What is the Angiography Error when Defining Myocardial Ischemia During Percutaneous Coronary Interventions?

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Summary

Background: The angiography has been used as a reference standard to define coronary artery disease (CAD), although its limitations are well-known. The significance of the myocardial fractional flow reserve (FFR) in the assessment of CAD is well established.

Objective: The aim of this study was to evaluate the accuracy of angiography when defining ischemic lesions and its correlation with FFR.

Methods: Two hundred and fifty consecutive patients (471 arteries) were included in this study. All stenoses ≥ 50% at the angiography visual estimate (AVE) were assessed by FFR measurements. When FFR was < 0.75, stenting was performed; when FFR was ≥ 0.75, no interventional treatment was carried out. Offline quantitative coronary angiography (QCA) was performed in all stenoses, which were divided in intermediate (< 70% - 327) and severe (125). The correlation coefficients between the diameter of the stenosis (%DS) and FFR and the accuracy of VA of the angiography when assessing ischemia were determined.

Results: FFR could be obtained in 452 lesions (96%). Mean %DS and FFR were 56 ± 8% and 0.74 and 76 ± 6% and 0.48 for moderate and severe stenoses, respectively. Concordance between QCA and FFR was poor, especially in intermediate stenoses (Spearman's rho = - 0.33, p<0.0001). Visual assessment resulted in an accuracy of 57% and 96% in intermediate and severe lesions, respectively.

Conclusions: Neither the visual assessment of an angiogram nor QCA can accurately predict the significance of most intermediate coronary stenoses, which emphasizes the importance of associating it to a functional evaluation of the coronary circulation, resulting in an adequate treatment of these stenoses. (Arq Bras Cardiol 2008;91(3):162-167)

Keywords: Coronary angiography; angioplasty, transluminal, percutaneous; transluminal, stents, myocardial ischemia.

Introduction

It is well known that the presence of myocardial ischemia verified at the myocardial scintigraphy is one of the most important prognostic factors in patients with coronary artery disease (CAD)[1,2]. However, many percutaneous coronary interventions (PCI) are performed based solely on angiographic criteria, without previous assessment of the existence of ischemia[3]. Additionally, despite its unquestionable qualities, the angiography presents known limitations when estimating the real severity of coronary obstructions, particularly in cases with moderate stenosis[4,5].

On the other hand, the significance of the fractional flow reserve (FFR) in defining myocardial ischemia has been largely established[6-8]. It is known that vessels that present FFR ≥0.75 can be safely treated with conservative therapies, whereas a FFR <0.75 is a sign of myocardial ischemia and the patients, in these cases, could benefit from percutaneous or surgical revascularization procedures[9-11].

The aim of this study was to assess, in all patients (and lesions) submitted to PCI at the Interventionist Cardiology Service of Santa Helena Hospital do Coracao within a certain period of time, the accuracy of the angiography visual estimate (AVE) and the quantitative coronary angiography (QAT) when identifying the lesions responsible for the myocardial ischemia, comparing their results with those obtained by FFR.

Methods

The present study included 250 patients referred for elective coronary angioplasty from October 2004 to April 2005.

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Patients with chronic coronary occlusion or angiographically significant disease in the left coronary trunk were excluded. All patients had undergone diagnostic coronary angiography two days to three weeks before the intervention.

Figure 1 shows the study design. Three independent cardiologists, blinded to the patients' symptoms, evaluated the angiographies of all patients selected for the angioplasty. They classified the coronary lesions in two categories, according to the AVE:

1) significant lesions at the AVE, of which treatment indication was angioplasty with or without stenting;

2) non-significant lesions at the AVE, of which treatment indication was not to treat. In case of lack of consensus regarding the visual impression of the cardiologists, the decision to treat or no to treat was based on the simple majority.

Cardiac catheterism and intracoronary pressure measurements

The catheterism was carried out via femoral artery, using guide catheters 6F or 7F without lateral orifices. Before the angiography, 10,000 IU of IV heparin and 0.5 mg of intracoronary nitroglycerin were administered. Subsequently, the intracoronary pressure measurements were carried out in all vessels with stenosis ≥50% at the AVE, using a 0.014" guide wire (*PressureWire® 4 Sensor*, RADI *Medical Systems, Uppsala*, Sweden) positioned at the distal bed of each coronary to be analyzed, one at a time[12]. IV adenosine was administered through the sheath placed in the femoral vein at a dose of 140 μg/kg/min to induce maximum hyperemia. FFR was determined automatically as the ratio between the mean distal pressure of the coronary and the mean pressure of the aorta (measured by the guide catheter), during maximum hyperemia[6]. All the stenoses responsible for ischemia (FFR <0.75) were treated by percutaneous intervention, as long as technically possible. Stenoses of which FFR were ≥0.75 were not submitted to PCI.

Quantitative coronary angiography (QCA) and lesion classification

The quantitative coronary angiography (QCA) was performed offline by choosing the angiographic projection in which the lesion showed to be more severe, using a software with an algorithm of automatic detection of arterial borders (CAAS II, Pie Medical Imaging, Maastricht, The Netherlands), as previously described[13].

The coronary lesions were then classified in two groups:

I) Moderate lesions: between 40% and 70% by the QCA;

2) Severe lesions: ≥70% by QCA.

Statistical analysis

All the variables were tested for normality by the Shapiro-Wilks and/or Kolmogorov-Smirnov tests. At the descriptive analysis, the numerical variables were presented as means±standard deviations (SD) and interquartiles and the categorical variables

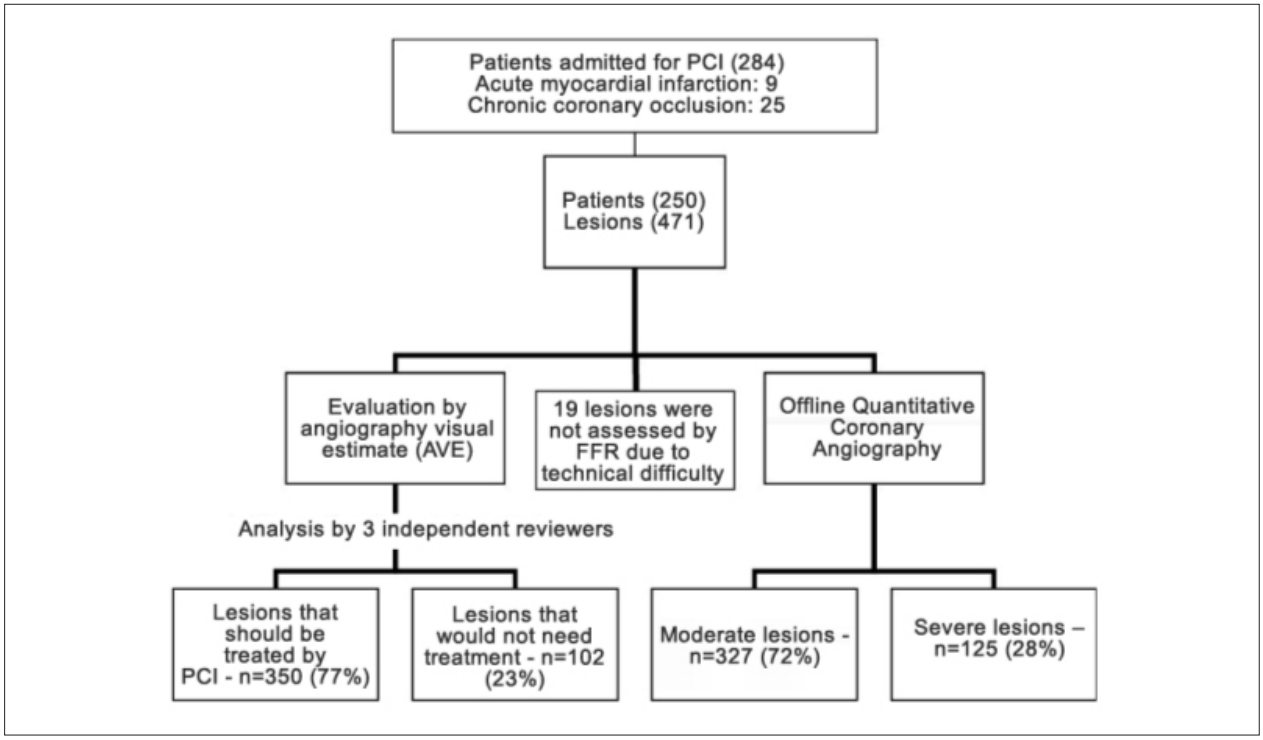

Figura 1 - General view of the study protocol and group formation. From the third level on, the numbers refer to the lesions and not to the patients. PCI: percutaneous coronary intervention.

as numbers (n) and percentages (%). The Chi-square test and Fisher's exact test were used for the categorical variables; the non-paired Student's t test and Mann-Whitney test were used for continuous variables. The angiographic characteristics and the FFR were compared between the groups with moderate and severe lesions. Spearman correlation coefficient (rho) between the QCA and the FFR was calculated for both groups. The sensitivity, specificity, positive predictive value, negative predictive value and the accuracy of the AVE when defining whether a certain lesion was responsible for ischemia were also determined, using the FFR as the reference standard. The statistical analysis was carried out with the Stata SE 9.1 program (Stata Corporation, Houston, Texas). Values of $p<0.05$ were considered statistically significant and they were all two-tailed.

Results

During a period of seven consecutive months, 284 patients were admitted at our Service to undergo coronary angioplasty with or without stenting. Of these, 9 had acute myocardial infarction (AMI) and 25 presented chronic coronary occlusion and were excluded from the study. Thus, 250 patients were included in the study.

The clinical characteristics of these patients can be seen in Table 1. Most of the patients (70%) presented stable angina and multiarterial disease (uniarterial: 30%; biarterial: 43%; triarterial: 27%). After the analysis of the FFR, the distribution of patients with significant lesions in one, two, or three vessels was altered, as shown in Figure 2.

Table 1 – Clinical characteristics of the patients

	Patients (n = 250)
Age	**61.0±10.4**
Female sex, %	37.6
Symptoms [n (%)]	
Stable angina	175 (70)
Silent ischemia	57 (22.8)
Unstable angina	18 (7.2)
Risk factors [n (%)]	
Arterial Hypertension	211 (84.4)
Dyslipidemia	120 (48.0)
Family history of CAD	102 (40.8)
Smoking	63 (25.2)
Diabetes	57 (22.5)
Previous AMI [n (%)]	121 (48.4)
Previous CTA [n (%)]	39 (15.6)
Previous MRS [n (%)]	8 (3.2)
Ejection fraction (EF) %	59±16
Multiartery disease [n (%)]	176 (70.4)

Values represented as means±SD; MRS - myocardial revascularization surgery; AMI - acute myocardial infarction; PTCA - percutaneous transluminal coronary angioplasty.

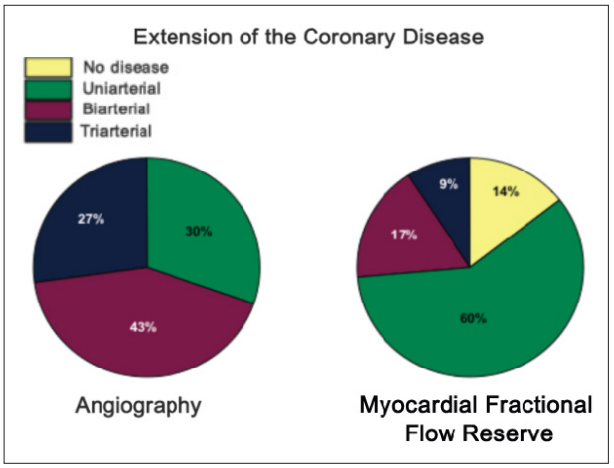

Figure 2 - Extension of the coronary disease evaluated by angiography compared to the functional extension of the disease according to the FFR.

The FFR measurement was attained successfully in 452 (96%) analyzed lesions. It was not possible to measure the FFR in 19 stenoses, due to technical problems (extreme tortuosity, unsuccessful lesion-crossing with the guide wire or very distal lesion). The angioplasty with stenting was performed in 256 stenoses related to 193 patients, with 100% of success of the procedure in this group of lesions.

Angiography visual estimate versus FFR

There was complete agreement among the cardiologists in charge of reviewing the angiographies in relation to the treatment strategy per lesion in 65% of the stenoses and disagreement in 35% of them, between one of the reviewers and the other two.

The PCI was indicated in 350 lesions based on the angiographic criterion of visual estimate of the lesion. After the measurement of the FFR, it was verified that 30% of these stenoses (105) were not responsible for ischemia (FFR ≥ 0.75) and no interventionist treatment was performed. However, the reviewer cardiologists considered that 100 stenoses did not have functional significance and should be only followed and treated with medications. The FFR measurement showed that 40% of these lesions (41) were ischemic (FFR <0.75) and needed some type of intervention when technically possible.

The capacity of the AVE in detecting myocardial ischemia, using the FFR as the reference standard, resulted in high sensitivity (85.7%), but low specificity (36.7%), positive (70%) and negative (59.8%) predictive values. The accuracy of the AVE was 68% in the group of studied lesions. When only the moderate lesions were considered, the accuracy of the AVE was 57% *versus* 96% in severe lesions. The interpretation error regarding lesion severity in moderate lesions was in both directions, that is, apparently severe lesions that showed to be harmless and lesions with benign angiographic characteristics that showed to be ischemic.

Table 2 – Angiographic and hemodynamic characteristics – analysis per lesion

	Lesions	Groups of lesions		
	(n=452)	Moderate (n=327)	Severe (n=125)	p value
Coronary artery [n (%)]				0.34
Anterior descending	215 (47.6)	162 (49.5)	53 (42.4)	0.92
Circumflex	125 (27.6)	89 (27.2)	36 (28.8)	0.26
Right coronary	112 (24.8)	76 (23.2)	36 (28.8)	0.29
ACC/AHA B2 or C [n (%)]	173 (38.3)	96 (29.3)	77 (61.6)	<0.0001
Diameter of reference (mm)	2.71 (2.34; 3.02)	2.69 (2.34; 3.06)	2.72 (2.36; 2.99)	0.88
Minimum luminal diameter (mm)	1.02 (0.76; 1.32)	1.16 (0.95; 1.4)	0.66 (0.54; 0.77)	<0.0001
Degree of stenosis (%)	62±12	56±8	76±6	<0.0001
Length of lesion (mm)	13.6 (9.1; 19.4)	13.1 (8.7; 19.0)	14.5 (9.8; 20.4)	0.06
Fractional flow reserve	0.7 (0.56; 0.81)	0.74 (0.68; 0.83)	0.48 (0.38; 0.57)	<0.0001

Values represented as means±SD; (Degree of stenosis) and median (interquartiles) – other numerical variables; ACC/AHA - American College of Cardiology/ American Heart Association.

QCA versus FFR

The angiographic characteristics of the moderate and severe lesions are shown in Table 2. An inverse correlation was observed between the degree of stenosis by QCA and the FFR (Figure 3), which was better in the severe lesions (*rho* = – 0.55; p<0.0001) then in the moderate ones (*rho* = – 0.33; p<0.0001). In the group of moderate lesions, the cutoff above which more than 90% of the lesions were ischemic was 64%; similarly, stenoses below 40% by QCA presented a low possibility of being responsible for ischemia (<10%).

In the present study, the pre-PCI minimum luminal diameter (MLD) was not a good parameter to infer ischemia. FFR values > or < 0.75 occurred in all MLD ranges.

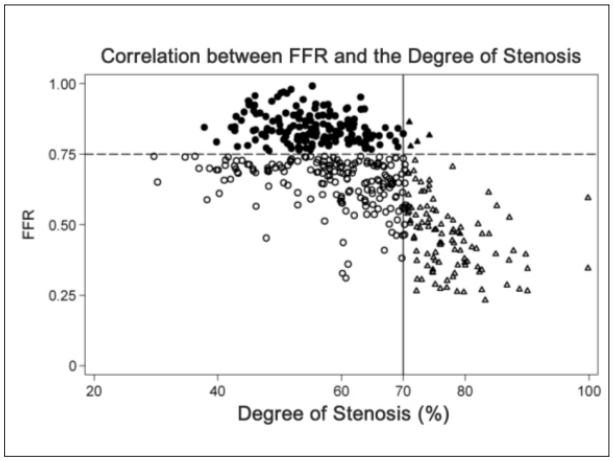

Figure 3 - Correlation between the degree of stenosis measured by QCA and the FFR. The circle corresponds to the moderate lesions and the triangle to the severe lesions. It can be noticed that, while most of the severe lesions present FFR< 0.75, indicating ischemia, the moderate lesions are distributed homogeneously above and below the FFR cutoff value (0.75).

Discussion

The results of the present study confirm the limitations of the angiography when allowing the precise identification of hemodynamically significant stenoses. This method showed to be imprecise to promote the identification of obstructions that disturb the coronary flow, especially in cases where the decrease in lumen diameter was defined as moderate, i.e., between 40% and 70% by the QCA.

Several studies have demonstrated that the treatment of patients with evidence of ischemia is beneficial and yields good mid- and long-term results; however, to revascularize based on anatomical criteria is debatable and does not seem to present any advantage in relation to the conservative treatment[1,9-11]. Considering the consensus of the American College of Cardiology/American Heart Association (ACC/AHA) to justify a PCI, it is necessary to prove the existence of ischemia[14,15]. Considering that, in many cases, the patients are referred to PCI with no objective evidence of ischemia[3] and as the FFR is an effective and specific index per lesion to indicate whether a certain stenosis is responsible for the ischemia[6-9], the present study suggests that many patients, especially the multiarterial ones, are referred to PCI without an adequate selection of the lesions to be treated, especially in the group of moderate lesions.

It is also known that the myocardial scintigraphy and other non-invasive methods to detect ischemia, although well-established, also present limitations. Lima et al[16] carried out a study in which they assessed 143 patients with triarterial CAD documented by angiography, to evaluate whether the association of ventricular function assessment with perfusion through single photon emission computed tomography (SPECT) increases the detection in multiple vascular sites. They observed that only 46% of the patients with significant triarterial disease showed a "multivascular pattern" at the SPECT. In contrast, the FFR measured in the atherosclerotic vessels in the uniarterial as well as multiarterial disease

provides the interventionist cardiologist precise functional and spatial information with an accuracy of more than 90% and can be evaluated at the same time of the coronary angiography, showing to be a cost- and time-saving measure for the patient and the health system[6-9].

The incorporation of the physiological information to the diagnosis repertoire of the interventionist cardiologist can be very useful in decision-making during PCI, especially in moderate stenoses, which are the most often found in daily practice. The FFR has been validated in experimental models as well as in studies in humans, under several different clinical conditions in recent years[8,17-19]. It is a simple, reproducible[6,7] and safe method as well as being independent from the hemodynamic state and suffer little influence of the microcirculation. Its correlation with the non-invasive methods such as myocardial scintigraphy, the dobutamine stress echo test and the stress test is very good and additionally, it has the advantage of being specific for each vessel and obstruction[8,12].

The AVE as well as the QCA are limited methods when evaluating moderate lesions. Fischer et al[4] assessed 83 moderate lesions (between 40% and 70%) and compared the angiography visual estimate and the QCA with the FFR in the detection of ischemic lesions. Their findings suggested that the AVE as well as the QCA were little effective when predicting the functional meaning of most of the moderate stenoses, especially those lesions < 60%.

These data were corroborated by the present study, which showed that moderate lesions at the angiography can induce to error, not only when the cardiologist indicates the need for revascularization in cases where there is no ischemia, but also in cases where patients with reduced myocardial perfusion do not receive the most adequate treatment. Sant'Anna et al[20], using the FFR as a routine tool in all elective angioplasties during a certain period of time, showed that 32% of the coronary lesions and 48% of the patients would have received inadequate treatment if only the AVE result had been considered, emphasizing the usefulness of the FFR measurement as an auxiliary tool in decision-making during PCI.

There are several limitations to the present study: first, it is generally considered that the patient will be submitted the coronary angiography and later to the elective PCI after undergoing some type of non-invasive test, which did not occur in most cases of the present study. However, this is the routine in many services in Brazil and other parts of the world[3] and our study aimed at reflecting the actual situation of the practice of PCI in our country. Second, the process of assessment of the coronary lesions was subjective, based on individual experiences, although it still reflects, with higher accuracy, what happens in the real world. Furthermore, the three reviewers were cardiologists with a vast experience in the field of coronary angiography. Third, the cutoff value of FFR to define ischemia was 0.75, a value that was validated based on several studies[6-8], which, in turn, analyzed only selected populations of uniarterial, non-diabetic and non-revascularized patients.

The population of the present study was more heterogeneous and included diabetic patients, with previous infarction, some who had been revascularized and probably some cases of myocardial hypertrophy. It is possible that investigations aiming at the analysis of the FFR performance in these populations, whose characteristics are more similar to those in our study, will demonstrate that the FFR values related to the presence of myocardial ischemia are different from that used in the present study, which could alter the calculation of angiography accuracy. However, these data are not available yet and therefore, we adopted the cutoff of 0.75 as the one that allowed the discrimination of the cases with and without myocardial ischemia.

Conclusion

The present study showed that the coronary angiography has reduced diagnostic accuracy for the detection of ischemia in moderate lesions, clearly demonstrating the need to associate it to a functional method capable of correctly managing the treatment of these stenoses. However, angiographically demonstrated lesions (at the QCA) have high association with the presence of ischemia.

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

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