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A prospective multicenter validation study for a novel angiography-derived physiological assessment software: Rationale and design of the radiographic imaging validation and evaluation for Angio-iFR (ReVEAL iFR) study

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Background Angiography-derived physiological assessment of coronary lesions has emerged as an alternative to wire-based assessment aiming at less-invasiveness and shorter procedural time as well as cost effectiveness in physiology-guided decision making. However, current available image-derived physiology software have limitations including the requirement of multiple projections and are time consuming.

Methods/Design The ReVEAL iFR (Radiographic imaging Validation and EvALuation for Angio-iFR) trial is a multicenter, multicontinental, validation study which aims to validate the diagnostic accuracy of the Angio-iFR medical software device (Philips, San Diego, US) in patients undergoing angiography for Chronic Coronary Syndrome (CCS). The Angio-iFR will enable operators to predict both the iFR and FFR value within a few seconds from a single projection of cine angiography by using a lumped parameter fluid dynamics model. Approximately 440 patients with at least one de-novo 40% to 90% stenosis by visual angiographic assessment will be enrolled in the study. The primary endpoint is the sensitivity and specificity of the iFR and FFR for a given lesion compared to the corresponding invasive measures. The enrollment started in August 2019, and was completed in March 2021.

Summary The Angio-iFR system has the potential of simplifying physiological evaluation of coronary stenosis compared with available systems, providing estimates of both FFR and iFR. The ReVEAL iFR study will investigate the predictive performance of the novel Angio-iFR software in CCS patients. Ultimately, based on its unique characteristics, the Angio-iFR system may contribute to improve adoption of functional coronary assessment and the workflow in the catheter laboratory. (Am Heart J 2021;239:19–26.)

The key principle behind guidance of percutaneous coronary intervention (PCI) using wire-based physiology is ensuring that revascularization is performed only

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Abbreviations: ACS, Acute Coronary Syndrome; AHA, American Heart Association; CCS, Chronic Coronary Syndrome; ESC, European Society of Cardiology; FFR, Fractional Flow Reserve; iFR, instantaneous wave-Free Ratio; ITT, Intention-To-Treat; PCI, Percutaneous Coronary Intervention; PP, Per-Protocol; QCA, Quantitative Coronary Analysis; Pd, Distal Pressure; Pa, Aortic Pressure.

Clinical Trial Registration *URL:* https://clinicaltrials.gov

Unique Identifier: *NCT03857503*

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in flow limiting coronary stenosis.[1-3] Of note, in the recent guidelines of the European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) for the management of Chronic Coronary Syndrome (CCS), for patients with multivessel disease it was recommended to use wire-based pressure gradient assessment for confirming the existence of and localizing functionally significant lesions, even when pre-procedural non-invasive imaging modalities such as scintigraphy have revealed the presence of myocardial ischaemia.[2]

Fractional Flow Reserve (FFR) is measured with a pressure wire, and calculated as the ratio of mean pressure distal to the coronary lesion to the mean aortic pressure during the entire cardiac cycle under hyperemia, whereas the instantaneous wave-Free Ratio (iFR) is the ratio of pressure distal to the coronary lesion to aortic pressure selectively measured over the wave-free period of diastole under resting conditions. Both wire-based physiological parameters were endorsed in the ESC/EACTS guidelines as criteria of PCI appropriateness in patients with CCS.[2,3]

More recently, image-derived physiological coronary assessment, based on either conventional angiography or multi-slice computed tomography (MSCT), has been developed and, subsequently, validated against wire-based FFR measurement.[4-7] The current commercially-available angiography-derived FFR estimates rely on applying pressure and flow relations as derived by Gould L, et al. or Navier-Stokes equations in combination with three-dimensional anatomical models of the coronary vessel under study, which are generated from orthogonal angiographic views.[8] A meta-analysis of 11 studies investigating the diagnostic yield of this approach demonstrated that sensitivity and specificity of this kind of angiographic software to predict functional significance of lesions was 89% and 90%, respectively.[5] FFR_{CT} provides an estimate of FFR by using computational fluid dynamics under simulated hyperemic conditions; the simulation is applied to a three-dimensional MSCT coronary angiography. FFR_{CT} received FDA clearance (de-novo Class II) in 2014 and is reimbursed by multiple US health insurance systems. These image-derived FFR applications may be advantageous for patients as well as medical care providers since none require additional investigation with pressure wire, potentially reducing procedural time, risk, patient discomfort and cost.[9]

The Philips Angio-iFR medical software device (Philips, San Diego, US, Figure 1) is a novel medical software device that can provide both iFR and FFR estimates within seconds based on single angiographic projection, using a lumped parameter fluid dynamics model. The ReVEAL iFR (Radiographic imaging Validation and EvALuation for Angio-iFR) clinical trial is being undertaken to demonstrate the diagnostic accuracy of angiographic-derived iFR and FFR estimates for identifying functionally significant lesions as determined by wire-based iFR and FFR, respectively, in patients who have at least one epicardial coronary narrowing with a 40 to 90% diameter stenosis by visual angiographic assessment.

Methods

Study design

The ReVEAL iFR study is a prospective, multi-center study with centralized off-line analyses in an independent Corelab (CORRIB Corelab, Galway, Ireland) to validate the novel Philips Angio-iFR medical software device (**Figure 1**) with wire-based physiological assessment. Approximately 440 patients will be enrolled from 33 sites, in Europe (N = 14), Japan (N = 3), and United States (N = 16).

Study software for angiography-derived physiological assessment (Figure 1 and 2)

The Angio-iFR algorithm uses a lumped parameter fluid dynamics model employing an electric-hydraulic analogy [10,11]; the coronary hydraulic network model is created as an electrical circuit "powered" by the heart. The basic components of the coronary vasculature are modeled as follows: Volumetric Blood Flow (Q), Pressure (P), and the Vascular Resistance including coronary lesion (R) equates to electrical current (I), voltage (V), and resistance (R), respectively. In the hydraulic analog, a dynamic pump pushes a viscous fluid through pipes with various degrees of blockage or constriction. Figure 2 provides a diagram of the manner in which the coronary circulation is modeled.

Automated quantitative coronary angiography algorithms measure the luminal dimensions of coronary arteries and according to the measurement coronary arteries are divided into segments in which each segment's diameter is constant and does not change. The pressure drop associated with fluid passing through each segment can be derived via Poiseuille's Law:

$$\Delta P = \frac{8\eta LQ}{\pi r^4}$$

Where, ΔP is the pressure drop across the length of the vessel segment;

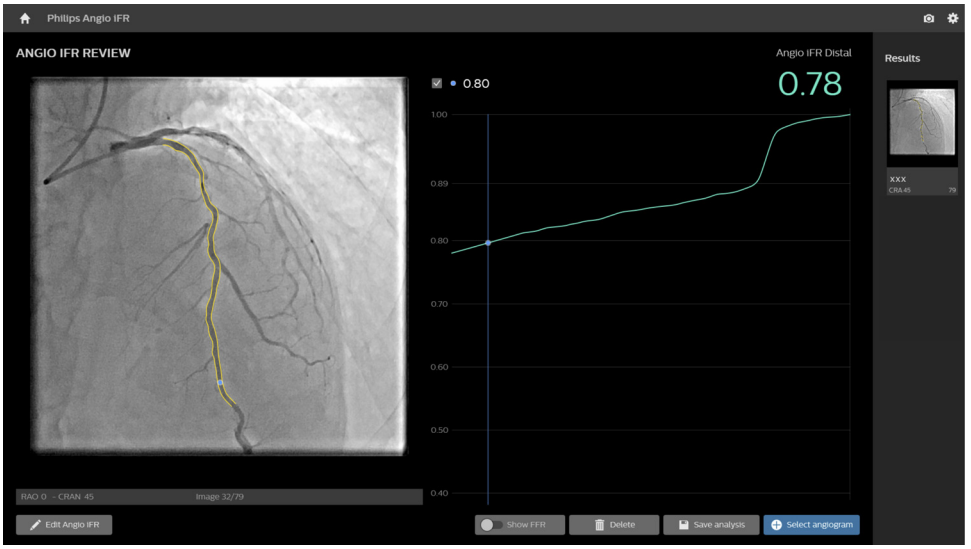
η is the dynamic viscosity of the blood moving through each vessel segment (represented by the variable, Poiseuille Friction, in Figure 2A);

L is the length of each vessel segment;

Q is the volumetric flow rate through each vessel segment; r is the radius of each vessel segment.

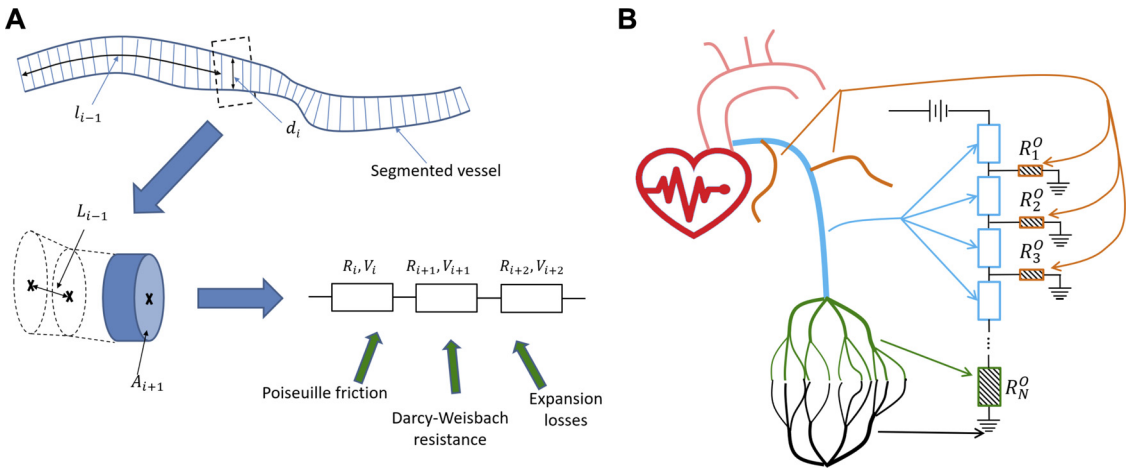
L and r are measured directly from the angiogram, and Q is a model parameter determined by the outlet conditions of the vascular system derived from the aortic pressure, and hence the pressure drop can be calculated. The equation does not hold, however, in very narrow segments, or for turbulent flow, close to the entrance of a

Figure 1



Angio-iFR medical software. The image is preliminary, which may be changed in the commercial version.

Figure 2



A lumped parameter fluid dynamics model of coronary circulation. (A) The correspondence between the vessel segmentation and the chain of resistors is illustrated for a small sample of cross sections. (B) Elements from the coronary artery system to the corresponding parts in the lumped model. The segmented coronary artery (blue) corresponds to the linear chain of resistors. Branching vessels (orange) correspond to orthogonal outlets. The microvascular resistance of the myocardium (green) is modeled as an outlet resistor. The venous system (black) corresponds to the electrical ground – or termination of all resistance.

vessel segment and after a focal lesion. These conditions are accounted for by extending the vascular resistance calculation with the Darcy-Weisbach friction and Borda-Carnot expansion loss variables as noted in Figure 2A. The three resistance effects are combined in a weighted sum using free training parameters as weights. The pressure drop across the length of the interrogated coronary segment is thus equivalent to the sum of the pressure drops across each individual segment in the same manner that series resistors are treated in an electrical circuit. Branching arteries are modeled as outlets reducing the local volumetric flow rate in the primary vessel, the

microvasculature is modeled as an outlet resistor, and the venous system is treated as the electrical ground – or the termination of the circuit (Figure 2B). This lumped parameter modeling approach is computationally efficient, and therefore enables real-time analysis during the coronary catheterization.

The software is composed of two separate models for estimating the functional significance of a lesion by FFR and iFR separately. The basic premise for the iFR indices is that autoregulation of the microcirculation causes the flow across the stenosis to remain constant until the stenosis becomes critical. For simulation of FFR and iFR, different boundary conditions are used. For estimation of FFR the hyperemic flow state is assumed, myocardial resistance is taken to be minimal and independent of the lesions, and all flow variation is thus considered to be associated with the epicardial lesion. For estimation of iFR, however, the myocardial resistance varies with the lesion resistance and the simulated flow is almost independent of the resistance associated with the lesion until the lesion becomes critically narrowed. The algorithm for FFR estimates was trained using invasively measured reference values together with 2D fluoroscopic angiography projections from 39 datasets (39 lesions in 28 patients). Variables were optimized to maximize the diagnostic accuracy of the software estimates compared to the respective invasive FFR measures. The algorithm for iFR estimates was optimized for the invasive iFR values in the same 39 datasets.

Study population

The inclusion and exclusion criteria are listed in Supplemental Table. Briefly, the study population is those presenting with Chronic Coronary Syndrome (CCS), having at least one epicardial coronary artery lesion with a 40-90% diameter stenosis by visual assessment on invasive coronary angiography. Angiographic exclusion criteria includes; left-main disease (isolated or non-isolated) when target vessel is left coronary artery; aorto-ostial right coronary artery disease when target vessel is right coronary artery; any (treated or untreated) chronic total occlusion (CTO) in the ipsilateral territory to the target vessel or untreated CTO in the contralateral territory to the target vessel; target vessel with severe tortuosity; target vessel with heavy calcification; target vessel with TIMI flow grade 1 or 0; target vessel with severe diffuse disease; bifurcation or trifurcation lesion; target lesion associated with myocardial bridge; and any vascular abnormality precluding optimal contrast opacification (Supplemental Table).

Study procedure

After confirmation of eligibility criteria, the following angiographic acquisition and physiological assessment will be performed. The study procedure will be conducted by using a guiding catheter of $\geq$5 French size.

After the mandatory administration of intracoronary nitrates, a single projection angiography of the coronary lesion is acquired twice at least 30 degrees apart without any guidewires.

After equalization of the pressure between pressure-wire measurement and aortic pressure, the pressure wire is further advanced into the target coronary artery beyond the lesion at least three times the length of the reference vessel diameter distal to the lesion, followed by acquisition of angiography in situ to be able to localize the exact position of the sensor of the pressure wire.

After the effect of any contrast or saline has abated, iFR spot measurements are recorded twice, as well as resting heart rate, Pd, Pa.

Intracoronary adenosine or other hyperemia agent is administered and once hyperemia is achieved, HR, FFR, Pd, and Pa measures are recorded to obtain FFR.

After hyperemia has abated, an iFR pullback is performed under continuous fluoroscopy, with iFR co-registration to the angiogram by the SyncVision system if it's available.

Pressure drift is checked when the sensor of the pressure wire is pulled back to the vessel ostium. If pressure drift is significant (Pd/Pa $<$0.98 or $>$1.02), the physiological measurements are repeated after second equalization.

Post procedure

Post-procedure care will be according to the institutional standard of care. Peri-procedural adverse events will be collected in 48 hours after the index procedure. When patients discharged prior to 48 hours after the index procedure, the patients will be followed up by phone to capture peri-procedural events.

Angiographic and pressure curve analysis in independent Corelab

After the acquisition of the angiographic and physiological data, the anonymized data are transferred to the independent Corelab (CORRIB Corelab, National University of Ireland Galway, Galway, Ireland). A dedicated screener will review the quality of angiography and physiological recordings according to the pre-specified quality criteria. The minimal evaluable criteria shall be the two sets of baseline angiograms documenting the target lesion/vessel with at least one matched iFR or FFR physiology record. Once the minimum evaluable criteria are confirmed, separate, dedicated analysts will perform the angiographic or physiological data analysis. The angiographic analyst will be blinded to the results of physiological data, whereas the physiological analyst will be blinded to the information derived from angiography. Invasive measurements of Pd, Pa, iFR and FFR will be confirmed using the Philips software (FFR v2.5 Modality of the s5/s5i/CORE and CORE Mobile Precision Guided Therapy System). The angiography is analyzed by

the Philips Angio-iFR medical software device (Philips IGTD, San Diego, US). In order to compare the results to the conventional angiography, Quantitative Coronary Angiography (QCA) is also performed with CAAS software (Pie Medical Imaging, Maastricht, the Netherlands). To make accurate correlation between angiographic-derived versus wire-derived iFR/FFR, the recorded position of the pressure sensor is superimposed in the angiographic data for colocalization of measurement. The angiographic analyst will select and analyze the frame of analysis in diastolic phase either based on ECG or angiography with minimum overlap and foreshortening of the lesion. The selection of frame and analysis will be compared with the analysis based on the frame that is automatically chosen by the Angio-iFR medical software device.

The mean value of wire-based iFR measurements, which should be recorded twice, will be used in the final analysis comparing iFR_{ref} and iFR_{angio}, taking into account the inherent measurement variability.

Endpoints

The primary endpoint of this imaging study is sensitivity and specificity of the image-derived iFR and FFR estimate for a given lesion compared to the corresponding invasive iFR and FFR values. The study is considered positive when both the image-derived iFR and FFR yield a sensitivity $\geq$75% and specificity $\geq$80%.

The powered secondary endpoints include (1) measurement agreement between angiography-derived FFR/iFR estimates and their respective matched invasive measures as demonstrated by Bland Altman Limits of Agreement; (2) Specificity of iFR/FFR estimates (dichotomized at the respective functional significance thresholds of 0.89 and 0.80) over visual determination of stenosis severity of $\geq$50%.

The intra-observer variability, inter-observer variability between two Corelab analysts, and intra-vessel variability between two iFR_{angio}/FFR_{angio} values based on different angiographic projections of the same target vessel are evaluated in a pooled set of 100 cases with a similar prevalence of the study population, using McNemar test and measurement agreement using the Bland-Altman test and the intraclass correlation coefficient (ICC). The angiographic analysis will be repeated twice by one analyst for intra-observer variability according to the instruction for use and Corelab standardized operational instruction, whereas a second analyst will perform analysis based on the same instructions to assess inter-observer variability. The intra-vessel variability will be assessed among cases which have at least two projections available for the analysis.

The other secondary endpoints are described in Supplemental Table II.

Sample size consideration

The study is powered to demonstrate the specificity of iFR_{angio} and FFR_{angio} compared to their respective invasive reference measures is $\geq$80%, and the sensitivity of iFR_{angio} and FFR_{angio} compared to their respective invasive reference measures is $\geq$75% using a two-sided binomial test with a significance level of 0.025 and power = 90%.

The variable disease prevalence based on positive FFR and iFR values impacts the sensitivity and specificity measures. The pooled DEFINE FLAIR and iFR SWEDEHEART demonstrated a prevalence of 50% and 55% according to iFR and FFR.[12] In the DEFINE FLAIR trial,[13] the prevalence of functionally significant coronary artery disease was 45% according to iFR, whereas in the FAVOR trial, the prevalence based on the invasive FFR was 32%.[14]

Based on these prevalence in the previous studies, minimum prevalence of the current study was assumed to be 30% regarding positive iFR measurement (iFR $\leq$0.89). Under this assumption, a sample size of 413 provides for a minimum power of 90% for both sensitivity and specificity with an alpha of 0.025. Supplemental Table 3 provides the actual power and alpha values for sensitivity and specificity for prevalence values ranging between 30 to 40% demonstrating increasing power for sensitivity but decreasing power for specificity associated with increasing prevalence.

The expected data quality failure rate is less than 15%, and the number of interrogated lesions per patient is expected to be 1.1 based on the DEFINE PCI study.[15] Hence, a total of 486 (413/0.85) vessels are needed, and enrolling 442 (486/1.1) patients would allow for both the expected number of diseased vessels and either missing or unevaluable data.

Statistics analysis

Safety analysis will be performed on patients enrolled into study and in whom the intervention began with the introduction of a pressure wire (Intention to Treat (ITT) population). The primary and secondary analyses of performance data will be performed including all patients for whom matched pairs of data as described previously and visual estimation of stenosis severity (i.e., %DS) data are available (per-protocol (PP) population). All variables will be summarized by descriptive statistics. The statistics for continuous variables includes mean, median, standard deviation, 95% confidence interval for the means, and the number of observations. For categorical variables, number events, event rate, and 95% confidence interval for the event rate will be presented.

Subgroup analysis

The differences between the angio-derived iFR/FFR against invasive iFR/FFR will also be assessed in the subgroups with or without tandem lesions.

Table. Current available angiography-derived FFR and Angio-iFR software

	Angio-iFR	μQFR	QFR	FFR_{angio}	vFFR	caFFR
Company	Philips	Pulse Medical	Medis/Pulse Medical	CathWorks	Pie Medical	RainMed
Estimated reference	iFR and FFR	FFR	FFR	FFR	FFR	FFR
Required angio projections	1 projection	1 projection	2 projections 25 degrees apart	≥2 projections 30 degrees apart	2 projections	2 projections 30 degrees apart
Required pressure data	No	No	No	No	Need	Need
Side branches	Incorporated	Incorporated	Not incorporated	Incorporated	Not incorporated	Not incorporated
Studies	ReVEAL iFR	Tu S, et al.	FAVOR pilot FAVOR II China FAVOR II EJ WiFi II FAVOR III	FAST-FFR	FAST	FLASH-FFR
C-statistics for predicting FFR≤0.8	NA	0.97	0.92-0.96	0.94	0.93	0.979
Time to computation	NA (expected to be very short time)	67±22 seconds	4.36 ± 2.55 min	*2.7 min	NA	4.54±1.48 min

FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; QFR: quantitative flow ratio.
*Time for manual correction and lesion identification were not included.

DISCUSSION

The main objective of the current study is to clinically validate the novel Angio-iFR medical software device with a reference of wire-based iFR/FFR in CCS patients undergoing angiography.

The angio-based physiological assessment is of great interest in current clinical practice of interventional cardiology. The potential clinical advantages of angiography-derived physiological assessment over wire-derived assessment are: (1) No requirement for a pressure wire and hyperemic agent; (2) Shorter procedure time; (3) Less patient discomfort; (4) Elimination of erroneous coronary pressure measurement by pressure wire; (5) Post-stenting FFR/iFR value can be assumed at baseline, which facilitate the PCI planning; and (6) Analyses can be performed at the time of the diagnostic procedure as well as post-procedure.

Currently, four technologies are commercially available for the angiography-derived physiological assessment: Quantitative Flow Ratio (QFR) (Medis Medical Imaging System, Leiden, the Netherlands, and Pulse Medical Imaging Technology, Shanghai, China); FFR_{angio} (CathWorks, Kefar Sava, Israel); vessel FFR (Pie Medical Imaging, Maastricht, the Netherlands); and caFFR (RainMed Ltd., Suzhou, China) (Table).

Among those software packages, QFR is the most well studied one so far. A systematic review and Bayesian meta-analysis indicated that the diagnostic performance of angiography-derived FFR does not differ between methods for computation (computational fluid dynamics vs. mathematical formula), type of analysis (online or offline analysis), or software packages.[5] The major limitation of angiography-derived FFR is thus far the lack of robust evidence in terms of clinical benefits that should be based on a prospective large randomized controlled trial (RCT) comparing established PCI strategies. However, the ongoing large RCTs (FAVOR III China, and FAVOR III EJ,) are expected to clarify the clinical efficacy of the angio-based physiological assessment. Another limitation is the requirement of two different projections to create a 3D vessel model, which could limit the utility of the technology especially in case of a retrospective analysis.

The current Angio-iFR software is unique in that the algorithm uses an electrical lumped parameter model; the angiographic simulation is based on one projection with short computation time of few seconds. This fast calculation is achieved by the in-depth background calculation and interpretation of the cine angiography. Among currently available angiography-derived physiological assessment software packages, the measurement of QFR takes on average 5 minutes for computation, [16,17] whereas caFFR requires 4.54 minutes.[18] FFRangio requires 2.7 minutes of computational time, without including manual processing time as well as data transfer.[19]

In addition, time to find another optimal projection for 3D vessel model reconstruction and additional settings (for example, caFFR requires a disposable pressure sensor for each study) was not included in those computational time, which might require additional few minutes. Of note, Tu S, et al. recently reported that development of a novel single-projection-derived QFR (μQFR) taking into account the side branches with the Murray law, which showed a substantially shorter computational time (67 ±22 seconds) than current available software (Table). [20,21] It would be of true

interest if the Angio-iFR software could achieve the similar, or even shorter, computational time with the highly automated procedure compared to other software including μQFR, while maintaining the diagnostic accuracy [21].

As described above, the analyzability and results of other commercially available software are strongly influenced by the acquisition of two projections, required to create 3D vessel model. Although prospective studies showed high analyzability of an angiography-derived FFR (90% - 99%), it is challenging especially in cases with complex diseases to acquire two separate angiographic projections without overlap or foreshortening. In fact, in the retrospective analysis of the SYNTAX II trial, the analyzability was 71.0% among patients with 3-vessel disease.[22] In addition, the potential efficacy of post-procedural QFR assessment in predicting recurrent cardiovascular events was also reported, where the analyzability of QFR was approximately 80%.[23,24] If the novel Angio-iFR software could demonstrate improved analyzability based on single view, this could facilitate the adoption of angiography-derived physiological assessment and post-PCI functional optimization in the catheter laboratory by integrating the assessments in a standard procedural workflow.[15,25]

In addition, this software provides simulated iFR values based on the resting coronary physiology and therefore may be able to provide further benefits over modelling the FFR value. Since the algorithms behind angiography derived physiological assessment typically rely on predictions of hyperemic microvascular resistance, and as resulting trans-stenotic hyperemic flow, using resting indices might bring an advantage over hyperemic indices. In non-hyperemic conditions, because of the autoregulation of microvascular circulation, coronary flow remains constant and does not significantly change according to the degree of coronary narrowing. However, during hyperemia, coronary flow becomes unpredictable after passing through a coronary narrowing with a diameter stenosis $\geq$40%.[8,26,27] For this reason, in case of a tandem lesions, iFR, but not FFR, can separately assess the functional severity of each individual stenosis in the same epicardial vessel.[26] In the iFR GRADIENT registry, the difference between predicted post-PCI iFR and observed actual post-PCI iFR was only 1.4% in tandem and diffuse coronary disease,[28] which was lower than those of FFR in previous reports (4% -11%).[27,29] Our subgroup analysis with or without tandem lesion may be able to clarify whether this benefit can be translated to angiographic-derived resting indices as well as the invasive indices.

Since this software can provide iFR and FFR based on a single view of angiography, it would be of great benefit for operators to visualize pressure gradients naturally co-registered in a working view during coronary intervention.

Limitation

This is a technical or mechanistic study to compare the novel angiography-derived physiological assessment versus wire-derived physiological assessment. The impact of the simulation on clinical outcomes is not investigated.

Conclusions

This will be the first trial to evaluate the novel angiography-based physiological assessment software to predict both iFR and FFR values among CCS patients undergoing coronary angiography.

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Disclosures

All other co-authors have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.05.004.

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