White paper

Angiography-based indices of coronary physiology

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Introduction

Over the past decades, pressure-wire-based physiological indices, with Fractional Flow Reserve (FFR) in particular, have emerged as the gold standard to assess the physiological significance of intermediate coronary lesions.

As of to date, the superiority of physiology-guided revascularization over angiography-guided revascularization is supported by a robust and still growing body of evidence. [1–3]

Data from the FAME (fractional flow reserve versus angiography for multivessel evaluation) and FAME 2 trials demonstrated that FFR-guided revascularization is superior to both optimal medical therapy and angiography-guided percutaneous coronary intervention (PCI) in terms of major adverse cardiac events (MACE) at 2 years. [1, 4] Moreover, the deferral of revascularization of physiologically non-significant stenosis appeared to be safe with favorable outcomes even after 15 years of follow-up. [3]

Nevertheless, the uptake of FFR in routine clinical practice has remained limited, reportedly due to the need for hyperemia associated with patient discomfort, additional pressure-wire instrumentation, and presumed additional time and costs. [5, 6]

In an attempt to abolish some of the aforementioned barriers, several non-hyperemic pressure ratios (NHPR), as instantaneous wave-free ratio (iFR), have been proposed.

The use of NHPR is backed by the results of DEFINE-FLAIR (functional lesion assessment of intermediate stenosis to guide revascularization) and iFR-SWEDEHEART (the instantaneous wave-free ratio versus fractional flow reserve in patients with stable angina pectoris or acute coronary syndrome) trials, which showed that an iFR-guided revascularization was non-inferior to a FFR-guided revascularization in terms of risk of MACE at 1 year. [7, 8] Based on the above mentioned studies, current guidelines recommend physiological lesion assessment of angiographically intermediate coronary stenosis, using either FFR or iwFR, when evidence of non-invasive ischemia testing is lacking. [9, 10] Although NHPR do not require hyperemia, they still require a pressure-wire and may still suffer from the risk of waveform artifacts and drift that appeared to be present in 10% and 17.5% of FFR tracings respectively according to a dedicated Core Lab analysis. [11]

The development of less invasive angiography based methods was possible thanks to the improvements in simplified computational fluid dynamics (CFD), and the introduction of 3-dimensional quantitative coronary angiography (3D QCA) which allowed to create an accurate reconstruction of the lumen geometry from the angiographic data, taking into account the 3D curvature of the vessel, lumen intruding plaque and presence of bifurcations and side branches. [12]

Recently, promising data have been released on the computation of angiography based FFR indices from a single angiographic view. [13] The concept is based on the potential negative impact of a second orthogonal projection in case of significant foreshortening or overlap in the second projection. Although operating with a single projection could potentially further extend the adoption of physiological assessment in the catheterization laboratory, caution is warranted in case of explicit lesion eccentricity in which the use of two projections remains advocated.

The fluid dynamics computation

Currently available angiography-based FFR indices use 2D or 3D anatomic models of the coronary vessels, constructed using at least one angiographic projection, combined with various approaches to fluid dynamics computation.

CFD is the most common way to solve the equations which describe the motion of fluids, the Navier-Stokes equations. [12] The solution of these equations provides information about blood flow velocity and pressure at any location in the coronary artery at any point of time. Although CFD-based models provide a detailed approach with high spatial resolution, it can be time consuming and computationally expensive.

To allow for faster computation, simplified approaches, built on the seminal work of Young, Tsai and Gould, have been proposed. [14–16]

Beside the geometrical reconstruction of the lumen geometry, all methods require input regarding the flow in the coronary segment under investigation. At the inlet of the model, boundary conditions for blood flow or pressure are required. Blood flow can be modelled as steady or transient flow, while pressure is obtained from patient-specific measurements or population-averaged data. [12, 17] The hyperaemic flow rates are obtained using a hyperemia-specific scaling law to lumen measurements or by applying a conversion based on physiological assumptions to the resting flow rate.

The inlet and the outlet can be coupled through a lumped parameter circuit model representing the coronary microcirculation. [17] Alternatively, at the outlet a constant pressure boundary is applied. [12, 17–19]

Currently available software

As of to date, four angiography-based FFR indices are commercially available (Table 1). Whereas the diagnostic performance of these angiography-based FFR indices was first explored in the pre-PCI setting (Table 2 and 3), more recent works explored the potential use of angiography-based FFR in the post-PCI setting as a tool to assess the direct impact of stent placement, the potential need for procedural optimization and to predict future adverse events (Table 4). Moreover, advances in software development currently allow to predict the functional outcome of a PCI, by simulating a "virtual" PCI and estimating post-PCI FFR values based on the pre-PCI angiogram.

That said, several limitations remain in the technology as it is available today. The latter include angiographic limitations (as severe tortuosity, overlapping vessels or aorto-ostial lesions) that will impact generic use of the technology in routine clinical practice and likely leave a place for conventional pressure-wire-based technologies.

This article provides an overview on the currently available clinical evidence on the use of angiography-based FFR indices.

Table 1: Features of commercially available angiography-based FFR software

Method	Fluid dynamics solution	Angiographic data inputs	Total computational time (min)	Approach
FFRangio	Flow resistance analysis	≥ 2 projection 30° apart	3.41*	Multi-vessel
QFR	Mathematical formula	2 projection 25° apart	3.9–5	Single-vessel
vFFR	Mathematical formula	2 projection 30° apart	Not reported	Single-vessel
caFFR	Real-time invasive pressure coupled with computational flow modeling	2 projection 30° apart	4.5	Single-vessel

Table 2: Major studies investigating the diagnostic performance of pre-PCI angiography-based fractional flow reserve with FFR as a reference

Study/Author	Software	Year	Study design	Number of vessel (patient)	AUC	Accuracy %
FAVOR Pilot Study	QFR	2016	Prospective	84 (73)	0.92	86
FAVOR II China study	QFR	2017	Prospective	332 (308)	0.93	93
Yazaki et al.	QFR	2017	Retrospective	151 (142)	0.93	89
The WIFI II Study	QFR	2018	Substudy	292 (191)	0.86	83
The FAVOR II Europe-Japan	QFR	2018	Prospective	317 (329)	0.92	87
Choi et al.	QFR	2020	Registry	599 (452)	0.95	91
Westra et al.	QFR	2019	Meta-analysis	969 (819)		87
Zuo et al.	QFR	2019	Meta-analysis	8213	0.92	
Kornowski et al.	FFRangio	2016	Prospective	101 (88)		94
Trobs et al.	FFRangio	2016	Retrospective	100 (73)	0.93	90
Pellicano et al.	FFRangio	2017		203 (184)		93
FAST FFR	FFRangio	2019	Prospective	319 (301)	0.94	92
Omori et al.	FFRangio	2019	Prospective	118 (50)		92
FAST study	vFFR	2019	Retrospective	100 (100)	0.93	
FAST EXTEND	vFFR	2020	Retrospective	294 (294)	0.94	88
FAST II	vFFR	2021	Prospective	500 (334)	0.93	90
FLASH FFR	caFFR	2019	Prospective	328	0.98	96

**Data on file, unpublished data provided by CathWorks.*

Table 3: Major studies investigating the diagnostic performance of angiography-based fractional flow reserve compared to NHPR with FFR as a reference

Study/Author	Software	Year	Study design	NHPR	Number of vessel (patient)	AUC angiography-based method vs. NHPR	Accuracy %
Stahli et al.	QFR	2019	Retrospective	Pd/Pa	516 (436)	QFR 0.86 (0.83–0.89) Pd/Pa 0.76 (0.72–0.80), p < 0.001	93 for QFR, 84 for Pd/Pa
Hwang et al.	QFR	2019	Retrospective	iFR	358 (264)	QFR 0.95 iFR 0.88, p < 0.001	91 for QFR, 81 for iFR , p < 0.001
Scoccia et al.	vFFR	2022	Post-hoc analysis	dPR	475	vFFR 0.94 (0.93–0.96) dPR 0.89 (0.86–0.92), p 0.005	86 for dPR 89 for vFFR (p = 0.14)
Nils P. Johnson et al.	FFRangio	2019	Post-hoc analysis	Pd/Pa, dPR, iFR	319 (301)		92 for FFRangio, 85 for Pd/Pa, 83 for iFR and dPR

Table 4: Summary of the studies investigating the impact of post-PCI angiography-based fractional flow reserve

Study/Author	Software	Year	Study design	Number of vessel (patient)	AUC	Annotations
HAWKEYE	QFR	2019	Prospective	751 (602)	0.77	To predict 2-year VOCE cutoff ≤ 0.89
Kogame et al.	QFR	2019	Retrospective	968 (440)	0.70	To predict 2-year VOCE cutoff ≤ 0.91
FAST POST	vFFR	2021	Retrospective	100 (100)	0.98	To predict FFR values < 0.90 TVF tertiles = 24.6%, 21.5% vs. 17.1%
FAST OUTCOME	vFFR	2022	Retrospective	832 (748)		To predict 5-year VOCE

Abbreviations:

AUC area under the curve
caFFR Computational pressure-flow dynamics derived FFR
dPR diastolic pressure ratio
FFR Fractional Flow Reserve
iFR instantaneous wave free ratio
MI myocardial infarction
Pd/Pa Distal coronary artery pressure to aortic pressure ratio
QFR quantitative flow ratio
TVF target vessel failure
vFFR vessel Fractional Flow Reserve
VOCE vessel-oriented composite endpoint

Quantitative Flow Ratio (QFR)

QFR (Medis Medical Imaging System, Leiden, the Netherlands, and Pulse Medical Imaging Technology, Shanghai, China) is computed combining flow equations with 2D or 3D reconstructions of the coronary artery using one or two angiographic projections at least 25° apart. Whereas coronary flow was previously derived from the TIMI frame count, the most recent version of the software no longer requires manual frame counting (Figure 1).

The superiority of the initially studied different QFR approaches, namely fixed-flow QFR, contrast-flow QFR, and adenosine-flow QFR, over 3D QCA in predicting FFR was assessed in the FAVOR Pilot Study (diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography), showing promising results. [20] Subsequently, data from two multicenter studies, FAVOR II Europe-Japan (diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve) and FAVOR II China (diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis), consistently showed a high diagnostic accuracy (86.6% in FAVOR II Europe-Japan and of 92.7% in FAVOR II China), and a high agreement between QFR and FFR (mean difference: -0.01 ± 0.06, in both studies). [21, 22]

These findings were confirmed by several subsequent retrospective and prospective studies, and proved to be consistent for both offline and online computed QFR (Table 2). [23–26]

Subsequent studies were performed focusing on head-to-head comparisons of QFR and NHPR in predicting FFR positive lesions. In these studies, QFR showed a superior diagnostic accuracy as compared with resting Pd/Pa ratio (AUC 0.86; 95% CI: 0.83–0.89 for QFR vs. 0.76; 95% CI: 0.72–0.80 for Pd/Pa; $p < 0.001$), and with iFR ($r = 0.86$ with FFR vs. 0.74 with iFR, $p < 0.001$, AUC 0.95 vs. 0.88, $p < 0.001$) (Table 3). [27, 28]

When tested against iFR as a reference index, QFR demonstrated a good correlation with iFR and a good diagnostic performance ($r = 0.74$, AUC 0.91). [29]

Since a substantial number of patients have combined epicardial and microvascular disease, a new algorithm for the assessment of microvascular disease has been recently developed based on QFR. This index of microcirculatory resistance (IMRangio) showed a good diagnostic performance, as compared to wire-based IMR, both in chronic and acute coronary syndromes (AUC 0.93 and 0.96). [30, 31]

Recently, computation of Murray law-based quantitative flow ratio (μQFR) from a single angiographic projection demonstrated an excellent diagnostic accuracy in identifying FFR positive lesions (93.0%, 95% CI: 90.3–95.8) and an overall good diagnostic performance, which was partially affected by the quality of the angiographic projections (AUC = 0.97 for optimal vs 0.92 for suboptimal projections, $p < 0.001$). Promising results were observed when μQFR was compared to 3D-QFR in a cohort of 35 patients (correlation 0.996, 95% CI: 0.993–0.997). [32]

The technology also demonstrated to be a promising tool when used in a post-PCI setting (Table 4). In the HAWKEYE study (prognostic value of QFR measured immediately after successful stent implantation: the international multicenter prospective HAWKEYE study), post-PCI QFR ≤ 0.89 was associated with a 3-fold increase in risk for the vessel-oriented composite endpoint (vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization). [33]

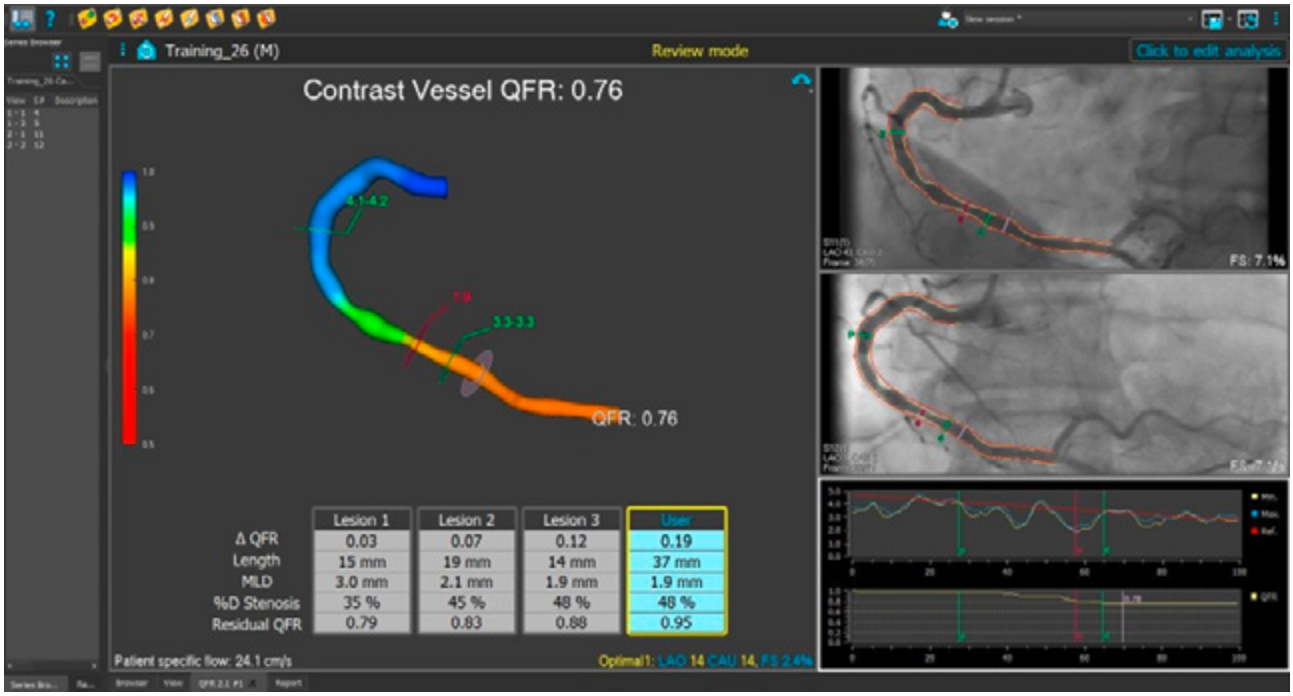
Building on these findings, the hypothesis that the physiological pattern of post-PCI residual disease obtained over QFR pull back is associated with vessel oriented composite outcome at 2 years was recently proven. [34]

Finally, a recent analysis from the DOCTORS (does optical coherence tomography optimize results of stenting) study population showed that residual QFR, defined as pre-PCI QFR analysis with virtual PCI, and post-PCI QFR analysis, correlate well with post-PCI FFR (correlation of residual QFR and of post-PCI-QFR with post-PCI FFR were 0.68; 95% CI: 0.53–0.78, and 0.79; 95% CI: 0.70–0.86). [35]

Promising outcome data from the multicenter, randomized FAVOR III China, comparing QFR-guided PCI with angiography-guided PCI, have been recently published. At 2 years, the primary endpoint of MACE was 8.5% for the QFR-guided group and 12.5% for the angiography-guided group ($p < 0.001$), mainly driven by a reduced rate of periprocedural myocardial infarction (MI), reduced rate of MI and lower rates of ischemia driven revascularization in the QFR arm. [36, 37] Of note, the results should be interpreted in light of the low anatomical complexity in the study (mean SYNTAX Scores QFR 9.3 ± 6.0 vs. angio 9.6 ± 6.3) as well as the remarkably low number of patients not undergoing revascularization as compared to previous studies. [7, 36]

Longer term follow-up, as well as the results of the ongoing FAVOR III Europe Japan trial (NCT03729739) and PIONEER IV (NCT04923191), assessing whether QFR-based diagnostic strategy yields non-inferior clinical outcomes as compared to a guideline-recommended strategy, are eagerly awaited.

Figure 1: Commercially available software for angiography-based FFR: QFR *with permission from Medis Medical Imaging Systems B.V.*



FFRangio

FFRangio (CathWorks, Ltd, Kfar Saba, Israel) provides a functional angiogram with a 3D reconstruction of the entire (right or left) coronary arterial system, using at least two angiographic projections 30° degrees apart. The coronary tree is modeled as an electric circuit where each segment acts as a resistor and the contribution of each narrowing to the total flow resistance is considered based on its impact on overall resistance. Subsequently, a lumped model is built, allowing the pressure drops and the flow rates to be estimated. FFRangio is then calculated as the ratio of the maximal flow rate in the stenosed artery compared with the maximal flow rate in the absence of the stenosis (Figure 2). [38, 39]

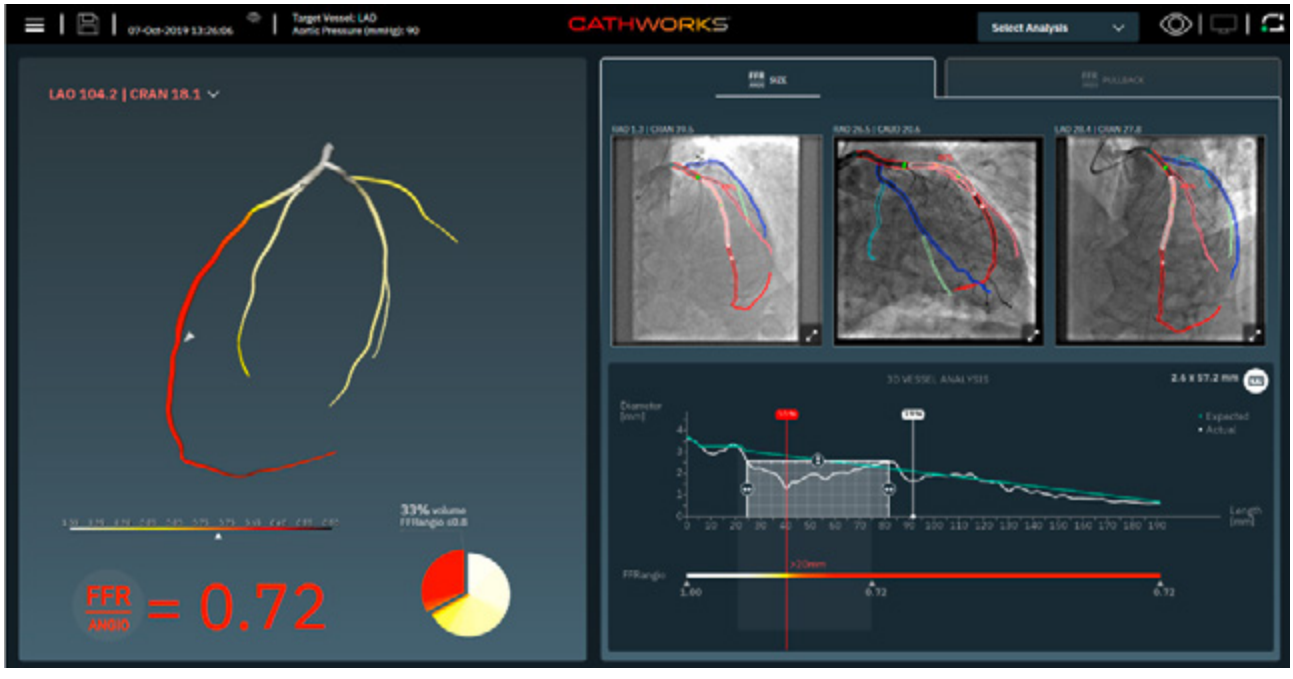
FFRangio showed a high diagnostic accuracy as compared to FFR in retrospective studies, when computed offline by experienced operators, as well as in prospective cohort studies, and appeared to be consistent across subgroups of patients (including age, sex, body mass index, diabetes, clinical presentation, and lesion types) (Table 2). [39–42]

The multicenter, prospective observational FAST-FFR study is currently the main evidence supporting the use of FFRangio. In 301 patients, online measurement of FFRangio, performed by trained local site personnel, showed 92% accuracy in predicting invasive wire-based FFR ≤ 0.80. [38]

Interestingly, in a head-to-head comparison between NHPR and FFRangio in predicting FFR ≤ 0.80, FFRangio agreed more often with invasive FFR than NHPRs, namely Pd/Pa, iFR and dPR (accuracy 92.4% for FFRangio, 85.3% for Pd/Pa, and 82.7% for iFR and dPR) (Table 3). [43]

Data regarding clinical outcomes of 492 patients whose treatment decision was based solely on the FFRangio recommended treatment (revascularization or deferral), have been recently presented, showing a rate of MACE at one year follow-up of 4.1% and 2.5% for the revascularization and deferral groups, respectively. [44]

Figure 2: Commercially available software for angiography-based FFR: FFRangio *with permission from CathWorks*



Vessel Fractional Flow Reserve (vFFR)

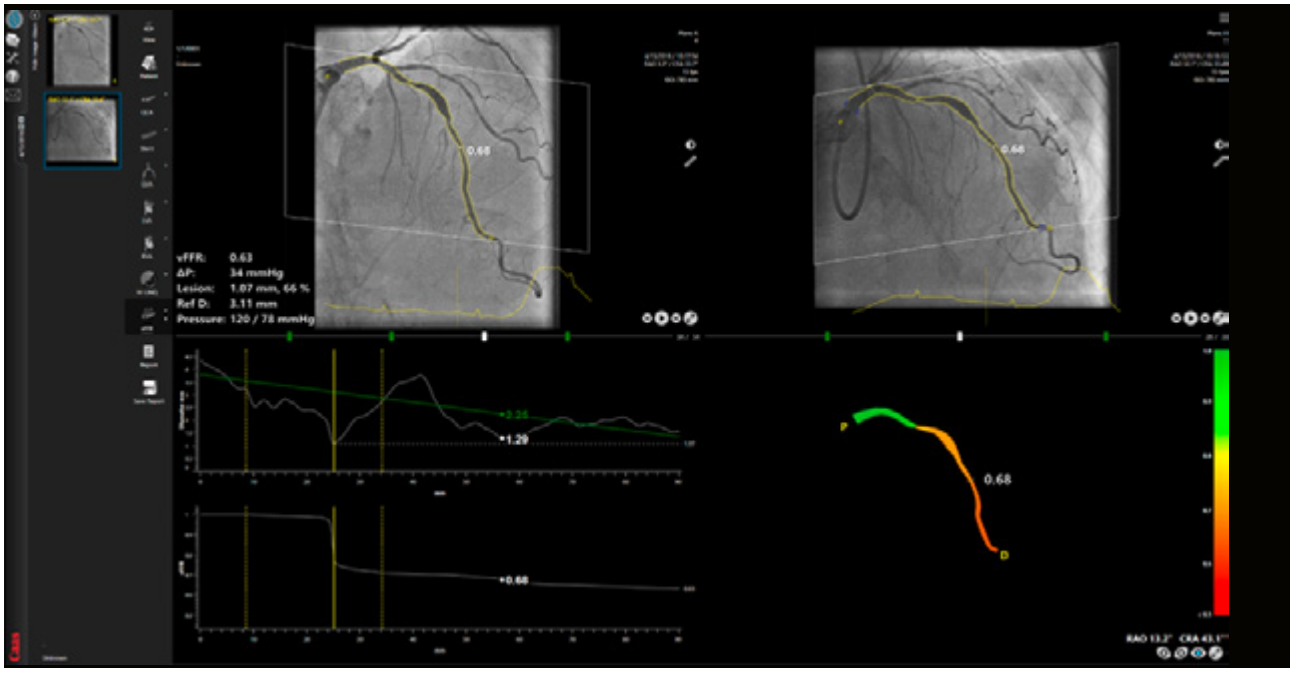
vFFR (CAAS, Pie Medical Imaging, Maastricht, the Netherlands) is obtained from two angiographic views with at least 30 degrees difference in rotation/angulation to generate the 3D QCA, using the invasively measured aortic root pressure as an input boundary condition. [45] The algorithm applies automated and harmonized optimal end-diastolic frame selection in the two orthogonal projections by ECG triggering and allows physiological lesion assessment of a specific target segment or vessel of interest, eliminating the need to perform an assessment of the full cardiac tree or manual frame counting (Figure 3). [45]

vFFR was first validated in two retrospective, single center studies, FAST I (validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study) and FAST EXTEND, showing an excellent diagnostic performance in predicting FFR among different vessel and anatomy subsets (AUC 0.93 and 0.94, respectively) (Table 2). [45, 46]

These positive findings were subsequently confirmed in the prospective, international, multicenter FAST II study (vessel fractional flow reserve (vFFR) for the assessment of stenosis severity: the FAST II study) which demonstrated a good correlation between vFFR, computed by local site personnel and by a blinded Core Lab, and pressure-wire-based FFR ($r = 0.74$; $p < 0.001$; mean bias 0.0029 ± 0.0642). Moreover, an excellent diagnostic accuracy of vFFR in identifying lesions with an invasive wire-based FFR ≤ 0.80 (AUC 0.93; 95% CI: 0.90–0.96; $p < 0.001$), also in more complex lesions, including bifurcations, tortuous and calcified lesions and patients presenting with non-ST elevation-acute coronary syndrome, was shown (Table 2). [47]

In a dedicated study focusing on patients with non-ostial left main coronary artery (LMCA) disease with good quality angiographic visualization and availability of intravascular ultrasound (IVUS) imaging data, vFFR showed a good correlation with left main coronary artery minimal lumen area (MLA) as assessed by IVUS ($r = 0.79$,

Figure 3: Commercially available software for angiography-based FFR: vFFR *with permission from Pie Medical Imaging B.V.*



p = 0.001) and a good diagnostic accuracy of vFFR ≤ 0.80 in identifying lesions with MLA < 6.0 mm^2 (sensitivity 98%, specificity 71.4%, AUC 0.95; 95% CI 0.89–1.00, p = 0.001). [48]

Moreover, vFFR computation in patients discussed within the heart team in whom the treatment decision was based on angiography alone demonstrated a discordance between vFFR confirmed lesion significance and revascularization in 29.8% of cases. [49]

In a head-to-head comparison between vFFR and dPR in predicting FFR ≤ 0.80, vFFR showed a stronger correlation and appeared to be a better discriminator than dPR (r = 0.82 versus r = 0.72, p < 0.001, AUCs 0.94 versus 0.89, p = 0.0053). In addition, in vFFR-dPR discordant cases, vFFR was more often concordant with FFR than dPR (58% vs. 42%, p = 0.001) (Table 3). [50]

Studies looking at the diagnostic value of vFFR with dPR as index reference showed a good correlation and diagnostic performance (r = 0.68, AUC 0.89). [51]

In the post-PCI setting, the retrospective, single center FAST POST (validation of novel 3-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve post stenting) was the first study to validate vFFR against microcatheter-based FFR, showing a good correlation and a high diagnostic accuracy to predict a conventional post-PCI FFR < 0.90 (r = 0.88, AUC 0.98, 95% CI: 0.96–1.00) (Table 4). [52]

Subsequent data from FAST OUTCOME (the prognostic value of angiography-based vessel fractional flow reserve after percutaneous coronary intervention) study demonstrated that post-PCI vFFR directly correlated to future adverse cardiac events. [53] When grouped in tertiles according to post-PCI vFFR values, vessels in the lower (vFFR < 0.88) and middle tertile (vFFR 0.88–0.93) had a higher risk of target vessel failure as compared to vessels in the upper tertile (vFFR ≥ 0.94) (24.6% and 21.5% vs. 17.1%; adjusted HR 1.84, p = 0.011, and 1.58, p = 0.040, respectively) at 5-years follow-up (Table 4). [53]

Finally, recent developments in vFFR software allowed to simulate the effect of "virtual" PCI and thus to predict the functional outcomes of PCI, through the estimation of post-PCI FFR (residual vFFR). Using pre-PCI virtual pull backs, residual vFFR showed a good correlation with invasive post-PCI FFR and post-PCI vFFR values (r = 0.84 and 0.77, respectively), and a good discriminative ability to identify post-PCI FFR < 0.90 (AUC 0.93 95% CI: 0.86–0.99). [54] Of note, restrictions may be in place for the availability of this option in CAAS workstation.

The safety and efficacy of a vFFR as compared to an FFR-guided revascularization strategy will be assessed in the ongoing multicenter, randomized FAST III (NCT04931771) and LIPSIA STRATEGY (NCT03497637) trials.

Computational pressure-flow dynamics derived FFR (caFFR)

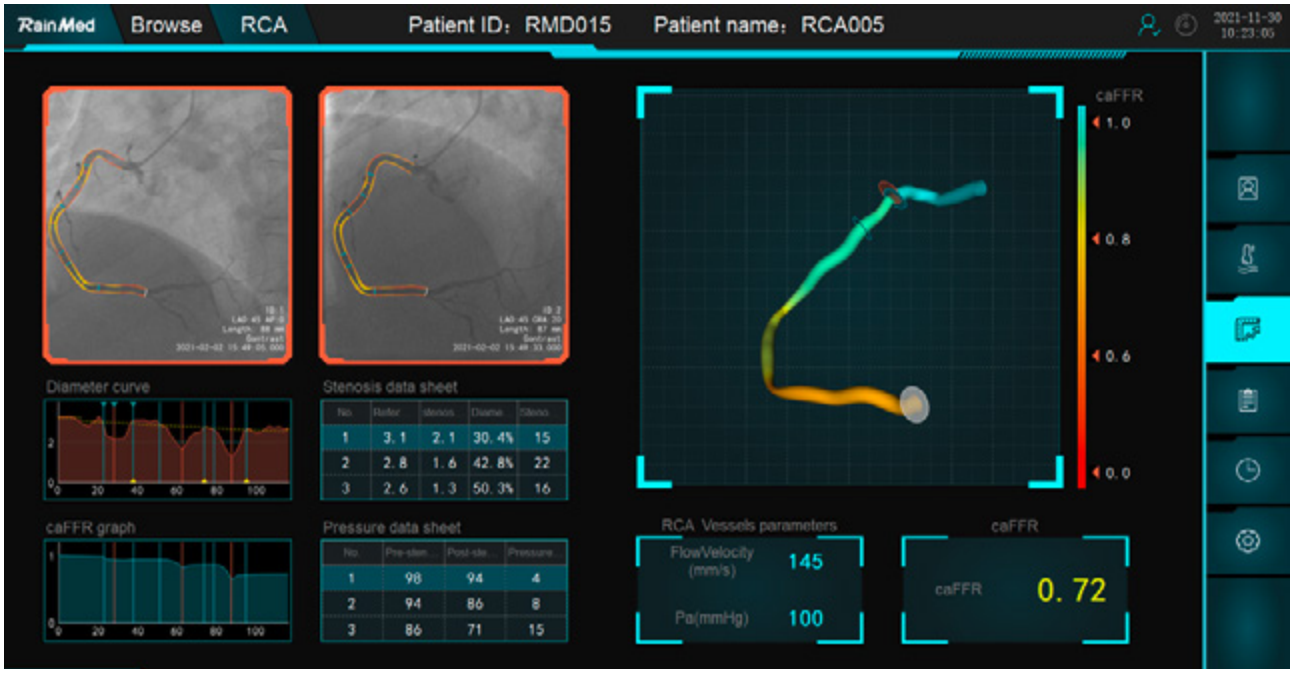
caFFR (Rainmed Ltd, Suzhou, China) requires two angiographic projections at different angles (separated by ≥ 30°) and the aortic pressure recorded by the FlashPressure pressure transducer, which is connected to the guide catheter and automatically determines mean aortic pressure over the third to eighth cycles following angiography. The flow velocity and the mean aortic pressure, recorded by the FlashPressure pressure transducer and transmitted to FlashAngio console, are used as an input to calculate the pressure drop along the generated mesh of the coronary artery (Figure 4). [55] Compared to the previous softwares, caFFR uses a real time invasive pressure, which allows to take the dynamic nature of blood pressure into account, instead of using a static value of aortic pressure, and to account for energy loss in lumen area proximal and distal to the stenosis. [55]

The currently available literature supporting the use of this software is limited to the prospective, multicenter FLASH FFR study (accuracy of computational pressure-fluid dynamics applied to coronary angiography to derive fractional flow reserve: FLASH FFR), where caFFR showed a high correlation and diagnostic accuracy as compared with FFR (r = 0.89, diagnostic accuracy 96%; 95% CI: 0.93–0.98), when computed by experienced operators in a low risk patients cohort (Table 2). [55]

Moreover, based on data from caFFR computation, a coronary angiography-derived index of microvascular resistance (caIMR) has been recently validated in a small cohort of patients with angina and without obstructive coronary artery disease, and it showed a good correlation and diagnostic performance as compared to wire-based IMR (r = 0.75, diagnostic accuracy 84%; 95% CI: 72%–0.93% and AUC 0.92). [56]

Although the first validation studies have shown favorable results, outcome data from the currently ongoing FLASH FFR II (NCT04575207), which compare caFFR-guided revascularization versus FFR-guided revascularization, are needed.

Figure 4: Commercially available software for angiography-based FFR: caFFR *with permission from RainMed Medical Technology Co., Ltd.*



Reproducibility

A common feature of all angiography-based FFR software is represented by the need for specific user interaction to refine geometrical vessel parameters and to select appropriate angiographic projections and frame. As such, the variations introduced by operators in each of these steps may potentially affect the reproducibility of the methods.

Data about time and amount of necessary manual contour corrections are available only for vFFR, which showed a highly accurate contour detection, and a percentage of manual contour correction needed in only 9.3% of vessels. [47]

With respect to reproducibility, in the FAST I and FAST II studies, vFFR showed a low interobserver variability when performed either by experienced operators (r = 0.95), and when performed by a blinded Core Lab and independent trained local site personnel (r = 0.87), which was consistent among specific lesion and patient subsets. [45, 47] Despite slight differences regarding the diagnostic performance between Core Lab and local site personnel in vFFR computation (r = 0.74 vs 0.74, AUC = 0.93 vs 0.90, diagnostic accuracy 90% vs 83%), the results indicate the reliability of physiological lesion assessment by trained local site personnel in the absence of a well-trained Core Lab. [48] In line with previous findings, vFFR showed a low variability and an excellent diagnostic agreement, when computed by an independent Core Lab in a blinded fashion (r = 0.89, coefficient of variation 3.9%). [57]

QFR demonstrated a good reproducibility when computed by two independent Core Labs (r = 0.96) or when performed online versus an independent Core Lab (r = 0.91). [24, 58] Nevertheless, the recently published QREP study demonstrated a modest reproducibility of QFR when computed by multiple observers with heterogeneous experience level (coefficient of variation 9.4%). The reproducibility appeared to be dependent on stenosis severity, angiographic quality, and specific observer. [59]

Finally, also FFRangio has shown good reproducibility (r = 0.88) when performed offline by experienced operators, however data about the agreement of on-site operators reproducibility are currently lacking. [38, 41]

Time to computation

Faster computation times of angiography-based physiology as compared to routine pressure-wire-based physiology is a major advantage that may help to drive the adoption of angiography-based FFR software. As of to date, data about comparative computation versus FFR are reported for QFR and caFFR. In the FAVOR II Europe-Japan trial the median time for QFR computation was significantly shorter than the time needed to measure FFR (5.0 min vs. 7.0 min respectively, $p < 0.001$). These results were subsequently confirmed in the FAVOR III China study, where QFR computation required 3.9 ± 1.4 minutes.

Data about time to computation for caFFR were highlighted in the FLASH FFR trial, showing that caFFR analysis required a total operation time of less than 5 min with less than 1 min computation time.

However, whether these differences can be replicated outside a clinical trial remains to be established.

A number of challenges remain and need to be addressed in order to standardize the workflow within the catheterization laboratory. Seamless integration of the software with local DICOM system, pressure signals and available workstations are crucial to achieve ease of use and fast computation times. With the integration of vFFR (CAAS, Pie Medical Imaging, Maastricht, the Netherlands) into the *syngo* Application Software running on ARTIS icono (Siemens Healthcare GmbH, Erlangen, Germany), a first step towards a more seamless workflow has been taken. Next to these technical prerequisites, the need for trained and certified personnel operating the workstation is imperative.

Future perspective

Angiography-based FFR is an appealing alternative to conventional pressure-wire physiological lesion assessment and has the potential to extend the uptake of physiology-guided PCI.

Whereas promising data have been recently released on the superiority of QFR vs. angiography-guided PCI, outcome data showing the non-inferiority of angiography-based revascularization compared to an FFR-guided strategy, are needed. As such, the results of currently ongoing dedicated randomized outcome trials (FAVOR III Europe Japan trial NCT03729739, PIONEER IV NCT04923191, FAST III NCT04931771, LIPSIA STRATEGY NCT03497637, FLASH FFR II NCT04575207) are eagerly awaited (Table 5).

Table 5: Ongoing outcome trials

	Device	Comparator	Trial design	Location/ site	No. of patients	Inclusion criteria (lesion)	Clinical Trial ID
FAVOR III EU-Japan	QFR	FFR	Non-inferiority	Europe/39 Japan/2	2000	Lesion ≥ 40% & ≤ 90% Ref diam ≥ 2.25	NCT03729739
PIONEER IV	QFR	Angio + IFR/FFR	Non-inferiority	Europe/30	2540	Lesion ≥ 50% Ref diam ≥ 2.25	NCT04923191
FAST III	vFFR	FFR	Non-inferiority	Europe/35	2228	Lesion ≥ 30% & ≤ 80%	NCT04931771
LIPSIA-STRATEGY	vFFR	FFR	Non-inferiority	German/7	1926	Lesion ≥ 40% & ≤ 90%	NCT03497637
Flash FFR II	caFFR	FFR	Non-inferiority	China/12	2132	Lesion ≥ 40% & ≤ 90% Ref diam ≥ 2.25	NCT04575207

The information in this section is based on ongoing research. The results are not available yet.

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Abbreviations

AUC	Area under the curve
caFFR	Computational pressure-flow dynamics derived FFR
caIMR	Coronary angiography-derived index of microvascular resistance
CFD	Computational fluid dynamics
CI	Confidence interval
ECG	Electrocardiogram
FFR	Fractional flow reserve
FFRangio	Angio-based fractional flow reserve
HR	Heart rate
iFR/iwFR	Instantaneous wave-free ratio
IMR	Index of microcirculatory resistance
IVUS	Intravascular ultrasound
LMCA	Left main coronary artery
MACE	Major adverse cardiac events
MI	Myocardial infarction
MLA	Minimal lumen area
NHPR	Non-hyperemic pressure ratios
PCI	Percutaneous coronary intervention
Pd/Pa	Distal coronary artery pressure to aortic pressure ratio
QFR	Quantitative flow ratio
TIMI	Thrombolysis in myocardial infarction
vFFR	Vessel fractional flow reserve
2D QCA	2-dimensional quantitative coronary angiography
3D QCA	3-dimensional quantitative coronary angiography
µQFR	Murray law-based quantitative flow ratio

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