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Typical symptoms are predictive of acute coronary syndromes in women

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Background Previous research suggests that the presentation of acute coronary syndromes (ACS) may differ in women and men. No study has prospectively evaluated the role of a comprehensive set of typical and atypical symptoms and whether different symptoms on presentation predict ACS diagnosis in women and men.

Methods and Results We directly observed 246 women and 276 men seen in the emergency department with symptoms suggestive of ACS and documented their symptoms verbatim. ACS was eventually diagnosed in 89 (36%) women and 124 (45%) men on the basis of standard electrocardiogram and cardiac enzyme criteria. Presence of typical symptoms (chest pain or discomfort, dyspnea, diaphoresis, and arm or shoulder pain) was significantly associated with a diagnosis of ACS in women but not in men. On the other hand, atypical symptoms were not related to ACS diagnosis in women, whereas in men some atypical symptoms (dizziness or faintness) were inversely associated with ACS ($P = .007$). In multivariate analysis, the only symptoms that showed significant or borderline associations with ACS in women were diaphoresis ($P = .019$) and chest pain or discomfort ($P = .069$). Chest pain or discomfort and other typical symptoms were not significantly associated with ACS in men. Adjusted relative risks for ACS associated with the presence of typical symptoms in women compared with men were close to 1.0, indicating no sex differences.

Conclusions Typical symptoms are the strongest symptom predictors of ACS in women, and they are as important in women as in men. Clinicians need to take very seriously any woman who has typical symptoms and pursue a full cardiac work-up. (Am Heart J 2002;143:283-8.)

Our knowledge of symptoms associated with acute coronary syndromes (ACS) is derived primarily from male samples. Acute ischemia is more likely to be missed in the emergency department (ED) in women than it is in men,[1] perhaps as a result of differences in symptom presentation. A number of studies have compared the symptom presentation of women and men with ACS.[2-10] In most of these studies, the prevalence of chest pain was similar in women and men. However, women were more likely to have atypical symptoms compared with men.[3,6-9]

By comparing the symptom prevalence in women and men with ACS, most of these studies have not addressed the issue of whether symptoms are associated with ACS differently in women and men. For example, a greater prevalence of atypical symptoms in women with ACS

compared with men may simply reflect the fact that these atypical symptoms are generally more common in women, even in the absence of diagnosed ACS.

The purpose of this study was to evaluate, in a prospective fashion, the role of a comprehensive set of typical and atypical symptoms on presentation as predictors of ACS in women and men. We hypothesized that although chest pain or discomfort and other typical symptoms predict ACS both in women and men, atypical symptoms would predict ACS in women but not in men.

Methods

Study sample

We conducted this study in the ED of Yale–New Haven Hospital, a 900-bed university teaching hospital and a regional cardiac referral center. Patients seen in the ED between September 1995 and August 1997 were considered for participation if they were ≥45 years old and reported ≥1 of a prespecified set of typical or atypical symptoms suggestive of ACS (Table I). Additionally, patients 18 to 44 years old were asked to participate if they had diabetes mellitus or ≥2 cardiac risk factors (history of coronary heart disease, systemic hypertension, hypercholesterolemia, smoking, obesity, family history of premature coronary heart disease, and postmenopausal status), and ≥1 typical or atypical symptoms suggestive of ACS. We included these additional criteria for younger patients to exclude patients at very low risk for ACS. Patients were approached for study participation after the ED staff had completed initial

Table I. Presenting symptoms suggestive of ACS

Typical chest and associated symptoms
   Substernal or left-sided chest pain (not related to trauma)
   Chest pressure, heaviness, tightness, or squeezing in chest
   Neck/throat pain or discomfort (not related to trauma)
   Jaw pain or discomfort (not related to toothache or trauma)
   Shoulder pain or discomfort (not related to degenerative joint disease or trauma)
   Arm pain or discomfort (not related to bursitis or trauma)
   Diaphoresis
   Dyspnea (not related to asthma, pulmonary infection, preexisting pulmonary problem, or renal failure)
Atypical chest and associated symptoms
   Chest pain in other location
   Numbness, tingling, pricking, or stabbing in chest
   Fullness or burning in chest
   Epigastric/indigestion-like/gas-like pain or discomfort (not related to gastrointestinal problem)
   Nausea or vomiting (not related to gastrointestinal problem)
   Upper extremity numbness or tingling (not related to stroke or carpal tunnel problem)
   Mid-back (between shoulder blades) pain (not related to degenerative joint disease or trauma)
   Pain/discomfort with deep breath or cough (not related to asthma or pulmonary infection, preexisting pulmonary problem)
   Dizziness, lightheadedness, or syncope (not related to stroke, neurologic problem, or hypertension)
   Fatigue or weakness (not related to stroke, neurologic problem, or hypertension)
   Palpitations (new onset, no history of arrhythmias)

assessment. In the event that patients were too sick to provide oral consent in the ED, they were approached when they were considered stable, within 24 hours of hospital admission. No patient died before we were able to obtain consent. A total of 527 patients met study criteria and were approached for participation. Of these, 522 patients agreed to participate (<1% refusal rate).

Data collection

During shifts of 2 to 5 hours across all 24 hours and all 7 days, nurse data collectors unobtrusively observed all the patients who met the study criteria as they came to the ED. Data on presenting symptoms were obtained by observing the patient-physician or patient-nurse interview, and symptoms were documented verbatim. Data on demographics and cardiac risk factors were gathered from the patient and the medical record. These data elements are defined in detail elsewhere.[8,11,12]

ACS included either acute ischemia or acute myocardial infarction (AMI). Acute ischemia was determined by electrocardiogram evidence of ST-segment depression, ST-segment elevation, or T-wave inversion or T-wave abnormalities different from the last electrocardiogram in at least 2 consecutive leads and by lack of cardiac enzyme elevation. Elevated cardiac enzymes (creatine kinase-MB [CK-MB] >5% of total CK in at least one set) indicated AMI.

Statistical analysis

All analyses were done using SAS 8.1 statistical software (SAS Institute, Cary, NC). We used χ^2 and t tests to examine the associations between ACS and baseline characteristics and symptoms in both women and men. Typical symptoms included chest pain or discomfort as a single variable (either chest pressure, heaviness, tightness/squeezing, or center or left chest pain), neck/jaw pain, arm or shoulder pain, diaphoresis, and dyspnea. Atypical symptoms included atypical chest pain or discomfort as a single variable (either chest

fullness, stabbing, burning, or right chest pain), indigestion, nausea or vomiting, upper extremity numbness or tingling, cough, pain with deep breath, palpitations, midback pain, dizziness/faintness, and fatigue. We also created an interval-level variable for the "number of presenting symptoms." Only those symptoms that were reported by at least 5% of women and men were included in the analyses.

To determine symptom predictors in women and men, we performed logistic regression analyses stratified by sex, with an α level of .20 for entering or staying in the model. In these models, typical and atypical symptoms reported by >5% women and men were included to identify the most important symptom predictors in the presence of many typical and atypical presenting symptoms. Age, diabetes, and number of presenting symptoms were forced in as control factors. Adjusted relative risks were estimated from generalized linear models for each of the symptom predictors. Last, we calculated individual relative risks of ACS for typical symptoms in women relative to men. In these analyses, we controlled for age, diabetes, and number of presenting symptoms. The adequacy of fit and the discriminatory power of all models were assessed according to standard methods.[13,14]

Results
Symptom predictors of ACS in women

In the sample of 246 women, 89 (36%) were ultimately diagnosed with ACS. As expected, older women and women with a history of coronary heart disease, myocardial infarction, or diabetes were significantly more likely to be diagnosed with ACS compared with women without these risk factors (Table II). For example, 47% of women with diabetes versus 32% of women without diabetes were diagnosed with ACS for that ED visit. The mean age of women with ACS was 69 ± 15 years, and the mean age of women without ACS was 64

Table II. Relationship between baseline characteristics and ACS in women and men

	Women (n = 246) % with ACS	Men (n = 276) % with ACS
White race		
Present	36	45
Absent	37	44
History of coronary heart disease		
Present	44*	48
Absent	28	41
Systemic hypertension		
Present	38	49
Absent	34	41
Obesity		
Present	38	46
Absent	33	46
History of myocardial infarction		
Present	49*	51
Absent	33	42
Diabetes		
Present	47*	46
Absent	32	45
Hypercholesterolemia		
Present	41	50
Absent	35	42
Other cardiac problems		
Present	39	35*
Absent	35	49
History of heart failure		
Present	40	45
Absent	35	45
Smoking		
Present	26	42
Absent	39	46

*P <.05 for within-group differences.

± 15 years (P = .017). In contrast, other cardiac risk factors such as hypercholesterolemia, obesity, hypertension, and heart failure were not significantly associated with a diagnosis of ACS.

Women who had typical symptoms such as chest pain or discomfort, diaphoresis, dyspnea, and arm or shoulder pain were significantly more likely to be diagnosed with ACS compared with women who did not report these symptoms (Table III). For example, 41% of women with chest pain or discomfort versus 28% of women without chest pain or discomfort were diagnosed with ACS for that ED visit. In contrast, none of the atypical symptoms were related to ACS. Overall, women who were ultimately diagnosed with ACS reported a higher number of symptoms (3.36 ± 1.74 symptoms) compared with women without ACS (2.78 ± 1.46 symptoms, P = .006).

In the multivariate model with all the typical and atypical symptoms entered simultaneously, diaphoresis was the strongest independent positive predictor of ACS in women (Table IV). Women with chest pain or discom-

Table III. Relationship between typical and atypical symptoms and ACS in women and men

	Women (n = 246) % with ACS	Men (n = 276) % with ACS
Typical symptoms		
Chest pain or discomfort (chest pressure, heaviness, tightness, squeezing, or center or left chest pain)		
Present	41*	49
Absent	28	38
Dyspnea		
Present	45*	41
Absent	30	47
Arm or shoulder pain		
Present	45*	47
Absent	32	44
Diaphoresis		
Present	53*	44
Absent	32	45
Neck or jaw pain		
Present	41	53
Absent	36	44
Atypical symptoms		
Nausea or vomiting		
Present	39	48
Absent	35	44
Dizziness or faintness		
Present	36	32*
Absent	36	50
Indigestion		
Present	38	45
Absent	36	45
Fatigue		
Present	36	41
Absent	36	45
Chest fullness, stabbing, numbness, burning, or right chest pain		
Present	34	50
Absent	36	44
Midback pain		
Present	50	17
Absent	35	46
Palpitations		
Present	35	29
Absent	36	46
Upper-extremity numbness		
Present	29	33
Absent	37	45
Unable to take deep breath		
Present	9	29
Absent	37	46
Cough		
Present	25	40
Absent	37	45

The positive predictive values associated with each symptom for women and men, respectively, are the percentages in the "Present" rows.
*P < .05 for within-group differences.

fort had an 81% higher risk for ACS, and women with arm or shoulder pain had a 60% higher risk for ACS. However, these latter symptoms did not reach statistical significance when included together in the model.

Table IV. Symptom predictors of ACS in women and men by logistic regression analysis

	Relative risk*	95% CI	P value
Women			
Chest pain or discomfort (chest pressure, heaviness, tightness, squeezing, or center or left chest pain)	1.81	.95-3.42	.069
Arm or shoulder pain	1.60	.83-3.10	.163
Diaphoresis	2.53	1.17-5.48	.019
Men			
Chest pain or discomfort (chest pressure, heaviness, tightness, squeezing, or center or left chest pain)	1.56	.86-2.82	.142
Dyspnea	.69	.40-1.19	.182
Dizziness or faintness	.49	.26-.93	.028

*Controlled for age, diabetes, and number of presenting symptoms.

Table V. Relative risk of ACS for typical symptoms in women relative to men

Typical symptoms	Relative risk*	95% CI	P value
Chest pain or discomfort (chest pressure, heaviness, tightness, squeezing, or center or left chest pain)	.83	.66-1.06	.129
Neck or jaw pain	.69	.40-1.15	.141
Diaphoresis	1.18	.87-1.59	.384
Arm or shoulder pain	.91	.64-1.30	.612
Dyspnea	1.00	.74-1.35	.993

Reference group is men presenting with typical symptoms.
*Controlled for age, diabetes, and number of presenting symptoms.

Symptom predictors of ACS in men

In the sample of 276 men, 124 (45%) were diagnosed with ACS for that ED visit. Older men were significantly more likely to be diagnosed with ACS, with a mean age of 64 ± 15 years versus a mean age of 58 ± 15 years for men without ACS (*P* = .005). Men with a history of other cardiac problems, such as valvular heart disease, primary arrhythmia, or nonischemic cardiomyopathy, were significantly less likely to be diagnosed with ACS than were men without this history (Table II).

Typical symptoms were not significantly related to a diagnosis with ACS in men (Table III). With regard to atypical symptoms, men who reported dizziness or faintness were significantly less likely to be diagnosed with ACS compared with men who did not report this symptom (Table III). There was no significant difference in the total number of symptoms between men with a diagnosis of ACS (2.55 ± 1.32 symptoms) and men without an ACS diagnosis (2.72 ± 1.40 symptoms).

In the model with all typical and atypical symptoms entered simultaneously, dizziness or faintness was an independent negative predictor of ACS in men (Table IV), whereas chest pain or discomfort and dyspnea were only mildly associated with a diagnosis of ACS in men. The fit of this model was poor (area under the ROC curve = 0.65, *P* = .06 for goodness-of-fit test), sug-

gesting that symptoms were not helpful in predicting ACS in men.

Comparison of symptom predictors of ACS in women and men

The positive predictive values of presenting with typical symptoms were similar in women and men. For example, 41% of women and 49% of men who had chest pain or discomfort were subsequently diagnosed with ACS for that ED visit (Table III). In addition, we found that the adjusted relative risks for ACS in women with typical symptoms compared with men with typical symptoms were close to 1.0, indicating no sex differences (Table V).

Discussion

The results of this prospective study indicate that typical symptoms are the strongest symptom predictors of ACS in women and are as important in women as in men. In contrast, we found no significant associations between atypical symptoms and ACS in women, whereas some atypical symptoms (dizziness or faintness) were inversely associated with ACS in men.

By comparing the symptom prevalence in women and men with ACS, previous research[3-8] has not addressed the issue of whether symptoms are associated with ACS differently in women and men. In fact,

we found that atypical symptoms such as nausea or vomiting and indigestion, which are reported in the literature[3,6-9] as more common in women with ACS, were not significantly associated with a diagnosis of ACS.

After controlling for age, diabetes, and number of presenting symptoms, we found that typical symptoms, such as diaphoresis and chest pain or discomfort, carried significant or borderline-significant positive relative risk for ACS in women. In contrast, typical symptoms were not significantly associated with ACS in men. In men, only dizziness/faintness was an independent negative symptom predictor of ACS. This unexpected finding may reflect the broad inclusion criteria of our study rather than truly signifying a protective characteristic in men with this symptom.

In contrast with our results, investigators for the Multicenter Chest Pain study found that diaphoresis, substernal chest pain, and pressing chest pain carried significant positive relative risks for AMI in both women and men.[2] A possible explanation for the difference in findings may be the result of different study enrollment criteria. Patients in the Multicenter Chest Pain study had to have a chief complaint of chest pain to be included, whereas the current study included all patients with symptoms suggestive of ACS, even if these symptoms did not include chest pain. In addition, we examined symptom predictors of ACS, which included both AMI and acute ischemia.

The Acute Cardiac Ischemia Time–Intensive Predictive Instrument (ACI-TIPI) trial found that the presence of chest pain, a chief complaint of chest pain, and nausea/vomiting were positive predictors of AMI in patients seen in the ED with symptoms suggestive of acute cardiac ischemia, whereas dizziness was a negative predictor of AMI.[10] These investigators found no sex-symptom interactions, indicating that these symptoms predicted AMI in women and men equally. A large number of patients (n = 2044, 19%) were excluded from the ACI-TIPI trial because of missing data (eg, no electrocardiogram reading), and this may in part explain the differences in findings in our study. Another difference from our study is the fact that we examined symptom predictors of AMI and acute ischemia rather than only AMI.

Our study has several limitations. First, we were unable to distinguish the chief complaint that prompted the patient to seek care from other associated symptoms. Identification of the chief complaint may be a more accurate measure to use when identifying symptom predictors of ACS. Second, patients with acute ischemia and AMI were collapsed into one group for our analyses to obtain an adequate sample size. Subtle differences in symptom predictors in women and men may exist, depending on whether a patient has acute ischemia or AMI. Third, our sample size may have been insufficient to detect less-strong predictors of ACS

in women and in men, as well as significant sex differences in presentation with typical symptoms. Fourth, patients who were not diagnosed with ACS and were discharged to home from the ED did not receive further follow-up. It is possible that some of these patients might have had coronary ischemia that was missed. However, the proportion of missed diagnoses for acute ischemia in the ED is small.[1]

In conclusion, our results do not support the suspicion that in women atypical symptoms are more strongly related to ACS than in men. In contrast, typical symptoms are the strongest symptom predictors of ACS in women. These findings indicate that attention to typical symptoms of acute ischemia or AMI can provide the most important symptom-based clues on the pretest probability of ACS in women. Clinicians need to take very seriously any woman who has typical symptoms, pursue a full workup, and not dismiss her symptoms as more likely the result of some other psychogenic, gastrointestinal, or musculoskeletal cause.

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