Prevalence, location, and extent of significant coronary artery disease in patients with normal myocardial perfusion imaging

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Background. **False-negative myocardial perfusion imaging (MPI) can by due to left main (LM) or three-vessel disease causing ''balanced ischemia''. However, so far prevalence of LM or three-vessel-disease in patients with normal MPI is unclear. We assessed prevalence, location, and extent of significant coronary artery disease (CAD) in patients with normal MPI.**

Methods. **Between 2006 and 2010, 256 patients with normal MPI who had invasive angiography because of persisting or worsening of the same initial symptoms were studied. Significant CAD was defined as stenosis > 70% or LM > 50%.**

Results. **A total of 93 patients (36%) had significant CAD. Significant CAD was observed more frequently in males, higher age and those with typical angina complaints. Significant LM disease was present in 7%, three-vessel disease in 10%, two-vessel disease in 22%, and single vessel disease (not left main) in 61%. In those with single vessel disease, the location was the LAD in 40%, the RCA in 30%, and the LCX in 30%.**

Conclusions. **In selected patients with normal MPI, one-third had significant CAD. The majority of these patients had single vessel disease (not left main). LM or three vessel disease, causing ''balanced ischemia'', is a less common cause of false-negative MPI. (J Nucl Cardiol 2014;21:284–90.)**

Key Words: Single-photon emission computed tomography • myocardial perfusion imaging • coronary artery disease

INTRODUCTION

Myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) provides valuable diagnostic and prognostic information in patients referred for non-invasive detection of myocardial ischemia.[1-4] However, its pure functional character renders it unable to detect atherosclerosis without hemodynamic consequences.

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Moreover, left main disease and three vessel disease may cause false-negative MPI.[5-8] So far, the location and extent of significant artery stenosis in patients with normal MPI are not clear.[7]

Therefore, the aim of our study was to assess the prevalence, location, and the extent of significant coronary artery stenoses in patients with normal MPI who underwent invasive coronary angiography because of persisting or worsening of the same initial symptoms.

MATERIALS AND METHODS

Study population

We performed a retrospective analysis of all 11,402 patients who underwent MPI-using ^{99m}Tc-Tetrofosmin

(Technetium-99m) SPECT in the Isala hospital, in Zwolle, the Netherlands between January 2006 and December 31st 2009. Of these patients, a total of 1,602 patients (14%) underwent invasive coronary angiography within 6 months after MPI because of persisting or worsening symptoms as expressed during their outpatient follow-up. Of the 1,602 patients, in 256 patients MPI was assessed as normal. Scans were considered normal if perfusion was assessed to be homogeneous throughout the myocardium and summed stress score was <3. These 256 patients constitute the population of this study.

Clinical information

At the time of SPECT examination, all patients completed a questionnaire regarding demographic information, prior medical history, cardiac risk factors, and current medication use. Furthermore, information regarding patient age, gender, weight, height, blood pressure, heart rate, and symptoms were prospectively obtained by a medical nurse. Pre-test likelihood of CAD was assigned according to Diamond and Forrester criteria.[9]

Diabetes was defined as confirmation of recurrent or persistent hyperglycemia with glycated hemoglobin (Hb A1C) $\geq$ 6.5%, or current use of oral anti-diabetic medication and/or insulin. Hypertension was defined as blood pressure higher than 140/90 mmHg as measured during at least three different times, or use of anti-hypertensive drugs for the indication hypertension. Smoking was defined as current consumption of at least 1 cigarette, cigar or pipe daily.

Hypercholesterolemia was defined as fasting total cholesterol of 5 mmol/l or more, or use of lipid-lowering therapy for the indication hypercholesterolemia.

Classification of Coronary Artery Disease

Invasive coronary angiography was performed with the standard Judkins or radial approach. All coronary angiograms were retrospectively re-interpreted visually by two experienced interventional cardiologists without knowledge of MPI. Coronary stenoses of 70% or greater were considered to be significant for the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) coronary territories. Significant Left main (LM) disease was defined as >50% diameter stenosis.[10-12] Patients were categorized as LM disease (both isolated and non-isolated), single vessel disease without LM, two vessel disease without LM, and three vessel disease without LM. Patients with previous coronary artery bypass graft (CABG) were categorized as having significant stenosis if they had graft dysfunction or any stenosis in a native coronary artery without graft.

SPECT-MPI Data Acquisition

All patients underwent a 1-day stress only or stress-rest ^{99m}Tc-Tetrofosmin MPI protocol. Patients were instructed to refrain from caffeine-containing beverages for at least 24 hours before the test. Pharmacologic stress was induced by intravenous administration of adenosine (continuous infusion at a rate of 140 μg/kg/minutes for 6 minutes) or dobutamine in case of contra-indication for adenosine (starting with 10 μg/kg/minutes and increased at 3-minutes intervals to a maximum of 50 μg/kg/minutes until 85% of the predicted heart rate had been reached). Adenosine was used in 95% of patients and dobutamine in 5% of patients. Whenever possible, patients performed additional low-level bicycle exercise to reduce side-effects of adenosine. ECG and blood pressure were monitored before, throughout, and following the infusion. A weight-adjusted dose of ^{99m}Tc-Tetrofosmin (standard 370, 500 MBq for patients >100 kg) was injected after 3 minutes of adenosine infusion. Patients scheduled for rest imaging received a dose of ^{99m}Tc-Tetrofosmin (standard 740 MBq, but 1000 MBq for patients >100 kg). For both, stress and rest SPECT images were acquired 45-60 min after tracer injection.

On the conventional dual-detector gamma camera Ventri, GE Healthcare), images were acquired using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 × 64 matrix, and an elliptical orbit with step-and-shoot acquisition at 6° intervals over a 180° arc (45° anterior oblique to 45° left posterior oblique) with 30 steps (30 views). All patients were imaged in supine position with arms placed above the head. Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images.

Gated SPECT analysis to calculate left ventricular volumes, ejection fraction and to assess wall motion abnormalities was done in nearly all patients when feasible, usually at stress but in some cases at rest. In 2009, stress and rest SPECT studies ($N = 81$) were followed by an unenhanced low-dose CT scan during a breath-hold to provide the attenuation map for attenuation correction. These scans covered the entire chest with scanning parameters: 5.0-mm slice thickness using a reconstruction algorithm with a 512 × 512 matrix, and 800 ms rotation times at 120 kV and 20 mA. Emission images as well as attenuation map data were entered in a dedicated reconstruction algorithm to provide 3D volume data (available in a Xeleris workstation, GE Healthcare). These were orientated in the standard way and displayed in the 3 traditional cardiac axes.

SPECT MPI Analysis

All MPI scans were analysed by an experienced cardiologist together with an experienced nuclear medicine physician. Segments were scored by consensus of two readers using a 20-segment model for the left ventricle using following five-point scoring system (0, normal; 1, equivocal; 2, moderate; 3, severe reduction in radiotracer uptake; and 4, absence of detectable tracer in a segment). A SPECT was considered normal if the summed stress score was <3.[13,14]

Statistical Analysis

Statistical analysis to compare baseline characteristics was performed with Chi-square and one-way analysis of variance (ANOVA) as available in SPSS software (version 20 for Windows; SPSS Inc., Chicago, Illinois, USA). Comparison of continuous data between both groups was performed using

the two-sided Student's t test. Quantitative variables were expressed as mean ± SD and categorical variables as frequencies, or percentage. P values of less than 0.05 were considered as statistically significant.

RESULTS

Baseline Characteristics

Mean age of the 256 patients was 63 ± 11 years, 47% were female and the mean body mass index (BMI) was 28 ± 4 kg/m^2. Hypertension and hypercholesterolemia were found in more than half of the patients. A total of 13% of patients had a history of previous percutaneous coronary intervention (PCI) and 11% had undergone a CABG before the SPECT. Aspirin, beta-blocker and statin were prescribed to the majority of the patients when they were referred to invasive coronary angiography. Fifty-four percent of patients had typical anginal complaints. The mean time between SPECT and subsequent invasive angiography was 66 ± 44 days (range 2-182 days).

Extent and Locations of Significant Coronary Artery Disease

A total of 93 patients (36%) had significant CAD, which was observed more frequently in males, with higher age, those with typical anginal complaints and those with a history of previous CABG (Table 1). The prevalence of significant CAD after the implementation of CT-based attenuation correction ($N = 81$) was 37% as compared to 36% in patients scanned without attenuation correction ($N = 175$, $P = 0.87$).

Among the 229 patients without previous CABG 78 patients (34%) had significant CAD. In the 27 patients with previous CABG 15 patients (56%) had significant CAD. The extent of significant coronary stenoses is shown in Figure 1. Seven percent had LM disease, 61% had 1 vessel disease, 22% had 2 vessel disease, and 10% had 3 vessel disease. Only 1 patient had isolated LM disease, while four patients had LM with three vessel disease. In the 86 patients with single vessel disease, the location of stenosis was almost equally distributed over the LAD, the RCA, and the LCX (Figure 2). In only 20 patients fractional flow reserve (FFR) measurement was performed, with a FFR value <0.80 in six patients. Of the 15 patients with previous CABG, only one developed new LM stenosis. The mean time between angiography and PCI or CABG was 17 days.

After a mean follow-up period of 5 years, 17 patients (6.6%) died, 8 of 93 patients with significant CAD versus 9 of 163 patients without significant CAD ($P = 0.34$). Of the 93 patients with significant CAD with angiography, within three months 58% were treated with PCI, 27% underwent a CABG and 15% were treated medically. Of the 163 patients without significant CAD at this angiography, three patients (2%) underwent coronary revascularisation during follow-up (9, 27, and 56 months after the MPI).

DISCUSSION

In this study, the prevalence, location, and extent of significant coronary artery disease was assessed in 256 patients with normal MPI who underwent invasive angiography within six months because of persistent anginal complaints. We found that in this selected population, one-third (93 patients) had angiographically significant coronary disease. Surprisingly, unprotected left main disease and/or three-vessel disease were present in only 11% of the patients with significant CAD. The majority of patients with significant CAD had single vessel disease, without a preference for a particular coronary artery. These findings suggest that balanced ischemia as cause of false-negative MPI may be less important than previously thought.

Besides true false-negative MPI,[5,15-17] significant stenoses in multiple coronary distribution areas are also associated with an underestimation of true extent of ischemia, since only the most severe stenosis will produce a regional flow defect. The combination of kinetics of available radiotracers uptake and the non-linear relationship between radiotracers uptake and absolute perfusion at high flow rates is regarded as possible explanation for this phenomenon.[18,19]

In a study[20] in patients with normal MPI and significant CAD as demonstrated by invasive angiography, 31% had LM or three vessel disease, but this study had a very small patient population (45 patients). Furthermore, it is remarkable that in that study only 11% were treated with coronary revascularization. Diamond et al. [21] also found a high prevalence (21%) of three-vessel and/or LM disease despite normal MPI, but this study included only 98 patients. In an unselected patient population with suspected CAD, of patients with normal MPI, 11% had LM or three-vessel disease.[22] Similar, two recently published studies found high prevalences of obstructive CAD in patients with normal MPI and extensive coronary atherosclerosis, however, these patients had predominantly single or two-vessel disease.[23,24] Combined with the results of our study, we think that balanced ischemia is only the cause of false-negative MPI in a minority of patients.

We found significant coronary artery disease in one third of our patients, confirming the importance of invasive angiography in patients with persisting or worsening of the initial symptoms suspicious for

Table 1. Comparison between significant and non-significant coronary artery disease, as assessed by invasive coronary angiography in patients with normal SPECT

Total cohort *N* = 256	**Significant CAD (*N* = 93)**	**Non-significant CAD (*N* = 163)**	***P* value**
Age (years)	65 ± 10	62 ± 11	0.007*
Length (cm)	173 ± 7	172 ± 10	0.35
Weight (kg)	82 ± 15	84 ± 16	0.53
BMI (kg/m^2)	27 ± 4	28 ± 5	0.17
Male gender	62 (67%)	74 (45%)	0.001*
Smoking	20 (22%)	42 (26%)	0.44
Hypertension	62 (67%)	94 (58%)	0.16
Hypercholesterolemia	67 (72%)	107 (66%)	0.29
Diabetes	22 (24%)	35 (22%)	0.69
Previous PCI	28 (30%)	32 (20%)	0.057
Previous CABG	15 (16%)	12 (7%)	0.03*
Use medication			
Aspirin	82 (88%)	103 (63%)	<0.001*
Beta-blocker	78 (84%)	122 (75%)	0.09
Calcium-channel blocker	29 (32%)	38 (23%)	0.17
Statin	67 (72%)	99 (61%)	0.07
Nitrate	44 (47%)	54 (33%)	0.03*
Typical Angina	62 (67%)	76 (47%)	0.002*
			0.31
Severity of complaints (CCS-classification)			
Class I–II	48 (52%)	102 (63%)	
Class III	38 (41%	54 (33%)	
Class IV	7 (7%)	7 (4%)	

Data are percentages or mean ± standard deviation.
SPECT, Single-photon emission computed tomography; *CAD*, coronary artery disease; *BMI*, body mass index; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft.

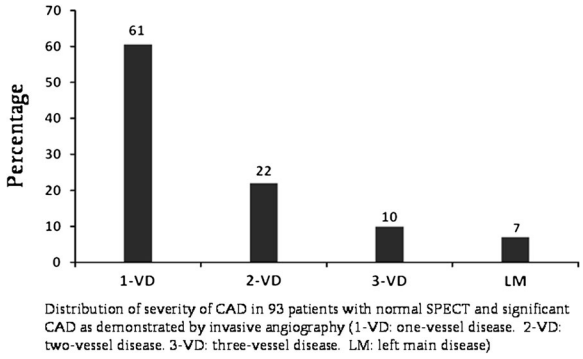

Figure 1. Distribution of extent of coronary artery stenosis in 93 patients with significant coronary artery disease.

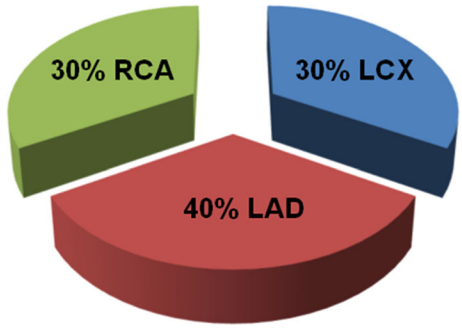

Figure 2. Location of significant coronary artery stenosis in 57 patients with single vessel disease (left main excluded).

coronary artery disease. There may be various explanations for false-negative MPI results. First, when comparing MPI with invasive angiography[25], it should be realized, that angiographic significant stenoses as shown by anatomic invasive angiography are often not reflecting myocardial ischemia.[16,26-30] So, in several cases MPI is in fact not false-negative but true negative, as the lesions are not of hemodynamic importance. True false MPI may be due to inadequate vasodilatation during stress, for example due to recent caffeine intake in adenosine stress or inadequate exercise in a physical stress test. Furthermore, inappropriate interpretation of supposed attenuation artefacts may result in false-

negative results. Another reason for false-negative MPI may be that small coronary vessels cannot cause ischemia as demonstrable by MPI.[31] Also development of collateral circulation can provide adequate perfusion to areas of myocardium supplied by a stenotic coronary artery leading to underestimation of the angiographic severity of epicardial lesion by perfusion imaging.[19] Moreover, not only (anatomical) invasive angiography, but also FFR, which may be seen as the new golden standard, can result in incorrect diagnoses. Reasons may be insufficient hyperemia, guiding catheter-related pitfall, electrical drift, diffuse disease rather than focal stenosis, small perfusion territory, severe microvascular disease, abundant collaterals, and severe left ventricular hypertrophy.[32]

Can MPI be improved, particularly to avoid false-negative results? Non-perfusion information can be used as indication for extensive and severe coronary artery disease, including transient ischemic left ventricular dilatation, increased lung radiotracer uptake, stress-induced global left ventricular dysfunction, and or wall motion abnormalities.[20] Knowledge of the clinical information and pre-test probability of CAD may improve interpretation of MPI.[33] CT-based attenuation correction may improve the overall diagnostic accuracy of MPI.[34]

Recently introduced ultrafast cardiac SPECT cameras with cadmium zinc telluride-based detectors may provide superior image quality allowing faster acquisition with reduced radiation doses.[35] Knowledge of the coronary calcium score may improve interpretation of myocardial perfusion scans, with higher sensitivity for detecting obstructive CAD without reducing the specificity.[36] The availability of multi-slice CT scanners and the recent advent of hybrid SPECT/CT and positron emission tomography/CT scanners may also improve the diagnostic potential of MPI.[37,38] Other potential future improvements in MPI are new tracers and new quantitative methods and software for image processing, evaluation, and data interpretation.[39]

Limitations

There are several limitations of our study. First, the data were retrospectively collected. Due to this, misclassification of baseline characteristics may have occurred. Also the use of pharmacological stress and the lack of implementing several non-perfusion markers in SPECT MPI analysis could be perceived as a limitation. Furthermore, visual anatomical assessment of angiograms can be weak due to poor correlation with FFR, however this reflects a real world situation which is current daily practice in most cardiology centers worldwide.

Of the patients with normal MPI, only a selected group had invasive angiography, mainly because of persisting symptoms. This means also that we cannot calculate sensitivity and/or specificity of MPI. We included also patients with a history of previous PCI and/or CABG, in these patients interpreting invasive angiography may be more difficult.

There is poor information about the presence of collaterals in the invasive coronary angiogram reports, especially in patients with a previous history of PCI and/or CABG. It's reasonable that the more collaterals are supplied to the coronary artery with a significant narrowing from the surrounding vessels, the bigger the chance of a normal MPI result.

Furthermore, we could not compare the angiographic results in the patients with normal MPI with the angiographic data of patients with abnormal MPI, since no data were collected of the patients with abnormal MPI. Finally, and possibly most important, in our population FFR was not routinely measured during invasive angiography.

NEW KNOWLEDGE GAINED

So-called balanced ischemia is only in a minority the cause of false-negative MPI.

CONCLUSION

In selected patients with normal SPECT MPI who were referred for invasive coronary angiography because of persisting or worsening of the same initial complaints, one-third had significant coronary artery disease. The majority of these patients (61%) had single vessel disease (not left main included). Probably, left main or three vessel disease, causing ''balanced ischemia'', is less important as cause of false-negative MPI.

Conflict of interest

The authors have indicated that they have no financial conflict of interest.

Disclosures

None.

References

1. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 Guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883-92.

2. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, et al. ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina-Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). Circulation 2003;107:149-58.
3. Shaw JL, Iskandrian AE. Prognostic Value of Gated Myocardial Perfusion SPECT. J Nucl Cardiol 2004;11:171-85.
4. Marcassa C, Bax JJ, Bengel F, Hesse B, Petersen CL, Reyes E, et al. Clinical Value, Cost-Effectiveness, and Safety of Myocardial Perfusion Scintigraphy: A Position Statement. Eur Heart J 2008;29:557-63.
5. Lima RSL, Watson DD, Goode AR, Siadaty MS, Ragosta M, Beller GA, 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.
6. Berman DS. Fourth Annual Mario S. Verani, MD Memorial Lecture: Noninvasive Imaging in Coronary Artery Disease: Changing Roles, Changing Players. J Nucl Cardiol 2006;13:457-73.
7. Berman DS, Kang X, Slomka PJ, Gerlach J, de Yang L, Hayes SW, et al. Underestimation of Extent of Ischemia by Gated SPECT Myocardial Perfusion Imaging in Patients with Left Main Coronary Disease. J Nucl Cardiol 2007;14:521-8.
8. 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.
9. Diamond GA, Forrester JS. Analysis of Probability as an aid in the Clinical Diagnosis of Coronary-Artery Disease. N Engl J Med 1979;300:1350-8.
10. Ragosta M, Dee S, Sarembock IJ, Lipson LC, Gimple LW, Powers ER. Prevalence of Unfavorable Angiographic Characteristics for Percutaneous Intervention in Patients with Unprotected Left Main Coronary Artery Disease. Catheter Cardiovasc Interv 2006;68:357-62.
11. Fajadet J, Chieffo A. Current Management of Left Main Coronary Artery Disease. Eur Heart J 2012;33:36-50.
12. Herzog BA, Buechel RR, Katz R, Brueckner M, Husmann L, Burger IA, et al. Nuclear Myocardial Perfusion Imaging with a Cadmium-Zinc-Telluride Detector Technique: Optimized Protocol for Scan Time Reduction. J Nucl Med 2010;51:46-51.
13. Berman DS, Kiat H, van Train K, Garcia E, Friedman J, Maddahi J. Technetium 99m Sestamibi in the Assessment of Chronic Coronary Artery Disease. Semin Nucl Med 1991;21:190-212.
14. Berman DS, Kiat H, Friedman JD, Wang FP, van Train K, Matzer L, et al. Seperate Acquisition Rest Thallium-201/Stress Technetium-99m Sestamibi Dual Isotope Myocardial Perfusion Single-Photon Emission Computed Tomography: A Clinical Validation Study. J Am Coll Cardiol 1993;22:1455-64.
15. Bateman TM, Maddahi J, Gray RJ, Murphy FL, Garcia EV, Conklin CM, et al. Diffuse Slow Washout of Myocardial Thallium-201: A New Scintigraphic Indicator of Extensive Coronary Artery Disease. J Am Coll Cardiol 1984;4:55-64.
16. Aarnoudse 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.
17. Ragosta M, Bishop AH, Lipson LC, Watson DD, Gimple LW, Sarembock IJ, et al. Comparison Between Angiography and Fractional Flow Reserve Versus Single-Photon Emission Computed Tomographic Myocardial Perfusion Imaging for Determining Lesion Significance in Patients with Multivessel Coronary Disease. Am J Cardiol 2007;99:896-902.
18. Marshall RC, Leidholdt EM Jr, Zhang DY, Barnett CA. Technetium-99m Hexakis 2-Methoxy-2-Isobutyl Isonitrile and Thallium-201 Extraction, Washout, and Retention at Varying Coronary Flow Rates in Rabbit Heart. Circulation 1990;82:998-1007.
19. Reyes E. Detection of Left Main Stem and Three-Vessel Coronary Artery Disease by Myocardial Perfusion SPECT Imaging. EuroIntervention 2010;6:G72-8.
20. Kostkiewicz M, Szot W. The Prognostic Value of Normal Myocardial Perfusion SPECT with Positive Coronary Angiography. Nucl Med Rev Cent East Eur 2012;15:22-5.
21. Diamond JA, Makaryus AN, Sandler DA, Machac J, Henzlova MJ. Normal or Near Normal Myocardial Perfusion Stress Imaging in Patients with Severe Coronary Artery Disease. J Cardiovasc Med (Hagerstown) 2008;9:820-5.
22. Hoilund-Carlsen PF, Johansen A, Christensen HW, Vach W, Moldrup M, Bartram P, et al. Potential Impact of Myocardial Perfusion Scintigraphy as Gatekeeper for Invasive Examination and Treatment in Patients with Stable Angina Pectoris: Observational Study Without Post-test Referral Bias. Eur Heart J 2006;27:29-34.
23. Ghadri JR, Pazhenkottil AP, Nkoulou RN, Goetti R, Buechel RR, Husmann L, et al. Very High Coronary Calcium Score Unmasks Obstructive Coronary Artery Disease in Patients with Normal SPECT MPI. Heart 2011;97:998-1003.
24. Mouden M, Ottervanger JP, Timmer JR, Reiffers S, Oostdijk AH, Knollema S, et al. Myocardial Perfusion Imaging in Stable Symptomatic Patients with Extensive Coronary Atherosclerosis. Eur J Nucl Med Mol Imaging 2013;41:136-43. doi:10.1007/s00259-013-2539-z.
25. Marie PY, Danchin N, Durand JF, Feldmann L, Grentzinger A, Olivier P, et al. Long-Term Prediction of Major Ischemic Events by Exercise Thallium-201 Single-Photon Emission Computed Tomography. Incremental Prognostic Value Compared with Clinical, Exercise Testing, Catheterization and Radionuclide Angiographic Data. J Am Coll Cardiol 1995;26:879-86.
26. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, et al. Measurement of Fractional Flow Reserve to Assess the Functional Severity of Coronary Artery Stenoses. N Engl J Med 1996;334:1703-8.
27. Bech GJ, Droste H, Pijls NH, De Bruyne B, Bonnier JJ, Michels HR, et al. Value of Fractional Flow Reserve in Making Decisions About Bypass Surgery for Equivocal Left Main Coronary Artery Disease. Heart 2001;86:547-52.
28. Botman KJ, Pijls NH, Bech JW, Aarnoudse W, Peels K, van Straten B, et al. Percutaneous Coronary Intervention or Bypass Surgery in Multivessel Disease? A Tailored Approach Based on Coronary Pressure Measurement. Catheter Cardiovasc Interv 2004;63:184-91.
29. Koolen JJ, Pijls NH. Coronary Pressure Never Lies. Catheter Cardiovasc Interv 2008;72:248-56.
30. Li J, Elrashidi MY, Flammer AJ, Lennon RJ, Bell MR, Holmes DR, et al. Long-Term Outcomes of Fractional Flow Reserve-Guided Vs. Angiography-Guided Percutaneous Coronary Intervention in Contemporary Practice. Eur Heart J 2013;34:1375-83.
31. Segall GM, Atwood JE, Botvinick EH, Dae MW, Lucas JR. Variability of Normal Coronary Anatomy: Implications for the Interpretation of Thallium SPECT Myocardial Perfusion Images in Single-Vessel Disease. J Nucl Med 1995;36:944-51.
32. Pijls NHJ, Tanaka N, Fearon WF. Functional Assessment of Coronary Stenoses: Can We Live Without It? Eur Heart J 2013;34:1335-44.

33. 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.
34. Sharma P, Patel CD, Karunanithi S, Maharjan S, Malhotra A. Comparative Accuracy of CT Attenuation-Corrected and Non-attenuation-Corrected SPECT Myocardial Perfusion Imaging. Clin Nucl Med 2012;37:332-8.
35. Mouden M, Timmer JR, Ottervanger JP, Reiffers S, Oostdijk AHJ, Knollema S, et al. Impact of a New Ultrafast CZT SPECT Camera for Myocardial Perfusion Imaging: Fewer Equivocal Results and Lower Radiation Dose. Eur J Nucl Med Mol Imaging 2012;39:1048-55.
36. Mouden M, Ottervanger JP, Timmer JR, Reiffers S, Oostdijk AHJ, Knollema S et al. The Influence of Coronary Calcium Score on Interpretation of Myocardial Perfusion Imaging (Abstract). ICNC11 2013.
37. Rana JS, Rozanski A, Berman DS. Combination of Myocardial Perfusion Imaging and Coronary Artery Calcium Scanning: Potential Synergies for Improving Risk Assessment in Subjects with Suspected Coronary Artery Disease. Curr Atheroscler Rep 2011;13:381-9.
38. Kaufmann PA, Di Carli MF. Hybrid SPECT/CT and PET/CT Imaging: The Next Step in Noninvasive Cardiac Imaging. Semin Nucl Med 2009;39:341-7.
39. Dilsizian V, Taillefer R. Journey in Evolution of Nuclear Cardiology: Will There be Another Quantum Leap with the F-18-Labeled Myocardial Perfusion Tracers? JACC Cardiovasc Imaging 2012;5:1269-84.