Comparison Between Young Males and Females with Acute Myocardial Infarction

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Objective - *To assess the differences between young males and females after acute myocardial infarction.*

Methods - *We retrospectively studied 236 patients (54 females and 182 males) after acute myocardial infarction and during hospital stay assessed the following parameters: risk factors; the treatment used; the pattern of coronary artery obstruction; left ventricular ejection fraction; complications; and, using a logistic regression model, the factors related to the occurrence of reinfarction and death.*

Results - *No significant difference was observed between the sexes in risk factors, pattern of coronary artery obstruction, and left ventricular function. The time interval between symptom onset and treatment was longer in females (p=0.03), who underwent thrombolysis (p=0.01) and angioplasty (p=0.03) less frequently than males did, but not myocardial revascularization. Female sex (OR = 5.98) and diabetes (OR = 14.52) were independent factors related to the occurrence of reinfarction and death.*

Conclusion - *Young males and females after acute myocardial infarction did not differ in coronary risk factors, and clinical and hemodynamic characteristics. Females had their treatment started later, and they underwent chemical thrombolysis and angioplasty less frequently than males did. Female sex and diabetes were related to the occurrence of reinfarction and death.*

Keywords: acute myocardial infarction, young, sex, clinical evolution

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The concept that acute myocardial infarction is not common in young individuals is based on the fact that it occurs in only 4 to 8% of this population [1,2]. If considered in absolute numbers however, acute myocardial infarction in this age bracket is not infrequent. Considering only the Brazilian hospitals accredited by the Public Health Care System (Sistema Único de Saúde), during the year 2000, 4,549 patients younger than 45 years of age were hospitalized due to acute myocardial infarction [3].

Acute myocardial infarction has a peculiar presentation in the young population with specific etiopathogenic, anatomic, and prognostic characteristics that differentiate these patients from the elderly [1,2,4-6]. As young patients with acute myocardial infarction get ill during their years of greater productivity, they suffer even more severe psychosocial and economic consequences [6,7].

Like the age factor, sex seems to influence the clinical presentation of acute myocardial infarction [7-11]. Females with acute myocardial infarction, in addition to being approximately 10 years older than males are, have a higher incidence of systemic arterial hypertension, diabetes mellitus, normal coronary arteries, and clinical signs of heart failure (even though their ejection fraction is not lower than that of males) [9-12]. It has not yet been defined whether the higher mortality in females with acute myocardial infarction occurs because they are affected at a more advanced age, because of the different incidences of several risk factors, or whether an independent association between female sex, morbidity, and mortality after acute myocardial infarction exists [8-11].

To better understand the characteristics of acute myocardial infarction in young patients, we assessed and compared the differences between the sexes in the incidence of risk factors for coronary artery disease, such as smoking, total hypercholesterolemia, high LDL-cholesterol levels, low HDL-cholesterol levels, hypertriglyceridemia, systemic arterial hypertension, diabetes mellitus, and familial history of early coronary artery disease. We also assessed the electrocardiographic location of acute myocardial infarction, the association between acute myocardial infarction and

pathological Q waves, the pattern of coronary artery obstruction, left ventricular ejection fraction, in-hospital clinical evolution, treatment, and complications after acute myocardial infarction. And finally we assessed the risk factors for reinfarction and death.

Methods

We retrospectively studied 236 patients with acute myocardial infarction admitted to the Instituto do Coração of the Hospital das Clínicas of the Medical School of the University of São Paulo from January 1996 to July 1999. This study was approved by the committee on ethics for analysis of research projects of the above-cited hospital.

We selected 25- to 45-year-old patients with the diagnosis of acute myocardial infarction established in the presence of at least 2 of the following criteria: a) clinical: report of pain in the anterior thoracic location, characterized as a pressure, tightness or a burning sensation > 20 minutes [13]; b) electrocardiographic: elevation of the ST segment ≥ 1mm, measured 0.02 seconds after the J point or pathological Q wave (duration m 0.03 seconds and amplitude m 3 mm) in at least 2 contiguous leads of the conventional electrocardiogram, including V7 and V8 [14,15]; c) enzymatic criteria: high levels (above 20 IU) of the myocardial fraction of creatine phosphokinase (normal value of 10 IU) [16].

Electrocardiograms were performed on hospital admission, after the initial treatment, at the emergency department and repeated daily or in the presence of symptoms or arrhythmias.

Blood samples were collected at the beginning of hospital admission and every 6 hours until normalization of the plasma enzymatic levels.

Patients with at least one of the following conditions were excluded: acute myocardial infarction during or following any surgical procedure; acute myocardial infarction in patients undergoing heart transplantation; patients with congenital cardiac or vascular malformations admitted to the hospital 48 hours after acute myocardial infarction symptom onset.

In this way, 236 patients (182 males and 54 females) with ages ranging from 27 to 45 (mean of 40.8±3.7) years were selected.

According to the presence of the pathological Q wave in at least 2 contiguous leads, acute myocardial infarction was classified as "Q-wave" and "non-Q-wave" myocardial infarction [15].

In regard to its electrocardiographic location, acute myocardial infarction was classified as [15] anterior (septal, anterolateral, high lateral, extensive location) - alteration in 1 or more of the following lead groups: V_1-V_3; V_4-V_6; D_1 and AVL; inferior (inferior, inferolateral, inferodorsal, laterodorsal, inferolaterodorsal location) - alteration in 1 or more of the following lead groups: D_2, D_3, AVF; D_1, AVL; V_5 and V_6; V_7 and V_8; undetermined - normal electrocardiogram or with left bundle-branch block.

The following risk factors were assessed: a) smoking: active smokers or those who had quit smoking within the 3 years preceding acute myocardial infarction were considered smokers [17]; b) hypercholesterolemia: total cholesterol > 200 mg/dL (measured during hospitalization) [18]; c) high LDL-cholesterol: LDL-cholesterol > 100 mg/dL (measured during hospitalization) [18]; d) low HDL-cholesterol: HDL-cholesterol < 35 mg/dL (measured during hospitalization) [18]; e) hypertriglyceridemia: triglycerides m 200 mg/dL [18]; f) systemic arterial hypertension: we considered as hypertensive those patients taking antihypertensive medication or with a history of systolic blood pressure m 140 mmHg or diastolic blood pressure m 90 mmHg, or both, based on an average of blood pressure measurements on at least 3 different days [19]; g) diabetes mellitus: patients with a history of 2 measurements of fasting plasma glucose m 126 mg/dL on 2 different days or patients with classical symptoms of diabetes associated with glycemia m 200 mg/dL [20]; h) familial history of early coronary artery disease: report of coronary artery disease in parents or siblings, < 55 years if males, or < 65 years if females [18].

According to the percentage of obstruction of the coronary artery lumen, the obstructive lesions were classified as follows [21,22]: noncritical – arterial lumen obstruction < 50%; critical – arterial lumen obstruction of 50% or more; and occlusive – total arterial lumen obstruction, with no flow through the artery.

After calculating the final diastolic (FDA) and final systolic (FSA) areas with planimetry, the ejection fraction was calculated with ventriculography in the right anterior oblique view and the following formula[23]: $\% EF = (FDA - FSA / FSA) \times 100^n$.

The following complications occurred early after acute myocardial infarction (in-hospital phase): arrhythmias – complete (right and left) bundle-branch block, (second-degree, high-degree, and total) atrioventricular blocks, atrial tachycardia, atrial fibrillation, atrial flutter, accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation [15,24]; heart failure – presence of the 3rd heart sound, clinical signs of pulmonary congestion (dyspnea, orthopnea, crepitant and subcrepitant rales), or arterial hypotension (systolic blood pressure < 90 mmHg) refractory to volume replacement by intravenous via [25]; mechanical complications [25] – mitral insufficiency (mitral reflux on left ventriculography), ventricular rupture (confirmed on surgical procedure or on autopsy), interventricular septal defect (presence of systolic flow through the interventricular septum on left ventriculography); postinfarction angina [25]; reinfarction [25] and death, considered major events during in-hospital evolution.

The descriptive analysis of the quantitative variables was performed by calculating the means and standard deviations, while the analysis of the qualitative variables was performed by calculating the absolute and relative frequencies [26].

The Student *t* test for independent samples [26] was used for comparison between the male and female sexes for the quantitative variables with normal distribution and

sample size > 30. When the supposed normality of data was rejected or the sample size was < 30, the comparison of the quantitative variables between the sexes was performed with the nonparametric Mann-Whitney test [27].

To compare proportions and test sex homogeneity of qualitative variables, the chi-square test was used [26], except in situations in which the expected frequencies of responses were lower than 5, which required the use of the Fisher exact test [26].

The variables associated with the occurrence of reinfarction and death were identified with a logistic regression model with a stepwise selection process [28]. For this multivariate analysis, the variables with $p < 0.25$ in the univariate analysis were selected.

The statistical significance level of 5% ($p < 0.05$) and 95% confidence interval were adopted in the study.

Results

The mean age was similar for females (41 ± 3.3 years) and males (40.7 ± 3.8 years). No statistically significant difference was observed between the sexes in regard to the risk factors assessed (tab. I). For cholesterol fractions, LDL-cholesterol values were available in 112 patients (94 males and 18 females) and HDL-cholesterol values were available in 119 patients (99 males and 20 females). The remaining risk factors were assessed in all patients.

The HDL-cholesterol levels were significantly lower in males (41.5 ± 14.4 in females and 33.2 ± 10.6 in males; p=0.02) (tab. II), but when the low HDL variable was tested, the probability was borderline (p=0.053) (tab. I).

Infarcts in the inferior wall occurred in 50% of the females and in 55.3% of the males (p=0.53) (fig. 1), while Q-wave infarcts had a similar distribution in both sexes (81.5% in females and 82.4% in males; p=0.87).

Coronary angiography was performed in 52 (96.3%) females and 165 (90.7%) males. Females had twice as many normal coronary angiographies as males did (17.3% and 8.5%, respectively), but the difference was not significant;

Table I - Age and risk factors of coronary artery disease in young individuals with acute myocardial infarction

Variable	Sex		P [1]
	Female	Male	
Age (years)	41 ± 3.3	40.7 ± 3.8	0.67
Smoking	34 (63%)	136 (74.7%)	0.09
High total cholesterol	22 (40.7%)	100 (54.9%)	0.07
High LDL-cholesterol	14 (77.8%)	83 (88.3%)	0.26
Low HDL-cholesterol	7 (35%)	58 (58.6%)	0.053
Hypertriglyceridemia.	12 (22.2%)	62 (34.1%)	0.099
Arterial hypertension	22 (40.7%)	96 (52.7%)	0.12
Diabetes mellitus	5 (9.3%)	17 (9.3%)	0.99
Familial history of early coronary artery disease	20 (37%)	89 (48.9%)	0.12

P- Descriptive level of probability with the chi-square test.

Table II – Plasma lipid levels in young patients with acute myocardial infarction

Lipids (mg/dL)	Sex		P [1]
	Female	Male	
Total cholesterol [2]	224.3 ± 69	225.9 ± 53.2	0.91
LDL-cholesterol [3]	139.9 ± 61.7	147 ± 42.5	0.64
HDL-cholesterol [4]	41.5 ± 14.4	33.2 ± 10.6	0.02
Triglycerides [2]	194.4 ± 130.8	234.4 ± 185.4	0.21

[1] Descriptive level of probability with the Student *t* test; [2] measured in 236 patients (54 females and 182 males); [3] calculated in 112 patients (18 females and 94 males); [4] measured in 119 patients (20 females and 99 males).

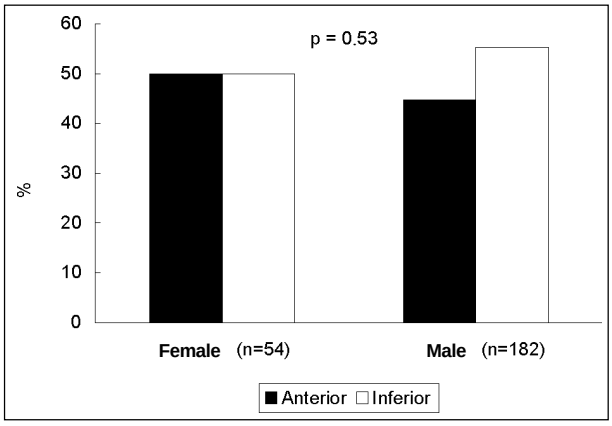

Fig. 1 – Electrocardiographic location of acute myocardial infarction in young patients.

42% of the patients, in both groups, had single-vessel disease (fig. 2).

Ventriculography was performed in 150 (63.6%) patients, whose left ventricular ejection fractions were calculated and were similar in males and females; 12.1% of the females and 6% of the males had left ventricular ejection fraction m 40% (tab. III).

The time (hours) elapsed between acute myocardial infarction symptom onset and treatment was significantly longer in females than in males (respectively 12.9 ± 14.6 and 7.6 ± 10.3; p=0.03) (fig. 3).

The use of thrombolytic agents and angioplasty was significantly lower in the female sex than in the male sex (p=0.01; p=0.03, respectively) (fig. 4). Myocardial revascularization was performed in 16.7% of the females and in

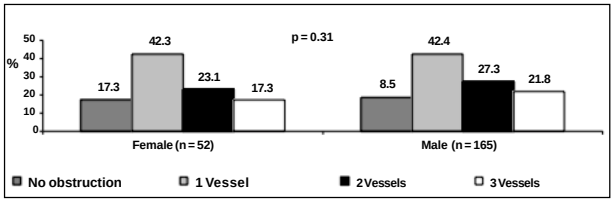

Fig. 2 - Pattern of coronary artery obstruction in young patients with acute myocardial infarction.

Table III – Left ventricular ejection fraction in young patients with acute myocardial infarction

Ejection fraction	Sex		P (1)
	Female (n=33)	Male (n=117)	
> 40%	29 (87.9%)	110 (94%)	0.26
≤ 40%	4 (12.1%)	7 (6%)	
Mean values	63.4 ± 19.1	66.4 ± 14.5	0.43

P- Descriptive level of probability with the chi-square test.

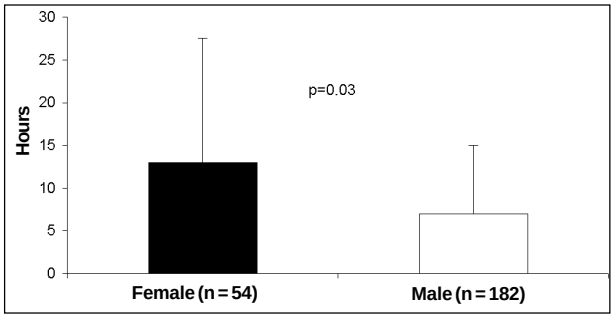

Fig. 3 - Time elapsed between symptom onset and treatment of acute myocardial infarction in young patients.

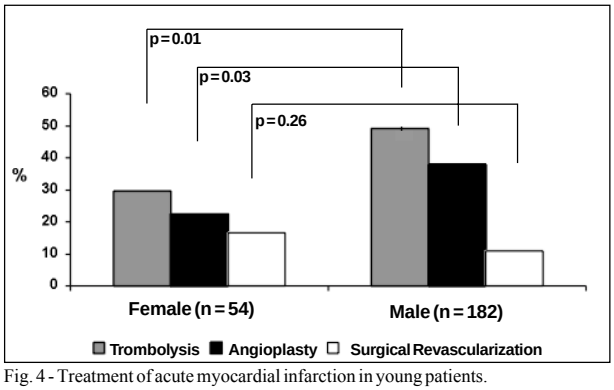

Fig. 4 - Treatment of acute myocardial infarction in young patients.

11% of the males, no significant difference being observed (p=0.26).

During hospital stay, complications occurred in 37% of the females and 30.8% of the males (p=NS). The analysis of the complications occurring alone (angina after acute myocardial infarction, heart failure, severe arrhythmias, mechanical complications, reinfarction, and death) did not show any significant difference between the sexes. Although not reaching significant levels (p=0.08), reinfarction was 3 times more common in females than in males (11.1% and 3.8%, respectively) (tab. IV).

Using the logistic regression model, the following parameters were assessed: sex, coronary risk factors, arterial pattern, and left ventricular ejection fraction. Of these variables, those that could foretell reinfarction or death, or both, were sex (OR = 5.98) and diabetes mellitus (OR = 14.52) (tab. V).

Table IV - In-hospital complications after acute myocardial infarction in young patients

	Sex		P
	Female (n=54)	Male (n=182)	
Postinfarction angina	9 (16.7%)	20 (11%)	(1) 0.26
Reinfarction	6 (11.1%)	7 (3.8%)	(2) 0.08
Heart failure	8 (14.8%)	28 (15.4%)	(1) 0.92
Severe arrhythmias	9 (16.7%)	21 (11.5%)	(1) 0.32
Mechanical complications	0	0	-
Death	3 (5.6%)	6 (3.3%)	(2) 0.43
Any complication	20 (37.1%)	56 (30.8%)	(1) 0.39

(1) Descriptive level of probability with the chi-square test; (2) descriptive level of probability with the Fisher exact test.

Table V - Probability of the occurrence of reinfarction and death in young patients after acute myocardial infarction

Variable	Estimated parameter	SD	P	Odds ratio"	IC) A 95%
Interception	-4.171	0.698	0.0001	-	-
Female sex	1.788	0.855	0.04	5.98	1.12; 31.97
Diabetes mellitus	2.675	0.917	0.003	14.52	2.41; 87.54

SD - standard deviation; P - descriptive level of probability; CI - confidence interval.

Discussion

In our study, patients up to 45 years of age were selected, according to the criterion in the literature, which considers a patient with acute myocardial infarction young if he or she is ≤ 40 or 45 years old [4-6,29-34]. The similarity of age between females and males allowed an adequate comparison between the sexes.

In our case series, no significant difference between males and females was observed in the risk factors for coronary artery disease. In acute myocardial infarction, in both sexes, high LDL-cholesterol and smoking were the most prevalent risk factors, while hypertriglyceridemia and diabetes mellitus were the least prevalent. Although HDL-cholesterol levels were significantly lower in males (tab. II), when the low HDL variable was tested, no significant difference occurred between males and females (borderline probability; tab. I).

The more elevated estrogen levels in young females and a shorter exposure of the young to the diverse risk factors of coronary artery disease, whose atherogenic effects on the cardiovascular system appear as years go by, may have contributed to the absence of statistically significant differences between the sexes in the risk factors of acute myocardial infarction [29-35].

We classified as smokers the active smokers and the individuals who had quit smoking in the 3 years preceding infarction, because population studies involving more than 1,000 patients have shown that 3 years after quitting smoking, the risk of acute myocardial infarction or death was similar to that of individuals who had never smoked [17]. The

fact that no significant difference was found between the sexes in the prevalence of smoking may suggest an increase in the smoking habit among young females. In more advanced age brackets, the prevalence of smoking is still higher among males as compared with that among females with acute myocardial infarction [8,36].

It has been reported in the literature that the isolated value of LDL-cholesterol plays a less significant role as a cardiovascular risk factor in females as compared with that in males [37-39]. On the other hand, a low HDL-cholesterol level has been considered an important predictor of mortality among females [7,35,37-41]. Currently, a meta-analysis carried out at the National Heart, Lung, and Blood Institute has shown that total hypercholesterolemia and high LDL-cholesterol levels correlate with a higher cardiovascular mortality in females younger than 65 years old, but not in the elderly [40].

The role of triglycerides as an independent risk factor of coronary artery disease is still controversial; some admit their greater importance in females, especially in the elderly [42-45], mainly due to an increase in thrombotic risk [45]. Our results indicate that, at least in young patients, lipid alterations did not correlate with reinfarction and death. However, the small number of patients in our study does not allow definitive conclusions.

Some authors have reported a low prevalence of systemic arterial hypertension in young patients with acute myocardial infarction [6,31]; our data are not in accordance with these results, because approximately half of our patients, males and females, had a history of systemic arterial hypertension.

One of the factors that may have contributed to the higher prevalence of systemic arterial hypertension in our study was the criterion used for diagnosing hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure m 90 mmHg) [19,46], because in the studies cited, the definition of systemic arterial hypertension requires more elevated blood pressure levels [6,31]. Confirming our observations, Mansur et al [47] reported that systemic arterial hypertension was the major risk factor of coronary artery disease in 321 females, both in premenopause and postmenopause.

Diabetes mellitus was the least prevalent risk factor in our study, present in 10% of the patients of both sexes. One possible justification for the lower prevalence of diabetes mellitus in young patients of both sexes after acute myocardial infarction could be the fact that the atherogenic effects of diabetes mellitus on the cardiovascular system appear throughout the years [37,48]. We do not know any study in the literature specifically about the coronary risk caused by diabetes mellitus in young individuals.

Finally, approximately half of the males and females in our case series had a familial history of early coronary artery disease with no statistically significant difference between the sexes. Our results have shown that a familial history of early coronary artery disease is an important cardiovascular risk factor in young patients of both sexes.

In our study, the obstructive lesions in the major coronary arteries m 50% were considered critical. Although alterations in coronary flow at rest occur only in the presence of stenoses of the vessel lumen greater than 70% [49], that criterion was adopted because the risks of acute myocardial infarction and sudden death do not proportionally relate to the degree of coronary obstruction [21,50,51], and most infarctions occur after disruption of plaques that do not cause alterations in the coronary flow at rest [50,51].

Most of our patients of both sexes had single-vessel disease in the coronary arteries. These results are in accordance with those of other reports showing the predominance of critical single-vessel coronary lesions in young patients with acute myocardial infarction [4-6]. Although females had twice as many normal coronary angiographies as compared with males, we found no significant difference in the arterial pattern between the sexes. The higher platelet activity and the more elevated fibrinogen levels in young females [52] as compared with those in young males could be 1 justification for this difference (although not significant), because acute myocardial infarction with normal coronary arteries may be due to alterations in coagulation in 12.2% of the cases [53].

Everything suggests that the endothelial dysfunction resulting from risk factors, such as smoking, dyslipidemia, and arterial hypertension, associated with coronary spasm and thrombosis, plays an important role in the genesis of acute myocardial infarction in younger patients [4-6]. The shorter evolution of atherosclerotic coronary artery disease and the absence of differences between the risk factors of acute myocardial infarction may have been factors that determined the absence of significant differences between the arterial pattern in male and female patients.

In regard to left ventricular ejection fraction, no significant difference was observed between males and females in our sample, and, in regard to the incidence of heart failure after acute myocardial infarction, occurring in approximately 15% of our patients, no significant difference between the sexes was observed. Several studies involving patients with symptomatic coronary artery disease have shown that the prevalence of heart failure in females is approximately twice that in males, even though left ventricular ejection fraction is equal or even higher in females [12,54-57]. This apparent paradox is attributed to the more frequent presence of diastolic dysfunction in females [10,54-57].

In our case series, as with those in other centers [12,58,59], the treatment of acute myocardial infarction in females started significantly later than in males. This may show that the suggestive symptoms of acute myocardial infarction in young females have not yet been properly appreciated either by the patients, who seek medical assistance late, or by the physicians. Even currently, females are more aware of the risks of cancer than of those of cardiovascular diseases [60].

The fact that the treatment of the females started later may have influenced their therapy, resulting in a higher use of chemical thrombolysis and angioplasty. In addition, the clinical history of acute myocardial infarction of a female

patient is many times atypical, causing frequent diagnostic errors that interfere with the indication for thrombolysis [61-66].

Several studies have reported that females undergo surgical myocardial revascularization less frequently than males do [67-71], a trend that has changed lately [72]. In our study, surgical indication was similar for males and females, maybe because of the absence of statistically significant differences between the sexes in the incidence of triple-vessel coronary artery disease and impairment of left ventricular function.

In regard to clinical evolution, no significant difference was observed between the sexes in the occurrence of complications. In the literature, after acute myocardial infarction, females have been reported to have mitral insufficiency, heart failure, ventricular rupture, bradyarrhythmias, and atrial fibrillation more frequently than males do; males have a higher incidence of ventricular tachyarrhythmia (fibrillation and tachycardia) [9,10,56,59]. In our study, the absence of differences between the sexes in age, prevalence of systemic arterial hypertension and diabetes mellitus, left ventricular ejection fraction, and coronary artery obstruction pattern may have contributed to the similar incidence of complications.

We diagnosed no mechanical complications after acute myocardial infarction. However, only 3 of the 9 patients who died underwent autopsy, which may have influenced this result.

Reinfarction and death were considered major events. Although significant (p=0.08) levels have not been reached in our study, the 3 times higher reinfarction incidence in females as compared with that in males is noteworthy (11.1% and 3.8%, respectively). Some studies have shown a higher reinfarction rate in females [10,59], but other reports have not found a significant difference [12,55]. This difference in reinfarction occurrence between males and females could be related to differences in the coagulation and fibrinolytic systems existing between the sexes at any age bracket [10,50,51].

On the other hand, in our study, a small number of deaths was observed, 3 females and 6 males, during hospital evolution. In terms of percentage, a higher mortality occurred in the female sex than in the male sex, but this difference was not statistically significant; the small number of deaths did not allow conclusions about this result.

Cardiovascular disease is the major cause of death among western females [11,73], and a number of studies have assessed the relation between sex and mortality after acute myocardial infarction; the results, however, are still controversial [9-11,56,66,74,75]. The greater mortality among females has been related to the fact that they are older and have a higher prevalence of comorbidities, such as systemic arterial hypertension and diabetes mellitus, as compared with males [9-11,74,75]. Some authors, however, consider the female sex as an independent predictor of mortality [10].

The role played by sex in the mortality rate becomes still less clear when the different age brackets of the patients experiencing acute myocardial infarction are analyzed. Vacarino et al [9], in a recent study of 155,565 females and 229,313 males, reported that, after acute myocardial infarction, the younger females have a higher in-hospital mortality compared with that of males of the same age (the younger the female, the higher the mortality). Malacrida et al [75], however, reviewing the evolution of 36,080 patients of the ISIS-3 study (9,600 females and 26,480 males) disagreed with these results, reporting a lower difference in mortality between males and females with age reduction and only a small sex-independent effect on mortality, which was slightly higher in the female sex (OR = 1.14).

In our study, female sex and diabetes were independent factors related to the occurrence of reinfarction and death.

We believe that several factors may have influenced these results, but the clinical differences between males and females may have been particularly relevant, as may the higher platelet activity and the more elevated fibrinogen levels in females [52].

On the other hand, diabetes mellitus causes hyperviscosity, endothelial dysfunction, a reduction in fibrinolysis, and an increase in platelet aggregation, in the coagulation factors, in fibrinogen, and in LDL-cholesterol oxidation [76-78]. These factors may contribute, alone or in association, to the occurrence of reinfarction and death.

In conclusion, our results do not show differences between the sexes after acute myocardial infarction in risk factors, coronary artery obstruction pattern, left ventricular ejection fraction, and in-hospital complications in patients aged 45 years or less. On the other hand, the treatment of female patients started later and females underwent chemical or mechanical thrombolysis less frequently than males did. Female sex and diabetes mellitus were identified as independent risk factors for reinfarction and death.

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