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# Risk stratification of coronary artery disease using radionuclides. Current status of clinical practice<sup>☆</sup>



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## A B S T R A C T

### Keywords:

Coronary artery disease  
Risk stratification  
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Cardiovascular risk factor

A discussion is presented on the current use of radionuclides for evaluation of coronary artery disease in relation to other available techniques. The review is focused on coronary artery disease risk stratification employing single photon emission computed tomography and positron emission tomography, as well as on ischemic cardiomyopathy and myocardial viability applications.

Concepts are presented regarding coronary blood flow reserve, diagnostic and prognostic values, criteria for its appropriate use, as well as current methods to reduce unnecessary patient irradiation, in order to optimize nuclear cardiology practice.

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## Estratificación de riesgo de enfermedad coronaria con métodos isotópicos. Estado actual de la práctica clínica

## R E S U M E N

### Palabras clave:

Enfermedad coronaria  
Estratificación de riesgo  
SPECT cardíaco  
PET cardíaco  
Factor de riesgo cardiovascular

Se discute el uso actual de los radioisótopos para la evaluación de la enfermedad coronaria con relación a otras técnicas disponibles. La revisión se centra en la estratificación de riesgo de enfermedad coronaria mediante tomografía de fotón único y de doble fotón, y su la aplicación en viabilidad miocárdica y miocardiopatía isquémica.

Se presentan conceptos sobre flujo absoluto y reserva de flujo coronario, valor diagnóstico y pronóstico, así como criterios de uso apropiados de las pruebas y también los métodos actuales para disminuir la radiación innecesaria de los pacientes, optimizando la práctica de la cardiología nuclear.

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## Introduction

The incidence of atherosclerosis and coronary artery disease (CAD) is continuously rising worldwide despite the important development of early diagnostic techniques, multiple primary and secondary prevention campaigns and the use of hypolipemiant drugs. In general terms, mortality by CAD has decreased due to better therapeutic management, even in advanced cases including the use of implantable devices and heart transplantation. However, the development of metabolic syndrome and diabetes mellitus (DM) have increased in different regions because of sedentary lifestyles and inadequate alimentation. In parallel, ischemia-related heart failure remains underdiagnosed in many parts of the world. In addition to the traditional cardiovascular risk factors (CVRF) such as age, sex, DM, arterial hypertension, family history of cardiovascular disease, dyslipidemia and smoking, other conditions are associated with a greater risk of cardiac events, among which DM of more than 5 years of poorly controlled glycemia as well as cerebrovascular diseases, peripheral artery disease and chronic

kidney disease are of note. Overweight, obesity, sedentarism, atrial fibrillation and left ventricular hypertrophy, autoimmune diseases, major depression, cocaine use and erectile dysfunction are also related to CAD and may have cumulative effects in subjects with endothelial and microvasculature disease. Inflammation has a well recognized relationship with CAD.<sup>1</sup>

For decades the traditional anatomical gold standard for the diagnosis of CAD has been coronary angiography with cut off values between 50 and 75% for arterial stenosis. However, in many patients this method underestimates real ischemia both in cases with lower values of stenosis as well as in those presenting only microvessel disease and underlying endothelial dysfunction. Measurement of the coronary calcium score recognizes CAD but does not directly signal the presence of myocardial ischemia. This score is important to help secondary prevention with the management of CVRF. Other anatomical imaging techniques such as cardiac computerized tomography (CT), angio-CT and cardiac magnetic resonance (CMR) provide complementary anatomical information, especially in the evaluation of myocardial infarction. Echocardiography is an inexpensive noninvasive diagnostic method of CAD which is widely available. Stress is required for the assessment of ischemia and pharmacologic stress is used more than exercise due to technical facilities, presenting a greater specificity but lower sensitivity than myocardial perfusion single photon emission computerized tomography (SPECT). It has the advantage of not using

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ionizing radiation and the disadvantage of being operator dependent. Its yield depends, in part, on the quality of the acoustic window of the patient. Ultrasonographic 3D analysis and strain have led to an improvement in the characterization of contractile synchrony which may be altered early in CAD. On the other hand, CMR requires trained operators, relatively complex software, and there are some difficulties in individuals carrying electronic implants, patients with tachycardia or subjects with altered renal function.

Measurement of the fractional flow reserve (FFR) is based on the difference in pressures in coronary stenosis and is currently considered as a more adequate functional standard than coronary angiography since it allows early detection of blood flow deficits. A value  $<0.8$  is considered to be abnormal, although there is an uncertain zone between 0.75 and 0.8. This technique has well known prognostic value, especially in cases of revascularization with angioplasty.<sup>2,3</sup>

Quantification of absolute basal flow as measured by positron emission tomography (PET) under pharmacologic stress allows early identification of patients with reduced coronary flow reserve both on a global and segmentary basis. This methodology is costly and its implementation is complex. On the other hand, it is also possible to evaluate endothelial dysfunction prior to manifestations of ischemia observed as vasoactive response corresponding to sympathetic stress. Protocols with this objective trigger endothelial nitric oxide synthase. Measurements with different PET tracers indirectly evaluate the increase in myocardial blood flow induced by the release of nitric oxide during stress. Alterations have been observed in diabetic patients, even those newly diagnosed, as well as in obese subjects and smokers.<sup>4–6</sup>

Since the 1980s, nuclear cardiology, especially with myocardial perfusion SPECT, has significantly contributed to the noninvasive detection and risk stratification in CAD as well as the study of patients with intermediate cardiovascular risk and in cases in which electrocardiography interpretation is difficult. Its utility in known cases of CAD and in the evaluation of therapy is also recognized. The most commonly used radiotracers are thallium-201 ( $^{201}\text{Tl}$ ) and technetium-labeled tracers. The first is a cation similar to potassium which presents redistribution and uses the sodium-potassium pump for introduction into myocytes. It is flow-dependent with a high myocardial extraction fraction (half life  $^{201}\text{Tl}$ : 72 h). The technetium radiotracers are  $^{99\text{m}}\text{Tc}$ -sestamibi and  $^{99\text{m}}\text{Tc}$ -tetrofosmin, which are also cations and are taken up by processes dependent on transmembrane potential. They have less effective extraction than  $^{201}\text{Tl}$  and similarly require cellular viability for penetrating myocytes. They accumulate in the cytoplasmic mitochondria with minimum redistribution (half life  $^{99\text{m}}\text{Tc}$ : 6 h) and are molecules which remain relatively fixed in the myocytes and need separate injections to compare the stress and rest phases. The technique allows the selection of patients with induced ischemia for further referral to an anatomical diagnostic procedure (*i.e.* coronary angiography) and for eventual coronary revascularization as well as optimization of medical management including that of CVRF.

There is debate about the overuse of ionizing radiation in some countries especially in the follow up of patients who might receive unnecessary exposure during the first year post-revascularization. There is consensus, however, that the use of isotopes could be improved. This is particularly true when focused on adequate indications and the selection of protocols able to respond to the request of the referring physician, considering the multiple variables which could reduce diagnostic safety and minimize the radiation dose received in usual clinical practice.

It should be taken into account that since perfusion SPECT studies presented a low specificity several decades ago, the concept of normalcy rate needs to be used to eliminate the reference bias and calculate the specificity in patients with a low pretest probability of CAD.<sup>7–9</sup>

## Comparison of invasive and noninvasive techniques in the diagnosis of coronary artery disease

The use of noninvasive diagnostic techniques should be considered in cases with symptoms of CAD or ventricular dysfunction depending on the pretest probability of the disease. With regard to noninvasive anatomical evaluation in CAD, the European multicenter EVINCI study (*Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease*)<sup>10</sup> evaluated 475 patients with stable angina and an intermediate probability of CAD. The patients underwent angio-CT and non-invasive functional tests (SPECT, PET, stress echocardiography or CMR), and it was reported that the diagnostic accuracy of angio-CT was significantly greater than that of functional tests. The definition of significant CAD in this study was  $>50\%$  stenosis of the left coronary artery,  $>70\%$  stenosis of the main coronary artery or 30 to 70% with  $\text{FFR} \leq 0.8$ . On the other hand, the PROMISE study (*Prospective Multicenter Imaging Study for Evaluation of Chest Pain PROMISE*)<sup>11</sup> randomized 10,000 symptomatic CAD patients mainly presenting angina or exercise dyspnea to undergo initial anatomical tests with either angio-CT or a functional test (exercise electrocardiography, nuclear stress test of stress echocardiography). Death, myocardial infarction, hospitalization for unstable angina or major complications of the procedure were considered to be major events and the average pretest probability was approximately 53%. The results of this study showed that the use of noninvasive approaches compared to functional tests did not improve the clinical prognosis at a median follow up of 2 years.

In a recent meta-analysis of different invasive and noninvasive techniques in CAD,<sup>12</sup> CMR demonstrated a high efficiency for the diagnosis of ischemia when the FFR was used as the gold standard. The anatomical methods such as angio-CT and coronary angiography had less specificity while functional evaluation of coronary atherosclerosis by stress echocardiography, SPECT and FFR-CT significantly improved the accuracy of CAD detection. The last tool is based on the application of computational fluid dynamics in conventional angio-CT. In this study SPECT presented better performance when the technique was assessed per patient compared to per vessel. It was also of note that the specificity of SPECT was greater than that of conventional coronary angiography which does not consider functional values.

## Risk stratification in coronary artery disease by single photon emission computerized tomography

The prognostic value and especially the negative predictive value of a negative nuclear ischemia test is well known. The risk of major cardiac events (death of cardiac origin or myocardial infarction) is low, being less than 1% over a 2–3 year period, even in patients with known CAD. However, this is not strictly true in patients with DM who have a higher risk of events of up to 2–3% and who may present cardiovascular events in as short a term as one year.

The addition of functional nuclear parameters improves the diagnostic value of multivessel disease. Transitory dilatation in stress compared to rest is a simple sign to observe, with values  $>1.2$  being considered as abnormal depending on whether the summed or end-diastolic image are used as well as the type of stress, radiotracer and technique used for calculation. Other independent findings such as a fall in left ventricular ejection fraction (LVEF) post-stress or transitory alterations of motility, visualization of the right ventricle post-stress and an increase in the pulmonary/myocardial activity index in the stress or post-stress images are able to indirectly detect ischemia in more than

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