Viability assessment with MRI is superior to FDG-PET for viability: Pro

Jamshid Maddahi, MD, FACC

INTRODUCTION

Debates are often used to highlight attributes and limitations of various diagnostic modalities in medicine. With this format, however, debaters may gravitate toward an extreme and unbalanced position, away from scientific facts and clinical realities. I accepted the invitation to debate the pro-MRI position on the assessment of myocardial viability with the intent to present a balanced point-of-view, especially that my own research has been focused on the use of PET for evaluating myocardial viability.

Rational management of patients with coronary artery disease (CAD) and poor left ventricular (LV) function relies on proper identification of the subgroup at high risk and those who have the highest potential of benefiting from a particular type of treatment. Before the advent of imaging techniques to determine myocardial viability, many patients with CAD and low ejection fractions (EFs) were relegated to medical therapy. It is now well recognized that patients with CAD and LV dysfunction have a high but variable mortality rate while receiving medical therapy. Many of these patients who have intractable heart failure are considered candidates for cardiac transplantation. Despite favorable survival after cardiac transplantation, this procedure cannot be performed in many heart failure patients who are potentially eligible because of the shortage of donor hearts, limited number of qualified transplant centers, and the expense of the procedure. In many patients with heart failure, LV dysfunction is reversible after myocardial revascularization.

From the Departments of Molecular and Medical Pharmacology (Division of Nuclear Medicine) and Medicine (Division of Cardiology), David Geffen School of Medicine at University of California at Los Angeles (UCLA), Los Angeles, CA.

Reprint requests: Jamshid Maddahi, MD, FACC, Departments of Molecular and Medical Pharmacology (Division of Nuclear Medicine) and Medicine (Division of Cardiology), David Geffen School of Medicine at University of California at Los Angeles (UCLA), 100 UCLA Medical Plaza #410, Los Angeles, CA 90095-7064; *jmaddahi@mednet.ucla.edu.*

J Nucl Cardiol 2010;17:292–7.
1071-3581/$34.00

doi:10.1007/s12350-010-9201-y

The potential for recovery of LV dysfunction after myocardial revascularization represents a practical clinical definition for myocardial viability. Two myocardial viability patterns have emerged as the most common conditions associated with chronic dysfunctional myocardium with the potential for recovery of dysfunction after revascularization: hibernating myocardium and repetitively stunned myocardium. The classic definition of hibernation postulated that myocardial function is reduced to match chronic and severe reduction of resting myocardial blood flow.[1] More recent evidence that resting perfusion is not always significantly reduced in areas of hibernating myocardium,[2] lead to the stipulation that repetitive stunning caused by repeated ischemic episodes may result in chronic LV dysfunction.[2]

MRI VS. PET: TECHNICAL ASPECTS

Technical aspects of MRI and PET are summarized and compared in Table 1. MRI is not associated with radiation exposure to the patient. Its inherent resolution is 1-2 mm in the imaging plane with slice thickness of about 4 mm. Contrast-enhanced MR imaging protocol consists of a bolus, intravenous injection of 0.1 to 0.2 mmol · kg^{-1} of Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), and imaging in approximately 20 min, using inversion-recovery-prepared T-1 weighted gradient echo pulse sequences. Image acquisition may be very fast, using a single or repeated breath-hold. At the time of delayed imaging, Gd-DTPA is accumulated and retained in the infarcted tissue, but washes out of the normal myocardium, resulting in delayed enhancement of the acutely infarcted myocardium or chronic scar tissue.[3-11] Due to its high resolution, MRI allows visualization of small subendocardial myocardial infarctions that may be missed by SPECT. In a study of 91 patients with suspected or known coronary artery disease,[12] MRI identified 100 of the 109 segments (92%) with subendocardial infarction (<50% transmural extent of the left-ventricular wall), whereas SPECT identified only 31 (28%). On a per patient basis, six (13%) individuals with subendocardial infarcts visible by MRI had no evidence of infarction by SPECT. Although MRI and PET have not been systematically compared for detection of subendocardial myocardial infarction, it is reasonable to assume

Table 1. Comparison of technical aspects of MRI and PET for assessment of myocardial viability

	MRI	PET
Radiation	None	Yes, but clinically acceptable
Contrast material	Gd may cause nephropathy	Radiotracers have no adverse events
Resolution	Higher, detects small subendocardial MI	Lower, small subendocardial MI may be missed
Imaging protocol	Rapid and straightforward	Longer and more complex

that MRI is superior to PET in this regard. Nevertheless, as patients with no evidence of infarction by nuclear imaging methods have excellent prognosis, the clinical significance of small subendocardial infarctions that are detected by MRI and missed by PET is unclear.

Concern for contrast-induced nephropathy existed with gadolinium-contrast as its hyperosmolarity and renal excretion via glomerular filtration were similar to iodinated radiocontrast.[13] Although early studies in low risk patients suggested a benign renal profile, recent studies raise the possibility of nephrotoxicity. In addition, reports of a previously rare condition entitled nephrogenic systemic fibrosis (NSF) have recently emerged in patients with advanced kidney disease and have been linked to exposure to gadolinium-contrast.[12] Nephrogenic systemic fibrosis is a debilitating disorder in which progressive and severe fibrosis of the skin and other systemic organs that leads to significant disability and is associated with increased mortality. Initially reported most commonly in end stage renal disease (ESRD) patients receiving dialysis, it is also described in patients with severe acute kidney injury (AKI) and advanced chronic kidney disease (stages 4 and 5) not requiring dialysis. In addition to underlying kidney disease, the risk of developing NSF is increased with larger doses of gadolinium (or multiple exposures), exposure to specific gadolinium chelates (non-ionic, linear), underlying pro-inflammatory states (in particular vascular endothelial dysfunction), and perhaps some currently unrecognized cofactors. Avoidance of gadolinium exposure appears to be the best approach for patients who maintain risk factors.

PET imaging of myocardial viability is based on imaging both myocardial perfusion and FDG uptake using two separate tracer injections and imaging. Myocardial perfusion may be imaged at rest or both at rest and during pharmacologic stress, using a PET perfusion tracer such as N-13 ammonia, Rubidium-82, or O-15 water. Alternatively, myocardial perfusion may be imaged using a Tc-99m labeled perfusion tracer (such as Tc-99m sestamibi or Tc-99m tetrofosmin) and SPECT imaging. Depending on the tracer that is used, the perfusion imaging protocol may be as short as 10 minutes (for resting Rb-82 imaging) or as long as about one hour (for rest-stress N-13 ammonia imaging). The protocol for FDG imaging is not always straightforward, especially in patients with diabetes mellitus (DM) because of poor uptake of FDG.[14-16] Generally, three different protocols have been used: (1) the standard protocol, consisting of oral glucose loading or a supplemental insulin bolus based on fasting glucose; (2) the niacin protocol, consisting of pretreatment with niacin to lower free fatty acids; and (3) the insulin clamp protocol, consisting of hyperinsulinemic euglycemic clamp. In a study by Vitale et al,[16] these three protocols were compared in 10 patients with non-insulin dependent DM, CAD, and severe LV dysfunction. The results demonstrated that the hyperinsulinemic euglycemic clamp yielded the highest FDG PET image quality, however, larger clinical trials are needed to assess whether accuracy is greater with this approach.

MRI and PET Patterns of Myocardial Viability

Table 2 outlines the underlying etiologies for myocardial contractile dysfunction and criteria that are used by PET[17-19] and contrast enhancement (CE) MRI[20-24] for assessing these conditions. In transmural or near transmural myocardial infarction, matched reduction (>50% normal) of perfusion and FDG uptake are noted. Similarly, with MRI contrast enhancement of >50% of myocardial wall thickness is present. In non-transmural myocardial infarction, matched reduction of $\leq$50% is noted on the perfusion and FDG images and MRI contrast enhancement involves $\leq$50% of myocardial wall thickness. In hibernating myocardium, PET shows the distinct pattern of mismatch (reduced perfusion and normal or near normal FDG uptake) and with MRI there is no contrast enhancement. In repetitively stunned myocardium, myocardial perfusion is normal or near normal and FDG uptake is normal. There is no MR contrast enhancement in this condition. In nonischemic myopathy, PET and MR show either a normal pattern or patchy pattern of perfusion-FDG and contrast enhancement. Of these conditions, only hibernating and repetitively stunned myocardium are associated with improvement of contractile dysfunction following revascularization.

Table 2. Different patterns of myocardial viability by MRI CE and PET

	MRI CE	PET
Transmural MI	>50% thickness	>50%, matched reduction of P and FDG
Non-transmural MI	≤50% thickness	≤50%, matched reduction of P and FDG
Hibernating	None	Reduced P, NI-near NI FDG (mismatch)
Repetitively stunned	None	NI-near NI P, NI FDG
Nonischemic myopathy	None or Patchy	NI or patchy P and FDG

CE, Contrast enhancement; *MI*, myocardial infarction; *P*, perfusion; *NI*, normal.

MRI VS. PET: CLINICAL EFFICACY

Prediction of Recovery of Function After Revascularization

Several studies have evaluated the positive and negative predictive values (PPV and NPV) of transmural extent of MRI delayed enhancement for prediction of recovery of function after revascularization [20-24]. In the initial study of Kim et al,[20] the likelihood of improvement in regional contractility after revascularization decreased progressively as the transmural extent of hyperenhancement (TEH) before revascularization increased. Re-analysis of their data shows that after revascularization, contractility did not improve (NPV) in 92% (168/182) of dysfunctional segments with >50% TEH, while it improved (PPV) in 66% (410/622) of dysfunctional segments with ≤50% TEH. Similarly, in the study of Selvanayagam et al,[21] NPV and PPV for MRI-delayed enhancement were 81% (71/88 segments) and 62% (326/524 segments). Van Hoe et al,[22] using 75% criterion for transmural extent of delayed enhancement, reported that NPV of MRI was 92% (22/24) and PPV was 75% (70/93). These studies[20-22] have consistently shown that the PPV of delayed enhancement is lower than its NPV (Figure 1). Importantly, PPV is even lower when segments with no enhancement are excluded from analysis. Using this analysis, PPV were, respectively, 53% (155/293), 51% (170/334), and 44% (14/32) in the studies of Kim et al,[20] Selvanayagam et al,[21] and Van Hoe et al.[22]

Kuhl et al[23] compared MRI and PET/SPECT in 29 patients with ischemic cardiomyopathy. The PPV was identical for both techniques (73%). However, MRI achieved a higher NPV (93%) as compared to PET/SPECT (77%). Lauerma et al,[24] comparing MRI and PET FDG, showed that sensitivity of MRI late enhancement was lower than FDG PET (62% vs. 81%), but specificities were comparable (84% vs. 86%). PPV and NPV, however, cannot be calculated from the presented data in this report, to allow comparison to the above-mentioned studies.

Possible explanation for relatively lower PPV of MRI for assessment of myocardial viability is shown in Figure 2. In dysfunctional myocardial segments with ≤50% transmural extent of MRI delayed enhancement, nontransmural myocardial infarction is present either alone or combined with hibernating myocardium. In the former condition, recovery of function following revascularization is not expected. Since MRI does not distinguish these two conditions from one another, its PPV is adversely affected. PET, however, does distinguish these two conditions from one another (resulting in improved PPV) by demonstrating the mismatch pattern in hibernating myocardium.

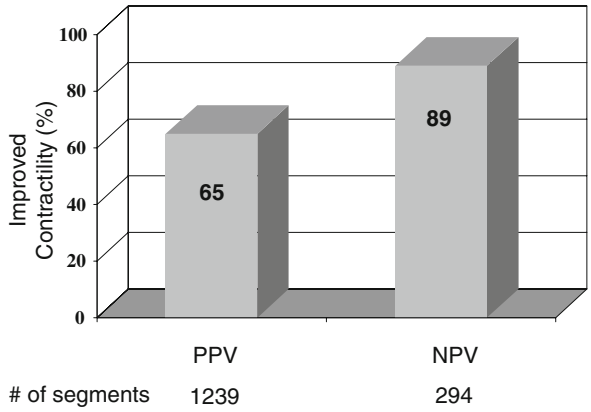

Figure 1. Average positive and negative predictive values of contrast-enhanced MRI for assessment of myocardial viability, derived from three studies.[20-22] *PPV*, Positive predictive value; *NPV*, negative predictive value.

MRI is superior to PET in assessing myocardial viability in thinned out myocardial regions (Figure 3). Significant thinning of viable myocardium reduces the apparent regional FDG uptake due to partial volume effect, resulting in a false negative PET finding. The diagnostic accuracy of MRI, however, is preserved in thinned out myocardium, because the appearance of contrast enhancement is not adversely affected.

Additional Factors that Influence Heart Failure Response to Revascularization

It has been shown that in addition to myocardial viability, other factors may influence recovery of LV

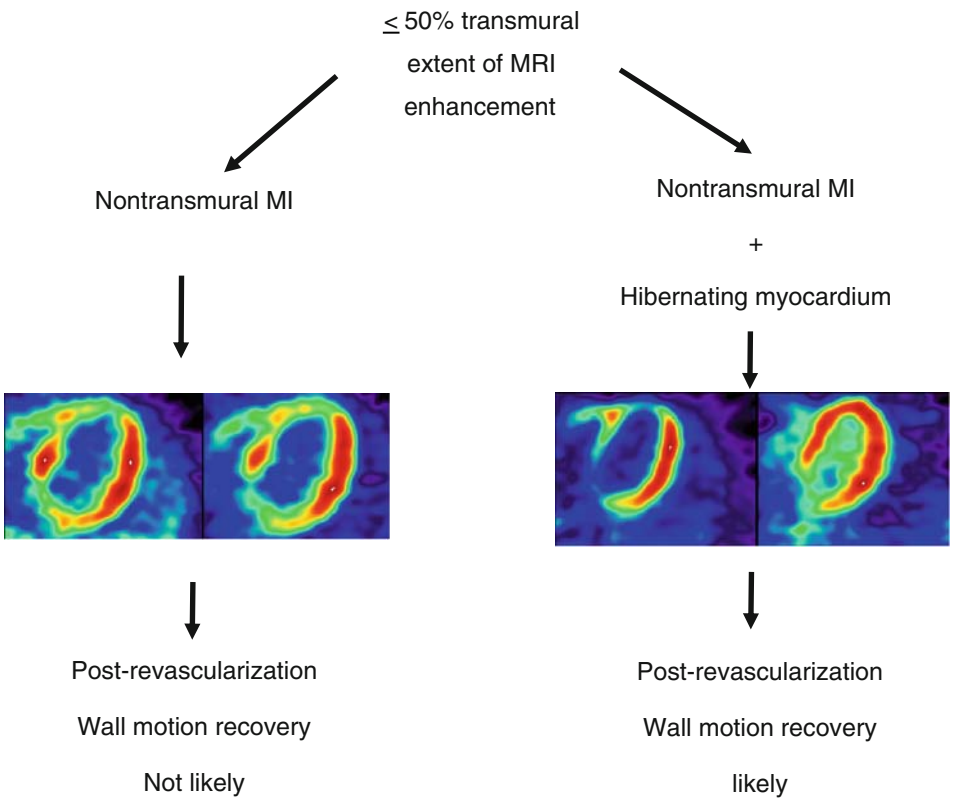

Figure 2. Possible explanation for superiority of PET for assessment of myocardial viability in myocardial segments with ≤50% transmural extent of MRI-delayed enhancement. Please see text for details.

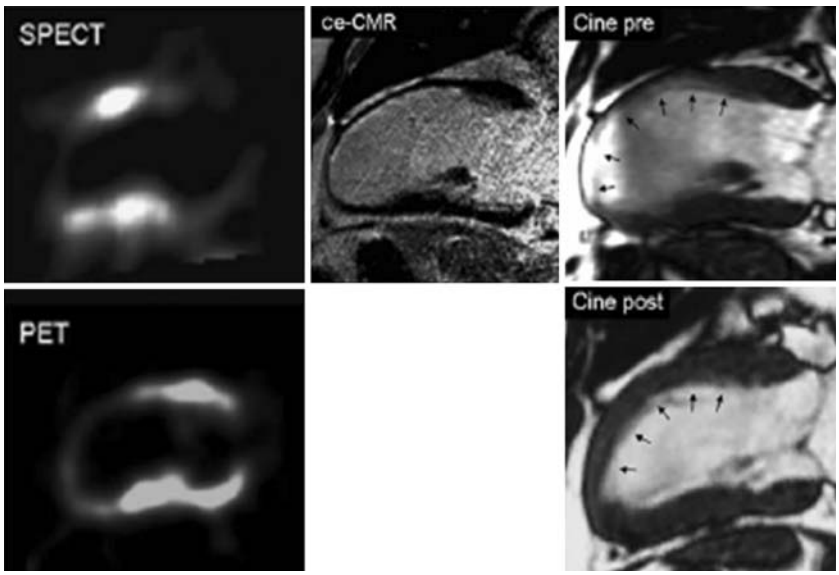

Figure 3. Discrepancy between MRI and PET for assessment of thinned out, hibernating myocardium (Kuhl et al[23]). Contrast-enhanced cardiac MR (ce-CMR) image shows thinned out anterior and apical myocardial walls without contrast enhancement, indicating presence of viable, hibernating myocardium. This is confirmed by significant improvement in thickening and motion of the anterior wall and apex from pre- to post-revascularization. SPECT perfusion-PET FDG images, however, did not demonstrate evidence of viability due to matched, >50% reduction of perfusion and metabolism (FDG uptake). When the viable, but hibernating myocardium is thin, FDG uptake appears significantly reduced due to partial volume effect.

Table 3. Comparison of clinical efficacies of MRI and PET imaging for assessment of myocardial viability

	MRI	PET
NPV	Relatively higher	Relatively lower
P PV	Overall, relatively lower	Overall, relatively higher
PPV in thinned myocardium	Relatively higher	Relatively lower
Prognostic data	Limited	Extensive
Valvular regurgitation evaluation	Possible	Not possible
Limitations of application in special populations	Critically ill, with pacemaker or claustrophobia	Suboptimal in diabetic patients

VPV, Negative predictive value; *PPV*, positive predictive value.

dysfunction after revascularization. These factors include LV size, LVEF, presence and extent of stress-induced ischemia (jeopardized myocardium), and presence of valvular regurgitation. MRI is uniquely suited for evaluation of concomitant valvular regurgitation, but the other factors may be assessed equally well by both modalities.

Prognostic Information

While the prognostic value of PET in predicting outcomes in patients with LV dysfunction is well documented in several studies,[17-19,25-31] limited data are available for MRI in this regard. Wu et al[32] showed that in patients with acute MI the extent of delayed enhancement was associated with an increased risk of adverse cardiovascular events during follow-up. In other studies, the extent of delayed enhancement predicted death better than LV size or ejection fraction[33] or was associated with inducible ventricular tachycardia on electrophysiologic testing.[34]

Table 4. Advantages of MRI vs. PET for assessment of myocardial viability

No radiation
Straightforward and rapid protocol
Better detection of small subendocardial MI due to a higher resolution
NPV is higher
PPV is maintained in thinned myocardium
More practical in diabetic patients
Additional evaluation of valvular regurgitation

Table 5. Limitations of MRI vs. PET for assessment of myocardial viability

Gadolinium-related nephropathy
Lower PPV
Limited prognostic data
Cannot be used in critically ill patients and those with a pacemaker or claustrophobia

Application in Special Populations

As summarized in Table 3, MRI method is not suitable for critically ill patients and those with a cardiac pacemaker. In addition, a certain percentage of patients may not tolerate the procedure due to claustrophobia. The PET technique, on the other hand, is suboptimal in patients with DM.

SUMMARY

Proper selection of MRI vs. PET for assessment of myocardial viability in a given clinical scenario is significantly enhanced by full knowledge of advantages and limitations of these two modalities. Tables 4 and 5 summarize these features and are intended to provide a balanced point-of-view and help clinicians in selection of the right modality for the right patient.

References

1. Rahimtoola SH. The hibernating myocardium. Am Heart J 1989; 117:211-21.
2. Wijns W, Vatner SF, Camici PG. Hibernating myocardium. N Engl J Med 1998;339:173-81.
3. Weinmann HJ, Laniado M, Mutzel W. Pharmacokinetics of GdDTPA/dimeglumine after intravenous injection into healthy volunteers. Physiol Chem Phys Med NMR 1984;16:167-72.
4. Schaefer S, Malloy CR, Katz J, Parkey RW, Buja LM, Willerson JT, et al. Gadolinium-DTPA-enhanced nuclear magnetic resonance imaging of reperfused myocardium: Identification of the myocardial bed at risk. J Am Coll Cardiol 1988;12:1064-72.

5. Judd RM, Lugo-Olivieri CH, Arai M, Kondo T, Croisille P, Lima JA, et al. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. Circulation 1995;92:1902-10.
6. Kim RJ, Chen EL, Lima JA, Judd RM. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. Circulation 1996;94:3318-26.
7. Flacke SJ, Fischer SE, Lorenz CH. Measurement of the gadopentetate dimeglumine partition coefficient in human myocardium in vivo: Normal distribution and elevation in acute and chronic infarction. Radiology 2001;218:703-10.
8. Rehwald WG, Fieno DS, Chen EL, Kim RJ, Judd RM. Myocardial magnetic resonance imaging contrast agent concentrations after reversible and irreversible ischemic injury. Circulation 2002;105: 224-9.
9. Klein C, Nekolla SG, Balbach T, Schnackenburg B, Nagel E, Fleck E, et al. The influence of myocardial blood flow and volume of distribution on late Gd-DTPA kinetics in ischemic heart failure. J Magn Reson Imaging 2004;20:588-93.
10. Klein C, Schmal TR, Nekolla SG, Schnackenburg B, Fleck E, Nagel E. Mechanism of late gadolinium enhancement in patients with acute myocardial infarction. J Cardiovasc Magn Reson 2007;9:653-8.
11. Saraste A, Nekolla S, Schwaiger M. Contrast-enhanced magnetic resonance imaging in the assessment of myocardial infarction and viability. J Nucl Cardiol 2008;15:105-17.
12. Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: An imaging study. Lancet 2003;361:359-60.
13. Perazella MA. Gadolinium-contrast toxicity in patients with kidney disease: nephrotoxicity and nephrogenic systemic fibrosis. Curr Drug Saf 2008;3:67-75.
14. Voipio-Pulkki L, Nuutila P, Knuuti J, et al. Heart and skeletal muscle glucose disposal in type 2 diabetic patients as determined by PET. J Nucl Med 1993;34:2064-7.
15. Ohtake T, Yokoyama I, Watanabe T, et al. Myocardial glucose metabolism in NIDDM patients evaluated by FDG-PET. J Nucl Med 1995;36:456-63.
16. Vitale GD, deKemp RA, Ruddy TD, Williams K, Beanlands RSB. Myocardial glucose utilization and optimization of ^{18}F-FDG PET imaging in patients with non-insulin-dependent diabetes mellitus, coronary artery disease, and left ventricular dysfunction. J Nucl Med 2001;42:1730-6.
17. Marshall RC, Tillisch JH, Phelps ME, et al. Identification and differentiation of resting myocardial ischemia and infarction in man with positron emission tomography ^{18}F-labelled fluorodeoxyglucose and N-13 ammonia. Circulation 1983;314:884-8.
18. Tillisch J, Brunken R, Marshall R, Schwaiger M, Phelps M, Schelbert H. Reversibility of cardiac wall motion abnormalities predicted by positron tomography. N Engl J Med 1986;314:884-8.
19. Maddahi J, Heinrich S, Brunken R, Di Carli M. Role of thallium-201 and PET imaging in evaluation of myocardial viability and management of patients with CAD and LV dysfunction. J Nucl Med 1994;35:707-15.
20. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445-53.
21. Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, et al. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. Circulation 2004;110:1535-41.
22. Van Hoe L, Vanderheyden M. Ischemic cardiomyopathy: Value of different MRI techniques for prediction of functional recovery after revascularization. AJR Am J Roentgenol 2004;182:95-100.
23. Kuhl HP, Lipke CS, Krombach GA, Katoh M, Battenberg TF, Nowak B, et al. Assessment of reversible myocardial dysfunction in chronic ischaemic heart disease: Comparison of contrasten-hanced cardiovascular magnetic resonance and a combined positron emission tomography-single photon emission computed tomography imaging protocol. Eur Heart J 2006;27:846-53.
24. Lauerma K, Niemi P, Hanninen H, Janatuinen T, Voipio-Pulkki LM, Knuuti J, et al. Multimodality MR imaging assessment of myocardial viability: Combination of first-pass and late contrast enhancement to wall motion dynamics and comparison with FDG PET-initial experience. Radiology 2000;217:729-36.
25. Eitzman D, Al-Aouar Z, Kanter HL, vom Dahl J, Kirsh M, Deeb GM, et al. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. J Am Coll Cardiol 1992;20:559-65.
26. Di Carli MF, Davidson M, Little R, Khanna S, Mody FV, Brunken RC, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. Am J Cardiol 1994;73:527-33.
27. Lee KS, Marwick TH, Cook SA, Go RT, Fix JS, James KB, et al. Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and revascularization. Circulation 1994;90:2687-94.
28. vom Dahl J, Altehoefer C, Sheehan FH, Buechin P, Schulz G, Schwarz ER, et al. Effect of myocardial viability assessed by technetium-99m-sestamibi SPECT and fluorine-18-FDG PET on clinical outcome in coronary artery disease. J Nucl Med 1997;38:742-8.
29. Di Carli MF, Maddahi J, Rokhsar S, Schelbert HR, Bianco-Batlles D, Brunken RC, et al. Long-term survival of patients with coronary artery disease and left ventricular dysfunction: Implications for the role of myocardial viability assessment in management decisions. J Thorac Cardiovasc Surg 1998;116:997-1004.
30. Huitink JM, Visser FC, Bax JJ, van Lingen A, Groenveld AB, Teule GJ, et al. Predictive value of planar 18F-fluorodeoxyglucose imaging for cardiac events in patients after acute myocardial infarction. Am J Cardiol 1998;81:1072-7.
31. Beanlands R, deKemp R, Smith S, Johansen H, Ruddy T. FDG PET imaging alters clinical decision making in patients with impaired ventricular function. Am J Cardiol 1997;79:1092-5.
32. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765-72.
33. Roes SD, Kelle S, Kaandorp TA, Kokocinski T, Poldermans D, Lamb HJ, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol 2007;100:930-6.
34. Bello D, Fieno DS, Kim RJ, Pereles FS, Passman R, Song G, et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. J Am Coll Cardiol 2005;45:1104-8.