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INTRAVASCULAR IMAGING (A. G. TRUESDELL, SECTION EDITOR)

Contrast Fractional Flow Reserve (cFFR) and Computed Tomography Fractional Flow Reserve (CT-FFR) Guidance for Percutaneous Coronary Intervention (PCI)

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Abstract

Purpose of Review In this review, we summarize both contrast fractional flow reserve (cFFR) and computed tomography fractional flow reserve (CT-FFR) as novel modalities to evaluate the hemodynamic significance of coronary artery stenoses and to guide percutaneous coronary intervention (PCI).

Recent Findings Implementation of cFFR can reduce the time, cost, effort, and patient discomfort associated with traditional adenosine FFR. Clinical outcomes following cFFR-guided revascularization are currently under investigation. Emerging data on the use of CT-FFR in patients with acute coronary syndromes may increase the use of this technology in acute settings, while virtual stenting applications to model the hemodynamic results of stent placement may help optimize PCI planning.

Summary Using contrast media already available for traditional angiography, cFFR yields results that are highly reproducible and correlate more closely with traditional adenosine FFR than the distal/aortic pressure ratio (Pd/Pa) or the instantaneous wave-free ratio (iFR). Based upon computational fluid dynamics, CT-FFR provides a non-invasive estimate of the traditional adenosine FFR and predicts ischemia more accurately than nuclear imaging. Therefore, CT-FFR has begun to take on a gatekeeper role to minimize unnecessary invasive angiography.

Keywords Contrast fractional flow reserve · Computed tomography fractional flow reserve · Percutaneous coronary intervention · cFFR · CT-FFR · PCI

Introduction

Fractional flow reserve (FFR) is a well-validated index for assessment of the physiological significance of coronary artery stenosis [1]. FFR is defined as the maximal blood flow to the myocardium supplied by a coronary artery in the presence of stenosis (Qs) divided by the theoretical maximal flow in the same distribution (Qn) [2]. Under maximal hyperemia, achieved with vasodilating agents such as adenosine, coronary resistance is constant and minimal; thus, a direct relationship exists between coronary flow and pressure. FFR can therefore be measured by the ratio of pressure gradient in the presence of stenosis (Qs) divided by the pressure gradient under normal circumstances (Qn), such that

$$FFR = Qs/Qn = (Pd-Pv)/(Pa-Pv)$$

where Pd is the pressure distal to stenosis, Pv is the venous pressure, and Pa is the aortic pressure. Assuming Pv is

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significantly smaller than Pd and Pa, the above equation can be simplified as FFR = Pd/Pa [3]. In the cardiac catheterization laboratory, this measurement may be made by passing a pressure-transducing wire through a guide catheter and measuring pressures simultaneously at the aortic level using the guide catheter and distal to the stenosis using the pressure-transducing wire, under maximal hyperemia.

FFR has been shown to be an effective tool to guide revascularization in the setting of intermediate stenosis severity and to improve clinical outcomes [4, 5]; however, FFR remains underutilized due to patient discomfort with hyperemic agents, time constraints, logistical challenges with the use of instruments, reimbursement policies, and operator opinions regarding coronary physiology [6, 7]. Several resting indices have emerged as alternatives to overcome these challenges and have been studied extensively in the last decade, most notably the instantaneous free-wave ratio (iFR). More recently, contrast FFR (cFFR) and computed tomography FFR (CT-FFR) have been developed as novel modalities to evaluate the hemodynamic significance of coronary stenoses. In this article, we will review cFFR and CT-FFR as well as the literature evaluating the use of these assessments to guide percutaneous coronary intervention (PCI).

FFR as the Gold Standard

Invasive FFR with adenosine is considered the gold standard for evaluating the hemodynamic significance of coronary artery stenosis. In 1996, Pijls et al. demonstrated that an FFR value ≤ 0.75 correlated well with inducible ischemia on nuclear stress testing [8]. In 2001, the DEFER trial measured FFR in 325 patients without evidence of ischemia on noninvasive testing [9]. Those with FFR > 0.75 were randomized to immediate angioplasty or deferral of angioplasty. At 24 months, cardiovascular event-free survival was similar in both groups (83% for angioplasty vs. 89% for deferral, $p = 0.27$), thus indicating that revascularization could be safely deferred in patients with FFR > 0.75. Subsequently, the 2009 FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial randomized 1005 patients with multivessel coronary artery disease (CAD) to undergo PCI with drug-eluting stent (DES) implantation guided by angiography alone versus angiography plus FFR; PCI was performed if FFR ≤ 0.80 [10]. The cutoff value of 0.80 was chosen to minimize the number of untreated ischemic lesions in the small transition zone (FFR 0.75–0.80). The composite incidence of death, myocardial infarction (MI), and repeat revascularization (PCI and/or coronary artery bypass grafting) at 1 year was 28% lower in the angiography + FFR group than in the angiography-only group. The FAME 2 trial enrolled patients with chronic stable CAD and FFR ≤ 0.80, randomizing them to optimal medical therapy versus PCI [11]. The study was stopped prematurely because of a significant difference in 2-year composite death, MI, and urgent revascularization between the two groups (4.3% with PCI vs. 12.7% with medical therapy, hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.19–0.53, $p < 0.001$), a difference that persisted at 5-year follow-up [5]. As a result, FFR ≤ 0.80 is now recognized as the threshold for revascularization. A recent study including patients from FAME 1 and FAME 2 demonstrated that the larger the increase in FFR post-PCI, the more symptom relief patients experienced [12]. Moreover, the incidence of clinical events (cardiac death, MI, revascularization) was lower with higher post-PCI FFR. This study highlighted the importance of measuring FFR before and after PCI.

European Society of Cardiology guidelines give a class I recommendation and US multisociety guidelines give a class IIa recommendation to measure FFR to assess the hemodynamic significance of intermediate stenoses, and revascularization is recommended in the setting of stable angina and abnormal FFR indices [13, 14]. FFR of ≤ 0.80 is also included in the most recent US multisociety appropriate use criteria as an indication for revascularization of non-culprit lesions of intermediate severity in the setting of acute coronary syndromes [15].

Contrast Fractional Flow Reserve

Contrast as a Hyperemic Agent

Despite these guideline recommendations, FFR is underutilized, as shown by a recent study of Veterans Affairs patients with stable ischemic heart disease and intermediate (40–69% diameter) stenoses on angiography. FFR guidance was utilized in only 16.5% of 17,989 cases [7], although it was associated with a 43% reduction in 1-year mortality. One reason for underutilization of FFR is vasodilator side effects: adenosine may cause chest pain, dyspnea, flushing, and AV block [16], while other vasodilators such as nitroprusside and papaverine have been limited by hypotension and bradycardia [17, 18].

While indices such as Pd/Pa and iFR may avoid vasodilation entirely [19, 20], radiographic contrast media itself can also serve as a well-tolerated hyperemic agent. The hyperemic potential of contrast was first identified in 1959 by Guzman et al., who injected five different types of contrast into the coronary circulation of mongrel dogs and observed an average of 60% increase in coronary blood flow compared to rest [21]. Sodium diatrizoate, a high osmolality agent, was used as a hyperemic agent by K Lance Gould in his groundbreaking canine experiments that formed the foundation of coronary physiology and myocardial perfusion [22]. Newer low osmolality non-ionic contrast agents act similarly and with fewer side effects. De Bruyne et al. demonstrated the hyperemic effect of intracoronary ioxehol injection in humans, although

the response was less than with papaverine or adenosine [23]. Most contrast agents appear to work similarly, with iomeprol, iopromide, and iodixanol being the most studied (Table 1). The principal benefit of using contrast as a hyperemic agent for computing FFR is that contrast is already available and being used for coronary angiography. A small amount of additional contrast may be injected after diagnostic angiography, and cFFR may be measured using a standard pressure wire.

Correlation with FFR

Multiple studies have shown a strong correlation between cFFR and FFR. RINASCI (Rapid Injection of Contrast Medium vs. Nitroprusside or Adenosine in Intermediate Coronary Stenoses) was the first study that prospectively tested the accuracy of cFFR compared to FFR [24]. Eighty patients with 104 intermediate coronary stenoses underwent intracoronary injection of 6 ml of a non-ionic radiocontrast material (iomeprol) followed by measurement of Pd/Pa ratio using a pressure wire. This index, termed contrast medium-induced Pd/Pa ratio (CMR) by the authors, is now called cFFR. Subsequently, FFR was measured under maximal hyperemia using intracoronary or intravenous adenosine. A strong correlation was seen between cFFR and FFR ($r^2 = 0.88$, $p < 0.001$) with close agreement between the two indices using Bland Altman analysis (0.02 ± 0.02, 95% CI of disagreement -0.03–0.07). Furthermore, receiver operating characteristics (ROC) curves showed excellent accuracy with cFFR cutoff of ≤ 0.83 for prediction of FFR value of ≤ 0.80 (area under the curve [AUC] 0.98 [95% CI 0.93–0.99] with a specificity of 97.4% and sensitivity of 85.7%). They also found that cFFR of 0.84–0.87 did not correlate well with FFR ($r = 0.38$, $p = 0.12$). The authors concluded that, in this "gray zone," the use of traditional adenosine FFR cannot be circumvented.

Johnson et al. conducted an international multicenter prospective study (CONTRAST [Continuum of Vasodilator Stress from Rest to Contrast Media to Adenosine Hyperemia for Fractional Flow Reserve Assessment]) comparing the diagnostic performance of novel indices (cFFR, Pd/Pa, iFR) with adenosine-derived FFR in 763 subjects [25]. Pressure tracings from individual sites were blinded and analyzed by a physiological core lab in a standardized manner. cFFR showed a higher accuracy for predicting FFR as compared to the other two indices (85.8% accuracy for CFFR vs. 78.5% for Pd/Pa and 79.9% for iFR, $p < 0.001$). MEMENTO-FFR (Multi-Center Evaluation of the Accuracy of the Contrast Medium Induced Pd/Pa Ratio in Predicting FFR) was the largest study to date to compare the diagnostic performance of cFFR with resting Pd/Pa and FFR [26]. MEMENTO-FFR retrospectively enrolled 926 patients at ten hospitals in four European countries. cFFR not only showed a robust correlation with FFR ($r = 0.90$, $p < 0.001$), but also strongly predicted FFR with AUC 0.95 (95% CI 0.94–0.96) on ROC curve analysis, both of which were significantly better than resting Pd/Pa. A cFFR threshold of ≤ 0.85 had an accuracy of 89% in identifying an FFR ≤ 0.80. A recently published meta-analysis of 18 studies analyzing various adenosine-free indices found that cFFR had the highest correlation with FFR along with best diagnostic accuracy as compared to other resting indices [33]. Table 1 summarizes all of the studies to date that have validated cFFR as an important

Table 1 Studies validating cFFR compared to FFR

Study (citation)	Country	Type of study	Number of patients	Number of lesions	Contrast material used	Contrast dose	cFFR threshold	AUC	cFFR accuracy vs. FFR	Sensitivity	Specificity
RINASCI [24]	Italy	Prospective	80	104	Iomeprol	6 ml	< 0.83	0.98	NR	85.7	97.4
CONTRAST [25]	International	Prospective	763	763	Iobitridol Iodixanol Iohexol Iomeprol Iopamidol Iopromide Ioversol Ioxaglate	8 ± 2 ml	< 0.83	0.930	85.8	75.8	95.3
MEMENTO- FFR [26]	International	Retrospective	926	1026	Iomeprol Iopromide Iodixanol	5–10	< 0.85	0.95	89	87	90
Topcu et al. [27]	Turkey	Prospective	28	34	Iomeron	6 ml	< 0.85	0.939	91.2	90.9	91.7
Spagnoli et al. [28]	France	Prospective	104	138	Iodixanol	10 ml	< 0.85	0.94	NR	95	73
Kanaji et al. [29]	Japan	Prospective	89	120	Iomeron	6 ml	< 0.77	0.96	92.5	94	91.4
Shiode et al. [30]	Japan	Prospective	93	109	Iopamidol	6–8 ml	< 0.82	0.980	NR	95.1	91.2
Van Wyk et al. [31]	New Zealand	Prospective	76	100	Iodixanol	8–10 ml	< 0.83 and > 0.87	NR	96	100	96.1
Cerrato et al. [32]	International	Prospective	86	108	Iomeron	6 ml	< 0.84	0.96	NR	93	96

diagnostic tool in evaluating the functional significance of intermediate CAD [27–32].

Reproducibility of cFFR

The reproducibility of cFFR and other resting indices (iFR, Pd/Pa) was also compared with FFR in the CONTRAST study [25]. cFFR demonstrated superior reproducibility compared with Pd/Pa and iFR with standard deviation (SD) between repeated measurements of 0.017, 0.023, and 0.033; by comparison, FFR had SD 0.019. Spagnoli et al. similarly demonstrated the reproducibility of cFFR in a group of 14 patients with very limited variability and small estimated bias (mean estimated bias 0.001 ± 0.014) [28].

cFFR in Special Populations

Several studies have examined the performance of cFFR in special patient populations. Post hoc analyses of the CONTRAST study demonstrated superior diagnostic performance of cFFR in both diabetic and female patients compared to iFR and Pd/Pa [34, 35]. Kobayashi et al. studied the impact of lesion location on the accuracy of cFFR, finding that cFFR was less accurate for left main and proximal left anterior descending coronary artery lesions with FFR ≤ 0.80 as the reference (accuracy 80.3% for LM and proximal LAD vs. 87.8% for other lesion locations) [36]. Nevertheless, cFFR still had a better diagnostic accuracy irrespective of lesion location as compared to resting indices (Pd/Pa, iFR).

Hybrid Approach

The MEMENTO-FFR investigators developed a hybrid algorithm incorporating cFFR for assessment and management of intermediate coronary artery stenoses (Fig. 1) [26]. For a positive cFFR (≤ 0.83), PCI was recommended; for a negative cFFR (≥ 0.89), PCI was deferred; and for equivocal cases (cFFR 0.84–0.88), traditional adenosine FFR was performed. Using this approach, adenosine was required in only 22% of cases. Recently, Cerrato et al. proposed a novel Pd/Pa-cFFR-FFR algorithm with initial use of resting Pd/Pa. cFFR was performed in cases of equivocal resting Pd/Pa values (0.89–0.96), and FFR was performed only for equivocal cFFR cases (0.84–0.87) [32]. This decision-making algorithm reduced the need for adenosine and additional contrast medium in 90% and 48% of cases, respectively.

Future Directions

To date, no prospective study has evaluated the outcomes following a cFFR-guided revascularization approach. Most of the data supporting cFFR are extrapolated from its reliable correlation with adenosine FFR. Adenosine Contrast Correlations in Evaluating Revascularization (ACCELERATION, NCT03557385) is an ongoing clinical trial comparing adenosine FFR with cFFR obtained using an automated contrast injector system. This trial will also provide data on long-term clinical outcomes following PCI performed using cFFR guidance.

Computed Tomography Fractional Flow Reserve

Computational fluid dynamic (CFD) models may be applied to anatomic data obtained from coronary computed tomography angiography (CTA) to calculate a non-invasive hemodynamic index dubbed CT-FFR [37]. Calculation of CT-FFR first requires creation of patient-specific anatomical models based upon data obtained from coronary CTA. Then, total and vessel/lesion specific coronary artery flow at baseline is calculated based on allometric scaling laws using the principle that baseline coronary artery flow is proportional to the left ventricular myocardial mass supplied by that artery. Baseline microcirculatory resistance is then determined using a form-function relationship between epicardial coronary vessel size and flow. Maximal hyperemia is subsequently simulated by decreasing the coronary resistance index to 0.24 ± 0.01, which approximates the effect of 140 μg/kg/min of intravenous adenosine. Finally, the Navier-Stokes equations of blood fluid dynamics are solved numerically to obtain CT-FFR values [38]. Presently, HeartFlow (Redwood City, CA) provides the only Food and Drug Administration (FDA) approved technology for CT-FFR. Commercial users perform coronary CTA and then upload images to HeartFlow servers. HeartFlow technologists perform segmentation of the coronary arteries and compute CT-FFR using CFD. The CT-FFR values are superimposed upon a tomographic map of the coronary tree and sent to the ordering provider. Since 2017, the median turnaround time for CT-FFR analysis has been 2.5 h [39]. Figure 2 provides an example of the rendering of CT-FFR from coronary CTA images.

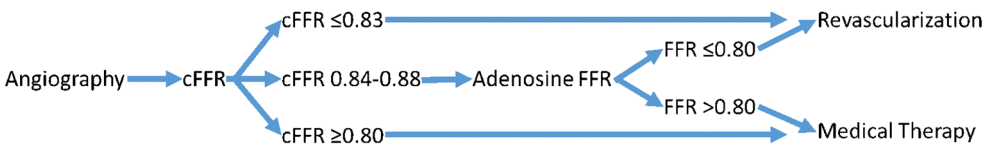

Fig. 1 Hybrid algorithm for functional evaluation of intermediate coronary artery stenosis, after Leone et al. [26]

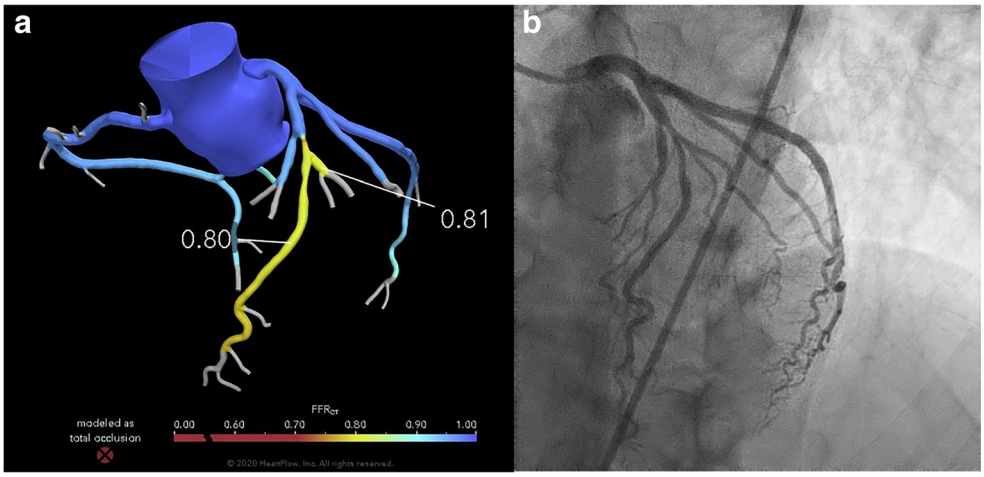

Fig. 2 CTA showing a left anterior descending coronary artery stenosis with HeartFlow CT-FFR quantification (**a**) and the corresponding invasive coronary angiography (**b**)

Validation of CT-FFR

Several studies have validated the use of CT-FFR as a promising tool for the diagnosis of hemodynamically significant CAD. The DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) and DeFACTO (Diagnostic Accuracy of Fractional Flow Reserve From Anatomic CT Angiography) studies showed that addition of CT-FFR to CTA improved accuracy compared to coronary CTA alone in diagnosing hemodynamically significant stenoses in stable patients suspected of having CAD with invasive FFR being the reference standard [40, 41]. The NXT (Analysis of Coronary Blood Flow using CT Angiography: Next Steps) trial was a prospective multicenter trial including 254 patients with suspected CAD who underwent CT-FFR prior to invasive coronary angiography [42]. Per-patient and per-vessel AUC of ROC curves for CT-FFR compared with invasive FFR were 0.90 (95% CI 0.87–0.94) and 0.93 (95% CI 0.91–0.95), respectively. A good correlation was seen between CT-FFR and invasive FFR ($r = 0.82$, $p < 0.001$). Diagnostic accuracy remained high in patients with intermediate coronary stenoses.

Of note, in addition to its superiority over coronary CTA alone, CT-FFR also outperforms other non-invasive imaging modalities for diagnosing ischemia. Driessen et al. performed a post hoc study of 208 patients enrolled in the PACIFIC (Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis) trial with suspected stable CAD [43]. CT-FFR was compared with coronary CTA alone, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) for ischemia diagnosis; invasive FFR was used as the gold standard. CT-FFR showed greater AUC than SPECT on a per-vessel and per-patient level (0.94 and 0.92, respectively, for CT-FFR and 0.83 and 0.81, respectively, for SPECT, $p < 0.01$). CT-FFR also performed better than PET on a per-vessel basis (AUC 0.87 for PET, $p < 0.01$) but not on a per-patient basis (AUC 0.91, $p = 0.56$).

CT-FFR as a Potential Gatekeeper for Invasive Coronary Angiography

Given its high diagnostic accuracy, CT-FFR has been proposed as a potential gatekeeper for invasive coronary angiography in stable patients with suspected CAD. Multiple studies have assessed clinical outcomes following incorporation of CT-FFR into decision-making algorithms and found that invasive angiography can be safely deferred in cases of negative CT-FFR (> 0.80). Additionally, CT-FFR can identify patients who will benefit most from revascularization. The PLATFORM [Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impact(s)] study was a randomized controlled trial of 584 patients undergoing evaluation of chest pain without known CAD and with intermediate probability of CAD [44]. Patients were assigned to initial CT-FFR testing versus "usual testing," which consisted of either non-invasive imaging or invasive angiography. The primary endpoint of performance of invasive angiography without obstructive CAD was significantly lower in those undergoing initial CT-FFR as compared to those who received usual care (12.4% vs 73.3%, risk difference 60.8%, $p < 0.0001$). Moreover, 1-year costs were 33% lower in the CT-FFR cohort when compared to those who received usual care.

In PLATFORM, major adverse events were infrequent and comparable in both groups [45]. Similarly, in a single-center Danish study of 1248 stable patients with suspected CAD, deferral of ICA for CT-FFR of > 0.80 did not result in any adverse cardiac events at a median 12-month follow-up [46]. Among 271 chest pain patients enrolled in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial who underwent coronary CTA prior to

invasive angiography, CT-FFR ≤ 0.80 was a significant predictor of major adverse cardiovascular events or revascularization (hazard ratio [HR] 4.3, 95% CI 2.4–8.9, $p = 0.033$) [47]. Reserving ICA for patients with CT-FFR ≤ 0.80 decreased the need for invasive angiography by 44% in patients without > 50% stenosis on traditional CTA. Similar results were reported by Ihdayhid et al., who not only found that a positive CT-FFR was a better predictor of composite endpoint of death, MI, and revascularization than coronary CTA alone, but also, that each 0.05 unit decrement in numerical CT-FFR value was independently associated with a greater incidence of the composite endpoint with an adjusted HR of 1.7 (95% CI 1.4–1.9, $p < 0.001$) [48].

CT-FFR in Special Populations

CT-FFR is currently being explored as a triage tool for acute chest pain patients. Chinnaiyan et al. randomized 555 acute chest pain patients without known CAD and negative serum cardiac biomarkers to CTA alone vs. CT-FFR [39]. The incidence of invasive angiography without obstructive CAD was higher in patients with a positive traditional CTA as compared to positive CT-FFR (56.5% vs. 8.0%, $p < 0.001$), and at 90 days, there was not a significant difference in major adverse cardiovascular events between the two groups. Thus, invasive angiography can be safely deferred for acute chest pain patients with negative CT-FFR.

The role of CT-FFR in evaluation of acute coronary syndrome patients has not yet been well studied. A clinical trial (NCT04052763) of CT-FFR in non-ST-elevation myocardial infarction (NSTEMI) patients is underway in Switzerland. This trial may help identify NSTEMI patients for whom invasive angiography may be avoided [49], an important consideration to reduce unnecessary invasive procedures in the era of high sensitivity troponin T assays.

Patients undergoing transcatheter aortic valve replacement (TAVR) have traditionally undergone pre-procedural CT aortography and invasive coronary angiography. The pending FORTUNA (Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVR, NCT03665389) trial will assess whether CT data alone can safely eliminate invasive angiography.

CT-FFR for Planning PCI and Future Directions

Because CT-FFR provides both anatomical and functional information about coronary stenoses, this tool is emerging as a promising one for planning PCI, especially in the setting of multiple lesions in the same vessel. Interventionalists can plan their approaches knowing the exact location of flow-limiting stenosis pre-procedurally. Virtual stenting simulation prior to PCI has also been developed to predict functional outcomes after PCI. In a 44-patient pilot study, Kim et al. compared predicted post-PCI CT-FFR with post-PCI adenosine FFR: CT-FFR modeling correlated positively with FFR with $r = 0.55$ ($p < 0.001$) and predicted 96% of post-PCI residual ischemia [50]. A novel PCI support application developed by HeartFlow is currently undergoing FDA review prior to a planned pivotal study: this intraprocedural tool aggregates data from CT-FFR, virtual stenting, and the actual location of a stent prior to deployment, providing interventionalists with real-time predictions of hemodynamic results.

Conclusion

cFFR and CT-FFR have emerged as powerful tools to evaluate the hemodynamic significance of coronary artery stenoses and thereby determine which lesions will benefit most from revascularization. Non-ionic contrast media is an attractive alternative to adenosine and other hyperemic agents, saving time and avoiding side effects while assessing coronary physiology. On the other hand, CT-FFR can non-invasively facilitate an appropriate revascularization strategy using simulation.

Techniques to assess coronary lesions continue to evolve. FFR estimation from real-time coronary angiography (FFRangio) is a novel technology that proposes to eliminate hyperemic agents and pressure wire-based FFR measurements altogether. Machine learning algorithms under development may provide real-time CT-FFR data without uploading CTA images to a third party server. With continued research, the tools of coronary physiology will further improve PCI planning, cost reduction, efficient care delivery, and patient outcomes.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Pijls NH, Son JAV, Kirkeeide RL, Bruyne BD, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation. 1993;87(4):1354–67.
2. Pijls NHJ, Gelder BV, PVD V, Peels K, Bracke FALE, Bonnier HJRM, et al. Fractional flow reserve. Circulation. 1995;92(11):3183–93.
3. Bruyne BD, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation. 1994;89(3):1013–22.
4. Pijls NHJ, van Schaardenburgh P, Manoharan G, Boersma E, Bech J-W, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. J Am Coll Cardiol. 2007;49(21):2105–11.

5. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. Five-year outcomes with PCI guided by fractional flow reserve. N Engl J Med. 2018;379(3):250–9.
6. Toth GG, Toth B, Johnson NP, Vroey FD, Serafino LD, Pyxaras S, et al. Revascularization decisions in patients with stable angina and intermediate lesions. Circulation: Cardiovascular Interventions. 2014;7(6):751–9.
7. Parikh RV, Liu G, Plomondon ME, Sehested TSG, Hlatky MA, Waldo SW, et al. Utilization and outcomes of measuring fractional flow reserve in patients with stable ischemic heart disease. J Am Coll Cardiol. 2020;75(4):409–19.
8. Pijls NHJ, de Bruyne B, Peels K, van der Voort PH, Bonnier HJRM, Bartunek J, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med. 1996;334(26):1703–8.
9. Bech GJW, Bruyne BD, Pijls NHJ, Muinck EDD, Hoorntje JCA, Escaned J, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis. Circulation. 2001;103(24):2928–34.
10. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van't Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213–24.
11. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. Fractional flow reserve–guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367(11):991–1001.
12. Fournier S, Ciccarelli G, Toth GG, Milkas A, Xaplanteris P, Tonino PAL, et al. Association of improvement in fractional flow reserve with outcomes, including symptomatic relief, after percutaneous coronary intervention. JAMA Cardiol. 2019;4(4):370–4.
13. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018;40(2):87–165.
14. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary. Circulation. 2011;124(23):2574–609.
15. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes. J Am Coll Cardiol. 2017;69(5):570–91.
16. Adjedj J, Toth GG, Johnson NP, Pellicano M, Ferrara A, Floré V, et al. Intracoronary adenosine: dose–response relationship with hyperemia. J Am Coll Cardiol Intv. 2015;8(11):1422–30.
17. Parham WA, Bouhasin A, Ciaramita JP, Khoukaz S, Herrmann SC, Kern MJ. Coronary hyperemic dose responses of intracoronary sodium nitroprusside. Circulation. 2004;109(10):1236–43.
18. Wilson RF, White CW. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. Circulation. 1986;73(3):444–51.
19. Mamas M, Horner S, Welch E, Ashworth A, Millington S, Fraser D, et al. Resting Pd/Pa measured with intracoronary pressure wire strongly predicts fractional flow reserve. J Invasive Cardiol. 2010;22:260–5.
20. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave–intensity analysis: results of the ADVISE (ADenosine vasodilator independent stenosis evaluation) study. J Am Coll Cardiol. 2012;59(15):1392–402.
21. Guzman SV, West JW. Cardiac effects of intracoronary arterial injections of various roentgenographic contrast media. Am Heart J. 1959;58(4):597–607.
22. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol. 1974;33(1):87–94.
23. De Bruyne B, Pijls Nico HJ, Barbato E, Bartunek J, Bech J-W, Wijns W, et al. Intracoronary and intravenous adenosine 5′-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow Reserve in Humans. Circulation. 2003;107(14):1877–83.
24. Leone AM, Scalone G, De Maria GL, Tagliaferro F, Gardi A, Clemente F, et al. Efficacy of contrast medium induced Pd/Pa ratio in predicting functional significance of intermediate coronary artery stenosis assessed by fractional flow reserve: insights from the RINASCI study. EuroIntervention. 2015;11(4):421–7.
25. Johnson NP, Jeremias A, Zimmermann FM, Adjedj J, Witt N, Hennigan B, et al. Continuum of vasodilator stress from rest to contrast medium to adenosine hyperemia for fractional flow reserve assessment. J Am Coll Cardiol Intv. 2016;9(8):757–67.
26. Antonio Maria L, Roberto M-R, Sergio BB, Nicolas A, Luis R, Pelaez JAF, et al. The multi-center evaluation of the accuracy of the contrast MEdium INduced Pd/Pa RaTiO in predicting FFR (MEMENTO-FFR) study. EuroIntervention. 2016;12(6):708–15.
27. Topcu S, Tanboğa IH, Aksakal E, Aksu U, Gulcu O, Birdal O, et al. Efficacy of coronary fractional flow reserve using contrast medium compared to adenosine. Postepy Kardiol Interwencyjnej. 2016;12(3):212–6.
28. Spagnoli V, Amabile N, Dillinger JG, Veugeois A, Logeart D, Henry P, et al. Myocardial fractional flow reserve measurement using contrast media as a first-line assessment of coronary lesions in current practice. Can J Cardiol. 2016;32(6):739–46.
29. Kanaji Y, Murai T, Lee T, Matsuda J, Usui E, Araki M, et al. Efficacy of pressure parameters obtained during contrast medium-induced submaximal hyperemia in the functional assessment of intermediate coronary stenosis in comparison with instantaneous wave-free ratio. Int J Cardiol. 2016;208:128–36.
30. Shiode N, Okimoto T, Tamekiyo H, Kawase T, Yamane K, Kagawa Y, et al. Contrast-induced hyperemia as an alternative to drug-induced hyperemia in the evaluation of the fractional flow reserve in coronary lesions. Intern Med. 2017;56(3):253–7.
31. Van Wyk P, Puri A, Blake J, Elliott JM, McClean D, Arshad M, et al. The utility of contrast medium fractional flow reserve in functional assessment of coronary disease in daily practice. Heart Lung Circ. 2018;27(2):212–8.
32. Cerrato E, Tomassini F, Salinas P, Pavani M, Conrotto F, Echavarria-Pinto M, et al. Simplified hybrid algorithms for pressure wire interrogation exploiting advantages of a baseline and contrast Pd/Pa ratio indexes to predict stenosis significance: insight from the SPARE multicenter prospective study. Catheter Cardiovasc Interv. 2018;92(6):1090–6.
33. Leone AM, Campo G, Gallo F, Pavasini R, Basile E, D'Amario D, et al. Adenosine-free indexes vs. fractional flow reserve for functional assessment of coronary Stenoses: systematic review and meta-analysis. Int J Cardiol. 2020;299:93–9.
34. Shah SV, Zimmermann FM, Johnson NP, Nishi T, Kobayashi Y, Witt N, et al. Sex differences in adenosine-free coronary pressure indexes: a CONTRAST substudy. J Am Coll Cardiol Intv. 2018;11(15):1454–63.
35. Gargiulo G, Stabile E, Ferrone M, Barbato E, Zimmermann FM, Adjedj J, et al. Diabetes does not impact the diagnostic performance of contrast-based fractional flow reserve: insights from the CONTRAST study. Cardiovasc Diabetol. 2017;16(1):7.
36. Kobayashi Y, Johnson NP, Berry C, De Bruyne B, Gould KL, Jeremias A, et al. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements. J Am Coll Cardiol Intv. 2016;9(23):2390–9.
37. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive

quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol. 2013;61(22):2233–41.
38. Min JK, Taylor CA, Achenbach S, Koo BK, Leipsic J, Nørgaard BL, et al. Noninvasive fractional flow reserve derived from coronary CT angiography: clinical data and scientific principles. JACC Cardiovasc Imaging. 2015;8(10):1209–22.
39. Chinnaiyan KM, Safian RD, Gallagher ML, George J, Dixon SR, Bilolikar AN, et al. Clinical use of CT-derived fractional flow reserve in the emergency department. JACC Cardiovasc Imaging. 2020;13(2, Part 1):452–61.
40. Koo B-K, Erglis A, Doh J-H, Daniels DV, Jegere S, Kim H-S, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: results from the prospective multicenter DISCOVER-FLOW (diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve) study. J Am Coll Cardiol. 2011;58(19):1989–97.
41. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo B-K, van Mieghem C, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA. 2012;308(12):1237–45.
42. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (analysis of coronary blood flow using CT angiography: next steps). J Am Coll Cardiol. 2014;63(12):1145–55.
43. Driessen RS, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. J Am Coll Cardiol. 2019;73(2):161–73.
44. Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRCT: outcome and resource impacts study. Eur Heart J. 2015;36(47):3359–67.
45. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM study. J Am Coll Cardiol. 2016;68(5):435–45.
46. Nørgaard BL, Hjort J, Gaur S, Hansson N, Bøtker HE, Leipsic J, et al. Clinical use of coronary CTA–derived FFR for decision-making in stable CAD. JACC Cardiovasc Imaging. 2017;10(5):541–50.
47. Lu MT, Ferencik M, Roberts RS, Lee KL, Ivanov A, Adami E, et al. Noninvasive FFR derived from coronary CT angiography: management and outcomes in the PROMISE trial. JACC Cardiovasc Imaging. 2017;10(11):1350–8.
48. Ihdayhid AR, Norgaard BL, Gaur S, Leipsic J, Nerlekar N, Osawa K, et al. Prognostic value and risk continuum of noninvasive fractional flow reserve derived from coronary CT angiography. Radiology. 2019;292(2):343–51.
49. Meier D, Skalidis I, De Bruyne B, Qanadli SD, Rotzinger D, Eeckhout E, et al. Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale. IJC Heart Vasc. 2020;27:100496.
50. Kim K-H, Doh J-H, Koo B-K, Min JK, Erglis A, Yang H-M, et al. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. J Am Coll Cardiol Intv. 2014;7(1):72–8.