An Update on Coronary Physiology

Pressure wire–based assessment of epicardial stenosis and the integration of multimodal assessment to assess the prognostic implications of epicardial coronary plaque.

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The coronary circulation is an intricate and dynamic network composed of the large epicardial vessels and the microvasculature, controlled by multiple physiologic mechanisms that maintain adequate myocardial perfusion despite ever-changing hemodynamic conditions.[1-3] Any or all of these components can be compromised by various mechanisms, causing cardiac dysfunction or ischemia. Epicardial stenoses can be visualized using one of the most fundamental tools of interventional cardiology, the coronary angiogram. However, comprehensive assessment of the functional significance of these epicardial stenoses requires more sophisticated techniques.

INVASIVE ASSESSMENT OF MYOCARDIAL ISCHEMIA

Pioneering work from Gould et al identified disturbed coronary flow in the presence of epicardial stenosis > 85% and > 50% at rest and during hyperemia, respectively. This facilitated the interpretation of the coronary angiogram and strengthened the initial belief that there was a cause-and-effect relationship between coronary stenosis and myocardial ischemia.[4] Significant progress has ensued in the intervening years, and we now appreciate that myocardial ischemia is not a single entity but a disease spectrum that may be due to focal epicardial stenosis, diffuse coronary artery disease (DCAD), microvascular dysfunction (MCD), or a combination of these components. Therefore, to comprehensively assess ischemia and target treatment in individuals, a thorough understanding of the underlying etiology of myocardial ischemia is required.

Initial invasive assessment of the ischemic potential of epicardial stenoses used coronary flow reserve (CFR) with fractional flow reserve (FFR) predominately after the pivotal DEFER,[5] FAME,[6] and FAME II[7] trials. Over the intervening decades, a number of alternatives to FFR have emerged to determine the ischemic potential of coronary lesions, including nonhyperemic pressure wire assessment, angiographic-based computational fluid dynamics, and intravascular imaging–derived assessment. This article focuses on pressure wire–based assessment of epicardial stenosis and the integration of multimodal assessment to assess the prognostic implications of epicardial coronary plaque. Invasive assessment of ischemia with nonobstructive coronary arteries is a large topic outside the scope of this article.

PRESSURE WIRE–BASED TECHNIQUES TO ASSESS THE ISCHEMIC POTENTIAL OF EPICARDIAL STENOSIS

Fractional Flow Reserve

Much of the available data on the invasive assessment of myocardial ischemia comes from the use of FFR. First proposed by Pijls et al,[8,9] FFR is calculated as the ratio of invasively measured coronary pressures, distal (Pd) and proximal (Pa) to an epicardial stenosis, under hyperemic conditions. Usually obtained with adenosine, it is assumed that the Pd/Pa ratio acts as a surrogate for the fractional peak flow across the lesion given that hyperemia induces minimal and constant myocardial resistance.[10] Several large clinical trials (most notably, DEFER,[5] FAME,[6] and FAME II[7]) have shown FFR to be both safe and efficacious in predicting the functional significance of a coronary stenosis, with a cutoff value of 0.75 used in DEFER and 0.80 used in the FAME trials. The relative ease and simplicity with which FFR can be obtained during daily clinical practice and its inclusion in the current guidelines[11,12] mean it is commonly used to investigate the physiologic significance of a coronary stenosis. Despite the evidence supporting FFR, it has a number of limitations, including that it does not provide insights into the status of nonobstructive coronary artery disease (CAD) or other key con-

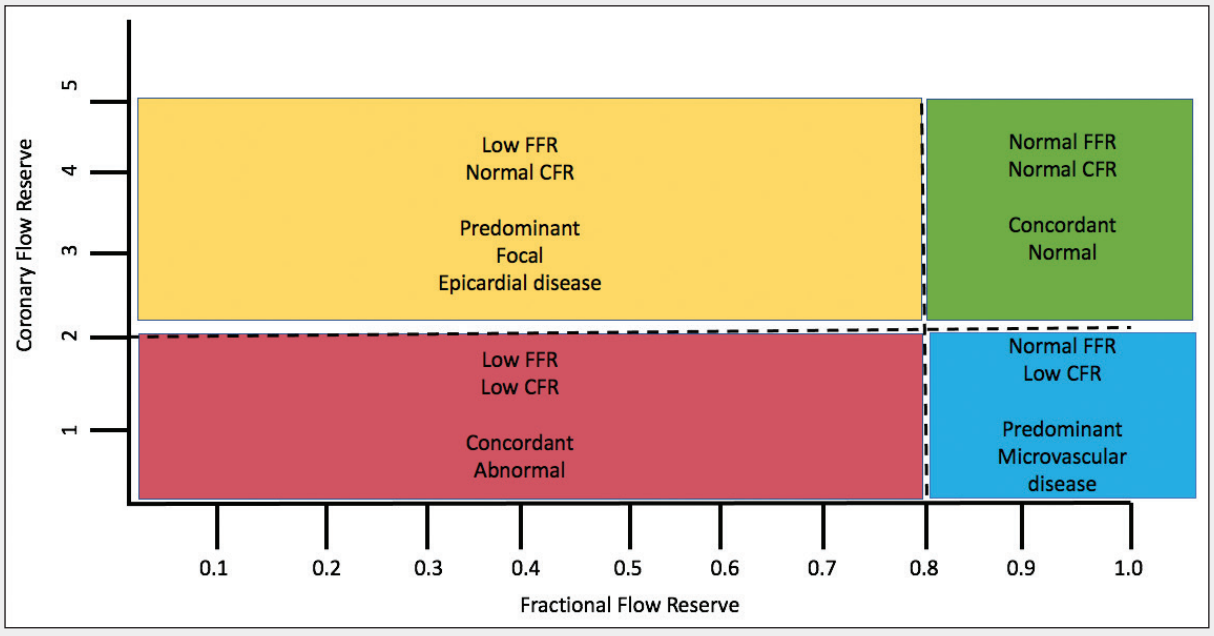

Figure 1. Interpretation of integrated FFR and CFR.

tributors to total myocardial flow, such as collaterals or microcirculation.

FFR is often thought of as the gold standard in the invasive evaluation of ischemia; however, FFR itself was validated against a number of noninvasive tools, each with varying sensitivity and specificity.[13] Although this might be considered a weakness of the validation mechanisms underpinning FFR, importantly, patients had to have a subsequent negative ischemia test (ie, demonstrate that the ischemia was clearly linked to the interrogated stenosis and that the ischemia test normalized after revascularization). The cutoff point of 0.80 is now widely accepted when deciding to treat or defer an epicardial stenosis. Although 0.80 was chosen for its sensitivity and specificity in predicting the safety of deferring stenting, the further away from the 0.75 to 0.80 value a measurement is, the more likely it is to reproducibly classify a stenosis.[14] Similarly, while a cut-off value of 0.80 predicts the likelihood of major adverse cardiac events (MACE), the majority of these events are driven by revascularization for angina, and it is not until values approach 0.67 that the hard endpoints of death and myocardial infarction begin to emerge.[15,16]

Recent work using hyperemic pullback pressure gradients has attempted to better classify patterns of CAD using invasive physiology.[17] By quantifying the distribution of epicardial resistance during an FFR pullback, CAD can be classified as focal, diffuse, or both. This may potentially influence revascularization decision-making, but clinical trials to determine its place in clinical decision-making and clinical outcomes are required.

Nonhyperemic Pressure Ratios

A number of nonhyperemic wire-based indices have been developed to assess the functional significance of epicardial stenoses. These assess either specific phases of (iFR: instantaneous wave-free ratio, dPR: diastolic pressure ratio, and DFR: diastolic hyperemia-free ratio) or the whole cardiac cycle (cFFR: contrast FFR, rest Pd/Pa, and RFR: resting full-cycle ratio).

iFR is the only alternative to FFR that has been evaluated in randomized controlled trials (DEFINE-FLAIR[18] and iFR-SWEDEHEART[19]). The trials showed that at 1 year, iFR was noninferior to FFR, with a primary endpoint of death, myocardial infarction, or unplanned revascularization. Although iFR is known to have a close pressure relationship to FFR, it is relatively insensitive to nonflow-limiting coronary stenosis. This can be explained by the fact that iFR is calculated during basal conditions and therefore the large pressure gradient that occurs during hyperemia due to a large increase in coronary flow is not observed with iFR. Approximately 20% of lesions will have discordant iFR and FFR values, but it is not clear whether the clinical outcomes differ based on physiology-guided treatment decisions using

TABLE 1. USE OF MULTIMODAL PHYSIOLOGY IN THE ASSI

Author	Year	Design	Study Outline	Clinical Setting	N, Lesions Total	N, Patients Total	Indices Used
Meuwissen et al[31]	2001	Cohort	To compare the outcomes of CFR and FFR in a cohort of patients with stable CAD	Stable patients	150	126	CFR, FFR, minimum microvascular resistance
Meuwissen et al[27]	2008	Cohort	To evaluate deferral of PCI in intermediate lesions using FFR, CFR, and HSR in patients with negative or nondiagnostic/ non-invasive stress tests	Stable patients	186	170	CFR, FFR, HSR
Echavarría-Pinto et al[34]	2013	Cohort	To investigate the prevalence of focal stenosis, diffuse athero-sclerosis, and MCD at different levels of FFR	Stable patients	91	78	CFR, FFR, IMR
van de Hoef et al[25]	2014	Cohort	To evaluate the physiologic basis and clinical outcomes associated with FFR and CFVR discordance in deferred stenting	Stable patients	157	157	CFVR, FFR
Lee et al[24]	2016	Cohort	To investigate the implications of CFR and IMR in patients with normal FFR	Stable patients	663	313	CFR, FFR, IMR
Johnson et al[45]	2021	Cohort	To assess clinical outcomes of combined pressure and flow assessment of coronary lesions	Stable Patients	668	455	CFR, FFR

Abbreviations: CAD, coronary artery disease; CFR, coronary flow reserve; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; HSR, hyperemic stenosis resistance
nary intervention; POCO, patient-oriented composite outcomes.

ESSMENT OF ANGIOGRAPHICALLY INTERMEDIATE LESION				
	Main Findings	**Clinical Outcome Measure**	**Other Outcome Measure**	**Results**
	Discordance between CFR and FFR was seen in 41 lesions. Maximum microvascular resistance showed a large variability and was significantly higher in the group with abnormal CFR and normal FFR (2.42 ± 0.77 mm Hg) compared to the group with normal FFR and abnormal CFR (1.91 ± 0.7 mm Hg), *P* = .034.	None	Correlation between CFR and FFR	–
	MACE incidence increased significantly with decreasing FFR and CFR and increasing HSR. A significantly higher MACE rate was observed when results were concordant abnormal or discordant between FFR and CFR compared to concordant normal values.	MACE	–	MACE ▪ Concordently normal CFR and FFR: 5.4% ▪ Discordent CFR and FFR: 19.7% ▪ Concordently abnormal CFR and FFR: 33.3% ▪ *P* = .008
	A substantial number of lesions with FFR > 0.8 had disturbed hemodynamics. Integrating FFR, CFR, and IMR allowed differentiation of patterns of IHD.	None	Coronary hemodynamic patterns as demonstrated with multimodal physiology	–
	Discordance between CFVR with FFR was characterized by magnitude of coronary microvascular resistance during basal and hyperemic conditions, implicating a pivotal role of the coronary microvasculature in the physiologically guided identification of CAD severity. Discordance between FFR and CFVR was associated with adverse outcome compared to cases where FFR and CFVR were concordantly normal. The adverse outcome of discordance between FFR and CFVR compared with cases in which FFR and CFVR were normal was attributable to cases where FFR is normal but CFVR abnormal, whereas discordance with abnormal FFR and normal CFVR was predominantly associated with equivalent clinical outcome compared with concordantly normal FFR and CFVR.	MACE	–	MACE at 1, 3, 5, and 10 y ▪ FFR ≥ 0.75 and CFVR ≥ 2: 2%, 4%, 10%, 28% ▪ FFR ≥ 0.75 and CFVR < 2: 36%, 46%, 50%, 59% ▪ FFR < 0.75 and CFVR ≥ 2: 8%, 8%, 31%, 51%
	CFR and IMR improved the risk stratification of patients with normal FFR. Low CFR and high IMR was associated with worse prognosis.	POCO	–	POCO ▪ CFR > 2, IMR < 23 U: 9.5% ▪ CFR > 2, IMR ≥ 23 U: 0% ▪ CFR ≤ 2, IMR < 23 U: 7% ▪ CFR ≤ 2, IMR ≥ 23 U: 27.9% ▪ *P* = .002
	All-cause death, myocardial infarction, and revascularization after 2 years was NOT noninferior between lesions with FFR ≤ 0.8 but CFR ≥ 2 and lesions with FFR > 0.8 and CFR ≥ 2	MACE	–	MACE ▪ Concordently normal CFR and FFR: 6.2% event rate ▪ Discordent CFR and FFR: 10.8% event rate ▪ *P* = .090

index; IHD, ischemic heart disease; IMR, index of microcirculatory resistance; MACE, major adverse cardiac events; MCD, microcirculatory dysfunction; PCI, percutaneous coro-

each modality. Vendor-specific software allows overlay of the iFR pullback curve onto the angiogram, thus allowing operators target lesions to achieve physiologically optimal PCI.[20] Compared to post-PCI iFR ≤ 0.95, achieving a post-PCI iFR ≥ 0.95 has been associated with improved event-free survival at 1 year, as well as a greater reduction in anginal symptoms.[21]

Coronary Flow Reserve

CFR is used both invasively and noninvasively to provide a global assessment of the coronary circulation, evaluating the ability of the coronary vasculature to increase its flow in response to increasing myocardial oxygen demand.[4,9,22] In the absence of obstructive epicardial coronary artery stenosis, the coronary vasculature can increase its flow up to four times above baseline with an intact autoregulatory system.[23] Therefore, failure of the coronary vasculature to increase its flow in the absence of a focal coronary stenosis implies the presence of either diffuse CAD or MCD. Despite being the initial tool in the invasive assessment of ischemia, the use of CFR to assess stenosis severity has been superseded by FFR. The use of CFR to assess the microcirculation continues, using either wire-based Doppler or thermodilution measurements.

Studies comparing FFR and CFR in the evaluation of the functional significance of epicardial stenoses frequently report discordance between modalities in up to 30% to 60% of lesions.[24-27] Integrating both positron emission tomography (PET) and invasive physiology, Johnson et al proposed classifying coronary vessels into four quadrants based on the cutoff values of CFR (> 2) and FFR (< 0.8) (Figure 1).[28] Concordance between CFR and FFR can be relatively easily interpreted. If both are normal (CFR > 2, FFR > 0.8), it can be assumed that myocardial ischemia is unlikely as there is no significant limitation to flow through the epicardial artery or impediment to the microvasculature in appropriately increasing flow. When both CFR and FFR are abnormal, myocardial ischemia occurs due to an inability of the autoregulatory mechanisms of the microvasculature to augment flow in response to increased resistance caused by the epicardial stenosis. In this case, revascularization of the coronary stenosis should restore flow through the coronary artery. If there is coexisting MCD, revascularization will not restore the autoregulatory mechanisms. Discordance between CFR and FFR leads clinicians to question which result is providing the correct answer; however, one should view them as complementary physiologic indices[29] and incorporate information from both techniques to provide the best possible treatment.

NORMAL FFR WITH ABNORMAL CFR

This pattern can perhaps be most easily explained by the presence of MCD causing a decreased CFR with normal or nonobstructive epicardial vessels reflecting the normal FFR values. Structural microcirculatory remodeling or microcirculatory plugging may exist, therefore limiting the maximal myocardial flow due to increased resistance in the arterioles and capillaries. This leads to a reduced distal pressure drop and a higher FFR than would be obtained in the absence of MCD.[30] This is supported by the work of Meuwissen et al who assessed CFR, FFR, and minimal microvascular resistance (a velocity-based index of microvascular resistance) during maximal hyperemia in 150 intermediate coronary lesions.[31] When the CFR-FFR discordant subjects were analyzed, there were no significant differences in the clinical or angiographic characteristics. In the group with a normal FFR but abnormal CFR, there was a significantly higher minimal microvascular resistance compared to the group with an abnormal FFR and normal CFR (2.42 ± 0.77 mm Hg vs 1.91 ± 0.7 mm Hg; $P < .05$), thus implying the presence of MCD in the group with normal FFR and abnormal CFR.

An alternative cause for this scenario is DCAD, which limits hyperemic flow to the point that the pressure gradient across the stenosis is low or nonexistent. In the presence of DCAD, there is a lack of convective accelerative flow and flow separation loss, leading to minimal pressure drop (normal FFR). However, within the diseased segment, there is a drop off in coronary flow, identified by the low CFR. Gould et al described the hemodynamic effects of DCAD on coronary flow in patients with angiographically mild CAD without myocardial perfusion defects using dipyridamole PET.[32] Despite demonstrating no segmental myocardial perfusion defects, which can be interpreted as a surrogate of normal FFR in this instance, investigators found a graded, longitudinal, base-to-apex myocardial perfusion gradient that was significantly different to that observed in healthy patients. This work was further supported by De Bruyne et al, who measured FFR in patients with nonstenotic CAD and controls without atherosclerosis. In coronary arteries with DCAD and no focal stenosis, a pressure gradient occurred along the length of the artery—a phenomenon not seen in normal coronary arteries.[33] These findings demonstrate that DCAD caused increased flow resistance and therefore promoted myocardial ischemia.

Echavarría-Pinto et al integrated microcirculatory resistance, using index of microcirculatory resistance (IMR), along with FFR and CFR into the investigation of intermediate coronary artery stenosis to further

elicit this discordance.[34] They found a high frequency of abnormal CFR and/or IMR in arteries with normal FFR (63% of cases), with IMR widely dispersed in vessels with FFR > 0.8 and CFR < 2 (n = 28; 39%). Given that high IMR reflects increased microvascular resistance and thus is a marker of MCD, this can differentiate ischemia predominantly due to MCD (normal FFR, low CFR, high IMR) from ischemia predominantly due to DCAD (normal FFR, low CFR, low IMR).

ABNORMAL FFR WITH NORMAL CFR

FFR assumes that the Pd/Pa ratio acts as a surrogate for the fractional peak flow across the lesion, given that hyperemia induces minimal and constant myocardial resistance. However, myocardial function depends on coronary blood flow and not coronary perfusion pressure alone.[35] The simplest explanation for abnormal FFR with normal CFR is that even a mild stenosis can generate a significant translesional pressure gradient if coronary flow increases sufficiently. This occurs most commonly in proximal stenoses or those with a large subtended myocardial mass. The presence of virtually no pressure gradient at rest but a significant gradient during hyperemia should alert one to the possibility of this phenomenon.[36] Incorporating IMR[34] once again provides us with an understanding: the lowest IMR values were found in this group, supporting the presence of a functional microcirculation. In this case, the epicardial lesion limits the conduction of blood through the vessel (FFR ≤ 0.80), although the overall myocardial blood supply in the territory is not significantly impaired (normal CFR).

PROGNOSTIC VALUE OF CFR, FFR, AND RESISTANCE

CFR was first used to assess epicardial stenosis severity,[4] but its utility in globally assessing the coronary circulation and stratifying cardiovascular risk has been extensively investigated both invasively and noninvasively.[25,34,37,38] Table 1 provides a summary of the key clinical trials assessing CFR and FFR use in combination.[24,25,27,31,34,45] Using PET studies, Murthy et al[38] evaluated myocardial perfusion and CFR in patients with and without CAD. They found that impaired CFR was associated with an adjusted 3.2- and 4.9-fold increase in the rate of cardiac death in patients with diabetes and patients without diabetes, respectively (P = .0004). Interestingly, diabetes has always been considered a cardiovascular risk factor; however, patients with diabetes with an impaired CFR without CAD experienced a similar rate of cardiac death to patients without diabetes with CAD (2.8% vs 2% per year; P = .33). In contrast, patients with diabetes without CAD with a preserved CFR had a very low rate of cardiac mortality, similar to patients without diabetes or CAD and a preserved CFR (0.3% vs 0.5% per year; P = .65), implying that CFR rather than diabetes itself is an important prognostic factor. Although FFR is now widely used in clinical practice to risk-stratify patients, deferred patients in both DEFER[39] and FAME[7] had a MACE rate of approximately 20% at long-term follow-up. These, along with other studies,[31,40-42] highlight the importance of looking beyond epicardial stenosis when attempting to risk stratify patients.

The combined prognostic value of CFR, FFR, and resistance was evaluated in 2008 by Meuwissen et al,[27] who investigated deferral of PCI in 186 intermediate stenoses interrogated with FFR, CFR, and hyperemic microvascular resistance. The authors found a significantly higher MACE rate in the group with concordantly abnormal CFR and FFR compared to the discordant and concordantly normal group (33.3% vs 19.7% vs 5.4%, respectively; P = .008). This initial work showing the additional prognostic benefit of adding CFR to FFR regenerated interest in the complementary information these measures can provide. More recent work from van de Hoef et al provides long-term follow-up (mean, 11.7 years) of 157 patients with intermediate stenosis investigated with FFR and coronary flow velocity reserve (CFVR).[25] Discordance was associated with an overall higher MACE rate than in the group with normal FFR and CFVR. The combination of a normal FFR and abnormal CFVR led to significantly more MACE early in the study, and this increased MACE rate remained significant throughout follow-up. In contrast, when a normal CFVR was associated with abnormal FFR, the MACE rate was equivalent to that in patients with normal FFR and CFVR up to 3 and 10 years, with cutoff points of 0.75 and 0.8, respectively. The increased MACE rate with an FFR cutoff value of 0.75 is in keeping with previous studies, supporting the concept that FFR values are a spectrum, with an increased event rate the further below the cutoff point of the stenosis is.[7,14,43,44]

Lee et al aimed to investigate the prognostic implications of CFR and IMR in patients evaluated with FFR.[24] In total, 663 vessels in 313 patients undergoing clinically indicated coronary angiography were assessed. Two-hundred thirty patients (516 vessels) with a normal FFR were divided into groups based on low and high CFR and then into four groups: (1) high CFR with a low IMR, (2) high CFR with a high IMR, (3) low CFR with a low IMR, and (4) low CFR with a high IMR. The primary outcome was patient-oriented composite outcome (POCO), a combination of all-

cause mortality, any myocardial infarction, and any revascularization. Patients were followed for a median of 658 days (IQR, 503.8-1139.3 days). The study showed that patients with a normal FFR and a low CFR had a higher incidence of POCO (hazard ratio, 4.189; 95% CI, 1.117-15.715; $P = .034$). The cumulative incidences of POCO were 9.5%, 0%, 7%, and 27.9% for groups 1, 2, 3, and 4, respectively ($P = .002$), and thus, patients with impaired flow due to MCD (low CFR, high IMR) had the worst outcomes. Because all patients had similar clinical and angiographic characteristics, the measurement of flow and resistance provided additional prognostic information in this group that, by FFR alone, would have been characterized as not having functionally significant disease.

These studies led to the prospective evaluation of revascularization deferral in arteries with an abnormal FFR (< 0.8) but normal CFR (> 2) in the multicenter DEFINE-FLOW trial.[45] Overall, 668 lesions in 455 individuals were evaluated, and only those with FFR < 0.8 and CFR < 0.2 were revascularized; all others were treated with optimal medical therapy. At 2-year follow-up, all-cause death, myocardial infarction, and revascularization rates were not noninferior in patients with an FFR ≤ 0.8 and a CFR ≥ 2 (10.8%) compared to an FFR > 0.8 and a CRF ≥ 2 (5.3%). In this study, the majority of MACE was driven by target vessel revascularization in all groups, with a lower target vessel failure predicted by a higher FFR (hazard ratio, 0.69 for a + 0.05 change in FFR; 95% CI, 0.53-0.90; Cox $P = .007$). Interestingly, the numerical event rates did not vary between those with an FFR > 0.80/CFR < 2 (13%), an FFR ≤ 0.80/CFR ≥ 2 (10.8%), and an FFR ≤ 0.80/CFR < 2 (12.8%). Some of these findings may be explained by increased shear stress causing a decrease in pressure (< FFR) in nonflow-limiting lesions (normal CFR) and leading to vulnerable plaques.[46]

FUTURE PERSPECTIVES

A number of additional indices, not widespread in clinical practice, may help further define ischemia and provide prognostic information. These include coronary flow capacity (CFC), which interprets CFR in relation to maximal flow (hyperemic average peak flow velocity).[42] CFC is potentially a useful addition to multimodal physiology as it integrates CFR and maximal hyperemic flow to investigate myocardial blood flow impairment due to a combination of obstructive CAD, diffuse CAD, and MCD. Ultimately, the combination of invasive physiologic indices, intracoronary imaging, and clinical factors may help identify the truly vulnerable plaque/patients who may benefit from revascularization, aid in the determination of revascularization technique (focal vs diffuse), and aid in the optimization of risk in those with ischemia not related to focal coronary stenosis.

CONCLUSION

The evidence supporting the complementary value of multimodal intracoronary physiological assessment to provide a comprehensive global evaluation of epicardial coronary stenoses is mounting. Although FFR has long been held up as a gold standard in evaluating the functional significance of a coronary stenosis, there are a number of limitations, including evaluation of the entirety of the vessel and assessment of potential vulnerable plaques. Furthermore, the presence of a negative FFR does not imply that the individual patient does not have myocardial ischemia and therefore a poorer clinical prognosis. Instead of viewing FFR, nonhyperemic pressure ratios, CFR, and measures of resistance as competing tools, the concept of multimodal physiology combining the information provided by all indices to achieve our ultimate goal and provide the best clinical outcomes to every patient should be adopted. Ongoing prospective clinical trials along with development of additional indices will provide us with further information on the prognostic value of this multimodal physiology approach. ■

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