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FUNCTIONAL TESTING AS THE MOST ACCURATE TOOL FOR RISK STRATIFICATION IN PATIENTS WITH MICRO- AND MACROVESSEL CORONARY ARTERY DISEASE

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Abstract

The scope of this review is to underline the diagnostic and prognostic significance of non-invasive tests, with special reference to myocardial perfusion scintigraphy and computed tomography angiography, to assess cardiac perfusion and anatomy in patients with micro- and macrovessel coronary disease.

From available data it appears that functional testing should still be considered as the most accurate tool for the evaluation of patients with macrovessel coronary disease. In fact, the determination of the cardiac global ischemic burden remains the most important tool for the clinical management of patients with different types of ischemic heart diseases. For this purpose, several instrumental techniques can be adopted.

Recent technological advancements have introduced the possibility to obtain physiologic evaluation of coronary stenosis by computed tomography angiography, thereby enabling this test to potentially provide an integrated anatomic-physiologic assessment of macrovessel coronary disease. Apart from the use of computational fluid dynamics to non-invasively calculate coronary fractional flow reserve, these advances also include evaluation of rest-stress myocardial perfusion from a typically acquired computed tomography angiography.

Finally, the pathophysiologic potential role of endothelial dysfunction and its relation with myocardial perfusion in determining prognosis is also discussed. A potential increasing future role of coronary plaque characterization is hypothesized.

Keywords: *coronary artery disease, endothelial dysfunction, myocardial perfusion scintigraphy, functional testing.*

Introduction

Despite the development of highly sensitive diagnostic tools for anatomic determination of micro- and macrovessel coronary artery disease (CAD), the determination of global cardiac ischemic burden remains the most important tool for the management of patients with different types of CAD. For this purpose, several instrumental techniques can be adopted.

In patients with suspected or established CAD, physiological testing remains the gold standard, especially in the prognostic evaluation of the disease. In this context, myocardial perfusion scintigraphy (MPS) appears as a very accurate technique. Indeed, as evident in patients with either epicardial or microvascular CAD, the presence and extent of inducible myocardial ischemia grossly correlate with clinical outcome and should therefore be considered as the most relevant factor to perform a close follow-up of these patients. In fact, anatomic evaluation of obstructive stenosis does not determine the hemodynamic significance of the visualized lesions and, therefore, it lacks the prognostic insight. The scope of this review is to underline the importance of evaluating the presence and extent of myocardial ischemia beyond the evaluation of coronary anatomy in the prognostic stratification of patients presenting with different types of CAD.

The significance of myocardial perfusion abnormalities in patients with microvascular coronary artery disease: The cardiac Syndrome X is characterized by angina-like chest pain and positive exercise test, in the presence of angiographically normal coronary arteries. Although multiple pathogenetic causes have been hypothesized [*Chierchia S, Fragasso G, 1996*], coronary microvascular dys-

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function appears as a likely mechanism in a sizeable proportion of patients. Some studies conducted in patients with cardiac Syndrome X reported reduced progression of the angiographic dye ("slow-flow") and suggested that this phenomenon could be possibly caused by small vessel disease [*Tambe AA et al., 1972; Przybojewski JZ, Becker PH, 1986; Van Lierde J et al., 1991; Burckhartt BA et al., 1998; Kapoor A et al., 1998*]. Furthermore, in small patient series with slow-flow, histologic evidence of small vessel coronary disease has been described [*Mosseri M et al., 1986; Mangieri E et al., 1996*]. More recently, direct evidence of transient reversible myocardial underperfusion during MPS occurring during slow-flow has been demonstrated and associated to a worse long-term prognosis [*Fragasso G et al., 2009*].

The conventional stress/rest MPS has also been confirmed to be a very useful prognostic tool in patients with Syndrome X [*Fragasso G et al., 2014*], where the observation of stress perfusion defects had traditionally been considered as a "false-positive" result. In this study, prognosis in patients with normal coronary arteries but scintigraphic evidence of relatively mild inducible myocardial hypoperfusion was not as good as in patients with normal perfusion, especially in terms of morbidity. In fact, in those Syndrome X patients who revealed transient scintigraphic perfusion defects, decreased survival and increased hospitalization, as well as severe and longer symptomatic burden requiring multidrug therapy were observed. More specifically, significant increment of the secondary end-points (cardiovascular hospitalizations) and greater symptomatic burden in the positive MPS group, clearly indicate worse functional prognosis in these patients. This observed incremental predictive value of MPS for future events has been proven in two other studies, demonstrating significant differences in the prognosis of patients between positive and negative MPS patients with angiographically "non-significant" CAD [*Delcour KS et al., 2009; Adamu U et al., 2010*]. On the other hand, these results also indirectly confirm the association between a negative MPS and very low event rates [*Soman P et al., 1999*].

Microvascular-induced myocardial ischemia: The concept that searching for ischemia rather than epicardial vessel stenosis could be more effective in risk stratification has different physiological explanations. The mechanisms by which prognosis in Syndrome X patients with positive MPS could be worse are probably related to an effective reduction of microcirculation vasodilatory reserve [*Cannon RO et al., 1983; Legrand V et al., 1985*] being the cause of symptoms, positive response to exercise testing and inducible scintigraphic defects [*Tweddel AC et al., 1992; Romeo F et al., 1993; Fragasso G et al., 1996*]. In fact, histologic evidence of small vessel coronary disease in patients with angina, normal coronary arteries and slow-flow has been previously shown [*Mosseri M et al., 1986; Mangieri E et al., 1996*]. Additionally, abnormal subendocardial hypoperfusion has been detected in patients with angina and angiographically normal coronary arteries by cardiac magnetic resonance imaging [*Panting JR et al., 2002*], supporting the concept that chest pain in these patients may be related to non-transmural myocardial ischemia. This hypothesis is supported by cardiac magnetic resonance spectroscopy data showing reduced myocardial ratios of phosphocreatine to adenosine triphosphate, consistent with cellular ischemia, in some women with chest pain and normal coronary arteries [*Buchthal SD et al., 2000*].

In patients with chest pain and normal angiograms, abnormalities of the coronary microcirculation have been attributed to endothelial dysfunction [*Motz W et al., 1991; Quyyumi AA et al., 1992; Egashira K et al., 1993; Piatti P et al., 2003*]. Although most studies have shown that patients with angina and normal coronary arteries bear a benign prognosis [*Pasternak RC et al., 1980 ; Proudfit WL et al., 1980; Isner JM et al., 1981; Kemp HG et al., 1986; Kaski JC et al.,1995*], recent investigations indicate that in patients with non-obstructive coronary disease and evidence of myocardial ischemia, the presence of endothelial dysfunction [*Suwaidi JA et al., 2000; Von Mering G et al., 2004*] and the long-term persistence of chest pain [*Johnson BD et al., 2006*] are associated with adverse cardiovascular events. In a study population of 42 women with angina and angiographically normal coronary arteries it has been shown that approximately 30% of those exhibiting severe endothelial dysfunction developed CAD during a 10-year follow-up [*Bugiardini R et al., 2004*]. It has also been recently shown that in patients with angina, positive exercise test

and normal coronary arteries, the presence of endothelial dysfunction is associated with potentially inducible myocardial hypoperfusion and a worse prognosis [*Fragasso G et al., 2009*]. Therefore, the occurrence of exercise-induced ST-segment changes and myocardial perfusion abnormalities, especially if associated with endothelial dysfunction, could predict a worse outcome and should not be regarded as a false-positive result.

The mechanisms beyond electrocardiographic (ECG) changes are difficult to discriminate in patients with angina who present with positive exercise ECG but unremarkable perfusion scintigraphy. Although these are often considered "false-positive" tests, they may reveal an earlier stage of microvascular dysfunction [*Brush J et al., 1988*]**.**

The significance of myocardial perfusion abnormalities in patients with epicardial coronary artery disease: The observed prognostic significance of myocardial perfusion abnormalities in patients with angina pectoris and normal epicardial coronary arteries appears particularly relevant in view of previous evidence suggesting that searching for ischemia rather than for the mere presence of atherosclerotic stenosis could represent a better prognostic tool even in patients with macroscopic CAD. In the COURAGE Trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), a strategy-driven trial randomizing 2287 patients to optimal medical therapy (OMT) with or without percutaneous coronary intervention (PCI), revealed no difference by treatment in the primary end point of death or acute myocardial infarction for a median 4.6 years of follow-up (p=0.62) [*Boden W et al., 2007*]. The COURAGE trial included a nuclear sub-study to measure ischemic burden in a subset of patients [*Shaw L et al., 2008*]. The primary aim of the nuclear sub-study was to compare changes in ischemic burden after randomization to PCI+OMT compared with OMT alone and to explore associations with patient outcome. The nuclear sub-study demonstrated that the magnitude of ischemia on MPS was proportional to the risk of death or myocardial infarction. Regardless of treatment assignment, the magnitude of residual ischemia on follow-up MPS was proportional to the risk of death or myocardial infarction and ≥5% reduction in ischemia by intervention was associated with a significant reduction of risk. It is remarkable that this study has reported to date the largest series on ischemia reduction with medical therapy in a clinical trial. From the OMT patients exhibiting significant ischemia reduction, the majority were also angina free, generally with mild residual ischemia on their follow-up MPS.

Relatively recent evidence supporting the non-inferiority of functional compared to anatomical testing for risk stratification has been provided by the Prospective Multicenter Imaging Study for Evalution of Chest Pain (PROMISE) Study [*Douglas P et al., 2015*]. The study included 10.003 symptomatic patients who were randomly assigned to a strategy of initial anatomical testing with the coronary computed tomographic angiography (CTA) or functional testing (exercise ECG, nuclear stress testing or stress echocardiography). The composite primary endpoints were death, myocardial infarction, hospitalization for unstable angina or major procedural complications. The secondary endpoints included invasive cardiac catheterization that did not show obstructive CAD and radiation exposure. In symptomatic patients with suspected CAD who required non-invasive testing, a strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes (over a median follow-up of 2 years). An insignificant improvement in performance was observed in the functional testing arm: during follow-up, 164 (3.3%) patients in the CTA group and 151 (3.0%) patients in the functional testing group had a primary end-point event (p=0.75). The results have shown that in symptomatic patients with suspected CAD who require non-invasive testing, an initial strategy of coronary anatomy assessment was not associated with better clinical outcomes than functional testing over a median follow-up of 2 years and was indeed associated to a greater radiation burden.

The fact that anatomy alone does not allow a prognostic evaluation of patients with stable forms of CAD is confirmed by previous studies showing that that myocardial infarction frequently develops from previously non-severe lesions. In addition, it is often difficult to predict the location of a subsequent infarct from analysis of the first coronary angiogram [*Ambrose J et al, 1988*].

Future clinical implications: Functional testing remains the gold standard in the prognostic evaluation of coronary artery disease. In this context, myocardial perfusion scintigraphy is the most sensitive technique [*Fragasso G et al., 1999*]. In patients with Syndrome X, positive functional testing has traditionally been considered as a false-positive result. Usually patients were reassured after a normal coronary angiogram, despite the presence of angina, abnormal stress ECG and frequent evidence of inducible myocardial ischemia on stress MPS. As evident in patients with epicardial CAD, the presence and extent of inducible myocardial ischemia grossly correlate with clinical outcome and should not be minimized but indeed taken into account to perform a close follow-up of these patients. The presence of inducible myocardial ischemia in patients with Syndrome X may predict future events: in such patients, morbidity and even mortality are higher than patients without inducible ischemia.

In patients with non-acute CAD, the COURAGE trial has evidenced that up-front percutaneous coronary intervention (PCI) based on angiographic stenosis severity does not reduce coronary events more than initial medical treatment [*Boden W et al., 2007*]. Additionally, randomized trials report better outcomes when PCI is guided by fractional flow reserve rather than by angiographic severity [*Pijls N et al., 2010*] [*De Bruyne B et al., 2012*], confirming the primary role of functional versus anatomic evaluation of CAD.

In several prospective multicentre trials, CTA has been proven as having high diagnostic accuracy for stenosis detection as compared to invasive angiography. Nevertheless, anatomic evaluation of obstructive stenosis does not determine the hemodynamic significance of the visualized lesions. Recent technological innovations have introduced the possibility to obtain physiologic evaluation of coronary stenosis by CTA, thereby enabling this test to potentially provide an integrated anatomic-physiologic assessment of CAD [*Koo B et al., 2011*]. Apart from the use of computational fluid dynamics to non-invasively calculate fractional flow reserve, these advances also include evaluation of rest-stress myocardial perfusion from a typically acquired CTA [*Feuchtner G et al., 2012*].

Nevertheless, true progress in the diagnosis, treatment, and prevention of CAD is dependent on understanding the mechanisms of coronary plaque progression. Autopsy studies have identified high-risk, or vulnerable, plaques that result in acute coronary syndromes or sudden cardiac death. Diagnostic techniques for vulnerable-plaque detection are needed. Recent advances in intravascular imaging have significantly improved the ability to detect high-risk, or vulnerable, plaque in vivo by using various methods. In the near future, plaque characterization will certainly have an increasing role in the management of CAD [*Tarkin J et al., 2016*].

In conclusion, functional testing remains the most useful tool for risk stratification in micro- and macrovascular CAD. Recent technical advancement allowing a combined anatomic and physiological approach by CTA could possibly become the best diagnostic/prognostic tool in the very near future.

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