Clinical update

Fundamentals in clinical coronary physiology: why coronary flow is more important than coronary pressure

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Wide attention for the appropriateness of coronary stenting in stable ischaemic heart disease (IHD) has increased interest in coronary physiology to guide decision making. For many, coronary physiology equals the measurement of coronary pressure to calculate the fractional flow reserve (FFR). While accumulating evidence supports the contention that FFR-guided revascularization is superior to revascularization based on coronary angiography, it is frequently overlooked that FFR is a coronary pressure-derived estimate of coronary flow impairment. It is not the same as the direct measures of coronary flow from which it was derived, and which are critical determinants of myocardial ischaemia. This review describes why coronary flow is physiologically and clinically more important than coronary pressure, details the resulting limitations and clinical consequences of FFR-guided clinical decision making, describes the scientific consequences of using FFR as a gold standard reference test, and discusses the potential of coronary flow to improve risk stratification and decision making in IHD.

Keywords Ischaemic heart disease • Coronary flow • Coronary pressure • Coronary flow reserve • Fractional flow reserve

Introduction

The interest in coronary physiology to guide clinical decision making is increasing at a time of drastic economic restrictions and growing attention towards the appropriateness of coronary stenting in stable ischaemic heart disease (IHD). For many practicing physicians, coronary physiology equals the measurement of coronary pressure for the calculation of fractional flow reserve (FFR). Indeed, accumulating evidence supports the contention that FFR-guided revascularization is superior to revascularization based on coronary angiography alone, and it appears that stenoses deemed haemodynamically important by FFR are generally better off treated by percutaneous coronary intervention (PCI) in combination with medical therapy, than by medical therapy alone. However, it is frequently overlooked that FFR is a coronary pressure-derived estimate of coronary flow impairment. It is not the same as the direct measures of coronary flow from which it was derived, and which are the critical determinants of signs and symptoms of myocardial ischaemia.

In this manuscript, we describe why coronary flow is physiologically and clinically more important than coronary pressure and relate this to the limitations and clinical consequences of using FFR as a surrogate of flow impairment to guide clinical decision making, as well as the scientific consequences of using FFR as a gold standard reference test, as is customary in recent literature. Moreover, we describe the clinical potential of direct assessment of coronary flow to improve risk stratification and decision making in stable IHD.

Fractional flow reserve: from surrogate to gold standard in stenosis assessment

Fractional flow reserve, the ratio between mean distal coronary pressure—measured using a coronary pressure wire advanced distal to the coronary stenosis of interest—and mean aortic pressure—measured through the guiding catheter—during maximal vasodilation, was initially derived as a pressure-derived proxy measure of relative coronary flow reserve (rCFR); an estimate of the vasodilator capacity in the narrowed artery as a fraction of the vasodilator capacity in the same artery without the stenosis. Its validation against

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direct measures of flow was performed in a healthy animal model, but FFR has since been applied to a clinical setting that involves a wide scale of cardiovascular risk factors affecting the coronary microcirculation. Nonetheless, this pressure-derived estimate of coronary flow impairment has shown to improve identification of stenoses that require revascularization using a discrete cut-off value in two randomized clinical trials.\(^5,13\) As a result, FFR is now purportedly the gold standard for invasive physiological assessment of coronary lesion severity, and is even used as a reference test for novel diagnostic modalities in the setting of stable IHD.

Unfortunately, among this promotion from surrogate parameter of blood flow impairment to gold standard reference test, details regarding the physiological basis and diagnostic characteristics of FFR have been lost for consideration.

Why can fractional flow reserve be wrong? Misinterpretation of its physiological basis

The use of coronary pressure to estimate coronary flow impairment is based on the assumption that coronary pressure is proportional-linear to coronary flow when coronary resistance is minimal and constant, a condition aimed to satisfy using administration of adenosine.\(^6\) However, the regulation of coronary vascular tone is complex, and is not only mediated by adenosine.\(^8\) As a result, the induction of ‘maximal’ hyperaemia, and hence, a constant coronary resistance required for the validity of FFR, is not achieved by the administration of adenosine alone.\(^5\) Moreover, even if constant coronary resistance could be achieved, the relationship between coronary pressure and flow is not proportional-linear; it has a non-zero pressure intercept and is incremental linear in the physiological range of perfusion pressures, the slope of which is variable (Figure 1). Finally, the application of aortic pressure and distal coronary pressure as estimates of flow in a healthy and stenosed coronary artery, respectively, assumes that the magnitude of minimal coronary resistance is equivalent in stenosed and healthy coronary vessels, even though a body of evidence has documented the opposite.\(^5\) Hence, at best, coronary pressure measurements allow a crude estimation of coronary flow impairment.

Although FFR is frequently advocated to be a stenosis-specific measure, it has to be borne in mind that the application of FFR in contemporary practice—the direct ratio between distal coronary pressure and aortic pressure during hyperaemia—actually forms the myocardial FFR: a pressure-derived estimate of the maximum achievable blood flow to the distal myocardium in the presence of a stenosis as a fraction of the maximum achievable blood flow to the distal myocardium in the absence of a stenosis.\(^7\) This includes contributive factors to total myocardial flow other than flow through the coronary artery of interest, particularly collateral flow. A normal FFR can therefore represent normal myocardial flow due to substantial collateral flow despite very severe stenosis.

Pivotal in the interpretation of the diagnostic characteristics of FFR is the acknowledgement that FFR is derived as a surrogate measure of coronary flow impairment. It is not the same as relative or absolute measures of coronary flow, which are the critical determinants of myocardial ischaemia.\(^6,9,10\) In this regard, it is crucial to understand that myocardial metabolism thrives on coronary blood flow, not on coronary perfusion pressure.\(^6\) Smalling and colleagues elegantly demonstrated that myocardial function is preserved regardless of perfusion pressure, down to FFR values \(\sim 0.4\), given that coronary flow remains stable.\(^1\) Since the pressure drop across a coronary stenosis is determined by the magnitude of coronary flow that goes through it, basic coronary haemodynamics dictate that a pressure drop across a stenosis increases with an increase in coronary flow, and vice versa (Figure 2).\(^5,12\) Hence, a low coronary flow may coexist with a normal FFR value, and a high coronary flow with an abnormal FFR value.\(^5,13\) The fact that such discordance between FFR and measurements of flow occurs in 30–40% of cases illustrates that FFR is frequently not a reliable estimate of coronary flow impairment.\(^13–15\) Since myocardial function depends on flow, and not on perfusion pressure,\(^11,15\) it seems detrimental to consider FFR a gold standard: a hypothesis that has been confirmed in several observational studies.\(^13–18\)

Consequences of applying fractional flow reserve as a dichotomous gold standard in clinical practice

The recent FAME II trial has unequivocally documented the clinical consequences of decision making based on FFR alone in...
temporary guidelines, did not require intervention up to 2 years of normal FFR, whom would thus be eligible for PCI according to contemporary practice. This trial investigated patients with stable IHD, in whom all stenoses eligible for PCI were evaluated with FFR. Those lesions in which FFR was normal (>0.80) were not intervened on and were considered the reference group. Those in which FFR was abnormal (<0.80) in at least one of the assessed coronary stenoses entered the trial and were randomized between optimal medical therapy plus stenting vs. optimal medical therapy alone. At 2-year follow-up, patients randomized to optimal medical therapy plus coronary stenting were found to fare significantly better, with less adverse cardiac events—a composite of (urgent) PCI, myocardial infarction, and cardiac death. Although these overall results suggest that FFR is indeed the go-to tool to guide coronary intervention, there is a flipside to the findings in FAME II. Looking at coronary revascularizations, almost 60% of patients with an abnormal FFR were thus not randomized but deferred based on contemporary revascularization guidelines,19 did not require intervention up to 2 years of follow-up. Moreover, of those patients that had a normal FFR (>0.80), and were thus not randomized but deferred based on the FFR, >10% actually suffered a major adverse cardiac event within the first 2 years of follow-up. The absence of randomized treatment allocation in this arm precludes conclusions as to whether these patients truly would not have benefitted from PCI. Hence, even though FFR-guided intervention may well limit the number of adverse events when compared with angiography-guided intervention, FFR should clearly not be considered a ‘gold standard’ reference test based on its clinical performance.

Why can fractional flow reserve be right? Re-interpretation of clinical data

Despite its fundamental limitations as a surrogate of flow, and the unequivocal consequences in terms of its accuracy to depict those stenoses that require PCI, many physicians blindly adhere to FFR for their decision making in stenoses of equivocal angiographic severity. This approach is based on the documented benefit of FFR-guided intervention in the FAME and FAME II trials, and its advocated use in angiographically intermediate stenoses in contemporary revascularization guidelines. However, for the correct interpretation of these studies, it is critical to acknowledge two interrelated facts. First, despite its dichotomous use in clinical practice, FFR reflects a risk continuum: risk for adverse events is largest in low FFR stenoses and lowest in stenoses with a high FFR. Second, the FAME and FAME II trial populations included all potential revascularization targets resulting in a wide range of FFR values, from normal FFR values to FFR <0.60, whereas contemporary revascularization guidelines advocate the use of FFR in stenoses of intermediate angiographic severity, which leads to clustering of evaluated stenoses within the intermediate FFR range. Since it was documented that the inclusion of very severe coronary stenoses governs the clinical benefit of FFR-guided intervention, it cannot be expected that its use to a restricted range of equivocal angiographic stenoses, as adopted in contemporary practice, bears a similar clinical benefit.

Going back to the early clinical validation of FFR, its optimal cut-off value derived from electrical manifestations of ischaemia during exercise testing was 0.66. It was also documented that coronary flow characteristics that determine the occurrence of objective signs and symptoms of myocardial ischaemia are dominantly associated with FFR values <0.65. Indeed, these cut-offs for ischaemia are drastically lower than the clinical cut-off value of 0.80 used in contemporary practice. A substantially lower ischaemic threshold of FFR than is currently applied may explain the relatively limited benefit of revascularization in all FFR-positive stenoses at the 0.80 cut-off value, where 60% of FFR-positive stenoses did not require any intervention up to 2 years of follow-up. The fact that the dominant effect of PCI over medical therapy alone was attributed to stenoses with FFR <0.65 in FAME II is consistent with this interpretation.

It is conceivable that the benefit of FFR-guided intervention dominantly occurs from treating stenoses with FFR-values that are truly associated with flow impairment, and hence, myocardial ischaemia, while the effect of FFR-guided decision making around the cut-off values is limited at best. This hypothesis was confirmed in an elegant patient-level pooled meta-analysis on the prognostic characteristics of FFR, documenting an optimal prognostic revascularization threshold for FFR of 0.68, which is notably similar to the FFR cut-off
values reported for flow impairment and myocardial ischaemia. Therefore, it may be concluded that the solitary use of FFR in stenoses of intermediate severity using a 0.80 cut-off value, as is advocated in clinical practice guidelines, is not endorsed by the aforementioned clinical trials.

**Microvascular disease: a diagnostic blind spot in fractional flow reserve-guided strategies**

Following decades of a stenosis-centred approach towards stable IHD, it is now recognized that dysfunction of the coronary microcirculation may contribute to, or may even be the sole determinant of signs and symptoms of myocardial ischaemia, and imparts a detrimental prognostic value. Nonetheless, even the most recent clinical practice guidelines on the management of stable IHD focus on the identification of ischaemia-inducing coronary stenoses, whereas microvascular disease is considered only after exclusion of significant epicardial disease. This is in contrast with a well-documented non-focal nature of atherosclerotic disease suggesting that, at the stage where signs and symptoms of stable IHD occur, it is a combination of epicardial and microvascular disease that dictates the inability to meet myocardial demand. Ultimately, the coronary microcirculation has a dominant function in the regulation of myocardial perfusion, and the loss of vasodilator reserve at this level, whether primary or secondary to epicardial disease, dictates the occurrence of myocardial ischaemia.

**Coronary microcirculation: bridging flow and function**

In the healthy coronary circulation, the epicardial conduit arteries comprise only up to 10% of coronary resistance, whereas the coronary arterioles maintain a high level of resistance and constitute the dominant site of myocardial flow regulation. In the healthy vasculature, these resistance vessels are responsible for maintaining stable coronary flow across a wide range of physiological perfusion pressures, a process termed coronary autoregulation, and to adapt myocardial flow to myocardial demand through metabolic vasodilation. As atherosclerosis develops and progresses, the resistance in the coronary arterioles is progressively exhausted: an increase in epicardial resistance or intrinsic disease of the microcirculation is counteracted by adaptive autoregulatory vasodilation of the coronary arterioles to maintain myocardial perfusion. Although myocardial perfusion is initially preserved, myocardial underperfusion occurs at complete exhaustion of the reserve vasodilatory capacity, leading to myocardial ischaemia. At exhaustion of the vasodilatory reserve of the resistance vessels, less prominent factors regulating coronary vascular tone exert greater influence on myocardial perfusion, such as activation of the renin–angiotensin system, and α-adrenergic vasoconstriction induced by sympathetic activation on the coronary circulation, contributing to the occurrence of myocardial ischaemia. Due to the transmural distribution of coronary blood flow and the impeding characteristics of cardiac contraction, the subendocardium is most sensitive to underperfusion, and will be the first to show signs of myocardial ischaemia. In myocardial ischaemia, regional myocardial function adapts to the reduction in myocardial perfusion, termed perfusion–contraction matching. This reduction in contractile function is not the energetic consequence of reduced tissue perfusion, but represents an adaptive response. Repetitive stress-induced myocardial underperfusion may ultimately lead to long-term myocardial hibernation by alterations in myocardial metabolism. These observations illustrate the complexity and importance of the coronary microcirculation in myocardial function and its role in the functional consequences of IHD.

**Microvascular functional status and fractional flow reserve**

Considering the dominant role of the coronary microcirculation in myocardial perfusion and function, the limitations of fractional flow reserve as an estimate of flow impairment play a critical role in two distinct ways. Obviously, in the absence of an epicardial stenosis no pressure drop will occur along the vessel and FFR will be normal. Nonetheless, this normal FFR does not imply that the coronary vasculature is normal, since microvascular disease may occur solitarily, and may be associated with disabling angina complaints and substantially impaired clinical outcome. This pertains to a wide variety of disturbances in the microcirculation, including structural remodeling, coronary micro-embolisation, and peri-interventional reflex coronary vasomotion. It is important to note that this also pertains to the acute and subacute phase of acute coronary syndromes, where neurohumoral activation interferes with the reactivity of the coronary resistance vessels. It is important to realize that FFR is insensitive in low-flow settings. Second, maximal coronary flow is impaired in the setting of microvascular disease, since it limits the vasodilator capacity of the coronary microcirculation. Because the pressure drop across a coronary stenosis, and hence FFR, depends on the magnitude of maximal trans-stenotic flow, FFR is unlikely to be abnormal in low-flow settings regardless of the haemodynamic significance of the coronary stenosis. Accordingly, the underestimation of physiological stenosis severity by FFR in the setting of microvascular dysfunction is known to increase with increasing impairment of the vasodilator capacity of the microvascular bed, both in the setting of stable IHD, as well as in the setting of acute coronary syndromes. The complex multi-level nature of IHD therefore creates a diagnostically and prognostically important blind spot in contemporary FFR-guided strategies.

**Beyond coronary pressure assessment of the coronary circulation: coronary flow assessment and coronary flow (velocity) reserve**

Several techniques allow the direct assessment of coronary or myocardial flow, and the evaluation of microvascular functional status in the clinical setting. Non-invasive modalities such as positron emission tomography and magnetic resonance imaging allow quantitative assessment of regional myocardial flow in milliliters per grams of tissue, as well as regional flow reserve. However, non-invasive tools
do not allow ad hoc evaluation of coronary flow during invasive coronary angiography. Invasive flow assessment is technically more demanding than coronary pressure measurements. It can be performed by means of the thermodilution or Doppler technique, both of which provide a measure of coronary flow velocity. The measurement of invasive coronary flow is substantially more challenging than coronary pressure measurements, which has largely dictated the clinical preference of coronary pressure over coronary flow, despite its inherent limitations. For example, thermodilution measurements require the administration of multiple brisk saline boluses to obtain coronary thermodilution curves and calculate mean transit times. Besides the requisite disturbance of coronary haemodynamics by saline injections, which can be perceived as a confounder especially in the assessment of basal flow levels, the assessment of coronary flow with the thermodilution technique requires several important precautions, which have been described in detail elsewhere. The Doppler technique provides a more direct assessment of flow velocity, but is technically more challenging and therefore likely more prone to measurement error if not performed by operators with ample experience. This owes to the fact that wire positioning is critical to obtain a good quality flow velocity profile, which has been described in detail elsewhere. Nonetheless, two advantages of the measurement of invasive flow velocity are the ability to directly evaluate the coronary artery of interest, as well as the fact that the magnitude of flow velocity is intrinsically corrected for the amount of perfused myocardial mass in the arterial distribution. Flow velocity in the coronary circulation is only moderately reduced at every bifurcation due to the diameter reduction of the daughter vessels. Since the reduction in coronary diameter with branching of the coronary tree is directly related to the amount of perfused myocardial mass by the observed laws of normalized shear stress. Flow velocity yields an inherent correction of absolute flow velocity values for the amount of perfused myocardial mass.

Coronary flow reserve, the ratio of coronary flow (velocity) during maximal vasodilation to coronary flow (velocity) during resting conditions, is a widely studied and well-validated flow-based physiological parameter, and has been applied successfully to a wide scala of invasive and non-invasive diagnostic modalities. Regardless of the modality applied, CFR has consistently shown paramount prognostic relevance in stable IHD. However, the assessment of CFR, similar to FFR, requires the induction of maximal vasodilation. As noted previously, the requisite of maximal hyperaemia is cumbersome in clinical practice, and a debate continues regarding the method to optimally induce coronary vasodilation in clinical practice, which has been discussed in detail elsewhere. Moreover, the usefulness of CFR for diagnostic purposes in obstructive coronary artery disease has been questioned as it is influenced by clinical and haemodynamic parameters. Combined with its relative technical complexity, this led to its abandonment at large in the physiological guidance of epicardial coronary revascularization when the easily applicable coronary pressure-derived FFR was introduced. Despite the resulting lack of technological advances in the field of invasive coronary flow assessment, perseverance of scientific efforts has now resulted in pivotal insights into the pathophysiology of stable IHD. The crux of these insights lies in the appreciation of disagreements between coronary flow- and pressure-based evaluations of the coronary circulation.

Fractional flow reserve and its discordance with coronary flow reserve

Where the clinical performance of FFR in large randomized clinical studies led to the assumption that disagreements between FFR and CFR were due to the limitations and diagnostic inefficiency of CFR, it is now recognized that pertinent coronary pathophysiology explains this phenomenon. This is plausible, since, in retrospect, the diagnostic characteristics of CFR in terms of its ability to identify ischaemia-producing coronary stenoses and prognostic value for the occurrence of adverse events have always been notably similar to that of FFR. It is now acknowledged that CFR and FFR actually interrogate different domains of the coronary circulation; dominantly the epicardial domain for FFR, though influenced by the microvasculature, and both the epicardial and microvascular domains for CFR, suggesting that the relative functional status of these domains influences the agreement between FFR and CFR. Accordingly, recent reports have illustrated that the relative involvement of the epicardial and microvascular domains of the coronary circulation indeed drives the occurrence of discordance between FFR and CFR, which notably occurs in 30–40% of vessels with stenoses of equivocal angiographic severity, and thus applies to a substantial proportion of patients in daily clinical practice.

Considering the dichotomous agreement between FFR and CFR, four quadrants can be identified (Figure 3). Fractional flow reserve and CFR may be concordantly normal, where both the flow characteristics in the circulation are normal and no substantial pressure loss occurs along the coronary artery of interest. On the opposite of the spectrum, FFR and CFR may be concordantly abnormal, indicating that an epicardial coronary stenosis is so severe that coronary flow is severely impaired, and a haemodynamically significant reduction in coronary perfusion pressure occurs even at low maximal trans-stenotic flow. The discordance between FFR and CFR is diagnostically more complex. When FFR is abnormal and CFR is above normal thresholds, the concerning stenosis is non-flow limiting. From basic stenosis haemodynamics, it can be appreciated that the large pressure drop across such a stenosis, and thus the low FFR, is due to an impaired vasodilator response of the coronary vasculature resulting in a large trans-stenotic flow-induced pressure gradient. These stenoses were documented to carry a low risk for adverse events during long-term follow-up, equivalent to those stenoses in which both FFR and CFR are normal (Figure 4). This finding is in accordance with the dependence of myocardial function on flow, and confirms the hypothesis that preservation or restoration of myocardial flow determines clinical outcomes. Hence, despite a substantial pressure drop across the stenosis, these lesions are not likely to be optimally managed by PCI.

On the other hand, when FFR is normal while CFR is impaired, three pathophysiological patterns may (co)exist. First, it may be an expression of diffuse epicardial coronary artery disease. Due to the lack of convective acceleration and flow separation losses,
responsible for pressure drops across focal stenoses, FFR tends to remain unimpaired in diffuse disease even though CFR can be drastically reduced. On the other hand, the normal FFR may be a reflection of an undiseased epicardial artery, whereas the reduction in CFR may be an expression of pure microvascular disease; this is likely when CFR is impaired but FFR approaches normal values. Finally, this pattern may be a reflection of a combination of microvascular and epicardial coronary artery disease, where the low-flow situation induced by the microvascular dysfunction prevents the generation of a large pressure drop across the stenosis, and hence FFR remains relatively normal despite the presence of a haemodynamically significant stenosis. Importantly, this patient population was found to be at high risk for adverse events (Figure 4), and constitutes an important blind spot in contemporary diagnostic strategies in IHD.15,17

Nonetheless, although physiologically plausible,15,32 and supported by non-invasive studies on CFR,17,18,49 direct clinical outcome data on discordance between FFR and CFR as presented in Figure 4 remain scarce and derived from relatively small observational studies.15 This is the subject of the ongoing prospective DEFINE-FLOW trial (NCT02328820), aiming to define the clinical pertinence of FFR/CFR discordance in a prospective multicentre setting.

A novel diagnostic approach to ischaemic heart disease: putting flow first

The above-mentioned considerations illustrate the diagnostic complexity of IHD that originates from the relative involvement of the epicardial coronary artery and the distal microvasculature, and the diagnostic blind spot that is created when FFR is measured solitarily. Therefore, it is crucial to develop diagnostic strategies that incorporate assessment of all levels of the coronary circulation in the primary evaluation of patients with suspected stable IHD in order to identify those patients that require further evaluation for potential revascularization targets or close follow-up in case of a high risk for adverse events.

Using flow to determine the eligibility for revascularization

If the critical aspect in the risk for future adverse events and the clinical benefit of revascularization is the presence of impaired coronary flow, a robust flow-based approach towards IHD would allow a more optimal patient selection. Although CFR would allow a comprehensive assessment of flow impairment of the coronary vasculature, its dependence on resting haemodynamics is an important theoretical limitation for its use as a primary diagnostic tool in IHD. However, the flow characteristic of a vascular territory may
be described by three variables, baseline flow, hyperaemic flow, and CFR, two of which are independent. Consequently, the integration of two of these variables allows a complete description of the flow characteristics of the vascular territory of interest. On this basis, it was recently suggested that integrating both CFR and maximal flow in a physiological concept, termed coronary flow capacity, allows comprehensive assessment of flow impairment in IHD (Figure 5). This concept has been linked unequivocally to objective signs and symptoms of myocardial ischaemia, and overcomes many of the limitations of using CFR alone since it is insensitive to alterations in resting haemodynamics. It also overcomes many of the limitations of using FFR alone as a first-line diagnostic tool in IHD, since it allows comprehensive assessment of both obstructive and non-obstructive causes of myocardial ischaemia.

Conceptually, a diagnostic approach in IHD aiming to identify flow impairment, regardless of its obstructive or non-obstructive origin, should be favoured over a diagnostic algorithm that only aims to address focal obstructive disease. A comprehensive flow-based approach would simply allow more adequate identification of patients in whom the expressed symptoms are indeed the results of perfusion impairment.

**Combining coronary pressure and flow to assess revascularization targets**

Once critical flow impairment is documented, further assessment should focus on the identification of revascularization targets and potential microvascular involvement. As noted previously, CFR is not an optimal tool for this purpose, since it is affected by both epicardial and microvascular involvement and therefore does not allow to identify their relative involvement. Fractional flow reserve is not optimal either, since microvascular disease may obscure the haemodynamic relevance of obstructive epicardial disease, and revascularization targets may be missed. Combining coronary pressure and flow assessment in clinical practice allows to calculate the resistance to coronary blood flow induced by the epicardial stenosis—by means of the hyperaemic or basal stenosis resistance index, and the coronary microcirculation—by means of the hyperaemic
Conclusions

Coronary flow is fundamentally more important for myocardial function than coronary pressure and therefore constitutes the parameter of interest for diagnostic strategies. Although FFR has yielded an important progress in the diagnosis of obstructive coronary artery disease as a pressure-derived estimate of blood flow impairment, it should be borne in mind that substantial limitations originate from the fact that FFR represents a surrogate of direct measures of coronary flow impairment from which it was derived. With the documentation of a complex multi-level involvement of the coronary circulation in IHD, and the suboptimal performance of FFR-guided intervention, it is no longer tenable to delay the introduction of more comprehensive diagnostic strategies that aim to directly identify perfusion impairment for clinical decision making.

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De Bruyne B, Pijls NHJ, Smith L, Wievegg M, Heyndrickx GR. Coronary thermo-

Barbato E, Aarnoudse W, Aengevaeren WR, Werner G, Klauss V, Bojara W,

Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A,

Mosher P, Ross J, McFate PA, Shaw RF. Control of coronary blood flow by an

Deussen A, Ohanyan V, Jannasch A, Yin L, Chilian W. Mechanisms of metabolic

Heusch G. The regional myocardial flow-function relationship: a framework for an

Heusch G, Libby P, Gersh B, Yellon D, Bohm M, Lopaschuk G, Opie L. Cardiovas-

Niccoli G, Falcioni E, Cosentino N, Fracassi F, Roberto M, Fabretti A, Panebianco M,

Doucette JW, Corl PD, Payne HM, Flynn AE, Goto M, Nassi M, Segal J. Validation of
dilution to assess flow reserve: experimental validation.

32. Liu Y, Guterman DD. Vascular control in humans: focus on the coronary micro-

33. Mosher P, Ross J, McFate PA, Shaw RF. Control of coronary blood flow by an


38. Heusch G, Libby P, Gersh B, Yellon D, Bohn M, Lopaschuk G, Opie L. Cardiovas-


40. Seiler C, Kirkeeide RL, Gould KL. Basic structure-function relations of the epicar-
