

Noninvasive Measurement of Coronary Fractional Flow Reserve: An Under-exploiting Newland

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INTRODUCTION

In patients with coronary artery disease (CAD), the most important factors regarding to both symptoms and outcomes are the presence and extent of inducible ischemia.^[1] Alleviation of ischemia with percutaneous coronary intervention (PCI) can improve symptoms and clinical outcomes. Stenting ischemic stenosis result in effective and durable relief of angina pectoris and improves outcome, while in opposite, stenting nonischemic stenosis deteriorates outcomes and is not cost-effective.^[2-4]

INVASIVE FRACTIONAL FLOW RESERVE

Fractional flow reserve (FFR) has emerged as a useful tool to determine the lesions that require revascularization and is now considered as the gold standard for invasive assessment of ischemia.^[5,6] FFR-guided therapy was shown to reduce major harmful cardiac events by approximately 28% compared with angiography-guided PCI^[7] and by 68% compared with optimal medical therapy alone,^[8] which is also cost effective.^[9] Measurement of FFR during invasive angiography was upgraded to an IA classification in multi-vessel PCI from the European Society of Cardiology for identifying hemodynamically significant coronary lesions when noninvasive evidence of myocardial ischemia is unavailable.^[5]

Numerous specific merits making FFR particularly suitable for the functional assessment of coronary stenosis and subsequent clinical decision-making, but the disadvantage should also be noted [Table 1].^[5,6,10] To overcome the limitations of invasive measurement of FFR, researchers have developed noninvasive measurements of FFR derived from coronary computed tomographic

angiography (CTA) (FFR_{CT}), angiography, and optical coherence tomography (OCT).

FRACTIONAL FLOW RESERVE DERIVED FROM COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Computed tomographic angiography is a noninvasive anatomic test with favorable diagnostic performance with which we can identify anatomically obstructive coronary stenosis.^[12] Recent progress in computational fluid dynamics (CFD) and image-based modeling, now allows determination of rest and hyperemic coronary flow and pressure from CTA scans, with no need for modification of acquisition protocols, additional imaging or administration of medications.^[12] Thus, FFR_{CT} was measured noninvasively based on these novel techniques. The scientific basis for FFR_{CT} has been well-described in details by Taylor *et al.*,^[12,13] and three procedures are required in the computation of FFR from coronary CT [Figure 1a].^[12,14] The scientific basis are as follows: (1) The baseline coronary blood flow is proportional to myocardial oxygen demand at rest for calculation of total resting coronary blood flow relative to patient-specific myocardial mass that can be quantified on the CT scan; (2) The resistance of the microcirculatory vascular bed at rest is inversely proportional to the size of the feeding vessel; (3) The coronary microcirculation has a predictable vasodilatory response to adenosine.

Most recently, prospective multicenter Diagnosis of Ischemia Causing Stenoses Obtained Via Noninvasive FFR study and the Determination of Fractional Flow Reserve by Anatomic CTA trial reported that FFR_{CT} was demonstrated to be superior to measures of stenosis severity for determination of lesion-specific ischemia.^[12,13,15] Noninvasive FFR_{CT} demonstrated per-vessel accuracy, sensitivity, specificity positive predictive value (PPV), and negative predictive

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Table 1: Comparisons of invasive FFR and noninvasive FFR

Comparisons	Advantages	Disadvantages
Invasive FFR	Unequivocally normal value of 1 Independent of gender and various cardiovascular condition ^[5,6,10] Well-validated in multi-vessel disease, previous myocardial infarction, and left main disease ^[11] Easy, rapid, and safe procedure in the catheterization laboratory	Potential hazard of plaque rupture Expensive, time-consuming and allergic actions Can not reflect the morphology change in lesion
FFR _{CT}	No need for modification of acquisition protocols and additional imaging ^[12] Combined anatomic and physiologic assessment in a single noninvasive test Applicable to various common cardiovascular conditions ^[12]	Impaired coronary CT image quality with numerous artifacts CTA is limited in the context of advanced and calcific CAD and in patients with irregular heart rhythm or motion artifact ^[19] Assumptions in the physiological models may affect assumed parameters such as fluid density and viscosity
FFR _{QCA}	No induction of hyperemic flow, and no hazard of passing an intracoronary wire May be superior to FFRCT without additional procedure time, equipment, training, cost ^[19] Permits longitudinal assessment of the entire coronary vessel or even the entire coronary tree	The accuracy and feasibility should be determined by multicenter robust studies before its use from bench to bedside ^[19]
FFR _{OCT}	Clarifies the roles of variables between anatomical and functional measurements of stenosis severity ^[31]	The diagnostic accuracy and meaningful cut-off value for stenting decisions is not defined yet

FFR_{OCT}: FD-OCT derived FFR; FFR_{CT}: FFR derived from computed tomographic angiography; FFR: Fractional flow reserve; FD-OCT: Frequency domain optical coherence tomography; QCA: Quantitative coronary angiography.

value (NPV) for lesions causing ischemia of 84.3%, 87.9%, 82.2%, 73.9%, and 92.2%, respectively and was found to be superior to CTA stenosis for diagnosing ischemic lesions which demonstrated an accuracy, sensitivity, specificity, PPV, and NPV of 58.5%, 91.4%, 39.6%, 46.5%, and 88.9%, respectively.^[12,16] There was a marked improvement in the ability to discriminate ischemia-causing stenosis with an area under the curve in the receiver operating characteristics curve of 0.95 for FFR_{CT} ($P < 0.0001$ compared to CT alone).^[17] This promising novel technology provides a combined anatomic and physiologic assessment of CAD in a single noninvasive test that can help select patients for invasive angiography and revascularization or best medical therapy. The recent landmark ABSORB^[18] trial first selects FFR_{CT} as the functional parameter to evaluate coronary stenosis severity instead of invasive FFR.^[19,20]

Nevertheless, the diagnostic performance of FFR_{CT} may be influenced by many potential limitations [Table 1]. As for image quality, however, closely adherence to coronary CTA image acquisition guidelines, particularly by use of beta-blockers to reduce heart rate and heart rate variability and administration of sublingual nitrates to dilate the coronary arteries can minimize artifacts.^[13,21] In conclusion, the validation of FFR_{CT} is very impressive, and this supernova is full of expectations in the future clinical research.

FRACTIONAL FLOW RESERVE DERIVED FROM ANGIOGRAPHY

Meanwhile, three group of researchers also developed noninvasive measurement of FFR from angiography data alone. In 1996, Molloy *et al.*^[22] developed the first-pass analysis technique to calculate the blood flow through the

signal strength of CAG. Computed from blood flow, they successfully assessed FFR based on angiography data (FFR_a) on swine models.^[23] The first-pass analysis technique can be used to measure absolute coronary blood flow by analyzing the propagation of a contrast material signal in the coronary system.^[22,24,25] The volume of the vascular bed supplied by a particular coronary artery is modeled as a container with a single input without any assumptions about the internal structure of the vascular bed or the nature of exit conduits. In the period of the cardiac cycle, coronary blood flow was reflected with the change in contrast volume. Power injection of contrast material was assumed to substitute for blood with contrast material. Since the concentration of iodine in the contrast material and a linear regression analysis between measured integrated gray levels and iodine massed in the calibration phantom were known, it is possible to convert gray level to volume using the calibration curve and the known iodine concentration of the contrast material.^[14,22] In this way, the difference in densitometric signal in the vascular bed can be converted to the volume of contrast material entering the vascular bed between successive images using system iodine calibration.^[26] In order to measure FFR_a, the ratio of blood flow under condition of a stenosis (Q_s) to theoretically normal blood flow (Q_N) was calculated. On the assumption that blood was momentarily replaced with contrast material, Q_s was acquired using a time-density curve and Q_N was calculated with the total coronary arterial volume using scaling laws.^[19] However, the accuracy of FFR_a was limited by the small sample size of swines, and this technique required curb of breathing motion, which might significantly restrict the development in real practice.

Decades later, Morris *et al.*^[1] used generic boundary conditions for CFD analysis to calculate virtual FFR (vFFR)

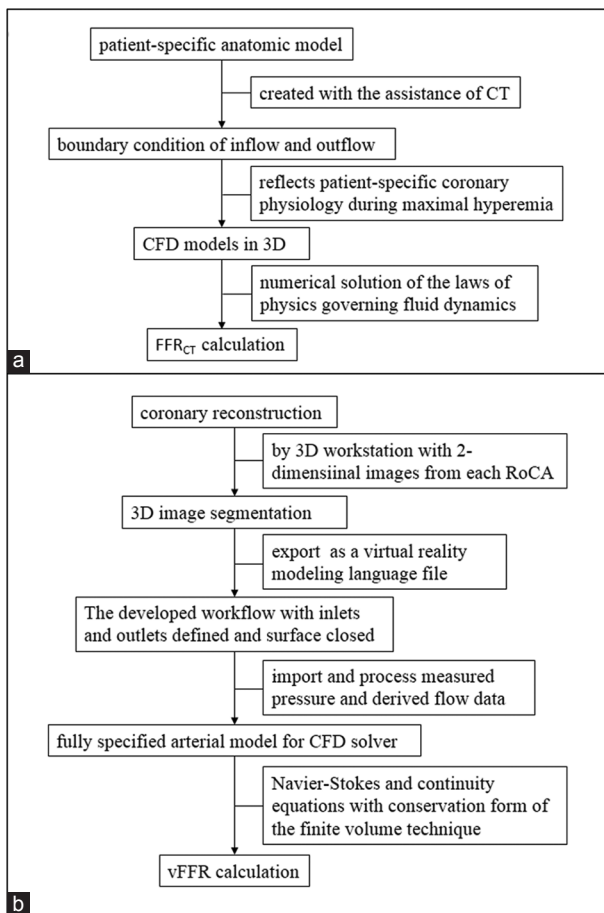


Figure 1: Calculation process of fractional flow reserve (FFR) derived from coronary computed tomographic (CT) angiography and virtual FFR. (a) Computation of FFR from coronary CT; (b) Computation of FFR from coronary angiography.

in CAD patients undergoing rotational coronary angiography. In computing vFFR from angiographic images, four procedures are involved [Figure 1b]. It was indicated that CFD model predicted which lesions were physiologically significant ($FFR < 0.80$) with accuracy, sensitivity, specificity, PPV and NPV of 97%, 86%, 100%, 100%, and 97% respectively.^[1] vFFR and pressure derived FFR values were compared. On average, the vFFR values deviated from FFR by ± 0.06 (mean delta = 0.02, standard deviation = 0.08), so vFFR and FFR were closely correlated ($r = 0.84$).^[1] It revealed that the FFR was reliably predicted without the need for invasive measurements or inducing hyperemia.

However, the interrogated lesions in Morris's study were simple lesions, and vFFR required over 24 h for the computation. Therefore, Tu *et al.*^[27] developed a novel approach on the basis of three-dimensional (3D) quantitative coronary angiography (QCA) and thrombolysis in myocardial infarction (TIMI). Frame count for fast computation of FFR (FFR_{QCA}) in CAD patients. In general, the strategy is to reconstruct anatomical models by 3D-QCA and subsequently apply CFD, using mean volumetric flow rate (VFR) at hyperemic derived by 3D-QCA and TIMI

frame count at the boundaries. First, the contrast medium transport time was calculated at hyperemic by TIMI frame count. Then, VFR at hyperemia was derived using the lumen volume of reconstructed coronary tree divided by the mean transport time. Next, in CFD, instead of using generic boundary conditions, this study apply the VFR at hyperemic and the mean pressure at the guiding catheter tip at the inlet, and apply fully developed flow condition at the outlets, leading to a fast simulation approach. It revealed that good correlation ($r = 0.81$; $P < 0.001$), with a mean difference of ($r = 0.81$; $P < 0.001$) was found between FFR_{QCA} and FFR_{CT} .^[27] What's more, FFR_{QCA} was assessed to have overall accuracy, sensitivity, specificity, PPV, and NPV of 88%, 78%, 93%, 82%, and 91%, respectively.^[27]

In conclusion, FFR_{QCA} might be superior to pressure derived FFR and FFR_{CT} [Table 1]. The primary difference between FFR_{QCA} and FFR_{CT} is that FFR_{CT} use empiric flow derivation based on average population-based physiological model assumptions under rest conditions while FFR_{QCA} uses individual hyperemic flow that better accounts for distal microvascular disease, providing a better approximation of invasive measures overall.^[28]

FRACTIONAL FLOW RESERVE DERIVED FROM OPTICAL COHERENCE TOMOGRAPHY

Most recently, it was suggested that vFFR could also be noninvasively calculated by frequency domain OCT (FD-OCT). FD-OCT merges to be another novel noninvasive method for the quantitative measure of stenosis severity, which provides cross-sectional images of coronary arteries and deployed stents with micron resolution and measures lumen dimensions with excellent reproducibility.^[29,30] It also provides information about plaque vulnerability, calcification, estimates the blood flow resistance and microvascular resistance of the vessel segments imaged. Through the volumetric analysis of FD-OCT images, FFR was calculated from the blood flow resistance and the microvascular resistance.^[31] Combined with a blood flow resistances model, it can overcome many limitations of conventional measures of stenosis severity based on QCA. FD-OCT derived FFR (FFR_{OCT}), showed a significant correlation with pressure derived FFR.^[31] Zafar *et al.* calculated FFR_{OCT} with microvascular resistance under maximal hyperemia (R_{mv}), blood flow resistance of the stenosis (R_s), and the blood flow resistance of the length of vessel outside the imaged segment (R_e). FFR was calculated as $(R_{mv} + R_e)/(R_{mv} + R_e + R_s)$ with R_{mv} measured by dividing the hyperemic microvascular resistance index and R_e calculated as the viscous flow resistance of the length of vessel outside the imaged segment using Poiseuille's law.^[31] R_s that is assumed to consist of a flow independent component that results from viscous and kinetic losses, and a result is calculated using the analytical method.

Stefano *et al.*^[32] were the first to determine the correlation between FFR and OCT derived lumen measurements in

14 patients with 18 stenosis, but no significant correlation between FFR and the OCT measured minimum lumen area (MLA) ($r = 0.167$, $P = 0.56$), minimum lumen diameter (MLD) ($r = -0.42$, $P = 0.13$), and percent area stenosis (%AS) ($r = 0.29$, $P = 0.29$) was found. Recently, Gonzalo *et al.*^[33] evaluated the diagnostic efficiency of OCT derived lumen measurements identifying the stenosis severity in 56 patients with 61 stenoses and reported poor but significant correlation between FFR and OCT measured MLA ($r = 0.51$, $P < 0.001$), MLD ($r = 0.4$, $P = 0.005$), and %AS ($r = 0.33$, $P = 0.02$). Zafar *et al.*^[31] carried out a feasibility study enrolled 20 patients to figure out the relationship between pressure-derived FFR and FFR_{OCT}. A moderate but significant correlation between pressure derived FFR and FFR_{OCT} ($r = 0.69$, $P < 0.001$) was detected, and Bland–Altman analysis showed that the mean differences between FFR and FFR_{OCT} were 0.05 ± 0.14 (limits of agreement: $-0.09-0.19$).^[31]

Frequency domain optical coherence tomography is a promising tool in assessing stenotic lesions. Firstly, since no clear guidelines on how to manage multiple lesions with a positive FFR in the distal segment, FD-OCT is important to identify the noncritical MLA in the proximal stenosis, leading to selective intervention of the distal stenosis and optimization of the stent deployment procedure.^[32]

Secondly, FD-OCT also has a positive effect under the conditions of acute coronary syndromes and negative FFR to evaluate any feature of plaque instability. However, since a meaningful cut-off value for stenting decisions is not driven yet, FFR_{OCT} may not be considered in primary stenting decisions. With further validation, FFR_{OCT} has the potential to become a valuable tool for the evaluation of coronary artery stenosis and may play a role in interventional procedural planning and decision-making.

PERSPECTIVE

In summary, FFR_{CT}, FFR_{OCA} and FFR_{OCT} have their own advantages and limitations respectively. It displays a significant superiority of the traditional invasive one and may be a potential diagnostic tool for lesion-specific ischemia and help to make optimal clinical decisions. However, the Newland discovered by Columbus needs hundreds of followers to create the prosperity. Therefore, these noninvasive assessment techniques of coronary FFR should be under exploiting.

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