

# Invasive physiological indices to determine the functional significance of coronary stenosis

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## ABSTRACT

Physiological measurements are now commonly used to assess coronary lesions in the cardiac catheterisation laboratory, and this practice is evidence-based and supported by clinical guidelines. Fractional flow reserve is currently the gold standard method to determine whether coronary lesions are functionally significant, and is used to guide revascularization. There are however several other physiological measurements that have been proposed as alternatives to the fractional flow reserve. This review aims to comprehensively discuss physiological indices that can be used in the cardiac catheterisation laboratory to determine the functional significance of coronary lesions. We will focus on their advantages and disadvantages, and the current evidence supporting their use.

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## 1. Introduction

Physiological measurements are being increasingly used in the cardiac catheterization laboratory to evaluate the functional significance of coronary stenoses. The fractional flow reserve (FFR) is used to assess whether coronary lesions should be revascularized. However, a multitude of physiological indices have been proposed for similar clinical application. The aim of this review is to provide a comprehensive discussion of the most common invasive physiological indices to assess coronary lesions, including their advantages, disadvantages and the evidence that supports their use.

### 1.1. Fractional Flow Reserve (FFR)

FFR is currently considered the gold standard for the physiological assessment of coronary artery stenosis in the catheterization laboratory. The FFR is derived from the ratio between the mean coronary blood pressure distal to a stenosed segment ( $P_d$ ) and the mean proximal coronary pressure ( $P_a$ ) during maximum coronary blood flow and a state of minimum microvascular resistance [1]. Essentially,  $FFR = P_d/P_a$  during

induced hyperemia. FFR is meant to represent the ratio of maximal myocardial blood flow in the territory supplied by the coronary stenosis being interrogated to the maximal myocardial blood flow in the same territory if the coronary artery in question was normal and without stenosis.

Measurement of FFR is performed by using a pressure-sensor wire or microcatheter to record pressure distal to the target lesion while simultaneously recording proximal coronary pressure via the guiding catheter. FFR is measured after administration of intracoronary nitroglycerin (100–200  $\mu$ g) to dilate the vessel, followed by adenosine to induce maximum hyperemia and minimum microvascular resistance [2]. Other vasodilators such as regadenoson, nicorandil, nitroprusside and dobutamine have been proposed for use as substitute vasodilators to induce hyperemia, but adenosine remains the gold standard for FFR measurement [2].

The results of the FAME-1 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME-2 trials which demonstrate clinical benefit in using FFR to guide revascularization decisions have led to the adoption of FFR use in clinical practice [3–5]. The role of FFR to guide revascularization has been adopted by international guidelines. The American College of Cardiology guidelines provides a class IIa recommendation for the use of FFR to evaluate intermediate lesions (30–70% stenosis) in patients with stable ischaemic heart disease [6]. The European society of cardiology 2014 revascularization guidelines provides a class IA recommendation for the use of FFR to guide revascularization in patients with stable ischaemic heart disease or silent angina [7].

*Abbreviations:* FFR, fractional flow reserve;  $P_a$ , proximal (aortic) pressure;  $P_d$ , distal coronary pressure; iFR, instantaneous wave-free reserve; cFFR, contrast Fractional Flow Reserve; CFR, coronary Flow Reserve; HSR, hyperaemic stenosis resistance; BSR, basal stenosis resistance.

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FFR use to guide revascularization was found to be cost-effective by reducing the number of unnecessary interventions [8], which can potentially lead to cost-savings of \$1200–\$5000 per patient [9]. FFR use was found to be more cost-effective than a nuclear imaging guided revascularization strategy [10].

Despite the fact that FFR use to guide revascularization is backed by a substantial body of evidence, and is cost-effective, it remains underutilised. This is likely due to a combination of factors including added procedural time, operator unfamiliarity, side effects and cost of adenosine, and lack of reimbursement for the procedure [11]. Consequently, there have been several attempts at developing alternative physiological approaches to detect ischemia in the cardiac catheterisation laboratory.

### 1.2. The instantaneous wave-free ratio (iFR)

The principle of iFR is based on the concept that coronary microvascular resistance is constant during the diastolic wave-free period, defined as beginning from 25% into diastole to 5 ms before the end of diastole, and that  $P_d/P_a$  measured during this period is a surrogate of coronary flow during maximal hyperaemia. Measurement of iFR requires the use of a pressure wire but obviates the need for adenosine. It therefore avoids the side-effects and symptoms associated with adenosine infusion and incurs less cost.

The ADVISE (**A**denosine **V**asodilator **I**ndependent **S**tenosis **E**valuation) study was the first to validate iFR in the clinical setting. A total of 131 patients with 157 stenoses were enrolled. iFR had good correlation with FFR ( $r = 0.90, p < 0.001$ ). The area under the curve was 0.93 for iFR cutoff 0.83 to predict FFR  $< 0.80$  with 85% sensitivity and 91% specificity [12].

Several comparative studies to validate iFR in patients with intermediate coronary artery stenoses followed. The VERIFY (**V**erification of **I**ntermediate **W**ave-Free Ratio and **F**ractional Flow Reserve for the **A**ssessment of **C**oronary Artery Stenosis Severity in **E**veryday **P**ractice) study, which was performed by a different group of investigators reported AUC 0.87 with high specificity of 96% but low sensitivity of 54% for iFR  $\leq 0.83$  to predict FFR  $\leq 0.80$ . In addition, these investigators found that adenosine infusion resulted in the iFR dropping from 0.82 to 0.64 ( $p < 0.0001$ ), and this demonstrated that microvascular resistance is not minimal during the diastolic wave-free period [13].

In response, proponents of the iFR conducted the CLARIFY study (**C**lassification **A**ccuracy of **P**ressure-Only **R**atios **A**gainst **I**ndices Using **F**low study). This demonstrated that vasodilators only affected the numerical value of iFR and not its diagnostic performance. When comparing iFR with iFRa (iFR measured with hyperemia) using the hyperemic stenosis resistance (HSR) index as the gold standard, the area under the curve of iFR was 0.93, iFRa was 0.94 and FFR was 0.96,  $p = 0.48$  [14]. However, the use of HSR as a reference is debatable as it has not been validated in any large scale studies.

iFR can also be used by way of a hybrid approach whereby iFR  $< 0.86$  is considered functionally significant and iFR  $> 0.93$  is considered not functionally significant, and if iFR falls within the grey zone of between 0.86 and 0.93, then the operator should perform FFR. The hybrid iFR approach can correctly classify patients into functionally significant or non-significant FFR 95% of the time, and obviated the need for adenosine 57% of the time [15,16]. Using this approach in the ADVISE II study, which involved 598 patients, resulted in 94.2% agreement between iFR and FFR, and eliminated the need for adenosine in 69.1% of the time [17].

Recently, two large randomised control trials tested the validity of using iFR to guide revascularization. Both studies demonstrated that using an iFR cut off of  $\leq 0.89$  was not inferior to FFR in guiding revascularization for the primary outcome of one year composite risk of major adverse cardiac events including death, nonfatal myocardial infarction and unplanned revascularization. The DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) trial

[18], which involved 2492 patients, showed that the rate of major adverse cardiac events was 6.8% in the iFR group and 7.0% in the FFR group with hazard ratio of 0.95 (95% CI 0.68 to 1.33;  $p = 0.78$ ) and  $p < 0.001$  for non-inferiority. The iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) trial [19], which involved 2037 patients, showed that the rate of major adverse cardiac events at one year was 6.7% for the iFR group and 6.1% for the FFR group with  $p = 0.007$  for non-inferiority. The use of iFR in these trials resulted in shorter procedure time and less patient discomfort when compared to FFR as adenosine infusion was not required for iFR measurement.

In both studies, the FFR arm had a greater number of revascularization procedures, resulting in a higher number of stents deployed (number of significant lesions detected in iFR group vs FFR group: 451 vs. 557,  $p = 0.004$  in the DEFINE-FLAIR trial and 457 vs. 528, in the iFR-SWEDEHEART trial,  $p < 0.001$ ). There are two ways to interpret this data. The first is to assume that there was a larger number of patients with significant lesions in the FFR arm in both trials. This assumption would suggest that the FFR cohorts should theoretically have worse outcome results, and this could have confounded the results of the studies. The second way to interpret this data is to assume that iFR is less sensitive in assessing stenosis severity when compared to FFR. It is our opinion that the second explanation is true, as this phenomenon was found independently in both studies, and encountering iFR negative but FFR positive is a common occurrence in the cardiac catheterisation laboratory.

The two major trials did not address the issue of discordance between iFR and FFR, which can affect up to 20% of patients, especially those with left main and LAD lesions [20]. It has been suggested that patients with high iFR and low FFR have preserved coronary flow (CFR) and higher myocardial blood flow compared to patients with low iFR and low FFR [21]. These patients tend to have less complex coronary disease and less comorbidities [22]. It remains unclear whether lesions with low FFR but normal iFR should be revascularized. In addition, a meta-analysis combining both these studies showed that use of iFR resulted in a numerically higher rate of subsequent death or myocardial infarction (relative risk 1.3,  $p = 0.09$ ) [20].

In patients with serial stenoses, FFR measurement of a specific lesion can be affected by upstream or downstream disease [23]. iFR has been proposed as a useful measurement in these situations. Theoretically, pressure gradients during resting conditions may be less susceptible to effects of inter-lesional dependence, and the use of iFR pullback with automated iFR-angiography co-registration provides an attractive tool to guide revascularization in this setting [24,25]. However, the use of iFR in this setting has only been validated in a small study involving 29 patients [24].

The accumulated data for iFR therefore suggests that it is a reasonable alternative to performing FFR in the cardiac catheterisation laboratory, with the advantage of obviating the need for adenosine administration. However, there is a need to determine the long-term outcome of unrevascularized patients who are iFR negative but FFR positive. A summary of studies comparing iFR to FFR is shown in Table 1, and a summary of clinical outcome studies involving FFR and iFR is shown in Table 2.

### 1.3. Resting $P_d/P_a$

In an effort to further simplify FFR, investigators have studied the use of baseline mean  $P_d/P_a$  over the entire cardiac cycle without hyperaemia. An initial single centre retrospective study showed a significant linear correlation between resting  $P_d/P_a$  and FFR  $r = 0.74$ , and area under the curve was 0.86 for resting  $P_d/P_a$  to predict FFR  $\leq 0.8$  [26]. Subsequent prospective studies demonstrated AUC of 0.88–0.89, specificity of 91.7–92%, and sensitivity of 60–68.9% for  $P_d/P_a \leq 0.91$  to predict FFR  $\leq 0.8$  [27,28].

**Table 1**  
Summary of studies comparing FFR and iFR.

Study	Design	Outcome
ADVISE [12]	Prospective comparative study evaluating 157 lesions in 131 patients	iFR <0.83 had 85% sensitivity, 91% specificity, 91% PPV and 85% NPV to predict FFR <0.8 (AUC 0.93)
ADVISE Registry [62] Johnson et al. [63] RESOLVE [29]	Retrospective registry including 339 stenoses in 312 patients Retrospective study with 1129 patients 1974 stenoses in 1768 patients	iFR <0.89 had AUC 0.89 and agreement accuracy of 94% to predict FFR ≤0.8 iFR <0.89 had AUC 0.86 to predict FFR <0.8 iFR ≤0.90 had 78.9% sensitivity, 82.4% specificity, 85.2% PPV and 73.3% NPV to predict FFR ≤0.80 (AUC 80.4%)
VERIFY [13]	Comparative study with 2 arms: 1. Prospective (n = 206) 2. Retrospective (n = 500)	Prospective arm: iFR ≤0.80 had 40% sensitivity, 99% specificity, 98% PPV and 47% NPV to predict FFR ≤0.8 (AUC 0.6) Retrospective arm: iFR ≤0.80 had 40% sensitivity, 99% specificity, 99% PPV and 44%NPV to predict FFR ≤0.8 (AUC 0.59)
CLARIFY [14]	Prospective study with 51 stenoses comparing iFR and FFR to predict positive HSR	iFR and FFR had equal accuracy in predicting positive HSR (AUC 0.93 for iFR vs 0.96 for FFR, p = 0.48)
Park et al. [64]	Retrospective analysis of 238 stenoses	iFR <0.9 had 76% sensitivity, 86% specificity, 82% PPV and 80% NPV to predict FFR ≤0.80 (AUC 0.9)
ADVISE in practice [65]	392 stenoses from 313 patients	iFR <0.9 had 81% sensitivity, 79% specificity, 71% PPV and 87% NPV to predict FFR ≤0.80 (AUC 0.87)
JUSTIFY-CFR [66]	Prospective study with 216 stenoses from 186 patients that compare iFR and FFR using CFVR as gold standard	AUC for iFR higher compared to FFR (0.82 vs 0.72 p < 0.001) to predict CFVR <2
ADVISE II [17]	Prospective study evaluating 919 stenoses from 797 patients	iFR <0.9 had 73% sensitivity, 87.8% specificity (AUC 0.9) to predict FFR ≤0.80. iFR ≤0.85 or ≥0.94 correctly classified FFR 91.6% of the time. Hybrid iFR-FFR approach increased classification accuracy to 94.2%.

Resting Pd/Pa has been shown to be comparable to iFR when using FFR as the gold standard in several studies. Resting Pd/Pa had similar overall diagnostic accuracy to iFR in the RESOLVE study (81.5% vs. 80.4% for iFR) [29]. The ADVISE II study demonstrated no difference between Pd/Pa and iFR with AUC of 0.90 for both Pd/Pa and iFR, p = 0.35. There was a strong correlation between Pd/Pa and FFR (r = 0.84, p < 0.001), and Pd/Pa correctly classified functionally significant lesions in 83.2% of cases [30]. The CONTRAST (Can CONTRast injection Better Approximate FFR Compared to Pure ReSting Physiology?) study was a large prospective multicenter study with 763 enrolled patients that compared resting Pd/Pa, iFR, and contrast FFR using FFR as the gold standard. This demonstrated no difference between resting Pd/Pa and iFR (diagnostic accuracy to predict FFR ≤0.8 was 78.5% vs. 79.9%, p = 0.78) [31]. The VERIFY 2 study concluded that both Pd/Pa and iFR have similar accuracy with 10% rate of lesion misclassification even with a hybrid approach [32].

Several studies have since focused on the comparison between iFR and resting Pd/Pa. One such study showed that resting Pd/Pa correlated strongly with iFR (R2 = 0.93; p < 0.001), and that resting Pd/Pa ≤ 0.91 was able to predict functionally significant iFR accurately with AUC 0.98 (p < 0.001) [33]. In patients who had coronary intervention deferred, iFR and Pd/Pa had similar ability to predict adverse clinical outcomes. However, iFR was found to be more sensitive to changes in

vessel diameter stenosis severity. iFR also had significantly lower variability in estimated event rates when compared to resting Pd/Pa (3.27 ± 3.39% vs. 3.85 ± 4.00%; p < 0.001) [34].

Using N-ammonia positron emission tomography derived coronary flow reserve as a gold standard, a recent study demonstrated that FFR, iFR and resting Pd/Pa were similar in its diagnostic accuracy by receiver operating characteristic curve analysis. However, FFR had better discrimination and reclassification ability when compared to the other two resting indices in predicting the presence of ischaemia [35].

It is therefore likely that Pd/Pa is similar in its diagnostic accuracy to iFR [36]. However, the cut off value of Pd/Pa has not been standardized [37]. The prospective use and outcomes of Pd/Pa guided interventions have not been tested in the clinical setting, and a randomised control trial is required for this.

1.4. Contrast FFR

Contrast medium is known to induce vasodilation and hyperemia [38]. Although the hyperaemia induced is often submaximal, contrast agents may be used to measure FFR. A prospective non-randomised study measured Pd/Pa after injection of 6 ml of iomeprol contrast, and defined this measurement “contrast FFR”. A highly significant correlation between contrast FFR and FFR was demonstrated (r = 0.94, p <

**Table 2**  
Summary of randomised clinical outcome trials involving FFR and iFR.

Study	Design	Outcome
<i>FFR studies</i>		
DEFER [50]	N = 325 patients with intermediate coronary stenosis Patients with FFR >0.75 randomised to PCI or medical management	Event free survival: 83% vs 89% (p = 0.27)
FAME [3]	N = 1005 patients with multivessel coronary disease (≥50% stenosis) randomised to angiographic vs FFR guided PCI	MACE: 18.3% vs 13.2% (p = 0.02) Death or myocardial infarction: 11.1% vs 7.3% (p = 0.04)
FAME 2 (5)	N = 888 stable patients with stable angina and FFR ≤0.8 randomised to PCI vs medical therapy	MACE: 4.3% vs 12.7% (p < 0.001) (driven largely by urgent revascularization)
DANAMI 3 – PRIMULTI [67]	N = 627 post primary-PCI patients randomised to FFR guided complete revascularization (2 days post STEMI) vs medical therapy prior to discharge	MACE: 13% vs 22% (p = 0.004) (driven largely by ischaemia driven revascularization)
COMPLETE – ACUTE [68]	N = 885 post primary-PCI patients randomised to FFR guided complete revascularization during index procedure vs medical therapy prior to discharge	MACE: 7.8% vs 20.5% (p < 0.001) (driven largely by urgent revascularization)
<i>iFR studies</i>		
DEFINE-FLAIR [18]	N = 2492 patients randomised to iFR guided PCI vs FFR guided PCI Non-inferiority analysis	MACE: 6.8% vs 7% (p = 0.83)
iFR-SWEDEHEART [19]	N = 2019 patients randomised to iFR guided PCI vs FFR guided PCI Non-inferiority analysis	MACE: 4.6% vs 4.6% (p = 0.84)

0.001). Contrast FFR  $\leq 0.83$  was highly specific (96.1%) and considerably sensitive (85.7%) with area under the receiver operating characteristic curve of 0.97 to predict FFR  $\leq 0.8$ . Disagreement was evident in 17% of the lesions, which had contrast FFR readings ranging from 0.84 to 0.87, and the study suggested that adenosine was only required when the contrast FFR value falls within this range [39].

The above-mentioned CONTRAST study revealed that the mean  $P_d/P_a$  value became progressively smaller for resting  $P_d/P_a$ , iFR, contrast FFR and FFR. This indicates that microvascular resistance becomes progressively lower in this sequence of measurements. Accuracy to predict FFR  $\leq 0.8$  was higher for contrast FFR when compared to resting  $P_d/P_a$  or iFR, and the accuracy was the same for  $P_d/P_a$  and iFR. Contrast FFR of  $\leq 0.83$  had an area under the receiver operating characteristic curve of 0.93 with sensitivity of 75.8% and specificity of 95.3% to predict FFR  $\leq 0.8$ . The use of contrast FFR in a hybrid approach also obviated the need for adenosine to a greater extent when compared to the resting indices, with only 37.2% of patients requiring adenosine administration [31].

In a multicentre study that involved 1026 coronary stenoses, contrast FFR  $\leq 0.85$  was found to have AUC 0.89 in predicting an FFR value  $\leq 0.80$ . Both resting  $P_d/P_a$ /FFR and contrast FFR/FFR hybrid approaches showed equivalent excellent accuracy (96%). However, a cFFR/FFR hybrid approach resulted in significantly lower number of lesions requiring adenosine (22% vs. 44%,  $p < 0.0001$ ) [40].

The results of these studies indicate that contrast FFR is feasible and has greater accuracy than iFR and resting  $P_d/P_a$  to predict functionally significant FFR, with minimal added complexity when compared to the resting indices. However, the use of contrast FFR has not been tested in a randomised control interventional trial, and there is no widespread consensus as to the amount of contrast required for FFR measurement. Moreover, the hyperemia induced by contrast is short-lived, and tends to last for only a short duration. This means that repeated measurements, such as in the setting of pullback interrogation to assess serial lesions can become complex, and incur high contrast usage. In terms of practical usage, if resting  $P_d/P_a$  or contrast FFR is  $\leq 0.8$ , this would obviate the need for adenosine administration.

### 1.5. Coronary flow reserve (CFR)

The coronary flow reserve (CFR) represents the ratio of maximum blood flow during hyperaemia in the coronary artery being interrogated to the resting blood flow of the same artery. It is predicated on the fact that functionally significant coronary stenosis will cause compensatory lower microcirculatory resistance, and lead to the blunting of further increases in blood flow during hyperaemia. CFR use predates FFR, and CFR provides an assessment of both epicardial and microcirculatory status within the territory of the coronary artery of interest [1]. CFR can be measured using temperature-sensor wires by thermodilution or by Doppler wires.

CFR correlates well with non-invasive myocardial perfusion studies. A CFR  $< 2$  indicates impaired flow and predicts unfavourable outcomes [41–43]. The correlation between CFR and FFR is modest ( $r = 0.34$ ,  $p < 0.001$ ) [44]. A discrepancy whereby normal CFR coincides with abnormal FFR or abnormal CFR coincides with normal FFR occurs in 30–40% of patients, and this is likely due to the heterogeneity in epicardial stenosis severity and microvascular dysfunction in individuals [44–46].

Studies using both CFR and FFR have shown that the status of the coronary microcirculation may be a better indicator of prognosis when compared to epicardial stenosis severity. Rates of major adverse cardiac events at ten years were 80% when FFR  $> 0.80$  and CFR  $< 2$  vs. 40% when FFR  $\leq 0.8$  and CFR  $\geq 2$  [46]. Deferral of intervention based on normal CFR was previously touted to be safe. However, adverse event rates were 6–9.1% after an average 1 year follow up in patients who had normal CFR and were not revascularized [47,48]. This compares to event rates of 6.9–21% after 5 years follow up when deferring based on normal FFR [49,50].

Although CFR is a better prognostic indicator, FFR remains a better tool in the cardiac catheterisation laboratory as it specifically assesses the functional significance of epicardial lesions and aids in the decision of whether to revascularise coronary lesions. Moreover, CFR is dependent on systemic haemodynamics and has less reproducibility when compared to FFR [51]. Specific measurement of both epicardial and microcirculatory status with a combination of indices such as the combination of FFR and the index of microcirculatory resistance (IMR), or the combination of hyperaemic stenosis resistance and hyperaemic microvascular resistance index [52], will provide a comprehensive assessment of the coronary circulation. The Combined Pressure and Flow Measurements to Guide Treatment of Coronary Stenoses (DEFINE-FLOW) (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect - Combined Pressure and Doppler FLOW Velocity Measurements) trial (NCT02328820) is currently evaluating the concept of combined FFR and CFR measurements and results are expected to be available in 2018.

### 1.6. Hyperaemic stenosis resistance and basal stenosis resistance

The accuracy of physiological assessment of coronary lesions can be increased by combining pressure and velocity measurements using a combination pressure-sensor and Doppler wire. The hyperaemic stenosis resistance index is calculated by the formula  $(P_a - P_d)/\text{average peak velocity during maximal hyperaemia}$ , and represents the resistance offered by the coronary lesion being assessed [53]. The validation of HSR against myocardial perfusion study showed that HSR with a cutoff 0.8 mmHg/cm per sec performed better than CFR and FFR (AUC 0.90 for HSR vs. 0.80 for CFR ( $p = 0.024$ ) and 0.82 for FFR ( $p = 0.018$ ) [54]. A study reported high HSR ( $> 0.80$ ) could be of value in predicting adverse events after PCI especially in the setting where there is discordance between FFR and CFR results [45].

Currently, HSR is considered by some to be the most accurate invasive measurement available to assess the functional significance of coronary lesions. This is true when faced with a patient with a normal coronary microcirculation as HSR provides the direct measurement of stenosis resistance and is independent of microcirculatory resistance. However, the HSR may be misleading in the setting of microcirculatory disruption.

Investigators have attempted to simplify the process of measuring HSR by measuring stenosis resistance using the same formula during basal conditions without hyperaemia, and this measurement was named the basal stenosis resistance (BSR). When comparing BSR, HSR, CFR and FFR with myocardial perfusion scintigraphy as a reference in 228 patients, BSR was found to be equivalent to CFR and FFR, but less accurate than HSR (AUC was 0.77 for BSR, 0.77 for FFR, 0.75 for CFR and 0.81 for HSR,  $p < 0.05$ ) [55]. Although BSR is not as accurate as HSR, it is comparable to FFR and resting parameters (AUC for predicting abnormal HSR was 0.99 for BSR, 0.96 for FFR, 0.95 for iFR and 0.95 for resting  $P_d/P_a$ ) [56].

Despite the accuracy of indices combining pressure and velocity measurements, their use is largely confined to the research setting. This is because Doppler measurements are technically demanding and prone to variability.

A summary of the advantages and disadvantages of all currently available physiological studies used in the catheterization laboratory to assess epicardial coronary lesions are shown in Table 3.

### 1.7. Other coronary physiology indices to assess the coronary microcirculation

The status of the coronary microcirculation can be assessed physiologically in the cardiac catheterisation laboratory by using a combination of pressure and flow measurements. Surrogates of flow can be derived by using temperature-sensor wires that enable thermodilution based measurements such as the index of microcirculatory resistance

**Table 3**  
Physiological indices to assess coronary stenosis.

Index	Interrogation target	Advantages	Disadvantages
FFR	Epicardial lesion-specific	- Simple cut off, low variability - Not affected by hemodynamic variables	- Need for hyperemic agent
iFR Pd/Pa	Epicardial lesion-specific Epicardial lesion-specific	- No need for hyperemic agents - No need for hyperemic agents - Available with all pressure measurement systems	- Requires equipment from one specific vendor - No RCT validating its use
Contrast FFR	Epicardial lesion-specific	- Better correlation with FFR than other resting indices - Available with all pressure measuring systems	- Short-lived contrast hyperemia - No consensus on contrast dose
CFR	Composite of epicardial lesion and microcirculation	- Good prognostic marker	- Inability to differentiate the effects of microvascular dysfunction from that of epicardial lesion - Need for hyperemic agents - Affected by hemodynamic variables - Technically demanding
HSR	Epicardial lesion-specific	- Combined pressure and flow evaluation - Established cutoff	- Need for hyperemic agents - Technically demanding
BSR	Epicardial lesion-specific	- Combined pressure and flow evaluation - No need for hyperemic agents	- Less accurate than HSR - No established cutoff - Technically demanding

[51] and absolute microcirculatory resistance, [57] or Doppler-sensor wires that enable velocity based measurements such as the hyperemic microvascular resistance index, [58] and zero-flow pressure [59]. Although indices that assess the coronary microcirculation have prognostic value in determining subsequent adverse events, [60,61] no interventional clinical trials have shown benefit in the use of these indices in the clinical setting. A summary of invasive coronary physiological indices that are available to assess epicardial lesions and the microcirculation are shown in Fig. 1.

**2. Conclusion**

The field of coronary physiology is rapidly evolving, and changing the practice of interventional cardiology. A substantial number of studies support the use of physiological indices to assess epicardial stenosis in the cardiac catheterisation laboratory, and an understanding into the differences between these indices will enable operators to apply them in the clinical setting. Future studies are required to determine whether

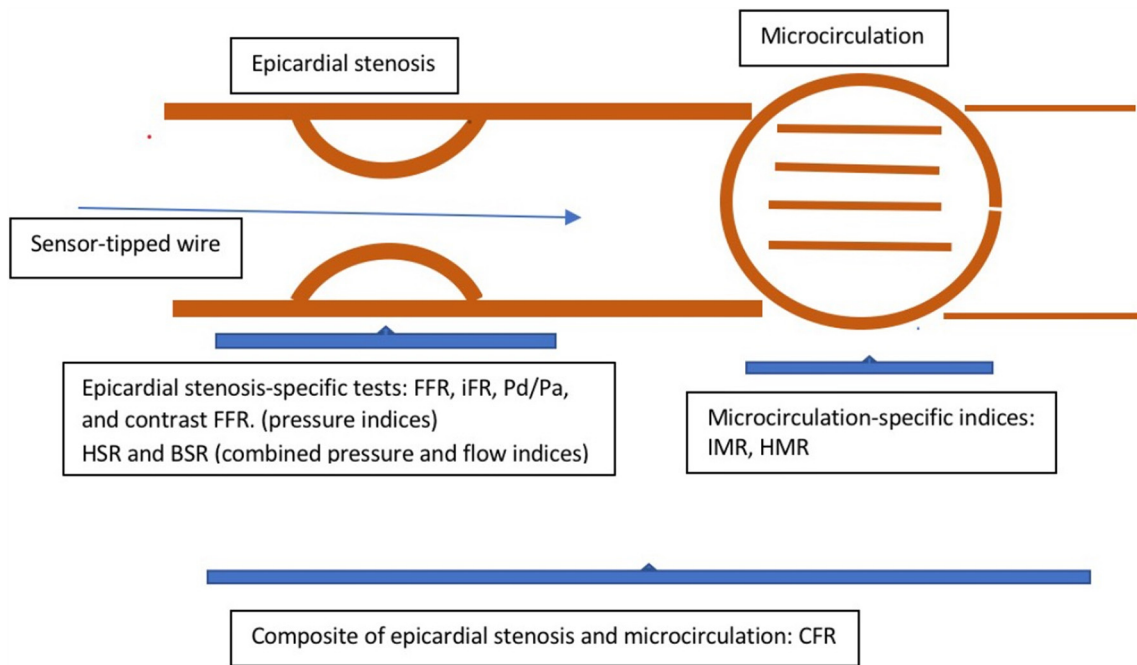
there is a role for physiological indices to assess the coronary microcirculation.

*2.1. Impact on daily practice*

Providing insights on the different invasive physiology indices to assess coronary lesions will aid in improving their utilization in everyday interventional practice. The availability of different options for functional assessment of intermediate coronary lesions will help overcome some of the limitations faced in the cardiac catheterisation laboratory.

**Conflict of interest**

Associate Professor Yong has received minor honoraria and research support from Abbott (formerly St Jude Medical) and research support from Philips (formerly Volcano). Professor Fearon is a consultant for Boston Scientific and has minor stock options with HeartFlow. He has



**Fig. 1.** Physiological indices to determine the functional significance of coronary stenosis categorised by interrogation territory and method. FFR: fractional flow reserve, iFR: instantaneous wave-free ratio, Pd: distal coronary pressure, Pa: proximal coronary pressure, HSR: hyperaemic stenosis resistance, BSR: basal stenosis resistance, IMR: index of microcirculatory resistance, HMR: hyperaemic microvascular resistance.

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Dr. Firas R AL-Obaidi has no conflict of interest to declare.

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