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Current Status of Myocardial Perfusion PET in the United States

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Abstract

While single photon emission computed tomography (SPECT) is by far the predominant modality for radionuclide myocardial perfusion imaging in the United States in 2017, there has been impressive growth in positron emission tomography (PET) and especially hybrid PET/computed tomography (CT) utilization. Advantages, clinical indications, and procedural standards have been documented by professional society publications. FDA clearances exist and payments are defined for governmental and commercial contractors. Current efforts are underway to standardize training and education for physicians and technologists who will perform PET perfusion studies, and to advance standards for performance, quality control, and reporting of myocardial blood flow quantification. Industry appears heavily invested in the future of PET perfusion, with recent FDA approval of a second Rubidium-82 generator and elution system, a new production facility capable of substantially increasing Rubidium-82 availability, and a novel fluorine-based perfusion tracer undergoing Phase 3 studies. Current paradigms appear to favor SPECT for less complicated patients who are able to exercise, and PET for more complicated or higher-risk patients who require pharmacologic stress.
Keywords: Myocardial blood flow, Myocardial perfusion imaging, Positron emission tomography, United States
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The potential value of positron emission tomography (PET) for myocardial perfusion imaging (MPI) has been recognized for more than 30 years. Utilization was basically limited to academic institutions interested in research studies until 1989, when rubidium-82 (Rb-82) was approved by the FDA for MPI. Subsequently, cardiology practices and larger hospitals began to transition selected patients from SPECT to PET for their MPI studies. Initially, images were acquired on dedicated BGO systems without cardiac gating. With introduction of newer LSO and LYSO detectors, imaging protocols evolved to permit higher count studies along with rest and peak hyperemia function. Currently, hybrid PET/CT scanners capable of list-mode acquisitions are increasingly used, simplifying routine quantification of absolute measurements of myocardial blood flow and providing assessments of coronary artery calcium. The only source of generators and a delivery system until late 2016 was Bracco Diagnostics (CardioGen). In 2010, strontium leakage into the Rb-82 eluent was discovered after thresholds of generator utilization were passed, leading to a 10-month interruption of service and institution of safety steps mandated by the FDA. In late 2016, a second generator and elution system (Ruby-Fill, Jubilant-DraxImage) was FDA approved. In 2007, N-13 NH3-ammonia was also approved for assessment of myocardial perfusion. While most sites are using Rb-82, a number of hospitals with on-site cyclotrons and practices with N-13 NH3-ammonia producing cyclotrons within about 15 minutes away use ammonia. In 2017, F-18 Flurpiridaz is undergoing Phase 3 testing as a PET MPI agent for both pharmacologic and exercise stress. Today, cardiac PET is being employed commonly in the United States for myocardial perfusion imaging, myocardial viability assessment, diagnosing cardiac sarcoidosis and following for therapeutic response, prosthetic valve and device infections, and for a number of niche applications such as vasculitis, differentiating cardiac tumors from thrombi, and transplant rejection. Current estimates are that cardiovascular PET is being performed on a routine basis at approximately 300 centers in the United States.

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PET myocardial perfusion imaging

The vast majority of cardiovascular PET studies are perfusion studies performed to assess coronary artery disease (CAD). There are approximately 200 sites using Rb-82 and 50 using N-13 NH3-ammonia. The majority of studies are performed with Rb-82 delivered in a generator sold on a 4, 5, or 6 weekly schedule by Bracco Inc. Some centers that have an on-site cyclotron or one within 15 minutes away capable of producing NH3-ammonia are using this rather than Rb-82.

Larger volume sites prefer Rb-82 for a number of reasons. The tracer is available 24/7; it permits very rapid through-put efficiency (full rest/stress studies can be accomplished every 30 minutes); the cost is fixed and therefore decreases per patient as volume increases; staff exposure to radiation is minimized; peak hyperemic regional and global left ventricular function can be compared to rest function; and there is strong documentation of value for flow quantification measurements. It is likely that Rb-82 will remain the agent of choice for higher-volume labs. The disadvantages are the high fixed costs limiting it to higher-volume sites; image quality is not as good as with NH3-ammonia or F18-flurpiridaz; and repeat imaging in the case of mishaps such as patient motion during acquisition is not practicable due to the short half-life (75 seconds) of Rb-82.

PET compared to SPECT for MPI

Exercise SPECT provides a large amount of information important for diagnosing CAD, estimating risk, and guiding decisions about need for coronary angiography and revascularization. In this test, the absence of perfusion defects comports a good outcome provided the patient demonstrates good exercise tolerance in absence of concerning findings such as major ST changes, arrhythmias, blood pressure drops during exercise, or progressive angina. Pharmacologic SPECT is considerably less comforting. Clinical response to the vasodilator adds little useful information. Interpretation lies almost entirely on the spatially-relative distribution of the tracer to the myocardium. Risk of events is higher for normal or abnormal perfusion findings after pharmacologic stress compared to exercise stress (1, 2). Some patients do not even have a vasodilator impact on coronary flow (3-5), and in absence of measuring flow, this is not discernable by the imager.

The evidence available is that for patients undergoing pharmacologic stress, PET outperforms SPECT for both diagnosis and risk stratification of CAD. The advantages include:

i) Superior image quality, independent of patient habitus (6, 7). With PET, all of the image data is attenuation corrected. The images have high count density and less scatter contamination especially from cardiac-adjacent structures. Image quality is the same for large and small patients, those with breast implants, and those that cannot raise their arms above their heads.
ii) Higher diagnostic accuracy. Several studies and meta-analyses (7-10) have shown that PET provides both higher sensitivity and specificity than SPECT for diagnosing any CAD, and especially for recognizing or ruling out the presence of multivessel CAD (7, 11, 12).
iii) Lower radiation. A typical rest/stress Tc-99m SPECT exposes a patient to about 12 mSv of radiation, compared to about 3 for a rest/stress PET study (13-15). This is an important consideration for younger patients, and for those with chronic CAD who are likely to receive high radiation burdens during their years of coping with this chronic disease.
iv) Faster acquisition protocols. Typical acquisitions for each image set is about 5 minutes, with a complete rest/stress Rb-82 study completed in 30 minutes. This is an important advantage for hospital in-patients, as it expedites their care including discharge if normal. It also results in improved image quality for those patients who find it difficult to lie still for protracted periods. Finally, PET/CT scanners have multiple potential uses aside from perfusion imaging. The rapidity of MPI scanning permits highly efficient utilization of these devices throughout the work day.
v) Routine flow quantification as a part of most studies, requiring no additional time or radiation exposure.
vi) Strong prognostic power. PET like SPECT contains important information about prognosis in relation to size, severity, and location of perfusion defects (6, 16, 17). This capability is further enhanced by assessment of cavity size, LVEF, and regional wall motion and thickening under peak hyperemic conditions rather than long post-stress as with SPECT studies. The addition of flow quantification has been shown to add prognostic information beyond that provided by perfusion defect analysis alone (18-22).

Based on a strong evidence base, the American Society of Nuclear Cardiology and the Society of Nuclear Medicine and Molecular Imaging jointly published a position statement on the clinical indications for myocardial perfusion PET (23). This addressed concerns from professional medical societies about patient-centered imaging, necessity for lowered radiation exposure associated with nuclear cardiac imaging (24), and the Centers for Medicare and Medicaid Services (CMS) clinical quality measures (25). The position statement endorsed PET as *preferred* for patients requiring pharmacologic stress. It *recommended* PET for 5 specific clinical scenarios:

i) when a prior non-PET stress imaging study was of poor quality, equivocal or inconclusive, affected by attenuation artifact, or discordant with clinical impression or with other test results such as coronary angiography;

ii) for patients with body characteristics known to often affect image quality, such as large breasts, breast implants, or BMI's above 30;

iii) when patients are judged to be at higher risk in the event of a misdiagnosis, such as those with chronic kidney disease, diabetics, prior CABG, prior infarcts, left ventricular dysfunction, and known or suspected extensive CAD;

iv) for younger patients with known CAD in order to keep lifetime exposure to radiation as low as possible from sequential perfusion imaging;

v) when myocardial blood flow quantification is requested.

The position statement was prepared by a Writing Group with input from 22 PET and SPECT experts from around the world, approved by several committees within ASNC and SNMMI, and ultimately by the leadership of both societies. The statement was then published simultaneously in both the Journal of Nuclear Medicine and the Journal of Nuclear Cardiology. It was mentioned by 55 independent news outlets, has been downloaded more than 1, 000 times, and was classified in the top 5% of articles by Altmetric. It's impact is now working its way into appropriate use criteria specific to PET, and has resulted in modified practice standards for providers and payers.

Absolute flow quantification

Quantification of rest and peak hyperemia flow and flow reserve is facilitated by newer generation scanners with 3D and list-mode acquisition capability. An estimated 25% of centers performing PET MPI routinely acquire flow measurements, using FDA-approved software distributed by several different vendors. Flow quantification is more difficult with the older generation dedicated scanners that about half of current providers are using. These require 4 infusions of Rb-82, as gating and dynamic acquisitions usually need to be done sequentially. Currently, the relevant medical imaging societies have published 2 advisories concerning flow quantification. The 2016 ASNC imaging guidelines/SNMMI procedure standard for PET nuclear cardiology procedures (26) lists 5 clinical scenarios where MBF measurements appear most helpful: symptomatic patients without known CAD; patients with known CAD in whom more specific physiologic assessment is desired; identifying or ruling out multivessel CAD; determining presence of microvascular dysfunction; and heart transplant patients where there is concern for coronary vasculopathy. This document also lists 4 clinical situations where reporting flow measurements may not be helpful or could be misleading: post-CABG patients and those who have had large infarcts, have severe left ventricular dysfunction, or severe chronic kidney disease. Importantly, some patients are non-responders to vasodilators (such as with malfunctioning or blocked receptors), so that flow reserve measurements near 1 may negate the value of an otherwise normal perfusion scan. This is especially important for patients who are being tested soon after hospital arrival, who have not been properly prepped for myocardial perfusion imaging.

PET MPI and the interventionalist

Interventionalists in the United States have become familiar with the importance of physiologic measurements for indeterminate severity lesions they encounter in the catheterization laboratory. As such, there is strong curiosity about non-invasively derived flow measurements as a gatekeeper to interventions. PET flow quantification helps in identifying those patients most likely to have or not to have multi-vessel disease. This helps to guide many decisions pre-procedure, such as whether to pre-load with anti-platelet medications and in what kind of setting the procedure should be performed. It also helps to identify situations where stenting may not be very useful, such as those in which the coronary stenosis is moderate severity but flow reserve is very low; such patients have severe microvascular disease and improving epicardial flow is unlikely to confer much benefit (27).

There should not be an expectation of a 1:1 correlation between fractional flow reserve (FFR) measured in the cath lab and PET-derived blood flow reserve, as the former measures a pressure gradient across an epicardial coronary lesion, while PET flow reflects the entire delivery system (the epicardial coronaries and the microvasculature). Surprisingly however, there is concordance of normal or abnormal FFR and PET flow in about 2/3 of patients (28).

Reimbursement for myocardial perfusion PET

Myocardial perfusion PET is paid for differently in the United States, depending on the site of service and the patient's insurance coverage. If the site of service is a hospital and the patient has Medicare (government insurance that covers everybody over age of 65), the payment rate was $1,322 in 2017, including the radionuclide, the stress agent, and all supplies, but excluding the stress test (an additional $232). If coronary artery calcium is also measured, there is an additional payment of $60. New for 2018 will be an add－on code for PET quantification of myocardial blood flow－the payment amount for this has not yet been released. In addition

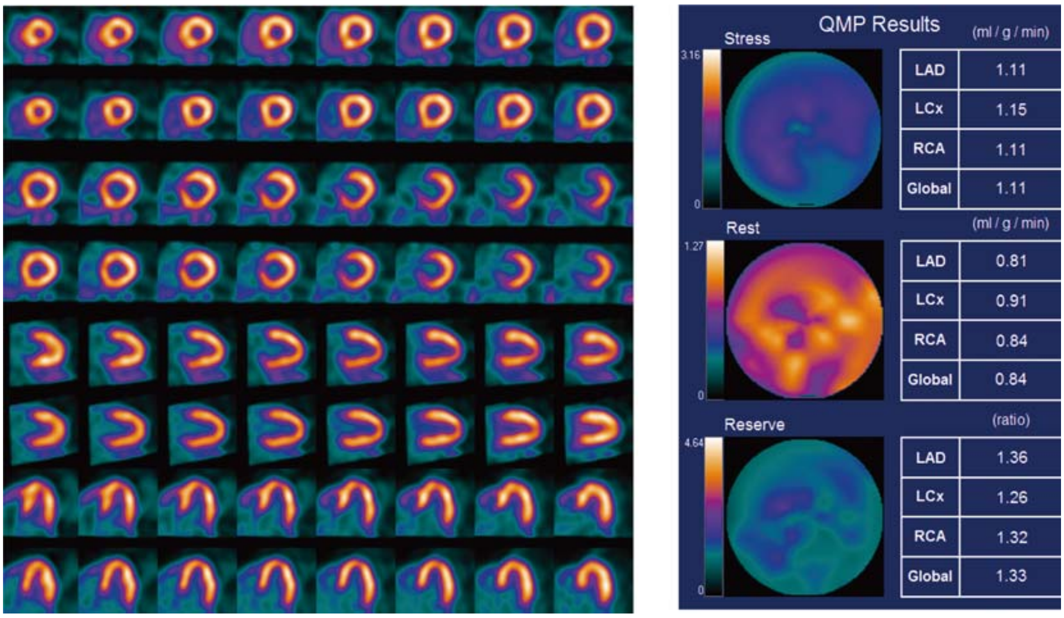

Fig. 1 Patient with atypical chest pain. PET images appear normal, but flow reserve is low. Coronary angiography revealed 3-vessel CAD and patient underwent coronary artery bypass surgery.

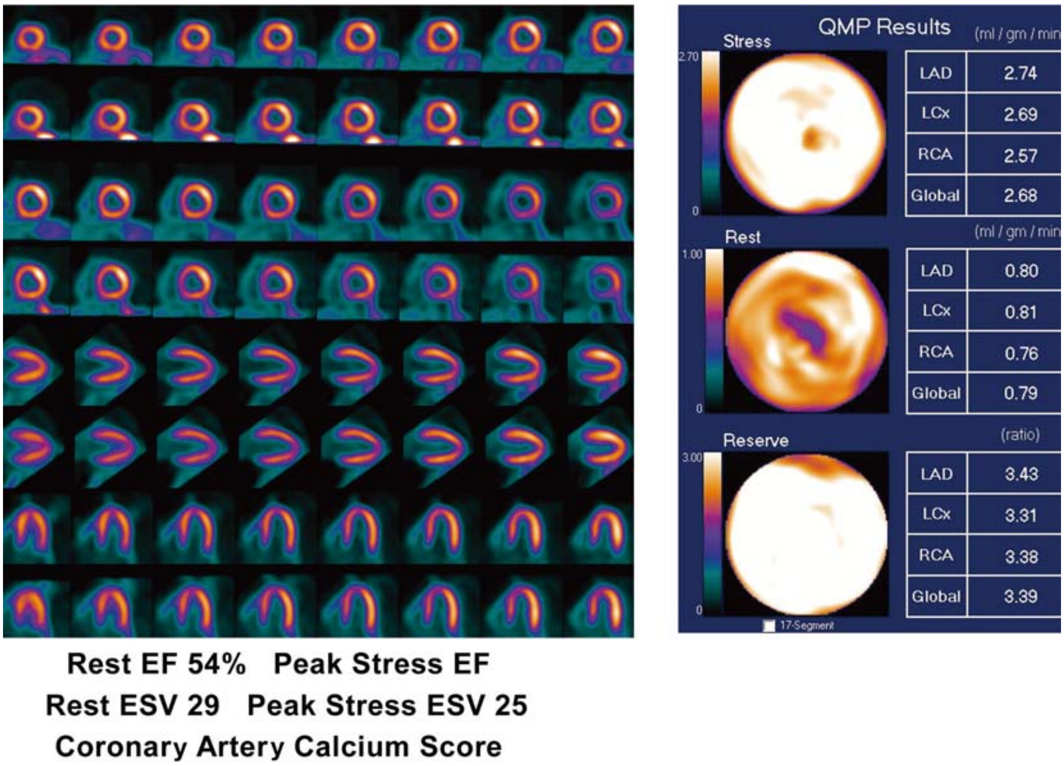

Fig. 2 A patient with chest pain was seen in the Emergency Room. ECG showed pre-excitation and serum troponin was normal. The PET images were normal, the coronary calcium score was 0, and flow reserve was normal. The findings were all consistent with healthy epicardial coronaries and a normal microvasculature, ensuring very low likelihood for cardiac events for at least the following 10 years.

to these "technical" payments, there is also approximately $200 for the professional fee covering the stress test, the MPI, and the coronary calcium interpretation.

This compares to the technical fees for rest/stress SPECT ($1,139 plus $232 for the stress test), stress echo ($450), coronary CTA ($265), and stress MR with contrast ($657).

For office-based providers, Medicare contractors and commercial insurance companies pay at highly variable rates. Medicaid does not pay for PET services.

Conclusions

The benefits of PET for selected patients is increasingly

Table 1 Summary of clinical indications for myocardial perfusion PET according to the ASNC/SNMMI Joint Statement.

Preferred: All patients unable to exercise.
Recommended:
1. When prior testing has been inconclusive or equivocal, affected by artifact, or discordant with clinical impression or the results of coronary angiography
2. When imaging might be expected to be challenging due to body habitus such as large breasts, breast implants, inability to keep arms up, or BMI >30
3. Higher risk patients where the implications of a misdiagnosis could result in patient harm, such as chronic kidney disease, diabetes, known extensive CAD (post-CABG, post-PCI), prior myocardial infarctions, Left ventricular dysfunction
4. Younger patients with established CAD in order to limit life-time exposure to imaging-associated radiation
5. When flow quantification is likely to be of benefit in decision-making

In general, SPECT is ideal for patients who can exercise and are less complicated; PET is favored for more complicated patients who require pharmacologic stress.

being recognized in the United States. Most imaging labs that adopt PET also retain SPECT. Within labs that have both PET and SPECT, an important decision-point is whether the patient can perform exercise. Those that cannot, are more likely to be imaged with PET. The more complicated the patient, the more likely PET will be selected. Routine flow quantification as a part of PET MPI is growing, and will be separately payable beginning in 2018. The relevant professional societies have taken strong positions about the significance of this newer modality for myocardial perfusion imaging, not as a replacement for SPECT but as a preferred and in some cases recommended modality rather than SPECT for selected clinical scenarios.

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Conflicts of interest

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References

1. Navare SM, Mather JF, Shaw LJ, et al. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: a meta-analysis. J Nucl Cardiol 2004; 11: 551-61.
2. Rozanski A, Gransar H, Hayes SW, et al. Comparison of long-term mortality risk following normal exercise vs adenosine myocardial perfusion SPECT. J Nucl Cardiol 2010; 17: 999-1008.
3. Wilson RF, Wyche K, Christensen BV, et al. Effects of adenosine on human coronary arterial circulation. Circulation 1990; 82: 1595-606.
4. Mishra RK, Dorbala S, Logsetty G, et al. Quantitative relation between hemodynamic changes during intravenous adenosine infusion and the magnitude of coronary hyperemia: implications for myocardial perfusion imaging. J Am Coll Cardiol 2005; 45: 553-8.
5. Bateman TM, Case JA. Variability in normal myocardial blood flow measurements: physiologic, methodologic, or protocol related? J Nucl Cardiol 2015; 22: 85-8.
6. Yoshinaga K, Chow BJ, Williams K, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? J Am Coll Cardiol 2006; 48: 1029-39.
7. Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. J Nucl Cardiol 2006; 13: 24-33.
8. Nandalur KR, Dwamena BA, Choudhri AF, et al. Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a meta-analysis. Acad Radiol 2008; 15: 444-51.
9. Mc Ardle BA, Dowsley TF, deKemp RA, et al. Does rubidium-82 have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. J Am Coll Cardiol 2012; 60: 1828-37.
10. Parker MW, Iskandar A, Limone B, 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: 700-7.
11. Ziadi MC, Dekemp RA, Williams K, et al. Does quantification

of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? J Nucl Cardiol 2012; 19: 670-80.
12. Naya M, Murthy VL, Taqueti VR, et al. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. J Nucl Med 2014; 55: 248-55.
13. Senthamizhchelvan S, Bravo PE, Lodge MA, et al. Radiation dosimetry of 82Rb in humans under pharmacologic stress. J Nucl Med 2011; 52: 485-91.
14. Hunter CR, Hill J, Ziadi MC, et al. Biodistribution and radiation dosimetry of 82Rb at rest and during peak pharmacological stress in patients referred for myocardial perfusion imaging. Eur J Nucl Med Mol Imaging 2015; 42: 1032-42.
15. Mattsson S, Johansson L, Leide Svegborn S, et al; ICRP. Radiation dose to patients from radiopharmaceuticals: a compendium of current information related to frequently used substances. Ann ICRP 2015; 44(2 Suppl): 7-321.
16. Dorbala S, Hachamovitch R, Curillova Z, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. JACC Cardiovasc Imaging 2009; 2: 846-54.
17. Dorbala S, Di Carli MF, Beanlands RS, et al. Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. J Am Coll Cardiol 2013; 61: 176-84.
18. Herzog BA, Husmann L, Valenta I, et al. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol 2009; 54: 150-6.
19. Ziadi MC, DeKemp RA, Williams KA, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. J Am Coll Cardiol 2011; 58: 740-8.
20. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation 2011; 124: 2215-24.
21. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation 2012; 126: 1858-68.
22. Farhad H, Dunet V, Bachelard K, et al. Added prognostic value of myocardial blood flow quantitation in rubidium-82 positron emission tomography imaging. Eur Heart J Cardiovasc Imaging 2013; 14: 1203-10.
23. Bateman TM, Dilsizian V, Beanlands RS, et al. American Society of Nuclear Cardiology and Society of Nuclear Medicine and Molecular Imaging Position Statement on the clinical indications for myocardial perfusion PET. J Nucl Med 2016; 23: 1227-31.
24. Cerqueira MD, Allman KC, Ficaro EP, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. J Nucl Cardiol 2010; 17: 709-18.
25. Centers for Medicare and Medicaid Services. Clinical quality measures basics. https: //www. cms. gov/regulations-and-guidance/legislation/ehrincentiveprograms/clinicalqualitymeasures.html
26. Dilsizian V, Bacharach SL, Beanlands RS, et al. ASNC imaging guidelines/ SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. J Nucl Cardiol 2016; 23: 1187-26.
27. Taqueti VR, Hachamovitch R, Murthy VL, 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.
28. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol 2013; 62: 1639-53.