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Current and Future Status of Blood Flow Tracers

Alberto Cuocolo · Corrado Cittanti · Wanda Acampa · Michele Larobina · Mario Petretta

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Abstract Myocardial perfusion imaging is important for the management of patients with suspected or known coronary artery disease. Nuclear cardiology is the most widely used noninvasive approach for the assessment of myocardial perfusion. The available single-photon emission CT (SPECT) flow agents are characterized by a rapid myocardial extraction and by a cardiac uptake proportional to blood flow. In addition, different positron emission tomography (PET) tracers may be used for the absolute quantitative measurement of myocardial blood flow and coronary flow reserve. However, the available SPECT and PET tracers for myocardial perfusion imaging have some limitations that must be considered to maximize their clinical applications and there is still a well-recognized need for the development of new perfusion tracers with more ideal properties. This review illustrates the current status and the future perspectives of blood flow tracers for SPECT and PET myocardial perfusion imaging.

Keywords Myocardial blood flow · coronary flow reserve · radiotracers · SPECT · PET

A. Cuocolo (✉)
Department of Biomorphological and Functional Sciences,
University of Naples Federico II,
Via Pansini 5,
80131 Naples, Italy
e-mail: cuocolo@unina.it

A. Cuocolo
SDN Foundation,
Institute of Diagnostic and Nuclear Development,
Naples, Italy

C. Cittanti
Department of Radiological Sciences, University of Ferrara,
Ferrara, Italy

W. Acampa · M. Larobina
Institute of Biostructures and Bioimages,
National Council of Research,
Naples, Italy

M. Petretta
Department of Clinical Medicine,
Cardiovascular and Immunological Sciences,
University of Naples Federico II,
Naples, Italy

Introduction

In current clinical practice the assessment of myocardial perfusion with radiotracers is an integral component of the evaluation of patients with suspected or known coronary artery disease (CAD) and it has been successfully performed for over 30 years. More than 10 million studies per year are executed worldwide with a rich literature confirming both high diagnostic and prognostic values of this approach. Its strengths include standardized protocols, ease of use, and well-established guidelines [1••] and, over these years, considerable technological advancement has been made to improve image quality and optimize acquisition protocols. However, the assessment of myocardial perfusion is closely related to development of more suitable radiopharmaceuticals. In particular, a myocardial perfusion imaging agent should ideally exhibit a high first-pass extraction linearly correlated with increasing flow in the hyperemic range, and must be labeled with a radioisotope having optimal half-life, suitable energy, and favorable dosimetry. Moreover, the clearance rates of the compound from the myocardium after initial uptake should be slow enough in comparison to background to allow acquisition of high-quality images. Finally, the technical feasibility of

performing an absolute quantitative measurement of myocardial blood flow would be highly desirable.

First historical attempts to perform myocardial perfusion imaging with potassium-43 and rubidium-81 in the early 1970s, despite a wide number of technical limitations, provided a conceptual framework for future developments in this field [2, 3]. The introduction of thallium-201 (^{201}Tl) in the mid-1970s represented a milestone in the development and widespread clinical use of myocardial perfusion imaging [4]. Indeed, this radiotracer had a great impact on diagnostic evaluation, risk stratification, and therapeutic decision-making in patients with CAD over the next two decades. However, ^{201}Tl has important limitations, like a relatively low energy of emitted photons, a physical half-life of 73 h, and an unfavorable biodistribution in testes and kidneys. These restrictions affect the amount of administrable dose to approximately 150 MBq, limiting image quality, in association with a relatively high-absorbed dose and thereby stimulating the research for better myocardial perfusion imaging agents.

When technetium-99 m (^{99m}Tc)–labeled compounds, such as methoxyisobutyl isonitrile (sestamibi) and 1,2-bis [bis(2-ethoxyethyl)phosphino] ethane (tetrofosmin), were approved for clinical use in the early 1990s, there was a rapid adoption of these radiopharmaceuticals [5]. Despite a lower first-pass extraction in the myocardium and higher uptake in bowel and liver in comparison to ^{201}Tl, these tracers have relatively higher-energy photons, a shorter physical half-life (6 h), and can be used in much higher doses limiting attenuation artifacts with superior single-photon emission CT (SPECT) image quality and providing a lower radiation burden than that achieved through ^{201}Tl imaging. Another major advantage of ^{99m}Tc-labeled agents over ^{201}Tl is that, in addition to perfusion data, post-stress assessment of left ventricular function (motion, thickening, and ejection fraction) can be accurately determined with ECG-triggered acquisition (gated-SPECT) using one injection and one imaging sequence. By providing this additional information gated-SPECT helps to significantly increase both specificity and prognostic value of myocardial scintigraphy [6•]. However, despite the success of these single-photon tracers, there is still the room for further improvement in myocardial perfusion imaging. In particular the presence of diffuse disease in all three main coronary arteries may decrease the sensitivity of conventional SPECT images for each individual vessel, and "balanced ischemia" may mask or minimize the presence of disease [7]. In this context, myocardial perfusion positron emission tomography (PET) offers many theoretical advantages over traditional single-photon techniques. These advantages include higher spatial and contrast resolution, resulting in higher image quality and improved diagnostic accuracy. Moreover, the possibility to quantify myocardial perfusion in absolute terms (ie, milliliters per gram per minute), that allows the noninvasive evaluation of coronary microcirculation and the identification of three-vessel disease, represents the major goal of PET. Despite the fact that clinical value of cardiac PET imaging was demonstrated more than 30 years ago [8], its use has been minimal because of several reasons. The main ones are represented by the need for an on-site cyclotron, high costs of PET scanners, lack of reimbursement, and limited availability of user-friendly software for cardiac image processing and display [9]. Nowadays, however, the increasing availability of PET facilities in a large number of nuclear medicine centers worldwide is rapidly changing many of these issues.

Current Status of SPECT Perfusion Tracers

The principal characteristics of the currently used SPECT perfusion tracers are illustrated in Table 1. Despite its several virtues and a rich history as a myocardial perfusion agent, ^{201}Tl has suffered in recent decades the increasing popularity of ^{99m}Tc-labeled agents. In fact, due to its favorable chemical and physical characteristics, ^{99m}Tc can be incorporated into a wide range of organic as well as inorganic molecules, and therefore, it became the radioiso-

Table 1 Principal characteristics of currently used SPECT and PET blood flow tracers

	Production	Physical half-life	Energy, *keV*	Extraction fraction,%
SPECT tracers				
^{201}Tl	Cyclotron	72 h	80,165	80
^{99m}Tc-sestamibi	Generator	6 h	140	65
^{99m}Tc-tetrofosmin	Generator	6 h	140	60
PET tracers				
^{13}N-ammonia	Cyclotron	10 min	511	95
^{82}Rb	Generator	1.3 min	511	50
^{15}O-water	Cyclotron	2.1 min	511	100

tope of choice for the development of the last generation of myocardial perfusion SPECT agents. In the attempt to obtain the ideal myocardial perfusion tracer a wide number of ^{99m}Tc compounds have been synthesized and experimentally tested in animals and men during the last 30 years. Based on their structural characteristics, these ^{99m}Tc-labeled myocardial perfusion imaging agents were divided into two main categories: lipophilic cationic agents, consisting of 1) isonitriles (sestamibi), 2) diphosphines (tetrofosmin), and 3) Q complexes; and lipophilic neutral agents, consisting of 1) teboroxime and 2) N-NOEt.

Although showing a high myocardial extraction and favorable biodistribution in animals, neutral compounds were affected by relatively rapid myocardial clearance and prominent sustained liver uptake. This unfavorable combination turns into a "challenge" the identification of best timing for acquisition and, de facto, precludes a routinely clinical use of these tracers. Q complexes even compare favorably with exercise-redistribution ^{201}Tl showing good preliminary biodistribution data in man, as for the ^{99m}Tc-N-NOEt. However, these complexes have not been submitted for FDA approval. Because of good myocardial image quality due to high contrast in uptake between left ventricle and lungs, sestamibi and tetrofosmin are the only compounds based on ^{99m}Tc chemistry that achieved the clinical routine. Therefore, nowadays the spectrum of single-photon-emitting radiopharmaceuticals approved for clinical use as myocardial perfusion tracers is limited to ^{201}Tl-chloride, ^{99m}Tc-sestamibi, and ^{99m}Tc-tetrofosmin. Several studies have attempted to highlight the possible superiority of a tracer on the other, analyzing and comparing their diagnostic and prognostic potential in various clinical settings and different patient subgroups. ^{201}Tl was used as a reference for evaluating clinical performance of ^{99m}Tc-based radiopharmaceuticals. As previously reported, there are technical differences between these tracers mainly related to the uptake modalities of the compounds [10] and to the imaging characteristics. These aspects, in particular if a pharmacologic stress is performed, may affect in different ways the biodistribution of the tracers accounting for the differences reported in literature in radiopharmaceuticals behavior, mainly in studies with limited groups of selected patients and specific clinical settings [11–13]. However, in data emerging from large prospective controlled trials performed over the past 20 years in order to assess the diagnostic accuracy of myocardial perfusion scintigraphy for the detection of CAD, a good correlation and a broadly comparable clinical behavior of the three tracers has been shown. In particular, in the largest study of 2560 patients randomized to each of the three compounds [14], overall sensitivity in the subset of patients undergoing angiography was 91% and specificity 87%, with no significant difference between the three tracers. However, according to the authors' conclusions, in obese patients and in women with large breasts the use of ^{99m}Tc agents should be preferred to reduce the impact of soft tissue attenuation artifacts. Moreover, the use of radiopharmaceutical-specific normal data files is recommended for quantitative analysis of SPECT images [15].

Current Status of PET Perfusion Tracers

PET has many advantages over SPECT, including higher spatial resolution and the ability to provide absolute quantitative measurements of physiologic parameters, such as regional myocardial blood flow and coronary flow reserve (Fig. 1). The most common tracers currently used for the assessment of myocardial perfusion with PET are nitrogen-13 (^{13}N) ammonia, rubidium-82 (^{82}Rb), and oxygen-15 (^{15}O) water [16]. The principal characteristics of these tracers are illustrated in Table 1. When injected, ^{13}N-ammonia is extracted by myocardial tissue with a very high extraction fraction where it is converted to ^{13}N-glutamine [17]. The clearance half time of ^{13}N-ammonia activity from the myocardium is slow enough that one can wait until blood pool activity is significantly lower than myocardial activity. ^{13}N-ammonia myocardial extraction is nonlinear and inversely related to blood flow. ^{13}N-ammonia provides excellent-quality images of the myocardium, because of the high single-pass extraction (approximately 70%–80% at physiologic flow rates), the relatively prolonged retention of tracer by the heart (biological half-life of 80–400 min) after intravenous administration, and the rapid blood-pool clearance (Fig. 2). Imaging with ^{13}N-ammonia requires either an on-site cyclotron or close proximity to a regional positron radiopharmaceutical source centre. ^{82}Rb is a cation and its uptake depends on myocardial perfusion [18]. An advantage of ^{82}Rb over ^{13}N-ammonia is the production by a generator without the need for a costly cyclotron. The single-pass extraction of ^{82}Rb by the myocardium is inversely and nonlinearly related to coronary blood flow. The quality of images obtained after intravenous administration of ^{82}Rb depends on the tracer infusion duration and imaging protocol. Although disappearance of tracer from arterial blood is rapid, infusion system with prolonged administration time results in high myocardial blood-pool activity. ^{15}O-water is a freely diffusible tracer with a short physical half-life (2.1 min) requiring an on-site cyclotron. To effectively obtain myocardial images, ^{15}O-water (because of its short half-life) requires administration with rapid data acquisition. Because water is distributed in both the vascular space and myocardium, visualization of myocardial activity with this tracer requires correction for activity in the vascular compartments, which makes the images difficult to interpret

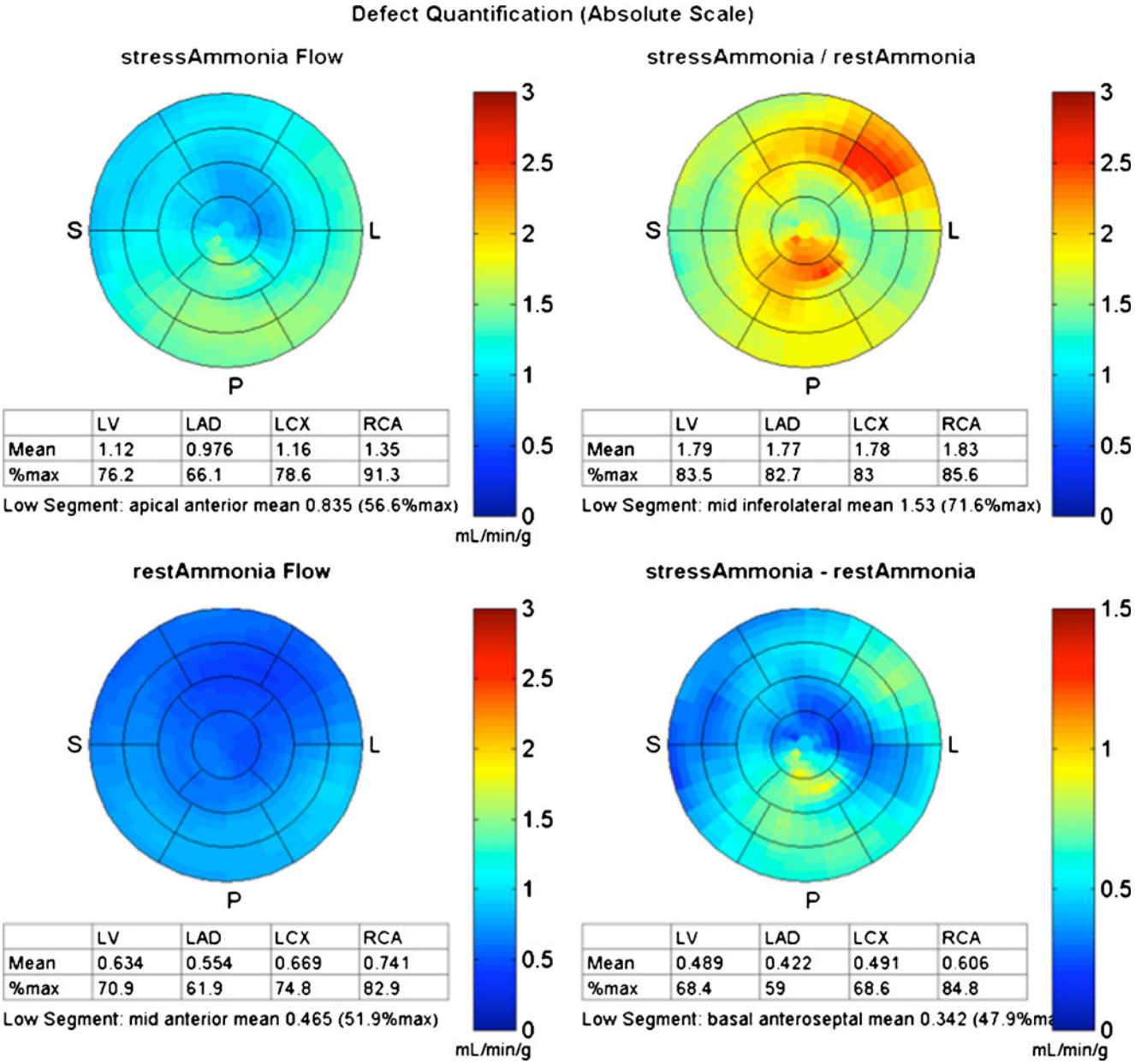

Fig. 1 Example of myocardial blood flow quantification with stress (dipyridamole) and rest ^{13}N-ammonia PET imaging in a patient with nonischemic dilated cardiomyopathy: 17-segment model polar maps of rest blood flow (*lower left*; color scale: 0–3.0 mL/min/g), stress blood flow (*upper left*; scale: 0–3.0 mL/min/g), flow reserve (*upper right*; scale: 0–3.0), and flow difference (*lower right*; scale: 0–1.5), which demonstrate a global impairment (absolute and percentage values are displayed in the *tables below*)

visually. The correction can be performed based on the early ^{15}O-water kinetic information or is accomplished by acquiring a separate scan that identifies either the intravascular compartment [19].

PET has a high sensitivity and specificity for the detection of myocardial ischemia. Studies that compared perfusion imaging with PET and SPECT in the assessment of CAD found PET to be superior to SPECT in terms of sensitivity, specificity, and predictive accuracy [20, 21]. Myocardial perfusion PET is particularly useful in reducing the number of false-positive SPECT studies due to attenuation artifacts. The higher sensitivity of PET can also be useful in the evaluation of quantitative myocardial blood flow. Gated-PET may provide additional information regarding peak stress ventricular function, which is an advantage to gated-SPECT. Patients in whom stress imaging with exercise is neither required nor feasible, and patients with a high likelihood of false-positive or false-negative studies by SPECT, are likely to benefit from PET imaging. This includes obese individuals and women with

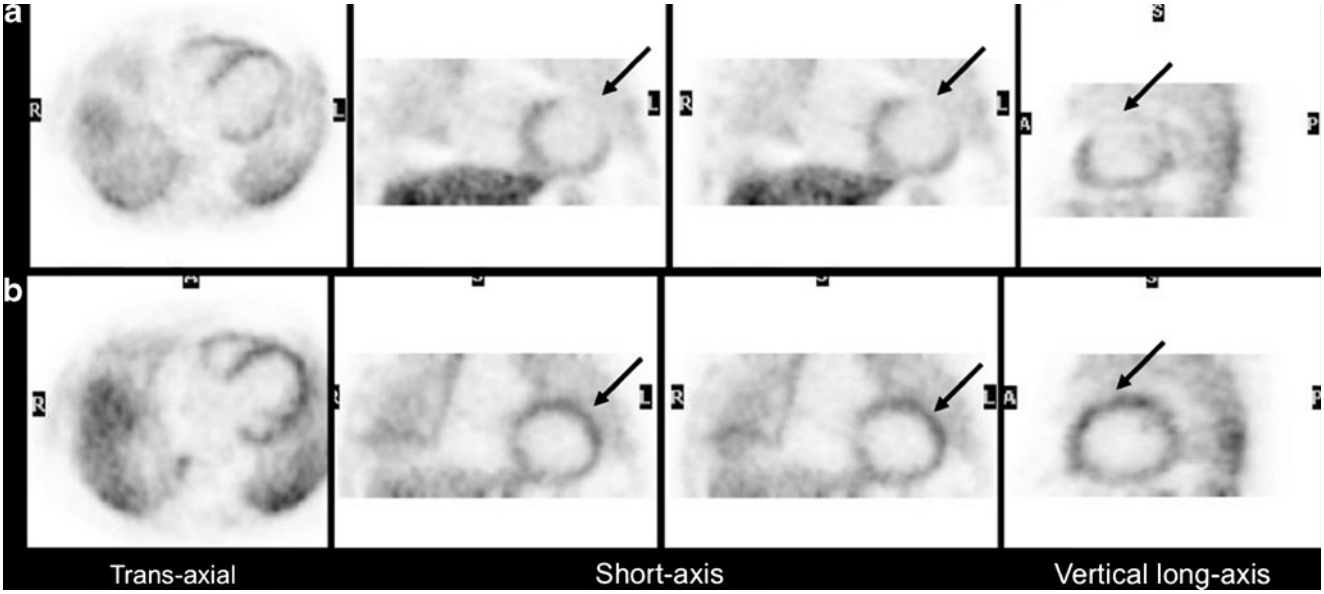

Fig. 2 Transaxial, short-axis, and long-axis images of PET myocardial perfusion obtained at stress (dipyridamole) and at rest with ^{13}N-ammonia in a patient with ischemic dilated cardiomyopathy and atypical chest pain. There is a moderately large flow deficit in the lateral and anterolateral walls (*arrows*) with stress **a** that is normal at rest **b**

large breasts, where SPECT imaging is less effective due to attenuation artifacts. Many patients with end-stage renal and liver disease have edema, ascites, and high-elevated diaphragms, sometimes with pericardial effusions, which may lead to non-uniform attenuation abnormalities [22]. Furthermore, patients with equivocal results with other noninvasive tests or conflicting results can benefit from PET imaging.

Future Perspectives of SPECT Perfusion Tracers

An ideal myocardial perfusion single-photon imaging agent has been sought in nuclear cardiology. The commercial agents ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin, despite the excellent and comparable clinical results achieved [14], do not have all the traits of an ideal tracer. In particular, a high first-pass extraction and linear relationship between flow and tracer uptake are key indicators of ideal behavior. As previously reported [23], sestamibi and tetrofosmin do not exhibit optimal values for these parameters. The major drawback in image quality for ^{99m}Tc compounds is the early hepatic uptake that may interfere with assessment of the inferior left ventricular wall, mostly in studies at rest or after dipyridamole or adenosine administration. Various strategies, such as delayed image acquisition or ingestion of a fatty meal, milk, chilled or carbonated water, have been proposed to deal with this limitation, with often contradictory results [24].

Thus, there is a clinical need for a radiotracer with high heart uptake and a substantially better heart-to-liver ratio than that of sestamibi and tetrofosmin. In fact, as underlined in an excellent editorial by Zaret [25], these radiopharmaceuticals "…stand in the middle, rather than at the end, of a journey in the pursuit of the ideal!" Despite this need, there has not been a great impetus in the development of new perfusion agents in the 10 years after FDA tetrofosmin approval in 1996. However, in the last few years with the goal of speeding up hepatic clearance while maintaining high myocardial image quality, a number of experimental studies addressed the issue of developing new radiopharmaceuticals toward the improvement of myocardial and liver kinetics in comparison with those of clinically available ^{99m}Tc compounds. In particular, attention is now focused on two distinct classes of radiopharmaceuticals: the first including an electrically neutral lipophilic compound labeled with ^{125}I, rotenone, and the second, grouping a class of cationic perfusion imaging agents, all labeled with ^{99m}Tc.

7'-Z-iodorotenone (ZIROT) is an inhibitor of complex I of the mitochondrial transport electron chain that has been labeled with ^{125}I. Z-iodorotenone is a neutral and lipophilic compound and has been shown to have high first-pass extraction (~ 84%) and better retention in comparison to sestamibi (~ 48% first-pass extraction) in isolated perfused rabbit heart studies [26]. While the absolute heart uptake of iodorotenone was similar to that of sestamibi and tetrofosmin, ZIROT demonstrated significantly superior ($P<0.001$) heart-to-lung ratios in rodents at 1 h post-injection [27]. However, biodistribution experiments in adult male Sprague–Dawley rats indicated that Z-iodorotenone heart-to-liver ratio was similar to that of sestamibi but signifi-

cantly lower than that of tetrofosmin [26]. Despite these preliminary experimental results suggesting favorable distribution characteristics of ZIROT in comparison to the currently used ^{99m}Tc tracers, no data are yet available in human models.

As mentioned above, ^{99m}Tc-N-NOEt represents the first reported example of a heart imaging agent characterized by the presence of a terminal Tc'N multiple bond. It has a square-pyramidal geometry in which two identical bidentate dithiocarbamate ligands are symmetrically bound to a Tc'N group in the basal plane of the square-pyramid [28]. Thereafter, a new class of asymmetric, cationic perfusion imaging agents has been synthesized in order to optimize the balance between myocardial extraction and liver uptake [29]. The molecular structure of this class of compounds has a common chemical feature that lies in a Tc≡N core bound to two different bidentate ligands, thereby giving rise to asymmetrical complexes carrying a single positive charge [30]. The first in order of time was the monocationic nitrido ^{99m}Tc complex DBODC whose biodistribution behavior was extensively studied in rats [29, 31] and dogs [32]. These preclinical results in animals showed that heart uptake of ^{99m}Tc-N-DBODC and washout from blood and lungs, as well as kinetic features, as determined in dogs, are similar to those of the commercial radiopharmaceuticals sestamibi and tetrofosmin. However, a prominent difference was observed in liver washout, which was remarkably rapid and quantitative, leading to a heart-to-liver ratio at 60 min after injection in rats approximately 10 times higher than that of sestamibi and tetrofosmin [30, 31, 33]. Based on these promising results a phase 1 study has been carried out [34••] showing that this tracer has the desirable characteristics of the highest heart uptake observed for a monocationic myocardial perfusion tracer in humans (Fig. 3) and a fast and quantitative washout from non-target organs surrounding the heart region (Table 2). Under these conditions, the heart region is quickly visualized at 5 min after injection, and liver activity appears to be significantly reduced also 30 min after tracer administration both in rest and in stress images, making ^{99m}Tc-N-DBODC a promising myocardial perfusion agent with improved imaging properties. Representative planar whole-body images of the biodistribution of ^{99m}Tc-N-DBODC in healthy volunteers are shown in Fig. 4.

Another monocationic nitrido-compound under evaluation is ^{99m}Tc-N-MPO [35]. In rats it accumulates in the mitochondrial fraction to the same extent as sestamibi as demonstrated by a myocardial subcellular distribution study. Moreover, its biodistribution data in Sprague–Dawley rats showed a heart-to-liver ratio significantly higher than that of sestamibi at all time points, and also slightly higher than that of ^{99m}Tc-N-DBODC. It has been postulated that multidrug resistance transport function of

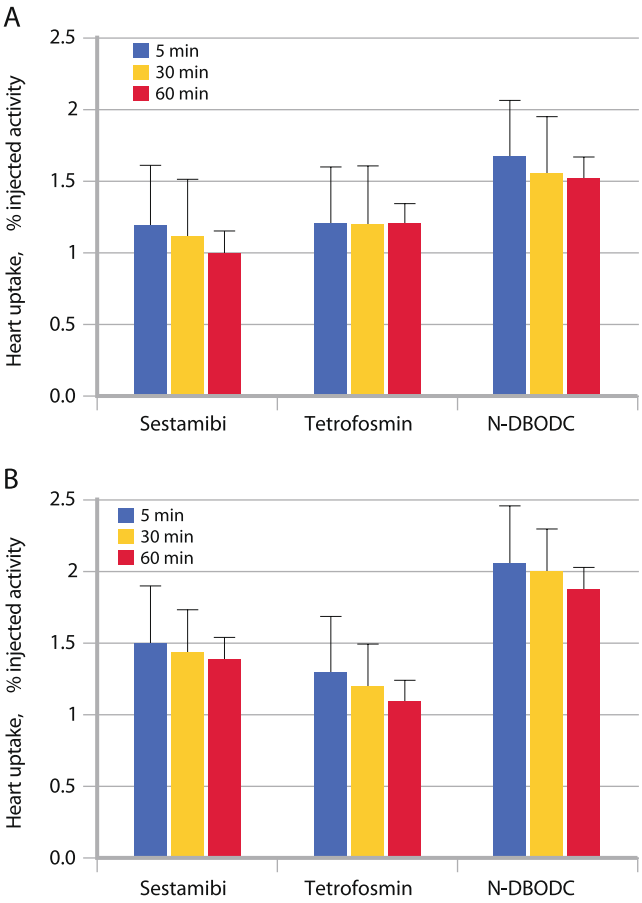

Fig. 3 Heart uptake (% injected activity) of ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, and ^{99m}Tc-N-DBODC in healthy volunteers under rest **a** and stress **b** conditions at different time intervals

hepatocytes and renal cells may be responsible for the fast clearance of ^{99m}Tc-N-MPO from liver and kidneys, respectively. However, additional comparison studies in guinea pigs [36] and dogs [37•] showed results below expectations: myocardial and liver uptake values were similar for the two tracers, resulting in only a mild to moderate advantage in heart-to-liver ratio of ^{99m}Tc-N-MPO over sestamibi. Unfortunately, no clinical data are yet available regarding the myocardial and liver kinetics of ^{99m}Tc-N-MPO in patients.

The last promising compound belonging to the core Tc≡N class is ^{99m}Tc-15 C5-PNP, a tricarbonyl complex with high solution stability and rapid clearance from blood and non-target organs in rodents [38]. This agent was recently evaluated in comparison with ^{99m}Tc-sestamibi in a male Sprague–Dawley rat heart model and despite heart-to-liver ratio values lower than that observed in a previous study [39], in vivo micro-SPECT acquisitions revealed cardiac perfusion images of similar quality with both tracers. In particular, a good visualization of the normal left ventricular wall and perfusion defects could be achieved 15 to 20 min after intravenous administration of ^{99m}Tc-15 C5-PNP. More-

Table 2 Heart-to-lung and heart-to-liver ratios measured at different times for ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, and ^{99m}Tc-N-DBODC in 10 healthy male volunteers under stress and rest conditions

	Heart-to-lung ratio		Heart-to-liver ratio	
	Rest	Stress	Rest	Stress
^{99m}Tc-sestamibi				
5 min	1.90±0.20	2.10±0.10	0.50±0.10	1.30±0.10
30 min	2.20±0.10	2.30±0.20	0.50±0.10	1.40±0.20
60 min	2.40±0.10	2.40±0.20	0.60±0.10	1.80±0.30
^{99m}Tc-tetrofosmin				
5 min	3.10±1.80	4.00±1.10	0.40±0.10	0.80±0.30
30 min	4.50±1.50	5.90±2.20	0.60±0.30	1.20±0.70
60 min	7.30±4.40	5.90±1.30	1.20±0.80	3.10±3.00
^{99m}Tc-N-DBODC				
5 min	2.17±0.20	2.55±0.29	0.33±0.07	0.66±0.19
30 min	2.33±0.21	2.49±0.45	0.48±0.10	0.94±0.38
60 min	2.40±0.26	2.58±0.41	0.74±0.13	1.26±0.28

over, the hepatic washout of this compound was significantly faster and greater than that of sestamibi leading to images with a significantly lower liver activity. If these encouraging preliminary data will be reproduced in humans, ^{99m}Tc-15 C5-PNP will be a welcome addition to currently approved perfusion agents.

It should be noted, however, that scientific research directed toward identifying new myocardial perfusion tracers never stops. An Italian group recently published the synthesis and biological evaluation of a new series of bidentate ligands aimed to increase the first-pass extraction of Tc ≡ N monocationic compounds, trying to keep unaltered their favorable imaging properties [40•]. The study shows that the incorporation of alicyclic dithiocarbamate in the $[^{99m}Tc(N)(PNP)]^{+}$ building block yields to a significant increase of the heart uptake at early injection point, suggesting that the first-pass extraction fraction of these novel complexes may be increased with respect to the other cationic ^{99m}Tc agents keeping almost unaltered the favorable target/non-target ratios.

Future Perspectives of PET Perfusion Tracers

^{82}Rb has the advantage of not requiring an on-site cyclotron and is currently the most widely used tracer for assessment of myocardial perfusion with PET. The kinetic properties of this radionuclide are similar to those of ^{201}Tl and it is appropriate for myocardial perfusion imaging using qualitative or semi-quantitative evaluation. On the other hand, its potential for absolute quantification of blood flow is still under investigation [41••]. ^{13}N-ammonia and ^{15}O-water are the most often used and validated PET tracers for quantification of myocardial perfusion [16]. However, they have short half-lives (10 and 2 min, respectively) and require on-site cyclotron, which limits their clinical use. Therefore, tracer availability still remains a major determinant for cardiac studies with PET.

Recently, many myocardial perfusion tracers labeled with fluorine-18 (^{18}F) have been developed: fluorodihydrorotenone, fluorobenzyl-triphenylphosphonium, fluorophenyl-triphenylphosphonium, fluoroethylrhodamine B, and BMS747158-02 [42, 43]. Due to half-life of 110 min, their availability is not limited to laboratories with on-site cyclotron, facilitating larger clinical use of PET cardiac imaging.

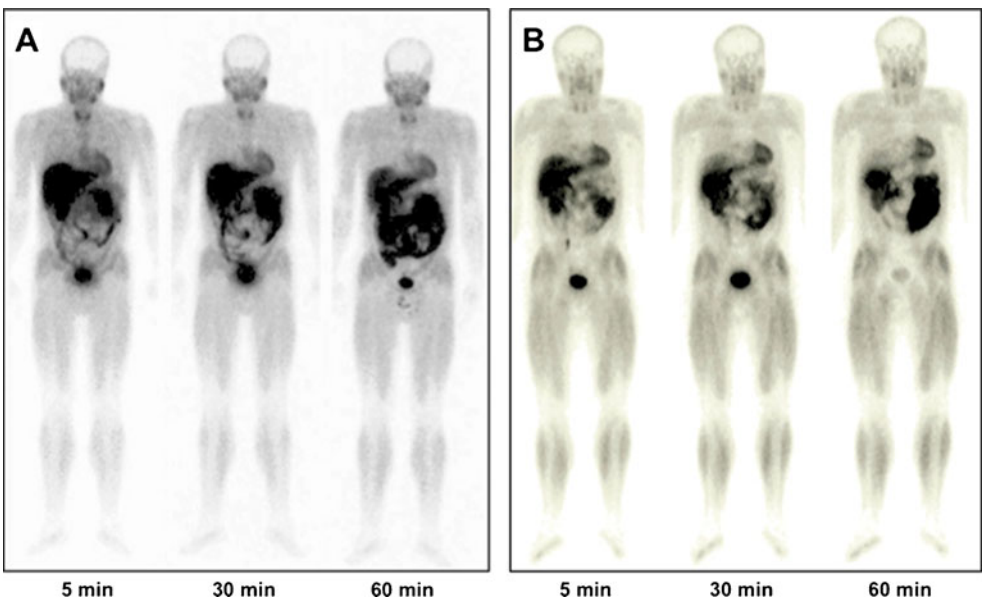

Fig. 4 Biodistribution of ^{99m}Tc-N-DBODC in two healthy volunteers under rest **a** and stress **b** conditions: planar whole-body images at different time intervals

The mechanisms of retention of ^{18}F-fluorodihydrorotenone [44] and ^{18}F-fluorobenzyl triphenyl phosphonium [45] in myocytes have not yet been completely clarified and may partly represent nonspecific binding to mitochondrial membranes. Recently, Shoup et al. [42] reported an excellent heart-to-blood ratio of ^{18}F-fluorophenyltriphenylphosphonium and a good correlation with ^{13}N-ammonia distribution in normal and LAD-occluded rabbits, suggesting that this radiopharmaceutical may have potential as a PET agent for characterizing mitochondrial damage and/or myocardial blood flow. ^{18}F-fluoroethylrhodamine B is another compound proposed as blood flow tracer [43]. However, with both these tracers no human studies have been reported.

A more promising myocardial perfusion tracer is ^{18}F-BMS747158-02, a pyridaben analogue and inhibitor of mitochondrial complex I (MTC I) of the electron transport chain in the inner mitochondrial membrane [46–48]. Because of its lipophilicity and high binding affinity to MCT I this tracer shows effective and rapid uptake in cardiomyocytes followed by very slow washout. In vivo PET studies with ^{18}F-BMS747158-02 have demonstrated excellent quality of myocardial images in different animal models. ^{18}F-BMS747158-02 first-pass myocardial extraction fraction in isolated rat and rabbit hearts is more than 90% and persistent even at very high flow rates. High, essentially flow independent extraction fraction of ^{18}F-BMS747158-02 implies an almost linear relationship between uptake and myocardial blood flow, which is an important tracer feature for assessment of flow reserve in stress testing. Experiences on the use of ^{18}F-BMS747158-02 in diseased myocardium are still limited. When injected during transient coronary artery ligation, the resulting perfusion defects were clearly delineated by ^{18}F-BMS747158-02 PET in rat and pig models [49•, 50••]. Because ^{18}F-BMS747158-02 binds to a mitochondrial enzyme, it is important to clarify whether alterations in the metabolic state of the myocardium, such as those related to work load, substrate supply, and ischemia, affect its regional retention. The effects of various chronic cardiac disease conditions, such as heart failure, on the relationship between tracer uptake and blood flow still remain to be studied. Although detailed pharmacokinetics of the tracer need to be determined in human studies, the results of the experimental studies demonstrating good image quality, stable kinetics, and high extraction over wide flow range indicate suitability of ^{18}F-BMS747158-02 for clinical protocols similar to those used with SPECT tracers. In particular, the tracer could be injected during physical exercise on a treadmill remote from the PET scanner followed by post-injection imaging similar to the SPECT protocols. Therefore, the important information on exercise-provoked symptoms as well as prognostic information related to exercise capacity can be explored. Provided that myocardial blood flow assessment can be improved, the need for doing rest and stress protocols would become less important as the absolute blood flow together with functional evaluation in gated images would provide diagnosis of inducible ischemia independently of coronary flow reserve. Finally, the use of ^{18}F-BMS747158-02 for assessment of myocardial infarction and viability in combination with FDG could also be an option in PET centers, which have FDG available.

Conclusions

Despite all of the successes achieved with the current generation of SPECT and PET myocardial perfusion tracers, there is still a recognized need for the development of new perfusion tracers with improved properties. All the available single-photon tracers for myocardial perfusion imaging have suboptimal extraction and biodistribution characteristics that must be carefully considered to maximize their clinical applications. In the last few years, the design of new ^{99m}Tc-labeled tracers has been guided by observation of the relationships between basic biological and chemical properties and corresponding myocardial images. Although ^{82}Rb has played an important role in expanding PET myocardial perfusion imaging to more clinical centers, this tracer also has some suboptimal characteristics, including the roll-off in tracer extraction at high flow rates, which is comparable to the other potassium analog, ^{201}Tl. In addition, the very short half-life of ^{82}Rb requires the use of pharmacologic stress. Thus, the quest for the ideal myocardial blood flow tracer is still in progress.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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