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 ($P < 0.01$), 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.
AMI: acute myocardial infarction.

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. 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. 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.

The influence of the following variables on the time of AMI symptom onset were recorded: sex, age (≥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 χ² 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. 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 rhythm; 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. 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.

To address the problems of the cosinor method, the system developed by Alberola et al 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.

Significance was set at α=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 rhythmmetric 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.
The periodicity of myocardial infarctions has been reported in numerous studies over the last twenty years. 

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 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
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 increased, etc.¹⁵,⁵⁰

Behar et al²⁹ and Zarich et al⁵¹ indicate that AMI symptoms in diabetic patients show a circadian rhythm with a single morning peak. In the work of Zarich et al,⁵¹ this circadian rhythm is no longer seen in patients with serious dysregulation of the autonomic nervous system. Hjalmarson et al²² and Gilpin et al²⁰ 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).³⁷ Finally, other authors have reported the absence of a circadian rhythm with respect to the onset time of AMI symptoms in pa-
tion of the reinfarction. The results reported in this res-

might be the cause of the changes seen in the presenta-

logical to think that their pharmacological treatments

sion requirement for prior ischemic heart disease, it is

3). Since the patients with reinfarction met the inclu-

pattern in which the morning peak was attenuated and

ce peaks might reflect this alteration, along with the

rhythm was found, with a bimodal incidence

vascular 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 inclu-
sion requirement for prior ischemic heart disease, it is

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vascular risks associated with the disease.

The changes in the regulation of the autonomic ner-
vous system experienced by diabetic patients may be
one of the main reasons for the loss of a standard cir-
cadian rhythm for AMI symptom onset. The 2 inciden-
time 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

concerns and the pharmacological treatment of cardio-

vascular 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 inclu-
sion 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 presenta-
tion of the reinfarction. The results reported in this re-

spect in the literature are contradictory. Hansen et al47
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 al22 and Gilpin et al,20 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 al29
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 compari-

son of incidence of AMI onset over 6 h intervals using

Figueras et al54 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)
that than 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 pa-

ents shows a standard pattern with a single morning
peak followed by a progressive decline. Reinfarction
patients, however, show a bimodal pattern, with cir-
cadian 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 suffe-

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 to-
wards a nocturnal low point (Figure 4).

The results of Hjalmarson et al22 are in agreement
with the present data with respect to the double peak
of incidence shown by smokers. Kinjo et al,35 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
Tofler et al,13 tobacco might increase platelet aggrega-
bility. Certainly there is a relationship between smo-
kng a cigarette and the activation of the sympathetic
mechanisms of the autonomic nervous system. Spa-
cing out smoking over the day might favor the attenua-
tion of the morning peak and the appearance of an
evening incidence plateau.

CONCLUSIONS

The onset time of AMI symptoms follows a sinu-
soidal curve with a morning peak and an early mor-
ing 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 he-
art disease or a prior cerebrovascular accident, and
among those with family histories of ischemic heart
disease (risk markers). Those with high blood pressu-
re and dyslipidemia (modifiable factors) also show
this pattern. However, patients with diabetes, who
smoke, or who suffer reinfarction, show a double in-
cidence peak in their curves.

Researchers of the ARIAM (Análisis
del Retraso en el Infarto Agudo de Miocardio)
Study Group

Advisory committee: M. Álvarez, J.J. Rodríguez, E.
Torrado, A. García, (Málaga, Spain).

Collaborators: J. Canovas (Hospital General, Ali-
cante); F. Guardiola, A. Roche (Hospital Virgen de
los Lírios, Alcoi, Alicante); L. Gómez, A. Pérez
(Clinica Benidorm, Alicante); J. Cardona, V. Madrid
(Hospital General Marina Alta, Denia, Alicante); A.
Mota (Hospital General, Elche, Alicante); J.A. Martín,
J.A. Rodriguez (Hospital General, Elda, Alicante); F.
Criado (Hospital del SVS, Benidorm, Alicante); J.
Ortega, M. Martínez (Hospital Vega Baja, Orihuela,
Alicante); G. Pérez (Hospital Universitario de San
Juan, Alicante); F. Barredo, J.F. Martínez (Hospital
Torrecádenas, Almería); J. Córdoba (Hospital La
Inmaculada, Huelva, Alicante); L.J. Fierro, M.
Ruiz (Hospital Comarcal de Poniente, El Egidio,
Almería); A. Montón (Hospital General Yagüe,
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