

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.¹ Yet, 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.^{2,3}

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.⁴⁻⁷ 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.⁸⁻¹⁰ 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.^{7,11-14} 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.¹⁵ 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.^{7,11-14}

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.^{16,17}

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.^{18,19} 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.^{18,19} 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).²⁰⁻²² 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.²³

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.²¹ 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.²⁴ 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.²¹

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.²⁵ Schuurbiets 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.²⁶ 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.^{27,28} 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,^{26,29} 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 Papafakis 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.³⁰ To compute the vFAI, the f_v and f_s parameters were derived from the artery-specific quadratic equation $\Delta P = f_v Q + f_s Q^2$ by performing two separate CFD simulations using the geometry resulting from 3D-QCA. After solving f_v and f_s , the vFAI was calculated as the ratio of the area under the curve ($P_d/P_a = 1 - f_v Q/P_a - f_s Q^2/P_a$) 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 currently commercially available software packages to calculate angiography-based FFR.³¹⁻³⁶

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 velocities³¹: (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).³² 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).³⁶ 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.³³ 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%).³⁴ 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.

CAAS Workstation QCA-3D. The CAAS Workstation QCA-3D software evolved by applying simplified methods for computation of 3D-QCA-based vessel FFR (vFFR; Figure 1) within CAAS Workstation 8.0. Based on well-validated 3D coronary reconstructions,^{26,29} the pressure drop is calculated instantaneously by applying physical laws as described by Gould et al.²⁷ Within these physical laws, patient-specific aortic rest pressure is incorporated, as measured during the catheterization procedure. The FAST study, which was a single-center observational study, aimed to validate the software to calculate vFFR offline to assess the correlation as compared with pressure wire-based FFR and study interobserver variability. The study demonstrated a high diagnostic accuracy of vFFR in identifying significant pressure wire-based FFR (area under the curve, 0.93; 95% confidence interval, 0.88–0.97) with low interobserver variability ($R = 0.95$; $P < .001$).³⁵ However, FAST was a single-center experience and the analyses were restricted to those recordings with optimal pressure wave forms. Previous

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

Company	Product Name	Acronym Index	Validation Study	Correlation With Pressure Wire FFR	Bias Mean ± SD	AUC CI (95% CI)	Interobserver Variability
Medis Medical Imaging Systems, BV	QAngio XA	QFR	FAVOR Pilot Study ³¹	0.77	0.001 ± 0.06	0.92 (0.85–0.97)	N/A
			FAVOR II China ³²	0.86	0.01 ± 0.06	0.96 (0.94–0.98)	N/A
			FAVOR II Europe-Japan ³⁶	0.83	0.01 ± 0.06	0.92 (0.89–0.96)	N/A
CathWorks	FFRangio system	FFRangio	Pellicano et al ³³	0.88	0.007 ± 0.05	N/A	R = 0.92
			FAST-FFR study ³⁴	0.80	-0.14 ± 0.12	0.94 (0.92–0.97)	N/A
Pie Medical Imaging	CAAS 3D-QCA	vFFR	FAST study ³⁵	0.89	0.01 ± 0.04	0.93 (0.88–0.97)	R = 0.95
			FAST II study*	*	*	*	*
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.³⁷ 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.^{38–41} Previous work from our group has provided more insights of the potential for a post-PCI FFR < 0.85 using high-definition intravascular ultrasound.⁴² 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 < 0.90.⁴³

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

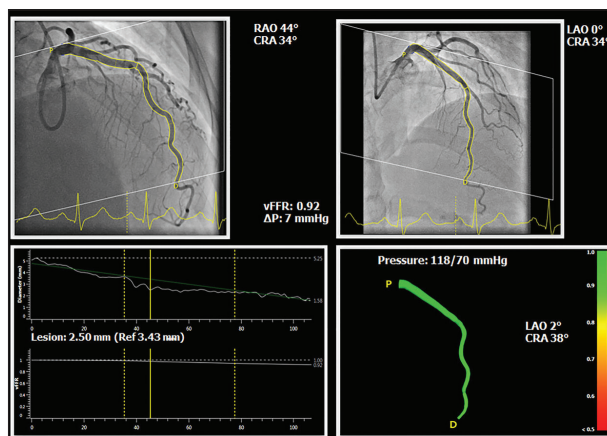


Figure 1. Example of vFFR analysis using CAAS Workstation software. 3D reconstruction of a coronary artery and computation of vFFR using two angiographic projections (with at least 30° apart) and invasively measured aortic root pressure. CRA, cranial; LAO, left anterior oblique; RAO, right anterior oblique.

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.³⁷

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 study 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. ■

- Uren NG, Melin JA, De Bruyne B, et al. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med*. 1994;330:1782-1788.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions [published erratum appears in *Circulation*. 2012;125:e412]. *Circulation*. 2011;124:e574-651.
- Neumann HJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541-2619.
- De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001.
- Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol*. 2007;49:2105-2111.
- Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-224.
- Nakamura M, Yamagishi M, Ueno T, et al. Prevalence of visual-functional mismatch regarding coronary artery stenosis in the CVIT-DEFER registry. *Cardiovasc Interv Ther*. 2014;29:300-308.
- Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv*. 2012;5:1029-1036.
- Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55:2816-2821.
- De Bruyne B, Bartunek J, Sys SJ, et al. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation*. 1996;94:1842-1849.
- De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371:1208-1217.
- Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703-1708.
- Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve: A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183-3193.
- Toth GG, Toth B, Johnson NP, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv*. 2014;7:751-759.
- Escaned J, Echavarría-Pinto M, García-García HM, et al. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE II international, multicenter study (Adenosine Vasodilator Independent Stenosis Evaluation II). *JACC Cardiovasc Interv*. 2015;8:824-833.
- Sen S, Escaned J, Malik IS, 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;59:1392-1402.
- Lighthart J, Masdjedi K, Wittberg K, et al. Validation of resting diastolic pressure ratio calculated by a novel algorithm and its correlation with distal coronary artery pressure to aortic pressure, instantaneous wave-free ratio, and fractional flow reserve. *Circ Cardiovasc Interv*. 2018;11:e006911.
- Sivaneeraj J, Ahn JM, Jeremias A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. *EuroIntervention*. 2018;14:806-814.
- 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;61:2233-2241.
- Koo BK, Erglis A, Doh JH, 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;58:1989-1997.
- Min JK, Berman DS, Budoff MJ, et al. Rationale and design of the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) study. *J Cardiovasc Comput Tomogr*. 2011;5:301-309.
- Lee BK, Kwon HM, Kim D, et al. Computed numerical analysis of the biomechanical effects on coronary atherogenesis using human hemodynamic and dimensional variables. *Yonsei Med J*. 1998;39:166-174.
- Douglas PS, De Bruyne B, Pontone G, et al. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM study. *J Am Coll Cardiol*. 2016;68:435-445.
- Slager CJ, Wentzel JJ, Schuurbaers JC, et al. True 3-dimensional reconstruction of coronary arteries in patients by fusion of angiography and IVUS (ANGUS) and its quantitative validation. *Circulation*. 2000;102:511-516.
- Schuurbaers JC, Lopez NG, Ligthart J, et al. In vivo validation of CAAS QCA-3D coronary reconstruction using fusion of angiography and intravascular ultrasound (ANGUS). *Catheter Cardiovasc Interv*. 2009;73:620-626.
- Gould KL, Kelley KO, Bolson EL. Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. *Circulation*. 1982;66:930-937.
- Kirkeeide RL. Coronary obstructions, morphology and physiologic significance. In: Reiber JHC, Serruys PW, eds. *Quantitative Coronary Arteriography*. Dordrecht, the Netherlands: Kluwer Academic Publishers; 1991:229-244.
- Girasis C, Schuurbaers JC, Muramatsu T, et al. Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation. *EuroIntervention*. 2013;8:1451-1460.
- Papafakis MJ, Muramatsu T, Ishibashi Y, et al. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire - fractional flow reserve. *EuroIntervention*. 2014;10:574-583.
- Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR Pilot Study. *JACC Cardiovasc Interv*. 2016;9:2024-2035.
- Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol*. 2017;70:3077-3087.
- Pellicano M, Lavi I, de Bruyne B, et al. Validation study of image-based fractional flow reserve during coronary angiography. *Circ Cardiovasc Interv*. 2017;10:e005259.
- Fearon WF, Achenbach S, Assali TEA, et al. Accuracy of fractional flow reserve derived from coronary angiography. *Circulation*. 2019;139:477-484.
- Masdjedi KM, van Zandvoort LJ, Balbi MM, et al. Validation of 3-dimensional quantitative coronary angiography based software to calculate vessel fractional flow reserve: Fast Assessment of Stenosis severity (FAST) study [published online May 14, 2019]. *EuroIntervention*.
- Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. *J Am Heart Assoc*. 2018;7:e009603.
- Matsumura M, Johnson NP, Fearon WF, et al. Accuracy of fractional flow reserve measurements in clinical practice: observations from a core laboratory analysis. *JACC Cardiovasc Interv*. 2017;10:1392-1401.
- Agarwal SK, Kasula S, Hacıoglu Y, et al. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. *JACC Cardiovasc Interv*. 2016;9:1022-1031.
- Leesar MA, Satran A, Yalamanchili V, et al. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. *EuroIntervention*. 2011;7:917-923.
- Pijls NH, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation*. 2002;105:2950-2954.
- Kasula S, Agarwal SK, Hacıoglu Y, et al. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. *Heart*. 2016;102:1988-1994.
- Daemen J, van Zandvoort L, van Bommel R, et al. CRT-30.03: Explanation of post procedural fractional flow reserve below 0.85: a comprehensive ultrasound analysis of the FFR Search registry [abstract]. *JACC Cardiovasc Interv*. 2018;11(suppl):S36.
- Masdjedi KM, van Zandvoort LJ, Balbi MM, et al. Validation of novel 3-dimensional quantitative coronary angiography based software to calculate vessel fractional flow reserve (vFFR) post stenting: Fast Assessment of Stenosis severity POST stenting, The FAST POST-study. Presented at: Transcatheter Cardiovascular Therapeutics (TCT) 2018; September 25, 2018; San Diego, CA.

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