

# The role of PET quantification in cardiovascular imaging

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**Abstract** Positron emission tomography (PET) has several clinical applications in cardiovascular imaging. Myocardial perfusion imaging with PET allows accurate global and regional measurements of myocardial perfusion, myocardial blood flow and function at stress and rest in a single examination. Simultaneous assessment of function and perfusion by PET with quantitative software is currently routine practice. Combination of ejection fraction reserve with perfusion information may improve the identification of severe coronary artery disease. Myocardial viability can be estimated by quantitative comparison of fluorine-18 fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) and rest perfusion imaging. Quantitative myocardial blood flow and myocardial flow reserve measurements are becoming routinely included in clinical assessments due to the enhanced dynamic imaging capabilities of the latest PET/CT scanners. Absolute flow measurements allow evaluation of

coronary microvascular dysfunction and provide additional prognostic and diagnostic information in coronary disease. Quantitative clinical software tools for computing myocardial blood flow from kinetic PET data in an automated and rapid fashion have been developed for use with several radiotracers:  $^{13}\text{N}$ -ammonia,  $^{15}\text{O}$ -water and  $^{82}\text{Rb}$ . The level of agreement between various software methods available for such analyses is excellent. Relative quantification of  $^{82}\text{Rb}$  PET myocardial perfusion tracer uptake, based on comparisons with normal perfusion databases, demonstrates high performance for the detection of obstructive coronary disease. Computerized analysis of myocardial perfusion at stress and rest reduces the variability of the assessment compared with visual analysis. New tracers, such as  $^{18}\text{F}$ -flurpiridaz may allow further improvements in myocardial blood flow quantification and disease detection. PET quantification can be enhanced by precise coregistration with CT angiography. In emerging clinical applications, the potential to identify vulnerable plaques by quantification of atherosclerotic plaque uptake of  $^{18}\text{F}$ FDG and  $^{18}\text{F}$ -sodium fluoride tracers in carotids, aorta and coronary arteries has been demonstrated.

Color figures online at <http://link.springer.com/article/10.1007/s40336-014-0070-2>.

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## Introduction

Positron emission tomography (PET) allows accurate measurement of relative myocardial hypoperfusion, absolute myocardial blood flow and contractile function at stress and rest, in a single scanning session, allowing diagnosis of coronary artery disease (CAD) [1] and

evaluation of long-term prognosis [2]. PET is considered the gold standard for measuring myocardial blood flow [3, 4] and it is also an important tool in assessment of the viability of the myocardium [5]. New cardiac PET imaging techniques are being developed to investigate plaque inflammation in the cardiovascular system [6]. The multitude of information that can be obtained from PET images necessitates the use of advanced quantitative techniques. Some parameters, such as absolute myocardial blood flow measurements, cannot be obtained by visual analysis alone. In addition, quantitative or semi-quantitative analysis of PET data, compared with visual interpretation, allows reduced inter- and intra-observer variability.

Software quantification methods for cardiac PET have evolved recently, and they allow rapid and largely automated extraction of various physiological parameters. Typically, a PET quantification software package allows integrated analysis of static, gated and dynamic datasets in a single session, facilitating inclusion of all quantification results in the clinical review. These various image datasets can be obtained from a single PET acquisition of the list-mode data—this is typically possible with the latest scanners. Static images are used to define the extent and severity of regional hypoperfusion at stress and rest. Viability imaging performed with a glucose analog—fluorine-18 fludeoxyglucose ( $^{18}\text{F}$ -FDG)—makes it possible to define the amount of myocardial scar (no uptake of  $^{18}\text{F}$ -FDG or perfusion tracer) and mismatch (uptake of  $^{18}\text{F}$ -FDG but no myocardial perfusion uptake). Gated PET images allow automated computation of left ventricular volumes, ejection fraction (EF) and other functional parameters, such as diastolic function. Finally, dynamic reconstruction of the data allows extraction of the time-activity curves from the blood pool and myocardium, and computation of absolute regional myocardial blood flow in ml/g/min at stress and rest and consequently myocardial flow reserve (MFR)—defined as the ratio of myocardial blood flow at stress and rest. These computations can be obtained within seconds, with minimal user interaction.

This review describes state-of-the-art PET quantification techniques, focusing particularly on applications currently in clinical use and summarizing their role in cardiovascular disease detection and management.

### Relative quantification of perfusion and ischemia

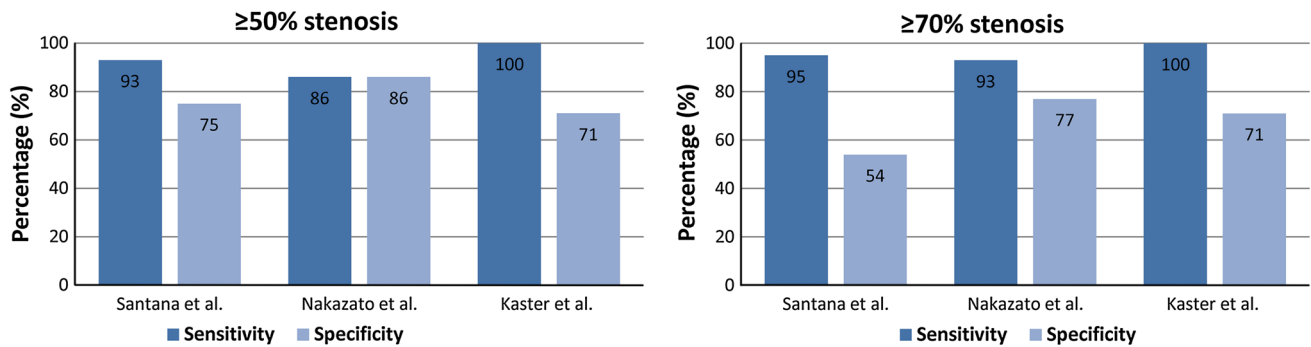
Positron emission tomography myocardial perfusion is recommended for diagnosis or risk stratification of patients who have non-diagnostic results on other imaging tests [7]. Cardiac PET/CT, through analysis of perfusion changes between stress and rest (ischemia) and comparison of perfusion studies with normal limits derived from images

of subjects with low likelihood of disease and normal perfusion findings, allows detection of obstructive CAD [8–10]. The relative quantification technique based on normal limits is widely used in single-photon emission computed tomography (SPECT) and has been adapted to PET imaging. Typically, an integrated score combining hypoperfusion severity and extent is derived using the polar map concept. Quantitative analysis of relative hypoperfusion has been shown to rival the accuracy of expert readers in the diagnosis of CAD by SPECT in large studies [11]. The key advantage of such quantitative analysis is its improved reproducibility compared with visual assessment [12].

In previous reports of cardiac PET diagnostic performance for CAD detection, the average sensitivity for detecting at least one coronary artery with significant stenosis was 89 % (range 83–100 %), and the average specificity was 89 % (range 73–100 %) [13], even though it is accepted that there is no 1-to-1 relationship between obstructive disease and ischemic stenosis [14]. Most of the early PET perfusion studies were obtained with stand-alone 2D PET scanners rather than with integrated PET/CT systems and utilized visual scoring of perfusion defects in a 17-segment model, which is analogous to SPECT perfusion scoring. Although automated relative quantification was initially developed for SPECT imaging, several recent studies report the use and performance of this method in PET/CT imaging. To date, three studies have reported  $^{82}\text{Rb}$  PET/CT diagnostic performance with quantitative analysis based on comparison with normal limits (Fig. 1) [9, 10, 15]. Kaster et al. [15] achieved perfect 100 % sensitivity for the detection of obstructive CAD when transient ischemic dilation results were integrated with perfusion results. Figure 2 shows examples of perfusion images and quantification results based on normal limits and the direct stress-rest comparison for  $^{82}\text{Rb}$ . Although separate normal limits are typically required for males and females in SPECT quantification, relative PET perfusion quantification methods use combined-gender normal limits; this is possible owing to the accurate CT attenuation correction available on PET/CT scanners [9, 10, 15]. It should be noted that due to variable characteristics of normal perfusion distribution for different tracers, for example reduced isotope concentration in the lateral wall on  $^{13}\text{N}$ -ammonia imaging [16], relative analysis of PET perfusion will require isotope-specific normal limits.

### Quantification of heart contractile function

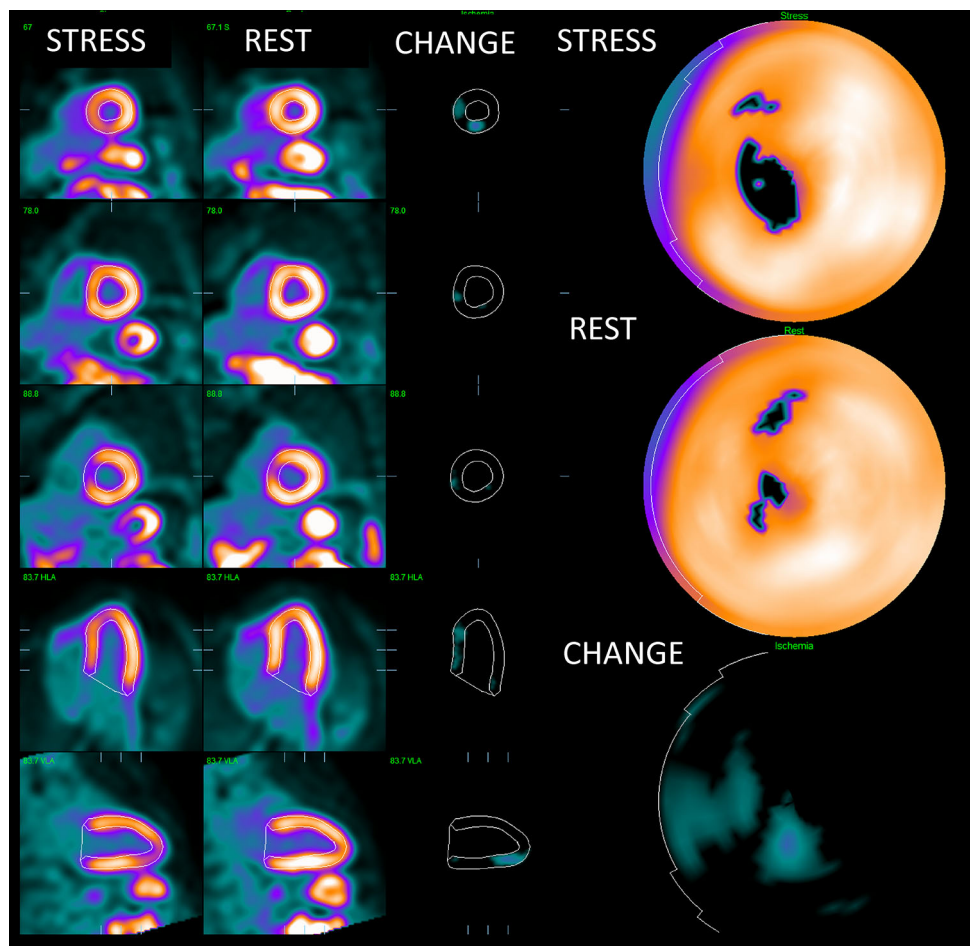
The quantitative analysis of myocardial contractile function has been extensively validated for myocardial SPECT [17], but such quantitative methods can be also applied to PET. A



**Fig. 1** Relative quantification accuracy. Results from three recent manuscripts by Santana et al. [9] ( $n = 76$ ), Nakazato et al. [10] ( $n = 167$ ), and Kaster et al. [15] ( $n = 110$ ), validating the use of

relative quantification with normal limits in myocardial perfusion PET studies for detection of coronary artery disease by three separate software tools (color figure online)

**Fig. 2** An example of relative quantification for myocardial perfusion PET. Co-registered stress and rest images with contours are shown on the left. The change images (CHANGE) in the middle show the ischemic region in the septal wall. Polar maps (right) show corresponding significant defect at stress. The quantification results were stress total perfusion deficit (TPD) = 10 %, rest TPD = 4 %, ischemia by change analysis = 5 %. Ejection fraction was normal. This patient had significant >70 % lesion in the proximal left anterior descending territory as confirmed by angiographic examination (color figure online)



typical contemporary protocol for PET imaging includes list-mode data acquisition at stress and rest. This allows retrospective reformatting and re-binning with cardiac gating and subsequently derivation of gated data. An excellent correlation of MRI and PET  $^{18}\text{F}$ -FDG imaging techniques for quantification of EF as well as systolic and diastolic volumes has been reported [18, 19]. Compared with SPECT images, PET images exhibit higher resolution and better definition of

the mitral valve plane due to accurate attenuation correction [10]. This allows more accurate detection of the myocardium and improved tracking of the mitral valve plane. High PET image resolution and  $^{18}\text{F}$ -FDG uptake in the right ventricle may also allow quantification of right ventricular function by PET [20].

PET contractile function analysis can be used in conjunction with perfusion analysis to improve patient

risk stratification. In a study including 1441 patients, stress EF measured from  $^{82}\text{Rb}$  PET provided an independent and incremental prognostic value compared with perfusion measures [21]. Functional measurements from PET may also include phase and dyssynchrony analysis. Although these techniques have not been extensively validated with PET, measurements of histogram bandwidth and phase standard deviation from  $^{15}\text{O}$ -water and  $^{18}\text{F}$ -FDG-PET scans were found to be very well correlated with SPECT [22]. Recently, in an analysis of 486 patients, left ventricular mechanical dyssynchrony was found to be an independent predictor of all-cause mortality in ischemic cardiomyopathy [23]. Furthermore, an analysis of dyssynchrony obtained from gated  $^{18}\text{F}$ -FDG-PET imaging was shown to identify responders to cardiac resynchronization therapy [24]. Another quantitative parameter related to contractile function, first described and validated for SPECT, is the transient ischemic dilation of the left ventricle. This measure has been found to improve the identification of patients with severe CAD by SPECT [25]. Rischpler et al. [26] demonstrated the use of the transient ischemic dilation ratio in  $^{82}\text{Rb}$  PET imaging as an independent predictor of mortality.

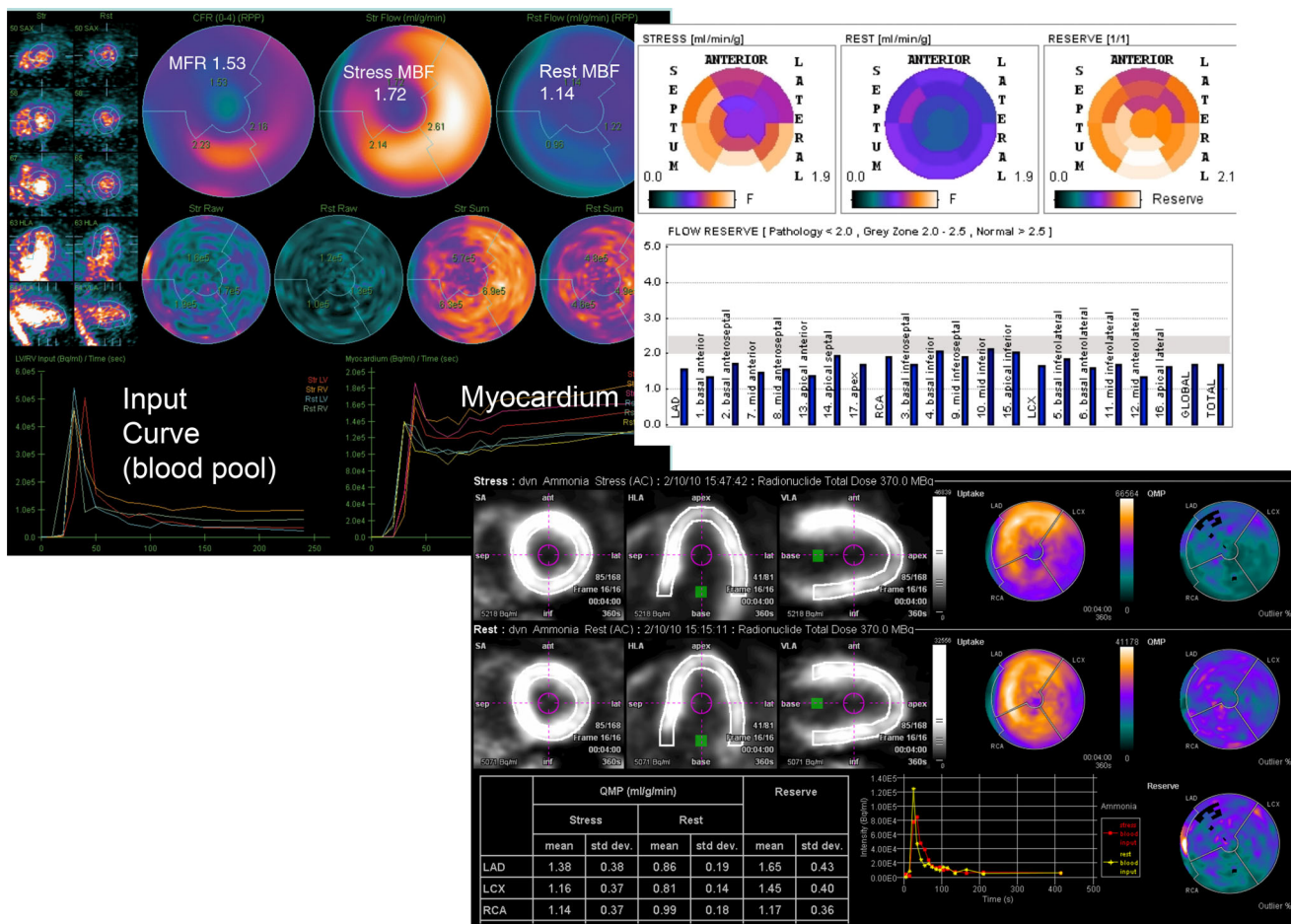
A key advantage of PET perfusion imaging over SPECT perfusion imaging (wherein images are typically acquired at least 15 min after injection) is the possibility of performing immediate imaging of heart contractile function during stress. Thus, with PET imaging, it is possible to assess the true peak stress function. In contrast, with SPECT, given that scans are typically performed 15–45 min after stress, only post-ischemic changes due to myocardial stunning can be observed. Therefore, PET imaging allows quantification of the EF reserve—defined as the change in EF between stress and rest. In 510 patients, Dorbala et al. [27] showed that the EF reserve obtained with  $^{82}\text{Rb}$  PET imaging was the only independent predictor of left main and triple-vessel disease. A very high negative predictive value (97 %) for excluding severe left main and triple-vessel disease was demonstrated if the EF reserve was higher than 5 %. The same group has also shown that left ventricular EF reserve has incremental prognostic value over clinical variables and resting EF obtained from  $^{82}\text{Rb}$  PET [28]. Recently, the use of EF reserve quantification was evaluated for the regadenoson stress agent and  $^{82}\text{Rb}$  PET imaging. The mean left ventricular EF reserve was shown to be significantly higher in patients with normal myocardial perfusion imaging results ( $6.5 \pm 5.4$  %) than in those with mild ( $4.3 \pm 5.1$  %,  $p = 0.03$ ) and moderate-to-severe reversible defects ( $-0.2 \pm 8.4$  %,  $p = 0.001$ ). Also, the mean left ventricular EF reserve was significantly higher in patients with a low likelihood of CAD ( $7.2 \pm 4.5$  %,  $p < 0.0001$ ) [29].

### Myocardial blood flow and myocardial flow reserve quantification

Myocardial blood flow and MFR measurements are becoming routinely included in clinical assessments due to the enhanced dynamic imaging capabilities of the latest PET/CT scanners. PET allows non-invasive measurements in units of milliliters of blood per minute, per gram of myocardium. These absolute measurements have been validated against invasive flow estimates obtained by microsphere techniques in numerous studies. PET is currently the most validated imaging technique for the quantitative evaluation of myocardial blood flow.

New software tools are now becoming available that will allow more widespread quantification of myocardial blood flow at stress and rest. These tools include kinetic models and algorithms for computing myocardial blood flow and MFR from kinetic PET data obtained using different radiotracers:  $^{13}\text{N}$  ammonia [30, 31],  $^{15}\text{O}$ -water [32] and  $^{82}\text{Rb}$  [33]. Current software tools utilizing these algorithms allow completely automated or semi-automated measurements of stress and rest flow. Figure 3 shows screenshots of the three implementations of recent clinical software for computation of myocardial blood flow and MFR. The input function is typically obtained from the first-pass blood pool analysis in the left ventricle or left atrium. Segmentation of the left ventricle and determination of the blood pool region can be accomplished automatically. Patient motion correction can also be applied to improve the robustness of the analysis. The computations are rapid, typically being accomplished within seconds. Both global and regional (or segmental) myocardial blood flow and MFR measurements are obtained, by kinetic modeling techniques, assuming the appropriate compartmental model, which is specific to a given radiotracer. The inter-scan reproducibility of software methods for absolute flow measurements has been reported to be in the order of 15 % [34]. The quantitative agreement between different software methods available for such analyses is also very good, as recently evaluated for  $^{82}\text{Rb}$  [35] and  $^{13}\text{N}$ -ammonia [36] models (Fig. 4). Clinically,  $^{82}\text{Rb}$  PET blood flow measurements have the widest application, since  $^{82}\text{Rb}$  does not require a cyclotron on site. Although the  $^{82}\text{Rb}$  is not a tracer with ideal imaging properties—for example it has a lower extraction fraction than other tracers—the  $^{82}\text{Rb}$  flow measurements have been well validated and calibrated to both  $^{13}\text{N}$ -ammonia [33] and  $^{15}\text{O}$ -water [37] measurements.

Absolute flow measurements and MFR estimation allow evaluation of several clinically important cardiovascular conditions. Flow measurements at stress and rest provide an integrated measure of the ischemic burden due to microvascular and macrovascular disease [38]. Myocardial flow measurements at stress may potentially allow identification



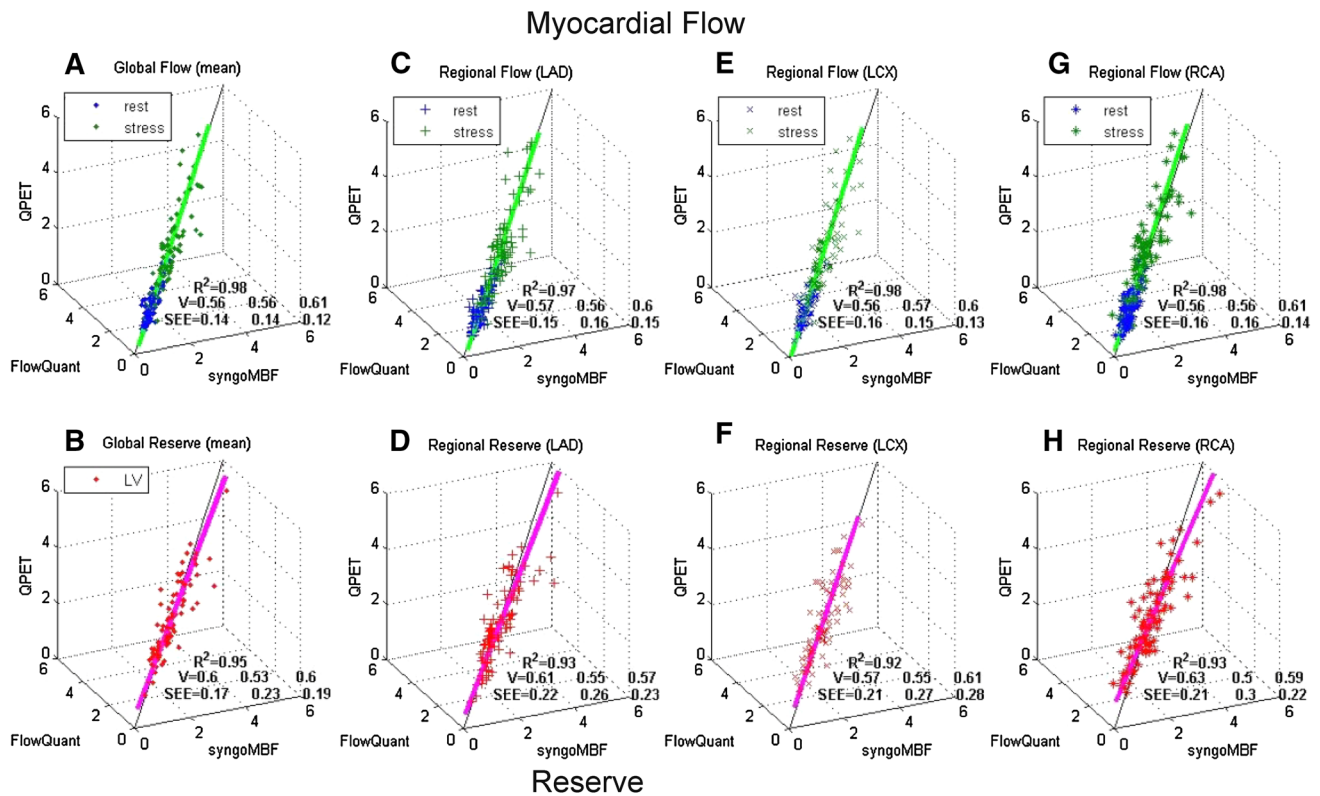
**Fig. 3** Results from different implementations of the absolute flow quantification methods demonstrating regional and segmental quantification of rest and stress myocardial blood flow and myocardial

flow reserve. Cedars Sinai QPET (top left) PMOD software (top right) and Siemens syngoMBF flow analysis (bottom) are shown (color figure online)

of endothelial dysfunction in early coronary disease [38]. In addition, resting myocardial flow heterogeneity and in particular gradient of flow reduction from the base to the apex of the left ventricle has been demonstrated to be a potential early marker of sub-clinical CAD [39]. The presence of a normal MFR can also confirm adequate pharmacological response in the absence of disease [40]. On the other hand, an MFR value <1 could be a hallmark of coronary steal, which is a dangerous clinical condition [41, 42]. Therefore, these quantitative measurements provide powerful additional prognostic and diagnostic information, which could be utilized clinically. Figure 5 shows an example of severely reduced MFR in all the territories observed in microvascular disease. Relative quantification shows only a small abnormality in this case. Patients in whom this condition is diagnosed by quantification of MFR could benefit from aggressive lipid-lowering therapy [43].

Currently, diagnoses of significant, obstructive CAD by PET are typically achieved by visual or quantitative assessment of the relative hypoperfusion at stress and rest rather than

by absolute flow quantification. Nevertheless, myocardial flow measurements have also been shown to be useful in the diagnosis of CAD, especially in the detection of multivessel CAD. It has been reported that quantification of <sup>82</sup>Rb net retention, to measure the stress-rest blood flow difference in the myocardium, defined a greater extent of disease than did standard quantification based on comparisons of the relative stress-rest perfusion difference [44]. Ziadi et al. [45] studied the incremental value of absolute MFR over standard relative quantification in 120 patients undergoing rest/stress <sup>82</sup>Rb imaging. They found that the MFR defined by PET was an independent predictor of triple-vessel CAD and provided added value to relative quantification by summed stress scoring. In a related study by Fiechter et al. [46], absolute measurements of MFR were found to increase the per-patient diagnostic accuracy of <sup>13</sup>N-ammonia from 79 to 92 % in 73 patients. Figure 6 shows an example of a PET <sup>82</sup>Rb scan with angiographically confirmed triple-vessel disease in which only two territories are identified as abnormal by relative quantification. These preliminary studies reporting increased



**Fig. 4** Agreement for the software packages on measurements of myocardial blood flow and myocardial flow reserve. 3D scatterplots of syngoMBF vs FlowQuant vs QPET values of rest and stress myocardial blood flow and myocardial flow reserve for global left ventricle (a, b) and regional vascular territories (c–h).  $R^2$  is the total

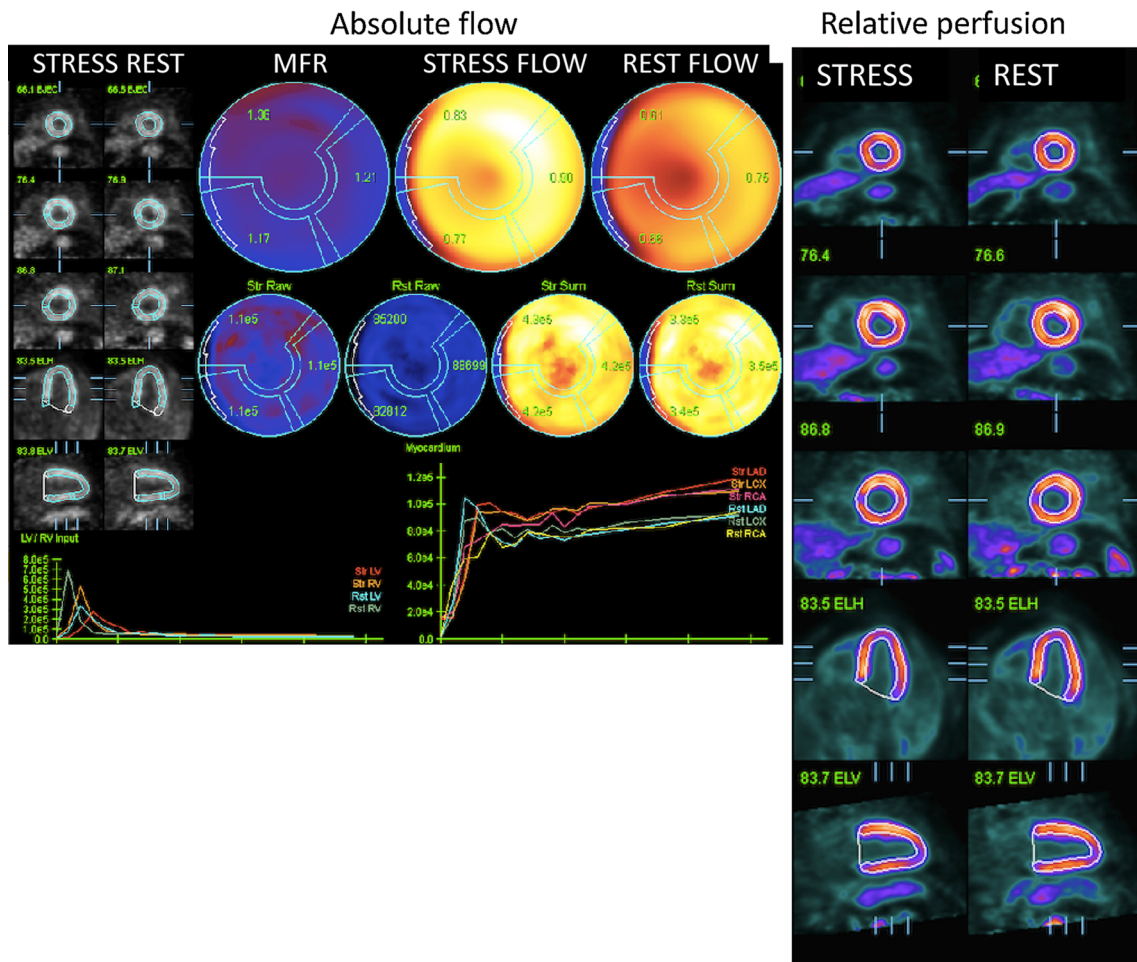
variance described by 3D unit basis vector (V) line of best fit. SEE is the standard deviation of residual errors from regression line of best fit for each of the three programs. Reproduced with permission from deKemp et al. [35] (color figure online)

diagnostic accuracy for detection of coronary disease with absolute flow measurements when combined with relative quantification will need to be confirmed in larger cohorts, since reduced absolute MFR measurements could be caused by factors other than CAD, or could be related to non-obstructive disease [38], thus reducing the specificity for the detection of the obstructive disease.

Quantification of MFR by PET has also recently been established as an important prognostic tool. MFR was shown to improve patient risk assessment compared with relative perfusion (summed stress scoring), and EF quantification alone [2]. Murthy et al., in a study of 2,782 patients, showed that the incorporation of MFR into cardiac death risk assessment resulted in correct reclassification of almost 35 % of intermediate-risk patients and a significant increase in c-index (from 0.82 to 0.84). Figure 7 shows the incremental prognostic value of MFR over ischemia measures. Based on this evidence, quantitative absolute myocardial flow measurements can be used to improve patient mortality risk stratification in addition to other PET measures, such as relative perfusion abnormality or EF.

The practicality of the routine clinical imaging with PET is challenged by the need for an on-site cyclotron (in the

case of  $^{13}\text{N}$ -ammonia and  $^{15}\text{O}$ -water imaging), or an on-site generator (in the case of  $^{82}\text{Rb}$  imaging). In addition,  $^{82}\text{Rb}$  does not have optimal imaging characteristics, due to its long positron range and low extraction fraction. A new imaging tracer,  $^{18}\text{F}$ -flurpiridaz, has recently been proposed for cardiac PET imaging [47]. This tracer exhibits high image contrast in the myocardium, and prolonged retention and superior extraction compared with SPECT tracers (Tc-99m or TI-201) or  $^{82}\text{Rb}$  PET. Cardiac PET imaging with  $^{18}\text{F}$ -flurpiridaz could be performed without a cyclotron on site, because of the relatively long half-life of this tracer. Although the longer half-life of  $^{18}\text{F}$ -flurpiridaz may result in higher patient doses compared with doses for  $^{82}\text{Rb}$  or  $^{13}\text{N}$ -ammonia PET, the reported doses are nevertheless less than 6.4 mSv for the full rest/stress study [48]. New myocardial blood flow quantification models have been proposed and validated for  $^{18}\text{F}$ -flurpiridaz. Sherif et al. [49] showed that the superior imaging characteristics of this tracer enable estimation of absolute flow values by simplified analysis of retention and standardized uptake values (SUVs). These properties of  $^{18}\text{F}$ -flurpiridaz open up new opportunities in the use of absolute quantification since SUV computations do not require the measurement of the



**Fig. 5** Example of severely reduced myocardial flow reserve (1.17–1.37) and reduced myocardial stress flow (0.83–0.77 ml/g/min) in all vascular territories in a patient with syndrome X (left).

This patient had a borderline abnormal relative perfusion scan with mildly decreased uptake at stress in the part of the inferior wall (right) (color figure online)

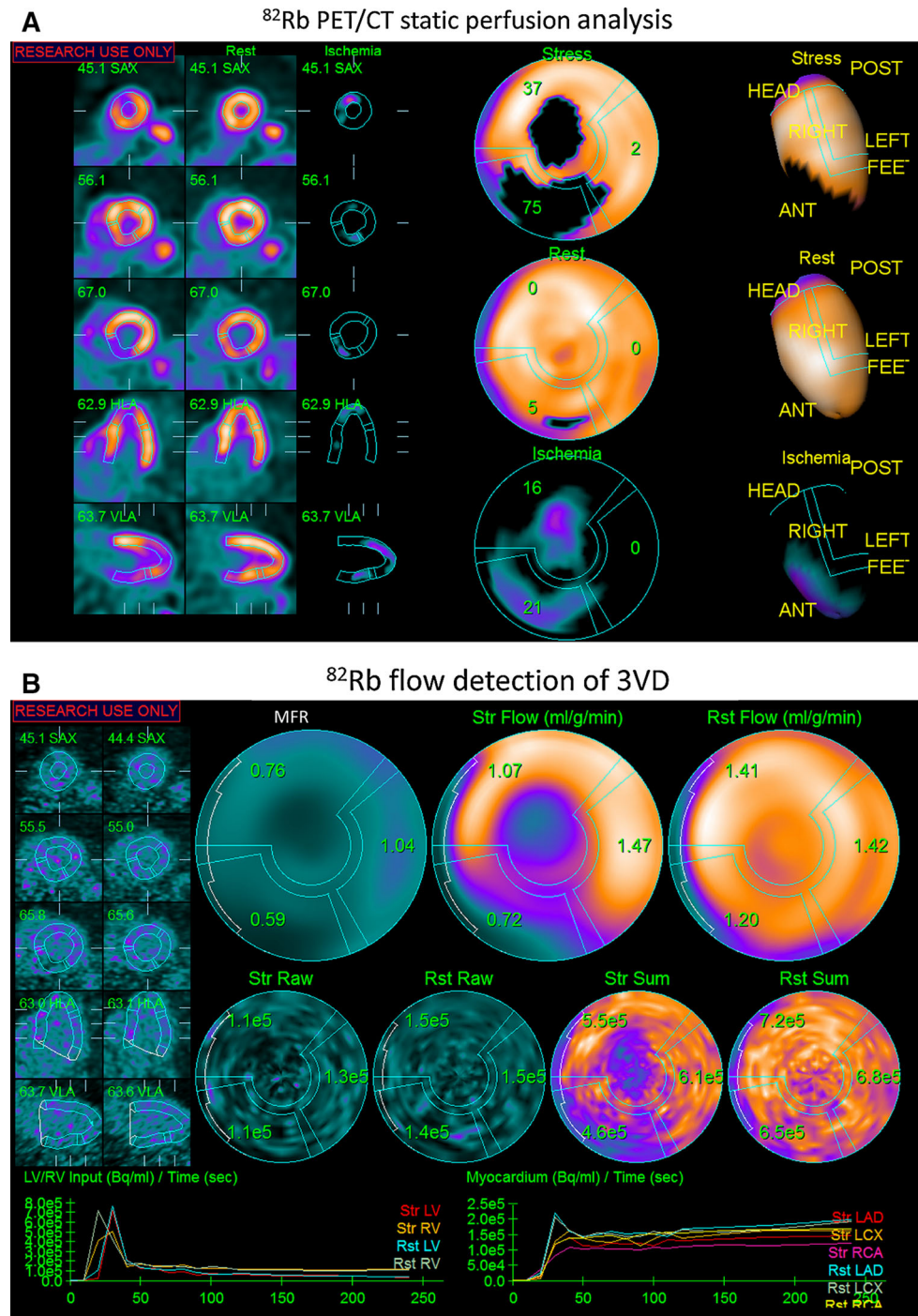
myocardial input function and thus would allow a treadmill exercise regimen outside of the scanner. Such simplified techniques may lead to a wider acceptance of the quantitative models. Furthermore, the high resolution of <sup>18</sup>F-flurpiridaz images may allow improved quantitative accuracy and may warrant the use of sophisticated techniques eliminating cardiac [50] and patient motion [51] to provide optimal quantitative results. In initial validation of <sup>18</sup>F-flurpiridaz, its diagnostic accuracy was reported to be higher than that of SPECT with visual scoring of static images in a phase II trial [48]; however, clinical application of this tracer for myocardial blood flow quantification has not yet been reported.

**Relative quantification of myocardial viability**

Positron emission tomography has been considered the most sensitive method and the “gold standard” for assessment of

myocardial viability [5, 52, 53]. In a simple static protocol, which has been accepted clinically, relative uptake of <sup>18</sup>F-FDG is measured and compared with perfusion at rest. PET viability imaging is used to identify patients with a significant amount of viable recoverable myocardium and can predict functional recovery [54]. The amount of viable myocardium has long-term prognostic implications [55–58]. Patients with viable myocardium will be more likely to benefit from revascularization than those who do not show such viable tissue. Typically, <sup>18</sup>F-FDG viability imaging is combined with a resting PET perfusion scan (using <sup>82</sup>Rb or <sup>13</sup>N-ammonia tracer) or even a resting SPECT scan. Regions which are hypoperfused at rest but are viable (have some <sup>18</sup>F-FDG uptake) are defined by combined assessment of both scans. If a certain degree of such mismatch between perfusion and viability is detected, it indicates that the patient may benefit from a revascularization procedure. Currently the usual clinical method for detecting such viability patterns is visual assessment of the mismatch between static images of

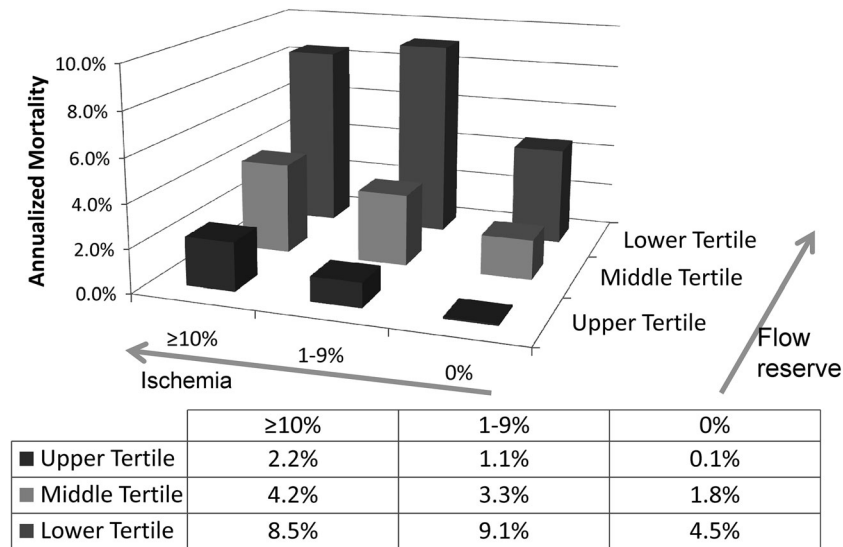
**Fig. 6** Example of added value of myocardial flow reserve (MFR) over ischemia quantification for diagnosis from  $^{82}\text{Rb}$  PET. Relative quantification of total perfusion deficit at stress and rest shows stress and ischemic abnormalities in left anterior descending and left circumflex territories but normal right coronary artery territory (a), while MFR is definitely abnormal in all vascular territories (0.76–1.04), with no flow reserve (MFR = 1.04) in the right coronary region (b). This case was angiographically confirmed as triple vessel disease (color figure online)



the resting perfusion defect and the static  $^{18}\text{F}$ -FDG-PET scan. However, visual methods for the identification of mismatch suffer from the usual problems of inter- and intra-observer variability. If a specific threshold is required for the decision on the intervention, automated quantitative techniques should be considered to ensure objective patient management. To this end, several relative quantification techniques which automatically compute the amount of mismatch and scar have been developed [17, 57, 59, 60].

In the first report on quantitative viability analysis, Beanlands et al. [59] proposed mismatch and scar scores derived from combined perfusion and viability polar maps. These parameters combine extent and severity of the defects. The Cedars-Sinai group has developed an integrated analysis of perfusion and viability in their software. Viability quantification is accomplished as follows: 3D left ventricular contours derived from resting PET or SPECT scans and  $^{18}\text{F}$ -FDG-PET images are co-registered in 3D to





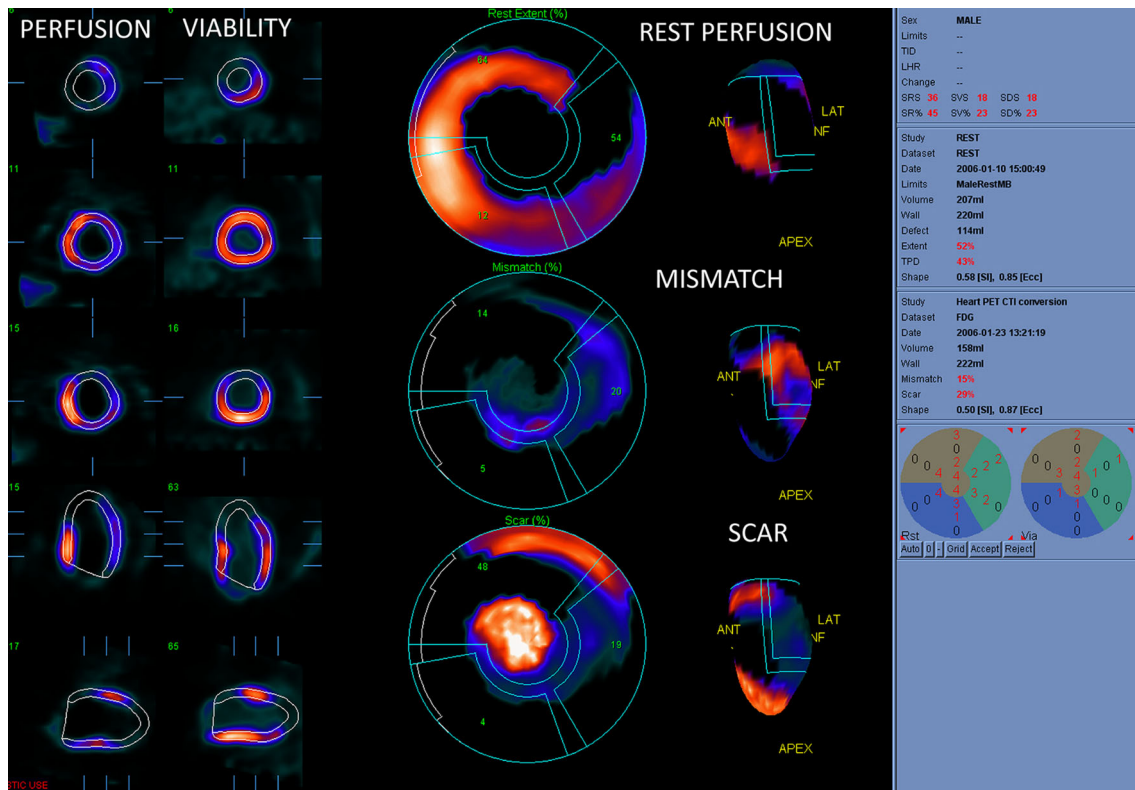
**Fig. 7** Incremental prognostic value of myocardial flow reserve (MFR) over ischemia measures. Unadjusted annualized cardiac mortality by tertiles of MFR and by categories of myocardial ischemia. The annual rate of cardiac death increased with increasing summed stress score and decreasing MFR. Importantly, lower MFR

consistently identified higher-risk patients at every level of myocardial scar/ischemia, also among those with visually normal positron emission tomography scans and normal left ventricular function. Reproduced with permission from Murthy et al. [2]

correct for rotational and positional errors between the two scans, using methods developed for alignment of stress/rest image pairs [61]. Subsequently, the contours derived from the rest perfusion data are applied to the spatially co-registered <sup>18</sup>F-FDG images. Quantification of the viability scores (mismatch and scar regions) is performed after direct image count normalization between the perfusion and viability scans. The method of assigning mismatch and scar scores is based on the approach taken in the PARR-1 study [59], which involves automatic registration and utilization of normal limits for resting perfusion. The viability analysis is performed in polar coordinates, with computation of scar and mismatch scores for each patient’s polar map within the spatial location of the resting perfusion defect, as defined by total perfusion deficit analysis [62]. When the normalized perfusion value at a given polar map location is lower than the normalized <sup>18</sup>F-FDG uptake, the mismatch score is calculated from the difference between the two values. The scar score is calculated relative to the normalized <sup>18</sup>F-FDG uptake in each polar map segment. When normalized perfusion exceeds <sup>18</sup>F-FDG uptake, the scar score is assigned a value equal to the normalized perfusion value in that segment. The total scar score in the entire polar map is then computed as the sum of all segmental scar and mismatch scores, and reported as a percentage of the total area of the left myocardium. An example of mismatch and scar quantification is shown in Fig. 8.

Quantitative analysis of mismatch and scar has been used in several clinical trials. The original technique

developed by the Ottawa group was utilized in the PARR-1 and PARR-2 trials [59, 63]. The objective of the PARR-1 trial by Beanlands et al. [59] was to determine whether the extent of the viability (mismatch or scar) is related to the amount of recovery of left ventricular function and to develop a model predicting recovery after revascularization, based on the viability imaging results. They found that the quantitative measure of scar was a significant independent predictor of left ventricular function recovery after revascularization. In a subsequent sub-study of the PARR-2 trial, the investigators found that in 182 patients with ischemic left ventricular dysfunction, the risk of cardiac death, myocardial infarction or cardiac-related re-hospitalization was reduced when a quantitative mismatch variable was above 7 % [63]. Quantitative analysis of mismatch and scar was also recently applied by Uebleis et al. [64] in 244 patients to evaluate the prognostic significance of <sup>18</sup>F-FDG-PET viability scanning for the prediction of patients with ischemic cardiomyopathy and left ventricular dysfunction. Their analysis showed that the patients with mismatch greater than 5 % (as established by the quantitative software) who did not undergo early revascularization had significantly higher mortality than the group who had similar mismatch (≥5 %) and did undergo the intervention. This study illustrates the role of quantitative viability imaging in the selection of patients for appropriate therapy. It would have been very difficult to derive such definite mismatch thresholds, which can be used to guide therapy, had quantitative analysis not been employed.



**Fig. 8** Viability quantification by PET. Rest perfusion images and viability images are shown (*two left columns*). Polar map quantification (*middle column* and 3D representation, *right column*) shows

resting perfusion defect with total perfusion deficit of 43 % (*top polar map*) Mismatch of 15 % (*middle polar map*) and scar of 29 % (*bottom polar map*) (color figure online)

### Absolute quantification of myocardial metabolism

Imbalances in cardiac metabolism are related to several cardiovascular disorders. PET techniques, by radiolabeling and measuring the kinetics of metabolic substrates, allow in vivo quantification of glucose uptake, oxygen consumption and fatty acid oxidation in the heart. The relative quantification of a radiotracer can be accomplished by static viability imaging as described earlier, but quantification of glucose metabolism in absolute units is possible only through dynamic quantitative  $^{18}\text{F}$ -FDG imaging [58, 65, 66]. Tracer kinetic compartmental models have been developed for the analysis of  $^{18}\text{F}$ -FDG metabolism and allow computation of regional glucose utilization rates in  $\mu\text{mol}/\text{min}/\text{g}$  both at stress and at rest [66]. The mismatch between blood flow and glucose utilization could be used to establish the presence of “metabolic ischemia”. Such quantitative imaging methods could perhaps play a role in the therapeutic management of patients with cardiomyopathy. The use of  $^{18}\text{F}$ -FDG for metabolic imaging and quantification is clinically feasible, since it does not require a cyclotron on site and  $^{18}\text{F}$ -FDG is a routinely available tracer.

In addition, oxidative metabolism of the myocardium can be assessed by  $^{11}\text{C}$ -palmitate [67] or  $^{11}\text{C}$ -acetate tracers [68, 69] tracers (although these tracers require a cyclotron on site). Quantitative kinetic models for  $^{11}\text{C}$ -acetate have been developed to derive, non-invasively, the regional myocardial clearance rates of  $^{11}\text{CO}_2$  (turnover rate constant in 1/min) from the myocardium [68, 69]. Based on invasive comparisons in canine studies, these values could be calibrated to absolute units ( $\mu\text{mol}/\text{min}/\text{g}$ ) reflecting the myocardial oxygen consumption.  $^{11}\text{C}$ -acetate imaging has been shown in human studies to identify hibernating myocardium potentially better than viability studies using  $^{18}\text{F}$ -FDG [70].  $^{11}\text{C}$ -palmitate tracer kinetic modeling is more complex than  $^{11}\text{C}$ -acetate modeling and it allows in vivo evaluation of the reduction of fatty acid oxidation in the ischemic myocardium [67, 71, 72]. The regional relative uptake and time-activity curves can be derived to estimate the clearance half times and the retention fraction of the  $^{11}\text{C}$ -palmitate from the myocardium [71]. This technique could potentially be used to evaluate the consequences of the ischemic injury. Nevertheless, these sophisticated quantitative techniques for evaluation of myocardial oxidative metabolism originally established and validated

primarily in animal models have, largely, not been used clinically to date.

### PET quantification and hybrid imaging

Virtually all PET scanners are offered currently by vendors in hybrid PET/CT configuration. Many of these systems feature high-end (64-slice or higher) CT components, capable of state-of-the-art CT coronary angiography (CTA). Several groups have investigated the feasibility of obtaining improved diagnostic performance by augmenting quantitative PET analysis with anatomical information from coronary CTA. Kajander et al. [73] studied the quantitative combined analysis of  $^{15}\text{O}$ -water PET blood flow and coronary CTA. They demonstrated that the combination of PET and coronary CTA achieves 95 % sensitivity and 100 % specificity, allowing higher diagnostic accuracy than either CTA or PET alone. In a similar study, Danad et al. [74] found that the diagnostic accuracy of quantitative  $^{15}\text{O}$ -water PET/CTA was superior to that of either  $^{15}\text{O}$ -water PET or CTA alone for the detection of clinically significant CAD.

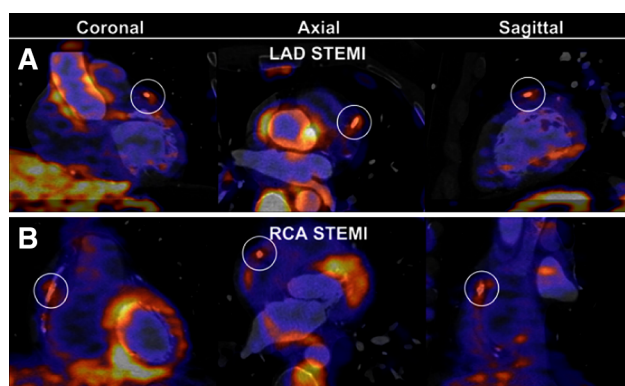
Combined quantitative analysis of PET and CTA requires perfect alignment of the PET and CT scans. This cannot be guaranteed simply by ensuring that the patient does not move on the bed, since CTA and PET are typically acquired with different breathing patterns. The alignment can be performed interactively; however, such manual intervention is likely to introduce inter-observer variability into the hybrid imaging results. Nakazato et al. [75] validated a fully automated technique for the alignment of PET and CTA. They found that despite CTA and PET scans being performed without the patient leaving the table, misalignments between PET and CTA were typically between 14 and 27 mm. The automated software successfully corrected these misalignments, allowing combined 3D visualization of coronary vessel anatomy and hypoperfusion. Subsequently, the quantitative results were modified in 11 out of 32 studies based on the co-registration with CTA [75]. Such 3D fusion of the anatomical and functional scans may allow more precise left ventricular contouring and vascular territory adjustment for subsequent quantitative analysis.

### Vulnerable plaque quantification

Positron emission tomography imaging could also be utilized to characterize atherosclerotic plaque deposits within vessel walls. Elevated macrophage content and associated histological evidence of inflammation are the major hallmarks of ruptured arterial plaques. Among the tracer

compounds for imaging macrophage accumulation,  $^{18}\text{F}$ -FDG is approved for human scanning and is used extensively for the detection and staging of tumors, and for imaging of the glucose utilization in viable myocardium [76] (see previous sections).  $^{18}\text{F}$ -FDG is currently the most validated PET compound for vulnerable plaque imaging [77]. High-end PET/CT with 64-slice (or higher) CT allows precise anatomical delineation of the plaque and vessel anatomy by CTA. PET studies of plaque inflammation in the carotid vessels [78] and in the aorta [79] have been reported. Thanks to the increased PET imaging resolution of the new hybrid PET/CT scanners, it may also be possible to image coronary arteries. Increased  $^{18}\text{F}$ -FDG signal along the course of the coronary arteries in patients with known CAD has been reported, but without direct confirmation that plaques existed at the sites of increased uptake [80]. Higher  $^{18}\text{F}$ -FDG signal at culprit plaque sites was shown in patients with acute coronary syndrome [81]. Another preliminary study with 64-slice PET/CT also found increased  $^{18}\text{F}$ -FDG uptake at culprit sites of acute myocardial infarction after coronary stenting [82]. The other PET tracer that can potentially depict coronary plaque biology and is approved for human scanning is  $^{18}\text{F}$ -sodium fluoride. Preliminary hybrid PET/CT imaging in coronaries with  $^{18}\text{F}$ -sodium fluoride has been performed [83]. It has also been shown, in a longitudinal  $^{18}\text{F}$ -FDG-PET/CT study, that focal arterial inflammation precedes subsequent calcification in the same location [84].

The quantification of vascular atherosclerotic plaques from PET images presents new challenges. In cases of plaque inflammation, small hot spots need to be differentiated from uptake in other adjacent structures. In the monitoring of the disease progression, the level of focal activity may need to be compared in patients with suspected inflammation versus controls, or versus previous studies. The analysis techniques are similar to the methods used in oncological imaging for tracer uptake quantification in tumors. Typically, SUVs or target-to-background ratios are used in the analysis of the vascular plaque uptake [82, 83, 85, 86]. Small plaque sizes and the need for partial volume correction, especially in the coronary vessels, may make quantification of SUVs problematic. New PET reconstruction techniques, which employ resolution recovery principles, can aid in the correction of the tracer activity localized in small lesions [87]. The regions of interest are most robustly guided by coregistered CTA, which provides the anatomical definition of the plaque boundaries. Although it is possible to judge tracer uptake in the vasculature by visual grading, the results are highly variable. Quantification of target-to-background ratios or SUVs allows detection of subtle, but significant increases the tracer concentration in inflamed plaques. In an example from our study of coronary plaque imaging with PET, we



**Fig. 9** PET  $^{18}\text{F}$ -FDG coronary uptake quantification. Examples of increased  $^{18}\text{F}$ -FDG uptake at stent site in patients with acute ST elevation myocardial infarction (STEMI). **a** A 54-year-old man imaged after percutaneous coronary stenting of proximal left anterior descending artery (LAD) for STEMI. Quantification of maximum target-to background ratio (maxTBR) at stent site was 2.1 (white circles). **b** A 49-year-old man imaged after stenting of proximal right coronary artery (RCA) for STEMI. maxTBR at stent site was 2.1. Reproduced with permission from Cheng et al. [82] (color figure online)

show the quantification of  $^{18}\text{F}$ -FDG atherosclerotic plaque uptake in two cases with acute coronary syndrome (Fig. 9).

### Future directions

As hybrid PET/CT scanners become more ubiquitous and image analysis becomes more automated, we will likely see some integration of the quantitative CT and or CTA results with PET results, since visual hybrid analysis of the data from these two modalities has been shown to have incremental diagnostic value [73]. Additionally, a calcium scoring scan, which can be readily obtained on any PET/CT scanner, could perhaps be used in conjunction with the PET images for enhanced diagnosis or prognosis. For example, Bybee et al. [88] studied patients with no history of prior CAD and normal PET perfusion scans and found a high prevalence of significant subclinical atherosclerosis in patients who had elevated calcium scores. Thus, it is possible that quantitative combination of multiple parameters obtained from both CT or CTA and multiple PET parameters could be developed to derive integrated quantitative scores expressing the risk of disease, as has been demonstrated for SPECT imaging [89].

Concerns about radiation dose will influence the use of hybrid PET/CT or PET/CTA scanning. In efforts to reduce the dose and scan time, software methods have been proposed for PET attenuation correction using CT calcium scoring scans [90], eliminating the need for CT attenuation map scans. On the other hand, it is also potentially possible to obtain calcium scores from the attenuation maps [91]

and use them as an additional independent marker of the disease. Low-dose protocols have been proposed for hybrid PET/CTA imaging [92]. It has been reported that hyperemic (stress) blood flow alone (without rest scan) may be sufficient for detection of obstructive CAD [74]. Therefore, combining physiological and anatomical imaging could be accomplished with PET stress-only/CTA imaging, which could significantly reduce the overall dose burden and scan duration [92, 93]. Furthermore, prospective gating and other dose-reducing techniques allow acquisition of high quality coronary CTA scans with doses lower than 1 mSv [94]. These novel CT acquisition techniques may facilitate more routine use of hybrid PET/CTA imaging and hybrid quantification. Finally, cardiac PET/MR has entered the clinical arena allowing further reduction of the overall radiation dose and may also offer some new clinical applications such as imaging of cardiac sarcoidosis [95].

It is also likely that cardiac respiratory gating [96, 97] and advanced PET reconstruction techniques, available with the new equipment, will increase resolution and allow better definition of motion for PET images. Further, it may allow improvement of the accuracy of the quantification methods by the analysis of the motion-frozen data [98]. Consequently, very high quality, high-resolution PET images free of patient and respiratory and cardiac motion could perhaps enable quantification of endocardial and epicardial perfusion and absolute myocardial blood flow. Such high-resolution quantification will, very likely, also be required for vulnerable plaque quantification in the coronary arteries to avoid partial volume and motion effects.

### Summary

Positron emission tomography cardiovascular imaging is a powerful clinical and research tool. It allows determination of the extent and severity of CAD, identification of early coronary disease by absolute myocardial flow measurements, detection of viable myocardium, determination of myocardial metabolism, measurement of cardiac function, and potential differentiation of vulnerable plaques from stable plaques. Additional synergistic possibilities exist when it is coupled with CTA. A multitude of clinically relevant cardiovascular imaging parameters can be obtained from PET imaging. Some of these variables are inherently quantitative and it is not possible to use visual analysis for their determination (such as absolute myocardial blood flow obtained from dynamic data, phase analysis or ejection fraction and systolic/diastolic volumes obtained from gated data). Other variables such as relative myocardial hypoperfusion, myocardial viability or tracer plaque uptake have traditionally been assessed by visual means,

but quantitative methods allow improved reproducibility and potentially also improved accuracy. The quantification of PET images allows objective determination of the disease likelihood and appropriate risk stratification. Virtually all quantitative functional and perfusion parameters can be obtained rapidly (typically in a matter of seconds) from reconstructed tomographic data with minimal user interaction. For these reasons, the use of advanced objective quantification methods in cardiovascular PET is becoming an integral part of clinical examinations and represents a primary advantage over other modalities.

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