Cardiovascular Intervention and Therapeutics (2019) 34:85–96
https://doi.org/10.1007/s12928-018-0559-0

EXPERT CONSENSUS DOCUMENT

Clinical use of physiological lesion assessment using pressure guidewires: an expert consensus document of the Japanese Association of Cardiovascular Intervention and Therapeutics

Yoshiaki Kawase[1] · Hitoshi Matsuo[1] · Takashi Akasaka[1] · Yasutsugu Shiono[1] · Nobuhiro Tanaka[1] · Tetsuya Amano[1] · Ken Kozuma[1] · Masato Nakamura[1] · Hiroyoshi Yokoi[1] · Yoshio Kobayashi[1] · Yuji Ikari[1]

Received: 20 November 2018 / Accepted: 20 November 2018 / Published online: 27 December 2018

Abstract
In this document, the background, concept, and current evidence are briefly summarized. The focus is on the clinical application of physiological lesion assessment from a practical standpoint for facilities that do not have ample experience. Finally, the characteristics of new resting indexes are summarized.

Keywords Coronary circulation · Coronary artery disease · Fractional flow reserve · Instantaneous wave-free ratio

Introduction

Fractional flow reserve (FFR) has become a gold standard index for the invasive assessment of physiological severity of coronary artery stenosis. Coronary angiography is the traditional imaging modality for visual evaluation of coronary lesion severity and guidance of percutaneous coronary interventions (PCI)s. However, coronary angiography is in reality a two-dimensional shadowgraph of the vessel lumen. It cannot depict the arterial vessel wall or plaque burden. Moreover, it cannot approximate the amount of myocardium subtended by the target vessel. Without a proper assessment of physiological lesion severity, PCIs might mitigate its preferable effects on patient outcome [1].

Considering the importance of discriminating the lesions most likely to derive clinical benefit from PCIs, the Japanese Central Social Insurance Medical Council has changed the requirement for the reimbursement of PCIs in April 2018.

Following this change, the role of physiological lesion assessment in catheter laboratories is expected to increase considering the low penetration rate of the non-invasive physiological test in Japan.

In addition, a new hyperemia-free index as an indication of PCIs, namely instantaneous wave-free period (iFR) has recently been validated and its non-inferiority in the prediction of 1-year outcome of FFR with the results of Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) and iFR Swedish angiography and angioplasty registry (SWEDEHEART) has been demonstrated [2, 3].

However, there are many catheter laboratories that do not have adequate experience with physiological lesion assessment using pressure guidewires. In addition, there are many differences in clinical situations between Japan and Western countries (available drugs, the timing of physiological lesion assessment, etc.). In this document we summarize not only the current evidence but also the practical use of physiological lesion assessment in Japan.

Concept of fractional flow reserve

The basic concept of FFR is presented in Fig. 1. The linear relationship between perfusion pressure and blood flow only exists when maximum hyperemia is achieved, although these correlations can be theoretically applicable in diastole [4, 5]. Therefore, the blood flow that passes through the stenosis is proportional to the perfusion pressure under maximum hyperemia.

To achieve maximum hyperemia, drugs that have a vasodilatory effect should be used to attenuate the auto-regulatory function of the coronary artery system.

✉ Yoshiaki Kawase
ykawase@heart-center.or.jp

[1] Gifu Heart Center, Gifu, Japan

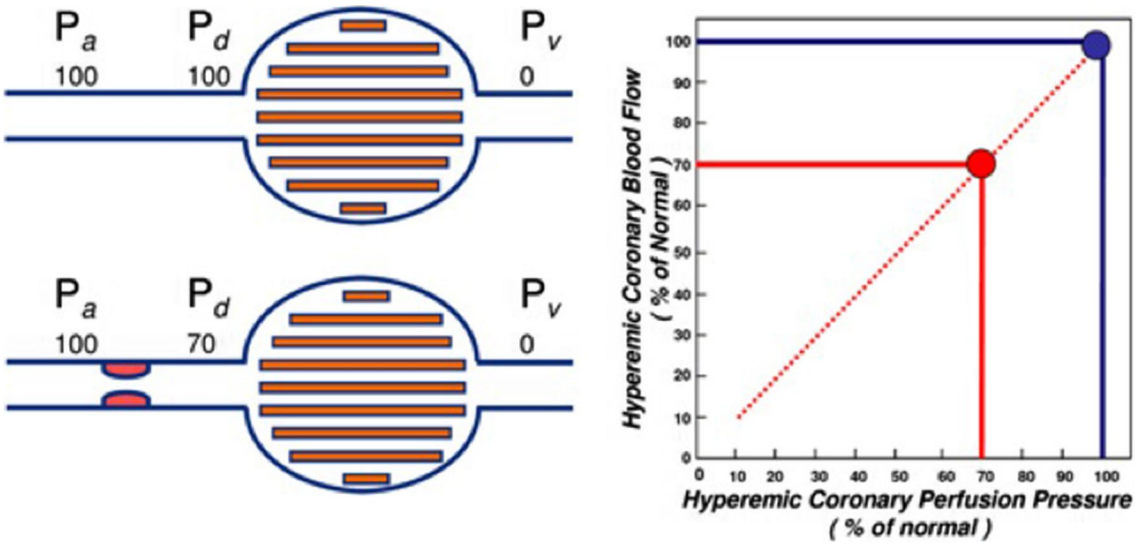


Fig. 1 The concept of FFR. Blue lines represent a case presenting no epicardial stenosis in the coronary artery. In this case the intracoronary pressure is 100 mmHg throughout the coronary artery, which indicates this coronary artery is performing at 100% of its capacity. Red lines represent a case with stenosis causing a hyperemic pressure gradient of 30 mmHg. This lesion caused a 30% decrease in performance relative to the maximum capacity in coronary flow. *Pa* aortic pressure, *Pd* distal coronary pressure, *Pv* central venous pressure

The FFR is defined as the maximum myocardial blood flow in the presence of stenosis divided by the theoretical normal maximum blood flow without a stenosis in the target coronary artery. This index represents the fraction of the performance of the coronary artery that can be achieved despite the coronary stenosis.

The normal value of this index is 1.0, regardless of the patient or the specific vessel studied [6]. This index is independent of changes in systemic blood pressure and heart rate [7]. And most importantly, FFR measurements show excellent reproducibility [8].

Although the threshold of FFR in the presence of ischemia has been reported to be < 0.75 [9], a FFR ≤ 0.80 is widely used as a cutoff value for the indication of PCIs [9, 10]. A FFR between 0.75 and 0.80 is considered the gray zone to avoid overlooking of lesions with ischemia for various reasons (please refer to the section "Pitfalls of FFR measurement"). Furthermore, independent of this explanation, the threshold point for the indication of medical treatment and revascularization has been reported to be 0.80 based on the relationship between the event rate and the FFR value [11, 12], and a FFR ≤ 0.80 is thought to be an indication for revascularization.

FFR and clinical outcome

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial [1], which showed no advantage of angio-guided PCIs over optimal medical therapy, provided the opportunity to seriously consider the application of PCIs. The report from the same group also indicated a correct approach. Shaw et al. showed the importance of the presence of ischemia at the target vessel and the importance of the reduction of this ischemia by PCIs to show the effect of PCIs on outcome [13].

Considering the clinical environment mentioned above, the role of physiological lesion assessment using pressure guidewires, which can be used in the catheter laboratories, is expected to increase in Japan.

There have been three landmark studies evaluating FFRs. The first study was the Deferral versus Performance of PTCA in patients without Documented Ischemia (DEFER study) [14]. In this study, the authors clearly demonstrated the safety of the deferral of lesions with an FFR value of equal to or more than 0.75. The concept underlined by the study was that non-ischemic lesions, provided optimal medical therapy is available, have an excellent outcome with rates of death and myocardial infarction of less than 1% per year. Considering the rate of acute stent thrombosis and procedure-related myocardial infarction, even the implantation of a current state-of-the-art stent cannot improve the outcome of these lesions [15]. The validity of this method for extended periods (up to 15 years) has been also demonstrated [16, 17]. The same evidence has been confirmed for the Japanese population [18].

The second landmark study was the Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study [19]. In this study the superiority of FFR-guide PCI over angiography-guided PCI in patients with multi-vessel coronary

artery disease was validated. The composite of death, myocardial infarction, and repeat vascularization was less frequent in FFR-guided PCI compared to angiography-guided PCI (13.2 vs. 18.3%, $p=0.02$).

The third and last landmark study was the FAME II study [10]. Unlike the COURAGE trial, which showed no superiority of angiography-guided PCIs over optimal medical therapy, the FAME II trial clearly showed the superiority of FFR-guided PCIs plus optimal medical therapy over optimal medical therapy alone. When the FFR of the target vessel was equal to or less than 0.80, the composite of death from any cause, myocardial infarction, and urgent revascularization were less frequently observed in the PCI plus the Medical Therapy group compared to the Medical Therapy-alone group (4.3 vs. 12.7%, $p<0.001$). This difference was mainly driven by the decrease of urgent revascularization requirement in the PCI plus Medical Therapy group compared to the Medical Therapy alone group (1.6 vs. 11.1%, $p<0.001$).

Based on these results, the current European guideline recommends FFR-guided revascularization as class I (level of evidence A) in stable patients without clear evidence of ischemia [20].

The validity of FFR-guided revascularization over angio-guided revascularization has also been shown in patients who underwent coronary artery bypass graft surgery [21, 22].

FFR was introduced over 20 years ago [23] and there has been a wealth of evidence reported in almost all subsets of coronary disease and clinical settings. However, the main purpose of this document is to act as a guide for facilities that do not have ample experience with FFR measurement. However, the main purpose of this document is to act as a guide for facilities that do not have ample experience with FFR measurement. Therefore, more detailed evidence supporting FFR should be referred to other reviews.

Use of FFR in real practice

Pressure guidewires

Four wire-type pressure measurement devices (so called pressure-wires) and one monorail microcatheter type device are presently available in Japan. The characteristics of each device are summarized in Table 1. All pressure wires are applicable with a diagnostic catheter. A 5-Fr or larger guiding catheter is required for monorail microcatheter type devices.

All devices can now provide resting indexes.

The position of the pressure sensor of the devices should be placed at least 2–3 cm distal to the stenosis to be assessed to avoid the influence of pressure recovery phenomenon. In general, to evaluate whether a target coronary artery is suffering from myocardial ischemia caused by stenosis in the epicardial coronary artery, the pressure sensor should be positioned at the very distal part of the coronary artery [24].

Diagnostic and guiding catheters

One of the large differences in Japan compared to Western countries in terms of FFR measurement is the usage of a small caliber diagnostic catheter. Nevertheless, regardless of the size used, it is not recommended to measure FFR using a diagnostic catheter [24]. The problems associated with the use of a small caliber diagnostic catheter are as follows: (1) unsatisfactory back up force and (2) blunted pressure signal due to the small lumen size. Considering the clinical environment in Japan, measuring the FFR with a 5-Fr diagnostic catheter is widely accepted. There has been a report that showed the feasibility of FFR measurement with a 4-Fr diagnostic catheter; [25] however, the author also described the limitations in selected cases. Therefore, facilities that do not have sufficient experience with FFR measurements are highly recommended to avoid using the 4-Fr diagnostic catheter for FFR measurements.

When using a guiding catheter, it is important to use a guiding catheter without side-holes. The side-holes of the

Table 1 Characteristics of pressure wire sensors

Provider	Product	System	Resting indexes	Size
Abbott Vascular	PressureWire	Electric	RFR	0.014″
Boston Scientific	Commet[a]	Optical fiber	dPR	0.014″
Opsens	OptoWire	Optical fiber	dPR	0.014″
Philips	WaveWire	Electric	iFR	0.014″
ACIST Medical Systems[b]	Navvus	Optical fiber	dPR	0.020″

RFR resting full-cycle ratio, *iFR* instantaneous wave-free period, *dPR* diastolic pressure ratio

[a]Commet is currently not available in Japan

[b]Monorail microcatheter type

guiding catheter are located 20- to 50-mm proximal from the tip of the catheter. The pressure signals from these side-holes usually derive from ascending aorta and differs to that recorded from the tip of the catheter. The expressed pressure recording in this case is the fusion of the pressure from the ostium of the coronary artery and the ascending aorta. Therefore, the guiding catheter with side-holes should be avoided for the measurement of FFR.

Maximal hyperemia

The drugs available also differ between Japan and Western countries. Regadenoson is not available and adenosine is not reimbursed for use in FFR measurement in Japan. Conversely, nicorandil is available to limited countries (Fig. 2) [26, 27].

Papaverine is an ideal coronary vasodilator [28]. However, considering its arrhythmic side effects, few facilities use this drug in daily practice [29].

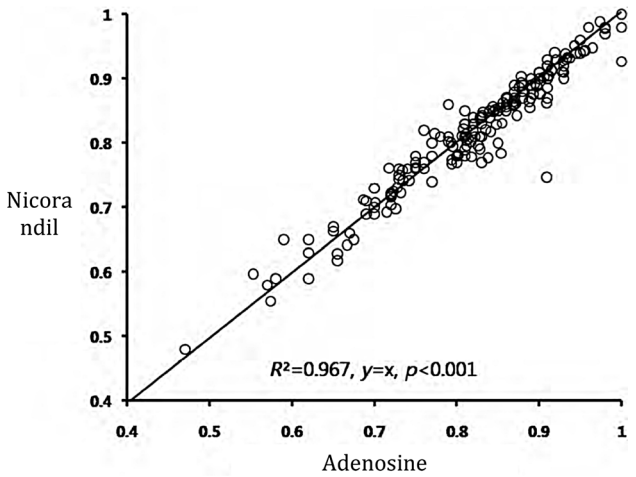


Fig. 2 Correlation between intravenous administration of adenosine (140 μg/kg/min) and intracoronary administration of nicorandil (2 mg). Adapted with permission from Jang et al. [27]

Intravenous continuous administration of adenosine-5′-triphosphate (ATP), a precursor of adenosine with the same vasodilator effect, is the current standard in Japan [30].

The list of available drugs for FFR measurement in Japan is summarized in Table 2. It is important to underline that premedication with nitrate, which is a common epicardial vasodilator in the catherization laboratory is essential for the measurement of both resting and hyperemic indexes to eliminate the presence of vasospasm in the epicardial coronary artery.

Although it is available only in a limited number of countries, nicorandil, a hybrid of nitrate and an ATP-sensitive potassium channel opener, is easy to use without the effects of caffeine intake unlike ATP and with less frequency of lethal arrhythmia than papaverine. Nicorandil also causes less hemodynamic changes compared to ATP infusion, which is preferable for patients with severe aortic valve stenosis [31].

Indications for FFR measurement

Although the main target for FFR measurement in real practice is a lesion with moderate stenosis (30–70% stenosis), there are cases where FFR shows a negative value with very tight stenosis (mismatch case) [32, 33]. Conversely, there are also cases where FFR shows a positive value with very mild stenosis (reverse-mismatch case) [32]. The reason for these phenomena seem to depend on the amount of myocardium subtended by the target lesion [34].

Although, the indication for PCIs for mismatch cases tends to be an area of debate, the awareness of the presence of reverse-mismatch cases is more important since these lesions tend to supply blood to a larger extent of the myocardium (ex. left main trunk) and the outcome of these patients is not benign [35, 36].

To avoid overlooking these lesions and applying physiological measurement to as many vessels as possible, iFR [37] and FFRCT, which are thought to be invasive or noninvasive alternatives to FFR, respectively, have some advantages over invasive FFR.

Table 2 Available agents for FFR measurement in Japan

Drug	Route	LCA dose	RCA dose	Complication/contraindication
ATP[a]	Intravenous	140 μg/kg/min		Asthma, atrioventricular block, hypotension
Papaverine	Intracoronary[b]	12 mg	8 mg	Torsade de Pointes (1–2%)
Nicorandil	Intracoronary[b]	2 mg	2 mg	Torsade de Pointes (< 1%)[c]

ATP adenosine-5′-triphosphate, *LCA* left coronary artery, *RCA* right coronary artery

[a]ATP is available for intracoronary administration. However, due to its short acting time it is not recommended for facilities which do not have ample experience with physiological assessment

[b]Slow (> 10 s) intracoronary injection is recommended

[c]The induction of arrhythmia with nicorandil is thought to be dose-dependent. The usage of nicorandil at clinically established doses is thought to be safe [71, 72]

Contraindications for FFR measurement

There are few contraindications for FFR measurement. An obvious contraindication is allergy to vasodilatory drugs such as adenosine, ATP, and so on, bronchial asthma, or COPD. Careful consideration is necessary when vasodilatory drugs are applied in patients with low blood pressure, hypertrophic obstructive cardiomyopathy, and severe aortic valve stenosis.

In this regard, iFR might overcome the problems described above, since there is no need for the use of vasodilatory drugs for measurement [38].

Although, it is not a contraindication, FFR measurement in the target vessel of ST elevated myocardial infarction in the acute setting is not recommended due to the presence of microvascular dysfunction in the targeted area [39]. Conversely, the feasibility of FFR measurement for the evaluation of non-culprit vessels in patients with ST elevated myocardial infarction, and for vessels with a history of ST elevated myocardial infarction has been shown [40–42].

The validity of FFR in patients with non-ST elevated myocardial infarction has also been shown in several studies [43, 44]. Nevertheless, evidence is limited, although there has also been a report suggesting that the FFR cutoff value should be higher in this setting [45]. Therefore, the application of FFR in decision-making for patients with non-ST elevated myocardial infarction should be carefully assessed, especially in cases with an FFR > 0.80.

The FFR does not consider the central vein pressure in its simplified formula; although, there is a report suggesting the validity of FFR values even with the presence of high central vein pressure [46]. It is advisable to refrain from FFR measurement in cases in which low blood pressure with increased central vein pressure is expected (e.g., in cases of cardiogenic shock or congestive heart failure).

With regard to anatomical limitations, a lesion with a very tight stenosis, severe winding of the target vessel (a cause of the accordion phenomenon), and the presence of very severe calcification might be sub-contraindications for FFR measurement.

Pitfalls of FFR measurement

The failure to achieve maximum hyperemia may represent a major pitfall of FFR measurement. The major checkpoints are as follows: (1) confirmation of the correct intracoronary injection of vasodilator drug (avoidance of the use of catheters with side-holes, slow injection of the drug to avoid back-flow of the injected drug, placement of the catheter tip in the coronary artery ostium, etc.); (2) recommendation to refrain from caffeine intake more than 24 h before the FFR measurement using adenosine and ATP; [47] (3) avoidance of the use of a vein from the lower extremity and distal forearm for continuous intravenous administration of vasodilator drug, and (4) confirmation of the position of the guiding catheter from the tight engagement to the coronary artery orifice.

The disturbance of the coronary flow merely due to the presence of a large-sized catheter at the ostium of the coronary artery, [48] neglecting to remove the wire introducer from the Y-connector, and the misplacement of the transducer are very simple yet easy to forget pitfalls occurring during the measurement of FFR.

The pressure signal drift in both directions can be the cause of misinterpretation of the FFR value. If one encounters more than a 2 mmHg pressure signal drift, the measurement should be repeated [49]. The careful preparation of the pressure wire should include: (1) flushing the wire tube with a sufficient amount of saline while the pressure wire is in the tube and (2) waiting 20–30 s after the equalization of the electronic pressure wire at the tip of the guiding catheter before advancing the wire into the coronary artery. Avoiding and confirming the presence of a pressure signal drift before the finalization of the measurement is mandatory [50].

The phenomenon is more critical when using resting indexes. Hyperemia usually increases the pressure gradient within a coronary artery by a factor of several times. Therefore, the signal-to-noise ratio during hyperemia is several-fold higher than under resting conditions. In other words, the resting indexes are more vulnerable to the influence of pressure signal drift compared with FFR.

Table 3 summarizes the additional pitfalls compromising the measurement of FFR.

FFR interpretation in real practice

FFR should be regarded as a continuous variable of risk [11]. This concept is important both for ischemia positive (FFR < 0.75) and negative (FFR > 0.80) lesions.

For ischemia positive lesions, the cutoff value of FFR is different among the indications for PCIs (FFR < 0.75–0.79) and the risk for endpoints like cardiac death and myocardial infarction (FFR < 0.64–0.67) [11, 51].

In this regard, the complexity of the target lesion and the amount of myocardium subtended by the target lesion should be considered [11]. For example, when the lesion is in the ostium of the right coronary artery, where a high rate of restenosis is expected [12], the FFR value should be carefully interpreted. A further example is that if the amount of myocardium subtended by the lesion is small, the threshold of FFR for the indication of PCIs may be lower provided the symptom is manageable with optimal medical therapy (Fig. 3a). Conversely, even if the far distal value of FFR is below the threshold of indication of PCIs, the lesion without a focal pressure gradient might not be

Table 3 Pitfalls in FFR measurement

Errors that increase FFR value		Errors that decrease FFR value	
Falsely higher Pd	Falsely lower Pa	Falsely lower Pd	Falsely higher Pa
The presence of signal drift Insufficient vasodilatation with drug Microvascular disease Hypotension Distal lesion	The wedge of the catheter The presence of thrombus or air in the catheter The presence of introducer needle at the Y-connector The presence of contrast media in the catheter The misplacement of the transducer of aortic pressure The leakage of pressure from the fluid-filled pressure transducer	The presence of signal drift The presence of accordion Phenomenon The presence of thrombus or dissection in the coronary artery	The misplacement of the transducer of aortic pressure The usage of a guiding catheter with side hole

Pa aortic pressure, *Pd* coronary artery pressure distal to the stenosis, *N/A* not applicable, *FFR* fractional flow reserve

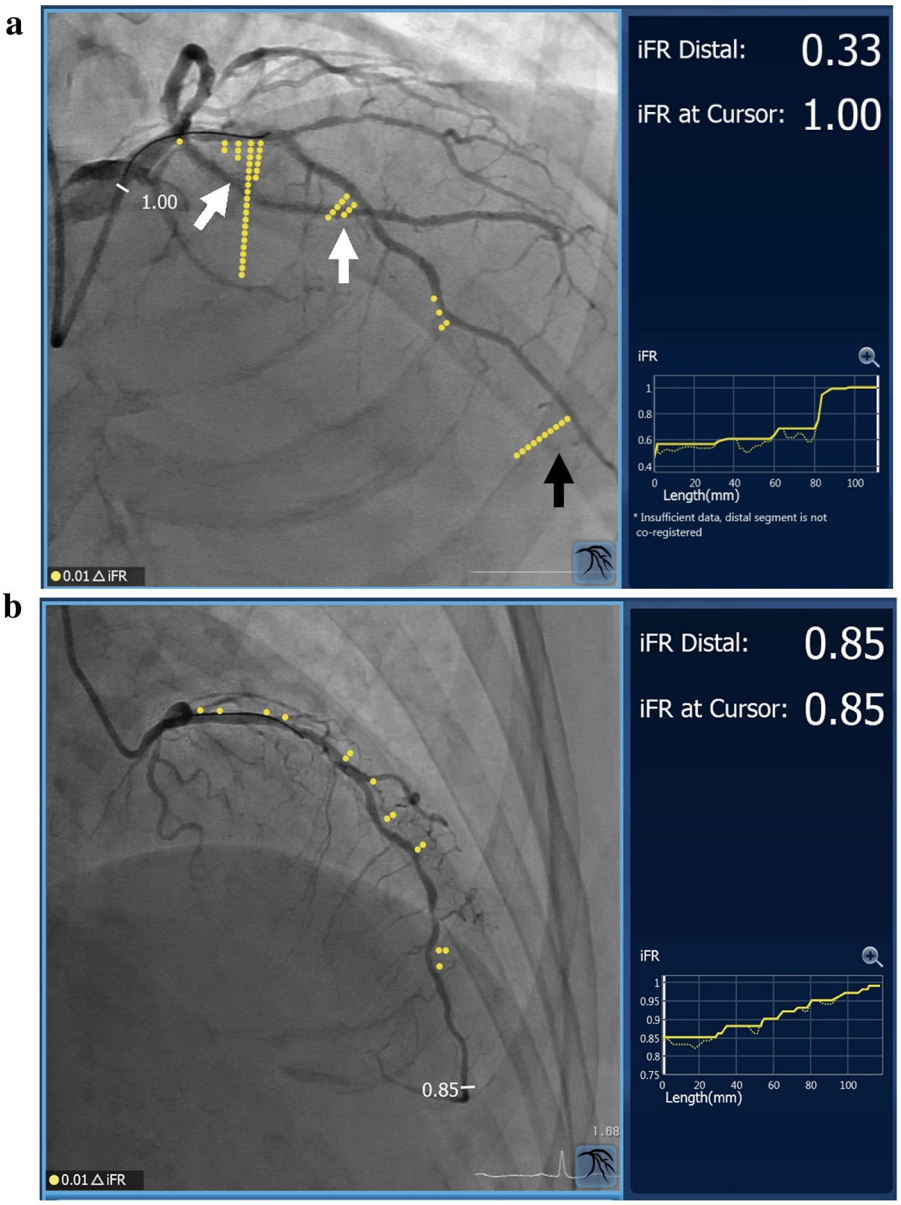


Fig. 3 **a** A representative case of focal pressure gradient in both the proximal and distal part of the left ascending coronary artery. The values indicated are iFR. Yellow dots: the delta iFR caused by each lesion. One dot corresponds to a delta iFR of 0.01. White arrows: the focal pressure gradient in the proximal part of the left ascending coronary artery. Considering the large amount of subtended myocardium, these lesions might be suitable for treatment with stent placement. Black arrow: focal pressure gradient in the distal part of the left ascending coronary artery. Considering the small amount of subtended myocardium, these lesions might not be suitable for treatment with stent placement depending on the response of the patient with optimal medical therapy. **b** A representative case of diffuse pressure across the left ascending coronary artery. The values indicated are iFR (Courtesy of Dr Nishina). Yellow dots: the delta iFR caused by each lesion. One dot corresponds to a delta iFR of 0.01. Considering the widely spread dots without a large focal pressure gradient, these lesions might not be suitable for treatment with stent placement

suitable for treatment using stent placement (Fig. 3b). The iFR is expected to play a role in discriminating these lesions [52, 53].

The last notion is that although FFR > 0.80 is usually considered a lesion without ischemia; however, strictly speaking this understanding is not true. More precisely, an FFR > 0.80 should be considered a lesion that is not likely to be a cause of ischemia; which means that the lesion is not an indication for stent implantation. If maximum hyperemia is correctly achieved for FFR measurement, the impairment of the performance of the vessel by this lesion may be less than 20%. Ischemia can be caused by other reasons such as microvascular dysfunction, vasospastic angina, hypertrophic cardiomyopathy, severe aortic stenosis, anemia, etc [54]. This means that in some patients, additional clinical factors should be considered for the diagnosis of myocardial ischemia.

A recent interesting report showed the importance of optimal medical therapy for deferred lesions based on FFR measurement [55]. The study showed significantly better outcome in patients with higher FFR value than lower FFR values. The author speculated that this paradoxical result was due to the less intensive optimal medical therapy, especially statin use, in patients with higher FFR values than patients with lower FFR values. The concept of deferring stent placement should be considered only when optimal medical therapy is provided to the patients by the physician.

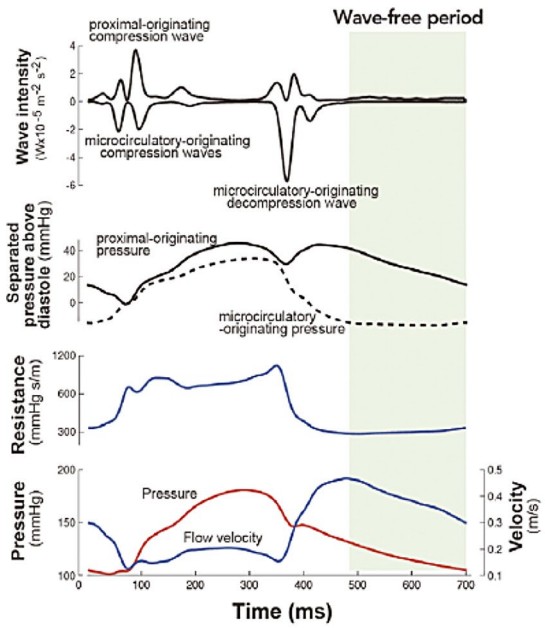
The concept of iFR

Davies et al. invented a wave-free period, which derives from wave-intensity analysis [56]. Resistance is thought to be low and stable during this period [57]. The iFR is calculated by distal coronary pressure (Pd) divided by aortic pressure (Pa) during the wave-free period, where a linear correlation between pressure and flow would be expected, under resting conditions, which means the induction of hyperemia is not required (Fig. 4). Following the results of two large randomized trials [2, 3], the current European guidelines have updated iFR-guided revascularization to class I (level of evidence A) in stable patients without any clear evidence of ischemia [20].

Concordance and discordance between the FFR and iFR

The concordance between the FFR and iFR measurements has been reported to be 80–85% [58–60]. The main mechanism of discordance between the FFR and iFR is thought to originate from the differences in the patient's conditions during the measurement (at rest and under maximal hyperemia).

Cook et al. showed a better concordance of iFR with coronary flow reserve (CFR) than with FFR [61]. The lesion showing a low pressure gradient at rest and a



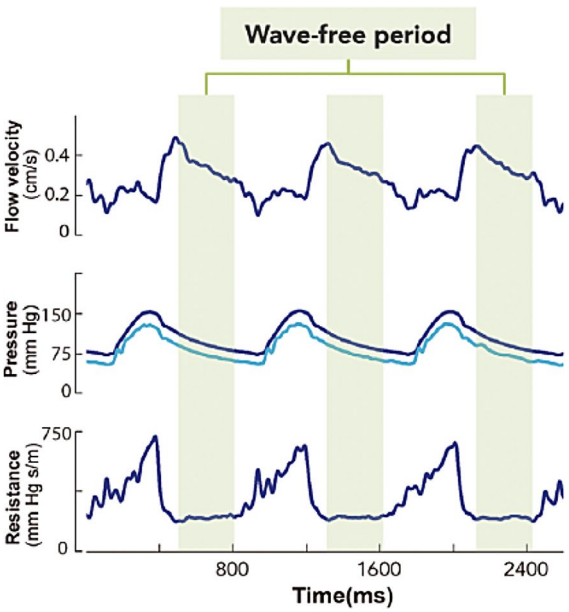


Fig. 4 The concept of the wave-free period. The influence of different waves propagating from the proximal and distal ends of the vessel on the coronary flow is shown with separate wave-intensity plots. These waves are absent during the wave-free period. The resistance is low and most stable during the wave-free period. Coronary pressure and flow show a liner relationship during the wave-free period. Adapted with permission from Sen et al. [58]

high-pressure gradient under maximum hyperemia might represent a case with a higher rate of hyperemic flow to resting flow that is comparable to the concept of high CFR [62].

Lee et al. reported different clinical and angiographical characteristics among the 4 groups classified according to the FFR and iFR (group 1: FFR > 0.80 and iFR ≥ 0.90, group 2: FFR > 0.80 and iFR < 0.90, group 3: FFR ≤ 0.80 and iFR > 0.90, group 4: FFR ≤ 0.80 and iFR < 0.90) [63]. The authors also reported outcomes of concordant and discordant groups of FFR and iFR. Since both the DEFINE-FLAIR and IFR-SWEDEHEART trial did not allow the simultaneous measurement of FFR and iFR, the outcomes of deferred lesions with discordant results between FFR and iFR could not be investigated. Therefore, Lee et al. provide essential information about the outcome of these groups [64]. According to the data, only the group with concordant abnormal results showed a significantly higher risk of clinical events compared with the concordant normal group. The discordant results between the FFR and iFR measurements were not associated with an increased risk of clinical events (Fig. 5).

Pullback curve analysis

It was considered difficult to predict the hemodynamic response to stenting in the presence of other flow limiting lesions before the advent of iFR, as hyperemic flow can be affected if the severity of stenosis exceeds 40–50% [65]. In the presence of two flow-limiting lesions, there is an interaction of coronary flow between lesions under hyperemia. The treatment of one lesion changes this interaction and leads to differences in the coronary flow that passes through the untreated lesion (Fig. 6) [66]. This phenomenon makes predicting post-PCI physiological results using FFR difficult. A solution to resolve this phenomenon exists, but it requires a complex formula including the value of wedge pressure that is not practical to measure at the time of diagnostic catheter [67]. Conversely, the resting flow is not affected by the lesion up to the almost sub-occlusion of the vessel. Therefore, without the presence of an extremely tight stenosis, the treatment of one lesion may cause negligible changes in resting flow passing through the residual stenosis. This characteristic of resting flow might allow the iFR to predict the post-PCI physiological outcome [52, 53].

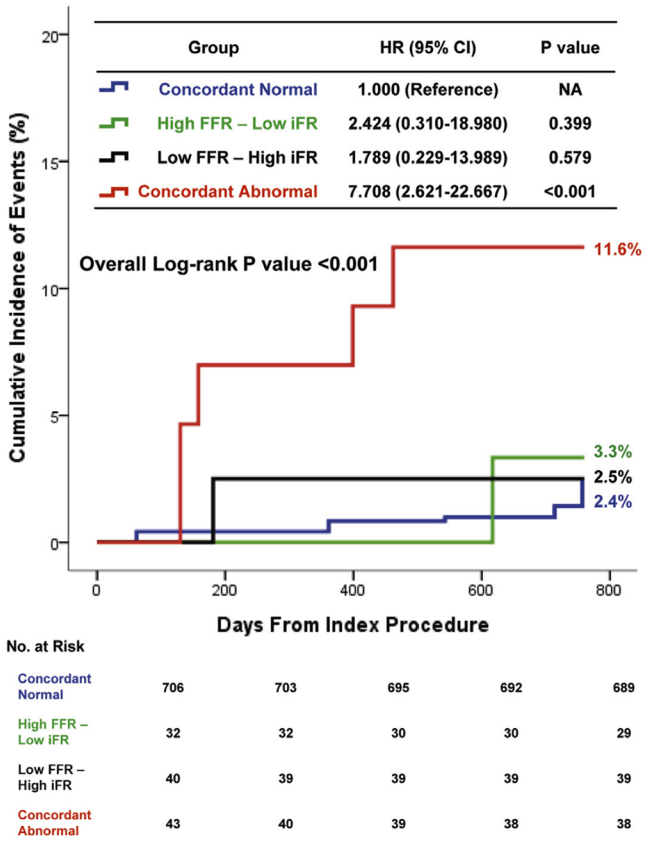


Fig. 5 Outcome of patient with discordant and concordant results from FFR and iFR assessment. *FFR* fractional flow reserve, *iFR* instantaneous wave-free ratio, *HR* hazard rate. Adapted with permission from Lee et al. [64]

FFR: fractional flow reserve, iFR: instantaneous wave-free ratio, HR: hazard rate. Adapted with permission from Lee, et al. [64]

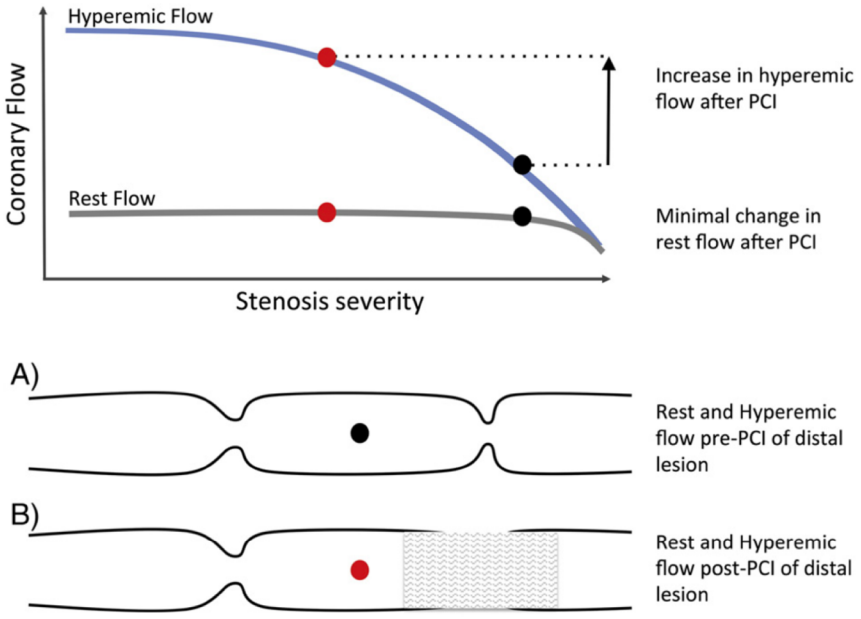


Fig. 6 The change in coronary flow passing through one lesion pre- and post-treatment of the other lesion. The treatment of one lesion can change the coronary flow passing through the other lesion under hyperemia. The change in coronary flow that passes through the lesion can change the pressure gradient induced by the lesion. This phenomenon is minimum under resting conditions and facilitates the prediction of the coronary flow that will pass through the lesion and the pressure gradient created by the lesion after treatment. *PCI* percutaneous coronary intervention. Adapted with permission from Nijjer et al. [66]

The treatment of one lesion can change the coronary flow passing through the other lesion under hyperemia. The change in coronary flow that passes through the lesion can change the pressure gradient induced by the lesion. This phenomenon is minimum under resting conditions and facilitates the prediction of the coronary flow that will pass through the lesion and the pressure gradient created by the lesion after treatment. Adapted with permission from Nijjer, et al. [66]
PCI: percutaneous coronary intervention.

Pitfalls of iFR measurement

The basic pitfalls for the measurement of iFR are almost identical to those of FFR, except that the achievement of maximum hyperemia is not a determining factor.

Instead, there are several important points to consider for the measurement of the resting indexes: (1) the administration of nitrate, which is a vasodilator of the epicardial coronary artery, is also necessary as in FFR measurement and (2) following the injection of any agent having vasodilatory effects (contrast medium, saline, etc.), the operator must wait until the vasodilator effect has subsided. In particular, after the administration of ATP, papaverine, or nicorandil, the measurement of resting indexes should occur after at least a 5-min delay. Although, not associated with the use of vasodilator drugs, hyperemia can be induced by ischemia caused by the occlusion of coronary artery, thus measurement of the resting indexes should take place at least several minutes after the occlusion of coronary artery during the PCI procedure [68]. (3) The resting indexes should be interpreted carefully in patients with left ventricular hypertrophy, in those undergoing hemodialysis, and in severe valvular heart disease, etc., since the validity of resting conditions values for these patients are controversial.

Other resting indexes

Resting indexes are now available with pressure wire systems. Table 4 describes the features of these new resting indexes that have been validated by several reports. Because the coefficients of determination between these new resting indexes with iFR is almost 1.0 ($r^2 > 0.98$), these indexes might be nearly identical to iFR [69, 70]. However, there is no clinical data available for these new resting indexes. Real-world data using these new resting indexes are requested in the near future.

Table 4 Resting indexes

Full name	IFR Instantaneous wave-free period	RFR Resting full-cycle ratio	DPR Diastolic pressure ratio
Provider	Philips	Abbott Vascular	Opsens Boston Scientific ACIST Medical Systems
Target for the analysis	Wave-free period	Full-cycle	Whole diastolic
Cutoff	0.89	0.89	0.89

Compliance with ethical standards

Conflict of interest Yoshiaki Kawase received payment for lectures from Boston Scientific Japan, Hitoshi Matsuo received payment for lectures from Boston Scientific Japan, Phillips Japan, and Abott Vascular Japan, Takashi Akasaka received payment for lectures from St. Jude Medical, received grants/research support from St. Jude Medical, ACIST Medical Systems Japan, Abott vascular Japan, and Boston Scientific Japan, Yasutsugu Shiono received payment for lectures from Philips Japan, received grants/research support from St. Jude Medical, and ACIST Medical Systems Japan, Nobuhiro Tanaka received payment for lectures from Boston Scientific Japan and Abott Vascular Japan, Tetsuya Amano received grants/research support from Abott Vascular Japan and Boston Scientific Japan, Ken Kozuma received payment for lectures from Abott Vascular Japan, received grants/research support from Abott Vascular Japan, Masato Nakamura received payment for lectures from Abott vascular Japan, Phillips Japan, and Zeon Medical, Hiroyoshi Yokoi received payment for lectures from Boston Scientific Japan, Yoshio Kobayashi received research grant/research support from Abbott Vascular Japan, Yuji Ikari received grants/research support from Boston Scientific Japan and St. Jude Medical.

References

1. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503–16.
2. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med. 2017;376:1824–34.
3. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med. 2017;376:1813–23.
4. Hoffman JI. Maximal coronary flow and the concept of coronary vascular reserve. Circulation. 1984;70:153–9.
5. Klocke FJ. Measurements of coronary flow reserve: defining pathophysiology versus making decisions about patient care. Circulation. 1987;76:1183–9.
6. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation. 1995;92:3183–93.
7. De Bruyne B, Paulus WJ, Pijls NH. Rationale and application of coronary transstenotic pressure gradient measurements. Cathet Cardiovasc Diagn. 1994;33:250–61.
8. Berry C, van 't Veer M, Witt N, Kala P, Bocek O, Pyxaras SA, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. J Am Coll Cardiol. 2013;61:1421–7.
9. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med. 1996;334:1703–8.
10. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991–1001.
11. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol. 2014;64:1641–54.
12. Lam MK, Sen H, Tandjung K, Lowik MM, Basalus MW, Mewes JC, et al. Clinical outcome of patients with implantation of second-generation drug-eluting stents in the right coronary ostium: insights from 2-year follow-up of the TWENTE trial. Catheter Cardiovasc Interv. 2015;85:524–31.
13. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation. 2008;117:1283–91.
14. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation. 2001;103:2928–34.
15. Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, et al. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: a pre-specified analysis from the PRODIGY study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY). JACC Cardiovasc Interv. 2014;7:20–8.
16. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49:2105–11.
17. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J. 2015;36:3182–8.
18. Tanaka N, Nakamura M, Akasaka T, Kadota K, Uemura S, Amano T, et al. One- year outcome of fractional flow reserve-based coronary intervention in Japanese daily practice- CVIT-DEFER Registry. Circ J. 2017;81:1301–6.
19. Tonino PA, De Bruyne B, Pijls NH, 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;360:213–24.
20. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2018. https://doi.org/10.1093/ejcts/ezy289.
21. Botman CJ, Schonberger J, Koolen S, Penn O, Botman H, Dib N, et al. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. Ann Thorac Surg. 2007;83:2093–7.
22. Fournier S, Toth GG, De Bruyne B, Johnson NP, Ciccarelli G, Xaplanteris P, et al. Six- year follow-up of fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. Circ Cardiovasc Interv. 2018;11:e006368.
23. 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;87:1354–67.
24. Toth GG, Johnson NP, Jeremias A, Pellicano M, Vranckx P, Fearon WF, et al. Standardization of fractional flow reserve measurements. J Am Coll Cardiol. 2016;68:742–53.
25. Moriyama N, Yamanaka F, Shishido K, Tobita K, Yokota S, Hayashi T, et al. The COFFEE Trial (COmparison of Fractional Flow Reserve Measurements through 4 FrEnch versus 6 FrEnch Diagnostic Catheter). JACC Cardiovasc Interv. 2018;11:414–6.
26. Inoue F, Hashimoto T, Fujimoto S, Uemura S, Kawamoto A, Dohi K. Estimation of coronary flow reserve by intracoronary administration of nicorandil: comparison with intracoronary administration of papaverine. Heart Vessels. 1998;13:229–36.
27. Jang HJ, Koo BK, Lee HS, Park JB, Kim JH, Seo MK, et al. Safety and efficacy of a novel hyperaemic agent, intracoronary nicorandil, for invasive physiological assessments in the cardiac catheterization laboratory. Eur Heart J. 2013;34:2055–62.
28. Wilson RF, White CW. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. Circulation. 1986;73:444–51.
29. Nakayama M, Tanaka N, Sakoda K, Hokama Y, Hoshino K, Kimura Y, et al. Papaverine-induced polymorphic ventricular tachycardia during coronary flow reserve study of patients with moderate coronary artery disease. Circ J. 2015;79:530–6.
30. De Bruyne B, Pijls NH, 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;107:1877–83.
31. Oi M, Toyofuku M, Matsumura Y, Motohashi Y, Takahashi K, Kawase Y, et al. Utility of nicorandil for the measurement of coronary fractional flow reserve. Cardiovasc Interv Ther. 2014;29:24–30.
32. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol. 2010;55:2816–21.
33. Koo BK, Kang HJ, Youn TJ, Chae IH, Choi DJ, Kim HS, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. J Am Coll Cardiol. 2005;46:633–7.
34. Nakamura M, Yamagishi M, Ueno T, Hara K, Ishiwata S, Itoh T, et al. Prevalence of visual-functional mismatch regarding coronary artery stenosis in the CVIT-DEFER registry. Cardiovasc Interv Ther. 2014;29:300–8.
35. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation. 2009;120:1505–12.
36. Lee JM, Koo BK, Shin ES, Nam CW, Doh JH, Hu X, et al. Clinical outcomes of deferred lesions with angiographically insignificant stenosis but low fractional flow reserve. J Am Heart Assoc. 2017. https://doi.org/10.1161/JAHA.117.006071.
37. Van Belle E, Gil R, Klauss V, Balghith M, Meuwissen M, Clerc J, et al. Impact of routine invasive physiology at time of angiography in patients with multivessel coronary artery disease on reclassification of revascularization strategy: results from the DEFINE REAL study. JACC Cardiovasc Interv. 2018;11:354–65.
38. Yamanaka F, Shishido K, Ochiai T, Moriyama N, Yamazaki K, Sugitani A, et al. Instantaneous wave-free ratio for the assessment of intermediate coronary artery stenosis in patients with severe aortic valve stenosis: comparison with myocardial perfusion scintigraphy. JACC Cardiovasc Interv. 2018;11:2032–40.
39. 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;64:1894–904.
40. 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;3:1274–81.
41. Lee JM, Kim HK, Lim KS, Park JK, Choi KH, Park J, et al. Influence of local myocardial damage on index of microcirculatory resistance and fractional flow reserve in target and nontarget vascular territories in a porcine microvascular injury model. JACC Cardiovasc Interv. 2018;11:717–24.
42. De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, et al. Fractional flow reserve in patients with prior myocardial infarction. Circulation. 2001;104:157–62.
43. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, et al. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC Cardiovasc Interv. 2011;4:1183–9.
44. Nam J, Briggs A, Layland J, Oldroyd KG, Curzen N, Sood A, et al. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. Cost Eff Resour Alloc. 2015;13:19.
45. Hakeem A, Edupuganti MM, Almomani A, Pothineni NV, Payne J, Abualsuod AM, et al. Long- term prognosis of deferred acute coronary syndrome lesions based on nonischemic fractional flow reserve. J Am Coll Cardiol. 2016;68:1181–91.
46. Toth GG, De Bruyne B, Rusinaru D, Di Gioia G, Bartunek J, Pellicano M, et al. Impact of right atrial pressure on fractional flow reserve measurements: comparison of fractional flow reserve and myocardial fractional flow reserve in 1,600 coronary stenoses. JACC Cardiovasc Interv. 2016;9:453–9.
47. Matsumoto H, Nakatsuma K, Shimada T, Ushimaru S, Mikuri M, Yamazaki T, et al. Effect of caffeine on intravenous adenosine-induced hyperemia in fractional flow reserve measurement. J Invasive Cardiol. 2014;26:580–5.
48. Aminian A, Dolatabadi D, Lefebvre P, Khalil G, Zimmerman R, Michalakis G, et al. Importance of guiding catheter disengagement during measurement of fractional flow reserve in patients with an isolated proximal left anterior descending artery stenosis. Catheter Cardiovasc Interv. 2015;85:595–601.
49. Pijls NH, Bruyne BD. Fractional flow reserve, coronary pressure wires, and drift. Circ J. 2016;80:1704–6.
50. Wakasa N, Kuramochi T, Mihashi N, Terada N, Kanaji Y, Murai T, et al. Impact of pressure signal drift on fractional flow

reserve-based decision-making for patients with intermediate coronary artery stenosis. Circ J. 2016;80:1812–9.
51. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, et al. Fractional flow reserve and cardiac events in coronary artery disease: data from a prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). Circulation. 2017;135:2241–51.
52. Kikuta Y, Cook CM, Sharp ASP, Salinas P, Kawase Y, Shiono Y, et al. Pre-angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT Registry. JACC Cardiovasc Interv. 2018;11:757–67.
53. Kawase Y, Kawasaki M, Kikuchi J, Hirata T, Okamoto S, Tanigaki T, et al. Residual pressure gradient across the implanted stent: an important factor of post-PCI physiological results. J Cardiol. 2018;71:458–63.
54. Balla C, Pavasini R, Ferrari R. Treatment of angina: where are we? Cardiology. 2018;140:52–67.
55. Yamashita J, Tanaka N, Shindo N, Ogawa M, Kimura Y, Sakoda K, et al. Seven-year clinical outcomes of patients with moderate coronary artery stenosis after deferral of revascularization based on gray-zone fractional flow reserve. Cardiovasc Interv Ther. 2015;30:209–15.
56. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, et al. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. Circulation. 2006;113:1768–78.
57. Siebes M, Kolyva C, Verhoeff BJ, Piek JJ, Spaan JA. Potential and limitations of wave intensity analysis in coronary arteries. Med Biol Eng Comput. 2009;47:233–9.
58. 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: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol. 2012;59:1392–402.
59. Escaned J, Echavarria-Pinto M, Garcia-Garcia HM, van de Hoef TP, de Vries T, Kaul P, et al. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE II international, multicenter study (ADenosine Vasodilator Independent Stenosis Evaluation II). JACC Cardiovasc Interv. 2015;8:824–33.
60. 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;168:739–48.
61. Cook CM, Jeremias A, Petraco R, Sen S, Nijjer S, Shun-Shin MJ, et al. Fractional flow reserve/instantaneous wave-free ratio discordance in angiographically intermediate coronary stenoses: an analysis using doppler-derived coronary flow measurements. JACC Cardiovasc Interv. 2017;10:2514–24.
62. Akasaka T, Yamamuro A, Kamiyama N, Koyama Y, Akiyama M, Watanabe N, et al. Assessment of coronary flow reserve by coronary pressure measurement: comparison with flow- or velocity-derived coronary flow reserve. J Am Coll Cardiol. 2003;41:1554–60.
63. Lee JM, Shin ES, Nam CW, Doh JH, Hwang D, Park J, et al. Discrepancy between fractional flow reserve and instantaneous wave-free ratio: clinical and angiographic characteristics. Int J Cardiol. 2017;245:63–8.
64. Lee JM, Shin ES, Nam CW, Doh JH, Hwang D, Park J, et al. Clinical outcomes according to fractional flow reserve or instantaneous wave-free ratio in deferred lesions. JACC Cardiovasc Interv. 2017;10:2502–10.
65. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol. 1974;33:87–94.
66. Nijjer SS, Sen S, Petraco R, Mayet J, Francis DP, Davies JE. The Instantaneous wave-Free Ratio (iFR) pullback: a novel innovation using baseline physiology to optimise coronary angioplasty in tandem lesions. Cardiovasc Revasc Med. 2015;16:167–71.
67. De Bruyne B, Pijls NH, 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;101:1840–7.
68. Kawase Y, Omori H, Kawasaki M, Tanigaki T, Hirata T, Okamoto S, et al. Postocclusional hyperemia for fractional flow reserve after percutaneous coronary intervention. Circ Cardiovasc Interv. 2017;10:e005674. https://doi.org/10.1161/CIRCINTERVENTIONS.117.005674.
69. Van't Veer M, Pijls NHJ, Hennigan B, Watkins S, Ali ZA, De Bruyne B, et al. Comparison of different diastolic resting indexes to iFR: are they all equal? J Am Coll Cardiol. 2017;70:3088–96.
70. Svanerud J, Ahn JM, Jeremias A, van't Veer M, Gore A, Maehara A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. EuroIntervention. 2018;14:806–14.
71. Kojima S, Ishikawa S, Ohsawa K, Mori H. Determination of effective and safe dose for intracoronary administration of nicorandil in dogs. Cardiovasc Res. 1990;24:727–32.
72. Miyazaki T, Moritani K, Miyoshi S, Asanagi M, Zhao LS, Mitamura H, et al. Nicorandil augments regional ischemia-induced monophasic action potential shortening and potassium accumulation without serious proarrhythmia. J Cardiovasc Pharmacol. 1995;26:949.