Emerging Tracers for Nuclear Cardiac PET Imaging

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Abstract

Myocardial perfusion imaging using positron emission tomography (PET) has several advantages over single photon emission computed tomography (SPECT). The recent advances in SPECT technology have shown promise, but there is still a large need for PET in the clinical management of coronary artery disease (CAD). Especially, absolute quantification of myocardial blood flow (MBF) using PET is extremely important. In spite of considerable advances in the diagnosis of CAD, novel PET radiopharmaceuticals remain necessary for the diagnosis of CAD because clinical use of current cardiac radiotracers is limited by their physical characteristics, such as decay mode, emission energy, and half-life. Thus, the use of a radioisotope that has proper characteristics and a proper half-life to develop myocardial perfusion agents could overcome these limitations. In this review, the current state of cardiac PET and a general overview of novel ¹⁸F or ⁶⁸Ga-labeled radiotracers, including their radiosynthesis, in vivo characterization, and evaluation, are provided. The future perspectives are discussed in terms of their potential usefulness based on new image analysis methods and hybrid imaging.

Keywords Coronary artery disease (CAD) · Myocardial imaging agents · ¹⁸F-labeled mitochondrial voltage sensors · ⁶⁸Ga-labeled cardiac imaging agents · Positron emission tomography

Introduction

Single photon emission computed tomography (SPECT) has played an important role in assessing myocardial blood flow (MBF) and in diagnosing CAD since the 1980s [1, 2]. However, the technical limitations of SPECT imaging using ^{99m}Tc-labeled radiotracers, such as the difficulty of photon attenuation correction and uptake of radiotracers in the liver, may limit the diagnostic accuracy of SPECT [3]. PET has a number of technical advantages over SPECT, such as higher spatial resolution, a standardized method for the correction of photon attenuation, and quantitative measurement of MBF [4]. However, the PET radioisotopes which are currently used in diagnosis of CAD have a short physical half-life ([¹³N]NH₃, 9.97 min; ⁸²Rb, 1.27 min; [¹⁵O]H₂O, 2.04 min). This means that these radioisotopes need an on-site cyclotron

or generator for their widespread use in the clinic [5]. Thus, the use of radioisotopes that have proper physical characteristics and a proper half-life to label myocardial imaging agents (MIA) could overcome these limitations. Previously, radiosynthesis and in vivo characterization of ¹⁸F-labeled phosphonium cations were reported and discussed [6]. In this review, the current state of cardiac PET and a general overview of novel ¹⁸F (including phosphonium cations) or ⁶⁸Ga-labeled radiotracers are provided. ¹⁸F (half-life, 109.8 min; β⁺, 97%) or ⁶⁸Ga (half-life, 67.7 min; β⁺, 88%) are popular radioisotopes used to develop small molecule radiopharmaceuticals for PET due to favorable decay characteristics. Furthermore, clinical perspectives of cardiac PET are discussed.

The Current State of Cardiac PET

There is a large need for PET in the management of CAD due to its advantages over SPECT, such as superior image quality, less radiation dose, and absolute quantification of MBF. In a recent report, the excellent image quality with PET was actually associated with superior diagnostic accuracy in the detection of functionally significant CAD, as compared to that of not only SPECT but also coronary CT [7]. Both sensitivity and specificity of PET were well above 80%, in contrast to

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SPECT with suboptimal sensitivity and coronary CT with suboptimal specificity. Absolute quantification of MBF by myocardial perfusion PET has also shown promise in the clinical management of CAD. PET-measured absolute MBF parameters have shown superior diagnostic values compared to relative analysis of a perfusion defect [8, 9]. PET-measured MBF parameters also show prognostic values. Even in the subgroup of patients with abnormal perfusion (summed stress score, ≥ 4), coronary flow reserve (CFR, < 2.0) measured by [^{13}N]NH $_3$ PET was still predictive of future cardiac events [10]. PET-measured CFR was predictive of cardiac events, being independent from angiographic severity of epicardial CAD. Bypass surgery, in comparison with percutaneous coronary intervention, was related to a better prognosis in patients with CFR < 2.0 [11]. PET-measured CFR is considered to reflect not only focal significant stenosis but also underlying diffuse atherosclerosis, and it may help to decide on the optimal treatment strategy in CAD patients [11, 12].

However, current myocardial perfusion PET radiotracers generally require an on-site cyclotron (except for ^{82}Rb) mainly due to their short half-lives. This results in limited distribution and clinical utilization of myocardial perfusion PET. Recent studies suggest that cadmium-zinc-telluride (CZT) SPECT may be a substitute for myocardial perfusion PET. It showed improved image quality as compared to conventional SPECT, improved diagnostic accuracy, less radiation exposure, and even quantification of MBF [13–17]. Although the measurement of MBF using CZT SPECT is in progress, the generally lower extraction fraction of $^{99\text{m}}\text{Tc}$ -labeled agents may increase image noise and is suboptimal for accurate calculation of MBF [18]. It was recently shown that the resting MBF measured by CZT SPECT was comparable to that measured by [^{13}N]NH $_3$ PET, but stress MBF and CFR were significantly underestimated [19]. The obtuse correlation curve between MBF values measured by CZT SPECT and [^{13}N]NH $_3$ PET reflects the suboptimal non-linear extraction fraction of myocardial SPECT agents, which is highlighted during vasodilator stress. With respect to the fact that the mainstay of functional assessment of CAD is based on stress perfusion, the concerns related to the low extraction fraction of SPECT agents ($^{99\text{m}}\text{Tc}$ -labeled agents) raise questions about its clinical reliability.

Thus, an ^{18}F -labeled myocardial perfusion agent was developed, and it was expected to provide comparable or even superior image quality compared to current PET agents, as well as wide availability due to its longer half-life [20–23]. This ^{18}F -labeled myocardial perfusion PET agent, ^{18}F -BMS-747158-02 ([^{18}F]flurpiridaz), is being clinically tested. It recently entered a clinical phase III open-label trial, in which its diagnostic accuracy for stenosis $\geq 50\%$ on invasive coronary angiography was compared with that of $^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile (MIBI). Contrary to our expectation, the specificity of [^{18}F]flurpiridaz PET—one of

the two co-primary endpoints of the phase III trial—failed to reach the threshold of non-inferiority to that of $^{99\text{m}}\text{Tc}$ -MIBI SPECT. Although further analyses in subgroups of female [24] and obese [25] patients showed superior diagnostic accuracy and met the non-inferiority threshold for specificity, the application of ^{18}F -flurpiridaz has not yet become a clinical reality.

Novel ^{18}F -Labeled Myocardial Perfusion Agents

Mitochondria play an important role in cell life and cell death. Especially, mitochondria constitute 20 to 30% of the myocardial intracellular volume as powerhouse [23]. Thus, unique protein or characteristics of mitochondria are a major target for developing of PET myocardial imaging agents.

First target of mitochondria for developing of PET myocardial perfusion agents is mitochondrial complex I (MC-1). MC-1 is the first enzyme of four electron transport complexes in the inner mitochondrial membrane. Radioisotope-labeled myocardial imaging agents which target the MC-1 are reported from the early 2000s, such as classical MC-1 inhibitor rotenone derivatives ([^{125}I]iodorotenone or [^{18}F]fluorodihydrorotenone) and pyridazinone derivative ([^{18}F]flurpiridaz) [23, 26, 27]. Rotenone derivatives showed higher uptake than $^{99\text{m}}\text{Tc}$ -MIBI in an isolated rabbit heart. However, the mechanism of rotenone derivatives in myocytes had not been fully cleared and a large amount of rotenone derivatives was retained nonspecifically in the mitochondrial membrane. [^{18}F]flurpiridaz represented high quality of myocardium image and had ability to visualize and quantify cardiac defects in different animal models including humans. However, the phase III trial failed due to already mentioned diagnostic accuracy.

Second target is the mitochondrial membrane potential (MP) in cardiomyocytes. The MP of cardiomyocytes is higher than that of normal epithelial cells, and loss of MP is a signal for cell death caused by myocardial ischemia [28, 29]. Quaternary ammonium and phosphonium cations accumulate in mitochondria of cardiomyocytes because the lipophilic cations (positive charge) move into the mitochondrion due to its high-density and electrochemical transmembrane potential (negative charge) in cardiomyocytes [30]. The myocardial uptake mechanism of these cations is similar to that of $^{99\text{m}}\text{Tc}$ -MIBI and $^{99\text{m}}\text{Tc}$ -tetrafosmin for SPECT [31]. Therefore, these radiolabeled cation derivatives are potential candidates for developing MIA.

Quaternary ammonium cations as myocardial perfusion PET agent were reported from 2011 [32–34]. These cations were labeled with ^{11}C due to drawback of longer half-life of ^{18}F . A waiting period of four to five half-lives is ideally needed between at rest and stress PET scan to avoid significant

interference. However, ^{18}F -based MIA prevent both scans during a single day or needed several hours like SPECT scan protocol using $^{99\text{m}}\text{Tc}$ -labeled MIA. Six kinds of ^{11}C -labeled ammonium cations were developed and [^{11}C]dimethyldiphenyl-ammonium trifluoromethane sulfonate ([^{11}C]DMDPA) showed the best performance among them in rat or pig models.

The reported ^{18}F -labeled tetraphenylphosphonium salt (TPP) derivatives are summarized in Fig. 1. ^{18}F -labeled TPP derivatives are classified into three types (type 1, short aliphatic or ether form linkers are adopted between the triphenylphosphonium and ^{18}F ; type 2, ^{18}F -substituted phenyl or benzyl group is attached to triphenylphosphine; and type 3, ^{18}F -labeled linkers are conjugated to triphenylphosphine derivatives by click chemistry) [30, 35–49]. Among these cations, 4- ^{18}F -fluorobenzyltriphenylphosphonium (^{18}F -FBnTP) showed promise for the first time as a myocardial perfusion PET agent. ^{18}F -FBnTP is metabolically stable and performs well in healthy and CAD models [30, 46, 48]. However, in vivo characteristics of ^{18}F -FBnTP, such as higher uptake and longer retention in the heart and more rapid wash out from the liver, need to be improved. ^{18}F -Labeled alkyl chain-conjugated triphenylphosphonium cations, [^{18}F]fluoroalkyltriphenylphosphonium cations ([^{18}F]FATPs), show improved characteristics through lipophilicity control [38, 41–44]. Lipophilicity of the radiotracer could control myocardial selectivity and hepatic clearance. Although little is known about the lipophilicity needed for high myocardial selectivity, the log P value range for cationic radiotracers is 0.5–1.3 to image organs with high mitochondrial density, as a result of their fast membrane-penetration kinetics [50]. The lipophilic interaction between the [^{18}F]FATPs and the lipid layer is attractive because the ^{18}F -labeled alkyl group increases the lipophilicity [51, 52]. Furthermore, ^{18}F -labeled TPP derivatives that have different functional groups, such as methyl, methoxy, *tert*-butyl, dimethylamine-substituted phenyl, and triazole formation, were investigated to assess their performance as MIA for PET [35, 40, 42, 53].

^{18}F -Fluorination of Tetraphenylphosphonium Cation Derivatives

Synthesis methods of ^{18}F -labeled TPP or TPP derivatives, such as 3-[^{18}F]fluoropropyltriphenylphosphonium cation, 4-[^{18}F]fluorobenzyltriphenylphosphonium cation ([^{18}F]FBnTP), and 4-[^{18}F]fluorobenzyltris-4-dimethylaminophenylphosphonium cation, have been summarized and reported previously [6].

^{18}F -labeled fluoroalkylphosphonium cations ([^{18}F]FATPs), including (5-[^{18}F]fluoropentyl)triphenylphosphonium cation ([^{18}F]FPTP), (6-[^{18}F]fluorohexyl)triphenylphosphonium cation

([^{18}F]FHxTP), (7-[^{18}F]fluoroheptyl)triphenylphosphonium cation ([^{18}F]FHtTP), (8-[^{18}F]fluorooctyl)triphenylphosphonium cation ([^{18}F]FOTP), (2-(2-[^{18}F]fluoroethoxy)ethyl)triphenylphosphonium cation ([^{18}F]FETP), and (2-(2-[^{18}F]fluoroethoxy)ethyl)tris(4-methoxyphenyl)phosphonium cation ([^{18}F]FETMP), were investigated to assess the appropriate range of lipophilicity for myocardial imaging using PET [37–39, 41–44]. Synthesis of [^{18}F]FATPs has been reported previously. In brief, α,ω -di-tosyloxyalkane was used as a precursor for the synthesis of [^{18}F]FATPs. After ^{18}F -fluorination, triphenylphosphine or tris(4-methoxyphenyl)phosphine was added to the reaction vessel and heated with no separation step. Finally, ^{18}F -labeled mixture was purified by semipreparative HPLC and the collected HPLC fraction was co-injected with its reference compound into an analytical HPLC system for identification. [^{18}F]FATPs were synthesized within 60 min with 10–20% RCY. Radiochemical purity was > 98% and average specific radioactivity was > 5.9 Tbq/ μmol .

Other ^{18}F -labeled TPP derivatives, such as 4-([^{18}F] fluoromethyl)benzyltriphenylphosphonium ([^{18}F]FMBTP), 3-([^{18}F] fluoromethyl)benzyltriphenylphosphonium ([^{18}F]mFMBTP), mitophos series (MitoPhos_04, MitoPhos_05, MitoPhos_07), and ^{18}F -labeled triethylene glycol derivative of BnTP ([^{18}F]FPEGBnTP), have been reported since 2014 [36, 40, 54]. [^{18}F]FMBTP and [^{18}F]mFMBTP have the same formula; however, the position of fluoromethyl structure is different. As a precursor, 1,4-bis(bromomethyl)benzene (for [^{18}F]FMBTP) or 1,3-bis(bromomethyl)benzene (for [^{18}F]mFMBTP) was used and radiotracers were synthesized by using a simple one-pot procedure. Their RCY values were approximately $52 \pm 9.3\%$ ($n = 7$, for [^{18}F]FMBTP) and $50.6 \pm 6.9\%$ ($n = 7$, for [^{18}F]mFMBTP). Both radiotracers showed excellent radiolabeling yields (> 50%) and radiochemical purities (> 99%). The specific activities of [^{18}F]FMBTP and [^{18}F]mFMBTP were approximately 30 and 38 GBq/ μmol , respectively. Furthermore, the performance of the methoxy group-substituted [^{18}F]FMBTP was reported [35].

The first mitophos compound ([^{18}F]MitoPhos_01) was reported in 2013 [55]. To achieve a suitable log P value to provide favorable biodistribution, the functional groups of the phenyl rings present around the phosphorus center were modified and synthesis of three novel phosphonium cations ([^{18}F]MitoPhos_04, [^{18}F]MitoPhos_05, and [^{18}F]MitoPhos_07) was reported, and they can be synthesized by using the common radiolabeled linker, [^{18}F]fluoroethylazide ([^{18}F]FEA), for click chemistry in the same reaction vial [40]. The conversion percentage of the [^{18}F]FEA to the labeled phosphonium cations was in the range of 80%. The specific activity of [^{18}F]MitoPhos_04 and [^{18}F]MitoPhos_07 was 49.6 ± 6.5 GBq/ μmol ($n = 3$) and 68 ± 18.8 GBq/ μmol ($n = 3$), respectively. The total synthesis time was less than 1 h. Furthermore, initial studies of three-tracer one-pot synthesis have shown promising preliminary results.

Fig. 1 Schematic structure of radioisotope-labeled tetraphenylphosphonium cation derivatives. **a** (4-[^{18}F]fluorophenyl)triphenylphosphonium cation ([^{18}F]TPP), **b** (3-[^{18}F]fluoropropyl)triphenylphosphonium cation, **c** (5-[^{18}F]fluoropentyl)triphenylphosphonium cation ([^{18}F]FPTP), **d** (6-[^{18}F]fluorohexyl)triphenylphosphonium cation ([^{18}F]FHxTP), **e** (7-[^{18}F]fluoroheptyl)triphenylphosphonium cation ([^{18}F]FHtTP), **f** (8-[^{18}F]fluorooctyl)triphenylphosphonium cation ([^{18}F]FOTP), **g** (2-(2-[^{18}F]fluoroethoxy)ethyl)triphenylphosphonium cation ([^{18}F]FETP), **h** (2-(2-[^{18}F]fluoroethoxy)ethyl)tris(4-methoxyphenyl)phosphonium cation ([^{18}F]FETMP), **i** (4-[^{18}F]fluorobenzyl)triphenylphosphonium cation ([^{18}F]FBnTP), **j** (4-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)benzyl)triphenylphosphonium cation ([^{18}F]FPEGbNTP), **k** tris(4-(dimethylamino)phenyl)(4-[^{18}F]fluorobenzyl)phosphonium cation, **l** (4-[^{18}F]fluoromethyl)benzyl)triphenylphosphonium cation ([^{18}F]FMBTP), **m** (3-(3-[^{18}F]fluoromethyl)benzyl)triphenylphosphonium cation ([^{18}F]mFMBTP), **n** (4-(4-[^{18}F]fluoromethyl)benzyl)tris(2-methoxyphenyl)phosphonium cation, **o** (4-(4-[^{18}F]fluoromethyl)benzyl)tris(3-methoxyphenyl)phosphonium cation, **p** (4-(4-[^{18}F]fluoromethyl)benzyl)tris(4-methoxyphenyl)phosphonium cation, **q** tris(4-tert-butylphenyl)(2-(1-(2-[^{18}F]fluoroethyl)-1H-1,2,3-triazol-4-yl)ethyl)phosphonium cation ([^{18}F]MitoPhos_04), **r** (2-(1-(2-[^{18}F]fluoroethyl)-1H-1,2,3-triazol-4-yl)ethyl)trip-tolylphosphonium cation ([^{18}F]MitoPhos_05), **s** tris(3,5-dimethylphenyl)(2-(1-(2-[^{18}F]fluoroethyl)-1H-1,2,3-triazol-4-yl)ethyl)phosphonium cation ([^{18}F]MitoPhos_07)

[^{18}F]FPEGbNTP was designed to develop a new BnTP derivative showing lower liver uptake and higher heart-to-liver ratio in comparison with [^{18}F]FBnTP [36]. It was hypothesized that the lipophilicity of [^{18}F]FBnTP would affect its accumulation in the liver and a lower lipophilic derivative would indicate faster clearance from the liver. Finally, [^{18}F]

pegylated BnTP was synthesized and its in vitro/in vivo performance was evaluated. Radiochemical yield of [^{18}F]FPEGbNTP was 13–23% ($n = 8$) and radiochemical purity of the drug solution was > 95%.

In Vivo Characteristics of ^{18}F -Labeled Tetraphenylphosphonium Cation Derivatives

Biodistribution results and microPET images of ^{18}F -labeled TPP derivatives are shown in Table 1 and Fig. 2. The lipophilicity, functional group of the triphenylphosphonium core, and structure of ^{18}F -labeled linker are summarized in Table 2. Directed ^{18}F -labeled TPP showed intense cardiac uptake in biodistribution (1.64% ID/g at 5 min after injection; ID, injected dose) and microPET studies (2.3 nCi/cm³ at 1 min after injection) [45]. A biodistribution study revealed that blood activity changed significantly from 5 to 60 min, reducing from 0.15 to 0.02% ID/g. At 5, 30, and 60 min, lung activity was 0.69, 0.36, and 0.38% ID/g, respectively, whereas liver uptake was 0.34, 0.18, and 0.17% ID/g, respectively. Heart-to-lung ratios at 5, 30, and 60 min were 2, 5, and 4, respectively. The cardiac uptake of ^{18}F -labeled TPP in rats showed a similar value to that of $^{99\text{m}}\text{Tc}$ -tetrofosmin or $^{99\text{m}}\text{Tc}$ -MIBI. The time-activity curve (TAC) generated from PET imaging of rats showed that ^{18}F -labeled TPP uptake by the heart wall was approximately fourfold higher than blood uptake for 60 min.

Table 1 Comparison of biodistribution at 60 min after i.v. injection of ^{18}F -labeled TPP derivatives into mice

	[^{18}F]TPP ^a	[^{18}F]FBnTP	[^{18}F]FPTP	[^{18}F]FHxTP	[^{18}F]FETP	[^{18}F]FETMP
Blood	0.02 ± 0.003	0.05 ± 0.01	0.04 ± 0.01	0.19 ± 0.03	0.23 ± 0.02	0.73 ± 0.63
Heart	1.57 ± 0.18	12.16 ± 2.4	21.23 ± 3.60	23.20 ± 2.70	19.96 ± 2.08	29.88 ± 7.59
Lung	0.38 ± 0.11	1.82 ± 0.3	2.96 ± 0.63	3.70 ± 0.12	4.01 ± 0.74	6.38 ± 1.21
Liver	0.17 ± 0.03	8.09 ± 3.9	3.05 ± 0.92	1.30 ± 0.12	2.03 ± 0.17	11.22 ± 1.48
Kidney	1.75 ± 0.38	24.70 ± 4.1	11.68 ± 3.73	12.68 ± 3.13	16.86 ± 2.73	41.10 ± 9.94
Muscle	0.26 ± 0.11	1.27 ± 0.4	6.16 ± 1.78	4.53 ± 0.54	4.42 ± 1.15	5.41 ± 1.93
Heart-to-liver	8	1.50	7.25	17.83	9.87	2.74
Heart-to-lung	4	6.68	7.28	6.27	5.05	4.75
Heart-to-blood	75	243	523.34	126.76	86.78	61.07
	[^{18}F]FMBTP	[^{18}F]mFMBTP	[^{18}F]FMBTP (<i>para</i>)	[^{18}F]FMBTP (<i>ortho</i>)	[^{18}F]FMBTP (<i>meta</i>)	[^{18}F]FPEGbNTP
Blood	0.41 ± 0.01	0.61 ± 0.05	0.97 ± 0.04	0.53 ± 0.08	0.31 ± 0.04	1.08 ± 0.05
Heart	31.17 ± 1.5	28.30 ± 2.36	21.68 ± 0.69	20.06 ± 3.27	15.65 ± 3.16	3.3 ± 0.22
Lung	4.1 ± 0.69	5.08 ± 0.32	6.58 ± 1.42	3.20 ± 0.46	4.08 ± 1.16	0.81 ± 0.01
Liver	1.89 ± 0.32	2.39 ± 0.56	2.30 ± 0.19	1.30 ± 0.41	1.06 ± 0.14	0.83 ± 0.02
Kidney	17.1 ± 3.72	19.73 ± 1.69	62.62 ± 5.86	43.47 ± 3.24	29.43 ± 4.71	3.64 ± 0.18
Muscle	6.91 ± 1.04	4.29 ± 0.67	5.37 ± 0.82	4.06 ± 0.81	3.73 ± 0.63	1.28 ± 0.06
Heart-to-liver	16.43	11.84	9.43	15.43	14.76	4.00
Heart-to-lung	7.46	5.57	3.29	6.27	3.84	4.10
Heart-to-blood	74.74	46.39	22.35	37.85	50.48	3.13

^a Biodistribution in Sprague Dawley rats. Data are expressed as the percentage of injected dose per gram of tissue (% ID/g)

Fig. 2 Coronal microPET images of normal rats (mouse) after intravenous injection of **a** [^{18}F]FBnTP (mouse), **b** [^{18}F]FPTP, **c** [^{18}F]FETP, and **d** [^{18}F]mFMBTP. H, heart; L (LIV), liver; RV, right ventricle; LV, left

ventricle; SUV, standardized uptake value (Reprinted with permission [41, 44, 46, 54])

Among 3- ^{18}F fluoropropyltriphenylphosphonium, [^{18}F]FBnTP, and 4- ^{18}F fluorobenzyltris-4-dimethylaminophenylphosphonium, only the in vivo

characteristics of [^{18}F]FBnTP were reported [46]. [^{18}F]FBnTP showed strongest uptake in the kidney, followed by the heart (12.16% ID/g) and liver (8.09% ID/g), and very

Table 2 The lipophilicity and the functional group of the triphenylphosphonium core and structure of ^{18}F -labeled linker of ^{18}F -labeled TPP derivatives

	Lipophilicity	Functional group of triphenylphosphonium core	Structure of ^{18}F -labeled linker
[^{18}F]FBnTP	-0.38	N/A	Fluorobenzyl
[^{18}F]FPTP	1.31 ± 0.02	N/A	Fluoropentyl
[^{18}F]FHxTP	1.78 ± 0.05	N/A	Fluorohexyl
[^{18}F]FHtTP	2.52 ± 0.01	N/A	Fluoroheptyl
[^{18}F]FOTP	2.91 ± 0.02	N/A	Fluorooctyl
[^{18}F]FETP	0.89 ± 0.02	N/A	(Fluoroethoxy)ethyl
[^{18}F]FETMP	1.27 ± 0.01	Methoxy (<i>para</i>)	(Fluoroethoxy)ethyl
[^{18}F]FMBTP	1.16 ± 0.003	N/A	4-(Fluoromethyl)benzyl
[^{18}F]mFMBTP	1.05 ± 0.01	N/A	3-(Fluoromethyl)benzyl
[^{18}F]FMBTP (<i>para</i>)	1.67 ± 0.01	Methoxy (<i>para</i>)	4-(Fluoromethyl)benzyl
[^{18}F]FMBTP (<i>ortho</i>)	1.53 ± 0.02	Methoxy (<i>ortho</i>)	4-(Fluoromethyl)benzyl
[^{18}F]FMBTP (<i>meta</i>)	0.54 ± 0.05	Methoxy (<i>meta</i>)	4-(Fluoromethyl)benzyl
[^{18}F]MitoPhos_04	2.03 ± 0.19	<i>tert</i> -Butyl	Triazole
[^{18}F]MitoPhos_05	1.31 ± 0.06	Methyl (<i>para</i>)	Triazole
[^{18}F]MitoPhos_07	1.83 ± 0.04	3,5-Dimethyl	Triazole
[^{18}F]FPEGnTP	-0.92	N/A	Triethylene glycol

N/A not applicable

low uptake in the blood (0.05% ID/g) at 60 min. Furthermore, [^{18}F]FBnTP demonstrated excellent characteristics as a cardiac imaging agent in murine and normal canine models. The myocardium-to-liver uptake ratio reached 1 at approximately 25 min after intravenous injection of [^{18}F]FBnTP in mice and the myocardium-to-liver uptake ratio was 1 in dog models for 90 min.

[^{18}F]FATPs showed excellent heart-specific uptake and wash out from the liver than the other ^{18}F -labeled TPP derivatives. The lipophilicity of [^{18}F]FATPs was controlled by the structure of ^{18}F -labeled linker and the functional group of the triphenylphosphonium core. The myocardial uptake of [^{18}F]FATPs was more than 20% ID/g for 2 h after radiotracer injection. The heart-to-liver ratio and the heart-to-blood ratio were more than 4 and 30, respectively, at 10 min. However, clearance of [^{18}F]FETMP from the liver occurred later than that of other [^{18}F]FATPs due to the functional group of the triphenylphosphonium core (heart-to-liver ratio at 10 min, 2.33 ± 0.36). [^{18}F]FATPs showed superior heart-background contrast on microPET imaging of murine models at each time point and better image quality than [^{13}N]NH₃, which is the clinical gold standard myocardial imaging agent for PET [37, 41–44]. The [^{18}F]FATPs images demonstrated good visualization of the heart, with excellent heart-to-liver and heart-to-lung ratios. The [^{18}F]FATPs TACs demonstrated rapid accumulation in the heart (1–2 min), with stable retention for 60 min. The heart-to-liver ratios of [^{18}F]FPTP, [^{18}F]FHxTP, and [^{18}F]FETP were 1.67 ± 0.21 , 2.49 ± 0.08 , and 2.6 ± 0.85 , respectively, whereas the heart-to-lung ratios of [^{18}F]FPTP, [^{18}F]FHxTP, and [^{18}F]FETP were 3.65 ± 0.2 , 5.67 ± 0.52 , and 6.31 ± 0.8 , respectively, 1 min after intravenous injection. In contrast, [^{13}N]NH₃ TAC revealed that the heart-to-liver ratio and the heart-to-lung ratio were 0.8 ± 0.14 and 0.93 ± 0.07 , respectively, at 5 min after injection. Furthermore, [^{18}F]FATPs were compared with [^{13}N]NH₃ by using myocardial infarction (MI) models. Sharply defined myocardial defects were present with [^{18}F]FATPs or [^{13}N]NH₃ (10 min). [^{18}F]FATPs showed similar values for defect size and contrast ratio; however, the [^{13}N]NH₃ images significantly underestimated infarct size soon after tracer injection (0–10 min, $P = 0.027$), which might be due to the spillover of radioactivity into the left ventricular or right ventricular myocardium [37]. Furthermore, [^{18}F]FATPs showed significantly higher first-pass extraction fraction value than those of [^{13}N]NH₃ in isolated rat hearts perfused by the Langendorff method (flow rates 4, 8, or 16 mL/min, $P < 0.05$) [6]. The flow rate would be relevant because the MBF of normal rats under isoflurane anesthesia is 4.2 ± 0.9 mL/min [56].

[^{18}F]FMBTP and [^{18}F]mFMBTP were reported in 2014 [54]. Both compounds were electropositive, and their log P values at pH 7.4 were 1.16 ± 0.003 ($n = 3$) and 1.05 ± 0.01 ($n = 3$), which were comparable to those of [^{18}F]FETMP (1.27 ± 0.01) and [^{18}F]FHxTP (1.78 ± 0.05). [^{18}F]FMBTP

showed high heart uptake ($25.24 \pm 2.97\%$ ID/g at 5 min after intravenous injection) and the activity was retained for 2 h ($28.99 \pm 3.54\%$ ID/g at 2 h). However, the liver uptake was decreased dramatically from $14.93 \pm 1.46\%$ ID/g (at 5 min) to $0.89 \pm 0.29\%$ ID/g (at 120 min). The heart-to-liver, heart-to-lung, and heart-to-blood ratios of [^{18}F]FMBTP were 5.04, 5.80, and 32.9, respectively, at 30 min postinjection, and they increased to 32.5, 7.61, and 151.9, respectively, at 120 min postinjection. Furthermore, [^{18}F]mFMBTP showed higher heart uptake ($31.02 \pm 0.33\%$ ID/g at 5 min postinjection) and better target-to-non target ratios at earlier time points. Both these new radiotracers showed moderate muscle uptake at all time points after injection ($6.91 \pm 1.04\%$ ID/g for [^{18}F]FMBTP and $4.29 \pm 0.67\%$ ID/g for [^{18}F]mFMBTP at 60 min), which was similar to that of the previously reported lipophilic cations of [^{18}F]FPTP ($6.16 \pm 1.78\%$ ID/g at 60 min p.i.) [10] and [^{18}F]FHxTP ($4.53 \pm 0.54\%$ ID/g at 60 min p.i.), respectively. Finally, in vivo PET studies were performed using [^{18}F]mFMBTP in rats and Beagle dogs. [^{18}F]mFMBTP showed an excellent image quality in rats for 2 h after intravenous injection. The highest myocardial uptake was reached rapidly at a very early time point after injection and it remained high across all time points to 2 h. With respect to liver uptake, it peaked at 5 min postinjection and rapid clearance was observed. It was even lower than lung uptake after 30 min postinjection. The heart-to-liver ratio increased obviously due to quick clearance from the liver (1.37, 6.62, 12.06, and 18.64 at 5, 30, 60, and 120 min postinjection, respectively). In the case of Beagle dogs, the heart could be clearly seen at 10 min after injection, and heart uptake did not obviously decrease till 2 h. The values for heart-to-liver and heart-to-lung uptake ratios were calculated as 1.54 and 6.00 at 10 min after injection, 2.83 and 15.19 at 30 min after injection, 3.98 and 38 at 60 min after injection, and 7.76 and 35.28 at 120 min after injection, respectively. The results of PET imaging in dogs showed a trend similar to biodistribution results in rats and mice. In addition to this, the influence of an additional methoxy group and its different positions on myocardium uptake and pharmacokinetic properties of [^{18}F]FMBTP were examined and reported in 2017 [35]. However, [^{18}F]FMBTP showed the highest heart uptake value.

Radiosynthesis and evaluation of ^{18}F -labeled triethylene glycol derivative of BnTP, [^{18}F]FPEGBnTP, were reported in 2016 [36]. However, in vitro cellular uptake and in vivo biodistribution of [^{18}F]FPEGBnTP were preliminarily evaluated to elucidate the possibility of its use as an MPI agent. Lipophilicity of [^{18}F]FPEGBnTP was compared with that of [^{18}F]FBnTP. Log P values of [^{18}F]FBnTP and [^{18}F]FPEGBnTP were -0.38 and -0.92 respectively, indicating that [^{18}F]FPEGBnTP is relatively less lipophilic than [^{18}F]FBnTP. [^{18}F]FPEGBnTP showed heart uptake of $3.33 \pm 0.22\%$ ID/g at 60 min after intravenous injection. In

contrast, liver and lung exhibited lower uptakes (0.83 ± 0.02 and $0.81 \pm 0.01\%$ ID/g at 60 min, respectively). However, radioactivity uptake in the blood ($1.08 \pm 0.05\%$ ID/g) was relatively higher than that in the liver and lung

⁶⁸Ga-Labeled Myocardial Perfusion Agents

¹⁸F-labeled MPI agents based on the lipophilic cation have been mentioned above; however, these agents depend on the presence of nearby cyclotrons. Recently, ⁶⁸Ga ($t_{1/2} = 68$ min) eluted from germanium/gallium (Ge/Ga) generators (parent–daughter combination system) showed high quality with excellent emission properties for clinical PET imaging [57]. The parent nuclide (⁶⁸Ge) onto a titanium column and the daughter nuclide (⁶⁸Ga) are simply eluted as ⁶⁸GaCl₃ with hydrochloric acid. This generator can be used for more than a year due to the long half-life of the parent nuclide ⁶⁸Ge ($t_{1/2} =$ days). Furthermore, the short half-life of ⁶⁸Ga can be eluted two or three times per day from the generator. Thus, the ⁶⁸Ge/⁶⁸Ga generator is appropriate for experimental or clinical application [58]. Many kinds of synthetic complexes of ⁶⁸Ga(III) have been reported as candidate PET tracers for cardiac nuclear imaging [58–71]. In this review, we have categorized them according to their characteristics, as perfusion imaging agents, MI imaging agents and cardiac metabolic imaging agents, and we have summarized them (Table 3).

⁶⁸Ga-labeled lipophilic cations have been reported as myocardial perfusion agents [59, 60, 62, 73, 74]. Among them,

⁶⁸Ga[(4,6-MeO₂sal)₂BAPEN]⁺ showed heart-specific accumulation. The myocardial uptake mechanism of ⁶⁸Ga-BAPEN is presumably similar to that of ^{99m}Tc-MIBI or [¹⁸F]FATPs because radiotracers are lipophilic and have monovalent ions with +1 charge. However, their labeling procedures are complicated and they need time-consuming operations. Thus, a practical kit was developed to overcome these limitations and to increase usage convenience [58]. In a biodistribution study with balb/c mice, ⁶⁸Ga-BAPEN showed strongest uptake in the kidney ($52.45 \pm 6.25\%$ ID/g), followed by the intestine ($18.90 \pm 4.05\%$ ID/g), liver ($17.73 \pm 2.53\%$ ID/g), and heart ($11.77 \pm 0.83\%$ ID/g) and low uptake in the muscle ($1.88 \pm 0.43\%$ ID/g) and blood ($0.39 \pm 0.04\%$ ID/g) at 1 h postinjection. Furthermore, ⁶⁸Ga-labeled hexadentate bis(salicylaldehyde) chelates (BAPDMEN) derived from BAPEN were reported and they showed promising preclinical results [72]. In rats, the myocardial uptake of the ⁶⁸Ga-labeled tracers exceeded that of ^{99m}Tc-MIBI after 1 min postinjection and it showed prolonged retention in the myocardium for 2 h. Tarkia et al. investigated and reported the myocardial uptake and plasma protein binding properties of BAPEN and BAPDMEN derivatives using a pig model [63]. A novel lipophilic monocationic Ga(III)-complex, ^{67/68}Ga-[3-isopropoxy-ENBDMPI]⁺, was reported in 2014 [64]. ^{67/68}Ga-[3-isopropoxy-ENBDMPI]⁺ showed specific heart uptake ($11.98 \pm 0.74\%$ ID/g) and low liver uptake ($7.44 \pm 0.44\%$ ID/g) at 60 min postinjection. They explained that low liver uptake was caused by expression of P-glycoprotein (Pgp) in hepatocytes. The uptake mechanism of lipophilic

Table 3 ⁶⁸Ga-labeled cardiac imaging agents

Category	Radiotracer	Target	Reference
Perfusion imaging	⁶⁸ Ga[(4,6-MeO ₂ sal) ₂ BAPEN] ⁺	Mitochondria	[58, 59]
	⁶⁸ Ga[(3-MeOsal) ₂ Me ₄ BAPEN] ⁺	Mitochondria	[63]
	⁶⁸ Ga[Ga(3-EtOsal) ₂ Me ₄ BAPEN] ⁺		
	⁶⁸ Ga[(sal) ₂ BAPDMEN] ⁺	Mitochondria	[63, 72]
	⁶⁸ Ga[(4-MeOsal) ₂ BAPDMEN] ⁺	Mitochondria	[72]
	⁶⁸ Ga[(4,6-MeOsal) ₂ BAPDMEN] ⁺		
	⁶⁸ Ga[(3-MeOsal) ₂ BAPDMEN] ⁺	Mitochondria	[63, 72]
	⁶⁸ Ga[(6-MeOsal) ₂ BAPDMEN] ⁺	Mitochondria	[72]
	⁶⁸ Ga[3-isopropoxy-ENBDMPI] ⁺	Mitochondria	[64]
Myocardial infarction imaging	⁶⁸ Ga-NOTA-NGR	Aminopeptidase N (CD13)	[65]
	⁶⁸ Ga-pentixafor	Chemokine receptor 4 (CXCR4)	[67]
	⁶⁸ Ga-NOTA-RGD	α _v β ₃ integrin	[66]
	⁶⁸ Ga-NODAGA-RGD		[68]
	⁶⁸ Ga-DOTA-peptide (phage display)	MMP-2, MMP-9	[69]
	⁶⁸ Ga-NOTA-undecanoic acid	Fatty acid oxidation	[70]
Cardiac metabolic imaging	⁶⁸ Ga-NOTA-dodecanoic acid		
	⁶⁸ Ga-NODAGA-undecanoic acid	Fatty acid oxidation	[71]
	⁶⁸ Ga-DTPA-undecanoic acid		

cation is opposed by the action of ATP-binding-cassette (ABC) membrane transporters, such as the multidrug resistance (MDR) Pgp (ABCB1) and MRP1 (ABCC1), which transport lipophilic cationic metal complexes out of the cells. Thus, ^{67}Ga -[3-isopropoxy-ENBDMPI] $^{+}$ is retained for a prolonged period in cardiomyocytes which are rich in mitochondria and lack Pgp, while hepatocytes which express Pgp along their canalicular surface rapidly excrete ^{67}Ga -[3-isopropoxy-ENBDMPI] $^{+}$ into the bile and intestines. They determined whether Pgp affected the accumulation of ^{67}Ga -[3-isopropoxy-ENBDMPI] $^{+}$ in vitro and in vivo conditions. Finally, they performed a microPET study with Sprague Dawley rats and images showed sustained retention of ^{67}Ga -[3-isopropoxy-ENBDMPI] $^{+}$ in the heart and rapid clearance from the liver (Fig. 3).

^{68}Ga -Labeled Agents for MI or Cardiac Metabolic Imaging

MI is a dynamic process that begins with coronary occlusion and causes heart muscle damage by decreasing or stopping blood flow to the heart. Because of this, MI is visualized to target biomarkers related to cell damage or healing process, such as inflammation, angiogenesis, and matrix metalloproteinases (MMPs) [65–69].

Peptide sequences, asparagine-glycine-arginine (NGR) motif binds to aminopeptidase N (CD13), which is expressed on inflammatory cells [65]. In the myocardium, CD13 is expressed in pathophysiological conditions such as acute

MI, where it facilitates inflammatory cell infiltration. Tillmanns J et al. synthesized ^{68}Ga -NOTA-NGR and compared it with [^{18}F]FDG or ^{68}Ga -NOTA-arginine-glycine-aspartic acid (RGD) motif binds to integrin $\alpha_v\beta_3$ receptors in myocardial ischemia and reperfusion (MI/R) rat models. The [^{18}F]FDG identified infarcted areas, where increased uptake of ^{68}Ga -NOTA-NGR was apparent. However, ^{68}Ga -NOTA-RGD showed higher liver uptake than ^{68}Ga -NOTA-NGR. Another agent related to the inflammatory process is ^{68}Ga -pentixafor [67]. Chemokine receptor 4 (CXCR4) is expressed on inflammatory cells after acute MI. CXCR4 belongs to the family of G-protein-coupled receptors and is involved in many kinds of biological processes, such as the entry of HIV-1, the development of metastasis, and several inflammatory conditions. Therefore, the CXCR4 receptor is an attractive biomarker to identify the activated inflammatory cells located in the MI area. ^{68}Ga -pentixafor is a ligand with high affinity and selectivity to hCXCR4-receptors ($\text{IC}_{50} = 5 \text{ nM}$) and it has been tried in human MI patients. As a result, ^{68}Ga -pentixafor PET images reveal markedly increased CXCR4 expression in the MI area, indicating an active inflammatory process.

The $\alpha_v\beta_3$ integrin is expressed on angiogenic vessels and is a potential biomarker for pathological processes. Its expression is upregulated in cancer lesions and metastases as well as in acute MI as part of the infarct healing process [66]. RGD is the principal integrin-binding domain present within extracellular matrix (ECM) proteins such as fibronectin, vitronectin, and fibrinogen. Thus, RGD or synthetic RGD derivatives provide several advantages for targeting integrin for molecular

Fig. 3 Representative microPET/CT images of ^{68}Ga -[3-isopropoxy-ENBDMPI] $^{+}$. Sprague Dawley rats were injected intravenously with ^{68}Ga -[3-isopropoxy-ENBDMPI] $^{+}$ and images were acquired 60 min postinjection (Reprinted with permission [64])

imaging applications [75]. ^{68}Ga -labeled RGD derivatives, such as ^{68}Ga -NOTA-RGD and ^{68}Ga -NODAGA-RGD were evaluated in MI rat and pig models [66, 68]. In PET studies, increased uptake is represented by both radiotracers in the MI area. It means that localized $\alpha_v\beta_3$ integrin expression in MI may be used as a biomarker to image MI.

MMPs are proteolytic enzymes that play a central role in the degradation of ECM proteins in MI [76, 77]. Especially, the expression of gelatinases MMP-2 and MMP-9 is elevated after myocardial injury. Thus, radioisotope-labeled MMP-2/9 target compound could be used as a PET agent for MI. ^{68}Ga -labeled specific MMP-2/9 binding peptide which was identified from the phage display library was evaluated in a MI rat model and it was reported in 2016 [69]. This radiotracer showed accumulation in the damaged rat myocardium after injury; however, its instability and inadequate *in vivo* characteristics make it unsuitable for further evaluation.

Fatty acids are the major energy source in the myocardium and a change in their metabolism reflects abnormality in the myocardium. Thus, radioisotope-labeled long-chain fatty acids have been investigated as imaging agents since the 1990s [78, 79]. Finally, several kinds of ^{68}Ga -labeled long-chain fatty acids were synthesized and evaluated [70, 71]. The first reported ^{68}Ga -labeled fatty acids were ^{68}Ga -NOTA-undecanoic acid and ^{68}Ga -NOTA-dodecanoic acid [70]. These radiotracers showed significant initial uptake in the myocardium; however, significant retention of the activity was found to be associated with blood. Thus, synthetic modification is needed to increase the potential of these radiotracers for myocardial imaging. Another work using ^{68}Ga -labeled fatty acids aimed to investigate the influence of different chelators of undecanoic acid on cardiac uptake and pharmacokinetics [71]. Jain K et al. synthesized ^{68}Ga -NODAGA-undecanoic acid and ^{68}Ga -DTPA-undecanoic acid and evaluated their *in vivo* characteristics. Biodistribution studies showed significant retention of ^{68}Ga -NODAGA-undecanoic acid in the myocardium. Moreover, rapid washout of ^{68}Ga -DTPA-undecanoic acid from the liver was observed. However, they suggested amalgamation of the structural features of the two radiotracers for the final design of the ^{68}Ga -labeled fatty acid complex that might help to achieve the desired pharmacokinetics for cardiac metabolic imaging.

Conclusion

The development of new radiotracers and/or novel utilization of existing radiotracers are essential steps in cardiac molecular imaging with PET. As described above, many radiotracers are awaiting implementation in the clinical workflow for various cardiac diseases. In parallel with these active research works, clinical efforts should be made to design PET more relevant for patient care.

For example, recent progress in PET in cardiac amyloidosis can provide a good opportunity to promote cardiac PET imaging. PET radiotracers including ^{18}F sodium fluoride (^{18}F]NaF), [^{11}C]Pittsburgh compound B (^{11}C]PIB), [^{18}F]florbetapir, and [^{18}F]florbetaben showed subtype-specific, promising results in cardiac amyloidosis. [^{18}F]NaF showed distinguished uptake in transthyretin (TTR) cardiac amyloidosis [80], while the others were highly specific for immunoglobulin light chain (AL) cardiac amyloidosis [81–83]. However, indications for PET imaging for a specific subtype have not been established; the interpretation of PET images can be variable due to diverse analytical methods suggested in recent studies. It is mandatory to establish/create comprehensive guidelines on PET imaging in the context of clinical diagnostic work-up of cardiac amyloidosis. The American Society of Nuclear Cardiology published a practical document of practice points for $^{99\text{m}}\text{Tc}$ pyrophosphate imaging for TTR cardiac amyloidosis [84]. Patient selection, imaging procedure, interpretation, and quantification methods were comprehensively included, making $^{99\text{m}}\text{Tc}$ PYP readily accessible. The same can be done for PET imaging of AL cardiac amyloidosis. It would complete the workflow of molecular imaging, covering the two major subtypes of cardiac amyloidosis.

Cardiac sarcoidosis is also a good disease candidate to promote cardiac PET imaging. ^{68}Ga -DOTANOC, a neuroendocrine tumor imaging agent, was recently introduced as it showed superior diagnostic accuracy as compared to [^{18}F]FDG [85]. Taking advantage of the accumulation in active inflammation, several ^{68}Ga -labeled somatostatin analogues are now being investigated in clinical trials. There are ongoing clinical efforts, although they are limited to [^{18}F]FDG PET. The revised major guidelines include specific [^{18}F]FDG PET findings as one of the diagnostic criteria, and they recommend PET for diagnosis and evaluation of the inflammatory activity in cardiac sarcoidosis [86, 87]. Volumetric parameters are now being applied to diagnosis and prognostic stratification [88, 89], in addition to the traditional maximal uptake value.

It is also encouraging that a relevant multimodality imaging approach is under investigation for these two disease entities, especially PET-magnetic resonance (MR) [80, 90, 91]. Excellent morphological evidence and tissue characterization are expected to have a synergistic effect with PET. Hybrid PET-MR can be one-stop-shop imaging capable of not only making the diagnosis but also evaluating TTR/AL subtyping or inflammation activity in amyloidosis and sarcoidosis, respectively.

Preclinical and clinical progress can trigger and promote/stimulate the development of each other. There are still challenges and competitors for nuclear cardiology imaging. But cardiac PET has a unique strength based on the infinite potential offered by the development of new radiotracers.

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Compliance with Ethical Standards

Conflict of Interest Dong-Yeon Kim, Sang-Geon Cho and Hee Seung Bom declare that there is no conflict of interest.

References

- Small GR, Wells RG, Schindler T, Chow BJ, Ruddy TD. Advances in cardiac SPECT and PET imaging: overcoming the challenges to reduce radiation exposure and improve accuracy. *Can J Cardiol*. 2013;29:275–84.
- Ohira H, Mc Ardle B, Cocker MS, Dekemp RA, Dasilva JN, Beanlands RS. Current and future clinical applications of cardiac positron emission tomography. *Circ J*. 2013;77:836–48.
- Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. *J Am Coll Cardiol*. 2004;44:1533–42.
- Knuuti J, Bengel FM. Positron emission tomography and molecular imaging. *Heart*. 2008;94:360–7.
- Siegrist PT, Husmann L, Knabenhans M, Gaemperli O, Valenta I, Hoefflinghaus T, et al. ^{13}N -ammonia myocardial perfusion imaging with a PET/CT scanner: impact on clinical decision making and cost-effectiveness. *Eur J Nucl Med Mol Imaging*. 2008;35:889–95.
- Kim DY, Min JJ. Radiolabeled phosphonium salts as mitochondrial voltage sensors for positron emission tomography myocardial imaging agents. *Nucl Med Mol Imaging*. 2016;50:185–95.
- Danad I, Rajmakers PG, Driessen RS, Leipsic J, Raju R, Naoum C, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–7.
- Lee JM, Kim CH, Koo BK, Hwang D, Park J, Zhang J, et al. Integrated myocardial perfusion imaging diagnostics improve detection of functionally significant coronary artery stenosis by ^{13}N -ammonia positron emission tomography. *Circ Cardiovasc Imaging*. 2016;9:e004768.
- Fiechter M, Ghadri JR, Gebhard C, Fuchs TA, Pazhenkottil AP, Nkoulou RN, et al. Diagnostic value of ^{13}N -ammonia myocardial perfusion PET: added value of myocardial flow reserve. *J Nucl Med*. 2012;53:1230–4.
- Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, et al. Long-term prognostic value of ^{13}N -ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. *J Am Coll Cardiol*. 2009;54:150–6.
- Taqeti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation*. 2015;131:19–27.
- Cho SG, Park KS, Kim J, Kang SR, Song HC, Kim JH, et al. Coronary flow reserve and relative flow reserve measured by ^{13}N -ammonia PET for characterization of coronary artery disease. *Ann Nucl Med*. 2017;31:144–52.
- Engbers EM, Timmer JR, Mouden M, Knollemans S, Jager PL, Ottervanger JP. Prognostic value of myocardial perfusion imaging with CZT SPECT camera in patients suspected for coronary artery disease. *J Nucl Med*. 2017;58:1459–63.
- Chikamori T, Hida S, Tanaka N, Igarashi Y, Yamashita J, Shiba C, et al. Diagnostic performance of a cadmium-zinc-telluride single-photon emission computed tomography system with low-dose technetium-99m as assessed by fractional flow reserve. *Circ J*. 2016;80:1217–24.
- Wells RG, Timmins R, Klein R, Lockwood J, Marvin B, deKemp RA, et al. Dynamic SPECT measurement of absolute myocardial blood flow in a porcine model. *J Nucl Med*. 2014;55:1685–91.
- Mouden M, Timmer JR, Ottervanger JP, Reiffers S, Oostdijk AH, Knollemans S, et al. Impact of a new ultrafast CZT SPECT camera for myocardial perfusion imaging: fewer equivocal results and lower radiation dose. *Eur J Nucl Med Mol Imaging*. 2012;39:1048–55.
- Song B, Lussato D, Guernou M, Queneau M, Geronazzo R. Comparison of myocardial perfusion imaging using thallium-201 between a new cadmium-zinc-telluride cardiac camera and a conventional SPECT camera. *Clin Nucl Med*. 2011;36:776–80.
- Garcia EV. Are SPECT measurements of myocardial blood flow and flow reserve ready for clinical use? *Eur J Nucl Med Mol Imaging*. 2014;41:2291–3.
- Nkoulou R, Fuchs TA, Pazhenkottil AP, Kuest SM, Ghadri JR, Stehli J, et al. Absolute myocardial blood flow and flow reserve assessed by gated SPECT with cadmium-zinc-telluride detectors using $^{99\text{m}}\text{Tc}$ -tetrofosmin: head-to-head comparison with ^{13}N -ammonia PET. *J Nucl Med*. 2016;57:1887–92.
- Nekolla SG, Reder S, Saraste A, Higuchi T, Dzewas G, Preissel A, et al. Evaluation of the novel myocardial perfusion positron-emission tomography tracer ^{18}F -BMS-747158-02: comparison to ^{13}N -ammonia and validation with microspheres in a pig model. *Circulation*. 2009;119:2333–42.
- Huisman MC, Higuchi T, Reder S, Nekolla SG, Poethko T, Wester HJ, et al. Initial characterization of an ^{18}F -labeled myocardial perfusion tracer. *J Nucl Med*. 2008;49:630–6.
- Yu M, Guaraldi MT, Mistry M, Kagan M, McDonald JL, Drew K, et al. BMS-747158-02: a novel PET myocardial perfusion imaging agent. *J Nucl Cardiol*. 2007;14:789–98.
- Yalamanchili P, Wexler E, Hayes M, Yu M, Bozek J, Kagan M, et al. Mechanism of uptake and retention of F-18 BMS-747158-02 in cardiomyocytes: a novel PET myocardial imaging agent. *J Nucl Cardiol*. 2007;14:782–8.
- Heller JM GV, Udelson JE, Beanlands R, Knuuti J, Bateman TM, Berman DS, et al. Improved assessment of CAD in women with flurpiridaz F-18 PET myocardial perfusion imaging: results of subset analysis of the flurpiridaz F-18 phase 3 study. *Circulation*. 2015;132:A18022.
- Bateman TMMJ, Udelson J, Beanlands R, Knuuti J, Heller GV, Berman D, et al. Improved assessment of CAD in obese subjects with flurpiridaz F-18 PET myocardial perfusion imaging: a subset analysis of the flurpiridaz F-18 301 phase 3 study. *J Am Coll Cardiol*. 2016;67:1578.
- Marshall RC, Powers-Risius P, Reutter BW, O'Neil JP, La Belle M, Huesman RH, et al. Kinetic analysis of ^{18}F -fluorodihydrotroponone as a deposited myocardial flow tracer: comparison to ^{201}Tl . *J Nucl Med*. 2004;45:1950–9.
- Marshall RC, Powers-Risius P, Reutter BW, Taylor SE, VanBrocklin HF, Huesman RH, et al. Kinetic analysis of ^{125}I -iodorotone as a deposited myocardial flow tracer: comparison with $^{99\text{m}}\text{Tc}$ -sestamibi. *J Nucl Med*. 2001;42:272–81.
- Summerhayes IC, Lampidis TJ, Bernal SD, Nadakavukaren JJ, Nadakavukaren KK, Shepherd EL, et al. Unusual retention of rhodamine 123 by mitochondria in muscle and carcinoma cells. *Proc Natl Acad Sci U S A*. 1982;79:5292–6.
- Chen LB. Mitochondrial membrane potential in living cells. *Annu Rev Cell Biol*. 1988;4:155–81.
- Madar I, Ravert H, Dipaula A, Du Y, Dannals RF, Becker L. Assessment of severity of coronary artery stenosis in a canine model using the PET agent ^{18}F -fluorobenzyl triphenyl

- phosphonium: comparison with ^{99m}Tc -tetrofosmin. *J Nucl Med.* 2007;48:1021–30.
31. Min JJ, Biswal S, Deroose C, Gambhir SS. Tetraphenylphosphonium as a novel molecular probe for imaging tumors. *J Nucl Med.* 2004;45:636–43.
 32. Jacobson O, Abourbeh G, Tsvirkun D, Mishani E. Rat imaging and in vivo stability studies using [^{11}C]dimethyl-diphenyl ammonium, a candidate agent for PET-myocardial perfusion imaging. *Nucl Med Biol.* 2013;40:967–73.
 33. Ilovich O, Abourbeh G, Bocher M, Freedman N, Billauer H, Dotan S, et al. Structure-activity relationship and preclinical evaluation of carbon-11 labeled ammonium salts as PET myocardial perfusion imaging agents. *Mol Imaging Biol.* 2012;14:625–36.
 34. Ilovich O, Billauer H, Dotan S, Freedman NM, Bocher M, Mishani E. Novel and simple carbon-11 labeled ammonium salts as PET agents for myocardial perfusion imaging. *Mol Imaging Biol.* 2011;13:128–39.
 35. Chen S, Zhao Z, Zhang Y, Fang W, Lu J, Zhang X. Effect of methoxy group position on biological properties of ^{18}F -labeled benzyl triphenylphosphonium cations. *Nucl Med Biol.* 2017;49:16–23.
 36. Tominaga T, Ito H, Ishikawa Y, Ito H, Ishiwata K, Furumoto S. Radiosynthesis and preliminary biological evaluation of a new ^{18}F -labeled triethylene glycol derivative of triphenylphosphonium. *J Label Compd Radiopharm.* 2016;59:117–23.
 37. Kim DY, Kim HS, Reder S, Zheng JH, Herz M, Higuchi T, et al. Comparison of ^{18}F -labeled fluoroalkylphosphonium cations with ^{13}N - NH_3 for PET myocardial perfusion imaging. *J Nucl Med.* 2015;56:1581–6.
 38. Kim DY, Kim HS, Min JJ. Radiosynthesis and evaluation of ^{18}F -labeled aliphatic phosphonium cations as a myocardial imaging agent for positron emission tomography. *Nucl Med Commun.* 2015;36:747–54.
 39. Kim DY, Kim HS, Jang HY, Kim JH, Bom HS, Min JJ. Comparison of the cardiac microPET images obtained using [^{18}F]FPTP and [^{13}N]NH $_3$ in rat myocardial infarction models. *ACS Med Chem Lett.* 2014;5:1124–8.
 40. Haslop A, Wells L, Gee A, Plisson C, Long N. One-pot multi-tracer synthesis of novel ^{18}F -labeled PET imaging agents. *Mol Pharm.* 2014;11:3818–22.
 41. Kim DY, Kim HS, Le UN, Jiang SN, Kim HJ, Lee KC, et al. Evaluation of a mitochondrial voltage sensor, (^{18}F -fluoropentyl)triphenylphosphonium cation, in a rat myocardial infarction model. *J Nucl Med.* 2012;53:1779–85.
 42. Kim DY, Kim HJ, Yu KH, Min JJ. Synthesis of ^{18}F -labeled (2-(2-fluoroethoxy)ethyl)tris(4-methoxyphenyl)phosphonium cation as a potential agent for positron emission tomography myocardial imaging. *Nucl Med Biol.* 2012;39:1093–8.
 43. Kim DY, Kim HJ, Yu KH, Min JJ. Synthesis of ^{18}F -labeled (6-fluorohexyl)triphenylphosphonium cation as a potential agent for myocardial imaging using positron emission tomography. *Bioconjug Chem.* 2012;23:431–7.
 44. Kim DY, Kim HJ, Yu KH, Min JJ. Synthesis of ^{18}F -labeled (2-(2-fluoroethoxy)ethyl)triphenylphosphonium cation as a potential agent for myocardial imaging using positron emission tomography. *Bioorg Med Chem Lett.* 2012;22:319–22.
 45. Shoup TM, Elmaleh DR, Brownell AL, Zhu A, Guerrero JL, Fischman AJ. Evaluation of (4-[^{18}F]fluorophenyl)triphenylphosphonium ion. A potential myocardial blood flow agent for PET. *Mol Imaging Biol.* 2011;13:511–7.
 46. Madar I, Ravert H, Nelkin B, Abro M, Pomper M, Dannals R, et al. Characterization of membrane potential-dependent uptake of the novel PET tracer ^{18}F -fluorobenzyl triphenylphosphonium cation. *Eur J Nucl Med Mol Imaging.* 2007;34:2057–65.
 47. Kim DY, Yu KH, Bom HS, Min JJ. Synthesis of (4-[^{18}F]fluorophenyl)triphenylphosphonium as a mitochondrial voltage sensor for PET. *Nucl Med Mol Imaging.* 2007;41:561–5.
 48. Madar I, Ravert HT, Du Y, Hilton J, Volokh L, Dannals RF, et al. Characterization of uptake of the new PET imaging compound ^{18}F -fluorobenzyl triphenyl phosphonium in dog myocardium. *J Nucl Med.* 2006;47:1359–66.
 49. Cheng Z, Subbarayan M, Chen X, Gambhir SS. Synthesis of (4-[^{18}F]fluorophenyl)triphenylphosphonium as a potential imaging agent for mitochondrial dysfunction. *J Label Compd Radiopharm.* 2005;48:131–7.
 50. Zhou Y, Liu S. ^{64}Cu -labeled phosphonium cations as PET radio-tracers for tumor imaging. *Bioconjug Chem.* 2011;22:1459–72.
 51. Demura M, Kamo N, Kobatake Y. Binding of lipophilic cations to the liposomal membrane: thermodynamic analysis. *Biochim Biophys Acta.* 1987;820:303–8.
 52. Ono A, Miyauchi S, Demura M, Asakura T, Kamo N. Activation energy for permeation of phosphonium cations through phospholipid bilayer membrane. *Biochemistry.* 1994;33:4312–8.
 53. Ravert HT, Madar I, Dannals RF. Radiosynthesis of 3-[^{18}F]fluoropropyl and 4-[^{18}F]fluorobenzyl triarylphosphonium ions. *J Label Compd Radiopharm.* 2004;47:469–76.
 54. Zhao Z, Yu Q, Mou T, Liu C, Yang W, Fang W, et al. Highly efficient one-pot labeling of new phosphonium cations with fluorine-18 as potential PET agents for myocardial perfusion imaging. *Mol Pharm.* 2014;11:3823–31.
 55. Haslop A, Gee A, Plisson C, Long N. Fully automated radiosynthesis of [1-(2-[^{18}F]fluoroethyl),1H[1,2,3]triazole 4-ethyl-ene] triphenylphosphonium bromide as a potential positron emission tomography tracer for imaging apoptosis. *J Labelled Comp Radiopharm.* 2013;56(6):313.
 56. Croteau E, Benard F, Bentourkia M, Rousseau J, Paquette M, Lecomte R. Quantitative myocardial perfusion and coronary reserve in rats with ^{13}N -ammonia and small animal PET: impact of anesthesia and pharmacologic stress agents. *J Nucl Med.* 2004;45:1924–30.
 57. Pagou M, Zerizer I, Al-Nahhas A. Can gallium-68 compounds partly replace ^{18}F -FDG in PET molecular imaging? *Hell J Nucl Med.* 2009;12:102–5.
 58. Yang BY, Jeong JM, Kim YJ, Choi JY, Lee YS, Lee DS, et al. Formulation of ^{68}Ga BAPEN kit for myocardial positron emission tomography imaging and biodistribution study. *Nucl Med Biol.* 2010;37:149–55.
 59. Tsang BW, Mathias CJ, Green MA. A gallium-68 radiopharmaceutical that is retained in myocardium: ^{68}Ga [(4,6-MeO $_2$ sal)2BAPEN] $^{+}$. *J Nucl Med.* 1993;34:1127–31.
 60. Tsang BW, Mathias CJ, Fanwick PE, Green MA. Structure-distribution relationships for metal-labeled myocardial imaging agents: comparison of a series of cationic gallium (III) complexes with hexadentate bis(salicylaldehyde) ligands. *J Med Chem.* 1994;37:4400–6.
 61. Cutler CS, Giron MC, Reichert DE, Snyder AZ, Herrero P, Anderson CJ, et al. Evaluation of gallium-68 tris(2-mercaptobenzyl)amine: a complex with brain and myocardial uptake. *Nucl Med Biol.* 1999;26:305–16.
 62. Plossl K, Chandra R, Qu W, Lieberman BP, Kung MP, Zhou R, et al. A novel gallium bisaminothiolate complex as a myocardial perfusion imaging agent. *Nucl Med Biol.* 2008;35:83–90.
 63. Tarkia M, Saraste A, Saanijoki T, Oikonen V, Vahasilta T, Strandberg M, et al. Evaluation of ^{68}Ga -labeled tracers for PET imaging of myocardial perfusion in pigs. *Nucl Med Biol.* 2012;39:715–23.
 64. Sharma V, Sivapackiam J, Harpstrite SE, Prior JL, Gu H, Rath NP, et al. A generator-produced gallium-68 radiopharmaceutical for PET imaging of myocardial perfusion. *PLoS One.* 2014;9:e109361.

65. Tillmanns J, Schneider M, Fraccarollo D, Schmitto JD, Langer F, Richter D, et al. PET imaging of cardiac wound healing using a novel ^{68}Ga -labeled NGR probe in rat myocardial infarction. *Mol Imaging Biol*. 2015;17:76–86.
66. Menichetti L, Kusmic C, Panetta D, Arosio D, Petroni D, Matteucci M, et al. MicroPET/CT imaging of $\alpha_v\beta_3$ integrin via a novel ^{68}Ga -NOTA-RGD peptidomimetic conjugate in rat myocardial infarction. *Eur J Nucl Med Mol Imaging*. 2013;40:1265–74.
67. Rischpler C, Nekolla SG, Kossmann H, Dirschinger RJ, Schottelius M, Hyafil F, et al. Upregulated myocardial CXCR4-expression after myocardial infarction assessed by simultaneous GA-68 pentixafor PET/MRI. *J Nucl Cardiol*. 2016;23:131–3.
68. Gronman M, Tarkia M, Kiviniemi T, Halonen P, Kuivanen A, Savunen T, et al. Imaging of alphavbeta3 integrin expression in experimental myocardial ischemia with [^{68}Ga]NODAGA-RGD positron emission tomography. *J Transl Med*. 2017;15:144.
69. Kiugel M, Kyto V, Saanijoki T, Liljenback H, Metsala O, Stahle M, et al. Evaluation of ^{68}Ga -labeled peptide tracer for detection of gelatinase expression after myocardial infarction in rat. *J Nucl Cardiol*. 2016;
70. Jindal A, Mathur A, Pandey U, Sarma HD, Chaudhari P, Dash A. Development of ^{68}Ga -labeled fatty acids for their potential use in cardiac metabolic imaging. *J Labelled Comp Radiopharm*. 2014;57:463–9.
71. Jain A, Mathur A, Pandey U, Sarma HD, Dash A. ^{68}Ga labeled fatty acids for cardiac metabolic imaging: influence of different bifunctional chelators. *Bioorg Med Chem Lett*. 2016;26:5785–91.
72. Hsiao YM, Mathias CJ, Wey SP, Fanwick PE, Green MA. Synthesis and biodistribution of lipophilic and monocationic gallium radiopharmaceuticals derived from N,N'-bis(3-aminopropyl)-N,N'-dimethylethylenediamine: potential agents for PET myocardial imaging with ^{68}Ga . *Nucl Med Biol*. 2009;36:39–45.
73. Green MA, Mathias CJ, Neumann WL, Fanwick PE, Janik M, Deutsch EA. Potential gallium-68 tracers for imaging the heart with PET: evaluation of four gallium complexes with functionalized tripodal tris(salicylaldimine) ligands. *J Nucl Med*. 1993;34:228–33.
74. Kung HF, Liu BL, Mankoff D, Kung MP, Billings JJ, Francesconi L, et al. A new myocardial imaging agent: synthesis, characterization, and biodistribution of gallium-68-BAT-TECH. *J Nucl Med*. 1990;31:1635–40.
75. Bellis SL. Advantages of RGD peptides for directing cell association with biomaterials. *Biomaterials*. 2011;32:4205–10.
76. Spinale FG, Janicki JS, Zile MR. Membrane-associated matrix proteolysis and heart failure. *Circ Res*. 2013;112:195–208.
77. Rohde LE, Ducharme A, Arroyo LH, Aikawa M, Sukhova GH, Lopez-Anaya A, et al. Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. *Circulation*. 1999;99:3063–70.
78. Knapp FF Jr, Kropp J. Iodine-123-labelled fatty acids for myocardial single-photon emission tomography: current status and future perspectives. *Eur J Nucl Med*. 1995;22:361–81.
79. Schwaiger M, Hicks R. The clinical role of metabolic imaging of the heart by positron emission tomography. *J Nucl Med*. 1991;32:565–78.
80. Trivieri MG, Dweck MR, Abgral R, Robson PM, Karakatsanis NA, Lala A, et al. ^{18}F -Sodium fluoride PET/MR for the assessment of cardiac amyloidosis. *J Am Coll Cardiol*. 2016;68:2712–4.
81. Lee SP, Lee ES, Choi H, Im HJ, Koh Y, Lee MH, et al. ^{11}C -Pittsburgh B PET imaging in cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2015;8:50–9.
82. Dorbala S, Vangala D, Semer J, Strader C, Bruyere JR Jr, Di Carli MF, et al. Imaging cardiac amyloidosis: a pilot study using ^{18}F -florbetapir positron emission tomography. *Eur J Nucl Med Mol Imaging*. 2014;41:1652–62.
83. Law WP, Wang WY, Moore PT, Mollee PN, Ng AC. Cardiac amyloid imaging with ^{18}F -florbetaben PET: a pilot study. *J Nucl Med*. 2016;57:1733–9.
84. Schwaiger M, Melin J. Cardiological applications of nuclear medicine. *Lancet*. 1999;354:661–6.
85. Gormsen LC, Haraldsen A, Kramer S, Dias AH, Kim WY, Borghammer P. A dual tracer ^{68}Ga -DOTANOC PET/CT and ^{18}F -FDG PET/CT pilot study for detection of cardiac sarcoidosis. *EJNMMI Res*. 2016;6:52.
86. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernay CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1304–23.
87. Ishida Y, Yoshinaga K, Miyagawa M, Moroi M, Kondoh C, Kiso K, et al. Recommendations for ^{18}F -fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. *Ann Nucl Med*. 2014;28:393–403.
88. Osborne MT, Hulten EA, Singh A, Waller AH, Bittencourt MS, Stewart GC, et al. Reduction in ^{18}F -fluorodeoxyglucose uptake on serial cardiac positron emission tomography is associated with improved left ventricular ejection fraction in patients with cardiac sarcoidosis. *J Nucl Cardiol*. 2014;21:166–74.
89. Ishiyama M, Soine LA, Vesselle HJ. Semi-quantitative metabolic values on FDG PET/CT including extracardiac sites of disease as a predictor of treatment course in patients with cardiac sarcoidosis. *EJNMMI Res*. 2017;7:67.
90. Hanneman K, Kadoch M, Guo HH, Jamali M, Quon A, Iagaru A, et al. Initial experience with simultaneous ^{18}F -FDG PET/MRI in the evaluation of cardiac sarcoidosis and myocarditis. *Clin Nucl Med*. 2017;42:e328–e34.
91. Lucke C, Oppolzer B, Werner P, Foldyna B, Lurz P, Jochimsen T, et al. Comparison of volumetric and functional parameters in simultaneous cardiac PET/MR: feasibility of volumetric assessment with residual activity from prior PET/CT. *Eur Radiol*. 2017;27:5146–57.