Functional assessment of coronary atherosclerosis in the catheterization laboratory: the key role of fractional flow reserve

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Patients with suspected coronary artery disease often undergo coronary angiography without prior non-invasive functional stress testing, mainly because of logistic reasons, shortcomings of the non-invasive tests, and a more widespread confidence in invasive techniques. The availability in the catheterization laboratory of the pressure-derived fractional flow reserve (FFR) has provided the interventional cardiologist with the ideal tool for appropriate decision-making based on the functional significance of the coronary stenosis detected at the angiogram. In fact, FFR allows a more refined and individualized understanding of the true severity of coronary artery disease, and, therefore, a more appropriate selection of the epicardial lesions to be treated, especially in patients with dubious lesions and complex disease. A clinical decision-making based on coronary pressure measurement results in a more effective strategy than placing stents on a "trial and error" basis. This is particularly true in case of drug-eluting stents where an approach based on an indiscriminate multi-stenting will annihilate the benefits of these new stents and be unacceptably expensive. In addition, many angiographically mild stenoses happen to be hemodynamically significant and, therefore, deserve revascularization, especially in the drug-eluting stent era.

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Introduction

Even though functional testing has proven to bear relevant prognostic information in patients with suspected coronary artery disease[1], often coronary angiography is not preceded by non-invasive stress testing[2] (Fig. 1). This results from a number of practical reasons: these tests are time-consuming, are often performed in different departments and the waiting lists for these tests prolong the hospital stay. In addition, there are conceptual shortcomings of the classical non-invasive stress tests (exercise ECG, dobutamine echocardiography and perfusion scintigraphy) which, often, do not provide the interventional cardiologists with information that really helps in the therapeutic decision-making process: among other factors, the intensity of stress is often submaximal, the ECG tracing interpretation may be difficult due to the presence of concomitant abnormalities (i.e. left bundle branch block, left ventricular hypertrophy, pacemaker, etc.), the chest echogenicity of these patients might be suboptimal, the interpretation is operator-dependent, and their spatial resolution is limited. Taken together, these reasons largely explain why many cardiologists prefer to perform a coronary angiogram as soon as they suspect the presence of coronary artery disease on the basis of the risk factors and the clinical history. While this approach is definitively more pragmatic it leaves many open questions in the catheterization laboratory even more so when considering the weak relationship between angiography and functional impact of the stenosis (Fig. 2). Since it has been shown that there is no prognostic benefit in treating hemodynamically non-significant stenoses[3], and conversely, that stenoses capable of inducing myocardial ischemia do require revascularization[4], it is important to obtain simple, swift and reliable functional information in the catheterization laboratory. Pressure-derived fractional flow reserve

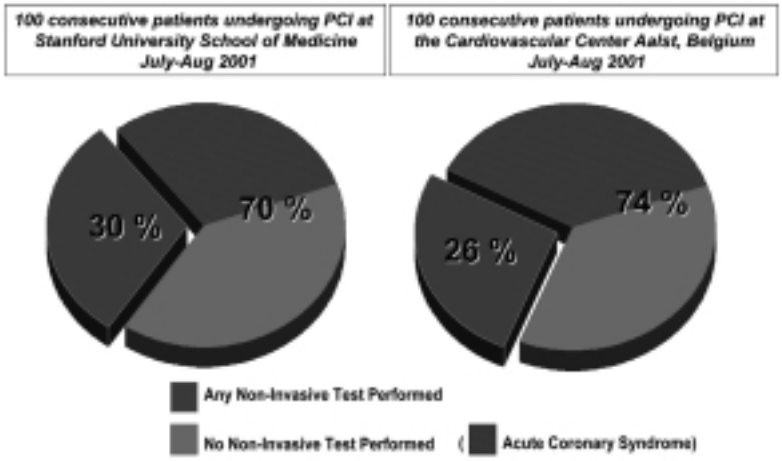

Figure 1. *Proportion of patients undergoing percutaneous coronary intervention (PCI) in an American* (left) *and in a European interventional center* (right) *with a non-invasive diagnostic test performed prior the intervention. Personal communication from Fearon and Barbato.*

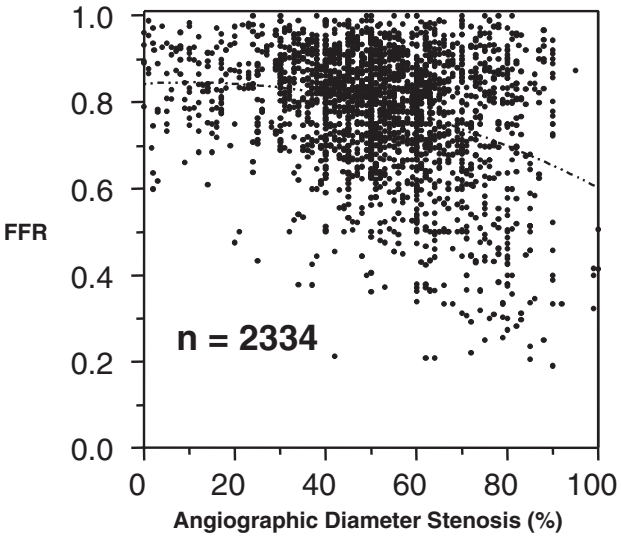

Figure 2. *Relationship between angiographic severity (assessed at quantitative coronary angiography) and functional severity of several coronary stenoses. FFR = fractional flow reserve.*

(FFR) has emerged as the ideal tool for appropriate decision-making in the catheterization laboratory. This review aims at summarizing the main features and the clinical applications of FFR.

The principle of fractional flow reserve

FFR has been defined[5] as the ratio of maximal achievable flow in the stenotic vessel to maximal achievable flow in the same vessel in the hypothetical case the stenosis was absent. Stated another way, this ratio between two flows provides relevant information about the degree of improvement of myocardial perfusion that might be expected after restoring the conductance of the epicardial vessel, i.e. by stenting the stenotic segment. It has been shown that this ratio of two flows can be calculated from the simple ratio of two pressures (distal coronary pressure and aortic pressure) provided these pressures are obtained during steady state maximal hyperemia[5,6]. In addition, it should be emphasized that FFR takes into account the contribution of collaterals to myocardial perfusion during hyperemia. The normal value of FFR is unequivocally equal to unity. The reproducibility of the measurements is excellent and FFR is not influenced by physiological variations of blood pressure and heart rate.

Practicalities

The pressure wire. The pressure monitoring guide wire that has been used for all validation studies is the PressureWire™ (Radi Medical Systems, Uppsala, Sweden). It is a 175 cm long wire with a diameter of 0.014". Its handling characteristics are similar to most angioplasty guide wires so that it can easily be used for any percutaneous coronary intervention (PCI). The sensor, which measures both pressure and temperature, is located 3 cm from the tip, at the junction between the radiopaque tip and the non-radiopaque shaft of the wire. Its proximal ending is connected to an interface, which displays both the aortic pressure recorded by the guiding catheter and the distal coronary pressure from the wire.

Coronary hyperemia. Maximal coronary hyperemia is paramount for FFR measurements. Suboptimal hyperemia could be responsible for an inaccurate physiologic assessment of coronary artery disease, translating into erroneous clinical decision-making. The most common hyperemic stimulus used in the catheterization laboratory is adenosine, either administered intracoronarily or intravenously[7-9]. To avoid submaximal coronary hyperemia, doses of adenosine higher than that previously recommended have recently been pro-

posed[10]. In details, an intracoronary bolus of 40 μg or an intravenous infusion of 140 μg/kg/min of adenosine have been demonstrated to induce hyperemia comparably to intracoronary papaverine, without significant risk for patients.

Varia. FFR measurements prolong the diagnostic procedure of about 6 min. In case of intravenous adenosine, a period of 3 min should be awaited in order to reach a steady state maximal hyperemia. Transient atrioventricular block might occur. As a 0.014" guide wire is inserted in the coronary artery, heparin should be given at dosages commonly used during PCI. The additional costs of FFR measurements are in the range of 800-1000 euros.

Cut-off values

Pressure-derived FFR has been extensively validated against non-invasive stress tests (Table I)[11-17]. Several studies have shown that signs of reversible myocardial ischemia were most often present when the value of FFR was < 0.75 whilst signs of ischemia could very rarely be elicited when the value was > 0.80. Unlike many other diagnostic tests, FFR therefore shows a very narrow "grey zone" between 0.75 and 0.80, which makes this index highly suitable for clinical decision-making in individual patients. These threshold values are valid also after subacute or chronic myocardial infarction[17]. Only in patients with very diffuse coronary atherosclerosis in whom a major alpha-adrenergic tone of the microvasculature can be expected, alpha-blockers might be given on top of adenosine to elicit a truly maximal hyperemia[18]. These data indicate that FFR provides similar information to a perfusion scintigram, with much higher spatial resolution. Therefore FFR can be proposed as a surrogate of non-invasive stress testing to assess the presence of reversible myocardial ischemia. In addition, FFR provides information during catheterization, so that it can immediately be translated in therapeutic procedure.

Clinical setting

Intermediate stenosis. The presence of an intermediate stenosis is a common finding in patients undergoing coronary angiography. However, the prognosis in such patients is not primarily determined by the angiographic presence and severity of the stenosis but by the extent and severity of inducible ischemia[19]. While it is widely accepted that revascularization of stenoses with objective evidence of ischemia is indicated, the appropriate treatment of stenoses unable to induce ischemia remains controversial. Since FFR is a reliable index that can be used as a surrogate for non-invasive testing, FFR allows to distinguish lesions that are responsible for inducing myocardial ischemia from those which are not. It has been demonstrated that only hemodynamically significant stenoses need to be treated and that dilation of functionally non-significant lesions is of no benefit for the patient. Indeed, the DEFER study[3] has demonstrated that a strategy based on deferring PCI in lesions with a FFR > 0.75 is safe and bears better long-term outcome than a strategy based on performing PCI only on the basis of the angiographic appearance of coronary stenoses (Fig. 3).

Multivessel disease. In patients with multivessel disease the spatial resolution of non-invasive testing is poor. In contrast, FFR performed in all three vessels provides in the catheterization laboratory precise functional information that cannot be obtained from non-invasive testing. It has recently been demonstrated that clinical decision-making based on the functional assessment of all coronary stenoses in patients with multivessel disease is reliable and safe. Berger et al.[20] demonstrated that FFR measurement not only distinguishes between functionally significant and non-significant stenoses, but also allows the latter be safely deferred. In addition, multivessel PCI guided by pressure measurement was compared to bypass surgery and yielded a similarly favorable outcome, not only in terms of adverse events but also in terms of reintervention and quality of life[21] (Fig. 4). Therefore, FFR allows a much more refined approach than the mere subjective

Table I. Comparison between fractional flow reserve and other non-invasive stress tests: threshold for reversible myocardial ischemia.

Author	Patients	Test	Threshold
De Bruyne et al.[11]	One-vessel disease (n=60)	Bicycle ECG	0.72*
Pijls et al.[12]	One-vessel disease pre + post PCI (n=60)	Bicycle ECG	0.74*
Pijls et al.[13]	One-vessel disease, intermediate stenosis (n=45)	Bicycle ECG + thallium scintigraphy + dobutamine echo	0.75*
Bartunek et al.[14]	One-vessel disease (n=75)	Dobutamine echo	0.78*
Abe et al.[15]	One-vessel disease (n=46)	Thallium	0.75*
Chamuleau et al.[16]	Multivessel disease (n=127)	MIBI-SPECT	0.74**
De Bruyne et al.[17]	Post-MI (n=57)	MIBI-SPECT	0.75-0.80*

MI = myocardial infarction; PCI = percutaneous coronary intervention; SPECT = single photon emission computed tomography. * 100% specificity; ** optimal cut-off value.

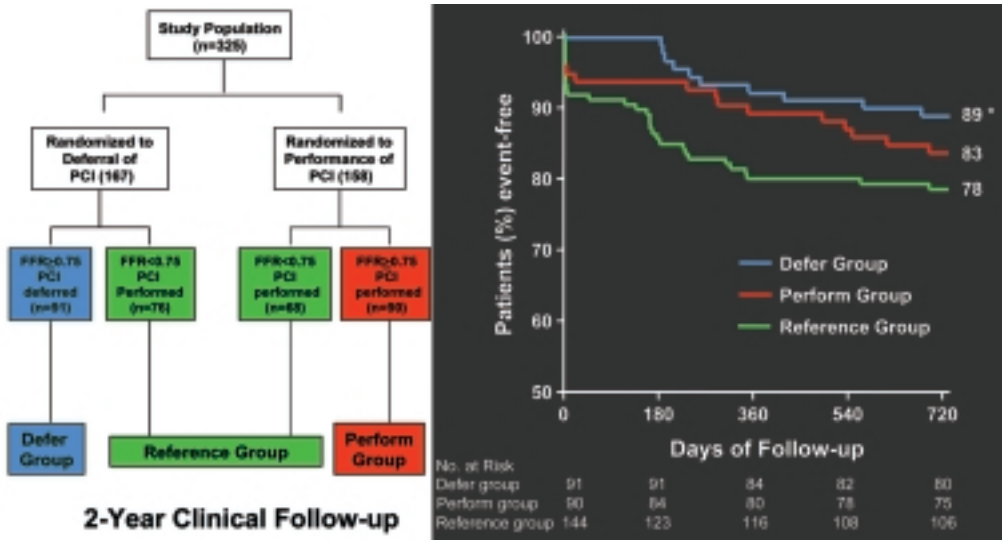

Figure 3. *DEFER study. On the* left*, the study design is schematically represented. On the* right*, the 2-year clinical follow-up is illustrated. The "DEFER group", which represents the group of patients where a non-functionally significant (fractional flow reserve-FFR > 0.75) coronary stenosis was diagnosed, had a greater proportion of patients free of events than the "perform group" (percutaneous coronary intervention-PCI performed even if FFR > 0.75). * p = 0.03 vs reference group.*

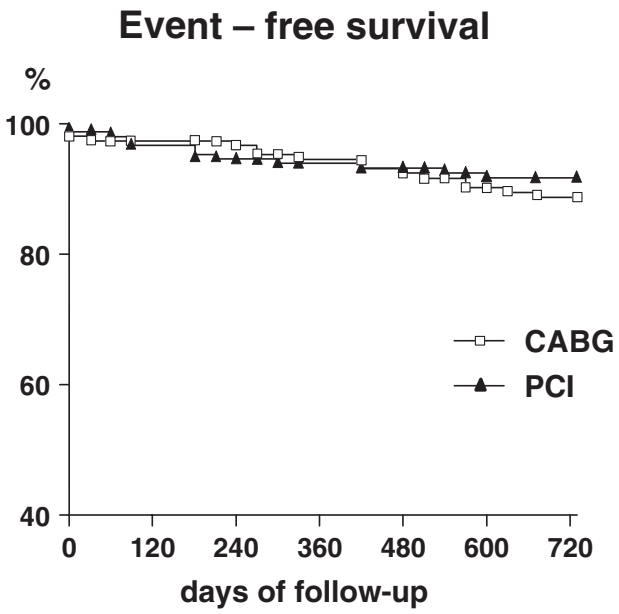

Figure 4. *Two-year clinical follow-up of patients with multivessel disease treated either with bypass surgery (CABG) or with a fractional flow reserve-guided percutaneous coronary intervention (PCI) of the functionally significant stenoses only. Fractional flow reserve-guided PCI results in a comparable outcome to CABG in multivessel disease patients.*

evaluation of the angiogram, especially in patients with diffuse and multivessel disease. These data also suggest that, in patients with multivessel disease, a tailored approach based on FFR measurements allows to safely treat more patients by PCI, even if they were initially scheduled to undergo multivessel bypass surgery.

Left main stenosis. In clinical practice, left main coronary artery disease is often diagnosed in patients as only a mild or moderate stenosis on the angiogram. Although such patients are intuitively at increased risk, it is unclear whether their prognosis will be improved by bypass surgery. On the other hand, if there is a rupture of an anatomically insignificant left main plaque, the result could be fatal. It is conceivable that a premature operation could lead to an inappropriate use of available grafts and early occlusion of either the native vessel or the graft, leaving the future risk of acute occlusion unaffected. This problem is exacerbated in several ways: first, reliable angiographic assessment and quantitative coronary angiography of a left main coronary artery disease stenosis is often difficult; second, it is not uncommon for left main coronary artery disease to be suspected but hard to quantify from the angiogram; third, classical non-invasive tests are often incapable of determining between inducible ischemia caused by left main coronary artery disease stenosis itself or by other abnormalities elsewhere in the coronary system; and finally, surgery for left main coronary artery disease is not without risk in itself. In doubt, surgical treatment is often chosen, encouraged by the fear of under treating these patients.

When there is a doubt for the need for left main coronary artery surgical revascularization, FFR can be used as a reliable and lesion specific index to document the presence of reversible ischemia caused by the left main stenosis. In fact, a strategy based on treating the left main stenoses which were functionally significant at FFR evaluation (FFR < 0.75), while deferring which were not (FFR > 0.75), has been demonstrated safe, accompanied by an excellent survival and freedom from events for up to 3 years of follow-up[22].

Diffuse atherosclerotic disease. Diffuse coronary atherosclerosis is a common finding at coronary angiography and mostly neglected as a potential cause of pa-

tient's complaints or abnormal perfusion scans. 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, and in 8% of cases, the FFR is lower than the ischemic threshold of 0.75[23]. This suggests that abnormal resistance of coronary arteries due to diffuse atherosclerosis without focal stenosis may contribute to stress-induced myocardial ischemia and flow maldistribution on perfusion scintigrams. In fact, it is the presence and the extent of inducible ischemia which determine the prognosis in these patients and not the angiographic appearance of the stenosis. As shown in figure 5, a pullback curve can be obtained under maximal hyperemia by retrieving the pressure wire from the distal coronary artery to the guiding catheter. With this maneuver, the individual contribution of every segment and every spot lesion can be studied. In this respect coronary pressure measurement is unique and such detailed spatial resolution cannot be obtained by any other invasive or non-invasive method.

Drug-eluting stents. The advent of drug-eluting stents (DES) may have given the impression that stents might be deployed in every single lesion, even those which are hemodynamically non-significant, because restenosis is no longer to be feared. There are, however, no data to support such a widespread use of DES. In addition, this approach is economically unaffordable. Recent data have shown that DES are not particularly cost-effective[24]. It is therefore very likely that their cost-effectiveness will be proved only when DES are placed in those lesions where they are mandatory (i.e. lesions capable of inducing ischemia). FFR appears therefore as the ideal tool to guide DES deployment in patients with multivessel disease. Conversely, in patients in whom only one or two stenoses are scheduled for stenting, other "minor" stenoses on the angiogram often happen to be hemodynamically significant and, therefore, do require stenting as well. It might be clear that FFR allows to avoid unnecessary PCI but conversely detects significant stenoses which would otherwise have been left untreated. Finally, this information can now be obtained "on the spot" allowing for optimal functional revascularization without delay.

Fractional flow reserve after stenting. After stenting a focal coronary stenosis, the clinical assumption is that a normal arterial resistance has been restored and, accordingly, that the post-stent FFR should be close to 1.

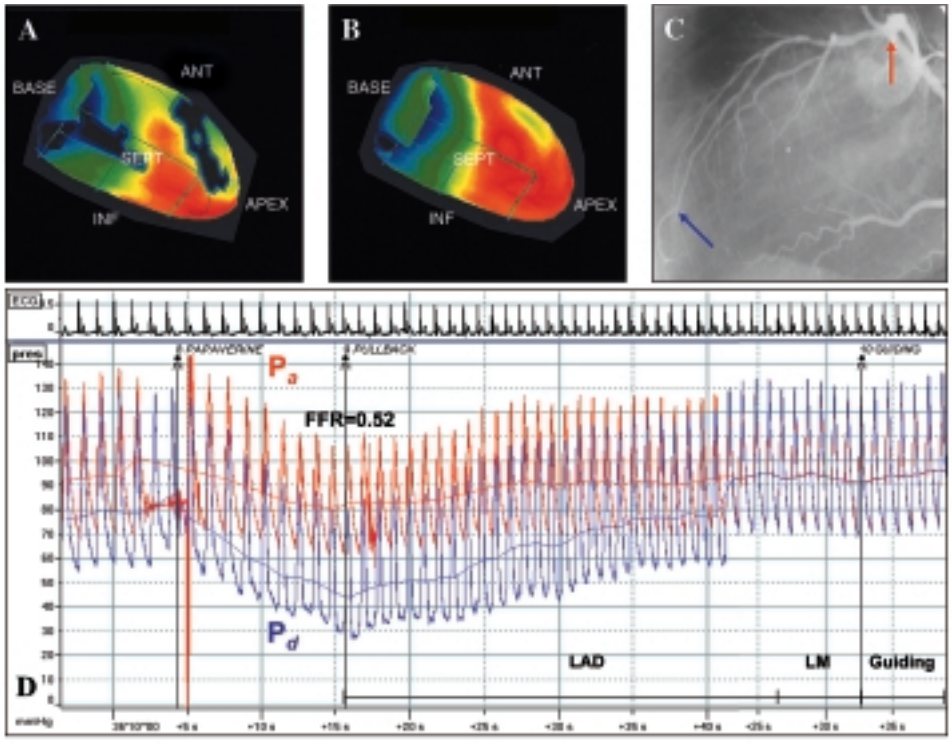

Figure 5. *Example of a patient with diffuse coronary atherosclerosis.* Panel A: *MIBI-single photon emission computed tomography during adenosine-induced hyperemia. A perfusion defect is visible in the anterior territory.* Panel B: *MIBI-single photon emission computed tomography at rest. The perfusion defect visible during hyperemia has disappeared.* Panel C: *coronary angiogram. In addition to diffuse irregularities, a mild focal stenosis is visible in the mid-left anterior descending coronary artery (LAD), distal to the origin of the first diagonal branch. The pressure wire was positioned in the very distal part of the LAD* (blue arrow) *and then, slowly pulled back under maximal hyperemia.* Panel D: *pressure tracing. The* red tracing *corresponds to the aortic pressure (P_a, recorded by the guiding catheter); the* blue tracing *corresponds to the distal coronary pressure (P_d, recorded by a pressure wire). After inducing steady state hyperemia, the pressure sensor was slowly pulled back from the distal position into the guiding catheter. The tracing demonstrates that there is a progressive increase in coronary resistance along the LAD and that the stenosis in the mid-LAD contributes only in part to this resistance (as shown by the steep 10 mmHg step-up at sensor pullback tracing). Myocardial ischemia in this case is the consequence of the diffuse atherosclerosis and there would be little benefit by stenting the mid-LAD. FFR = fractional flow reserve; LM = left main.*

Though this is true in a sizable proportion of patients, FFR measured in the distal part of the artery remains < 0.90 in many others, especially those with diffuse atherosclerosis. In addition to its usefulness as a diagnostic tool, FFR has been shown to carry important prognostic information[25] (Fig. 6, Table II): the major adverse cardiac event rate after 6 months increases dramatically with decreasing values of FFR measured in the distal part of the artery after stenting. The relation between the occurrence of major adverse cardiac events and FFR was more pronounced than with the vessel dimensions. A lower than normal value of FFR after stenting might be related to suboptimal stent deployment. Yet, it is more likely related to the diffuse atherosclerotic burden of the artery which, in turn, is a marker for the "aggressiveness" of atherosclerosis.

Other physiologic indices of the coronary circulation

Coronary flow reserve. Coronary flow reserve (CFR) is defined as the ratio between maximal achievable coronary flow during hyperemia and resting coronary flow. CFR can be practically measured with a Doppler-tipped 0.014" guide wire or alternatively measured with a thermo-pressure 0.014" guide wire (PW 5, Radi Medical System) by means of the thermodilution technique[26]. CFR in angiographically normal vessels from adult patients with coronary artery disease risk factors is 2.7 ± 0.6[27]. In spite of a large interindividual variation, clinical studies have demonstrated that a CFR < 2 was most often associated with an abnormal perfusion scintigram[28]. Moreover, in patients with a CFR > 2 and in whom a planned angioplasty was deferred, a favorable medium-term prognosis was documented[29].

Regardless of the method used to assess CFR, several factors hamper its use in current clinical practice: a) CFR takes into account the two compartments of the vascular bed: the epicardial vessel and the microcirculation (Fig. 7). This implies that in the absence of an epicardial vessel obstruction, an abnormal CFR could be related to microvascular dysfunction that may occur in left ventricular hypertrophy, chronic or acute ischemia, diabetes mellitus, or other rheological conditions[30,31]. To overcome this limitation the concept of the

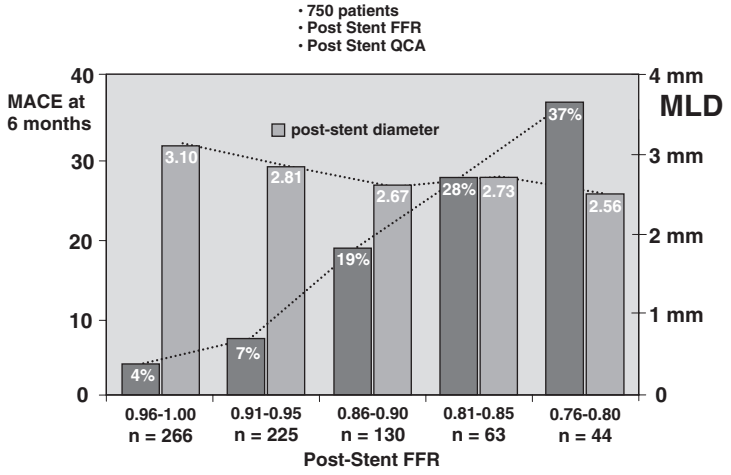

Figure 6. *Inverse relationship between fractional flow reserve (FFR) measured after stent implantation and major adverse cardiac events (MACE) at 6 months. In particular, an optimal stent deployment, with an FFR value > 0.96 results in 4% MACE. Values of FFR < 0.90 after stent implantation indicate a suboptimal result and a worse outcome. On the other hand, post-stent quantitative coronary angiography (QCA) does not correlate with 6-month MACE. MLD = minimal lumen diameter.*

Table II. Type and distribution of events in the different groups.

	All patients (n=744)	Final fractional flow reserve				
		0.75-0.80 (n=44)	0.81-0.85 (n=63)	0.86-0.90 (n=130)	0.91-0.95 (n=241)	0.96-1.00 (n=266)
Death	5 (0.7%)	1 (2.3%)	0	2 (1.5%)	2 (0.8%)	0
AMI	19 (2.6%)	7 (15.9%)	2 (3.2%)	6 (4.6%)	1 (0.4%)	3 (1.1%)
CABG	12 (1.6%)	4 (9.5%)	1 (1.6%)	3 (2.3%)	3 (1.2%)	1 (0.4%)
Re-PCI	54 (7.3%)	6 (13.6%)	13 (20.1%)	15 (11.5%)	11 (4.6%)	9 (3.4%)
Any events	76 (10.2%)	13 (29.5%)	14 (22.2%)	21 (16.2%)	15 (6.2%)	13 (4.9%)

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention. From Pijls et al.[25], modified.

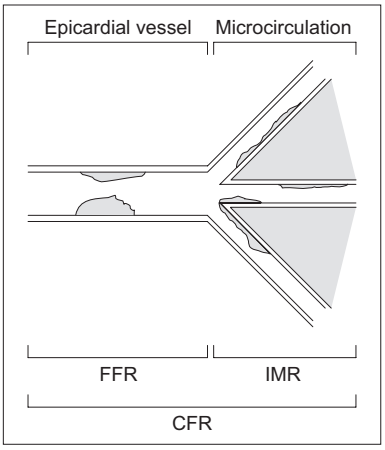

Figure 7. *Schematic representation of the two compartment models of coronary circulation: epicardial vessel and microcirculation. The fractional flow reserve (FFR) gives information on the epicardial vessel. The index of microvascular resistance (IMR) gives information on the microcirculation. The coronary flow reserve (CFR) gives information on both the epicardial vessel and microcirculation.*

relative CFR (rCFR) has been proposed. rCFR is the ratio of CFR as measured in the stenotic vessel to CFR as measured in the adjacent "angiographically normal" vessel. rCFR measurement adds an additional step, namely the measurement of flow velocities in a contralateral "normal" vessel. It can therefore not be performed in three-vessel disease; b) CFR varies with changes in blood pressure and heart rate[32]; c) in a considerable number of patients, the Doppler signal is easily disturbed by positional changes, motion of the patient, or respiration; d) CFR does not take into account the collateral circulation which has been shown to play a major role in the functional status and the prognosis of patients.

Index of microvascular resistance. The index of microvascular resistance (IMR) is a recently described index for the evaluation of the extent of microvascular disease[33-35]. IMR can be calculated with a 0.014" pressure wire (PW 4, Radi Medical System) by measuring, during maximal coronary hyperemia, the distal coronary pressure and mean transit time. *In vitro* and animal studies have shown promising features of this new index that correlated well with true myocardial resistance[33,35]. In addition, a recent work shows that IMR is a specific index of microvascular resistance[36], providing for the first time the ability to semi-quantify this part of the coronary circulation. IMR can be measured simultaneously with FFR and does not necessitate any additional equipment. Although acute and chronic ischemic syndromes are commonly due to coronary flow-limiting stenosis of the epicardial coronary artery, 10-20% of patients undergoing coronary angiography are found to have normal coronary artery or at least mild coronary stenosis not-justifying the clinical status. In addition, an angiographically significant epicardial coronary stenosis could not be the one responsible for patients' complaints in case of diffuse microvascular dysfunction in the myocardial territory perfused by that coronary artery. In this situation, treating this stenosis would expose the patients to significant procedural risk without any significant benefit. The combination of FFR and IMR measurements provides a complete functional assessment of the coronary circulation, allowing to evaluate separately the epicardial and microvascular compartments.

Summary and conclusion

FFR allows a more refined and individualized understanding of the true severity of coronary artery disease and, therefore, a more appropriate selection of the epicardial lesions to be treated, especially in patients with complex disease. Clinical decision based on coronary pressure measurement will be more effective than placing stents on a "trial and error" basis. Furthermore, with the advent of DES the population of patients with more complex disease selected for PCI has significantly increased. Yet, an approach based on an indiscriminate multi-stenting will annihilate the cost-effectiveness of these new stents.

When coronary angiography is the first diagnostic test in patients with risk factors for coronary artery disease and chest pain, FFR measurement provides an *ad-hoc* functional information, obviating for the lack of non-invasive stress testing. This implies that a complete functional work up and *ad-hoc* therapeutic procedure ("all-in-one") can now be performed in the catheterization laboratory.

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