REVIEW

Novel Angiography-Derived Techniques for Functional Assessment of Coronary Artery Disease

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Abstract

Background: The importance of coronary physiology in identifying hemodynamically significant lesions is well established.
Objective: The current review summarizes the most important studies of the novel techniques developed over the last decade that allow the computation of fractional flow reserve (FFR) from either invasive or computed coronary angiography.
Methods: A systematic review of all published research in PubMed and Google Scholar databases, regarding the angiography-derived functional assessment of coronary artery disease (CAD) has been performed. The following terms were used: "functional angiography", "quantitative flow ratio", "computed tomography-derived FFR", "FFR angiography" and "virtual FFR".
Results: Several multicenter clinical trials have presented the currently available techniques for physiological assessment of coronary artery stenosis, such as quantitative flow ratio (QFR), computed tomography-derived FFR, FFRangio and virtual FFR, their theoretical basis and methodology, as well as their diagnostic performance, using invasive FFR as reference standard.
Conclusion: A variety of novel angiography-derived techniques for physiological assessment of CAD exist, showing high diagnostic performance and are expected to increase the use of coronary physiology in the guidance of clinical decision making upon revascularization strategy. ***Rhythmos 2020;15(4):73-77.***

Keywords: fractional flow reserve; quantitative flow ratio; computed tomography-derived FFR; FFR angiography; virtual FFR; computational fluid dynamics

Abbreviations: CAD: coronary artery disease, FFR: fractional flow reserve, iFR: instantaneous wave-free ratio, CFD: computational fluid dynamics, QCA: quantitative coronary angiography, QFR: quantitative flow ratio, HFV: hyperemic flow velocity, CTA: computed tomography angiography, FFR_{CT}: computed tomography derived FFR, FFRangio: FFR-angiography, vFFR: virtual FFR.

Introduction

Physiological evaluation is the established clinical standard for the assessment of intermediate coronary stenosis in patients with stable coronary artery disease (CAD).[1-3] Current guidelines recommend the use of fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) to guide coronary revascularization.[4] Despite that, their adoption in clinical practice remains poor due to several technical difficulties, such as increased time consumption required for their performance, equipment and drug costs, patients' discomfort and contraindications to adenosine for FFR. In order to overcome these obstacles, several new methods based on computational fluid dynamics (CFD) and mathematic formulas for less invasive physiological assessment of coronary stenosis have emerged over the last decade,[5-8] with computed tomography-derived FFR (FFR_{CT}) and quantitative flow ratio (QFR) being the most widely studied. What follows is a review of these novel methods of functional assessment of coronary stenosis, including the theoretical basis and methodology behind their application and the clinical studies assessing their diagnostic performance.

Quantitative Flow Ratio (QFR)

In 2014 Tu et al introduced a new computer model for fast computation of FFR on the basis of 3-dimensional (3D) quantitative coronary angiography (QCA) and TIMI (Thrombolysis In Myocardial Infarction) frame count, using mathematical formulas taking into account Bernoulli's principle.[9] The novel computational FFR was denoted as quantitative flow ratio (QFR) (**Fig**. 1).

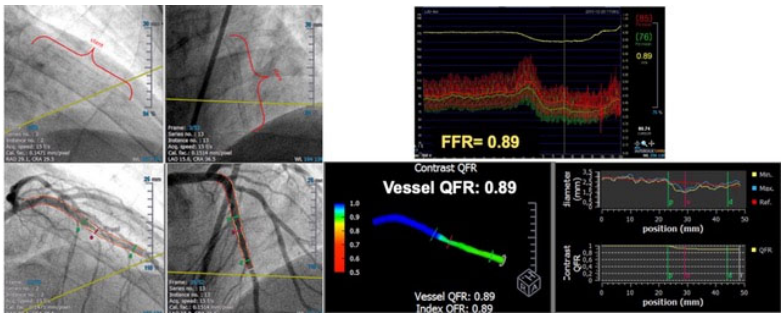

Figure 1. Example of QFR and FFR analysis in the same patient with in-stent restenosis. FFR value: 0.89. QFR value: 0.89

QFR Computation: Underlying principles and Methodology

The QFR computation is based on the following underlying principles: 1) coronary pressure remains constant through normal epicardial coronary arteries;[10] 2) the amount of pressure drop is determined by the stenosis geometry and the flow moving through the stenosis, described by the fluid dynamic equations;[11] 3) the stenosis geometry can be characterized by the deviation of the diseased lumen sizing with respect to the reference sizing, i.e., the healthy lumen as if there was no stenosis, by 3D QCA;[9] and 4) coronary flow velocity is preserved distally relative to proximal flow velocity[12] and the mass flow rate in the main coronary arteries decreases with the tapering

of the arteries due to the presence of side branches. Hence, the mass flow rate at each location along the interrogated vessel can be determined by the mean flow velocity and the reference sizing from 3D QCA.

Computation of QFR is performed offline, using a prototype software package (QAngio XA 3D prototype, Medis Medical Imaging System, Leiden, the Netherlands). In the first step, 2 diagnostic angiographic projections, at least 25^{o} apart, are selected and 3D reconstruction of the interrogated vessel without its side branches is performed, and 3D QCA data are readily available. Then, the software computes within a minute the following 3 QFR pullbacks based on the different mean hyperemic flow velocities (HFV): 1) a fixed empiric HFV of 0.35 m/s that has been derived from previous FFR studies[9] (fixed-flow QFR [fQFR]); 2) modelled HFV derived from coronary angiography without pharmacologically induced hyperemia (contrast-flow QFR [cQFR]), that is, the contrast flow is converted into the virtual hyperemic flow based on data derived from previous studies,[9] and cQFR is computed as if adenosine was actually used; and 3) measured HFV derived from coronary angiography during adenosine-induced maximum hyperemia (adenosine-flow QFR [aQFR]).[5]

QFR Studies

The first prospective study to report high diagnostic performance of QFR in comparison to FFR was the multicentre international FAVOR Pilot study, showing favourable results of cQFR that does not require pharmacologic hyperaemia induction[5]. The high diagnostic accuracy of QFR (using the cQFR model) in identifying hemodynamically significant coronary lesions was subsequently confirmed by two larger prospective multicentre trials, conducted in patients with stable CAD, the FAVOR II – China[13] and the FAVOR II – Europe-Japan studies[6] (diagnostic accuracy 92.7% and 86.8% respectively). Both studies showed superiority of QFR over angiographic assessment of intermediate coronary artery stenosis, using FFR as reference standard.

Since the publication of the studies that established the high diagnostic performance of QFR, a large number of prospective and retrospective trials have investigated its feasibility and diagnostic accuracy in different patients subsets, such as patients with coronary microcirculatory dysfunction,[14] in-stent restenosis,[15] stenosis identified by coronary CT[16], prior myocardial infarction,[17] non-culprit lesions in the acute phase of myocardial infarction,[18] severe aortic stenosis[19] and diabetes mellitus.[20]

In addition, the diagnostic performance of QFR has been evaluated using iFR as reference standard showing good correlation and classification agreement between these two adenosine-free indices, although the diagnostic accuracy of QFR seems to be higher in comparison to FFR than in comparison to iFR[21,22]. Applying the cut-off value of QFR $\leq$ 0.80 and iFR $\leq$0.89, the sensitivity and specificity of QFR have been reported between 80% and 85% and between 82% and 83% respectively.[21,23]

Computed Tomography Derived FFR (FFR_{CT})

In recent years computed tomography angiography (CTA) has been widely used to provide anatomic information regarding the presence and extend of CAD. Despite that, its specificity for predicting the hemodynamic significant of coronary stenosis, as defined by invasive FFR, is limited[24]. Over the last decade, it has become possible to measure FFR from standard CTA datasets. The Computed Tomography derived FFR (FFR_{CT}), based on CFD, requires the creation of an anatomical model of coronary vasculature, a mathematical model of coronary physiology and a computational model of the fluid dynamics[25]. Since its initial validation in 2011 in the Diagnosis of ISChemia-Causing Stenoses obtained via NoninvasivE Fractional FLOW Reserve (DISCOVER-FLOW) trial[26] , a large number of clinical studies have been conducted in order to evaluate the diagnostic accuracy of FFR_{CT} using invasive FFR as reference[27-30], leading to the approval of the method (HeartFlow, Inc., Redwood City, California) by the Food and Drug Administration in the United States and by the Conformité Européene in Europe[31].

FFR_{CT} Methodology

FFR_{CT} relies on standard CTA images acquired with multi-slice CT scanner (with at least 64 slices) using a standard protocol according to guidelines from the Society of Cardiovascular Computed Tomography[32]. The process of FFR_{CT} calculation is performed using either a HeartFlow or a Siemens software[33] which constructs a patient-specific 3D anatomical model of the epicardial coronary arteries, aorta, and myocardium. Machine learning techniques aid in creating a mesh of the coronary lumen[34]. For each vessel supplying the myocardium, resting and hyperemic microvascular resistance are quantified by using lumped parameter models of the heart, allometric scaling laws and form-function relationships that regulate blood flow, and known coronary resistance changes due to hyperemia. With a 3D anatomic model and microvascular resistance model, supercomputers solve 3D equations of blood flow for velocity and pressure using CFD, and FFR_{CT} is determined by normalizing the mean hyperemic pressure by the mean hyperemic pressure in the aorta[25]. The total time from submitting data to receiving results has decreased over time, and FFR_{CT} results are routinely returned within 2–3h.

FFR_{CT} Studies

The diagnostic performance of FFR_{CT} was initially evaluated in three large pivotal multicenter trials (DISCOVER-FLOW, DeFACTO and NXT trial), using invasive FFR as reference standard[26,27,30]. In terms of cut-off points, all studies used the same one to define positive results ($FFR_{CT} \leq 0.80$; $FFR \leq 0.80$). FFR_{CT} was found to be superior to CTA in discriminating hemodynamically significant lesions in all three studies, although in DeFACTO study the diagnostic accuracy of FFR_{CT} and CTA was only 73% (95% CI 67% to 78%), which did not meet the primary endpoint of the 70% of the lower bound of the 95%CI[27]. On the other hand, diagnostic accuracy, sensitivity and specificity were high in the DISCOVER-FLOW (84.3%, 87.9% and 82.2% respectively) and NXT trial (81%, 88% and 79%).

Several meta-analyses of the diagnostic accuracy of FFR_{CT} have been performed.[33,35-37] A previous meta-analysis of 18 studies showed comparable pooled sensitivities of FFR_{CT} and CTA, but FFR_{CT} had higher per-patient specificity compared to CTA alone (77% vs 43%).[35] Similar results were also reported by a more recent meta-analysis of 16 studies published between 2011 and 2019, including 1852 patients that showed higher specificity of FFR_{CT} in comparison to CTA both at per-patient (71% vs 32%) and per-vessel analysis (82% vs 46%).[37] Finally Cook and colleagues in a meta-analysis of studies comparing FFR_{CT} to invasive FFR (using cut-off value 0.8 in both) found an overall diagnostic accuracy of FFR_{CT} of 82%.[36]

FFRangio

FFRangio (developed by CathWorks, Ltd) is a novel technology providing a 3D functional angiography mapping of the coronary tree.[7] It is based on a rapid flow analysis of a dynamically derived lumped model that can assess FFR using routine angiograms and hemodynamic data.

FFRangio Methodology

The primary element of FFRangio is the proprietary 3D rebuild of the coronary tree from 2-dimensional images, after which the system scans the entire reconstructed tree in 3D and analyses each branch as well as each bifurcation (or trifurcation), looking for narrowed regions. This is followed by hemodynamic evaluation, where the contribution of each narrowing to the total resistance to flow is taken into account and a subsequent lumped model is built. This allows pressure drops and flow rates to be estimated. The accumulated volume of the coronary tree and the total coronary length, calculated from a reconstruction of its geometry, enable an estimation of normal supply through an assessment of the microcirculatory bed resistance. The solution of the lumped model based on the inlet and outlet boundary conditions allows to evaluate ratios of flow rate for stenosed versus "healthy" coronary regions.[38]

At least 2 angiographic projections of the vessel to be measured are needed (acquired at 15 frames/sec). Care is taken to fill the artery as completely as possible with contrast medium and to image the entire coronary tree at each view. Following the acquisition of the angiogram the user enters the mean aortic pressure. The coronary tree is reconstructed in 3D based on at least 2 projections whereby epipolar ray tracing together with mathematical constraints enforcing the tree's structure is utilized. The system scans the reconstructed tree looking for narrow regions and hyperemic flow is derived from automatic resistance-based lumped mapping along the entire coronary bed. The FFR values at each point are color-coded and superimposed on the 3D epicardial model and cut-off values of 0.80 identical to standard invasive FFR apply. FFRangio does not utilize pharmacologic drug induced hyperemia[39].

FFRangio Studies

The first in-human study of FFRangio (2016), including analysis of 101 lesions, showed high reproducibility and diagnostic accuracy of the method in comparison to invasive FFR.[38] Subsequently, two larger validation studies confirmed the high diagnostic accuracy of FFRangio using invasive FFR as reference and cut-off value of 0.80.[7,40] The FAST-FFR study, a large prospective multicenter study (including analysis of 319 vessels) indicated very high sensitivity, specificity and diagnostic accuracy of FFRangio for predicting pressure wire-derived FFR (93.5%, 91.2% and 92.2% respectively). The correlation of FFRangio and invasive FFR remained high over the entire range of FFR values[40].

Virtual FFR (vFFR)

In the same philosophy, as the QFR and FFRangio investigators, of using coronary angiogram for wire-free computation of FFR, Morris and his colleagues invented another technique to virtually calculate FFR, based on CFD, the virtual FFR (vFFR).[41]

vFFR Methodolgy and Studies

Although the initial vFFR method had shown good diagnostic accuracy in comparison to invasive FFR, in VIRTU-1 trial, it required >24hours to produce a result[42]. Subsequently, the same study group developed a novel "pseudotransient" analysis protocol for computing vFFR based on angiographic images and steady-state CFD that generates results in 189 seconds using a desktop PC,

making the method attractive for future use in clinical practice by interventional cardiologists.[41] In the Morris model, a translesional pressure drop across a narrowed arterial segment is computed, in which the drop in pressure is described by a quadratic function of flow during steady state over a pressure cycle, as opposed to requiring calculations of all points over the complete phasic cycle as required in most CTA FFR original algorithms[43]. Further description of the complex computations behind vFFR calculations are beyond the scope of this review. The VIRTU-FAST study, published in 2017, showed that vFFR can be accurately computed from coronary angiography in <4 min. Interestingly, the study's sensitivity analysis showed that physiological lesion significance was influenced less by coronary or lesion anatomy (33%) and more by microvascular physiology (59%).[41]

Clinical implications

The usefulness of hemodynamic assessment of coronary artery stenosis in guiding revascularization plan has been well established over the last decades. A large number of publications have shown that several novel techniques for fast, wire-free computation of FFR with high diagnostic accuracy and reproducibility are currently available. The new methods of angiography-derived functional assessment of coronary lesions seem to be promising in spreading the use of coronary physiology, making it available to more patients, providing all the benefits of physiological guidance without the limitations that restrict the use of invasive techniques. This may eventually lead to improved clinical outcomes, since the angiography-derived functional assessment of CAD is superior to coronary angiogram alone and to avoidance of unneeded revascularization.

Conclusions

Computed "virtual" coronary physiology seems to represent part of a new era of coronary angiography. The novel less invasive techniques of hemodynamic assessment of CAD, despite some limitations and methodological challenges that need to be resolved, will open up coronary physiology to the majority of patients either offline or preferably in the catheterization laboratory. Ongoing prospective randomized clinical trials, evaluating the safety of these new techniques in clinical decision making at long term follow-up, are expected with great interest from the interventional cardiologists community.

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