Silent ischemia: Silent after all?

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OBJECTIVE: To examine the association of nonpain symptoms in men and women with exercise-related silent ischemia, as well as the independence of these findings from other clinical factors.

METHODS: A prospective study of 482 women and 425 men (mean age 58 years) undergoing exercise stress testing with myocardial perfusion imaging. Analyses were performed on 60 women and 155 men with no angina but medical perfusion imaging evidence of ischemia during exercise.

MEASURES: The presence of various non-pain-related symptoms. Ischemia is indicated by myocardial perfusion defects on exercise stress testing with single photon emission computed tomography.

RESULTS: Women reported more nonangina symptoms than men ($P<0.05$). They experienced fatigue, hot flushes, tense muscles, shortness of breath and headaches more frequently ($P<0.05$). Symptoms relating to muscle tension and diaphoresis were associated with ischemia after controlling for pertinent clinical covariates. However, the direction of association differed according to sex and history of coronary artery disease events or procedures. Sensitivity of the detection models showed modest improvements with the addition of these symptoms.

CONCLUSIONS: While patients who experience silent ischemia experience a number of nonpain symptoms, those symptoms may not be sufficiently specific to ischemia, nor sensitive in detecting ischemia, to be of particular help to physicians in the absence of other clinical information.

Key Words: Coronary artery disease; Sex; Silent ischemia; Symptoms

At a symptom level, ischemia is generally associated with angina pain. However, ischemic episodes are asymptomatic (silent) in as many as 80% of cases (1-3). Myocardial infarctions can also be silent in up to 68% of cases (1,4). Several studies have associated silent ischemia (SI) with an adverse prognosis, particularly in high-risk individuals (5-22). For example, patients experiencing SI during daily activities were four to 16 times more likely (in patients with a history of coronary artery disease [CAD]) to suffer from various fatal and non-fatal cardiac events than patients without SI (12).

Whether this outcome is related to the disease state or results from behavioural factors, such as delay in seeking medical attention, is not clear. It is possible that a lack of pain or recognition may reduce motivation to engage in preventive behaviours (19), decrease compliance with medical treatment or interfere with appropriate self-regulatory behaviours (eg, cessation of physical activity) during ischemic episodes. A lack of pain markedly contributes to the underdiagnosis of CAD in the general population, because medical tests and treatments are most frequently performed in patients complaining of angina (16), despite the fact that chest pain appears to be marker of ischemia with relatively low specificity (11,23).

L'ischémie silencieuse : L'est-elle vraiment ?

OBJECTIF : Examiner l'association des symptômes non douloureux chez les hommes et les femmes à l'ischémie silencieuse reliée à l'exercice, ainsi que l'indépendance de ces observations par rapport à d'autres facteurs cliniques.

MÉTHODOLOGIE : Une étude prospective de 482 femmes et 425 hommes (âge moyen de 58 ans) subissant une épreuve à l'effort avec imagerie par perfusion myocardique. Les auteurs ont analysé 60 femmes et 155 hommes ne faisant pas d'angine mais démontrant une ischémie à l'effort d'après l'imagerie par perfusion médicale.

MESURES : Présence de divers symptômes non douloureux. L'ischémie est indiquée par des anomalies de la perfusion myocardique pendant l'épreuve à l'effort avec tomographie d'émission monophotonique.

RÉSULTATS : Les femmes ont déclaré plus de symptômes non angineux que les hommes ($P<0,05$). Elles ressentaient plus de fatigue, de bouffées de chaleur, de tensions musculaires, d'essoufflements et de céphalées ($P<0,05$). Les symptômes reliés aux tensions musculaires et à la diaphorèse s'associaient à l'ischémie après le contrôle des covariables cliniques pertinentes. Cependant, la direction de l'association différait selon le sexe et les antécédents d'événements ou d'interventions coronaropathiques. La sensibilité aux modèles de détection a révélé de modestes améliorations avec l'ajout de ces symptômes.

CONCLUSIONS : Les patients qui souffrent d'ischémie ont des symptômes non douloureux, mais qui ne sont peut-être ni assez caractéristiques de l'ischémie ni assez sensibles à la déceler pour être utiles aux médecins en l'absence d'autre information clinique.

It is possible that patients with SI experience subtler symptoms that can be useful in alerting physicians to the possibility of their CAD risk. However, Pennebaker and Watson (24) demonstrated that people attend to sensations that fit their expectations of a disease state. Thus, if a particular symptom profile does not correspond to a patient's model of ischemia or CAD, the patient may disregard it and not report it. This is particularly true if the sensation reflects a normal bodily process or state. In support of this, Barsky et al (25) discovered a history of mild, subtle symptoms during careful clinical questioning of patients who had suffered from silent myocardial infarctions – symptoms that patients had dismissed as being irrelevant.

We conducted a prospective correlational investigation of the symptoms of men and women experiencing ischemia during exercise stress testing with nuclear imaging. A standardized approach to the measurement of pain and nonpain symptoms was used. We anticipated that patients with SI experience nonpain symptoms and that, based on findings in patients with angina (26-28), men and women differ in the frequency in which these symptoms are reported. Finally, we explored whether patients with and without ischemia can be distinguished from each other on the basis of these nonpain symptoms after controlling for pertinent clinical and psychosocial variables.

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Figure 1 Flow of patients from recruitment to diagnosis of ischemic status. Note that ischemia status could not be determined by myocardial perfusion imaging (MPI) for 10 of the patients in the study

PATIENTS AND METHODS

The research protocol was accepted by the hospital scientific and ethics committees. Written, informed consent was obtained from all participants.

Patients

Four hundred twenty-five men and 482 women were recruited who were referred for exercise stress assessment using myocardial perfusion imaging (MPI) with technetium-99m-sestamibi at a tertiary hospital specializing in cardiology between 2000 and 2003.

Exclusion criteria included inability to speak or read French or English, age younger than 18 years, inpatient status, documented cardiac event or procedure (eg, angioplasty) in the previous two months, another significant and incapacitating health problem (eg, cancer), substance abuse and cognitive deficit.

Fifty-five men and 58 women refused to participate because they lacked time ($n=12$), were not interested ($n=38$), were too tired, stressed or uncomfortable ($n=10$), or for no precise reason ($n=53$). Age could be obtained for 52 of them ($X_{\text{age}} = 60$ years).

For the present manuscript, only patients who did not report angina pain on exercise testing were retained for analyses. Figure 1 shows the flow of patients from recruitment efforts to diagnosis of ischemia using MPI.

Procedure

Patients scheduled to undergo exercise MPI testing were evaluated on two consecutive days. Information on the medical, sociodemographic and psychological status of patients was obtained at baseline (day 1), while pain and symptom data were obtained immediately following exercise (day 2). A more detailed description of the procedure and measures has been previously published (27).

Instruments

Symptom checklist: A 23-item checklist was designed to assess the more subtle symptoms associated with ischemia. It included symptoms typically associated with angina (eg, breathlessness, tight feeling in the chest) and symptoms reportedly more prevalent in women (eg, nausea, fatigue). Participants could add other symptoms if they were not found on the list.

Dermatome pain map (29,30): A graphic that includes two line drawings of the human body and assesses anatomical pain location.

Short form of the McGill Pain Questionnaire (31): The short form

of the McGill Pain Questionnaire measures qualitative and quantitative aspects of pain.

Chest pain quality scale: A scale used to classify patients' daily chest pain (if present) as typical, atypical or nonspecific angina.

Psychiatric symptom index (32): A 29-item measure of psychological status.

Medical assessment

MPI results were used as the principal indicator of the presence of myocardial ischemia, because these have been shown to be more sensitive and specific in the diagnosis of CAD than standard electrocardiogram results (33). The images were reviewed by one of three trained nuclear imaging specialists, who based the decision on clinical impression.

The exercise stress tests were performed on a treadmill using the Bruce protocol. The protocol was ceased when the patient reported considerable pain, was out of breath, presented with significant anomalies on electrocardiogram (eg, greater than 3 mm ST segment deviation) or had achieved at least 90% of the maximal heart rate expected for his/her age. The metabolic estimated cost (number of metabolic equivalents) achieved during exercise was noted for each patient.

Statistical analysis

ANOVAs and χ^2 analyses were performed to examine sociodemographic and medical differences among patients with and without MPI evidence of ischemia on exercise stress testing.

All primary analyses were performed separately for individuals with and those without a history of CAD events or procedures. This decision was based on evidence of clinical heterogeneity among these groups, and on preliminary analyses showing that patients with a history of CAD versus those without exhibited differences in symptom profile, as well as in the association of these symptoms with ischemia status.

Sex differences in symptom profile among patients with silent ischemia during exercise

To identify sex-related differences in symptoms reported by patients with SI during exercise, χ^2 analyses were performed. Although not discussed in detail in the results section, these analyses were also performed in patients with neither pain nor ischemia to aid in the interpretation of the detection models described below.

Detection of ischemia from nonpain symptoms reported during exercise stress testing

Binary logistic regressions were performed to examine whether subtle nonpain symptoms experienced during exercise stress testing can aid in detecting patients who showed evidence of exercise-induced ischemia during testing.

To ensure greater stability of measure for the nonpain symptoms and to reduce problems with collinearity among related symptoms (eg, difference between tense muscles and stiff muscles), logistic regression analyses were performed on groupings of symptoms. A factor analysis with varimax rotation was performed on all symptoms reported by at least five men or women to identify which symptoms grouped together. Three factors were identified. Factor 1 (cardiovascular or neurological) accounted for 21% of the variance and included palpitations, throbbing in the head or neck, dizziness, fatigue, headache and shortness of breath. Factor 2 (diaphoresis) accounted for 12% of the variance and included perspiration and hot flushes. Factor 3 (muscle tension) accounted for 11% of the variance and included 'tense' and 'stiff' muscles. Weakness and trembling loaded poorly on all factors and thus were considered separately.

Clinical covariates were forced into block 1 of the detection models. A variable was considered to be covariate if its association with MPI status (indicating absence or presence of myocardial ischemia) reached $P < 0.20$ in univariate logistic regressions. The

TABLE 1
Sociodemographic profile of men and women without pain during exercise single photon emission computed tomography

Variable	Men			Women		
	Without ischemia (n=126)	With ischemia (n=155)	P	Without ischemia (n=257)	With ischemia (n=60)	P
Marital status, n (%)			0.233			0.978
Single	11 (9)	6 (4)		32 (13)	8 (13)	
Married/living with someone	98 (78)	128 (83)		166 (65)	38 (63)	
Separated/divorced/widowed	17 (14)	21 (14)		59 (23)	14 (23)	
Education, n (%)			0.167			0.23
Elementary school	25 (20)	31 (20)		66 (26)	22 (37)	
High school	52 (41)	47 (30)		88 (34)	19 (32)	
College/university	49 (39)	74 (48)		101 (39)	19 (32)	
Smoking, n (%)	20 (16)	24 (16)	0.929	35 (14)	19 (32)	0.001
Psychological status (mean $\pm$ SD)	12.4 $\pm$ 9.75	11.9 $\pm$ 8.96	0.635	17.5 $\pm$ 12.45	18 $\pm$ 12.23	0.806

TABLE 2
Medical profile of men and women without pain during exercise single photon emission computed tomography

Variable	Men			Women		
	Without ischemia (n=126)	With ischemia (n=155)	P	Without ischemia (n=257)	With ischemia (n=60)	P
Age (mean $\pm$ SD)	57.5 $\pm$ 10.13	60.4 $\pm$ 8.72	0.010	56.9 $\pm$ 9.82	59.7 $\pm$ 10.54	0.049
Body mass index (kg/m ²) (mean $\pm$ SD)	27.3 $\pm$ 3.83	27.5 $\pm$ 4.07	0.796	26.1 $\pm$ 4.41	26.7 $\pm$ 5.56	0.324
History of angina, n (%)	27 (21)	64 (41)	0.002	52 (20)	15 (25)	0.518
History of coronary events or procedures, n (%)	48 (38)	91 (59)	0.001	30 (12)	20 (33)	0.000
Hypertension, n (%)	48 (38)	71 (46)	0.347	117 (46)	29 (48)	0.713
Diabetes, n (%)	17 (14)	26 (17)	0.774	30 (12)	9 (15)	0.698
Hypercholesterolemia, n (%)	74 (59)	103 (67)	0.346	105 (41)	30 (50)	0.364
Family history of heart disease, n (%)	83 (66)	112 (72)	0.157	209 (81)	46 (77)	0.639
Family history of hypertension, n (%)	43 (34)	57 (37)	0.593	155 (60)	26 (43)	0.030
Family history of diabetes, n (%)	51 (41)	45 (29)	0.058	108 (42)	23 (38)	0.707
Beta-blockers, n (%)	44 (35)	63 (41)	0.364	60 (23)	25 (42)	0.003
Anticoagulants, n (%)	67 (53)	112 (72)	0.001	100 (39)	34 (57)	0.009
Lipid-lowering agents, n (%)	72 (57)	99 (64)	0.294	76 (30)	30 (50)	0.002
Type of daily angina pain, n (%)			0.092			0.495
Typical pain	2 (2)	11 (7)		20 (8)	6 (10)	
Atypical pain	11 (9)	20 (13)		46 (18)	14 (23)	
Nonspecific pain	22 (18)	25 (16)		53 (21)	8 (13)	
Patients tested in the morning, n (%)	81 (64)	105 (68)	0.542	150 (59)	44 (73)	0.035
Metabolic equivalents achieved during exercise testing (mean $\pm$ SD)	8.8 $\pm$ 1.82	8.2 $\pm$ 1.59	0.003	7.2 $\pm$ 1.50	6.6 $\pm$ 1.56	0.008

symptom variables, on the other hand, were entered into a backward logistic regression in block 2. Only significant or near-significant symptom findings are reported. Because there was considerable heterogeneity among men and women, the detection models were performed separately by sex and, as mentioned above, by history of CAD.

RESULTS

Three hundred forty-seven participants showed MPI evidence of ischemia. Results for the first set of analyses presented below are based on the 155 men and 60 women whose ischemia was silent during testing (representing 62% of all ischemic patients). The second set of

analyses included all patients who did not experience angina pain during testing (including 126 men and 257 women with neither pain nor ischemia).

Patient characteristics

Mean scores and proportions for demographic and medical data for men and women as a function of ischemia status are presented in Tables 1 and 2.

Nonpain symptoms reported by patients with SI

The most common symptoms were shortness of breath (67%), fatigue (41%), perspiration (39%), palpitations (17%), dizziness (15%), hot

TABLE 3
Symptoms experienced by patients without a history of coronary artery disease

Symptom	With ischemia, n (%)			Without ischemia, n (%)		
	Men (n=64)	Women (n=40)	P	Men (n=78)	Women (n=225)	P
Weakness	7 (11)	8 (20)	NS	6 (8)	51 (23)	0.004
Trembling	3 (5)	4 (10)	NS	4 (5)	21 (9)	NS
Cardiovascular/neurological						
Palpitations	6 (9)	9 (23)	0.064	5 (6)	60 (27)	0.000
Throbbing in head/neck	1 (2)	5 (13)	0.020	5 (6)	22 (10)	NS
Dizziness	8 (13)	9 (23)	NS	18 (23)	67 (30)	NS
Fatigue	21 (33)	21 (53)	0.047	23 (30)	101 (45)	0.017
Headache	1 (2)	5 (13)	0.020	5 (6)	22 (10)	NS
Shortness of breath	36 (56)	31 (78)	0.028	40 (51)	169 (75)	0.000
Diaphoresis						
Perspiration	35 (55)	13 (33)	0.027	36 (46)	73 (32)	0.030
Hot flushes	5 (8)	8 (20)	0.067	5 (6)	37 (16)	0.027
Muscle tension						
Tense muscles	5 (8)	11 (28)	0.007	8 (10)	36 (10)	NS
Stiff muscles	6 (9)	5 (13)	NS	4 (5)	16 (7)	NS

NS Not significant

TABLE 4
Symptoms experienced by patients with a history of coronary artery disease

Symptom	With ischemia, n (%)			Without ischemia, n (%)		
	Men (n=91)	Women (n=20)	P	Men (n=48)	Women (n=30)	P
Weakness	8 (9)	3 (15)	NS	3 (6)	6 (20)	0.064
Trembling	4 (4)	2 (10)	NS	2 (4)	3 (10)	NS
Cardiovascular/neurological						
Palpitations	16 (18)	6 (30)	NS	4 (8)	7 (23)	0.064
Throbbing in head/neck	2 (2)	1 (5)	NS	1 (2)	3 (10)	NS
Dizziness	12 (13)	4 (20)	NS	4 (8)	8 (27)	0.029
Fatigue	34 (37)	12 (60)	0.063	19 (40)	13 (43)	NS
Headache	1 (1)	2 (10)	0.026	1 (2)	4 (13)	0.048
Shortness of breath	62 (68)	16 (80)	NS	32 (67)	25 (83)	NS
Diaphoresis						
Perspiration	25 (28)	11 (55)	0.017	22 (46)	10 (33)	NS
Hot flushes	10 (11)	6 (30)	0.028	5 (10)	7 (23)	NS
Muscle tension						
Tense muscles	9 (10)	2 (10)	NS	11 (23)	3 (10)	NS
Stiff muscles	6 (7)	1 (5)	NS	6 (13)	2 (7)	NS

NS Not significant

flushes (14%), muscle tension (13%) and weakness (12%). Overall, women experienced significantly more symptoms during the exercise stress test compared with men (3.5 ± 2.54 versus 2.2 ± 1.96 ; $F(1,211) = 15.230$, $P=0.000$), irrespective of CAD history. Women reported fatigue, shortness of breath, throbbing in the head or neck, headaches, hot flushes and tense muscles more frequently than men. The direction of sex-related differences in symptoms relating to diaphoresis depended on history of CAD events or procedures (Tables 3 and 4).

Detection of ischemia from nonpain symptoms

Results can be seen in Tables 5 through 8. There was a lack of uniformity in symptoms and clinical factors associated with ischemia across the four groups. For example, age was significantly associated with ischemia in women with a history of CAD, but not for other groups. Smoking was significant for women (regardless of CAD history), but

not for men. With respect to the main analyses, two groups of symptoms predominated: diaphoresis and muscle tension. Diaphoresis was significantly and positively associated with ischemia for both men and women; for men, it was among patients without a history of CAD, while for women, it was for those with a history of CAD. On the other hand, having muscle tension decreased the probability of having ischemia among men with a history of CAD, while for women with no history of CAD, it increased the probability of detecting ischemia.

Post hoc analyses

To understand why the direction of the sex-related difference in diaphoresis was dissimilar depending on whether patients had a history of coronary events, exploratory ANOVAs and χ^2 analyses were performed on variables thought to have the potential to influence this symptom domain, in part, through sympathetic nervous system activation.

TABLE 5
Detection of ischemia in men with no history of coronary artery disease

Variable entered	P	OR	95% CI
Block 1 (forced in)			
Hypertension	0.408	0.694	0.291 to 1.651
Family history of diabetes	0.018	0.382	0.173 to 0.845
METS achieved during exercise testing	0.966	0.995	0.795 to 1.246
Use of anticoagulants	0.115	1.897	0.855 to 4.211
Use of ACE inhibitors	0.008	4.733	1.502 to 14.910
Model $\chi^2=20.403$	0.001		
Block 2 (backward logistic regression)			
Diaphoresis	0.020	4.754	1.277 to 17.703
Model $\chi^2=5.722$	0.017		
Full model $\chi^2=26.125$	0.000		

Block 1: sensitivity 46%; specificity 76%; positive predictive value 61%; negative predictive value 64%. Full model: sensitivity 62%; specificity 78%; positive predictive value 69%; negative predictive value 72%. ACE Angiotensin-converting enzyme; METS Metabolic equivalents

TABLE 6
Detection of ischemia in men with a history of coronary artery disease

Variable entered	P	OR	95% CI
Block 1 (forced in)			
Type of daily angina pain*	0.004	0.435	0.247 to 0.765
Family history of hypertension	0.282	1.624	0.671 to 3.932
Use of lipid-lowering agents	0.074	0.346	0.108 to 1.106
Time of day tested	0.311	0.648	0.280 to 1.501
Smoking	0.593	0.75	0.261 to 2.154
METS achieved during exercise testing	0.487	1.126	0.806 to 1.572
Age	0.006	1.085	1.023 to 1.152
Model $\chi^2=27.208$	0.000		
Block 2 (backward logistic regression)			
Muscle tension	0.042	0.184	0.032 to 0.944
Model $\chi^2=4.315$	0.038		
Full model $\chi^2=31.523$	0.000		

*A smaller number indicates more typical angina symptoms. Block 1: sensitivity 86%; specificity 53%; positive predictive value 77%; negative predictive value 68%. Full model: sensitivity 85%; specificity 57%; positive predictive value 78%; negative predictive value 68%. METS Metabolic equivalents

Among patients without a history of CAD events or procedures, men exerted more physical effort during exercise stress testing ($P=0.000$), they exhibited greater increases in systolic blood pressure (SBP) during testing ($P=0.000$), and they were more often diagnosed with diabetes ($P=0.046$) and hypercholesterolemia ($P=0.024$). Controlling for these variables eliminated the sex-related difference in diaphoresis.

However, among patients with a history of CAD, women were more frequently diagnosed with diabetes ($P=0.045$), more frequently smoked ($P=0.008$) and were more frequently diagnosed with hypertension. On the other hand, they showed smaller increases in SBP during exercise testing and achieved fewer metabolic equivalents than men. Controlling for these variables did not alter the results: women with a history of CAD more frequently reported diaphoresis than men.

DISCUSSION

The present study of a large, consecutive series of men and women referred for exercise-stress testing with MPI for evaluation of suspected or known CAD showed a high prevalence of SI (62%). This is in keeping with the literature on ischemia (1-3,6,10) and myocardial infarction (4).

TABLE 7
Detection of ischemia in women with no history of coronary artery disease

Variable entered	P	OR	95% CI
Block 1 (forced in)			
Time of day tested	0.002	0.226	0.086 to 0.596
Age	0.174	1.030	0.987 to 1.074
Diabetes	0.247	0.379	0.073 to 1.963
METS achieved during exercise testing	0.039	0.743	0.560 to 0.985
Family history of hypertension	0.094	0.530	0.252 to 1.115
Family history of diabetes	0.325	0.671	0.303 to 1.486
Smoking	0.018	3.109	1.215 to 7.953
Model $\chi^2=29.485$	0.000		
Block 2 (backward logistic regression)			
Muscle tension	0.053	3.410	0.986 to 11.797
Model $\chi^2=3.564$	0.059		
Full model $\chi^2=33.049$	0.000		

Block 1: sensitivity 8%; specificity 99%; positive predictive value 50%; negative predictive value 86%. Full model: sensitivity 16%; specificity 98%; positive predictive value 60%; negative predictive value 87%. METS Metabolic equivalents

TABLE 8
Detection of ischemia in women with a history of coronary artery disease

Variable entered	P	OR	95% CI
Block 1 (forced in)			
Use of beta-blockers	0.178	2.526	0.656 to 9.730
Diabetes	0.241	2.435	0.549 to 10.790
Smoking	0.009	11.61	1.832 to 73.590
Age	0.292	1.041	0.966 to 1.123
Model $\chi^2=12.998$	0.011		
Block 2 (backward logistic regression)			
Diaphoresis	0.069	4.985	0.883 to 28.151
Model $\chi^2=3.581$	0.058		
Full model $\chi^2=16.579$	0.005		

Block 1: sensitivity 45%; specificity 87%; positive predictive value 69%; negative predictive value 70%. Full model: sensitivity 60%; specificity 80%; positive predictive value 67%; negative predictive value 75%

Patients with SI reported a number of symptoms during exercise. Most common were shortness of breath (dyspnea), fatigue and perspiration. Consistent with the literature on angina (27,28), women experienced more symptoms during the exercise stress test than men. This was particularly true for fatigue, hot flushes, tense muscles, shortness of breath and headaches. Women visiting the emergency department for nontraumatic chest pain frequently present with more symptoms of fatigue than men, while men report diaphoresis more frequently in these settings (28). In the current study, however, the expected sex-related differences in perspiration were observed only among patients without a history of CAD. In the latter group, it is likely that greater comorbidity (particularly diabetes), exertion and sympathetic activation during exercise stress testing in men were responsible for the diaphoresis, because controlling for these variables eliminated sex-related differences. In patients with a history of CAD, however, perspiration was reported more frequently in women. These women also exhibited greater comorbidity (diabetes and hypertension) and smoked more – factors associated with sympathetic hyperactivity. On the other hand, during exercise-induced ischemia, they did not exhibit SBP hyper-reactivity, compared with men. Moreover, statistically controlling for these variables did not change the results in

patients with a history of CAD – more women reported diaphoresis during exercise stress testing than men. The reasons for these differences remain to be elucidated.

Dyspnea is considered to be an anginal equivalent by many clinicians and researchers (1). In a study by Coodley (34), up to 25% of older patients with known CAD reported dyspnea as the primary symptom in the absence of angina. In the current study, 78% of women and 63% of men did. According to Gregoratos (35), dyspnea reflects elevated left ventricular end-diastolic pressure resulting from myocardial ischemia superimposed on reduced ventricular compliance. The latter is found frequently in hypertensive patients. Close to one-half of patients examined in the current study suffered from hypertension.

Patients with silent myocardial infarctions have also been reported to frequently present with neurological and gastrointestinal symptoms, including syncope, vertigo, fainting, abdominal pain and nausea (1,35). In the current sample of patients with SI, neurological symptoms (eg, weakness, fatigue, dizziness) were frequent, particularly in women. Gastrointestinal symptoms, on the other hand, were rarely reported.

Unfortunately, the reported symptoms were only partially useful in discriminating between patients with and without ischemia. Cardiovascular and neurological symptoms were reported to a similar extent, irrespective of ischemic status. On the other hand, diaphoresis was associated with close to a fivefold chance of experiencing exercise-related ischemia among women with a history of CAD and among men without CAD. Women without a CAD history who complained of muscle tension had a 3.4 greater chance of experiencing ischemia. We have previously reported (36) similar findings in women who also experienced angina pain on exercise stress testing. In men with a CAD history, however, muscle tension was related to a lower incidence of ischemia. In men with angina, atypical symptoms, such as muscle tension, have frequently shown limited or inverse relations with ischemia (12,36,37). The reasons for these group differences are unclear, but they likely reflect differences in clinical and pathological processes.

While the present study was the first, to our knowledge, to systematically and prospectively examine symptom profiles in both men and women with SI, several limitations merit mention. In women, the smaller sample size might have led to insufficient power of the analyses to detect weaker predictors of ischemia. There is concern that the models may be overfit and should therefore be seen as hypothesis-generating at this time. SI was defined based on a single event. Nonetheless, because the goal of the manuscript was to identify nonpain symptoms associated with SI, measured simultaneously, it was not considered to be essential that patients should be excluded if they had experienced angina in the past. An additional limitation concerns the fact that the participants were mainly French-speaking and white. Further research in other ethnic groups would be helpful in assessing the applicability of these results beyond Caucasians. Finally, patients attended a cardiac

tertiary hospital, where the prevalence of CAD is higher than in other institutions. Indeed, a large proportion of participants (particularly among the men) had a history of coronary events or procedures and significant comorbidities (eg, hypertension). The high-risk profile of most of the recruited patients may have obscured findings. Research has shown that as the a priori likelihood of developing myocardial ischemia and heart disease increases, chest pain loses its significance as an additional predictive factor (15). This may also be true of other symptoms. We addressed this issue by analyzing the results separately for patients with and without a CAD history, and did, indeed, show clinical and symptomatic heterogeneity among these groups.

The impacts of these nonpain symptoms are not negligible. First, sensitivity of the detection models improved by 16% in men with no history of CAD, 8% in women with no history of CAD and 15% in women with a history of CAD. When used in conjunction with other clinical data, the presence of these symptoms may aid to alert physicians to the possible presence of ischemic events in these patients. On the other hand, patients who present with nonspecific symptoms, such as diaphoresis, fatigue or muscle tension, may be more likely to be misdiagnosed than patients who report more typical angina. Most physicians will evaluate and treat their patients based on the presence of typical angina symptoms, rather than rely on documentation of myocardial ischemia (18). Similarly, patients may delay longer in seeking treatment for nonspecific symptoms, such as occasional muscle tension or diaphoresis. This may place those with unrecognized CAD at greater risk for morbidity and mortality (37,38).

Given studies indicating a similar or worse prognosis in patients with silent compared with painful myocardial ischemia or infarcts (6,7,9,10,14,17,20), particularly among high-risk individuals (15,18,21,36,39,40), continued research on the origin and detection of SI are clearly needed to improve patient care and education. In the meantime, it is suggested that patients reporting perspiration and/or muscle tension (in women) on physical effort be followed up for testing, particularly if other symptoms commonly associated with CAD or ischemic processes, such as dyspnea and fatigue, are also present. In the long-term, the costs of testing false-positives are likely to be outweighed by those associated with the late diagnosis and treatment of true-positives. Similarly, it may be cautious to teach patients in whom SI has been detected to temporarily cease or reduce the intensity of ongoing physical activity when they experience these symptoms.

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