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Impaired Coronary Vascular Reactivity and Functional Capacity in Women

Results From the NHLBI Women's Ischemia Syndrome Evaluation (WISE) Study

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OBJECTIVES We investigated the relationship between coronary vascular reactivity and functional capacity as assessed from the Duke Activity Status Index (DASI) in a cohort of women evaluated for suspected ischemia.

BACKGROUND Reduced functional capacity and impaired vascular reactivity are associated with poor prognosis, but an association between vascular reactivity and functional capacity is unknown.

METHODS A total of 190 women enrolled in the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study had baseline clinical assessment and coronary artery flow velocity response to adenosine ($CFVR_{ado}$). We compared these results with self-reported DASI metabolic equivalents (METs).

RESULTS Mean age was 55 ± 11 years (range 21 to 83 years), and only 18% had coronary stenosis ≥50%. Women with a $CFVR_{ado}$ <2.5 (n = 98) had mean DASI of 15.1 ± 13.6, compared to women (n = 92) with $CFVR_{ado}$ ≥2.5, whose mean DASI was 21.0 ± 15.2 (p = 0.004). This relationship was maintained after adjusting for age and presence of coronary artery disease. $CFVR_{ado}$ of ≥2.5 was associated with a DASI of >20 (odds ratio 3.03, 95% confidence interval 1.56 to 5.90, p = 0.001).

CONCLUSIONS Women with reduced $CFVR_{ado}$ were significantly more likely to have reduced functional capacity. Impairment in coronary vascular function and reduced levels of activity may both play a role in the poorer prognosis observed in the WISE study women; however, the relationship between the two is still unclear. (J Am Coll Cardiol 2006;47:44S–9S) © 2006 by the American College of Cardiology Foundation

Exercise capacity is among the most important predictors of cardiovascular adverse outcomes in healthy men (1) and women (2) as well as in those with coronary artery disease (CAD) (3). The factors contributing to impaired exercise capacity appear multifactoral and include increasing age, sedentary lifestyle, depression, obesity, and other comorbidities as well as impaired cardiovascular function. Recent research has suggested similar correlations between exercise capacity and mortality in asymptomatic women, independent of other cardiovascular risk factors (2,4). The mechanisms to explain this relationship are not clear. In addition to traditional exercise testing, the Duke Activity Status Index (DASI) is a well validated measure of functional capacity that can be expressed as metabolic equivalents (METs) and has been shown to correlate with adverse outcomes (5–7). In the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study, women evaluated for suspected ischemia all had assessments of functional capacity, including DASI scores, and a subgroup also had assessments of coronary vascular reactivity. Previous analyses of this relatively healthy group of women have demonstrated that both lower DASI scores and impaired large coronary artery endothelial function are associated with adverse cardiovascular outcomes (8,9). In this work, we investigated the relationship of DASI score to vascular reactivity assessed from coronary flow response to adenosine ($CFVR_{ado}$) in these women.

METHODS

Study population. The WISE study is an NHLBI-sponsored four-center study that aims to improve diagnostic testing in the evaluation of ischemic heart disease in women. A total of 936 women with chest pain (mean age 58±12 years; range 21 to 86 years), presenting for clinically indicated angiograms to evaluate suspected myocardial ischemia, were enrolled from 1996 to 2000. The institutional

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Abbreviations and Acronyms

CAD	= coronary artery disease
$CFVR_{ado}$	= coronary flow velocity response to adenosine
CI	= confidence interval
DASI	= Duke Activity Status Index
METs	= metabolic equivalents
NHLBI	= National Heart, Lung, and Blood Institute
WISE	= Women's Ischemia Syndrome Evaluation

review board at each site approved the study, participant consent was obtained at enrollment, and all data were monitored by an independent data and safety monitoring committee. Major exclusion criteria were comorbidity that would compromise follow-up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, severe congestive heart failure, recent myocardial infarction, significant valvular or congenital heart disease, and a language barrier to questionnaire testing. Full details of the protocol and design of the WISE study have been previously published (10). The present study population consisted of the 190 WISE study participants who had measurements of coronary vascular function with adenosine.

Baseline evaluation. Baseline evaluation consisted of a physical exam and collection of clinical data, including the DASI questionnaire. Demographic, clinical, and angiographic data were collected at the WISE study data coordinating center in Pittsburgh, Pennsylvania. Qualitative and quantitative coronary angiographic analyses were carried out by a core laboratory (Rhode Island Hospital, Providence, Rhode Island) according to methodology and definitions previously published from the WISE study (11). We defined any angiographic stenosis of >50% of luminal diameter as significant CAD. The CAD severity score was derived as an aggregate of percentage of luminal stenosis, extent and location of stenosis, and degree of collateral vessels (11).

Measurement of functional capacity. The DASI is a score derived from a 12-item self-reported questionnaire that captures a person's ability to perform various routine activities. These activities have been shown to accurately estimate peak oxygen consumption (5,6). By dividing the DASI score by 3.5, MET levels were derived. Women with a DASI score of <20, which corresponds to 5.7 METs, were considered functionally impaired (12).

Measurement of coronary microvascular function. To assess coronary vascular function, testing was performed in a left coronary artery branch (left anterior descending coronary artery [n = 137] or circumflex coronary artery [n = 53]) without obstructive atherosclerosis (diameter stenosis <50%) after vasoactive medications had been withdrawn for at least 48 h. To assess blood flow velocity reserve, a Doppler-tipped guidewire (0.014-inch FloWire; Jomed/Cardiometrics, Mountain View, California) was advanced through the diagnostic catheter, and recordings were made once a stable Doppler signal in the proximal or mid vessel was obtained. Intracoronary bolus injections of 18 μg adenosine (Adenocard; Fujisawa USA, Deerfield, Illinois) were administered into the left main coronary artery. The coronary flow velocity increase resulting from dilation of the microvasculature was measured (11). A $CFVR_{ado}$ of <2.5 was taken to represent impaired coronary vascular function. (13).

Statistical analysis. The primary analysis in this report is the relationship between functional capacity as assessed by DASI scores and a measure of coronary reactivity using $CFVR_{ado}$. The relationships among these measurements and other demographic and CAD risk factor variables were also investigated. For comparing women with normal ($CFVR_{ado}$ ≥2.5) versus impaired ($CFVR_{ado}$ <2.5) coronary reactivity, and normal (DASI ≥20) versus impaired (DASI <20) functional capacity, unadjusted means ± standard deviations or frequencies (%) were calculated. We also used tertile analysis to examine the gradient between high, medium, and low $CFVR_{ado}$ and high, medium, and low DASI in this study population. The Mantel-Haenszel chi square was used to evaluate the p value for trend. Because demographic and/or clinical data tend to have skewed distributions, we used Wilcoxon rank sum tests to compare continuous variables, chi square tests to compare categorical variables, and Spearman rank correlations to describe the relationship between continuous variables. Logistic regression analysis was used to adjust these for age and CAD. Stepwise logistic regression analysis was used to model normal versus low functional capacity as a function of coronary reactivity and other coronary risk factors. Variables considered for inclusion in the model included the baseline characteristics listed in Tables 1 and 2, and variables were then chosen for entry into multivariable models based upon univariate associations of $p \leq 0.10$. In order to account for possible modulator effects, we then forced all other variables from Tables 1 and 2 into the models, one at a time. Summary statistics for the regression models included the *c*-statistic (a measure of association of predicted probabilities and observed prevalence of a binary outcome) and R^2 (re-scaled for use in logistic regression). For all analyses, a two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the women are shown in Table 1. In general, these 190 women in the coronary vascular function substudy population are very similar to the total WISE study cohort (10). The mean age was 55 ± 11 years and 18% were nonwhite minorities, primarily African American. Three-quarters were postmenopausal, and about half were obese (body mass index ≥30 kg/m^2) and had hypertension or dyslipidemia. Seventy percent of the WISE study women had a family member with premature heart

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Table 1. Characteristics of Women With Coronary Flow Velocity Reserve Assessments

	Overall (n = 190)	$CFVR_{ado}$ <2.5 (n = 98)	$CFVR_{ado}$ ≥2.5 (n = 92)	Unadjusted p Value
Age (yrs)	55 ± 11	56 ± 12	53 ± 9	0.01*
Postmenopausal (%)	75	77	72	0.40
Nonwhite race (%)	18	13	23	0.08
BMI (kg/m^2)	31.2 ± 7.3	31.1 ± 6.3	31.3 ± 8.3	0.52
Waist-hip ratio	0.88 ± 0.13	0.89 ± 0.14	0.87 ± 0.13	0.03
Waist circumference	38.1 ± 7.5	38.6 ± 7.3	37.6 ± 7.8	0.31
Systolic BP (mm Hg)	135 ± 20	139 ± 21	131 ± 17	0.007*
Diastolic BP (mm Hg)	77 ± 10	77 ± 9	76 ± 11	0.56
Pulse pressure (mm Hg)	58 ± 17	62 ± 19	55 ± 14	0.009*
History of hypertension (%)	56	61	50	0.12
History of dyslipidemia (%)	51	57	44	0.08
Diabetes (%)	21	26	16	0.12
Hemoglobin	13.0 ± 1.4	13.0 ± 1.5	13.0 ± 1.3	0.68
Family history of CAD (%)	70	70	70	0.98
Past smoker (%)	57	58	56	0.82
Current smoker (%)	20	17	23	0.34
CAD ≥50% stenosis (%)	18	23	14	0.13
CAD severity score	8.6 ± 6.2	9.4 ± 7.2	7.7 ± 4.8	0.09
DASI	18.0 ± 14.6	15.1 ± 13.6	21.0 ± 15.2	0.004*
DASI <20 (%)	66	78	54	0.0007*
Medication use				
Current HRT (%)	44	39	49	0.14
Ever used HRT (%)	54	49	60	0.16
Beta-blockers (%)	29	38	20	0.006*
Statins (%)	17	20	13	0.18
ACE inhibitors (%)	25	28	22	0.35
Aspirin (%)	49	54	44	0.19
Calcium antagonists (%)	27	26	28	0.79
Nitrates (%)	19	20	18	0.74

*$p < 0.05$ after adjusting for age and presence of significant CAD.

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; $CFVR_{ado}$ = coronary flow velocity response to adenosine; DASI = Duke Activity Status Index; HRT = hormone replacement therapy.

disease. Twenty percent had a history of diabetes mellitus, currently smoked, or had significant angiographic CAD. Somewhat more than half of the women had an impaired $CFVR_{ado}$ (<2.5). This population was also characterized by impaired functional capacity, with a mean DASI of 18.0 ± 14.6 (equivalent to 5.1 METS), and two-thirds having a DASI of <20. Only 10% indicated that they could participate without difficulty in strenuous sports, which included swimming (question 12 in the DASI). Women with impaired $CFVR_{ado}$ were significantly older, had higher systolic blood pressure, pulse pressure, and beta-blocker use, and more frequently had impaired functional capacity. No other laboratory values or medication use were significantly different. The differences between women with normal and impaired $CFVR_{ado}$ persisted even after adjusting for age and presence of CAD (Table 1).

Baseline characteristics of the women categorized by impaired versus normal functional capacity (DASI <20 vs. >20) are summarized in Table 2. The group with impaired functional capacity had significantly lower $CFVR_{ado}$ compared to the group with normal functional capacity (2.4 ± 0.7 vs. 2.7 ± 0.7; p = 0.004). Women with impaired functional capacity also had significantly higher CAD severity scores, and a higher proportion had significant CAD (24% vs. 8%; p = 0.007). Use of aspirin, calcium antagonists, and nitrates was seen in significantly higher percentages of women with impaired functional capacity compared to those with normal functional capacity. After adjusting for age and presence of CAD, only normal $CFVR_{ado}$ (p = 0.01), and nitrate use (p = 0.01) remained significantly predictive. The presence and severity of CAD also remained significant after adjustment for age.

The Spearman rank correlation between DASI and $CFVR_{ado}$ was 0.20 (p = 0.005). Figure 1 characterizes the women by tertiles for both DASI and $CFVR_{ado}$. For each increasing tertile of CFVR, a higher proportion of women had normal functional capacity and a decreasing proportion of women had low functional capacity (p for trend = 0.02).

Independent predictors of normal versus reduced functional capacity are summarized in Table 3. When modeled using a stepwise regression and adjusting for baseline differences, the best independent predictors of normal functional capacity were: $CFVR_{ado}$ ≥2.5 (odds ratio [OR] 3.03, 95% confidence interval [CI] 1.56 to 5.90; p = 0.001), CAD severity score (OR 0.92, 95% CI 0.85 to 0.99; p = 0.04), and diastolic blood pressure (OR 1.03, 95% CI 1.001 to 1.07; p = 0.04) (Table 3). Substituting presence/absence of obstructive CAD did not greatly affect the model,

Table 2. Characteristics of Women by Assessment of Functional Capacity

	DASI <20 (n = 126)	DASI ≥20 (n = 64)	p Value (Unadjusted)	p Value (Adjusted for Age and CAD)
Age (yrs)	54 ± 11	55 ± 10	0.75	0.28
Postmenopausal (%)	76	73	0.66	0.36
Nonwhite race (%)	18	19	0.83	0.42
BMI (kg/m^2)	31.4 ± 7.4	30.9 ± 7.3	0.51	0.85
Systolic BP (mm Hg)	135 ± 20	136 ± 19	0.61	0.95
Diastolic BP (mm Hg)	76 ± 10	78 ± 10	0.21	0.10
Pulse pressure (mm Hg)	59 ± 17	57 ± 17	0.32	0.28
History of hypertension (%)	59	50	0.25	0.28
History of dyslipidemia (%)	56	41	0.08	0.20
Diabetes (%)	24	16	0.19	0.44
Family history of CAD (%)	70	69	0.83	0.89
Current smoker (%)	23	14	0.14	0.20
CAD ≥50% stenosis (%)	24	8	0.007	0.006
CAD severity score	9.4 ± 6.6	6.9 ± 5.0	0.002	0.01
$CFVR_{ado}$	2.4 ± 0.7	2.7 ± 0.7	0.004	0.01
$CFVR_{ado}$ ≥2.5 (%)	40	66	0.0007	0.001
Medication use				
Current HRT (%)	44	44	0.97	0.92
Ever used HRT (%)	55	54	0.92	0.76
Beta-blockers (%)	32	22	0.12	0.18
Statins (%)	18	14	0.46	0.54
ACE inhibitors (%)	25	25	0.46	0.54
Aspirin (%)	56	38	0.02	0.08
Calcium blockers (%)	32	19	0.06	0.08
Nitrates (%)	25	8	0.004	0.01

Abbreviations as in Table 1.

although nitrate use entered as a significant covariate. Similarly, limiting the analysis to only those without CAD did not change the model. To exclude the modulating effect of other variables, we added each variable from Tables 1 and 2 in turn to the models. These were not independent predictors of functional capacity, nor did their addition to the model affect the robust relationship between $CFVR_{ado}$ and DASI.

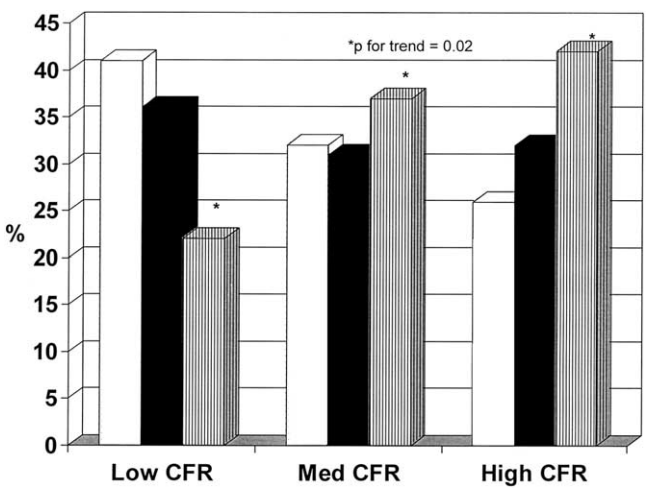

Figure 1. Percentage of women with low, medium, and high Duke Activity Status Index (DASI) by coronary flow velocity (CFR). DASI tertiles: 0 to 9.8 (n = 63), 9.9 to 19.9 (n = 63), 20 to 58.2 (n = 62). $CFVR_{ado}$ tertiles: 0.58 to 2.22 (n = 63), 2.23 to 2.69 (n = 65), 2.7 to 4.48 (n = 62). **Open bars** = low DASI; **solid bars** = medium DASI; **ruled bars** = high DASI.

DISCUSSION

Our results suggest a significant relationship between impaired coronary flow reserve and overall functional capacity in women with suspected ischemic heart disease. In previous studies, DASI has been shown to be a reliable and valid assessment of functional capacity as expressed in METs (5). The observed relationship between DASI and coronary flow reserve was independent of age and CAD and offers one possible link to explain the resulting impairment in functional capacity observed in these women. The mechanism responsible for the observed impairment of coronary vascular function on the overall functional capacity is unknown.

Exercise capacity has been shown to be an important prognostic predictor in patients with cardiovascular disease. In a study involving more than 6,000 men who underwent clinically indicated exercise electrocardiogram treadmill, a low metabolic equivalent was associated with mortality (1). Peak exercise capacity measured by METs was the strongest predictor of death in patients with cardiovascular disease and also in normal subjects (14). Exercise capacity was a stronger predictor of mortality than traditional risk factors for cardiovascular disease. Furthermore, in patients with heart failure, decreased functional capacity has been shown to be associated with worse cardiovascular outcomes (15). In addition to the high-risk patient groups, impaired exercise capacity has been shown to correlate with cardiovascular death in asymptomatic men (1). In a recent analysis from the Women Take Heart project, exercise capacity was found

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Table 3. Independent Predictors of Normal Versus Reduced Functional Capacity (DASI ≥20 vs. <20)

Predictor	Odds Ratio	95% CI	p Value
1. Model obtained by stepwise regression (c-statistic = 0.72; R^2 = 0.16)			
$CFVR_{ado}$ ≥2.5	3.03	1.56–5.90	0.001
CAD severity score	0.92	0.85–0.99	0.04
Diastolic BP	1.03	1.001–1.07	0.04
2. Model obtained when not entering CAD severity score (c-statistic = 0.69; R^2 = 0.18)			
$CFVR_{ado}$ ≥2.5	2.76	1.44–5.30	0.002
CAD ≥50% stenosis	0.34	0.12–0.95	0.04
Nitroglycerin use	0.26	0.10–0.74	0.01
3. Model obtained by stepwise regression for women without CAD only (n = 154) (c-statistic = 0.67; R^2 = 0.13)			
$CFVR_{ado}$ ≥2.5	3.02	1.51–6.04	0.002
Nitroglycerin use	0.33	0.11–0.94	0.04

The following variables were entered into the logistic model were not independent covariates: age, race, waist-hip ratio, systolic blood pressure, diastolic blood pressure (BP), pulse pressure, history of dyslipidemia, and use of beta-blockers, aspirin, calcium blockers, or nitrates. The above and the following variables were forced into the models one at a time, but their inclusion did not affect the relationship between CFVR ≥2.5 and DASI ≥20: postmenopausal status, body mass index, waist circumference, history of hypertension or diabetes, hemoglobin, family history of CAD, current or ever smoking, current or ever hormone replacement therapy, and use of statins, angiotensin-converting enzyme inhibitors.

CAD = coronary artery disease; $CFVR_{ado}$ = coronary flow velocity response to adenosine; CI = confidence interval; DASI = Duke Activity Status Index.

to be a strong independent predictor of all-cause death in asymptomatic women as well (2). This relationship held even after adjusting for traditional cardiac risk factors. For each MET increase in exercise capacity, a 17% reduction in mortality rate was seen. More recent WISE study data have shown that lower functional capacity, assessed by DASI, was associated with higher prevalence of coronary heart disease risk factors and angiographic CAD at baseline and associated with higher risk of adverse events during intermediate follow-up and was independent of both traditional cardiovascular risk factors and anthropometric measurements (9).

The exact mechanisms responsible for this observed relationship are unclear. In our study, impaired overall functional capacity was independently associated with coronary microvascular dysfunction. Impaired vascular function is believed to be integral to the formation of atherosclerotic heart disease. The identification of endothelial dysfunction in the absence of significant occlusive disease presents a global pattern of dysfunction in the macro- and microcirculation and has been postulated to represent one of the earliest manifestations of atherosclerosis (16). Impaired vascular function has been shown to be independently associated with adverse cardiovascular outcomes in the absence of epicardial coronary disease (17). This is the first study to demonstrate that non–endothelial-dependent microvascular dysfunction is associated with decreased functional capacity in women. Decreased functional capacity in the WISE study women has been recently shown to be correlated with adverse outcome (9). Disordered vascular smooth muscle and endothelial interactions may contribute to the ability of the coronary vessels to respond to changes in perfusion pressure and metabolic demands during ischemia and infarction. This and other nonatherosclerotic mechanisms could contribute to the decreased functional capacity and poor outcomes observed in women with ischemic heart disease.

Interventions targeting decreased functional capacity have resulted in improvements in both symptoms and measures of microvascular function. Eriksson et al. (18) compared an eight-week exercise training program to a control group in patients with syndrome X. The exercise training resulted in a significant increase in exercise capacity with less anginal pain. There was a trend toward an endothelium-dependent blood flow increases after training (p = 0.06). Recent work by Woo et al. (19) suggests improvements in arterial endothelial function after six weeks to one year of diet versus diet and exercise in a group of 82 obese but otherwise healthy children. At one year, there was significantly less carotid intimal thickening in the group that continued to diet and exercise and sustained improvement in arterial endothelial function. Data from Hambrecht et al. (20) have demonstrated that impairment in coronary artery endothelial function could be reversed by a short-term moderate level of exercise training. Our data, which demonstrates that increasing levels of functional capacity are associated with increases in $CFVR_{ado}$, would support the hypothesis that if vascular dysfunction is reversible, an intervention that increases functional capacity should increase vascular function. Hambrecht et al. (20) also observed that exercise training resulted in improvements in agonist-mediated endothelium-dependent vasodilatory capacity of the left internal mammary artery in patients with CAD. There was a significant increase in endothelial nitric oxide synthase protein expression in the training group compared with the control group. We have observed that hemoglobin levels show an association with DASI scores, vascular reactivity, and adverse cardiovascular outcomes in the WISE study population (21). Thus we could postulate a possible interaction among nitric oxide metabolism, hemoglobin levels, and impaired microvascular function (22), which all ultimately may contribute to reduced functional capacity and worsened cardiovascular outcome. This interaction also opens another possible therapeutic target for future studies.

The American Heart Association has expressed the need to find noninvasive screening tests that predict cardiac risk (23). In women, the need for better risk stratification is extremely important, given the gender-related diagnostic dilemmas. Because, as shown here, lower DASI scores correlate with impaired coronary vascular function and elsewhere with higher risk for adverse outcomes, the DASI may be a simple and easy to use tool that contributes to the global risk assessment. This instrument is easy to use and cheap and needs further study to confirm our findings.

Study limitations. Our study evaluated a relatively small group of women with chest pain and ischemic-type symptoms warranting referral for coronary angiography, which may lead to a referral bias and limited generalization of the results. We measured coronary vascular response at only one point in time, so unknown or unmeasurable factors could potentially alter the responses at that point in time. Our cross-sectional design precludes inferring a causal relationship between vascular reactivity and functional capacity.

Conclusions. Women with reduced $CFVR_{ado}$ were significantly more likely to have reduced functional capacity as assessed by the DASI. The DASI may offer a simple noninvasive measure of global cardiovascular risk that is linked to impairment in coronary vascular function.

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