Angiography-Based FFR: Reevaluating the Role of the Pressure Wire

Reviewing the nuances of coronary angiography–based FFR and results of initial validation studies.

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Assessment of coronary stenosis severity by a visual estimate of the coronary angiogram has traditionally served as the cornerstone for the diagnosis of patients with known or suspected coronary artery disease (CAD). In contrast to visual assessment, quantitative coronary angiography (QCA) allows for a more accurate estimation of both the diameter stenosis and length of a coronary lesion, parameters that proved to contribute to resistance to blood flow. As such, QCA-based percentage diameter stenosis is commonly used to detect the presence of obstructive CAD. However, in the current era, the use of coronary physiology to assess coronary stenosis severity is gaining importance and is recommended by international revascularization guidelines to guide revascularization strategies.

FRACTIONAL FLOW RESERVE

In the past decade, a wealth of data have become available demonstrating pitfalls of angiographic lesion assessment. To overcome these limitations, fractional flow reserve (FFR) has emerged as the mainstay of functional hemodynamic assessment of coronary artery lesions and is presently regarded as the gold standard for identifying stenoses that cause myocardial ischemia. Several reports have described the discordance between anatomic and functional assessment of coronary lesions, showing that mismatch (ie, anatomically significant but hemodynamically nonsignificant lesions) and reverse mismatch (ie, anatomically nonsignificant but hemodynamically significant lesions) were far from rare. As such, angiographic-FFR mismatch was found in 43.4% of lesions, whereas reverse angiographic mismatch was found in 23.2%. With subsequent clinical validation studies demonstrating significantly better short- and long-term outcomes with FFR-guided percutaneous coronary intervention (PCI) as compared with angiography-guided PCI, FFR has become an established modality in the evidence-based management of patients with CAD. Unfortunately, even 25 years after the introduction of FFR and despite indisputable evidence supporting the benefit of FFR to guide clinical decision-making, adoption into daily practice has been limited. This has been hypothesized to be due to the need for pressure wires or microcatheters, time-consuming FFR procedures, and (in some countries) expensive hyperemic agents with known adverse events, such as dyspnea and arrhythmias and/or intolerance due to pulmonary disease. However, the majority of these arguments were refuted in clinical trials in which the use of FFR was not associated with longer procedure times and/or higher costs.

NONHYPEREMIC PRESSURE RATIOS

In recent years, the instantaneous wave-free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (Pd/Pa) were introduced as alternative invasive indices to assess the severity of coronary artery stenosis without the need for hyperemic agents. Although Pd/Pa represents the ratio from the mean resting distal pressure to aortic coronary pressure during the entire cardiac cycle, iFR is based on the same ratio measured during the so-called wave-free period, the period during diastole in which the microvascular resistance is low and constant. Because the proprietary algorithm of iFR is linked to a single vendor, several validation studies were recently performed to find more generic options to calculate so-called nonhyperemic pressure ratios (NHPRs). As such, a good correlation was found between iFR and several NHPRs, including the diastolic pressure ratio and resting full-cycle ratio, among others. Although NHPRs have emerged as adenosine-free, faster, and easier methods to achieve physiologic assessment, the need for a costly pressure wire or microcatheter remains a fact. For these reasons, the search for cheaper, faster, and more patient-friendly methods to assess coronary physiology remains imperative to increase its use in routine daily practice. Therefore, a modality combining functional and anatomic evaluation of epicardial coronary artery lesions in a single noninvasive test
would help increase the use of coronary physiology in catheterization laboratories worldwide.

**COMPUTATIONAL FLUID DYNAMICS AND FFRCT**

There has been a growing interest in noninvasive FFR derived from coronary CTA (FFRCT) using the concepts of computational fluid dynamics (CFD). CFD is a well-known and widely used method in mechanical engineering to solve complex problems by analyzing behaviors including fluid flow, heat transfer, and associated phenomena using computer simulations. The governing equations of fluid dynamics, (ie, the Navier-Stokes equations) can be calculated to obtain coronary flow and pressure. To simulate realistic coronary blood flow, a domain of interest must be defined and boundary conditions must be specified. The isolation and generation of boundary conditions are challenging steps in integrating CFD to assess the physiologic significance of CAD.

The prospective, multicenter DISCOVER-FLOW trial demonstrated a diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 84.3%, 87.9%, 82.2%, 73.9%, 92.2%, respectively, for FFRCT, and 58.5%, 91.4%, 39.6%, 46.5%, 88.9%, respectively, for coronary CTA to identify a positive FFR as assessed using conventional pressure wires. In the PLATFORM study, the use of FFRCT was associated with a reduction of unnecessary coronary angiographic procedures, while maintaining the same number of patients who underwent PCI. Therefore, FFRCT proved to be a reliable gatekeeper to invasive coronary angiography and revascularization, which may have significant health and economic implications. However, as FFRCT is based on the reconstruction of an accurate anatomic model of the epicardial coronary arteries derived from coronary CT scan data, any artifacts that significantly compromise image quality can impact assessment of the lumen and limit diagnostic accuracy of FFRCT. Although the technology is quickly gaining momentum in patient screening and even more comprehensive procedural planning, the technology is still hampered by long computation times and, at present, a lack of reimbursement in the majority of countries.

**CORONARY ANGIOGRAPHY (3D-QCA)–BASED FFR**

Despite excellent results of FFRCT studies, there is an ongoing search for tools that allow online physiologic lesion assessment with the potential to be integrated into daily clinical practice. In 2000, the ANGUS study demonstrated that three-dimensional (3D) reconstruction of coronary arteries can be successfully performed by combining orthogonal angiographic projections of the coronary along with intravascular ultrasound images. Schuurbiers et al demonstrated that the CAAS Workstation QCA-3D system (Pie Medical Imaging) allows 3D reconstruction of human coronary arteries based on biplane angiographic projections. Validation of the CAAS QCA-3D system against the ANGUS system (3D reconstruction based on fusion of angiography and intravascular ultrasound) showed that both the 3D geometry and lumen areas were highly correlated and set the stage for more comprehensive CFD.

Within the last few years, the CAAS Workstation software (Pie Medical Imaging) has been modified to integrate a simplified method for calculating 3D-QCA–based FFR. The software allows instantaneous calculation of pressure drops by applying physical laws including viscous resistance and turbulent effects of coronary flow, as described by Gould et al and Kirkeeide. Within these physical laws, both Gould et al and Kirkeeide incorporated viscous and separation loss effects into coronary flow behavior. The proposed methods are based on a single angiographic x-ray projection. Within the CAAS Workstation, the geometry of the coronary artery is derived from well-validated 3D coronary reconstruction technique, which reduces the effects of foreshortening, out-of-plane magnification, and nonsymmetric coronary lesions during the pressure drop calculations.

One of the first studies validating the software with more extensive CFD was performed by Papafaklis et al in which a method for fast virtual functional assessment of intermediate coronary lesions using routine x-ray angiography (ie, virtual Functional Assessment Index [vFAI]) was described. To compute the vFAI, the $f_s$ and $f_q$ parameters were derived from the artery-specific quadratic equation $\Delta P = f_s, Q + f_q, Q^2$ by performing two separate CFD simulations using the geometry resulting from 3D-QCA. After solving $f_s$ and $f_q$, the vFAI was calculated as the ratio of the area under the curve $(P_d/P_a = 1 - f_s, Q/P_a - f_q, Q^2/P_a)$ for a flow ranging from 0 to 4 mL/s. The authors concluded that vFAI showed a high diagnostic performance and incremental value to QCA for predicting FFR.

**Validation Studies of Coronary Angiography–Based FFR**

The software and algorithms of (at present) three different vendors matured over time applying several assumptions, such as using steady flow instead of transient flow, which proved to have only limited impact on the average pressure distribution over the cardiac cycle, significantly reducing computation times from hours to seconds. Table 1 summarizes the commercially available software packages to calculate angiography-based FFR.

**QAngio XA.** The FAVOR pilot study assessed the diagnostic accuracy of quantitative flow ratio (QFR) as measured offline in three ways based on the different mean hyperemic flow velocities: (1) fixed empiric hyperemic flow velocity (fQFR), (2) modeled hyperemic flow velocity derived from angiography without drug-induced hyperemia (cQFR), and (3) measured hyperemic flow velocity...
derived from angiography during adenosine-induced hyperemia (aQFR). The authors observed a good agreement with FFR for all three QFR values with mean differences of 0.003 ± 0.068; 0.001 ± 0.059; and 0.001 ± 0.065 for fQFR, cQFR, and aQFR, respectively. The diagnostic accuracy for identifying a positive FFR (FFR < 0.80) was 80%, 85%, and 87% for fQFR, cQFR, and aQFR, respectively. In the prospective, multicenter FAVOR II China study, a contrast flow model used a frame count method to derive contrast flow velocity from coronary angiography calculated offline QFR (QAngio XA, Medis Medical Imaging BV). On a vessel and patient level, the diagnostic accuracy of QFR in identifying hemodynamically significant coronary stenosis was 97.7% and 92.4%, respectively. The FAVOR II Europe-Japan trial demonstrated the superiority of online computation of QFR in a multicenter setting as compared with two-dimensional QCA in terms of sensitivity and specificity with pressure wire–based FFR as the gold standard (86.5% vs 44.2% [P < .001] and 86.9% vs 76.5% [P = .002], respectively). However, both FAVOR studies only enrolled selected patients, excluding bifurcation lesions and diameter stenosis < 30% or > 90%, and no interobserver variability was assessed. At present, both the FAVOR III China (NCT03656848) and FAVOR III Europe Japan (NCT03729739) are enrolling patients. FAVOR III China is a prospective, multicenter, blinded, randomized superiority trial comparing the clinical outcome and cost-effectiveness of QFR-guided PCI versus angiography-guided PCI. The FAVOR III Europe Japan study aims to assess if a QFR-based diagnostic strategy yields a noninferior 12-month clinical outcome as compared with a pressure wire–based FFR strategy in 2,000 patients with stable angina or stabilized non–ST-segment myocardial infarction and intermediate coronary stenosis in up to 40 international sites.

**FFRangio System.** Another technology that provides functional angiographic mapping of the entire coronary tree is the FFRangio system (CathWorks). FFRangio is a computational method based on rapid flow analysis for the assessment of FFR. FFRangio uses the patient’s hemodynamic data and routine angiograms to generate a complete 3D coronary tree with color-coded FFR values at any epicardial location. Hyperemic flow ratio is derived from an automatic resistance-based lumped model of the entire coronary tree using allometric scaling laws. Pellicano et al demonstrated a high concordance between off-site measured FFRangio and pressure wire–based FFR. FFRangio was recently validated in the FAST-FFR study, a prospective multicenter trial that compared the accuracy of on-site FFRangio with pressure wire–based FFR. The study demonstrated a high sensitivity (94%), specificity (91%), and accuracy (92%). A limitation of this study was the lack of information regarding the total time needed to calculate FFRangio. At present, no inter- or intraobserver variability has been reported for FFRangio.

### TABLE 1. AVAILABLE SOFTWARE FOR CORONARY ANGIOGRAPHY-BASED FFR CALCULATION

<table>
<thead>
<tr>
<th>Company</th>
<th>Product Name</th>
<th>Acronym Index</th>
<th>Validation Study</th>
<th>Correlation With Pressure Wire FFR</th>
<th>Bias Mean ± SD</th>
<th>AUC CI (95% CI)</th>
<th>Interobserver Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medis Medical Imaging Systems, BV</td>
<td>QAngio XA</td>
<td>QFR</td>
<td>FAVOR Pilot Study</td>
<td>0.77</td>
<td>0.001 ± 0.06</td>
<td>0.92 (0.85–0.97)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FAVOR II China</td>
<td>0.86</td>
<td>0.01 ± 0.06</td>
<td>0.96 (0.94–0.98)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FAVOR II Europe-Japan</td>
<td>0.83</td>
<td>0.01 ± 0.06</td>
<td>0.92 (0.89–0.96)</td>
<td>N/A</td>
</tr>
<tr>
<td>CathWorks</td>
<td>FFRangio system</td>
<td>FFRangio</td>
<td>Pellicano et al</td>
<td>0.88</td>
<td>0.007 ± 0.05</td>
<td>N/A</td>
<td>R = 0.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FAST-FFR study</td>
<td>0.80</td>
<td>-0.14 ± 0.12</td>
<td>0.94 (0.92–0.97)</td>
<td>N/A</td>
</tr>
<tr>
<td>Pie Medical Imaging</td>
<td>CAAS 3D-QCA</td>
<td>vFFR</td>
<td>FAST study</td>
<td>0.89</td>
<td>0.01 ± 0.04</td>
<td>0.93 (0.88–0.97)</td>
<td>R = 0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FAST II study*</td>
<td>*</td>
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</tbody>
</table>

Abbreviations: 3D, three-dimensional; AUC, area under the curve; CI, confidence interval; FFR, fractional flow reserve; N/A, not available; QCA, quantitative coronary angiography; QFR, quantitative flow reserve; SD, standard deviation; vFFR, vessel FFR.

*Multicenter, international, prospective, observational validation study of vFFR, ongoing (NCT03791320).
work showed the high prevalence of suboptimal FFR curves in clinical practice (up to 30%), suggesting an additional benefit when using techniques based on angiography and simplified flow models. A larger international, prospective, multicenter trial (FAST II, NCT03791320) is currently ongoing to assess the diagnostic accuracy of both online and core lab–assessed vFFR as compared with conventional pressure wire–based FFR for intermediate coronary artery lesions in patients with stable and unstable CAD.

Poststenting Angiography-Based FFR

FFR has been predominantly used to assess coronary stenosis severity prior to PCI. However, there is increasing interest in the use of post-PCI physiologic assessment considering that several studies have shown that post-PCI FFR is a strong and independent predictor of clinical outcome. Previous work from our group has provided more insights of the potential for a post-PCI FFR < 0.85 using high-definition intravascular ultrasound. Stent underexpansion was the most frequently identified cause, found in 74% of the cases, followed by clear focal signs of luminal narrowing (54%), focal lesions distal to the stent (30%), residual lesions proximal to the stent (29%), and stent malapposition (22%). The latter results further support the hypothesis that post-PCI FFR increases the likelihood of identifying residual disease that might warrant additional treatment and optimize long-term results. However, at present, post-PCI FFR is rarely performed due to a number of reasons, including pressure wires that were used pre-PCI and are damaged, additional time needed to repeat the FFR assessment, expense and side effects of hyperemic agents, and because the majority of interventionalists still strongly believe in their ability to achieve a satisfactory PCI result based on angiography alone. A 3D-QCA–based physiologic lesion assessment after PCI could therefore drastically change the way we adjudicate our results in daily practice. The FAST POST study demonstrated good correlation between conventional invasive post-PCI FFR and 3D-QCA–based FFR and had a high diagnostic accuracy to identify a conventional post-PCI FFR < 0.90.

ADVANTAGES AND LIMITATIONS OF ANGIOGRAPHY-BASED FFR

Coronary angiography–based FFR has several potential advantages as compared with conventional pressure wire–based FFR. The computations of angiography-based FFR are fast and have the potential to provide wireless FFR stenosis assessment for almost all angiographic procedures, either pre-, periprocedural, and post-PCI. Second, although pressure wire–based complications are unlikely, this risk would be eliminated with angiography-based FFR. Pressure wire–based FFR requires the use of intracoronary or intravenous drugs to achieve a hyperemic condition and has potential side effects; these drugs would not be required and thus FFR assessment would be more patient-friendly. Recent research concluded that even in dedicated multicenter trials, a significant amount of drift might occur with pressure wire–based FFR, in addition to an up to 30% likelihood that FFR values are based on dampened pressure waveforms due to inadequate position of the guiding catheter or suboptimal flush.

Coronary angiography–based FFR is still in an early stage of development, and no outcome studies have been performed confirming the applicability of the technique in routine clinical practice. As previously mentioned, none of the currently available software solutions have been tested to guide clinical decision-making in routine practice. In all studies, the calculation of angiography-based FFR was performed by highly trained individuals, which might have influenced the FFR results in a positive way. Second, as with any new technology introduced into clinical practice, there is a learning curve on how and how not to use the technology. At present, accurate performance is only possible if dedicated online image exports are made. The images subsequently need to be assessed by adequately trained staff familiar with the concepts of QCA. Optimal angulations, avoidance of overlap, and accurate contour correction proved to be key to achieve optimal results, and more specifically, all of these can only work after acquiring decent-quality angiograms. Although this might sound trivial, previous studies showed that up to 65% of routine angiograms are of insufficient quality to be used in 3D-QCA–based FFR software due to insufficient luminal contrast opacification, overlap, or lack of adequate orthogonal projections.

The accuracy of the software in complex vessels (eg, bifurcations, left main disease, heavily calcified vessels, diffusely diseased vessels) remains to be determined in larger patient cohorts. Furthermore, the image acquisition requirements and the user interface of an angiography-based FFR system should be seamlessly incorporated into the standard work of the catheterization laboratory. Additionally, the CFD...
equations require several assumptions from a population model regarding myocardial blood flow rates as a function of the myocardial arterial branches and the resistance of the myocardium. Because coronary flow velocity is a highly sensitive variable that is influenced by clinical and hemodynamic parameters (including heart rate, blood pressure, left ventricular end-diastolic pressure, left and/or right ventricular hypertrophy, and systemic diseases such as diabetes mellitus and large vessel disease), there will probably be patient-specific errors related to abnormal coronary physiology, which may account for outliers in the correlation between angiography-based FFR and pressure wire–based FFR.

CONCLUSION

There is a clear need to simplify the use of coronary physiology to increase its uptake in daily clinical practice. The advent of coronary angiography–based FFR looks promising, and the first clinical validation studies of at least three different vendors showed results that are almost too good to be true. Once the technology becomes more widely available, it might fundamentally change the way both diagnostic coronary angiography and PCI will be performed. For the time being, the results of planned and ongoing clinical outcome studies are eagerly awaited to determine the value of angiography-based FFR in daily clinical practice.

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