Abnormal Coronary Vasomotion as a Prognostic Indicator of Cardiovascular Events in Women

Results From the National Heart, Lung, and Blood Institute–Sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Background—Coronary vascular dysfunction has been linked to atherosclerosis and adverse cardiovascular outcomes in men, but these relationships have not been firmly established in women.

Methods and Results—As part of the Women's Ischemia Syndrome Evaluation (WISE) sponsored by the National Heart, Lung, and Blood Institute, 163 women referred for clinically indicated coronary angiography underwent coronary reactivity assessment with quantitative coronary angiography and intracoronary Doppler flow before and after intracoronary administration of acetylcholine, adenosine, and nitroglycerin and were then followed up for clinical outcomes. History of hypertension was present in 61%, dyslipidemia in 54%, diabetes in 26%, and current tobacco use in 21% of women enrolled. Seventy-five percent had no or only mild epicardial coronary artery disease (CAD). Over a median follow-up of 48 months, events occurred in 58 women. On bivariate analysis, women with an event had significantly less change in coronary cross-sectional area (ΔCSA) in response to acetylcholine ($P=0.0006$) and nitroglycerin ($P=0.04$). In addition, women with abnormal coronary dilator response to acetylcholine had less time free from cardiovascular events ($P=0.004$). In multivariable analysis, after controlling for age, hypertension, diabetes, dyslipidemia, tobacco use, and CAD severity, %ΔCSA with acetylcholine ($P=0.001$) independently predicted events. When the outcome was restricted to only death, myocardial infarction, congestive heart failure, and stroke, %ΔCSA with acetylcholine remained a significant predictor ($P=0.006$).

Conclusions—In women in this study, impaired coronary vasomotor response to acetylcholine was independently linked to adverse cardiovascular outcomes regardless of CAD severity. (***Circulation***. 2004;109:722-725.)

Key Words: coronary disease ■ endothelium ■ acetylcholine ■ prognosis ■ women

Coronary vascular dysfunction is believed to be a precursor for atherosclerosis and has been linked to progression of coronary artery disease (CAD) and development of cardiovascular-related events, such as death, myocardial infarction (MI), stroke, and unstable angina.[1–3] Recently, others have suggested that impaired coronary reactivity to acetylcholine (Ach) is an independent predictor of poor prognosis and predicts cardiovascular events in patients with epicardial CAD.[1–5] In another recent study, better coronary microvascular response to Ach was associated with improved survival.[6] These findings were in the context of both obstructive and nonobstructive CAD and support the hypothesis that coronary dysfunction is instrumental in both the development of CAD and its progression. Most of the studies that suggested a relationship between coronary dysfunction and adverse cardiovascular outcome were in mixed populations of men and women.[4,5] This relationship was seen predominately in high-risk patients and in studies with fewer women. We hypothesized that coronary dysfunction would be a determinant of adverse outcomes in women presenting with suspected myocardial ischemia. We investigated this prospectively in a cohort of women referred for clinically indicated coronary angiography who also underwent extensive testing of coronary vascular function.

Methods

Patients

We studied 163 women enrolled in the National Heart, Lung, and Blood Institute (NHLBI)–sponsored Women's Ischemia Syndrome Evaluation (WISE) who were referred for coronary angiography for investigation of suspected myocardial ischemia. The WISE is a 4-center study evaluating novel diagnostic techniques and pathophysiological mechanisms in women with suspected myocardial ischemia. The WISE protocol, approved by the relevant institutional review boards, has been described in detail elsewhere.[7] All study participants gave written informed consent before undergoing evaluation. Demographic data were recorded with standardized questionnaires. The University of Florida and the University of Pittsburgh sites participated in the coronary reactivity testing, and all data were read at a core laboratory (University of Florida).

Assessment of Coronary Vascular Function

Vasoactive medications were withdrawn for ≥48 hours, and coronary reactivity testing was performed in an epicardial coronary artery free of obstructive CAD (<50% diameter). The left anterior descending coronary artery was the preferred vessel, followed by the left circumflex coronary artery. To assess blood flow velocity, a Doppler-tipped guidewire (0.014-inch FloWire, JOMED/Cardiometrics) was advanced through the diagnostic catheter. Recordings were made once a stable Doppler signal in the proximal or mid vessel was obtained. Intracoronary bolus injections of 18 μg of adenosine (Adenocard, Fujisawa USA), a predominantly non–endothelium-dependent microvascular dilator, were administered into the left main coronary artery. Coronary flow reserve, the increase in flow resulting from dilation of the small arteries and arterioles, was measured, as well as flow-related dilation of epicardial vessels with intact endothelial function.[8]

Endothelium-dependent function was assessed directly with intracoronary infusion of Ach. A 10^{-6} mol/L Ach solution (Miochol-E, CibaVision) was infused at 0.8 mL/min for 3 minutes, which gave an estimated coronary concentration of 0.182 μg/mL. This was followed by infusion of 10^{-4} mol/L Ach for 3 minutes, which gave an estimated concentration of 18.2 μg/mL.[9,10] The 10^{-6} mol/L Ach was used for safety purposes and resulted in minimal changes in flow and diameter. Therefore, the 10^{-4} mol/L Ach data are reported. Nitroglycerin (NTG; 200-μg IC bolus) was then infused to assess non–endothelium-dependent epicardial coronary reactivity.[11]

Quantitative Coronary Angiography

Angiograms and flow recordings were made at baseline and after administration of each vasoactive drug. A return to baseline flow velocity was documented before each new reactivity test. Pulsed-wave Doppler flow spectra were used to calculate time-averaged peak velocity (APV). Coronary cross-sectional area (CSA) was calculated from the diameter measured 5 mm distal to the tip of the Doppler wire with the equation πR. Coronary volumetric blood flow (CBF) was calculated with the equation CBF=CSA×APV×0.5.[12] Epicardial response to Ach also was assessed by measuring coronary diameter at baseline and after Ach infusion by quantitative coronary angiography. For quantitative coronary angiography, angiograms were analyzed by investigators blinded to patient data at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI) as described previously.[13] Standard digital coronary angiographic images on CD-ROM were analyzed by a computer-based edge-detection method. Cine film images of lumen diameters were quantified by a projector-based cross-hair technique. Luminal diameters were determined at baseline and in response to vasoactive agents 5 mm distal to the Doppler wire tip. A CAD severity score was calculated.[13]

Definitions

Coronary flow velocity reserve was defined as the ratio of peak coronary APV after administration of vasoactive agents to the baseline coronary APV. Volumetric coronary flow reserve was the ratio of the peak calculated coronary flow after vasoactive agents to calculated baseline flow. Epicardial endothelial function was assessed by comparing the diameter after Ach infusion with baseline diameter at the same site. A normal response to Ach was dilation from baseline, whereas an abnormal response was defined as either no dilation or constriction with Ach.

TABLE 1. Characteristics of Women in the Study

Characteristics	
Age, y	55.6±10.1
Body mass index, kg/m^2	32.4±7.8
History of hypertension, n (%)	99 (61)
History of diabetes, n (%)	42 (26)
Family history of CAD, n (%)	106 (65)
Postmenopausal, n (%)	125 (77)
Any history of birth control pill use, n (%)	85 (52)
Any history of hormone replacement therapy, n (%)	95 (58)
History of smoking, n (%)	
Never	71 (44)
Past	57 (35)
Current	34 (21)
CAD, n (%)	
None (<20% stenosis)	74 (45)
Minimal (20%–50% stenosis)	49 (30)
Significant (>50%)	40 (25)

For age and body mass index, values are mean±SD. For body mass index, n=149 women; for all other categories, n=163 women.

Follow-Up

Follow-up was completed with the standardized WISE questionnaire administered at 6 weeks and then yearly after coronary reactivity testing. The outcome variable was defined as the number of women with a first cardiovascular event recorded >3 days after reactivity testing and included death or hospitalization for worsening angina, MI, congestive heart failure, ischemic stroke, other vascular event, or coronary revascularization (percutaneous coronary intervention or CABG).

Statistical Methods

All analyses were performed with SAS software release 8.0 (SAS Institute) and S-plus software release 6.1 (Insightful Corporation). Data on CSA in response to reactivity testing for women with or without events were compared by 2-sample t tests. Event rates were estimated with Kaplan-Meier survival curves for categorical variables, and probability values for these estimates were calculated with the log-rank statistic. For the survival analyses, failure to dilate (≤0%Δ in CSA) was considered abnormal for endothelium-dependent response to Ach and flow-mediated epicardial response to adenosine. For NTG, a non–endothelium-dependent epicardial vasodilator, a ≤15%Δ in CSA was considered abnormal. Cox proportional hazards modeling was used to examine the joint effect of covariates on time to first cardiovascular event. A priori, CAD status, hypertension, diabetes, dyslipidemia, age, current smoking, and menopause status were included in all models. Because of varying sample sizes, individual models were generated for each reactivity variable, to assess its independent effect. On the basis of these results, additional models were fit to assess the impact of multiple reactivity variables on time to first event. All tests were 2 tailed, and a probability value of <0.05 was considered statistically significant.

Results

Pertinent clinical characteristics for women in the study group are summarized in Table 1. Mean age of the women was 56 years, with a median follow-up of 48 months (range 4 days to 73 months). The majority were postmenopausal and had a history of hypertension, dyslipidemia, family member with
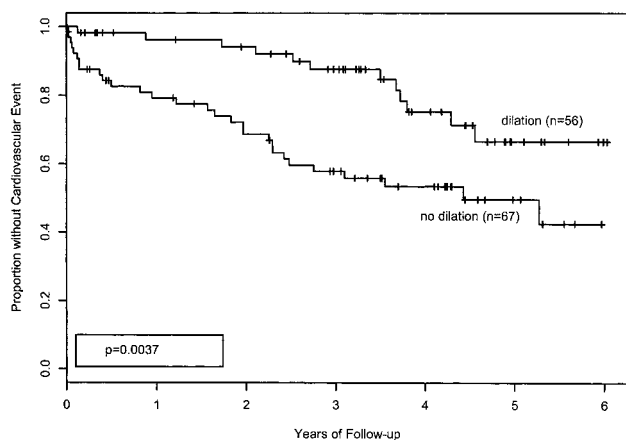
TABLE 2. Index (First) Events During Follow-Up

Event	No. of Cases
Death	5
Hospitalization for nonfatal event	
MI	2
CHF	3
Stroke	7
PCI	14
CABG	0
Angina	22
Other vascular event	5
No. of women with adverse event	58

MI indicates myocardial infarction; CHF, congestive heart failure; and PCI, percutaneous coronary intervention.
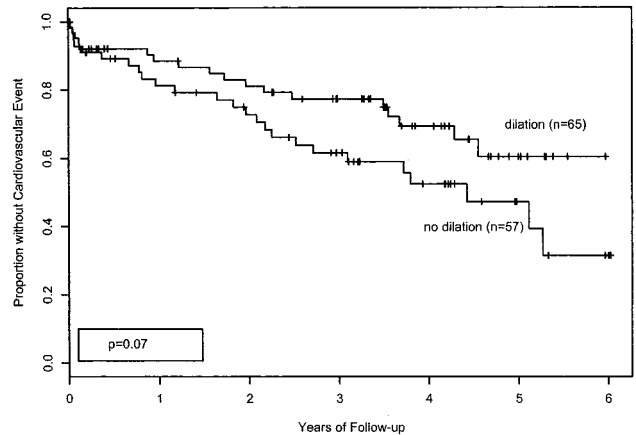
cardiac disease, birth control use, or hormone replacement. Twenty-two percent were current tobacco users. Body mass index (BMI) measurements were obtained on 149 women; 83% had a BMI >25, and 58% had a BMI >30. Participants were divided into 3 groups based on angiographic findings: 74 (45%) had no CAD, defined as <20% stenosis; 49 (30%) had minimal CAD, defined as 20% to 49% stenosis; and 40 (25%) had severe CAD, defined as stenosis ≥50%.

Of the 163 women studied, 58 (36%) had first events (Table 2), defined as death or hospitalization for cardiovascular cause. Of these, 22 (38%) died or had hospitalization for MI, congestive heart failure, stroke, or other vascular event. On bivariate analysis, women with an event had significantly less change in CSA (mean±SD) in response to Ach ($-7.9\pm20.9\%$; $P=0.0006$) and to NTG ($14.2\pm22.5\%$; $P=0.04$) than those without an event (Ach 7.8±24.5%, NTG 25.1±35.7%). Reduced microvascular responses (APV and volumetric ratio) to these agents were not associated with events (data not shown).

In addition, women with abnormal coronary dilator response to Ach had less time free from cardiovascular events ($P=0.004$; Figure 1). Trends were noted for %ΔCSA response after adenosine ($P=0.07$; Figure 2) and NTG
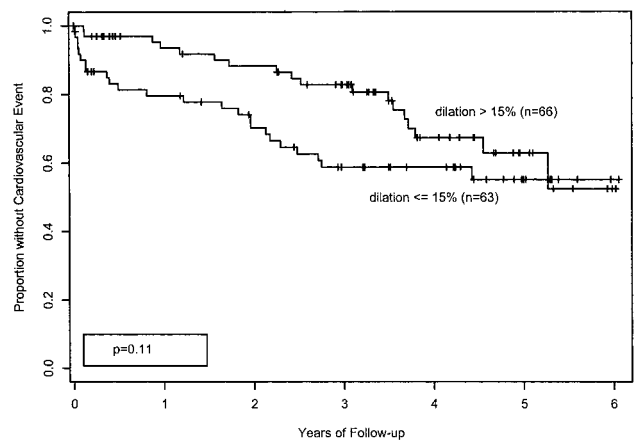

Figure 2. Relation between epicardial coronary CSA response to adenosine and risk of cardiovascular event. Kaplan-Meier analysis of event-free survival.

($P=0.11$; Figure 3) when analyzed for event-free survival. Early differences in event-free survival were seen with response to NTG, but owing to later events in the dilation group, statistical significance was not achieved.

Reactivity variables were evaluated individually for association with time to first cardiovascular event, controlling for age, CAD status, hypertension, dyslipidemia, current smoking status, and menopause status. Variables that were observed to significantly improve this basic model included %ΔCSA in response to Ach ($P=0.001$) and NTG ($P=0.03$), as well as APV ratio in response to Ach ($P=0.04$) and NTG ($P=0.02$). On multivariable regression analysis, degree of CAD and %ΔCSA to Ach were the only variables that predicted adverse cardiovascular events (all $P<0.05$; Table 3). When the outcome was restricted to death, MI, congestive heart failure, or stroke, response to Ach remained a significant ($P=0.006$) predictor of outcomes.

Discussion

Abnormal coronary vasomotion is believed to be a precursor to atherosclerotic disease[4] and has been suggested to predict adverse cardiovascular outcomes, including death, MI, and

Figure 1. Relation between epicardial coronary CSA response to ACh and risk of cardiovascular event. Kaplan-Meier analysis of event-free survival.

Figure 3. Relation between epicardial coronary CSA response to NTG and risk of cardiovascular event. Kaplan-Meier analysis of event-free survival.

TABLE 3.   Cox Proportional Hazards Regression (Final Model) Results for Predictors of Adverse Outcome Risk

Variable	Hazard Ratio	95% Confidence Interval
Minimal CAD	2.842	1.255–6.440
Severe CAD	3.853	1.641–9.047
Hypertension	0.868	0.426–1.767
Diabetes	0.751	0.310–1.819
Dyslipidemia	0.511	0.250–1.045
Age	0.990	0.950–1.032
Current smoker	0.965	0.419–2.223
Postmenopausal	0.881	0.353–2.202
% CSA change in response to Ach	0.971	0.953–0.988

CSA indicates cross-sectional area; Ach, acetylcholine.

cerebrovascular events.[1–5,14] In the present study, an abnormal response to Ach was found to be an independent predictor of adverse cardiovascular events, including hospitalization for worsening angina, MI, congestive heart failure, stroke, revascularization, other vascular events, and death in women evaluated for suspected ischemia. Abnormal response to Ach also predicted adverse outcomes when analyzed for only cardiovascular deaths, MI, congestive heart failure, and stroke. This relationship persisted even after we controlled for factors known to contribute to adverse cardiovascular-related events, including degree of CAD, hypertension, diabetes, dyslipidemia, age, current smoker, and menopause status. Furthermore, women with impaired coronary vascular response to Ach had decreased time free of adverse cardiovascular events.

Previous studies have shown that abnormal coronary vasomotion is a predictor of adverse cardiovascular outcomes. However, most of these studies have been in high-risk patients with fewer female patients.[1–5] The present data confirm previous reports that indicate that an abnormal coronary response to Ach is an independent predictor of adverse cardiovascular outcomes and extends this relationship to women being evaluated for suspected ischemia. In the present study, 75% of the women had no or only minimal epicardial CAD. Therefore, this work also extends the observed relationships between abnormal coronary reactivity and adverse outcomes to lower-risk women who do not have significant angiographic CAD. Interestingly, significant relationships between abnormal reactivity and adverse outcomes were observed only with reactivity measures related to endothelial dysfunction.

Previous WISE analyses have shown that coronary microvascular dysfunction is correlated with traditional atherosclerotic risk factors,[15] but more recent analysis reveals that although these relationships remain statistically significant, the *r* values are low (eg, <0.20). Hence, these risk factors do not account for most of the variability in coronary microvascular function (Wessel et al, unpublished data, 2004). Given that abnormal coronary vasomotion in the form of endothelial dysfunction is believed to be a precursor of clinical atherosclerosis and a predictor of adverse cardiovascular events but is poorly predicted by current diagnostic tests, such testing may be valuable for further risk stratification of women being evaluated for suspected ischemia.

Study Limitations

The WISE study only included a relatively small cohort of women with signs and/or symptoms suggestive of ischemia who were referred for clinically indicated coronary angiography. This may have resulted in a referral bias. Also, reactivity testing results were from a single testing period, which may not necessarily reflect the status of the coronary artery over time.

Conclusions and Clinical Implications

Coronary endothelial dysfunction, which is potentially modifiable, is increasingly suggested as a contributor to cardiovascular morbidity and even mortality. The results of the present study confirm the suggestion that this dysfunction is an independent predictor of adverse outcomes and extend this relationship to women under evaluation for suspected ischemia. Further investigation of pathophysiological mechanisms and therapeutic interventions of coronary dysfunction, both at the macrovascular and the microvascular level, are needed.

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