




The Evolution of Virtual Physiologic Assessments and Virtual Coronary Intervention to Optimize Revascularization

Kara M. Stout¹ · Kostantinos D. Boudoulas² · Thomas J. Povsic³ · S. Elissa Altin⁴ · Aravdeep S. Jhand¹ · Steven R. Bailey⁵ · Andrew M. Goldsweig¹ 

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Abstract

Purpose of Review In this review, we summarize the use of virtual physiologic functional assessments of coronary artery disease and their utility to guide virtual coronary intervention (VCI).

Recent Findings Virtual fractional flow reserve (vFFR), coronary angiography–derived fractional flow reserve (FFR_{angio}), virtual contrast FFR (cFFR), and quantitative flow reserve (QFR) are four technologies that generate computer-based FFR measurements comparable to the gold standard of pressure-wire-based FFR. VCI capitalizes on this technology by utilizing pre- and post-vFFR assessments to predict the physiologic response to stenting.

Summary Physiologic assessment of coronary lesion significance has become a cornerstone of decision-making for revascularization. FFR and non-hyperemic pressure ratio use is limited by the requirement for an intracoronary wire and the additional time required. Virtual physiologic assessments address these shortcomings with accuracy comparable to FFR. Building on this technology, VCI simulation has the potential to revolutionize the approach to percutaneous revascularization.

Keywords Virtual physiologic assessment · vFFR (virtual fractional flow reserve) · FFR_{angio} (coronary angiography–derived fractional flow reserve) · cFFR (virtual contrast FFR) · QFR (quantitative flow reserve) · VCI (virtual coronary intervention)

Introduction

Each year in the USA, percutaneous coronary intervention (PCI) is performed in 7801 adults per million for acute coronary syndromes (ACS) and in 922 per million for stable coronary artery disease (CAD) [1]. Revascularization has been

shown to reduce death and recurrent myocardial infarction (MI) in patients with ACS [2, 3].

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial showed that revascularization with PCI or coronary artery bypass grafting, in comparison with optimal medical therapy (OMT), did not result in a significant reduction in major adverse cardiovascular events (MACE) or death among patients with stable ischemic heart disease at 3.2 years [4]. Of note, this trial did exclude a significant number of participants due to an ejection fraction less than 35%, class III or IV heart failure symptoms, or screening coronary computed tomography angiography (CCTA) demonstrating no obstructive CAD or unprotected left main stenosis [4].

One explanation for the lack of observed reduction in MACE or death in ISCHEMIA could be the reliance upon imprecise anatomic guidance during coronary angiography, rather than a physiologic assessment, as fractional flow reserve (FFR) was used in only 20.3% of cases [4]. In particular, angiography-only assessments of CAD can be problematic with lesions of intermediate severity (40–70% obstruction) [5•] because additional variables including the lesion length,

✉ Andrew M. Goldsweig
andrew.goldsweig@unmc.edu

¹ Division of Cardiovascular Medicine, University of Nebraska Medical Center, 982265 Nebraska Medical Center, Omaha, NE 68198-2265, USA

² Division of Cardiovascular Medicine, Ohio State University, Columbus, OH, USA

³ Division of Cardiovascular Medicine, Duke University, Durham, NC, USA

⁴ Division of Cardiovascular Medicine, Yale University, New Haven, CT, USA

⁵ Division of Cardiovascular Medicine, Louisiana State University, Shreveport, LA, USA

collateral flow, and functional status of the myocardial microvascular bed downstream have not been assessed [6, 7]. When FFR was used to guide PCI in patients with stable ischemic heart disease in the FAME II (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, there was a composite reduction in death, myocardial infarction, and unplanned hospitalization requiring revascularization in comparison to OMT alone at 5 years of follow-up, with the greatest difference driven by a reduction in urgent revascularization [8].

To evaluate intermediate coronary lesions more accurately, physiological assessment has become one of the cornerstones of revascularization, ensuring that only functionally significant lesions are treated [5•]. In this article, we review the origins of invasive physiologic assessment pre- and post-PCI and its evolution into a virtual coronary investigation. Based upon this technology, real-time virtual coronary intervention (VCI) has the potential to become the next step in the evolution of our current approach to revascularization.

The Emergence of a Physiologic Assessment for PCI: FFR

FFR, a well-validated index for the physiologic assessment of coronary lesions, is defined as the ratio of the distal coronary pressure (Pd) to the proximal aortic pressure (Pa) at maximum hyperemia [9]. At maximum hyperemia, achieved most commonly by intravenous or intracoronary adenosine, resistance is constant and minimal, and the coronary pressure correlates to coronary blood flow, allowing for a physiologic assessment of the stenosis [9]. In a normal coronary artery, the FFR equals 1.0 [10].

Pijls et al. demonstrated that an FFR value of < 0.75 correlated with inducible ischemia on multiple non-invasive stress testing modalities, with positive FFR results reverting to normal after revascularization [11]. Deferral of revascularization based on an $\text{FFR} \geq 0.75$ resulted in no mortality difference at 15-year follow-up in the DEFER (Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis) trial [12]. The subsequent FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial then demonstrated that FFR-guided PCI (using a cutoff for revascularization of $\text{FFR} \leq 0.80$) is associated with a lower incidence of death, MI, or repeat revascularization at 1 year in comparison to PCI guided by angiography alone [10, 13, 14]. Thereafter, in FAME II, patients with stable CAD were randomized to FFR-guided PCI plus OMT or OMT alone [8]. This trial was prematurely terminated due to a significantly lower rate of the primary composite endpoint of death, MI, or urgent revascularization in the PCI group (4.3%) in comparison to the OMT group (12.7%) [8].

Based on these studies, FFR-guided PCI for angiographically intermediate stenoses to assess for hemodynamic significance received a Class I, Level of Evidence A recommendation in the 2018 from the European Society of Cardiology and a Class IIa, Level of Evidence A recommendation from the 2011 American College of Cardiology/American Heart Association and Society for Cardiovascular Angiography and Interventions guidelines [15, 16].

Despite the evidence and specialty societal recommendations for the use of FFR, global adoption has remained low, with utilization in less than 6% of procedures [17]. This is likely due in part to a combination of a prolongation of procedural time, added costs of the wire and vasodilating agent, patient discomfort with adenosine, and the potential risk of guide catheter and wire-related procedural complications [17, 18••]. In addition, technical challenges with pressure drift, inadequate induction of maximal hyperemia, or aortic waveform distortion limit accuracy and reproducibility [18••]. Nonetheless, the benefits of physiologically guided PCI have led to the American College of Cardiology/American Association for Thoracic Surgery/American Heart Association/American Society of Echocardiography/American Society of Nuclear Cardiology/Society for Cardiovascular Angiography and Interventions/Society of Cardiovascular Computed Tomography/Society of Thoracic Surgeons 2017 Appropriate Use Criteria for Coronary Revascularization in Patients with Stable Ischemic Heart Disease to recommend that FFR may be helpful in defining a need for revascularization and may substitute for stress test demonstrated ischemia [19].

Non-hyperemic Pressure Ratios

Non-hyperemic pressure ratios (NHPR) provide an alternative functional assessment without the need for adenosine. The instantaneous wave-free ratio (iFR) is measured as the mean ratio of the instantaneous phasic distal coronary pressure to aortic pressure during the wave-free period (WFP) [17, 20]. The WFP begins 25% of the way into diastole and concludes 5 ms before the end of diastole; this period is characterized by the lack of new waves propagating from the distal or proximal ends of the vessels [20]. During this time, there is a direct correlation between intracoronary pressure and flow, and microvascular resistance is minimal and stable [20].

The ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study and the ADVISE Registry were the first comparisons of iFR versus FFR [20, 21], establishing an iFR value of 0.89 to predict a functionally significant FFR of 0.80 [21]. Several additional studies found no significant difference between iFR and FFR performance for stenosis-specific myocardial ischemia assessed by reference standards of either positron emission tomography [22, 23] or myocardial

perfusion scintigraphy [24]. iFR was found to be non-inferior to FFR in guiding PCI for patients with both stable angina and ACS with more PCI deferrals with iFR and no difference in MACE including all-cause death, non-fatal MI, or unplanned revascularization at 1 year in the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization), with 6.8% of the iFR group versus 7.0% of the FFR group ($p < 0.001$), and iFR SWEDEHEART (Evaluation of iFR in Stable Angina or Acute Coronary Syndrome) trials, with 6.7% of the iFR group versus 6.1% of the FFR group ($p = 0.007$) [17, 25, 26]. In addition, there were fewer reported adverse procedural symptoms with iFR over FFR [25, 26].

Shortcomings of a Pressure Wire Physiologic Assessment Despite Advances in iFR Technology

Despite equivalence in hard clinical outcomes, there has been interest in understanding the differences in these technologies, especially identifying the 20% discordance between FFR and iFR measurements when evaluated by a core laboratory analysis [27, 28]. This discrepancy may be related to specific lesion characteristics, inadequate hyperemia, or varied responses to microvascular dysfunction [20]. Predominantly focal lesions were more likely to have a FFR ≤ 0.80 and iFR > 0.90 , while diffuse lesions were more commonly found to have an FFR > 0.80 and iFR ≤ 0.89 [28]. Given that FFR relies on hyperemia, it may be difficult to assess accurately the individual contributions of different portions of a diseased segment [5•], making iFR a more appealing functional assessment in this subset. In addition, diffuse disease is associated with changes in longitudinal pressure gradients affecting resistance and microvascular dysfunction [29].

FFR and iFR Performance in Specific Subgroups

Following an MI, an increase in left ventricular end-diastolic pressure can precipitate an increase in microvascular resistance, falsely elevating FFR measurements [30]; however iFR is less affected [18••]. In patients with multivessel coronary artery disease, iFR may also be preferred over FFR to avoid multiple rounds of hyperemia [25, 26].

The assessment of CAD in patients with severe aortic stenosis (AS) is challenging given the influence of AS on the development of left ventricular hypertrophy, increased afterload, and changes in microcirculatory and extravascular resistance, leading to microvascular dysfunction which appears similar to CAD [31]. Ahmad et al. reported a significant reduction in the FFR of angiographically intermediate

coronary lesions after transcatheter aortic valve replacement (TAVR) in patients with AS, while iFR calculations were unchanged after TAVR [32]. This may reflect coronary microcirculatory adaptation both to underlying CAD and AS as independently contributory variables. Like the challenges with the use of FFR in diffuse CAD discussed previously, it is not possible to distinguish the independent influences of CAD and AS with a hyperemia assessment, while it is possible to isolate the differences using iFR [32].

Despite iFR being a preferred physiologic assessment over FFR in these clinical settings after an MI, with MVCAD, or with AS, an important caveat is that precise algorithms and supporting data are vendor-specific: the iFR technology belongs to Philips/Volcano (Amsterdam, the Netherlands) [18••]; Abbott (Chicago, IL) systems calculate a resting full-cycle ratio (RFR), and Boston Scientific (Marlborough, MA) systems calculate a diastolic hyperemia-free ratio (dFR). Both RFR and dFR demonstrate excellent agreement with iFR and the same discriminatory agreement for low FFR [33]. Nevertheless, all these non-hyperemic pressure ratios still prolong procedural time, add to overall costs, and carry the risks of placing a guidewire and guide catheter in a diseased coronary artery [18••, 26].

A Gateway to the Future with a Virtual Physiologic Assessment

Virtual FFR (vFFR) provides an assessment of physiologic lesion significance without the risks of an invasive wire-based technique. It utilizes a combination of computational fluid dynamics (CFD) and coronary imaging [34]. CFD analyses are best described by differential equations of the conservation of mass and momentum, commonly utilizing the Navier-Stokes Model [34–36]; however, these equations can only be solved under circumstances of steady or pulsatile flow in an idealized circular cylindrical geometry [37].

CFD models require anatomical and physiological inputs to calculate the vFFR [34]. The luminal surface of an artery is identified, analyzed, and segmented from invasive angiography or CCTA, and a two- or three-dimensional model is generated [37], which is then discretized into volumetric elements [34, 36]. CT-based vFFR may be limited by insufficient image quality for accurate segmentation due to “stair-step” artifact from respiratory movement or arrhythmias, phase misregistration, or calcification causing “blooming or streaking” [34, 37]. Rotational coronary angiography allows for the selection of two optimal projections, free from foreshortening or inadequate opacification, but this technology is not widely available [34]. Other modalities such as intravascular ultrasound and optical coherence tomography may add further anatomic data but at the cost of intracoronary wire placement and an additional expensive procedure [34].

To calculate vFFR, the boundary inlet and outlet conditions are set by dedicated software, and this final closed surface is meshed to provide a virtual model [38]. The inlet pressure of the aortic root is simple to calculate from the direct measurement of the aortic pressure (or using the non-invasive cuff pressure and an adjustment equation with CCTA images) [34]. The outlet boundary, including both the coronary vasculature and ascending aorta, is very difficult to assess due to the heterogeneity of coronary microvascular circulation [34]. Morris et al. applied a generic downstream boundary condition based on a Windkessel model, which used downstream pressure and flow over a cardiac cycle to calculate microvascular resistance for each patient [35, 38]. These measurements were then averaged over their patient cohort to provide a universal boundary condition [35, 38]. While this generic boundary condition has been widely adapted, it is important to realize that the error for this generic application was halved when using individual invasive measurements, as discussed below [38].

Lastly, the optimal method for CFD simulation is challenging. Coronary circulation is dynamic and pulsatile, and a transient or time-dependent simulation is the most accurate method. This requires CFD to solve for millions of degrees of freedom simultaneously and hundreds of thousands of times over a cardiac cycle, which requires an average of 24 h to compute [34]. However, a limited steady-state CFD analysis can be performed over 2 min using a simplified estimate of dynamic blood flow [34].

Virtual Physiologic Assessments Utilizing Computational Fluid Dynamics

The VIRTU-1 (VIRTUal Fractional Flow Reserve from Coronary Angiography) study was a single-center, observational study of 19 patients who underwent contrast single-axis rotational coronary angiography (Philips, Best, the Netherlands), and all vessels with >50% stenosis were assessed by invasively measured FFR. Two clear projections from similar phases of the cardiac cycle were used to reconstruct arteries on a Philips 3D workstation [38]. The inflow and outflow settings utilized the aortic pressure and the Windkessel model, as described above. Hemodynamically significant lesions (FFR ≤ 0.80) were distinguished from non-significant lesions (FFR > 0.80) with 97% accuracy using vFFR [38]. This model quantified invasive FFR to within ± 0.06 using the vFFR assessment [38].

This full-transient-coupled method, requiring 24–36 h in processing time, was then compared to novel “steady” and “pseudo-transient” methods by Morris et al. [39]. Prediction of pulsatile physiology using a steady-state flow assumption is based on the work of Gorlin and Gorlin in 1951, who validated a formula for estimating mitral valve orifice area using a

mean, steady state as a surrogate for pulsatile flow [40]. Morris et al. created a pseudo-transient vFFR (vFFR_{ps-trns}) that approximates the temporal variation of the pressure distal to a lesion, which, when combined with the proximal pressure, was used to calculate the vFFR. The vFFR_{ps-trns} calculation uses several constructed variables including z_1 and z_2 from a quadratic equation to represent the diseased vessel, impedance, resistance, compliance, and four parameters describing the timing and amplitude of the intramural myocardial systolic pressure [39]. This model is compared to a steady vFFR (vFFR_{steady}) which reduces the outlet parameters to a single time-averaged resistance of the coronary microvasculature [39]. The mean error of vFFR_{ps-trns} and vFFR_{steady} compared to invasive FFR was $\pm 0.86\%$ and $\pm 0.50\%$, respectively. Both vFFR_{ps-trns} and vFFR_{steady} independently showed interclass correlation coefficients with FFR of 0.999 (95% confidence interval [CI]: 0.998–0.999; $p < 0.001$) [39].

These calculations by Morris et al. utilized individual, invasive pressure measurements for the input and output data [39]. When the generic value for microvascular resistance as discussed in the initial VIRTU-1 study [38] was used as the distal boundary condition, the diagnostic accuracy for baseline and hyperemic conditions fell from 100 to 52% [39]. This improved to 82% when comparing artery-specific lesions under hyperemic conditions [39]. These data confirm the inferior accuracy of generic boundary conditions and remain an area for further research.

Expanding an Imaging-Based Physiologic Assessment: Vessel FFR, vFAI, cFFR, QFR, and FFR_{angio}

Several virtual FFR modalities and technologies have been developed to simplify the use and increase the adoption of these functional assessments. Advancements have included the following methods: vessel FFR, virtual functional assessment index (vFAI), contrast FFR (cFFR), quantitative flow ratio (QFR), and coronary angiography-derived FFR (FFR_{angio}) (Table 1).

Building on the foundation of CFD, the FAST (Fast Assessment of STenosis) study aimed to create and then validate a new three-dimensional quantitative coronary angiography (3D-QCA)-based software to calculate vessel FFR using a phantom model. In the first phase of the study, Masdjedi et al. created an in vitro model to validate the calculations performed by CAAS Workstation 8 (Pie Medical Imaging, Maastricht, the Netherlands) software. This in vitro model was comprised of a chamber mimicking the left ventricle with artificial valves, and water-driven systemic and coronary circulations modeled using input impedances from the behavior of the systemic circulation and outputs modeled using the Windkessel principle [41••]. The pressure drop over

Table 1. Summary of invasive physiologic assessments of coronary stenoses

	FFR	iFR	vFFR	FFRangio	QFR	cFFR
Definition	-Ratio of the distal coronary pressure to the proximal aortic pressure at maximum hyperemia	-Mean ratio of the instantaneous phasic distal coronary pressure to aortic pressure during the wave-free period	-Angiograms acquired in ≥ 2 different projections 30° apart and an integrated mathematical approach	-Angiograms acquired in ≥ 2 different projections 30° apart utilizing rapid flow analysis	-Angiograms acquired in ≥ 2 different projections 25° apart with an integrated mathematical approach utilizing a contrast frame count	-Angiograms acquired in ≥ 2 different projections 30° apart recorded while contrast was injected at 4 ml/s with an integrated mathematical approach
Physiologic significance	≤ 0.80	≤ 0.89	≤ 0.80	≤ 0.80	≤ 0.80	≤ 0.94
Published clinical studies	-FAME -FAME II -DEFER -DANAMI-3-PRIMUMULTI -COMPARE-ACUTE	-ADVISE -ADVISE Registry -iFR-SwedeHeart -DEFINE FLAIR -85% (ADVISE)	-FAST -FAST II (ongoing)	-FAST-FFR -93.5% (95% CI, 88–97%) (FAST-FFR)	-FAVOR Pilot -WIFI II -FAVOR II China -FAVOR II -FAVOR III (ongoing) -77% (95% CI, 66–85) (WIFI II) -86.5% (95% CI, 78.4–92.4) (FAVOR II Europe-Japan) -94.6 (95% CI, 88.7–98.0) (FAVOR II China) -86% (95% CI, 79–91) (WIFI II) -88.9% (95% CI, 81.6–91.1) (FAVOR II Europe-Japan) -91.7 (95% CI, 87.1–95.0) (FAVOR II China) -83% (WIFI II) -86.8% (FAVOR II Europe-Japan) -92.4% (FAVOR II China)	-FLASH FFR
Sensitivity for predicting hemodynamically significant stenosis		N/A	N/A	-93.5% (95% CI, 88–97%) (FAST-FFR)		-92.2% (95% CI, 85.7–92.7) (FLASH FFR)
Specificity for predicting hemodynamically significant stenosis		-91% (ADVISE)	N/A	-91.2% (95% CI, 86–95%) (FAST-FFR)		-87.3% (95% CI, 82.1–91.5) (FLASH FFR)
Predictive performance for FFR ≤ 0.80		-88% (ADVISE) -94% (ADVISE Registry)	-93% (FAST)	-92.2% (FAST-FFR)		-89.0% (95% CI, 85.1–92.2%) (FLASH FFR)
Advantages	-Outcome data at 15 years (DEFER) -Well validated with non-invasive physiologic assessments [11]	-iFR is non inferior to FFR for guiding PCI at 2 years (DEFINE-FLAIR, iFR SWEDEHEART) -Validated with non-invasive studies [20–22] -Hyperemia independent -Quicker than FFR -Ability to assess serial lesions [28] -Fewer reported adverse procedural symptoms (DEFINE-FLAIR, iFR SWEDEHEART)	-Hyperemia independent -Pressure-wire not needed -Low inter-user variability	-Hyperemia independent -Pressure-wire not needed -Visualization of the entire coronary tree could improve management of complex anatomy	-Hyperemia independent -Pressure-wire not needed -Measurement does not rely on generic boundary conditions -Shorter time to perform than FFR (Favor II Europe-Japan)	-Hyperemia independent -Pressure-wire not needed -May provide a rapid assessment of the entire coronary tree and post PCI -Utilizes real-time aortic pressure during angiography accounting for dynamic changes with PCI

Table 1. (continued)

FFR	iFR	vFFR	FFRangio	QFR	cFFR
<p>Disadvantages</p> <ul style="list-style-type: none"> -Pressure wire required (additional cost and wire and guide catheter-related complications) -Discomfort with hyperemia -Poor assessment of serial lesions [28] -Poor assessment post MI [30] -Poor assessment with MVCAD [17, 25] -Poor assessment with aortic stenosis [31] 	<ul style="list-style-type: none"> -Pressure wire required (additional cost and wire and guide catheter-related complications) -Specific software needed for computation 	<ul style="list-style-type: none"> -No outcomes evidence -Not validated against noninvasive functional testing -Specific angiographic views required -Specific software needed for computation -Utilizes generic boundary conditions 	<ul style="list-style-type: none"> -No outcomes evidence -Not validated against noninvasive functional testing -Specific angiographic views required -Specific software needed for computation 	<ul style="list-style-type: none"> -No outcomes evidence -May require extra user interaction to accurately depict stenoses from the 3D QCA -Not validated against noninvasive functional testing -Specific angiographic views required -Coronary flow velocities do not account for changes in hemodynamics or differences in coronary artery flow 	<ul style="list-style-type: none"> -No outcomes evidence -cFFR data comes from a sub-study from a prospective, multicenter trial -Not validated against noninvasive functional testing -Specific software needed for computation -Utilizes generic boundary conditions -Unclear utility for complex lesions

the phantom lesions was compared to the reference standard computations of CFD [38, 39, 42] and the CAAS Workstation 8 software. Pulsatile and constant flow-based measurements corresponded well, supporting the previous assumption by Morris et al. that a single, steady-flow value assessment is adequate [39, 41]. There was also an excellent agreement between the in vitro model and CAAS Workstation vessel FFR pressure drop results ($r > 0.99$; $p < 0.002$) [41••].

The FAST study then retrospectively compared invasive FFR with vessel FFR. Computation of the vessel FFR utilized conventional angiography, in comparison with rotational coronary angiography in the VIRTU-1 study. Three two-dimensional images of two vessels acquired in projections at least 30° apart in angulation were utilized to model entire vessels and adjust for overlapping and foreshortening, and one view was used to see the position of the FFR wire. Vessel FFR had a good linear correlation with invasive FFR ($r = 0.89$; $p < 0.001$) and accuracy for identifying patients with significant FFR values (area under the receiver operating characteristic curve [AUC] of 0.93; 95% CI: 0.88–0.97) [41••]. Additionally, there was low inter-user variability ($r = 0.95$; $p < 0.001$) [41••]. This vFFR platform is commercially available in the USA and Europe (PIE Medical Imaging, Biltoven, the Netherlands, Figure 1).

Papfaklis et al. also used a similar steady-state CFD analysis with the CAAS QCA-3D system to compute a virtual functional assessment index (vFAI) based on the distal pressure to proximal pressure ratio over a lesion for flows of 1–4 ml per second, normalized against the flow of a normal artery over this range [43]. Siogkas et al. expanded vFAI technology past a coronary angiography-based assessment to utilize CCTA and intravascular ultrasound [44, 45]. The limitation of vFAI is that it is entirely a function of geometric stenosis, ignoring significant changes in the coronary microvasculature; therefore, it cannot be a surrogate for FFR [43, 44].

The FLASH FFR trial introduced a different CFD model with the FlashAngio software (Rainmed Ltd., Suzhou, China), which in combination with thrombolysis in myocardial infarction (TIMI) frame counts from two angiographic projections $\geq 30^\circ$ apart was used to calculate a virtual contrast FFR (cFFR) [46•]. The diagnostic accuracy of a significant virtual cFFR ≤ 0.94 to predict an FFR ≤ 0.80 was 89.0% (95% CI: 85.1–92.2%) [46•]. While encouraging, these data come from a sub-study of FLASH FFR, and larger focused trials to validate virtual cFFR as an independent physiologic assessment are needed.

The FAVOR (Functional Assessment by Various Flow Reconstructions) pilot study introduced quantitative flow ratio (QFR) as another method for computation of FFR based upon 3D-QCA with end-diastolic frames from two angiographic projections at least 25° apart to create a three-dimensional reconstruction of a vessel [47]. The estimated contrast flow velocity is then determined utilizing a contrast frame count,

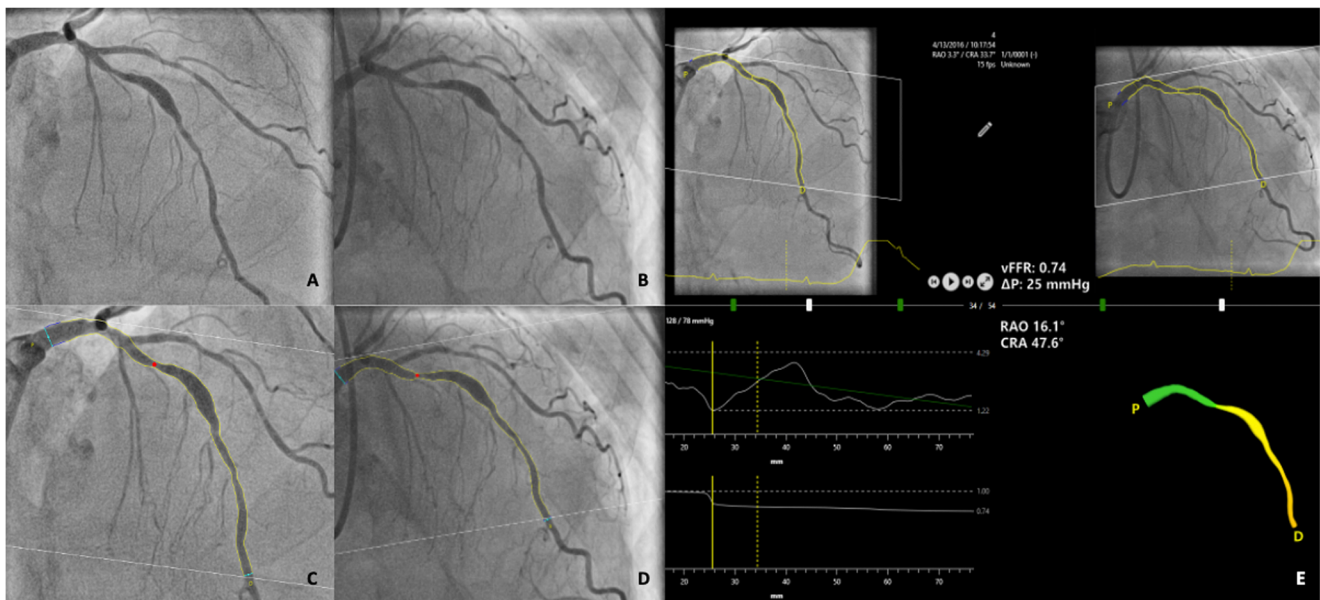


Figure 1. Utilizing two angiograms $\geq 30^\circ$ apart (A, B), the CAAS virtual fractional flow reserve (vFFR) software maps the stenosis of interest (C, D) and generates a three-dimensional reconstruction (E), from which the vessel FFR physiologic assessment may be calculated at any specified

point along the coronary artery in addition to anatomic information including the percentage stenosis, reference and lesion diameters, and the lesion borders. Images courtesy of PIE Medical Imaging

and QFR is computed with the QAngio XA 3D/QFR system (Medis Medical Imaging Systems, Leiden, The Netherlands) [47]. This computation relies on estimating the coronary pressure drop based on stenosis geometry and on the assumption that the flow velocity is preserved across lesions. The mass flow rate of coronary arteries decreases with artery tapering and side branches; hence, the mass flow rate at a specific point of a vessel can be determined by the mean flow velocity and the reference sizing from 3D-QCA [47]. The performance of QFR to predict an $\text{FFR} \leq 0.80$ was 83% in the WIFI II (Wire-Free Functional Imaging II) trial, 86.8% in the FAVOR II Europe-Japan trial, and 92.7% in the FAVOR II China trial [48–50]. In FAVOR II Europe-Japan, the QFR was computed in a median time of 5 min versus 7 min for FFR [49]. One additional benefit of QFR over vFFR and vessel FFR calculations is that QFR does not rely on generic boundary conditions [49]. Conversely, a drawback of QFR is that coronary flow velocity may be impacted by heart rate, blood pressure, left ventricular end-diastolic pressure, and right/left ventricular hypertrophy [41••]. Furthermore, flow in the left coronary artery is predominantly diastolic and in the right coronary artery is both systolic and diastolic [41••]. These variables could lead to significant differences in inter-observer or inter-study contrast frame counts and QFR measurements that were not addressed in the FAVOR II or WIFI II trials [41••].

Coronary angiography-derived FFR ($\text{FFR}_{\text{angio}}$) utilizes two or more single-plane angiograms with a minimum separation of 30° and the CathWorks console (Kfar Saba, Israel) to reconstruct the coronary artery network as an electric circuit [51•]. Each segment acts as a resistor, and the vessel resistance

is calculated based on its length and resistance. Normal maximal flow is based on the volume of the vessel and the total coronary length. The $\text{FFR}_{\text{angio}}$ is then calculated as the ratio of maximal flow rate in the stenosed artery to the maximal flow in the absence of the stenosis, utilizing a value of ≤ 0.80 as physiologically significant [51•]. The FAST-FFR ($\text{FFR}_{\text{angio}}$ Accuracy versus Standard FFR) trial demonstrated the diagnostic accuracy of $\text{FFR}_{\text{angio}}$ to predict an $\text{FFR} \leq 0.80$ to be 92.2% (95% CI, 88.7–94.8) [51•]. One benefit of $\text{FFR}_{\text{angio}}$ is the ability to map the entire coronary tree, which could assist with complex anatomy [51•].

Physiologic Assessment After PCI: a Measurement of Success

Post-PCI hemodynamic assessment can be performed to ensure optimization of stenting results and can predict the long-term risk of adverse outcomes. Agarwal et al. found that post-PCI FFR reclassified 21% of angiographically satisfactory PCI results as persistently ischemic (with post-PCI FFR of ≤ 0.81) [52]. These findings were echoed in the DEFINE PCI trial (Physiologic Assessment of Coronary Stenosis Following PCI), where residual ischemia (assessed with a post-PCI iFR < 0.90) was found in 21.9% of vessels after angiographically satisfactory PCI [53]. Of these vessels, 81.6% had residual discrete lesions proximal or distal to the stent, and 18.4% had diffuse disease [53]. While the shortcomings of FFR in the setting of diffuse disease has been previously discussed, these findings also challenge the validity of iFR to assess

serial lesions with a more diffuse pattern. To date, this potential shortcoming of iFR efficacy has not been validated against FFR [28].

Agarwal et al. described how lesions with a final FFR ≤ 0.86 predicted a significantly higher risk of major cardiac events (23% vs. 17%, $p = 0.02$); however, it is unknown if acting on a post-PCI low FFR valve is beneficial. A meta-analysis by Rimac et al. suggested that a post-PCI FFR ≥ 0.90 showed a lower risk of repeat PCI (odds ratio [OR] 0.43; 95% CI: 0.34–0.56; $p < 0.001$) and MACE (OR 0.71; 95% CI: 0.59–0.85; $p = 0.0003$). Despite these advances, Tebaldi et al. report that wire-based physiologic assessment after PCI is performed in only 13% of pressure-wire-guided procedures [54].

The Evolution of Virtual Coronary Interventions

As an extension of their previous work with CFD and vFFR, Gosling et al. have designed a paradigm for VCI, which allows an idealized virtual stent to be inserted and the resultant vFFR calculated [55••]. This prospective study analyzed angiographic and pre- and post-PCI invasive FFR measurements using conventional coronary angiography with VCI and vFFR measurements. The VIRTUheart workflow was used as an offline analysis with a Philips 3D workstation to obtain vessel geometry, stent dimensions, and position with input and output measurements from the VIRTU-1 study that were utilized [38, 39]. CFD analysis was allowed in all vessels and computational time averaged 95 s per case.

Before PCI, the mean FFR was 0.66 ± 0.14 and vFFR was 0.68 ± 0.13 [55••]. The diagnostic ability of vFFR to predict ischemia (FFR ≤ 0.80) was 93% [55••]. After PCI, the mean FFR was 0.90 ± 0.05 and vFFR was 0.92 ± 0.05 [55••]. Gosling et al. thereby demonstrated that vFFR analysis can be produced in minutes, no more time than a post-PCI FFR assessment, and without the risk of an additional wire or adverse effects of hyperemia.

Additionally, this novel application of vFFR allows simulated stent placement based on invasive angiography with pre- and post-PCI physiologic assessments. The ability to predict the outcome of different stenting techniques provides operators with the capability to select the optimal patient-specific approach to PCI, and the final vFFR value can be used to predict the future risk of MACE [56, 57]. VCI also overcomes the shortcomings of FFR and iFR to assess tandem and diffuse lesions by treating them virtually [55••].

Conclusion

Physiologic assessment of CAD is a cornerstone of decision-making to guide and evaluate revascularization, and

importantly FFR-guided PCI has been shown to reduce MACE. The development of vFFR and vessel FFR may help with limitations of FFR and iFR. Initial computational time challenges of vFFR have been overcome with incorporation of a non-inferior steady-state model in place of a fully transient CFD model. Continued research in coronary microvascular disease, improvements in the generic output parameters, and advancements in coronary flow hemodynamic models will provide more accurate assessments of vFFR, vFAI, virtual cFFR, QFR, and FFR_{angio}. Nascent VCI technology represents a burgeoning field of personalized revascularization strategies beyond conventional angiography with computer-simulated stenting including pre- and post-PCI virtual FFR analysis to predict the physiologic response to PCI with a high degree of accuracy. We now await additional clinical trials addressing the benefits of these approaches on clinical outcomes; technology dissemination and reimbursement must also be addressed to increase the application of these novel technologies.

Declarations

Conflict of Interest Dr. Goldsweig reports grant support from the National Institute of General Medical Sciences, 1U54GM115458, and the UNMC Center for Heart and Vascular Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. None of the other authors report any conflicts of interest to disclose.

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