

Present and future of clinical cardiovascular PET imaging in Europe—a position statement by the European Council of Nuclear Cardiology (ECNC)

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Abstract This position statement was prepared by the European Council of Nuclear Cardiology and summarises the current and future potential of PET as a clinical cardiovascular diagnostic imaging tool. The first section describes how methodological developments have positively influenced the transition of PET from a research tool towards a clinical diagnostic test. In the second section, evidence in support of its superior diagnostic accuracy, its value to guide decision making and to predict outcome and its cost effectiveness is summarised. The third section finally outlines new PET-based approaches and concepts, which will likely influence clinical cardiovascular medicine in the future. The notion that integration of cardiac PET into healthcare systems and disease management algorithms will advance quality of care is increasingly supported by the literature highlighted in this statement.

Keywords PET · Cardiology PET · PET-CT · FDG ·
Molecular imaging · Myocardial blood flow

Introduction

Despite a rapid increase of PET in oncology, the clinical use of PET in cardiology in Europe has remained limited to few specialised centres. Unlike in the United States, the increasing availability of PET and PET-CT in numerous nuclear medicine departments has not yet changed this situation. Abundance of other mature functional imaging modalities, absence of commercially available PET tracers and lack of reimbursement in many countries have been major inhibitors in the past.

However, a number of elements are now leading to significant changes and to an increasing clinical perception of PET as a powerful cardiac imaging tool. Based on success in North America, there is a major professional and commercial interest in perfusion tracers that can be used without an on-site cyclotron. Also, hybrid PET-CT scanners, the current standard of PET imaging, are now increasingly available with high-end CT systems that are capable of high-resolution cardiac imaging. These enable a routine combined assessment of anatomy and function/biology, which will increase acceptance of PET among often morphology-oriented clinical cardiologists. Emerging concepts such as microvascular disease, which precedes the development of overt clinical coronary artery disease (CAD) and represents a prognostic factor in many cardiac pathologies, have been brought up based on PET and its unique strength to measure myocardial perfusion in absolute terms. Finally, there is increasing evidence that PET will play a key role in the clinical translation of novel concepts of molecular

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medicine and personalised medicine, such as monitoring of new therapies, evaluation of atherosclerotic plaque biology and identification of individuals at elevated risk for development of heart failure or arrhythmia/sudden death.

The European Council of Nuclear Cardiology (ECNC), a joint organ of cardiovascular imaging experts of the European Association of Nuclear Medicine and the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology, has identified cardiac PET as a major opportunity for the field, with the potential for significant growth in Europe. ECNC has therefore decided to provide a brief position statement on current status and future potential of cardiac PET in Europe, with the intention to increase awareness among professionals and stimulate further clinical development and growth of the technique.

Methodologic considerations

Limitations of myocardial SPECT imaging

The role of myocardial single-photon emission computed tomography (SPECT) in the diagnostic/prognostic evaluation and follow-up of CAD does not need any further demonstration [1–3]. Its use is generalised, even if its accessibility is still more limited in Europe than in the USA [4]. Its accuracy in the assessment of ischaemia, viability and ventricular function makes it an important and cost-effective clinical tool [5–7]. However, myocardial SPECT imaging suffers from limitations, which give room to other techniques for the evaluation of CAD.

In spite of some established attempts to compensate, non-uniform attenuation artefacts decrease the specificity of the technique or lead to inconclusive tests, especially in women and obese patients, but sometimes without any clear explanation [8, 9]. Additionally, inferior image resolution and heart-to-background ratios may explain some false-negative results. Absence of absolute quantification may limit the diagnostic value in patients with multi-vessel disease particularly in case of balanced ischaemia [10–12]. SPECT only allows a semi-quantitative assessment of changes in regional tissue perfusion, but its physical limitations do not permit quantification of blood flow [13]. Finally, the extraction fraction of SPECT tracers is more severely limited at higher flow rates than that of PET tracers, contributing to a limited usefulness in high flow settings such as patients with beginning disease or monitoring of preventive measures [14].

Technical advantages of PET

PET imaging provides not only superior spatial and temporal resolution over SPECT [15] but also routine and

robust attenuation correction. With coincidence detection, the probability of attenuation for the two photons is uniform along the line between the two detectors and can be readily corrected using attenuation coefficients from a transmission image. While external transmission sources were previously used, the current standard using PET-CT systems is to acquire a low-dose X-ray CT for attenuation correction. This has resulted in a technical challenge, namely the misalignment of CT and PET data due to respiratory or patient motion, which may result in artefacts [16–18]. But several approaches, including software-based realignment [16, 18] or modified CT protocols [17, 19], have been introduced to overcome this problem. The overall result of attenuation correction is a better image uniformity, particularly in women where breast attenuation is critical, and in obese patients. The direct consequence is an increase in specificity and normalcy rate compared to SPECT and a decrease in the number of uncertain interpretations. In a study of 2,748 patients, e.g. the number of uncertain scans was significantly reduced from 37% with ^{201}Tl SPECT to 21% with ^{82}Rb PET [20].

The recent generation of PET systems with novel detector materials such as LSO and LYSO yields significant further improvement of image quality. These scanners provide high count-rate performance and are especially beneficial to exploit the full potential of 3D acquisition [21]. Listmode acquisition is now also available for routine use, allowing for multiple image reconstructions from a single dataset, including static, gated and dynamic images. This increases flexibility and provides multiple options for advanced image processing: ECG-gated datasets can be used at rest and during pharmacologic stress in order to determine functional response to stress [22, 23]. ECG gating can be implemented together with respiratory gating [24]. This may allow for creation of “motion-frozen” images, which will reduce distortion and facilitate correction for respiratory misalignment [25]. Finally, these advantages may be combined with the creation of dynamic imaging sequences for routine measurement of tracer kinetics and non-invasive absolute quantification of biologic and physiologic processes by compartmental modelling.

Clinical cardiac PET tracers

Characteristics of the most common radiotracers used in clinical cardiac PET are summarised in Table 1 and outlined in the following [26].

Myocardial perfusion All PET perfusion tracers allow for short-imaging protocols and repeated studies due to their short half-lives. A PET perfusion study can thus be readily accomplished in a fraction of the time necessary for myocardial perfusion SPECT [2, 26].

Table 1 Tracers for clinical cardiac PET imaging (modified from [26])

Tracer	Half-life	Tissue positron range (mm)	Myocardial uptake mechanism
H ₂ ¹⁵ O	2 min	1.1	Free diffusion (perfusion)
¹³ NH ₃	10 min	0.7	Diffusion/metabolic trapping (perfusion)
⁸² Rb	78 s	2.6	Na/K-ATPase (perfusion)
¹⁸ F-FDG	110 min	0.2	Glucose transport/hexokinase (viability)

¹³NH₃ has a first-pass extraction of 80% and requires energy for myocardial retention. Uptake is linear over a wide range of myocardial blood flow except at very high flow rates. Imaging with ¹³NH₃ requires either an on-site cyclotron or proximity to a regional positron radiopharmaceutical source centre. Images are of high quality and resolution.

H₂¹⁵O is potentially superior to other tracers since it is metabolically inert and freely diffusible across capillary and cell membranes. However, it is a drawback that the tracer is not accumulated in myocardium but reaches equilibrium between tissue compartments. Thus, images of regional myocardial perfusion distribution are not readily produced by standard image reconstruction and image processing for blood pool subtraction is needed [27].

⁸²Rb is a potassium analogue that has a first-pass extraction of 65% and also requires energy for myocardial uptake; it requires active transport via Na/K-ATPase, which is dependent on coronary flow. Also, with ⁸²Rb, the extraction fraction decreases in a nonlinear manner with increasing blood flow, and this effect is more pronounced when compared to ammonia, although still superior when compared to ^{99m}Tc-labelled SPECT compounds [28, 29]. Image resolution and quality are somewhat compromised due to high energy of positrons emitted during the decay of ⁸²Rb and due to lower count rates as a result of the ultra-short half-life (Fig. 1). An advantage of ⁸²Rb over ¹³NH₃ and H₂¹⁵O is that it is produced by a ⁸²Sr/⁸²Rb generator without the need for a costly cyclotron. The commercial availability of ⁸²Rb generators is considered to be a key element for a more widespread application of clinical myocardial perfusion PET. This has been demonstrated in the United States, where ⁸²Rb is the most frequently employed cardiac PET tracer and experiences exponential growth in recent years. Most recently, first reports about the clinical use of ⁸²Rb in Europe have been published [30], suggesting that initial steps towards a more widespread use in Europe have been taken.

Myocardial viability ¹⁸F-FDG is widely available due to its success as a metabolic imaging tracer in clinical oncology. It is known for decades that the tracer is of high value to determine myocardial glucose utilisation as an indicator of myocardial viability. Increased ¹⁸F-FDG uptake can be observed in ischaemic tissue, whereas markedly reduced or absent uptake indicates scar formation. ¹⁸F-FDG uptake is

heterogeneous in normal myocardium in the fasting state, and therefore oral glucose loading, nicotinic acid derivatives or infusion of insulin and glucose have been used to enhance myocardial ¹⁸F-FDG uptake [31]. Images obtained in nondiabetic patients and in patients with non-insulin-dependent diabetes, after insulin infusion, are of higher quality than those obtained after oral glucose loading [32]. Also, bolus injections of insulin have been suggested as possible alternatives [33]. In Europe, oral administration of acipimox (Nedios, Byk, The Netherlands) is also possible. Acipimox is a nicotinic acid derivative, which lowers free fatty acid plasma levels efficiently, resulting in excellent ¹⁸F-FDG uptake with good image quality [34, 35]. Acipimox can be administered orally, and it further simplifies cardiac ¹⁸F-FDG imaging. When such protocols for patient preparation are being followed, cardiac ¹⁸F-FDG is generally of high diagnostic quality.

Radiation exposure

Radiation exposure from medical procedures is increasingly discussed [36] not only for the patient but also for the staff

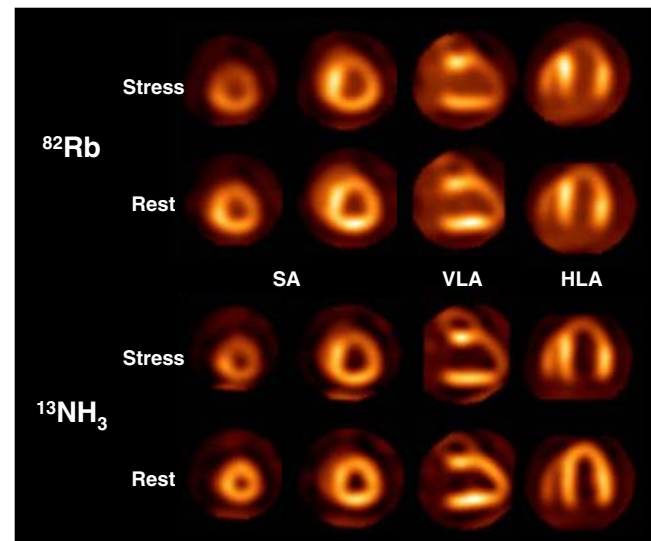


Fig. 1 Myocardial perfusion PET images using ⁸²Rb (top) and ¹³NH₃ (bottom) at rest and during adenosine-induced vasodilation stress in a dog model of coronary stenosis in the mid left anterior descending artery. Both studies were performed in the same animal, during the same imaging session. SA Short axis, VLA vertical long axis, HLA horizontal long axis

employed in imaging laboratories. Positron emitting tracers typically provide less radiation burden to the patient when compared to SPECT tracers due to their short half-lives. Radiation doses during routine stress-rest perfusion PET are clearly lower than ^{99m}Tc -SPECT values and significantly lower than dual-isotope SPECT protocols (Table 2) [37].

Although the high energy photons as such may theoretically represent a higher radiation burden for staff involved in PET imaging, the detected radiation doses are reasonable. Due to differences in radiotracer administration, scan acquisition and stress-testing tasks, the doses with PET are even lower than those obtained with ^{99m}Tc tracers [38].

From a radiation protection standpoint, PET thus also represents a superior technique over conventional SPECT imaging.

Summary—methodological considerations

PET incorporates several technical advantages over SPECT for cardiac imaging, including better spatial and temporal resolution, robust attenuation correction and listmode data acquisition. These improve diagnostic accuracy, reader confidence and versatility, which will be increasingly important because obesity prevalence increases and poses a challenge for image quality and because diagnostic and therapeutic options for CAD also increase so that only the most accurate test will be successful.

Clinical cardiac PET tracers have better physiologic characteristics than SPECT tracers and shorter physical half-lives. This enables absolute quantification (together with the technical advantages of PET) and thereby increases diagnostic information content. It also shortens the length of imaging protocols versus SPECT, improving patient comfort and throughput. Today, ^{82}Rb is the most frequently used clinical cardiac PET tracer and a driving force for increased clinical acceptance because it is a generator product and can be used independent of a cyclotron.

Table 2 Patient radiation exposure by the most frequent diagnostic nuclear imaging procedures (based on reference [37])

Study	Total body effective dose (mSv)
^{201}Tl stress and re-injection (110+37 MBq)	25.1
^{99m}Tc -sestamibi 1 day (370+1,100 MBq)	10.7
^{99m}Tc -sestamibi 2 days (1100+1,100 MBq)	16.0
$^{201}\text{Tl}/^{99m}\text{Tc}$ Dual isotope (110+1,100 MBq)	27.3
^{82}Rb stress-rest PET (1100+1,100 MBq)	7.5
$^{13}\text{NH}_3$ stress-rest PET (500+500 MBq)	2.0
H_2^{15}O stress-rest PET (900+900 MBq)	1.7
^{18}F -FDG PET viability (259 MBq)	4.9

Lower radiation exposure from short-lived PET tracers is another advantage of cardiac PET over SPECT, which is becoming increasingly important in times of growing public awareness and concern towards radiation from medical imaging procedures.

Present clinical impact of cardiac PET

Diagnosis of coronary artery disease

In a 2005 review, Machac et al. listed eight studies that compared PET perfusion with coronary angiography, representing a total of nearly 800 patients. The mean sensitivity was 93% and specificity was 92% for detection of significant coronary stenoses [26]. More recently, Di Carli and Hachamovitch also reviewed the literature and reported a weighted sensitivity of 90% and specificity of 89% to detect CAD as derived from nine studies including 877 patients, scanned mostly with ^{82}Rb PET [39]. These meta-analyses confirm the very high diagnostic accuracy of PET for detection of CAD.

Also, in three studies, which directly compared ^{201}Tl SPECT and ^{82}Rb or $^{13}\text{NH}_3$ PET myocardial perfusion imaging, the mean sensitivity was 91% for PET and 81% for SPECT, with respective specificities of 93% versus 85% to detect CAD [26]. Even when compared to up-to-date SPECT methods using ^{99m}Tc -labelled tracers and gated acquisition, the specificity was still significantly higher for PET (93%) compared with SPECT (73%, $p=0.02$), as reported by Bateman et al. [40]. In particular, the specificity of PET to detect CAD in women in this study was 86% versus 64% for SPECT ($p=0.009$). Finally, Di Carli et al. recently reported very similar results for the accuracy of ^{82}Rb imaging with hybrid PET-CT in a group of 64 patients with suspected CAD, with a sensitivity of 93%, a specificity of 83%, and an overall diagnostic accuracy of 87% [41].

In summary, myocardial perfusion PET is particularly useful in reducing the number of false-positive scans due to attenuation artefacts. This explains the superior specificity over SPECT (Fig. 2). The correction of attenuation obtained with PET is more accurate than in SPECT because of the uniform attenuation of high energy photons. This is of particular importance in the clinical setting in obese populations and in women, in whom attenuation artefacts are frequent. Obesity is very common in patients with suspected CAD, with recent data suggesting a prevalence as high as 78% [41]. The higher sensitivity of PET to detect CAD can be explained by better spatial resolution and better tracer extraction allowing for detection of more subtle perfusion abnormalities.

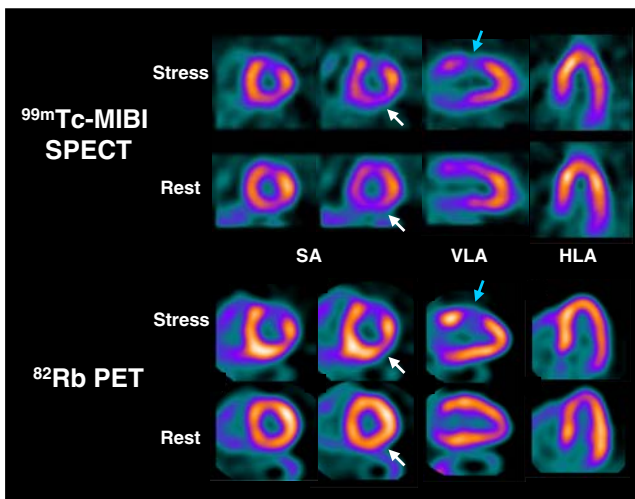


Fig. 2 Myocardial perfusion SPECT (*top*) and PET (*bottom*) images in a patient with known triple vessel CAD, new onset of angina and a body mass index of 35 kg/m². PET shows reversibility in anterolateral (*blue arrows*) and inferolateral region (*white arrows*), confirmed by high-grade stenoses of first diagonal and left circumflex arteries at angiography. Note that inferolateral reversibility is difficult to discern on SPECT due to attenuation. SA Short axis, VLA vertical long axis, HLA horizontal long axis

Prognostic evaluation of CAD

It has been increasingly emphasised that the biggest value of perfusion imaging lies in its predictive potential for adverse cardiac events. This allows the clinician to choose an individual therapeutic strategy based on the patient's risk. Very large patient groups have shown the incremental prognostic value for SPECT myocardial imaging, and published data for myocardial perfusion PET are also available. In a series of 685 patients studied with dipyridamole ⁸²Rb PET, a normal scan had a 90% event-free survival for 41 months, compared with 87%, 75% and 76% in case of small, moderate and extensive defects, respectively [42]. Also, the prognostic value of dipyridamole ⁸²Rb PET imaging was evaluated in another study in 367 patients divided into three groups according to their summed stress score (normal, mild, moderate to severe abnormalities). The annual hard event rate was 0.4%, 2.3% and 7%, respectively, in the three groups. The PET data were the strongest predictors of total cardiac events. In obese patients, the annual total event rate was 11% with an abnormal scan and 1.5% with a normal scan [43]. Finally, Schenker et al. recently reported about the prognostic value of myocardial perfusion and coronary calcium score, as obtained in a single cardiac PET-CT study in 695 patients with intermediate pre-test likelihood of CAD [44]. The authors observed an increasing prevalence of abnormal PET with increasing coronary calcium score but interestingly also observed abnormal perfusion in 16% of patients with a normal

calcium score. Risk-adjusted survival analysis demonstrated a stepwise increase in cardiac events with increasing calcium scores in patients with and without ischaemia on PET. And, among patients with normal PET myocardial perfusion imaging, the annualised event rate in patients with no calcium was lower than in those with high calcium (2.6% versus 12.3%, respectively), while in patients with ischaemia on PET, the annualised event rate in those with no calcium was lower than in those with high calcium (8.2% versus 22.1%). These data suggest that CT calcium scoring and PET perfusion imaging are complementary for the assessment of cardiovascular risk. Both can be integrated to stratify patients into different risk-based categories.

Cost-effectiveness considerations for myocardial perfusion PET

All across Europe, resources dedicated to healthcare are limited, and the question of cost-effectiveness of medical procedures is crucial. This question is even more crucial in the field of cardiology, where the possibilities of imaging are extensive and often redundant. As shown above, myocardial perfusion PET has greater sensitivity and specificity to diagnose CAD when compared to SPECT. But despite the demonstration of greater accuracy, it has not yet replaced other non-invasive approaches to detect CAD. In addition to limited availability, this may be because PET is more expensive than other non-invasive tests for CAD detection. But looking only at the costs of a single test is a short-sighted approach. Estimation of the total costs of diagnostic tests for CAD requires consideration of the indirect and induced costs of management algorithms based on the test. False-positive non-invasive tests may, e.g. result in unnecessary invasive angiography, which carries additional costs and risks, or it may even result in unnecessary treatment, which may carry greater costs and potential risks. A missed diagnosis due to a false-negative test on the other hand may result in otherwise preventable adverse events, which will impair quality of life. Analysis of the utility of clinical approaches thus also has to account for the impact of medical care on the quality, as well as quantity of life. Patterson et al. used a mathematical model to compare the cost-effectiveness of exercise ECG, SPECT, PET and invasive angiography to diagnose CAD. Their model accounts for costs per effect or cost per utility unit (including cost of diagnostic and therapeutic measures, including those that yield false-positive results, as well as those that yield false-negative results) in different populations of patients. They observed that PET, despite high costs of a single test, shows the lowest cost per effect or cost per utility unit in patients with a pre-test likelihood of CAD below 70%, which is attributed to its superior diagnostic accuracy and avoidance of false-positive and

false-negative studies. Only for a pre-test likelihood above 70% was direct angiography the most cost-effective approach [45]. Gould et al., using a somewhat less complex model, had earlier come to similar conclusions [46].

Merhige et al. recently confirmed these theoretical predictions in a prospective clinical trial [47]. The authors compared downstream invasive procedure utilisation, costs and outcomes after PET and SPECT in large patient populations matched for pre-test likelihood of CAD. With PET, the use of invasive angiography was reduced by more than 60% and the revascularisation rate by 50%, with no difference in death or myocardial infarction rates at 1-year follow-up. These favourable results were explained by an improvement in image quality, enhanced certainty of interpretation and diagnostic accuracy [47].

It is of note that the aforementioned cost-effectiveness analyses were done in the healthcare environment of the United States. Some of the cost analyses may not be directly transferable to Europe because specific reimbursements may vary between healthcare systems, but the basic costs associated with diagnostic procedure are not very different between healthcare systems, and prevalence and risk profile of CAD, as well as diagnostic performance of tests, should be comparable among Western countries. It is thus to be expected that myocardial perfusion PET as a diagnostic procedure will also be cost effective in European healthcare systems.

Finally, it should be noted that other factors supporting cost effectiveness, such as the higher patient throughput and patient comfort due to shorter imaging protocols for PET versus SPECT, have not been considered in the aforementioned analyses.

Assessment of myocardial viability

Myocardial viability tests are targeting a smaller, more specific subpopulation of CAD patients with advanced disease and left ventricular (LV) dysfunction. The decision to move forward with revascularisation in those patients is a crucial one because they are at high procedure-related risk. This emphasises the need for diagnostic procedures to guide therapeutic decision making. Historically, PET techniques played a key role in establishing viability testing in general by supporting the notion that perfusion assessment alone may not be enough to predict functional recovery after revascularisation and by defining the pathophysiological state of ischaemically jeopardised but viable “hibernating myocardium” through preserved glucose metabolism in hypoperfused myocardial areas (Fig. 3) [48].

Comparison with other viability tests ^{18}F -FDG PET has been found to be superior to ^{201}Tl SPECT for the evaluation of myocardial viability [49]. Although positive

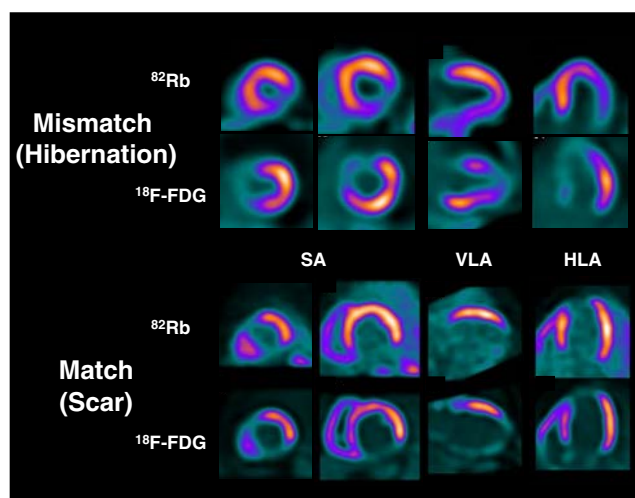


Fig. 3 PET patterns of myocardial viability, as determined by measurement of rest perfusion, using ^{82}Rb , and glucose utilisation, using ^{18}F -FDG. A mismatch with reduced perfusion and preserved/increased ^{18}F -FDG uptake in inferolateral wall, indicating hibernating myocardium, is shown on top. Note that ^{18}F -FDG uptake in ischaemically compromised myocardium can be higher than that of normally perfused myocardium, emphasising the need for combined assessment of perfusion and metabolism to avoid misinterpretation of metabolic images. Bottom shows a matched perfusion/metabolism defect in inferior wall, consistent with scar. SA Short axis, VLA vertical long axis, HLA horizontal long axis

findings with SPECT are mostly in agreement with PET, severe ^{201}Tl defects (<50% relative uptake) have been shown to be associated with ^{18}F -FDG evidence of viability in up to 50% of segments [50]. ^{201}Tl re-injection following redistribution imaging increases the number of reversible defects and the detection of viable myocardium. It has been suggested that ^{201}Tl re-injection may be comparable to ^{18}F -FDG for the assessment of viability in patients with severe ‘fixed’ thallium stress-redistribution perfusion defects [51], but the weight of the evidence favours the use of ^{18}F -FDG PET [52]. The PET approach was also superior to $^{99\text{m}}\text{Tc}$ -labelled perfusion agents in the assessment of myocardial viability [53]. ^{18}F -FDG uptake can be observed in 64% of segments with severe defects on resting $^{99\text{m}}\text{Tc}$ perfusion SPECT, but preserved ^{18}F -FDG uptake is less likely in severe SPECT defects [53, 54]. It is of note that one randomised study found no difference in accuracy between SPECT and PET for viability assessment [55], but results of this study need to be interpreted with caution because included patients had a relatively preserved ejection fraction and thus did not represent the typical viability imaging population of patients with severe heart failure and ejection fractions below 35%. The results of ^{18}F -FDG SPECT are generally comparable to ^{18}F -FDG PET [56].

PET has also been shown to be more sensitive than low-dose dobutamine echocardiography for assessment of

myocardial viability [57–59]. Low-dose dobutamine echocardiography may underestimate viability in regions with low flow [60], and ^{18}F -FDG uptake has been observed in segments that appear non-viable on low-dose dobutamine echocardiography. Ninety-seven percent of segments with improved wall motion following infusion of dobutamine show viability by PET, whereas only 29–57% of PET viable segments are viable on low-dose dobutamine echocardiography [58].

Finally, magnetic resonance imaging of the delayed enhancement of gadolinium-DTPA has emerged as an attractive means to identify myocardial scars. It has been shown that the likelihood of functional recovery decreases as a function of increasing transmural extent of scars [61] and that the test is more sensitive to detect smaller amounts of nontransmural scar when compared to PET [62]. But overall specificity of delayed enhancement for prediction of functional recovery is limited [63]. While PET actively identifies ischaemically compromised but viable myocardium, which poses the patient at risk, it should be noted that delayed enhancement MRI targets non-viable scar but does not provide information about the degree of ischaemic compromise of viable myocardium.

Predictive value ^{18}F -FDG PET is accurate to predict improvement of regional wall motion and global LV ejection fraction following revascularisation. Although results differ depending on the criteria used to detect viability, the sensitivity and positive predictive value of PET are high. PET is most predictive of improvement when blood flow is reduced by >50%, with relatively high glucose uptake. A recent pooled analysis of 24 ^{18}F -FDG PET studies (756 patients) demonstrated a weighted mean sensitivity and specificity of 92% and 63% for regional functional recovery, with a positive and negative predictive value of 74% and 87%, respectively [64]. Additionally, three studies (253 patients) using ^{18}F -FDG PET were available for prediction of global ejection fraction improvement; pooling of these three studies yielded a sensitivity and specificity of 83% and 64%, respectively, with a positive and negative predictive value of 68% and 80%, respectively, to predict improvement of global function after revascularisation.

Symptomatic improvement is considered another important aspect of revascularisation, which may be subjectively more relevant to patients than improvement of contractile function. According to Schinkel et al. [64], three studies (122 patients, all using ^{18}F -FDG PET) focussed on improvement of exercise capacity. Overall, the mean exercise capacity (expressed in METS) was 4.4 before and 5.7 after revascularisation in patients with viable myocardium and 5.1 before and 5.9 after revascularisation in patients without viable myocardium.

Many factors affect surgical outcome besides ^{18}F -FDG uptake, including adequacy of revascularisation and long-term graft/vessel patency. Importantly, it is critical to revascularise patients as soon as possible because improvement is less likely to occur when surgery is delayed after documentation of dysfunctional but viable myocardium [65]. This has recently been confirmed in a large study analysing more than 700 patients, in which all underwent ^{18}F -FDG PET, where patients with rapid intervention had significantly better outcome when compared to those with delayed or no intervention [66].

Several retrospective studies have focussed on outcome of patients with ischaemic heart disease and ventricular dysfunction relative to their PET results and their treatment strategy. A recent meta-analysis [64] identified ten studies (1,046 patients), which have evaluated the prognostic role of ^{18}F -FDG PET. The annualised mortality rates obtained from pooled analysis were 4% for those with viability undergoing revascularisation versus 17% for those with viability not undergoing revascularisation, and they were 6% for those without viability undergoing revascularisation versus 8% for those without viability not undergoing revascularisation.

Finally, one recent randomised trial assigned 430 patients to either management assisted by ^{18}F -FDG PET or standard care. The study overall only showed a nonsignificant trend towards reduction in cardiac events for ^{18}F -FDG PET-assisted management versus standard care. In those who adhered to PET recommendations regarding revascularisation, however, and in patients without recent angiography, significant survival benefits were observed [67].

Cost-effectiveness considerations for PET viability imaging

Issues similar to those mentioned above for perfusion PET need to be considered about cost-effectiveness of viability PET imaging. The costs of a single test are high, but costs for unnecessary treatment in the viability setting of patients with advanced heart failure are even higher. Avoidance of one unnecessary coronary bypass graft surgical procedure, or even of an unnecessary cardiac transplantation, justifies the conduction of multiple non-invasive diagnostic tests if they are appropriate for guidance of clinical decision making. It has clearly been shown that viability imaging influences decision making [68], and this is supported by its high level of evidence for diagnostic and prognostic usefulness, which exceeds that of other viability imaging techniques.

One study applied an economic model to investigate the cost-effectiveness of viability PET in patients referred for surgical revascularisation in the United Kingdom [69]. Based on diagnostic accuracy and outcome data from the

literature and their own hospital, the authors compared three strategies (bypass for all patients, medical therapy for all patients, PET-guided decision for bypass or medical therapy) and concluded that PET may be cost effective to select patients with poor LV function for coronary artery bypass grafting.

Rare patient populations

Some studies have indicated a clinical usefulness of cardiovascular PET imaging in diseases other than CAD. These indications are rare, but the respective patients will often be referred to academic centres for their workup, where PET is more likely to be available and thus should be considered as a useful tool.

Systemic inflammatory diseases ^{18}F -FDG is a marker of inflammation. PET may thus represent a tool for the assessment of myocardial involvement in systemic and inflammatory disorders. Although sarcoidosis is often benign, the specific setting of cardiac sarcoidosis is associated with a poor prognosis and induces a prolonged corticosteroid therapy. Several authors recently suggested that fasting ^{18}F -FDG may identify cardiac sarcoidosis and assessment of disease activity by imaging inflammatory lesions, possibly in association with PET perfusion imaging (Fig. 4) [70–72]. This technique was shown to be superior to perfusion SPECT and ^{67}Ga scintigraphy [73, 74]. Also, high uptake of ^{18}F -FDG has been evidenced in great vessels in aortitis and Takayashu disease, where the intensity of uptake seems to be related to disease activity, which may help in therapeutic management of these patients [75, 76].

Paediatric patients Children constitute a particular population in the setting of congenital heart disease and coronary anomalies. They need high sensitivity and high-resolution

imaging due to the limitation of injected dose and the small heart size. Radiation protection aspects are crucial. The short half-life of PET tracers is a major advantage allowing higher doses with lower radiation exposure, and the higher resolution of PET scanners provides good quality images for detection of perfusion defects and for assessment of myocardial viability so that PET may be especially preferred over SPECT in this specific population [77].

Summary—current clinical status

- Myocardial perfusion PET has excellent diagnostic accuracy for detection of CAD, which is superior to myocardial perfusion SPECT. An increasing number of studies also support its incremental prognostic value. Obese patients and women seem to benefit most from the diagnostic superiority of PET.
- There is increasing evidence that perfusion PET can be cost effective for the general workup of CAD due to its superior accuracy. Higher costs of the test are outweighed by saved costs from avoided unnecessary subsequent invasive angiographies and interventions.
- PET measurements of perfusion and glucose metabolism historically have been the driving force in the establishment of myocardial viability imaging. Patients with advanced ischaemic heart disease and LV dysfunction are the target group. The accuracy of viability PET for prediction of functional recovery is well documented, and the evidence that test results influence therapeutic decision making and outcome beneficially is strong when compared to other available techniques.
- Cost-effectiveness considerations similar to perfusion PET apply to viability PET. Higher costs of the test are outweighed by saved costs from avoided inappropriate therapeutic decisions.

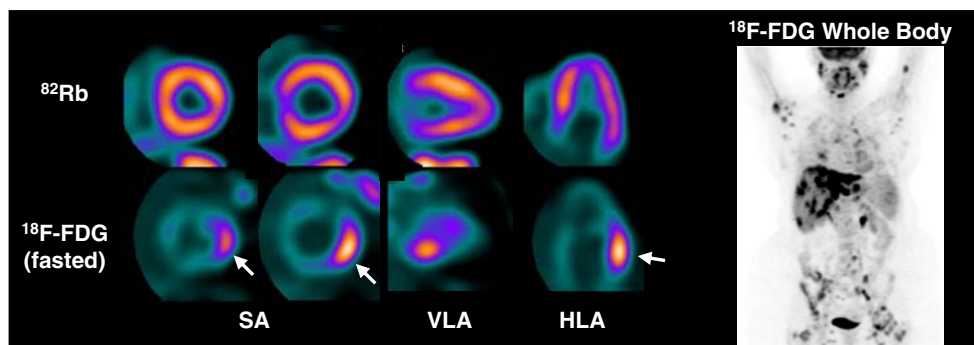


Fig. 4 Resting perfusion and fasting ^{18}F -FDG images in a patient with sarcoidosis and ventricular tachycardia, with no evidence of CAD. Regional myocardial inflammation is identified in basal lateral wall (arrows), suggesting myocardial inflammation. ^{82}Rb uptake is

mildly reduced in the same region, suggesting additional presence of fibrosis. Whole-body ^{18}F -FDG images show extensive involvement of multiple other organ systems, including lung, liver, lymph nodes and bone. *SA* Short axis, *VLA* vertical long axis, *HLA* horizontal long axis

New developments

PET has been used for decades as a very powerful research tool. The following section is not designed to provide a complete overview over the very broad and diverse applications of PET in cardiovascular research. Dedicated review articles are recommended for this purpose. This section rather aims at highlighting those innovative techniques and novel developments, which are likely to have a rapid direct impact on the application of PET as a clinical cardiac imaging tool in the future.

Hybrid PET-CT

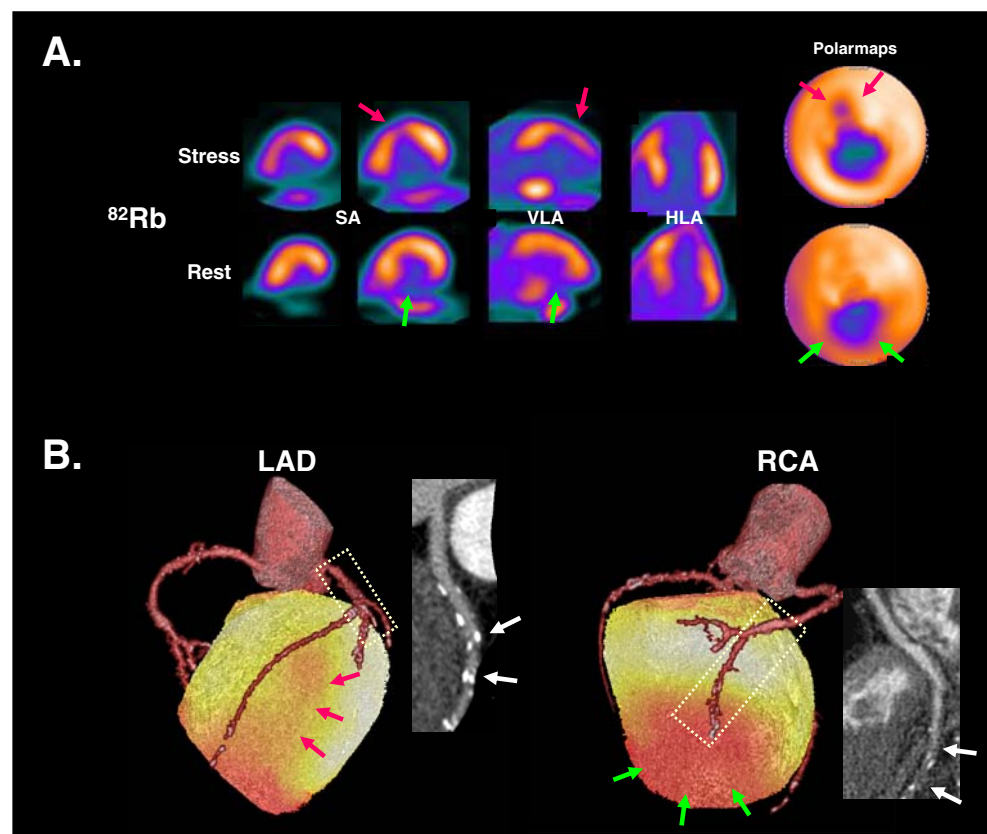
All PET systems are currently manufactured as PET-CT scanners. The number of slices of the integrated CT component has rapidly evolved from two to 16 and now 64 slices so that coronary CT angiography (CTA) became a reality using hybrid systems. The applications of multi-slice CT for cardiac imaging on standalone CT systems have recently been summarised in collaboration with ECNC [78]. When integrated with PET, the novel hybrid machines now have the potential to determine coronary artery calcium score, anatomy of the coronary arteries and the functional consequences of CAD either at stress (for

assessment of induced ischaemia), or at rest (for viability) in association with LV contractile function (Fig. 5).

Although it has been demonstrated for many years that functional tests provide major prognostic information that is superior and additional to the anatomic information, the existence of coronary CTA for integration with PET will probably modify the application of the test. The precise potential and practical role of each of the modalities and of their combination will require extensive further research. There is some evidence, however, that information derived from CT is complementary rather than competitive to the information derived from PET.

Firstly, it has recently been shown that coronary calcium scoring and myocardial perfusion PET, as acquired on a hybrid PET-CT system, provide complementary prognostic information [42]. And secondly, regarding CTA, increasing data indicate that the major strength is its high negative predictive value, so its utility as a standalone test is highest in patients with low prevalence of CAD [79, 80]. Major current limitations include a relatively low positive predictive value and the difficulty to assess luminal narrowing quantitatively, especially in case of calcium distribution. A combination of morphologic and functional imaging thus may be attractive in patients with intermediate or higher pre-test likelihood of CAD. This is supported by the

Fig. 5 Integrated assessment of coronary morphology and function by hybrid PET-CT in a patient with new onset of heart failure and chest pain. **a** Myocardial perfusion images and polarmaps using ^{82}Rb at rest and during dipyridamole stress. There is a fixed defect in inferior wall suggesting prior myocardial infarction (green arrows) and a smaller reversible defect in distal anterior wall suggesting ischaemia (red arrows). SA Short axis, VLA vertical long axis, HLA horizontal long axis. **b** Fusion of stress PET with four-slice CT angiography. The left anterior descending artery (LAD, left) shows diffuse calcifications with additional soft plaque (white arrows), co-localising with the anterior wall ischaemia (red arrows). The right coronary artery (RCA, right) shows predominantly soft plaque with significant luminal narrowing and distal occlusion (white arrows), co-localising with the fixed perfusion defect (green arrows)



findings of several studies that only less than half of the significant stenoses as evaluated by multidetector CT are associated with the occurrence of myocardial ischaemia as detected by SPECT or PET [81–84].

F-18-labelled perfusion tracers

Recently, promising new ^{18}F -labelled perfusion tracers have been introduced. BMS-747158-02 is a pyridaben analogue, which binds avidly to mitochondria. Initial in vivo studies showed rapid myocardial uptake, which was not inhibited by cold pyridaben analogues and slow washout [85]. Myocardial uptake increased proportionally to flow in a rabbit heart model and was higher than that of SPECT tracers [86]. Finally, first-pass extraction fraction was 0.94 in isolated rat hearts, and in vivo image contrast was reportedly superior [87].

Another compound, ^{18}F -fluorobenzyl triphenyl phosphonium, a lipophilic cationic agent, also showed favourable uptake and retention kinetics by the myocardium [88]. In a recent study in dogs, its uptake in ischaemic and non-ischaemic myocardium was compared with microspheres in the presence of coronary stenoses of different severity. The ratio between ischaemic and non-ischaemic tissue correlated linearly with microsphere flow disparity and flow defect contrast was nearly three times greater than with $^{99\text{m}}\text{Tc}$ -tetrofosmin [89].

These ^{18}F -labelled compounds obviously represent very attractive alternatives to current PET perfusion tracers and, once approved for clinical use, are likely to further boost the clinical acceptance of cardiac PET. The ^{18}F label will allow for commercial distribution similar to ^{18}F -FDG, so that PET centres without a cyclotron will benefit. Also, the tracers would be available in single patient doses, which is an advantage over ^{82}Rb , where the laboratory needs to commit to a whole generator for a month and thus requires high patient throughput for cost effectiveness. Also, due to the longer half-life, the tracers will allow for imaging after injection at peak exercise on a treadmill remote to the PET scanner. And finally, image quality and relationship with true flow seem to be superior for these tracers when compared to the currently most frequently used other perfusion imaging agents. Of note, however, clinical experience with these ^{18}F -labelled perfusion tracers has not yet been reported, and protocols remain to be developed and established.

Quantification of myocardial blood flow in the clinical environment

The ability to quantify myocardial blood flow (MBF) and coronary flow reserve (CFR) in absolute terms represents another major advantage of PET over SPECT. It requires a

multi-frame dynamic acquisition, accurate correction of photon attenuation, correction of activity curves for decay and partial volume effects and a compartmental model for calculation of MBF. PET with H_2^{15}O or $^{13}\text{NH}_3$ is considered the non-invasive gold standard for assessment of MBF and CFR [90]. MBF and CFR show some degree of spatial heterogeneity on the individual level, but very small temporal heterogeneity, offering a high repeatability. Normal values are changing slightly with gender and age [91, 92]. Baseline MBF increases with aging, but since hyperaemic MBF decreases simultaneously, aging is associated with a decrease in CFR. Probably as an effect of estrogens on the vascular tone, baseline MBF is higher in females, but CFR is lower [93].

Quantitative PET flow measurements have contributed to a paradigm shift in the perception of CAD. For years, the involvement of macroscopic vessels, i.e. angiographically identifiable coronary arteries, was considered as the primary pathophysiologic correlate of cardiovascular disease. It is now widely accepted that the involvement of the microcirculation plays a key role in the pathogenesis of many cardiac disorders and that the evaluation of microvascular dysfunction has the potential for an important clinical tool. CFR represents the increase of MBF during maximal coronary microvascular dilatation in response to pharmacologic stress. It represents the functional capacity of the coronary microcirculation and thus endothelial dysfunction.

Traditionally, flow quantification by PET, using H_2^{15}O or $^{13}\text{NH}_3$, has been used in subject groups of limited size either to study the effect of potential risk factors (such as smoking, hyperlipidemia, diabetes or insulin resistance) on coronary microcirculation [94–97] or to study the microcirculatory effects of novel therapeutic and preventive interventions [98–100].

Also, the measurement of CFR by PET may provide important prognostic information. Neglia et al. [101] found that reduced CFR was a strong predictor of poor prognosis in patients with idiopathic LV dysfunction independently of the degree of LV functional impairment and of the presence of overt heart failure. Also, in patients with hypertrophic cardiomyopathy, CFR, as measured with PET, was an independent predictor of clinical deterioration and death [102]. And finally, it has been shown that impaired vascular reactivity as identified by PET can predict subsequent onset of clinically overt CAD [103].

With the increasing success of myocardial perfusion PET as a clinical imaging tool, there is also increasing effort to implement flow quantification into clinical diagnostic algorithms. Quantitative flow measurements may be useful in several clinical situations such as detection and evaluation of extensive CAD with balanced ischaemia on qualitative images [104], evaluation of the significance of

a given lesion, evaluation of collateral flow [105], identification of endothelial dysfunction in pre-clinical disease and reliable monitoring of therapeutic strategies. For the purpose of a more widespread utilisation of flow quantification in the clinics, quantitative algorithms for ^{82}Rb , the most frequently used clinical tracer, need to be validated. ^{82}Rb has certain limitations, which are essentially the pronounced nonlinear relationship of its myocardial extraction with the flow rate, resulting in substantial underestimation at higher flow, the high positron energy yielding lower image resolution, and the low count rates of studies due to ultra-rapid decay. Several methods have been used with ^{82}Rb to achieve sufficient accuracy for evaluation of CFR in clinical situations, using either a compartmental model or more simple estimations such as the normalised ratio of stress/rest uptake [105–107]. Machac and co-workers also proposed a simple method using the summed blood pool activity and the relation between the extraction fraction and blood flow obtained in animals; this method yields an excellent reproducibility of 97% [108]. Attempts have been made to improve the accuracy of ^{82}Rb PET in quantification of MBF. The problem of noisy time–activity curves can be improved by noise-reduction methods [109]. Factor analysis has been also applied to better separate the myocardium and arterial time–activity curves [110]. It is expected that these techniques will help to implement flow quantification into clinical PET practice soon and that accuracy and information content of cardiac PET will thereby be further enhanced.

Atherosclerotic plaque evaluation

Although atherosclerosis is a chronic process, which develops over decades, its most dangerous complication results from a sudden thrombotic occlusion of a coronary artery at a vulnerable and unstable site, manifesting as an acute coronary event [111]. These unstable plaques are often only moderately stenotic and may not impair blood flow at rest or during exercise. Early identification of patients with unstable coronary plaques may develop into a useful tool for risk assessment. Despite considerable improvements in morphological and functional non-invasive imaging techniques, no parameters have been established so far to accurately predict the stability or vulnerability of atherosclerotic plaques, as well as reliable tools for monitoring therapeutic responses.

In this setting, the combined non-invasive assessment of plaque structure and metabolic activity is of interest. ^{18}F -FDG uptake has been demonstrated to be a measure of metabolic activity of atherosclerotic plaque [112–115]. Autoradiographic studies confirmed that uptake of ^{18}F -FDG was located in inflammatory cells, predominantly macrophages, and was directly proportional to plaque

macrophage content [116]. Rudd et al. demonstrated a relationship between carotid plaque, ^{18}F -FDG uptake as a marker of inflammation and patients' symptoms [117]. In addition, the same group showed the high reproducibility of the technique [118]. A recent paper established that ^{18}F -FDG imaging indeed can be used to assess the severity of inflammation in carotid plaques in patients, with a high correlation between ^{18}F -FDG uptake and ex vivo macrophage assays [119]. A recent clinical study has shown that the 3-month simvastatin treatment attenuated plaque inflammation as measured with ^{18}F -FDG PET. This study also used a co-registration of ^{18}F -FDG data and CT, which helps in localising the uptake to individual atherosclerotic walls [120].

These reports using ^{18}F -FDG clearly confirmed the principle of non-invasive characterisation of inflamed plaques by PET. ^{18}F -FDG has the advantage of being commercially available and ready for clinical use, but it also has disadvantages in its lack of specificity. Other molecular markers, including tracers for apoptosis, angiogenesis and matrix metalloproteinases, are currently being investigated and may be promising candidates for identification of vulnerable plaques in the future [121]. Of note, this concept is expected to be limited to carotids and other major vessels for the near future. Coronary plaques represent a very small and moving target that is very difficult to visualise by PET, and major technical challenges are still to be overcome in order to visualise coronary atherosclerosis biology non-invasively in the future.

Molecular targeting in cardiovascular disease

The role of molecular imaging in the management of cardiovascular disease is expected to dramatically increase in the next years. There is a strong need for novel imaging strategies to gain insight into pathogenesis, progress of disease and assessment of new therapeutic interventions for numerous conditions and targets such as heart failure, thrombosis, atherosclerosis, vulnerable plaques, apoptosis and angiogenesis.

Multiple new PET tracers are undergoing evaluation for this purpose and are already used in animal experiments. The details of these new compounds are beyond the scope of this article, but it can be postulated that PET, due to its high sensitivity and quantitative nature, will represent one of the methods of choice for these purposes and that translation into clinical practice will happen.

Assessment of molecular and cellular therapies

Novel, very specific therapeutic approaches have been introduced into the cardiovascular arena, including the application of stem cells for myocardial regeneration, the

use of genetic manipulations to treat arrhythmia or other diseases or the use of recombinant proteins, e.g. to induce angiogenesis. The increasing specificity of these therapeutic approaches has also resulted in an increasing demand for more specific diagnostic approaches. Several questions about the best clinical situation for therapy, the best method of agent delivery and the efficiency of therapy still remain unanswered. PET represents a method of choice to provide quantitative answers to such questions in the pre-clinical setting, as well as in patients, with the potential for rapid translation into the clinical setting [122]. A simple but very practical example is the use of ^{18}F -FDG for in vitro labelling of bone marrow cells and subsequent quantification of their in vivo retention in the myocardial target region. This approach has already been pursued in human studies in order to establish methods of cell preparation to maximise their retention [123].

PET strategies to monitor such therapies may also include a combination of existing techniques targeting downstream functional effects, with novel approaches targeting upstream molecular events. An elegant example is represented by the work of Wagner and co-workers, who used PET/CT for in vivo characterisation of angiogenesis-directed molecular intervention, i.e. adenoviral transfer of a VEGF gene [124]. The study combined the imaging of the gene transfer and expression by the use of a co-expressed reporter gene, the phenotypic effect on microcirculation by quantitative perfusion imaging with ^{13}N , the induced changes of expression of $\alpha_v\beta_3$ integrin using ^{18}F -galactosyl-RGD and finally the use of CT for co-localisation of these effects and assessment of ventricular function.

Summary—new developments

- The latest generation of hybrid PET-CT scanners incorporates multi-slice CT components, which are capable of coronary calcium scoring and contrast-enhanced coronary angiography. This facilitates integrated assessment of cardiac morphology and function. Initial studies suggest that the information derived from CT and PET is complementary, not competitive for the evaluation of CAD.
- Promising new ^{18}F -labelled myocardial perfusion tracers are under development and, once clinically established, will likely increase the acceptance of cardiac PET as a routine diagnostic tool.
- Absolute quantification of myocardial blood flow by dynamic PET has contributed to an improved understanding of the pathophysiology of CAD for decades. It is ready for routine clinical application and will likely increase the power of PET further by characterising patients without evidence of regional, visually detectable perfusion heterogeneity.
- The potential of PET to introduce tracers targeting biologic and molecular mechanisms relevant to cardiac disease and therapy is basically unlimited. Ongoing research efforts will continue to provide novel specific compounds for translation into the clinical environment. With this flexibility, PET has the potential to take a central role as a diagnostic tool in personalised, molecular cardiovascular medicine of the future.

Conclusions

There is a considerable, growing body of evidence supporting the usefulness of PET for imaging of myocardial perfusion and viability in the clinical setting. Diagnostic accuracy is high, the prognostic value is established, and cost-effectiveness analyses suggest that the high costs of the test are outweighed by avoidance of costlier, unnecessary follow-up procedures or therapeutic interventions because of superior accuracy. Simultaneous advances of PET cameras and tracer methodology (such as the advent of cardiac hybrid PET-CT, clinical implementation of absolute flow quantification and novel perfusion tracers) are further facilitating the integration of PET as a high-end diagnostic test in clinical cardiology. All this is in synchrony with clinical needs for advanced, specific imaging strategies responding to the rapid evolution of new cardiovascular concepts and therapies. Along with the ever-increasing availability of PET scanners through the success in oncology, this will hopefully expedite a broader clinical acceptance of cardiac PET in European healthcare systems.

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