View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 5, NO. 6, 2012

© 2012 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2012.01.023

# Safety of Coronary Reactivity Testing in Women With No Obstructive Coronary Artery Disease

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

Janet Wei, MD,* Puja K. Mehta, MD,* B. Delia Johnson, PHD,† Bruce Samuels, MD,* Saibal Kar, MD,‡ R. David Anderson, MD,§ Babak Azarbal, MD,‡ John Petersen, MD,§ Barry Sharaf, MD,‖ Eileen Handberg, PHD,§ Chrisandra Shufelt, MD,* Kamlesh Kothawade, MBBS,* George Sopko, MD,¶ Amir Lerman, MD,# Leslee Shaw, PHD,** Sheryl F. Kelsey, PHD,† Carl J. Pepine, MD,§ C. Noel Bairey Merz, MD*

*Los Angeles, California; Pittsburgh, Pennsylvania; Gainesville, Florida; Providence, Rhode Island; Bethesda, Maryland; Rochester, Minnesota; and Atlanta, Georgia*

**Objectives** This study evaluated the safety of coronary reactivity testing (CRT) in symptomatic women with evidence of myocardial ischemia and no obstructive coronary artery disease (CAD).

**Background** Microvascular coronary dysfunction (MCD) in women with no obstructive CAD portends an adverse prognosis of a 2.5% annual major adverse cardiovascular event (MACE) rate. The diagnosis of MCD is established by invasive CRT, yet the risk of CRT is unknown.

**Methods** The authors evaluated 293 symptomatic women with ischemia and no obstructive CAD, who underwent CRT at 3 experienced centers. Microvascular function was assessed using a Doppler wire and injections of adenosine, acetylcholine, and nitroglycerin into the left coronary artery. CRT-related serious adverse events (SAEs), adverse events (AEs), and follow-up MACE (death, nonfatal myocardial infarction [MI], nonfatal stroke, or hospitalization for heart failure) were recorded.

**Results** CRT-SAEs occurred in 2 women (0.7%) during the procedure: 1 had coronary artery dissection, and 1 developed MI associated with coronary spasm. CRT-AEs occurred in 2 women (0.7%) and included 1 transient air microembolism and 1 deep venous thrombosis. There was no CRT-related mortality. In the mean follow-up period of 5.4 years, the MACE rate was 8.2%, including 5 deaths (1.7%), 8 nonfatal MIs (2.7%), 8 nonfatal strokes (2.7%), and 11 hospitalizations for heart failure (3.8%).

**Conclusions** In women undergoing CRT for suspected MCD, contemporary testing carries a relatively low risk compared with the MACE rate in these women. These results support the use of CRT by experienced operators for establishing definitive diagnosis and assessing prognosis in this at-risk population. (Women's Ischemia Syndrome Evaluation [WISE]; NCT00832702) (J Am Coll Cardiol Intv 2012;5:646–53) © 2012 by the American College of Cardiology Foundation

From the *Division of Cardiology, Women's Heart Center, Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; †Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; ‡Division of Cardiology, Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; §Division of Cardiology, University of Florida, Gainesville, Florida; ‖Division of Cardiology, Brown University, Providence, Rhode Island; ¶Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; #Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; and the **Program in Cardiovascular Outcomes Research and Epidemiology, Emory University, Atlanta, Georgia. This work was supported by contracts from the National Heart, Lung, and Blood Institute, nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, and N01-HV-68164; grants U0164829, U01 HL649141, U01 HL649241, T32HL69751, and 1R03AG032631 from the National Institute on Aging; General Clinical Research Center grant MO1-RR00425

In patients undergoing angiography for stable angina, the proportion of women and men with no obstructive coronary artery disease (CAD) is increasing over time (1). Compared with men, women have a higher incidence of signs and symptoms of myocardial ischemia, yet 30% to 50% of women who undergo coronary angiography do not have obstructive CAD (2–4). The absence of obstructive CAD is not benign, as 38% of women with acute myocardial infarction (MI) and no obstructive CAD have been found to have plaque rupture or ulceration using intravascular ultrasound (5). Women with angina in the absence of obstructive CAD are often inappropriately reassured and even dismissed without further investigation or treatment: yet angina among women, regardless of coronary angiographic findings, is associated with increased mortality (6,7). The National Heart, Lung, and Blood Institute–sponsored WISE (Women's Ischemia Syndrome Evaluation) studies have documented that approximately one-half of these symptomatic women with no obstructive CAD have microvascular coronary dysfunction (MCD), which produces ischemia and is associated with an adverse cardiovascular prognosis compared with asymptomatic women (3,4,8–11). Both coronary artery spasm and endothelial dysfunction have been shown to be predictors of morbidity and mortality in patients with angina (12–16). Coronary spasm may result in MI, ventricular arrhythmias, and sudden cardiac death (15,17,18). Recent data show that women without obstructive CAD who have a low coronary flow reserve (CFR) are at higher risk of major adverse cardiac events (MACE) compared with those with normal CFR (19). Treatment directed at endothelial function can reduce angina, coronary spasm, heart failure, and stroke (20–23); therefore, it is important to establish the diagnosis in order to institute appropriate medical management.

See page 654

Invasive coronary reactivity testing (CRT) using vasoactive agents to evaluate macrovascular and microvascular responses is considered the reference standard for a definitive diagnosis of MCD (24). However, it is not routinely performed for a variety of reasons, including a lack of standardized protocols and concerns over catheterization laboratory time. Furthermore, limited data exist on the safety of contemporary CRT in women suspected of having MCD. We evaluated the safety of CRT performed at 3 experienced centers in women with angina, evidence of myocardial ischemia by stress testing, and no obstructive CAD (3,25).

## Methods

Women with angina and evidence of myocardial ischemia underwent CRT at 3 experienced clinical centers that participate in WISE: the University of Pittsburgh, the University of Florida, Gainesville, and Cedars-Sinai Medical Center. Inclusion criteria: women with angina, myocardial ischemia by stress testing, and absence of obstructive CAD (<50% luminal obstruction in 1 or more epicardial coronary arteries on angiography). Exclusion criteria: contraindications to angiography and invasive CRT (hypersensitivity to contrast media, active bleeding, bleeding diathesis, renal dysfunction); prior or planned percutaneous coronary intervention or coronary artery bypass grafting; acute MI within 30 days; primary valvular heart disease; cardiogenic shock or intra-aortic balloon pump; inability to withhold nitrates, calcium channel agents, and alpha- and beta-adrenergic blockers for 24 h before testing; New York Heart Association functional class III or IV heart failure; ejection fraction <40%; hypertrophic obstructive cardiomyopathy; severe lung, renal, or hepatic disease; life expectancy <6 months, age <21 years; or pregnancy. All study participants gave written informed consent before undergoing evaluation. Demographic data were recorded with standardized questionnaires. CRT data were read onsite (at the Cedars-Sinai Cardiovascular Intervention Center) or at the WISE Angiographic Core Laboratory (Brown University). The institutional review boards at each site approved the study.

**Abbreviations and Acronyms**

**AE** = adverse event(s)
**CAD** = coronary artery disease
**CFR** = coronary flow reserve
**CRT** = coronary reactivity testing
**IC** = intracoronary
**MACE** = major adverse cardiovascular event(s)
**MCD** = microvascular coronary dysfunction
**MI** = myocardial infarction
**QCA** = quantitative coronary angiography
**SAE** = serious adverse event(s)

**CRT protocol.** Patients fasted for 12 h and withheld caffeine, long-acting nitrates, and other vasoactive agents for 24 h before testing. Patients were instructed to discontinue nicotine and avoid sublingual nitroglycerin 4 h before the

from the National Center for Research Resources; and grants from the Gustavus and Louis Pfeiffer Research Foundation, Danville, New Jersey; The Women's Guild of Cedars-Sinai Medical Center, Los Angeles, California; The Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, Pennsylvania; QMED, Inc., Laurence Harbor, New Jersey; the Edythe L. Broad Women's Heart Research Fellowship, Cedars-Sinai Medical Center, Los Angeles, California; and the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, California. Dr. Samuel received speaker's honoraria from Abbott Vascular and is a consultant for Volcano Corporation. Dr. Shufelt received an investigator research effort funding (>10,000/year) from Gilead. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Wei and Mehta contributed equally to this work.

Manuscript received November 3, 2011; revised manuscript received January 13, 2012, accepted January 20, 2012.

procedure. Pre-mixed acetylcholine in 3 concentrations (0.182, 1.82, and 18.2 μg/ml) was prepared within 3 h of the scheduled procedures.

Outpatient diagnostic coronary angiography was performed via the percutaneous femoral approach. A pigtail catheter was used to measure aortic and left ventricular pressures. Patients with significant CAD, coronary artery anomalies, or bridging were excluded. For borderline lesions, at the discretion of the interventionalist, intravascular ultrasound and/or fractional flow reserve were used to confirm absence of obstructive stenosis.

After angiography, women were given body weight–adjusted heparin for anticoagulation, and the activated clotting time was maintained above 250 s. CRT was performed by infusing vasoactive substances through a guiding catheter placed in the left main coronary artery. Doppler guidewire (0.014-inch diameter, FloWire, JOMED/Cardiometrics/Volcano, San Diego, California) was positioned in the proximal left anterior descending coronary artery (Fig. 1). The following coronary functions were tested:

1. Nonendothelial-dependent microvascular function determination: After an adequate flow reading was obtained by the ComboMap Pressure and Flow System (JOMED/Cardiometrics/Volcano), baseline average peak velocity was recorded (Fig. 2). Intracoronary (IC) bolus injections of incremental doses of adenosine (18 μg, 18 μg, and 36 μg) were administered to create maximal hyperemia. The catheter was flushed with saline after each adenosine injection, and an average peak velocity reading was obtained 5 s after the saline flush. Adenosine CFR was calculated by ComboMap as a ratio of average peak velocity to average baseline velocity. This process was repeated and recorded for each dose of adenosine after the peak velocity returned to baseline. A CFR ≤2.5 in response to adenosine was considered abnormal (14,19).
2. Endothelial-dependent microvascular and macrovascular dysfunction determination: Graded IC acetylcholine concentrations of 0.182 and 18.2 μg/ml were infused (2 ml over 3 min). An intermediate dose of 1.82 μg/ml was infused at the discretion of the angiographer if it was deemed unsafe to proceed directly to a higher dose of 18.2 μg/ml, based on the coronary reactivity from the lower dose (i.e., 0.182 μg/ml) of acetylcholine. Doppler measurement of peak velocity was obtained at the end of each acetylcholine infusion. Normal endothelial-dependent microvascular response was defined as a coronary blood flow increase >50% at the highest dose of acetylcholine. Post-acetylcholine cine image was obtained for each concentration for quantitative coronary angiography (QCA). We ensured that coronary flow returned to baseline before each infusion. Normal acetylcholine response, or endothelial-dependent macrovascular coronary function, was defined as coronary artery dilation >5%. Coronary blood flow response to acetylcholine was calculated from the Doppler-derived time-velocity integral and vessel diameter by the following equation: Coronary blood flow = $\pi$ (average peak velocity/2) (vessel diameter/2)$^2$. Vessel diameter was calculated 5 mm distal to the Doppler wire.
3. Nonendothelial-dependent macrovascular function determination: After completion of acetylcholine infusions and the return of coronary flow velocity to baseline, IC nitroglycerin (200 μg) was injected to evaluate nonendothelial-dependent macrovascular function. Average baseline and peak velocity were recorded. A cine image within 30 s of IC nitroglycerin

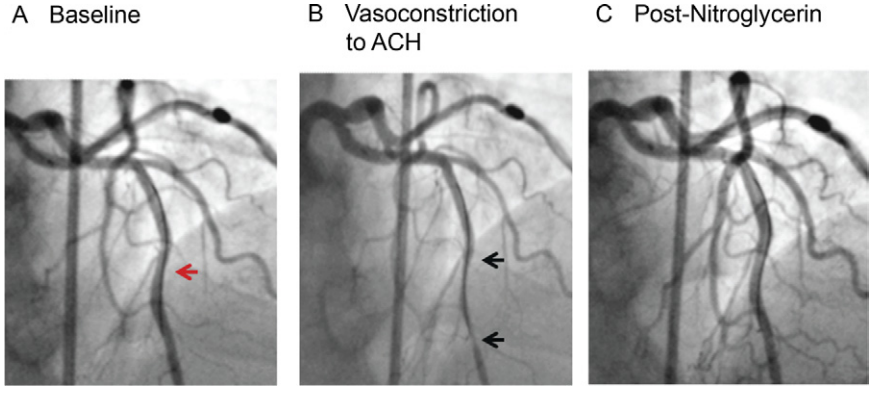


**Figure 1. Coronary Angiogram and CRT**

The figure shows Doppler flow wire in the left anterior descending artery **(red arrow) (A)**. In response to acetylcholine (ACH) infusion, there is abnormal coronary artery vasoconstriction **(black arrows)**, indicating endothelial dysfunction **(B)**. This is resolved by intracoronary nitroglycerin **(C)**. CRT = coronary reactivity testing.

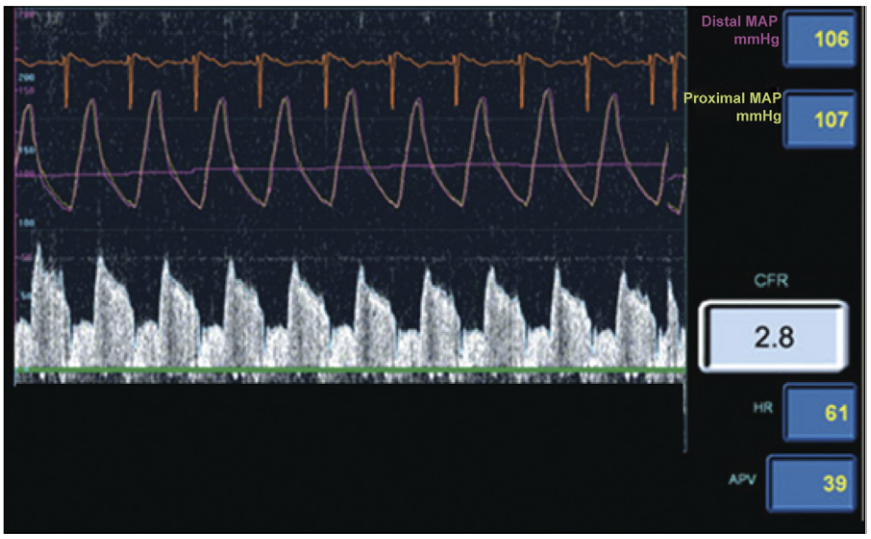


**Figure 2. Example of Doppler Wire Tracing**

The figure depicts a coronary flow velocity map showing an average peak velocity of 39 cm/s and a coronary flow reserve of 2.8 in response to adenosine, as determined by a Doppler flow wire in the coronary artery. Adenosine tests nonendothelial-dependent microvascular vasodilatory capacity. Coronary blood flow is calculated based on the change in diameter of the vessel and the change in velocity in response to acetylcholine. Acetylcholine tests endothelial-dependent vasomotor function.

was obtained for QCA. Normal nitroglycerin response was defined as a diameter increase >20%.

The angles, skew rotation, and table height were kept constant during the procedure. QCA measurements were made in the segment 5 mm distal to the tip of the Doppler wire. For each time interval, the diameter was measured in the same segment. Heart rate and blood pressure were recorded before and after administration of adenosine, acetylcholine, and nitroglycerin.

**Periprocedural adverse events.** Adverse events (AEs) and serious adverse events (SAEs) during and immediately post-CRT were recorded. SAEs were defined as those that required termination of the protocol and immediate hospitalization (hemodynamic instability, coronary artery dissection, MI, stroke, and death). AEs were defined as events related to the procedure that did not require hospitalization (such as deep venous thrombosis, transient coronary air embolism, nonsustained arrhythmias, and transient hypotension not requiring treatment). SAEs and AEs were adjudicated by a clinical events committee.

**Table 1. Patient Demographics (N = 293)**

| | |
|---|---|
| White/Caucasian | 247 (84%) |
| Age, yrs | 54 ± 10 |
| History of smoking | 140 (48%) |
| Dyslipidemia | 94 (32%) |
| Hypertensive | 102 (35%) |
| Diabetic | 29 (10%) |

Values are n (%) or mean ± SD.

**Outcomes during follow-up.** As per WISE protocol, women were followed up for 6 weeks and then annually for death, nonfatal MI, nonfatal stroke, and hospitalization for heart failure. The MACE rate was calculated as the percentage of patients with a first event.

## Results

The patient demographics are shown in Table 1. Results of CRT are reported in Table 2; not all patients underwent all aspects of reactivity testing, as this was site-dependent.

**Table 2. Results of CRT**

| | |
|---|---|
| Abnormal nonendothelial microvascular function (CFR ≤2.5 in response to 18 μg of adenosine) | 138/293 (47%) |
| Abnormal endothelial microvascular function (≤50% change in CBF in response to high-dose acetylcholine) | 112/220 (51%) |
| bnormal endothelial macrovascular function (<5% increase in diameter in response to high-dose acetylcholine) | 127/220 (58%) |
| AAbnormal smooth muscle function (nonendothelial macrovascular function (<20% increase in diameter to nitroglycerin) | 136/225 (60%) |
| Coronary vasospasm (>50% reduction in diameter to high-dose acetylcholine compared with baseline) | 11/220 (5%) |
| Coronary vasospasm (>70% reduction in diameter to high-dose acetylcholine compared with post-nitroglycerin diameter) | 5/220 (2.3%) |

Values are n/N (%).
CBF = coronary blood flow; CFR = coronary flow reserve; CRT = coronary reactivity testing.

**Table 3. CRT-Related SAEs**

| Patient Age (Yrs) | Target Vessel | Complication | Treatment |
|---|---|---|---|
| 53 | LAD | Before initiation of protocol, a focal spasm in the LCX was visualized while the Doppler wire was in the LAD, causing an MI and prolonged chest pain. | Patient was given IC nitroglycerin and verapamil, as well as sublingual and intravenous nitroglycerin. She was admitted with a peak CPK of 532 and positive MB fraction. |
| 58 | LAD | A nonflow-limiting coronary dissection of the mid LAD resulted from advancement of the Doppler wire. Focal vasospasm and staining were visualized after the acetylcholine injection. IC nitroglycerin appropriately dilated the vessel. | TIMI flow grade 3 was present, and no intervention was needed. Patient was given clopidogrel and monitored overnight. She did not experience additional chest pain. There were no electrocardiographic changes. |

CPK = creatine phosphokinase; CRT = coronary reactivity testing; IC = intracoronary; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MB = myocardial band; MI = myocardial infarction; SAE = serious adverse event(s); TIMI = Thrombolysis In Myocardial Infarction.

CRT-related SAEs occurred in 2 women (0.7%) and included 1 coronary artery dissection (0.3%) and 1 ST-segment elevation MI due to coronary artery spasm (0.3%) (Table 3). CRT-related AEs occurred in 2 women (0.7%), and included 1 with transient air microembolism (0.3%) and 1 with deep venous thrombosis on the side of the groin access site (0.3%) >30 days after the CRT (Table 4). The combined CRT-related AE/SAE rate was 1.4%. There was no CRT-related mortality.

The prevalence of epicardial coronary vasospasm in our women was 5%, when vasospasm was defined as acetylcholine response of >50% coronary artery diameter reduction from baseline diameter (26). When defined as >70% coronary artery diameter reduction to acetylcholine from baseline, vasospasm occurred in 2 patients (0.9%). We also compared acetylcholine response to post-nitroglycerin diameter. Five patients (2.3%) had a >70% reduction in diameter due to acetylcholine compared with their post-nitroglycerin diameter.

The cohort was then followed for a period of 5.4 years, with 32 MACE observed in 24 women, including 5 deaths (1.7%), 8 nonfatal MIs (2.7%), 8 nonfatal strokes (2.7%), and 11 hospitalizations for heart failure (3.8%). The composite MACE rate to first event was 8.2% (24 of 293).

## Discussion

Although invasive CRT is used to diagnose MCD in patients without obstructive CAD, the safety of CRT has not been well established, especially among women. The results of our study demonstrate that invasive CRT is relatively safe to evaluate MCD in symptomatic women with evidence of ischemia but no obstructive CAD. Compared with diagnostic coronary angiography, which carries a <2% risk of complications (26,27), addition of CRT does not appear to significantly raise procedural risk. Specifically, the combined CRT-related AE/SAE risk (1.4%) was substantially lower than the 5.4-year follow-up MACE rate (8.2%). Prior studies have documented that MCD is associated with an adverse cardiovascular prognosis compared with asymptomatic women (3,4,8–10). Although clinical trials testing whether medical therapy reduces MACE in patients with MCD are needed, existing intermediate outcome trials suggest that endothelial function improves with treatment (20–23), as do signs and symptoms of ischemia (28). Accordingly, establishment of the diagnosis of MCD in these patients is important for appropriate medical management.

Coronary blood flow is regulated by various endothelial-dependent and nonendothelial-dependent factors. Nonendothelial-dependent factors include myocardial metabolism, myocardial compressive forces, aortic pressure, and neurohumoral substances (29). We measured CFR directly by the Doppler wire in response to adenosine, a nonendothelial-dependent vasodilator (30). Acetylcholine was used to test endothelium-dependent function, as it stimulates nitric oxide release from the endothelial cells. Nitroglycerin response was used to test nonendothelial-dependent macrovascular function. Procedural success rates were high in our study, and one-half of patients in our patient population had an abnormal CRT (Table 2).

**Table 4. CRT-Related AEs**

| Patient Age (Yrs) | Target Vessel | Complication | Treatment |
|---|---|---|---|
| 66 | LAD | An air microembolism to RCA was noticed during insertion of an infusion catheter, causing chest pain for 2 min. | Supplemental oxygen was delivered by face mask, with spontaneous recovery. |
| 52 | LAD | Patient was diagnosed with a deep venous thrombosis more than 30 days after her coronary reactivity study. | Anticoagulation was initiated as indicated. |

AE = adverse event(s); RCA = right coronary artery; other abbreviations as in Table 3.

**Safety of IC Doppler flow measurement.** IC Doppler measurement currently has a Class IIb recommendation for assessment of the severity of coronary flow abnormalities in patients with angina, ischemia by stress testing, but no obstructive CAD (31). The Doppler wire used in our study is a 0.014-inch-diameter flexible, steerable guidewire with a piezoelectric ultrasound transducer integrated into the tip (32,33). The Doppler wire may cause coronary spasm, which was previously seen in 1% of patients undergoing IC Doppler examination (34). Wire-induced spasm was relieved by IC nitroglycerin, similar to our contemporary study findings. A smaller study of 44 patients reported that no Doppler wire–related complications occurred in patients with normal or mild CAD (35). In our study, there was 1 coronary artery dissection (0.3%) that may have been due to the Doppler wire. The dissection likely occurred during placement of the Doppler wire before reactivity testing. Focal vasospasm and staining of the mid left anterior descending coronary artery were then noted during acetylcholine injection. No intervention was needed as the dissection was stable, with no limitation of flow.

**Safety of IC adenosine.** The safety and use of IC boluses of adenosine is well established (36–38). In a study of 39 patients by Wilson et al. (39), IC boluses (2 to 16 $\mu$g) produced small, brief, dose-dependent reductions in mean arterial pressure and did not significantly change the PR, QRS, or QT intervals on the electrocardiogram, even when the drug was injected directly into the right coronary artery. However, in a study by Qian et al. (34) of 906 patients, 14 patients experienced arrhythmias (7 asystole, 4 second-degree atrioventricular block, 1 third-degree atrioventricular block, 1 severe sinus bradycardia, 1 ventricular fibrillation), all of whom received an IC bolus of 12 $\mu$g of adenosine in the right coronary artery. One patient experienced sinus bradycardia and hypotension after 18 $\mu$g of IC adenosine in the left anterior descending artery after stent implantation (34). In our study of 293 patients, neither the 18-$\mu$g nor the 36-$\mu$g dosages of adenosine resulted in any arrhythmias, and all cases were performed in the left coronary artery, showing that contemporary testing safety has improved and is safe.

**Safety of IC acetylcholine.** Acetylcholine has been used to evaluate coronary vasomotor function. Sueda et al. (40) performed 1,000 acetylcholine tests in Japanese men with and without obstructive CAD from 1991 to 2004. Incremental doses of 20/50/80 $\mu$g into the right coronary artery and 20/50/100 $\mu$g into the left coronary artery were injected over 20 s. They reported 17 of 1,000 patients (1.7%) who experienced a major adverse reaction during acetylcholine infusion, including 11 with nonsustained ventricular tachycardia (1.1%), 1 with sustained ventricular tachycardia (0.1%), 1 with ventricular fibrillation (0.1%), 3 with shock due to left main stem spasm (0.3%), and 1 with cardiac tamponade (0.1%). No serious complications, such as death, stroke, or acute MI, were observed in this study.

More recently, the CASPAR (Coronary Artery Spasm in Patients with Acute Coronary Syndrome) study investigators injected incremental doses of acetylcholine (2/20/100 $\mu$g over 3 min) into the left coronary artery and/or right coronary artery of 86 patients (15). Coronary vasospasm was detected in 42 patients (49%). Ischemic ST-segment changes were seen in 20 patients (17 ST-segment depressions, 3 ST-segment elevation), but there were no clinical adverse events. In a study of nifedipine's effect on endothelial dysfunction, investigators infused acetylcholine (0.36, 3.6, and 18 $\mu$g/ml at 2 ml/min for 3 min) in either the left anterior descending artery or circumflex artery of 641 patients (41). Transient electrocardiographic changes were reported in 5 patients, whereas diffuse coronary vasoconstriction with hemodynamic instability occurred in 5 patients (0.78%) (1 [0.16%] required resuscitation). One patient (0.16%) developed acute coronary syndrome and cardiac arrest in the catheterization laboratory, possibly related to acetylcholine.

In our similarly sized study, acetylcholine infusions were well tolerated, without significant hemodynamic changes, again suggesting that contemporary testing safety has improved. Although some patients did experience chest pain at higher doses of acetylcholine, we were careful in monitoring coronary flow throughout acetylcholine infusion to assess for significant spasm. Five patients (2.3%) developed acetylcholine-induced vasospasm, which immediately resolved after nitroglycerin injection, with no further sequelae. The higher doses of acetylcholine used in the CASPAR study (2/20/100 $\mu$g) likely caused more coronary vasospasm than the lower doses of acetylcholine used in our study (0.364/3.64/36.4 $\mu$g). Our case of coronary artery dissection was likely due to the Doppler wire rather than vasospasm from acetylcholine.

**Study limitations.** As per WISE protocol, CRT was performed in the left anterior descending coronary artery in all patients. Safety of CRT in the right coronary artery or left circumflex artery was not evaluated. Acetylcholine is not directly infused into the left anterior descending artery, but rather infused through the guiding catheter in the left main coronary artery, and thus the concentration of the acetylcholine may be diluted in the left anterior descending artery. Because vasoactive substances are infused in the left main artery, both the circumflex and the left anterior descending artery are susceptible to vasoconstrictive effects. The protocol stipulated for the Doppler wire to be maintained in the proximal left anterior descending coronary artery. Therefore, the safety of CRT when the Doppler wire is placed more distally is unknown. It is also difficult to accurately perform QCA in distal vessels due to their smaller diameter.

## Conclusions

In women undergoing CRT for suspected MCD, contemporary testing is relatively safe with a low adverse event rate

when using standardized protocols for IC adenosine, acetylcholine, and nitroglycerin delivery in experienced centers. These results support the use of CRT by experienced operators for diagnostic and prognostic purposes in patients with persistent angina, evidence of myocardial ischemia, and no obstructive CAD. Prior studies investigating therapy directed at improvement of MCD have shown reduction of angina, vasospasm, heart failure, and stroke. Additional studies are needed to demonstrate improvement in cardiovascular outcomes.

**Reprint requests and correspondence:** Dr. C. Noel Bairey Merz, Division of Cardiology, Women's Heart Center, Cedars-Sinai Medical Center, 444 South San Vicente Boulevard, Suite 600, Los Angeles, California 90048. E-mail: merz@cshs.org.

## REFERENCES

1. Jespersen L, Hvelplund A, Abildstrom SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J 2012;33:734–44.
2. Anderson RD, Pepine CJ. Gender differences in the treatment for acute myocardial infarction: bias or biology? Circulation 2007;115:823–6.
3. Reis SE, Holubkov R, Conrad Smith AJ, 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;141:735–41.
4. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol 2009;54:1561–75.
5. Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation 2011;124:1414–25.
6. Carpiuc KT, Wingard DL, Kritz-Silverstein D, Barrett-Connor E. The association of angina pectoris with heart disease mortality among men and women by diabetes status: the Rancho Bernardo study. J Womens Health (Larchmt) 2010;19:1433–9.
7. Hemingway H, Langenberg C, Damant J, Frost C, Pyörälä K, Barrett-Connor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. Circulation 2008;117:1526–36.
8. Johnson BD, Shaw LJ, Pepine CJ, 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;27:1408–15.
9. von Mering GO, Arant CB, Wessel TR, 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;109:722–5.
10. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. Arch Intern Med 2009;169:843–50.
11. Lanza GA, Buffon A, Sestito A, et al. Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. J Am Coll Cardiol 2008;51:466–72.
12. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106:653–8.
13. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899–906.
14. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr., Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948–54.
15. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: the CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) study. J Am Coll Cardiol 2008;52:523–7.
16. Wakabayashi K, Suzuki H, Honda Y, et al. Provoked coronary spasm predicts adverse outcome in patients with acute myocardial infarction: a novel predictor of prognosis after acute myocardial infarction. J Am Coll Cardiol 2008;52:518–22.
17. Sovari AA, Cesario D, Kocheril AG, Brugada R. Multiple episodes of ventricular tachycardia induced by silent coronary vasospasm. J Interv Card Electrophysiol 2008;21:223–6.
18. MacAlpin RN. Cardiac arrest and sudden unexpected death in variant angina: complications of coronary spasm that can occur in the absence of severe organic coronary stenosis. Am Heart J 1993;125:1011–7.
19. Pepine CJ, Anderson RD, Sharaf BL, et al. 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;55:2825–32.
20. Bonetti PO, Barsness GW, Keelan PC, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J Am Coll Cardiol 2003;41:1761–8.
21. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol 2002;40:505–10.
22. Yasue H, Mizuno Y, Harada E, et al. Effects of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers. J Am Coll Cardiol 2008;51:1742–8.
23. Pauly DF, Johnson BD, Anderson RD, et al. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: a double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). Am Heart J 2011;162:678–84.
24. Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation 2005;111:363–8.
25. Bairey Merz CN, Shaw LJ, Reis SE, et al. 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:S21–9.
26. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, (Committee on Coronary Angiography). J Am Coll Cardiol 1999;33:1756–824.
27. Kennedy JW. Complications associated with cardiac catheterization and angiography. Cathet Cardiovasc Diagn 1982;8:5–11.
28. Mehta PK, Goykhman P, Thomson LE, et al. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. J Am Coll Cardiol Img 2011;4:514–22.
29. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA 2005;293:477–84.
30. Abebe W, Makujina SR, Mustafa SJ. Adenosine receptor-mediated relaxation of porcine coronary artery in presence and absence of endothelium. Am J Physiol 1994;266:H2018–25.
31. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography). Circulation 1999;99:2345–57.
32. Doucette JW, Corl PD, Payne HM, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. Circulation 1992;85:1899–911.

33. Bach RG, Kern MJ. Practical coronary physiology. Clinical application of the Doppler flow velocity guide wire. Cardiol Clin 1997;15:77–99.
34. Qian J, Ge J, Baumgart D, et al. Safety of intracoronary Doppler flow measurement. Am Heart J 2000;140:502–10.
35. Mechem C, Kern MJ, Aguirre F, Cauley M, Stonner T. Safety and outcome of angioplasty guidewire Doppler instrumentation in patients with normal or mildly diseased coronary arteries (abstr). Circulation 1992; 86:I323.
36. Rieber J, Jung P, Schiele TM, et al. Safety of FFR-based treatment strategies: the Munich experience. Z Kardiol 2002;91 Suppl 3:115–9.
37. Jeremias A, Whitbourn RJ, Filardo SD, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. Am Heart J 2000; 140:651–7.
38. De Bruyne B, Pijls NH, Barbato E, et al. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. Circulation 2003;107:1877–83.
39. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. Circulation 1990;82:1595–606.
40. Sueda S, Oshita A, Nomoto T, et al. Recommendations for performing acetylcholine tests safely: STOP Dangerous Complications Induced by Acetylcholine Tests (STOP DCIAT). J Cardiol 2008;51:131–4.
41. Lüscher TF, Pieper M, Tendera M, et al. A randomized placebo-controlled study on the effect of nifedipine on coronary endothelial function and plaque formation in patients with coronary artery disease: the ENCORE II study. Eur Heart J 2009;30:1590–7.

**Key Words:** coronary reactivity ■ endothelial dysfunction ■ microvascular dysfunction.