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STATE-OF-THE-ART REVIEW

The Pullback Pressure Gradient

A Physiologic Index to Differentiate Focal From Diffuse Coronary Artery Disease

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ABSTRACT

Fractional flow reserve is the most widely used physiologic index to establish the functional significance of epicardial coronary artery disease (CAD). Fractional flow reserve guides clinical decisions toward or against coronary revascularization based on a single binary decision threshold indicative of myocardial ischemia. CAD pathophysiological patterns can be evaluated by assessing the distribution of pressure losses along the coronary vessel, often displayed as a "pullback curve." Until recently, the information provided by the pullback curves was visually and subjectively interpreted, which is associated with interobserver variability. The pullback pressure gradient is a novel index that addresses this gap by assessing the longitudinal distribution of the CAD, quantifying it on a scale from 0 to 1, with higher values indicative of predominantly focal CAD and lower values of predominantly diffuse CAD. This review provides a comprehensive analysis and critical appraisal of pullback pressure gradient and future directions. (JACC Adv. 2025;4:101679)

Fractional flow reserve (FFR)—an index that represents the relative coronary flow reduction compared with the same vessel hypothetically without coronary artery disease (CAD)—is the most extensively studied physiologic index to evaluate the functional significance of epicardial CAD. FFR is a flow index derived from pressure measurements obtained with a pressure wire during hyperemia.[1-4] More recently, other image-based modalities have been used to compute FFR.[5,6] The use of FFR is associated with improved clinical outcomes by guiding revascularization decisions and identifying patients who benefit from percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery. The presence or absence of functional significance is most commonly based on a threshold value of 0.80.[4,7-9] FFR informs on the epicardial resistance to hyperemic flow, and even though it is a result of cumulative pressure losses along the vessel, the CAD pattern—for example, focal or diffuse CAD—is not quantified by the metric.

FFR measures the total epicardial resistance along the coronary artery, correlates with myocardial ischemia, and informs about the potential for revascularization.[10] FFR-guided PCI is superior to angiographic-guided PCI in reducing major adverse cardiovascular events.[4,7-9] Distal FFR, however, does not assess the distribution of pressure losses along the vessel, and patients with similar distal FFR measurements can have different CAD phenotype

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

FFR = fractional flow reserve

FFR_{CT} = coronary computed tomography angiography-derived fractional flow reserve

iFR = instantaneous wave-free ratio

MSA = minimal stent area

PCI = percutaneous coronary intervention

PPG = pullback pressure gradient

QFR = quantitative flow ratio

TVR = target vessel revascularization

TVF = target vessel failure

distributions. As compared with patients with focal pressure loss, diffuse CAD is associated with lower effectiveness of PCI with low post-PCI FFR, higher residual angina, and higher incidence of clinical events.[11,12]

A pressure "pullback," which should be routinely performed to check for drift, also allows assessing the distribution of pressure losses along the coronary vessel. The inspection of the pullback curve allows the identification of focal pressure gradients that can be a target for PCI. The pullback maneuver, however, lacks standardization, and assessments are based on subjective interpretations leading to interoperator variability.[1,13,14]

The pullback pressure gradient (PPG) is a novel physiologic index that quantifies the pattern of CAD by analyzing the longitudinal distribution of epicardial resistance rather than the total pressure losses (**Central Illustration**).[15] PPG incorporates both the focality of coronary stenosis and the extent of the vessel affected by CAD. This review provides a comprehensive analysis and critical appraisal of PPG and future directions.

FFR PULLBACKS: STATE-OF-THE-ART AND UNMET NEEDS. Standardized methods to measure FFR have been described.[14] To acquire lesion-specific FFR, the pressure wire sensor should be positioned *at least* 20 to 30 mm distal to the most distal stenosis at a distance where poststenotic laminar flow is restored. To evaluate FFR, however, and establish whether a coronary artery is responsible for myocardial ischemia in the myocardial territory it supplies, the pressure sensor should be positioned in the distal part of the coronary artery where the vessel diameter is at least 2.0 mm by visual estimation.[14] Studies addressing PPG have positioned the pressure-wire sensor in the distal coronary segment and recorded the position by contrast angiography.[15,16] Hyperemia is subsequently induced using hyperemic agents such as adenosine or papaverine, and pressure tracings are recorded (**Figure 1**). To determine the FFR value, the nadir of the distal coronary pressure (Pd) is divided by the aortic pressure (Pa).[14]

To assess the distribution of epicardial resistance, a slow manual pullback of the pressure wire is performed over 20 to 30 seconds at a constant speed without stopping wire withdrawal during maneuver. The wire position and angiographic landmarks can serve as markers. Drops in FFR along the pressure tracing indicate changes in epicardial resistance.[14,17]

HIGHLIGHTS

- PPG provides insights into the epicardial distribution of the CAD and predicts post-PCI fractional flow reserve, the likelihood of symptom relief, and improvement in quality of life.
- Randomized studies comparing PPG-guided PCI are needed. The ideal treatment strategy for patients with diffuse CAD according to the PPG remains uncertain and requires further investigation.

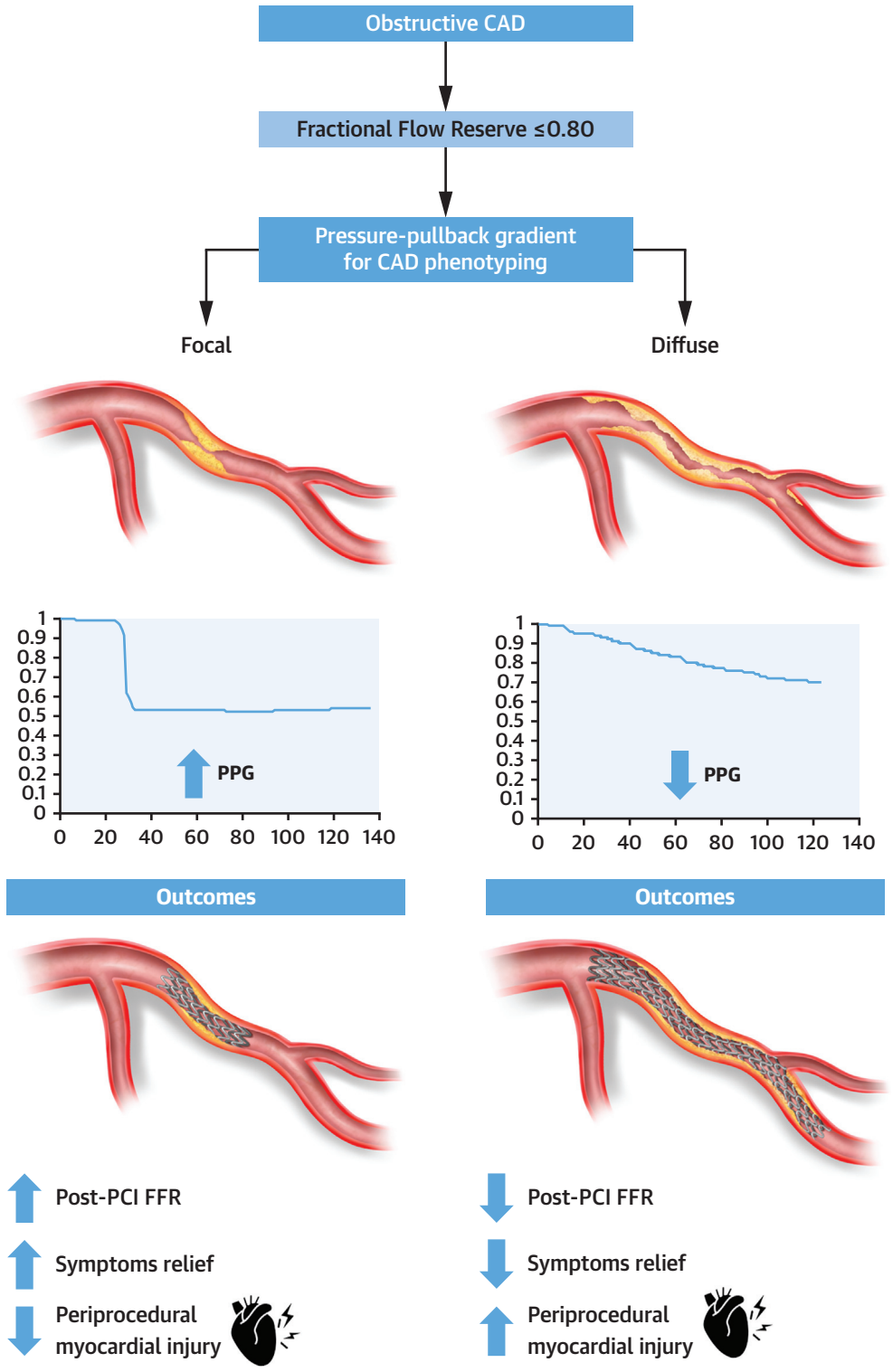
PRESSURE-WIRE BASED PPG: CONCEPT AND CALCULATION. The PPG standardizes FFR pullback analysis and allows the assessment of CAD patterns in a continuum from predominantly focal to predominantly diffuse CAD with an excellent inter- and intra-observer agreement. PPG is calculated from 2 components: 1) the largest FFR gradient measured in the pullback; and 2) the extent of functional disease in the vessel. Specifically, PPG considers the maximum FFR gradient over 20% of the pullback relative to the total delta FFR along the vessel. Extension of functional disease is measured by FFR deterioration across the vessel and is quantified as an FFR drop above a threshold per percent of the pullback. The final equation to calculate the PPG index has been defined as follows[15]:

PPG formula using motorized pullback.

$$\text{PPG index} = \left\{ \frac{\text{MaxPPG20mm}}{\Delta\text{FFRVessel}} + \left(1 - \frac{\textit{length of functional disease (mm)}}{\textit{Total vessel length (mm)}}\right)\right\} \div 2$$

PPG was initially validated using hyperemic pressure wire-based motorized pullbacks. The pressure wire (PressureWire X, Abbott Vascular) was positioned in the distal coronary segments with at least 2 mm diameter, estimated via angiographic visualization. Intracoronary nitrates were administered, followed by intravenous adenosine at 140 μg/kg/min through a peripheral or central vein to maintain a hyperemic state for at least 2 minutes. A device gripped the pressure wire tip, and a motorized pullback machine performed the maneuver at a speed of 1 mm/s.[15] Pressure gradients were recorded along the vessel, and PPG was calculated using code.

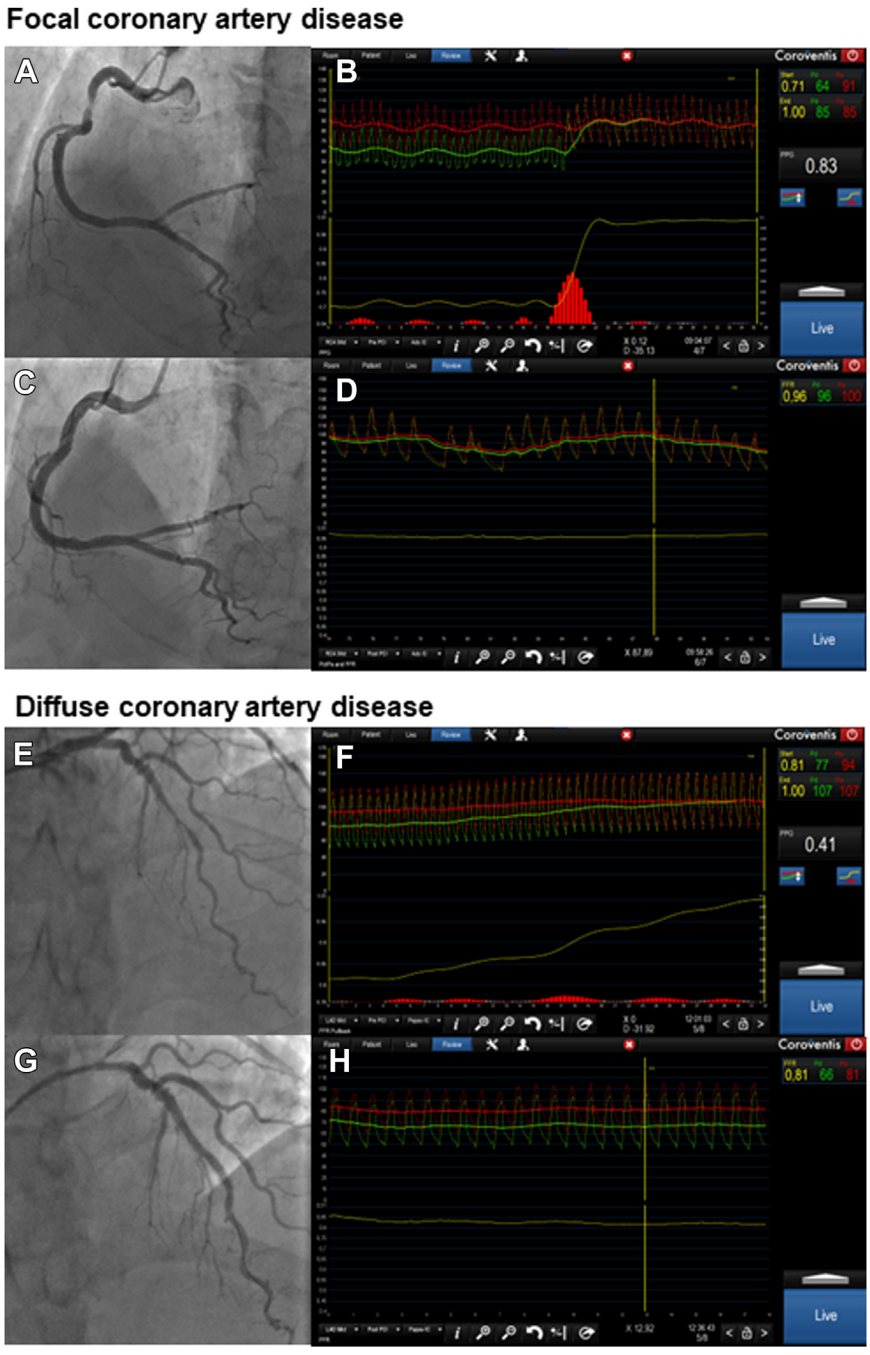
CENTRAL ILLUSTRATION **Pathophysiological Coronary Artery Disease Patterns and Pullback Curves**



Carvalho PEP, et al. JACC Adv. 2025;4(5):101679.

CAD = coronary artery disease; FFR = fractional flow reserve; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient.

FIGURE 1 Focal vs Diffuse Coronary Lesion Patterns



(A) Pre-PCI invasive angiography of the right coronary artery (RCA); (B) pre-PCI FFR pullback curve and PPG; (C) post-PCI invasive angiography of the RCA; (D) post-PCI pullback curve showing optimal post-PCI FFR; (E) pre-PCI invasive angiography of the left anterior descending artery (LAD); (B) pre-PCI FFR pullback curve and PPG; (C) post-PCI invasive angiography of the LAD; (D) post-PCI pullback curve showing suboptimal post-PCI FFR. FFR = fractional flow reserve; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient.

In the motorized pullback technique, $MaxPPG_{20mm}$ is defined as maximum FFR variation over 20 mm. ΔFFR_{vessel} is the pressure difference between the ostium and the distal vessel. The length with functional disease was defined as length with an FFR drop of at least 0.0015 per millimeter. Therefore, the PPG is a continuous index where values close to 1 represent focal CAD and values close to 0 indicate diffuse CAD.[15]

Although the original validation used a motorized device (Volcano R 100), this prolongs the procedure, and motorized pullback devices are cumbersome to use, not widely available, and may require longer intravenous adenosine infusions. Therefore, PPG was subsequently validated using manual pullbacks, which are more convenient for routine clinical practice as they only take an additional 20 to 30 seconds to perform with a constant and slow manual pullback of the pressure wire. These have been proven to correlate with procedural outcomes in the multicenter PPG global study, which included 993 patients across 23 centers worldwide.[16,18] The PPG formula has been simplified for manual pullbacks by adjusting the distance values in millimeters to relative pullback duration (seconds). In manual pullback formula, MaxPPG 20 mm is defined as the maximum FFR change in 20% of the pullback duration. FFRvessel is the pressure difference between the ostium and the distal vessel. The length with functional disease was defined as length with an FFR drop of at least 0.0015 per millimeter. This approach is reproducible and is not affected by the pullback duration.[19]

PPG formula using manual pullback.

$$\frac{\text{MaxPPG over 20\% of the duration}}{\Delta\text{FFRVessel}} + (1 - \textit{Proportion of pullback with FFR deterioration}) \div 2$$

ALTERNATIVES TO WIRE-BASED PPG. CCTA-based PPG. As shown in Table 1, PPG can be derived from any pressure pullback curve. Coronary computed tomography angiography (CCTA)-derived FFR (FFR_{CT}) uses computational fluid dynamics to mathematically model coronary flow and vessel resistance (Figure 2). Therefore, FFR_{CT} pullbacks can be used to calculate PPG. In a study by Dai et al,[5] FFR_{CT} was assessed using dedicated software (RuiXin-FFR, Raysight Medical). FFR_{CT} pullback curves were digitized from the FFR_{CT} system, and the PPG index was calculated as mentioned above.

Angiographic-based FFR PPG. Angiographic data can also be used to derive an angiographic FFR pullback across the vessel length, and hence PPG can also be estimated from angiographic-based FFR (Figure 2). This technique employs a computational model based on a 3-dimensional vessel reconstruction to determine FFR and build pullback curves.[6] Another option is using Murray law-based quantitative flow ratios (QFRs), which applies a computational method to a single angiographic view, considering side branch diameters and fractional flow division (Medis Medical Imaging System).[6,20-23]

In a pooled analysis of the P3 (Precise Percutaneous Coronary Intervention Plan; NCT03782688) study and the TARGET-FFR (Trial of Angiography vs Pressure-Ratio-Guided Enhancement Techniques—Fractional Flow Reserve; NCT03259815) randomized clinical trial, Seki et al[24] evaluated the accuracy of angiography-derived FFR (virtual FFR [vFFR], CAAS Workstation 8.5, Pie Medical Imaging) compared to wire-based FFR pullbacks. The analysis revealed moderate agreement between the 2 modalities, with 42.3% of vessels with diffuse disease and 26.4% of vessels with focal disease being misclassified by vFFR-based PPG. This could be explained by a limitation of coronary angiography in detecting diffuse disease, leading to an underestimation of pressure losses.[25] Nonetheless, patients with high PPG derived from vFFR curves reported less angina after PCI.[24]

MORPHOLOGICAL CORRELATES

PPG AND PLAQUE PHENOTYPE. PPG has been associated with lesion and plaque characteristics. In the P3 study, PPG was cross-matched with plaque morphology obtained through CCTA and optical coherence tomography. The higher the PPG (eg, the more focal the disease), the greater the plaque burden at the minimum luminal area region and the low-attenuation plaque burden. Lipid-rich plaques and thin-cap fibroatheromas were more common in focal than diffuse disease.[26] In patients with PPG >0.65 and FFR ≤0.70 the prevalence of vulnerable plaques was as high as 88.2%.[27] These plaque characteristics are associated with higher risk of future ischemic adverse events, and intervention may be beneficial.[28,29]

Similar results were observed in the Global PPG study (NCT04789317).[30] In a subgroup analysis of 261 patients (264 vessels) with pre-PCI FFR and intravascular ultrasound pullbacks, patients with focal disease (high PPG) had a higher prevalence of small minimum luminal area (<4 mm^2), lipid-rich plaque, and attenuated plaques compared with those with diffuse disease (high PPG). Conversely, patients with diffuse disease had a higher prevalence of calcified plaque (77.5% vs 59.5%; $P = 0.003$) and a higher, though not statistically significant, prevalence of calcified nodules (40.5% vs 32.0%; $P = 0.195$).[30] In a

TABLE 1 Comparison Between PPG Derived From Different Modalities

	Modalities		
	Pressure-Wire FFR	**Angiography-Derived FFR**	**FFR_{CT}**
Pros	Robust evidence Manual or motorized pullback with similar results	Wireless physiological assessment	Wireless physiological assessment Available before cardiac catheterization
Cons	Wire-based Hyperemia needed	Assessed in the catheterization laboratory Lacks validation	Highly dependent on image quality Lacks validation
Pressure-wire	✓	✗	✗
Hyperemia	+	✗	✗
FFR drop threshold to define the length of functional disease	0.0015/mm	0.0015/mm 0.0250/mm[a]	0.0015/mm
Technologies used in the published studies	PressureWire X (Abbott Vascular)	QFR (Medis Medical Imaging System) μQFR (version V2, Pulse Medical) vFFR (CAAS 8.5 Workstation, Pie Medical Imaging)	RuiXin-FFR (Raysight Medical)
Certainty of the evidence	+++	++	+
FDA-cleared	✓	✓	✓
Clinically available	✓	✓	✓

[a]1 study considered a major gradient when QFR drop was ≥0.025/mm; however, a 0.0015 threshold was used to calculate PPG.

FDA = Food and Drug Administration; FFR = fractional flow reserve; FFRCT = coronary computed tomography angiography-derived fractional flow reserve; QFR = quantitative flow ratio.

subanalysis of the P3 study by Sakai et al,[26] patients with diffuse CAD (low PPG) had higher calcium score, longer calcium length, and higher calcium burden. These plaque phenotyping findings suggest that patients with focal disease are at a greater risk of ischemic events and are more likely to benefit more from PCI, whereas patients with diffuse disease have higher calcium burden associated with stent underexpansion, stent malapposition, and stent delivery failure and lower post-PCI FFR.[31]

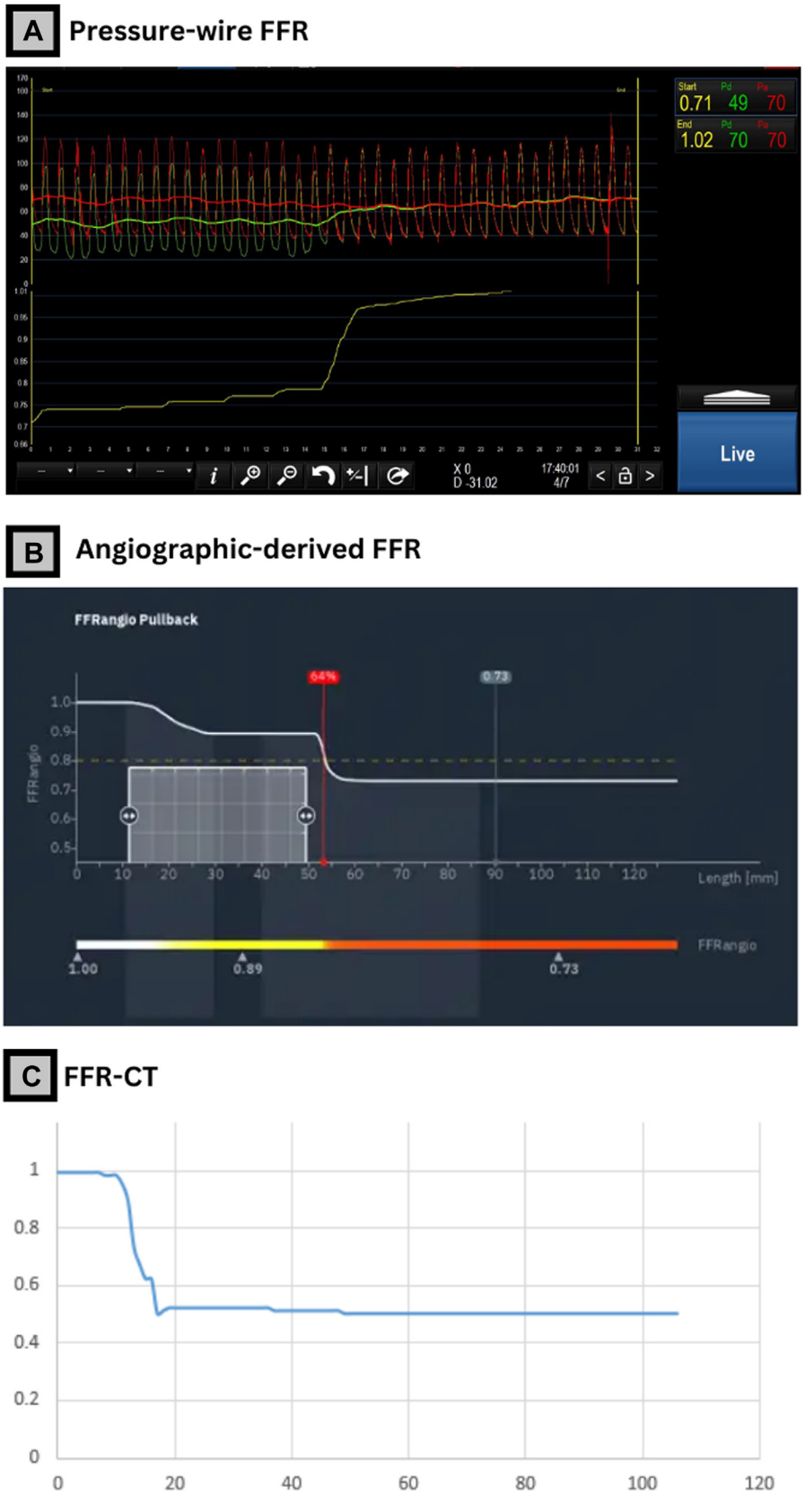
Using FFR_{CT} to calculate PPG in 359 patients pre-PCI, Dai et al[5] evaluated high-risk plaque characteristics according to CCTA and PPG to predict outcomes. In this study, high-risk plaque and low PPG were independently associated with periprocedural myocardial infarction and postprocedural myocardial injury. Patients with low PPG and more than 3 high-risk plaque characteristics had the highest risk of major adverse cardiac events.[5] The use of these parameters showed an incremental prognostic value as compared with the use of solely pre-PCI clinical data.

PPG AND INTRAVASCULAR IMAGING CORRELATION. PPG also correlates with intravascular imaging data after PCI. Patients with focal CAD are more likely to have larger minimal stent area (MSA) post-PCI, as well as larger proximal and distal reference areas, and require shorter stent length, as compared with those with diffuse CAD.[32] Kotuko et al measured PPG using μQFR from pre-PCI angiograms in 206 patients with chronic CAD: post-PCI MSA was larger in patients with focal CAD according to PPG dichotomization (mean difference: 1.09 mm^2; 95% CI: 0.44-1.77 mm^2). Proximal and distal reference luminal areas were also larger, and stent length was shorter in patients with focal CAD (mean difference: −3.765 mm; 95% CI: −6.289 to −1.255 mm).[32]

Similar findings were presented by Mizukami et al showing that MSA was larger in patients with focal disease (6.3 ± 2.3 mm^2 vs 5.3 ± 1.8 mm^2, $P = 0.015$) with significant correlation between MSA and PPG ($r = 0.25$; $P = 0.012$). Stent length was also longer in patients with diffuse disease (29.7 ± 13.2 mm for focal vs 37.2 ± 15.8 mm for diffuse disease, $P = 0.012$). Post-PCI, stent edge dissections were more frequent in the diffuse CAD group compared with the focal CAD group but did not reach statistical significance (5.4% focal and 15.4% diffuse; $P = 0.10$).[33]

In a subanalysis of the P3 study by Ohashi et al,[33] the post-PCI optical coherence tomography assessment identified higher rates of incomplete stent apposition in patients with diffuse CAD (11.3% in the focal subgroup vs 44.2% in the diffuse subgroup,

FIGURE 2 Fractional Flow Reserve Pullback Curves of Pressure Wire and Angiography-Derived Fractional Flow Reserve



Pullback pressure tracings using different modalities to assess the FFR including (A) pressure-wire FFR, (B) angiogram-derived FFR, and (C) FFRCT. FFR = fractional flow reserve; FFRCT = coronary computed tomography angiography-derived fractional flow reserve.

$P = 0.002$). In contrast, similar rates of stent edge dissection, stent underexpansion, and irregular tissue protrusion were found between groups.[29]

Overall, patients with focal disease achieved larger post-PCI MSA compared with those with diffuse CAD. Lower MSA is associated with a higher risk of stent thrombosis, in-stent restenosis, target vessel revascularization (TVR), and suboptimal post-PCI FFR.[34,35] Whether the PPG index should be used as a continuous or dichotomous binary decision threshold to predict post-PCI MSA requires additional study.[33]

CLINICAL OUTCOMES

PROCEDURAL OUTCOMES. PPG predicts post-PCI FFR, and greater improvements in post-PCI FFR have been associated with lower incidence of adverse event rates and greater angina relief.[36-38] However, even in patients with optimal stent expansion, post-PCI FFR may be suboptimal, especially in those with diffuse CAD.[39] Suboptimal FFR post-PCI is linked to higher rates of cardiac death, target vessel myocardial infarction, and TVR.[38,40]

In the study from Mizukami et al, post-PCI FFR was higher in focal CAD (0.91 ± 0.07 vs 0.86 ± 0.05, $P < 0.001$), and PPG accurately predicted post-PCI FFR (area under the curve [AUC]: 0.81; 95% CI: 0.73-0.88).[33] In a subanalysis of the TARGET-FFR, the proportion of patients achieving post-PCI FFR ≥0.90 was higher in patients with focal disease (52.6% vs 15.8%; $P < 0.001$) as compared with diffuse CAD. Multivariable analysis showed that PPG was independently associated with post-PCI FFR.[41]

Similar results were observed in PPG derived from angiography-derived FFR virtual pullback curves. In a study from Shin et al,[21] 234 patients with QFR pullback curves were analyzed. Patients with predominantly focal disease (QFR-PPG ≥0.78) had a higher mean post-PCI invasive hyperemic FFR as compared with predominantly diffuse disease (<0.78) (0.87 ± 0.06 vs 0.82 ± 0.06). Post-PCI analysis from the PANDA III study (Comparison of BuMAeG Based Biodegradable Polymer Stent With EXCEL Biodegradable Polymer Sirolimus-eluting Stent in "Real-World" Practice; NCT02017275), which included 1,335 patients and 1,607 target vessels, showed that patients with optimal post-PCI QFR (>0.91) predominantly present residual disease with high QFR-PPG (>0.78). In contrast, patients with suboptimal post-PCI QFR (<0.91) mostly presented with residual diffuse disease per QFR-PPG (≤0.78).[20]

The Global PPG study enrolled 1,004 (1,057 vessels) patients and analyzed periprocedural and in-hospital outcomes of patients with focal vs diffuse CAD according to the PPG index classification and showed that PPG can be used to predict periprocedural outcomes.[18] In this study, periprocedural myocardial infarction was higher in patients with diffuse CAD (5.9% vs 9.8%, $P = 0.04$) with a trend toward higher risk for in-hospital target vessel failure (TVF) (6.2% vs 9.8%, $P = 0.056$). PPG altered decision-making in 13.9% of the patients: of those, 36.2% were referred to surgical revascularization, and 63.8% to medical therapy. These changes occurred mainly in patients with diffuse CAD.

POSTPROCEDURAL OUTCOMES. The impact of PPG on long-term outcomes is yet to be explored. In the study from Ohashi et al, only 1 TVF event occurred in a patient with a focal disease group at 2 years of follow-up.[41] In the study from Mizukami et al, after 12 months of follow-up, TVR rates were similar between groups (OR: 0.85; 95% CI: 0.58-1.24).[33]

In a subanalysis of the TARGET-FFR trial, residual angina was present in 39.8% of patients overall, but more common in patients with diffuse CAD (51.9%) than in patients with focal CAD (27.5%) according to the PPG. PPG moderately predicted post-PCI angina-free status (AUC: 0.65; 95% CI: 0.52-0.78). In addition, patients with focal CAD had significantly higher scores on the Seattle Angina Questionnaire (SAQ) (mean difference: 11.5 points; 95% CI: 2.8-20.3; $P = 0.010$).[42]

After 12 months of follow-up, the PPG global study demonstrated that PPG was independently associated with angina relief and target-vessel failure. The angina frequency SAQ score was significantly higher in patients with focal disease compared to those with diffuse disease at 1 year post-PCI (95.3 ± 9.9 vs 92.5 ± 15.0; $P = 0.006$). Additionally, 77% of patients with focal CAD reported no angina at 1 year, compared to 70.9% of patients with diffuse CAD ($P = 0.0280$). Target-vessel failure was more prevalent in patients with diffuse CAD receiving PCI compared with those with focal disease. Among patients with diffuse disease identified by PPG, those treated with coronary artery bypass grafting or optimal medical therapy had lower rates of target-vessel failure compared to those receiving PCI.

Likewise, in the pooled analysis of the P3 study and the TARGET-FFR trial, angiography-derived FFR (vFFR) was used to calculate PPG. After 3 months of follow-up, patients with focal disease according to vFFR-based PPG had higher scores on the SAQ compared to those with diffuse disease. However, vFFR-based PPG demonstrated poor capacity to predict freedom from angina (AUC: 0.55; 95% CI: 0.46-0.64), with no significant differences in quality of life

post-PCI between focal and diffuse disease. These results highlight the need for further validation using noninvasive imaging and virtual-derived pullback curves.[25]

In a substudy of a population derived from the PANDA III study, PPG was calculated from QFR virtual pullback curves. Low pre-PCI QFR-PPG (≤0.78) was associated with a higher cumulative incidence of a composite outcome, including cardiac death, target-vessel-related myocardial infarction, and ischemia-driven target-vessel revascularization at a 2-year follow-up (HR: 1.93; 95% CI: 1.08-3.44). This association remained significant even after multivariate adjustment for potential confounding factors.[22]

While FFR cutoffs determine the need for revascularization, PPG provides insights into the epicardial distribution of the disease and forecasts PCI outcomes. PPG is also associated with periprocedural myocardial infarction with low PPG values (diffuse CAD) linked with higher periprocedural cardiac troponin concentrations. Postprocedure, it predicts post-PCI FFR, delta FFR, the likelihood of symptom relief, and improvements in quality of life.

COMPARISON WITH OTHER APPROACHES

PPG has been more widely calculated using pressure-wise (PressureWire X, Abbott Vascular)-based FFR.

In 2 large randomized controlled trials evaluating nonhyperemic pressure ratios, instantaneous wave-free ratio (iFR) (Philips) was noninferior to FFR to guide PCI, leading to its widespread adoption given its ease of use without the need for hyperemia.[43,44] In PPG Global, a subgroup of patients underwent resting and hyperemic pullback. PPG derived from resting conditions showed an excellent agreement with PPG derived from FFR.[45] These results suggest the PPG can be extracted from resting indexes with acceptable accuracy.

The iFR pullback approach using the SyncVision system (Philips) allows angiographic iFR coregistration. In addition, PCI planning can be achieved with angiographic iFR pullback coregistration that facilitates prediction of post-PCI iFR and may influence decision-making and guide revascularization.[46,47] The ongoing DEFINE GPS (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting; NCT04451044) randomized controlled trial is investigating the role of PCI guided by iFR coregistered with the angiogram vs angiographic guidance alone.[48] There may be opportunities for comparative studies evaluating contemporary pullback approaches including iFR with angiographic coregistration vs FFR with PPG pullbacks.

In studies utilizing pressure-wire FFR, PPG was calculated using the CoroFlow software (Coroventis Research AB). The derivation from other modalities, including angiography-derived and FFR_{CT}, could promote broader adoption of the PPG concept. Opportunities also exist to better define the length of functional disease as determined by an FFR drop of at least 0.0015 per millimeter, as only modalities that provide such granularity can accurately reproduce the PPG calculations as originally derived.

FUTURE DIRECTIONS

In patients classified with diffuse CAD according to PPG, the benefit of PCI remains uncertain. When PCI is pursued, diffuse CAD is associated with the use of more and longer stents, increasing the likelihood of side branch occlusion, stent-induced dissection, periprocedural myocardial infarction, and potentially TVF. Even with surgical revascularization, diffuse CAD is associated with higher rates of graft occlusion.[49,50] Therefore, PPG is an emerging index that may enhance decision-making based on the diffuseness of CAD (**Figure 2**).

PCI reduces epicardial coronary resistance, increases myocardial perfusion, and improves symptoms.[39] Post-PCI, however, residual angina is common and significantly impacts quality of life and predicts mortality.[51] Diffuse atherosclerosis is one of the key causes of residual angina.[39] In patients with stable CAD, large randomized controlled trials comparing an initial invasive strategy with PCI vs optimal medical therapy have not shown benefits of PCI. For these patients, assessing disease diffuseness using PPG is even more important, may complement decision-making, and help identify patients most likely to derive a benefit from PCIs.[52]

The main limitation of the evidence supporting PPG is the process of patient selection. In most studies, patients intended to be treated with PCI were included. Therefore, the applicability of PPG in more complex patients, for example, diffuse multivessel disease, requires further investigation. Prospective studies are limited by short follow-up periods and the lack of prespecified PPG cutoff for decision-making. To date, there is no randomized controlled trial analyzing the impact of PPG-guided revascularization. Despite that, studies have shown increased rates of procedural adverse events in patients with low PPG.[18,33] Given the potential of PPG to influence decisions in patients considered for PCI, this approach

TABLE 2 PPG Studies' Design and Main Findings

First Author, Year (Ref #)	Sample Size	Modality	Focal vs Diffuse Cutoffs	Clinical Value
Pressure-wire FFR				
Collet et al 2019 (P3 study)[15]	117 patients (158 vessels)	Invasive Hyperemic FFR with motorized pullback	Not specified a cutoff, but analyzed outcomes per tertiles	Validation of PPG as a tool to discriminate focal vs diffuse epicardial atherosclerosis
Sonck et al 2022 (single-center study)[19]	116 maneuvers (96 manual and 20 motorized)	Invasive Hyperemic FFR with motorized or manual pullback	Not applicable	Validation of manual pullback maneuvers to accurately allow PPG calculation
Candreva et al 2021 (P3 study)[57]	72 patients (85 vessels)	Invasive Hyperemic FFR with motorized pullback	Not applicable	PPG also accurately assesses serial lesions and may be used to inform revascularization decision-making.
Collet et al 2022 (TARGET FFR trial)[42]	103 patients	Invasive Hyperemic FFR with manual pullback	Median value—focal (≥0.66) and diffuse (<0.66)	Patients with high PPG (focal disease) reported greater angina relief and quality of life as compared with low PPG (diffuse disease)
Mizukami et al 2022 (P3 study)	113 patients (116 vessels)	Invasive Hyperemic FFR with motorized pullback	Highest tertiles (0.73)—focal (>0.73) and diffuse (≤0.73)	Study comparing motorized FFR and OCT pullbacks before and after PCI. Focal CAD (high PPG) was associated with higher post-PCI FFR and larger MSA
Ohashi et al 2023 (TARGET FFR trial)[41]	114 patients	Invasive Hyperemic FFR with motorized pullback	Highest tertiles (0.74)—focal (≥0.74) and diffuse (<0.74)	PPG correlated with post-PCI FFR and delta FFR, with higher values achieved in patients with focal disease (high PPG)
Sakai et al 2023 (P3 study)[26]	117 patients (120 vessels)	Invasive Hyperemic FFR with motorized pullback	Median value—focal (>0.66) and diffuse (≤0.66)	Focal CAD (high PPG) is associated with higher plaque burden and lipid-rich plaques. Patients with diffuse CAD (low PPG) had more calcified plaques.
Yang et al 2024 (P3 study)[27]	95 patients	Invasive Hyperemic FFR with motorized pullback	Mean value—focal (>0.65) and diffuse (≤0.65)	PPG correlation with CCTA and OCT plaque analysis. PPG is a predictor of vulnerable plaque, especially lesions with low FFR.
Ohashi et al 2024 (P3 study)[29]	102 patients (105 vessels)	Invasive Hyperemic FFR with motorized pullback	Median value—focal (≥0.69) and diffuse (<0.69)	Focal CAD (high PPG) is associated with larger MSA and a higher incidence of tissue protrusion. Stent malaposition is more frequent in diffuse CAD (low PPG).
Collet et al 2024 (PPG Global)[18]	1,004 patients (1,057 vessels)	Invasive Hyperemic FFR with manual pullback	Median value—focal (≥0.62) and diffuse (<0.62)	PPG correlated with post-PCI FFR and predicted optimal revascularization. PPG influenced treatment decision in 14% of the patients. Patients with low PPG (diffuse disease) had a higher incidence of periprocedural MI. At the 1-y follow-up, residual angina was more frequent in patients with diffuse disease, and TVF was more frequent among patients with diffuse disease undergoing PCI.
Angiographic-derived FFR				
Dai et al 2021 (single-center study)[6]	103 patients (143 vessels)	QFR virtual pullback	Median value—focal (≥0.74) and diffuse (<0.74)	Study shows feasibility of PPG index calculated from QFR virtual pullback curves. QFR demonstrated lower accuracy in diffuse disease (low PPG).
Biscaglia et al 2021 (HAWKEYE study)[58]	111 patients (120 vessels)	QFR virtual pullback	Focal (>0.71 [highest tertile]) and diffuse (≤0.54 [lowest tertile])	As observed in invasive hyperemic FFR, pre-PCI QFR pullback curve has a strong correlation with post-PCI QFR, with higher values observed in patients with focal disease.
Dai et al 2021 (PANDA III study)[23]	1,003 patients (1,044 vessels)	QFR virtual pullback	Median value—focal (>0.769) and diffuse (≤0.769)	Patients with low PPG had a higher incidence of 2-y vessel-oriented composite outcome. The incidence of VOCO was similar between patients with low PPG receiving PCI (8.4%) as compared with those treated conservatively (7.8%).

Continued on the next page

TABLE 2 Continued

First Author, Year (Ref #)	Sample Size	Modality	Focal vs Diffuse Cutoffs	Clinical Value
Shin et al 2021 (Combined 4 studies)[a,21]	341 patients	QFR virtual pullback	Median—focal (≥0.78) and diffuse (<0.78)	Incidence of TVF after PCI was higher in patients with predominantly diffuse disease.
Dai et al 2021 (PANDA III study)[22]	1,395 patients (1,685 vessels)	QFR virtual pullback	Used cutoff from Shin et al 2021 (0.78)	Prognostic value of pre-PCI QFR-PPG retained after PCI. Of note, even in patients with high post-PCI QFR, vessels with low pre-PCI QFR-PPG presented a higher risk of VOCO at 2 y.
Dai et al 2022 (PANDA III study)[20]	1,335 patients (1,607 vessels)	QFR virtual pullback	Used cutoff from Shin et al 2021 (0.78)	Residual disease post-PCI assessed using post-PCI QFR is independently associated with VOCO.
Dai et al 2023 (CZT-SPECT registry)[59]	28 patients (34 vessels)	QFR virtual pullback	Not applicable	PPG-QFR correlates with myocardial blood flow assessed by CZT-SPECT.
Kotuko et al 2023 (ASET-JAPAN study)[32]	206 patients (217 vessels)	μQFR virtual pullback	Used cutoff from Shin et al 2021 (0.78)	Pre-PCI μQFR-PPG is an independent predictor of post-PCI μQFR. Diffuse CAD was associated with smaller MSA and higher plaque burden in the stented segment.
Seki et al 2024 (P3 study and TARGET-FFR trial pooled analysis)[25]	298 patients (300 vessels)	vFFR pullbacks	Median value—focal (≥0.67) and diffuse (<0.67)	vFFR moderately agreed with wire-based FFR pullbacks. Nonetheless, patients with focal CAD (high vFFR-PPG) reported greater angina relief.
CCTA-derived FFR				
Dai et al 2023 (single-center study)[5]	359 patients	FFR_{CT} (RuiXin-FFR) virtual pullback	Lower tertile 0.61—focal (>0.61) and diffuse (≤0.61)	Low FFR_{CT} is an independent predictor of periprocedural MI, especially in patients with high-risk plaque characteristics.

[a]This study included data from the Samsung Medical Center Institutional Registry (Long-Term Outcomes and Prognostic Factors in Patient Undergoing CABG or PCI; NCT03870815), Heart Transplantation Cohort (Physiologic Assessment of Microvascular Function in Heart Transplant Patients; NCT02798731), Algorithm-PCI registry (Automated Algorithm Detecting Physiologic Major Stenosis and Its Relationship with Post-PCI Clinical Outcomes study; NCT04304677), and COE-PERSPECTIVE (Influence of FFR on the Clinical OutcomEs of PERcutaneouS Coronary Intervention; NCT01873560) studies.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; FFR = fractional flow reserve; FFRCT = coronary computed tomography angiography-derived fractional flow reserve; MSA = minimal stent area; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient; QFR = quantitative flow ratio; TVF = target vessel failure; VOCO = vessel-oriented composite outcomes.

may improve patient triage and enhance safety in PCI procedures by reducing PCI-related adverse events.[53]

It is important to interpret the PPG individually as a continuous variable rather than a dichotomous cutoff to differentiate between focal and diffuse CAD. The higher the PPG index, the more focal the disease, and the greater the likelihood that PCI will benefit the patient. Conversely, a lower PPG index indicates more diffuse disease, suggesting a lower benefit from PCI revascularization. The cutoffs to define focal and diffuse disease varied across studies and were based on the population analyzed rather than a fixed value. As shown in **Table 2**, the median value of the population's PPG was used to distinguish between focal and diffuse CAD in most studies. In the PPG global study, the largest prospective study using PPG to guide revascularization, a median-based cutoff of 0.62 was used to differentiate between focal CAD (PPG ≥0.62) and diffuse CAD (PPG <0.62). In studies with angiographic-derived FFR PPG, higher median values were found and used to dichotomize focal vs diffuse, with values ranging between 0.67 and 0.78.[21,23,25] Dai et al analyzing 1,444 vessels, defined 0.769 QFR-derived PPG as the best cutoff to predict vessel-oriented composite outcome at 2 years using AUC data. These findings suggest an overestimation of "focality" of angiographic-derived PPG.

The PPG represents a novel application of coronary physiology that allows for the diagnosis of the pattern and to predict the magnitude of flow improvement with PCI. Several angiographic, lesion, and plaque characteristics should be considered to determine revascularization suitability and type. Further randomized trials with long-term follow-up are warranted to explore the current findings of observational studies. The PPG Primetime trial will randomize patients to PPG-guided revascularization according to the PPG strategy vs standard of care. Further studies are warranted, particularly, PPG-guided PCI compared with FFR-guided PCI. Moreover, the best treatment for patients with diffuse disease, according to the PPG, requires further investigation. As most observational studies only included patients with physiologically significant

lesions (FFR ≤0.80), the role of PPG in guiding decisions in lesions with FFR >0.80 is unknown.

Theoretically, PPG can be derived from any pullback curve, including hyperemic and non-hyperemic pressure ratios, CCTA-derived FFR, angiographic-derived FFR, and even intravascular imaging-derived FFR. Currently, only Coroflow software (v3.7, Coroventis Research AB) has PPG integrated, with PPG derived from other modalities being mostly used for research purposes in a retrospective fashion. There are opportunities to integrate the PPG equation across different modalities, which could lead to broader adoption in real-world clinical practice.

While PPG data has mostly been validated using pressure wires in the cardiac catheterization laboratory, preprocedural PPG assessment using CCTA requires additional study as they may predict PCI outcomes by forecasting plaque morphology, post-PCI FFR, maintenance of angina, suboptimal stent placement, and increased rates of periprocedural outcomes.[18,26,29,33] PPG may complement FFR_{CT}-based virtual PCI planning and help inform preferred revascularization strategies based on predicted post-PCI FFR_{CT} and procedural risks.

Widespread adoption of preprocedural PPG enables a comprehensive physiologic characterization of CAD before patients are referred to the catheterization laboratory. This approach can aid in case triage, shared decision-making, and preprocedural PCI planning. Invasive PPG assessment is not expected to incur additional costs, as the same pressure wire used to assess distal physiology can also perform the pullback maneuver. Additionally, only an extra 20 to 30 seconds would be needed in cases requiring hyperemic pressure ratios.[19]

Cost-effectiveness analyses have shown that physiology-guided PCI resulted in a cost reduction in the long-term analysis as compared with angiography-guided PCI.[54-56] Similar or even better outcomes are anticipated with PPG-guided revascularization. While FFR assess the severity of the epicardial resistance, PPG evaluates the longitudinal epicardial distribution of pressure loses. In practice, PPG complements FFR assessment and may defer PCI in some patients with hemodynamically significant diffuse disease. As demonstrated in the PPG global study, 14% of the patients had their treatment modified after the PPG assessment, with most being deferred from PCI to receive alternative treatments.[18] Therefore, PPG not only predicts PCI outcomes but also tailors the procedure, leading to greater symptom relief, improved quality of life, higher post-PCI FFR, and potentially lower rates of TVF.

CONCLUSIONS

PPG is an emerging approach that provides a standardized and objective method to distinguish focal from diffuse CAD with predictive capability. It complements FFR, and its measurement provides insights about the underlying plaque morphology and informs procedural risk and decisions about therapeutic strategies. As compared to patients with low PPG indicative of diffuse CAD, those with high PPG have more focal CAD that, following PCI, are more likely to have favorable clinical outcomes and symptom relief and result in higher post-PCI FFR values. PPG represents a novel complementary approach to phenotype CAD and forecast outcomes that may optimize PCI results by improving patient selection.

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REFERENCES

1. Pijls NHJ, 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(26):1703-1708. https://doi.org/10.1056/NEJM199606273342604

2. De Bruyne B, Baudhuin T, Melin JA, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation*. 1994;89(3):1013-1022. https://doi.org/10.1161/01.CIR.89.3.1013

3. Pijls NHJ, Van Son JAM, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87(4):1354-1367. https://doi.org/10.1161/01.CIR.87.4.1354

4. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367(11):991-1001. https://doi.org/10.1056/NEJMOA1205361

5. Dai N, Chen Z, Zhou F, et al. Coronary CT angiography-derived plaque characteristics and physiologic patterns for peri-procedural myocardial infarction and subsequent events. *Eur Heart J Cardiovasc Imaging*. 2023;24(7):897-908. https://doi.org/10.1093/EHJCI/JEAD025

6. Dai N, Hwang D, Lee JM, et al. Feasibility of quantitative flow ratio-derived pullback pressure gradient index and its impact on diagnostic performance. *Cardiovasc Interventions*. 2021;14(3):353-355. https://doi.org/10.1016/J.JCIN.2020.10.036

7. Patricio L, Tonino PAL, De Bruyne B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *Rev Port Cardiol*. 2009;28(2):229-230. https://doi.org/10.1056/NEJMOA0807611

8. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med*. 2018;379(3):250-259. https://doi.org/10.1056/NEJMOA1803538

9. Pijls NHJ, 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(21):2105-2111. https://doi.org/10.1016/J.JACC.2007.01.087

10. Scarsini R, Fezzi S, Leone AM, et al. Functional patterns of coronary disease: diffuse, focal, and serial lesions. *JACC Cardiovasc Interv*. 2022;15(21):2174-2191. https://doi.org/10.1016/J.JCIN.2022.07.015

11. Baranauskas A, Peace A, Kibarskis A, et al. FFR result post PCI is suboptimal in long diffuse coronary artery disease. *EuroIntervention*. 2016;12(12):1473-1480. https://doi.org/10.4244/EIJ-D-15-00514

12. De Bruyne B, Hersbach F, Pijls NHJ, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. *Circulation*. 2001;104(20):2401-2406. https://doi.org/10.1161/HC4501.099316

13. Gosling RC, Morris PD, Lawford PV, Hose DR, Gunn JP. Personalised fractional flow reserve: a novel concept to optimise myocardial revascularisation. *EuroIntervention*. 2019;15(8):707-713. https://doi.org/10.4244/EIJ-D-18-00668

14. Toth GG, Johnson NP, Jeremias A, et al. Standardization of fractional flow reserve measurements. *J Am Coll Cardiol*. 2016;68(7):742-753. https://doi.org/10.1016/J.JACC.2016.05.067

15. Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol*. 2019;74(14):1772-1784. https://doi.org/10.1016/J.JACC.2019.07.072

16. Munhoz D, Collet C, Mizukami T, et al. Rationale and design of the pullback pressure gradient (PPG) global registry. *Am Heart J*. 2023;265:170-179. https://doi.org/10.1016/J.AHJ.2023.07.016

17. Nijjer SS. Using physiology pullback for percutaneous coronary intervention guidance: is this the future? *Interv Cardiol Clin*. 2023;12(1):41-53. https://doi.org/10.1016/J.ICCL.2022.09.005

18. Collet C, Munhoz D, Mizukami T, et al. Influence of pathophysiological patterns of coronary artery disease on immediate percutaneous coronary intervention outcomes. *Circulation*. 2024;150(8):586-597. https://doi.org/10.1161/CIRCULATIONAHA.124.069450

19. Sonck J, Mizukami T, Johnson NP, et al. Development, validation, and reproducibility of the pullback pressure gradient (PPG) derived from manual fractional flow reserve pullbacks. *Catheter Cardiovasc Interv*. 2022;99(5):1518-1525. https://doi.org/10.1002/CCD.30064

20. Dai N, Zhang R, Yuan S, et al. Prognostic implications of quantitative flow ratio-derived physiological 2-dimensional residual disease patterns after stenting. *JACC Cardiovasc Interv*. 2022;15(16):1624-1634. https://doi.org/10.1016/J.JCIN.2022.06.021

21. Shin D, Dai N, Lee SH, et al. Physiological distribution and local severity of coronary artery disease and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2021;14(16):1771-1785. https://doi.org/10.1016/J.JCIN.2021.06.013

22. Dai N, Yuan S, Dou K, et al. Prognostic implications of prestent pullback pressure gradient and poststent quantitative flow ratio in patients undergoing percutaneous coronary intervention. *J Am Heart Assoc*. 2022;11(11):24903. https://doi.org/10.1161/JAHA.121.024903

23. Dai N, Zhang R, Hu N, et al. Integrated coronary disease burden and patterns to discriminate vessels benefiting from percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2022;99(1):E12-E21. https://doi.org/10.1002/CCD.29983

24. Seki R, Collison D, Ikeda K, et al. Validation of virtual fractional flow reserve pullback curves. *Catheter Cardiovasc Interv*. 2024;104(6):1178-1188. https://doi.org/10.1002/CCD.31222

25. Strepkos D, Sara JDS, Carvalho PEP, et al. Angiography-derived fractional flow reserve: newer data and future directions. *Am J Cardiol*. 2025;238:1-8. https://doi.org/10.1016/J.AMJCARD.2024.11.021

26. Sakai K, Mizukami T, Leipsic J, et al. Coronary atherosclerosis phenotypes in focal and diffuse disease. *JACC Cardiovasc Imaging*. 2023;16(11):1452-1464. https://doi.org/10.1016/J.JCMG.2023.05.018

27. Yang S, Hwang D, Sakai K, et al. Predictors for vulnerable plaque in functionally significant lesions. *JACC Cardiovasc Imaging*. 2025;18(2):195-206. https://doi.org/10.1016/J.JCMG.2024.07.021

28. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J*. 2020;41(3):383-391. https://doi.org/10.1093/EURHEARTJ/EHZ520

29. Ohashi H, Mizukami T, Sonck J, et al. Intravascular imaging findings after PCI in patients with focal and diffuse coronary artery disease. *J Am Heart Assoc*. 2024;13(5):32605. https://doi.org/10.1161/JAHA.123.032605

30. Sakai K, Ali Z, Mizukami T, et al. TCT-722 coronary artery plaque distribution in functional focal and diffuse disease. *J Am Coll Cardiol*. 2024;84(18):B287. https://doi.org/10.1016/J.JACC.2024.09.867

31. Shah M, Najam O, Bhindi R, De Silva K. Calcium modification techniques in complex percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2021;14(5):e009870. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009870

32. Kotoku N, Ninomiya K, Masuda S, et al. Preprocedural physiological assessment of coronary disease patterns to predict haemodynamic outcomes post-PCI. *EuroIntervention*. 2023;19(11):E891-E902. https://doi.org/10.4244/EIJ-D-23-00516

33. Mizukami T, Sonck J, Sakai K, et al. Procedural outcomes after percutaneous coronary interventions in focal and diffuse coronary artery disease. *J Am Heart Assoc*. 2022;11(23):e026960. https://doi.org/10.1161/JAHA.122.026960

34. Song HG, Kang SJ, Ahn JM, et al. Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv*. 2014;83(6):873-878. https://doi.org/10.1002/CCD.24560

35. Piroth Z, Toth GG, Tonino PAL, et al. Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. *Circ Cardiovasc Interv*. 2017;10(8):e005233. https://doi.org/10.1161/CIRCINTERVENTIONS.116.005233

36. Neleman T, van Zandvoort LJC, Tovar Forero MN, et al. FFR-guided PCI optimization directed by high-definition IVUS versus standard of care: the FFR REACT trial. *JACC Cardiovasc Interv*. 2022;15(16):1595-1607. https://doi.org/10.1016/J.JCIN.2022.06.018

37. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. *JACC Cardiovasc Interv*. 2016;9(10):1022-1031. https://doi.org/10.1016/J.JCIN.2016.01.046

38. Hwang D, Koo BK, Zhang J, et al. Prognostic implications of fractional flow reserve after coronary stenting: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(9):e2232842. https://doi.org/10.1001/JAMANETWORKOPEN.2022.32842

39. Crea F, Bairey Merz CN, Beltrame JF, et al. Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. *Eur Heart J*. 2019;40(29):2455-2462. https://doi.org/10.1093/EURHEARTJ/EHY857

40. Fournier S, Ciccarelli G, Toth GG, et al. Association of improvement in fractional flow reserve with outcomes, including symptomatic relief, after percutaneous coronary intervention. *JAMA Cardiol*. 2019;4(4):370-374. https://doi.org/10.1001/JAMACARDIO.2019.0175

41. Ohashi H, Collison D, Mizukami T, et al. Fractional flow reserve-guided stent optimisation in focal and diffuse coronary artery disease. *Diagnostics (Basel)*. 2023;13(15):2612. https://doi.org/10.3390/DIAGNOSTICS13152612

42. Collet C, Collison D, Mizukami T, et al. Differential improvement in angina and health-related quality of life after PCI in focal and diffuse coronary artery disease. *JACC Cardiovasc Interv*. 2022;15(24):2506-2518. https://doi.org/10.1016/J.JCIN.2022.09.048

43. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376(19):1813-1823. https://doi.org/10.1056/NEJMOA1616540

44. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376(19):1824-1834. https://doi.org/10.1056/NEJMOA1700445

45. Storozhenko T, Collison D, Johnson N, et al. TCT-722 diagnostic performance of nonhyperemic pressure ratios versus fractional flow reserve stratified by coronary artery. *J Am Coll Cardiol*. 2023;82(17):B290-B291. https://doi.org/10.1016/J.JACC.2023.09.734

46. Nijjer SS, Sen S, Petraco R, et al. Pre-Angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. *JACC Cardiovasc Interv*. 2014;7(12):1386-1396. https://doi.org/10.1016/J.JCIN.2014.06.015

47. Kikuta Y, Cook CM, Sharp ASP, et al. Pre-Angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT registry. *JACC Cardiovasc Interv*. 2018;11(8):757-767. https://doi.org/10.1016/J.JCIN.2018.03.005

48. Study details | distal evaluation of functional performance with intravascular sensors to assess the narrowing Effect: guided physiologic stenting | ClinicalTrials.gov. Accessed July 22, 2024. https://clinicaltrials.gov/study/NCT04451044

49. Shiono Y, Kubo T, Honda K, et al. Impact of functional focal versus diffuse coronary artery disease on bypass graft patency. *Int J Cardiol*. 2016;222:16-21. https://doi.org/10.1016/J.IJCARD.2016.07.052

50. Dourado LOC, Bittencourt MS, Pereira AC, et al. Coronary artery bypass surgery in diffuse advanced coronary artery disease: 1-year clinical and angiographic results. *Thorac Cardiovasc Surg*. 2018;66(6):477-482. https://doi.org/10.1055/S-0037-1601306

51. Mozaffarian D, Bryson CL, Spertus JA, McDonell MB, Fihn SD. Anginal symptoms consistently predict total mortality among outpatients with coronary artery disease. *Am Heart J*. 2003;146(6):1015-1022. https://doi.org/10.1016/S0002-8703(03)00436-8

52. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31-40. https://doi.org/10.1016/S0140-6736(17)32714-9

53. Munhoz D, Mizukami T, Sonck J, et al. TCT-726 impact of the pull back pressure gradient (PPG) on PCI planning and decision-making. *J Am Coll Cardiol*. 2024;84(18):B289. https://doi.org/10.1016/J.JACC.2024.09.871

54. Fearon WF, Bornschein B, Tonino PAL, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation*. 2010;122(24):2545-2550. https://doi.org/10.1161/CIRCULATIONAHA.109.925396

55. Fearon WF, Nishi T, De Bruyne B, et al. Clinical outcomes and cost-effectiveness of fractional flow reserve-guided percutaneous coronary intervention in patients with stable coronary artery disease: three-year follow-up of the FAME 2 trial (fractional flow reserve versus angiography for multivessel evaluation). *Circulation*. 2018;137(5):480-487. https://doi.org/10.1161/CIRCULATIONAHA.117.031907

56. Hong D, Kim H, Lee H, et al. Long-term cost-effectiveness of fractional flow reserve-based percutaneous coronary intervention in stable and unstable angina. *JACC Adv*. 2022;1(5):100145. https://doi.org/10.1016/J.JACADV.2022.100145

57. Candreva A, Mizukami T, Sonck J, et al. Hyperemic hemodynamic characteristics of serial coronary lesions assessed by pullback pressure gradients. *Catheter Cardiovasc Interv*. 2021;98(5):E647-E654. https://doi.org/10.1002/CCD.29868

58. Biscaglia S, Uretsky BF, Tebaldi M, et al. Angio-based fractional flow reserve, functional pattern of coronary artery disease, and prediction of percutaneous coronary intervention result: a proof-of-concept study. *Cardiovasc Drugs Ther*. 2022;36(4):645-653. https://doi.org/10.1007/S10557-021-07162-6

59. Dai N, Zhang B, Gong Z, et al. Quantitative flow ratio derived pullback pressure gradient and CZT-SPECT measured longitudinal flow gradient for hemodynamically significant coronary artery disease. *J Nucl Cardiol*. 2023;30(5):1992-2002. https://doi.org/10.1007/S12350-023-03245-Z

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