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Přehledový článek | Review

The concept of functional revascularization

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ABSTRACT

Detection and reduction of inducible myocardial ischemia is a key moment in management of patients with stable coronary artery disease. It has been shown that coronary angiography as well as non-invasive stress testing fails to inform about true hemodynamic significance of individual stenosis in certain subsets of coronary anatomies. Intervention of non-significant lesion is associated with worse prognosis than optimal medical treatment. Using invasive measurement of myocardial fractional flow reserve (FFRmyo) for decision to perform or defer percutaneous coronary intervention was superior to angiographical guidance. Revascularization of functionally significant lesions and medical management of non-significant ones is the base of concept of functional revascularization and FFRmyo may be a tool which provides information needed for such a clinical decision.

SOUHRN

V léčbě nemocných s ischemickou chorobou srdeční je klíčovým momentem detekce a odstranění indukovatelné ischemie myokardu. Je známo, že v určitých případech ani angiografie, ani neinvazivní zátěžové testy nejsou schopny podat správnou informaci o skutečné hemodynamické významnosti stenózy koronární tepny a že intervence nevýznamné stenózy zhoršuje prognózu ve srovnání s konzervativní léčbou. Bylo rovněž prokázáno, že indikace k intervenci na podkladě výsledku měření frakční průtokové rezervy (FFR) je spojena s lepšími výsledky než vedení angiografií. Intervence pouze hemodynamicky významných stenóz a konzervativní léčba u funkčně nevýznamných je základem konceptu funkční revaskularizace. Pro stanovení skutečné hemodynamické významnosti by měření FFR mohlo být tím pravým nástrojem.

Background

It has been documented that the presence of significant myocardial ischemia is a negative prognostic factor in patients with stable coronary artery disease (CAD) [1–3]. Reduction of ischemic burden is associated with improved long-term prognosis. It can be successfully achieved by medical therapy or revascularization procedures [3]. The nuclear sub-study of the COURAGE trial [4] as well as other studies demonstrated better efficiency of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) when compared to medical treatment in relieving myocardial ischemia [3,5]. In certain subsets of patients (left main disease, triple-vessel disease), CABG is able to improve the patients' prognosis when compared to medical management as was documented in dated, though for clinical practice still relevant trials [5–7]. When deciding on indication and possibly type of revascularization invasive coronary angiography still plays a pivotal role. It is well established, relatively

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safe and available method which offers very good temporal and spatial resolution and has been used as a road map for revascularization procedures for several decades. Though for many years it has been also recognized that the ability of coronary angiography to define functional significance of coronary stenosis is rather limited. Coronary lesions with 40–70% stenosis diameter were found to be both significant and non-significant [8–10]. Despite the recent development of techniques of coronary angiography and image post-processing, including 2D a 3D quantitative analysis or computed tomography coronary angiography, there is still a substantial limitation of contrast angiography in assessment of functional significance [11,12]. Further, many physicians still rely only on visual estimation of coronary stenosis even though it has been shown to be unreliable [11,12]. Many patients undergoing coronary angiography have not been non-invasively tested for inducible myocardial ischemia or these tests were not conclusive [13]. In some patients with multivessel disease it may not be possible to make a sound relation between stress test result and coronary anatomy or result could be false negative due to balanced ischemia.

Myocardial fractional flow reserve

The myocardial fractional flow reserve (FFRmyo) is an invasive method for an assessment of functional significance of epicardial coronary artery stenosis and has been used in clinical practice for more than a decade. It is based on intracoronary pressure measurement during pharmacologically induced maximal hyperemia using dedicated coronary micromanometric guidewire [14–18]. Position of micromanometr can be easily assessed during angiography, thus allowing very good spatial resolution and assessment of individual lesions and diseased arteries. FFRmyo could be considered as "in-cathlab" surrogate for stress testing as it was found to have an excellent sensitivity and specificity when compared to conventional stress test such as myocardial perfusion scans, stress echocardiography and ECG stress testing [16,19].

Probably main clinical application of FFRmyo is an assessment of borderline significant stenosis and this indication is also supported by recently published guidelines [20,21]. Several published data suggested that deferral of intervention of borderline stenosis with FFR value more than 0.75 or 0.80 is safe and associated with very good outcome during mid- and long-term follow-up [12,22–25]. The very first randomized trial using FFRmyo in relatively low-risk patients (the DEFER trial) documented better outcome in patients with deferred PCI when compared to stented group with ischemic FFRmyo and control stented group with non-ischemic FFRmyo [26] (Table 1).

Landmark trial FAME published in 2009, included 1 005 patients with multivessel disease and randomized them to angiography or FFR-guided PCI. Patients randomized to undergo FFR had absolute reductions in the primary composite end point of death, MI, CABG surgery, or repeat PCI of 5.1% and 5.3% at one year and 18 months, respectively (Table 2).

At two years, the 22.2% of patients randomized to angiography-guided PCI had a primary end point compared with 17.7% in the FRR-guided treatment arm, an absolute reduction of 4.5%. Similar to earlier analyses, the reduction was driven by a reduction in the rate of MI.

Table 1 – Clinical outcomes in the DEFER [26] and the COURAGE [29] trials. In DEFER trial there was a group of patient with non-ischemic FFR treated by PCI. At the time when the trial was designed it was no clear that deferral of PCI based on FFR measurement is safe. Of interest are the differences between conservative arm of DEFER (non-ischemic lesions) and conservative arm of COURAGE (probably mix of ischemic and non-ischemic lesions).

	DEFER 5 years (n = 325)			COURAGE 4.6 years (n = 2 287)	
	Conservative FFR ≥ 0.75	PCI FFR ≥ 0.75	PCI FFR ≤ 0.75	PCI	Conservative (OMT)
Mortality (all cause) (%)	6.6	5.7	9.0	7.6	8.3
Mortality (cardiac) (%)	3.3	2.3	6.0	2.1	2.2
Spontaneous myocardial infarction (%)	0	5.6	9.7	10.0	11.4
Revascularization (%)	8.9	9.1	13.4	21.1	32.6
Mortality + spontaneous myocardial infarction (%)	6.6	11.3	18.7	17.6	19.7

FFR – myocardial fractional flow reserve; OMT – optimal medical treatment; PCI – percutaneous coronary intervention.

Table 2 – Outcome of patients in FAME study – 2-year follow-up [27] comparing results in angio-guided and FFR-guided stenting groups

	Angio-guided (n = 496)	FFR-guided (n = 509)	*p*
Mortality (all-cause) (%)	19 (3.8)	13 (2.6)	0.25
Myocardial infarction (%)	48 (9.7)	31 (6.1)	0.03
CABG, repeated PCI (%)	61 (12.3)	53 (10.4)	0.35
Mortality + myocardial infarction (%)	63 (12.7)	54 (10.4)	0.03
Mortality + myocardial infarction, CABG, repeated PCI (%)	110 (22.2)	90 (17.7)	0.07

The cost-analysis showed that the treatment with FFR was cost-effective, mainly because patients in the FFR arm received fewer stents. The rate of complication related to lesion with deferred PCI was low with only 1 MI related to deferred stenosis (out of 517 deferred lesions). The cut-off value of FFRmyo for PCI was 0.80 and less [10,27].

There were 3 large randomized trials comparing different revascularization strategies (multivessel PCI vs. CABG in SYNTAX trial [28]) or comparing revascularization with optimal medical treatment (OMT) (COURAGE trial [29]) and above mentioned FAME trial [27]. After excluding patients with left main disease from the SYNTAX trial and including only patients with triple-vessel disease (SYNTAX 3VD) a comparison of these trials regarding the incidence of major adverse cardiac events (MACE) could be made. Despite different angiographical baselines (more advanced anatomy in SYNTAX 3VD) the rate of MACE in PCI arms of all these trials was similar at around 20% at 1-year follow-up. FFR guided strategy in FAME trial had 13% of MACE. Hypothetically one of the factors causing this difference could be a non-necessary stenting in SYNTAX 3VD, COURAGE and FAME angio-guided arm populations, where stented lesions were not functionally significant despite their angiographic appearance.

Concept of functional revascularization

To understand the concept of functional revascularization in patients with stable CAD it is important to acknowledge different combined mortality and MI rate associated with ischemic and non-ischemic stenoses and their treatment (medical versus interventional). From previous studies it is known that such an event rate is about 1% per year for a functionally non-significant stenosis if treated appropriately by medication [26,29–31]. Conversely it is between 5% and 10% per year for a functionally significant stenosis if only treated by medication [4,32] and approximately 3% per year for a stented lesion whether it was functionally significant or not [4,30,32,33].

This means that stenting of a functionally significant stenosis could improve outcome, but stenting a functionally non-significant stenosis would worsen outcome.

It may also change a routine practice in coronary cardiac surgery [31]. Cornelis et al. showed that 1-year patency of venous grafts depends also on lesion functional significance when assessed by FFRmyo. The occlusion rate was strikingly higher in non-significant lesions [34]. By avoiding unnecessary grafting some patients could be treated by PCI instead or having less grafts, possibly all arterial. Recently presented large French FFR registry documented such a trend in clinical practice [35].

Case report

This gentleman, who is 74 years old, was referred for cardiac catheterization. His main complain were palpitations secondary to persistent atrial fibrillation which were occasionally associated with chest discomfort. He denied exertional chest pains. He had refused to undergo ablation therapy for atrial fibrillation in the past. His coronary angiography revealed two-vessel disease. There was a 50–70% of proximal left anterior descending (LAD) and serial 50% stenosis of left circumflex artery (LCx). Right coronary artery had mild disease.

FFRmyo of both arteries was performed using intracoronary bolus of Adenosine, 150 μg. FFR of LAD was 0.64 (Fig. 1), FFRmyo of LCx was 0.84 (Fig. 2). The patient was referred for single coronary bypass (LIMA-LAD) and MAZE procedure. Disease of LCx should be managed medically.

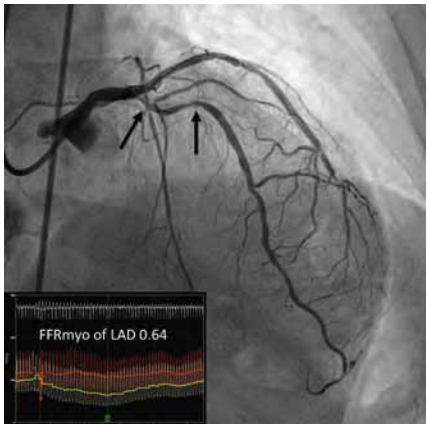

Fig. 1 – Angiogram of the left coronary artery. There are proximal stenoses of LAD (arrows). Bottom left – FFRmyo recording in LAD – 0.64 indicating hemodynamic significance.

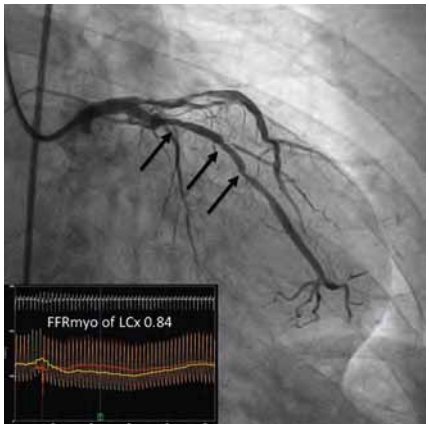

Fig. 2 – Angiogram of the left coronary artery. There are proximal stenoses of LCx and obtuse marginal branch (arrows). Bottom left – FFRmyo recording in LCx. The value of 0.84 does not suggest hemodynamic significance.

Conclusion

There could be a shift of paradigm for indication of revascularization in patients with stable CAD. Functional measurement prior to indication of revascularization may decrease the rate of implanted stents or inserted grafts. It could also change the classification of patient according to number of diseased vessels, usually down-grading as less stenoses were functionally significant. It is not realistic to advocate FFR measurement for all stenoses in range of 40–70% and also expect that measurement of all borderline stenosis would have significant impact on daily routine practice. Yet it is important to recognize that initial data suggest that FFRmyo could be a valuable tool in these clinical situations with potential to improve patient outcome.

In the future we will get more data from FAME2 trial comparing PCI and OMT and we need more adequately designed trials comparing PCI and CABG in different patient subsets.

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