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ORIGINAL ARTICLE

Comparison between Myocardial Ischemia Evaluation by Fractional Flow Reserve and Myocardial Perfusion Scintigraphy

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Abstract

Background: Moderate coronary artery lesions can be, or not, responsible for myocardial ischemia. The functional analysis of these lesions can be performed by invasive and noninvasive methods.

Objective: To compare the functional analysis of moderate coronary lesions by fractional flow reserve and myocardial perfusion scintigraphy.

Methods: 47 patients with stable coronary artery disease and at least one moderate coronary artery obstruction were prospectively studied. They were submitted to fractional flow reserve and myocardial perfusion scintigraphy with a median interval of 24.5 days between January 2013 and December 2015. There was no change in clinical status or revascularization procedure between the exams. The population variables were described as medians and interquartile range. Fractional flow reserve was performed in one left main coronary artery; 37 left descending coronary arteries; 12 circumflex arteries and 4 right coronary arteries. Fractional flow reserve < 0.8 was considered positive. The comparative analysis between the results of the tests was performed by two-tailed Fisher's test and a p-value ≤ 0.05 was considered significant.

Results: Fractional flow reserve < 0.8 was found in the left main coronary artery (100%); 13 in the left descending coronary artery (35.14%); 6 in circumflex artery (50%) and 2 in the right coronary artery (50%). Among the patients with positive fractional flow reserve, 83% had myocardial ischemia demonstrated by the myocardial perfusion scintigraphy (p = 0.058). When analyzing specifically the left descending coronary artery, 83% of the patients with negative fractional flow reserve showed no ischemia at the myocardial perfusion scintigraphy, but 69% of the patients with positive fractional flow reserve showed no ischemia at the myocardial perfusion scintigraphy (p = 0.413).

Conclusion: Disagreements can occur between the results of the functional analysis of moderate coronary lesions by invasive and noninvasive tests. (Int J Cardiovasc Sci. 2018;31(4)333-338)

Keywords: Myocardial Ischemia; Praqctional Flow Reserve, Myocardial; Myocardial Perfusion / Diagnostic Imaging; Microvascular Angina.

Introduction

The presence of myocardial ischemia is one of the important prognostic factors in coronary artery disease (CAD) and in the decision-making on the best treatment to be implemented. The combination of coronary anatomy and information on the hemodynamic implication of the obstructive lesion is essential to define the treatment strategy to be carried out in patients with CAD.

The fractional flow reserve (FFR) measurement is a valuable tool to evaluate the functional severity of a coronary stenosis, identifying changes in coronary flow resistance. The FFR can be obtained in the hemodynamic laboratory and can be performed together with the angiography. The FFR is defined as the maximum blood flow to the myocardium in the presence of a certain stenosis, divided by this flow, if there was no such stenosis. The FFR can be determined by dividing the

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mean pressure distal to the coronary lesion by the mean aortic pressure during maximal adenosine-induced vasodilation. The FFR has a normal value of 1, and values less than 0.8 indicate myocardial ischemia. Studies have shown that coronary vessels with FFR ≥ 0.8 can be clinically treated, with cardiovascular event rates similar to those of patients with normal noninvasive tests (< 1% per year). Patients with FFR ≤ 0.8 could benefit from percutaneous or surgical revascularization procedures.[1-3]

Although the FFR has its defined role in moderate lesions and is not very useful in angiographically severe lesions, it helps in the decision-making regarding when to revascularize patients with multivessel disease. In these patients, it helps to define the revascularization strategy, as well as to better evaluate its extent, according to the functional evaluation of stenosis in critical coronary sites.[4]

Myocardial perfusion scintigraphy (MPS) with tomographic images has been validated by several studies in the evaluation of diagnosis and prognosis for patients at risk of cardiovascular events. The functional repercussion of coronary lesions constitutes one of the main purposes of the method, which is based on the perfusion deficit assessment in myocardial segments irrigated by partially occluded arteries. Risk stratification is based on the ability to identify patients according to the test results. SPECT with normal or slightly altered perfusion has an excellent prognosis, with a low mortality risk (< 1%) per year. The risk associated with perfusion alterations varies according to the ischemia extent and severity. The greater the perfusion defects, the higher the likelihood of future events. In those with moderate perfusion defects, the incidence of events is 1 to 3% per year, being > 3% in patients with major perfusion defects.[5]

Most percutaneous coronary interventions are performed based on angiographic criteria alone, with no objective evidence of myocardial ischemia. Coronary angiography has limitations in establishing functional severity, because the stenosis degree of a lesion does not always correlate with functional impairment in the myocardium.6 Thus, it is important to complement anatomical data with functional tests capable of adequately guiding the therapeutic approach regarding a myocardial revascularization procedure. Several studies have been carried out to evaluate the agreement between the FFR with functional methods (MPS, dobutamine stress echocardiogram and exercise testing) to define the presence of myocardial ischemia, with the FFR having the advantage of being specific for each vessel and obstruction.[7] In multi-vessel patients, MPS tends to underestimate or overestimate the functional importance of coronary stenosis when compared to FFR.[8]

The functional tests are performed in a minority of patients referred to coronary angioplasty at *Instituto Nacional de Cardiologia*. In this sense, the FFR can be a useful tool in the hemodynamics room to aid in decision-making regarding whether or not to perform a percutaneous coronary intervention, saving time and costs to the health system. The objective of the present study was to compare the functional analysis between FFR and MPS in patients with moderate lesions at the coronary angiography.

Methods

This is a prospective, observational study of patients of both genders, aged 18 years or older, admitted to the Department of Coronary Disease unit or referred to the Hemodynamic Service of *Instituto Nacional de Cardiologia*, who had an FFR indication after the coronary angiography by the multidisciplinary "Heart team". The sample size of 47 patients was selected by convenience.

Patients with no previous MPS were submitted to the examination. Coronary lesions were classified as moderate (between 50 and 70%) and severe (≥ 70%) according to visual estimation.

Patients with moderate lesions and those for whom there was doubt regarding the indication of myocardial revascularization were included in the study. Patients with chronic occlusion, ST-segment elevation acute myocardial infarction, unstable patients, those with severe valvular disease or cardiomyopathies from other causes, patients with contraindications to the use of adenosine and to scintigraphy (pregnant women, infants and women with suspected pregnancy) were excluded from the study.

The study was approved by the Ethics and Research Committee of *Instituto Nacional de Cardiologia*, and all the participants agreed to sign the Free and Informed Consent Form. The present study has no sources of funding.

Fractional flow reserve measurement

Coronary catheterization was performed with 6 and 7F guide catheters. Prior to the angiography, 10,000 u of intravenous heparin and intracoronary nitroglycerin at a dose of 0.25 to 0.5 mg were administered. Then, pressure measurements were performed in vessels with stenosis ≥ 50% by visual estimation using a guidewire with a

sensor at its tip and was positioned in the distal bed of each coronary to be analyzed. Intravenous adenosine at the dose of 140 mg/kg/minute was administered for 2 to 3 minutes to induce maximal hyperemia.

The FFR was established as the ratio between the mean distal coronary pressure and the mean aortic pressure, measured by the guide catheter during maximal hyperemia. Stenoses with FFR < 0.8 were considered positive for ischemia.

Myocardial perfusion scintigraphy

The MPS was performed using the Single-Photon Emission Computed Tomography (SPECT) technique, using technetium-99m sestamibi (Tc-99m MIBI) with the 2-day protocol at rest and exercise or dipyridamole stress test. The images were semi-quantitatively analyzed using a 17-segment model. The test was considered abnormal when it disclosed evidence of one or more ischemic areas. The percentage of ischemic area was not evaluated in all patients.

Statistical analysis

A descriptive analysis of the selected patients' basal characteristics was performed by calculating medians and interquartile ranges. The assessment of the association between the presence of ischemia in the MPS and FFR was assessed using the two-tailed Fisher's exact test. A p-value < 0.05 was considered statistically significant. The STATA/MP software by StatCorp LP, version 14.2, was used for data analysis.

Results

When characterizing the sample of assessed patients, 47 individuals with stable coronary disease and a median age of 65.4 years (interquartile range between 58.03 and 69.59 years) were selected. Most were women (66%) and had stable angina (82%); and 7% were post-acute myocardial infarction.

Regarding left ventricular function, only 14% had moderate to severe dysfunction. The ejection fraction calculated by the Teichholz method showed a median of 64.5%, with an interquartile range between 45% and 71% (Table 1).

The stress assessment by MPS was performed in 68% with dipyridamole and in 32% through an exercise stress test. The interval between MPS and FFR was 24.5 days between January 2013 and October 2015.

Table 1. Patients' characteristics

Age, years	65.45 (58.03-69.59)
Female, %	65.96
Ethnicity, %	
White	63.83
Mixed-race	25.53
Black	10.64
Diagnosis, %	
Stable angina	82.98
Previous AMI	14.89
Others	2.13
SAH	91.11
Dyslipidemia	91.11
Diabetes Mellitus	42.22
Smoker	40.00
Cerebrovascular disease	8.89
Kidney failure	4.44
Sedentary lifestyle	86.67
Obesity	13.95
Family history	52.27
LVEF < 50%	14.28
EF Teichholz	64.5 (45-71)
Three-vessel anatomy or LMCA	38.80

AMI: acute myocardial infarction; SAH: systemic arterial hypertension; LVEF: left ventricular ejection fraction; EF: ejection fraction; LMCA: left main coronary artery.

In the analyzed sample of patients, 38.8% had a three-vessel lesion or had a left main coronary artery lesion. FFR was performed in the following territories: one left main coronary artery, 37 anterior descending arteries (ADA), 12 circumflex arteries and 4 right coronary arteries.

In the comparative analysis of the MPS and FFR results, 83% of the patients with positive FFR also had positive MPS, but with a non-significant p value (0.058) and 53.57% of the patients with positive MPS had a negative FFR (Figure 1).

When discriminating the assessment of the ADA territory, 83% of patients with negative FFR also had negative MPS, but in those who obtained positive FFR

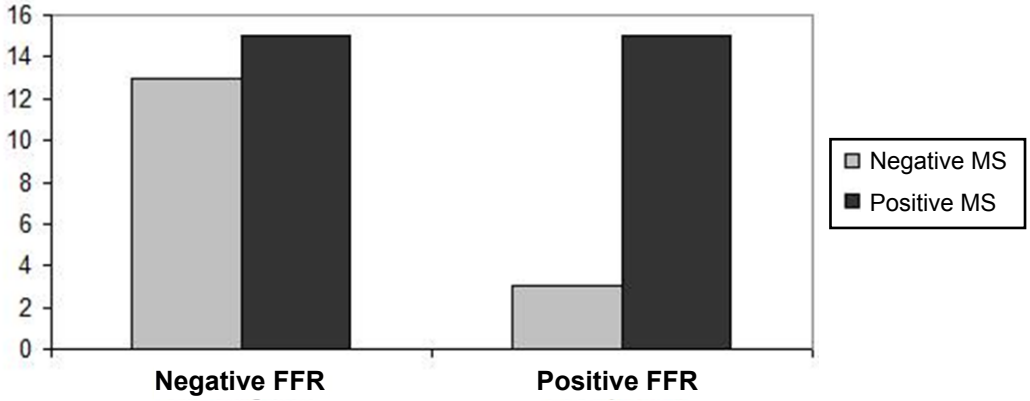

Figure 1 - *Myocardial scintigraphy (MS), according to the fractional flow reserve (FFR).*

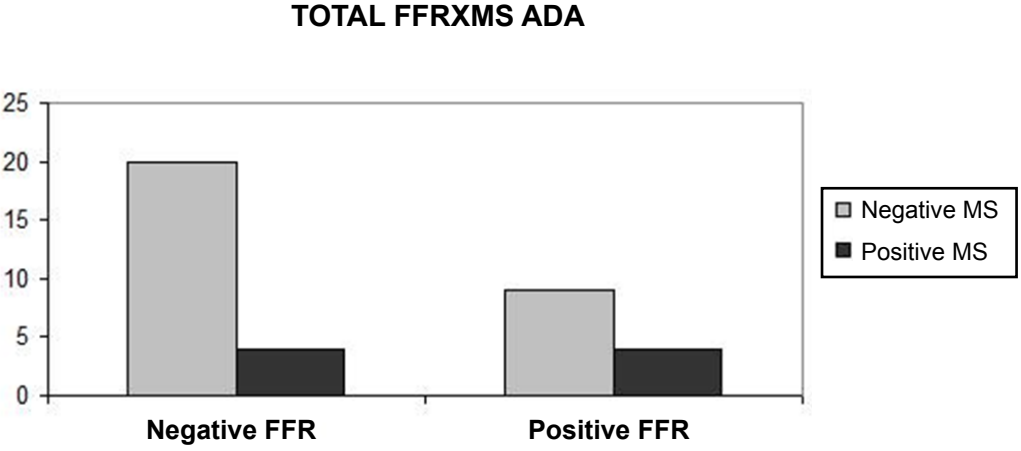

Figure 2 - *Myocardial scintigraphy (MS) in the anterior descending artery (ADA) according to the fractional flow reserve (FFR).*

results, MPS was negative in 69% – both results showed a non-significant p value (0.413) (Figure 2).

Discussion

When assessing ischemia, the agreement between MPS and FFR is a weak one.[8,9] In the present study, we observed the non-agreement between the methods, although 83% of patients with positive FFR had positive MPS; the *p* value was not significant.

Such disagreement becomes more evident in patients with multivessel disease, since MPS tends to underestimate the functional importance of the lesions.[8] The FFR reflects the pressure gradient in a single vessel; on the other hand, the MS makes a comparison of the functional stenosis severity between the vessels. The perfusion defect in MPS is defined by comparison with the region of higher perfusion, considering that this region is normal, but often it is also an altered region – although less affected.[10] In the assessed sample, 38.8 % of the patients had left main coronary artery or three-vessel disease, which may have contributed to a disagreement between the results.

Another factor to be considered regarding the agreement analysis is the presence of microvascular disease, which influences the FFR assessment,[10] although

other invasive evaluations can be performed to better quantify the microvascular disease. The coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) improve risk stratification in patients with negative FFR, being an independent prognostic factor.[11-13] The CFR represents the vasodilation capacity of the coronary vascular bed during hyperemia, being measured by thermodilution indicators. A low CFR value (≤ 2) indicates microvascular dysfunction. Additionally, the microvascular resistance index also provides data on microvascular function, being measured by through the distal coronary pressure multiplied by the mean transit time of 3 mL of saline bolus during adenosine-induced hyperemia, with the normal value being < 20, whereas the altered value is > 30.[11-13] In the total sample, the FFR was negative in 53.57% of the patients who had a positive MPS, a result that can be explained by the presence of microvascular disease, which was confirmed by the abovementioned methods.

No significant agreement was observed in the ADA-specific analysis, but 83% of the patients with negative scintigraphy also had a negative FFR.

There was no significant data on agreement or disagreement in our sample, possibly due to the number of patients studied, requiring that a larger sample be assessed.

Conclusion

Disagreements may occur between the functional analysis results of moderate coronary lesions by invasive and non-invasive tests. This fact can have important consequences in the use of the scintigraphy to establish the optimal revascularization strategy, mainly in multivessel patients. Therefore, fractional flow reserve is good technique to be used together with coronary angiography, especially in patients with multivessel lesions, since anatomic and functional stratifications can be obtained in a single procedure. Regarding patients with microvascular disease, the fractional flow reserve is not defined as an ideal strategy to evaluate ischemia.

Author contributions

Conception and design of the research: Pittella F, Paço P, Leandro SM, Felix R, Issa AFC. Acquisition of data: Paço P, Leandro SM, Tadeu J, Felix R, Issa AFC. Analysis and interpretation of the data: Pittella F, Paço P, Tadeu J, Felix R, Issa AFC. Statistical analysis: Paço P, Issa AFC. Writing of the manuscript: Paço P, Issa AFC. Critical revision of the manuscript for intellectual content: Pittella F, Felix R, Issa AFC. Supervision / as the major investigador: Leandro SM, Felix R, Issa AFC. Conducting examinations: Leandro SM, Felix R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number 5272. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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