High-risk coronary artery disease, but normal myocardial perfusion: A matter of concern?

Shu Yokota, MD,[a] Mohamed Mouden, MD, PhD,[a] and Jan Paul Ottervanger, MD, PhD, FESC[a]

[a] Department of Cardiology, Isala Hospital, Zwolle, Netherlands

Received Apr 23, 2015; accepted Apr 23, 2015
doi:10.1007/s12350-015-0167-7

See related article, pp. 530–541

Use of non-invasive cardiac imaging is recommended in numerous clinical scenarios in order to provide diagnostic and prognostic information to guide clinical decision making.[1] Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is well validated and has proven value in identifying patients at high risk of a serious cardiac event, whereas a normal MPI study confers a benign prognosis with a low annual serious cardiac event rate of 0.6% per year.[2] However, there has always been concern that MPI can miss high-risk coronary artery disease (CAD) as in patients with balanced ischemia due to flow-limiting three-vessel CAD or left main stenosis,[3,4] while this group is particularly prone to adverse cardiac events and may have benefit of revascularization.[4,5]

In the current issue of the journal, Nakanishi et al studied the prevalence and predictors of high-risk CAD in patients with normal MPI.[6] Subsequent invasive coronary angiography was performed within 60 days after normal MPI in 580 patients in two centers. High-risk CAD was defined as 3 vessels with ≥70% stenosis, 2 vessels with ≥70% stenosis including proximal left anterior descending, or left main with ≥50% stenosis. Overall, 36% in this highly selected group of patients had evidence of anatomically obstructive CAD, with high-risk CAD in 7.2% of all patients. Predictors for high-risk CAD were the presence of mild/equivocal perfusion defects, transient ischemic left ventricle dilatation or abnormal ejection fraction, and a pre-test probability of ≥66%. Although MPI can miss both high-risk CAD and stenoses in small coronary arteries, the charm of the paper by Nakanishi et al is that they focused on high-risk CAD. Although their number of false-negative MPI with 7.2% of patients high-risk CAD is impressive, it should be realized that these 42 patients are selected from a total of 25,698 patients with normal MPI (0.16%). Moreover, since the angiographic presence of high-risk CAD in their study was not proven by fractional flow reserve (FFR) measurements, probably a substantial part of these stenoses was functionally not significant.

Several previous studies suggested that MPI may underestimate high-risk CAD in selected patients. Berman et al demonstrated in 101 patients with proven left main stenosis (by invasive angiography) that 13% had normal perfusion by visual analysis.[7] Lima et al demonstrated similar findings for 143 patients with severe three-vessel CAD, in which one-fifth had normal MPI results.[8]

There are several potential reasons for SPECT-MPI missing high-risk CAD. Visual analysis of MPI images provides information on relative rather than absolute perfusion for each myocardial region. Therefore, global but uniform reduction in coronary vasodilator reserve may result in a homogeneous decreased distribution of radiotracer, potentially leading to false-negative MPI results.[8,9] Several other reasons for false-negative MPI findings include insufficient coronary vasodilatation due to unrecognized ingestion of caffeine-containing products, attenuation and motion artifacts and plateauing of myocardial tracer uptake at high flow rates.[9-11] Finally, a false-negative MPI may be in fact not false negative, since invasive angiography, without functional measurement of the stenosis, may overestimate the functional severity.

IMPROVEMENTS OF SPECT

Several advances of MPI may improve the accuracy for detecting high-risk CAD (Table 1). The previously

Reprint requests: Jan Paul Ottervanger MD, PhD, FESC, Department of Cardiology, Isala hospital, Zwolle, Netherlands *J.Ottervanger@diagram-zwolle.nl*
J Nucl Cardiol 2016;23:542–5.
1071-3581/$34.00

Table 1. Potential improvements in MPI to detect high-risk CAD

Improvement	Expected benefit
Attenuation correction	+
Incorporating non-perfusion markers	++
CZT camera	+
Additional coronary calcium scoring	+
Hybrid imaging with simultaneous coronary CT	++
Risk factor analysis and clinical variables	+
PET MPI	+
Myocardial blood flow quantification	++
Physiological stress in selected patients	+/−
More sensitive interpretation of SPECT MPI	+/−

mentioned studies by Lima et al and Berman et al[7,8] found that the incorporation of several non-perfusion imaging findings, such as ECG-gating and transient ischemic left ventricle dilatation, significantly improved the detection of high-risk CAD. Duvernoy et al demonstrated that implementation of attenuation correction for SPECT MPI significantly improved the detection of significant left main disease.[11] Recently introduced solid-state SPECT cameras with cadmium zinc telluride (CZT) detectors are associated with higher sensitivity and energy resolution compared to conventional SPECT providing improved image quality.[12] In addition, CZT SPECT may facilitate dynamic SPECT acquisition for quantitative assessment of myocardial blood flow reserve which could potentially enhance detection of individuals with high-risk CAD.[13] Furthermore, use of pre-test probability and risk factors may improve interpretation of SPECT.[14] Possibly, hybrid imaging combining MPI with anatomical information obtained from coronary CT angiography will improve the detection of functionally relevant CAD and could be of value in depicting true high-risk CAD.[15]

Myocardial perfusion imaging with positron emission tomography (PET) may be preferred when available for its higher accuracy in detecting relevant CAD due to improved temporal and spatial resolution, more accurate attenuation correction, and the potential for absolute myocardial blood flow quantification.[16] Naya et al demonstrated that normal myocardial flow reserve on MPI measured with 82Rb PET was associated with a low likelihood of high-risk CAD.[17] Conversely, Ziadi et al found a reduced myocardial flow reserve to be an independent predictor of severe obstructive three-vessel CAD providing incremental value over relative MPI.[18] In another study, Dorbala et al showed that an increase of left ventricle ejection fraction reserve $\geq$5% yields a high negative predictive value for three-vessel CAD.[19]

ALTERNATIVES FOR MPI

The benefits of cardiac perfusion magnetic resonance imaging (MRI) as an alternative imaging modality to nuclear MPI has been suggested. However, also MRI has limitations. In patients with angiographically proven three-vessel CAD, it was demonstrated that perfusion defects in all three vascular territories remained undetected in more than 40% of patients by stress perfusion MRI.[20]

A recent meta-analysis suggested that stress echocardiography has a better discriminatory capacity than MPI for the detection of high-risk CAD.[21] However, there are some relevant limitations to this technique that prevent the large-scale use in daily practice. These limitations include the poor imaging quality in a substantial part of patients, time-consuming acquisition, the inability to image the entire left ventricle, and the interobserver and inter-institutional variability due to visual analysis and lack of quantitation.

With regard to non-invasive anatomical imaging, simultaneous coronary artery calcium scoring has the potential to increase detection of obstructive CAD and the presence of high-risk CAD in patients referred for MPI.[22] Coronary computed tomography angiography accurately excluded high-risk CAD in patients with suggestive symptoms in a recent study.[23] However, the performance in detecting high-risk CAD was suboptimal owing to the high number of false-positive observations made by overestimating the severity of stenosis.

The current standard for the anatomic diagnosis of CAD remains invasive coronary angiography, however, its invasive nature carries a non-negligible risk and adds significant costs.[24] An immediate invasive strategy may be recommended for risk stratification in patients who are amenable to, and candidates for coronary revascularization in patients with reduced left ventricular ejection fraction <50% and typical angina, in case of severe stable angina (Canadian Cardiovascular Society class 3) or when clinical profile suggests a high event risk, particularly if the symptoms are inadequately responding to medical therapy.[25,26] Under such circumstances, the indication for revascularization should depend on the result of intra-procedural FFR testing when indicated. In addition, invasive coronary angiography can also be considered when non-invasive test results suggest intermediate- or high-risk CAD, and for

patients who are not able to exercise, or have non-diagnostic stress results when the findings at angiography are expected to result in important changes to therapy. Importantly, although patients without evidence of ischemia generally have a benign prognosis, coronary revascularization may still be recommended from symptomatic point of view for patients with any stenosis >50% with limiting angina or angina equivalent unresponsive to optimal medical treatment.

IS FALSE-NEGATIVE MPI REALLY FALSE NEGATIVE?

Rather than inadequacy of MPI, the underestimation of ischemia in patients with high-risk CAD by different imaging modalities may reflect at least in part the inadequacy of the purely anatomical angiographic endpoint in these studies. Visual assessment of coronary stenoses by invasive angiography without pressure-derived FFR measurement may overestimate the frequency of high-risk obstructive CAD.[27] Similarly, quantitative coronary angiography failed to accurately predict the functional significance of coronary lesions.[28] In a sub-analysis of the fractional flow reserve versus angiography for multivessel evaluation (FAME) study, only 14% of patients with angiographic three-vessel CAD had concordant three-vessel functional CAD determined by invasive FFR measurements.[29] Similarly, Lindstaedt et al found discordance between angiographic assessment and FFR measurement with frequent overestimation of left main stenosis severity.[27] In addition, collateral (micro)circulation can maintain adequate myocardial perfusion, leading to underestimation of the angiographic severity of coronary lesions.

Nakanishi and colleagues are to be congratulated with their study. Continuing research should be encouraged to demonstrate the safety and accuracy of all our diagnostics and therapeutics in real life. In fact, their study demonstrated the safety of MPI, with only 0.16% high-risk CAD in patients with normal MPI. Furthermore, their study showed limitations in our routine clinical practice, in defining significant CAD purely on (invasive) anatomical imaging. Future studies should focus on demonstrating the functional significance of coronary stenoses, especially in those with normal MPI. Finally, MPI should and can be further improved, and hopefully in the future the number of false-negative MPI will be even lower, without increasing the number of false-positive findings.

References

1. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine: endorsed by the American College of Emergency Physicians. Circulation. 2009;119:e561-87.
2. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99 m sestamibi imaging. J Am Coll Cardiol. 1998;32:57-62.
3. Chamuleau SA, Meuwissen M, Koch KT, et al. Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate stenosis. Am J Cardiol. 2002;89:377-80.
4. Lopes NH, da Silva Paulitsch F, Gois AF, et al. Impact of number of vessels disease on outcome of patients with stable coronary artery disease: 5-year follow-up of the Medical, Angioplasty, and bypass Surgery Study (MASS). Eur J Cardiothorac Surg. 2008;33:349-54.
5. Jones EL, King SB 3rd, Craver JM, et al. The spectrum of left main coronary artery disease: variables affecting patient selection, management, and death. J Thorac Cardiovasc Surg. 1980;79:109-16.
6. Nakanishi R, Gransar H, Slomka P, et al. Predictors of high risk coronary artery disease in subjects with normal SPECT myocardial perfusion imaging. J Nucl Cardiol, current issue.
7. Berman DS, Kang X, Slomka PJ, et al. Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. J Nucl Cardiol. 2007;14:521-8.
8. Lima RS, Goode AR, Siadaty MS, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. J Am Coll Cardiol. 2003;42:64-70.
9. Aernoudse WH, Botman KJ, Pijls NH. False-negative myocardial scintigraphy in balanced three-vessel disease, revealed by coronary pressure measurement. Int J Cardiovasc Intervent. 2003;5:67-71.
10. Reyes E. Detection of left main stem and three-vessel coronary artery disease by myocardial perfusion SPECT imaging. Eurointervention. 2010;6 Suppl G:G72-8. doi:10.4244/EIJV10I1A26. Review.
11. Duvernoy CS, Ficaro EP, Karabajakian MZ, Rose PA, Corbett JR. Improved detection of left main coronary artery disease with attenuation-corrected SPECT. J Nucl Cardiol. 2000;7:639-48.
12. Garcia EV, Faber TL, Esteves FP. Cardiac dedicated ultrafast SPECT cameras: new designs and clinical implications. J Nucl Med. 2011;52:210-7.
13. Shiraishi S, Sakamoto F, Tsuda N, et al. Prediction of left main or 3-vessel disease using myocardial perfusion reserve on dynamic thallium-201 single-photon emission computed tomography with a semiconductor gamma camera. Circ J. 2015;79:623-31.
14. Simons M, Parker JA, Donohoe KJ, Udelson JE, Gervino EV. The impact of clinical data on interpretation of thallium scintigrams. J Nucl Cardiol. 1994;1:365-71.
15. Kajander S, Joutsiniemi E, Saraste M, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. Circulation. 2010;122:603-13.
16. 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.

17. 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.
18. 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.
19. Dorbala S, Vangala D, Sampson U, Limaye A, Kwong R, Di Carli MF. Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: A 82Rb PET/CT study. J Nucl Med. 2007;48:349-58.
20. Chung SY, Lee KY, Chun EJ, Lee WW, Park EK, Chang HJ, Choi SI. Comparison of stress perfusion MRI and SPECT for detection of myocardial ischemia in patients with angiographically proven three-vessel coronary artery disease. AJR Am J Roentgenol. 2010;195:356-62.
21. Mahajan N, Polavaram L, Vankayala H, Ference B, Wang Y, Ager J, Kovach J, Afonso L. Diagnostic accuracy of myocardial perfusion imaging and stress echocardiography for the diagnosis of left main and triple vessel coronary artery disease: A comparative meta-analysis. Heart. 2010;96:956-66.
22. Kamínek M, Metelková I, Budíková M, Koranda P, Henzlova L, Havel M, Sovová E, Kincl V. Diagnosis of high-risk patients with multivessel coronary artery disease by combined cardiac gated SPET imaging and coronary calcium score. Hell J Nucl Med. 2015;18:31-4.
23. Dharampal AS, Papadopoulou SL, Rossi A, et al. Diagnostic performance of computed tomography coronary angiography to detect and exclude left main and/or three-vessel coronary artery disease. Eur Radiol. 2013;23:2934-43.
24. Noto TJ Jr, Johnson LW, Krone R, Weaver WF, Clark DA, Kramer JR Jr, Vetrovec GW. Cardiac catheterization 1990: A report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). Cathet Cardiovasc Diagn. 1991;24:75-83.
25. Members Task Force, Montalescot G, Sechtem U, et al. ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of. Cardiology. 2013;34:2949-3003.
26. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130:1749-67.
27. Lindstaedt M, Spiecker M, Perings C, et al. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? Int J Cardiol. 2007;120:254-61.
28. Christou MA, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive imaging for evaluation of myocardial ischemia. Am J Cardiol. 2007;99:450-6.
29. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol. 2010;55:2816-21.