Review Article

Fractional Flow Reserve: An Indispensable Diagnostic Tool in the Cardiac Catheterisation Laboratory

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The goal of any treatment is to improve a patient's prognosis and/or symptoms. Accordingly, any diagnostic tool should help guide decision making in order to achieve optimal treatment for a patient. The vast majority of patients with suspected coronary artery disease never undergo any form of non-invasive test before having a coronary angiogram.[1] While coronary angiography is widely accepted as the "gold standard" investigation to diagnose coronary artery disease, and has contributed hugely to our understanding of coronary anatomy, it is highly subjective and does not provide any information about the haemodynamic significance of a stenosis.[2,3] Ideally, coronary angiography should be performed using an adjunctive investigation that can be done rapidly and simply, whilst providing the physician with important, reliable and objective information on the haemodynamic significance of a stenosis. Such a measurement already exists in routine clinical practice, namely fractional flow reserve. In this article we will review the basic principles and applications of fractional flow reserve, which is now recognised as a vital tool in the assessment of coronary stenoses in the cardiac catheterisation laboratory.

Coronary circulation

In simple terms, the coronary circulation can be considered as a two-compartment model. The first compartment consists of epicardial vessels, also referred to as "conductance vessels" because they do not offer any resistance to blood flow. The second compartment consists of arteries <400 μm, or "resistive vessels". In the presence of a coronary stenosis, myocardial flow is primarily controlled by resistive vessels.

The function of the coronary arterial circulation is to provide nutrients to the myofibrils. There is a close correlation between the luminal cross-sectional area of a normal coronary artery at each point along its length and the corresponding regional myocardial mass.[4]

The main parameters of circulatory function are flow, pressure and resistance. Flow and resistance both depend on the myocardial mass to be perfused. Under normal conditions, coronary pressure in the distal part of an epicardial artery should be equal to central aortic pressure. The pressure should be constant over the entire length of the epicardial arteries, even during maximal hyperaemia. Thus, in contrast to the size of the arteries and to the flow (velocity), coronary pressure in a normal coronary tree is independent of the myocardial mass, the age of the patient, systemic haemodynamics and the status of the microvasculature.[5,6]

Myocardial blood flow represents ap-

proximately 5% of the total cardiac output. The constant work of the heart means that resting myocardial oxygen demand is high and the extraction of oxygen by the myocardium is close to maximum, more so than in any other organ in the body. Further oxygen supply can only be met if myocardial blood flow is increased. If myocardial flow decreases below 90% of its normal resting levels, myocardial function starts to decrease. This suggests that the regulation of myocardial blood flow is remarkably tight and this is necessary to avoid wall motion abnormalities.[7-9]

Myocardial blood flow is influenced by a combination of neurohumoral, endothelial, endocrine, paracrine, metabolic, and physical factors. These act synergistically, making it almost impossible to study the individual effects of these factors on myocardial blood flow.[10-12]

Physiological indices of the coronary circulation

Several indices of coronary physiology have been proposed for the estimation of coronary circulatory function to guide clinical decision making. Fractional flow reserve is the best validated of these indices. In the first part of this section, we will briefly describe these indices and then we will focus mainly on fractional flow reserve.

Coronary flow reserve (CFR)

Coronary flow reserve is defined as the ratio of hyperaemic blood flow (Q_{max}) to resting myocardial blood flow (Q_{rest}): i.e. CFR = $Q_{max}/Q_{rest.}$ The normal value for CFR is still not well defined and normal values differ from study to study.[13,14] There is some consensus of opinion, however, suggesting that a value more than 4 should be considered as normal, which means that microvascular resistance can decrease by a factor of 4.[15] Since absolute myocardial flow is not easy to determine, surrogate markers of flow are commonly used, such as flow velocities assessed by the Doppler Wire (FloWire, Volcano Inc., Rancho Cordova, CA, USA) or mean transit time (T_{mn}) assessed by the PressureWire (RadiMedical Systems Inc., Uppsala, Sweden). Regardless of the method used to measure CFR, this technique has several limitations: (1) resting flow is highly variable; (2) hyperaemic flow is directly dependant on systemic blood pressure; (3) the hyperaemic and resting measurements are not performed simultaneously but successively; and (4) CFR is not specific for an epicardial stenosis, as the CFR value depends on both epicardial vessels and microcirculation. When CFR is low it is impossible to distinguish whether this value is related to an epicardial artery stenosis alone, microcirculatory dysfunction alone, or a combination of both. The limitations described above have meant that CFR is not routinely used in clinical practice to assess the haemodynamic significance of coronary stenoses. Thus it has only limited value in clinical decision making.

The index of microvascular resistance (IMR)

The resistance of a vascular system is defined as the ratio of the pressure gradient to the flow across that particular system. Accordingly, the *resistance* (R) of the coronary microvascular compartment is the ratio R = $(P_d - P_v)$ /Q, where P_d represents *distal coronary arterial pressure*, P_v represents *coronary venous pressure*, or right atrial pressure and Q represents *blood flow through the myocardial vascular bed*. In the coronary circulation P_v is often almost negligible. Fearon et al introduced the concept of the IMR,[16] considering that the mean transit time during maximal hyperaemia is inversely proportional to hyperaemic flow. Therefore, during maximal hyperaemia IMR = $P_d /(1/T_{mn}) = P_d \times T_{mn,}$ where P_d is the *distal coronary pressure* and T_{mn} is the *mean transit time*. IMR is specific for the microcirculation and is simple to obtain, as P_d and T_{mn} can be obtained simultaneously with the Pressure Wire (St Jude Medical, Minneapolis, MN, USA). This technique has been well validated in animals[16] and was recently used in the setting of acute coronary syndromes to predict clinical outcomes[17] and assess the effect of treatment.[18] A normal value of IMR is below 30.[19]

Fractional flow reserve

Definition

Fractional flow reserve (FFR) is defined as the ratio of the maximal blood flow achievable in a stenotic vessel to the normal maximal flow in the same vessel, which represents the fraction of maximum flow that can still be maintained despite the presence of the stenosis. FFR represents the extent to which maximal myocardial blood flow is limited by the presence of an epicardial stenosis. FFR can be calculated as the ratio of two pressures –distal coronary pressure (P_d) and aortic pressure (P_a)– provided they are both measured during maximal hyperaemia (Figure 1). FFR takes into account the contribution of collaterals to myocardial perfusion during hyperaemia and its

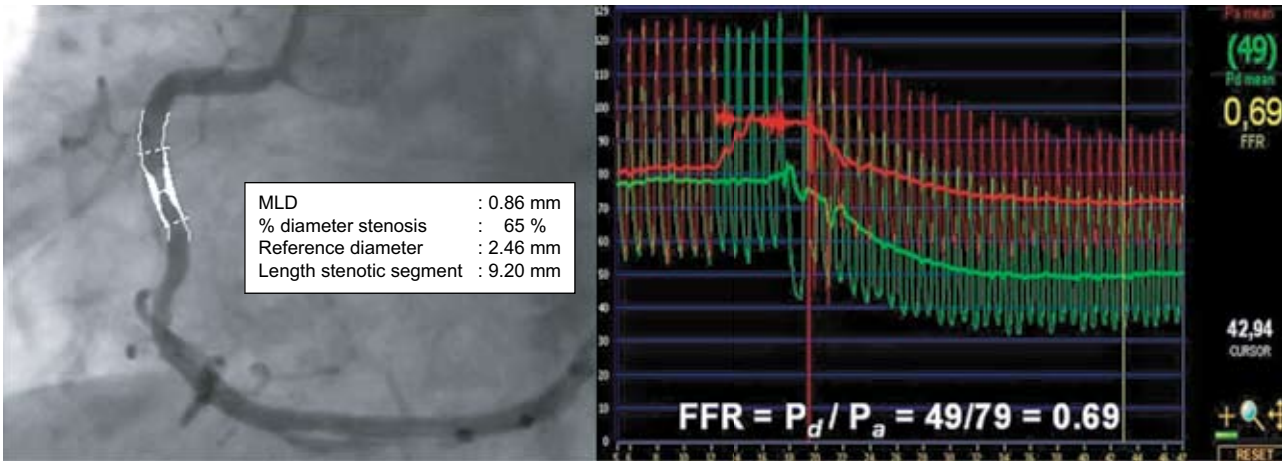

Figure 1. Typical example of physiological assessment of an atheromatous lesion in the mid right coronary artery, using a pressure wire. Simultaneous aortic pressure (Pa) and distal coronary pressure (Pd) recordings during maximal hyperaemia as induced by intracoronary adenosine. Fractional flow reserve (FFR) is 0.69, meaning that the stenosis is haemodynamically significant. MLD – minimum lumen diameter.

normal value is unequivocally equal to unity.[20] The reproducibility of FFR measurements is excellent and it is not influenced by physiological variations in blood pressure and heart rate.[21]

Practicalities in measuring FFR

Catheter

Although diagnostic catheters can be used successfully to help measure FFR,[21] their use is not recommended for several reasons. Firstly, the internal lumen of a diagnostic catheter is smaller than that of a guide catheter. A smaller lumen leads to higher levels of friction, which in turn hampers wire manipulation. Furthermore, the pressure measurements are less accurate and the option to proceed directly to percutaneous coronary intervention (PCI) is not available. Using a guide catheter from the beginning eliminates all of these problems. In particular, the advantage of using a guide catheter while using a pressure wire to measure the FFR across the lesion of interest means that *ad hoc* PCI is immediately possible.

Wires

Two pressure wire systems are available in the market for measuring intracoronary pressure, namely the PressureWire (St Jude Medical, Minneapolis, MN, USA) and the Volcano WaveWire (Volcano Inc., Rancho Cordova, CA, USA). The sensor is located 30 mm from the tip in both wires, at the junction between the radiopaque and radiolucent portions. The most recent generations of these 0.014 inch wires have similar handling characteristics to those of most standard angioplasty guide wires.

Hyperaemia

Maximal vasodilatation of both epicardial and resistance arteries is absolutely necessary in order to measure FFR. A bolus of 200 mg of isosorbide dinitrate (or any other form of intracoronary nitrates) eliminates any form of vasoconstriction in epicardial vessels. The pharmacological agents most often used to induce hyperaemia in resistance arteries are adenosine (via the intracoronary or intravenous routes) and papaverine. A dose of 40 μg of adenosine as an intracoronary bolus or 140 μg/kg/min as an intravenous infusion, have been demonstrated to induce hyperaemia comparable to intracoronary papaverine, without any significant risk to patients.[23,24]

Anticoagulation

As soon as a device is advanced into the coronary tree, the same anticoagulation regimens are used as for PCI. Heparin is administered using a weight adjusted dose and is monitored using activated coagulation time (ACT). In general an ACT value of at least 250 s is desirable.

Unique characteristics of FFR

FFR has a number of unique characteristics that make it particularly suitable for the functional assessment

of coronary stenoses and subsequent clinical decision making in the catheterisation laboratory. First of all, FFR has an unequivocally normal value that is easy to refer to but is rare in clinical medicine. In a normal epicardial artery there is virtually no decline in pressure at rest or during maximal hyperaemia and so P_d/P_a is equal or very close to unity.

Moreover FFR has a well defined cut-off value, which has been evaluated in several studies and compared to several decision-making modalities, most commonly radionuclide perfusion imaging.[25] Stenoses with an FFR measurement of <0.75 are almost invariably able to induce myocardial ischaemia (cut-off with specificity 100%, sensitivity 88%, positive predictive value 100%, and overall accuracy 93%).[26] Stenoses with an FFR >0.80 are almost never associated with exercise-induced ischaemia.[27] This means that the "grey zone" for FFR (between 0.75 and 0.80) spans over 6-7% of the entire range of FFR values.

FFR is not influenced by systemic haemodynamics. In contrast to many other indices measured in the catheterisation laboratory, changes in systemic haemodynamics do not influence the value of FFR in a given coronary stenosis.[28] This is not only due to the fact that aortic and distal coronary pressures are measured simultaneously, but also to the extraordinary capability of the microvasculature to vasodilate repeatedly to exactly the same extent. In addition, FFR has been shown to be independent of gender and risk factors such as hypertension and diabetes.[21] These characteristics contribute to the accuracy of the method and have helped to establish its role as a valuable tool to aid clinical decision making.

FFR takes into account the contribution of collaterals

Whether blood flow in an epicardial artery moves in an anterograde fashion, or retrogradely through collaterals, does not really matter for the myocardium. Distal coronary pressure during maximal hyperaemia reflects both anterograde and retrograde flow, according to their respective contribution. This holds true for the stenoses supplied by collaterals but also for stenosed arteries providing collaterals to another more critically diseased vessel.

FFR has unequalled spatial resolution

During FFR measurements, the exact position of the sensor can be continuously monitored and directly visualised in the coronary vessel using fluoroscopy. By pulling back the sensor during maximal hyperaemia the operator is provided with an instantaneous assessment of the abnormal resistance of the arterial segment located between the guide catheter and the sensor. In this way, FFR makes possible "per segment" accuracy with a spatial resolution down to as little as a few millimetres.

Clinical applications

FFR in angiographically intermediate stenoses

FFR is most frequently used to evaluate the functional relevance of a coronary artery stenosis whose haemodynamic significance is otherwise uncertain.[27] Cardiologists regularly describe an angiographic coronary narrowing of uncertain functional significance, using poorly standardised and highly subjective terminology. Examples of these terms include "a mild-to-moderate stenosis", "a dubious lesion", "an intermediate stenosis", "a moderate stenosis" or "a non-flow–limiting lesion", to name but a few. Although angiographic assessment is often the only decision-making modality available to many institutions, to treat a coronary artery lesion based on angiography alone is insufficient in the assessment of an equivocal coronary stenosis (Figure 2). Moreover, it has been reported that up to

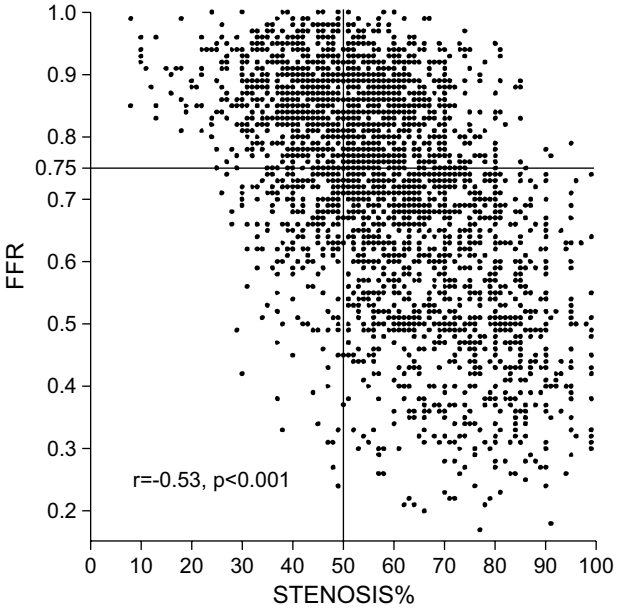

Figure 2. In this scatter graph we can see the correlation between the percentage diameter stenosis (%DS) and the fractional flow reserve (FFR) values in a large population of 2,500 patients. There is a statistically significant correlation between %DS and FFR, but the scatter is extremely large so that decision making for an individual patient is often difficult.

71% of PCIs are performed in the absence of any sort of functional evaluation.[1] This scenario, often referred to as the *oculo-stenotic reflex*, is even more worrisome now that safety concerns have arisen because of late stent thrombosis in the era of drug eluting stents.[28,29]

FFR measurements correlate well with the non-invasive assessment of coronary artery disease. In a study of 45 patients with angiographically dubious stenoses, it was shown that FFR was more accurate than exercise ECG, myocardial perfusion scintigraphy or stress echocardiography in assessing the functional severity of stenoses.[27] The results of these non-invasive tests are often contradictory, which renders appropriate clinical decision making difficult.[30] Moreover, the clinical outcome of patients in whom PCI has been deferred, because the FFR indicated that there was no haemodynamically significant stenosis, is very favourable. In this population the risk of death or myocardial infarction is approximately 1% per year, and this risk is not decreased by PCI.[31,32] Taken together these results strongly support the use of FFR measurement when deciding if an "intermediate" lesion needs revascularisation

FFR in left main disease

Significant left main coronary artery (LMCA) stenosis is an accepted indication for surgical revascularisation. Angiography alone has limited accuracy and wide inter-observer variability in the assessment of actual stenosis severity, especially in LMCA lesions.[33] In general, angiography tends to underestimate the functional significance of LMCA lesions. There are several reasons why the angiographic assessment of LMCA stenoses is imprecise. These include overlapping of the catheter with the origin of the left anterior descending and left circumflex arteries, spill-over of contrast medium, and incomplete mixing of blood and contrast medium in the proximal part of the LMCA. All of these potential pitfalls render the evaluation of a lesion at the ostium of the LMCA challenging even for the most experienced operator. Moreover, the LMCA is frequently short and, when present, atherosclerosis is often diffusely distributed so that a normal segment is lacking. This leads to an underestimation of the "reference" segment and therefore underestimation of the LMCA stenosis by both visual estimation and quantitative coronary analysis. Finally the myocardial mass supplied by the LMCA is large; thus, the amount of blood that flows through it is also large. Substantial trans-stenotic flow, in turn, induces large pressure gradients, especially during maximal hyperaemia. Consequently ambiguous LMCA disease sometimes results in considerable uncertainty when deciding on the best therapeutic strategy for the patient. FFR can be measured at the time of coronary angiography and identifies coronary lesions responsible for ischaemia. Several small studies and one larger study, published recently,[34-38] showed that an FFR-aided strategy for equivocal LMCA lesions is safe and related to a favourable clinical outcome.

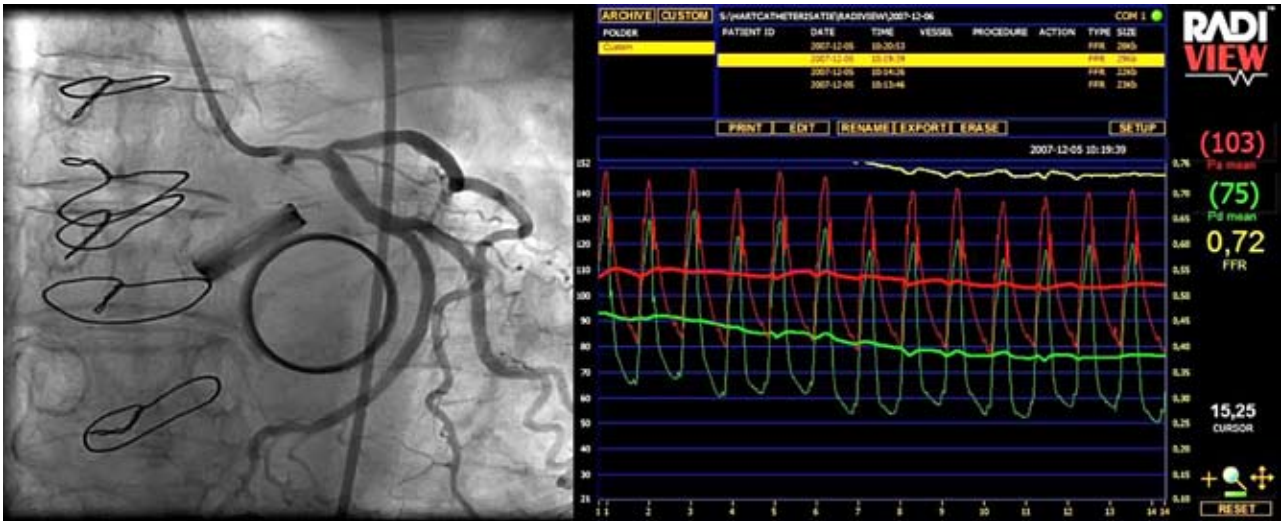

Figure 3. An example of angiographically mild left main coronary artery disease, in a patient previously operated on for valvular heart disease. However, haemodynamic assessment using a pressure wire showed that the fractional flow reserve (FFR) was 0.72 and so the patient was referred for revascularisation.

Therefore, it is reasonable to measure FFR in all patients with equivocal LMCA lesions before blindly deciding on the revascularisation strategy (Figure 3).

FFR in multi-vessel disease

Patients with "multi-vessel disease" actually represent a very heterogeneous population. In these patients, FFR measurement could prove vital, as it may completely alter the revascularisation strategy, i.e. PCI versus coronary artery bypass grafting. The more judicious use of stents, while still achieving complete relief of myocardial ischaemia, could improve the clinical outcome and decrease healthcare costs. In patients with multi-vessel disease, determining which lesion(s) warrant stenting and which do not can be difficult if one chooses to use non-invasive imaging modalities. For example myocardial perfusion scintigraphy is limited in its ability to accurately localise lesions responsible for ischaemia.[39,40] A recent randomised multi-centre study (FAME study) in 1005 patients showed that routine measurement of FFR during PCI with drug-eluting stents in patients with multi-vessel disease, as compared with the standard strategy of PCI guided by angiography, significantly reduced the rate of the primary composite endpoint of death, myocardial infarction, and repeat revascularisation at 1 year.[41] Thus, performing PCI on all stenoses that have been identified by angiography, regardless of their potential to induce ischaemia, diminishes the benefit of relieving ischaemia by exposing the patient to an increased stent-related risk, whereas systematically measuring FFR can maximise the benefit of PCI by accurately discriminating those lesions for which revascularisation will provide the most benefit from those for which PCI may only increase the risk. Moreover, the FFR-guided strategy reduces the number of stents used, decreases the amount of contrast agent used, does not prolong the procedure and is cost-saving.[42]

FFR after myocardial infarction

It is well established that, following myocardial infarction, myocardial myocytes are partially replaced by scar tissue. Therefore, the total mass of functional myocardium supplied by a given stenosis in an infarct related artery will tend to decrease and thus hyperaemic flow and gradient will both decrease as well. In this case FFR will increase, reflecting the functional importance of the stenosis that supplies "less" myocardium. In other words, when viable myocardial mass supplied by a certain stenosis decreases, the functional significance of the stenosis decreases accordingly. Moreover, recent data have shown that FFR measurements before angioplasty, in stenoses that supply an infarcted area, identify viable myocardium that may recover following revascularisation and may thus be used as an alternative to non-invasive viability testing.[41-43] These data support the application of the established FFR cut-off value in the setting of partially infarcted territories.

FFR in diffuse disease

Histopathology studies and, more recently, intravascular ultrasound have shown that atherosclerosis is diffuse in nature and that a discrete stenosis in an otherwise normal artery is actually rare. The presence of diffuse disease is often associated with a progressive decrease in coronary pressure and flow, and increases epicardial resistance, which correlates with the total atherosclerotic burden.[45] It has been demonstrated that more than half of atherosclerotic arteries without focal stenoses have a significantly higher resistance to flow than that observed in normal arteries, while in 8% of cases the FFR is lower than the ischaemic threshold of 0.75.[46,47] In a diffusely atheromatous vessel with sequential angiographically visible stenoses, a pullback trace can be obtained under maximal hyperaemia by pulling back the pressure wire from the distal coronary artery to the guiding catheter. Using this manoeuvre, the individual contribution of every segment and every spot lesion can be studied.

FFR post stenting, in bifurcation and coronary artery bypass graft lesions

Although restenosis rates after PCI have been significantly reduced with the use of stents, there is still a considerable number of patients who undergo target vessel revascularisation after PCI, because of excessive intimal hyperplasia, inadequate stent deployment or plaque shift to adjacent coronary segments. This is often not detected by angiography alone; therefore, additional methods such as FFR are necessary to immediately assess the stent result and to evaluate the adjacent vessel segments. In a large multi-centre registry of 750 patients, FFR was obtained after technically successful stenting. A post-PCI FFR value <0.9 was still present in almost one third of patients and was associated with an unfavourable clinical outcome. Moreover, post-stenting FFR was the strongest

independent predictor of 6-month clinical outcome.[48]

Bifurcation stenoses are particularly difficult to evaluate by angiography, because of overlapping vessel segments, radiographic artefacts, and because the nature of bifurcations means that PCI is often more challenging compared to regular PCI. There are some data supporting the use of FFR in guiding PCI for bifurcation lesions. Two recent studies by Koo et al[49,50] used FFR in the setting of bifurcation stenting. Their findings suggested that, in the case of side branches that looked "pinched" after stenting, the severity of the ostial stenosis in the side branch was often grossly overestimated by angiography. When kissing balloon dilation was performed in these side-branch ostial stenoses with an FFR <0.75, the FFR at 6 months was >0.75 in 95% of all cases.

Assessment of stenosis severity in coronary artery bypass grafts by FFR should not be theoretically different from the FFR assessment of native vessels. Stated another way, FFR is capable of determining whether or not a stenosis is functionally significant in a bypass graft. However, there are only very limited clinical outcome data in patients with bypass grafts in whom decisions regarding revascularisation have been based upon FFR measurements. Only one small study, by Aqel et al, showed that an FFR cut off value of 0.75 had an acceptable specificity and negative predictive value when compared to stress myocardial perfusion imaging in 10 patients with coronary bypass grafts.[51] Although it seems intuitive to use an FFR value of <0.75 as the cut-off when assessing bypass grafts, this should be done with caution until more clinical outcome data are available.

Future clinical implications of FFR

After considering the clinical use of FFR over such a broad spectrum of cases in the catheterisation laboratory, we believe that the diagnostic work-up of patients with known or suspected coronary artery disease might be drastically shortened and improved in the near future (Figure 4). The conventional teaching[52] is that patients with suspected coronary stenosis should first undergo non-invasive functional testing. These are often referred to as the so-called 'gate-keepers' of the catheterisation laboratory. Patients are referred for diagnostic coronary angiography if (and only if) non-invasive testing indicates that there is reversible myocardial ischaemia. At angiography, a stenosis >50% (or >70% for some physicians) is often considered to be sound justification for revascularisation. We have, however, often seen that the results of non-invasive functional tests performed sequentially are inaccurate and/or contradictory. In addition, the angiographic degree of stenosis is a battered gold standard, leading to a large number of inappropriate decisions regarding revascularisation.[29] However, it is worth repeating that non-invasive testing is actually performed in only a minority of patients undergoing angioplasty, even patients with stable coronary artery disease.[53]

In contrast to this conventional approach, we pro-

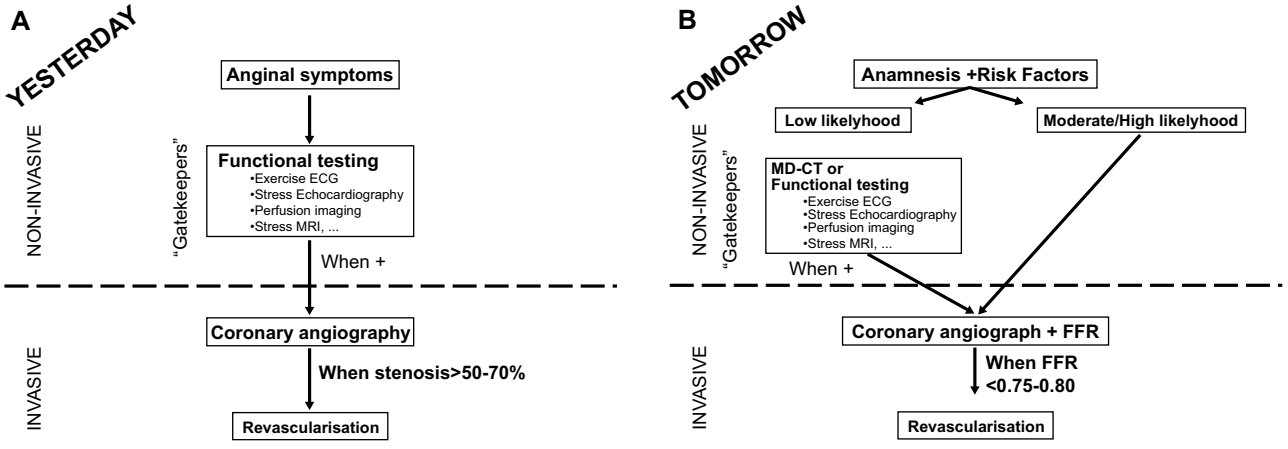

Figure 4. Diagnostic work-up of patients with suspected or known coronary artery disease (CAD). The conventional algorithm (Panel A) is based on two cornerstones: the positivity of non-invasive functional stress testing and the 50% or 70% diameter stenosis criteria at coronary angiography. The proposed algorithm (panel B) restricts the non-invasive approach to patients in whom the likelihood of CAD is low. Patients with a moderate or high likelihood of CAD are sent directly to the catheterisation laboratory provided fractional flow reserve (FFR) measurements can be obtained during the coronary angiogram. MD-CT – multi-dimensional computed tomography; MRI – magnetic resonance imaging.

pose that more emphasis should be given to a careful interrogation of the patient's history, including a precise analysis of risk factors. If, on this basis, an experienced cardiologist comes to the conclusion that "this person might well have significant coronary artery stenoses" it might be more efficacious to send the patient directly to the catheterisation laboratory *if and only if*, in the catheterisation laboratory, FFR measurements can be obtained and the revascularisation strategy is guided by the integration of clinical, anatomical (angiographic), and functional (FFR) information.

Conclusion

Pressure-derived FFR is a theoretically robust and practically simple means of assessing the functional consequences of epicardial coronary atherosclerosis. Accordingly, FFR should be considered as the myocardial perfusion "imaging modality" in the catheterisation laboratory. FFR is done together with coronary angiography and it is the only true "all-in-one" approach for patients with suspected or known coronary artery disease. Ultimately it combines unequalled physiological information with the best possible anatomical information derived from angiography, leading to immediate revascularisation if required.

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