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Přehledový článek | Review article

Myocardial perfusion imaging in coronary artery disease

Magdalena Kostkiewicz[a,b]

[a] *Department of Cardiovascular Diseases, Jagiellonian University, Collegium Medicum, Hospital John Paul II, Krakow, Poland*
[b] *Department of Nuclear Medicine, Hospital John Paul II, Jagiellonian University, Collegium Medicum, Krakow, Poland*

ARTICLE INFO

Article history:
Received: 22. 8. 2015
Received in revised form: 26. 9. 2015
Accepted: 28. 9. 2015
Available online: 31. 10. 2015

Klíčová slova:
Ischemická choroba srdeční
PET
Radionuklidové zobrazování perfuze myokardu
SPECT

SOUHRN

Radionuklidové zobrazování perfuze myokardu (myocardial perfusion imaging, MPI) lze použít k prokázání přítomnosti ischemické choroby srdeční (ICHS), stratifikaci rizika i k vedení léčby pacientů s již potvrzeným onemocněním. Uvedená metoda je schopna lokalizovat hemodynamicky významné stenózy koronárních tepen i zhodnotit rozsah a závažnost jejich obstrukce podle přítomnosti a rozsahu defektů perfuze. Normální výsledek MPI znamená nepřítomnost koronární obstrukce, a tedy i klinicky významného onemocnění. Předností vyšetření srdce metodou PET je oproti SPECT její vyšší prostorové a časové rozlišení i nižší radiační zátěž pacienta. Zdá se, že hybridní vyšetření srdce kombinací SPECT nebo PET s údaji z CT nabízí přesnější a spolehlivější diagnostické a prognostické informace o pacientech se středně vysokým rizikem rozvoje ICHS. V poslední době byl zaznamenán významný pokrok ve smyslu přesnější kvantifikace průtoku krve myokardem a koronární průtokové rezervy. Několik studií rovněž prokázalo, že kombinace zobrazení apoptózy a tvorby matrixových metaloproteináz může být prospěšná při zobrazování nestabilních plátů a vyhledání skupin asymptomatických pacientů s vysokým rizikem, pro něž znamená vyšetření zobrazovací metodou největší přínos.

Keywords:
Coronary artery disease
PET
Radionuclide myocardial perfusion imaging
SPECT

ABSTRACT

Radionuclide myocardial perfusion imaging (MPI) can be used to demonstrate the presence of coronary heart disease and to risk stratify and guide management of patients with known disease. It has the ability to localise haemodynamically important coronary stenoses, and assess the extent and severity of coronary obstruction by the presence and extent of perfusion defects. A normal stress MPI indicates the absence of coronary obstruction and hence of clinically significant disease. Cardiac PET has the advantage from SPECT of higher spatial and temporal resolution, and a decreased radiation exposure to patients. Hybrid cardiac imaging combining SPECT or PET with CT data appears to offer superior diagnostic and prognostic information in patients with intermediate risk for CAD. A significant progress in better quantification of myocardial blood flow and coronary flow reserve has recently been seen. Also several studies have demonstrated that the combination of imaging apoptosis and matrix metalloproteinases production can help imaging vulnerable plaque and identifying the group of high-risk asymptomatic patients who will benefit most by an imaging procedure.

Address: Magdalena Kostkiewicz, MD, PhD, Department of Cardiovascular Diseases, Jagiellonian University, Collegium Medicum, Hospital John Paul II, Krakow, Poland, e-mail: kostkiewiczmagda@gmail.com
DOI: 10.1016/j.crvasa.2015.09.010

Please cite this article as: M. Kostkiewicz, Myocardial perfusion imaging in coronary artery disease, Cor et Vasa 57 (2015) e446–e452 as published in the online version of the *Cor et Vasa* available at http://www.sciencedirect.com/science/article/pii/S0010865015001034

Introduction

The accurate noninvasive diagnosis and functional evaluation of coronary artery disease (CAD) is an important step in selecting the appropriate management strategy. A complete assessment of CAD requires both anatomical and functional information. This can be obtained in a variety of ways and the common imaging techniques overlap in their capabilities, particularly for the assessment of myocardial viability, function, and coronary anatomy. Several noninvasive imaging options are available for the assessment of suspected or known coronary artery disease and for a long-term prognosis of the disease. Radionuclide tests occupy a central position within the cardiac imaging modalities, and among them myocardial perfusion imaging (MPI) has an obvious place because of its perfect validation for assessing myocardial perfusion. Patients with ECG abnormalities, poor exercise capacity, or intermediate pretest likelihood of disease according to the ECS guidelines, would be the best candidates for this noninvasive imaging [1].

The introduction of ^{201}Tl myocardial perfusion imaging as an adjunct to ECG treadmill studies in the mid-1970s has evolved into the discipline of nuclear cardiology today [2]. MPI provides direct assessment of myocardial perfusion and therefore has an important role in the diagnosis of CAD in patients presenting with chest pain and intermediate pretest likelihood. Techniques such as SPECT and PET currently allow evaluating occlusive coronary atherosclerosis by estimation of myocardial perfusion as well as effects of myocardial hypoperfusion on metabolic activity and contractile function. An inducible perfusion abnormality indicates impaired perfusion reserve, which in turn usually corresponds to epicardial coronary obstruction.

Diagnosis and prognosis of obstructive CAD

Exercise–ECG stress testing has an established role in assessment of patients for the detection of occlusive CAD and with known CAD; however, the progression from ECG-based stress testing to current SPECT and PET technologies has led to improvements in both diagnostic efficacy (sensitivity and specificity for detecting CAD) and resolution (identifying the culprit lesion for chest pain and myocardial ischemia) [3]. An additional advantage of myocardial perfusion-based stress testing over ECG-only testing is the applicability to patients with underlying ECG abnormalities that mask dynamic ischemic ECG changes. Nevertheless, many patients referred for stress testing have functional limitations from pulmonary, orthopedic, peripheral vascular or neurologic conditions that prevent sufficient physical exercise. Ischemic ECG signals may be uninterpretable among patients with abnormal baseline ST segment depression of >1 mm, electronic pacing, left bundle-branch block, or preexcitation pattern. These inadequacies as well as the limited sensitivity and specificity of ECG-based SPECT stress test have led to the development of alternate methods of stressors with pharmacologic agents that either simulate exercise, such as an adrenergic agent (dobutamine), or induce vasodilation (adenosine or dipyridamole) [4].

Myocardial uptake of a radiotracer used for MPI is a function of both delivery of the radiotracer to the cell surface (which is flow-dependent) and subsequent extraction and retention into the cell (which is dependent on cell membrane integrity and viability). Intravascular radiotracer is extracted by myocardial tissue in proportion to blood flow. Thus, the same mechanisms leading to insufficient oxygen delivery and subsequent ECG-detected myocardial

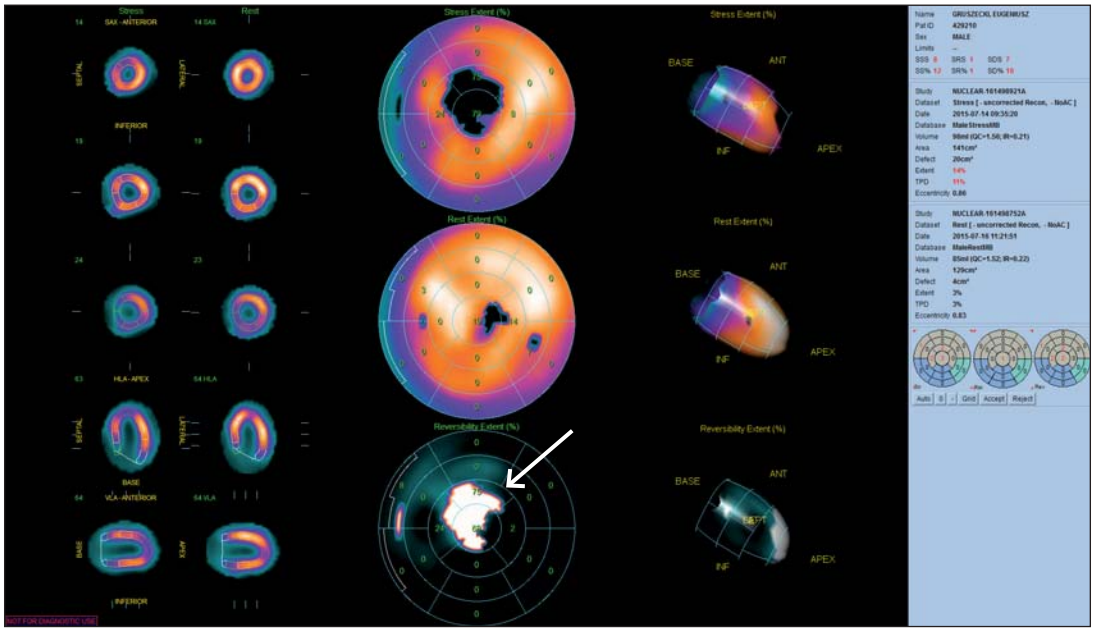

Fig. 1 – Myocardial perfusion SPECT study viewed in slices and polar maps under stress and rest. Polar maps show perfusion, defect extent, wall thickening, and segmental scoring of perfusion defect severity. Stress perfusion defect in the apex and, majority of which significantly improves (reverses) in rest study (arrow). Masses of one or more stress defects and reversible portions of defects are automatically tabulated, along with stress total severity score. SSS – stress scores; SRS – rest scores; difference scores. Software – Emory Cardiac Toolbox. Department of Nuclear Medicine Hospital John Paul II Krakow, Poland.

ischemia on the treadmill can be assessed directly by interrogating regional myocardial perfusion. Regions of decreased myocardial uptake on SPECT and PET can then be correlated with specific coronary artery vascular territories and with a culprit atherosclerotic lesion responsible for the patient's symptoms. A repeated radiotracer injection and imaging after stress and at rest allows differentiating between reversible and fixed perfusion defects. Reversible defects correlate with myocardial ischemia as seen by dynamic ECG changes between resting and stress conditions. If the defect size decreases from rest to stress, this signifies hypoperfused but viable myocardium (hibernation), which predicts a high possibility for recovery of function after revascularization [4] (Fig. 1).

The distribution of radiotracers in various regions of the LV reflects the physiologic consequence of the coronary artery vascular territories, the extent of epicardial luminal narrowing and downstream adaptation by the resistance vessels and collaterals. Metabolic adaptation likely represents one of the earliest responses to myocardial ischemia, which is regulated to protect the structural and functional integrity of the heart. Ischemia may be transitory and reversible, or permanent and irreversible, leading to myocardial infarction. Myocardial ischemia may also lead to postischemic stunning, hibernation, and preconditioning. A decrease in oxygen delivery to the myocardium results in the downregulation of mitochondrial oxidative metabolism and reduced contractile function targeting intracellular metabolic processes. Radiotracers reflect changes in blood flow and myocardial extraction and this has become the basis for subsequent cardiac SPECT and later PET tracers for perfusion imaging. For SPECT, a family of technetium-99m (^{99m}Tc) based radiotracers was developed in the 1990's including now ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin. Despite widespread clinical use, those radiotracers are imperfect due partly to their nonlinear myocardial extraction at high flow rates and high initial hepatic uptake, which can make difficult interpretation of defects in the inferior wall due to adjacent photon scatter. Radiotracers that have minimal hepatic uptake or more rapid washout are continuously under investigation to ameliorate some of these limitations [5].

Typical protocols for a complete PET study for perfusion and viability in CAD include an initial rest myocardial perfusion image with ^{82}Rb (rubidium) or ^{13}N ammonia ($^{13}NH_3$). ^{82}Rb is a potassium analog that has a first-pass extraction of 65%. A major advantage of ^{82}Rb over $^{13}NH_3$ is that it is produced by an ^{82}Sr/^{82}Rb generator without the need for a cyclotron. Then it is followed by the rest ^{18}F-fluorodeoxyglucose (^{18}F-FDG) acquisition where the patient is first fasted for 6–12 h and then receives a glucose load or hyperinsulinemic clamp [6]. The most widely used radiopharmaceutical to assess viable myocardium is ^{18}F-FDG. As a glucose analog, ^{18}F-FDG is transported into myocytes by the glucose transporter and can enter metabolic glucose pathways. Increased ^{18}F-FDG uptake can be observed in ischemic tissue; markedly reduced or absent uptake indicates scar formation. Normal myocardium demonstrates uptake of both the perfusion and metabolism radiotracer and scar demonstrates little to no uptake of either the metabolic or perfusion tracer matched defect. Hibernating and thus viable myocardium is detected as having reduced perfusion and preserved metabolism mismatched defect. Matched metabolism and perfusion defects are unlikely to recover following revascularization depending on the extent of left ventricular involvement [7] (Fig. 2).

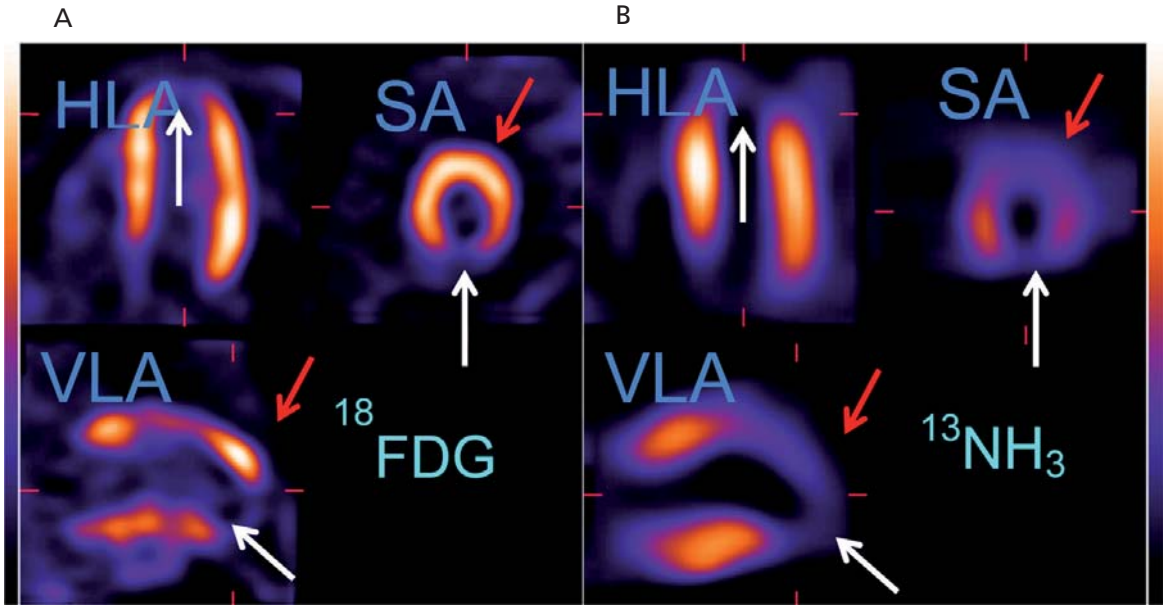

Fig. 2 – PET with NH_3 and ^{18}F-FDG to assess myocardial viability. Panel (A) myocardial metabolism, panel (B) – myocardial perfusion. Regional myocardial ^{18}F-FDG uptake (A) is disproportionately enhanced compared with regional myocardial blood flow assessed by $^{13}NH_3$ (B), metabolism – perfusion mismatch and is indicative of hibernating myocardium (*red arrows*). The lack of ^{18}F-FDG uptake compared with lack of regional myocardial blood flow is indicative of scar (*white arrows*). HLA – horizontal long axis; SA – short axis; VLA – vertical long axis. (Reproduced with permission of G. Romanowicz, MD, PhD, Department of Nuclear Medicine, Medical University of Gdansk, Poland)

There is an extensive literature evaluating the sensitivity and specificity of SPECT myocardial perfusion imaging for detecting CAD. For intermediate-risk patients, noninvasive imaging has a well-established role to diagnose CAD in many different clinical scenarios [1,5]. An analysis of 32 studies including 4480 patients with known or suspected CAD demonstrated mean sensitivity and specificity of 87% and 73%, respectively, for exercise myocardial SPECT for detecting a >50% stenosis [8]. An analysis of 16 studies of patients with known or suspected CAD including 2492 patients demonstrated sensitivity and specificity of 89% and 75%, respectively, for vasodilator stress with dipyridamole or adenosine for the detection of a >50% stenosis SPECT myocardial perfusion images provides important prognostic information [8]. In a meta-analysis, including 19 studies of >39 000 patients with an average of 2.3 years of follow-up, the event rate with a negative SPECT MPI was 0.6% [9]. In a meta-analysis of 177 studies (108 SPECT MPI studies, 4 PET MPI studies, and 5 both PET and SPECT studies), the sensitivity of PET was 92.6% and the specificity was 81.3%. SPECT had a lower sensitivity at 88.3% but a similar specificity of 75.8% [10]. Another meta-analysis also compared these 2 modalities. The sensitivities and specificities with ^{82}Rb PET were 90% (CI 0.88–0.92) and 88% (CI 0.85–0.91), respectively, whereas SPECT results were 85% [11]. Consequently, PET may significantly improve diagnostic accuracy compared with SPECT. Rest and stress ejection fraction, left ventricular volumes, and transient ischemic dilation can be assessed with SPECT MPI. These additional data enable further prognostication. Inclusion of left ventricular end-systolic volume (ESV) improved risk prediction: patients with ESV $\geq$ 70 ml had more events compared with those with ESV less than 70 ml [12].

When compared with SPECT, PET also has the advantage of quantitative analysis of myocardial blood flow and calculation of coronary flow reserve (CFR) with pharmacologic stress. With SPECT, transient ischemic dilation of the left ventricle or decrease in ejection fraction during stress may suggest multivessel disease [12]. Similarly, PET with CFR may even more accurately determine myocardium at risk. For example, while a perfusion defect may implicate single-vessel CAD, abnormal findings on CFR may correctly reclassify the patient as having multivessel CAD.

A growing consensus endorses PET as the most effective imaging technique for myocardial perfusion imaging and points to some very clear advantages compared with SPECT. PET imparts a higher specificity than SPECT, which is most likely a consequence of its superior attenuation correction, increased count-density images, and superior spatial resolution. Such improvements include the ability to extract myocardial blood flow reserve and coronary flow reserve measurements [13]. PET has improved spatial resolution as 2–3 mm as compared with the 6- to 8-mm resolution of conventional SPECT imaging [14].

MPI PET has been extensively evaluated and has been shown to be both sensitive and specific for the diagnosis of CAD. A meta-analysis including 14 studies (840 patients) demonstrated a sensitivity of 0.92 (95% CI 0.90 to 0.94) and specificity of 0.85 (95% CI 0.79 to 0.90) for the detection of CAD [15].

There are multiple studies directly comparing the diagnostic utility of PET as compared with SPECT that have demonstrated similar or superior diagnostic accuracy for PET. On a per-patient basis, PET had a higher diagnostic accuracy (91% versus 76%) and higher specificity (100% versus 66%) for detection of a 50% or greater coronary artery stenosis [16].

Stress myocardial perfusion imaging provides also strong prognostic information with identification of low-risk patients. As patients typically referred for stress have an intermediate probability of having CAD, patients with unequivocally normal stress myocardial perfusion SPECT studies have a <1% rate of having a risk of future cardiac events (death or acute myocardial infarction) [17]. Similar to SPECT, patients with a normal ^{82}Rb PET study exhibited only 0.4% annual cardiac event rates [18]. Therefore, in diagnosing CAD, PET with analysis of myocardial blood flow has the potential to affect clinical practice in two important ways. First, normal myocardial blood flow may offer such a high negative predictive value to exclude obstructive CAD that further invasive testing is not needed, even in higher risk patients. Second, abnormal CFR may improve classification of ischemia [19]. The extent and severity of myocardial ischemia and myocardial viability can serve as useful guides for deciding between revascularization and medical therapy. Patients without significant myocardial ischemia by SPECT or PET may not benefit from revascularization and would be ideally managed with maximal medical therapy. In retrospective studies, revascularization is associated with improved survival compared with medical therapy in patients with moderate to severe ischemia (ischemia exceeding 10% of LV mass) [20]. Results from retrospective studies have been similar in diabetics and in the elderly. In diabetic patients, coronary artery bypass grafting was associated with improved survival among patients with moderate to severe ischemia as detected by SPECT MPI [21]. Among elderly patients without known CAD, a benefit from revascularization was observed only in patients with ischemic myocardium ≥15% [22].

Hybrid cameras: PET/CT and SPECT/CT

Integrated SPECT/CT and PET/CT scanners are gaining popularity as hybrid molecular imaging devices which can acquire SPECT and CT in a single exam [23]. With the introduction of hybrid PET/CT or SPECT/CT systems, complementary information of coronary anatomy and its physiologic significance on myocardial blood flow reserve can be realized immediately, at the same imaging session [24]. Cardiac CT angiography, with resolution of 0.7- to 1-mm range, is suited to provide information on the presence and extent of occlusive CAD, PET and SPECT, on the other hand, are more suited to determine the functional consequences of isolated or sequential anatomic lesions and the status of myocardial viability. The combination of these anatomic and functional data is particularly relevant in patients who have an intermediate finding on either myocardial perfusion or CT angiography and has been shown to improve sensitivity and specificity of scintigraphic techniques. The integration of PET and multidetector CT scanners has interesting capabilities in cardiology. This technology enables detection and quan-

tification of the burden of calcified and noncalcified plaques, quantification of vascular reactivity and endothelial health, identification of flow-limiting coronary stenoses, and, potentially, identification of high-risk plaques (through fusion of anatomy and biology with molecularly targeted PET) in the coronary arteries in the same setting [25]. Integrated PET/CT offers an opportunity to assess the presence and magnitude of subclinical atherosclerotic disease burden and to measure myocardial blood flow (in mL/min/g of myocardium) as a marker of endothelial function [26].

Myocardial perfusion imaging SPECT/CT and PET/CT facilitates CAD management in both the elective and the acute settings by providing valuable information on diagnosis as well as prognosis [17]. Stress myocardial perfusion imaging provides strong prognostic information with identification of low-risk patients. As patients typically referred for stress have an intermediate probability of having CAD, patients with unequivocally normal stress myocardial perfusion SPECT/CT studies have a <1% rate of having a future cardiac event (death or acute myocardial infarction) [17]. By providing concurrent quantitative information about myocardial perfusion and metabolism with coronary and cardiac anatomy, PET/CT offers the opportunity for a comprehensive noninvasive evaluation of the consequences of atherosclerosis in the coronary arteries and the myocardium [27].

Future directions

The current myocardial perfusion imaging toolset has limited sensitivity for screening patients who are at risk for acute coronary syndrome. Therefore, identification of subclinical coronary artery atherosclerosis to enhance primary prevention of CAD, acute myocardial infarction, and sudden cardiac death requires a paradigm shift in the perspectives of next-generation imaging techniques. New methods to detect endothelial dysfunction and early, preclinical atherosclerotic plaques vulnerable to rupture are likely to play critical roles in the realization of this new goal for cardiac stress testing. Rather than assessing for perfusion by cardiomyocyte uptake, radiotracers complexed with molecular markers will be used to specifically target and to connect components of interest within atherosclerotic lesions. The metabolic assessment of such PET techniques coupled with anatomic assessment by CT should allow identification and, potentially, prediction of vulnerable plaques in the future.

Quantitative PET flow measurements have been used to demonstrate improvement in endothelial dysfunction and myocardial ischemia in patients with advanced CAD after medical treatment [28]. Further studies are needed to elucidate the role of PET-based coronary flow quantification in improving screening for preclinical CAD and the potential to guide therapeutic decisions. Molecular imaging offers opportunities to devote the continuously improving comprehension of the pathophysiology of atherosclerosis at the molecular and cellular levels for identification of the vulnerable plaque. There is potential for imaging unstable atherosclerotic plaques by targeting monocyte recruitment proteins, foam cells, matrix metalloproteinases, and apoptosis with molecular markers that are conjugated to a PET radiotracer [29].

Mismatches between myocardial innervation and perfusion are common in patients with CAD. Regional denervation of the heart in the post ischemic myocardium may persist for 15 days or longer after an ischemic event. In the post myocardial infarction setting, the territory of abnormal ^{123}I-MIBG tracer uptake (corresponding to sympathetic denervation) often exceeds the final infarct size, and such patients are at higher risk for subsequent ventricular arrhythmias. MIBG studies are promising in selecting heart failure patients for ICD therapy [30].

Further understanding of CAD pathophysiology at the molecular and cellular levels will allow radionuclide imaging to evolve into a primary prevention tool by earlier detection of atherosclerosis as well as identification of vulnerable plaques and adaptations in myocardial metabolism. Radionuclide tracers reflect physiologic processes at the cellular level. Nuclear imaging techniques will be also suited for cardiac molecular imaging because of their relatively high intrinsic sensitivity and excellent depth cellular penetration [31,32].

Conclusions

Both SPECT and PET cameras capture the photons emitted by a radiotracer and convert the information into digital data representing the magnitude of tracer uptake and the location of the emission in the heart. By acquiring dynamic (ECG-gated) scintigraphic data, information on regional and global LV function can be assessed in cinematographic mode. Thus, the addition of myocardial perfusion imaging to ECG monitoring during stress tests provides information about the resolution of regional ischemia, assessment for regional wall motion abnormalities, and myocardial viability. Clear competitive advantages of PET over SPECT include higher spatial and temporal resolution, reliable attenuation and scatter correction, and validated tracer kinetic models for measurement of myocardial perfusion and metabolism. By providing concurrent quantitative information about myocardial perfusion and/or metabolism with coronary and cardiac anatomy, SPECT/CT and PET/CT offers the opportunity for a comprehensive noninvasive evaluation of the consequences of atherosclerosis in the coronary arteries and the myocardium.

Conflict of interest
No conflict of interest.

Funding body
None.

Ethical statement
I declare that the research was conducted according to Declaration of Helsinki.

References

[1] The Task Force on the management of stable coronary artery disease of the European Society of Cardiology 2013 ESC guidelines on the management of stable coronary artery disease, European Heart Journal 34 (2013) 2949–3003.

[2] H.W. Strauss, K. Harrison, J.K. Langan, et al., Thallium-201 for myocardial imaging: relation of thallium-201 to regional myocardial perfusion, Circulation 51 (1975) 641–645.
[3] R.J. Gibbons, G.J. Balady, J.T. Bricker, et al., ACC/AHA 2002 guideline update for exercise testing: summary article – a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines), Journal of the American College of Cardiology 40 (2002) 1531–1540.
[4] R.C. Hendel, D.S. Berman, M.F. Di Carli, et al., Appropriate use criteria for cardiac radionuclide imaging, Journal of the American College of Cardiology 53 (2009) 2201–2229.
[5] O. Sogbein, M. Pelletier-Galarneau, T. Schindler, et al., New SPECT and Q6 PET radiopharmaceuticals for imaging cardiovascular disease, BioMed Research International 2014 (2014) Article ID 942960.
[6] F. Bengel, T. Higuchi, M. Javadi, R. Lautamäki, Cardiac positron emission tomography, Journal of the American College of Cardiology 54 (2009) 1–15.
[7] J.J. Bax, V. Delgado, Myocardial viability as integral part of the diagnostic and therapeutic approach to ischemic heart failure, Journal of Nuclear Cardiology 22 (2015) 229–245.
[8] F.J. Klocke, M.G. Baird, B.H. Lorell, et al., ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging), Circulation 108 (2003) 1404–1418.
[9] L.J. Shaw, A.E. Iskandrian, Prognostic value of gated myocardial perfusion SPECT, Journal of Nuclear Cardiology 11 (2004) 171–185.
[10] B.A. Mc Ardle, T.F. Dowsley, R.A. deKemp, et al., Does rubidium-82 have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease, Journal of the American College of Cardiology 60 (2012) 1828–1837.
[11] R. Hachamovitch, S.W. Hayes, J.D. Friedman, et al., Stress myocardial perfusion single-photon emission computed tomography is clinically effective and cost effective in risk stratification of patients with a high likelihood of coronary artery disease (CAD) but no known CAD, Journal of the American College of Cardiology 43 (2004) 200–208.
[12] T. Sharir, G. Germano, P.B. Kavanagh, et al., Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography, Circulation 100 (1999) 1035–1042.
[13] K. Mahdoubi, Molecular Imaging, Springer, 2013.
[14] S.L. Bacharach, J.J. Bax, J. Case, et al., PET myocardial glucose metabolism and perfusion imaging, Part 1: Guidelines for data acquisition and patient preparation, Journal of Nuclear Cardiology 10 (2003) 543–556.
[15] K.R. Nandalur, B.A. Dwamena, A.F. Choudhri, et al., Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a meta-analysis, Academic Radiology 15 (2008) 444–451.
[16] T.M. Bateman, G.V. Heller, A.I. McGhie, et al., Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT, Journal of Nuclear Cardiology 13 (2006) 24–33.
[17] D.S. Berman, R. Hachamovitch, L.J. Shaw, et al., Roles of nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance: noninvasive risk stratification and a conceptual framework for the selection of noninvasive imaging tests in patients with known or suspected coronary artery disease, Journal of Nuclear Medicine 47 (2006) 1107–1118.
[18] K. Yoshinaga, B.J. Chow, K. Williams, et al., What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? Journal of the American College of Cardiology 48 (2006) 1029–1039.
[19] M.A. Lodge, H. Braess, F. Mahmoud, et al., Developments in nuclear cardiology: transition from single photon emission computed tomography to positron emission tomography–computed tomography, Journal of Invasive Cardiology 17 (2005) 491–496.
[20] R. Hachamovitch, S.W. Hayes, J.D. Friedman, et al., Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography, Circulation 107 (2003) 2900–2907.
[21] P. Sorajja, P. Chareonthaitawee, N. Rajagopalan, et al., Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting, Circulation 112 (2005) 311–316.
[22] R. Hachamovitch, X. Kang, A.M. Amanullah, et al., Prognostic implications of myocardial perfusion single-photon emission computed tomography in the elderly, Circulation 120 (2009) 2197–2206.
[23] C.N. Patel, F.U. Chowdhury, A.F. Scarsbrook, Hybrid SPECT/CT: the end of unclear medicine, Postgraduate Medical Journal 85 (2009) 606–613.
[24] H.W. Strauss, J. Narula, T. Nakahara, Finding calcium in noncalcified lesions: 18F-fluoride offers insights into atheroma evolution, Journal of Nuclear Medicine 56 (2015) 974–975.
[25] T. Schindler, H. Schelbert, A. Quercioli, V. Dilsizian, Emerging role of Q7 PET imaging, Journal of the American College of Cardiology: Cardiovascular Imaging 3 (2010) 623–640.
[26] F.J. Wackers, SPECT detection of coronary artery disease, in: V. Dilsizian, J. Narula (Eds.), Atlas of Nuclear Cardiology, Current Medicine, Inc., Philadelphia, PA, 2003, 63–77.
[27] M. Carli, S. Dorbala, J. Meserve, et al., Clinical myocardial perfusion PET/CT, Journal of Nuclear Medicine 48 (2007) 783–793.
[28] T.H. Schindler, H.R. Schelbert, PET quantitation of myocardial blood flow, in: V. Dilsizian, J. Narula (Eds.), Atlas of Nuclear Cardiology, 2nd ed., Current Medicine, Inc., Philadelphia, PA, 2006, 67–96.
[29] J.R. Davies, J.H. Rudd, P.L. Weissberg, J. Narula, Radionuclide imaging for the detection of inflammation in vulnerable plaques, Journal of the American College of Cardiology 47 (2006) C57–C68.
[30] R. Arora, K.J. Ferrick, T. Nakata, et al., I-123 MIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator, Journal of Nuclear Cardiology 10 (2003) 121–131.
[31] S.R. Underwood, P. Bondt, A. Flotats, et al., The current and future status of nuclear cardiology: a consensus report, European Heart Journal: Cardiovascular Imaging 15 (2014) 949–955.
[32] M. Vesely, V. Dilsizian, Nuclear cardiac stress testing in the era of molecular medicine, Journal: of Nuclear Medicine 49 (2008) 399–413.