Fractional Flow Reserve by Tomography Diagnostic Performance in the Detection of Coronary Stenoses Hemodynamically Significant

Desempenho Diagnóstico da Reserva de Fluxo Fracionado Por Tomografia na Detecção de Estenoses Coronárias Hemodinamicamente Significativas

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Abstract

Background: Coronary computed tomography angiography is a noninvasive anatomic test for the diagnosis of coronary artery disease. The coronary fractional flow reserve is the gold standard method to determine if coronary stenosis is hemodynamically significant but requires an invasive procedure. Fractional flow reserve measurement by tomography is a new method to determine the hemodynamic significance of coronary luminal reduction.

Objective: To compare the accuracy of the invasive fractional flow reserve with the fractional flow reserve measurement by tomography.

Method: Patients submitted to invasive coronary computed tomography angiography and fractional flow reserve were included in the study. Flow-restricted stenosis was defined by fractional flow reserve measurement by tomography and fractional flow reserve $\leq$ 0.8, and anatomically significant coronary artery disease was defined as stenosis $\geq$ 50%. Diagnostic performance of fractional flow reserve measurement by tomography and stenosis by coronary computed tomography angiography was accessed with invasive fractional flow reserve as the gold standard.

Results: Among the patients, 33% had fractional flow reserve $\leq$0.8. There was no significant difference between the fractional flow reserve measurement by tomography and fractional flow reserve averages (0.87 versus 0.84; $p = 0.4$). The correlation between the values of the methods was $r = 0.77$, and concordance was moderate ($k = 0.54$). When fractional flow reserve $\leq$ 0.75 was analyzed, the concordance between the methods was absolute. The sensitivity, specificity, positive predictive value and negative predictive value of fractional flow reserve measurement by tomography were, respectively, 50%, 100%, 100% and 75%, for the threshold of 0.8. The mean difference between fractional flow reserve and fractional flow reserve measurement by tomography was -0.033 (95%CI -0.072-0.007), with concordance limits between -0.176 and -0.1111.

Conclusion: Fractional flow reserve measurement by tomography is a new method with high diagnostic performance in the detection of hemodynamically significant coronary stenoses and significantly elevates the specificity of the isolated coronary computed tomography angiography.

Keywords: Coronary Disease; Myocardial Ischemia; Diagnostic Imaging; Tomography.

Resumo

Fundamento: *A angiotomografia de coronárias é um teste anatômico não invasivo para diagnóstico de doença arterial coronariana. A reserva de fluxo fracionado coronariano é o método padrão-ouro para determinar se a estenose coronariana é hemodinamicamente significativa e requer procedimento invasivo. A mensuração da reserva de fluxo fracionado por tomografia é um novo método para determinar a significância hemodinâmica da redução luminal coronária.*

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Objetivo: *Comparar a acurácia da reserva de fluxo fracionado invasiva com a reserva de fluxo fracionado por tomografia.*

Método: *Pacientes submetidos à angiotomografia de coronárias e à reserva de fluxo fracionado invasiva foram incluídos neste estudo. Estenose com limitação de fluxo foi definida por reserva de fluxo fracionado por tomografia e reserva de fluxo fracionado ≤ 0,8. Doença arterial coronariana anatomicamente significativa foi definida por estenose ≥ 50%. O desempenho da reserva de fluxo fracionado por tomografia e da estenose pela angiotomografia de coronárias foi acessado com a reserva de fluxo fracionado invasiva como padrão-ouro.*

Resultados: *Dentre os pacientes, 33% tinham reserva de fluxo fracionado ≤ 0,8. Não houve diferença significativa entre as médias de reserva de fluxo fracionado por tomografia e reserva de fluxo fracionado (0,87 versus 0,84; p=0,4). A correlação entre os valores dos métodos foi r = 0,77, com concordância moderada (k=0,54). Quando analisada a reserva de fluxo fracionado ≤ 0,75, a concordância entre os métodos foi absoluta. Sensibilidade, especificidade, valor preditivo positivo e negativo da reserva de fluxo fracionado por tomografia foram, respectivamente, 50%, 100%, 100% e 75%, para o limiar de 0,8. A média da diferença entre reserva de fluxo fracionado e reserva de fluxo fracionado por tomografia foi de -0,033 (IC95% -0,072-0,007), com limites de concordância entre -0,176 e -0,111.*

Conclusão: *A reserva de fluxo fracionado por tomografia é um novo método, com alto desempenho diagnóstico na detecção de estenoses coronárias hemodinamicamente significativas, e eleva significativamente a especificidade da angiotomografia de coronárias isolada.*

Palavras-chave: *Doença das Coronárias; Isquemia Miocárdica; Diagnóstico por Imagem; Tomografia.*

Introduction

Coronary computed tomography angiography (CCTA) is a noninvasive test that enables the direct visualization of coronary artery disease (CAD). CCTA has a high negative predictive value (NPV), and although it presents a good correlation with coronary angiography (CAG) regarding degree of stenosis, its specificity decreases as the degree of CAD increases with coronary calcification and diffuse disease. It does not identify the hemodynamic repercussions of these injuries[1,2].

In this sense, based on the evidence from randomized clinical studies that identified no benefits for the survival of patients undergoing revascularization exclusively by anatomical analysis[3,4], the current guidelines suggest the anatomical-functional approach for coronary revascularization.

For this purpose, coronary fractional flow reserve (FFR) is the gold standard method for measuring the hemodynamic repercussions of coronary stenosis, which is measured by the ratio between the mean pressure distally to the coronary stenosis and the mean aortic pressure during maximum flow (hyperemia), resulting in the identification of lesions that restrict downstream blood flow. Previous studies reported that the use of FFR to guide revascularization decreased combined clinical events (death, non-fatal infarction, repeated revascularizations) and urgent revascularizations[5,6] in addition to being cost-effective[7]. Despite robust results, the use of FFR is not part of the daily routine in hemodynamics laboratories[8] due to the additional cost, need to use drugs to induce hyperemia, and invasive nature of the procedure[9].

FFR measurement by computed tomography (FFRct) is a new noninvasive method of determining the hemodynamic significance of coronary luminal reduction with the same tomographic images used to assess anatomy. Multicentric studies showed the incremental diagnostic value of CCTA[10-12] by reducing unnecessary CAG[13]. This study aimed to compare the accuracies of invasive FFR versus FFRct calculated at the examination center.

Method

Patients undergoing CCTA and invasive FFR during an interval of up to three months between October 2016 and July 2017 were included in the study. Cases of previous coronary revascularization, a poor-quality CCTA image, and high rate of coronary calcification were excluded.

CCTA was performed on a CT scanner with two X-ray sources (Somatom Definition Flash, Siemens AG Healthcare, Forchheim, Germany). Collimation was 2 × 64 × 0.6 mm (two array detectors with 64 0.6-mm-thick detector rows) with a gantry rotation time of 280 ms. The z-axis was applied, resulting in the acquisition of 2 × 128 slices per rotation. All patients received sublingual nitrate 5 mg. Oral or intravenous beta block (metoprolol tartrate) was used to reach a heart frequency of 60 bpm if inicial heart rate was above 70 bpm.

The FFRct analysis was performed using syngo.via Frontier cFFR 3.1 software (Siemens AG Healthcare). This is a console-based procedure that uses machine-learning techniques and big data from coronary databases and features quick performance and results (~20–30 min). The model uses both anatomical and physiological data to calculate FFRct. The coronary tree anatomy and the left ventricle myocardium are derived from a standard CCTA. A three-dimensional coronary tree is used to semi-automatically segment a lumen model and calculate the myocardial mass. Coronary flow at rest is estimated by the principles of allometric laws that describe the relationship between form and function[14]. In the next step, vascular resistance is calculated using a parameter estimation process[15].

The algorithm simulates coronary flow using principles of fluid dynamics. Different methods are used in non-stenotic arteries and stenotic regions. Hyperemia can be simulated by changing the computational parameters (reducing the coronary resistance index). Thus, virtual FFR values can be calculated over the entire coronary territory.

Catheterization was performed via the femoral approach using 6F or 7F guide catheters. After appropriate calibrations and equalizations were made, under full heparinization and with the intracoronary administration of nitroglycerin, the 0.014″ guidewire (Pressure-Wire CERTUS, St. Jude) was positioned in the distal end of the target vessel to measure intracoronary pressure in all vessels with a stenosis ≥ 50%. Adenosine was administered by continuous infusion (140 mcg/kg/min) to induce maximum hyperemia. The FFR was automatically determined as the ratio between the distal mean coronary pressure and the mean aortic pressure during maximum hyperemia measured with a guide catheter.

Independent observers analyzed the stenosis by CCTA, FFRct, and invasive FFR. Flow-limiting stenosis was defined by FFRct and FFR ≤ 0.8, while anatomically significant CAD was defined as stenosis ≥ 50%.

The diagnostic performance of FFRct and stenosis by CCTA was assessed with invasive FFR as the gold standard.

Categorical variables are expressed as percentages, while continuous variables are expressed as mean ± standard deviation. The relationship between FFR and FFRct was quantified using a correlation coefficient. The concordance between methods was assessed by Bland-Altman analysis. FFRct performance was analyzed using sensitivity (SE), specificity (SP), positive values (PPV), negative predictive values (NPV), and accuracy (percentage of patients correctly diagnosed by FFRct). P values < 0.05 were considered statistically significant.

Results

A total of 36 patients underwent CCTA and FFR between October 2016 and July 2017. Of them, 21 were excluded: 11 with previous revascularization, six with a high coronary calcification index (Agatston calcium score > 1200), and four with image artifacts that limited the FFRct analysis.

The 15 patients included in the study had a mean age of 59 years, were predominantly male (93%), and presented a mean calcium score of 337. The anterior descending artery was the most commonly analyzed vessel (73%) (Table 1).

CCTA showed that 66% of the stenoses analyzed by FFRct were moderate, three were major (20%), one was mild, and one was minimal (Figure 1). CAG showed that 80% of the stenoses were classified as moderate versus 20% as mild.

Of the total number of patients analyzed (n = 15), 33% had an FFR ≤ 0.8 (Table 2). There was no significant difference between the mean FFRct and FFR (0.87 × 0.84, p = 0.4). The two cases of mild and minimal stenosis detected by CCTA showed no hemodynamically significant stenosis by FFR and FFRct. The correlation between the values of the methods was r = 0.77 (Figure 2), while the concordance was moderate (k = 0.54). The concordance between methods was absolute at an FFR ≤ 0.75.

The SE, SP, PPV, and NPV of the FFRct for hemodynamically

Table 1 - Patient and lesion characteristics.

	Age	Sex	FFR	FFRtc	Vessel	CT reduction	CAG reduction	Calcium score
1	55	M	0.66	0.7	DA	4	3	410.8
2	66	M	0.8	0.89	CD	4	3	138.2
3	68	M	0.79	0.93	DA	3	3	742.8
4	46	M	0.65	0.72	DA	3	3	817.1
5	55	M	0.67	0.7	DA	3	3	1.037.2
6	60	M	0.94	0.98	CX	3	3	4.8
7	58	M	0.85	0.95	DA	3	3	373.7
8	56	M	0.98	0.95	CD	3	3	34
9	47	M	0.96	0.94	DA	3	2	117.9
10	55	M	0.92	0.91	CX	2	3	557.5
11	46	M	0.89	0.92	DA	3	2	46.9
12	76	F	0.93	0.82	DA	1	2	126,4
13	59	M	0.79	0.93	DA	4	3	29.6
14	79	M	0.89	0.82	DA	3	3	292.6
15	62	M	0.92	0.97	DA	3	3	329.6

Luminal reduction by CT and CAG: 4 = severe luminal reduction, 3 = moderate luminal reduction, 2 = mild luminal reduction, and 1 = minimal luminal reduction. CAG, coronary angiography. CD, right coronary artery. CT, computed tomography. CX, circumflex artery. DA, descending artery. F, female. FFR, fractional flow reserve. FFRct, FFR on computed tomography. M, male.

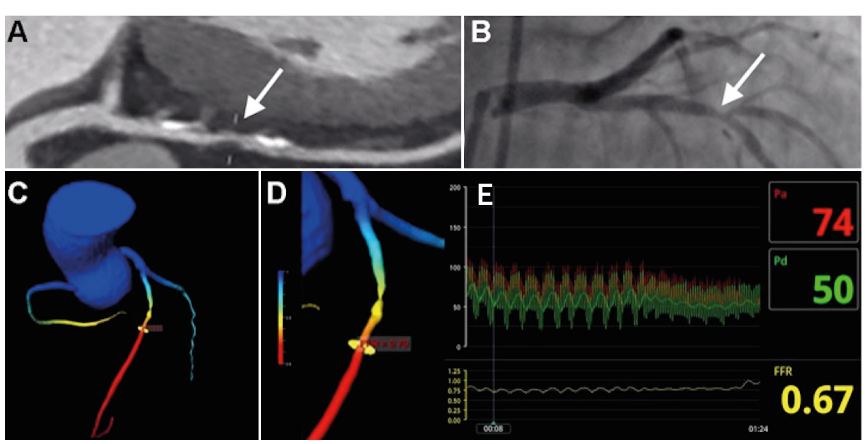

Figure 1 – *A - Anterior descending artery with mixed plaque and significant stenosis. B - CAG image confirming significant stenosis. C and D - FFRct images showing a value of 0.7 post-stenosis. E - FFR pressure curves with a value of 0.67. CAG, coronary angiography; FFR, fractional flow reserve; FFRct, FFR measured on computed tomography.*

significant injuries were 50%, 100%, 100%, and 75%, respectively, for a threshold of 0.8. The diagnostic performance of CCTA for hemodynamically significant lesions presented an SE of 100%, SP of 22%, PPV of 46%, and NPV of 100%. The CCTA accuracy was 53% but increased to 86% when associated with FFRct (p = 0.003).

The Bland-Altman analysis (Figure 3) showed that the mean difference between FFR and FFRct was -0.033 (95% confidence interval, -0.072 to 0.007) with a concordance threshold of -0.176 to -0.111.

Discussion

In this cohort of patients undergoing CCTA and CAG with FFR, the diagnostic accuracy of FFRct was superior to that of CCTA for detecting hemodynamically significant lesions determined by the standard reference for invasive FFR. The FFRct increased the capacity of a differential diagnosis for lesions that cause ischemia versus isolated CCTA analysis, especially in lesions with moderate stenosis.

CCTA has been increasingly used as a noninvasive method to investigate CAD with high diagnostic performance compared to CAG[1]. However, the method has a slightly reduced specificity compared to its high sensitivity due to overestimating the degree of stenosis; considering significant stenoses subsequently confirmed by CAG, only a few cause ischemia[16].

This anatomical-physiological discordance is not restricted to CCTA analyses. The nuclear sub-study of the COURAGE study showed that only 32% of patients had moderate to severe ischemia, while 40% had mild or no ischemia on single photon emission CT, with all presenting coronary lesions with significant stenosis on CAG[17]. This scenario shows that, even in cases of severe stenosis, other factors interfere with the onset of ischemia.

Thus, the confirmation of revascularization using only on an anatomical evaluation is limited. The Prospective Multicenter Imaging Study for Evaluation of Chest Pain study showed that the evaluation strategy based on CAG findings was safe and clinically effective. However, there was an increase in the rate of CAG and revascularization of about 50% compared to that of functional tests with no difference in clinical outcomes. Most interventions may have been performed in stenoses without hemodynamic repercussions, that is, not causing ischemia[18].

The inclusion of the physiological measure of stenosis by FFR to CAG was clinically and economically efficient[5]. In the FAME study, the group of patients undergoing revascularization based on an anatomical-functional assessment (CAG with FFR) had better event-free survival than those undergoing revascularization based only on anatomical assessment. This approach has been considered the gold standard for decision-making on coronary revascularization.

However, the invasive nature of the procedure has inherent risks. FFRct, as a noninvasive method not requiring new procedures during image acquisition, is a promising tool in the diagnostic arsenal of cardiology.

The DISCOVER-FLOW study, the first to validate this method, included 103 patients and 159 vessels and reported that FFRct presented an accuracy of 0.84 for

Table 2 – Participant characteristics.

	All patients (N = 15)	
Age	59 ± 9.8	
Male sex	14 (93.3%)	
FFR	0.84 ± 0.11	
FFRtc	0.87 ± 0.09	
Vessel	11 DA (73.33%) 2 CX (13.33%) 2 CD (13.33%)	
	CT	CAG
Luminal reduction	3 severe (20%) 10 moderate (66.6%) 1 mild (6.6%) 1 minimal (6.6%)	0 severe 12 moderate (80%) 3 mild (20%) 0 minimal
Calcium score	337.27 ± 322.44	

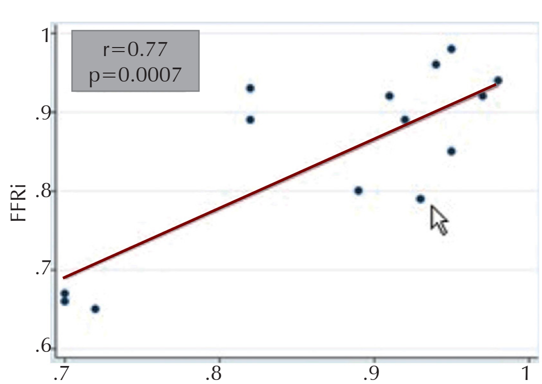

Figure 2 – *Linear regression of FFRct and FFR.*

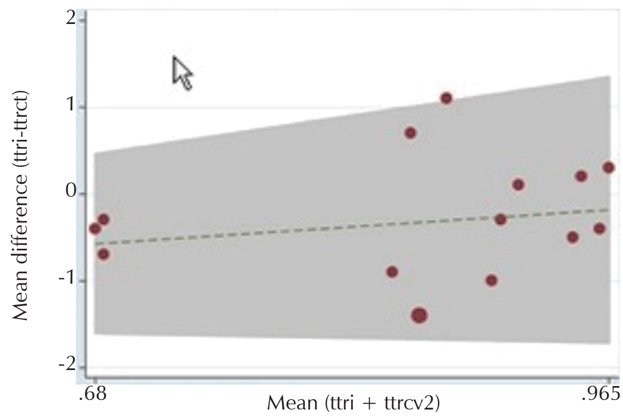

Figure 3 – *Bland-Altman analysis.*

detecting hemodynamically significant lesions, while CCTA has an accuracy of 0.58, results that corroborate those of the present study, which reported an accuracy of 0.86 for FFRct and of 0.53 for CCTA[10]. Subsequently, the DeFACTO study evaluated whether FFRct associated with CCTA could improve the diagnostic accuracy per patient and reported that 54.4% of the patients presented with an FFR < 0.8 and that the area under the ROC curve increased from 0.68 to 0.81 with CCTA and FFRct, respectively[11]. The results of the multicenter Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) study were also presented[12]. The NXT study included 254 patients and reported that FFRct had high accuracy (0.9) and provided a differential diagnosis for hemodynamically significant stenoses. The sensitivity and specificity for identifying myocardial ischemia were 86% and 79% for FFRct, 94% and 34% for CCTA, and 64% and 83% for CAG, respectively.

In these studies, the FFRct calculation was based on the principles of fluid dynamics. This technique based on fluid dynamics uses complex mathematical algorithms to create a three-dimensional computational model derived from CCTA images. Supercomputers and long hours were needed to solve these equations, which required a specialized and independent laboratory. The present study used a new software model with machine-learning intelligence. The FFRct analysis, now incorporated into the workstation where the CCTA is analyzed, is becoming fast and practical (about 30 minutes). In addition, it has easy clinical applicability since it does not require additional procedures, such as new image acquisition, protocol modification, medication administration, exposure to additional radiation, and additional contrast administration.

Despite the excellent diagnostic performance of FFRct with a cutoff point <0.8, this value is questionable. Considering a cutoff point of 0.75 in this small study population, the accordance was absolute for excluding or confirming flow-limiting coronary stenoses. Kruk et al.[19] reported that the ideal cutoff point for identifying lesions with FFR < 0.8 was an FFRct < 0.75. The SP and PPV increased from 72% to 93% and 68% to 85%, respectively, when FFRct had cutoff points of 0.8 and 0.75.

The limitation of this method should also be considered. The accuracy of the FFRct measurement is highly dependent on image quality. As a result, examinations of the coronary arteries with contours not defined by movement artifacts have impaired analyses and are often unable to analyze the FFRct. A high degree of calcification also limits the FFRct evaluation. Since the presence of coronary calcification often leads to an overestimation of the volume of calcium due to shadow or beam-hardening artifacts that obscure the vessel lumen, the real edges of the atherosclerotic plaque are not visualized; therefore, there is a tendency to determine luminal stenosis in this segment.

In the present study, a total of ten patients were excluded due to the aforementioned limitations, corresponding to 47.6% of the excluded patients. This may reflect limited use of the method in older equipment, which require a longer acquisition time, are more susceptible to movement artifacts, and are available in tertiary and quaternary services, where patients tend to have more coronary atherosclerotic disease.

However, a study comparing diagnostic accuracy in patients with a high coronary calcification index and patients with a low calcium score showed no difference in diagnostic accuracy[20]. The patients were allocated to quartiles according to the Agatston calcium score, and there was no statistical difference in FFRct diagnostic accuracy, SE, and SP between the different quartiles in the analysis by patient and that by vessel. The area under the ROC curve for patients with calcium scores of 416–3,599 was 0.86 (95% confidence interval, 0.76–0.96), while that for patients with calcium scores of 0–415 was 0.92 (95% confidence interval, 0.88–0.96) (p = 0.45). FFRct accuracy and SP were significantly superior to those of the stenosis quantification analysis to determine flow-limiting coronary lesions in all quartiles per patient (p < 0.001) and per vessel (p < 0.05) with similar SE. Despite the good results, this is a single study and a subgroup analysis, and further studies are necessary to extrapolate this result.

Furthermore, this study is an initial analysis of software not yet available in clinical practice; thus, it has inherent limitations. It was a single-center study with a small sample methodologically inferior to previous studies. Therefore, numerical comparisons should be interpreted with caution. More robust studies with higher methodological power are needed to confirm the diagnostic accuracy of this new method and better establish the ideal value of FFRct to ensure its cost-effective and safe clinical use.

Conclusion

FFRct is a new diagnostic method with potential to improve the diagnostic accuracy of CCTA for detecting hemodynamically significant coronary stenoses. FFRct significantly increased the SP of isolated CCTA, allowing the exclusion of hemodynamically significant lesions, especially in cases of moderate stenoses.

Authors' contributions

The authors of this study participated in the conception and design of the research, data collection, data analysis and interpretation, statistical analysis, manuscript writing and critical review. No funding was received in support of this study.

Conflict of interest

The authors have declared that they have no conflict of interest.

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