Review Article

Coronary Angiography With Pressure Wire and Fractional Flow Reserve

State of the Art in the Diagnosis of Coronary Stenosis

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Summary

Background: Approximately 800 000 coronary angiography procedures are performed in Germany each year, mainly in order to identify coronary artery stenoses. As a rule, revascularization is indicated only when coronary artery stenoses cause relevant ischemia, but this cannot be determined unequivocally by angiography alone. Pressure wire measurement and the measurement of fractional flow reserve (FFR) enable direct evaluation of the hemodynamic relevance of coronary artery stenoses during diagnostic coronary angiography.

Methods: This review is based on publications retrieved by a selective search in PubMed focusing especially on large randomized trials, registry studies, and meta-analyses on either pressure wire measurement or FFR.

Results: According to a registry study from France, the hemodynamic evaluation of a stenosis during coronary angiography affected decisions about revascularization in 43% of cases. Randomized multicenter trials have shown that a combined end-point consisting of death, myocardial infarction, or revascularization arose significantly less commonly in the FFR group than in the group receiving angiography without FFR (13.2% versus 18.3%; $p = 0.02$), and that patients with one or more hemodynamically significant coronary artery stenoses ($FFR \leq 0.80$) benefited more from revascularization than from medical management alone (event rate, 8.1% versus 19.5%; $p < 0.001$). It was also shown that revascularization yields no benefit if relevant ischemia has been ruled out, even if the angiogram shows high-grade coronary artery stenoses.

Conclusion: All cardiac catheter laboratories should be capable of performing pressure wire measurements and measurements of FFR and should do so regularly if ischemia due to coronary artery stenosis cannot be demonstrated non-invasively. A pathological FFR measurement is an indication for revascularization.

Cite this as:

Gaede L, Möllmann H, Rudolph T, Rieber J, Boenner F, Tröbs M: Coronary angiography with pressure wire and fractional flow reserve—state of the art in the diagnosis of coronary stenosis. *Dtsch Arztebl Int* 2019; 116: 205–11. DOI: 10.3238/arztebl.2019.0205

With about 800 000 investigations annually, coronary angiography is one of the most commonly performed invasive diagnostic procedures in Germany (1, 2). In the United States, approximately 1 million diagnostic cardiac catheterizations and approximately 480 000 percutaneous coronary interventions (PCI) were performed on an inpatient basis in 2014 (outpatient data are not available) (3).

Coronary angiography is primarily used to identify stenoses of the coronary arteries. However, there is a common misconception among physicians—and also patients—about the significance of angiography and angiographic severity of stenosis. Although the detailed visualization of a patient's coronary anatomy achieved by coronary angiography is essential for any revascularization, the association between angiographic degree of stenosis and resulting ischemia is less clear than is generally assumed (4).

Thus, in its new 2018 Guidelines on Myocardial Revascularization, the European Society of Cardiology (ESC) recommends that for any coronary stenosis with an angiographic degree of stenosis below 90%, the presence of ischemia should be verified before any decision on revascularization is made (5). Acute myocardial infarction is an exemption. Relevant ischemia can be detected by noninvasive methods, such as:

- Cardiac stress test
- Stress echocardiography
- Myocardial perfusion imaging
- Stress magnetic resonance imaging (MRI)
- Positron emission tomography (PET).

On the other hand, relevant ischemia can be demonstrated during coronary angiography by means of intracoronary pressure wire assessment, typically measuring fractional flow reserve (FFR). This technique allows to assess whether a stenosis is inducing ischemia and consequently whether the patient would benefit from revascularization or not. The most recent guidelines on myocardial revascularization, published in 2012, also recommend FFR measurement to inform the decision which lesions should be revascularized (6). In the following, the technique and the significance of FFR measurement will be discussed together with the available evidence.

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Methods

This review is based on a selective search of the literature in the PubMed database which also included English-language articles. On 27 April 2018, we performed the search using the search terms “fractional flow reserve“, “FFR“, “iFR“ (instantaneous wave-free ratio), each in combination with “randomized trial“ and “registry“.

We excluded studies published before 2015 to ensure that only studies on current revascularization techniques, especially studies on last-generation drug-eluting stents (DES), were retrieved. Of the 291 remaining search results, we screened out all reviews and randomized trials with less than 200 patients and all registries with less than 500 patients to avoid bias resulting from the non-publication of negative study results (7). We also included the ESC Guidelines on Myocardial Revascularization and the studies cited in it.

Coronary artery disease and revascularization

The treatment of coronary artery disease (CAD) has two primary goals: symptom alleviation and improvement of prognosis. It consists of pharmacotherapy, on the one hand, and surgical revascularization or percutaneous coronary intervention (PCI) on the other.

While the advantage of PCI with stent implantation in patients with myocardial infarction has been clearly demonstrated in prospective randomized trials, its benefit in patients with stable CAD has always been subject to controversy. In view of the recently published findings of the ORBITA trial, doubts about the benefits of PCI plus stent implantation have repeatedly been expressed—at times with extensive media coverage (8–10). However, it has been clearly shown that PCI plus stent implantation has a relevant impact of prognosis in patients with significant myocardial ischemia, defined as an ischemic area of at least 10% of the total myocardium (11). The ESC guidelines, which are accepted in Germany, therefore recommend revascularization by bypass surgery or PCI in patients with a stenosis of a least 50% of the lumen diameter (visually assessed) and concomitant relevant ischemia (5).

Degree of stenosis and ischemia

Interestingly, there is no close correlation between the angiographic degree of stenosis of an atherosclerotic coronary artery lesion and the resulting myocardial ischemia (12). The physiological significance of a stenosis is only partially dependent on lumen reduction. This is explained by:

- Differences in size of the dependent myocardium
- Anatomical and physiological factors, such as length and morphology of the stenosis
- Variable limitations of vasomotion and autoregulation of microvascular beds.

Consequently, apparently high-grade coronary artery stenoses do not necessarily induce relevant myocardial ischemia in the supplied territory,

whereas coronary lesions with non-high-grade angiographic appearance may well cause relevant ischemia. For these reasons, morphological evaluation of a stenosis cannot be relied on as the sole criterion for the decision to perform PCI or bypass surgery. Therefore, it is recommended to include non-invasive ischemia tests, such as stress echocardiography, myocardial perfusion imaging, and stress MRI, in the work-up for CAD. These tests should generally be performed prior to invasive coronary angiography (5). However, none of the noninvasive ischemia tests offers 100 percent sensitivity or specificity (for example, stress MRI: sensitivity 67–94%, specificity 61–85%) (5).

Pressure wire measurement, fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR)

With the current practice in Germany, in 46% of patients with stable CAD the presence of ischemia has not been reliably confirmed by noninvasive testing prior to coronary angiography and potential PCI (1). In addition, even if ischemia has been detected by noninvasive testing, it is often difficult to clearly decide based on the coronary angiography findings which lesions require revascularization, because patients often have multivessel disease or the ischemic area does not match with the territory of the coronary artery which appears to have the highest-grade stenosis. Therefore, it is crucial to enable the possibility of lesion-specific ischemia detection during coronary angiography.

The invasive detection of relevant ischemia is based on the principle that the blood pressure drops across a coronary stenosis. The ischemia caused by the coronary stenosis is proportional to the magnitude of this drop in blood pressure. In 1993, De Bruyne et al. were the first to directly measure this drop. They introduced a wire fitted with a miniaturized pressure sensor into the coronary artery and compared the mean coronary pressures proximal and distal to the stenosis while the microvascular resistance was minimized pharmacologically (13).

This principle is still used today: During coronary angiography, a thin wire or a special catheter with integrated pressure sensor is introduced into the coronary artery and placed distal to the stenosis. After pharmacological induction of maximal vasodilation, e.g. by intravenous or intracoronary administration of adenosine, mean coronary artery pressure distal to the stenosis was compared with the mean pressure in the aorta. The ratio of these 2 pressures is called fractional flow reserve (FFR). The ratio is 1.0, if no flow limitation and thus no ischemia is present. Initially, Pijls et al. set a threshold of 0.75 to define a significant coronary stenosis. This value was determined by matching FFR results with the results of noninvasive ischemia tests, such as exercise ECG, scintigraphy or stress echocardiography (14). Consequently, the first studies used 0.75 as the threshold value at and beyond that a coronary stenosis was regarded as “significant“ (15, 16). The FAME studies

Figure: Next to the angiographic image, visualization of the hemodynamics during the examination is shown. The red curve represents the aortic pressure, the red line the mean aortic pressure. The yellow curve represents the coronary artery pressure and the yellow line the mean coronary artery pressure.

a) Visually high-grade angiographic stenosis of a diagonal branch of the left anterior descending artery (LAD) (white arrow).

The fractional flow reserve (FFR)—determined by comparing the aortic pressure (red) and the mean coronary artery pressure distal to the stenosis (yellow) after adenosine administration—is 0.84. Thus, the stenosis is classified as not hemodynamically relevant, and consequently would not benefit from revascularization. The red arrow shows where the pressure sensor is located.

b) Visually moderate stenosis of the LAD (white arrow).

The FFR—determined by comparing the aortic pressure (red) and the mean coronary artery pressure distal to the stenosis (yellow)—is 0.74. Thus, the stenosis is classified as hemodynamically relevant and the patient would benefit from revascularization. The red arrow shows where the pressure sensor is located.

c) High-grade stenosis of the LAD (large white arrow), followed by 2 non-high-grade stenoses in the middle-third of the artery (small white arrows).

The FFR—determined by comparing the aortic pressure (red) and the mean coronary artery pressure distal to the stenosis (yellow)—is 0.64, indicating relevant ischemia. The red arrow shows where the pressure sensor is located.

d) The finding of Figure c immediately after percutaneous coronary intervention (PCI) of the proximal stenosis with placement of a drug eluting stent (large white arrow).

The FFR is now 0.91. Thus, the residual stenoses (small white arrows) are not hemodynamically relevant. The red arrow shows where the pressure sensor is located.

and the studies conducted since then used a threshold of 0.80 to reduce the rate of false negative FFRs.

Based on the evidence from these studies, both in everyday clinical practice and in the European and US guidelines a stenosis is considered hemodynamically relevant and prognostically significant—and thus to be treated by revascularization—if the ratio is ≤ 0.80 (5, 6). The *Figure* provides 3 examples to illus-

trate the role of FFR measurements in the treatment decision making process compared to visual assessment of angiography images alone. For the identification of reversible ischemia, FFR measurement has a sensitivity of 88% and a specificity of 100%. Likewise, the positive predictive value (PPV) is 100% (12, 14).

It is also possible to make a measurement without induction of maximal hyperemia, i.e. without

administration of adenosine. Example of such “resting indices” include Pd/Pa (comparison of mean pressure values without vasodilation), RFR (resting full-cycle ratio), and iFR (instantaneous wave-free ratio) (17–22). The results of two large randomized studies on the resting index iFR, DEFINE-Flair (n = 2492) and iFR-SWEDEHEART (n = 2037), were published in 2017. It was found that revascularization planning based on iFR was not inferior to FFR measurement with regard to the clinical endpoints death, myocardial infarction and unplanned revascularization (event rates iFR-SWEDEHEART FFR 6.1% versus iFR 6.7%; p = 0.53; event rates DEFINE-Flair FFR 7.0% versus iFR 6.8%; p = 0.78) (23, 24).

The invasive determination of the hemodynamic significance of a stenosis using a pressure wire is associated with few complications. Nevertheless, besides the transient discomfort which patients may experience following adenosine administration, there is a very low risk (<0.2%) of coronary artery injury associated with the use of guiding catheters and intracoronary wires (23, 25).

Significance of FFR measurement

In the large French R3F registry, measuring FFR resulted in a change of treatment regimen in 43% of the 1075 patients (26). Besides registries, large randomized trials in which FFR was used to inform decision making found that revascularization decisions frequently differed from those based solely on angiographic interpretation and that the clinical outcomes were significantly improved compared with exclusively angiography-guided management. This applied to both patients with stable angina pectoris and patients with acute coronary syndrome.

FFR measurement in patients with stable angina pectoris

The DEFER trial included 325 patients with de-novo stenosis and an angiographic, visually estimated degree of stenosis of >50% diameter reduction (27). Patients (n = 181) with an FFR >0.75 were randomized to receive either treatment with PCI (“Perform PCI”, n = 91) or a conservative procedure (“Defer”, n = 90). Patients with an FFR <0.75 (n = 144) were revascularized and defined as the reference group. After 1 year and after 5 years of clinical follow-up, no disadvantage was found for patients with an FFR >0.75 who did not undergo PCI (event-free survival in the Perform-PCI group versus Defer group: 73% versus 79% after 5 years, p = 0.52) (15). To the contrary: Over a follow-up period of 15 years, even less myocardial infarctions were observed in the Defer group compared with the Perform-PCI group (10.0% versus 2.2%; risk ratio [RR] 0.22; p = 0.03) (16).

The FAME study, which was published in 2009, randomly assigned patients with coronary two- or three-vessel disease and angiographic stenoses ≥50% to either angiography-guided (n = 496) or FFR-

guided revascularization (n = 509) (12). In the FFR-guided arm, PCI was performed if the FFR was ≤ 0.80. Altogether, 1387 stenoses were successfully evaluated. In 874 stenoses, the FFR was ≤ 0.80. In the FFR-guided group, the composite endpoint (death, myocardial infarction and revascularization) occurred significantly less frequently compared to the angiography-assessed PCI group (13.2% versus 18.3%; p = 0.02) after 1 year. No difference in mortality was found between the 2 groups (28). The 5-year follow-up data confirmed the long-term safety of FFR-guided PCI in patients with multivessel disease. The MACE rate (composite endpoint of death, myocardial infarction, repeat revascularization) in the angiography-guided patient group was 31%, in the FFR group 28% (RR: 0.91; p = 0.31) (29).

The FAME-2 study showed that patients with an FFR value ≤ 0.80 benefited from revascularization (30). The study included patients with one-vessel or multivessel disease and assessed all stenoses >50% using FFR. If the FFR of a stenosis was ≤ 0.80 (n = 888), the patients were randomly assigned to PCI or medical treatment alone. After inclusion of 880 patients, FAME-2 was halted prematurely because the primary endpoint (combination of death, myocardial infarction, and urgent revascularization) occurred significantly less frequently in the PCI group compared with the medical therapy group. After a 2-year follow-up period, the primary endpoint was observed in 8.1% of patients with abnormal FFR who underwent PCI (versus 19.5% with medical therapy alone; odds ratio [OR] 0.39; 95% confidence interval: [0.26; 0.57]; p < 0.001) (30).

The 5-year follow-up data confirmed the differences already observed after one year (31, 32). The FAME-2 study has been criticized because the “urgent revascularization” endpoint was primarily responsible for the difference found (4.0% versus 16.3%; OR: 0.23; [0.14; 0.38]; p < 0.001) (30). However, revascularization was only defined as “urgent” if the patient experienced constantly increasing or persistent symptoms of angina pectoris. This is equivalent to unstable angina pectoris and thus not a “soft” endpoint.

FFR measurement in patients with acute coronary syndrome

The COMPARE-ACUTE study, evaluating 885 patients with acute ST-segment elevation myocardial infarction and multivessel disease showed for the first time that FFR-guided complete revascularization was superior to treatment of the infarct-related artery only. In addition to treatment of the infarct-related artery, 55.3% of patients (163 of 295) in the FFR-guided group underwent revascularization of at least one non-infarct-related artery. In the control group, only the infarct-related artery was revascularized. At 12 months, the composite endpoint of mortality, myocardial infarction, cerebrovascular event, and revascularization occurred in the group with complete revascularization guided by FFR significantly less frequently (7.8%

versus 20.5%, $p < 0.001$). However, this finding was mostly driven by a lower rate of subsequent revascularizations. In the control group, two-thirds of the coronary interventions performed during the follow-up period was indicated for treatment of stable angina pectoris (33). This finding raises the question of whether FFR-guided revascularization is superior to angiography-guided complete revascularization in patients with acute coronary syndrome. However, until now no valid data capable of answering this question have become available.

The results of DEFER and FAME show that conservative management of stenoses which are not hemodynamically relevant is safe with optimized pharmacotherapy, and may be able to prevent acute myocardial infarction. On the other hand, the FAME-2 study and the COMPARE-ACUTE study demonstrated that patients with abnormal FFR (≤ 0.80) benefit from revascularization. This finding was also confirmed by the large IRIS-FFR registry which followed up more than 5000 patients over a period of almost 2 years (34).

It might be worth noting that the large randomized trials were at least to some extent sponsored by FFR wire manufacturers; thus, potential conflicts of interest should be taken into consideration.

A meta-analysis of 11 double-arm studies comparing FFR-based with only angiography-guided PCIs was published in 2017. The study, which included a total of 51 350 patients, confirmed that FFR-guided PCI is associated with lower rates of in-hospital myocardial infarction and myocardial infarction after 9 months (OR: 0.53; [0.40; 0.70], $p = 0.00001$). Likewise, the MACE rates were lower (OR: 0.63; [0.47; 0.86], $p = 0.004$). However, no differences were found for all-cause mortality (OR: 0.84; [0.59; 1.20], $p = 0.34$) and repeat revascularization (OR: 0.83; [0.50; 1.37], $p = 0.46$) (35).

Based on this evidence, the 2018 European guidelines recommend to measure FFR if noninvasive detection of ischemia is unavailable or if the findings are inconclusive (5). Currently, however, there is a lack of data on the impact of the regular use of FFR measurement on the number of revascularization interventions and on clinical event rates.

Reasons for the infrequent use of FFR measurement

In view of the solid available evidence, it is surprising that FFR measurements are only infrequently performed during invasive coronary angiography. While in 2011 approximately 10 200 FFR measurements were recorded across Germany, this number increased to approximately 38 200 measurements annually by 2016 (36). An analysis from the ALKK registry (Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte e. V.) showed that in the period from 2010 to 2013 altogether 100 977 PCIs were performed, but only 3.2% of the patients were evaluated based on intracoronary pressure measurements. There was significant variation in this percentage values among the 38 participating

Key messages

- The management of coronary artery disease with “symptom alleviation” and “improvement of prognosis” as the primary goals embraces pharmacotherapy or surgical revascularization/stent implantation.
- Only in the presence of hemodynamically significant coronary stenosis, revascularization offers a prognostic advantage. Clinically, fractional flow reserve (FFR) is used for ruling in or out lesion-specific relevant ischemia, as long as no or only inconclusive noninvasive ischemia detection is available.
- Likewise, determining resting indices, such as Pd/Pa (comparison of the mean pressure values without vasodilation), RFR (resting full-cycle ratio), and iFR (instantaneous wave-free ratio), allows to determine the fractional flow reserve without the need to induce maximal hyperemia.
- Both the European and the US guidelines assume for stenoses with $\text{FFR} \leq 0.8$ that they are prognostically significant and thus require revascularization.
- Patients without inducible ischemia ($\text{FFR} > 0.80$) have a good prognosis with optimized pharmacotherapy.

hospitals: from 0.1% to 8.8%. Here again, an increasing use of pressure wire measurements was noted during this 3-year period (37). In other European countries, the rates of FFR-guided PCI are significantly higher. In 2015, the leaders were Denmark (31%) and Belgium (29%) (38, 39).

A survey conducted in 2012 among 1089 interventional cardiologists identified lack of availability (47%) and problems with reimbursement (39%) as the primary reasons for the infrequent use of FFR guidance (40). In Germany, however, FFR measurement is included in the diagnosis-related group (DRG) system. In many cases, reimbursements cover the costs, but some situations, such as acute coronary syndrome or very complex PCI, are still problematic. Other recent explanations by experts for the still infrequent use include:

- Insufficiently trained medical and nursing staff
- Lack of acceptance, and
- Technical complexity.

Conclusion

With the introduction of pressure wire measurement to determine FFR, the hemodynamic relevance of coronary stenoses can be determined during coronary angiography. The information obtained by measuring intracoronary pressures can sometimes come as a surprise; for example, angiographic high-grade stenoses may turn out to be without hemodynamic relevance, or significant ischemia may be found to be induced by moderate-grade stenoses.

The available evidence from studies clearly indicates that: stenoses with normal FFR measurement do

not need revascularization. In this situation, the prognosis with pharmacotherapy alone is not inferior to the prognosis with PCI. On the one hand, there should be a general understanding that not the degree of stenosis but the extent of ischemia determines whether a patient will benefit from the revascularization of a lesion. On the other hand, it must be ensured that pressure wire measurement is always readily available during coronary angiography and used when needed.

Acknowledgement

The authors would like to thank Prof. Dr. S. Achenbach for his stimulating specialist comments during manuscript composition as well as his critical review and revision.

Conflict of interest statement

Dr. Gaede received consultancy fees and lecture fees from Abbott Vascular. She received research support (third-party funding) from St. Jude Medical.

Prof. Möllmann received consultancy fees, reimbursement of continuing medical education and travel expenses as well as lecture fees and study support (third-party funding) from Abbott Vascular, Boston Scientific, and St. Jude Medical.

Prof. Rudolph received reimbursement of congress fees from St. Jude Medical. She received lecture fees from St. Jude Medical, Abbott Vascular, and Philips. She received consultancy fees from Abbott Vascular.

PD Dr. Rieber received consultancy fees from Philips, Boston Scientific, and Abbott Vascular. He received reimbursement of travel expenses from Philips. He received lecture fees and authorship/co-authorship fees for a publication related to the topic from Philips and Abbott Vascular.

Dr. Boenner received study support (third party funding) from Abbott Vascular.

Dr. Tröbs received consultancy fees from Abbott Vascular.

Manuscript received on 20 September 2018; revised version accepted on 4 February 2019

Translated from the original German by Ralf Thoene, MD.

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CLINICAL SNAPSHOT

Cervical Emphysema in Boerhaave Syndrome

A 70-year-old man presented with dyspnea, sinus tachycardia, fever, and poor general status after repeated vomiting with no obvious cause. His oxygen saturation was 82%. Chest radiography showed bilateral cervical emphysema together with signs of mediastinal emphysema (*Figure*). Thoracic computed tomography confirmed the mediastinal emphysema and revealed a pleural effusion. On the assumption of mediastinitis and threatened sepsis, calculated antibiotic treatment was initiated. Gastroscopy demonstrated a circa 2-cm long rupture of the distal esophagus, thus confirming Boerhaave syndrome and meaning that surgical treatment was indicated. The operation was performed via the transabdominal route, and the lesion was oversewn and covered with a fundus patch. Despite intensive care the patient died of sepsis. Boerhaave syndrome describes spontaneous perforation of all layers of the esophageal wall as a consequence of a sudden strong increase in intraesophageal pressure, as may occur in vomiting. The incidence is low; the mortality amounts to 10 to 40%. Boerhaave syndrome must be treated as a life-threatening emergency. The presence of soft tissue emphysema may be a valuable diagnostic sign.

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Conflict of interest statement: The authors declare that no conflict of interest exists.

Translated from the original German by David Roseveare

Cite this as: Swol J, Mannke B, Ficker JH: Cervical emphysema in Boerhaave syndrome. *Dtsch Arztebl Int* 2019; 116: 211. DOI: 10.3238/arztebl.2019.0211

Orange arrows: Left thoracic mediastinal emphysema. White arrows: Bilateral cervical soft tissue emphysema. The opacity in the left lower field corresponds to a pleural effusion.