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Onset of Acute Myocardial Infarction during Sleep

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Summary

Background: Analysis of the chronology of acute cardiovascular events may provide important pathophysiologic information. There is a circadian pattern in the onset of acute myocardial infarction (AMI) with a mid-morning peak, ascribed to the catecholamine surge that accompanies awakening and assuming the upright posture. However, in up to 27% of patients the onset of AMI occurs during sleep (without apparent precipitating factors). The reasons for this finding are unknown.

Hypothesis: The aim of the study was to determine why the onset of symptoms of AMI occurs during sleep in some individuals rather than being precipitated by known trigger factors such as physical exertion.

Methods: Using the database from a large multicenter clinical trial, patients were grouped according to whether or not they were awakened from sleep by the symptoms of AMI.

Results: In all, 870 of 3,309 patients (26%) were awakened by AMI. In general, these patients were older and sicker, with poorer left ventricular function, lower quality of life indices, more frequent heart failure, lower ejection fractions, higher incidence of angina, and a greater frequency of atrial arrhythmias. On multivariate analysis, only low ejection fraction and older age were independently associated with awakening by the symptoms of AMI.

Conclusions: Patients who are older and sicker are more likely to be awakened from sleep by the onset of symptoms of AMI. Although the reasons are unknown, we speculate that these individuals are less active and therefore less vulnerable to established trigger factors such as vigorous physical exertion.

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Introduction

Analysis of the timing of acute cardiovascular events has the potential for providing important clues to their pathophysiology. Numerous studies have demonstrated a circadian pattern in the onset of acute myocardial infarction (AMI) with a peak in mid to late morning and/or late afternoon and early evening.[1–4] The morning peak has been ascribed to the effects of the surge in catecholamines that accompanies awakening and assuming the upright posture.[5, 6] The pathogenesis of the afternoon–evening peak is less clear. These peaks have been shown actually to increase in prominence when the onset is adjusted for the time of awakening.[7, 8] Other known trigger factors of myocardial infarction include heavy physical exertion, sexual activity, and emotional stress.[9–13] In contrast, 10–27% of patients have the onset of symptoms of AMI during sleep (with no apparent precipitating factors),[7–9, 14, 15] but the characteristics of these patients have not been well delineated. We hypothesized that this patient group might somehow be different from individuals in whom the onset of the acute event occurs during activity. Accordingly, we utilized the large database from the Cardiac Arrhythmia Suppression Trial (CAST) to examine the characteristics of the patient population who were awakened from sleep by the onset of AMI.

Methods

The institutional Committee on Human Research approved the study protocol in all participating institutions. Written informed consent was obtained from all subjects. The CAST was a prospective, placebo-controlled, randomized, double-blind study designed to test the hypothesis that suppression of unsustained ventricular arrhythmias by antiarrhythmic drugs in survivors of AMI would reduce the incidence of arrhythmic death. A detailed description of the CAST methodology has been provided elsewhere.[16, 17] The following is a brief review of the more important aspects of the trial, with more detailed information in the area relevant to the present analysis.

Patient Population

Patients were screened for inclusion in the trial between June 13, 1987, and August 1, 1991. Patients < 80 years of age were eligible if they demonstrated an average of ≥ 6 premature ventricular depolarizations/h on baseline 24-h ambulatory electrocardiographic (ECG) (Holter) monitoring and had an ejection fraction ≤ 55% within 90 days or ≤ 40% within 2 years of a documented AMI. Specifically excluded were patients with ≥ 15 consecutive beats of ventricular tachycardia at a rate of ≥ 120 beats/min > 6 days after infarction, symptomatic bradycardia (without a permanent pacemaker), New York Heart Association (NYHA) functional class IV congestive heart failure, significant (creatinine ≥ 2.5 mg%) renal failure, or any other conditions likely to limit life span. Also excluded were patients already receiving class I or III antiarrhythmic drugs or those with contraindications to any of the three study drugs (encainide, flecainide, moricizine).

After the first 22 months of the study, eligibility criteria were altered so that the upper limit of ejection fraction was 40% in all patients, the time from the qualifying myocardial infarction was shortened to ≤ 90 days, and up to 30 s of ventricular tachycardia was allowed if the individual was asymptomatic.

Before initiating the study medication, all patients underwent a detailed baseline medical history and physical examination. Patients were specifically questioned about the timing of the onset of symptoms of their qualifying AMI relative to the time of awakening on that day. Symptoms considered typical for AMI included severe discomfort anywhere in the anterior chest, back, neck, or shoulder for ≥ 30 min, frequently associated with nausea, vomiting, diaphoresis, or dyspnea.

Study Design

Patients were grouped according to whether or not they were awakened from sleep by the symptoms of AMI. Continuous variables between groups were compared with a one-way analysis of variance (ANOVA); categorical variables by chi-square test. P values < 0.05 were considered statistically significant. Stepwise regression analysis was used to select the predictors for a multivariate model. All demographic and clinical variables, but not quality of life variables, that were univariately related ($p < 0.10$) to awakening by AMI were considered as candidate variables for multivariate analysis. Standard stepwise methods with a $p < 0.05$ entry criterion were utilized to construct a logistic regression model where the outcome was "awakening by myocardial infarction."

Results

Data regarding timing of onset of AMI were available for 3,309 patients. Of these, 870 (26%) indicated that they were awakened by symptoms of AMI and 2,439 (74%) were not. The demographic characteristics of the two study groups are shown in Table I. The patients awakened from sleep were, in general, older, with poorer left ventricular function, lower quality of life indices, a decreased level of activity due to poor health, more frequent heart failure, higher incidence of angina pectoris, and a greater frequency of atrial fibrillation or flutter. More of them had ejection fractions ≤ 20%; 24% more were > 75 years of age; and 29% more were in NYHA functional class II and III. There was no gender difference between groups, and no significant difference in mean serum cholesterol or in the incidence of hypertension, diabetes, or cigarette smoking.

The ECG characteristics of the study groups are shown in Table II. These were derived from the ECG and Holter monitor recording obtained at the time of the the CAST qualifying examination. Those awakened from sleep had a higher resting heart rate and a higher incidence of left bundle-branch block. There was no difference between groups in PR interval or QRS duration, the incidence of left ventricular hypertrophy or abnormal Q waves, or the frequency of ventricular premature beats.

In the multivariate analysis, only low ejection fraction and older age were independently associated with awakening by the symptoms of AMI. The odds that a patient with an ejection fraction < 20% (n = 266) was awakened by symptoms were 1.48 times larger than those in a patient with an ejection fraction > 20% (odds ratio [OR] = 1.48, 95% confidence interval [CI] 1.14, 1.94, p = 0.0039) (Fig. 1A). "Age squares" entered the model (OR = 1.009 per 100 squared years, 95% CI 1.002, 1.016, p = 0.0079) such that the odds of awakening with a myocardial infarction were 10.5% higher for a change from 50 to 60 years old (n = 878), 12.5% higher for a change from 60 to 70 years old (n = 1291), and 14.6% higher for a change from 70 to 80 years old (n = 655) (Fig. 1B).

Discussion

Although there have been important advances in preventive cardiology in recent years, AMI remains an all too frequent and catastrophic event. Despite the identification of major risk factors and improved diagnostic modalities, there are currently no accurate means of predicting impending AMI in asymptomatic individuals. If those at greatest risk could be identified, then appropriate prophylactic measures might be undertaken. Current research has focused on the atherosclerotic plaque and the factors that cause it to become unstable, precipitating an acute event. Prior studies in this area have addressed the role of specific activities as potential trigger factors.[9–13] However, in up to 25% of cases, the onset of AMI occurs during sleep, in the absence of any apparent precipitating factors.[7–9, 14, 15] Since this represents a considerable number of acute events, information about the pathophysiology would be of considerable importance.

The major finding of the present study is that patients awakened from sleep by the onset of symptoms of AMI tend to be older and have a higher incidence of severe cardiac disease and symptomatic angina pectoris, and that this relationship is most pronounced in the subgroup that is oldest (≥ 76 years) and the subgroup that has the lowest ejection fraction (≤ 20%). Although the mechanisms involved in these findings are unknown, we speculate that these individuals are likely to be less

TABLE I Clinical characteristics of the study population grouped according to whether or not they were awakened by the symptoms of acute myocardial infarction

Characteristic	Awakened by Sx	Not awakened by Sx	p Value
No. of patients (3309) (%)	870 (26.3)	2439 (87.7)	
Age (years)	62.4 ± 10	61.4 ± 10	0.0096
Male gender (%)	706 (81.1)	1994 (81.8)	NS
Caucasian (%)	698(80.2)	1969 (80.7)	NS
Ejection fraction	0.35 ± 0.10	0.36 ± 0.10	0.02
Cholesterol (mg %)	214.3 ± 49	213.2 ± 49	NS
H/o heart failure (%)	160 (18.4)	371 (15.2)	0.03
H/o of angina (%)	436 (50.1)	1126 (46.2)	0.04
Hypertension (%)	302 (34.7)	770 (31.6)	NS
Diabetes (%)	197 (22.6)	520 (21.3)	NS
Previous MI (%)	396 (45.5)	1033 (42.4)	0.10
Decreased activity due to health (%)	296 (34)	734 (30.1)	0.03
H/o CABG/PTCA (%)	182 (20.9)	468 (19.2)	NS
H/o smoking (%)	707 (81.3)	1990 (81.6)	NS
H/o A fib/A flut (%)	29 (3.4)	48 (2.0)	0.02
QL symptoms (1-6)	1.9 ± 1.2	1.8 ± 1.2	0.04
QL mood (1-6)	1.5 ± 1.1	1.4 ± 1.0	0.3
Sitting BP	126 ± 19	125 ± 19	NS

Abbreviations: Sx = symptom, H/o = history of, MI = myocardial infarction, CABG = coronary artery bypass graft, PTCA = percutaneous transluminal coronary angioplasty, A fib = atrial fibrillation, A flut = atrial flutter, QL symptoms = quality of life related to symptoms (0 = no symptoms and 6 = symptoms all of the time), QL mood = quality of life related to mood with (0 = the best mood and 6 = the worst mood), BP = blood pressure, NS = not significant.

TABLE II Electrocardiographic characteristics of the study population grouped according whether or not they were awakened by the onset of symptoms of acute myocardial infarction

Characteristic	Awakened by Sx	Not awakened by Sx	p Value
No. of patients	870	2439	—
QRS width (ms)	0.947 ± 0.02	0.940 ± 0.02	NS
QT interval (ms)	0.38 ± 0.4	0.38 ± 0.4	NS
Abnormal Q waves (%)	611 (73.7)	1776 (75.7)	NS
PVC/h on Holter	126 ± 249	125 ± 243	NS
LBBB (%)	31 (3.6)	53 (2.2)	0.025
Sitting heart rate (beats/min)	76.1 ± 13	75.0 ± 13	0.03

Abbreviations: PVC = premature ventricular contractions, LBBB = left bundle-branch block. Other abbreviations as in Table I.

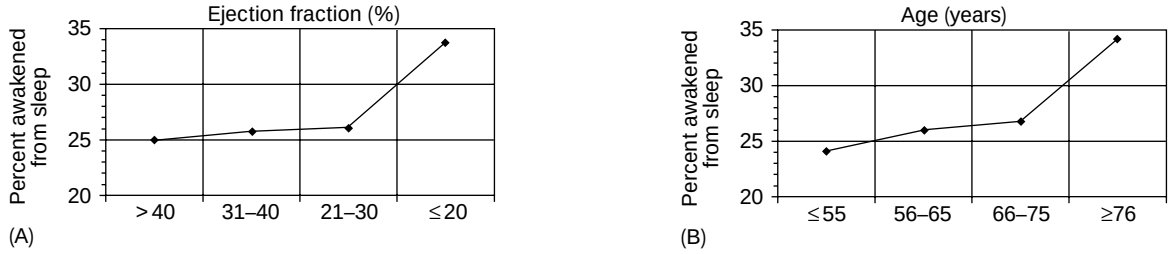

FIG. 1 (A) The relationship between ejection fraction and the probability of being awakened from sleep by the onset of symptoms of acute myocardial infarction. The patients with ejection fractions ≤ 20% are 1.48 times more likely to be awakened by the onset of symptoms than patients with ejection fractions > 20%. (B) The relationship between age and the likelihood of being awakened from sleep by the onset of acute myocardial infarction. Similar to the pattern observed with ejection fraction, there is an abrupt increase in the oldest age group.

active and therefore less vulnerable to established trigger factors such as vigorous physical exertion and sexual activity. In fact, a higher percentage of these patients admitted to decreased physical activity because of poor health.

This hypothesis is supported by a study of Pell and D'Alonzo, who examined the clinical and epidemiologic aspects of AMI in 1,356 employed patients between 25 and 64 years of age.[18] They found that younger men were almost three times more likely to be engaged in heavy activity or severe exertion at the time of symptom onset than their older co-workers. Similarly, French and Dock, and also Yater *et al.* describe a much lower incidence of AMI occurring during sleep (10 and 13.1%, respectively) in populations that were considerably younger than ours.[14,15] In contrast, Ridker *et al.* found that 26.3% of patients were awakened by the symptoms of AMI (compared with 26.2% in our study) in the population of the Physicians Health Study, which was 20–30 years older than in the two studies described above.[19] Stewart *et al.* recently reported the results of a study based upon a standardized questionnaire in 2,468 consecutive patients admitted to a coronary care unit with a first myocardial infarction between 1975 and 1993.[9] They found that patients with exercise-related symptom onset were more likely to be younger and male, while those who had onset of symptoms in bed were more likely to be older and have a history of stable or unstable angina. The study did not distinguish between those individuals who were asleep at the time of symptom onset and those who were merely in bed (perhaps, in some cases, because they were feeling ill).

Limitations

Our data should be interpreted in light of several methodologic limitations. Although our hypothesis was defined prospectively, prior to data analysis, the information was obtained at the time of the baseline examination, which may have occurred as long as 2 years after the qualifying myocardial infarction. Thus, the data exclude patients who died from the acute infarct (or from other causes) and may be applicable only to a select population of survivors. In addition, this time differential raises the possibility that our findings could be partly due to biased recall. However, when we analyzed the percentage of patients awakened by symptoms as a function of the time interval between their index myocardial infarction and their CAST baseline examination, we found no significant differences between groups (i.e., there was no significant difference among those patients examined within 14 days of their myocardial infarction, 15–28 days, 29–42 days, 43–90 days, etc.). Second, we have no information about the type of medication that individuals were receiving at the time of the acute event. Some of these medications, such as beta blockers or salicylates, may have some effect upon trigger factors of AMI and may have affected our findings. However, only 30% of patients were receiving beta blockers (and a smaller percentage were receiving salicylates on a regular basis) at the time of their baseline examination,[16] and it is likely that an even smaller percentage of individuals were receiving these medications prior to their qualifying myocardial infarction. Third, for the purposes of the present analysis, we have assumed that the onset of symptoms of AMI is synonymous with the onset of the event. In certain individuals, such as those with a stuttering onset or those with prolonged episodes of pre- or postinfarction angina, the actual initiation of myocardial necrosis may be difficult to determine without hourly serum enzyme determinations. Similarly, symptoms may be an unreliable indicator in patients with altered pain perception, such as diabetics and the very elderly. However, these limitations would apply similarly to both groups so that any systematic bias is unlikely. Finally, practice patterns change; for example, it is likely that a higher percentage of patients are prescribed beta blockers and aspirin following AMI now than was true 10 years ago. Accordingly, the applicability of our data to present day practice may be limited.

Conclusions

Patients who are awakened from sleep by the symptoms of acute myocardial infarction appear to be older and sicker than individuals who develop symptoms during activity. These data suggest that these former individuals may be less likely to be exposed to recognized trigger factors such as heavy exertion or sexual activity. Further studies are warranted to attempt to identify factors that are likely to precipitate acute myocardial infarction in individuals who are largely sedentary.

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Images in Cardiology: Osborn Waves of Severe Hypothermia

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A 50-year-old alcohol-addicted man was admitted unconscious with a core body temperature of 26° C. Blood tests revealed normal serum values for sodium, chloride, potassium, and calcium. Alcohol was negative in serum. The patient was rewarmed by conventional means (warmed air and infusions). No serious disturbances of cardiac rhythm occurred, respiration remained sufficient, and the patient survived without serious complications.

The initial electrocardiogram (ECG) (Fig. 1A, 26° C) showed a normal heart rate of approximately 80 beats/min with intermittent atrial fibrillation. PQ and QTc intervals were prolonged (280 and 600 ms, respectively) as was the QRS complex, which displayed the typical Osborn waves of hypothermia most pronounced in V_3–V_6, I–III, and aVF. Similar ECG alterations have been described in normothermic patients with hypercalcemia, acute central nervous system abnormalities, or acute inferior wall myocardial infarction, and they have been referred to as Osborn wave, J wave, camel hump, or hypothermic hump.

During rewarming the patient's ECG gradually normalized. After 4 h (Fig. 1B, 30° C) a regular ectopic atrial rhythm was observed and QTc interval had shortened to 503 ms. The Osborn waves were markedly reduced. In the final ECG after 24 h (Fig. 1C, 36.7° C) Osborn waves had disappeared and only a slightly prolonged QTc interval (453 ms) remained.

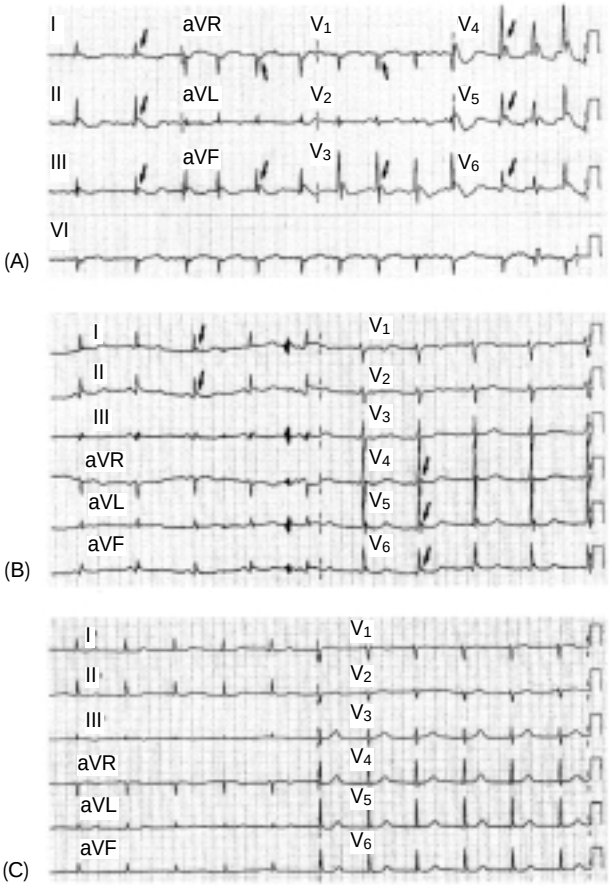

FIG. 1 Twelve-lead electrocardiograms at (A) admission, (B) after 4 h, and (C) after 24 h. See text for explication.

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