Review Article

Current status of myocardial perfusion imaging radiopharmaceuticals for SPECT and PET imaging modalities

Fadimana Nur Aydinbelge*, Murat Sadic, Meliha Korkmaz

Department of Nuclear Medicine, Ankara Training and Research Hospital, Ankara, Turkey

*Correspondence:
Dr. Fadimana Nur Aydinbelge,
E-mail: fnuraydinbelge@gmail.com

ABSTRACT

Coronary artery disease (CAD) is the leading cause of death and remains a major health problem worldwide. Myocardial perfusion imaging (MPI) with single photon emission tomography (SPECT) and positron emission tomography (PET) has been established as the main functional nuclear cardiology noninvasive technique for CAD over the past years. The studies has been shown that the use of MPI as a useful and important imaging modality for the diagnosis, risk stratification and treatment planning for CAD. The purpose of this article is to review properties of the radiopharmaceuticals used for myocardial perfusion imaging with SPECT and PET.

Keywords: Myocardial perfusion imaging, PET, Radiopharmaceutical, SPECT

INTRODUCTION

In nuclear cardiology practice, MPI is widely used as the major nuclear cardiology technique to the evaluation of regional myocardial blood flow and assessment of myocardial viability under rest and stress conditions for patient with CAD for decades.[1]

Myocardial perfusion scintigraphy (MPS) is an imaging method that utilizes an intravenously radioactive tracer to delineate the distribution of blood flow in myocardium during both stress with physical and pharmaceutical exercise test and at rest.[2] Principally, radioactive tracer must arrive to the myocardium and viable myocardial cells must be uptake radiotracer.

For successful imaging, a significant amount of radiotracer must remain in the cell. If a patient has hemodynamically significant coronary artery disease or myocardial cells that have lost viability due to myocardial infarction (MI), the concentration of radiotracer can decrease in this areas.[3] MPI depends on that basic mechanism. The evolution of this technique over the years has occurred parallel to advances in instrumentation, MPI can be recorded with SPECT, SPECT/computed tomography (CT), PET and PET/CT.[4,5] Myocardial perfusion imaging with SPECT or PET have also been considered an important tool and a noninvasive technique that is used for the diagnosis, the mainstay of risk stratification, assessment of myocardial viability and left ventricular function, treatment planning and prognostic assessment of patient with suspected or known CAD.[4]

The indications of MPI are evaluation of patients with suspected or having CAD, assessment of presence, location, extent and severity of myocardial ischemia and infarction, hemodynamic significance of coronary artery stenosis demonstrated by CT or invasive coronary angiography, assessment of myocardial viability in ischemic heart disease, also detection of stunned or hibernating myocardium.[3,6]

Additionally, myocardial perfusion PET is receiving increasing attention owing to its unique capability of absolute myocardial blood flow estimation.

PET/MRI seems to be particularly promising for nuclear cardiology imaging tool in the future for restrictive diseases, such as cardiac sarcoidosis and amyloidosis. Considering these advances, the current challenges of nuclear cardiology will become opportunities if more collaborative efforts are devoted to this exciting field of nuclear medicine.[7] Although current tracers used for perfusion imaging have provided valuable clinical information, further advances are needed to enhance the detection rate of coronary artery lesions as well as the capability of monitoring subtle changes in defect size with medical therapy aimed at alleviating stress-induced ischemia and/or improving coronary endothelial function.[4] The purpose of this article review property of current and future SPECT or PET radiopharmaceuticals for MPI.

SINGLE PHOTON RADIOPHARMACEUTICALS

A variety of radiopharmaceuticals which are used for the diagnosis and management of ischemic heart disease are summarized in Table 1. The selection among radiopharmaceuticals is determined with respect to the patient's physical characteristic which has an important role for the diagnosis and management of ischemic heart disease.

Table 1: Comparison of cardiac imaging tracers in spect.

	Tl -201	Tc-99m sestamibi	Tc-99m tetrofosmin	Tc-99m teboroxime	Tc-99m-N-NOET
Photon energy	67-82 kEv	140 keV	140 keV	140 keV	140 keV
Physical half life	73 h	6h	6h	6h	6h
Chemical class/charge	Elemental cation	Isonitrile cation	Diphosphine cation	Boronic asid compound	Bis (N-ethoxyl, N-ethyldithiocarmato)nitrido complexes
Mechanism uptake	Active transport (Na/K ATPase pump)	Passive diffusion	Passive diffusion	Passive diffusion	Passive diffusion
Myocyte localization	Cytosol	Mitochondria	Mitochondria	mitochondria	mitochondria
Preparation	Cyclotron	Generator/kit	Generator/kit	Generator/kit	Generator/kit
First-pass extraction fraction	Higher (85%)	Lower (55%-65%)	Lower (50%)	Higher (>90%)	Higher (75%-85%)
Heart uptake	3%	1.0%-1.4%	1.2%	2.2%	3.0%
Myocardial clearance	Rapid	Slow	Rapid	Rapid	Slow
Body clearance	Renal	Hepatic	Hepatic	Hepatic	Hepatic
Counting statics	Fair	Better	Better	Better	Better
Injected dose	Lower	Higher	Higher	Higher	Higher
Myocardial perfusion at high blood flow	Same	Same	Same	Same	Same
Redistribution	Significant	Minimal	Minimal	Minimal	Significant

Three single photon myocardial imaging tracers are commercially available for clinical use: Tc-99m tetrafosmin, Tc-99m sestamibi and thalium-201 chloride.[8] Tc-99m tetrafosmin and Tc-99m sestamibi are preferred to use imaging agents due to Tc-99m have better quality images, higher photon energy peak for gamma camera imaging and lower effective radiation dose to the patient than thalium-201 chloride.[9] An ideal radiopharmaceutical for optimal myocardial perfusion imaging should have the following characteristics: myocardial uptake directly proportional to blood flow, high extraction fraction, high myocardium-to-background ratio, good myocardial cell retention and photon flux.[9] Taking into consideration the advantages and disadvantages of each radiopharmaceuticals which give the best clinical information that should be selected.

Thallium-201 chloride

Thallium-201, which is a cyclotron-produced and potassium analogue, enters the myocardial cell membrane via the sodium-potassium adenosine triphosphatase (ATPase) pump dependent exchange mechanism.[1,9] It decays by electron capture with a physical half-life of 73

hours and has x-rays of energy 67-82 kEv and gamma rays of 135-167 kEv.[5,10] Tl-201 has lower image quality than technetium labelled agents that limited its use.[8] About 85% of the administered amount of Tl-201 is extracted by the myocardial cell following the first coronary capillary circulation, which is higher than the Tc-99m labeled MPI radiotracers.[11] About 4% of injected activity is localizing in the myocardium and taken up by viable myocardial cells in proportion to coronary blood flow.[8] After the initial extraction, redistribution of Tl-201 occurs rapidly within the myocardial cells, starting 20 minutes after administered dose.[4] For stress studies, imaging should be performed within 10 minutes later and rest studies begins 3-4 hours after radiotracer administration. It is cleared by kidneys that lead to a radiation dose to the kidneys of 1 rad/mCi.[11,12] Total body absorbed dose is 2.4 rem/4mCi (2.4 cGy/1480 MBq).[5]

Technetium- 99m

Technetium-99m is a widely used clinically in nuclear medicine. Tc-99m is produced by the extracted from a molybdenum-99 generator.[5] Tc-99m has a half-life of 6 hours and has gama energy of about 140 keV.[9] The energy of Tc-99m is higher than that of thallium, but lower than that of PET radiotracers.[6] Tc-99m-labeled radiopharmaceuticals used for MPI are as follows: Tc-99m sestamibi, Tc-99m tetrofosmin, Tc-99m teboroxime, Tc-99m-N-NOET.[1]

Tc-99m Sestamibi

Sestamibi is lipophilic complex cation and an isonitril compound (chemical name: hexakis 2-methoxyisobutyl isonitrile).[5] Tc-99m sestamibi is taken up by myocardium in proportion to coronary blood flow. First pass myocardial extraction fraction for sestamibi is in the range of 55% to 65%.[1] It diffuses passively across both the myocardial cell membrane and mitochondrial membrane8. Myocardial uptake ratio is approximately 1.2%-1.5% of the injected dose.[9] It is localized within mitochondria because of its large negative transmembrane potentials, reflecting viability.[13] This allows for an imaging time at several hours after administered radiotracer, depend on its half-life. Because of the progresive liver and lungs clearance of Tc-99m sestamibi, renal and bilier excretion; improving the myocardium-to-background activity ratios improve with time. After exercise stress studies, imaging performed 15-30 minutes later and rest studies begins 30 to 90 minutes after radiotracer administration because of faster background clearance.[5,14] The colon receives the highest radiation dose at 5.4 rems/30 mCi (5,4 cGy/1110 MBq). The whole body radiation effective dose is 0.9 rem/30 mCi (0.9 cGy/1110 MBq).[5]

Tc-99m Tetrofosmin

Tetrafosmin is a member of diphosphine family, chemical name is bisbis (2-ethoxyethyl) phosphinol ethane, and lipophilic cation that localizes mitochondria in the myocardial cell.[1] Tc-99m tetrafosmin and Tc-99m sestamibi are similar to myocardial uptake retention and blood clearance features.[9] The liver clearance of Tc-99m Tetrafosmin is faster than that of Tc-99m sestamibi.[12] First- pass extraction is about 54% which is lower than that of Tl-201 and Tc-99m sestamibi.[1] Myocardial uptake occurs by 5 minutes after injection and approximately 1.2% of administered dose remains in the myocardium.[9] Stress imaging should be started 15 minutes after exercise; rest studies should be started 30 minutes after intravenous injection because of faster hepatic clearance.[5] The gallbladder is the radiation target organ, receiving 5.4 rems/20 mCi (5.4 cGy/1110 MBq). The whole body radiation effective dose is 0,8 rem/30 mCi (0.8 cGy/1110 MBq).[5]

Tc-99m Teboroxime

Teboroxime is chemically different from Thallium and other Tc-labelled radiotracers. It is neutral lipophilic agent and a member of boronic acid adducts of technetium dioximes.[15] It accumulates in the myocardium in proportion to blood flow. Tc-99m teboroxime passes through the myocardial cell by passive diffusion due to it has a neutral lipophilic compound.[9] The first pass myocardial extraction fraction of Tc-99m teboroxime is over 90% and washout from the myocardium is rapid and approximately 2.2% of administered dose remains in the myocardium.[1] It does not redistribute.[5] Teboroxime requires very rapid imaging because of it has a very short myocardial retention time and rapid myocardial clearance.[5,6] So, this property has limited its use. The administered dose is higher than that of other radiotracers to obtain better counting statics for imaging.[9] The whole body absorbed dose of 0.83 rad.[16]

Tc-99m-N-NOET

Tc-99m (N-ethoxy-N-ethyl-dithiocarbamato) ni-trido (N-NOET) is a neutral lipophilic imaging agent.[17] Myocardial uptake is directly correlated with coronary blood flow.[1] It keeps by calcium channel membranes, does not keep by mitochondria.[18] The first-pass myocardial extraction fraction is high in the 75% to 85% range.[9] It exhibits to undergo redistribution in human clinical studies that like Tl-201; thus, a single injection is sufficient for stress and rest imaging.[19] The heart/lung uptake ratio of 99mTc-N-NOET is lower than that of other technetium agents and Tl-20120. The uptake of Tc-99m-N-NOET is shown to reflect reperfusion coronary blood flow and not viability in an experimental model of acutely reperfused myocardial infarction.[20]

PET RADIOTRACER FOR MYOCARD PERFUSION IMAGING

PET has been widely used to non-invasive imaging of heart disease over the past decades. PET has several advantages over SPECT that are better temporal, contrast

and spatial resolution and greater sensitivity, which provide to measure the capability of quantifying myocardial perfusion, myocardial blood flow (MBF) and myocardial flow reserve (MFR).[3,12,21] Due to its inherently quantitative nature, its superior detection sensitivity, and its advantageous spatial and temporal resolution over conventional nuclear techniques, PET has been considered a "gold standard" for noninvasive assessment of myocardial perfusion and viability. PET has high quality myocardial images compared with SPECT because of higher count rate, better attenuation correction and fewer attenuation artifacts.[22,23] However, usage of myocardial PET imaging has limitations that not easily avaliable in many hospitals for routine and higher cost than SPECT.[12] There are three agents commonly available and currently used for myocardial imaging with PET: Rubidium 82 (Rb-82) chloride, nitrogen 13 (N-13) ammonia, oxygen 15 (O-15) water.[1] In recent years, fluorine-18 labeled compounds for myocardial perfusion imaging have been developed and undergone clinical evaluation.[24] The detailed properties of PET tracers are shown on Table 2.

Table 2: Properties of cardiac PET radiotracers.

	NH$_3$-13	Rb-82	O-15	F-18 FDG	F-18 Flurpiridaz
Half-life	10 min	76 sec	122 sec	110 min	110 min
Production Method	On-site cyclotron	Sr-82/Rb-82 generator	On-site cyclotron	Regional cyclotron	Regional cyclotron
Average positron energy (MeV)	0.49	1.48	0.74	0.25	0.25
RMS Positron range (mm)	0.6	2.6	1.0	0.2	0.2
Positron range	2.5	8.6	4.1	1.0	1.0
Myocardial uptake mechanism	Diffusion/ Metabolic trapping (perfusion)	Na/K ATPase (perfusion)	Free diffusion	Glucose transport/ hexokinase (viability)	Mitochondrial binding (perfusion)
Myocardial extraction fraction	80%	65%	100% (diffusible)	1-3%	94%
Image Quality	Excellent	Good	Poor	Excellent	Excellent
Image resolution	Intermediate	Lowest	Intermediate	Highest	Highest
Image interpretation	Yes	Yes	No	Yes	Yes
Quantification of MBF	Yes	Yes	Yes	Yes	Yes
Stress modality	Pharmacologic or exercise (exercise is feasible but not practical)	Pharmacologic	Pharmacologic	Pharmacologic or exercise	Pharmacologic or exercise
Current status	FDA-approved	FDA-approved	FDA-not approved	FDA-approved	Tested in clinical III trials

Nitrogen 13 (N-13) Ammonia

Usage of N-13 ammonia may be preferred for assessment of myocardial perfusion with PET. Its usage is limited, because N-13 ammonia has short physical half-life (10-minute) and requiring one site cyclotron production.[12] In the bloodstream, neutral ammonia (NH$_3$) in equilibrium with its charged ammonium (NH$_4$) ion forms N-13 ammonia.[25] It diffuses passively across plasma and cell membranes, then is converted to N-13 glutamine via glutamine synthetase enzyme and is trapped inside the cell.[24] It has high first pass extraction (80%) and long tissue retention because of metabolic trapping.[1] The tracer uptake occurs also the brain, liver and kidneys.[5]

The positron range of N-13 ammonia is 2.53 mm resulting in good image resolution.[24] The radiation absorbed dose is low than the most clinically used radiotracers.[5] The bladder and the whole body effective dose is 0.2 rem/20 mCi (0.2 cGy/740 MBq).[5]

Rubidium 82 (Rb-82) Chloride

Rb-82 chloride is currently Food and Drug Administration (FDA)-approved cardiac PET radiotracers which are used for the assessment of suspected or having CAD and has some clinically limitations; an ultra-short half-life (76 seconds) and the half-life of parents is 26 days.[1,26] Rb-82 is produced by a commercially available

strontium-82/Rb-82 generator system equipped with automated infusion pump that can be eluated every 10 minutes.[25] Rb-82 is a monovalent cation and a potassium analog that is taken up into the myocardial cells by the Na/K ATPase pump.[25] Because of these properties of Rb-82 is similar to Tl-201.[27] Myocardial extraction of Rb-82 is lower (60%) than that of N-13 ammonia.[5] Rb-82 has 8.6mm positron range resulting in lower image resolution and quality than the other that of MPI tracers.[24] The highest radiation dose is received by kidneys, heart and lungs. The whole body effective dose is 0.8 rads/40 mCi (0.8 cGy/1480 MBq).[5]

Oxygen-15 Water

O-15 is an important radiotracer that can be used for the quantitative measurement of myocardial blood flow because it diffuses freely across plasma membranes.[25] It has a half-life of 2.2 minutes.[5] Its production requires an on-site cyclotron and limits the O-15 usage.[12] It has a first-pass extraction of 95% that is not affected by metabolic factors.[5] The positron range of O-15 is 4.14mm resulting in an intermediate image resolution and image quality lower than that of other PET myocardial perfusion agents.[24] It is a FDA not-approved radiotracer so currently not used for clinical imaging in United States.[3]

Fluorine-18 Fluorodeoxyglucose

F-18 FDG is an FDA-approved glucose analogue that is widely used in clinical oncology.[26] F-18 FDG uptake is established to determine myocardial viability.[7] It is taken into the myocardial cell and undergone phosphorylation like the same mechanism of glucose.[23] Unlike glucose, the resulting F-18 FDG 6-phosphate (approximately 1% to 4% of injected dose) trapped in the myocyte because it is not metabolized.[5] The urinary bladder receives the highest radiation dose at 3.0 rads/40 mCi (3.0 cGy/1480 MBq).[5] The whole body effective dose is 1.1 rem/15 mCi (1.1 cGy/575 MBq).[5]

FUTURE PET RADIOPHARMACEUTICAL

Several Fluorine-18 labeled radiotracers have been developed in recent years. These are F-18 flurpiridaz (formerly known as F-18 BMS747158-02) and F-18 fluorobenzyltriphenylphosphonium (F-18 FBnTP).[28] F-18 flurpiridaz and F-18 FBnTP are very promising new PET perfusion tracer that allow quantitative assessment of regional perfusion.[12] F-18 has advantages of high positron range (97%) and longer half-life (110 minutes) which to administer at peak exercise stress protocols.[5,12,24] F-18 labeled radiotracers may be produced at regional cyclotrons in similar way as F-18-FDG.[10]

F-18 FBnTP, is a member of a new class of positron-emitting lipophilic phosphonium cation, which can pass biological membranes by passive diffusion.[12] It is localized intact mitochondria due to the negative

mitochondrial membrane potential, like the Tc-99m sestamibi and Tc-99m tetrafosmin.[29]

F-18 flurpiridaz is radionuclide-labeled analog of an insecticide called pyridaben, which inhibits an enzyme in the mitochondrial complex I (MC-1) (known as NADH: ubiquinone oxidoreductase).[30] It has been investigated in phase III clinical trials.[7] The studies show that F-18 flurpiridaz with PET myocardial imaging had higher sensitivity and similar specificity than the patients undergoing invasive angiography.[31] F-18 flurpiridaz may provide an important development in current non-invasive imaging of CAD based on its favorable dosimetry, linear extraction across MBF, improved spatial resolution and longer half-life.[31]

OTHER PET TRACERS

Other tracers such as Carbon-11 (C-11) acetate have been used for PET perfusion imaging.[23] C-11 acetate is a radioactive isotope of natural element.[12] It has half-life of 20.4 minutes.[5] C-11 acetate is taken up by myocardial cells, rapidly converted acetylCoA and readily metabolized to C-11 CO_2 through TCA cycle with oxidative phosphorylation.[32] Clearance of C-11 acetate which provides a quantitative index of myocardial oxidative metabolism is measured externally with gamma probes in the myocardium.[33] Thus, it has been used for the noninvasive measurement of myocardial oxygen consumption (MVO_2).[34]

Cu-62 PTSM is a physical half-life of 9.7 minutes and the zinc-62/copper-62 generator system- produced tracer that has been used in the past.[35] The generator has a half-life 9.3 hours so requiring daily delivery.[23] Cu-62 ETS which is newer than Cu-PTSM exhibits higher stress/rest myocardial ratio and lower liver uptake compared to Cu-62 PTSM.[36]

Gallium-68 labeled imaging agents are being discovered as potential PET perfusion tracers. Germanium-68/Gallium-68 (Ge-68/Ga-68) generator systems are convenient as a source of PET radiotracers due to the long physical half-life of Ge-68 (271 days) and a suitable Ga-68 daughter half-life (67.7 minutes).[37] In recent years, myocardial uptake has been demonstrated with a ligand labeled with Ga-67 for SPECT suggesting potential for these ligands as PET MPI tracers.[23]

CONCLUSION

Over the years, many different radiopharmaceuticals cited in this review have been used SPECT or PET MPI. Each of the available radiotracers has advantages and disadvantages, which should be understood and taken into consideration when one of them is choosing. In the future, new perfusion agents should be developed and validated in the experimental laboratory for clinical applicable tracers.

REFERENCES

1. Beller GA, Bergmann SR. Myocardial perfusion imaging agents: SPECT and PET. J Nucl Cardiol. 2004;11(1):71-86.
2. Hung GU. Diagnosing CAD: additional markers from myocardial perfusion SPECT. J Biomed Res. 2013;27(6):467-77.
3. Hung GU, Wang YF, Su HY, Hsieh TC, Ko CL, Yen RF. New Trends in Radionuclide Myocardial Perfusion Imaging. Acta Cardiol Sin. 2016;32(2):156-66.
4. Won KS, Song BI. Recent trends in nuclear cardiology practice. Chonnam Med J. 2013;49(2):55-64.
5. Ziessman HA, O'Malley JP, Thrall JH, Fahey FH eds. Cardiac System. Nuclear Medicine: The Requisites. 4th ed. Philadelphia, PA: Elsevier Saunders. 2014:378-423.
6. Gibbons RJ. Myocardial perfusion imaging. Heart 2000;83(3):355-60.
7. Lee WW. Recent Advances in Nuclear Cardiology. Nucl Med Mol Imaging. 2016;50(3):196-206.
8. Verberne HJ, Acampa W, Anagnostopoulos C, Ballinger J, Bengel F, De Bondt P, et al. EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. Eur J Nucl Med Mol Imaging. 2015;42(12):1929-40.
9. Husain SS. Myocardial perfusion imaging protocols: is there an ideal protocol? J Nucl Med Technol. 2007;35(1):3-9.
10. Grunwald AM, Watson DD, Holzgrefe HH Jr, Irving JF, Beller GA. Myocardial thallium-201 kinetics in normal and ischemic myocardium. Circulation. 1981;64(3):610-8.
11. Pagnanelli RA, Basso DA. Myocardial perfusion imaging with 201Tl. J Nucl Med Technol. 2010;38(1):1-3.
12. Lin X, Zhang J, Wang X, Tang Z, Zhang X, Lu J. Development of radiolabeled compounds for myocardial perfusion imaging. Curr Pharm Des. 2012;18(8):1041-57.
13. Dahlberg ST. Assessment of myocardial perfusion with Tc-99m: image is everything. J Nucl Cardiol. 2009;16(4):493-6.
14. Leppo JA, DePuey EG, Johnson LL. A review of cardiac imaging with sestamibi and teboroxime. J Nucl Med. 1991;32(10):2012-22.
15. Zheng Y, Ji S, Tomaselli E, Ernest C, Freiji T, Liu S. Effect of co-ligands on chemical and biological properties of (99m)Tc(III) complexes (99m)Tc(L)(CDO)(CDOH)2BMe (L=Cl, F, SCN and N3; CDOH2=cyclohexanedione dioxime). Nucl Med Biol. 2014;41(10):813-24.
16. ES C, SS H. Nuclear Cardiac Imaging: Terminology and Technical Aspects. Radiology. 2004;233(2):566.
17. Fagret D, Ghezzi C, Vanzetto G. 99mTc-N-NOET imaging for myocardial perfusion: can it offer more than we already have? J Nucl Med. 2001;42(9):1395-6.
18. Riou L, Ghezzi C, Mouton O, Mathieu JP, Pasqualini R, Comet M, et al. Cellular uptake mechanisms of 99mTcN-NOET in cardiomyocytes from newborn rats: calcium channel interaction. Circulation. 1998;98(23):2591-7.
19. Fagret D, Marie PY, Brunotte F, Giganti M, Le Guludec D, Bertrand A, et al. Myocardial perfusion imaging with technetium-99m-Tc NOET: comparison with thallium-201 and coronary angiography. J Nucl Med. 1995;36(6):936-43.
20. Vanzetto G, Glover DK, Ruiz M, Calnon DA, Pasqualini R, Watson DD, et al. 99mTc-N-NOET myocardial uptake reflects myocardial blood flow and not viability in dogs with reperfused acute myocardial infarction. Circulation 2000;101(20):2424-30.
21. Parker MW, Iskandar A, Limone B, Perugini A, Kim H, Jones C, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis. Circ Cardiovasc Imaging. 2012;5(6):700-7.
22. Dilsizian V. SPECT and PET Myocardial perfusion imaging: tracers and techniques. In: Dilsizian V, Narula J, eds. Atlas of nuclear cardiology. 4th ed. New York, NY: Springer Science & Business Medi. 2013:55-93.
23. Lalonde L, Ziadi MC, Beanlands R. Cardiac positron emission tomography: current clinical practice. Cardiol Clin. 2009;27(2):237-55.
24. Maddahi J, Packard RR. Cardiac PET perfusion tracers: current status and future directions. Semin Nucl Med. 2014;44(5):333-43.
25. Machac J. Cardiac positron emission tomography imaging. Semin Nucl Med. 2005;35(1):17-36.
26. Bengel FM, Higuchi T, Javadi MS, Lautamaki R. Cardiac positron emission tomography. J Am Coll Cardiol. 2009;54(1):1-15.
27. Yoshinaga K, Klein R, Tamaki N. Generator-produced rubidium-82 positron emission tomography myocardial perfusion imaging-From basic aspects to clinical applications. J Cardiol. 2010;55(2):163-73.
28. Rischpler C, Park MJ, Fung GS, Javadi M, Tsui BM, Higuchi T. Advances in PET myocardial perfusion imaging: F-18 labeled tracers. Ann Nucl Med. 2012;26(1):1-6.
29. 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 18F-fluorobenzyl triphenyl phosphonium: comparison with 99mTc-tetrofosmin. J Nucl Med. 2007;48(6):1021-30.

30. 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(6):782-8.

31. Mahmarian JJ, Chang S, Nabi F. Nuclear cardiology: 2014 innovations and developments. Methodist Debakey Cardiovasc J. 2014;10(3):163-71.

32. Naya M, Tamaki N. Imaging of Myocardial Oxidative Metabolism in Heart Failure. Curr Cardiovasc Imaging Rep. 2014;7:9244.

33. Brown M, Marshall DR, Sobel BE, Bergmann SR. Delineation of myocardial oxygen utilization with carbon-11-labeled acetate. Circulation 1987;76(3):687-96.

34. Sun KT, Yeatman LA, Buxton DB, Chen K, Johnson JA, Huang SC, et al. Simultaneous measurement of myocardial oxygen consumption and blood flow using 1-carbon-11acetate. J Nucl Med. 1998;39(2):272-80.

35. Green MA, Mathias CJ, Welch MJ, McGuire AH, Perry D, Fernandez-Rubio F, et al. Copper-62-labeled pyruvaldehyde bis (N4-methylthiosemicarbazonato) copper(II): synthesis and evaluation as a positron emission tomography tracer for cerebral and myocardial perfusion. J Nucl Med. 1990;31(12):1989-96.

36. Lacy JL, Haynes NG, Nayak N, Mathias CJ, Wallhaus TR, Stewart R, et al. PET Myocardial Perfusion Imaging with Generator Produced Radiopharmaceuticals. 62Cu-PTSM and 62Cu-ETS. Clin Positron Imaging. 1999;2(6):317.

37. 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(1):83-90.