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STATE-OF-THE-ART REVIEW

Invasive Coronary Physiology After Stent Implantation

Another Step Toward Precision Medicine

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ABSTRACT

Intracoronary physiology is routinely used in setting the indication for percutaneous coronary intervention (PCI) but seldom in assessing procedural results. This attitude is increasingly challenged by accumulated evidence demonstrating the value of post-PCI functional assessment in predicting long-term patient outcomes. Besides fractional flow reserve, a number of new indexes recently incorporated to clinical practice, including nonhyperemic pressure and functional angiographic indexes, provide new opportunities for the physiological assessment of PCI results. Largely, the benefit of these tools is derived from longitudinal analysis of the treated vessel, which allows precise identification of the vessel segment accounting for a suboptimal functional result and enabling operators to perform accurate PCI optimization. In this document the authors review available evidence supporting why physiological assessment should be extended to immediate post-PCI with the aim of improving patient outcomes. A step-by-step guide on how available physiological tools can be used for such purpose is provided. (J Am Coll Cardiol Intv 2021;14:237–46) © 2021 by the American College of Cardiology Foundation.

The impact of coronary physiology on clinical decision making according to its timing of use and the rationale and methodology of microcirculatory assessment have been elegantly addressed in recent state-of-the-art reviews (1,2). In the present paper we dissect the clinical implications of functional post-percutaneous coronary intervention (PCI) assessment. The main aim is to provide deeper insight and a step-by-step guide to identify suboptimal results of PCI, consider additional corrective measures, and ultimately improve patient outcomes through the application of new intracoronary indexes and functional coronary imaging tools.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

FFR = fractional flow reserve

FFR_{angio} = angiographic fractional flow reserve

iFR = instantaneous wave-free ratio

PCI = percutaneous coronary intervention

Pd/Pa = ratio of resting distal to aortic coronary pressure

PPG = pull back pressure gradient

QFR = quantitative flow ratio

vFFR = vessel fractional flow reserve

WHY SHOULD OPERATORS APPLY PHYSIOLOGY AFTER STENT IMPLANTATION?

Although in routine clinical practice acute procedural success is most frequently gauged only by visual angiographic assessment, use of intracoronary imaging techniques has demonstrated inadequate stent expansion with residual in-stent stenoses in a significant percentage of patients with angiographically successful interventions (3). Apart from stent-related issues, residual ischemia causing target vessel failure may also be a consequence of overlooked focal stenoses or diffuse disease outside the target PCI segment, vulnerable plaques left untreated, atheromatous disease progression, microvascular disease, and epicardial or microvascular spasm (2). All these mechanisms contribute to the high percentage of patients with recurrent angina at 1 year after PCI (20% to 30%) (4).

In 2002, results of an international registry showed that the higher was the post-PCI fractional flow reserve (FFR) value, the lower the probability of an adverse event at follow-up (5). Consequently, several studies with more contemporary technologies have shown a relationship between post-PCI FFR and major adverse cardiac events, with various dichotomous predictive cutoff values (3). Recently, post-PCI physiology value was integrated in a risk prediction model along with clinical and angiographic data and was determined to be the most important predictor of long-term outcome (6). In addition, 2 elegant studies demonstrated how physiology guarantees a greater ability to predict outcome, compared with angiography alone (7,8). The analysis of 607 patients from the FAME 2 (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation 2) trial in whom revascularization was not performed demonstrated that the natural history of coronary stenoses is better predicted by physiology (FFR) compared with angiography (7). The same concept was demonstrated by the lack of predictive ability of the residual SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score after complete functional revascularization (8).

All this supports the suggestion that functional post-PCI assessment should be considered an important part of physiology-guided revascularization.

HIGHLIGHTS

- Physiology assessment post-PCI predicts outcome but is rarely used in clinical practice.
- Pullback can identify stent-related issues, overlooked lesions, and diffuse disease.
- Focal drops at pullback indicate the need of post-dilation or stent implantation.
- Diffuse disease demands aggressive medical therapy.
- Powered trials comparing physiology- and angio-guided PCI optimization are warranted.

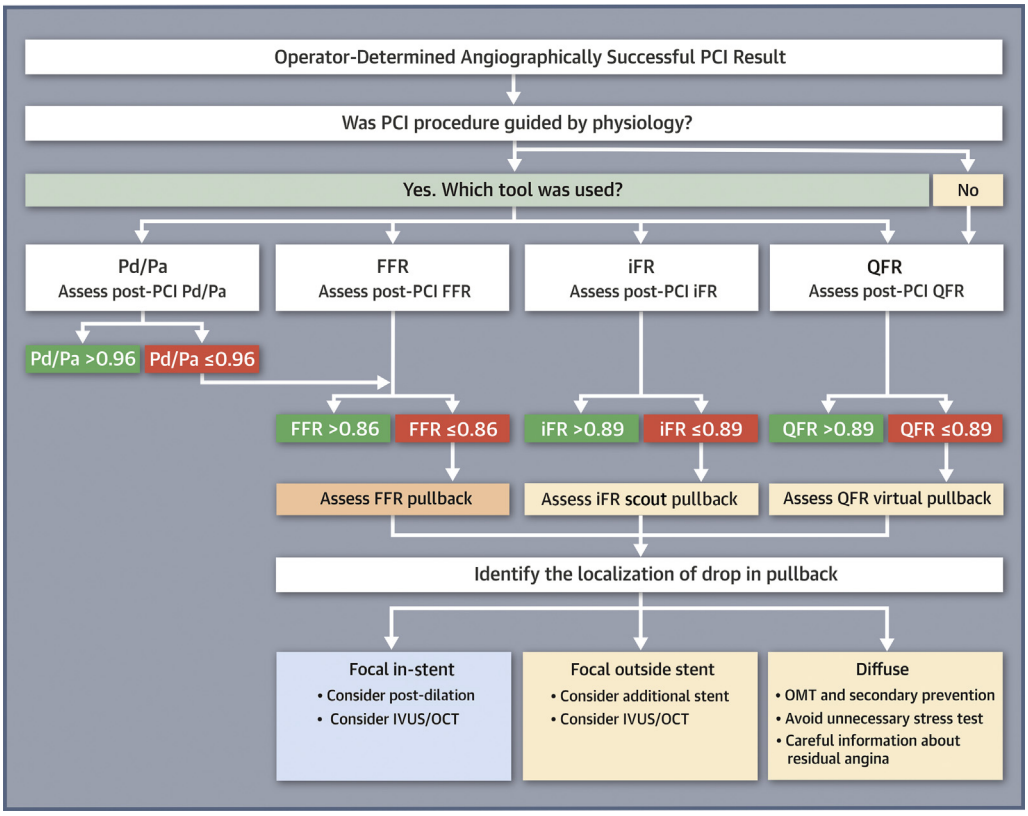
WHY DO OPERATORS RARELY APPLY PHYSIOLOGY AFTER STENT IMPLANTATION?

Although post-stent FFR has been shown to correlate with long-term outcome, its penetration in clinical practice is low. In the recent ERIS (Evolving Routine Standards of FFR Use) study, post-PCI FFR was used in <10% of lesions investigated with physiology pre-PCI (9). Most interestingly, even when the FFR result after PCI was suboptimal, in 79% of the cases, no further action was performed (9). Reasons for the low use of functional assessment post-PCI and for subsequent intervention are multiple. First, physiology is used after PCI mostly in cases in which it was used pre-PCI. Second, randomized clinical trials addressing the use of FFR to assess PCI results have not been performed, so clear instructions and cutoffs for its use are lacking. Third, the need to administer adenosine several times during the same procedure results in increased procedure time, cost, and adverse side effects. Fourth, in case of a post-PCI suboptimal functional result, it may be difficult to ascertain the underlying cause. Fifth, reproducibility of physiological measurements can be challenging in the post-PCI setting, and operator's experience significantly affects the reliability of the assessment.

HOW SHOULD OPERATORS APPLY PHYSIOLOGY AFTER STENT IMPLANTATION?

Although the post-PCI FFR value has been linked to long-term outcome, how to "react" to a suboptimal FFR value, after an angiographically "perfect" stenting result, has been contentious, largely because of

CENTRAL ILLUSTRATION **Flowchart for Guide Physiology-Guided Percutaneous Coronary Intervention Optimization Considering Current Methods**



Biscaglia, S. et al. J Am Coll Cardiol Intv. 2021;14(3):237–46.

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; OCT = optical coherence tomography; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; Pd/Pa = ratio of resting distal to aortic coronary pressure; QFR = quantitative flow ratio.

the lack of dedicated studies and the existence of multiple mechanisms influencing post-PCI values, each requiring different actions from the operator. Ongoing trials such as FFR-REACT (FFR-Guided PCI Optimization Directed by High-Definition IVUS Versus Standard of Care and TARGET-FFR (An Evaluation of a Physiology-Guided PCI Optimisation Strategy) may fill this gap (10,11). Understanding the mechanisms of abnormal physiological values is key in making the right choice on which actions should be performed to improve PCI outcomes.

There are at least 5 main causes of abnormal FFR values documented after PCI (1–3). First, stent-related issues, including stent underexpansion and stent edge dissection, may compromise intrastent or intraluminal dimensions and cause intrasegment pressure loss. Second, additional stenoses to the target PCI site may be present, whose hemodynamic significance had been overlooked or escaped identification by FFR. For example, the functional severity of stenoses located proximally to the target PCI site may be concealed by hemodynamic crosstalk during FFR interrogation (12). Third, the presence of diffuse vessel disease, which in many cases remains unnoticed from an angiographic standpoint, can produce a suboptimal functional result. Fourth, coronary spasm or simply increased vasomotor tone may be present, despite or in the absence of intracoronary nitrates. And fifth, pseudostenoses may develop, caused by straightening of vessel bends by the pressure guidewire, typically occurring in tortuous coronary arteries.

Untreated lesions and stent-related issues are likely treatable in most cases. With diffuse disease, however, it is unlikely that further stenting will significantly improve the outcome in view of the propensity for long stent lengths to increase risk for restenosis. In

TABLE 1 Recent Clinical Studies Evaluating the Role of Post-PCI Physiology

First Author, Year	N	Primary EP	Follow-Up (Months)	Threshold	Results	Note
Hakeem et al., 2019 (14)	574	MACE	30	Pd/Pa ≤0.96, FFR ≤0.86	Pd/Pa ≤0.96 and FFR ≤0.86 in 25% vs. Pd/Pa >0.96 and FFR >0.86 in 15%	In a fully adjusted Cox regression analysis, Pd/Pa was an independent predictor of MACE (HR: 2.07; 95% CI: 1.3–3.3; p = 0.002)
Jeremias et al., 2019 (16)	500	iFR <0.90	NA	iFR <0.90	iFR <0.90 in 24%	Causes of iFR <0.90 • Diffuse disease: 18.4% • In-stent drop: 31.3% • Untreated lesion: 50.3%
Biscaglia et al., 2019 (18)	602	VOCE	21	QFR <0.90	QFR <0.90 in 25% vs. QFR ≥0.90 in 3.5%	Causes of QFR<0.90 • Diffuse disease: 34% • In-stent drop: 13% • Untreated lesion: 32% • Combination: 21%
Kogame et al., 2019 (19)	393	VOCE	24	QFR <0.91	QFR <0.91 in 12% vs. QFR ≥0.91 in 3.7%	The impact of low post-PCI QFR on 2-yr VOCE was greater in vessels treated without IVUS guidance compared with vessels treated with IVUS guidance (p for interaction = 0.063)

CI = confidence interval; EP = endpoint; FFR = fractional flow reserve; HR = hazard ratio; iFR = instantaneous wave-free ratio; IVUS = intravascular ultrasonography; MACE = major adverse cardiac events; NA = not available; PCI = percutaneous coronary intervention; Pd/Pa = ratio of resting distal to aortic coronary pressure; QFR = quantitative flow ratio; VOCE = vessel-oriented composite endpoint.

conclusion, physiological indexes can be used to detect and discriminate among different underlying mechanisms of suboptimal PCI results associated with long-term adverse events (**Central Illustration**).

Pressure guidewires may theoretically obtain a longitudinal FFR map of the whole vessel. Pressure pull back is a key tool in understanding which coronary segment accounts for residual intracoronary pressure gradients. However, FFR pull back never became supported by prospective studies, and its adoption was hampered by the need to perform intravenous administration of adenosine. Yet some evidence was obtained on this topic. Agarwal et al. (13) showed that post-PCI FFR was in the ischemic range in 21% of lesions after angiographic successful PCI. The investigators performed an FFR pull back characterizing the underlying issue leading to subsequent intervention in 95.8% of lesions in the ischemic subgroup. Further intervention improved FFR from 0.78 ± 0.07 to 0.87 ± 0.05 ($p < 0.0001$). One of the main advantages of an FFR pull back is that hyperemia amplifies gradients and improves the signal-to-noise ratio. There are specific challenges in the interpretation of FFR pull back, such as the evaluation of serial lesions (3) and the need for at least 5 beats at each pull back position to ensure measurement reliability. These limitations are among the main causes of its underuse in clinical practice (9).

The strategy of "functional optimized coronary intervention," namely, defining procedural success using a physiological measure throughout the entire spectrum of coronary stenoses (50% to 99%), has been tested and was successfully performed in 92% of cases, thus demonstrating its feasibility (14).

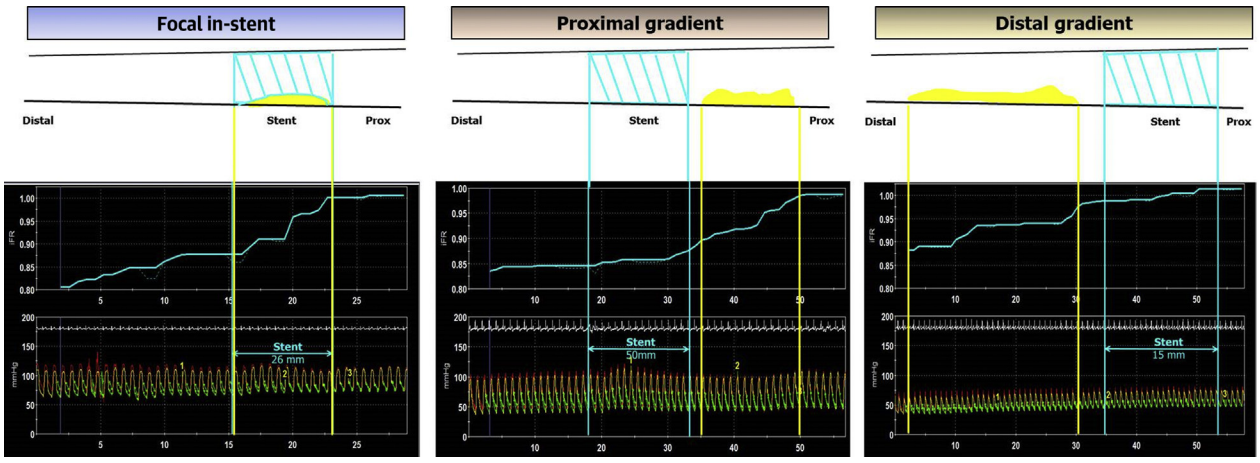
HOW MIGHT NEW TECHNOLOGIES HELP IN APPLYING POST-PCI PHYSIOLOGY?

New indexes and tools have been developed in an effort to overcome barriers to the widespread adoption of functional assessment. Nonhyperemic pressure indexes, including instantaneous wave-free ratio (iFR), ratio of resting distal to aortic coronary pressure (Pd/Pa), and other resting indexes, have enabled functional evaluation without pharmacological arteriolar vasodilation, while angiography-based functional assessment (quantitative flow ratio [QFR], angiographic FFR [FFR_{angio}], and vessel FFR [vFFR]) have eliminated the need for a dedicated pressure wire.

Importantly, these newer tools may allow operators to understand the mechanism underlying an abnormal physiologic value after angiographically successful intervention. In fact, the real novelty related to their development is the shift from a binary interpretation of physiology (positive or negative) to a quantitative, site-specific one. For these reasons, they are extremely appealing post-PCI, and several studies have been recently conducted to validate them in this setting (**Table 1**).

PD/PA. Pd/Pa (the baseline ratio of pressure distal to the lesion and aortic pressure) is a simple measure that may allow selection of those cases needing FFR. Hakeem et al. (15) investigated whether a combined strategy of Pd/Pa with or without FFR post-PCI could predict long-term clinical outcomes better than either marker alone in 664 lesions who had documented FFR and Pd/Pa pre- and post-PCI (**Table 1**). The analysis demonstrated the complementary role of Pd/Pa

FIGURE 1 Examples of Different Post-Percutaneous Coronary Intervention iFR Traces According to Underlying Coronary Artery Disease Mechanisms (In-Stent Drop, Proximal Gradient, Distal Gradient)

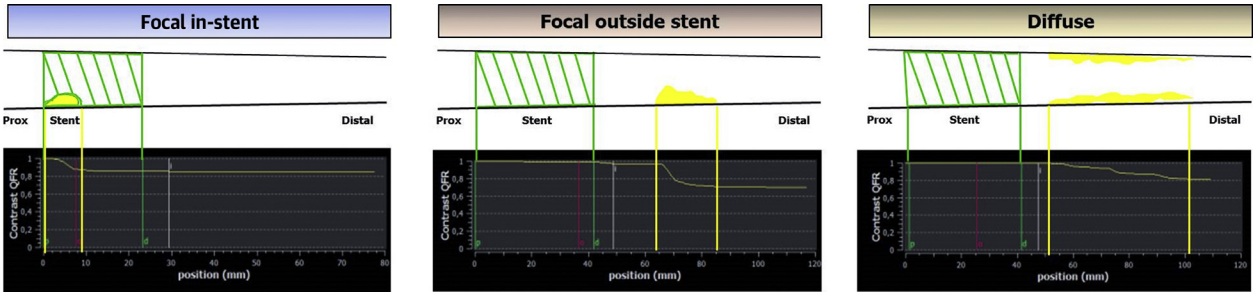


Blue lines delimit the proximal and distal ends of the stent. **Yellow lines** delimit the diseased portion of the vessel. iFR = instantaneous wave-free ratio; Prox = proximal.

to FFR post-PCI. The investigators suggested a post-PCI assessment with Pd/Pa; if >0.96, the procedure can be confidently concluded. Otherwise, FFR should be performed and if ≤0.86, pull back should be performed to elucidate the mechanism of the suboptimal result. The limit of Pd/Pa, however, is the inability to discriminate among different patterns of coronary artery disease (CAD) causing the suboptimal result, which is possible only through an FFR pull back.

iFR. iFR is a resting physiological index without need for drug-induced hyperemia. Beyond the avoidance of adenosine, iFR has distinct advantages in performing hemodynamic mapping of the entire vessel using pressure guidewire pull back (iFR Scout pull back system, Philips Medical Systems, Best, the Netherlands). Its main downside is the necessity for proprietary software from a single vendor. In contradistinction to FFR, iFR pull back curves are obtained on the basis of a beat-by-beat analysis and displayed by specific software that avoids fluctuations of the pull back curve associated with the Venturi effect. In theory, under resting conditions, flow is more constant, consistent, and predictable across in-series stenoses; as such, iFR pull back has a theoretical advantage and requires empirical testing (Figure 1). iFR pull back may identify lesions, estimate length, and integrate with coronary angiography (16). The same approach has been taken in the post-PCI

FIGURE 2 Examples of Different Post-Percutaneous Coronary Intervention QFR Traces According to Underlying Coronary Artery Disease Mechanisms (In-Stent Drop, Physiological Miss, Diffuse Disease)



Green lines delimit the proximal and distal ends of the stent. **Yellow lines** delimit the diseased portion of the vessel. Prox = proximal; QFR = quantitative flow ratio.

TABLE 2 How to Perform and Interpret Physiology Post-PCI

	FFR	iFR	QFR
How to perform post-PCI physiology			
Step 1	Angiographically satisfactory PCI		
Step 2	Inject nitroglycerin (100–200 μg) and flush with saline (in case of FFR, intravenous administration of adenosine is required)		
Step 3	Disengage catheter and perform manual or motorized pull back		Take 2 angiographic projections at least 25° apart avoiding foreshortening and overlap
Step 4	Check for drift		Perform post-PCI QFR analysis
Step 5	Assess the value and the presence of in-stent drop, physiological miss, and/or diffuse disease		
How to interpret post-PCI physiology			
Focal drop	Change in the angle of the FFR pull back curve between pull back sites	Abrupt drop-down in the iFR curve with ΔiFR ≥0.03 in <15 mm	Abrupt pressure drop-down with ΔQFR >0.05 in <10 mm
Diffuse disease	Progressive and constant FFR decrease without significant drop-down	Progressive and constant iFR decrease without significant drop-down	Progressive and constant QFR decrease without significant drop-down

Abbreviations as in Table 1.

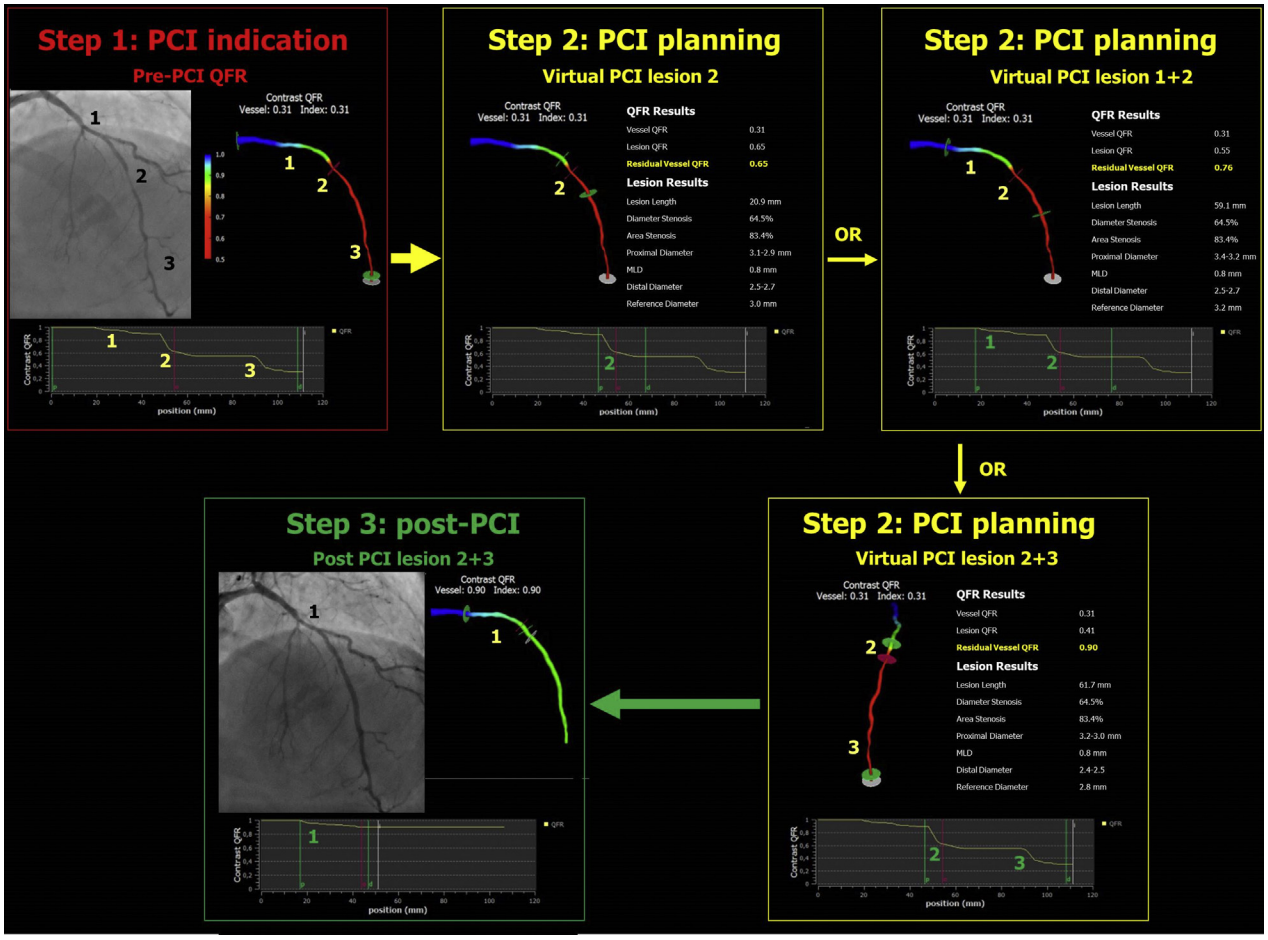
setting in the DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI) study, although the pull back was performed manually. A blinded iFR pull back was performed after angiographically successful PCI in 562 vessels in 500 patients in whom iFR had been used also pre-PCI to guide revascularization. Residual low iFR (expressed as an iFR value post-PCI <0.90) was present in 24% of patients. Among patients with ischemic post-PCI iFR, 81.6% had untreated focal stenoses that were angiographically inapparent, and 18.4% had diffuse disease. Among iFR detected focal lesions, 38.4% were located within the stented segment, while 61.6% were amenable to treatment with additional PCI (**Table 1, Figure 1**) (17). Limitations of the study included a large percentage of serial or tandem lesions that may have increased the proportion of abnormal iFR after PCI than previously reported. Importantly, the results of iFR were not shared with the operator at the time of the index procedure, so it is unclear what proportion of these persistently abnormal iFR values could have been "corrected" by undertaking further interventions during the index procedure.

QFR. QFR is an angiographically derived estimate of FFR developed as an alternative to wire-based intracoronary physiology. There are several third-generation quantitative coronary angiographic systems able to simulate FFR from conventional angiography (e.g., QFR, vFFR, FFR_{angio}). There appears to be no major differences in their diagnostic performance (18). One advantage of QFR is that, being an angiography-based reconstruction without the need for a wire, its application in the post-PCI setting is not related to its use before PCI. In addition, it allows generation of a pull back curve and discrimination of the physiological contribution of each single lesion as well as diagnosis of diffuse disease. The value of QFR to assess the functional results of PCI was tested in the prospective HAWKEYE (Angio-Based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation) study. Seven hundred fifty-one vessels in 602 patients undergoing angiographically satisfactory second-generation DES implantation were analyzed (19). At the end of the procedure, the operator acquired projections for QFR computation performed offline by an independent core laboratory. Receiver-operating characteristic curve analysis identified a post-PCI QFR best cutoff of ≤0.89 (area under the curve 0.77; 95% confidence interval: 0.74 to 0.80; $p < 0.001$). After correction for potential confounding factors, post-PCI QFR ≤0.89 was associated with a 3-fold increase in risk for the vessel-oriented composite endpoint at 2 years (hazard ratio: 2.91; 95% confidence interval 1.63 to 5.19; $p < 0.001$). In a retrospective evaluation of the SYNTAX II trial, the post-PCI QFR threshold for prediction of a vessel-oriented composite endpoint at 2 years was similar, at <0.91 even in patients with anatomic complexity such as 3-vessel disease (20).

Furthermore, a very important finding of the HAWKEYE study was the demonstration that QFR could discriminate among different CAD patterns. In vessels with suboptimal functional results, the site of the QFR drop was in-stent in 13% of the cases, while a focal drop outside the stent was identifiable in 32% of the cases. Thirty-four percent of vessels showed diffuse disease, while in 21% a combination of the aforementioned possibilities was present (**Table 1, Figure 2**).

Currently QFR requires off-line analysis. If it can be performed in real time, it may become an important

FIGURE 3 **Illustrative Case of Virtual PCI QFR**



Step 1: quantitative flow ratio (QFR) is used as a gatekeeper for percutaneous coronary intervention (PCI). The QFR analysis shows 3 pressure step-downs (see 1, 2, and 3 both in angiogram and in QFR trace). Step 2: once PCI is deemed indicated, it is possible to plan different treatment strategies ("virtual PCI") obtaining the "residual vessel QFR," which is the QFR value once the segment between p and d (in **green** in the QFR traces) is treated. P and d can be decided and moved by the operator to obtain different post-PCI scenarios (see examples in step 2). Step 3: the operator decided to treat lesions 2 and 3 according to pre-PCI QFR assessment and to perform post-PCI QFR that confirmed the previous estimation.

tool to optimize interventions. In addition, QFR analyzability depends on the quality of angiography, and it is feasible in about 80% of cases (19,20). Moreover, QFR is not applicable in specific lesion subsets, such as left main, bifurcation, and ostial lesions.

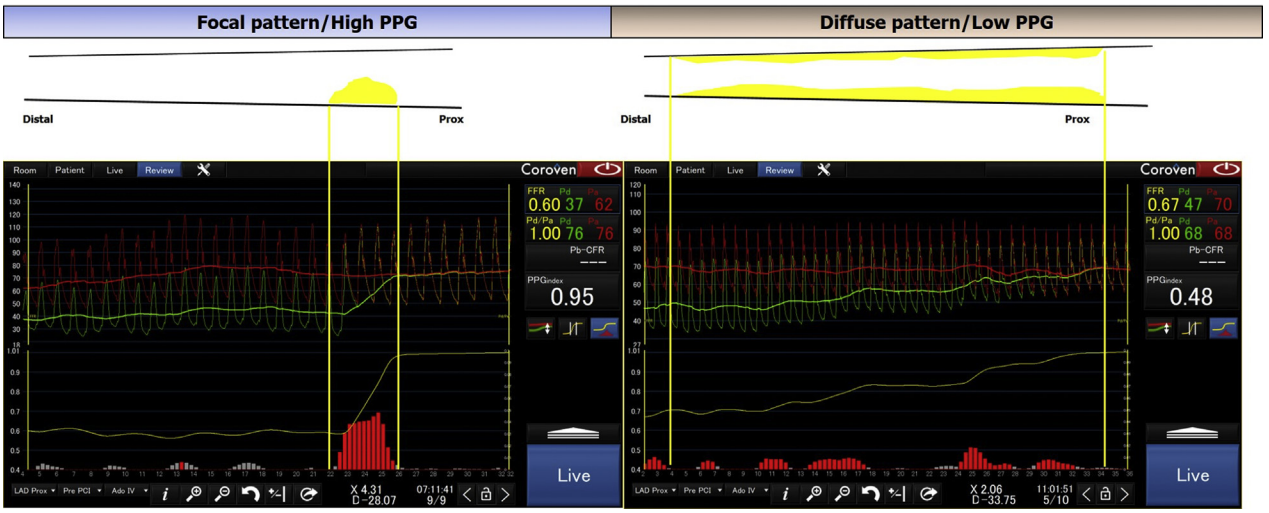
WHEN SHOULD OPERATORS APPLY PHYSIOLOGY AFTER STENT IMPLANTATION?

The development of multiple and complementary strategies enables operators to apply physiology-guided PCI in almost all cases. The only exception is the "culprit" lesion in ST-segment elevation myocardial infarction and possible high-risk "culprit" lesions in non-ST-segment elevation myocardial infarction, in which the microcirculation subtended by the infarct-related coronary artery might be impaired. **Table 2** summarizes how to perform and interpret post-PCI physiologic assessment. In the **Central Illustration** we provide a flowchart to optimize all PCIs combining the use of the different physiology tools, while in **Figures 1 to 3** we provide examples of the different mechanisms of CAD for each technology.

WHAT SHOULD OPERATORS EXPECT IN THE COMING YEARS? VIRTUAL PCI IS COMING

Angiography-guided PCI optimization is still the most used approach in clinical practice. For this reason, the next step in terms of physiology-guided PCI

FIGURE 4 Examples of Different Pre-Percutaneous Coronary Intervention FFR Traces With PPG Index According to Underlying Coronary Artery Disease Mechanisms (High PPG/Focal Disease, Low PPG/Diffuse Disease)



Yellow lines delimit the diseased portion of the vessel. PPG = pull back pressure gradient; Prox = proximal.

optimization should be conducting a randomized controlled trial comparing physiology-guided versus conventional angiography-guided PCI optimization, adequately powered for hard clinical endpoints.

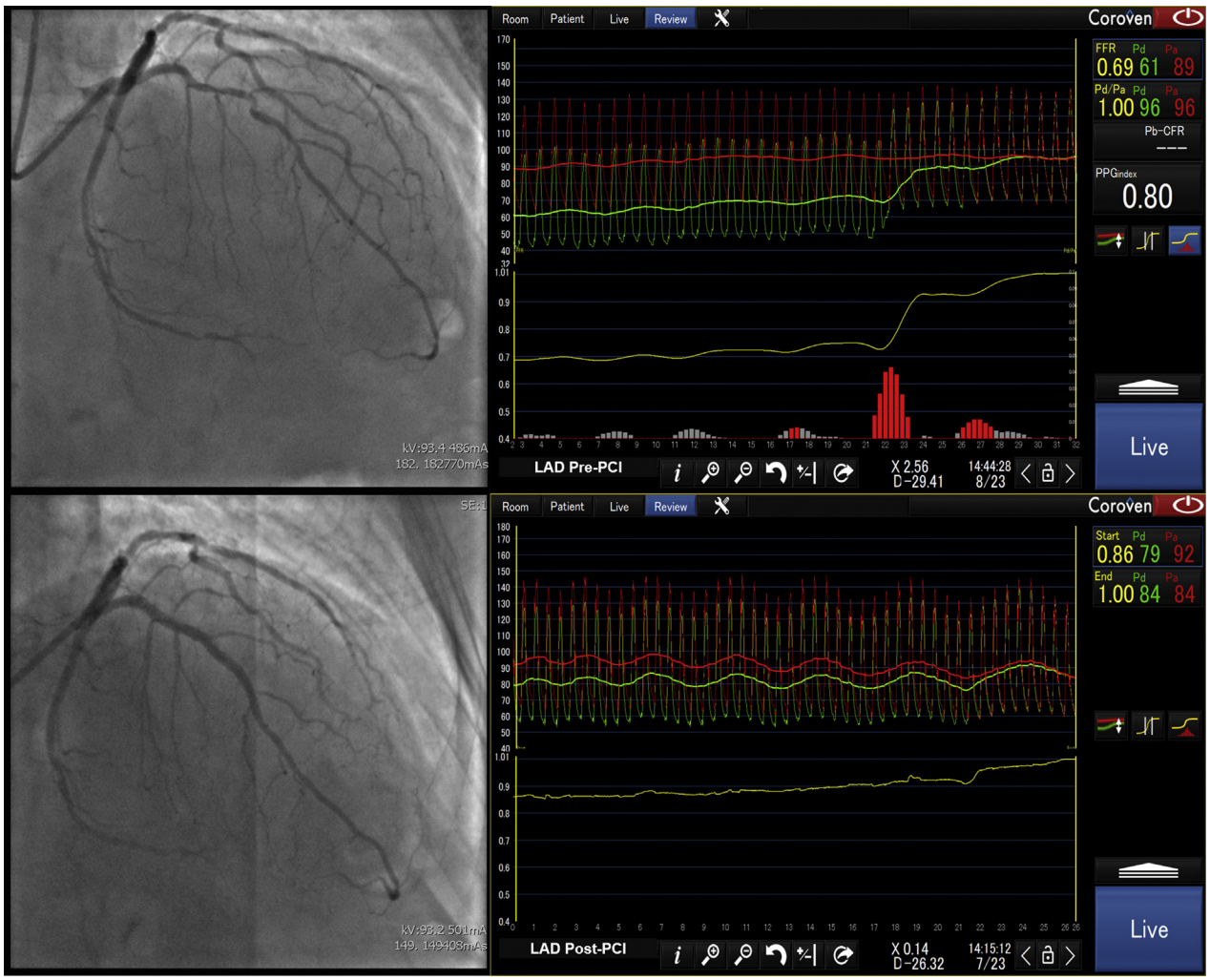
A full physiology-guided procedure is theoretically possible thanks to the virtual PCI tools that are already available for iFR, QFR, and computed tomographic FFR (**Figure 3**). Recently, the ability of FFR to discriminate pathophysiological patterns of CAD using coronary pressure pull back has been prospectively evaluated (21). The investigators proposed a quantitative assessment, namely, the pull back pressure gradient (PPG) index, to discriminate between focal and diffuse disease. The PPG index is a continuous metric with values close to 0 indicating diffuse disease, whereas those close to 1 suggest focal disease and are useful in the pre-PCI setting to predict post-PCI vFFR (**Figure 4**). However, a limitation of this technique is the necessity for a motorized system for FFR pull back and prolonged adenosine infusions (21). A new online automatic evaluation of the PPG index with manual pull back will be soon available to overcome this limitation.

These tools make it possible to obtain not only a single physiological value to determine the need for PCI but also a full physiological map of the vessel with point-by-point detailed information of the functional impact of a given stenosis. In addition, it is possible to simulate the treatment of 1 or more lesions (virtual PCI) to estimate the final functional value post-PCI (**Figure 5**). Functional assessment can be easily checked also after PCI and eventually guide further optimization. The final goal is to achieve optimal physiological results in all procedures. Seminal experiences of virtual PCI have been recently published (22). A validation of virtual intervention with pre-PCI iFR pull back was performed in serial lesions and diffuse CAD in 32 coronary arteries by Nijjer et al. (16). Obviously, the results of these proof-of-concept studies are only hypothesis generating, but they pave the way for future studies comparing physiology-guided virtual PCI with conventional angiography-guided PCI. To this end, coregistration of angiographic, imaging, and physiological information could have an additional value for PCI optimization (23). The DEFINE GPS (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting) trial will randomize more than 3,000 patients to evaluate patient outcomes of PCI guided by an integrated coregistration platform, which aggregates data from an instant iFR measurement and angiography compared against the current standard-of-care treatment guided by angiography alone (NCT04451044).

CONCLUSIONS

Current evidence supports the concept that angiography has major limitations in depicting the

FIGURE 5 **Illustrative Case of Virtual PCI With FFR and PPG Index**



The **top panel** shows a severe angiographic lesion in the mid segment of the left anterior descending coronary artery with an fractional flow reserve (FFR) value in the distal vessel of 0.69. In the **right top panel**, a manual FFR pull back tracing is shown (Coroventis Research, Uppsala, Sweden). The **red bars** depict pressure drops by millimeter. An important drop was identified in the mid segment of the vessel. The functional pattern of coronary artery disease (CAD) was quantified by the pull back pressure gradient (PPG) index of 0.80 (i.e., predominant focal functional CAD). In the **bottom panel**, the results after percutaneous coronary intervention (PCI) are shown. FFR post-PCI was 0.86, and the pull back identified a small pressure step up followed by diffuse pressure losses in the distal segment.

functional results of PCI and that the performance of physiological interrogation at the end of the procedure can identify suboptimal PCI results associated with poorer patient outcomes. Nonhyperemic pressure indexes (iFR, resting full-cycle ratio, diastolic pressure ratio, Pd/Pa) and angiography-based FFR (QFR, FFR_{angio}, and vFFR) provide additional opportunities to those offered by FFR for post-PCI functional assessment. Overall, these new technologies provide much more than binary information about the presence or absence of flow-limiting stenoses, allowing identification of the mechanism of suboptimal result and the exact location of the problem in the investigated vessel, both key aspects in choosing corrective interventional measures or, in specific patients, coadjuvant medical therapy as the best complementary treatment for PCI. The next evolution of physiology-guided PCI is to use the possibility of mapping physiologically the vessel before PCI and simulating the result of PCI in advance. Virtual PCI is

the natural step forward for physiology in the precision medicine era. Randomized studies are warranted to demonstrate the benefit of this approach on outcome.

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