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Myocardial fractional flow reserve

Its role in guiding PCI in stable coronary artery disease

Introduction

The concept of myocardial fractional flow reserve (FFR) was introduced into clinical practice by N. Pijls and B. de Bruyne in the early 1990s. Despite considerable initial resistance and scepticism among the interventional cardiac community, FFR must now be considered an accepted adjunctive technique in catheterization laboratories around the world. Abundant data have been accumulated over time demonstrating the value of intracoronary pressure measurements to improve patient care in coronary artery disease (CAD). This article will elucidate the role of FFR in the guidance of percutaneous coronary interventions (PCI) in patients with stable CAD.

The concept of FFR

FFR is a specific index of the functional significance of coronary artery stenoses which expresses maximal achievable blood flow in a coronary vessel as a fraction of normal maximal blood flow to the same myocardial territory if the patient were completely healthy [1]. Put another way, FFR represents the extent to which maximal myocardial blood flow is limited by the presence of epicardial stenoses. An FFR of 0.68 means that maximal myocardial blood flow reaches only 68% of its normal value. FFR can be measured easily during coronary angiography by the ratio of distal coronary pressure measured with a coronary pressure guidewire to aortic pressure measured simultaneously with the guiding catheter during maximum hyperemia. It is not only lesion-specific, but also accounts for the many complex variables influencing coronary flow including lesion severity, lesion length, and collateral flow. The index is independent of changes in systemic blood pressure, heart rate, or myocardial contractility. The mathematics, experimental basis, technique, limitations, and validation of FFR have been well described [2, 3, 4]. The value below which a stenosis is deemed "significant" is controversial. Although the initial validation studies determined that an FFR <0.75 most strongly correlated with ischemia (sensitivity 88%, specificity 100%, overall accuracy 93%) [1], there is a small zone of FFR uncertainty between 0.75 and 0.80. These "borderline" values may, in fact, be significant in some cases and require clinical judgement [5]. For the sake of improved sensitivity, however, many clinicians currently consider an FFR ≤0.80 as "ischemic" [6].

Rationale for FFR in the cath lab

Although noninvasive stress imaging should be the gold standard for the evaluation of patients with known or suspected CAD prior to coronary angiography, only a minority of patients have had noninvasive stress tests before presentation in the catheterization laboratory [7, 8]. Furthermore, noninvasive stress tests are often inadequately performed or yield inconclusive results. As a consequence, the selection of stenoses to be stented is guided merely by the standard coronary angiogram in most cases. This observation is supported impressively when looking at the 2008 database figures from 556 catheterization laboratories in Germany. Nationwide, the rate of 'ad hoc' interventions in 303,832 PCIs was 70.7% [9]. Obviously, there is considerable discrepancy between current practice and adherence to the guidelines on PCI and myocardial revascularization, which require objective evidence of (large) ischemia in patients with stable angina [10, 11].

An angiographic approach may be reasonable when the angiogram clearly demonstrates either a normal coronary artery or a severely stenosed one in the presence of typical angina. However, in most other clinical scenarios (quantitative) angiography has well-known limitations [12, 13]. Most importantly, angiographic information frequently does not correlate with the functional significance of a coronary lesion [14, 15, 16, 17]. Therefore, even experienced investigators are often unable to predict the significance of coronary stenoses based

on the angiogram [18]. This uncertainty may result in inappropriate care with PCI of lesions not causing ischemia or failure to revascularize significant ones.

The presence of myocardial ischemia causes symptoms and is predictive of future events [19, 20, 21, 22]. Revascularization of stenotic coronary lesions that induce ischemia has the potential to improve a patient's functional status and outcome [6, 21, 23]. For stenotic lesions that do not induce ischemia, however, the benefit of revascularization is less clear. Medical therapy alone is likely to be equally effective if not superior [6, 23]. Therefore, the decision to revascularize a coronary artery stenosis should be guided by evidence of myocardial ischemia.

The tools at our disposal to detect myocardial ischemia are numerous and yet limited. The best established stress imaging techniques are echocardiography and perfusion scintigraphy, which have several advantages over conventional exercise ECG testing, including superior diagnostic performance and the ability to quantify and identify areas of ischemia. Reported sensitivities and specificities of stress echocardiography are between 53%–93% and 70%–100%, respectively, under study conditions [24]. Stress echocardiography is highly user-dependent and requires adequate training and experience. Furthermore, many patients are poor candidates for the test due to inadequate image quality. Myocardial perfusion scintigraphy is more sensitive than echocardiography, but less specific. The reported sensitivity ranges from 70%–98%, but specificity only reaches 40%–90% [24].

Although noninvasive stress imaging may well help to discern the significance of a coronary artery lesion when there is single-vessel disease, these techniques have limitations in identifying the hemodynamic significance of individual stenoses in patients with multivessel CAD [25, 26]. Because myocardial perfusion imaging relies on relative flow heterogeneity, it usually identifies ischemia caused by the most severe stenosis. It may misclassify other vascular zones supplied by less diseased but still significantly narrowed arteries as normal [27].

Abstract · Zusammenfassung

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Abstract

Revascularization of coronary artery lesions should be based on objective evidence of ischemia, as recommended by the guidelines of the European Society of Cardiology. However, even in the case of stable coronary artery disease and elective percutaneous coronary intervention (PCI), pre-procedural noninvasive stress test results are available in a minority of patients only. It is common practice for physicians to make decisions on revascularization in the catheterization laboratory after a cursory review of the angiogram, despite the well-recognized inaccuracy of such an approach. Myocardial fractional flow reserve (FFR) measured by a coronary pressure wire is a specific index of the functional significance of a coronary lesion, with superior diagnostic accuracy for the detection of ischemia than any noninvasive stress test. FFR trials on patients with single and multivessel disease, such as the DEFER and FAME studies, have demonstrated that the clinical benefit of PCI with respect to patient outcome is greatest when revascularization is limited to lesions inducing ischemia, whereas lesions not inducing ischemia should be treated medically.

Keywords

Coronary artery disease · Fractional flow reserve · Intracoronary pressure measurement · Multivessel disease · Percutaneous coronary intervention

Fraktionelle myokardiale Flussreserve. Stellenwert in der PCI-Führung bei stabiler KHK

Zusammenfassung

Die Revaskularisation von Koronarstenosen sollte entsprechend den Leitlinien der Europäischen Gesellschaft für Kardiologie auf dem objektiven Ischämienachweis im Versorgungsgebiet eines Zielgefäßes beruhen. In der klinischen Praxis liegt dieser Nachweis jedoch nur bei einer Minderzahl von Patienten mit stabiler koronarer Herzerkrankung vor. Üblich ist die angiographische Einschätzung des Schweregrades einer Läsion, obwohl die Ungenauigkeit dieses Vorgehens durch vielfältige Daten belegt ist. Die fraktionelle myokardiale Flussreserve (FFR) ist ein spezifischer Index zur Evaluation der Einschränkung der Leitungsfunktion eines Koronargefäßes. Die FFR-Messung zeichnet sich durch eine überlegene Sensitivität, Spezifität und diagnostische Genauigkeit gegenüber allen nichtinvasiven Stresstestmodalitäten aus. Die DEFER- und die FAME-Studie konnten den Stellenwert der FFR bei der koronaren Ein- und Mehrgefäßerkrankung eindrücklich nachweisen. Ihre Ergebnisse stellen das Konzept der vollständigen Revaskularisation auf der Basis anatomischer Kriterien infrage und weisen auf die Überlegenheit eines integrativen Ansatzes angiographischer und physiologischer Informationen im Sinne einer vollständigen funktionellen Revaskularisation hin. Die Beurteilung der funktionellen Signifikanz unklarer linkskoronarer Hauptstammstenosen mittels FFR ermöglicht die Stratifizierung im Hinblick auf ein weiteres konservatives oder chirurgisches therapeutisches Vorgehen. In der klinischen Routine bietet die Kombination aus angiographischer und unmittelbar verfügbarer funktioneller Diagnostik mittels FFR die Möglichkeit einer raschen Evaluation des funktionellen Koronarstatus. Zudem liegen sowohl Durchführung als auch Interpretation in den Händen des für die weitere Therapie verantwortlichen Untersuchers.

Schlüsselwörter

Koronare Herzerkrankung · Fraktionelle Flussreserve · Intrakoronare Druckmessung · Mehrgefäßerkrankung · Perkutane Koronarinterventionen

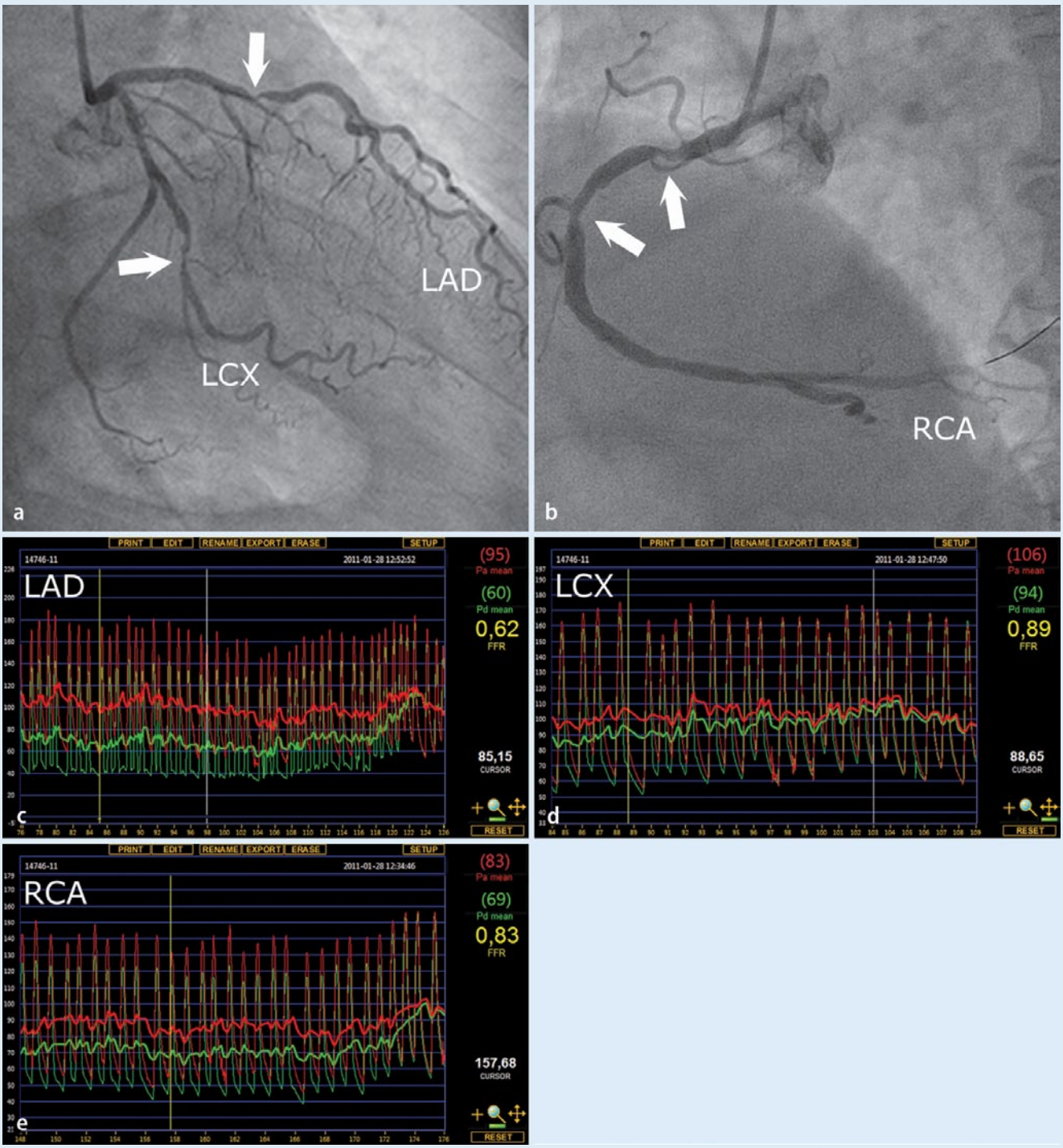

Fig. 1 ▲ Example of a typical FAME patient who presented with angina. Diagnostic angiography indicates three-vessel coronary artery disease (**a**, **b**). However, physiologic evaluation by FFR (**c–e**) reveals functional one-vessel disease of the LAD (FFR <0.80). The patient was therefore treated by PCI in the LAD only. At short-term follow-up he was asymptomatic. Phasic and mean aortic pressure curves are illustrated in *red* (*Pa*), while phasic and mean distal coronary pressure curves are illustrated in *green* (*Pd*). Online FFR values (during maximum hyperemia) are illustrated in *yellow* on the right side-bar, corresponding to the position of the *yellow marker line* to the left. *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *white arrows* indicate angiographically significant stenoses

In a recent study by Melikian et al. [28], myocardial perfusion scintigraphy underestimated the number of ischemic territories in 36% of patients with multivessel disease (MVD) compared to FFR.

A further limitation, which applies to both noninvasive modalities, is the poor spatial and segmental resolution in the case of several abnormalities within the same artery, as well as the impossibility to distinguish diffuse epicardial disease from focal stenosis [26]. Newer stress imaging techniques such as cardiac magnetic resonance imaging complement the noninvasive stress test modalities [29], but do not improve diagnostic accuracy significantly.

As a vessel-specific index, pressure derived FFR is superior to all noninvasive modalities for the detection of myocardial ischemia with respect to its sensitivity, specificity, diagnostic accuracy, and spatial and segmental resolution [30]. This resulted in the following Class IA recommendation in the 2010 European Guidelines on myocardial revascularization: "FFR-guided PCI is recommended for detection of ischemia-related lesion(s) when objective evidence of vessel-related ischemia is not available" [11].

FFR in single-vessel disease and intermediate lesions

One of the first 'landmark' studies of FFR was the DEFER study (FFR to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenoses) [23]. The study included 325 patients referred for PCI of a single, angiographically significant de novo stenosis of intermediate severity. Noninvasive tests were either negative, inconclusive or had simply not been performed. Immediately after inclusion and before any physiologic measurement was performed, patients were randomized to deferral or performance of PCI. Next, FFR was measured. If FFR was <0.75, the randomization was ignored on the basis of ethical reasons since such FFR results revealed clear evidence of ischemia and PCI was performed (Reference group, n=144). However, if FFR was ≥0.75, the randomization was executed, resulting in one group of patients in whom PCI was deferred and treated medically (Defer group, n=91), and one group in whom stenting was performed despite the fact that their stenosis was most likely not of functional significance (Perform group, n=90). After 5 years of follow-up, event-free survival did not differ between the latter two groups (80% and 73%, respectively), but was significantly worse in the Reference group (63%; p=0.03). The composite rate of death and acute myocardial infarction (MI) in the Defer, Perform, and Reference groups was 3.3%, 7.9%, and 15.7%, respectively (p=0.21 for Defer vs. Perform group; p=0.003 for the Reference group vs. both other groups). The percentage of patients free from chest pain at follow-up was not different between the Defer and Perform groups. The study showed that 5-year outcome after deferral of PCI of an intermediate coronary stenosis based on FFR ≥0.75 is excellent. The risk that a hemodynamically nonsignificant stenosis will cause death or acute MI is <1% per year and is not decreased by stenting [neither bare-metal nor drug-eluting stents (DES)].

The assumption that 'prophylactic' PCI of a stenotic lesion not inducing ischemia is beneficial overall must be considered a misconception. PCI of a functionally nonsignificant stenotic lesion increases the chance of an adverse event since the risk of thrombosis and restenosis associated with the placement of the stent, as well as with the attendant risk of subsequent repeat revascularization, MI, or death, clearly exceeds the low risk associated with a hemodynamically nonsignificant stenosis in which a stent has not been placed.

FFR in multivessel CAD

The results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [31] reminded us that PCI offers no benefit over medical therapy with respect to death or MI reduction in low- to intermediate-risk patients with multivessel CAD. However, a substudy of COURAGE showed that, in the population with greatest relief of ischemia, PCI reduced the rate of death and MI [21]. In concert with the COURAGE study, it must be recognized that not all multivessel angiographic CAD is physiologically equivalent CAD. Using FFR to assess all three vessels, Sant'Anna et al. [32] have shown that the incidence of "significant" three-vessel angiographic CAD drops from 27% to 9%, two-vessel drops from 43% to 17%, and single-vessel disease increases from 30% to 60%, simplifying decision-making in this difficult patient group.

The results of two single-center, nonrandomized studies suggested that in patients with MVD, PCI of hemodynamically nonsignificant stenoses can be safely deferred [33, 34]. These studies led to the larger prospective randomized, multicenter FAME trial (FFR versus Angiography for Multivessel Evaluation) [6]. The FAME study investigators addressed the hypothesis that an FFR-guided PCI approach with DES was superior to the current practice of conventional angio-guided PCI in patients with multivessel CAD amenable for PCI, at the exclusion of left main stenosis and primary PCI for acute MI. The FAME protocol directed the investigator to stent a lesion if it involved stenosis of at least 50% and if the investigator thought that stenting was warranted on the basis of the available clinical data, including the results of noninvasive testing, if performed. The protocol did not mandate treatment of all stenoses of 50% or more. Lesions to be stented had to be indicated before randomization, in order to avoid any possible bias. Once all stenoses were identified, 1005 patients were randomized 1:1 to either standard PCI as planned (n=496) or to prior FFR interrogation of all lesions deemed significant by angiography (n=509). In patients randomized to FFR guidance, PCI using DES was eventually performed only for lesions with FFR ≤0.80 (taken as the threshold for stress-inducible ischaemia).

Although the number of angiographically significant stenoses was identical between groups (2.7+0.9 vs. 2.8+1.0), the FFR-PCI group used fewer stents per patient (1.9±1.3 vs. 2.7±1.2, p<0.001) and less contrast medium (272 ml vs. 302 ml, p<0.001). More importantly, at 1-year follow-up, the FFR-PCI group had few-

er MACE (13.2% vs. 18.4%, p=0.02) and fewer combined deaths or MIs (7.3% vs. 11%, p=0.04) compared with the angio-PCI group. At 2 years, the significance of combined mortality or MI consolidated in favor of the FFR-guided group (8.4% vs. 12.9%, p=0.02) [35]. In addition to improving prognosis, symptomatic freedom from angina after 1 year was achieved in 81% of patients in the FFR-guided group compared to 78% in the angio-guided group (p=0.20).

What is unique about the FAME study is that the results suggest for the first time that stenting of lesions with an FFR >0.80 in the current era may actually be detrimental. The rationale for this apparent paradox is that, although adverse DES-related events occur uncommonly, they are more frequent than the rate of events of a lesion managed by optimal medical therapy alone. Another important finding of the FAME study is that assessment by FFR of the number of functionally significant diseased coronary arteries in patients with angiographic MVD often leads to a reduction in the number of diseased coronary arteries from a functional point of view—an observation in line with the above-mentioned study by Sant'Anna [32]. Of all patients with angiographic three-vessel disease (vd) in the FFR group, 86% had only two or even less functionally significant diseased coronary arteries (3-vd=14%, 2-vd=43%, 1-vd=34%, 0-vd=9%) [15]. A typical "FAME patient" is illustrated in **Fig. 1**.

In the randomized, controlled Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial [36], PCI with DES for the treatment of MVD including left main disease was inferior to coronary artery bypass graft (CABG) surgery in patients with angiographic three-vessel disease. In the SYNTAX study, PCI was guided by angiography alone. In both arms of the SYNTAX study, the treatment goal was complete revascularization from an angiographic point of view. In contrast, in the FFR-guided arm of the FAME study, the goal was complete functional revascularization. The outcome in the SYNTAX PCI group was inversely related to the extent and severity of the disease, as captured by the SYNTAX score [37]. The SYNTAX score was designed to reflect the complexity of coronary lesions with higher scores indicating more complex disease. The MACE rates per tertile of the SYNTAX score (<=22, 23–32, >=33) showed a stepwise increase: 13.6%, 16.7%, 23.4% (p<0.007). The two treatment groups had similar rates of death from any cause, stroke, or MI (7.6% for PCI and 7.7% for CABG). However, patients undergoing PCI were more likely than those undergoing CABG to require repeat revascularization (13.5% vs. 5.9%). The fewer the number of DES implanted in the PCI group (Syntax average=4.6 stents per patient), the better the outcome at follow-up [36].

Although indirect comparison among studies should be made with caution, it seems to be a reasonable assumption that if the PCI arms in the SYNTAX trial had been FFR-guided, this would have improved the outcome of PCI simply by reducing the number of stents needed to achieve 'complete functional revascularization'. Performing PCI on all stenoses that have been identified by angiography, regardless of their potential to induce ischemia, diminishes the benefit of relieving ischemia by exposing the patient to an increased stent-related risk, whereas systematically measuring FFR can maximize the benefit of PCI by accurately discriminating the lesions for which revascularization will provide the most benefit from those for which PCI may only increase risks. This new paradigm challenges both the design and the implications of recent and future trials.

FFR in left main stenosis

A correct clinical assessment of left main stem CAD lesions is of prognostic relevance. Although recently questioned [38, 39], the clinical significance of left main disease is defined by our guidelines as a left main stem lesion of >50% diameter stenosis and CABG is still conventionally regarded as the standard of care for significant left main disease in patients eligible for surgery [11]. The basis for these recommendations is somewhat scant, derived from only 150 randomized patients from two separate trials comparing CABG versus medical treatment, as well as data from the CASS registry, all dating back to the mid-1970s [39]. Because the long-term natural history of nonsignificant stenoses is very favorable, it was hypothesized that only patients with ischemia inducing left main stenosis as detected by FFR would benefit from a revascularization procedure [40, 41]. It has been shown that correct evaluation of the functional significance of equivocal left main CAD is not possible by visual assessment when compared to FFR measurement results [16]. Data from eight studies, in which the decision to treat patients either by CABG or medically was based on the FFR measurement result, comprise a total of 591 patients to date. The outcome data consistently show that medical treatment of a functionally nonsignificant left main stenosis is associated with excellent survival and low event rates [39, 42, 43].

Thus, the evolving role of FFR in the presence of left main CAD primarily consists of unmasking which lesions should be revascularized and which lesions should be treated medically. The debate on whether significant left main disease is eligible for PCI rather than surgery is a different and ongoing matter [11].

Conclusion

As to the practice of PCI, there is now mounting evidence that this form of therapy provides best results when focusing on the relief of ischemia, implying that stents should only be targeted at hemodynamically significant stenoses. In patients with stable CAD, in particular in the presence of MVD, identification of the hemodynamically significant lesions requires anatomic orientation by angiography combined with functional evaluation. The combination of diagnostic angiography and FFR measurements provides a unique opportunity to obtain anatomic and functional information with excellent diagnostic accuracy, performed and interpreted by the same investigator who is responsible for the subsequent treatment strategy.

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