Clin. Cardiol. 30, 69–74 (2007)

Clinical Investigations

Coronary Microvascular Reactivity is Only Partially Predicted by Atherosclerosis Risk Factors or Coronary Artery Disease in Women Evaluated for Suspected Ischemia: Results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE)

Timothy R. Wessel, M.D., Christopher B. Arant, M.D., Susan P. McGorray, PH.D., Barry L. Sharaf, M.D., FACC,* Steven E. Reis, M.D., FACC,† Richard A. Kerensky, M.D., FACC, Gregory O. von Mering, M.D., FACC, Karen M. Smith, M.D., FACC, Daniel F. Pauly, M.D., PH.D., FACC, Eileen M. Handberg, PH.D., Sunil Mankad, M.D., FACC,‡ Marian B. Olson, M.S.,† B. Delia Johnson, PH.D.,† C. Noel Bairey Merz, M.D., FACC§, George Sopko, M.D.,# Carl J. Pepine, M.D., MACC

University of Florida, Division of Cardiovascular Medicine, Gainesville, Florida; *Rhode Island Hospital, Division of Cardiology, Providence, Rhode Island; †University of Pittsburgh, Department of Epidemiology, Pittsburgh, Pennsylvania; ‡Allegheny General Hospital, Division of Cardiology, Pittsburgh, Pennsylvania; §Cedars-Sinai Medical Center, Division of Cardiology Los Angeles, California; and #National Heart, Lung, and Blood Institute, National Institutes of Health, Division of Heart and Vascular Disease, Bethesda, Maryland, USA

Summary

Background: Altered coronary reactivity is frequent in women with findings of myocardial ischemia without significant obstructive disease. This suggests a defect in coronary microvascular function. The adenosine-related component of this altered reactivity has been described in male and mixed gender populations, while the factors influencing this component of coronary reactivity in symptomatic women have received limited attention. Accordingly, the relationship between adenosine-related microvascular coronary reactivity and risk factors in symptomatic women evaluated for suspected ischemia remains uncertain.

Hypothesis: Abnormal coronary microvascular reactivity to adenosine is predicted by atherosclerosis risk factors in women.

Methods: As part of the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE), we investigated the relationship between risk factors and coronary microvascular reactivity as flow velocity reserve to intracoronary adenosine ($CFVR_{Ado}$) in 210 women referred for angiography to evaluate suspected ischemia.

Results: Univariate analyses identified associations between $CFVR_{Ado}$ and multiple risk conditions; however, after adjusting for age, none remained significant. The best multivariable model using combinations of risk conditions to predict $CFVR_{Ado}$ yielded an R^2 of only 0.18.

Conclusions: Among women with suspected ischemia, risk factors account for <20% of observed variability in $CFVR_{Ado}$. Therefore, other as yet unidentified factors must primarily account for coronary microvascular reactivity to adenosine.

Key words: women, risk factors, microcirculation, adenosine

Clin. Cardiol. 2007; 30: 69–74.

Supported by NHLBI contracts NO1-HV-68161, NO1-HV-68162, NO1-HV-68163, and NO1-HV-68164, and grants UO1-HL64829-01, UO1-HL64914-01, and UO1-HL65924-01. GCRC grant MO1-RR00425 from the National Center for Research Resources, and grants from the Gustavus and Louis Pfeiffer Research Foundation, Denville, New Jersey, and The Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, Pennsylvania.

Address for reprints:

Carl J. Pepine
Chief, Division of Cardiovascular Medicine
University of Florida College of Medicine
P.O. Box 100277
Gainesville, FL 32610-0277
e-mail: pepincj@medicine.ufl.edu

Received: May 10, 2006
Accepted with revision: September 13, 2006

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/clc.19

Introduction

Women with chest discomfort suggesting myocardial ischemia are less likely than men to have obstructive coronary artery disease (CAD)[1] but have substantial risk for repeated testing, hospitalization, and disability.[2] Altered coronary reactivity, proposed as a mechanism contributing to these findings, has been linked to risk factors and proinflammatory processes promoting atherosclerosis and is related to adverse outcomes.[3–14] Coronary reactivity may be tested by several stimuli. The vasodilator stimulus is often adenosine (Ado) and a gender-specific contribution to Ado-induced coronary arteriole dilation has been reported.[15] In the Women's Ischemia Syndrome Evaluation (WISE), diminished reactivity was frequent even without obstructive CAD.[1] Myocardial perfusion alterations in response to Ado–induced vasodilation are not infrequent in women without obstructive CAD[16] and do not necessarily correlate with endothelial dysfunction.[17] Yet, our understanding of variables associated with Ado-mediated coronary microvascular reactivity is incomplete. Therefore, we investigated the relationship between atherosclerosis risk conditions, including inflammatory markers and coronary microvascular reactivity, to Ado in women referred for coronary angiography.

Methods

The WISE is a National Heart, Lung, and Blood Institute (NHLBI)-sponsored study to improve the diagnostic evaluation of ischemic heart disease in women. Institutional Review Boards at each site approved the protocol, which is in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant. Data were monitored by an independent Data and Safety Monitoring Committee. Of 936 women undergoing clinically indicated angiograms, a subgroup of 210 had coronary reactivity testing at the Universities of Florida and Pittsburgh sites. These women gave informed consent to add this testing, had no stenosis warranting intervention, and had an appropriate coronary segment for Doppler flow recording. Details of the WISE protocol and design are published.[18]

Baseline evaluation included comprehensive clinical and laboratory data (Table 1). Inflammatory markers were measured from blood collected at entry, frozen on site ($-70\,^{\circ}C$) and analyzed by core lab. Serum amyloid A and high-sensitive-C-reactive protein (hs-CRP) were measured on a Hitachi 911 analyzer (Roche Diagnostics, Basel, Switzerland) by high-sensitivity methods.[19] Reagents for hs-CRP were from Denka Seiken (Niigata, Japan). Interleukin-6 was measured by enzyme-linked immunosorbent assay (ELISA) (Quantikine hs human interleukin-6, R&D Systems, Minneapolis, Minn., USA).[20] Qualitative and quantitative coronary angiographic analyses were done by core lab blinded to patient data.[21] Any >50% diameter stenosis was defined as obstructive CAD, 20–50% as mild CAD, and <20% as no CAD. A CAD severity score was defined as an aggregate of % stenosis, extent and location of stenosis, and degree of collateral vessels.[21]

Reactivity testing was performed in a left coronary artery branch (e.g., left anterior descending [n = 157] or circumflex [n = 53]) free of stenosis. A Doppler-tipped guidewire (0.014-in FloWire, JOMED/Cardiometrics, Mountain View, Calif., USA) was advanced through the diagnostic catheter, and when a stable Doppler signal was obtained, intracoronary bolus injections of 18 mcg Ado (Adenocard, Fujisawa USA, Deerfield, Ill., USA) were administered into the left main coronary artery.[21] Coronary flow velocity was recorded at baseline and after Ado (usually three times), with return to baseline before each bolus. Pulsed-wave Doppler flow spectra were used to calculate time-averaged peak velocity, and all recordings were analyzed by core lab (University of Florida). Coronary flow velocity reserve ($CFVR_{Ado}$) was defined as the ratio of hyperemic time-averaged peak velocity after Ado to baseline time-averaged averaged peak velocity.

Statistical Analyses

Values are expressed as mean ± standard deviation or percentages. Correlation coefficients (Pearson or Spearman, depending on the normality of data distribution as assessed by Shapiro-Wilk test) are used to examine the relationship between the reactivity variable and continuous risk conditions. For categorical risk conditions, two-tailed *t*-tests and analyses of variance are used to test for mean difference in reactivity variable. Linear regression models examined effects of risk conditions on reactivity measures. Variables considered for inclusion in each model appear in Table 1. Variables were then chosen for entry into multivariable R-square models based upon univariate associations. Numerous exploratory multivariate combinations were examined, and a forward selection procedure was used to determine the best models. These analyses were done in all women and in a subgroup without angiographic evidence of flow limiting stenoses (e.g., ⩽50% diameter reduction). All tests were two-sided. Because these analyses were exploratory, p values <0.1 were considered significant for the individual risk condition results to enter into multivariable models.

Results

Baseline Characteristics and Coronary Reactivity

Pertinent baseline characteristics appear in Table 1. Most (80%) women had no severe CAD: 49% had no angiographic CAD, 31% had mild CAD, and only 20% had obstructive CAD (Table 1). Comparing those with

TABLE 1 Characteristics of women with coronary reactivity assessment

Characteristic	%	Characteristic	Mean ± SD
White/Caucasian	83	Years of age (n = 210)	54.8 ± 9.7
History of		Years since last menses	18.9 ± 10.6
Diabetes mellitus	25	Body mass Index (kg/m^2)	32.2 ± 7.9
Hypertension	55	Systolic blood pressure (mmHg)	135 ± 21
Dyslipidemia	54	Diastolic blood pressure (mmHg)	76 ± 11
Cigarette smoking currently	20	Duke Activity Status Index score	17.5 ± 15.1
Cigarette smoking in past	35	Total cholesterol (mg/dl)	183 ± 39
Menopause	76	HDL cholesterol (mg/dl)	50 ± 12
Family history of premature CAD	64	LDL cholesterol (mg/dl)	109 ± 35
Medication use current		Triglycerides (mg/dl)	135 ± 103
Aspirin	52	Plasma glucose (mg/dl)	106 ± 48
Statin	22	Hemoglobin (g/dl)	12.7 ± 1.4
ACE inhibitor	24	Serum creatinine (mg/dl)	0.8 ± 0.2
Beta blocker	33	Ejection fraction (%)	65 ± 10
Medication use ever		CAD severity score	9.0 ± 6.7
Hormone replacement therapy	58	Serum amyloid A (mg/dl)	1.1 ± 2.5
Oral contraceptive pills	63	C-reactive protein (mg/dl)	0.8 ± 1.5
		Interleukin-6 (pg/ml)	3.8 ± 2.9
Coronary artery disease			
None (<20% stenosis)	49%		
Mild (20–50% stenosis)	31%		
Obstructive (>50% stenosis)	20%		

Abbreviations: ACE = angiotensin-converting enzyme, CAD = coronary artery disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SD = standard deviation.

no, mild, or obstructive angiographic CAD, the $CFVR_{Ado}$ were 2.8 ± 0.7, 2.6 ± 0.7, and 2.4 ± 0.7, respectively ($p = 0.02$ for trend).

Univariate analyses with continuous variables identified associations between decreasing $CFVR_{Ado}$ and increasing age ($p < 0.001$), years since last menses ($p = 0.01$), systolic blood pressure (SBP) ($p = 0.02$), high-density lipoprotein (HDL) level ($p = 0.02$), serum amyloid A level ($p = 0.05$), angiographic CAD severity score ($p = 0.01$), and Duke Activity Status Index (DASI) score ($p = 0.02$). Using univariate analyses with categorical variables, we found lower $CFVR_{Ado}$ was associated with histories of diabetes ($p = 0.004$), hypertension ($p = 0.03$), dyslipidemia ($p = 0.04$), birth control pill use ($p = 0.02$), current angiotensin-converting enzyme (ACE) inhibitor use ($p = 0.02$), menopause ($p = 0.07$), degree of angiographic CAD ($p = 0.02$), and family history of premature heart disease ($p = 0.03$). The other CAD risk conditions (Table 1) including low-density protein (LDL), CRP, and diastolic blood pressure did not correlate closely with $CFVR_{Ado}$. Figure 1 shows scatter plots of $CFVR_{Ado}$ with several representative conditions.

In the women with <50% angiographic stenoses ($n = 153$), we found univariate correlations between lower $CFVR_{Ado}$ and age ($r = -0.20$, $p = 0.02$), years since last menses ($r = -0.21$, $p = 0.03$), history of hypertension ($p = 0.07$), and birth control pill use ($p = 0.08$). Notably, in both the all patients and restricted analyses, none of the variables had a $p < 0.05$ after adjusting for age.

Multivariate Modeling

The best multivariate models predicting reduced $CFVR_{Ado}$ using combinations of traditional risk conditions (such as age, diabetes, hypertension, dyslipidemia, family history of premature CAD, post menopause, and angiographic CAD severity score; or age, HDL level, DASI score, smoking, diabetes, and family history of premature CAD) only yielded R^2 of 0.16 for $CFVR_{Ado}$. When inflammatory markers were included, serum amyloid A level was the only marker that contributed, resulting in an R^2 of only 0.18. This indicates that, while associations do exist between recognized atherosclerosis risk conditions and coronary microvascular reactivity in these women, these conditions account for <20% of the observed variability in $CFVR_{Ado}$.

Discussion

Although $CFVR_{Ado}$ significantly decreased as degree of angiographic CAD increased, most (80%) of these women had no obstructive CAD. Although prior studies indicate that flow responses to Ado depend on smooth muscle and endothelial function at the level of both the coronary epicardial and microvessels, our patients had no obstructive lesions in the left coronary branch where flow was measured. So it is unlikely that epicardial coronary dilation contributed significantly to $CFVR_{Ado}$. Our findings confirm previous reports of impaired coronary

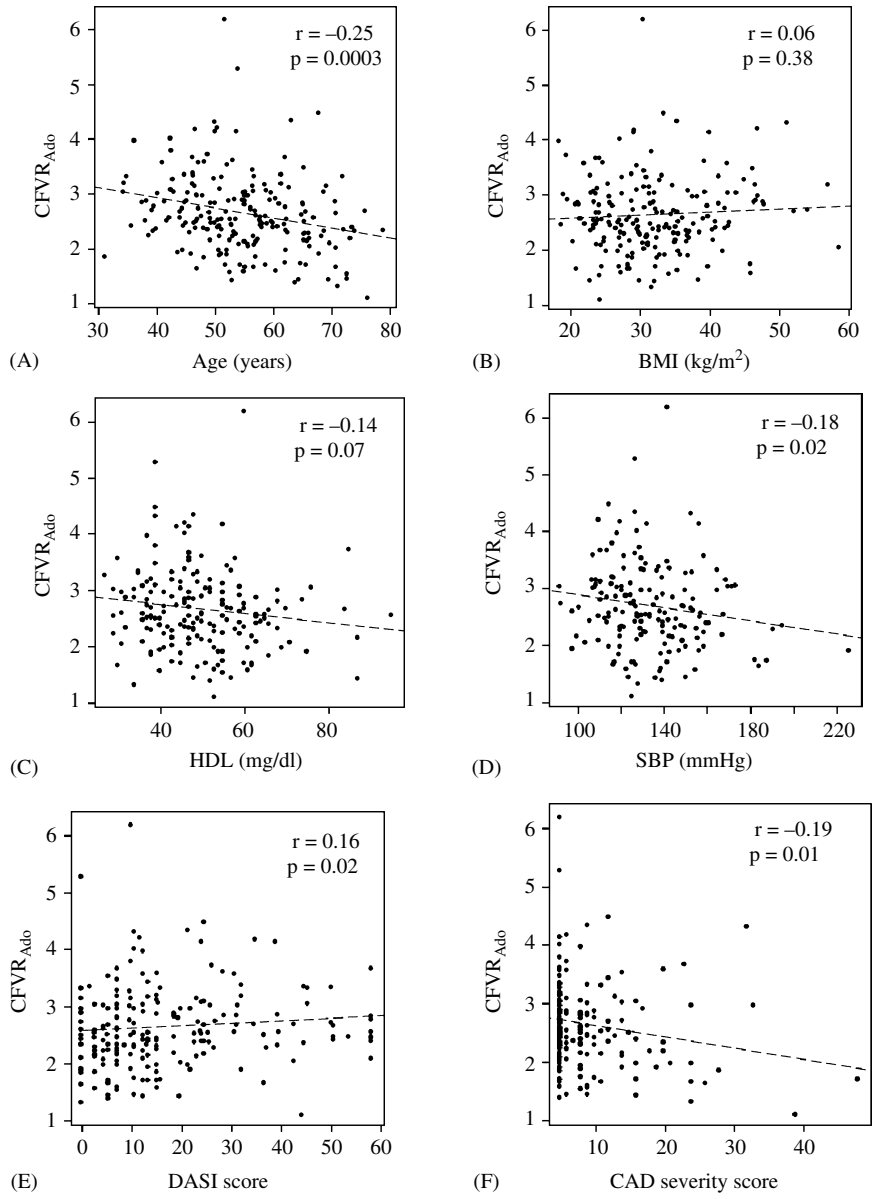

FIG. 1 Correlation between coronary reserve and age (A), BMI (B), HDL level (C), SBP (D), DASI score (E), and CAD severity score (F). CFVRAdo = coronary flow velocity reserve with intracoronary adenosine, BMI = body mass index, HDL = high-density lipoprotein, SBP = systolic blood pressure, DASI = Duke Activity Status Index, CAD = coronary artery disease.

microvascular reactivity to Ado[1,22,23] in women, including those without obstructive CAD. Yet, in the WISE, such women had a surprisingly high risk for adverse cardiovascular events during follow-up.[24,25] Our results indicate that, while a large number of atherosclerosis risk conditions were associated with $CFVR_{Ado}$, age was the only independent predictor regardless of severity of angiographic coronary atherosclerosis. In multivariate modeling with both traditional and newer atherosclerosis risk conditions, including body mass index (BMI) and inflammatory markers, risk conditions accounted for a small portion of $CFVR_{Ado}$ variability. Thus, these conditions are unlikely explanations for the major component of Ado-related microvascular dysfunction. Other studies indicate that a substantial portion of variability in endothelial-dependent coronary reactivity also remains unexplained by traditional risk factors.[3] An alternate interpretation would be that $CFVR_{Ado}$ variability reflects an Ado-mediated endothelial action; however, most of the women in the WISE have endothelial dysfunction,[5,6] so it is not likely that endothelial-mediated dilation would be prominent. Also, there is evidence indicating that the response to true endothelium-independent vasodilators such as nitroglycerin is impaired in patients

with traditional risk factors.[26] The implications of our findings are that novel risk conditions for reduced coronary microvascular reactivity merit further investigation.

Our univariate analyses revealed some interesting associations. The inverse association of $CFVR_{Ado}$ with serum amyloid A levels is intriguing, as serum amyloid A levels predicted CAD and adverse outcomes in the WISE.[27] The univariate association of $CFVR_{Ado}$ with both endogenous and exogenous hormone exposure (e.g., years since last menses and birth control pill use) could relate to delayed onset of coronary disease in women compared with men, indirectly implying a protective effect of endogenous female hormones. Higher HDL levels and current ACE inhibitor use correlating with lower $CFVR_{Ado}$ are likely chance occurrences considering the large number of variables examined. High-density lipoprotein and ACE-inhibitor use were not independently associated with $CFVR_{Ado}$ after adjusting for age.

Study Limitations

Although this is the largest group of women undergoing coronary reactivity testing with Ado, they had symptoms and signs of myocardial ischemia prompting referral for coronary angiography; therefore, an indication bias limits generalization of our results to other patient groups. Heterogeneity of the study population in terms of age, BMI, BP, CAD severity, and hormonal state may have precluded delineation of statistically significant associations between individual risk factors and $CFVR_{Ado}$. Unknown factors, including individual variability in Ado dose-responses or the microvascular effects of individual risk conditions, could potentially affect $CFVR_{Ado}$. While similar doses of intracoronary Ado provide near-maximal increase in coronary flow in 90–92% of cases,[28] the 18 mcg dose may not have achieved maximal hyperemia in every patient.[29] Also, no systematic assessment of left ventricular hypertrophy was undertaken. Although this could influence $CFVR_{Ado}$, an echocardiographic analysis from a WISE cohort suggested that limited $CFVR_{Ado}$ could not be explained by left ventricular hypertrophy.[1] The ratio of hyperemic to resting flow velocity depends on the level of flow at rest and, thus, may be diminished by higher resting coronary flow velocities (e.g., higher heart rate, BP, or both). For this reason it is possible that the age-dependent decline in $CFVR_{Ado}$ observed is related to previously reported age-related progressive increase in resting SBP. Nevertheless, previous analyses from WISE documented that $CFVR_{Ado}$ agrees closely with volumetric flow reserve.[24] Furthermore, the association between age and $CFVR_{Ado}$ persisted after controlling for SBP.

Conclusions

In women undergoing angiography for suspected ischemia, the coronary flow response to Ado is often impaired. While this response was associated with risk conditions for atherosclerosis, these conditions account for <20% of the observed variability in Ado-related coronary reactivity. Further investigations of novel risk factors for altered coronary reactivity as well as the outcomes of these women are warranted.

References

1. Reis SE, Holubkov R, Conrad Smith AJ, Kelsey SF, Sharaf BL, et al.: Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: Results from the NHLBI WISE study. *Am Heart J* 2001;141:735–741
2. Shaw LJ, Merz CN, Pepine CJ, Reis SE, Bittner V, et al.: The economic burden of angina in women with suspected ischemic heart disease: Results from the National Institues of Health-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Circulation* 2006;114:894–904
3. Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, et al.: Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002;106:653–658
4. Schindler TH, Nitzsche EU, Schelbert HR, Olschewski M, Sayre J, et al.: Positron emission tomography-measured abnormal responses of myocardial blood flow to sympathetic stimulation are associated with the risk of developing cardiovascular events. *J Am Coll Cardiol* 2005;45:1505–1512
5. von Mering GO, Arant CB, Wessel TR, McGorray SP, Bairey Merz CN, et al.: 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). *Circulation* 2004;109:722–725
6. Vita JA, Keaney JF Jr, Larson MG, Keyes MJ, Massaro JM, et al.: Brachial artery vasodilator function and systemic inflammation in the Framingham Offspring Study. *Circulation* 2004;110:3604–3609
7. Moreau P, d'Uscio LV, Luscher TF: Structure and reactivity of small arteries in aging. *Cardiovasc Res* 1998;37:247–253
8. Rizzoni D, Palombo C, Porteri E, Muiesan ML, Kozakova M, et al.: Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens* 2003;21:625–631
9. Nitenberg A, Valensi P, Sachs R, Dali M, Aptecar E, et al.: Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. *Diabetes* 1993;42:1017–1025
10. Kaufmann PA, Gnecchi-Ruscone T, Schafers KP, Luscher TF, Camici PG: Low density lipoprotein cholesterol and coronary microvascular dysfunction in hypercholesterolemia. *J Am Coll Cardiol* 2000;36:103–109
11. Dagres N, Saller B, Haude M, Husing J, von Birgelen C, et al.: Insulin sensitivity and coronary vasoreactivity: Insulin sensitivity relates to adenosine-stimulated coronary flow response in human subjects. *Clin Endocrinol (Oxf)* 2004;61:724–731
12. Jesmin S, Sakuma I, Hattori Y, Kitabatake A: In vivo estrogen manipulations on coronary capillary network and angiogenic molecule expression in middle-aged female rats. *Arterioscler Thromb Vasc Biol* 2002;22:1591–1597
13. Lamping KG, Christensen LP, Tomanek RJ: Estrogen therapy induces collateral and microvascular remodeling. *Am J Physiol Heart Circ Physiol* 2003;285:H2039–H2044
14. Opherk D, Schuler G, Wetterauer K, Manthey J, Schwarz F, et al.: Four-year follow-up study in patients with angina pectoris and normal coronary arteriograms ("syndrome X"). *Circulation* 1989;80:1610–1616
15. Heaps CL, Bowles DK: Gender-specific K(+)-channel contribution to adenosine-induced relaxation in coronary arterioles. *J Appl Physiol* 2002;92:550–558
16. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, et al.: Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346:1948–1953

17. Bottcher M, Botker HE, Sonne H, Nielsen TT, Czernin J: Endothelium-dependent and -independent perfusion reserve and the effect of L-arginine on myocardial perfusion in patients with syndrome X. *Circulation* 1999;99:1795–1801
18. Merz CN, Kelsey SF, Pepine CJ, Reichek N, Reis SE, et al.: The Women's Ischemia Syndrome Evaluation (WISE) study: Protocol design, methodology and feasibility report. *J Am Coll Cardiol* 1999;33:1453–1461
19. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, et al.: Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *J Am Med Assoc* 2002;287:1153–1159
20. Rifai N, Joubran R, Yu H, Asmi M, Jouma M: Inflammatory markers in men with angiographically documented coronary heart disease. *Clin Chem* 1999;45:1967–1973
21. Sharaf BL, Pepine CJ, Kerensky RA, Reis SE, Reichek N, et al.: Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study Angiographic Core Laboratory). *Am J Cardiol* 2001;87:937–941
22. Hasdai D, Holmes DR Jr, Higano ST, Burnett JC Jr, Lerman A: Prevalence of coronary blood flow reserve abnormalities among patients with nonobstructive coronary artery disease and chest pain. *Mayo Clin Proc* 1998;73:1133–1140
23. Wessel TR, Arant CB, Olson MB, Johnson BD, Reis SE, et al.: Relationship of physical fitness vs. body mass index with coronary artery disease and cardiovascular events in women. *J Am Med Assoc* 2004;292:1179–1187
24. Reis SE, Holubkov R, Lee JS, Sharaf B, Reichek N, et al.: Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol* 1999;33:1469–1475
25. Johnson BD, Shaw LJ, Pepine CJ, Reis SE, Kelsey SF, et al.: Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: Results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. *Eur Heart J* 2006;27:1408–1415
26. Clarkson P, Celermajer DS, Donald AE, Sampson M, Sorensen KE, et al.: Impaired vascular reactivity in insulin-dependent diabetes mellitus is related to disease duration and low density lipoprotein cholesterol levels. *J Am Coll Cardiol* 1996;28:573–579
27. Johnson BD, Kip KE, Marroquin OC, Ridker PM, Kelsey SF, et al.: Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: The National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;109:726–732
28. Jeremias A, Whitbourn RJ, Filardo SD, Fitzgerald PJ, Cohen DJ, et al.: Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J* 2000;140:651–657
29. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, et al.: Coronary pressure measurement after stenting predicts adverse events at follow-up: A multicenter registry. *Circulation* 2002;105:2950–2954