



Role of nuclear medicine assessing patients with suspected coronary artery disease

Roberto F.E. Pedretti^{1,2}, Luca Genovese², Luca Alberti², Alessandro Cecilia², Martina Cellamare², Matteo Crippa², Gianmarco Dacquino², Aurora Danza², Matteo Della Torre², Federico Ferrari Bravo², Giuseppe Galati², Francesco Torlone², Simona Sarzi Braga²

¹University of Milano-Bicocca, School of Medicine and Surgery

²IRCCS MultiMedica, Cardiovascular Department

ABSTRACT

Keywords

Coronary artery disease; single photon emission computed tomography; positron emission tomography; non-invasive tests



© 2024 The Authors
Published by SITECS

Nuclear medicine is a critical component in the field of cardiology as it provides diagnostic and prognostic insights that are essential for the effective management of heart disease.

Both single photon emission computed tomography (SPECT) and positron emission tomography (PET) play a significant role in assessing the likelihood of ischemic heart disease based on pre-test probabilities. Both SPECT and PET should be integrated into the clinical pathway according to the patient's individual risk profile, symptoms, and initial test results. The guidelines recommend using these imaging modalities to refine risk stratification, particularly in intermediate-risk patients, and to guide further invasive diagnostic or therapeutic procedures based on the imaging findings.

Received 5 April 2024; accepted 27 April 2024

Initial evaluation of patients with suspected ischemic heart disease

According to the 2019 European Society of Cardiology (ESC) guidelines on chronic coronary syndromes, a patient with suspected ischemic heart disease, commonly referred to as coronary artery disease (CAD), is typically identified based on risk factors, clinical presentation, and initial non-invasive evaluation [1].

The presence of risk factors such as hypertension, dyslipidemia, diabetes, smoking, a family history of early coronary artery disease, and obesity increases the likelihood of coronary artery disease. Symptoms can be summarized as dyspnea, typical angina pectoris characterized by chest pain or discomfort that occurs with exertion or emotional stress and is relieved by rest or nitroglycerin, atypical angina and non-anginal chest pain when not all the criteria for typical angina are met.

A detailed initial assessment, including medical history, physical examination, and diagnostic tests like an electrocardiogram (ECG), is

used to define the pre-test probability of CAD, based on age, sex, and the nature of chest symptoms.

Subsequent management can range from lifestyle modifications and medical treatment for low-risk patients to more aggressive interventions such as revascularization for those at high risk.

Noninvasive diagnostic evaluation

Non-invasive tests to assess ischemia include several techniques, such as exercise testing, stress echocardiography, myocardial perfusion imaging by nuclear imaging with Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), and cardiac magnetic resonance (CMR). These tests help to detect myocardial ischemia and evaluate the need for further invasive investigations such as coronary angiography.

Each non-invasive diagnostic test has a particular range of clinical likelihood of obstructive CAD where the usefulness of its application

Corresponding Author

Roberto F.E. Pedretti: roberto.pedretti@unimib.it

is maximal [1]. Given the clinical likelihood of obstructive CAD and the likelihood ratio of a particular test, one can assess the post-test probability of obstructive CAD after performing such a test [1]. Using this approach, one can estimate the optimal ranges of clinical likelihood for each test, in which they can reclassify patients from intermediate to either low or high post-test probability of CAD [2].

Patients can be categorized as having low, intermediate, and high pre-test probability of having ischemic heart disease and the choice of diagnostic tests is guided by these categories [1]:

- Low Pre-test Probability (<15%): For these patients, non-invasive testing might often be unnecessary, and routine testing is not recommended as it could lead to false positives and unnecessary further invasive procedures.
- Intermediate Pre-test Probability (15-85%): This group benefits the most from non-invasive imaging tests like stress echocardiography, SPECT and PET. SPECT is commonly used due to its availability and efficacy in detecting areas of reduced myocardial perfusion indicative of CAD. PET, while less commonly available, provides higher accuracy and better quantification of myocardial blood flow, and may be particularly useful in certain complex cases.
- High Pre-test Probability (>85%): In these patients, direct invasive strategies such as coronary angiography are often considered appropriate due to the high likelihood of significant coronary artery disease. However, PET can be used in specific scenarios to assess myocardial viability, especially when considering revascularization options.

Coronary Computed Tomography Angiography (CTA) is the preferred test in patients with a lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality. It detects subclinical coronary atherosclerosis but can also accurately rule out both anatomically and functionally significant CAD. It has higher accuracy values when low clinical likelihood populations are subjected to examination [3]. Trials evaluating outcomes after coronary CTA to date have mostly included patients with a low clinical likelihood [4, 5].

The non-invasive functional tests for ischemia typically have better rule-in power. In outcome trials, functional imaging tests have been associated with fewer referrals for downstream coronary angiography compared with a strategy relying on anatomical imaging [6-8].

The clinical significance of high-risk ischemic patterns

Before revascularization decisions can be made, functional evaluation of ischemia (either non-invasive or invasive) is required in most patients. Therefore, functional non-invasive testing may be preferred in patients at the higher end of the range of clinical likelihood if revascularization is likely or if the patient has previously been diagnosed with CAD.

When severe myocardial ischemia, indicative of substantial coronary artery obstruction, is identified, it represents a key determinant in the decision-making process for proceeding with interventional procedures. Patients displaying severe ischemia are often recommended for coronary angiography, which can lead to interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). These procedures aim to restore adequate blood flow to the ischemic areas, thereby improving symptoms, cardiac function, and overall prognosis [9, 10].

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial provided significant insights into the impact of the extent of myocardial ischemia on therapeutic decision-making in patients with stable CAD.

This trial explored the outcomes of patients with moderate to severe ischemia who were treated either with conservative medical therapy alone or with an initial invasive strategy involving angiography and possible revascularization [11].

The trial demonstrated that the initial invasive strategy did not significantly reduce the risk of major cardiovascular events compared to medical therapy alone in the overall cohort. However, subgroup analyses suggested that patients with more extensive ischemia might benefit more from revascularization in terms of symptom relief and quality of life improvements [11].

These findings emphasize the importance of personalized treatment strategies based on the extent of ischemia. While the results challenge the necessity of routine invasive procedures for all patients with moderate to severe ischemia, they highlight the need for a tailored approach, considering the individual patient's ischemic burden and symptomatic status.

Clinicians are required to carefully assess the extent of myocardial ischemia using non-invasive imaging techniques in stable CAD patients [1].

The ESC Guidelines summarize the definitions of high event risk for the different test modalities in patients with established chronic coronary syndromes [1, 12-14]:

- Exercise ECG: cardiovascular mortality >3% per year according to Duke Treadmill.
- Score SPECT or PET perfusion imaging: area of ischemia $\geq 10\%$ of the left ventricle myocardium.
- Stress echocardiography: ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia.
- CMR: ≥ 2 of 16 segments with stress perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments.

The role of nuclear medicine in patients with suspected CAD

Nuclear medicine is a critical component in the field of cardiology, offering diagnostic and prognostic insights that are essential for the effective management of heart diseases. This branch of medicine utilizes radioactive substances, known as radiotracers, to create images of the heart and study its function and structure in detail.

Both SPECT and PET play significant roles in assessing the likelihood of ischemic heart disease based on pre-test probabilities [1]. Guidelines outline specific scenarios in which SPECT and PET are particularly valuable, emphasizing their utility in refining diagnostic accuracy and guiding clinical decision-making [1].

Myocardial perfusion imaging with SPECT has been generally regarded as the reference standard for the evaluation of myocardial perfusion [1]. SPECT imaging is a robust tool for diagnosing CAD by evaluating myocardial perfusion deficits during stress testing. It is particularly useful for assessing the severity and extent of ischemia, helping to guide decisions about the necessity for angiography or revascularization [1].

Otherwise, PET offers several advantages over SPECT, including higher spatial resolution, the ability to quantitatively assess myocardial blood flow, and reduced radiation exposure to the patient [1]. PET is highly effective in evaluating myocardial viability and differentiating between scarred and hibernating myocardium, which is crucial for planning revascularization in patients with severe ischemia or complex coronary anatomy [1].

Both SPECT and PET should be integrated into the clinical pathway according to the patient's individual risk profile, symptoms, and initial test results. The guidelines recommend using these imaging modalities to refine risk stratification, particularly in intermediate-risk

patients, and to guide further invasive diagnostic or therapeutic procedures based on imaging findings.

A patient-centric approach, using the best available diagnostic tools to inform treatment strategies, thereby optimizing care for patients with suspected or confirmed CAD, is advocated to apply the best cost-effectiveness approach to an increasing disease.

Acknowledgements

This work has been supported by Italian Ministry of Health Ricerca Corrente - IRCCS MultiMedica

References

- [1] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020; 41:407-77.
- [2] Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J* 2018; 39:3322-30.
- [3] Gueret P, Deux JF, Bonello L, et al. Diagnostic performance of computed tomography coronary angiography (from the Prospective National Multicenter Multivendor EVASCAN Study). *Am J Cardiol* 2013; 111:471-8.
- [4] Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015; 372:1291-300.
- [5] SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015; 385:2383-91.
- [6] Greenwood JP, Ripley DP, Berry C, et al. Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: The CE-MARC 2 Randomized Clinical Trial. *JAMA* 2016; 316:1051-60.
- [7] Siontis GC, Mavridis D, Greenwood JP, et al. Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomised controlled trials. *BMJ* 2018; 360:k504.
- [8] Karthikeyan G, Guzik Salobir B, Jug B, et al. Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: An international, multi-center, randomized controlled trial (IAEA-SPECT/CTA study). *J Nucl Cardiol* 2017; 24:507-17.
- [9] Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012; 60:e44-e164.
- [10] Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; 356:1503-16.
- [11] Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med* 2020; 382:1395-407.
- [12] Mark DB, Shaw L, Harrell FE, Jr., et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991; 325:849-53.
- [13] Shaw LJ, Berman DS, Picard MH, et al. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. *JACC Cardiovasc Imaging* 2014; 7:593-604.
- [14] Johnson NP, Toth GG, Lai D, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014; 64:1641-54.