Comprehensive assessment of coronary fractional flow reserve

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Abstract

Fractional flow reserve (FFR) is considered nowadays as the gold standard for invasive assessment of physiologic stenosis significance and an indispensable tool for decision-making in coronary revascularization. Robust studies have shown that FFR is more effective in accurately identifying which lesions should be stented, and revascularization guided by FFR improves the outcome of coronary artery disease in patients. Therefore, FFR has been upgraded to a class A recommendation in current guidelines when the ischemic potential for specific target lesions is controversial. This article reviews the laboratory practice, functional evaluation of FFR as a gold standard and its emerging clinical application. In addition, novel noninvasive technologies of FFR measurement are discussed in depth.

Key words: fractional flow reserve, stenosis, revascularization, noninvasive.

Introduction

The goal of any diagnostic tool is to guide decision-making and apply optimal treatment to individuals [1–3]. Thus, it is necessary and could be of great benefit for patients to improve diagnostic tools along with the technical development. Patients with suspected coronary artery disease (CAD) might suggest the presence of myocardial ischemia, of which revascularization is significant as it has the potential to improve the outcomes presented by abundant data [4–6]. However, revascularization of stenotic lesions without inducible ischemia is not beneficial and even harmful [7]. Therefore, the decision should be guided by the evidence of myocardial ischemia, which could be suggested with functional diagnosis [7].

Coronary angiography, contributing hugely to the understanding of coronary anatomic stenosis, still plays a pivotal role in invasive imaging of the coronary arteries, despite the consensus that it is highly subjective and very limited in evaluating hemodynamic significance of the stenosis [1, 8, 9]. Ideally, it needs a diagnostic tool providing reliable and objective information of the functional significance of a stenosis, such as fractional flow reserve (FFR).

The FFR is an accurate and lesion-specific index to indicate whether a stenosis is responsible for ischemia [9]. It has been well established that

FFR is a reliable and feasible measurement tool of CAD, including angiographic intermediate stenosis, multi-vessel disease, left main coronary artery stenosis, and bifurcation lesions, and of significant benefit in guiding percutaneous coronary intervention (PCI) [5, 6, 10–13]. Thus, current guidelines recommend FFR as level of evidence 'A' when the ischemic potential for specific lesions is controversial [14]. This article reviews the basic concept, laboratory practice, functional evaluation, emerging clinical applications and novel techniques of FFR measurement.

Fractional flow reserve definition

The concept of FFR, a lesion-specific index of the functional significance of CAD, was introduced into clinical practice by Pijls and De Bruyne in the early 1990s [15]. It is defined as the ratio of maximum myocardial blood flow in a stenotic artery to maximum blood flow if the same artery were normal [2, 9, 16, 17]. In other words, it is a fraction of the maximal normal flow with the hypothetical completely normal case that the microvasculature resistance is minimal and constant [2, 9]. Therefore, FFR could represent the extent to which maximal myocardial blood flow is limited by the presence of an epicardial stenosis [1, 15]. A value of 0.70 means that maximal blood flow reaches only 70% of its normal or the stent focal stenosis bringing FFR to 1.0 represents an increase in maximal flow of 30%.

Although FFR represents mathematically the ratio of 2 pressures (the coronary pressure distal to the stenosis and the aortic pressure), it reflects indeed the ratio of 2 hyperemic flows (maximal flow in the presence of the stenosis to the maximal flow in the hypothetical absence of the stenosis). Based on the concept, FFR is linearly related to maximum blood flow irrespective of the patient and artery. Moreover, it is proved to be independent of changes in hemodynamics, including heart rate, systemic blood pressure and myocardial contractility [9, 15, 16]. Nevertheless, it should be pointed out that vessels with high-grade lesions, but with extensive collaterals or bypass grafts, may have a near-normal FFR value, since the pressure difference depends on total blood supply including collateral or dual circulation [16].

Fractional flow reserve measurements

Catheters

The use of guiding catheters is recommended, while the use of diagnostic catheters is technically feasible but not recommended, due to higher levels of friction hampering wire manipulation [1, 9]. The guide catheter could eliminate all of these problems and enable the practitioner to perform the so-called ad hoc PCI.

Wires

There are two wire systems commercially available measuring intracoronary pressure, namely the PressureWire (St. Jude Medical Inc., Minneapolis, Minnesota and Uppsala, Sweden) and the Volcano WaveWire (Volcano Inc., Rancho Cordova, CA, USA), both of which locate the sensor at the junction between the radiopaque and radiolucent portions with 30 mm from the distal tip [1, 9]. The former also provides thermodilution capabilities that allow measurement of the index of myocardial resistance and absolute coronary blood flow. Recently, a "wireless" version, PressureWireVR Aeris, was developed in which the signals are transmitted by radiofrequency to a receiver directly connected to the conventional catheterization laboratory physiologic monitoring system, therefore omitting any dedicated interface [9, 18].

Hyperemia

Based on the concept and principles of FFR, it is essential to induce maximal vasodilation of the two compartments of the coronary circulation (the epicardial or "conductance" arteries and the microvasculature or "resistance" arteries). Inducing both maximal and steady-state coronary hyperemia is of clinical significance to make use of FFR measurements. Several pharmacological agents have been used to induce coronary hyperemia, such as adenosine, papaverine, adenosine 5'-triphosphate (ATP), dipyridamole and dobutamine, etc. [19, 20]. A seminal study that enrolled 21 patients with an isolated coronary stenosis carried out by De Bruyne *et al.* [20] demonstrated that an intracoronary bolus of ATP or adenosine (20 to 40 µg) induces a similar level of hyperemia as an intracoronary bolus of 20 mg papaverine. However, the former often fails to induce true steady-state hyperemia. Only intravenous ATP or adenosine (140 µg/kg · min) and intracoronary 20 mg papaverine could induce complete steady-state hyperemia to enable a pressure pullback maneuver [20]. Among these agents, continuous administration of adenosine via the femoral vein is a standard method to achieve coronary hyperemia for FFR measurement [21–23]. However, adenosine is expensive with multiple side effects and contraindicated in patients with reactive airway disease. Regadenoson, a selective A_{2A} receptor agonist, is an approved hyperemic agent for pharmacological stress imaging [19]. Given its potent arteriolar vasodilator capability, sodium nitroprusside is recommended and often used in the treatment of no-reflow in the setting of ST-segment elevation myocardial infarction (STEMI) [24]. Recent studies have confirmed that regadenoson and nitroprusside were also of high efficiency in maximal

vasodilatation of coronary circulation [19, 21, 23, 24]. Furthermore, the femoral vein access requires an additional invasive procedure and is difficult to use during transradial coronary catheterization. Therefore, Lindstaedt *et al.* and Seo *et al.* suggested that continuous intravenous infusion of adenosine via the forearm vein/ antecubital vein is a convenient and effective way to induce steady hyperemia [22, 23]. The pharmacologic options available to induce hyperemia are summarized in Table I [2, 9, 17–21, 23–25].

Although maximal hyperemia is indispensible for the diagnosis of CAD, enhanced α-adrenergic microvascular vasoconstriction may influence pharmacological agents to induce maximal hyperemia [26, 27]. Accordingly, Barbato *et al.* designed a study to evaluate the influence of α-adrenergic tone on adenosine-induced hyperemia and then assess the impact, if any, on FFR-guided clinical decision making [26]. The study enrolled 85 patients with an intermediate coronary stenosis and normal left ventricular function who were then divided into the following three groups: before and after intracoronary bolus of phentolamine, an α_1-, α_2-adrenergic blocke (12 μg/kg, 33 patients); urapidil, a selective α_1-adrenergic blocker (10 mg, 32 patients) and saline (10 ml, 20 patients). It demonstrated that phentolamine and urapidil induced a slight but statistically significant decrease in FFR. However, only 6 patients presented a change in FFR from $p \geq 0.75$ to < 0.75 and no patients from $p \geq 0.80$ to < 0.75 which could influence the decision making. Therefore, the administration of α-adrenergic blockers in addition to adenosine causes a small and clinically irrelevant level of residual microvascular tone [26].

The results were further corroborated by a study investigating the effect of phentolamine in patients with or without microvascular disease [27]. Aarnoudse *et al.* found that no differences in hyperemic response to adenosine were observed, whether or not α-blockade was given before adenosine administration in 15 patients who did not have microvascular disease. In contrast, although FFR levels statistically significantly decreased in 15 patients with microvascular disease, the further decrease in microvascular resistance after addition of phentolamine was small and did not affect decision making on the basis of a 0.75 cut-off value. It was concluded that there was no need for routine use of α-blocking agents when measuring FFR, not even in patients with signs of microvascular dysfunction. In selected patients who have clear microvascular dysfunction, in which FFR is in the gray zone (0.75 to 0.80), additional intracoronary administration of phentolamine can be used to ensure the presence of truly maximum hyperemia [27].

Anticoagulation

Once the device is advanced into the coronary tree, the same anticoagulation regimens should be applied for PCI: heparin adjusted to weight, validated by a monitored activated coagulation time of at least 250 s, or a fixed number of units per time and/or body weight, in accordance with the local routine [1, 9].

Practical tips

Firstly, it is paramount to unpack the pressure monitoring guide carefully, considering kinking of the pressure monitoring guide. Then, do not damage the sensor while shaping the tip. Although several types of needles are available to introduce the wire into the valve of the Y-connector, a thin needle is recommended but allowing minimal backflow and could be kept in the Y-connector during the procedure, which greatly facilitates the handling of the wire and does not diverge from routine. Similarly, to avoid leakage and loss of aortic pressure, the valve on the Y-connector should be tightly closed. It is essential to equalize both pressures electronically and wait for 5–10 s in the position to ensure absence of drift, which could be distinguished from a true

Table I. Available vasodilators for FFR measurement

Targeted circulation	Pharmacological agents	Infusion method	Dosage
Epicardial vasodilation	Isosorbide dinitrate	IC	At least 200 μg bolus and 30 s before the first measurements
Microvascular vasodilation	Adenosine or ATP	IC	At least 30 μg bolus in the RCA, 40–80 μg in the LCA
		IV	140 μg/kg · min (femoral vein or forearm/antecubital vein)
	Papaverine	IC	10–16 mg in the RCA, 15–20 mg in the LCA
	Regadenoson	IV	A single, weight-unadjusted bolus of 400 μg
	Nitroprusside	IC	0.6 μg/kg, usually 30–50 μg was recommended

ATP – Adenosine triphosphate, IC – intracoronary, IV – intravenously, RCA – right coronary artery, LCA – left coronary artery.

pressure gradient by the identical morphology of the tracings. Once drift is suspected, it is recommended to re-equalize the pressures with the sensor just outside the tip of the guiding catheter. To correct the artifact of whipping and accordion effect, the wire could be pulled back a few millimeters [18].

Fractional flow reserve as functional gold standard

Although in most other clinical scenarios (quantitative) angiography has some limitations, an angiographic approach had been used for years as a gold standard for decision making in treating coronary lesions [15, 28, 29]. Apparently, coronary angiography might be reasonable when it demonstrates either a normal coronary artery or a severely stenotic one in the presence of typical angina, but no correlation with the functional significance of a coronary lesion [15, 30]. Thus, even experienced investigators are often unable to predict the significance of stenosis based on the angiography, which might result in inappropriate PCI of lesions not causing ischemia or failure to revascularize significant ones [15].

After decades of development, FFR has evolved into the gold standard for invasive assessment of physiologic stenosis significance [9, 14]. It is an accurate and lesion-specific index to indicate whether a stenosis or coronary segment can be responsible for ischemia, which has shown that deferring stenting in an FFR-negative stenosis (i.e., in the non-ischemic zone) is safe and associated with excellent long-term outcome. On the other hand, revascularization of an FFR-positive stenosis (i.e., in the ischemic zone) is associated with a significant decrease in ischemia and an improved outcome [3, 9, 31, 32].

Recently, many novel techniques, including quantitative coronary angiography (QCA), coronary CT angiography (CCTA), cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI), intravenous ultrasound (IVUS), optical coherence tomography (OCT), dynamic 3-dimensional CMR, have emerged with FFR as a functional gold standard for the assessment of hemodynamically significant lesions [33–41] (Table II). The results suggested that minimal lumen diameter (MLD) and lesion length (LL) measured by QCA were well correlated with FFR values, which indicated that both MLD and LL had physiological significance in coronary lesions [33–35, 38, 39]. Transluminal attenuation gradient (TAG) and corrected coronary opacification (CCO), as two of the novel analyses of CCTA, have not been physiologically validated [36]. Choi *et al.* compared the diagnostic performance of TAG and CCO with invasive FFR, which showed that they had a moderate correlation with physiological coronary artery stenosis [36].

However, the cutoff value of FFR which deemed a stenosis as functionally "significant" is controversial. Although the initial validation studies determined that an FFR < 0.75 most strongly correlated with ischemia (sensitivity 88%, specificity

Table II. The FFR as functional gold standard in various novel measurements of coronary stenosis

Reference	Diagnostic method		No. of patients	No. of lesions	FFR cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
30	QCA	LL/MLD4 ratio ≤ 12	41 (30 male)	46	0.80	–	94	–	–	82
31	QCA	MLD ≥ 1.6 mm	106	121	0.75	63	82	–	96	–
32	QCA	LL > 16.1 mm	136	163	0.80	86	94	–	–	–
33	CCTA	TAG ≤ –0.654	63	97	0.80	47.5	91.2	–	79.2	71.2
		CCO > 0.063				65.0	61.4	–	54.2	71.4
34	CMR-MPI	Patient-based	103 (66% male)	–	0.80	89	88	88	85	91
		Vessel-based				80	93	90	79	94
35	IVUS	MLA < 3.09 mm^2	185 (66.4% male)	205	0.80	69.2	79.5	–	–	–
36	OCT	MLA < 1.91 mm^2	59	62	0.75	93.5	77.4	–	–	–
		MLD < 1.35 mm				90.3	80.6	–	–	–
		Percent lumen area stenosis > 70.0%				96.8	83.9	–	–	–
37	CMR	Patient-based	64	159	0.75	91	90	91	–	–
		Vessel-based				79	92	88	–	–

QCA – Quantitative coronary angiography, LL – lesion length, MLD – minimum luminal diameter, CCTA – coronary CT angiography, TAG – transluminal attenuation gradient, CCO – corrected coronary opacification, CMR-MPI – cardiac magnetic resonance myocardial perfusion imaging, IVUS – intravenous ultrasound, MLA – minimum lumen area, OCT – optical coherence tomography, "–"– not available.

100%, overall accuracy 93%), there is a small zone of FFR uncertainty between 0.75 and 0.80 [42]. These "borderline" values may, in fact, be significant in some cases and require clinical judgment. For the sake of improved sensitivity, however, many clinicians currently consider an FFR ≤ 0.80 as "ischemic" [5, 6, 15, 16]. It was advised that sound clinical judgment (taking into account the character of symptoms, results of noninvasive tests if available, and whether a gradient is focal or diffuse) should balance the final decision between 0.75 and 0.80 [9].

Clinical application of fractional flow reserve

Traditionally, the applications of FFR in angiographic intermediate stenosis, multi-vessel disease, left main coronary artery stenosis, bifurcation lesions, post-intervention, diffuse disease or after myocardial infarction (MI) have been proved of great benefit by their robust clinical outcome [1, 2, 9, 15, 43–46]. Recently, studies further validated the application of FFR in stable CAD, serial stenosis in one vessel, small vessel stenosis, unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and intermediate stenosis of coronary artery bypass grafts (CABGs) (Table III).

Stable coronary artery disease

The Fractional Flow Reserve versus Angiography For Multivessel Evaluation (FAME) studies have found superior clinical outcomes with FFR-based PCI compared with conventional angiography-based treatment [5]. But for stable CAD patients, advocates for PCI continue to search for sound evidence that revascularization improves prognosis, though it is well established that PCI in patients with stable but symptomatic CAD relieves angina and improves quality of life [47–49]. Thus, De Bruyne *et al.* in the FAME α trial measured the FFR in patients with stable CAD and found that FFR-guided PCI plus best available medical therapy (MT) reduced urgent revascularization, but not death or nonfatal myocardial infarction, compared with MT alone in patients with stable CAD [6, 48]. However, the debate goes on whether FFR-guided PCI plus best available MT is superior to best available MT alone, and even the opposite conclusion was drawn: MT was superior because it reduced the need for revascularization [50, 51]. The proportion of patients with an elective revascularization was 100% in the PCI group vs. 8.6% in the MT group, an absolute reduction of 91.4 percentage points, which is 10 times as high as the absolute reduction of 9.5% in urgent revascularization attributable to PCI [51]. Moreover, there is concern that investigators may have had a lower threshold for recommending revascularization for a patient in the MT group who had recurrent angi-

Table III. Emerging clinical applications and outcomes of FFR-guided PCI

Reference	No. of patients	Follow-up [years]	Application	Cutoff value of FFR	Death or myocardial infarction			Revascularization			Other events	
					Surgical/ FFR-guided group (%)	Deferred/ angio-guided group (%)	Value of *p*	Surgical/ FFR-guided group (%)	Deferred/ angio-guided group (%)	Value of *p*	Surgical/ FFR-guided group (%)	Deferred/ angio-guided group (%)
De Bruyne *et al.*	888	5	Stable CAD	0.80	15 (3.4)	17 (3.9)	0.22	14 (3.1)	86 (19.5)	< 0.001	6 (1.3)	3 (0.7)
Kim *et al.* [44]	131	1.37 ±0.85	Serial stenosis in one vessel	0.80	1	0	NC	1	0	NC	0	0
Puymirat *et al.* [45]	717	3.3	Small vessel stenosis	0.80	13 (6)	65 (14)	0.003	22 (10)	86 (18)	0.006	0	6 (1.3)
Sels *et al.* [46]	1005	2	UA/NSTEMI	0.80	15 (10.0)	30 (16.9)	0.624	20 (13.3)	25 (14.0)	0.556	4 (2.7)	10 (5.6)
			SA		28 (7.8)	34 (10.7)		34 (9.5)	38 (11.9)		3 (0.8)	10 (3.1)
Di Serafino *et al.* [72]	223	4	CABGs	0.80	12 (18)	50 (33)	0.041	9 (14)	33 (22)	0.17	10 (15)	46 (30)

*PCI – Percutaneous coronary intervention. *Surgical group/deferred group, #FFR-guided group/angio-guided group, NC – not calculated, UA – unstable angina, NSTEMI – non-ST-segment elevation myocardial infarction, SA – stable angina, CABGs – coronary artery bypass grafts.*

na rather than attempting to continue managing the symptoms with aggressive medical measures. Besides, ischemia was not assessed by means of noninvasive testing in patients who had lesions with an FFR of 0.8 or less [52]. The authors would have studied long-term outcomes ideally as the follow-up period was probably too short for restenosis to emerge [48, 52]. We hoped that this trial would extend our scientific knowledge far beyond previously published studies [5, 49, 53–56], but this trial did not provide additional guidance to physicians treating individual patients with stable angina with little evidence of long-term, incremental benefit on prognostically important clinical outcomes [48, 52]. However, landmark analyses were performed in the FAME α trial according to a landmark point at 7 days [6]. They found that the strategy of PCI plus the best available MT was more beneficial 7 days after randomization, with interactions between time and treatment with respect to the primary end point, as well as with respect to death and MI, suggesting that the benefit of PCI plus the best available MT might become more pronounced with an increasing duration of follow-up [6].

Serial stenosis in one vessel

When several stenoses are present in the same artery, the concept and the clinical value of FFR are still valid to assess the effect of all stenoses together which can be calculated for each stenosis individually [9]. However, this is neither practical nor easy to perform, and has only been demonstrated in an animal model and a small human study over a decade ago [57, 58]. Recently, Kim *et al.* reported the clinical outcomes of 131 patients with serial moderate stenosis treated with drug-eluting stents using an FFR-guided approach. With the event rate at a median of 509 days being low with 1 in-stent restenosis, 1 MI, 1 non-cardiac death, and no events related to deferred lesions, it was concluded that the FFR-guided revascularization strategy using pullback pressure tracing in serial stenosis was safe, effective and maximizes the benefit of PCI with drug-eluting stents in patients with multiple stenosis in one vessel [44]. Nevertheless, this was not a study of a physiologically guided approach versus a standard angiographic access. Besides, the accuracy of clinical events was limited by the small sample size. Therefore, it would be hard to justify a randomized trial where the current strategy of FFR-guided treatment of each stenosis is compared with stenting of all moderate lesions when a net ischemic effect is present [59].

Small vessel stenosis

The PCI of small coronary vessels represents 30–50% of catheter-based coronary interventions performed worldwide each year [60–62]. Despite the morphological appearance, in fact, only one-third of the lesions seen in small vessels turned out to be functionally significant [63]. The PCI of small-vessel stenosis remains questionable as it does not improve clinical outcome of non-functionally significant lesions but with potential procedural or stent-related risks. Thus, Puymirat *et al.* enrolled 717 patients (495 angio-guided, 222 FFR-guided) with stable or unstable angina in small native coronary vessels (reference vessel diameter and stent size < 3 mm) from January 2004 to December 2008 [45]. With a follow-up in 97.5% of the patients, the conclusion was drawn that FFR-guided PCI of small coronary arteries is safe and results in better clinical outcomes when compared with an angio-guided PCI. This is the largest retrospective registry of an FFR-guided PCI strategy in small-vessel disease with the longest clinical follow-up. However, as a retrospective and non-randomized clinical trial, it must be acknowledged that factors cannot be accounted for that influence the operator's decision to adopt a particular strategy. Moreover, only patients with stable and unstable angina were recruited. Therefore, the inclusion of patients with NSTEMI or STEMI might lead to higher operator-dependent bias.

Unstable angina or non-ST-segment elevation myocardial infarction

The study of FFR-guided PCI in patients with UA and NSTEMI is limited. Several retrospective and a few prospective studies have indicated that in such patients FFR can be used in a similar way as in patients with stable angina (SA) [64–66]. On the other hand, using FFR to guide PCI in multivessel disease resulted in significant reduction of MI and mortality at 2 years shown in the FAME study [67]. Recently, Sels *et al.* in a FAME study included 1005 patients with multi-vessel disease amenable to PCI and randomized them to either angiography-guided PCI of all lesions ≥ 50% or FFR-guided PCI of lesions with an FFR ≤ 0.80 [46]. Patients admitted for UA or NSTEMI with positive troponin but total creatine kinase < 1000 U/l were eligible for inclusion. It was found that the benefit of using FFR to guide PCI in multi-vessel disease does not differ between patients with UA or NSTEMI, compared with patients with SA. There was concern about the use of FFR in acute coronary syndromes limited by microvascular obstruction, although it is still debatable [68–71]. However, in UA or NSTEMI with creatine kinase < 1,000 U/l as defined in the FAME study, the degree of microvascular obstruction, if present, was limited or rapidly transient so that the usefulness of FFR for selection of lesions was not affected by UA or NSTEMI [46].

Intermediate stenosis of coronary artery bypass grafts

Appropriateness of PCI in bypass grafts is crucial, especially in intermediate equivocal stenosis, to avoid exposing patients to unacceptable higher procedural risks without significant clinical benefit [72]. Although FFR-guided PCI of native intermediate coronary stenosis is safe and associated with an improved long-term clinical outcome, it is unknown whether this applies to CABGs. Thus, Di Serafino *et al.* included 223 patients with CABGs and with SA or UA and at least one intermediate stenosis of an arterial or a venous bypass graft from January 2000 until June 2011 [72]. Patients were then divided into 2 groups: FFR-guided (n = 65, PCI performed in case of FFR ≤ 0.80) and angio-guided (n = 158, PCI performed based on angiographic evaluation). They found that FFR-guided PCI of intermediate stenosis in CABGs is safe and results in a better clinical outcome as compared with an angiography-guided PCI. This clinical benefit was more pronounced in arterial grafts. In saphenous vein grafts, the FFR-guided strategy was associated with a significant reduction in PCI rate and procedural-related MI, with no excess risk up to 4 years' follow-up. In addition, a significant overall reduction in procedural costs has also been observed [72]. However, this study has limitations inherent to all retrospective registries, that is, underreporting of events and bias related to the operator's decision as to the revascularization strategy. The sample size is also limited, reflecting the low adoption of FFR in CABGs. Moreover, only patients with SA and UA were included; therefore, the conclusions cannot be extended to patients with NSTEMI and STEMI.

New technologies for fractional flow reserve measurement

Despite extensive evidence regarding the reliability of pressure-wire-derived FFR, it is an invasive, costly and time-consuming procedure. Additionally, the procedure associated with advancing a pressure wire across the lesion may increase the potential risks of plaque rupture and damage of the vessel wall [30]. With the interdisciplinary technology and skills, studies of novel FFR measurement based on coronary angiography and CT angiography present great potential.

Angiographic volume-derived fractional flow reserve measurements

A novel angiographic volume-derived FFR (FFR_V) has recently been investigated with coronary blood flow and arterial lumen volume based on first pass distribution analysis and scaling laws [30, 73–75]. It was found that pressure-wire measurements of FFR correlated linearly with FFR_V according to the equation: $FFR = 0.41\ FFR_V + 0.52$ ($p < 0.001$) and the correlation coefficient and standard error of estimate were 0.85 and 0.07, respectively [75]. Thence, this angiographic technique was deemed a potential assessment of the physiological severity of a coronary stenosis during routine diagnostic cardiac catheterization without a need to cross a stenosis with a pressure wire [75, 76].

However, this angiographic technique was only validated in a small sample size of a swine model [30, 75, 76], which may reduce its reliability and validity. Furthermore, only coronary angiograms without respiratory motion were analyzed for angiographic FFR, which cannot always be expected in a clinical setting [30, 75]. Finally, FFR_V obtained from the process of coronary angiography is still considered an invasive technique, although without a pressure wire.

Noninvasive fractional flow reserve from coronary computed tomography angiography

The CCTA is an effective noninvasive method for direct visualization of coronary artery disease, despite its diagnostic accuracy being in need of improvement [77, 78]. However, recent technological innovations enable non-invasive calculation of FFR from CCTA [79].

To evaluate the diagnostic performance of this new method, the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenosis Obtained Via Noninvasive Fractional Flow Reserve) study involved 103 patients with 159 vessels undergoing CCTA, invasive coronary angiography and FFR. It showed that noninvasive FFR derived from CCTA (FFR_{CT}) had a high diagnostic performance for the detection and exclusion of coronary lesions leading to ischemia [80]. However, the value of FFR was influenced not only by stenosis severity but also by the amount of viable myocardium subtended by the epicardial coronary branch harboring the stenosis. Therefore, similar stenosis might result in a different FFR value in the presence of viable or scarred myocardium [81]. Of note 17% of patients had a history of MI, though it was claimed that patients with recent MI were excluded [82]. Moreover, it showed that the limits of agreement between FFR_{CT} and invasive FFR increased in a manner that was inversely proportional to FFR [83]. Further study revealed that FFR_{CT} was superior to anatomic assessment of stenosis in CCTA for the diagnosis of ischemia-causing lesions [84]. With the potential of improved risk stratification and more appropriate use of invasive resources, it was believed that CCTA should be the first choice approach in the context of novel diagnostic strategies, if the diagnostic accuracy of FFR_{CT} could be improved [85]. However, in a larger follow-up trial of 252 patients, per-patient sensi-

tivity was 90%, but specificity was only 54% [86]. Lower specificity dampened the enthusiasm for the method when the trial was presented recently at the European Society of Cardiology meeting [87]. Although the well-conducted multicenter study did not achieve its prespecified primary goal for the level of per-patient diagnostic accuracy, it was believed that FFR_{CT} plus CT was associated with improved diagnostic accuracy and discrimination compared with CCTA alone [86, 88]. Furthermore, in patients with an intermediate stenosis diagnosed by CTA, FFR_{CT} demonstrated significantly higher diagnostic performance than anatomic assessment alone [77].

Our previous study also developed a noninvasive method for measuring fractional flow reserve (FFRni) through three-dimensional modeling [89]. The differences in the calculation process between FFR_{CT} and FFRni are mainly as follows. The calculation of FFR_{CT} adopted a method to couple lumped parameter models of the microcirculation to the outflow boundaries of the 3D model calculation in which coronary flow and pressure were unknown a priori [90]. Thus, it took approximately 5 h/examination to complete the cumbersome workload [80]. However, we utilized finite element analysis of the Flotran computational fluid dynamics module of ANSYS 11.0 to solve the hemodynamic calculation problems in a given fluid environment, which greatly reduced the computation time to about 3 h/examination.

Prospects and limitations of fractional flow reserve

Considering the clinical use of FFR in a broad spectrum in the catheterization laboratory, we recommend a practical algorithm for management of patients with chest pain adapted from Bugiardini and Bairey Merz (Figure 1) [91, 92]. However, FFR measurement makes no sense in the setting of acute ST-segment elevation MI, which can be applied only when several days have passed [9]. Although it has been validated to apply FFR during primary PCI, the specific ability to assess the hemodynamic severity of lesions is still controversial [93, 94]. Moreover, maximal hyperemia and the guiding catheter significantly contribute to the accuracy of FFR. Finally, the safety of crossing a stenosis with a pressure wire highly depends on the physicians' experience and skills.

Conclusions

Fractional flow reserve is a cost-effective measurement to determine the functional significance of coronary artery lesions and an indispensable tool for decision making in revascularization. There is mounting evidence that FFR-guided decisions to treat or defer the therapy of CAD patients are safe and improve clinical outcomes. As a practical means of assessing hemodynamic significance of stenosis, FFR was easily and rapidly obtained in the catheterization laboratory. The emerging techniques of noninvasive FFR with less clinical risk and higher significant accuracy are encouraging. However, a large sample size with invasive FFR as a reference standard is needed before its application from bench to bedside.

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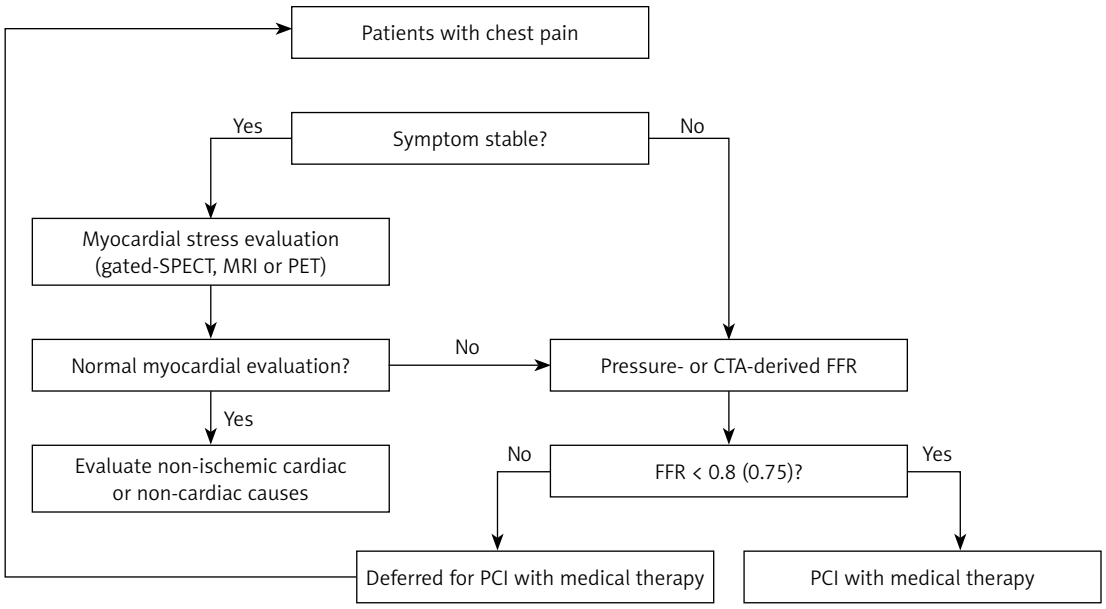

Figure 1. A practical algorithm for management of patients with chest pain

Conflict of interest

The authors declare no conflict of interest.

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