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Myocardial Perfusion Imaging for the Evaluation of Ischemic Heart Disease in Women

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Abstract

Purpose of the Review To review the value of myocardial blood flow and coronary flow reserve (CFR) measurements, as assessed by positron emission tomography (PET), in women with suspected ischemic heart disease.

Recent Findings CFR is a noninvasive measure of coronary vasomotor function that integrates the hemodynamic effects of epicardial coronary stenosis, diffuse atherosclerosis, and microvascular dysfunction on myocardial tissue perfusion and has emerged as an imaging marker of cardiovascular risk, independently of the degree of obstructive coronary artery disease (CAD).

Summary Normal coronary arteries or nonobstructive CAD is a common finding in women with ischemia. Thus, assessment of risk based on a coronary stenosis approach may fail in women. PET is able to quantify absolute myocardial blood flow and CFR which may help to elucidate other mechanisms involved such as microvascular dysfunction and diffuse epicardial CAD, responsible for the disease in women.

Keywords Women · Ischemic heart disease · Myocardial perfusion imaging · Coronary flow reserve · Cardiac risk

Introduction

In the multimodality era, selecting an initial strategy for evaluation of ischemic heart disease (IHD) is often challenging [1]. Patient pre-test probability of coronary artery disease (CAD), the sensitivity and specificity of each method and the prevalence of obstructive CAD, among other factors, play a central role in such decision. The American College of Cardiology has recently summarized appropriate use criteria for the utilization of noninvasive and invasive methods guiding the physicians to detect and assess cardiac risk in symptomatic patients [2]. In general, exercise stress test is recommended for low risk patients with interpretable electrocardiogram (ECG) and cardiac imaging for those with intermediate probability for CAD [2]. There is much debate in the literature over the best strategies for evaluation of CAD in symptomatic women [3]. This is mainly related to the fact that women exhibit normal coronary arteries or nonobstructive CAD in up to 50% of the cases. Detecting IHD in women in the setting of nonobstructive CAD is of clinical relevance because this population has an increased risk of cardiac events [4, 5•]. A complex interaction between focal stenosis, diffuse epicardial coronary narrowing, and microvascular dysfunction are often responsible for their symptoms and cardiac risk [6, 7•]. Therefore, traditional evaluation based on the physiological consequences of a significant epicardial coronary stenosis may fail in women [7•, 8, 9•]. In most of the cases, radionuclide myocardial perfusion imaging only identifies the

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coronary vascular territories subtended by severe epicardial stenosis. In consequence, this technique may underestimate the diagnosis of the disease in women with the frequent clinical scenario of nonobstructive CAD [9•].

Coronary flow reserve (CFR) is a noninvasive measure of coronary vasomotor function that integrates the hemodynamic effects of epicardial coronary stenosis, diffuse atherosclerosis, and microvascular dysfunction on myocardial tissue perfusion, and is considered a more sensitive indicator of myocardial ischemia than the relative assessment of myocardial perfusion [9•]. Recently, CFR has emerged as an imaging marker of cardiovascular risk both in men and women, independently of the degree of obstruction of the epicardial coronary arteries [10•]. Therefore, CFR measurements could be considered as a powerful aid in the diagnosis of ischemia in patients without obstructive epicardial CAD [11].

The present review will focus on the role of CFR measurements as a marker of risk in women with IHD.

Assessment of Coronary Flow Reserve

CFR can be measured noninvasively by positron emission tomography (PET), transthoracic Doppler echocardiography and cardiac magnetic resonance imaging [11]. PET is an imaging technology that allows the assessment of relative and absolute myocardial perfusion as well as left ventricular function at rest and during stress [12, 13]. Dynamic PET imaging is the most validated technique that affords robust and reproducible measurements of absolute myocardial blood flow (MBF) in ml/min/g at rest and during pharmacological stress, which allows the calculation of CFR as the ratio between MBF at stress and MBF at rest [14, 15]. CFR estimated by PET can be used for diagnosis of myocardial ischemia, even in absence of obstructive CAD [9•]. The ability of PET of combining relative myocardial perfusion with absolute MBF measurements improves the diagnostic and prognostic value of the technique, making PET the method of election to reveal IHD in women due to the high prevalence of coronary microvascular dysfunction and nonobstructive CAD observed in this population [3]. Other technical advantages for PET imaging that increases its diagnostic accuracy are the following: (a) routine attenuation correction (decreasing false positives results due to breast attenuation in women or by adipose tissue in those with elevated body mass index), (b) a uniform independent resolution, (c) a low radiation dose for the patient using short-lived radiopharmaceuticals as compared to conventional myocardial perfusion SPECT imaging, and (d) a short time of the myocardial perfusion rest/stress study completion [12, 13, 16].

In order to quantify MBF by PET, the most utilized radiotracers are Rubidium-82 (Rb-82) and N-13 Ammonia [15]. In brief, MBF values are estimated by image-derived time-activity curves of the flow tracer from the arterial blood pool and myocardial regions and fit to a mathematic model representing the tracer kinetics over time. The rate of myocardial tracer uptake affords an estimate of absolute MBF [17]. Several software packages are commercially available to calculate absolute MBF at rest and during stress. Thresholds of MBF at rest in healthy individuals may vary between 0.4 and 1.2 ml/g/min, and hyperemic MBF between 1.8 and 2.3 ml/g/min (depending on the PET blood flow tracer). Consequently, normal individuals are expected to have a CFR larger than 2 [18]. Because CFR is a ratio, factors affecting MBF at rest or during hyperemia such as age, sex, cardiac oxygen consumption, endothelial dysfunction, and coronary risk factors, among others, may influence its calculation [14, 15]. While an abnormal CFR increases the likelihood of significant obstructive CAD, it cannot differentiate significant epicardial stenosis from nonobstructive disease, diffuse atherosclerosis or microvascular dysfunction [19]. Clinical interpretation of MBFs and CFR requires understanding range values and the physiological and anatomical variables that can affect these measurements [14, 18].

In selected cases, computed tomography (CT) coronary angiography and coronary artery calcium (CAC) score calculations can be performed in combination with myocardial perfusion PET imaging (either in hybrid PET/CT scanners or by sequential PET/CT protocols) [3, 11]. This noninvasive approach allows integrating epicardial anatomy with the MBF and CFR measurements, thereby increasing the sensitivity of the diagnosis of CAD [20–22]. The interaction between epicardial CAD and noninvasive MBF estimates is discussed below.

Diagnostic Accuracy and Risk Stratification of Women by PET Imaging: Comparison with Single Photon Emission Computed Tomography Myocardial Perfusion Imaging

The American Society of Nuclear Cardiology, in the Consensus Statement about myocardial perfusion in women for the evaluation of stable IHD, recommends the exercise treadmill as the initial diagnostic test for symptomatic intermediate risk women who are capable of performing exercise and have an interpretable resting ECG [3].

Because of the unique characteristics mentioned before, PET is an imaging modality of particular interest for the diagnosis of ischemia in women where cardiac imaging has clinical indication. A meta-analysis of the cardiac PET literature demonstrated high sensitivity (92%) and specificity (85%) for the detection of CAD [23, 24]. Two meta-analyses comparing Rb-82 and N-13 Ammonia PET data with single photon emission computed tomography (SPECT) demonstrated a higher

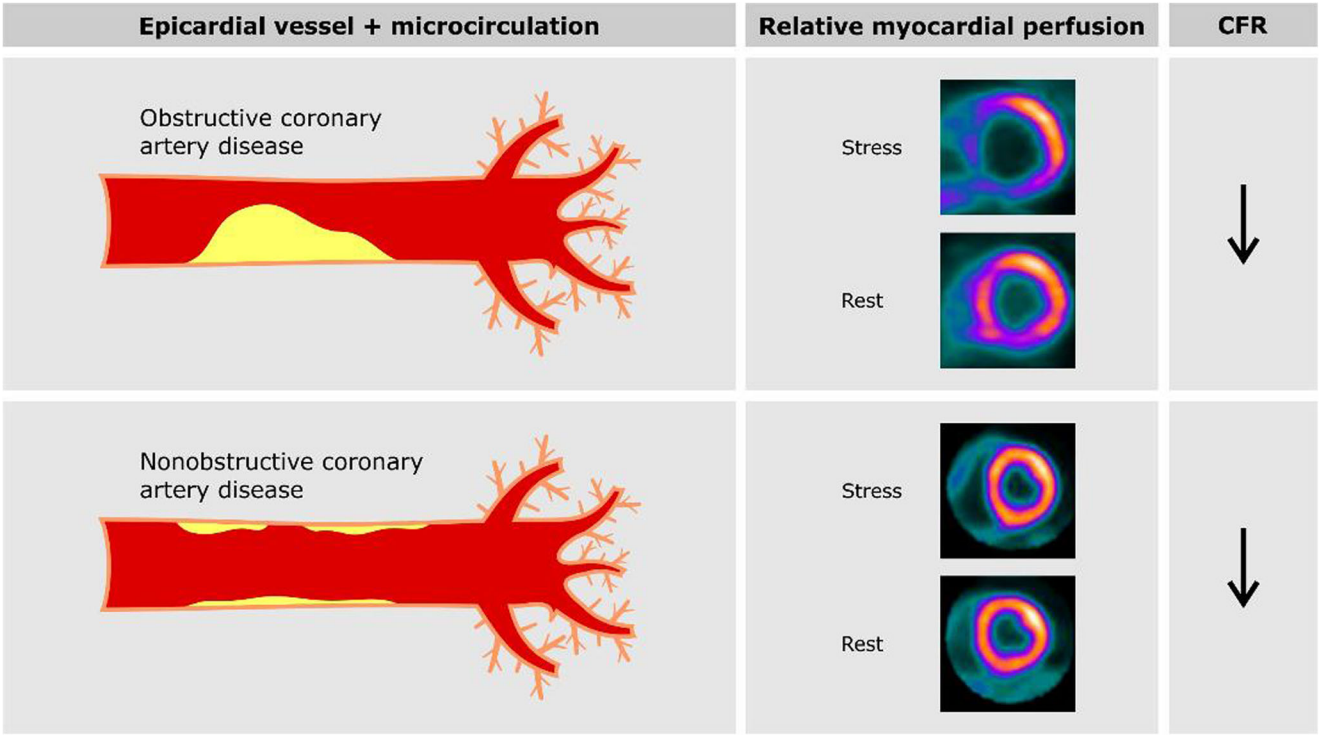


Fig. 1 This figure depicts the differences between detection of myocardial ischemia in patients with and without obstructive coronary artery disease. Patients with significant obstructive coronary artery disease exhibit stress myocardial perfusion defects and an impaired coronary flow reserve. In contrast, patients with nonobstructive coronary artery disease often present normal relative myocardial perfusion images while a reduced CFR uncovers myocardial ischemia. CFR coronary flow reserve

diagnostic accuracy for the first technique, with a 3–5% increase in specificity and 4–5% increase in sensitivity [25, 26].

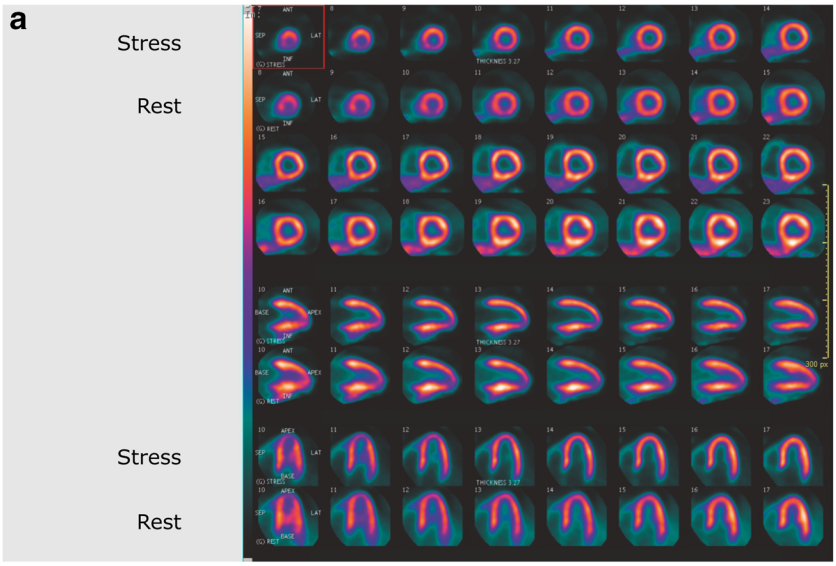
The higher diagnostic accuracy of PET in comparison with conventional SPECT was confirmed for women and men (88% vs 67%, $p = 0.009$) [27]. The evidence in more than 7000 patients indicates that a normal PET scan is associated with an excellent prognosis [28]. A normal scan indicates low risk (< 1% annual cardiac event rate) while an abnormal scan indicates worsening prognosis (> 4.2% annual event rate). Importantly, it has found a graded increase in risk of CAD events with more severe and extensive perfusion defects [28]. In sex-specific analysis of the PET Prognosis Multicenter Registry, Kay et al. [29] have shown that stress myocardial perfusion with Rb-82 provided significant and clinically meaningful risk stratification in both genders. In fact, there was a proportional relationship between CAD mortality and stress Rb-82 PET myocardial perfusion defect size and extent, as assessed by percentage of myocardium involved. The unadjusted 5-year CAD mortality ranged from 0.9 to 12.9% for women ($p < 0.0001$) and from 1.5 to 17.4% for men ($p < 0.0001$) for 0% to ≥ 15% abnormal myocardium at stress. Of note, in this study, the percentage of abnormal stress myocardium was independently predictive of CAD mortality in both men and women. The finding of sex equity in risk stratification with Rb-82 PET is in agreement with evidence from SPECT and other stress imaging modalities [29]. Furthermore, assessment of PET myocardial perfusion imaging in conjunction with left ventricular function by gated imaging stratifies risk and adds important prognostic information in women and men [29, 30]. The combined measurements of resting left ventricular ejection fraction and stress myocardial perfusion defects, as assessed by percentage of abnormal myocardium, were strong predictors of CAD mortality in both genders [29].

Prognostic Value of Microvascular Dysfunction in Women: Quantification of MBF and CFR by PET

Women symptomatic for chest pain undergoing coronary angiography frequently exhibit less obstructive epicardial CAD than men, nevertheless they have a worse prognosis [7•]. In fact, women with stable angina and nonobstructive CAD are three times more likely to experience a cardiac event within the first year of cardiac catheterization than symptomatic men with nonobstructive CAD [5•]. In the absence of focal epicardial stenosis, the presence of diffuse epicardial coronary narrowing, impaired endothelial shear stress and microvascular dysfunction are often responsible for symptoms and the IHD in women [4, 8]. Therefore, noninvasive testing predominantly based on identifying

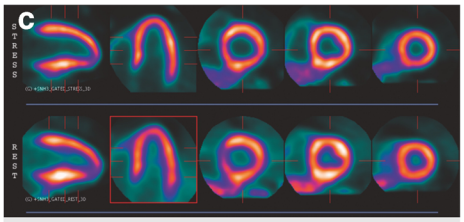
obstructive CAD can underestimate the diagnosis of the disease in females [31]. PET with the distinct advantage of quantifying absolute MBF and CFR can identify more accurately women at risk even in absence of significant obstructive CAD (Fig. 1). Previous observational PET studies have demonstrated alterations in the coronary microcirculation (by quantification of MBF and CFR) in women with risk factors for CAD and without stress-regional myocardial perfusion defects [32, 33]. Such patients appear to be at increased risk for cardiac events, since CFR has been recently considered a noninvasive biomarker of cardiac risk [34–36]. An impaired CFR (< 2) has been associated with a 3.4-fold increase and CFR less than 1.5 with a 5.6-fold increase hazard in the risk of CAD death as compared to a preserved CFR (≥ 2) [37]. Of note, CFR represents a noninvasive continuous marker of cardiovascular risk: the cardiac event rate for those patients with CFR < 2 increases exponentially as CFR decreases [9•]. Furthermore, noninvasive assessment of CFR by PET provides incremental risk stratification beyond measures of clinical risk, including estimations of left ventricular systolic function and the extent and severity of myocardial ischemia (by semiquantitative analysis), resulting in an incremental risk reclassification of patients with known or suspected CAD [35–37]. PET-CFR and MBF measurements also provide incremental risk stratification over coronary artery calcifications (reflecting atherosclerotic burden). In one study that included 901 symptomatic patients with normal rest/stress PET perfusion images and without obstructive CAD, CFR and not CAC provided significant incremental risk stratification over clinical risk score for prediction of major adverse cardiac events (MACE). Interestingly, in this study, the rate of MACE increased in the presence of impaired CFR even among patients with CAC of zero [38]. Likewise, we found in a small cohort of 22 women with signs and symptoms of ischemia and without obstructive CAD by coronary angiography, abnormalities in the microcirculatory function in absence of CAC as assessed by hybrid PET/CT imaging. Of note, 23% of the women presented cardiac events at 2 years of follow-up and one woman had a cardiovascular hard event. Furthermore, 32% of the patients had persistent chest pain, a common finding in women with ischemia and nonobstructive epicardial CAD (unpublished data). Together, these findings suggest that there is complementary information between epicardial atherosclerotic burden and coronary microcirculatory function. In symptomatic patients with nonobstructive CAD, CFR can be considered a marker of disease activity (as opposed to disease burden) reflecting mainly endothelial and smooth muscle dysfunction [12, 38]. It has also been described the association between CFR, angiographic epicardial CAD, and cardiovascular outcomes [10•]. The authors included 329 patients referred for coronary angiography after stress PET and followed by a median of 3.1 years. They found a modest correlation between CFR and CAD prognostic index and both parameters were independently associated with cardiac events. Patients with low CFR experienced rates of events similar to those of subjects with high angiographic scores, and those with low CFR who underwent coronary revascularization by coronary artery bypass grafting experienced event rates comparable to those with preserved CFR (independently of revascularization). Thus, global CFR confers risk independently of luminal angiographic severity. This concept has recently been explored in symptomatic women and men without overt CAD. Murthy et al. [39] investigated 405 men and 813 women referred for evaluation of suspected CAD and without myocardial perfusion defects at rest and during stress by PET. MACE were assessed over a median follow-up of 1.3 years. Coronary microvascular dysfunction (CFR < 2) was a powerful predictor of MACE and resulted in favorable net reclassification improvement after adjustment for clinical risk and left ventricular function. Importantly, these findings were regardless of gender. Thus, coronary microvascular dysfunction as assessed by PET uncovers men and women at increased clinical risk. More evidence has been recently reported by Taqueti et al. [40] in a cohort of 324 consecutive patients referred for invasive coronary angiography following rest/stress Rb-82 PET and a median follow-up of 3 years. They have shown that women have a significantly higher risk of adverse cardiac events despite of a lower burden of obstructive epicardial CAD (adjusted hazard ratio, 2.05; 95% confidence interval, 1.05–4.02; $p = 0.03$). This excess in cardiovascular risk in women was independently associated with severely impaired CFR (< 1.6) in absence of obstructive CAD by invasive coronary angiography. The authors conclude that a very low CFR may be a critical link to understanding the "hidden biological risk" of IHD in women despite the lower burden for obstructive epicardial CAD as compared to men [41]. These findings are of clinical importance because, as described before, women with IHD have often nonobstructive CAD, and absolute quantification of MBF may allow reclassifying their risk, especially in the setting of normal relative myocardial perfusion (i.e., no flow-limiting CAD) [13] (Fig. 2). This "hidden phenotype" of cardiac risk (low CFR and nonobstructive CAD) is not exclusive for women with IHD, other special populations like patients with diabetes, metabolic syndrome, chronic kidney disease, heart failure with preserved ejection fraction, among others, exhibit this pattern which may represent a novel target for cardiac risk reduction [9•].

So far, all the evidence described comes from single-center studies. Randomized and multicenter trials are desirable to standardize the routine clinical indication of MBF and CFR measurements in women with IHD, in particular for those without focal epicardial CAD. Development of focused sex-specific diagnostic strategies is of clinical relevance to reduce morbidity and mortality in women [7•, 31].



b

Coronary Territory	Rest MBF (ml/g/min)	Stress MBF (ml/g/min)	CFR (Stress/Rest)
LAD	0.78	1.38	1.77
LCx	0.84	1.35	1.60
RCA	0.80	1.26	1.57



	Stress (G)	Rest (G)
ESV	38 ml	35 ml
EDV	95 ml	82 ml
EF	60 %	57 %

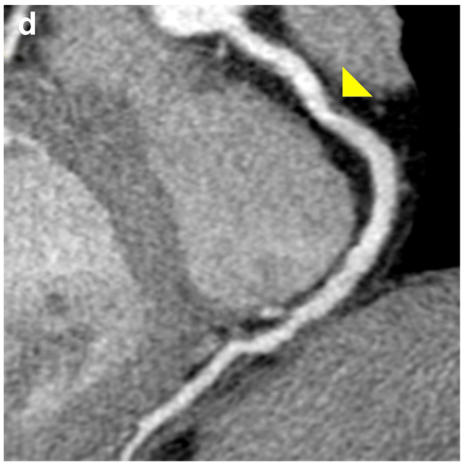


Fig. 2 A 63-year-old woman with stable angina. She has history of hypertension, diabetes, and hypercholesterolemia. **a** PET short-axis, long-vertical and long-horizontal cuts at rest and during dipyridamole-induced hyperemia show a preserved relative myocardial perfusion. **b** Quantification of myocardial blood flow by N-13 Ammonia shows a reduced CFR in the three vascular territories. **c** PET-gated images at rest shows a preserved left ventricular ejection fraction with an adequate increase during stress. **d** Cardiac computed tomography reveals nonobstructive coronary artery disease. Abbreviations: PET positron emission tomography, LAD left anterior descending, LCx left circumflex, RCA right coronary artery, MBF myocardial blood flow, CFR coronary flow reserve

Conclusion

Compelling evidence underscores the importance of the adverse prognosis of coronary microvascular dysfunction in absence of obstructive CAD in women with IHD. In this context, measurements of absolute MBF and CFR by PET imaging give helpful diagnostic information regarding the function of the coronary microcirculation. Observational PET studies have demonstrated that quantification of MBF and CFR can identify and predict cardiac risk in women with IHD, even in absence of overt CAD.

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Compliance with Ethical Standards

Conflict of Interest Roxana Campisi and Fernando D. Marengo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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