Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: Results from the NHLBI WISE study

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Background Chest pain in the absence of obstructive coronary artery disease (CAD) is common in women; it is frequently associated with debilitating symptoms and repeated evaluations and may be caused by coronary microvascular dysfunction. However, the prevalence and determinants of microvascular dysfunction in these women are uncertain.

Methods We measured coronary flow velocity reserve (coronary velocity response to intracoronary adenosine) to evaluate the coronary microvasculature and risk factors for atherosclerosis in 159 women (mean age, 52.9 years) with chest pain and no obstructive CAD. All women were referred for coronary angiography to evaluate their chest pain as part of the Women's Ischemia Syndrome Evaluation (WISE) study.

Results Seventy-four (47%) women had subnormal (<2.5) coronary flow velocity reserve suggestive of microvascular dysfunction (mean, 2.02 ± 0.38); 85 (53%) had normal reserve (mean, 3.13 ± 0.64). Demographic characteristics, blood pressure, ventricular function, lipid levels, and reproductive hormone levels were not significantly different between women with normal and those with abnormal microvascular function. Postmenopausal hormone use within 3 months was significantly less prevalent among those with microvascular dysfunction (40% vs 60%, $P = .032$). Age and number of years past menopause correlated with flow velocity reserve ($r = -0.18$, $P = .02$, and $r = -0.30$, $P < .001$, respectively). No significant associations were identified between flow velocity reserve and lipid and hormone levels, blood pressure, and left ventricular ejection fraction.

Conclusions Coronary microvascular dysfunction is present in approximately one half of women with chest pain in the absence of obstructive CAD and cannot be predicted by risk factors for atherosclerosis and hormone levels. Therefore, the diagnosis of coronary microvascular dysfunction should be considered in women with chest pain not attributable to obstructive CAD. (Am Heart J 2001;141:735-41.)

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Chest pain typical for angina pectoris is less likely to be associated with obstructive epicardial coronary artery disease (CAD) in women than in men.[1] Although women with chest pain in the absence of CAD are at low risk for adverse cardiac events, they are frequently limited by debilitating symptoms that may prompt repeated diagnostic evaluations and hospitalizations. These women are commonly diagnosed with Syndrome X, defined as chest pain, an ischemic stress test response, and angiographically normal coronary arteries.[2] Syndrome X may result from coronary microvascular dysfunction, which is a disordered function of the smaller coronary resistance vessels (<100 to 200 μm). However, the prevalence of coronary microvascular dysfunction in women with chest pain in the absence of obstructive CAD is uncertain.[3,4] Furthermore, the patho-

physiology and clinical determinants of coronary microvascular dysfunction in women have not been elucidated. Evaluation of the prevalence and mechanism of microvascular dysfunction in women with chest pain may provide the basis for its early diagnosis, which would allow for timely initiation of palliative therapy and decrease costs of repeated medical evaluations for "noncardiac" chest pain. Accordingly, we assessed the functional integrity of the coronary microvasculature and risk factors for atherosclerosis in 159 women who were referred for diagnostic cardiac catheterization to evaluate chest pain and were found to have no angiographically documented obstructive CAD.

Methods

The Women's Ischemia Evaluation (WISE) study is a 4-center study focused on developing new diagnostic techniques and advancing our understanding of pathophysiologic mechanisms for ischemic heart disease in women.[5] Women referred for clinically indicated coronary angiography to evaluate chest pain were candidates for enrollment. As part of WISE, a subgroup of 159 women without obstructive CAD (<50% diameter stenosis in all coronaries) underwent invasive evaluation of the functional integrity of their coronary microvasculature and comprehensive risk factor analysis.

Risk factor analysis

All women provided written informed consent. Demographic data including historical risk factors for atherosclerosis were obtained by means of self-report questionnaires. Fasting blood was sent to the WISE hormone core laboratory for measurement of reproductive hormones. Validated steroid and protein assay methods were used to determine levels of total estrogen, progesterone, estrone, and estradiol.[6] The sensitivity and the between-assay coefficients of variation, respectively, were 15% and 16% for estrone, 8% and 12% for estrogen, and 3.7% and 4.2% for estradiol.[7] Additional fasting blood samples were sent to the WISE core lipid laboratory that participates in the Centers for Disease Control and Prevention (CDC) lipid standardization program. Plasma total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by enzymatic assay, and low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation. The coefficients of variation for TC, HDL, and triglycerides were 1.80%, 1.23%, and 3.93%, respectively.

Invasive evaluation of coronary flow velocity reserve

Women with angiographically normal or with only minimal coronary artery luminal irregularities (<50% stenoses in all coronaries according to WISE core angiographic laboratory assessment by quantitative techniques[8]) underwent invasive assessment of the functional integrity of their coronary microvasculature. Because the microvessels regulate myocardial blood flow, coronary microvascular dysfunction is associated with impaired coronary flow reserve (ie, attenuated maximal coronary hyperemia), which can be evaluated by measurement of coronary flow velocity (or flow) responses to hyperemic stimuli. To measure coronary flow velocity reserve, a 0.014-inch or 0.018-inch Doppler-tipped guide wire (Endosonics, Rancho Cordova, Calif) was advanced through a coronary catheter engaged in the left main or right coronary artery and positioned in the left anterior descending (n = 112), ramus intermedius (n = 2), left circumflex (n = 42), or right coronary artery (n = 3). Pulsed-wave Doppler ultrasonography was used to measure time-averaged peak coronary flow velocity, which was calculated on-line over 2 cardiac cycles through a 2-mm sample volume at a location approximately 5 mm distal to the tip of the guide wire. To assess the functional integrity of the coronary microcirculation, coronary velocity was measured at baseline and during peak hyperemia induced by a hand-injected intracoronary bolus of adenosine (18 μg in the left main or 12 μg in the right coronary artery, Adenocard, Fujisawa USA, Deerfield, Ill) diluted in 2 mL of normal saline solution and followed by a 5-mL saline solution flush. Coronary flow velocity reserve was defined as the ratio of the average peak coronary velocity after adenosine to baseline velocity. Coronary microvascular dysfunction was defined as a coronary flow velocity reserve of <2.5, which is the lower limit of normal flow reserve in arteries free of significant obstructive CAD[9-11] and has been adopted as the standard clinical definition of normal microvascular function.

Stress testing

Data were collected from exercise electrocardiographic stress tests, dobutamine stress echocardiography, and radionuclide perfusion stress tests that were performed for clinical indications in 122 patients. On the basis of standard clinical definitions of ischemia, patients were classified as having ischemic, normal, or indeterminant responses to stress testing.

Statistical analysis

The data are summarized as mean ± SD or percent changes when appropriate. Women were divided into 2 groups, based on their coronary flow velocity reserve and with a cut-point of 2.5. Differences in distributions of factors between flow velocity reserve groups were assessed by means of the Mann-Whitney test for continuous factors and the chi-square test (with exact *P* values calculated because of frequently small expected cell values) for dichotomous factors. Associations between flow velocity reserve and continuous factors were assessed by means of the Spearman correlation coefficient. Odds ratios for the outcome of impaired flow velocity reserve for women with a particular risk factor were calculated by means of logistic regression. *P* values of ≤.05 are reported as statistically significant.

Results

The 159 women, 85.5% of whom were white, had a mean age of 52.9 ± 10.6 years and were mostly postmenopausal (81.0%). The cohort had a maximum diameter coronary stenosis of 13.7% ± 18.2%. Of these women, 19.6% were current smokers, 17.1% had diabetes, 45.5% and 53.8% reported histories of hyperlipidemia and hypertension, respectively, and 43.6% of all women were using postmenopausal hormones (50.4% of postmenopausal women).

Table I. Comparison of risk factors between women with normal and those with abnormal microvascular function

	Abnormal CFR <2.5	Normal CFR ≥2.5
n	74	85
Age (y)	54.0 ± 11.5	52.0 ± 9.7
White (%)	89.2	82.4
Years since last menses*	19.5 ± 10.0	14.8 ± 8.4
Systolic blood pressure (mm Hg)	137.6 ± 20.9	131.7 ± 17.3
Maximum coronary stenosis (%)	14.5 ± 18.6	13.0 ± 17.9
Ejection fraction (%)	66.0 ± 9.6	64.3 ± 9.8
Cholesterol (mg/dL)		
Total	183.7 ± 42.6	179.4 ± 46.4
LDL	106.5 ± 36.9	98.9 ± 44.0
HDL	52.2 ± 11.4	51.5 ± 12.8
Triglycerides (mg/dL)	125.3 ± 88.6	144.7 ± 188.8
Hormone levels		
Progesterone (ng/dL)	0.6 ± 2.1	1.2 ± 2.9
Estrone (pg/mL)	109.0 ± 98.8	164.7 ± 248.7
Estradiol (pg/mL)	33.5 ± 28.2	53.7 ± 52.1
Bioavailable estradiol (pg/mL)	17.3 ± 16.8	26.2 ± 28.6
FSH (mIU/mL)	32.5 ± 25.5	23.9 ± 20.2
LH (mIU/mL)	13.6 ± 10.2	13.1 ± 11.9
History of (%)		
Current cigarette smoking	17.6	21.4
Diabetes	18.9	15.5
Hyperlipidemia	48.5	42.7
Hypertension	58.1	50.0
Menopause	79.7	82.1
Pharmacologic therapy (%)		
Hormone replacement in postmenopausal women (last 3 mo)†	39.7	59.7
Antihypertensive therapy	41.9	39.3
Aspirin	47.3	39.3
Lipid-lowering agent‡	25.7	14.3
Stress test response		
n	59	63
Ischemic (%)	37.3	27.0
Indeterminant (%)	27.1	22.2
Normal (%)	35.6	50.8

Continuous data are expressed as mean ± SD.
CFR, Coronary flow reserve; *FSH,* follicular stimulating hormone; *LH,* luteinizing hormone.
*$P < .01$.
†$P < .05$.
‡$P = .07$.

Table II. Correlations between coronary flow reserve and clinical characteristics

Characteristic	Spearman correlation coefficient
Age	−0.18*
Years since last menses	−0.30†
Systolic blood pressure	−0.12
Maximum diameter stenosis	−0.05
Ejection fraction	−0.15
Cholesterol (mg/dL)	
Total	−0.08
LDL	−0.12
HDL	−0.07
Triglycerides (mg/dL)	0.06
Hormone levels	
Progesterone (ng/dL)	0.11
Estrone (pg/mL)	0.13
Estradiol (pg/mL)	0.14
Bioavailable estradiol (pg/mL)	0.12
FSH (mIU/mL)	−0.15
LH (mIU/mL)	−0.05

FSH, Follicular stimulating hormone; *LH,* luteinizing hormone.
*$P < .05$.
†$P < .001$ for significance of test that correlation is equal to zero.

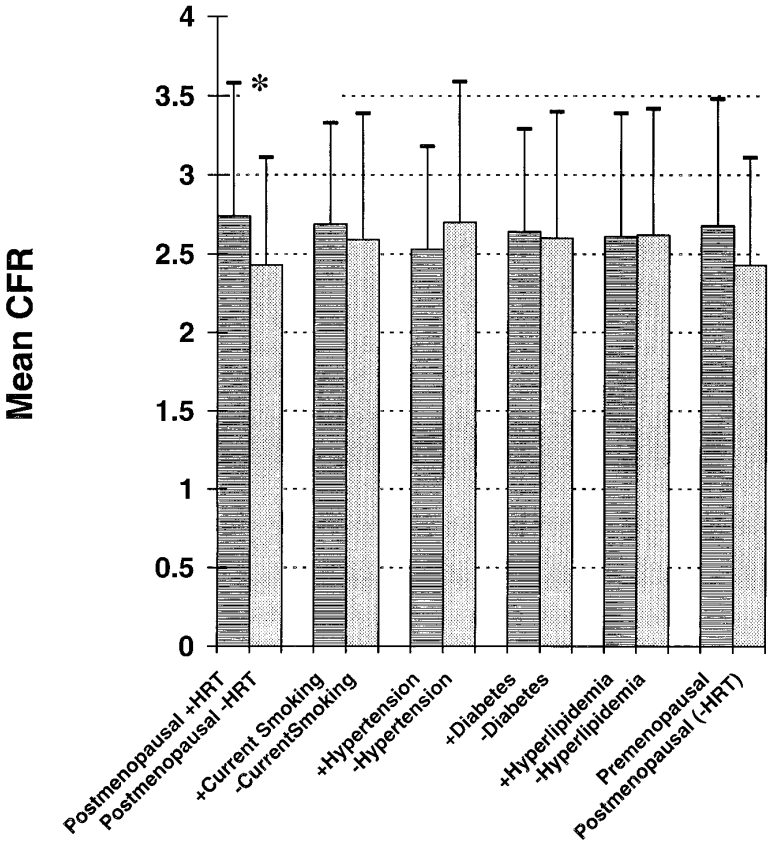
Comparison of women with and those without coronary microvascular dysfunction

Seventy-four (47%) of the 159 women had reduced coronary flow velocity reserve suggestive of microvascular dysfunction (mean, 2.02 ± 0.38). Eighty-five (53%) had normal coronary flow velocity reserve consistent with functionally intact coronary microvasculature (mean, 3.13 ± 0.64). Table I reports the clinical characteristics of women with and those without coronary microvascular dysfunction. These data demonstrate that when compared with the 85 women with normal coronary flow velocity reserve, the 74 women with reduced flow velocity reserve (ie, microvascular dysfunction) had similar demographic characteristics (age, race), baseline blood pressure, ventricular function, plasma lipid levels (TC, LDL, HDL, triglycerides), and plasma levels of the reproductive hormones estrone, estradiol, progesterone, and follicular stimulating and luteinizing hormones. Hormone use among postmenopausal women was significantly less prevalent among those with microvascular dysfunction (hormone use within 3 months reported in 39.7% of women with microvascular dysfunction vs 59.7% of those with normal function, $P = .032$). Among postmenopausal women, those with abnormal flow velocity reserve were several more years past menopause than those with normal microvascular function (19.5 vs 14.8 years, $P = .009$). The use of anithypertensive therapy, aspirin, and lipid-lowering agents did not differ between groups. There was a nonsignificant lower frequency of normal stress test responses in women with abnormal (35.6%) versus normal (50.8%) microvascular function ($P = .10$).

Determinants of coronary microvascular dysfunction

To evaluate factors potentially associated with coronary microvascular dysfunction in women, pertinent clinical variables were examined for correlation with coronary flow velocity reserve (Table II). A weakly significant negative correlation (Spearman $r = -0.18$, $P = .02$) was found between coronary flow velocity reserve and age. For postmenopausal women, a stronger association ($r = -0.30$, $P < .001$) was observed between flow velocity reserve and their reported number of years

Figure 1



Coronary flow velocity reserve in women with and those without traditional cardiac risk factors. Error bars denote standard deviation. *CFR,* Coronary flow velocity reserve; *HRT,* hormone replacement therapy in postmenopausal women. *Asterisk, P* = .017.

since menopause. However, the most notable finding is the lack of any significant associations between coronary flow velocity reserve and plasma lipid levels, circulating reproductive hormone levels, and baseline blood pressure and left ventricular ejection fraction.

Figure 1 compares coronary flow velocity reserve between women with and those without reported risk factors for atherosclerosis. These data demonstrate that in 125 women who were postmenopausal, those who used hormone replacement therapy within 3 months before evaluation had significantly higher coronary flow velocity reserve than hormone nonusers (2.74 ± 0.83 vs 2.43 ± 0.68, $P = .017$). In the entire cohort of premenopausal and postmenopausal women, no statistically significant differences were noted in mean flow velocity reserve between women who were current cigarette smokers and nonsmokers (2.69 ± 0.64 vs 2.59 ± 0.80), hypertensives and normotensives (2.53 ± 0.65 vs 2.70 ± 0.89), women with and those without diabetes (2.64 ± 0.65 vs 2.60 ± 0.80), or those with and those without reported hyperlipidemia (2.61 ± 0.78 vs 2.62 ± 0.80). There was a trend toward the 30 premenopausal women having higher flow velocity reserve than the 62 non–hormone-using postmenopausal women (2.68 ± 0.80 vs 2.43 ± 0.68, $P = .08$). In addition, differences in flow velocity reserve by these factors remained insignificant when patients were analyzed by subgroups of postmenopausal hormone users versus nonusers, suggesting that hormone use does not negate the influence of risk factors for atherosclerosis on flow velocity reserve.

To further evaluate determinants of coronary microvascular dysfunction in these women with chest pain who were found to have no obstructive CAD during diagnostic coronary angiography, odds ratios (OR) for the outcome of reduced flow velocity reserve in women with specific risk factors were calculated. Among postmenopausal women, hormone users were 56% less likely than nonusers to have impaired flow velocity reserve (OR = 0.44; 95% confidence interval,

0.22 to 0.91, $P = .026$). However, the distributions of traditional risk factors for atherosclerosis previously examined in Figure 1 were not significantly different in women with abnormal versus normal microvascular function. The corresponding ORs (with 95% confidence intervals) for impaired coronary flow velocity reserve were 0.78 (0.35 to 1.73) for current cigarette smoking (versus nonsmokers), 1.39 (0.74 to 2.60) for hypertension, 1.27 (0.56 to 2.92) for diabetes, and 1.27 (0.66 to 2.45) for hyperlipidemia.

Discussion

Women with chest pain in the absence of obstructive coronary atherosclerosis pose both a diagnostic and a therapeutic challenge. Although many of these women are diagnosed with "noncardiac" chest pain, an alternative mechanism for their symptoms is coronary microvascular dysfunction. Identification of this disorder is important because known treatments provide effective symptom relief, and its diagnosis can limit the need for repeated evaluations of "noncardiac" chest pain.[12-14] The current study suggests that (1) approximately half of women with chest pain and no significant angiographically documented CAD have physiologic evidence of coronary microvascular dysfunction, (2) postmenopausal women who do not use hormone replacement therapy are more likely than hormone users to have microvascular dysfunction, and (3) traditional risk factors for atherosclerosis are not associated with disordered coronary microcirculation in women with chest pain in the absence of obstructive CAD.

Epidemiologic studies suggest that angina is the most common initial presentation of CAD in women.[15] However, women with chest pain typical and atypical for angina are less likely to have obstructive CAD than men with similar symptoms.[1] Therefore, women with chest pain are frequently diagnosed with the clinical entities of Syndrome X (angina, ischemic stress test response, no obstructive CAD) or "noncardiac" chest pain.[2] Differentiation between these mechanisms of chest pain is important because noncardiac chest pain is not associated with cardiovascular sequelae and may require further medical evaluation and treatment. In contrast, Syndrome X, which is thought to be caused by microvascular dysfunction, is associated with inducible metabolic ischemia and can be treated by improving microvascular vasomotor tone with oral L-arginine, a precursor to vascular nitric oxide, and estrogen.[3,12,14,16-18]

Our results suggest that coronary microvascular dysfunction is present in approximately one half of women with chest pain in the absence of angiographically documented obstructive CAD. The pathophysiologic mechanism of coronary microvascular dysfunction in women without obstructive CAD has not been identified. Coronary microvascular tone is regulated in part by the endothelium, suggesting that microvascular dysfunction may be caused by endothelial dysfunction of the microvessels. This mechanism is supported by clinical studies in predominantly male cohorts, which have suggested that factors associated with endothelial dysfunction such as hypertension in the absence of left ventricular hypertrophy, diabetes, and hyperlipidemia are also associated with coronary microvascular dysfunction and that L-arginine improves symptoms in patients with abnormal coronary flow reserve.[12,19-21] Although these findings suggest that microvascular tone in men may be regulated by the endothelium of the coronary microvessels, our observation that risk factors for endothelial dysfunction do not appear to influence microvascular function in women suggests a possible sex difference in microvascular pathophysiology. However, our study did not directly evaluate coronary microvascular reponses to endothelium-dependent vasodilators. Therefore, we cannot state with absolute certainty that the observed lack of a relation between risk factors for atherosclerosis and coronary flow reserve is caused by the sex-specific differences in endothelial physiology.

Alternatively, microvascular physiology in women may be regulated by myocytes present in the media of the coronary microvessels. A myogenic mechanism can explain the current finding that a longer time since last menses (ie, longer duration of menopausal estrogen loss) is associated with worse coronary flow velocity reserve and that postmenopausal women who recently used estrogen were significantly more likely than estrogen nonusers to have normal microvascular function. In supraphysiologic concentrations, estrogen is an in vivo vasodilator that acts on arterial myocytes by inducing myocyte hyperpolarization, altering ATP-sensitive potassium channel kinetics in the myocytes, and inhibiting calcium and endothelin-1–induced, myocyte-mediated arterial constriction.[22-25] Estrogen also stimulates production of prostacyclin, which induces myocyte-mediated, endotheliumin-independent vasodilation.[26,27] Therefore, our findings, when viewed in the context of the lack of associations between risk factors for atherosclerosis and coronary flow velocity reserve, are consistent with the hypothesis that coronary microvascular dysfunction in women may be related to disordered microvascular myocyte function.

Limitations

This study is limited because it did not systematically evaluate the relation between coronary flow velocity reserve and a potential extrinsic factor that may alter vasoregulation of the coronary microvasculature, left ventricular hypertrophy. However, we have previously reported that coronary flow velocity reserve is not related to echocardiographically quantified left ventricular mass in women with chest pain in the absence of

obstructive CAD.[28] Furthermore, this study did not demonstrate an association between coronary flow velocity reserve and a history of hypertension, which is a risk factor for left ventricular hypertrophy.

The generalization of the current results to the overall population of women with chest pain is also limited. The WISE study enrolled only women who were clinically referred for diagnostic coronary angiography to evaluate chest pain. Therefore, the results might have been influenced by a referral bias and may only be applicable to women with the most severe chest pain. Another limitation is that some women were receiving pharmacologic therapy for risk factors for atherosclerosis at the time of evaluation of coronary microvascular physiology, which might attenuate relations between risk factors for atherosclerosis and coronary flow reserve. However, the data suggest that historical presence of risk factors for atherosclerosis and levels of lipids and reproductive hormones assessed at the time of angiography do not predict microvascular dysfunction in women with chest pain in the absence of obstructive CAD.

Our study found a nonsignificant lower frequency of normal stress responses in women with abnormal versus normal microvascular function. This lack of a strong, statistically significant association between stress-induced ischemia and microvascular function suggests that it is unlikely that stress testing will provide a highly sensitive and specific assessment of coronary microvascular dysfunction in women with chest pain and no obstructive CAD. However, the conclusions made from our observation are limited because our patients did not undergo stress testing with a uniform exercise protocol with imaging. Furthermore, recent studies suggest that more sophisticated measures of myocardial metabolism may be necessary to detect inducible myocardial ischemia in these women.[16]

Conclusions

Our results indicate that coronary microvascular dysfunction (ie, abnormally attenuated coronary flow velocity reserve) is present in approximately half of women with chest pain in the absence of obstructive CAD. Because microvascular dysfunction is associated with significant disability and is potentially treatable with vasoactive therapies, our findings suggest that it should be considered as a potential diagnosis in women with chest pain and no obstructive CAD. Our observation that risk factors for endothelial dysfunction do not correlate with coronary flow velocity reserve in these women suggests that further studies should evaluate the pathophysiologic mechanism of microvascular dysfunction. In addition, the relation found between reproductive hormones and coronary microvascular function in postmenopausal women must be further defined to determine whether postmenopausal hormone replacement can improve abnormal coronary microvascular physiology.

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