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Assessment of myocardial blood flow and coronary flow reserve with positron emission tomography in ischemic heart disease: current state and future directions

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Abstract Positron emission tomography (PET) is a versatile imaging technology that allows assessment of myocardial perfusion, both at a spatially relative scale and also in absolute terms, thereby enabling noninvasive evaluation of myocardial blood flow (MBF) and coronary flow reserve (CFR). Assessment of MBF using FDA-approved PET isotopes, such as ^{82}Rb and ^{13}N-ammonia, has been well validated, and several software packages are currently available, thereby allowing for MBF evaluation to be incorporated into routine workflow in contemporary nuclear laboratories. Incremental diagnostic and prognostic information provided with the knowledge of MBF has the potential for widespread applications. Improving the ability to identify the true burden of obstructive epicardial coronary stenoses and allowing for noninvasive assessment of coronary micro circulatory function can be achieved with MBF assessment. On the other hand, attenuated CFR has been shown to predict adverse cardiovascular prognosis in a variety of clinical settings and patient subgroups. With expanding applications of MBF, this tool promises to provide unique insight into the integrity of the entire coronary vascular bed beyond what is currently available with relative perfusion assessment. This review intends to provide an in-depth discussion of technical and clinical aspects of MBF assessment with PET as it relates to patients with ischemic heart disease.

Keywords Myocardial blood flow · Positron emission tomography · Coronary artery disease · Coronary flow reserve

Abbreviations

CAD	Coronary artery disease
CFR	Coronary flow reserve
MBF	Myocardial blood flow
MPI	Myocardial perfusion imaging
PET	Positron emission tomography

Introduction

Positron emission tomography (PET) is emerging as an indispensable tool in contemporary nuclear cardiology laboratories and is no longer considered merely a research tool. Utilization of PET for cardiac indications is rapidly growing, facilitated by wider availability of radiotracers and accessibility of PET scanners [1]. In addition, this promising technology has the advantage of improving efficiency and throughput in laboratories routinely incorporating PET in their workflow [2]. Moreover, preferential use of PET for myocardial perfusion imaging (MPI) has been advocated, when available, as an approach towards enhancing patients' safety with radionuclide imaging due to the shorter half-life of PET radiotracers [3, 4]. As such, PET technology is uniquely positioned as a versatile noninvasive modality with the potential for different cardiac applications [5].

There are many advantages of cardiac PET including the evaluation of relative and absolute myocardial perfusion for detection of flow-limiting coronary artery disease (CAD) [6]

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with superior image quality and diagnostic accuracy compared to conventional single-photon emission computed tomography (SPCET) [7, 8]. It also affords the ability to perform quantitative assessment of myocardial blood flow (MBF) in absolute units (ml/min/g). Furthermore, cardiac PET is reliable for evaluation of myocardial viability [9] and is emerging as a promising tool for imaging of atherosclerosis, arterial wall inflammation, and detection of cardiac involvement in systemic diseases, such as sarcoidosis [10, 11].

The interest in noninvasive quantification of MBF is not new and has long been sought as a means for better understanding of coronary physiology [12]. The ability to measure MBF, both at rest and under hyperemic conditions, and thereby determining coronary flow reserve (CFR), allows for systematic evaluation of the integrity of the entire coronary vascular bed, beyond the ordinary assessment of obstructive lesions in epicardial vessels. The feasibility of performing flow quantification in clinical settings using ^{82}Rb, ^{13}N-ammonia, and ^{15}O-water and the reproducibility of such measurements allow for easier incorporation of MBF in routine practice [13]. This enhanced ability to combine relative MPI with MBF measurements is arguably a major advantage of cardiac PET, further enhancing the diagnostic [14] and prognostic value of cardiac PET MPI [15–17].

The aim of this review is to focus on the basic concepts, technical considerations, and clinical applications of noninvasive assessment of MBF/CFR using PET. The review will mainly focus on the applications of noninvasive MBF/CFR in patients with CAD and ischemic heart disease. Other applications will be reviewed in other papers in this issue.

Technical considerations

Tracers

The high spatial and temporal resolutions, along with the low radiation dosimetry, all make PET an ideal test for noninvasive evaluation of MBF and CFR. Currently, three PET radiotracers are available for MBF evaluation: ^{15}O-water, ^{13}N-ammonia, and ^{82}Rb. Both ^{15}O-water and ^{13}N-ammonia have been validated against radioactive microsphere in animal model [18, 19], whereas ^{82}Rb has been mainly validated in comparison to ^{13}N-ammonia [20, 21].

^{15}O-water is considered the gold standard for flow evaluation owing to its ideal properties. It is inert, freely diffusible and has a linear relation to MBF with first pass extraction of tissue approaching unity [19, 22]. In addition, its short half-life and low radiation allow for repetitive measurements in relatively short time [23]. However, low signal-to-noise ratio resulting from free diffusion of the tracer between target tissue and background leads to inadequate image quality for relative perfusion assessment. Additionally, ^{15}O-water requires onsite cyclotron and has a short half-life, thereby limiting its use in routine clinical practice [19, 22, 23].

In comparison, the two widely used tracers (^{13}N-ammonia and ^{82}Rb) have a nonlinear relation to MBF with a roll-off phenomenon. The first-pass retention fraction of ^{13}N-ammonia and ^{82}Rb at rest is 85 and 65%, respectively, with declining rates at higher blood flow [1, 24, 25]. ^{13}N-ammonia diffuses through capillary and interstitial tissue to the myocytes, and a portion of the retained tracer diffuses back to the blood, while another portion remains trapped in the metabolic glutamine pool [26]. The superb quality of the relative perfusion imaging of ^{13}N-ammonia allows for the evaluation of ischemia, and the relatively longer half-life, almost 10 min, allows for potential use of exercise as a stress modality in addition to vasodilators. However, its use is hurdled by the need for onsite cyclotron for production.

^{82}Rb is a potassium analogue and therefore requires an active Na-K ATPase transporter and is generator-produced, making it more attractive for widespread clinical use [27]. It has similar diagnostic accuracy to ^{13}N-ammonia [28], but its exceptionally short half-life (76 s) allows for performance of stress and rest imaging in almost identical situations [29]. The characteristics of the different radiotracers are summarized in Table 1.

Imaging techniques

MBF is quantified from the dynamic PET images through application of mathematical models. Dynamic imaging is a rapid image acquisition which usually starts 10 s before the injection of the radioactive tracer to track the initial transport

Table 1 Summary of basic characteristics of available PET radiotracers

Characteristic	Rubidium^{82}	N^{13}-ammonia	O^{15}-water
Supplied	Generator	Cyclotron	Cyclotron
Half-life	76 s	9:96 min	2.09 min
Uptake mechanism	Active extraction	Active extraction	Freely diffusible
Positron range in water	1.6 mm	0.28 mm	0.5 mm
Image quality	Very good	Excellent	Uninterpretable
Radiotracer uptake characteristics	Adequate	Very good	Excellent

and the exchange of the tracer between the blood and myocardium. Dynamic images are performed at rest and maximum hyperemia to quantify the MBF and subsequently calculate the CFR by dividing the stress MBF over the rest MBF.

Yoshida et al. validated a simplified two-tissue compartment model for quantification of MBF by ^{13}N-ammonia and ^{82}Rb accounting for transport kinetics of each tracer [28]. This model has also proven feasible in humans using ^{82}Rb [30]. However, unlike ^{13}N-ammonia, ^{82}Rb has no radioactive metabolite and it does not bind to plasma protein, and therefore, a one-tissue compartment model maybe utilized for ^{82}Rb-derived MBF assessments. One-tissue compartment model has been validated against ^{13}N-ammonia in human subjects by Lortie et al. [21] and has been further validated in two additional studies against ^{15}O-water [31, 32]. Currently, ^{82}Rb is the most widely used tracer in clinical practice since due to its ease of delivery being generator-produced. There are several mathematical extraction models available for MBF quantification with ^{82}Rb, among which the one-tissue compartment model is the simplest and most widely used. Most of these models result in slightly different estimates of rest and peak MBF; however, these differences in CFR are relatively small (Fig. 1a–c). In addition, correlations between CFR and stress MBF measures made with the same input function were high, regardless of extraction model used as was shown in a large cohort of patients (n = 2783) referred for PET MPI [33]. Furthermore, the same investigators found that the prognostic value with CFR, and to a much lesser extent stress MBF, was persistent regardless of the utilized extraction model.

It is worth mentioning that there is a linear relationship between the resting MBF and rate pressure product (RPP) [34]. Since the CFR is the ratio of stress MBF to rest MBF, it is essential to correct resting MBF to the baseline RPP to avoid erroneous low CFR. The correction is calculated according to the formula Corrected MBF = MBF × (mean RPP at rest in PET study/ideal RPP) [35].

Correlation between CFR and FFR

Fractional flow reserve (FFR) is an invasive measure of hemodynamic significance of epicardial coronary stenoses. FFR represents the ratio between intracoronary pressure distal to a luminal stenosis under hyperemic conditions and central aortic pressure. Lesions with FFR values <0.8 or <0.75 were associated with inducible ischemia and, therefore, are considered hemodynamically significant [36, 37]. A strategy of FFR-guided coronary interventions was superior to angiography-guided interventions and to medical therapy alone in terms of preventing future cardiovascular events [38, 39], and use of FFR in the invasive catheterization laboratory for evaluation of indeterminate coronary lesions is currently recommended [40, 41].

In comparison to FFR, CFR measures global flow augmentation in response to vasodilation, whereas FFR provides lesion-specific measure of severity as a function of change in coronary pressure. In addition, FFR is independent of heart rate or blood pressure, unlike CFR which is corrected for both parameters [42]. Comparative studies showed good correlation between CFR and FFR, mainly among patients with single-vessel CAD [43]. Yet, discrepancies between CFR and FFR do exist, and they point to the differences in pathophysiology invoked with focal stenotic lesions in epicardial vessels (leading to an abnormal FFR) and that seen in diffuse disease of large conduit vessels or impaired microcirculatory function (resulting in attenuated CFR) [44]. Combining CFR and FFR not only helps advance our understanding of coronary physiology but also provides an opportunity to improve patients' outcomes through identifying novel targets for medical therapies and interventional options [45].

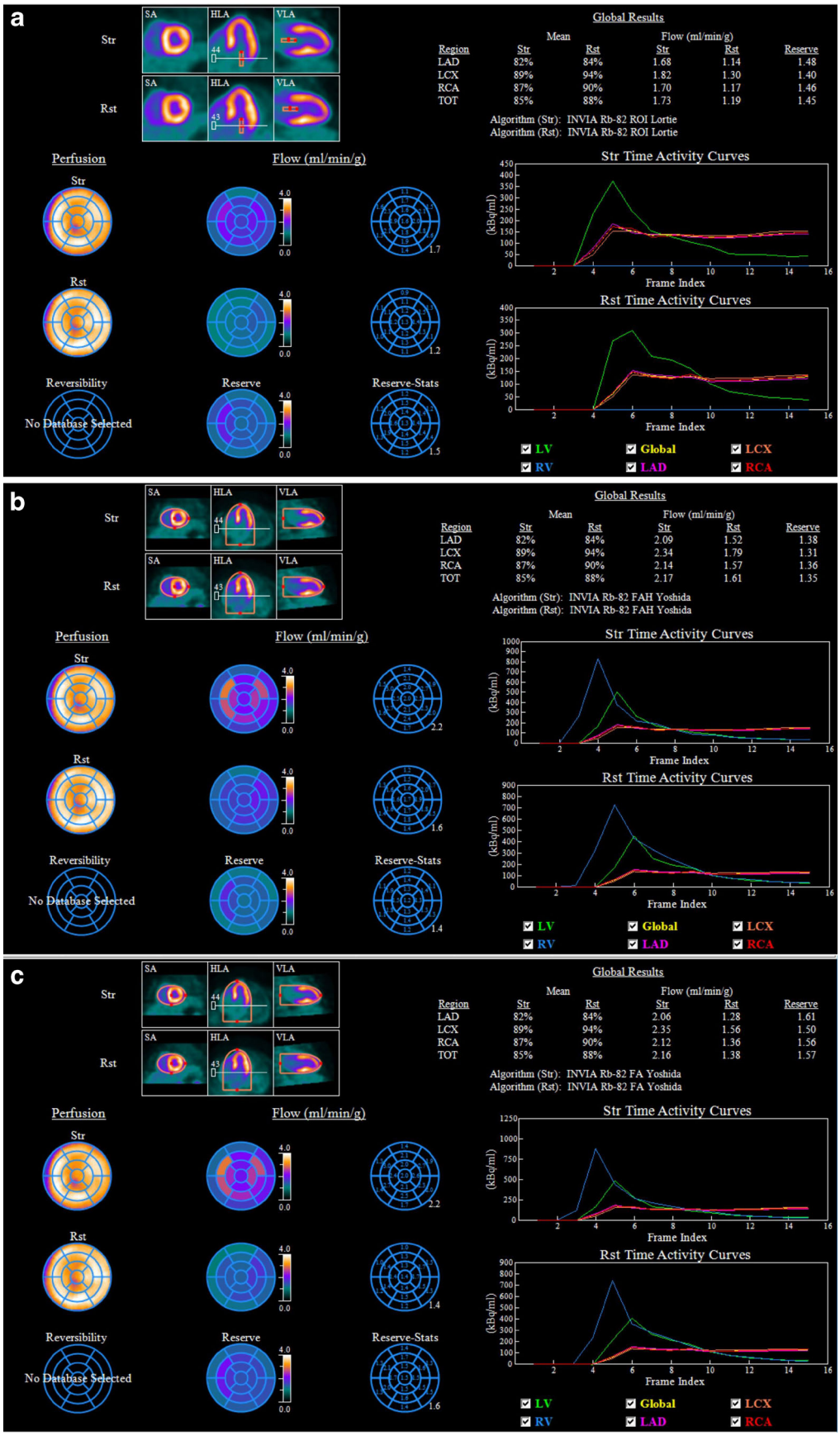
Clinical applications

Noninvasive CFR has been shown to be useful in multiple clinical scenarios. It aids in the diagnosis of diffuse CAD and adds incremental prognostic value to readily available clinical information.

Diagnosis of multivessel or left main CAD

Even though a large body of evidence has accumulated over the years to support the role of single-photon emission computed tomography (SPECT) perfusion imaging in risk stratification and guiding revascularization in patients with suspected CAD [46, 47], the concern about underestimating the true severity of CAD remains the Achilles' heel of relative myocardial perfusion assessment [48]. This is predominantly attributed to the potential for missing perfusion abnormalities in situations with "balanced" flow reduction in epicardial vessels, such as severe left main stenosis or the presence of hemodynamically significant stenoses in all three coronary territories [49]. In a study of 101 patients with angiographic left main CAD (≥50% stenosis) and no prior myocardial infarction or coronary revascularization that underwent SPECT MPI, only 56% of patients had a high-risk scan. Combining visual perfusion data and nonperfusion variables, especially transient ischemic dilation, 83% of patients were identified as high risk [50].

Detection of left main coronary disease may be improved with the incorporation of nonperfusion and gated functional findings to qualitative assessment of relative perfusion scans [50]. Additionally, determining "left ventricular ejection fraction reserve"—which is feasible during PET MPI since assessment of left ventricular systolic function occurs at peak stress—provides incremental diagnostic advantage for detecting left main or three-vessel disease [51]. Overall, PET


a
Str
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Global Results
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Flow (ml/min/g)
Region Str Rst Str Rst Reserve
LAD 82% 84% 1.68 1.14 1.48
LCX 89% 94% 1.82 1.30 1.40
RCA 87% 90% 1.70 1.17 1.46
TOT 85% 88% 1.73 1.19 1.45
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Flow (ml/min/g)
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Frame Index
Reversibility
Reserve
Reserve-Stats
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LV
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Mean
Flow (ml/min/g)
Region Str Rst Str Rst Reserve
LAD 82% 84% 2.09 1.52 1.38
LCX 89% 94% 2.34 1.79 1.31
RCA 87% 90% 2.14 1.57 1.36
TOT 85% 88% 2.17 1.61 1.35
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LAD 82% 84% 2.06 1.28 1.61
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TOT 85% 88% 2.16 1.38 1.57
Algorithm (Str): INVIA Rb-82 FA Yoshida
Algorithm (Rst): INVIA Rb-82 FA Yoshida

◀ **Fig. 1** Panel **a** shows myocardial blood flow and flow reserve with a one-compartment model of 82Rb kinetics and a nonlinear extraction function while panels **b** and **c** show myocardial blood flow and flow reserve estimates from different two-compartment models. Please note that myocardial blood flow showed significant differences between the different methods while the flow reserve showed smaller difference

appears to have superior sensitivity in detecting multivessel CAD when compared to SPECT [52].

The potential complementary role of MBF to relative MPI in detecting multivessel CAD was examined in a cohort of 120 patients without prior CAD who underwent ^{82}Rb PET MPI and subsequent invasive coronary angiography [14]. The majority of patients (88%) with multivessel CAD had reduced CFR (<2). Moreover, CFR added incremental predictive power to relative MPI in detecting presence of multivessel CAD. Thus, preserved CFR predicts a low likelihood of multivessel CAD. On the other hand, while there is higher likelihood of multivessel CAD when CFR is impaired, not all patients with low CFR have three-vessel CAD; other causes of low CFR need to be entertained including endothelial dysfunction and diffuse coronary disease.

These data suggest that global CFR quantification has the potential to improve diagnostic accuracy for detection of multivessel CAD when combined with relative MPI, especially given the limited utility of SPECT in this patient population [53]. Similar data were also seen using ^{15}O-water among 104 patients with intermediate pretest likelihood of CAD, where the absolute quantification of MBF was found to have superior diagnostic accuracy compared to relative perfusion analysis in detecting patients with multivessel disease using invasive coronary angiography as a gold standard [54].

Similarly, Naya et al. found that normal CFR excluded high-risk CAD in patients who underwent both rest/stress ^{82}Rb PET MPI and subsequent invasive coronary angiography [55]. In this investigation of 290 patients without prior history of CAD, a preserved CFR (>1.93) with normal or mildly-moderately abnormal MPI (<10% of left ventricular mass) excluded the presence of multivessel or left main coronary disease with a negative predictive value of 97%.

Detection of microvascular dysfunction and subclinical CAD

Qualitative or semiquantitative MPI identifies stress-induced perfusion defects, which indicates the presence of flow-limiting coronary stenoses. If only relative perfusion assessment is used, the case in patients undergoing SPECT MPI, the opportunity to diagnose early atherosclerosis is commonly missed. Studies have shown that subclinical CAD, manifesting as coronary artery calcification or endothelial dysfunction, is prevalent among patients with normal perfusion patterns [15, 56]. Attenuation of hyperemic MBF is seen among patients with cardiovascular risk factors [57, 58], and CFR measurements (using ^{13}N-ammonia PET) were lower among patients without overt CAD who had higher coronary heart disease risk [59]. Hence, CFR can be considered as a noninvasive marker of coronary microvascular health.

Such patients with impaired CFR appear to be at increased risk for adverse cardiovascular events [15–17], even in the setting of angiographically normal epicardial coronary arteries [60] (see "Prognosis and risk stratification" section). This ability to uncover CAD in its subclinical stages afforded by noninvasive CFR assessment helps identify subsets of patients at risk for future cardiac events who may benefit from early institution of aggressive risk factor control [61]. Furthermore, response to preventative medications can be assessed on serial measurements over time, demonstrating favorable changes in CFR with proper interventions [62, 63].

Differentiating diffuse epicardial CAD from microvascular dysfunction

Combining available noninvasive parameters of left ventricular perfusion (relative perfusion pattern, presence of transient cavity dilation, hyperemic MBF and CFR) and function (gated wall motion analysis at peak stress and LVEF reserve) allows enhanced ability to differentiate between various phenotypes of CAD [64]. Patients with focal stenoses (or severe diffuse disease) affecting multiple epicardial vessels and those with pronounced global microvascular disease may not be adequately differentiated on the basis of relative perfusion analysis alone; stress MBF and CFR play a complementary role (Fig. 2). However, in many different clinical situations, assessment of coronary anatomy by either coronary calcium scoring, CT angiography [65], or invasive angiography is necessary to make this distinction.

Prognosis and risk stratification

Several studies have established the prognostic utility of PET-determined MBF and CFR measurements in predicting future major adverse cardiac events (MACE) and their ability to offer incremental risk stratification beyond traditional markers of risk (Table 2) [15–17, 60, 66–74].

Herzog et al. were the first to demonstrate abnormal CFR (<2) using ^{13}N-ammonia PET to be independently predictive of future cardiac death, nonfatal MI, late revascularization, or cardiac hospitalization (HR 2.9, 95%CI [1.2–6.6], $p < 0.05$) [15]. Furthermore, impaired CFR provided further risk stratification among patients with normal qualitative regional perfusion within the first 3 years after the test, with lower event rates seen among patients with normal CFR (6.3 vs 1.4%, $p < 0.05$). These findings were the first steps on the road towards establishing the prognostic value of MBF and CFR [75].

Consequently, the prognostic utility of CFR using ^{82}Rb was evaluated prospectively [17]. In this study by Ziadi

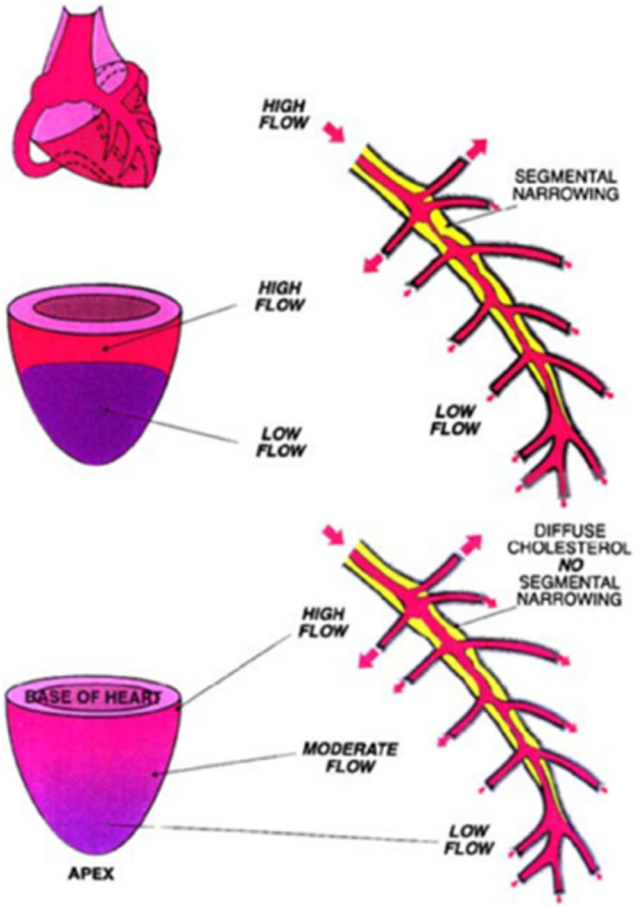

Fig. 2 Schematic representation of differences in myocardial perfusion between patients with severe focal stenosis and patients with severe diffuse disease. Reproduced with permission from Al-Mallah et al. Patients with severe focal stenosis demonstrate a perfusion defect by relative perfusion assessment and also have attenuated MBF/CFR in the territory of the affected vessel (*top*) while patients with severe diffuse disease may have normal (or near normal with base-apex gradient described by Gould et al.) relative perfusion pattern but will have global reduction in CFR (*bottom*)

et al., abnormal CFR was shown to be a predictor of cardiac death and myocardial infarction, regardless of the status of relative perfusion scan. Incidence of MACE was lower in patients with normal CFR relative to those with low CFR, whether MPI was normal (3.8 vs 9%, $p = 0.003$), or abnormal (9 vs 24%, $p < 0.001$). Figure 3 summarizes prognostic utility of impaired CFR in predicting MACE.

Similar findings to those shown were further corroborated by data in patients with chronic kidney disease [68], diabetes [69], and end-stage renal disease on dialysis [73]; in patients referred for coronary revascularization [71]; and in women [70]. Moreover, reclassification indexes have specifically demonstrated the ability of noninvasive markers of coronary vascular dysfunction to reclassify patients across the continuum of cardiovascular risk [68, 69, 73]. In addition, recent data suggested that peak MBF may also be used in the risk stratification of patients undergoing PET MPI [76].

PET MBF/CFR assessment may also be of help in other clinical scenarios. Taqueti et al. found that elevation of cardiac troponin among 761 patients without overt flow-limiting CAD to be associated with impaired global CFR, where a CFR <2 was associated with a 2-fold increase in the risk of having abnormal troponin level (HR 2.2, 95%CI [1.4–3.5], $p = 0.0015$) [72]. Additionally, CFR modified the effect of troponin elevation on the study endpoint of cardiac death, nonfatal MI, and late revascularization. Among patients with elevated troponin, the event rate was significantly lower for those with intact CFR compared to those with impaired CFR (0.9 vs 7.4%, $p = 0.046$). In fact, event rates were not statistically different between those with or without troponin elevation as long as CFR was ≥2 (0.9 vs 1.7%, $p = 0.58$).

Moreover, data on the role of PET-determined flow measurements and gender-based differences in cardiovascular risk are particularly enlightening. In a cohort of consecutive patients ($n = 324$) referred for invasive coronary angiography following rest/stress ^{82}Rb PET and a median follow up of 3 years, women were found to have a significantly higher risk of adverse cardiac events in spite of a lower burden of obstructive disease on invasive coronary angiography (HR 2.05, 95%CI [1.05–4.02], $p = 0.03$) [70]. Interestingly, this observed excess risk in women was no longer seen after adjusting for CFR (HR 1.81, 95%CI [0.91–3.59], $p = 0.10$), and only women with attenuated CFR (<1.6) demonstrated higher rates of cardiac events. As such, the authors concluded that CFR was responsible for a significant proportion of cardiovascular risk observed in women and that impaired CFR needs to be addressed as "hidden biological" risk factor for future cardiac events, which may represent a novel target for cardiac risk reduction.

MBF/CFR in special populations

In addition, CFR and MBF have been shown to provide incremental risk stratification in patient subgroups with increased cardiac risk. Table 3 summarizes the prognostic utility of CFR in such special populations.

Diabetes

The prognostic value of MPI in diabetics is well documented [77]. In addition, Murthy and colleagues studied 2783 consecutive patients (1172 diabetics and 1611 nondiabetics) who underwent quantification of CFR and were followed up for a median of 1.4 years, Impaired CFR was associated with an adjusted 3.2- and 4.9-fold increase in the rate of cardiac death for diabetics and nondiabetics, respectively ($p = 0.0004$). It is important to note that diabetic patients without known CAD with impaired CFR experienced an annualized rate of cardiac death comparable to that for nondiabetic patients with known CAD (2.8 vs 2.0%; $p = 0.33$). Conversely, diabetics without

Table 2 Utility of noninvasive MBF and CFR quantification for prediction of major adverse cardiac events (MACE)

Study (publication year)	Radiotracer	Flow measurement (threshold)	Study population	End point	Findings
Herzog et al. (2009) [15]	^{13}N-NH$_3$	CFR (abnormal if <2)	229 patients with clinically indicated MPI and complete FU (median 5.5 years), 66% with prior CAD, 18% with DM. Single center. Retrospective study	Cardiac death Nonfatal MI Hospitalization Late revasc.	Abnormal CFR was predictor of CD (3.1 vs 0.5%, $p < 0.05$) and MACE (6.3 vs 1.4%, $p < 0.05$)
Ziadi et al. (2011) [17]	^{82}Rb	CFR (abnormal if <2)	677 patients with clinically indicated MPI and complete FU (median 1.1 years), 58% with prior CAD, 29% with DM. Single center. Prospective study	Cardiac death Nonfatal MI Hospitalization Late revasc.	Abnormal CFR was predictor of CD/MI (2 vs 1.3%, $p = 0.03$) and MACE (9 vs 3.8%, $p < 0.05$) with normal MPI. CD/MI (11.4 vs 1.1%, $p = 0.05$) and MACE (24 vs 9%, $p < 0.05$) with abnormal MPI
Fukushima et al. (2011) [66]	^{82}Rb	CFR (abnormal if <2.1) Absolute MBF (abnormal if <1.9 ml/min/g)	224 patients with clinically indicated MPI and complete FU (median 1 year), 39% with prior CAD, 34% with DM. Single center. Retrospective study	Cardiac death Nonfatal MI Heart failure hosp. Invasive angiography	CFR is an independent predictor of MACE (HR 2.9, 95%CI [1.3–6.7], $p < 0.05$)
Murthy et al. (2011) [67]	^{82}Rb	CFR tertiles	2783 patients with clinically indicated MPI and complete FU (median 1.4 years), 42% with prior CAD, 36% with DM. Single center. Retrospective study	Cardiac death	Impaired CFR is predictive of CD; middle vs highest CFR tertile (HR 3.4, 95%CI [1.5–7.7], $p = 0.003$); lowest vs highest CFR tertile (HR 5.6, 95%CI [2.5–12.4], $p < 0.0001$)
Farhad et al. (2013) [16]	^{82}Rb	Tertiles of stress MBF and CFR	318 patients with clinically indicated MPI and complete FU (median 1.7 years), 35% with prior CAD, 34% with DM. Single center. Retrospective study	Cardiac death Nonfatal MI Late revasc. Cardiac hospitalization	Stress MBF, but not CFR, added incremental predictive value for MACE beyond SDS

CAD coronary artery disease, *CD* cardiac death, *CFR* coronary flow reserve, *HR* hazard ratio, *MACE* major adverse cardiac events, *MBF* myocardial blood flow, *SDS* summed difference score

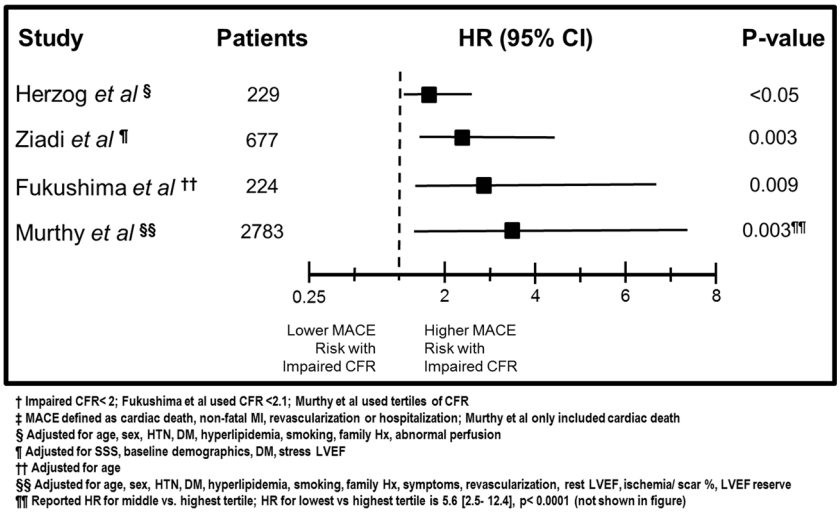

Fig. 3 Impaired CFR as a predictor of major adverse cardiac events (MACE). Risk of MACE with impaired CFR in published literature. Cutoff points for CFR and definitions are included

known CAD and preserved CFR had very low annualized cardiac mortality, which was similar to patients without known CAD or diabetes mellitus and normal stress perfusion and systolic function (0.3 vs 0.5%; $p = 0.65$).

Chronic kidney disease

Since cardiovascular mortality is the main cause of death in this population, accurate risk stratification is essential [78, 79]. SPECT is an important modality to assess these patients. However, there are still patients who experience event despite being labeled a low risk by SPECT. A study of end-stage renal disease (ESRD) clinically referred for myocardial perfusion PET imaging found that the addition of global CFR in ESRD patient resulted in risk reclassification in 27% of patients. Thus, global CFR may provide independent and incremental risk stratification for all-cause and cardiovascular mortality in this patient population [73].

Women

The multicenter PET registry demonstrated in 6037 women and men that stress Rb-82 PET provides significant and clinically meaningful effective risk stratification of women and men, supporting this modality as an alternative to comparative imaging modalities [80]. Rb-82 PET findings were particularly helpful at identifying high-risk, older women. Furthermore, among patients who undergo PET MPI with CFR assessment and eventually undergo coronary angiography, women have higher pretest likelihood, a significantly lower burden of obstructive CAD in comparison with men and higher event rate (adjusted hazard ratio, 2.05; 95% confidence interval, 1.05–4.02; $p = 0.03$). This higher excess cardiovascular risk in women was independently associated with impaired CFR [70]. Thus, CFR may be a helpful marker in women with nonobstructive disease who have higher event rate despite low-risk angiograms.

Cardiac allograft vasculopathy

Alterations in coronary vasomotor function have been described previously in cardiac transplant recipients and blunted vasodilator capacity, assessed using invasive Doppler flow measurements, predicted development of cardiac allograft vasculopathy, and cardiac death in post-transplant patients [81]. Similarly, PET-determined CFR demonstrated an inverse correlation with plaque volume as assessed using intravascular ultrasound in a group of 27 heart transplant recipients followed longitudinally post-transplant [82].

MBF/CFR in the guidelines

Given its clinical value, the most recent PET guidelines from the American Society of Nuclear Cardiology suggested that quantitative absolute MBF measurements with PET appear most helpful [9] in patients without known prior history of cardiac disease who present with symptoms suspicious for myocardial ischemia, patients with known CAD, in whom more specific physiological assessment is desired, patients with suspected multivessel CAD or microvascular dysfunction, and patients with suspected transplant vasculopathy. In contrast, there are particular patients for whom reporting hyperemic blood flow or flow reserve *may not add diagnostic value* or can be ambiguous or misleading, including patients post-CABG who can have diffuse reduction on MBF despite patent grafts, patients with large transmural infarcts, and patients with advanced severe chronic renal dysfunction and/or severe LV dysfunction. While the diagnostic value of CFR in these patients is not clear, the prognostic value

Table 3 Prognostic role of CFR in special patient populations

Study (publication year)	Subgroup	CFR threshold	Study population	End point	Findings
Murthy et al. (2012) [68, 69]	Chronic kidney disease	CFR <1.5	866 patients with CKD, clinically indicated MPI and complete FU (median 1.3 years), 55% with prior CAD, 45% with DM. Single center. Retrospective study	Cardiac death	Adjusted CD with low CFR is higher (HR 2.1, 95%CI [1.3–3.5], $p < 0.05$). Improved reclassification (NRI 0.142)
Murthy et al. (2012) [68, 69]	Diabetes	CFR <1.6	2783 patients with clinically indicated MPI and complete FU (median 1.4 years), 42% with prior CAD, 42% with DM. Single center. Retrospective study	Cardiac death	Higher CD in patients with CFR <1.6 (both DM+, DM−). DM+ patients without CAD had similar cardiac mortality to DM− patients with CAD (2.8 vs 2%, $p = 0.33$)
Taqueti et al. (2015) [71, 72]	Elevated cardiac troponin	CFR <2	761 patients with MPI for elevated troponin and complete FU (median 2.8 years), no prior CAD, 32% with DM. Single center. Retrospective study	Cardiac death Nonfatal MI Late revasc.	Impaired CFR is associated with elevated troponin. CFR modifies effect of troponin on endpoint
Taqueti et al. (2015) [71, 72]	Patients with subsequent coronary angiography/ revascularization	CFR <1.6	329 consecutive patients with clinically indicated MPI and subsequent angiogram, complete FU (median 3.1 years), 33% prior CAD, 40% with DM. Single center. Retrospective study	All-cause mortality Cardiac death Nonfatal MI Heart failure hosp.	Impaired CFR was a predictor of events independent of CAD. No difference in event rate among patients with high CFR, regardless of revascularization mode. The lowest event rate among those with low CFR was seen with CABG as mode of revascularization.
Shah et al. (2016) [73]	ESRD	Unit change in CFR	168 dialysis-dependent ESRD patients with clinically indicated MPI and complete FU (median 3 years), 43% prior CVD, 61% with DM. Single center. Retrospective study	All-cause mortality Cardiac death	CFR independently predicted all-cause mortality (HR 0.01, 95%CI [0.01–0.14], $p < 0.001$) and cardiac death (HR 0.01, 95%CI [0.01–0.15], $p = 0.002$)[a]
Taqueti et al. (2017) [70]	Women/men referred to coronary angiography	Multiple (2, 1.6, and 1.2)	329 patients (43% F) with MPI referred for angiography and complete FU (median 3 years), 33% prior CAD, 40% with DM. Single center. Retrospective study	Cardiac death Nonfatal MI HF hospitalization	Lower CFR was predictive of MACE after adjusting for angiographic severity of disease (HR 1.69, 95%CI [1.04–2.76], $p = 0.03$)

CAD coronary artery disease, *CD* cardiac death, *CFR* coronary flow reserve, *CKD* chronic kidney disease, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *HR* hazard ratio

[a] Log-transformed hazard ratio per 0.5 increases in CFR

of CFR in these patients has been demonstrated before [73, 83].

Conclusion

The increasing availability of PET MPI in many contemporary nuclear cardiology practices has provided us with robust noninvasive tools to evaluate the integrity of the coronary tree. In particular, MBF and CFR lend themselves as sources of valuable diagnostic and prognostic information in patients with known or suspected CAD. Current literature supports a strong role for MBF and CFR in improving the yield of MPI studies beyond relative perfusion analysis. Additionally, the ability to routinely assess MBF and CFR provides unique insight about coronary physiology and helps offer new and novel therapeutic alternatives to patients at risk for or with established CAD.

Compliance with ethical standards

Conflict of interest Firas Al Badarin is a speaker of Lantheus Medical Imaging.

Ahmed Aljizeeri declares that he has no conflict of interest.

Fatimah Almasoudi declares that she has no conflict of interest.

Mouaz Al-Mallah declares that he has no conflict of interest.

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