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Review article

Interpreting results of coronary computed tomography angiography-derived fractional flow reserve in clinical practice

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ABSTRACT

The application of computational fluid dynamics to coronary computed tomography angiography allows Fractional Flow Reserve (FFR) to be calculated non-invasively (FFR_{CT}), enabling computation of FFR from coronary computed tomography angiography acquired at rest both for individual lesions as well as along the entire course of a coronary artery. FFR_{CT}, validated in a number of accuracy studies and a large clinical utility trial, is beginning to penetrate clinical practice. Importantly, while accuracy trials compared FFR_{CT} to invasively measured FFR at a single point in the coronary tree, clinical reports of FFR_{CT} provide information regarding a patient's entire coronary vasculature. Specifically, in distal coronary segments, calculated FFR_{CT} values may be low and below 0.80 even in the absence of localized stenoses within the course of the artery. As a result, the reporting physician needs to understand how to interpret the findings in a clinically useful and thoughtful fashion. This review provides a brief overview of the background of both invasively measured and computationally derived FFR, explains changes in FFR along the course of normal coronary arteries and those affected by coronary atherosclerosis, and outlines the relevance of measurement location when interpreting and reporting FFR and FFR_{CT} results.

1. Introduction

Fractional flow reserve (FFR) is the current gold standard for the invasive assessment of lesion-specific ischemia and to guide revascularization in patients with stable ischemic heart disease.[1,2] The application of computational fluid dynamics (CFD) to coronary computed tomography angiography (coronary CTA) allows FFR to be calculated non-invasively, providing information on FFR both specific to a coronary lesion and also along the entire epicardial coronary artery tree based on coronary CTA data sets acquired at rest.[3] FFR derived from coronary CTA datasets (FFR_{CT}) has been validated through a number of accuracy studies and a large clinical

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utility trial.[4–9]

Importantly, in accuracy trials single measurements at specified locations within the coronary artery tree (typically, distal to a stenosis) were compared between non-invasive FFR_{CT} and invasive FFR. However, the clinical use of FFR_{CT} provides caretakers with FFR values along the entire course of the epicardial coronary arteries, including vessels without localized stenosis. As a result, the reporting physician needs to understand how to interpret the reported FFR_{CT} values at various locations in a clinically useful and thoughtful fashion. This review provides a brief overview of the science and clinical utility of both invasively measured and computationally derived FFR, outlines implications of interpreting FFR_{CT} across the entire length of a coronary artery, and provides case examples to illustrate the interpretation of FFR_{CT} both in straightforward and complex situations.

2. Science and background of FFR

FFR is the ratio of pressure distal to a stenosis to pressure in the aorta, measured under conditions of maximal coronary hyperemia. With the understanding that pressure is directly proportional to flow, FFR represents the ratio of maximum blood flow in a stenotic artery to maximum blood flow in the same artery if it were normal. An FFR value of 0.93 means the myocardium is receiving 93% of the blood flow it would receive if the vessel were entirely normal. While anatomic percent stenosis is evaluated at the location of the lesion, FFR is measured distal to a stenosis and measures the cumulative impact of all disease proximal to the measurement location.

Studies comparing invasive FFR or FFR_{CT} to anatomical imaging, including quantitative coronary angiography, coronary CTA or intravascular ultrasound, have consistently demonstrated an unreliable relationship between anatomic measures of stenosis and lesion-specific ischemia.[10,11] Even severe stenoses do not always result in significant pressure gradients, and a significant percentage of intermediate lesions do not cause ischemia. In a study of over 1300 coronary artery lesions, 65% of all stenoses with 50%–70% diameter reduction and 20% of all stenoses with 71%–90% diameter reduction were not hemodynamically significant ($FFR \leq 0.80$).[12] Furthermore, 33% of lesions graded between 31% and 50% and 13% of lesions graded between 0% and 30% diameter stenosis had FFR values ≤ 0.80.[13]

The DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) study evaluated patients with single-vessel disease and demonstrated that deferring revascularization for patients with $FFR > 0.75$ was safe with 15 year follow-up data.[14] FAME I (Fractional Flow Reserve versus Angiography for Guiding percutaneous coronary intervention [PCI] in Patients with Multivessel Coronary Artery Disease) and FAME II trials studied patients with multivessel disease and found that an FFR-guided revascularization strategy in relation to symptom relief, clinical outcomes and costs was superior to angiography-guided PCI.[15,16] FAME I demonstrated a significant reduction in major adverse cardiovascular events when deferring revascularization in lesions with FFR values > 0.80. FAME II found that PCI in lesions with FFR values < 0.80 decreased the need for urgent revascularization. Recently, it was shown that deferring invasive coronary angiography (ICA) in patients with $FFR_{CT} > 0.80$ had favorable prognosis.[17] In addition, the lower the FFR value, i.e. the depth of ischemia, the greater the risk of clinical adverse events.[18] In addition, lesions with lower FFR values receive greater benefit from revascularizaton.[19]

FFR may have a differential impact depending on value and stenosis location. For example, a proximal left anterior descending (LAD) 70% diameter stenosis with an FFR value of 0.78 portends a different prognosis compared to a distal LAD lesion with an FFR value of 0.78.[20] This is likely secondary to the larger extent of myocardium at risk in the proximal LAD lesion.

Accordingly, both anatomy and physiology are important when considering the clinical significance of a coronary lesion. When interpreting coronary CTA and FFR_{CT} analysis the interpreting physician needs to address the following clinical questions:

- Is there a coronary stenosis anatomically amenable to revascularization by PCI or coronary artery bypass graft (CABG) surgery?
- Does the stenosis result in a significant pressure gradient across the lesion thereby causing lesion-specific ischemia?

3. Non-invasive FFR derived from coronary CTA

The scientific basis for FFR_{CT} has been described in detail by Taylor et al.[3] Computation of FFR_{CT} involves (a) construction of an accurate patient-specific 3D anatomic model of the epicardial coronaries, (b) specifying microcirculatory models for coronary blood flow during maximal hyperemia and (c) performing a computational solution of the laws of physics governing fluid dynamics.

While not currently commercially available, there is growing data evaluating the diagnostic performance of reduced order models and 1D processing of the image data without the use of supercomputers for coronary CTA-derived FFR.[21–24] These algorithms will require more extensive testing prior to clinical use and require physician work effort to produce the anatomical models needed (approximately 1 h) with average computational run times of 10–52 min but offer the potential for onsite solutions.[23]

4. Defining significant FFR_{CT} values

The hemodynamic significance of coronary lesions has been defined in clinical trials at FFR thresholds ranging from 0.75 to 0.80.[15,16,25] Coronary stenoses with FFR values < 0.75 are most often associated with signs of ischemia whereas lesions with FFR values > 0.80 are rarely associated with inducible ischemia. FFR values between 0.75 and 0.80 have been described as a “gray zone” or borderline.[26,27]

5. Diagnostic performance and outcomes of FFR_{CT}

To date, three prospective multicenter clinical trials on diagnostic accuracy of FFR_{CT} using invasive FFR as the reference standard have been completed, with the most recent NXT trial reporting per-vessel sensitivities and specificities of 84% and 86%, respectively.[4–6] In the invasive arm of the recent prospective PLATFORM (Prospective LongitudinAl Trial of FFRCT: Outcome and Resource Impacts) clinical utility trial, a diagnostic strategy guided by FFR_{CT} resulted in cancellation of 61% of previously planned ICA without any subjects with ICA canceled experiencing an adverse event in 1 year follow-up.[7] As well, the use of a combined coronary CTA and FFR_{CT} strategy resulted in a reduction in the incidence of ICA showing non-obstructive disease by 83%. Importantly, this was done while both reducing health care costs and improving the quality of life of the patients enrolled.[7–9] To optimize the diagnostic accuracy and clinical utility of FFR_{CT}, coronary CTA image acquisition should follow current, accepted acquisition guidelines particularly focusing on heart rate control and nitroglycerine-mediated coronary dilatation.[28]

6. Interpretation of FFR_{CT} values

Non-invasive FFR_{CT} provides FFR values throughout the coronary tree. Values distal to stenoses as well as the lowest FFR_{CT} value

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at the distal end of each vessel are derived. This is distinct from invasive FFR where pressure measurements are usually recorded and reported only at a single point distal to a focal lesion and not in very distal vessel segments. FFR_{CT} assesses FFR_{CT} drop along the length of vessels even in the absence of focal stenoses, as well as gradients along the length of coronary arteries with diffuse atherosclerosis. Despite these differences, the primary role of FFR_{CT} both clinically and as evaluated in clinical trials, is to act as an alternative to invasive FFR by evaluating the FFR_{CT} distal to a focal stenosis (Figs. 1 and 2).

De Bruyne and colleagues have reported that diffuse coronary artery disease (CAD) without focal stenosis, which is frequently read as a "normal" coronary angiogram, may cause a continuous pressure drop along the vessel length leading to ischemia.[29] Their data highlight that diffuse disease even without focal obstructive disease can be hemodynamically significant. Among patients with normal coronary arteries with no CAD by ICA, they showed that the FFR value in the distal LAD was >0.90. Appropriate management of diffuse CAD with progressive pressure loss (FFR_{CT} drop) along the length of a vessel without a focal treatable lesion is not straightforward and will require further investigation including clinical registries and studies providing insight into clinical outcomes (Fig. 3).

At present, the lowest FFR_{CT} value at the distal end of the coronary vessel should not be used alone when considering referral for ICA. Clinical decision making should incorporate additional information such as anatomy, presence and location of stenoses, vessel size, suitability for revascularization, other FFR_{CT} values, patient symptoms, and clinical judgment. A precipitous drop in FFR_{CT} across a focal anatomic stenosis suggests the presence of lesion-specific ischemia, particularly if the FFR_{CT} value is $\leq$ 0.75. On the other hand, a gradual decrease in FFR_{CT}, without a focal stenosis, particularly for borderline or "gray zone" values (0.76–0.80), warrants consideration of other possibilities (diffuse CAD, serial lesions, small vessel size relative to myocardial mass, inadequate nitrate response) (Fig. 4). The ability to interrogate the impact that each

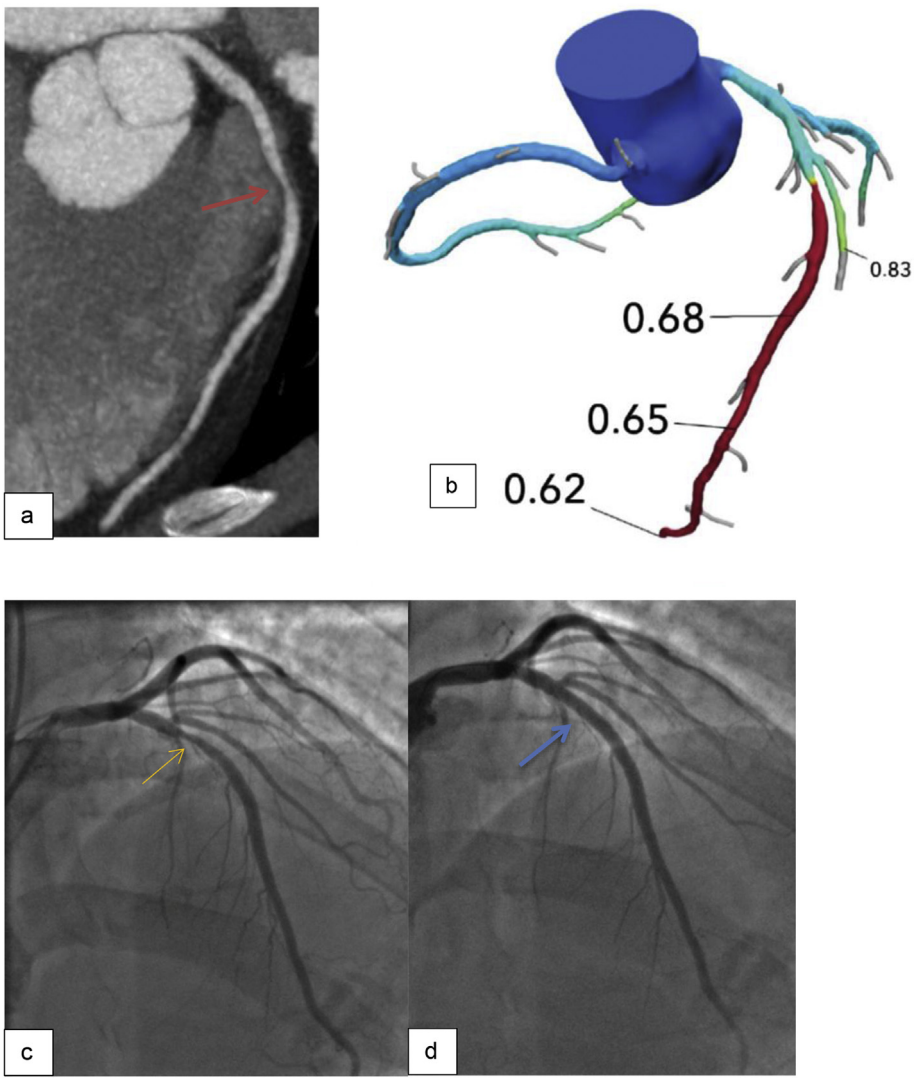

Fig. 1. Hemodynamically significant lesion of intermediate stenosis degree. 55-year-old caucasian male with hypertension and dyslipidemia presented with stable chest pain and an abnormal resting EKG. Multiplanar reformat of coronary CTA of the LAD **(a),** FFR_{CT} **(b)** and ICA pre-**(c)** and post-**(d)** PCI. Interpretation: LAD demonstrates a mid-non-calcified moderate stenosis **(red arrow)** that is hemodynamically significant. FFR_{CT} distal to the stenosis was 0.68. The patient underwent successful PCI **(blue arrow)** of the mid-LAD stenosis **(orange arrow)**. FFR_{CT} indicates fractional flow reserve derived from coronary computed tomography angiography (coronary CTA) datasets; EKG, electrocardiogram; ICA, invasive coronary angiogram; LAD, left anterior descending artery; PCI, percutaneous coronary intervention. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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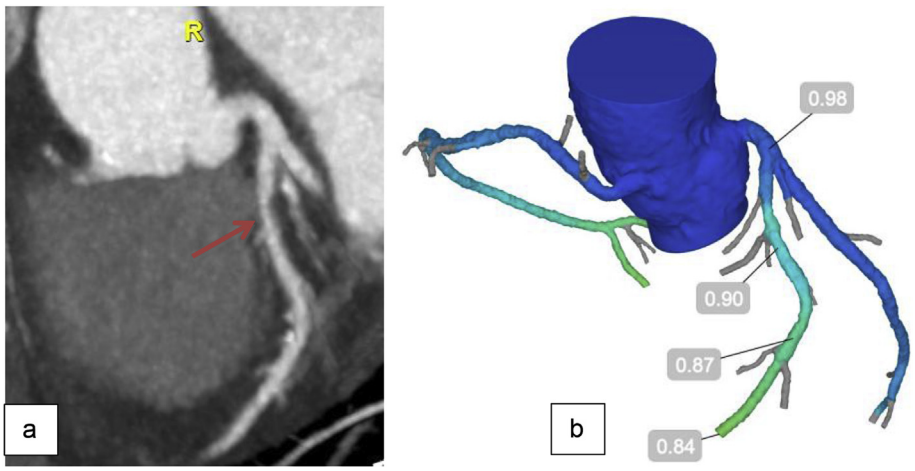

Fig. 2. Hemodynamically insignificant intermediate lesion. 78-year-old caucasian female presenting with dyspnea on exertion and non-specific EKG changes. Multiplanar reformat of coronary CTA of the LAD **(a)** and FFR_{CT} **(b)**. Interpretation: LAD demonstrates a proximal non-calcified moderate stenosis **(red arrow)** that is not hemodynamically significant. FFR_{CT} distal to the stenosis was 0.90. The patient was initiated on medical therapy. FFR_{CT} indicates fractional flow reserve derived from coronary computed tomography angiography (coronary CTA) datasets; LAD, left anterior descending artery; EKG, electrocardiogram; ICA, invasive coronary angiography. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

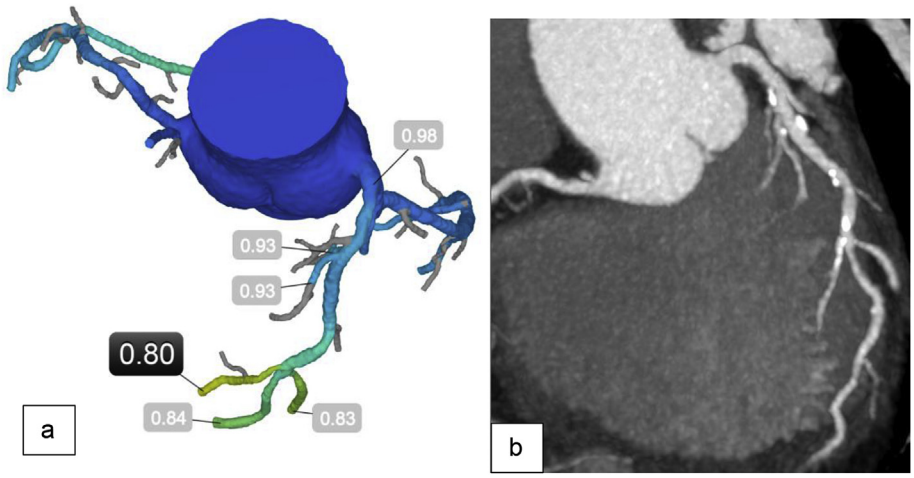

Fig. 3. Diffuse coronary artery disease with borderline $FFR_{CT.}$ 62-year-old male presenting with atypical chest pain. FFR_{CT} **(a)** and curved multiplanar reformat of coronary CTA of the LAD **(b)**. Interpretation: LAD demonstrated diffuse calcified and non-calcified mild disease without focal stenosis with an FFR_{CT} value of 0.80 distally. No discrete lesion was identified causing a focal significant pressure gradient. This finding may be explained by diffuse coronary artery disease. The interpreting physician decided to treat the patient medically without ICA. There was no discrete target for PCI and the FFR_{CT} value was in the gray zone. At 10 month follow-up the patient was symptom free and did not experience an incident event. FFR_{CT} indicates fractional flow reserve derived from coronary computed tomography angiography (coronary CTA) datasets; LAD, left anterior descending artery; ICA, invasive coronary angiogram; PCI, percutaneous coronary intervention.

individual lesion has on coronary physiology has proven clinically helpful to inform decisions around revascularization strategies.[30]

The combined results from coronary anatomy and FFR_{CT} should be communicated to the referring clinician to help guide downstream therapeutic decision making. The physician interpreting the FFR_{CT} analysis should consider the entire physiological model and integrate the findings with both the clinical history provided and the anatomical findings identified on the coronary CTA. Simply providing the lowest FFR_{CT} value is insufficient and can serve to confuse rather than inform clinical decision making. This requires time to ensure all available data inform an addendum to the initial report or are incorporated into a single integrated report in a clear and thoughtful fashion to aid downstream decision making.

It is important to note that published studies reporting on the diagnostic performance of FFR_{CT} utilized separate angiography/FFR and FFR_{CT} core laboratories as well as a separate integration core laboratory designed to ensure that the FFR_{CT} value selected from the model coincided with the location of the pressure sensor for the invasive FFR measurement.[4–6] If the measurement location of invasive FFR and FFR_{CT} do not correspond, the values will be different. In clinical practice the reported FFR_{CT} values are typically provided prior to ICA and measurement of FFR and thus may not reflect the precise location of the FFR pressure wire transducer. Thus, if during ICA, the location of the pressure sensor on the FFR wire is at a more proximal location compared to the FFR_{CT} value reported on the FFR_{CT} analysis, then the FFR_{CT} value will likely be lower. If the pressure sensor with invasive FFR is just distal to a specific lesion of interest, a simple comparison to the lowest FFR_{CT} value in the very distal vessel may lead to an apparent discordance with measured FFR. It is important that this be considered when correlating angiographic FFR values in relation to the location of reported FFR_{CT} values. In addition, it is known that discordance

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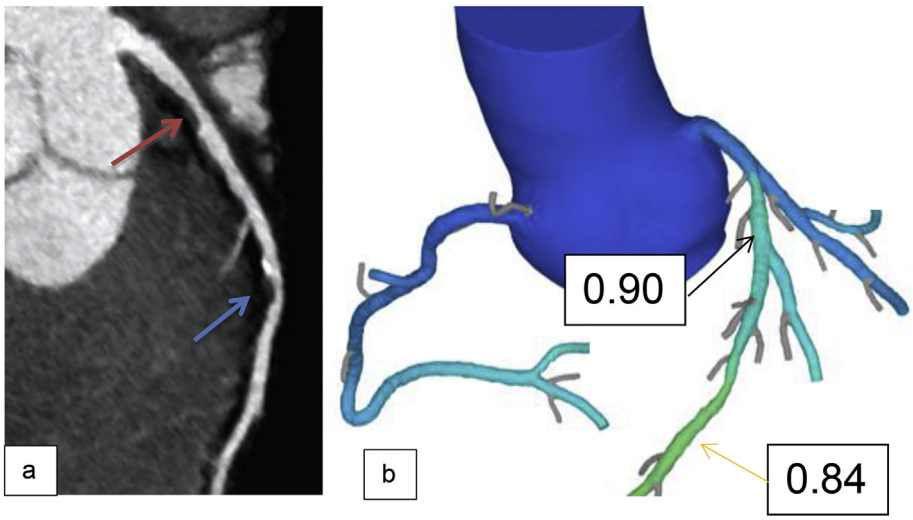

Fig. 4. Serial lesions that are not hemodynamically significant. 55-year-old male with a family history of coronary artery disease presented with atypical chest pain. Multiplanar reformat of coronary CTA of the LAD **(a) and (b)** FFR_{CT}. Interpretation: LAD demonstrates serial proximal (**red arrow**) and mid (**blue arrow**) primarily non-calcified moderate stenoses that cumulatively are not hemodynamically significant. Black and orange arrows represent the FFR_{CT} value distal to the proximal and mid stenoses, respectively. The interpreting physician decided to treat the patient medically without ICA. FFR_{CT} indicates fractional flow reserve derived from coronary computed tomography angiography (coronary CTA) datasets; LAD, left anterior descending artery; invasive coronary angiography. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

between FFR_{CT} and invasive FFR can result from inadequate dosing or non-administration of nitroglycerine prior to coronary CTA image acquisition.[31] When using sublingual nitrates, spray is preferred over tablets in accordance with the recently published SCCT CTA acquisition guidelines, as the bioavailability of the tablet is less rapid, potentially compromising coronary CTA image quality and FFR_{CT} analysis.[28]

7. Importance of image quality

Clinical interpretation of FFR_{CT} in conjunction with anatomic assessment of CAD by coronary CTA is dependent on appropriate coronary luminal modeling. Inadequate signal or contrast relative to noise and coronary motion or misalignment artifacts may compromise the ability to conduct plaque, lumen, coronary CTA interpretation and FFR_{CT} analysis. Misalignment artifact has consistently been shown to most affect the suitability of coronary CTA data sets for calculation of FFR_{CT}.[31] Guideline-directed coronary CTA acquisition methods are designed to optimize image quality and minimize artifacts while applying techniques that may reduce radiation exposure according to the "as low as reasonably achievable" (ALARA) principle.

8. Conclusion

FFR_{CT} is distinct from invasive FFR and other non-invasive cardiac stress tests as it provides per-lesion and per-vessel physiological information across the entire coronary tree which, during the course of interpretation, must be carefully reviewed and thoughtfully conveyed to the referring clinician. Efforts to better standardize reporting are essential to realizing the potential of FFR_{CT} to positively impact the clinical management of patients with CAD. This requires work effort on the part of the interpreting physician to provide functional data based on the FFR_{CT} analysis in order to improve clinical decision making for the patients.

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