EuroIntervention

Is functional assessment necessary in patients with stable angina?

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Abstract

Strategies during elective PCI procedures in patients with stable angina and multivessel disease are in the majority of catheterisation laboratories, more often than not based, solely on the angiographic analysis on the spur of the moment. This despite the knowledge that angiographic images are often lacking the discriminating power to predict accurately the exact physiologic impact of individual lesions. Evidence is however accumulating telling us that routine stenting of non significant lesions is at best of no additional benefit for the patient. The introduction of dedicated angioplasty guidewires equipped at the tip with a miniature pressure-sensor has greatly expanded the possibilities to accurately evaluate the functional importance of any lesion during diagnostic coronary angiogram by measuring the FFR index. This index, based on the measurements of the trans-stenotic coronary gradient during maximal vasodilatation, is accurate, and easy to implement. Results from several important trials (e.g.,DEFER) have brought to our attention the fact that non significant coronary lesions as documented by FFR measurements, in patients with single vessel disease can safely be left untreated. Recently, the remarkable results from the FAME trial have made a strong case for integrating functional evaluation as a routine work up especially in the presence of angiographic ambiguous lesions referred for PCI in patients with multivessel disease.

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Introduction

The physiologic concept on which Andreas Gruentzig in 1977 initially proposed and subsequently developed his technique of percutaneous transluminal coronary angioplasty was straight forward: relieving clinical symptoms in patients with single vessel coronary artery disease through a non-invasive mechanical dilatation by means of high pressure balloon inflations. The causal relationship between the angiographic coronary obstruction and ischaemic symptoms or other signs of ischaemia was central to his thesis. In other words the coronary stenosis to be dilated needed to be severe enough to induce ischaemia during stress. The disappearance of the symptoms and/of other signs of reversible ischaemia after a successful dilatation were therefore taken as proof of concept[1].

What was initially a delicate procedure, not devoid of potential serious risks, became soon a simple task with minimal complications thanks to the rapid technical improvements of balloon catheters, guidewires, the simplification of the procedure, the introduction of coronary stents together with a growing understanding of the pathophysiological role of platelets and the improved efficacy of newer more potent antiplatelet drugs.

These driving forces were all responsible for the rapid growth and expansion of the field of indication in patients with stable angina, from patients with one vessel disease to patients with multivessel disease, whereby the initial concept; i.e., the relationship between angiographic stenosis and ischaemia, became somewhat blurred and soon to be replaced by what has been jokingly called the oculostenotic reflex, often leading to undiscriminating stenting of all lesions technically amenable for PCI with no questions asked about stenosis severity[2].

In addition, the development and accessibility of newer non-invasive imaging modalities such as MDCT coronary artery scans as a screening tool to detect coronary atherosclerosis in the population at large was responsible for a significant increase in referrals for diagnostic coronary angiograms often to be followed by ad hoc stenting based on the sole operator's angiographic analysis.

Ultimate goal of revascularisation

Revascularisation today, whether by means of PCI or CABG, in symptomatic patients with stable angina due to multivessel obstructive coronary artery disease is aimed at normalising myocardial perfusion in one or more territories thereby reducing or eliminating symptoms and potentially reducing the risk of future cardiac events and/or improving survival. While the beneficial effects of revascularisation on clinical symptoms is clear beyond reasonable doubt, the protective effect against subsequent cardiovascular events and/or survival in this group of stable patients is not entirely settled which was again demonstrated in the COURAGE trial[3].

Optimal medical therapy (OMT)

The COURAGE trial has reminded us of the value of optimal medical therapy in patients with stable angina and inducible ischaemia. A strategy of PCI plus optimal medical therapy versus optimal medical therapy alone showed, in a large population with significant coronary artery disease, no significant difference in the composite endpoints (death, non-fatal myocardial infarction or reduction of major cardiovascular events). This was seen during a follow-up period between 2.5 to 7.0 years, notwithstanding a significant greater beneficial effect on angina symptoms in the PCI group[3,4]. The message from this trial, which in some way disturbed the community of interventional cardiologists, reads as follow: In patients with stable coronary artery disease with controlled symptoms under a regimen of optimal medical therapy, even in patients diagnosed with multivessel disease, PCI can safely be differed, but with the knowledge that one-third of these patients will require some type of revascularisation during follow-up at one point in time.

When revascularisation by means of PCI is considered, the question arises in patients with multivessel disease: complete versus culprit vessel revascularisation.

Complete versus culprit vessel revascularisation in multivessel disease

An argument that is often surfacing when discussing the survival benefit of revascularisation is the issue of complete versus incomplete revascularisation where only one or more culprit lesions are treated. Complete revascularisation has been systematically advocated by cardiac surgeons, based on non-randomised surgical studies in patients with multivessel disease in which improved survival with complete revascularisation was demonstrated[5]. The extrapolation from these results to PCI was an easy step. Although a seemingly logical step, the results of these surgical studies have been challenged on the basis of non randomisation as well as on the basis of selection bias. In fact, for CABG no level-I evidence so far has been presented to support this contention.

Patients with multivessel disease referred for PCI often have lesions in coronary arteries other than the culprit vessel. The decision whether to treat only the culprit lesion(s) or to treat all amenable lesions often depends on the operator's choice of the moment. Factors such as lesion characteristics, presence of total occlusions, amount of myocardium at risk as well as non-patient related factors such as time constraint, extra cost of additional material, overloaded cathlab schedules may all influence his decision. In practice "ischaemic-driven" revascularisation is more often the rule than not[6].

Retrospective analyses of large databases, with all its inherent limitations, have suggested that incomplete revascularisation in patients with multivessel disease yielded a less than optimal outcome as compared to complete revascularisation[7].

Few randomised trials are available addressing this issue for PCI treatment, whether complete revascularisation would also be beneficial in patients with multivessel disease. Ijsselmuiden et al[8] reported in a small group of 219 patients no significant difference in the outcome between complete versus culprit lesions revascularisation at four years suggesting that the decision whether to perform culprit vessel or complete revascularisation can be made on an individual patient basis.

Added value of functional evaluation for decision making during PCI

Coronary angiography still remains today the standard procedure to detect, locate and evaluate the haemodynamic severity of coronary stenoses in patients with typical or suspected angina pectoris

symptoms. As long as the disease is confined to a single concentric lesion in one vessel segment, the diagnostic challenge is usually limited to what is currently referred to as an intermediate or ambiguous lesion in the face of atypical symptoms. It is current knowledge that standard angiography, even assisted by computed analysis (QCA) is able to deceive the cardiologist due to the limitations of its two dimensional character and its limiting ability to visualise only the lumen[2]. The uncertainty of complete normalcy of the selected reference segment for comparison casts a permanent shadow on the calculations of percent diameter stenosis used routinely to classify stenosis severity. Lesions graded between 30% and 80% are notoriously often either functionally underestimated or overestimated. It stands to reason that the presence of multiple lesions in more than one vessel, involving complex lesions, ostial involvement, the presence of calcifications, tortuosity and vessel overlap will only add to the diagnostic uncertainties related to the haemodynamic significance of each lesion.

The above listed arguments may also explain why the anatomical assessment of lesion severity by computed tomography coronary angiography does not correlate well with the functional assessment of FFR. This is particularly true for the evaluation of intermediate stenoses[9].

Intravascular ultrasound (IVUS) imaging

Intravascular ultrasound imaging is superior to standard angiographic analysis for accurate quantification of vessel diameter and cross sectional area and yet, it does not give us true functional information about severity of coronary stenosis[10]. IVUS generates cross-sectional images of the coronary artery from which accurate measurements of the degree of obstruction are derived as well as information of the arterial wall and plaque composition. Several studies have demonstrated a linear relation between coronary flow reserve measured by guidewire Doppler velocimetry and the minimal luminal cross-sectional area derived from IVUS images[11]. A minimal luminal cross-sectional area ≥4.0 mm^2 has high diagnostic accuracy in predicting a coronary flow reserve of ≥2. This cut-off value has been used to discriminate between a flow limiting stenosis and a non-flow limiting stenosis. Deferring PCI on the basis of this cut-off value was associated with an especially low event rate at one year of 4.4% and TLR rate of 2.8%[12].

Myocardial perfusion imaging

In patients with a textbook history of exercise-induced-angina a diagnostic coronary angiography can be ordered without further delay. Additional testing may help localise the culprit vessel especially if only one vessel is diseased. In the presence of multivessel disease the story gets a little more complicated when in addition to the culprit lesion several other lesions on different vessels are present.

Over the years nuclear imaging has made significant advances to image the heart under stress conditions and to detect the presence of coronary artery disease.

Myocardial perfusion imaging with ^{99m}Tc-labeled perfusion agents combined with quantitative assessment has a high sensitivity (85%) for the detection of the presence of coronary artery disease. In addition it can be used to demonstrate perfusion abnormalities in the vascular territory subtended by the target vessel and so detect the severity of a lesion in case of single vessel disease. However, in the presence of multivessel disease myocardial imaging is less reliable to assess the individual severity of multiple different lesions. Indeed myocardial imaging is based on relative flow heterogeneity between segments and tends to identify ischaemia in segments subtended by the most severe coronary artery obstruction. Moderate but still significant stenoses may therefore go unnoticed on the myocardial perfusion scan[13] (Figure 1).

Fractional flow reserve

The development of specific guidewires, equipped with miniature pressure/flow sensors has introduced coronary physiology, until

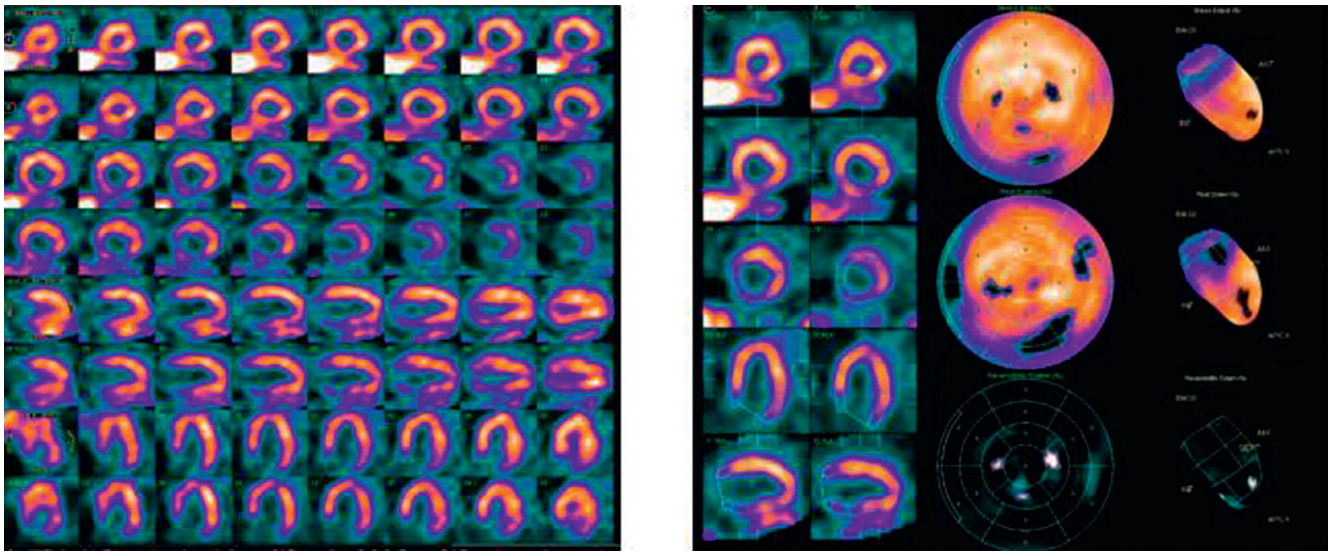

Figure 1. A MIBI scan (from the patient discussed in Figure 2 and Figure 3) did not reveal reversible ischaemia. A dobutamine stress echo was positive for symptoms but did show regional wall abnormalities.

then confined to the experimental laboratory, into the catheterisation room. Measurements of the trans-stenotic pressure gradient and/or coronary flow velocity reserve during diagnostic catheterisation allow the operator to accurately quantify the full functional impact of a specific coronary lesion on distal perfusion. Since coronary flow velocity measurements are influenced by alterations of the microcirculation most laboratories have favoured the use of intra coronary pressure measurements to assess stenosis severity using the index of "fractional flow reserve" (FFR)[14].

This simple index, expressed as the ratio between the coronary pressure distal to the stenosis and the pressure proximal to the stenosis measured during maximal coronary vasodilatation, describes the percent maximal achievable coronary flow reserve in the area subtended by the stenotic artery. A number of reasons make this index unique. First, the FFR index has a sound mathematical basis and has been extensively validated both in experimental conditions as well as in patients; secondly, this index is not affected by lesion geometry (location, length, severity), nor by haemodynamic conditions (systemic pressure, heart rate, contractile state), nor by abnormalities of the microcirculation; third, this index is lesion-specific and ideally suited for interrogating multiple lesions in patients with multivessel disease: fourth, easily implemented during routine diagnostic work up during a diagnostic procedure and perfectly reproducible. For all these reasons the FFR index is superior to any known other test in accurately assessing individual lesion severity.

It has been repeatedly demonstrated that a coronary stenosis with an FFR ≤0.75 (that is to say with a maximal coronary flow reserve of less than 75% of normal) is flow limiting during maximal stress and thus prone to induce myocardial ischaemia[15]. The superiority of FFR over myocardial perfusion imaging in detecting ischaemic vascular zones has recently been documented in patients with multivessel disease[16]. In this study, 67 patients (201 vascular territories) with 2 or 3 vessel disease underwent prospectively myocardial perfusion imaging (rest/stress adenosine) and FFR measurements of all vessels. The results showed a poor concordance between the two techniques. Myocardial perfusion imaging underestimated the number of ischaemic territories in as much as 36% of these patients.

This sensitive index which accurately and unequivocally determines the functional impact of a coronary lesion was used to investigate the appropriateness of stenting haemodynamically non significant lesions which is often performed in many institutions without strong evidence to do so. The DEFER trial was set up to answer this important question in patients referred for a single lesion PCI[17]. From this study two conclusions stand out. First, the prognosis of a functionally non-significant lesion (FFR≥0.75) treated medically is excellent with a five year rate of death or AMI related to that stenosis of <1% per year and not improved after stenting. Thus, PCI is of no benefit in case of non flow limiting stenosis. Secondly, functionally significant lesions (FFR≤0.75) are at the greatest risk for death and MI in the next five years after PCI, a figure significantly worse than that in patients with non significant lesions.

A shift in paradigm

The landmark trial "FAME" published last year in the New England Journal of Medicine[18] teaches us an important lesson: routine measurements of FFR using PCI in patients with multivessel coronary artery disease as a guide for decision making as to which stenosis to stent and which not (in this trial drug-eluting stents were used) reduced significantly the rate of composite endpoints (death, nonfatal myocardial infarction and repeat revascularisation) at one year from 13.2% versus 18.3%; p=0.02) when compared to a standard angiographic guided strategy. Strikingly, the number of implanted stents, the contrast load as well as the overall procedural time and costs were significantly less, yet the functional improvements were similar.

The proposed explanation for these remarkable results is double and reads as follow: It is current knowledge that the presence and the extent of inducible ischaemia is the most important prognostic factor in patients with coronary artery disease[12].

1. PCI of only flow-limiting lesions (FFR≤0.80 was used in this trial as a cut-off value) in patients with multivessel disease will reduce the overall ischaemic burden as well as the risks for future ischaemic events. This outweighs the risk of potential stent thrombosis and/or restenosis associated with stenting in general.
2. PCI of a non-flow-limiting stenosis (FFR≥0.80) will add the potential risk associated with stenting which is deemed higher than the low risk for future cardiac events associated with not stenting a non flow limiting lesion. In other words, the beneficial effect from stenting flow-limiting lesions is increased by a positive effect of not stenting non-flow-limiting lesions.

These results strongly support a shift in paradigm: Introducing routine functional assessment using the FFR index during PCI in patients with multivessel disease should result in complete functional rather than angiographic revascularisation of all flow-limiting stenoses and defer revascularisation of non-flow-limiting lesions under continuous optimal medical treatment (Figures 2, 3).

Summary

From the above it is clear that the practice of undiscriminating stenting of all angiographic documented lesions in patients with multivessel disease in the name of full revascularisation has no scientific ground. In other words, besides documenting carefully all coronary obstructions during coronary angiography, it is the responsibility of the operator to judge, and, not to guess, the severity of each lesion separately in order to decide which lesion to stent and which not to stent. FFR measurements are sensitive and easy to implement, as an adjunctive invasive act, to reliably assess the functional impact of all lesions in patients with multivessel disease. In doing so (and at a minimal cost of a little extra time, contrast and radiation) the operator will avoid stenting lesions which appear angiographically significant, but, in fact, are not flow-limiting and/or omit stenting angiographic-looking non-significant lesions which, in fact, are flow- limiting. This modified new strategy will benefit this group of patient with multivessel disease brought into the cathlab for PCI.

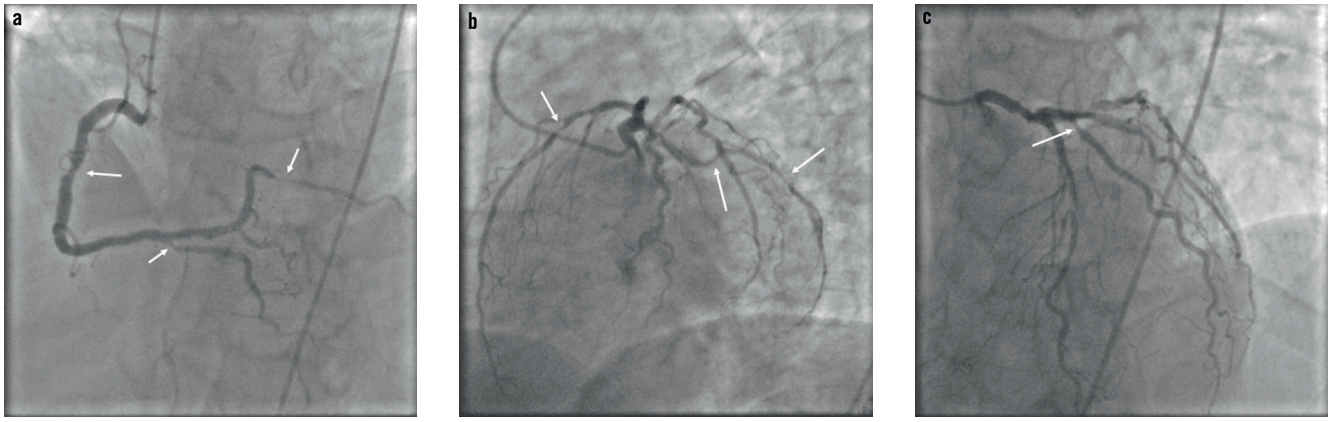

Figure 2. A 56-year old active male presented with recurring angina (typical) especially when riding his bicycle (CCS 2) two years post-stenting of the RCA (segment 3) and POBA of the postero-lateral branch. Risk factors were arterial hypertension and hyperlipidaemia. This example illustrates this point well. a. A coronary angiogram of the RCA showing a severe restenosis in the posterolateral branch, a moderate lesion of segment two and an intermediate lesion of the origin of the RPD. b. A LAD showing a severe lesion on segment seven and an intermediate lesion at the origin of a large diagonal branch. c. A LCx showing a significant lesion on the marginal branch and a intermediate lesion of the mid LCx.

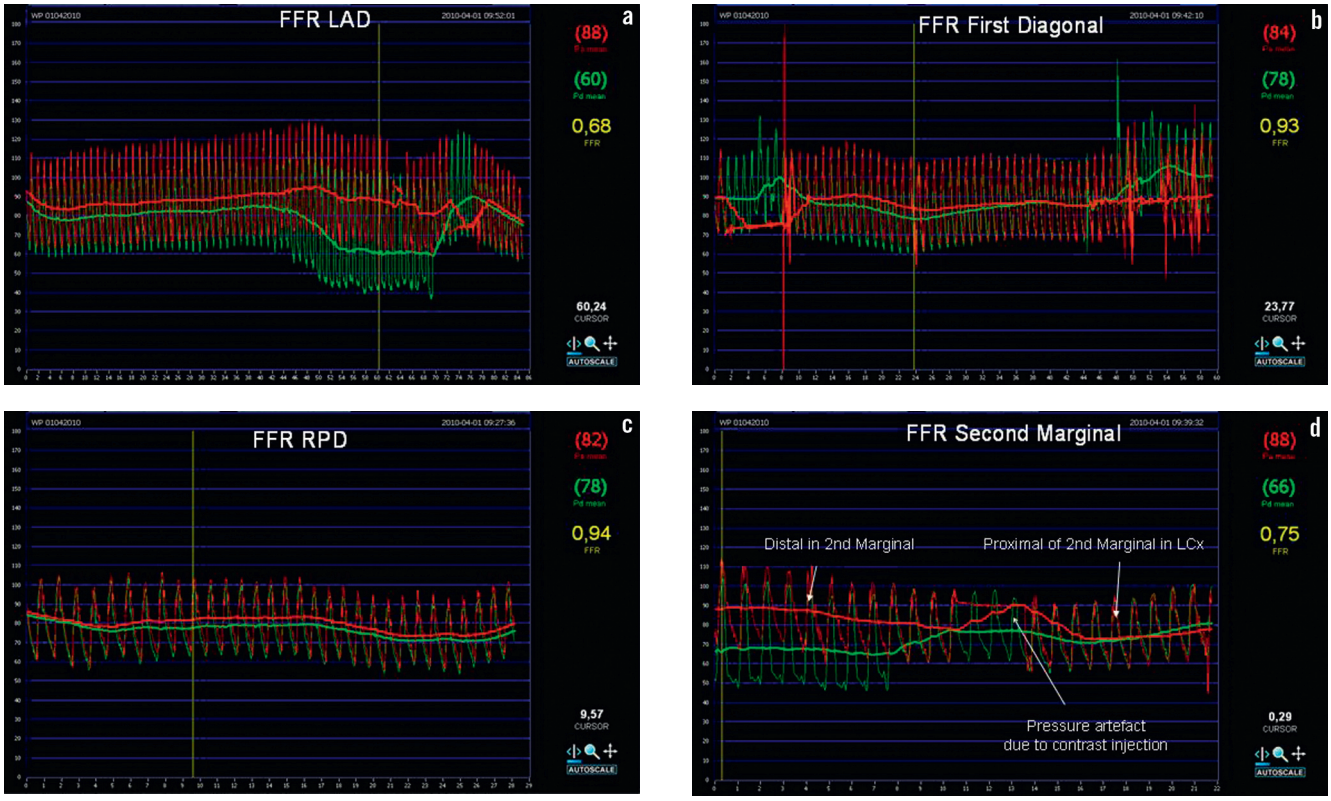

Figure 3. FFR interrogation of all lesions revealed that the lesions on the ostial RPD, diagonal branch and proximal LCx were non-flow-limiting. Therefore, only the mid LAD and postero-lateral branch were stented. The proximal LCx, the diagonal branch and the RPD were not treated. a. FFR interrogation of the LAD: 0.68; b. FFR interrogation of the diagonal branch: 0.93; c. FFR interrogation of the ostial RPD: 0.94; d. FFR interrogation of the marginal branch: 0.75. FFR after pull back in the LCx just distal to the intermediate lesion: 0.98.

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