



Advances in Coronary Physiology

Sukhjinder S Nijjer, MD; Sayan Sen, MD; Ricardo Petraco, MD; Justin ER Davies, MD

Pressure-wire technology, most typically fractional flow reserve (FFR), has provided interventional cardiologists with a means of determining the physiological importance of a stenosis during angiography. There has been renewed interest in coronary physiology in the light of guideline recognition, ongoing clinical research and new technologies changing the paradigm of how assessment is performed in the catheter laboratory. We reflect on FFR, with regards the potential effects of changing hemodynamics on FFR and the latest evidence with regards to outcomes. We also review the instantaneous wave-free ratio (iFR), a new pressure-only index, measured at rest, that is under active evaluation in several international randomized controlled trials. We review the accumulated evidence and discuss the important physiological concepts between pressure and flow that underlie the approach to using resting indices. Finally we investigate future developments, including physiological mapping with iFR-Pullback and the potential to predict the hemodynamic effect of stenting.

Key Words: Coronary circulation; Fractional flow reserve; Instantaneous wave-free ratio; Instantaneous wave-free ratio-Pullback

Patient outcomes are improved and costs are reduced when coronary physiology is used to guide coronary revascularization.^{1,2} However, the majority of patients are still managed using the angiographic visual appearance of a stenosis, sometimes without formal ischemia assessment.³ Conceptually, revascularization targeted to ischemia-causing stenoses maximizes the benefit while minimizing risk.^{4,5} Guidelines⁶ and appropriateness criteria reflect the added value of invasive physiology,^{7,8} and together with new technologies there has been renewed interest in coronary physiology.⁹

In this review, we consider the latest advances in coronary physiology. We reflect upon new data for fractional flow reserve (FFR), as well as new technologies, such as the instantaneous wave-free ratio (iFR), which allows assessment of coronary stenosis severity under rest conditions and permits stenosis mapping with anatomical co-registration.

FFR

FFR is the standard for clinical physiological assessment in the catheter laboratory and is supported by sound concepts and randomized data.¹⁰ FFR as a concept requires stable and minimal microvascular resistance for pressure measurements to equate to flow. In clinical practice this is most commonly achieved using adenosine; if maximal hyperemia is not achieved, there is potential for the pressure ratio calculated not to be the true FFR. Rigorous attention to detail is necessary in the application of physiology in the catheter laboratory and we reflect upon important areas that affect the interpretation of results.

Physiological Effect of Hemodynamic Changes During Vasodilator Use

The AFFECTS study assessed changes in aortic and coronary pressures in response to central infusion of adenosine, during both peak and stable hyperemia.¹¹ Seven distinct different patterns were noted (**Figure 1**). Infusion of adenosine triggers pulmonary receptors to give an initial peripheral vasoconstriction and a rise in systemic blood pressure (BP).^{11,12} Shortly after, adenosine increases large artery compliance, causing a fall in peripheral resistance and aortic reservoir pressure. Systemic BP falls, leading to a fall in proximal pressure (Pa); AFFECTS showed a mean fall of 10.2 ± 10.5 mmHg in Pa.¹¹ This fall in Pa accounted for more than half of the change in distal pressure (Pd) in response to centrally administered adenosine.¹¹ That is, half of the change in Pd, which is perceived to be due to a reduction in microcirculatory resistance, was related to a reduction in the aortic proximal driving pressure. This is intuitive, because the purpose of hyperemia is to create conditions in which pressure and flow are linearly related; any situation in which the pressure falls will cause flow to fall also. Therefore when Pa is reduced, then Pd and the ratio (Pd/Pa), which acts as surrogate of flow, will be reduced by the same proportion.

Because FFR can be calculated during either initial peak or stable hyperemia, and because Pa and Pd can differ at these 2 time points according to the 7 possible responses to adenosine, it is possible FFR values will differ at peak and stable hyperemia. For example, for a given Pd, if in peak hyperemia the Pa is high, then a low FFR may be calculated; if Pa then falls during stable hyperemia, a higher FFR will result.

This is observed practically: Echavarria-Pinto et al showed

Received February 3, 2015; revised manuscript received March 20, 2015; accepted March 23, 2015; released online April 13, 2015
International Centre of Circulatory Health, Imperial College London, London, UK

Mailing address: Justin ER Davies, MD, International Centre of Circulatory Health, Imperial College London, 59-61 North Wharf Road, London, W2 1LA, UK. E-mail: Justin.Davies@imperial.ac.uk

ISSN-1346-9843 doi:10.1253/circj.CJ-15-0044

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

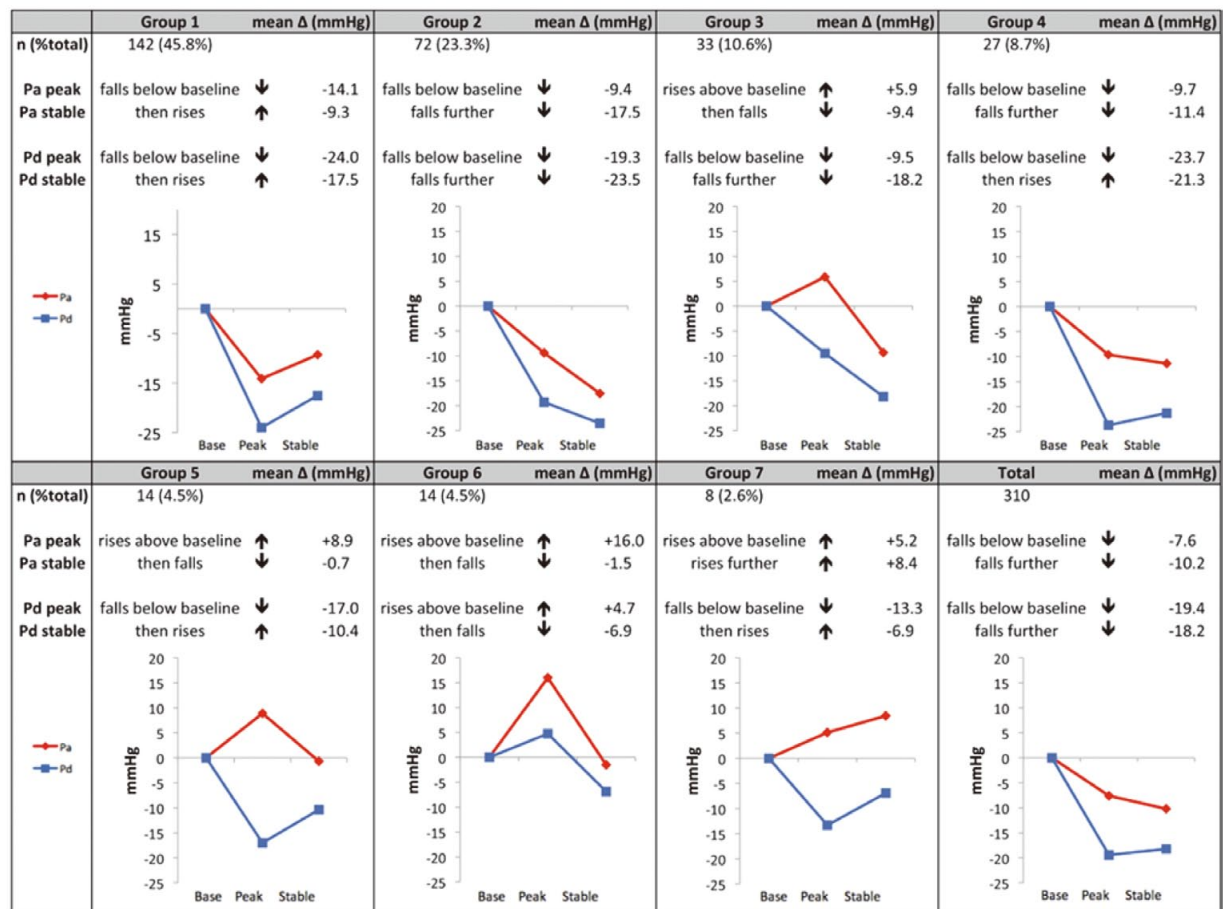


Figure 1. The 7 different hemodynamic responses to adenosine infusion. Both proximal (Pa) and distal (Pd) pressures change during adenosine infusion – with differential behaviors during peak and stable hyperemia. This will affect the ratios of Pd/Pa calculated at peak and stable hyperemia. Reproduced with permission from Tarkin JM, et al.¹¹

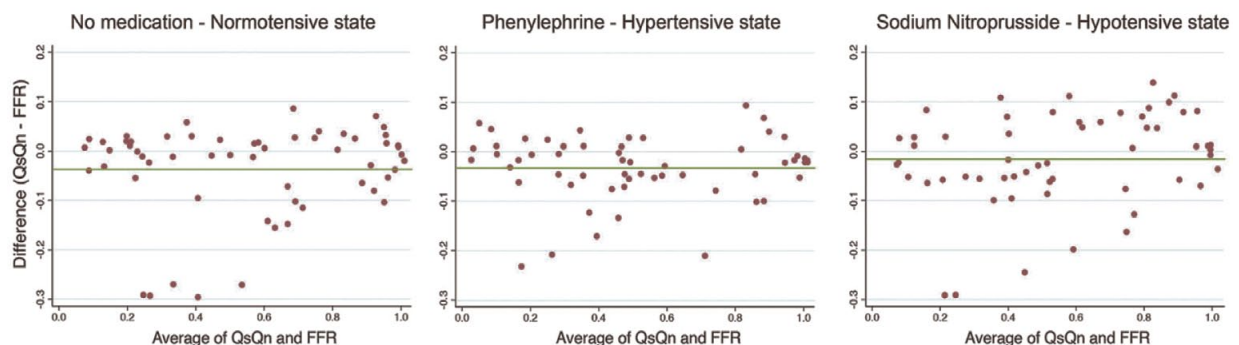


Figure 2. Bland-Altman graphs of Qs/Qn with fractional flow reserve (FFR). The original validation work for FFR measured a true FFR by directly measuring flow velocity in the presence and absence of a stenosis (Qs/Qn). This was compared with FFR, and when plotted with different hemodynamic states had high correlation and R^2 values. However, re-plotting the data of the 5 dogs presented in the published paper as a Bland-Altman plot shows that the Qs/Qn values are less tightly associated as may be suggested by correlations.

the lowest Pd/Pa ratio during hyperemia occurred during the peak phase rather than stable phase in almost one-fifth cases.¹³ In nearly 3% of cases this produced FFR values that suggested different revascularization decisions at peak and stable hyperemia.¹³ This result is important because the validation work and clinical outcome data for FFR were based on values calculated in the stable phase, not the lowest number recorded. These findings may be more frequent in an unselected real-world cohort that did not specifically exclude poor quality traces.

The choice of hyperemic agent will have a differential effect on hemodynamics.¹⁴ Adenosine (both intravenous and intracoronary) reduced BP significantly more than intracoronary nicorandil (a fall of 12.9 ± 9.1 mmHg vs. 9.2 ± 6.7 mmHg, $P < 0.001$).¹⁴ Regadenoson reduced BP even more than adenosine, but the changes in the reported subset were smaller, perhaps reflecting methodological differences (adenosine caused a rise in BP 3.2 ± 12.1 vs. regadenoson -2.7 ± 11.1 , $P < 0.001$).¹⁴ Although no relationship between the difference in FFR values between the 2 hyperemic agents and the change in hemodynamics was found, this is perhaps because FFR was calculated only during “maximal hyperemia” (likely to be the lowest ratio), with no actual comparison of the peak and stable values. Therefore, the true effect of pressure changes on the ratio remains unexplored in that dataset.

When Pa falls considerably, paradoxical vasoconstriction of the microcirculatory bed can occur to preserve tissue perfusion. This is observed as a paradoxical rise in Pd during intravenous adenosine infusion,^{15,16} particularly if stenoses are severe or infusion time is long. Although 1 min is typical, many centers and studies use 4 min as originally validated (eg, FUTURE (NCT01881555)).¹⁷

These findings are consistent with previous theoretical models that suggested FFR is affected by changes in hemodynamics.¹⁸ Indeed, the original animal data showing the pressure independence of FFR has been reviewed using a Bland-Altman analysis,¹⁹ demonstrating there can be a difference between pressure-based FFR and true flow-based FFR (Figure 2).

Altering the Doses of Hyperemic Agents

Additional doses of hyperemic agent are often given when FFR values are close to the threshold, ostensibly to ensure resistance is at its lowest and ensure lower FFR values cannot be achieved.²⁰ However, higher intravenous doses have been shown to adversely affect hemodynamics²¹ and higher doses have no validation in clinical outcome studies. The current thresholds for treatment (whether 0.80 or 0.75) were derived at much lower doses of adenosine (IC $20\text{--}40\mu\text{g}$ bolus, IV $140\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$),²² and higher doses may require different thresholds. As such, keeping to recommended doses helps standardize assessment and allows interpretation with the clinical outcome studies.

The route of hyperemic agent administration varies among centers. Although the landmark trials used intravenous infusion, many prefer intracoronary adenosine boluses.²³ The reasons include avoiding the need for additional femoral punctures or infusion pumps, increased cost efficiencies and lower incidence of side-effects.²⁴ Intracoronary dosing may avoid hemodynamic confounding because central aortic pressure is less likely to change,²¹ even when intracoronary infusions are used.²⁵ Although classification agreement is good across a wide spectrum of stenoses,²⁴ in more clinical populations the classification match between intracoronary and intravenous dosing can fall to 78%, near the 0.80 threshold.¹⁴ Therefore,

revascularization decisions may be affected by using an intracoronary approach in truly intermediate stenoses.

Role of FFR in Diagnostic Angiography

Physiology may have specific traction during diagnostic angiography to guide revascularization decisions earlier in the patient's clinical pathway. This patient cohort differs from those in whom revascularization by percutaneous coronary intervention (PCI) was already selected, as seen in the DEFER and FAME studies. Two important studies add significantly to our understanding of how such changes will alter future paradigms of the management of coronary disease.

In the RIPCORD study,²⁶ 200 patients undergoing coronary angiography had a management plan made based only on the angiographic findings. FFR was then measured in all vessels with ≥ 2.25 mm diameter and used to guide a second management plan. One-quarter of the patients had a change in management after measurement of FFR; 9 of 72 patients (12.5%) in whom medical therapy was chosen on the basis of angiography were recommended for revascularization when the FFR was known. Similarly, one-quarter of patients first recommended for revascularization required medical therapy once the FFR was known.² In total, one-third of vessels were considered significantly changed after FFR assessment.

The R3F study²⁷ was a larger study with a similar design, enrolling over 1,075 consecutive patients undergoing coronary angiography in 20 French centers. Unlike RIPCORD, patients were only included if at least 1 ambiguous lesion was present, and FFR was performed only in the vessel of interest. Although the overall proportion of medical therapy, PCI and coronary artery bypass grafting appeared similar, with only a modest but statistically significant change, individual patients had a marked change in plan, with 464 (43%) patients having a different management plan made after FFR disclosure. Importantly, from a safety perspective, the event rate after 1 year of follow-up was identical in the cohort of patients who were reclassified by FFR and those in whom angiographic-guided plans were concordant with the FFR findings (11.2% vs. 11.9% major adverse cardiac event (MACE) rate, $P = 0.78$).

Taken together, RIPCORD and R3F strongly suggest that routine coronary physiology should be considered in all patients referred for coronary angiography.

Outcomes of FFR-Guided Revascularization

The key question for the open-label FAME-2 study^{28,29} was whether patients with ischemia defined by FFR have improved outcomes if treated by PCI compared with optimal medical therapy alone. The study group was 1,600 stable patients scheduled for FFR assessment of any angiographically visible stenoses ($>50\%$). Those with $\text{FFR} \leq 0.80$ were randomized to FFR-guided PCI with optimal medical therapy or medical therapy alone, while those with $\text{FFR} > 0.80$ were treated medically and followed in a registry. The study was stopped early, after 888 patients had been randomized, because of increased events in the medical therapy arm. The primary endpoint, a composite of death, nonfatal myocardial infarction (MI) or urgent revascularization within 2 years was significantly lower in those undergoing PCI rather than medical therapy (8.1% vs. 19.5%, hazard ratio [HR] 0.39 [0.26–0.56], $P < 0.001$).²⁹ Events were driven by urgent revascularization, with 18 patients (4%) in the PCI arm vs. 72 (16.3%) in the medical arm needing PCI (HR 0.23, [0.14–0.38], $P < 0.001$) with no difference in mortality (HR 0.74, [0.26–2.14], $P = 0.58$) or MI (HR 0.85, [0.50–

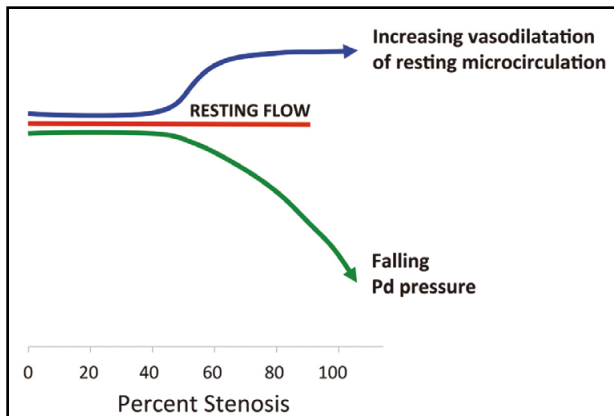


Figure 3. Schematic representation of the behavior of resting coronary physiology in the face of increasing stenosis severity. Resting flow-velocity is preserved across all severities of stenosis until near occlusion. To maintain flow, the microcirculation dilates at rest at the expense of the distal coronary pressure. Measuring pressure alone at rest gives an indication of how important the stenosis is to the given coronary bed – if there is no transtenotic gradient, then there has been no microcirculatory compensation in response to the stenosis and the stenosis is less likely to be truly flow-limiting.

1.45], $P=0.56$).²⁹ Those patients who had been deferred with an FFR >0.80 had a low primary endpoint of 3% at 7 months²⁸ and 9% (15 patients) at 2 years.²⁹ There was little difference between the deferred population (FFR >0.80) and those with FFR ≤ 0.80 who had undergone PCI (HR 0.90, [0.49–1.64], $P=0.72$).

FAME-2 provides excellent contemporary data and learning points for future trials. It can be seen that blinding patients and operators to the physiological values will have great importance. RIPCORD and R3F demonstrate that physician behavior and management plans are altered when the FFR value is known. Knowledge of the unblinded FFR value may have altered management of patients in FAME-2 and accounted for some of the early revascularization decisions. Furthermore, it is unclear how patients react to the knowledge that they have a stenosis known to be causing ischemia. In those with FFR ≤ 0.80 who had medical therapy, a dramatic cumulative increase in class IV angina (pain at rest) was observed. The increase was most marked in those reporting symptoms and less so in those with objective markers of instability such as ECG changes or troponin rise. This suggests knowledge of stenosis significance may have influenced patients' perception of symptoms. Trials such as the DEFINE-FLAIR study (NCT 02053038),³⁰ which is enrolling 2,500 patients into an outcomes-based iFR-FFR comparison, will have patients and those conducting follow-up blinded to the physiological arm or values to minimize such bias.

FFR as Marker of Ischemia

If revascularization is performed for ischemia, a continuous benefit should be expected related to the severity of ischemia, and FAME-2 demonstrates that the FFR value is related to the number of events. First, decisions were made using the 0.80 threshold; although not specifically validated during the original FFR studies, there is data to suggest there are increased events when stenoses between 0.75–0.80 are deferred,^{31,32}

suggesting that the higher 0.80 cut-point is prudent. An FFR of 0.65 had significant interaction with the primary endpoint at 7 months (when FFR ≤ 0.65 , events in the PCI arm were 7 vs. 35, HR 0.08 [0.03–0.26], when FFR >0.65 , events were 12 vs. 21, HR 0.46 [0.21–1.01], $P=0.01$ for interaction).²⁸ At 2 years, however, the interaction only showed a trend towards significance ($P=0.07$).²⁹ This suggests that the majority of benefit for revascularization is when stenoses are truly ischemic (FFR ≤ 0.65), and this value is similar to the mean FFR in FAME-1 in stenoses undergoing PCI (0.60 ± 0.14).¹

Further supporting data come from a comprehensive meta-analysis of study (9,173 lesions) and patient-level (6,961 lesions) data from FFR studies reporting events.³³ Clinical events increase as the FFR decreases and revascularization demonstrates the greatest benefit the lower the FFR value. Using patient-level data, the optimal FFR threshold to predict benefit from revascularization over medical therapy for a composite of death, MI and revascularization was found to be 0.67.³³

Taken together, the real value of the FFR is in the assessment of the severity of all stenoses rather than just the intermediate stenoses. Because anatomical parameters poorly predict the FFR value, limiting FFR to only “intermediate” stenoses will poorly identify potential ischemia; rather, all stenoses should be assessed to maximize gain.

FFR in Acute Coronary Syndromes (ACSs)

There are limited data for the value of FFR in the ACS setting.³⁴ Value may be added if nonculprit stenoses can be assessed at the time of catheterization to avoid later investigation. Concerns have regarded a possible sub-hyperemic response and underestimation of severity because of microvascular dysfunction leading to a sub-hyperemic response to adenosine, resulting in underestimation of stenosis severity. Repeating FFR measurement 6 weeks after MI (both ST-segment elevation MI [STEMI] and non-STEMI) shows little change in the mean FFR value for the study group, though there can be significant change on a per-patient basis.³⁵ Certainly in STEMI, microvascular responsiveness changes over time, showing significant worsening of FFR in nonculprit vessels when repeated measurements are made 1 day after STEMI and more so at 6 months.³⁶

The FAMOUS-NSTEMI study³⁷ was designed, but not powered, to assess the differences in health outcomes when both culprit and nonculprit vessels undergo FFR-guided treatment vs. angiographic-guidance during NSTEMI. The study group was 350 NSTEMI patients with 706 stenoses ($\geq 30\%$ severity) amenable to revascularization who had 704 FFR measurements and were randomized to FFR-guided or angiographic-guided PCI (FFR was not disclosed); 430 (61.1%) stenoses had FFR ≤ 0.80 and 80% of each arm had at least 1 physiologically significant vessel. In the FFR-guided arm, 22.7% patients were treated by medical therapy compared with 13.2% in the angiographic arm ($P=0.02$). Despite this, the number and length of stents was similar in both groups, and there was no difference in the in-hospital costs.

Prospective follow-up noted no difference in clinical events at 1 year,³⁷ with Kaplan-Meier plots showing convergence of a combination of death, MI or heart failure admission. Because both arms had similar stent rates, stent-related complications could be responsible or alternatively, patients with NSTEMI deferred for stenting may have had a catch-up of events (ie, they were under-treated initially). Breakdown of events according to culprit and nonculprit vessel would help interpretation.

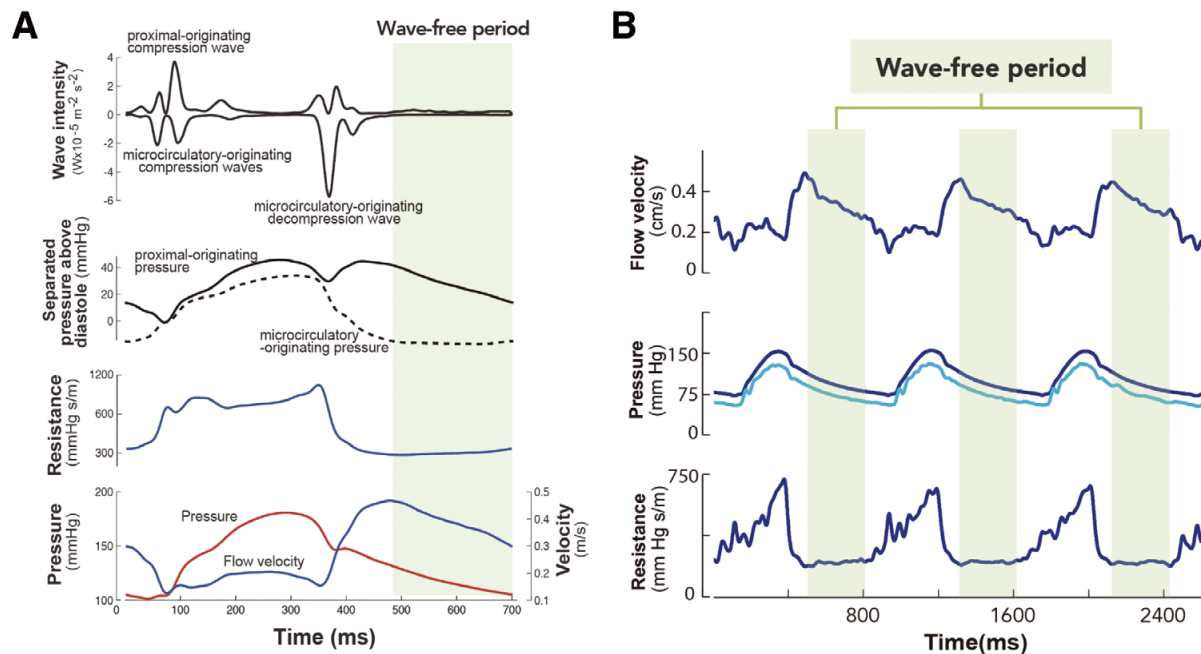


Figure 4. (A) Separated wave intensity plot shows how multiple different waves propagating from the proximal and distal ends of the vessel influence coronary flow. The waves are quiescent during the wave-free period in diastole. Instantaneous resistance plotted throughout the cardiac cycle demonstrates that resistance is lowest and most stable during the wave-free period. Coronary pressure and flow are linearly related during the wave-free period. (B) Flow velocity, proximal and distal pressure traces and instantaneous resistance demonstrate the stability of the wave-free period beat to beat. Flow velocity over the wave-free period is higher than that over the whole cycle, giving greater discrimination between stenosis severities than the whole cycle at rest. Adapted with permission from Sen S, et al.⁴² Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis.

Larger studies with greater delineation of the drivers of events are required, but FAMOUS clearly demonstrates it is technically feasible to perform pressure-wire assessments during cardiac catheterization for NSTEMI patients.

Uses of Resting Physiology

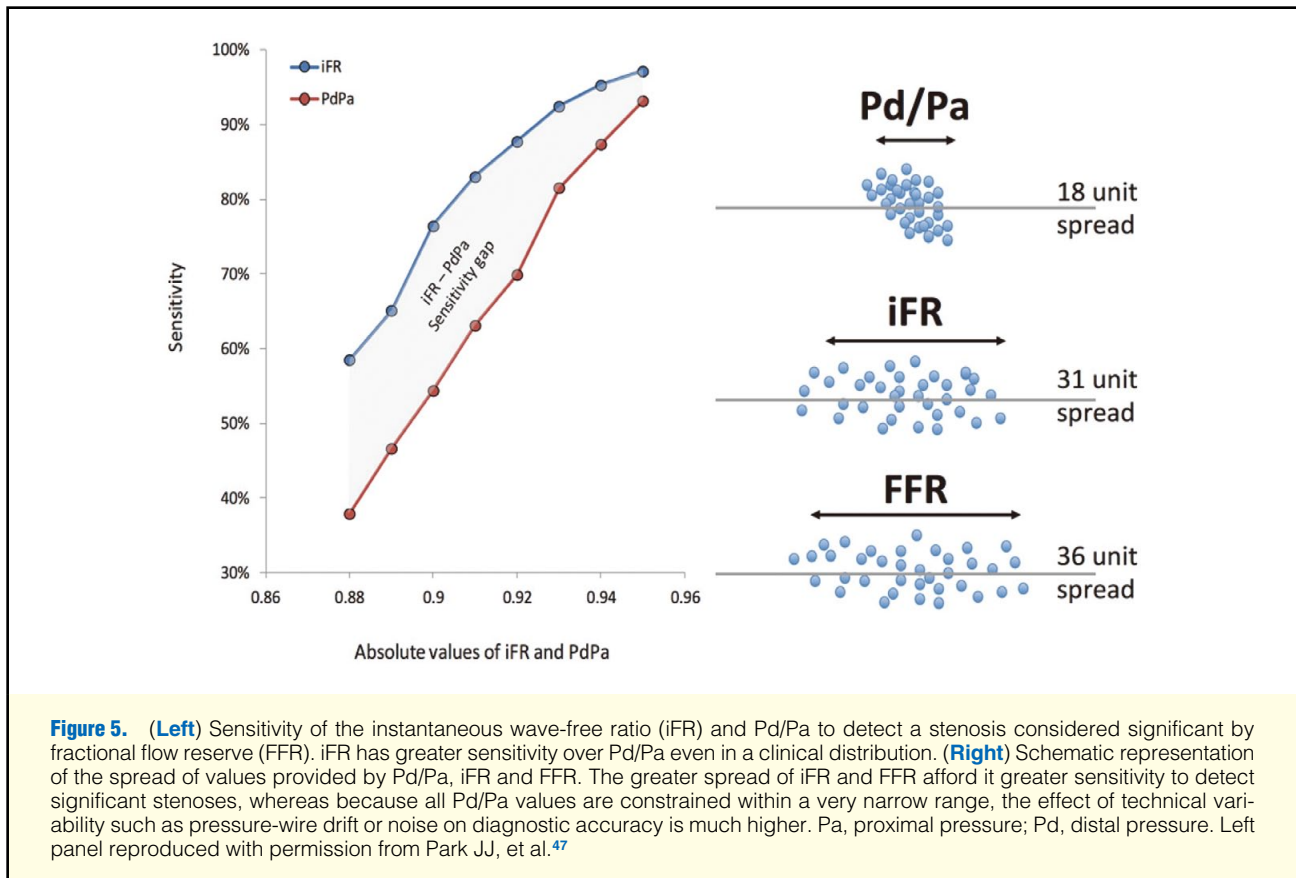
Coronary stenosis assessment at rest has been available since the dawn of coronary intervention,³⁸ but has been limited by bulky low-fidelity equipment. Exogenous hyperemic agents had to be used to aid discrimination between stenoses by increasing flow across them. However, exogenous induction of hyperemia does not increase flow uniformly across all severities of stenosis. Positron emission tomography (PET)-derived quantification of blood flow shows that adenosine increases blood flow most in unobstructed vessels or those with <50% diameter stenosis.³⁹ In those with >50% stenosis, namely those considered for suitable for revascularization, there was no significant increase in flow.³⁹ Resting blood flow was preserved across all severities of stenosis, and this likely occurs by compensatory microcirculatory vasodilatation in response to the stenosis at the expense of Pd, which falls even at rest (Figure 3). Because pressure falls at rest with stenosis severity, then a resting index should be sufficient to quantify severity, provided there is sufficient flow velocity to distinguish between stenoses.

iFR: an Alternative Tool to Assess Stenosis Significance

iFR is a resting index of stenosis severity that provides a physiological quantification of the effect of a stenosis on the coronary circulation. iFR is measured during a specific period of diastole known as the wave-free period, when flow is intrinsically at its highest compared with the whole cycle. By measuring during a higher flow velocity, the capacity to discriminate between stenosis severities at rest is amplified and maximal compared with any other phase of the cardiac cycle.

The wave-free period was originally isolated by application of wave-intensity analysis. Wave intensity demonstrates that the forces propagating from the proximal vessel (the aorta) conflict with those travelling from the distal end (the microcirculation) (Figure 4).^{40,41} Competing interaction between the waves occurs throughout systole and the largest microcirculatory wave occurs at the beginning of diastole to explain why coronary flow is predominantly diastolic. During diastole the waves are quiescent,⁴² and during this wave-free period, microcirculatory resistance is at its lowest and most stable compared with the rest of the cardiac cycle. During this time, pressure and flow velocity are linearly related (Figure 4) and pressure ratios can assess the flow limitation imposed by a stenosis.⁴² The wave-free period exists as a proportion of diastole changing with alterations of the R-R interval. This means that iFR can be calculated during irregular rhythms (eg, atrial fibrillation) and can be calculated for heart rates normally acceptable for physiological assessment (30–130 beats/min).

The ADVISE study⁴² was the first-in-human assessment of



iFR. After describing the wave-free period using combined pressure and flow velocity measurements, computer algorithms were developed to reliably identify the wave-free period using pressure-only technology. The pressure-only iFR algorithm was compared with FFR in 157 stenoses with a good correlation (0.90) and receiver-operating characteristic (ROC) area under the curve (AUC) of 93%.

The ADVISE family of studies demonstrated that in 15–20% cases the iFR, a resting index, was numerically lower than a hyperemic index.^{42,43} This observation may have been underreported in clinical practice because many would avoid hyperemia when the resting gradient was already significant. Similar findings have been observed by Seto et al.⁴⁴ and are explained by the AFFECTS study.¹¹ This phenomenon is more frequent in severe stenoses in which vasodilator reserve is depleted and the trans-stenotic flow is dependent on the proximal driving pressure. Even small hemodynamic perturbations can trigger compensatory microcirculatory vasoconstriction in an effort to preserve perfusion. This is observed as an apparently rising Pd or FFR ratio with continued infusion.

In a small number of cases, a stenosis may have trivial resting gradient but a large hyperemic gradient. Without measurement of flow, this would suggest the resting gradient was “incorrect”. However, coronary flow reserve (CFR) flow studies, whether by PET or invasive measurement, confirm that these events are consistent with a considerable increase in flow across a mild stenosis that gives a false-positive hyperemic pressure gradient (ie, not truly a flow-limiting stenosis). When patients with stenoses such as this are deferred, prognosis appears to be excellent. These concepts are revisited later.

iFR Assessed in Clinical Populations

The ADVISE-Registry compared iFR and FFR in a routine clinical population and found a classification match of 80%,⁴⁵ which is similar to the classification match between repeated measures of FFR in the DEFER study (85% match).⁴⁵ Therefore, the capacity of iFR (or any other index trying to match FFR) to agree with FFR will be constrained by the intrinsic variability of FFR and its capacity to agree with itself. Adjusting for this, taking maximal agreement as 85% (80/85) gives an agreement of 94%.

DEFER suggested FFR classification could change in 15% of cases when measurements were repeated 10 min apart.⁴⁶ Lesser change is noted if measurements are 2 min apart;¹⁰ greater change when 6 weeks apart.³⁵ Values closest to the cut-point have the greatest propensity to change; datasets made up of data-points away from the cut-point will have less change. Datasets in which values around the cut-point appear to be absent have the least change. Because the ADVISE-Registry included unselected consecutive cases performed as part of routine care, the lesion distribution was unimodal with a mean FFR of 0.81 ± 0.09 . With the majority of data-points close to the cut-point, this maximized the chance that small changes in either iFR or FFR would give classification mismatch. Previous FFR validation studies differed: they demonstrated bimodal distributions with a paucity of values at the cut-point.⁴⁵ This would aid validation against other parameters but not be representative of performance in clinical populations and lead to inadvertent bias.

An independent study from South Korea demonstrated similarity to the ADVISE-Registry.⁴⁷ In this rigorously col-

lected dataset, resting indices iFR and the whole-cycle resting Pd/Pa had excellent diagnostic accuracy compared with FFR, with iFR demonstrating greater discriminatory power than Pd/Pa. Pd/Pa values are typically clustered around a narrow range, where even a small artifact or drift will affect the diagnostic efficiency. iFR values for the same dataset were more widely spread, with a dispersion range similar to the FFR, meaning that iFR provided greater diagnostic stability over a wider range (Figure 5).

CLARIFY Study: Assessing the Effect of Hyperemia on the Wave-Free Period

Given the limitations of iFR-FFR comparisons, where the upper limit of agreement will always be determined by the accuracy of the reference parameter, it is reasonable to compare iFR and FFR to third-party parameters of ischemia. The CLARIFY study compared iFR and FFR to the hyperemic stenosis resistance (HSR) index.⁴⁸ The HSR is a combined pressure and flow-velocity index that essentially calculates the gradient of the pressure-flow curve,⁴⁸ as originally described by Gould.⁴⁹ Because it indexes transtenotic gradients by flow velocity, it corrects for false-positive pressure gradients; that is, situations where high flow velocities under hyperemic conditions generate apparently important gradients by turbulence alone without any true flow limitation. In CLARIFY, both iFR and FFR had equal diagnostic efficiency to match an ischemic classification with HSR (both 92%, with no significant difference between the 2 tests).⁵⁰

The CLARIFY study further addressed key questions brought by the cardiology community. One was whether iFR would be lower in the presence of adenosine, and whether the administration of adenosine over the wave-free period with further improve diagnostic categorization. CLARIFY confirmed that iFR could be numerically lower when measured during adenosine-mediated hyperemia (referred to as iFRa) often far lower than the FFR.⁵⁰ During iFRa, microvascular resistance was consistently lower than was achievable by adenosine alone over the whole cardiac cycle; that is, resistance was lower than that measured during FFR.⁵⁰ Therefore, for those who wish to always make measurements at the lowest resistance possible, iFRa is the ideal parameter. However, despite the marked additional reduction in resistance and lower values, iFRa was not diagnostically superior to iFR. There was no statistical differences among iFRa, FFR and iFR in diagnosing ischemia when compared to the third-party hyperemic ischemia parameter, HSR.⁴⁸ The optimal threshold for ischemia for iFRa was 0.66, corresponding to its much lower values. The implication is that it is certainly possible to elicit lower numbers by combining hyperemia with the wave-free period, but there is no diagnostic advantage in doing so.

CLARIFY confirmed the findings of PET studies showing that adenosine increased flow most in mild stenoses: in CLARIFY, invasive assessment of microvascular resistance showed that mild stenoses had the greatest response to adenosine, with limited effect in significant stenoses.⁵⁰ In contrast, the wave-free period had a more consistent reduction in microvascular resistance across all severities. In stenoses classed as ischemic by HSR, there was no difference in the resistance reduction offered by adenosine and the wave-free period.⁵⁰ In nonsignificant stenoses, adenosine hyperemia produced a greater reduction in resistance than offered by the wave-free period, but without any additional diagnostic advantage, as the classification match was identical between parameters.⁵⁰ This suggests that the wave-free period provides sufficient information for diagnostic classification of stenosis

severity and that the addition of hyperemia adds little.

iFR Comparative Studies With Markers of Ischemia

During the validation of FFR, it was evaluated against noninvasive parameters of ischemia such as exercise testing⁵¹ and PET. In many cases, these noninvasive parameters were themselves validated by their capacity to detect anatomical coronary disease. To avoid circular arguments, third-party assessments provide an alternative arbiter of ischemia. iFR has now been compared with other parameters of ischemia in a number of studies. Each demonstrates that a resting index has the capacity to provide as much information as a hyperemic index, even when compared with a reference standard that requires hyperemic stress.

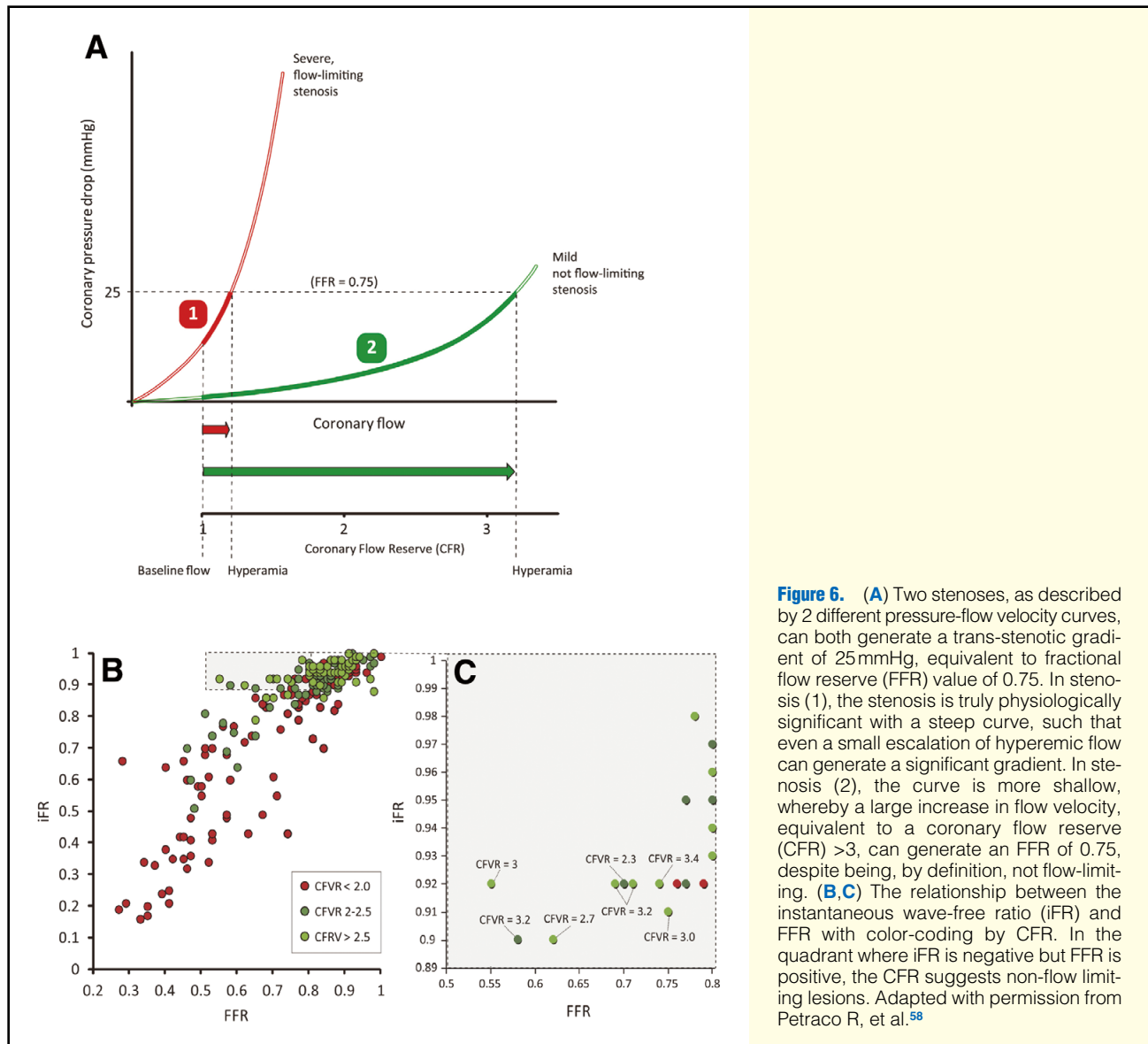
The CLARIFY study has already been discussed, and demonstrated equivalent capacity of iFR and FFR to assess ischemia classified by HSR.⁵⁰ A second, larger study similarly assessed iFR and FFR against HSR in 120 stenoses. In that study, iFR was found to have a significant higher classification match than FFR (89% vs. 82%, $P < 0.01$).⁵²

A third study assessed iFR, FFR and the basal stenosis resistance (BSR) index⁵³ against a comprehensive combined ischemic reference of myocardial perfusion scintigraphy (MPS) and HSR.⁵⁴ Stenoses were considered ischemic if both the MPS and HSR were positive, which is pertinent because it confirms both a perfusion maldistribution (MPS) as well as an epicardial stenosis (HSR) as the source of the perfusion defect. No significant difference was found between each index,⁵⁴ and the results were consistent with other nonselective cohorts using MPS.⁵⁵

A fourth study compared iFR and FFR against PET, which is recognized as the gold standard for quantifying myocardial blood flow (MBF).⁵⁶ De Waard et al performed ($[^{15}\text{O}]\text{H}_2\text{O}$) PET imaging in 34 patients with 49 intermediate coronary stenoses followed by invasive pressure-wire assessment. Both iFR and FFR had a 76% classification agreement with PET, and both had similar AUC for ROC analysis (0.85 for FFR and 0.86 for iFR, $P = 0.71$).⁵⁶ Both iFR and FFR had an identical pattern of agreement and disagreement with PET MBF. This is a remarkable finding and akin to the finding that FFR was related to MBF on PET imaging in 22 patients, which validated FFR as a test for ischemia.⁵⁷

Finally, iFR and FFR have been compared with invasive CFR.⁵⁸ Calculated using a Doppler flow-velocity wire and presented as a ratio of hyperemic flow-velocity to resting flow-velocity, CFR is a strongly prognostic index.⁵⁹ $\text{CFR} > 2$ is non-flow-limiting whereas less than this suggests a significant stenosis. When iFR, FFR and CFR were measured in 216 stenoses, iFR had closer agreement with CFR than does FFR, with a statistically significant higher AUROC (iFR 0.82 vs. FFR 0.72, $P < 0.001$).⁵⁸ Even when constrained to the physiological range of 0.60–0.90, iFR maintained a stronger association with CFR than FFR (AUROC 0.78 vs. 0.59, $P < 0.001$).⁵⁸ This suggests iFR has a closer association with both hyperemic flow velocity and CFR than FFR. This is understood when it is appreciated that significant FFR values can occur in the presence of high flow velocity across a mild but not flow-limiting stenosis (Figure 6). This mechanism may account for discrepancies between iFR and FFR. In the JUSTIFY-CFR cohort, when iFR was negative and FFR was positive, $\text{CFR} > 2$ was noted in 97% of cases (Figure 6). These findings suggest that when iFR and FFR appear to disagree, iFR provides a greater degree of information about the state of coronary flow than does FFR.

These findings support the concern many physiologists



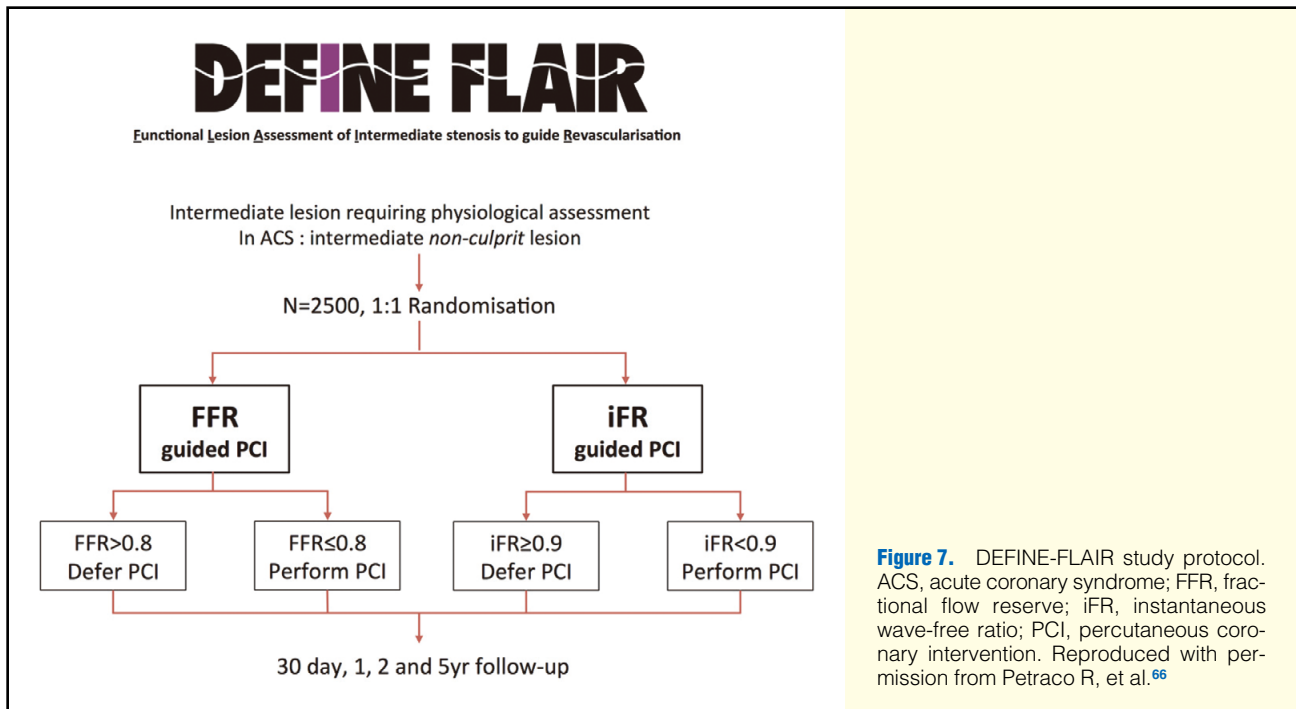
have expressed for some time: that FFR has only modest agreement with CFR.⁶⁰ Johnson et al studied 438 stenoses and found FFR and CFR matched only in 60%.⁶⁰ There are 2 areas of discrepancy to consider: when FFR is positive (≤ 0.80) but the CFR is normal (>2.0), and second, when FFR is negative (>0.80) but the CFR is abnormal (<2.0). The first situation is vexing, as the pressure-based index suggests revascularization while the flow-based index shows the flow can increase sufficiently without intervention.

One possible explanation of the discrepancies between FFR and CFR has been inadequate hyperemia. Because both indices require maximal hyperemia, in the same manner that FFR is affected by inadequate hyperemia, CFR readings may underestimate true flow values. This has been suggested because many studies have used lower doses of intracoronary adenosine than are currently used in practice. However, giving further vasodilator to increase hyperemic flow would mean both indices move even further in opposite directions: FFR would become more positive ($\text{FFR} < 0.80$) and CFR would become more negative ($\text{CFR} > 2.0$). Therefore, the discrepancy cannot

be resolved by higher doses. Furthermore, higher doses could mean assessments that are congruent could become incongruent: an FFR value close to 0.80 with a $\text{CFR} > 2.0$ with higher doses could have an FFR that dips below 0.80 while CFR will only rise.

Although FFR has outcome data, such discrepancies are under-described in FFR trials. Van de Hoef et al reported 10-year follow-up data of patients with discrepant pressure and flow measurements who were deferred for PCI. In those with a positive FFR (≤ 0.80) but normal CFR (>2.0), MACE rates were no different from those in patients with a negative FFR (>0.80) and a normal CFR (>2.0).⁶¹ That is, managing these patients according to their normal flow value achieved the same result regardless of the FFR.⁶¹ Those with a negative FFR (>0.80) but abnormal CFR (<2.0) had very high MACE rates, suggesting this pool of patients are not getting appropriate revascularization. This finding may account for the highly variable event rate (2.5–11% at 1 year) reported after deferring stenoses with $\text{FFR} > 0.80$.⁶²

By combining iFR and FFR it is possible to more closely



attain an estimate of hyperemic flow. If the iFR is negative and FFR is positive, the data suggest these stenoses are likely to represent those with high probability (97%) of CFR >2.0 for which clinical outcomes are identical between PCI and deferral.^{58,61} Whereas if the iFR is positive and the FFR negative, this suggests a low CFR.^{58,61} In such cases it may be prudent to revascularize if anatomically feasible; further studies assessing the value of this are underway.

Clinical Application of iFR: Using the iFR-FFR Hybrid Approach

While awaiting outcome data, a prudent application of iFR in the clinical setting is to apply the hybrid iFR-FFR strategy.⁶³ The aim is to achieve a high diagnostic agreement with FFR that has outcome data, while reducing the need to administer adenosine. iFR is measured in all patients; if the value found is within a narrow range then adenosine is administered to calculate FFR. Many different hybrid iFR-FFR approaches are possible according to the classification match sought: a match of 95% requires adenosine if iFR values are between 0.86 and 0.93, sparing almost 60–70% of patients from adenosine administration.^{63–65}

External validity of the iFR-FFR hybrid approach has been provided by ADVISE-II and the ADVISE-In-Practice studies. ADVISE-II was a prospective global double-blind multicenter study of 690 truly intermediate stenoses (mean FFR 0.83 ± 0.11).^{64,65} In nearly 70% of cases, adenosine administration could be avoided by using the hybrid approach while maintaining 94% overall classification match with an FFR-only approach. ADVISE-In-Practice was the first study to use the commercially available iFR console.⁶⁶ In this international, multicenter study of 392 stenoses in 313 patients, iFR had a high classification match with FFR (80% using the FFR 0.80 cut-point; 88% with ischemic threshold of 0.75 and 92% if the FFR gray-zone was accounted for).⁶⁶ Using the hybrid approach, 61% of the patients could be spared from adenosine, with a

94% classification match with FFR.⁶⁶

The hybrid approach has been adopted in routine clinical practice and is being used in SYNTAX-II (NCT 02015832)⁶⁷ in which 3-vessel disease on angiography will undergo revascularization according to the physiological findings on iFR-FFR assessment. Because physiological assessment can convert angiographic 3-vessel disease to lesser severities,^{26,68} SYNTAX-II may show that rapid assessment with iFR-FFR can assist in focusing revascularization to functionally important stenoses in patients otherwise treated surgically.

Clinicians experienced in using iFR are increasingly using it alone as a single physiological parameter, with a single threshold of significance (an iFR <0.90 is treated with revascularization, whereas iFR ≥0.90 is deferred). These thresholds were determined against an FFR threshold of 0.80 in the large and independent RESOLVE study, which combined many different datasets.⁶⁹ The validity and safety of such an approach is being assessed in 2 international studies: DEFINE-FLAIR³⁰ and the iFR-SWEDEHEART.⁷⁰

Ongoing Outcome Studies Using iFR

Clinical outcomes studies are underway to determine the safety of using an iFR-only approach to guide revascularization.

DEFINE-FLAIR is a multicenter international, double-blind outcome study that will be the largest physiology study performed to date (Figure 7): 2,500 patients with intermediate stenoses will be randomized to either an iFR-guided approach (treatment threshold iFR <0.90) or an FFR-guided approach (treatment threshold FFR ≤0.80). Both stable patients and those with ACS (nonculprit vessels) are included. The study is powered to test MACE at 1 year for noninferiority between iFR and FFR. FLAIR is unique because not only will the patients be blinded to the physiological parameter used, but those performing patient follow-up will also be blinded. Other endpoints include the cost efficiencies between iFR and FFR.

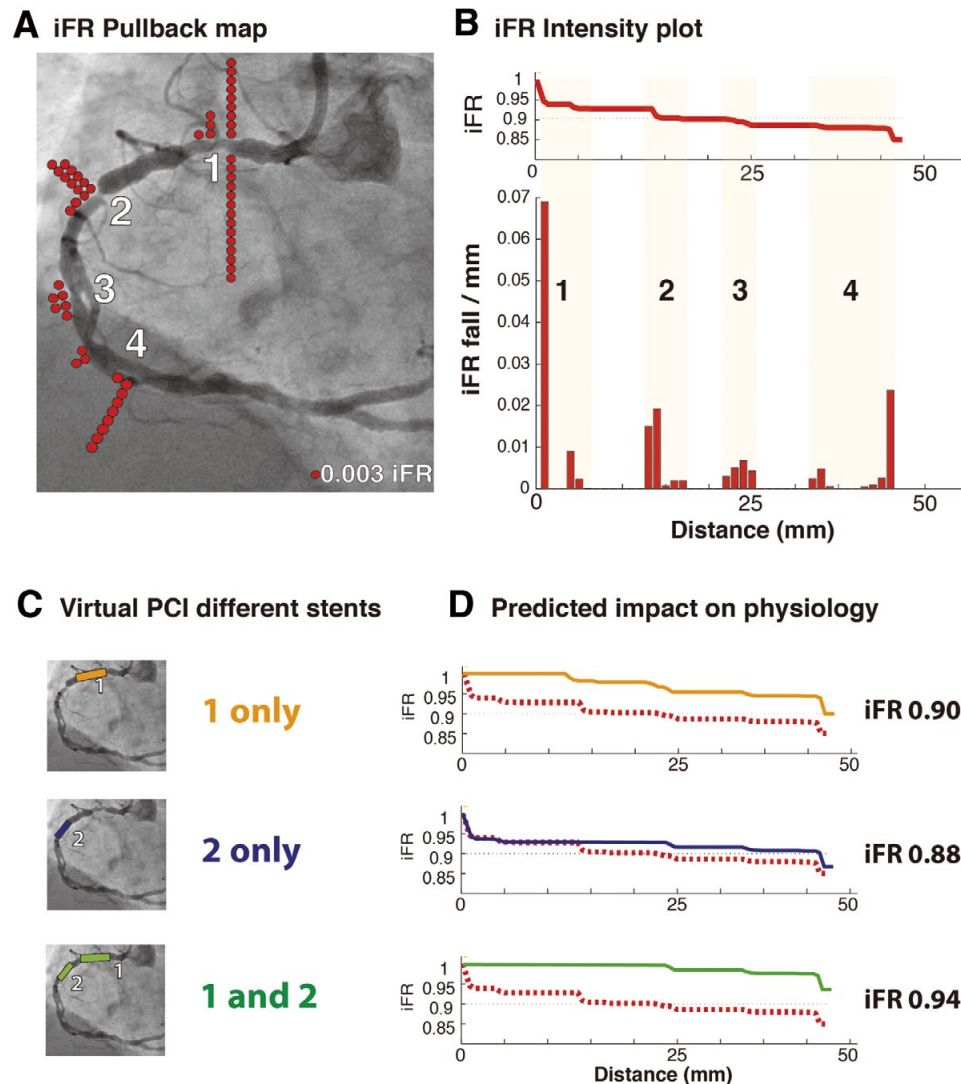


Figure 8. (A) The iFR-Pullback data can be mapped onto the coronary angiogram with pressure loss or iFR intensity plotted as red dots to demonstrate colocalization with the angiographic stenosis. (B) The iFR Intensity can be plotted separately with a measure of physiological lesion length. (C) Virtual-PCI can be performed by selective removal of a stenosis. (D) The expected result of removing a stenosis can be plotted with the prediction of the post-PCI iFR to enable the best stenting option to be selected. iFR, instantaneous wave-free ratio; PCI, percutaneous coronary intervention. Adapted with permission from Nijer SS, et al.⁷⁶

The iFR-SWEDEHEART (NCT 02166736) study is simultaneously being performed in Sweden as part of the pioneering Swedeheart registry. In this study, 2000 patients will be randomized to either iFR or FFR and have follow-up within the registry system. Because the clinical outcomes and study design have been harmonized with those of DEFINE-FLAIR, the combined studies will provide data on 4,500 patients and approximately 7,500 coronary stenoses.

iFR in ACS

At present, iFR has very limited data in the setting of ACS. The FORECAST study is an independent study using offline iFR calculation that demonstrated the feasibility of iFR measurements in nonculprit vessels in ACS patients.⁷¹ In 123

stenoses in 82 patients with ACS and stable disease, an iFR threshold of 0.92 best matched an FFR of 0.80 with a diagnostic concordance with FFR of 81.3%.⁷¹ No difference in diagnostic efficiency between ACS patients and those with stable disease was found and all apparent discrepancies were within the FFR 0.75–0.80 gray-zone.⁷¹ Furthermore, when using a hybrid iFR-FFR approach, they found 68% of patients would be spared adenosine. Further data will come from the DEFINE-FLAIR study, which is including patients with ACS.

iFR-Pullback and Virtual-PCI

iFR can be calculated beat-to-beat during pressure-wire pullback, which enables the identification of stenoses and their physiological significance at rest without the need for a long

infusion of hyperemic agent. The first iFR-Pullback study⁷² suggested important advantages to performing a resting pull-back.

During resting conditions there is less flow interaction between stenoses. Hyperemic flow velocity is readily attenuated by the presence of any stenosis; even minor or diffuse disease can reduce the level of hyperemic flow compared to the flow levels found in normal vessels. Therefore even trivial stenoses or diffuse disease have the capacity to confound hyperemic assessments pressure assessments.^{73–76} In the resting state, resting coronary flow is preserved despite the presence of even severe stenoses;³⁹ this suggests a transtenotic pressure drop distal to a stenosis will be resultant only from stenoses proximal to the pressure sensor with less confounding from distal disease. If iFR-Pullback is performed, all the gradients in the vessel can be determined to quantify the severity of each lesion in the vessel.

This leads to an exciting new domain. Computer ‘Virtual-PCI’ algorithms can ‘remove’ a stenosis on an iFR-Pullback trace (Figure 8) and then compute the residual gradients to estimate an expected post-PCI iFR,⁷⁶ under the assumption that any intervention is perfect without any residual gradient in the treated segment.⁷² In the first iFR-Pullback study, real-world post-PCI iFR values could be predicted with high accuracy and without a significant systematic bias.⁷²

The predicted value could provide a target physiological value for the real-world intervention. The process could also permit the evaluation of the potential physiological benefit of multiple different ‘virtual’ stenting strategies. Potentially acceptable physiological results could be achieved by a more limited stenting approach (potentially reducing stented-related complications). Alternatively, iFR-Pullback could reveal more extensive stenting is required to achieve hemodynamic improvement.

This technology is rapidly advancing, thanks to simultaneous developments in pressure-wires, computing power, X-ray imaging and angiographic co-registration systems. Computer tracking of pressure-wire movement could allow manual hand-guided pullback with simultaneous live angiographic co-registration. This would facilitate ease of use and rapid decision making.

Practical Use of Resting Indices

All resting measurements should adequate nitrates have been given to ensure epicardial stability, ensure pressure normalization (‘equalization’) has been performed, and avoid wire manipulation during measurement. Patients were not routinely sedated for any of the ADVISE family of studies; all measurements were simply made with a pressure wire without hyperemic agent administration.

Active normalization for iFR is essential because not only must the pressure ratio be 1.0 at the ostium, but any phase-delays between the traces must be removed; measurements with phase delays can invoke significant error.⁶⁶

Intracoronary nitrates are used not to produce hyperemia, rather to maximize epicardial vessel diameter, and to prevent wire-induced spasm, which can induce a pseudo-stenosis. After any injection of contrast or nitrate, a short delay of 15–20s should be allowed prior to measurement; because nitrates should be administered soon after guide catheter engagement, there is no practical delay, as this time elapses with wire preparation and passage through the catheter. After PCI, the process of balloon removal, re-administration of nitrates and flushing of the catheter is sufficient to allow a

resting state to be restored to allow measurement. If adenosine has been administered, time should be allowed for recovery, which can vary among patients. Finally, manipulation of the wire or pressure manifolds during readings, whether at rest or hyperemia, will alter the values and should be avoided.

Conclusions

There has been an exciting renewal of interest in coronary physiology. Despite the complexity inherent to detailed interrogation of vessel ischemia, patient outcomes are expected to improve. Established technologies such as FFR should be promoted, but with awareness of potential pitfalls. New, potentially disruptive technologies such as iFR may simplify physiological assessment in the catheter laboratory and provide significant added benefit with iFR-Pullback with Virtual-PCI.

Acknowledgments

The authors thank Dr Rasha Al-Lamee, Dr Jason Tarkin and Dr Christopher Cook.

Disclosures

Dr Justin Davies, Consultant to Volcano Corporation and Medtronic. Dr Justin Davies and Imperial College own intellectual property regarding iFR, which is licensed by the Imperial College to Volcano Corporation. Imperial College London is coordinating the FLAIR study, which is supported by an unrestricted grant from Volcano Corporation. All the authors have had travel expenses to conferences supported by industry, including Volcano Corporation, St Jude Medical, Medtronic, Pfizer and Astra Zeneca.

Funding

This review was supported by the Medical Research Council (UK), British Heart Foundation (BHF) and the NIHR Imperial Biomedical Research Centre.

References

1. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van't Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360**: 213–224.
2. Fearon WF, Bornschein B, Tonino PAL, Gothe RM, Bruyne BD, Pijls NHJ, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation* 2010; **122**: 2545–2550.
3. Puymirat E, Muller O, Sharif F, Dupouy P, Cuisset T, de Bruyne B, et al. Fractional flow reserve: Concepts, applications and use in France in 2010. *Arch Cardiovasc Dis* 2010; **103**: 615–622.
4. Patel MR, Rao SV. Ischemia-driven revascularization: Demonstrating and delivering a mature procedure in a mature way. *Circ Cardiovasc Qual Outcomes* 2013; **6**: 250–252.
5. Kim YH, Park SJ. Ischemia-guided percutaneous coronary intervention for patients with stable coronary artery disease. *Circ J* 2013; **77**: 1967–1974.
6. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; **34**: 2949–3003.
7. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate Use Criteria for Coronary Revascularization – Focused Update: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2012; **59**: 857–881.
8. Nallamothu BK, Tommaso CL, Anderson HV, Anderson JL, Cleveland JC, Dudley RA, et al. ACC/AHA/SCAI/AMA – Convened PCPI/NCQA 2013 Performance Measures for Adults Undergoing Percutaneous Coronary Intervention: A report of the American

- College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convended Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. *Circulation* 2014; **129**: 926–949.
9. Koo BK. The present and future of fractional flow reserve. *Circ J* 2014; **78**: 1048–1054.
 10. Pijls NHJ. Fractional flow reserve to guide coronary revascularization. *Circ J* 2013; **77**: 561–569.
 11. Tarkin JM, Nijjer S, Sen S, Petraco R, Echavarria-Pinto M, Asress KN, et al. Hemodynamic response to intravenous adenosine and its effect on fractional flow reserve assessment: Results of the Adenosine for the Functional Evaluation of Coronary Stenosis Severity (AFFECTS) Study. *Circ Cardiovasc Interv* 2013; **6**: 654–661.
 12. Biaggioni I. Contrasting excitatory and inhibitory effects of adenosine in blood pressure regulation. *Hypertension* 1992; **20**: 457–465.
 13. Echavarria-Pinto M, Petraco R, van de Hoef TP, Gonzalo N, Nijjer S, Tarkin JM, et al. Fractional flow reserve and minimum Pd/Pa ratio during intravenous adenosine infusion: Very similar but not always the same. *EuroIntervention* 2014 October 22, doi:10.4244/EIJY14M10_09.
 14. Lim WH, Koo BK, Nam CW, Doh JH, Park JJ, Yang HM, et al. Variability of fractional flow reserve according to the methods of hyperemia induction. *Catheter Cardiovasc Interv* 2014 November 20, doi:10.1002/ccd.25752.
 15. Chamuleau SAJ, Siebes M, Meuwissen M, Koch KT, Spaan JAE, Piek JJ. Association between coronary lesion severity and distal microvascular resistance in patients with coronary artery disease. *Am J Physiol Heart Circ Physiol* 2003; **285**: H2194–H2200.
 16. Gould KL, Lipscomb K, Calvert C. Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. *Circulation* 1975; **51**: 1085–1094.
 17. Hospices Civils de Lyon. Functional Testing Underlying Coronary Revascularisation (FUTURE) [Internet]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2013 [cited 2014 Dec 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01881555> (accessed December 30, 2014).
 18. Siebes M, Chamuleau SAJ, Meuwissen M, Piek JJ, Spaan JAE. Influence of hemodynamic conditions on fractional flow reserve: Parametric analysis of underlying model. *Am J Physiol Heart Circ Physiol* 2002; **283**: H1462–H1470.
 19. Pijls NH, van Son JA, 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**: 1354–1367.
 20. De Luca G, Venegoni L, Iorio S, Giuliani L, Marino P. Effects of increasing doses of intracoronary adenosine on the assessment of fractional flow reserve. *JACC Cardiovasc Interv* 2011; **4**: 1079–1084.
 21. Jeremias A, Filardo SD, Whitbourn RJ, Kernoff RS, Yeung AC, Fitzgerald PJ, et al. Effects of intravenous and intracoronary adenosine 5'-triphosphate as compared with adenosine on coronary flow and pressure dynamics. *Circulation* 2000; **101**: 318–323.
 22. Bruyne BD, Pijls NHJ, Barbato E, Bartunek J, Bech JW, Wijns W, et al. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation* 2003; **107**: 1877–1883.
 23. Toth G, Hamilos M, Pyxaras S, Mangiacapra F, Nelis O, De Vroey F, et al. Evolving concepts of angiogram: Fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J* 2014; **35**: 2831–2838.
 24. Jeremias A, Whitbourn RJ, Filardo SD, Fitzgerald PJ, Cohen DJ, Tuzcu EM, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J* 2000; **140**: 651–657.
 25. Koo BK, Kim CH, Na SH, Youn TJ, Chae IH, Choi DJ, et al. Intracoronary continuous adenosine infusion. *Circ J* 2005; **69**: 908–912.
 26. Curzen N, Rana O, Nicholas Z, Gollidge P, Zaman A, Oldroyd K, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain? The RIPCOR Study. *Circ Cardiovasc Interv* 2014; **7**: 248–255.
 27. Van Belle E, Rioufol G, Pouillot C, Cuisset T, Bougrini K, Teiger E, et al. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: Insights from a large French multicenter fractional flow reserve registry. *Circulation* 2014; **129**: 173–185.
 28. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012; **367**: 991–1001.
 29. De Bruyne B, Fearon WF, Pijls NHJ, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014; **371**: 1208–1217.
 30. Imperial College London. Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation (DEFINE-FLAIR) [Internet]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2013 [cited 2014 Dec 28]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02053038> (accessed December 28, 2014).
 31. Shiono Y, Kubo T, Tanaka A, Ino Y, Yamaguchi T, Tanimoto T, et al. Long-term outcome after deferral of revascularization in patients with intermediate coronary stenosis and gray-zone fractional flow reserve. *Circ J* 2014; **79**: 91–95.
 32. Courtis J, Rodés-Cabau J, Larose E, Déry JP, Nguyen CM, Proulx G, et al. Comparison of medical treatment and coronary revascularization in patients with moderate coronary lesions and borderline fractional flow reserve measurements. *Catheter Cardiovasc Interv* 2008; **71**: 541–548.
 33. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, et al. Prognostic value of fractional flow reserve: Linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014; **64**: 1641–1654.
 34. Shah NR, Al-Lamee R, Davies J. Fractional flow reserve in acute coronary syndromes: A review. *JACC Heart Vasc* 2014; **5**: 20–25.
 35. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010; **3**: 1274–1281.
 36. Cuculi F, De Maria GL, Meier P, Dall'Armellina E, de Caterina AR, Channon KM, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2014; **64**: 1894–1904.
 37. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: The British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J* 2015; **36**: 100–111.
 38. Grüntzig A, Senning A, Siegenthaler W. Nonoperative dilatation of coronary-artery stenosis: Percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979; **301**: 61–68.
 39. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med* 1994; **330**: 1782–1788.
 40. Davies JE. Evidence of a dominant backward-propagating “suction” wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation* 2006; **113**: 1768–1778.
 41. Hadjiloizou N, Davies JE, Malik IS, Aguado-Sierra J, Willson K, Foale RA, et al. Differences in cardiac microcirculatory wave patterns between the proximal left mainstem and proximal right coronary artery. *Am J Physiol Heart Circ Physiol* 2008; **295**: H1198–H1205.
 42. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis. *J Am Coll Cardiol* 2012; **59**: 1392–1402.
 43. Nijjer SS, Sen S, Petraco R, Sachdeva R, Cuculi F, Escaned J, et al. Improvement in coronary haemodynamics after percutaneous coronary intervention: Assessment using instantaneous wave-free ratio. *Heart* 2013; **99**: 1740–1748.
 44. Seto AH, Tehrani DM, Bharmal MI, Kern MJ. Variations of coronary hemodynamic responses to intravenous adenosine infusion: Implications for fractional flow reserve measurements. *Catheter Cardiovasc Interv* 2014; **84**: 416–425.
 45. Petraco R, Escaned J, Sen S, Nijjer S, Asress KN, Echavarria-Pinto M, et al. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: Results of the ADVISE registry. *EuroIntervention* 2013; **9**: 91–101.
 46. Petraco R, Sen S, Nijjer S, Echavarria-Pinto M, Escaned J, Francis DP, et al. Fractional flow reserve-guided revascularization: Practical implications of a diagnostic gray zone and measurement variability on clinical decisions. *JACC Cardiovasc Interv* 2013; **6**: 222–225.
 47. Park JJ, Petraco R, Nam CW, Doh JH, Davies J, Escaned J, et al. Clinical validation of the resting pressure parameters in the assessment of functionally significant coronary stenosis: Results of an independent, blinded comparison with fractional flow reserve. *Int J Cardiol* 2013; **168**: 4070–4075.
 48. Meuwissen M, Siebes M, Chamuleau SAJ, van Eck-Smit BLF, Koch

- KT, de Winter RJ, et al. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. *Circulation* 2002; **106**: 441–446.
49. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res* 1978; **43**: 242–253.
 50. Sen S, Assres KN, Nijjer S, Petraco R, Malik IS, Foale RA, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration: Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). *J Am Coll Cardiol* 2013; **61**: 1409–1420.
 51. Plein S, Motwani M. Fractional flow reserve as the reference standard for myocardial perfusion studies: Fool's gold? *Eur Heart J Cardiovasc Imaging* 2013; **14**: 1211–1213.
 52. Sen S, Nijjer S, Petraco R, Malik IS, Francis DP, Davies J. Instantaneous wave-free ratio: Numerically different, but diagnostically superior to FFR? Is lower always better? *J Am Coll Cardiol* 2013; **62**: 566.
 53. Van de Hoef TP, Nolte F, Damman P, Delewi R, Bax M, Chamuleau SAJ, et al. Diagnostic accuracy of combined intracoronary pressure and flow velocity information during baseline conditions: Adenosine-free assessment of functional coronary lesion severity. *Circ Cardiovasc Interv* 2012; **5**: 508–514.
 54. van de Hoef TP, Meuwissen M, Escaned J, Sen S, Petraco R, van Lavieren MA, et al. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: Diagnostic accuracy for stenosis-specific myocardial ischemia. *EuroIntervention* 2014 August 30, doi:10.4244/EIJY14M08_17.
 55. Yanagisawa H, Chikamori T, Tanaka N, Hatano T, Morishima T, Hida S, et al. Correlation between thallium-201 myocardial perfusion defects and the functional severity of coronary artery stenosis as assessed by pressure-derived myocardial fractional flow reserve. *Circ J* 2002; **66**: 1105–1109.
 56. De Waard G, Danad I, da Cunha RP, Teunissen P, van de Hoef T, Rajmakers P, et al. Hyperemic FFR and baseline iFR have an equivalent diagnostic accuracy when compared to myocardial blood flow quantified by [¹⁵O]H₂O PET perfusion imaging. *J Am Coll Cardiol* 2014; **63**: A1692.
 57. Bruyne BD, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans: Validation with positron emission tomography. *Circulation* 1994; **89**: 1013–1022.
 58. Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: Results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). *Circ Cardiovasc Interv* 2014; **7**: 492–502.
 59. Chamuleau SAJ, Tio RA, de Cock CC, de Muinck ED, Pijls NHJ, van Eck-Smit BLF, et al. Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. *J Am Coll Cardiol* 2002; **39**: 852–858.
 60. Johnson NP, Kirkeeide RL, Gould KL. Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? *JACC Cardiovasc Imaging* 2012; **5**: 193–202.
 61. van de Hoef TP, van Lavieren MA, Damman P, Delewi R, Piek MA, Chamuleau SAJ, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv* 2014; **7**: 301–311.
 62. Depta JP, Patel JS, Novak E, Gage BF, Masrani SK, Raymer D, et al. Risk model for estimating the 1-year risk of deferred lesion intervention following deferred revascularization after fractional flow reserve assessment. *Eur Heart J* 2015; **36**: 509–515.
 63. Petraco R, Park JJ, Sen S, Nijjer SS, Malik IS, Echavarría-Pinto M, et al. Hybrid iFR-FFR decision-making strategy: Implications for enhancing universal adoption of physiology-guided coronary revascularisation. *EuroIntervention* 2013; **8**: 1157–1165.
 64. Escaned J. ADVISE II: Late Breaking Clinical Trials. TCT 2013 Oral Presentation. <http://www.tctmd.com/show.aspx?id=122086> (accessed April 5, 2015).
 65. Escaned J, Mauro EP, García-García HM, Van de Hoef TP, de Vries T, Kaul P, et al. Prospective assessment of the diagnostic accuracy of the instantaneous wave-free ratio to assess coronary stenosis relevance: Results of ADVISE II (ADenosine Vasodilator Independent Stenosis Evaluation II), an International Multicenter Study. *JACC Cardiovasc Interv* 2015 (in press).
 66. Petraco R, Al-Lamee R, Gotberg M, Sharp A, Hellig F, Nijjer SS, et al. Real-time use of instantaneous wave-free ratio: Results of the ADVISE in-practice. An international, multicenter evaluation of instantaneous wave-free ratio in clinical practice. *Am Heart J* 2014; **168**: 739–748.
 67. European Cardiovascular Research Institute. A trial to evaluate a new strategy in the functional assessment of 3-vessel disease using the SYNTAX II score in patients treated with PCI [Internet]. Bethesda (MD): National Library of Medicine (US); 2014 [cited 2014 Dec 28]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02015832> (accessed December 28, 2014).
 68. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PAL, et al. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 2011; **58**: 1211–1218.
 69. Jeremias A, Maehara A, Gèneux P, Assres KN, Berry C, De Bruyne B, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: The RESOLVE Study. *J Am Coll Cardiol* 2014; **63**: 1253–1261.
 70. Uppsala University. Evaluation of iFR vs. FFR in stable angina or acute coronary syndrome (iFR Swedeheart) [Internet]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2014 [cited 2014 Dec 28]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02166736> (accessed December 28, 2014).
 71. Indolfi C, Mongiardo A, Spaccarotella C, Torella D, Caiazzo G, Polimeni A, et al. The instantaneous wave-free ratio (iFR) for evaluation of non-culprit lesions in patients with acute coronary syndrome and multivessel disease. *Int J Cardiol* 2015; **178**: 46–54.
 72. Nijjer SS, Sen S, Petraco R, Escaned J, Echavarría-Pinto M, Broyd C, 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**: 1386–1396.
 73. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* 1974; **34**: 48–55.
 74. Bruyne BD, Pijls NHJ, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-derived fractional flow reserve to assess serial epicardial stenoses theoretical basis and animal validation. *Circulation* 2000; **101**: 1840–1847.
 75. Pijls NHJ, Bruyne BD, Bech GJW, Liistro F, Heyndrickx GR, Bonnier HJRM, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery validation in humans. *Circulation* 2000; **102**: 2371–2377.
 76. Nijjer SS, Sen S, Petraco R, Allamee R, Mayet J, Francis DP, et al. The instantaneous wave-free ratio (iFR) pullback: A novel innovation using baseline physiology to optimise coronary angioplasty in tandem lesions. *Cardiovasc Revasc Med* 2015 January 29, doi: 10.1016/j.carrev.2015.01.006.