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REVIEW ARTICLE

Clinical use of quantitative cardiac perfusion PET: rationale, modalities and possible indications. Position paper of the Cardiovascular Committee of the European Association of Nuclear Medicine (EANM)

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Abstract Until recently, PET was regarded as a luxurious way of performing myocardial perfusion scintigraphy, with excellent image quality and diagnostic capabilities that hardly justified the additional cost and procedural effort. Quantitative perfusion PET was considered a major improvement over standard qualitative imaging, because it allows the measurement of parameters not otherwise available, but for many years its use was confined to academic and research settings. In recent years, however, several factors have contributed to the renewal of interest in quantitative perfusion PET, which has become a much more readily accessible technique due to progress in hardware and the availability of dedicated and user-friendly platforms and programs. In spite of this evolution and of the growing evidence that quantitative perfusion PET can play a role in the clinical setting, there are not yet clear indications for its clinical use. Therefore, the Cardiovascular Committee of the European Association of Nuclear Medicine, starting from the experience of its members, decided to examine the current literature on quantitative perfusion PET to (1) evaluate the rationale for its clinical use, (2) identify the main methodological requirements, (3) identify the remaining technical difficulties, (4) define the most reliable interpretation criteria, and finally (5) tentatively delineate currently acceptable and possibly appropriate clinical indications. The present position paper must be considered as a starting point aiming to promote a wider use of quantitative perfusion PET and to encourage the conception

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and execution of the studies needed to definitely establish its role in clinical practice.

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

Introduction

Clinical interest in myocardial perfusion PET has increased over the years. The widespread implementation of PET scanners for oncological indications has refuelled interest in cardiac indications. In addition there is a large body of evidence that shows the clinical value of PET-derived quantitative measurements such as myocardial blood flow (MBF) and coronary flow reserve (CFR). The aim of this narrative review was to define better the role of quantitative myocardial perfusion PET in current clinical practice, and to make suggestions for its correct execution, interpretation and reporting.

Historical perspective

In the history of PET applications, cardiology and neurology preceded oncology for clinical implementation. As early as the late 1980s the use of perfusion and metabolic PET, the latter performed with ^{18}F-FDG, was the most established modality for the detection of viable hibernating myocardium [1]. At that time perfusion PET was regarded as an expensive but more accurate alternative to SPECT. Moreover, it had the advantages of reliable attenuation correction and of short acquisition protocols [2]. However, while PET in oncology grew exponentially, the use of myocardial perfusion PET remained confined to a few centres, mostly because of the need for a radiopharmaceutical department with an on-site cyclotron for radiopharmaceutical production (^{13}N-ammonia, ^{15}O-water and ^{11}C-acetate) and for the very high cost of ^{82}Rb generators. In practice and in terms of reimbursement, the well-shown advantage of higher diagnostic accuracy was not large enough to justify the effort (and expense) needed to transfer routine cardiac imaging from SPECT to PET [3].

In recent years, however, various factors, including the widespread availability of PET scanners, more frequently combined with an on-site cyclotron, the increased availability of ^{82}Rb generators, and the expectations aroused by the development of ^{18}F-labelled perfusion tracers, which would obviate the need for an on-site cyclotron, have renewed interest in PET in cardiology [4]. This renewed interest is supported by a large body of evidence demonstrating the advantages of performing MBF quantification, which supports its specific role mainly in complex heart diseases, for example multivessel coronary artery disease (CAD) [5].

Advantages of quantitative over qualitative PET perfusion imaging in the clinical setting

Diagnosis of coronary artery disease

PET perfusion imaging has now reached the level of evidence for class Ia recommendation in the noninvasive work-up of CAD in patients with intermediate pretest probability [6, 7]. In this context, the contribution of quantitative cardiac perfusion PET is to help define the total ischaemic burden. This is mainly relevant in identifying patients with balanced three-vessel CAD, which could be missed using relative tracer uptake only, as done with myocardial perfusion SPECT and qualitative PET imaging [8]. There are abundant data indicating that the haemodynamic relevance of an isolated coronary stenosis is not easily predictable and that there is a wide variability in perfusion abnormalities for any given stenosis pattern depending, for example, on variations in the microvascular bed [9, 10]. Various studies have demonstrated that quantitative perfusion PET provides significant added value in the evaluation of multivessel CAD [11–15]. Usually in this setting the most apparent perfusion defect can be attributed to the "culprit" lesion. Conversely, quantitative evaluation allows correct identification of any perfusion abnormalities in the remaining coronary perfusion territories [16–18] (Fig. 1).

By using previously identified stress MBF and CFR thresholds, Johnson et al. have been able to construct a model that offers a high diagnostic reliability for the objective assessment of CAD burden in an individual patient [16]. The possible coexistence of CAD and coronary microvascular dysfunction (CMD) must be taken into account, and this may limit the specificity of quantitative PET for multivessel epicardial lesions as compared to a pure morphological reference standard [7, 15, 17, 18] (Fig. 2). On the other hand, the persistence of an abnormal CFR after coronary revascularization implies an unfavourable outcome, demonstrating the prognostic role of CMD in patients with CAD [19]. In addition, the presence of CMD is also one of the reasons for the frequent disagreement between the intracoronary derived CFR and fractional flow reserve (FFR) [17]. In contrast, additional signs on PET, such as transient left ventricular dilation or a decrease in left ventricular ejection fraction after stress, may help differentiate between three-vessel CAD and diffuse CMD [20].

Quantitative perfusion PET has been used to detect preclinical CAD and to classify the degree of response to risk factor correction, for instance through life-style changes or drug therapy. Many of these studies have focused on the demonstration of endothelium-related abnormalities in MBF and CFR elicited by means of the cold pressor test (CPT) [21]. In theory, the detection of an anomalous response to either the CPT or to maximal pharmacological vasodilation, which is the standard stress modality for PET studies, could play a role in guiding primary prevention of CAD [18, 22]. The list of

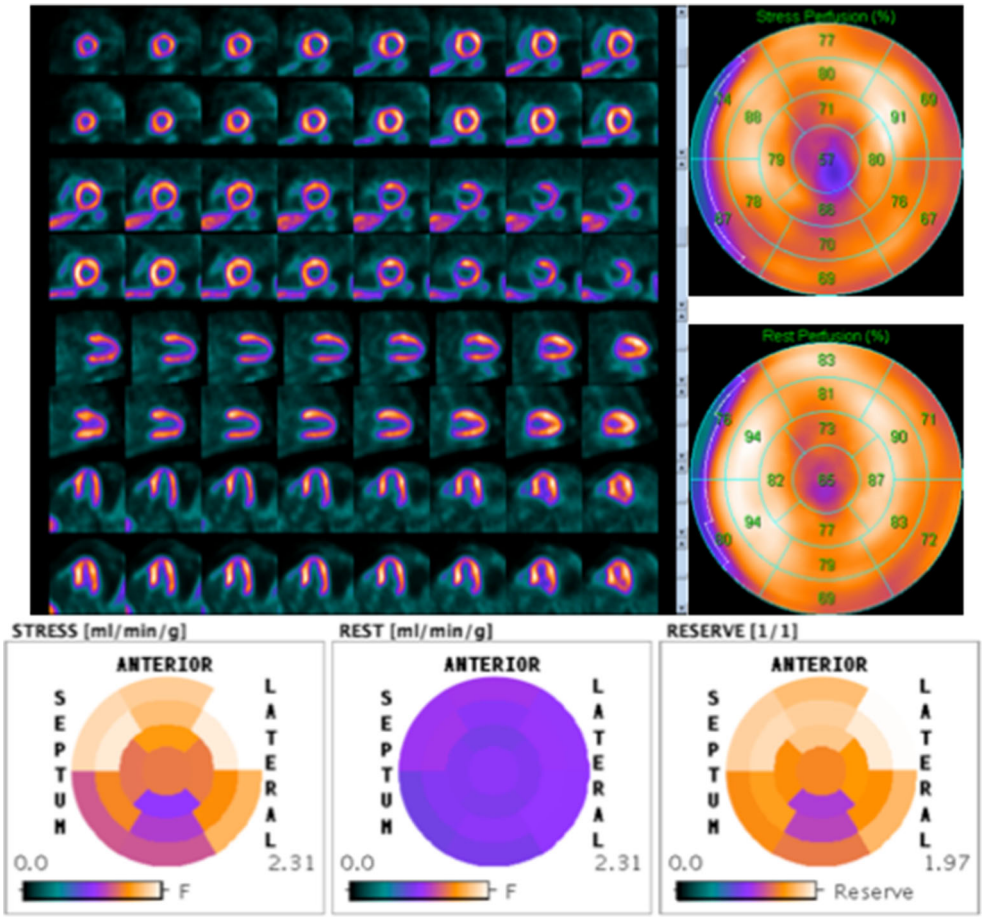

Fig. 1 Myocardial perfusion PET with ^{13}N-ammonia in a patient with severe CAD who had already undergone multiple revascularization procedures, with worsening effort angina and positive stress testing. The stress (dipyridamole) and rest images (from *top to bottom*: short axis, vertical long axis and horizontal long axis), and the stress (*top right*) and rest (*middle right*) polar maps show an almost normal resting perfusion with apical thinning and a limited mild perfusion defect involving the apex and the distal inferior wall. The results of perfusion quantification show normal resting MBF, but decreased maximal hyperaemic MBF in most ventricular segments, with a corresponding abnormal CFR (<2) in all three coronary artery territories. On coronary angiography, the right coronary artery was found to be subоccluded, the left anterior descending artery had a 60 % stenosis and the left circumflex artery had an 80 % stenosis

conditions in which abnormal quantitative PET findings have been demonstrated is very long [21]. Because perfusion abnormalities precede other signs of atherosclerosis, the demonstration of an effective reduction in the level of risk factors by means of life-style changes and/or therapeutic intervention could be of major value, but large-scale clinical studies are still lacking [21]. Quantitative perfusion PET has been demonstrated to be advantageous for the following clinical indications:

1. Atherosclerotic cardiac disease including CAD
   (a) Detection of preclinical disease
   (b) Definition of the total ischaemic burden
   (c) Detection of balanced three-vessel CAD
   (d) Prognostic stratification
2. Non-atherosclerotic cardiac diseases
   (a) Detection of coronary microvascular dysfunction

– Hypertrophic cardiomyopathy
– Fabry-Anderson disease
– Amyloidosis
   (b) Prognostic stratification

– Dilated cardiomyopathy
– Hypertrophic cardiomyopathy

Prognosis

Using the traditional visual (semiquantitative) interpretation, PET has been found to be superior to SPECT for establishing the prognosis, even in patients with a normal perfusion pattern on ^{201}Tl and ^{99m}Tc-sestamibi scans [23, 24]. ECG gating of the PET acquisition further improves the prognostic capabilities of PET imaging [25]. MBF and CFR measured during the CPT have been shown to have prognostic implications [26]. More importantly, it has been convincingly demonstrated that MBF and CFR assessed during maximal pharmacological vasodilation have remarkable prognostic relevance [27–35]. Quantitative PET is also able to evaluate the relationship between CFR and left ventricular ejection fraction after myocardial infarction [36]. Most recently, two studies have shown that the adverse prognostic value of an impaired CFR is independent of the angiographic extent and severity of CAD [37,

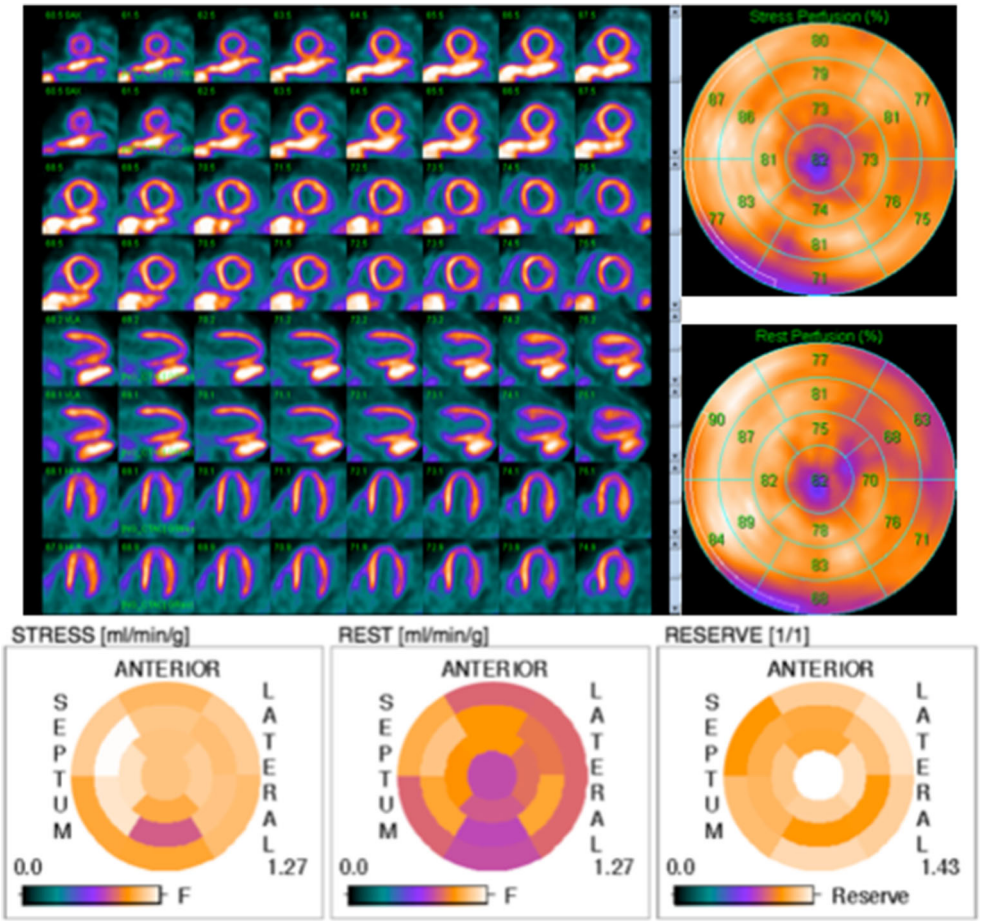

Fig. 2 Myocardial perfusion PET with ^{13}N-ammonia in a patient with a history of previous radiotherapy and chemotherapy for lymphoma with mediastinal involvement, now reporting effort dyspnoea. Same image disposition as in Fig. 1. There is apparently normal perfusion both under stress and at rest. The results of perfusion quantification show normal resting MBF, but severely and diffusely decreased maximal hyperaemic MBF (<1.3 mL/min/g), with a corresponding severely abnormal CFR (<1.5) in all three coronary artery territories. Coronary CT angiography was then performed to differentiate between extensive CAD and CMD, and showed severe three-vessel disease

38]. Therefore the physiological consequences of coronary stenoses, and not just their anatomical features, should be the considered in patient management and in therapeutic decision-making [17]. Unfortunately, no prospective trials demonstrating the real value of a (quantitative) PET-guided revascularization strategy have yet been performed and published.

Other cardiac diseases

Another major contribution of quantitative myocardial PET is to allow CMD detection in various conditions beyond CAD (listed in section Diagnosis of coronary artery disease). The main application of CMD assessment is in patients with cardiomyopathies, mainly hypertrophic cardiomyopathy (HCM). Here, CMD is responsible for the frequently reported anginal symptoms and has been demonstrated to be a powerful prognostic factor [39–42]. In patients with dilated cardiomyopathy, the severity of CMD similarly plays a prognostic role [43]. In a recent study, the adverse prognostic value of an abnormal CFR has been confirmed in patients with dilated cardiomyopathy independently of its origin, ischaemic or non-ischaemic [44]. Also in patients with Fabry-Anderson disease, CMD is frequently encountered and implies more severe heart involvement [45]. Lately, CMD has been found in patients with cardiac amyloidosis, explaining the symptoms of effort angina and dyspnoea in these patients [46].

Technical requirements and clinical protocols

Quantitative myocardial perfusion PET requires the highest technical standard. In this section the issues that are specific to quantitative studies are emphasized.

PET scanner

In PET the current state-of-the-art is a PET/CT scanner with three-dimensional (3-D) acquisition capabilities. Quantitative perfusion PET needs a dynamic acquisition starting with injection of the radiopharmaceutical. The high amounts of radioactivity can cause difficulties to older bismuth germanate (BSO) scanners. Here, either improved electronics or two-dimensional (2-D) imaging (septa in) should be performed in order to avoid the unwanted increase in randoms and scattered events together with dead-time related problems [47]. For the last difficulty, it is also possible to slow the rising time of the input curve and the related sampling frequency

without impairing the quality of the quantitative assessment [48]. Indeed, the use of older devices, including 2-D scanners with line source attenuation correction, is still regarded as acceptable for cardiac studies, but, in quantitative PET, might have a major effect on MBF measurements [49].

Because of the limited thickness of the ventricular wall, high spatial resolution is required, and thus the use of iterative and resolution recovery algorithms, which is nowadays the standard for most PET scanners, appears most reasonable. However, various problems specifically related to the use of iterative methods, resolution recovery algorithms and time-of-flight (TOF) correction in the setting of quantitative PET have been reported [50–56]. For instance, three recent studies showed differences ranging from 5 % to almost 20 % in rest and stress MBF when 3-D ordered subsets expectation maximization (OSEM) and TOF plus point spread function modelling reconstructions were compared [57–59]. On the other hand, TOF has been shown to significantly improve image quality and intraobserver and interobserver reproducibility of ^{13}N-ammonia PET [59]. Further studies are warranted to define the real impact of these factors on the clinical reliability of PET measurements.

Radiopharmaceuticals

^{15}O-Water

A diffusible, inert tracer such as ^{15}O-water is ideal for perfusion quantification, and indeed, because of the lack of persistent uptake in the myocardium and very short half-life (125 s), it can exclusively be used for measurement of MBF [60, 61]. Although the use of factor analysis allows identification of the heart and definition of volumes of interest (VOI) without the need for an additional blood pool scan, no true morphological images are available and gated PET studies are highly demanding [18, 62]. Apart from the high extraction fraction, the other main advantage of ^{15}O-water in the clinical setting is the ability to perform a tight time schedule and the effectiveness of MBF quantification, as demonstrated by a wide experience in a few selected centres, mainly in combination with coronary CT angiography (CCTA) by means of hybrid imaging [63] (Fig. 3; Table 1).

^{13}N-Ammonia

^{13}N-Ammonia also requires an on-site cyclotron, but its production is easier than that of ^{15}O-water. Because of its longer half-life (9.96 min), the time schedule for a complete rest–stress study is slightly longer than with ^{15}O-water [60]. Owing to the good myocardial uptake, high-quality images can be obtained and gated PET is feasible with good results, although the delay in the acquisition with respect to stress is slightly longer than with ^{82}Rb [18, 60, 64]. The extraction fraction is quite high (80 % at rest) and even though a limited roll-off phenomenon at high MBF might theoretically affect the analysis, several published studies have demonstrated the feasibility and reliability of MBF quantification using ^{13}N-ammonia [65–68] (Table 1).

^{82}Rubidium

The main advantage of ^{82}Rb is that it is a generator-produced tracer with an established clinical track record [18, 60, 64]. Image quality is lower than with ^{13}N-ammonia due the wide positron range [60]. Because of the lower extraction fraction (65 % at rest) and the ensuing roll-off phenomenon, ^{82}Rb is not ideal for MBF quantification [18, 60]. Nevertheless, quite reliable methods have been developed to use this tracer for MBF quantification [69–71]. However, the reproducibility of MBF measurements appears lower than those with ^{15}O-water and ^{13}N-ammonia [18]. Additional specific problems of quantitative PET must be kept in mind, such as infusion rate capabilities of the generator, their changes related to the generator's life time, dose balance to avoid saturation and dead-time losses during the dynamic phase without impairing the quality of later frames [64, 72–74]. Moreover, ^{82}Rb is the only radionuclide used for perfusion PET for which the presence of prompt gammas have some relevance, with possible increases in dead-time, particularly in 3-D imaging [75]. Prompt gamma correction can improve qualitative ^{82}Rb perfusion PET, but its importance in quantitative PET has not been established [76] (Table 1).

Examination procedure

Generally, the acquisition of a quantitative PET study does not greatly differ from that of a standard qualitative cardiac PET scan.

Patient preparation

The patient should abstain from caffeine-containing food and drinks for at least 12 h and should have fasted overnight or for at least 6 h. Washout of cardioeffective drugs should be considered in selected cases, according to the study indications and the advice of the referring cardiologist. Theophylline-containing medications must be stopped at least 48 h before the scan.

Rest and stress study

Using the currently available PET perfusion tracers the entire study (rest and stress) can be completed during one single session, with the standard approach to perform the rest study first [64]. However, various data suggest that stress MBF could be effective for ruling out CAD without the need for CFR assessment and thus for resting MBF, so the execution of

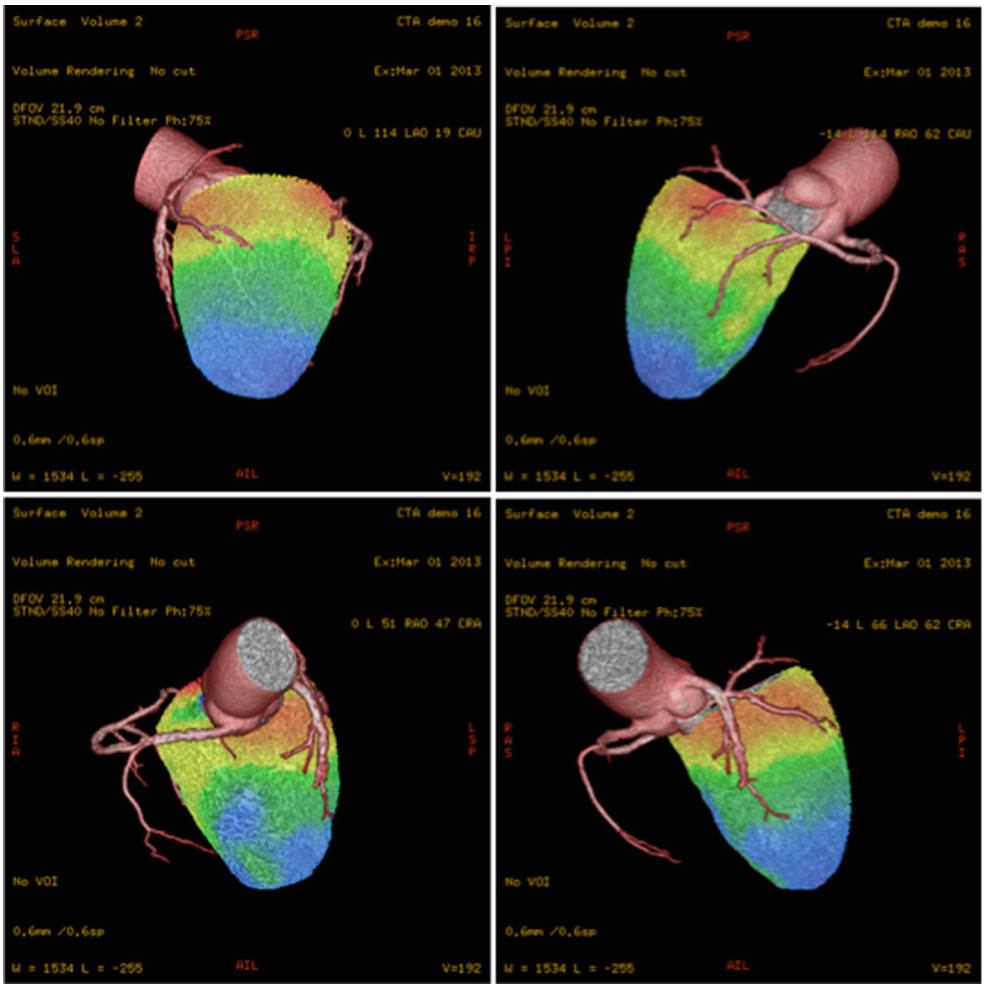

Fig. 3 Fused ^{15}O-water PET and coronary CT angiography in a 47-year-old man with multiple risk factors, atypical left hand pain during exertion and ischaemic ECG changes. CT reconstructions show significant stenoses in the left anterior descending and left circumflex arteries. The right coronary artery shows no stenosis. Stress myocardial perfusion is reduced (*blue*) in the areas supplied by the left anterior descending and left circumflex arteries. Image courtesy of Prof. J. Knuuti, MD, PhD, Turku, Finland

stress-only scans could be considered, at least in selected patients [12, 77, 78]. The main drawback of this approach is the required immediate processing of the stress study in order to decide on the subsequent strategy. The time needed for this could interfere with patient throughput, and this delay could be longer if quantitative measurements are obtained. In the future, the use of ^{18}F-flurpiridaz or other fluorinated compounds, which require a longer interval between the two studies, might make the stress-first (and possibly stress-only) approach much more reasonable [60].

To quantify MBF various framing schemes (i.e. number and duration) have been proposed for the dynamic acquisition. Predefined frames are now less frequently used, whilst postprocessing of list-mode acquisitions is most likely the best choice [64, 78]. Ultimately, the number and duration of frames should be based on the software and model that will be used for MBF quantification. By definition, in case of quantitative perfusion PET, the patient must be injected inside the scanner and thus pharmacological testing with coronary vasodilators is probably the only appropriate option. The only type of stress that mimics some kind of physical stimulation is the CPT, which has been reported to cause endothelium-dependent MBF activation [27]. However, despite several interesting reports of its value, the CPT is not yet widely used in clinical routine.

Traditionally, as with SPECT MPI, dipyridamole and adenosine are clinically the most used pharmacological stressors for quantitative perfusion PET. Most recently, the use of regadenoson has been reported for PET imaging, where it offers particular advantages of improved applicability and practicability, mainly with regard to the time line of application, compared to the two "traditional" stressors [79–81]. However, the delay in radiopharmaceutical injection after administration of regadenoson could affect the degree of hyperaemia achievable, although the clinical consequences of these differences are uncertain [82, 83].

Combination with ECG-gated PET

The acquisition of ECG-gated PET images with ^{15}O-water PET is technically very challenging and only very limited data are available yet on this subject. Most likely extrapolation of these data to clinical practice will take some time. However, acquisition of gated PET images with the other perfusion

Table 1 Comparison of the available tracers for quantitative perfusion PET

	Advantages	Disadvantages	Threshold values for CAD detection
^{15}O-Water	1. Freely diffusible (linear relationship with MBF) 2. Robust and reliable compartmental modelling 3. Intrinsically quantitative 4. Tight time schedule 5. Wide experience, particularly with hybrid imaging	1. Cyclotron product 2. Very short half-life (complex tracer handling) 3. Absence of morphological myocardial images 4. Complex VOI definition 5. Conventional gated PET impossible	Maximal MBF <2.3 mL/min/g, CFR <2.5
^{13}N-Ammonia	1. Short positron range 2. Reliable compartmental modelling 3. High-quality myocardial images 4. High-quality gated PET 5. Wide experience	1. Cyclotron product 2. Nonlinear extraction fraction 3. Metabolic interferences 4. Prolonged patient schedule	Maximal MBF <1.85 mL/min/g, CFR <2
^{82}Rb	1. Generator product 2. Very tight time schedule 3. Gated PET possible 4. Wide experience, but largely with qualitative imaging	1. Wide positron range 2. Dose-related dead-time losses (3-D imaging) 3. Prompt gamma interference (3-D imaging) 4. Suboptimal extraction fraction 5. Complex compartmental modelling 6. Higher variability of estimated parameters	Maximal MBF <1.4 mL/min/g, CFR <1.7

tracers is readily available. In order to combine the dynamic study needed for MBF and the gated acquisition, it is better to perform a list-mode acquisition. The data can later be properly rebinned to obtain the two datasets. Alternatively, in the case of ^{13}N-ammonia the dynamic acquisition can be followed by a second gated acquisition. With ^{82}Rb, due to its very short half-life, this option might require a second tracer injection [64]. The reliability of gated PET measurements as compared to measurements with other established modalities and the role of functional changes between the rest and stress studies for diagnosis and prognosis have been convincingly demonstrated [20, 84].

Hybrid imaging

Because of the widespread availability of PET combined with fully diagnostic CT scanners, it is also reasonable to consider the possibility of hybrid imaging for quantitative PET. With regard to the combination of diagnostic CT and cardiac PET, either for coronary calcium scoring or for CCTA, there are no specific technical problems related to the choice of performing quantitative PET. Indeed, there are some very interesting reports on the reliability of such a hybrid solution in the case of ^{15}O-water PET [63]. This approach, however, requires a state-of-the-art CT scanner with at least 64 slices, increases the radiation burden and prolongs the PET/CT scanner occupation time [64]. On the other hand, off-line image fusion may be an interesting alternative. The combination of qualitative myocardial perfusion and CCTA has been suggested for optimal identification of the vascular territories in the individual patient, but most recently the true diagnostic impact of this procedure has been questioned [85, 86]. On the other hand, most interesting results have been reported using the combination of CCTA with MBF parametric images, which have so far mainly been developed for ^{15}O-water, so that the real effect on perfusion of each obstruction can be assessed. Nevertheless, the possibility of obtaining these parametric images has recently also been demonstrated for ^{13}N-ammonia (Fig. 4) [63, 87].

Sources of error

Attenuation correction

Attenuation correction itself can cause artefacts if not properly performed, and therefore the possibility of differences between emission images acquired during normal breathing and CT should be taken into account [73, 88–90]. The possibility of minor misalignment should always be considered even in the absence of overt patient motion. Whilst CT provides a "frozen" image of a specific phase of breathing, PET data are acquired during the full cycle of normal respiratory motion [73]. The evaluation of minor differences between CT and PET images can be particularly challenging in dynamic studies, because of the poor quality of PET images.

Patient motion

Ensuring that the patient is in the most comfortable position possible during cardiac PET should avoid motion affecting the acquisition, particularly because the patient should have arms

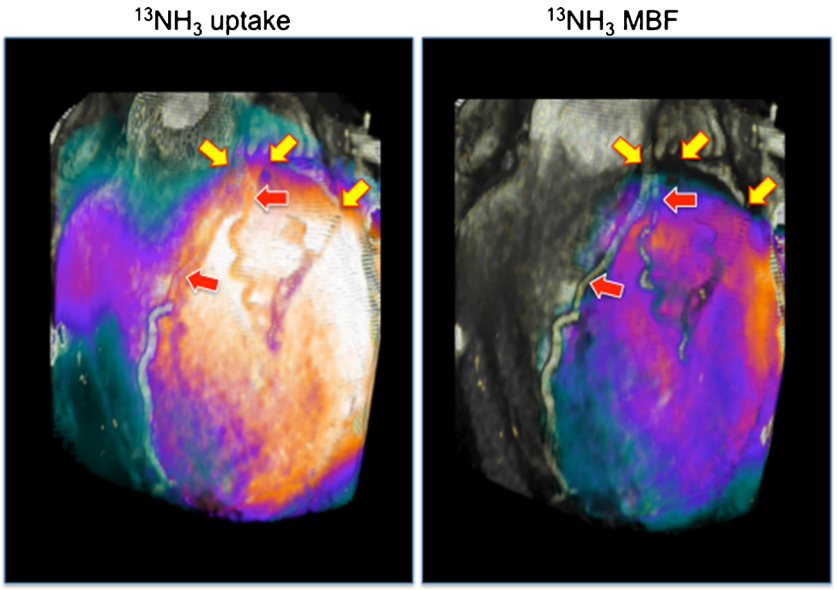

Fig. 4 Off-line fusion of $^{13}NH_3$ PET and coronary CT angiography in the patient described in Fig. 2. In the *left panel* the standard stress $^{13}NH_3$ uptake image shows a limited perfusion defect in the distal left anterior descending artery territory in spite of multiple obstructions in both the left anterior descending and the left circumflex arteries (*arrows*). However, as shown in the *right panel*, using parametric $^{13}NH_3$ MBF images, a severe diffuse reduction in maximal MBF is demonstrated in almost the whole anterolateral wall (*orange-yellow* maximum of the image scale, set to 1.5 mL/min/g)

above the head during the acquisition. Patient motion, particularly irregular breathing, may affect the frame sequence from which the time–activity curves will be extracted. The patient should therefore be requested to breathe normally and not to speak during the few minutes of the dynamic phase. Respiratory gating is desirable and respiratory correction from dynamic data has recently been reported, but this is so far not yet routinely implemented in cardiac studies [91, 92]. It is thus important to have the option to correct the position of abnormal frame(s) before proceeding with MBF measurements [73].

Cardiac contraction

As already mentioned, gating of dynamic sequences is currently not possible. Moreover, the possible adverse influence on the noise ratio of reducing the counts of every single time-frame by splitting it according to the cardiac cycle should be considered. However, myocardial contraction remains a major limitation in optimizing the spatial resolution of cardiac studies [93].

Image processing and MBF measurement

Image reconstruction

Because high resolution is needed, in general the most advanced reconstruction methods are desirable. The main issues related to the relationship between the reconstruction procedure and the subsequent MBF quantification are dealt with above. A thorough examination of many of these problems with the main focus on ^{82}Rb has recently been published [49]. In the clinical practice of quantitative PET, these issues must be kept in mind in order to choose the best possible compromise given the characteristics of the scanner used.

Processing software

PET scanner vendors are becoming aware of the potential importance of cardiac PET. As a consequence, dedicated processing packages are now available, sometimes associated with additional costs [94]. Some of these packages include the same capabilities as SPECT cameras, with qualitative perfusion analysis, possibly offering comparison with a normal database, and gated image quantification, including ventricular volumes and ejection fractions. Other packages, however, already consider the possibility of performing MBF measurements [94]. Alternatively, various platforms are available for off-line processing of dynamic studies, usually exported as DICOM files [94].

Image preparation

Before processing, some programs allow correction for patient motion affecting the frame sequence. These platforms and the programs already implemented in the scanner software usually allow reorientation of the heart along its axes, and identification of the right and left ventricular VOIs and the myocardial VOI from which the tracer time-activity curves will be extracted. With most programs an automatic procedure is available, with some degree of operator interaction to correct for reorientation and VOI definition mistakes.

Compartmental models

There are different approaches to MBF quantification, mainly based on compartmental models of tracer kinetics [95]. They

are generally based on the fitting of the time–activity curves to derive the parameters for the input function and for the myocardial tracer uptake. These parameters will afterwards be included in the equation of the selected model to derive the kinetic parameter that best depicts MBF. Various correction factors are usually considered, for example for activity spillover from blood into the myocardium, as well as for partial volume effect and system resolution [96–98].

Several studies have demonstrated a high intraobserver and interobserver reproducibility of quantitative PET [99–108]. Other studies have compared the reliability of the different models used for quantification of MBF, and have shown different degrees of agreement, and that there are methodological inequalities that must be taken into account if the results from different laboratories have to be compared [95, 109–117]. In general, however, the reproducibility of MBF calculated using the same model but different platforms is good-to-excellent [112, 114, 115, 117]. Moreover, CFR is often more reliable for comparisons because, as the ratio between stress and rest MBF, it is less affected by possible differences between platforms [116, 118]. Most importantly, there is a wide consensus that PET measurements are quite robust and compare well with other quantitative parameters in terms of test–retest variability [17].

Interpretation and reporting of results

Which parameters should be considered?

The parameters that can be derived from quantitative PET are resting and maximal MBF and their ratio, usually identified as CFR or MBF reserve. These parameters are generally calculated for the whole left ventricular myocardium and usually for the coronary territories and/or the ventricular walls. In studies performed with ^{15}O-water, anatomical images are not available, but can be derived from MBF parametric images. Conversely, both ^{13}N-ammonia and ^{82}Rb allow direct visual evaluation of perfusion images and their qualitative assessment [119]. A semiautomatic procedure based on comparison with a normal database can sometimes be used [120]. Additionally, gated PET can be analysed by means of various programs, mostly those already extensively employed for gated SPECT [20, 31, 84].

Which criteria should be applied?

In the literature a wide array of criteria have been proposed for classifying quantitative perfusion PET results as normal or abnormal. The tracer used is the main variable. Furthermore, in order to obtain a correct CFR value, it is important to correct the baseline MBF for the resting rate pressure product, which can sometimes be abnormally high, for instance in anxious subjects [121]. With ^{15}O-water previous studies have shown that a CFR threshold of 2.5 is the most effective for identifying patients with CAD defined as lumen narrowing of >50 % on coronary angiography plus FFR <0.8 [63, 104]. However, more recent studies have suggested that stress MBF can be as effective as CFR for detecting CAD (and possibly more effective), with the potential advantage with high values of making the resting study unnecessary [77, 122]. In a large study to identify the best possible thresholds, a stress MBF cut-off of 2.3 mL/min/g had a diagnostic accuracy of 86 % at the per-patient level and 85 % at the per-vessel level, and in the same population a CFR cut-off of 2.5 had a diagnostic accuracy of 78 % at the per-patient level and 81 % at the per-vessel level [77]. Moreover, MBF parametric images produced with ^{15}O-water have been used to examine the possibility of assessing the difference in MBF between the endocardial and epicardial layers [123]. The transmural perfusion gradient has not so far been shown to add significantly to the diagnostic performance of quantitative PET [124]. However, this particular approach could become of increasing importance in other conditions in which MBF is impaired because of CMD, in particular HCM [87, 125].

For ^{13}N-ammonia, the first proposed thresholds were 1.52 mL/min/g for stress MBF and 2.74 for CFR, with a slight superiority of the latter for detecting a significant coronary stenosis [126]. Later, different thresholds were proposed (1.85 mL/min/g for stress MBF and 2 for CFR), but in this study, stress MBF appeared more effective than CFR [12]. The CFR threshold of 2 was later confirmed in another study [13]. A lower threshold of 1.44 has also been proposed for CFR, but this was based on a different approach to MBF quantification using a graphic method [109, 127].

Surprisingly, for the most used perfusion tracer, ^{82}Rb, the thresholds are less well defined. Anagnostopoulos et al. suggested 1.7 for CFR and 1.4 mL/min/g for stress MBF as possible thresholds for differentiating patients with >50 % stenosis on coronary angiography [128]. More recently, in a very large patient population, Johnson et al. identified a similar threshold for CFR (1.74), but a very low stress MBF threshold (0.91 mL/min/g) for identifying patients with ischaemia as defined by typical angina or diagnostic electrocardiographic changes during dipyridamole infusion [16].

No data on the clinical reliability of ^{18}F-flurpiridaz for MBF quantification have been published as this tracer has not yet been clinically approved. However, the feasibility of quantitative perfusion imaging with this radiotracer has been demonstrated [129].

Indications for PET perfusion imaging

So far there are no specific guidelines for the use of quantitative PET. The current guidelines of ACC/AHA/ASNC for the use of radionuclide imaging suggest the use of PET as an alternative to SPECT, without mentioning the role of quantitative PET [6]. Even in guidelines on advanced imaging, the specific role of quantitative PET is only mentioned in passing

[130]. Similarly, the more recent appropriateness guidelines suggest equality between PET and SPECT in the context of (qualitative) MPI [131]. The Japanese guidelines on cardiac nuclear medicine mention the value of quantitative PET for assessing the severity of ischaemia and CMD, and for detecting preclinical disease and determining treatment effects [132]. In Europe, the possible role of PET, but not specifically of quantitative PET, has been explored more recently in the setting of hybrid imaging [133, 134], and finally considered specifically for risk stratification in stable coronary disease [135]. Similarly, PET is broadly reported as an alternative to other noninvasive techniques in the European guidelines on coronary revascularization [136].

Therefore any attempt to present clinical indications for quantitative perfusion PET remains somehow arbitrary and is open to criticism. Nevertheless, given the accumulated evidence of the added value of MBF and CFR over standard visual evaluation of PET images, it seems reasonable to define some specific clinical scenarios in which the use of quantitative PET appears most valuable. In addition, the use of PET is associated with a lower radiation burden than other diagnostic modalities such as SPECT and CCTA, and fulfils the current necessity for dose reduction [4, 137–143]. Thus, independently of quantification, myocardial PET perfusion is preferred in younger patients, and especially women.

Diagnosis, assessment and prognostication of CAD

For diagnostic purposes, MPI is in general indicated only in patents with intermediate pretest probability of CAD. In this scenario, however, particularly when there are reasons to suspect multivessel disease, the use of quantitative PET would be advantageous. Quantitative PET can be used to establish the diagnosis and simultaneously define the total ischaemic burden, thereby better stratifying patients for coronary revascularization [7, 17].

The practical usefulness of the detection of abnormalities in MBF as a sign of preclinical atherosclerosis in patients with low pretest probability has not yet been demonstrated. More realistically, the use of quantitative PET could be considered in the increasing number of patients in whom the results of CCTA, or even those of intracoronary angiography (ICA), are inconclusive because of the presence of intermediate lesions or of other signs suggestive of atherosclerosis [7, 144, 145]. Similarly, in patients without significant coronary lesions but with anginal symptoms, the use of quantitative PET would be reasonable to evaluate the haemodynamic consequences of minimal obstructions or to make a diagnosis of CMD [146]. Patients with known anomalous coronary artery anatomy, fistulas or bridging, especially patients with chest pain, are a particular group eligible for quantitative myocardial perfusion PET [147, 148].

Although in general imaging for risk-stratifying patients is underutilized, the excellent prognostic value of quantitative perfusion PET-derived parameters make it an ideal tool for this purpose.

Use of quantitative PET in other heart diseases

A completely normal quantitative perfusion PET scan would reasonably exclude the presence of haemodynamically significant CAD in patients with anginal chest pain but with possible non-atherosclerotic heart disease. Much more importantly, there is enough evidence to emphasize the importance of an accurate assessment of MBF for identifying the presence of CMD in patients with cardiomyopathies, in particular HCM [41]. Less certain, but undoubtedly promising, is the use of quantitative PET for the assessment of therapeutic responses in these patients [18, 149].

Quantitative PET in comparison with other imaging modalities

The general advantages of PET as compared to SPECT have already been mentioned, and MBF quantification is one of the most important. However, the new gamma cameras with cadmium-zinc-telluride (CZT) technology could potentially be used in quantitative assessment even with single-photon tracers, although there is as yet no definitive demonstration of their reliability [150]. The differences between the physiological approach to CAD as compared to the anatomical one based on CCTA or ICA have also been described [17]. The measurement of FFR during ICA can certainly improve the evaluation of the haemodynamic significance of any single obstruction, but there remain important differences between this approach and CFR calculation [17]. There have also been attempts to add flow measurement capabilities to CCTA, but they are still in the developmental phase, and have the additional problems of the radiation burden and contrast medium-related concerns [151]. Possibly more promising, because no ionizing radiation is used, is the measurement of MBF by means of magnetic resonance imaging (MRI) [152]. Good correlations between MRI PET measurements have been reported [127]. However, the possible concerns about paramagnetic contrast media and the contraindications to MRI in cardiac patients with implanted devices must be taken into account [153]. Finally, the availability of dedicated MRI scanners with appropriate software and adequately trained personnel is relatively limited.

Future perspectives

Together with further improvements in PET technology such as solid-state scanners, improved gating capabilities and

implementation of advanced reconstruction algorithms, the imminent availability of the ^{18}F-labelled tracer ^{18}F-flurpiridaz is the most exciting development in quantitative perfusion PET [60]. However, this anticipated advance should not prevent the use of quantitative PET wherever possible. In particular, in centres that have already made the great investment necessary for changing to ^{82}Rb PET for a large part of their MPI routine should consider performing MBF quantification in at least all patients with the indications listed above. Similarly, all groups with an on-site cyclotron, particularly if some initial experience with ^{13}N-ammonia qualitative PET is available, should also be encouraged to perform quantitative PET. Because of its more demanding methodology it is less likely that new centres will consider performing ^{15}O-water studies.

In recent years, radiopharmaceutical production systems that deliver a single patient dose of a few PET radioisotopes and biomarkers have been developed. Due to their small footprint and self-shielding, these "baby cyclotron" systems offer the advantage of being easily incorporated into an existing clinical setting, just close to, for example, a PET scanner. At present, the only featured target is ^{18}O, thus leading to a unique ^{18}O(p,n)^{18}F nuclear reaction, and the production cycle of a single dose of ^{18}F takes no less than 35 min. Because of the limited beam current (<5 μA), and the suboptimal peak proton energy (7.5 MeV), the 9.96 min decay half-life of ^{13}N would make the ^{16}O(p,α)^{13}N reaction practically unfeasible. The only exception to this rule seems to be a ^{13}N-only dedicated superconducting mini-cyclotron system (Ionetix ION-12sc). However, because of the declared technical characteristics (as low as 10 μA beam current and 12 MeV peak proton energy, while the major reaction efficiency for ^{13}N production is at 8 MeV), and the absence of scientific papers demonstrating its capabilities, there are major doubts as to the reliability of such a system.

In such a scenario of augmented awareness of the merits of quantitative perfusion PET and of increasing confidence in its feasibility, the effective introduction of an ^{18}F-labelled radiopharmaceutical would permit quantitative PET imaging to be performed in all patients in whom this technology could have major clinical benefit. In turn this would probably further encourage the vendors to implement the platforms and programs needed for MBF measurement, making their use much easier for the clinician. An increasing number of patients could be studied with exercise qualitative PET, a modality so far never utilized and in which the impossibility of MBF quantification could be at least partly compensated for by the more physiological stimulation of the coronary reserve. However, what still remains to be accomplished is the planning and execution of dedicated trials that would finally define the clinical role of quantitative perfusion PET as a specific imaging modality.

Compliance with ethical standards

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