Review Article

Clinical Relevance of Coronary Fractional Flow Reserve: Art-of-state

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Abstract

Objective: The objective was to delineate the current knowledge of fractional flow reserve (FFR) in terms of definition, features, clinical applications, and pitfalls of measurement of FFR.

Data Sources: We searched database for primary studies published in English. The database of National Library of Medicine (NLM), MEDLINE, and PubMed up to July 2014 was used to conduct a search using the keyword term "FFR".

Study Selection: The articles about the definition, features, clinical application, and pitfalls of measurement of FFR were identified, retrieved, and reviewed.

Results: Coronary pressure-derived FFR rapidly assesses the hemodynamic significance of individual coronary artery lesions and can readily be performed in the catheterization laboratory. The use of FFR has been shown to effectively guide coronary revascularization procedures leading to improved patient outcomes.

Conclusions: FFR is a valuable tool to determine the functional significance of coronary stenosis. It combines physiological and anatomical information, and can be followed immediately by percutaneous coronary intervention (PCI) if necessary. The technique of FFR measurement can be performed easily, rapidly, and safely in the catheterization laboratory. By systematic use of FFR in dubious stenosis and multi-vessel disease, PCI can be made an even more effective and better treatment than it is currently. The current clinical evidence for FFR should encourage cardiologists to use this tool in the catheterization laboratory.

Key words: Clinical Application; Features; Fractional Flow Reserve; Limitation

Introduction

Coronary angiography still plays a pivotal role in invasive imaging of the coronary arteries. However, it is limited in its ability to determine the physiologic significance of coronary stenosis.[1,2] It is important to emphasize that in coronary artery disease, the most important factor related to outcome is the presence and extent of inducible ischemia.[3,4] A functionally significant stenosis should be revascularized if technically possible.[5-7] On the other hand, if a stenosis has no functional significance, medical treatment is excellent with an infarction and a mortality rate of <1% per year.[7,8] Intracoronary (IC) physiologic measurement of myocardial fractional flow reserve (FFR) was introduced and has proven to be a reliable method.[9] An FFR value of 0.80 or less identifies ischemia-causing coronary stenoses with an accuracy of more than 90%.[9-11] An incontrovertible proof of the benefit of FFR-guided multivessel percutaneous coronary intervention (PCI) compared with standard angiography was provided in the large randomized, multicenter FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study.[7,12] In that study, it was demonstrated that all types of adverse events were decreased by 30% in the 1st year after PCI when guided by FFR. The information provided by FFR is similar to that obtained with myocardial perfusion studies, but it is more specific and has a better spatial resolution, because every artery or segment is analyzed separately, and masking of one ischemic area by another, more severely ischemic, zone is avoided.[13,14] Despite all the benefits, there are several pitfalls related to FFR measurement and a few clinical situations, in which it is not reliable and should not be applied.

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Definition of Fractional Flow Reserve

Fractional flow reserve is defined as the ratio of maximum blood flow in a stenotic artery to maximum blood flow if the same artery is normal assuming that these measurements are obtained when the microvasculature resistance is minimal and constant (maximal hyperemia).[9,10,15-17] This ratio of the two flows is expressed as the ratio of two pressures,

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which can be easily measured by a pressure wire and the guiding catheter, respectively. Therefore, FFR equals Pd/Pa, where Pd is the distal coronary pressure across the stenosis, and Pa is the aortic pressure, both measured at maximum coronary hyperemia. FFR shows how far maximal myocardial blood flow is limited when epicardial stenosis is presence. FFR of 0.60 means that the maximum blood flow (and oxygen supply) to the myocardial distribution of the respective artery only reaches 60% of what it would be if that artery was completely normal. An increase to 0.90 after stenting indicates that maximum blood supply has now increased by 50%. Therefore, FFR is linearly related to maximum blood flow, and its normal value is 1.0, irrespective of the patient, artery, blood pressure, and so forth. The measurement of FFR is independent of changes in systemic blood pressure, heart rate, or myocardial contractility and is highly reproducible.[15,18] The concept of FFR is explained in Figure 1.

Fractional Flow Reserve Practicalities

Catheters

In general, a 6F guiding catheter is used because the lumen of such catheter is large and smooth and easily accommodates advancement of a pressure guidewire. However, a recent study by Legalery *et al*.[19] has demonstrated that FFR measurement can also be safely performed through a conventional 4F diagnostic catheter. The use of diagnostic catheters is technically feasible. However, due to the higher levels of friction hampering wire manipulation, the smaller internal caliber prejudicing pressure measurements and the inability to perform ad hoc PCI using diagnostic catheters, the use of guiding catheters is recommended.[20]

Wires

At present, two Food and Drug Administration (FDA)-approved pressure wire systems are available: Pressure Analyzer (RADI Medical Systems, Uppsala, Sweden) and WaveMap (Volcano Therapeutics Inc., Rancho Cordova, USA). Both are 0.014-inch in diameter and, therefore, allow all possible coronary interventions without needing another guidewire. The sensor is located 30 mm from the tip, at the junction between the radiopaque and radiolucent portions. The last generations of these 0.014-inch wires have similar handling characteristics to most standard angioplasty guide wires. The PressureWireVR from St. Jude Medical (St Pauls, MN, USA)/Radi Medical Systems (Uppsala, Sweden) also offers a thermodilution capability that allows measurement of the index of myocardial resistance and absolute coronary blood flow. In addition, the later wire also exists in a "wireless" version: PressureWireVR Aeris in which the signals are transmitted by radiofrequency to a receiver directly connected to the conventional catheterization laboratory physiologic monitoring system, therefore eliminating the need for any dedicated interface.

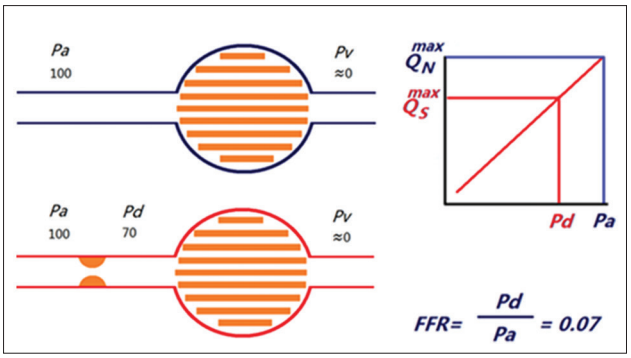

Figure 1: Concept of fractional flow reserve. In the case of stenosis responsible for a hyperemic pressure gradient of 30 mmHg (red lines), the driving pressure will no longer be 100 mmHg but 70 mmHg (Pd). Since the relationship between driving pressure and myocardial blood flow is linear during maximal hyperemia, myocardial blood flow will only reach 70% of its normal value. This numerical example shows how a ratio of two pressure (Pd/Pa) corresponds to a ratio of two flows (QmaxS/QmaxN).

Hyperemia

To measure FFR, it is absolutely essential to achieve maximal vasodilatation of the two vascular compartments of the coronary circulation, namely the epicardial (conductance arteries) and the microvascular arteries (resistance arteries). If maximal vasodilatation is not achieved, the pressure gradient across a lesion will be smaller than expected, and FFR will be overestimated. Consequently, the severity of the lesion will be underestimated. Practically speaking, a desirable hyperemic stimulant should fulfill the following criteria: Rapid onset and short duration of action, low cost, lack of significant side effects, and stable steady state. Several hyperemic stimulants, delivered either through IC injection or as a continuous intravenous (IV) infusion, have been used for this purpose, including adenosine,[21] adenosine 5'-triphosphate (ATP),[22-24] and papaverine.[25] IC papaverine is cheap and creates maximum hyperemia for approximately 30–60s, but has the disadvantage of inducing arrhythmias in some patients. IC adenosine or ATP creates hyperemia for a few seconds only and can be used in patients with 1-vessel disease and no other abnormalities. It does not allow for performance of a pressure pullback recording. IV administration of adenosine (particularly by the central venous route) is the gold standard for creating hyperemia, acts within 1 min, creates a steady state level of maximum hyperemia and is safe. The disadvantage is an unpleasant feeling in the chest or the throat of the patient (which is harmless, and that should be emphasized). IV adenosine is contraindicated in cases of severe asthma. ATP can be used as an equivalent to adenosine (similar dosage). In the experience of the Catharina Hospital in more than 11,000 patients undergoing FFR measurements, IV adenosine was used in 98%, and only two serious adverse events were observed (0.02%).[26] The different hyperemic drugs and their actions are summarized in Table 1.

The new hyperemic agents such as regadenoson and nicorandil, for invasive physiologic assessment, were also available now.[21] Nair *et al*.[27] compared the hyperemic efficacy between

Table 1: Hyperemic agents and their actions

Agent	Peak effect	Side effects	Comments
ATP	Duration of infusion	Dyspnea, chest pain	Does not allow pullback
Papaverine	60 s	Transient AV block	Not used commonly
Nitroprusside	30 s	Hypotension	Not well-studied
Dobutamine	Duration of infusion	Tachycardia	Slow onset
Regadenoson	2-3 min	Dyspnea, chest pain, headache	Not well-studied with FFR

ATP: Adenosine triphosphate; AV: Atrioventricular; FFR: Fractional flow reserve.

a selective A_2A receptor antagonist, regadenoson (400 μg, IV bolus) and adenosine in 25 patients with intermediate coronary stenosis and found that a single IV bolus of regadenoson was as effective as an IV infusion of adenosine. Jang *et al*.[28] compared the hyperemic efficacy of a bolus administration of nicorandil (IC, 2 mg) with continuous infusion of adenosine in 210 patients. In this study, hyperemic efficacy of nicorandil was not inferior to that of adenosine (0.82 ± 0.10 vs. 0.82 ± 0.10; for noninferiority, $P < 0.001$) and there was a strong linear correlation between the FFR measured by IV infusion of adenosine and nicorandil ($R^2 = 0.934$). Moreover, nicorandil caused less change in mean blood pressure, heart rate, PR interval, and less severe chest pain than adenosine ($P < 0.05$). While transient atrioventricular block occurred in 16 patients with adenosine, none was detected with nicorandil. These novel agents and methods of adenosine administration will cause less discomfort in patients and reduce the complexity of invasive physiologic assessment.

Anticoagulation

As soon as any device is advanced into the coronary tree, the use of the same anticoagulation regimens as routinely used during a PCI is recommended: Heparin adjusted to weight, validated by a monitored activated coagulation time of at least 250 s, or a fixed number of units/time and/or body weight, in accordance with the local routine.

Clinical Relevance of Fractional Flow Reserve

Intermediate coronary lesion

The potential of angiography to evaluate the hemodynamic severity of an intermediate lesion is limited. Moreover, angiographic assessment is often the only decision-making modality for performance of angioplasty, especially in the absence of any sort of functional evaluation.[29] In patients with angiographically dubious stenoses, it has been shown that FFR is more accurate than exercise electrocardiography, myocardial perfusion scintigraphy, and stress echocardiography for assessing hemodynamic significance.[10] These results strongly supported the use of FFR measurements as a guide for decision-making about the need for revascularization in "intermediate" lesions.

Left main coronary artery

The presence of a significant stenosis in the left main coronary artery (LMCA) is a critical prognostic importance, and it determines the type of treatment.[18] The evaluation of hemodynamic severity is essential, and noninvasive testing is often noncontributive.[30] There are significant interobserver variations in the assessment of LMCA lesions.[31] the LMCA is generally short, and when present, atherosclerosis is often distributed diffusely, so that a normal segment is lacking, which leads to an underestimation of the "reference" segment and thus to an underestimation of LMCA stenoses by both visual estimation and quantitative coronary angiography; the myocardial mass that depends on the LMCA is large, so the amount of blood that flows through it is great, and substantial trans-stenotic flow, in turn, induces large pressure gradients, especially during hyperemia.[32] FFR can identify LMCA stenosis responsible for ischemia. Several studies showed that an FFR-guided strategy for equivocal LMCA lesions is safe and related to a favorable clinical outcome.[32-36] Left main disease is rarely isolated. When tight stenoses are present in the left anterior descending (LAD) or the left circumflex coronary artery (LCx), the presence of these lesions will tend to increase the FFR measured across the left main. The influence of a LAD/LCx lesion on the FFR value of the left main will depend on the severity of this distal stenosis but, even more, on the vascular territory supplied by this distal stenosis. For example, if the distal stenosis is in the proximal LAD, its presence will markedly affect the stenosis in the left main. If the distal stenosis is located in a small second marginal branch, its influence on the left main stenosis will be minimal. Nevertheless, even in the presence of other stenoses in addition to LMCA stenosis, the distal FFR value indicates to what degree maximum perfusion of the different left coronary artery territories is decreased. In a recent prospective study by Hamilos *et al*.,[32] an excellent outcome of FFR-guided revascularization was found in 213 consecutive patients with equivocal LMCA disease, whether or not in conjunction with LAD or LCx stenosis.

Tandem lesions

Tandem lesions [Figure 2] are defined as two separate lesions with >50% stenosis each (with visual assessment on conventional angiography) in the same coronary artery, separated by an angiographically normal segment.[37,38] Theoretically, the FFR can be calculated for each stenosis individually.[39] However, it is important to realize in such cases that each of several stenoses will influence hyperemic blood flow and therefore FFR across the other one. De Bruyne *et al*.[37] have developed equations for predicting the FFR of each individual lesion separately in the case of tandem lesions, and these equations have been validated successfully in animals and humans.[39] Practically, as for diffuse disease, a pull-back maneuver under maximal hyperemia is the best way to appreciate the exact location and physiologic significance of sequential stenoses and to guide the interventional procedure step-by-step. After the most severe stenosis (i.e., the stenosis with the largest gradient) has been stented, the pull-back recording can be repeated, and it can be decided whether and where a second stent should be placed.

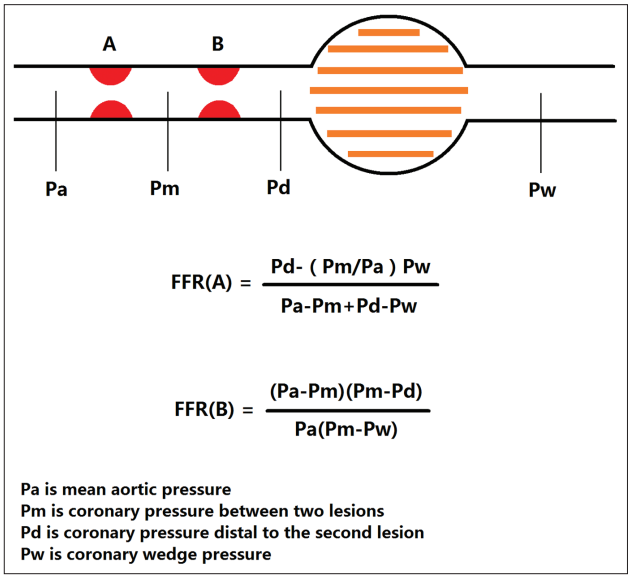

Figure 2: Simplified schematic illustrating an epicardial vessel with two stenoses.

Fractional flow reserve in bifurcation lesions

Overlapping of vessel segments and radiographic artifacts make bifurcation stenoses particularly difficult to evaluate on angiography, whereas PCI of bifurcations is often more challenging than for regular stenoses. The principle of FFR-guided PCI applies in bifurcation lesions, two studies by Koo *et al*.,[40,41] used FFR in the setting of bifurcation stenting. The results of these studies can be summarized as follows: (1) After stenting the main branch, the ostium of the side branch (SB) often looks pinched. Yet such stenoses are grossly overestimated by angiography: Few of these ostial lesions with a stenosis diameter <75% were found to have FFR <0.75; and (2) When kissing balloon dilation was performed only in ostial stenoses with FFR <0.75, the FFR at 6 months was >0.75 in 95% of cases. These studies favor an approach in bifurcation lesions of stenting the main branch and kissing balloon dilation thereafter only if FFR of the SB is <0.75. If FFR of the SB is >0.75, the outcome is excellent without further intervention.

Multivessel coronary disease

For patients with multivessel coronary disease, it is important to know which particular lesion is physiologically significant and responsible for reversible ischemia. FFR can help to identify one or more culprit lesions in this type of patients so that catheter-based treatment of culprit lesions can be performed. Studies conducted by Chamuleau *et al*.[42] showed that FFR was more useful than single-photon emission computed tomography for clinical decision-making and risk stratification in patients with multivessel disease. Recent study by Botman *et al*.[43] also demonstrated that in patients with multivessel disease, intervention undertaken in those patients with one or two physiologically-significant lesions identified by FFR <0.75 yielded a favorable outcome similar to that of patients with three or more culprit lesions who undergo surgical treatment.

Diffuse and long lesions

De Bruyne *et al*.[44] suggested that in diffusely atherosclerotic coronary arteries at angiography, coronary pressure measurement is useful in quantifying the severity of the lesion. A pressure pull-back curve is needed in a diffusely affected coronary vessel. This can be done by withdrawing the pressure-sensing guidewire from a distal to a proximal position very slowly during a steady-state maximum hyperemia induced by IV ATP or adenosine.[44] This curve represents the pressure gradient over the entire length of the vessel, and clearly demonstrates the exact location and severity of the lesion. This so-called pull-back curve is extremely useful in guiding spot-stenting in a vessel with long and diffuse lesions.

Transplant vasculopathy

Cardiac allograft vasculopathy (CAV) is the major cause of mortality and morbidity after the 1st year of heart transplantation.[45] Techniques that can be used as tools for decision-making to either justify intervention procedures on unstable CAV patients or to avoid unnecessary intervention would clearly benefit interventional cardiologists. Casella *et al*.[46] reported a case in which FFR measurement was used to guide and monitor the results of coronary balloon angioplasty on a CAV patient and the results seem very promising. In addition, a recent study by Fearon *et al*.[47] on 53 cardiac transplant patients further suggested that the use of physiologic assessment techniques was feasible for screening asymptomatic cardiac transplant recipients for angiographically unapparent transplant arteriopathy.

Myocardial infarction

In the case of prior myocardial infarction (MI), the mass of viable myocardium is smaller, and impairment of resistance vessels might blunt pharmacologically induced maximal hyperemia. However, as both the decrease of viable myocardium and impairment of coronary resistance vessels are matched in the infarcted area, FFR is still a reliable indicator. Claeys *et al*.[48] provided data that FFR is minimally affected (+5%) in patients with severely impaired microvascular function and may still be applied to patients with recent MI. De Bruyne *et al*.[11] have demonstrated that FFR assessment criteria are also valid in detecting reversible ischemia in patients at least 6 days after MI. Another study conducted by Usui *et al*.[49] comparing FFR and thallium-201 myocardial imaging also showed that pressure-derived FFR is reliable in assessing coronary artery stenosis in patients with previous MI, with a sensitivity of 79% and specificity of 79%.

Unstable angina

In patients with unstable angina, it is commonly believed that maximal hyperemic flow can be lower than in patients with stable angina. Consequently, the 0.75 cut-off value of FFR might not be valid in these patients, and the appropriate value needs to be determined. However, a recent study by Leesar *et al*.[50] for patients with unstable angina or non-ST-segment elevation MI further demonstrated that the FFR assessment criteria were also valid in these patient

groups. A decision-making strategy based on the 0.75 cut-off is superior to a more conservative approach based on stress perfusion scintigraphy.

Coronary artery bypass graft lesions

In theory, the assessment of stenosis severity in coronary artery bypass graft lesions (CABGs) by FFR should not be different from FFR assessment of native vessels. At present, there are no clinical outcome data available regarding the use of FFR in graft stenosis. Therefore, FFR should be used with caution in bypass graft stenosis. Nevertheless, in patients requiring CABG for multivessel revascularization, angiographic lesions of uncertain significance would benefit from FFR, providing prognostic information regarding potential of future bypass graft patency. Botman *et al*.[51] showed that the rate of occlusion was approximately three times higher when the bypass was placed on a native artery with a hemodynamically nonsignificant stenosis. This study suggested that FFR could have serious implications for best long-term CABG outcomes.

Diabetes mellitus

In patients with diabetes mellitus (DM), structural abnormalities in the microvascular system may blunt the maximal hyperemic response to potent hyperemic agents, and as a result, the FFR may not reliably reflect the degree of ischemia in this patient group. However, recently, a research team in Japan provided data that the cut-off value of 0.75 for FFR can also reliably detect myocardial ischemia in patients with DM. Yanagisawa *et al*.[52] compared the pressure-derived FFR for detecting inducible ischemia with SPECT imaging in diabetic patients with a mean hemoglobin A1c of 7.3%. The FFR cut-off value of 0.75 was still applicable and reliable in patients with DM, with a sensitivity of 83% and a specificity of 75%.

Special Features of Fractional Flow Reserve

Fractional flow reserve has a theoretical normal value of 1 for every patient, artery, and myocardial bed

In a normal epicardial coronary artery, there is virtually no decrease in pressure, not even during maximal hyperemia.[44] This means that normal epicardial arteries do not contribute to the total resistance to coronary blood flow, it is obvious that Pd/Pa will equal or be very close to unity.

Fractional flow reserve has a well-defined cut-off value with a narrow gray zone between 0.75 and 0.80

Stenoses with FFR <0.75 are almost invariably able to induce myocardial ischemia, whereas stenoses with FFR >0.80 are almost never associated with exercise-induced ischemia. The gray zone for FFR (between 0.75 and 0.80) spans <10% of the entire range of FFR values.

Fractional flow reserve is not influenced by systemic hemodynamic

In the catheterization laboratory, systemic pressure, heart rate, and left ventricular contractility are prone to change. These indices do not influence the value of FFR in a given coronary stenosis.[18,53]

Fractional flow reserve takes into account the contribution of collaterals

Distal coronary pressure during maximal hyperemia reflects both antegrade and retrograde flows according to their respective contribution.[8,9] This holds true for the stenoses supplied by collaterals but also for stenosed arteries providing collaterals to another more critically diseased vessel.

Fractional flow reserve specifically relates the severity of the stenosis to the mass of tissue to be perfused

The larger the myocardial mass traverse by a vessel is the larger the hyperemic flow, and in turn, the larger the gradient and the lower the FFR for a given stenosis.[54] It also means that the hemodynamic significance of a particular stenosis may change if the perfusion territory changes (as is the case after MI).

Practical Tips and Tricks

Be open-minded

At the beginning of an FFR program, a lesion that appears to be significant on the angiogram happens to be hemodynamically not significant and conversely. The operator has to be open to a change in mindset. Remember that pressure never lies whether we like it or not.

Be consistent in your fractional flow reserve-based decisions

It is important to be consistent in decision-making regarding FFR. If, after measuring an FFR of 0.9, you would decide to perform a PCI anyway or, conversely, if after measuring an FFR of 0.7, you would decide to leave a stenosis in a vessel supplying a large territory, then it is better not to perform the test at all.

Equalization is essential

After a long procedure, differences may sometimes occur between aortic and coronary pressures. Morphology of the distal pressure can cause the difference between true pressure gradient (ventricularized) and drift (exactly the same morphology).

Whipping

When the guide wire sensor hits the coronary wall, an artifact can be seen in the form of a brief but pronounced increase (spike) in the pressure signal measured by the wire. To correct this artifact, the wire should simply be pulled back (or advanced) a few millimeters.

Avoid side-holes catheters

With side-holes catheters, the guiding pressure will result in a pressure "somewhere in between" coronary and aortic pressure (side holes and end hole).

Pullback pressure

A pull-back pressure recording at maximum hyperemia provides important information during an interventional procedure, which can help objectively select which of several stenoses is most appropriate for percutaneous transluminal coronary angioplasty. This information will also allow

clinicians to avoid performing unnecessary procedures that increase the risk of restenosis without a hemodynamic benefit. The pull-back pressure recording can be repeated during the procedure to evaluate the result of what has been done already and what should still be done.

Limitation of Fractional Flow Reserve

Fractional flow reserve value at gray zone cannot be used for decision-making

The FFR provides a well-defined cut-off value for deciding whether to revascularize immediately or to defer intervention;[8,55] however, it is particularly challenging to assess lesion with FFR value at gray zone.[56] Studies of stenoses with FFR 0.75–0.80 have shown conflicting outcome data.[57,58] As the value of FFR gets closer to its cut-off, certainty falls to less than 80% within 0.77–0.83, reaching a nadir of 50% around 0.8.[59] According to Petraco *et al*.,[59] it would be rational for clinicians to make revascularization decisions based on broadened clinical judgment (including other perfusion imaging modalities, considering anatomical features and risk-benefit profile) and all available information to deliver safe and suitable care for individual patients whose FFR value falls at gray zone. Despite the considerable contribution that FFR evaluations can be used for decision-making during coronary angiography,[60] FFR should not be used as a gatekeeper. The operator's subjective judgment may continue to play an important role in selected cases, mainly in the borderline ranges.[55]

Fractional flow reserve measurement does not reflect the actual value during the acute phase of myocardial infarction

During the acute phase of MI, infarct-related resistive vessel dysfunction can cause serious microvascular impairment.[61,62] This impairment causing the myocardial microvascular resistance remains high,[63,64] thus maximal hyperemia cannot be fully achieved. Uren *et al*.[65] demonstrated that basal and hyperemic myocardial flows per gram or perfusable tissue were lower in infarcted regions than in regions remote from the infarction up to 6 months after MI. In addition, thrombus embolization, myocardial stunning, acute ischemic microvascular dysfunction, and other factors make reaching a complete microvascular vasodilation unlikely.[20] Maximal hyperemia or minimal microvascular resistance is crucial for FFR.[56,66] Failure to achieve minimal microvascular resistance results into an underestimation of the functional severity of the coronary stenosis. Thus, during the acute phase of MI, FFR measurement cannot reflect the actual value. When a several days have passed (usually 6 days are considered sufficient), FFR can be applied as in routine practice.

Fractional flow reserve measurement is not reliable for assessing myocardial bridge patients

Myocardial bridge (MB) is a condition that occurs when the myocardium overlies the epicardial segment of a coronary artery.[67,68] Although one-third of the population may have MB,[69] it is usually a benign condition. Even though often clinically silent, MB may present as angina, MI, arrhythmias, left ventricular dysfunction, and even sudden cardiac death.[67,68,70] Stenotic lesion of MB is a dynamic stenosis that occurs during systole and often gets carried over to early and mid-diastole.[71] Bioengineering models and invasive coronary testing have shown that the dynamic stenosis of MB differs significantly from the fixed type of atherosclerotic epicardial stenosis.[72-74] The flow pattern in the bridge segment is characterized by abrupt flow acceleration in early diastole, followed by immediate deceleration and the subsequent plateau of mid-to-late diastolic flow.[73] These phenomena of phasic compression of the artery extending into the mid diastole and the altered flow pattern are not seen in atherosclerotic lesions.[72,73] Recently, Bernhard *et al*.[72] showed that pressure measurements across serial stenoses are different and more complex than single, fixed stenoses. It is thus very likely that pressure measurements across a dynamic obstruction with serial varying stenoses, as within the MB tunnel, may be more complex as well. Singh *et al*.[71] observed several patients with angina and MB, in which the stenotic area was measured using FFR. The first patient had an abnormal exercise test with atypical chest pain, and the FFR was abnormal across the MB. Despite stent implantation and the use of drug-eluting stent, he continued to have symptoms and developed early in-stent restenosis. The second patient had no symptoms with a normal stress test, but the FFR value across the MB was abnormal. The author concluded that there is a possibility that FFR may be abnormal in most patients with MB despite the absence of ischemia and may not be as reliable as in patients with fixed coronary stenoses.[71]

Conclusion

Fractional flow reserve is a valuable tool to determine the functional significance of coronary stenosis. It combines physiological and anatomical information, and can be followed immediately by PCI if necessary. The technique of FFR measurement can be performed easily, rapidly, and safely in the catheterization laboratory. By systematic use of FFR in dubious stenosis and multivessel disease, PCI can be made an even more effective and better treatment than it is currently. Despite all of the advantages, there are several pitfalls related to FFR measurement and a few clinical situations in which it is not reliable. The current clinical evidence for FFR should encourage cardiologists to use this tool in the catheterization laboratory.

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