Clinical Investigations

Risk Factors Related to the Occurrence of Silent Myocardial Ischemia in Mexicans

ALBERTO UNZUETA-MONTOYA, M.D., JORGE ESCOBEDO-DE LA PEÑA, M.D., M.P.H., M.SC., FACP,* ARTURO TORRES-Y GUTIÉRREZ RUBIO, M.D., ALBERTO UNZUETA, JR., M.D., GUILLERMO ORDOÑEZ-TOQUERO, M.D., PATRICIA PÉREZ-REYES, M.D.,* HÉCTOR HERNÁNDEZ-Y HERNÁNDEZ, M.D.

Hospital of Cardiology, National Medical Center "Siglo XXI," Mexican Institute of the Social Security; *Epidemiology Division, Coordination of Community Health, Mexican Institute of the Social Security, Mexico, D.F., Mexico

Summary

Background: Silent myocardial ischemia is a growing world health problem. It has been related to factors that promote an increase in myocardial oxygen demand or affect coronary vasomotor tone. Coronary artery disease has shown an increasing trend in Mexico in this century.

Hypothesis: The aim of the study was to estimate the strength of the association between some risk factors and the occurrence of silent myocardial ischemia.

Methods: A cross-sectional study was conducted and 249 individuals were screened by 24-h Holter electrocardiogram. Silent myocardial ischemia was diagnosed in patients with painless transient ST-segment depression. All subjects were interviewed for coronary risk factors and total serum cholesterol was measured.

Results: Silent ischemia was diagnosed in 115 patients (46%), who were older (59 ± 9 vs. 57 ± 11 years; $p = 0.01$). In a logistic regression analysis, a lower risk for silent ischemia was found in patients with thrombolysis [odds ratio (OR) 0.28; 95% confidence interval (CI) 95% 0.14–0.53], or those who followed their medical treatment (OR 0.16; CI 95% 0.04–0.68). The major risk factors were hypercholesterolemia (OR 1.6; CI 95% 0.9–2.9) and more severe coronary artery disease (OR 2.5; CI 95% 1.1–5.7).

Conclusions: Some coronary risk factors are related to silent ischemia. It is still important to diagnose this entity, but modification of its related risk factors should be kept in mind to diminish its occurrence and its severe consequences.

Key words: silent myocardial ischemia, risk factors, coronary artery disease, ambulatory monitoring, thrombolysis, ST-segment depression

Introduction

Silent myocardial ischemia is a common manifestation of coronary artery disease (CAD) regardless of the absence of clinical symptoms.¹ It is even more frequent than angina in patients with CAD. Silent ischemia has been frequently related to adverse coronary events and sudden cardiac death, and it is an independent predictor of mortality even in patients with stable angina.^{2,3}

Silent ischemia may be present in 2.5% of asymptomatic individuals and in up to 50% of patients after myocardial infarction (MI).⁴ Despite control of anginal symptoms with drugs, more than 40% of patients with stable angina have silent ischemia during ordinary daily activities.³

Risk factors that promote an increase in myocardial oxygen demand or affect coronary vasomotor tone contribute to the occurrence of silent ischemia.¹ Several risk factors have been related to silent ischemia, all well-established risk factors for overt CAD.^{5–7} Hypertension^{5,6} and smoking,⁷ but not diabetes⁸ have been related to silent ischemia. In healthy volunteers, age, gender, obesity, and high-density lipoprotein (HDL) levels were risk factors for exercise-induced silent ischemia.⁷

Both the extent of CAD and the degree of left ventricular dysfunction are strong predictors of the prognosis after MI. However, these data are not always available in patients with CAD. Silent myocardial ischemia is thus an alternative prognostic factor in patients who have survived an MI.² Since silent myocardial ischemia is considered to be present in patients

Address for reprints:

Alberto Unzueta-Montoya, M.D.
Retorno 62 No. 6
Colonia Avante
Coyoacán
04460 México, D.F.
México

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with CAD or coronary artery spasm,⁸ it is important to differentiate risk factors related to CAD from those related to silent ischemia once CAD is present.

Coronary artery disease is a growing problem in Mexico⁹ and it is one of the main causes of hospitalization and death. Several studies have recently analyzed the occurrence of CAD in Mexicans,^{10, 11} as well as those prognostic factors that predict an adverse outcome in those patients with CAD who have survived a first MI.¹² The authors conducted this study to identify risk factors related to the occurrence of silent ischemia in patients with known CAD.

Methods

A cross-sectional study was conducted in a group of patients with CAD and long-term stable angina; these patients were included in a clinical trial for silent myocardial ischemia. They had been attended at the Cardiology Hospital of the National Medical Center, at the Mexican Institute of the Social Security, at least 6 months before inclusion into the study. Coronary artery disease was diagnosed in patients with a clinical onset of MI documented by ECG, or in patients with at least 75% reduction in lumen diameter of the major coronary arteries as measured by coronary angiography. Major coronary arteries were defined as the left anterior descending, left circumflex, and right coronary arteries.

In all, 249 individuals were screened by 24-h Holter electrocardiogram (ECG), and silent myocardial ischemia was diagnosed in those patients with a painless transient ST-segment depression. An episode of ST-segment depression was defined as ≥ 1 mm horizontal or downsloping ST-segment depression, persisting at 80 ms after the J point and lasting ≥ 60 s in consecutive beats. Each episode needed to be apart from another one for at least 1 min. The same criteria were used when there was an ischemic ST-segment elevation, defined as ≥ 1 mm upsloping above the isoelectric line compared with the baseline ST segment.

Ambulatory ECG was performed with a Hewlett Packard 43400 electroanalyzer, HP vectra QS 20 hardware (Hewlett Packard, Seattle, Wash., USA), and new wave Holter software, following the American Heart Association recommendations.¹³ After careful skin preparation, electrodes were placed on the anterior thorax surface to obtain the register of potentials at leads V₁ and aVF. Patients were instructed to carry out their usual daily activities. They were asked to fill out a comprehensive structured daily report that included any symptoms felt, their duration, and whether any drug was taken for chest pain relief.

Baseline ECG recording was made for each patient before and after hyperventilation, and in the supine, prone, sitting, and standing positions to ensure that the ST segment was not affected by posture. Electrocardiographic tracings of all episodes suggesting silent myocardial ischemia were obtained at 25 mm/s speed for review. The total number of episodes and their total duration in min were determined in each patient in a 24-h period. All ST-segment abnormalities, either depression or up-

sloping, were classified as symptomatic or silent according to the presence of angor as registered on the patient's report.

Patients were excluded if they had a ≥ 1 mm ST-segment abnormality during baseline ECG recording; if they had a recent (< 90 days) MI; unstable angina, arrhythmia, cardiac pacemaker insertion, severe valvular cardiopathy, left or right bundle-branch block; if they were receiving digitalis therapy; or if they had chest pain during the Holter ECG. None of the patients included in the study had angina during the 24-h ambulatory period.

All recordings were analyzed by two independent physicians and one of the authors (A.U.), all of whom were blinded to the patients' conditions. In case of discrepancy of opinions among the three observers, the tapes were reanalyzed, and if discrepancy persisted the patient was excluded from the study. All subjects were also interviewed for known coronary risk factors. Previous treatment, either medical or surgical, was also registered and total serum cholesterol was measured.

Categorical variables were compared with a chi-square test, whereas continuous variables were analyzed using analysis of variance (ANOVA) or the Kruskal-Wallis test. A logistic regression analysis was conducted to control for potential confounders. Odds ratios were calculated to assess association and 95% CIs were also estimated. A nonparametric Mantel and Haenszel X test was used for hypothesis testing, and a chi square for trend (X^2_{trend}) was used to evaluate a dose-response effect in ordinal categorical variables.

Results

Table I illustrates the subdivision of our patient population, based on the presence or absence of silent myocardial ischemia. We studied 202 men (81%) and 47 women (19%). During ambulatory ECG, silent myocardial ischemia was diagnosed in 115 patients (46%). The mean age of the study population was 58.1 years (± 10.04); however, those with silent myocardial ischemia were older (59.8 ± 9.3 years) than those without ischemia (56.7 ± 10.5 years; $p = 0.01$).

TABLE I Total number of patients with and without silent myocardial ischemia and the presence of the studied risk factors

Variable	With silent ischemia (n = 115)	Without silent ischemia (n = 134)
	No. (%)	No. (%)
Gender		
Male	89 (77)	113 (84)
Female	26 (23)	21 (16)
Hypertension	38 (33)	51 (38)
Hypercholesterolemia	60 (52)	51 (38)
Diabetes	43 (37)	41 (31)
Thrombolysis	21 (18)	62 (42)
Drug therapy	104 (90)	131 (98)
Previous myocardial infarction	97 (84)	131 (98)

TABLE II Findings during ambulatory electrocardiogram monitoring in patients with silent myocardial ischemia

Total transient silent ischemic events (n)	243
Total silent ischemic time (min)	11,436
Number of silent episodes/patient/24 h	
Mean ($\pm$ SD)	2.11 ($\pm$ 2.24)
Median (range)	1 (1–16)
Duration of silent ischemia/patient/24 h	
Mean (min) ($\pm$ SD)	99 ($\pm$ 149)
Median (min) (range)	52 (1–1,037)
Number of transient silent ischemic events	Number of subjects (%)
1	61 (53.0)
2	33 (28.7)
3–5	14 (12.2)
≥ 6	7 (6.1)
Total silent ischemic time (min)	
1–30 min	40 (34.8)
31–60 min	25 (21.7)
>60 min	50 (43.5)

Abbreviation: SD = standard deviation.

There were 243 episodes of transient silent ischemia, and the total silent ischemic time was 11,436 min (Table II). Sixty-one patients (53%) had only one episode of silent myocardial ischemia, and 7 patients (6.1%) had six or more episodes. Fifty patients (43.5%) had total silent ischemia of >60 min, which has been correlated with a poorer prognosis (Table II).

Table III shows the ORs derived from a crude analysis, relating some risk factors to the occurrence of silent myocardial ischemia. Men had a lower risk for silent ischemia, although with a lack of precision. Neither diabetes nor hypertension were related to the occurrence of silent myocardial ischemia. However, hypertensive subjects with silent myocardial ischemia had a longer duration of hypertension (median 10 vs. 6 years; Kruskal-Wallis 3.9; $p = 0.05$). On the other hand, diabetics with silent myocardial ischemia also had a longer median duration of their disease (12 vs. 10 years; Kruskal-Wallis 2.0;

$p = 0.16$) compared with diabetics without silent myocardial ischemia. In fact, diabetics had a higher median duration of ischemia (66 vs. 40.1 min; Kruskal-Wallis 4.8; $p < 0.05$).

In the bivariate analysis, a dose-response effect was observed in the occurrence of silent myocardial ischemia according to the number of affected vessels (Table III). Patients with triple-vessel disease had a three-fold higher risk of silent myocardial ischemia (OR 3.2; CI 95% 1.02–8.4; $X^2_{\text{trend}} 7.5$; $p = 0.006$). Patients with hypercholesterolemia were more prone to have silent ischemia, whereas those who had received thrombolysis or had been taking drugs for CAD, had a lesser frequency of silent ischemia.

In a multiple logistic regression analysis (Table IV), after controlling for potential confounders (age, gender, diabetes, hypertension), a lower risk for silent myocardial ischemia was found in patients with thrombolysis (OR 0.28; CI 95% 0.14–0.53), or those who followed their medical treatment (OR 0.16; CI 95% 0.04–0.68). The major risk factors for silent myocardial ischemia were hypercholesterolemia (OR 1.6; CI 95% 0.9–2.9) and a more severe CAD (OR 2.5; CI 95% 1.1–5.7). Patients with double-vessel disease showed no difference in risk compared with those with single-vessel disease, but those with the most extensive CAD (triple-vessel disease) had a two and a half-fold higher risk of silent ischemia after adjusting for potential confounders.

Discussion

Myocardial ischemia is a common expression of CAD and angina has been considered its major symptom. However, angina is a relatively insensitive and nonspecific predictor of significant coronary occlusive disease, and there could be severe and potentially lethal coronary stenosis even if it is not present.^{1, 14} On the other hand, lack of angina does not preclude the presence of multivessel CAD, nor does it imply a better prognosis.¹⁵ Severity of anginal symptoms is not related to the extent of ischemic heart disease nor to the incidence of sudden death.¹⁵

The responsible mechanisms of the lack of angina during an episode of silent myocardial ischemia have not been elucidated; however, several hypotheses have been raised to explain the absence of pain. A high threshold for pain or a

TABLE III Odds ratios derived from a bivariate analysis to assess the effect of each risk factor on the occurrence of silent ischemia

Variable	OR	95% CI	p Value
Hypercholesterolemia	1.78	1.03–3.06	0.03
Thrombolysis	0.26	0.14–0.48	<0.001
Angiogram			
Double-vessel disease	1.17	0.47–2.91	0.71
Triple-vessel disease	3.20	1.23–8.44	<0.01
Drug therapy	0.22	0.05–0.88	<0.01
Sex (male)	0.64	0.32–1.27	0.16
Diabetes	1.35	0.77–2.39	0.26
Hypertension	0.80	0.46–1.41	0.41

Abbreviations: OR = odds ratio, CI = confidence interval.

TABLE IV Odds ratios derived from multiple logistic regression analysis to assess the independent effect of each risk factor on the occurrence of silent ischemia while controlling for potential confounders

Variable	OR	95% CI	p Value
Hypercholesterolemia	1.6	0.93–3.18	0.09
Thrombolysis	0.28	0.14–0.53	<0.001
Triple-vessel disease	2.51	1.10–5.73	0.03
Drug therapy	0.16	0.04–0.53	<0.001
Male	0.50	0.23–1.07	0.08

Abbreviations as in Table III.

generalized defective perception of painful stimuli¹ as well as psychological or cultural factors may play a role. Catecholamine effects¹⁶ and endorphins¹⁷ have also been related to silent myocardial ischemia. Whatever the mechanisms for myocardial ischemia are, they may certainly change from patient to patient and in response to the type of CAD and the presence of other risk factors.¹

Some well-known risk factors for CAD, such as age and hypercholesterolemia, were identified as risk factors for silent ischemia. These risk factors have also been identified in other studies.^{7, 18} Diabetes mellitus, an important risk factor for CAD,^{10, 11} was not related to the occurrence of silent ischemia. Other authors have been equally unable to relate diabetes to silent ischemia.^{19–21} We studied 84 patients with diabetes (34% of the studied sample). Half of the diabetic patients (51%) and 44% of those without diabetes had silent ischemia. Other studies¹⁹ have shown similar figures on the occurrence of myocardial ischemia in diabetics (54%) and nondiabetics (47%). In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study,²⁰ the prevalence of silent ischemia was higher in nondiabetics (39%) than in diabetics (36%); and in a population-based study, it was slightly higher in diabetics (5.4%) than in nondiabetics (4.7%). These reported differences, as well as those observed in this study, have shown a high probability of being due to chance alone.^{19–21} However, some studies have reported a positive relation between diabetes and silent ischemia.^{22, 23} When diabetic patients²² were compared with nondiabetic subjects with CAD, the occurrence of silent ischemia was higher in diabetics (36%) than in the control group (17%), and does not seem to differ with gender and age.²³

It has been argued that diabetic patients may have a higher prevalence of silent ischemia because of autonomic neuropathy since they show significant autonomic impairment.²⁴ An abnormal perception of ischemia, caused by impairment of nerve conduction in pain pathways, could explain an increased prevalence of silent ischemia in diabetics. In this study we found no difference beyond chance in the occurrence of silent ischemia. However, diabetic patients with silent ischemia had a longer duration of diabetes and a higher median total duration of silent ischemia. In spite of these conflicting results, diabetics may be a high-risk group for silent ischemia, closely related to the duration of the metabolic disease.

Hypertension seemed to be no risk factor for silent ischemia. Hypertensive patients with silent myocardial ischemia had a longer duration of hypertension, and this finding is concordant with other reports.⁵ It has been reported that transient myocardial ischemia can be frequently observed in hypertensive patients with a normal coronary angiogram.⁶ However, hypertension has not been recognized as a risk factor for silent ischemia,⁷ although systolic blood pressure may be related to its presence.¹⁸

The frequency of silent ischemia was greater in patients with more severe types of CAD, and those with triple-vessel disease had a three-fold higher risk. It has been reported that the number and duration of episodes of ST-segment change increase with increasing severity of ischemic disease, although there is a substantial overlap between the groups.²⁵ A

higher incidence of silent ischemia in subjects with triple-vessel disease, when compared with those with single- or double-vessel disease, is consistent with findings in other reports.^{2, 3} Silent myocardial ischemia may thus be an important marker of more severe CAD, which has been highly related to the worst prognosis.^{2, 3, 12}

Thrombolytic treatment has undoubtedly favorably modified the natural history of MI, although it has been related to a higher incidence of recurrent thrombotic events (reinfarction, unstable angina). Silent ischemia has been proposed as a prognostic factor for recurrent ischemic events, in particular early reinfarction, in patients treated with thrombolysis.²⁶ In the multivariate analysis of this study, a 72% risk reduction in the occurrence of silent ischemia, while controlling for other risk factors, was observed in patients who had been treated with thrombolysis. To our knowledge, no prior study has compared the occurrence of silent ischemia in patients whether or not they have been treated with thrombolysis.

Conclusions

Coronary artery disease is one of the most important health problems in Mexico, as well as in most industrialized countries. Although there is still a lack of evidence on the importance of asymptomatic silent ischemia, it may be important to identify those subjects at higher risk of developing it. Some studies have reported a higher mortality in patients with silent ischemia;^{2–4} therefore, identifying high-risk subjects may be of potential benefit to reduce the associated higher mortality rates.

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