CLINICIAN UPDATE

Syndrome X and Microvascular Coronary Dysfunction

C. Noel Bairey Merz, MD; Carl J. Pepine, MD

Case presentation: A 44-year-old woman is referred for worsening chest pain since 2007, with abnormal stress testing in May 2008, followed by coronary angiography in June 2008. She had several prior hospitalizations to evaluate possible myocardial infarction, and 1 with an elevated troponin level in 2001. She has a history of breast cancer in 2007. She currently reports daily exertional substernal chest pain that radiates to her left arm and hand that is relieved with rest. She works as an undercover police officer, frequently has to chase suspects, and is concerned about being able to do her job. A review of cardiac risk factors is negative. She takes tamoxifen with vitamins, and her physical examination and resting ECG are normal. Review of the prior coronary angiography confirms absence of obstructive coronary artery disease and normal left ventricular function.

To further evaluate the basis for her symptoms, she underwent coronary reactivity testing (CRT), which demonstrated a limited coronary flow reserve (CFR) to adenosine and coronary blood flow reserve (Figure 1) as well as coronary artery constriction with acetylcholine, indicative of endothelial dysfunction (Figure 2). Adenosine stress cardiac magnetic resonance imaging was consistent with microvascular coronary dysfunction (MCD; Figure 3).

MCD Is a High-Risk Subset of Cardiac Syndrome X

Management of patients with angina and evidence of myocardial ischemia on stress testing without obstructive coronary artery disease by angiography (previously referred to as cardiac syndrome X, or CSX) is a challenge. Patients with this syndrome may have persistent chest pain, evidence of angina, and ischemic-type ST-segment depression or noninvasive perfusion or wall-motion abnormality during stress testing. Common knowledge based on early reports suggested a benign prognosis; however, data from the National Heart, Lung, and Blood Institute (NHLBI)–Women's Ischemia Syndrome Evaluation (WISE) document that up to 50% of these patients may have MCD, which is associated with an adverse prognosis.[1] On the basis of the WISE experience,[1] the largest and most completely investigated cohort with midlife women and this syndrome, patients with MCD frequently have atherosclerosis on intravascular coronary ultrasound[2] and face a 2.5% annual adverse cardiac event rate, which includes myocardial infarction, stroke, hospitalization for congestive heart failure, and sudden cardiac death.[3,4] Thus, MCD appears to be a high-risk subgroup within CSX.

In the absence of obstructive coronary artery disease, the small arteries and arterioles downstream from epicardial coronary arteries are the major sites of resistance to myocardial blood flow. The structure and function of these microvessels have a role in myocardial perfusion and its regional distribution within the myocardium and transmurally. Microvascular dysfunction may include the following, alone or in combination: (1) Altered resting vascular smooth muscle tone secondary to either endothelial or smooth muscle cell dysfunction; (2) altered responses to constrictor or dilator stimuli; (3) reduced number of arterioles and capillaries (eg, rarefaction); and (4) structural alterations that contribute to decreased lumen size, increased wall-to-lumen ratio, increased stiffness, and remodeling. Myocardial capillary rarefaction has been described in dilated cardiomyopathy[5] and cardiac transplant vasculopathy[6] and is present in noncardiac vessels in both hypertension[7] and CSX.[8] Recently, it has been shown that vascular smooth muscle

From the Women's Heart Center, Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA (C.N.M.B.), and the Division of Cardiovascular Medicine, University of Florida, Gainesville, FL (C.J.P.).

Correspondence to C. Noel Bairey Merz, MD, Women's Heart Center, 444 S San Vicente Blvd, Suite 600, Los Angeles, CA 90048. E-mail merz@cshs.org

(*Circulation*. 2011;124:1477-1480.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.974212**

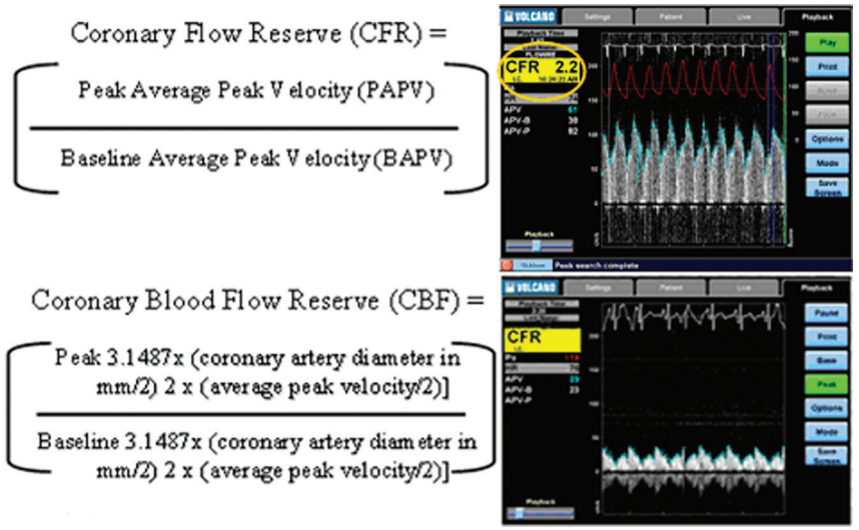

Figure 1. Intracoronary Doppler blood flow velocity waveforms in response to intracoronary adenosine and acetylcholine. Coronary flow reserve (CFR) is the ratio of average peak velocities before and after adenosine. Coronary blood flow (CBF) reserve is the ratio of average peak CBF before and after acetylcholine.

cells have a profound influence on endothelial cell biology, which suggests a regulatory interaction not previously appreciated.[9] Coronary microcirculation abnormalities are important prognostic determinants in acute and chronic coronary syndromes,[10] as well as diabetes, hypertrophic cardiomyopathy, and transplant coronary vasculopathy,[11] and in CSX from our studies in the WISE.[4]

Invasive Diagnosis of MCD

Therapeutic success hinges on diagnostic certainty. For risk stratification and planning an optimal management strategy, CRT with intracoronary infusions of adenosine, acetylcholine, and nitroglycerin to assess microvascular and macrovascular (epicardial) endothelial and nonendothelial function should be considered in subjects with signs and symptoms of ischemia when no obstructive coronary artery disease is found. With a standard adenosine-Doppler wire protocol, as is used for CFR measurement,[12] quantitative and qualitative coronary angiography, and intracoronary acetylcholine and nitroglycerin,[3] possible mechanistic pathways for MCD can be assessed.[12] The benefit of this diagnostic testing probably outweighs the risk of diagnostic uncertainty and absence of risk reduction

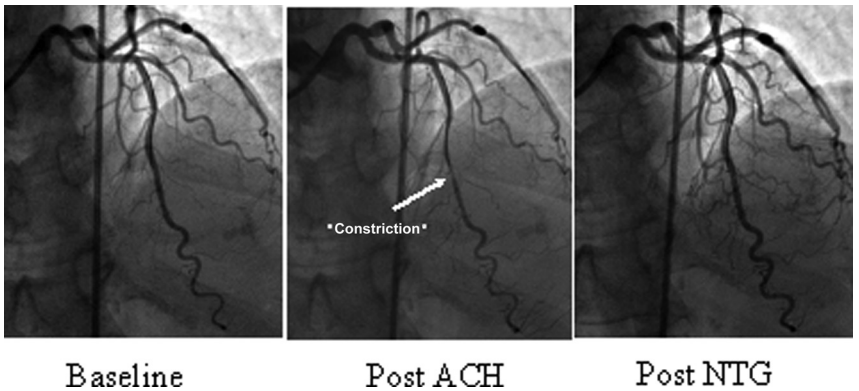

Figure 2. Intracoronary acetylcholine (ACH) demonstrating constriction of the coronary arteries (arrow) and intracoronary nitroglycerin (NTG) coronary angiography demonstrating dilation.

therapy.[4] However, potentially serious complications such as coronary artery dissection can occur, so CRT should be performed only by experienced interventional cardiologists in appropriate at-risk subjects. It is also important to understand that CFR, the principal non–endothelium-dependent CRT measure, is influenced by myocardial oxygen demand. Therefore, measures of CFR must account for heart rate, blood pressure, and left ventricular filling pressure and contractility.[13]

Our patient has evidence of endothelial dysfunction of her epicardial coronaries (eg, constriction to acetylcholine). This dysfunction likely extends to the microvasculature, and she also has evidence of arteriolar dysfunction (eg, low CFR with adenosine). Her epicardial coronary dilator response to exogenous nitroglycerin appears normal.

Noninvasive Diagnosis of MCD

Although evidence of abnormal myocardial perfusion secondary to abnormal CRT can be detected noninvasively by single-photon emission computed tomography, positron emission testing, and stress cardiac magnetic resonance imaging,[1] the sensitivity and specificity of these measures remain incompletely characterized. The reference standard for diagnosis of MCD remains the invasive CRT. An ongoing NHLBI-sponsored WISE Ancillary Study is investigating the utility of cardiac magnetic resonance imaging for diagnosis and prognosis (risk assessment) of MCD in women.[14] If preliminary reports[14–16] are confirmed, cardiac magnetic resonance imaging will be the only method currently applicable for clinical use to evaluate the transmural distribution (eg, endocardial versus epicardial) of coronary blood flow.

Treatment of CSX and MCD

Current angina/CSX guidelines do not specifically address MCD.[17,18] Treatment should focus on 2 main goals: (1) Antiatherosclerosis and antiischemia

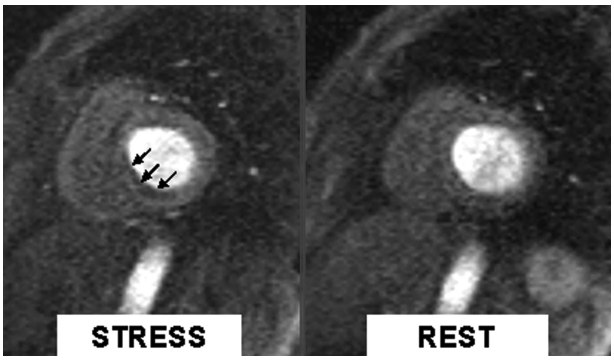

Figure 3. Adenosine stress perfusion base-ventricle cardiac magnetic resonance imaging (left) and rest perfusion base-ventricle cardiac magnetic resonance imaging (right). Arrows indicate areas of reduced myocardial perfusion, worsened during stress (left).

therapy to reduce adverse cardiac event risk and (2) relief of angina to improve quality of life. Because of the high prevalence of coronary atherosclerosis and adverse prognosis observed in these subjects, we also incorporate the National Cholesterol Education Program expert panel's guidelines (Adult Treatment Panel III)[19] for therapeutic lifestyle change,[20] low-dose aspirin, and statin therapy in these patients as coronary heart disease equivalents.

Table. Treatment of Subjects With Angina, Evidence of Myocardial Ischemia, and No Obstructive Coronary Artery Disease

Microvascular coronary dysfunction
Abnormal endothelial function
Angiotensin-converting enzyme inhibitors
Statins
L-Arginine supplementation
Aerobic exercise
Enhanced external counterpulsation
Abnormal nonendothelial function
β-blockers/α-β-blockers
Nitrates
Antianginal/antiischemic
Ranolazine
Xanthine derivatives
Abnormal smooth muscle function (Prinzmetal angina)
Calcium antagonists
Nitrates
Abnormal cardiac nociception
Low-dose tricyclic medication
Spinal cord stimulation
Cognitive behavioral therapy

Reprinted from Mehta and Merz[20] with permission.

Trial evidence supports use of β-blockers, angiotensin-converting enzyme inhibitors, nitrates, calcium antagonists, ranolazine, xanthine derivatives such as aminophylline, enhanced external counterpulsation, cognitive behavioral therapy, low-dose tricyclic antidepressants, and neurostimulation to improve angina symptoms, stress test parameters, and endothelial function (Table). Notably, the α-blocker doxazosin is not beneficial, and its association with increased stroke and heart failure risk in ALLHAT (the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) should exclude this agent even if the woman has hypertension. Low-dose hormone therapy[1] does not appear to be effective, and L-arginine supplementation had an adverse effect in postmyocardial infarction patients, despite improving signs and symptoms in a CSX population. Diltiazem fails to improve CFR in these patients. However, β-blockers consistently demonstrate superiority over nitrates and calcium antagonists in randomized clinical trials. An exploratory WISE Ancillary Trial testing sildenafil in this patient group suggested improved CFR.

Conclusions

Among subjects with CSX, defined as persistent chest symptoms that suggest angina, evidence of ischemia, and no obstructive coronary artery disease, MCD is highly prevalent and is associated with an adverse prognosis. CRT remains the reference standard for diagnosis; noninvasive testing for MCD is currently under investigation and appears promising. Therapeutic lifestyle change, low-dose aspirin, and lipid-lowering therapy are recommended because of the high prevalence of coronary atherosclerosis and elevated risk of adverse cardiovascular events. Limited trial evidence suggests that use of antiischemia and antianginal therapy, most consistently with β-blockers, may improve symptoms, stress test parameters, and endothelial and/or microvascular coronary function. Although large outcome trials are being planned in MCD subjects, sufficient but evolving data exist to incorporate specific recommendations for this population into existing angina and acute coronary syndrome guidelines. Key points for the clinician include recognition of ischemia and deployment of guideline-endorsed therapy for angina and reduction of cardiac risk factors.

Case Follow-Up and Disposition

The patient was prescribed simvastatin 40 mg by mouth every day, aspirin 81 mg by mouth every day, carvedilol 6.25 mg by mouth twice daily, and sublingual nitroglycerin 0.4 mg as needed and before physical exertion. At 2-year follow-up, she reports decreased symptoms, has maintained her job, and has had no further hospitalizations for angina or suspected acute coronary syndrome.

Sources of Funding

This work was supported by contracts from the NHLBI (Nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, and N01-HV-68164); a General Clinical Research Centers grant (MO1-RR00425) from the National Center for Research Resources; and grants from the Gustavus and Louis Pfeiffer Research Foundation, Denville, NJ, the Women's Guild of Cedars-Sinai Medical Center, Los Angeles, CA, the Edythe L. Broad Women's Heart Research Fellowship, Cedars-Sinai Medical Center, Los Angeles, CA, and the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, CA. Dr Pepine is supported by NIH/NHLBI grants 5 U01 HL087366-04, 5 R01 HL091005-03, 5 R01

HL090957-03, and 2 U01 GM074492-06; NIH/AG (National Institute on Aging) grant 3 U01 AG022376-05A2S1; and NIH/National Center for Research Resources grant 5 UL1 RR029890-02.

Disclosures

Dr Bairey Merz has received research grants from the WISE (NIH/NHLBI 5 R01 HL090957); honoraria from the Women-Heart Coalition, Los Robles Medical Center, Monterey Community Hospital, Primed, Los Angeles OB-GYN Society, and the North American Menopause Society; and consulting fees from the NHLBI. Dr Pepine has received research grants from WISE (NIH/NHLBI U01 HL6489 and NIH/NHLBI 5 R01 HL090957).

References

1. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Lerman A, Quyyumi AA, Sopko G. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study, part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol*. 2006;47:S21–S29.
2. Khuddus MA, Pepine CJ, Handberg EM, Bairey Merz CN, Sopko G, Bavry AA, Denardo SJ, McGorray SP, Smith KM, Sharaf BL, Nicholls SJ, Nissen SE, Anderson RD. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol*. 2010;23:511–519.
3. von Mering GO, Arant CB, Wessel TR, McGorray SP, Bairey Merz CN, Sharaf BL, Smith KM, Olson MB, Johnson BD, Sopko G, Handberg E, Pepine CJ, Kerensky RA. 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.
4. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, Johnson BD, Sopko G, Bairey Merz CN. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia: results from the National Heart, Lung, and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol*. 2010;55:2825–2832.
5. Tsagalou EP, Anastasiou-Nana M, Agapitos E, Gika A, Drakos SG, Terrovitis JV, Ntalianis A, Nanas JN. Depressed coronary flow reserve is associated with decreased myocardial capillary density in patients with heart failure due to idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 2008;52:1391–1398.
6. Escaned J, Flores A, Garcia-Pavia P, Segovia J, Jimenez J, Aragoncillo P, Salas C, Alfonso F, Hernandez R, Angiolillo DJ, Jimenez-Quevedo P, Banuelos C, Alonso-Pulpon L, Macaya C. Assessment of microcirculatory remodeling with intracoronary flow velocity and pressure measurements: validation with endomyocardial sampling in cardiac allografts. *Circulation*. 2009;120:1561–1568.
7. Rakusan K, Flanagan MF, Geva T, Southern J, Van Praagh R. Morphometry of human coronary capillaries during normal growth and the effect of age in left ventricular pressure-overload hypertrophy. *Circulation*. 1992;86:38–46.
8. Antonios TF, Kaski JC, Hasan KM, Brown SJ, Singer DR. Rarefaction of skin capillaries in patients with anginal chest pain and normal coronary arteriograms. *Eur Heart J*. 2001;22:1144–1148.
9. Balcells M, Martorell J, Olive C, Santacana M, Chitalia V, Cardoso AA, Edelman ER. Smooth muscle cells orchestrate the endothelial cell response to flow and injury. *Circulation*. 2010;121:2192–2199.
10. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*. 2000;101:1899–1906.
11. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830–840.
12. Phan A, Shufelt C, Merz CN. Persistent chest pain and no obstructive coronary artery disease. *JAMA*. 2009;301:1468–1474.
13. Kern MJ, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, Higano ST, Lim MJ, Meuwissen M, Piek JJ, Pijls NH, Siebes M, Spaan JA. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation*. 2006;114:1321–1341.
14. Shufelt C, Kar S, Slivka M, Thomson L, Yang Y, Berman D, Polk D, Tolstrup K, Merz CB. Cardiac magnetic resonance imaging and coronary reactivity testing: a useful noninvasive tool. *J Am Coll Cardiol*. 2008;51:A231.
15. Ishimori ML, Martin R, BErman DS, Goykhman P, Shaw LJ, Shufelt C, Slomka PJ, Thomson LE, Schapira J, Yang Y, Wallace DJ, Weisman MH, Bairey Merz CN. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. *JACC Imaging*. 2011;4:2733.
16. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med*. 2002;346:1948–1953.
17. Fraker TD Jr, Fihn SD, Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Gardin JM, O'Rourke RA, Williams SV, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 Chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to Develop the Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina. *Circulation*. 2007;116:2762–2772.
18. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation*. 2007;116:e148–e304.
19. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
20. Mehta PK, Bairey Merz CN. Treatment of angina in subjects with evidence of myocardial ischemia and no obstructive coronary artery disease. In: Bonow RO, ed. *Braunwald's Heart Disease*. 9th ed. Philadelphia, PA: Elsevier; 2011.