Imaging Microvascular Dysfunction and Mechanisms for Female-Male Differences in CAD

Monica B. Patel, MD, Linh P. Bui, MD, Richard L. Kirkeeide, PhD, K. Lance Gould, MD

ABSTRACT

Microvascular dysfunction or disease is most commonly associated with diffuse epicardial coronary atherosclerosis and endothelial dysfunction, whereas it is less common as a distinct, separate, isolated pathophysiology. The different manifestations of coronary artery disease in women relate in part to their smaller coronary arteries, higher coronary blood flow, and higher endothelial shear stress, which have profound effects on endothelial function and development or resistance to atherosclerosis, its symptomatic presentation, outcomes, and treatment. The complex interactions of focal stenosis, diffuse epicardial atherosclerotic coronary narrowing, and microvascular dysfunction make definitive diagnosis and management difficult by use of standard noninvasive and invasive physiological and anatomic technologies. However, quantitative rest-stress myocardial perfusion, best documented by positron emission tomography, combined with clinical circumstances usually provides a definitive diagnosis to guide management, including vigorous risk factor management and revascularization for patients with physiologically severe epicardial stenosis by quantitative positron emission tomography. (J Am Coll Cardiol Img 2016;9:465–82) © 2016 by the American College of Cardiology Foundation.

Several recent excellent reviews detail the clinical manifestations of coronary artery disease (CAD) in women compared with men (1–3). Dominant themes include the continued wide prevalence of CAD in women, atypical angina, diffuse epicardial coronary atherosclerosis, microvascular dysfunction, inaccurate diagnostic tests, delayed or late acute coronary syndromes associated with high mortality, and differential responses to medical treatment or invasive procedures in women compared with men.

Three prominent components of CAD in women (focal stenosis, diffuse epicardial atherosclerosis, and microvascular disease) have different relative importance and interact variably among individuals (and with time, in the same individual) differently than in men (1–3). Moreover, there is no standardized definition or unique stand-alone measurement for each of these 3 components separately because of their complex dynamic interacting association. Therefore, imaging microvascular disease inherently also involves the coronary pathophysiology of angina without angiographic stenosis and perfusion imaging for the broad spectrum of abnormalities or imaging artifacts in women that require differentiation from specific, separate, isolated microvascular disease or no coronary abnormalities, by invasive or noninvasive technologies.

As the basis for imaging microvascular disease, invasive pressure-flow velocity measurements provide important insights (4–6). In a recent study of 139 patients with angina and no stenosis >50% diameter narrowing (4), 77% were women. Invasive measurements were made of coronary flow reserve (CFR), fractional flow reserve (FFR), endothelial dysfunction, an index of microcirculatory resistance, and atherosclerosis by intravascular ultrasound (IVUS). These patients had a high prevalence of diverse coronary abnormalities. All patients had coronary atherosclerosis by IVUS. Mean CFR was

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4.1 ± 1.7, with a range of 1.3 to 9.9. Endothelial dysfunction was found in 44% by stringent criteria of >20% decrease in coronary artery diameter after intracoronary acetylcholine and in 76% by any degree of vasoconstriction versus normal vasodilation. In 51% of these patients, invasive pressure-derived FFR was below the threshold of 0.8 used to guide percutaneous coronary inter- vention (PCI). Fifty-eight percent had myocardial bridging with no effect on FFR or CFR. Over all, only 23% had normal endothelial function, normal coronary function, no myocardial bridging, and no coronary explanation for angina (4). On multivariate analysis, coronary abnormalities were significantly related to age, diabetes, fasting blood glucose, hypertension, body mass index, and blood homocysteine levels.

Consequently, imaging microvascular dysfunction requires that each of the 3 pathophysioligies (focal stenosis, diffuse epicardial atherosclerosis, and microvascular disease) be addressed within the larger framework of quantitative myocardial perfusion imaging in women. Of necessity, it must also consider issues that prevent the differentiation of these various pathophysiolgies from false positive and false negative imaging, CFR-FFR discordance, and other potential mechanisms for angina in the absence of the coronary abnormalities that constitute nearly one-fourth of cases (4). Finally, even a standard of quantitative perfusion imaging is necessary for validity and clinical usefulness of imaging microvascular disease. Our analysis of imaging microvascular disease, therefore, directly relates to mechanisms underlyng the fundamental differences of CAD in women compared with men that are potentially answerable by regional and global quantitative perfusion in women or men.

WOMEN VERSUS MEN: MECHANISMS RELATING ARTERIAL SIZE, CORONARY BLOOD FLOW, ARTERIAL WALL SHEAR STRESS, FLUID DYNAMICS, HORMONES, CLINICAL PRESENTATION, OUTCOMES, AND RESPONSE TO TREATMENT OR PROCEDURES

The smaller size of coronary arteries in women than men is well established (7-9) and corresponds to smaller left ventricular (LV) mass, as summarized in Table 1 (9). Myocardial perfusion or coronary blood flow is higher in women than in men, as reported in Table 1 based on 4,328 rest-stress positron emission tomography (PET) studies expanded from our original publications, which detailed patient groups and methodology (10,11). Small arteries with high flow have fully developed flow profiles and high endothelial shear stress. Large arteries with low flow have less developed or disordered flow profiles with low endothelial shear stress. Endothelial shear stress and its effects have been well documented for specific coronary arterial anatomy, such as proximal and opposing arterial walls at branch points, arterial bends, or developing stenosis (12-17).

However, principles of fluid dynamics relating to focal atheroma have not been extended to the generalized physiological consequences of small arterial size and high coronary flow in relation to other characteristics of CAD in women, particularly diffuse CAD. Our synthesis in this review extends these anatomically localized specific principles into an explanation of male-female differences in manifestations of CAD that integrates fluid dynamics, clinical coronary physiology, and quantitative perfusion imaging.

The schema of the Central Illustration integrates these diverse aspects of CAD in women compared with men through the common physiological mechanism of endothelial shear stress. Although endothelial shear stress varies with pulsatile flow, the average calculated shear stresses in Table 1 provide essential insights into male-female differences in manifestations of CAD. As in the Central Illustration and Table 1, large coronary arteries with slow flow have nonlaminar flow and low shear. Small coronary arteries with high flow have fully developed flow profiles and high endothelial shear. Instantaneous flow velocity profiles and instantaneous endothelial shear stresses vary spatially within and between arteries and with time because of pulsatile flow, arterial bending, branches, changing arterial diameters caused by pulsatile pressure, and lumen irregularities or stenosis. However, these average shear values are within ranges that have major effects on endothelial function and development of or resistance to atherosclerosis (12-17), as shown in the Central Illustration.

ENDOTHELIAL LOW SHEAR STRESS. Low endothelial shear stress increases low-density lipoprotein (LDL) transport through “leaky” endothelial cell junctions and increases inflammation, platelet activation, and thrombosis, as well as heterogeneous remodeling, focal atheroma, and excessive heterogeneous expansive remodeling with associated plaque instability (12-17). These adverse effects are mediated by low shear, which down-regulates endothelial nitric oxide (NO), NO synthase, endothelial NO synthase.
(eNOS) gene expression, eNOS phosphorylation, and manganese superoxide dismutase expression and up-regulates endothelial NADPH oxidase, thereby increasing superoxide ion (12-17).

Leaky junctions between vascular endothelial cells account for 90% of LDL transport across endothelium into cell walls (13). Low shear stress increases LDL nitration and LDL oxidation, which leads to up-regulation of adhesion molecules and recruitment of monocytes that develop into diffuse or focal atheroma. Importantly, physiological concentrations of estrogen substantially block low shear-mediated LDL oxidation and increase endothelial NO production, which has been shown to reduce LDL transport across the endothelium into the cell wall. Estrogens also reduce the arterial stiffness associated with pressure-driven leaky cell junctions (13).

Low shear stress with focal stenosis and unstable plaque is associated with heterogeneous excessive positive remodeling (12,16). Stable stenosis is associated with negative remodeling caused by fibroma formation. However, physiologically milder remodeling preserves lumen size during progressive atherosclerosis without instability, thereby leading to diffuse disease.

ENDOTHELIAL HIGH SHEAR STRESS. High endothelial shear stress inhibits LDL transport and focal atherogenesis by reducing leaky endothelial cell junctions and inhibits inflammation, platelet activation, and thrombosis. It also promotes mild stable uniform remodeling and inhibits focal atheroma, stenosis, and plaque instability. These beneficial effects are mediated by up-regulation of endothelial NO, eNOS gene expression, eNOS phosphorylation, and manganese superoxide dismutase expression and down-regulation of endothelial NADPH oxidase, thereby decreasing superoxide ion (12-17).

The net effects of arterial size and shear and their associated effects lead to stable diffuse CAD in women until late in life, after withdrawal of estrogens that interact with shear stress. Endothelial shear stress and its effects are a complex, heterogeneously varying regional-, time-, and age-related continuum with great individual differences. The antiatherosclerotic effects of high shear might not prevent the development of CAD from high risk factors but might modify it to a diffuse disease without the early segmental stenosis seen in men. Consequently, with given risk factors, some women never develop CAD, others develop it prematurely as men do, and others have delayed focal disease, whereas in many women, coronary atherosclerosis is modified by these shear-dependent mechanisms into diffuse disease without focal stenosis.

CLINICAL MANIFESTATIONS AND ENDOTHELIAL SHEAR. Shear effects on CAD in women might also explain 2 prominent clinical features. The first is atypical nonexertional angina related to diffuse coronary narrowing. With the focal stenosis commonly seen in men, increased coronary flow with exercise is associated with a stenosis pressure gradient that is proportional to flow raised to the second power (flow²) (Central Illustration), thereby reducing coronary perfusion pressure with consequent subendocardial underperfusion and angina. However, for diffuse disease in women, increased coronary flow is linearly associated with flow (flow)³, thereby causing less pressure gradient, less subendocardial ischemia, and less angina with exercise.

The second prominent characteristic is the high mortality in post-menopausal women late in life when they do develop focal stenosis. Late stenosis in women is superimposed on severe diffuse disease that has developed silently during their middle years to produce a large burden of atherosclerosis in small arteries, which incurs higher risk than in men, who have more focal disease that presents earlier in life. With estrogen withdrawal, its partial protection against atheroma formation in low shear regions of

### Table 1

<table>
<thead>
<tr>
<th>Arterial Diameter (mm)</th>
<th>Women</th>
<th>Men</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>3.91 ± 0.67</td>
<td>4.35 ± 0.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAD</td>
<td>3.24 ± 0.58</td>
<td>3.54 ± 0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LCx</td>
<td>2.75 ± 0.64</td>
<td>3.18 ± 0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RCA</td>
<td>3.26 ± 0.65</td>
<td>3.7 ± 0.70</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Mean size of all arteries | 3.29 | 3.7 |

| Myocardial perfusion (ml/min/g) for women (n = 1,150) and men (n = 3,178) |
|-----------------------------|-----------------------------|-----------------------------|
| Rest                        | 0.97 ± 0.09                 | 0.73 ± 0.04                 | <0.00001 |
| Stress                      | 2.36 ± 0.42                 | 1.94 ± 0.4                  | <0.00001 |
| CFR                         | 2.57 ± 0.59                 | 2.74 ± 0.71                 | <0.00001 |

<table>
<thead>
<tr>
<th>Left ventricular bed size (g)</th>
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<tbody>
<tr>
<td>LM</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>LCx</td>
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<tr>
<td>RCA</td>
</tr>
</tbody>
</table>

| Mean size, all beds | 86 | 110 |

| Shear (dynes/cm²) for mean arterial size and female/male bed size above |
|-------------------------------|-----------------------------|-----------------------------|
| LM                            | 16.3                        | 11.4                        |
| LAD                           | 19.2                        | 14.1                        |
| LCx                           | 15.5                        | 9.6                         |
| RCA                           | 9.4                         | 6.2                         |

| Mean size, all arteries       | 15.1                        | 10.4                        |

*From Kucher et al. (9). †From Gould et al. (10,11) for patients with risk factors or documented coronary artery disease. ‡From Hiteshi et al. (7). §Assumes developed flow; LAD = left anterior descending coronary artery; LCx = left circumflex; LM = left main; LV = left ventricular; RCA = right coronary artery.
Microvascular Dysfunction and Female-Male Manifestations of CAD

branches or bending is lost, which leads to “accelerated” clinical manifestations related to the focal stenosis added to diffuse disease.

Hence, the long “silent” period of diffuse coronary atherosclerosis development in women may essentially evolve a more lethal combination of diffuse plus late focal disease than commonly seen in men. Although men also commonly develop clinically significant microvascular dysfunction, their higher prevalence of focal stenosis with distinct symptomatology earlier in life than women overshadows manifestations of their microvascular dysfunction.

Global reduction of CFR, which reflects the global burden of diffuse epicardial atherosclerosis, carries high cardiovascular risk (18–21). This high-risk global disease may contravene any potential benefit from revascularization of focal stenosis (21). Quantification of the physiological severity of the focal versus diffuse disease associated with microvascular dysfunction is therefore essential for assessment of the risks and benefits of procedures versus medical treatment alone (18–21). Deferring aggressive risk factor management or lipid treatment on the basis of sex may enable the progression of silent diffuse disease that manifests later high risk preventable by vigorous risk factor management, particularly given that women respond better to lipid-lowering treatment than men (22), with worse outcomes from bypass surgery (23).

**CORONARY BLOOD FLOW, SHEAR STRESS, CARDIOVASCULAR FITNESS, AND MICROVASCULAR FUNCTION.** Women have higher resting heart rates than men, and after 60 years of age, they have higher peak heart rates (24,25), which is consistent with higher resting perfusion than men and implies higher shear stress (Table 1). However, women are less physically active in their leisure time and have lower peak VO2 and lower cardiovascular fitness, which is associated with higher mortality rates in lower strata of fitness/metabolic equivalents (25,26). For deconditioned women, the endothelial dysfunction associated with reductions of eNOS expression and NO production associated with low coronary blood flow and low shear stress can be reversed by physical training that increases coronary flow with increased shear stress during exercise (27–29). Sustained laminar shear stress in physiological ranges activates signaling pathways that induce expression of several atheroprotective and antithrombogenic genes. These genes encode for products that serve antioxidant, anti-inflammatory, anticoagulant, and antiapoptotic functions (30).

**VASCULAR AGING WITH INITIATION OF MENOPAUSE AND MICROVASCULAR FUNCTION.** In women, adverse changes in cardiovascular disease risk factors, such as hypertension, dyslipidemia, and adiposity, occur with hormonal changes of menopause, vascular aging, and the declining coronary endothelial dysfunction associated with cardiovascular morbidity and mortality (31). The decline of endothelial function in women is delayed approximately 1 decade later than in men but accelerates after menopause (32,33). Declines in ovarian function and estrogen levels in late perimenopausal transition initiate rapid deterioration in endothelial function with decreased NO production, increased oxidative stress, increased proinflammatory cytokines, increased large artery stiffness associated with leaky endothelial cell junctions, and increased vascular vulnerability (34). These changes reflect and interact with loss of the estrogen-mediated benefit of high shear stress.

With aging, risk factors commonly increase in association with the increasing prevalence of
Microvascular dysfunction. Lack of regular exercise is a prominent feature of aging and is in contrast to people who exercise regularly, control their weight, and eat healthy food, which is associated with a low risk of microvascular disease. Moreover, regular exercise may relieve the angina of microvascular disease as effectively or more effectively than standard treatment with nitrates and beta blockers (now the subject of a randomized trial, Microvascular Disease Exercise Trial [MOVE]; NCT02045459). Although forearm-mediated vasodilation increased by 50% with endurance training in men compared with sedentary men, endurance training in post-menopausal women had no benefit on forearm-mediated vasodilation compared with sedentary women. This observation suggests that estrogen is necessary to produce a beneficial effect from endurance exercise training on endothelial function in women (35,36), paralleling the loss of estrogen protection against the adverse effects of low shear at arterial bends and branches. Experimentally, 17β-estradiol (E2) reversed the oxidative stress caused by disordered flow and oscillatory shear stress (17); however, replacement of estrogen does not prevent or lessen the occurrence of CAD in women.

**QUANTITATIVE PERFUSION IMAGING IN WOMEN FOR MICROVASCULAR DISEASE**

This background of CAD in women that is related to arterial size and coronary blood flow establishes the basis for reviewing quantitative perfusion imaging and microvascular disease. There is no single report, series of patients, or conceptual framework for imaging microvascular disease because of the many diverse pathophysiology for different syndromes, thus labeled a wastebasket term.

Accordingly, this review develops the major concepts by means of a series of clinical cases, each of which illustrates a specific concept or principle in the wide ranges of interacting microvascular dysfunction, diffuse epicardial atherosclerotic narrowing, segmental stenosis, endothelial dysfunction, and atypical chest pain seen commonly in women, as well as in men. The case images create a picture of what high-quality quantitative perfusion imaging tells an informed observer that may not be familiar or imaginable to most cardiologists, which it is hoped will be corrected in part by this paper.

**CONCEPTS IN QUANTITATIVE PERFUSION IMAGING OF MICROVASCULAR DISEASE**

Although the underlying pathophysiology of angina and acute coronary syndromes in women are different from men, clinical manifestations are primarily related to epicardial coronary atherosclerosis, as evidenced by intracoronary IVUS, which identified atherosclerosis in systematic patient studies (4). However, from a practical clinical viewpoint, primarily microvascular disease can be differentiated from focal obstructive epicardial coronary stenosis by quantitative perfusion imaging without an angiogram, as illustrated in the cases below.

Reduced global quantitative stress perfusion or CFR is commonly called microvascular disease (18-20); however, this term is imprecise and often incorrect, because microvascular dysfunction is most commonly associated with diffuse epicardial coronary atherosclerosis and endothelial dysfunction without regional flow-limiting stenosis (4). Because of its close association with atherosclerosis, treatment of microvascular disease requires treatment of associated risk factors, in which intense long-term preventive treatment generally leads to regression of atherosclerotic volume (37) with improved coronary perfusion capacity. The case examples of microvascular and epicardial disease emphasize vigorous risk factor treatment with or without invasive procedures for large areas of severe low-ischemic perfusion quantified by PET.

**CONCEPT 1. MICROVASCULAR DISEASE WITHOUT EPICARDIAL CORONARY STENOSIS.** Figure 1 illustrates severe isolated microvascular dysfunction without obstructive CAD. This 78-year-old woman with a strong family history of CAD, controlled hypertension, and treated hyperlipidemia had angina with jaw and arm radiation for 11 years at rest and exertion, which progressed to limit her walking to 100 ft and was relieved in part with nitroglycerin. Five coronary angiograms that showed no obstructive CAD over a period of years led to her referral for a dipyridamole stress PET-computed tomography (CT) scan. Figure 1 shows normal topographic views of relative uptake of rubidium Rb-82 as described previously (10,11,21,38-40). Global stress flow (Figure 1C) of 1.27 ml/min/g and CFR (Figure 1D) of 1.4 during dipyridamole stress represent moderate to severe impairment close to the threshold associated with angina and electrocardiography (ECG) changes, as listed in Table 2 (10,11,21,38-40). There was no regional stress-induced perfusion defect; a CT scan for attenuation correction showed no coronary calcium, and stress ejection fraction was 70% on gated perfusion images.

To assess potential caffeine inhibition in this patient after PET, we measured caffeine levels of 5.7 μg/ml at 24 h and 1.8 μg/ml at 48 h, with none
detectable at 72 h after the last caffeine intake, where the detection limit for our laboratory is 1.0 µg/ml. On repeat PET after 5 days abstinence from caffeine, when no caffeine was detected in her blood with the same dipyridamole stress, scanner, and protocol, the stress perfusion increased from 1.27 to 1.63 ml/min/g and CFR increased from 1.4 to 2.0, which was still significantly reduced (not shown) but modestly higher than for stress perfusion with detectable blood caffeine. These results indicate microvascular dysfunction with no stenosis or significant diffuse narrowing because of lack of coronary calcium at her age and normal angiograms. The case also illustrates how caffeine inhibition mimics microvascular disease. Such definitive cases of pure microvascular dysfunction are uncommon compared with the more common mixed diffuse or focal epicardial coronary atherosclerosis associated with microvascular disease, as illustrated below. This patient’s angina was not relieved by beta-blockers, long-acting nitrates, calcium-channel blockers, or ranolazine but was partially relieved by frequent sublingual nitroglycerine.

CONCEPT 2. DIFFUSE SEVERE EPICARDIAL Atherosclerosis and Microvascular Dysfunction. The 77-year-old asymptomatic woman in Figure 2 had a prior myocardial infarction during cholecystectomy with an angiogram that showed mild nonobstructive CAD; no intervention was performed. Risk factors included hypertension, hyperlipidemia, diabetes, and a strong family history of CAD; she had diastolic dysfunction according to echocardiography, with an ejection fraction of 60%, and no chest pain. She was referred for PET before knee surgery. With dipyridamole stress, she had severe angina and 2 mm of ST-segment depression that required aminophylline reversal after image acquisition. CT for attenuation correction showed a 1-cm-long calcification of the left anterior descending coronary

**FIGURE 1** Microvascular Disease Without Epicardial Coronary Stenosis

Single anterior views of relative rest (A) and stress (B) images. On the color scale, white indicates highest relative activity (100%) scaled to progressively lower uptake from yellow, to green, to blue. The histogram shows percentage of the left ventricle in the color-coded ranges. For the same patient, global stress perfusion (C) and coronary flow reserve (CFR) (D) were moderately to severely reduced, scaled according to their color bar with a histogram for percentage of left ventricle in color-coded ranges. Other views (right [septal], lateral, and inferior topographic views) were all similar. Generic coronary artery distributions are indicated by artery shadow overlay. D1 and D2 = diagonal branches; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RI = Ramus Intermedius.
artery (LAD). Gated perfusion images showed severe transient ischemic dilation of the LV consistent with diffuse subendocardial underperfusion. The rest (Figure 2A) and stress (Figure 2B) relative PET images showed no large or severe stress defect. There was a longitudinal midanterior to apex perfusion gradient in the distribution of the distal LAD, which indicates diffuse arterial narrowing (41,42). Global stress perfusion was moderately and diffusely reduced to 1.86 ml/min/g, and CFR was reduced to 1.09 diffusely in part because of diffuse epicardial narrowing, as evidenced by the base to apex longitudinal perfusion gradient and the angiogram. This case illustrates diffuse epicardial coronary atherosclerosis combined with microvascular disease sufficient to cause global subendocardial ischemia with angina and abnormal ST-segment depression during dipyridamole stress. All risk factors were well controlled except for exercise, which was limited by knee and hip joint disease.

<table>
<thead>
<tr>
<th>TABLE 2 Clinical Correlates With CFR and Stress Flow (N = 1,876 Rest-Stress PET Cases)</th>
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<tbody>
<tr>
<td>Clinical Class (Without PET Data)</td>
</tr>
<tr>
<td>Number of PET cases</td>
</tr>
<tr>
<td>Regional stress flow*</td>
</tr>
<tr>
<td>Regional CFR</td>
</tr>
<tr>
<td>Global stress flow</td>
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<td>Global CFR</td>
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*cc/min/gm.

CAD = coronary artery disease; CFR = coronary flow reserve; PET = positron emission tomography.

FIGURE 2 Diffuse Severe Epicardial Atherosclerosis and Microvascular Dysfunction

Single anterior views of normal relative rest (A) and stress (B) uptake images. For the same patient, stress perfusion (C) and CFR (D) were diffusely reduced because of diffuse epicardial narrowing and in part because of high resting perfusion caused by resting high blood pressure and anxiety. Abbreviations and displays as in Figure 1.
CONCEPT 3. OCCLUSIVE, DIFFUSE EPICARDIAL CAD WITHOUT MICROVASCULAR DISEASE. The 59-year-old woman whose case is presented in Figure 3 had 4-vessel coronary bypass surgery 6 months previously for atypical angina without improvement in symptoms. Risk factors included hypertension, hypercholesterolemia, diabetes, a strong family history of CAD, and smoking (1 pack/day for 35 years), which led to the PET examination. A repeat angiogram performed by her cardiologist showed all 4 bypass grafts were occluded. All coronary arteries were patent but interpreted as severe 3-vessel stenosis, for which repeat bypass was recommended. The surgeon (and senior author) saw only diffuse luminal irregularities on the angiogram without severe stenosis and referred the patient for PET imaging.

Relative rest and dipyridamole stress images showed a small moderate to severe stress-induced defect in a first diagonal distribution comprising 11% of the LV from the histogram beside the stress color bar. In the basal inferior myocardium, maximum

Rest and stress relative uptake images with coronary flow capacity map combining stress flow (in ml/min/g) and CFR, color scaled as for prior images. Dark blue indicates myocardial steal wherein stress flow falls below rest flow. The coronary flow capacity map combines stress flow and CFR as reported previously (10,11,21,38–42), with color-scaled ranges of stress flow and CFR. Groups of subjects were as follows: red for healthy young volunteers <40 years old without risk factors or any medical conditions; orange for older volunteers or patients with risk factors only and with no known coronary artery disease (CAD); yellow for patients with known CAD documented by coronary events or angiography with or without revascularization; green for patients with regional stress defects and either angina or >1 mm of ST-segment depression on ECG during the dipyridamole stress; and blue for patients with both during dipyridamole stress. Color-coded percentage of left ventricle (LV) in each range is listed below the coronary flow capacity map. Max = maximum; min = minimum; OM1 and OM2 = obtuse marginal branches; PDA = posterior descending artery; RCA = right coronary artery; other abbreviations as in Figure 1.
CFR was 3.7 and stress flow was 2.1 ml/min/g, both of which are high within normal limits, which indicated an absence of global microvascular dysfunction, as shown on the coronary flow capacity map that integrated both stress flow (in ml/min/g) and CFR according to the color-coded scale. Global CFR of 2.1 (compared with maximal CFR) was mildly reduced, consistent with diffuse disease, but was adequate, with no other low perfusion near the ischemia threshold of 1.7 (Table 1). In the small severe mid-anterolateral stress defect, CFR was 0.66, which indicated myocardial steal with severe angina during dipyridamole stress, wherein absolute stress flow fell to 66% of rest flow, associated with collaterals beyond an occluded first diagonal branch (reversed with intravenous aminophylline).

Retrospective review of the angiogram with background contrast enhancement revealed a small diagonal with a flush occlusion at its origin from the LAD that was not seen on any prior angiogram before or after bypass surgery. It was the source of the patient’s angina and explained the lack of symptomatic benefit after bypass surgery to other arteries with non-flow-limiting diffuse atherosclerosis.

The high CFR and coronary flow capacity despite occluded bypass grafts indicated a lack of significant flow-limiting stenosis of the arteries with occluded bypass grafts. Her angina arose from the overlooked occluded diagonal branch. With preserved stress flow and CFR outside the first diagonal distribution, the angiographically apparent diffuse epicardial disease was not flow limiting, and microvascular function was intact, with high flow capacity in light of the maximum CFR of 3.7 outside the diagonal distribution. This case illustrates the importance of regional quantitative perfusion imaging integrated with global quantitative perfusion imaging to assess the severity of focal, diffuse epicardial and microvascular disease. The patient was taking metoprolol succinate, isosorbide mononitrate, and ranolazine for angina; her blood pressure and lipid levels were well controlled, but the patient’s weight at 214 lb was over the target of 155 lb, with no exercise and continued smoking.

CONCEPT 4. MISSED DIAGNOSIS OF EPICARDIAL CORONARY STENOSIS MASQUERADING AS MICROVASCULAR DISEASE.
Epicardial coronary stenosis in women may be misdiagnosed as microvascular disease because of inadequate quantitative perfusion imaging,
misreading of coronary angiograms (as in the prior case), or a mindset oriented toward male manifestations and interventions in cardiology practice. The 58-year-old woman whose case is depicted in Figure 4 had mitral valve prolapse, mild treated hypertension, past smoking, a strong family history of CAD, vague chest discomfort, and total cholesterol of 207 mg/dl, triglycerides of 71 mg/dl, LDL of 118 mg/dl, and high-density lipoprotein (HDL) of 74 mg/dl without lipid medication. Lipoprotein(a) was 9 mg/dl, and LDL pattern A and homocysteine levels were normal. Other risk factors, weight, and diet were well controlled. One year previously, a CT coronary artery calcium score was 118 in the LAD. She developed 3 weeks of exertional angina but had a normal ECG stress test and normal standard nuclear stress single-photon emission computed tomography (SPECT); she was told that she had no heart disease and no risk factors by her cardiologist. Because of persisting exertional angina, she requested a second opinion.

Her PET showed a severe dipyridamole-induced perfusion defect in the distribution of a diagonal...
branch off the LAD but with adequate perfusion in the septal and apical distribution of the LAD. Angiography confirmed severe diagonal stenosis associated with “branch steal” (41,42) caused by mild LAD stenosis proximal to a more severe stenosis of the diagonal branch. PCI opened both arteries, with resolution of her angina. In this case, standard diagnostic testing and clinical assessment overlooked significant coronary stenosis that otherwise was attributable to microvascular angina. Atorvastatin lowered her total cholesterol to 151 mg/dl, triglycerides to 62 mg/dl, LDL to 61 mg/dl, and HDL to 80 mg/dl, with 12-year follow-up free of events or symptoms.

CONCEPT 5. LEFT MAIN STENOSIS OR BALANCED STENOSIS VERSUS MICROVASCULAR DYSFUNCTION.

The patient in Figure 5 had treated hyperlipidemia, hypertension, and dyslipidemia, with total cholesterol of 182 mg/dl, triglycerides of 408 mg/dl, and HDL of 22 mg/dl 20 years previously, when she started taking atorvastatin 40 mg/day. This enabled her to maintain total cholesterol of 108 mg/dl, triglycerides of 99 mg/dl, LDL of 54 mg/dl, and HDL of 32 mg/dl over the next 20 years, with controlled blood pressure but no regular exercise. An angiogram 16 years previously showed mild CAD with no procedures performed, and she remained asymptomatic until her recent mild exertional angina. Dipyridamole stress at PET as image acquisition was completed caused mild angina and 4 mm of ST-segment depression; her blood pressure dropped to
98/51 mm Hg, which was reversed by aminophylline, followed by metoprolol as blood pressure recovered.

Stress perfusion images showed a large, severe anterior, septal, and apical stress defect comprising 60% to 70% of the LV. Stress flow and CFR were severely reduced into the low-flow ranges of severe ischemia over most of the LV, much larger than on relative images, interpreted as severe balanced 3-vessel or left main disease. Angiography confirmed severe left main stenosis at the trifurcation of the LAD, left circumflex artery, and first septal perforator, which led to successful bypass surgery.

These stress images of left main stenosis may not always be distinguished from severe global microvascular dysfunction; however, the clinical response to dipyridamole indicated severe epicardial disease, because such a fall in blood pressure with vasodilatory stress is uncommon with pure microvascular dysfunction in the absence of epicardial stenosis.

CONCEPT 6. OCCLUSIVE CAD WITH NORMALIZING COLLATERAL FLOW AND MICROVASCULAR FUNCTION. The 67-year-old woman whose case is depicted in Figure 6 had a strong family history of CAD with 1 risk factor (she had smoked 3 packs per day for 40 years but quit 11 years before the PET examination). She had bilateral arm tingling and chest tightness at rest for 2 years before developing exertional angina that led to the PET. Dipyridamole PET showed a distal anterior, anteroseptal, and apical defect with myocardial steal indicating collateral perfusion distal to a severe mid-LAD stenosis or occlusion. An angiogram confirmed a long, tapering, severe mid-LAD stenosis with slow antegrade flow and significant competitive collateral flow via large collaterals from the right coronary artery. Revascularization was deferred because of the presence of good collaterals, good LV function, and resolution of symptoms on beta blockers.
On atorvastatin, follow-up PET 3 years later showed remarkable improvement, with only a mild mid to distal anterior stress defect (not shown). Ten years later, PET showed a normal stress image (Figure 6B), which indicated extensive collateral development or recanalization to prevent steal and provide normal coronary flow capacity. Ten-year PET showed exceptionally high stress flow of 3.3 ml/min/g, comparable to healthy young volunteers, thereby excluding microvascular disease despite occlusive collateralized epicardial disease.

**CONCEPT 7. HIGH-QUALITY PERFUSION IMAGING TO DIFFERENTIATE SEVERE GLOBAL MICROVASCULAR DYSFUNCTION FROM SEVERE DIFFUSE FLOW-LIMITING EPICARDIAL CORONARY NARROWING.** In Figure 7A, global stress perfusion is reduced to 1.18 ml/min/g, which indicates global uniform severe microvascular dysfunction. In Figure 7B, stress perfusion has a base to apex longitudinal perfusion gradient, which indicates diffuse epicardial coronary narrowing as described previously (41,42). At the base, stress flow reaches 2.59 ml/min/g, which is in the range of healthy young volunteers, thereby ruling out global microvascular dysfunction. The fluid dynamic mechanism of the base to apex longitudinal perfusion gradient is “branch steal,” documented experimentally and by quantitative PET in humans (42).

As is common in many patients, regional stress flow defects in specific arterial distributions may be superimposed on globally reduced stress perfusion. This pattern of regional on global perfusion abnormalities indicates epicardial coronary disease in addition to microvascular dysfunction, which reduces global stress perfusion. These quantitative perfusion patterns combined with coronary calcium and clinical circumstances usually provide adequate differentiation of stenosis and diffuse epicardial and microvascular disease without angiography.

**CONCEPT 8. SEVERE ANGINA AT VERY HIGH STRESS FLOW AND CFR WITH NO FLOW-LIMITINGstenosis.**

The 68-year-old patient in Figure 8 had angina that
led to PCI 4 and 5 years previously, with an angiogram that showed patent stents and no residual stenosis. Risk factors included controlled hypertension, treated hyperlipidemia, and past heavy smoking (quit 15 years previously). However, angina continued with emotional stress and inconsistently with exercise despite the use of beta-blockers, long-acting nitrates, and calcium channel blockers. Consequently, the cardiologist requested a PET study, performed with regadenoson stress. Relative rest (Figure 8A) and stress (Figure 8B) PET images were normal. A coronary flow capacity map (Figure 8C) showed excellent flow capacity (red), comparable to that of young volunteers. Rest perfusion (Figure 8D) of 1.04 ml/min/g, stress perfusion (Figure 8D) at 3.22 ml/min/g, and CFR at 3.18 were all excellent, nearly 3 times higher than the low-flow threshold that causes angina and ECG changes.

However, as image acquisition was completed, typical severe angina developed (grade 10 on a scale of 1 to 10), radiating across the chest into the left arm and jaw, the worst the patient had ever experienced.
crying out for relief. Intravenous aminophylline and metoprolol with sublingual nitroglycerine reduced angina within a minute, and it disappeared within 3 minutes. LV ejection fraction from ECG gated perfusion images was 75% at rest, increasing to 78% during regadenoson stress with severe angina but no ECG changes.

In this case, severe angina during high coronary flow with normal ECG and contractile function was not due to myocardial ischemia. Regadenoson is primarily an adenosine A2 receptor agonist that mediates hyperemia, as documented by this patient’s high stress perfusion. However, regadenoson binds weakly to adenosine A1 receptors that mediate cardiac pain. Severe chest pain during high coronary perfusion without ischemia suggests abnormal adenosine A1 receptor function mediating cardiac pain because of an excess density of A1 receptors or unusual regadenoson binding to A1 receptors in addition to A2 receptors. Some degree of angina is not uncommon with vasodilator stress despite high coronary flow, likely reflecting adenosine A1 receptor-mediated chest pain.

**CONCEPT 9. MYOCARDIAL PERFUSION IMAGING IN WOMEN: OVERDIAGNOSIS.** The 63-year-old woman in Figure 9 had a non-ST-segment elevation myocardial infarction with chest pain and enzyme rise. Risk factors included family history of CAD, elevated lipoprotein(a) to 114 mg/dl, total cholesterol of 197 mg/dl, triglycerides of 72 mg/dl, LDL subtype A of 120 mg/dl, and HDL of 63 mg/dl on no lipid medications with normal blood pressure and glucose. An angiogram confirmed an occluded first diagonal branch off the LAD, a reported moderate to severe stenosis of LAD, and a non-ST-segment elevation of 60%. Elective PCI was recommended despite the patient being asymptomatic after the acute event.

On PET imaging conducted for a second opinion, excellent global coronary flow capacity ruled out other significant stenosis or diffuse flow-limiting or microvascular disease, particularly in the LAD distribution. There was a small, mild to moderate stress defect in the distribution of the occluded diagonal branch. Collateral flow was sufficient to prevent steal, with perfusion well above ischemic levels consistent with absence of symptoms, contravening...
the prior recommended elective PCI. Comprehensive personalized quantitative PET imaging prevented unnecessary procedures, with no further events or symptoms through 7-year follow-up on atorvastatin.

**CONCEPT 10. MYOCARDIAL PERFUSION IMAGING IN WOMEN: FAILURE TO EXCLUDE CAD VERSUS MICROVASCULAR DISEASE.** The 43-year-old asymptomatic woman in Figure 10 had a routine positive treadmill test that led to positive SPECT perfusion stress, interpreted as anterior ischemia, for which an angiogram was recommended by her cardiologist despite the absence of risk factors. PET conducted for a second opinion showed normal stress relative uptake images (Figure 10A) and a coronary flow capacity map (Figure 10B) with high stress flow (Figure 10C) of 3.02 ml/min/g and CFR (Figure 10D) of 4.09, which contravened the previously recommended coronary angiogram. Positive stress tests or SPECT perfusion imaging may lead to unnecessary angiograms, the results of which are normal, thereby raising the question of microvascular disease known to cause relative SPECT stress defects that cannot be differentiated from attenuation artifacts.

**CONCEPT 11. IMPROVED CORONARY FLOW CAPACITY WITH OPTIMAL RISK FACTOR CONTROL.** The 76-year-old asymptomatic woman in Figure 11 had dense coronary calcification with serial normal relative uptake images 5 years apart on a research protocol with optimal risk factor control (at target weight, regular exercise, attainment of lipids, blood pressure, and glucose goals). Stress perfusion and coronary flow capacity map showed quantitative improvement beyond variability of repeated serial measurements.

**CONCEPT 12. QUALITY STANDARDS FOR QUANTITATIVE PERFUSION IMAGING OF MICROVASCULAR, DIFFUSE EPICARDIAL, AND OBSTRUCTIVE CAD.** Each of the quantitative perfusion images shows the range of focal, diffuse epicardial and microvascular disease encountered routinely in clinical practice. Each case also illustrates a principle of coronary physiology essential for quantitative perfusion imaging to guide personalized management of CAD. We use PET as the best established method, supported by a large literature and by our long experience with it (10,11,21,38–42). Other technology, such as magnetic resonance imaging, may provide comparable data, but whatever technology or protocols are used must

**FIGURE 11** Improved Coronary Flow Capacity With Optimal Risk Factor Control

Anterior and septal views of stress perfusion and coronary flow capacity at baseline and 5-year follow-up showing increased percentage of left ventricle in high flow ranges. Abbreviations as in Figure 3.
meets simple yet demanding quality tests to quantify perfusion for clinical decisions.

The following simple standard performance test combines measurement accuracy for rest perfusion and stress perfusion (in ml/min/g) and CFR for correct clinical decisions. It is based on long-standing human and experimental coronary physiology literature even before clinical PET, on clinical invasive measurements (4), and on our published data (10,11,21,38–42), now expanded to more than 4,500 clinical and protocol studies, including serial repeat studies for reproducibility in more than 300 volunteers.

Any technology or protocol for quantitative perfusion imaging as demonstrated here must prove its capacity to routinely measure the following in the clinic: 1) rest perfusion of 0.2 ml/min/g in transmural scar in at least 5 patients, to test low perfusion accuracy; and 2) regional and global CFR of 4.0 and stress perfusion of 3.0 ml/min/g on 2 sequential rest-stress PET perfusion studies in the same subject with ±12% variability for at least 15 young healthy volunteers with no risk factors, no smoking, no obesity, and no measureable blood caffeine levels (43). We emphasize that the goal is accurate quantitative coronary physiology, not technology that is simply the tool used to measure physiology.

SUMMARY

The term microvascular dysfunction or disease is imprecise and frequently incorrect, because microvascular dysfunction is most commonly associated with focal or diffuse epicardial coronary atherosclerosis and heterogeneous endothelial dysfunction in women compared with the focal stenosis that develops earlier in life in men. Compared with men, different manifestations of CAD in women are associated with their smaller coronary arteries, higher coronary blood flow, and higher endothelial shear stress, which have major effects on endothelial function and resistance to coronary atherosclerosis.

In women in particular, complex interactions of focal stenosis, diffuse epicardial coronary narrowing, related endothelial shear stress, and microvascular dysfunction often make definitive diagnosis and management difficult by use of standard noninvasive or invasive physiological and anatomic technologies. However, quantitative rest-stress myocardial perfusion, best documented by PET, combined with clinical circumstances can usually differentiate the complex interacting pathophysiologies of microvascular, diffuse epicardial, and focal stenotic CAD to guide vigorous risk factor management and procedures for large areas of severe low ischemic stress flow by quantitative PET.

REFERENCES


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