Original article

doi:10.5633/amm.2027.0206

CLINICAL OUTCOMES OF CORONARY INTERVENTIONS GUIDED BY THE USE OF FRACTIONAL FLOW RESERVE AND NON-HYPEREMIC PRESSURE RATIONS

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Fractional flow reserve (FFR) represents the gold standard for assessing the functional significance of angiographically borderline coronary lesions. Non-hyperemic pressure ratios (NHPR), which represent ratios during diastole or during the entire cardiac cycle at rest, are also important. The aim of this research was to demonstrate favorable long-term outcomes of coronary interventions guided by FFR and NHPR. The research was carried out as a retrospective study of patients with coronary disease which coronary interventions in the Cath Lab of the Cardiology Clinic of the University Clinical Center Niš were conducted by FFR and NHPR. The periprocedural characteristics of all included 25 cases and total of 35 lesions, were obtained. Of the 8 patients for whom revascularization was indicated, only one patient had complete surgical revascularization (coronary artery bypass graft – CABG), while the other 7 patients underwent a percutaneous coronary intervention (PCI) procedure. After the PCI procedure, the measurement of the FFR value was

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repeated. The average follow-up time was 15 months. After the follow-up period 10 patients had complaints. Out of 10 patients with typical anginal symptoms, exercise tests were performed in 8 patients, and all were negative for myocardial ischemia. None of the patients who underwent revascularization or had no revascularization experienced non-fatal target vessel myocardial infarction (NF-TVMI) and repeated target lesion revascularization (TLR) during follow-up. With this research, we established favorable outcomes of coronary interventions guided by FFR and NHPR.

Keywords: fractional flow reserve, non-hyperemic pressure ratios, percutaneous coronary intervention, coronary artery bypass graft

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Originalni rad

doi:10.5633/amm.2027.0206

Klinički ishodi koronarnih intervencija vođenih upotrebom frakcione rezerve protoka i nehiperemijskim indeksima pritiska

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Rezerva frakcionog protoka (engl. *fractional flow reserve* – FFR) predstavlja zlatni standard za procenu funkcionalnog značaja angiografski graničnih koronarnih lezija. Za procenu hemodinamske značajnosti koronarnih lezija značajni su i nehiperemijski indeksi pritiska (engl. *non-hyperemic pressure ratios* – NHPR) koji predstavljaju indekse pritiska tokom dijastole ili tokom celog srčanog ciklusa u mirovanju. Cilj ovog rada bio je demonstrirati povoljne dugoročne ishode koronarnih intervencija vodjenih FFR-om i NHPR za krajnji ishod nakon dugoročnog praćenja. Istraživanje je sprovedeno kao retrospektivno ispitivanje bolesnika sa koronarnom bolesti kod kojih su koronane intervencije u angio sali Klinike za kardiologiju UKC Niš bile vođenje FFR i NHPR. Objedinjene su periproceduralne karakteristike svih uključenih 25 slučajeva, odnosno ukupno 35 lezija. Od 8 pacijenata kojima je indikovana revaskularizacija, samo kod jednog pacijenta kompletna revaskularizacija je postignuta hirurški (engl. *coronary artery bypass graft* – CABG), dok je kod ostalih 7 pacijenata radjena perkutana koronarna intervencija (engl. *percutaneous coronary*

intervention – PCI). Nakon PCI procedure ponovljeno je merenje FFR vrednosti. Prosečno vreme praćenja iznosilo je 15 meseci. Nakon perioda praćenja 10 pacijenata je imalo tegobe. Od 10 pacijenata sa tipičnim anginoznim tegobama, testovi fizičkim opterećenjem odradjeni su kod 8 pacijenata, i svi su bili negativni na miokardnu ishemiju. Ni jedan pacijent kome je uradjena revaskularizacija ili se od iste odustalno nije doživeo nefatalni infarkt miokarda ciljnog krvnog suda (eng. non-fatal target vessel myocardial infarction-NF-TVMI) i ponovljenu revaskularizaciju ciljne lezije (eng. target lesion revascularization-TLR) tokom praćenja. Ovim istraživanjem ustanovili smo povoljne ishode koronarnih intervencija vodjenih FFR i NHPR.

Ključne reči: rezerva frakcionog protoka, nehiperemijski indeksi pritiska, perkutana koronarna intervencija, kompletna revaskularizacija je postignuta hirurški

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INTRODUCTION

FFR (fractional flow reserve) is the gold standard for assessing the functional significance of angiographically borderline coronary lesions. (1) FFR is a pressure index used during coronary angiography to assess the potential of coronary stenosis to cause myocardial ischemia. (2) Non-hyperemic pressure ratios (NHPR) are also important for assessing the hemodynamic significance of coronary lesions, which represent pressure ratio during diastole or during the entire cardiac cycle at rest, which provide a physiological quantification of the effect of stenosis on the coronary circulation. (2, 3)

In addition to its diagnostic role, numerous studies have confirmed the importance of the use of FFR in the management of revascularization procedures, since its use leads to a reduction in the incidence of adverse cardiovascular events, a reduction in the number of implanted stents, as well as a more favorable economic relationship between costs and benefits. (4, 5, 6)

The importance of NHPR is particularly highlighted, as these indexes can shorten the procedure time, improve cost efficiency, as well as patient comfort (2).

AIM

The aim of this work was to demonstrate favorable long-term outcomes of coronary interventions guided by FFR and NHPR for final outcome after long-term follow-up.

MATERIAL AND METHODS

The research was carried out as a retrospective study of patients with coronary disease, in whom coronary interventions with FFR and NHPR was performed in the Cath lab of Interventional Cardiology, and who were patients and users of the services of the Cardiology Clinic of the University Medical Center Niš.

During this study, the usual methods of collecting complete medical documentation, fluoroscopic images from coronary angiography and PCI, laboratory analyzes and echocardiography findings, as well as documentation from CABG revascularization in the case of patients who had complete revascularization achieved by surgery, were applied.

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Clinical examinations of the patients were carried out at the Cardiology Clinic of the University Clinical Center Niš or by telephone. During clinical controls, standard, non-invasive methods for taking arterial and venous blood, as well as auscultatory blood pressure measurement and echocardiographic examination of the heart were applied.

Statistical processing of the collected data was performed in the SPSS (Statistical Package for Social Science) program, Statistics for Windows, version 13 (SPSS Inc., Chicago, Ill., USA). Tested parameters are represented as a percentage, and continuous variables are represented by mean value (X) and standard deviation (SD) and minimum and maximum values.

RESULTS

Demographic characteristics are presented in Table 1. Men made up 72% of all included patients, the average age of the subjects was 62 ± 7 years.

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Table 1. The demographic characteristic and the statistical results of the investigated parameters

Parameters	Values (N=25)
Men	18 (72%)
Age	62 ± 7 Min 50 Max 74
Ejection fraction (EF)	53 ± 10 % Min 38 Max 70
Diabetes mellitus	Yes-8 (32%) Type 2- 6 (75%) Type 1- 2 (25%)
Hypertension	24 (98%)
Smoking	Current 5 (20%) Former 8 (32%) Non-smokers 12 (48%)
Chronic kidney disease	1 (4%)
BMI	26.6 ± 4,4
Access	Radial 19 (76%) Femoral 6 (24%)
Prior IM	12 (48%)
Prior PCI	11 (44%)

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Table 2 shows the periprocedural characteristics of all included 25 cases, i.e. a total of 35 lesions for which hyperemic and non-hyperemic indices were measured. Out of the total number of cases, 10 patients had two-vessel disease, so hyperemic and non-hyperemic ratios were calculated on both arteries.

Table 2. Angiography characteristics of Lesions Assessed by Fractional Flow Reserve and Non-Hyperemic Pressure Ratios

Characteristics	Values (N=25) (total N of lessions 35)
Lesion territory	
Left main	9 (25.7%)
Left anterior descending artery	16 (45.7%)
Right coronary artery	2 (5.7%)
Left circumflex artery	7 (20%)
Diagonal	1 (2.8%)
Lesion location	
Proximal	9 (25.7%)
Mid	17 (48.6%)
Distal	9 (25.7%)
Angiographic vessel disease	
1 vessel	15 (60%)
2 vessels	10 (40%)
FFR and NHPR	
FFR mean	0.82 ± 0.1
NHPR mean	0.86 ± 0.1
POST PCI FFR mean	0.88 ± 0.05

The angiographic characteristics of the lesions indicated for medical treatment and the characteristics of the lesions indicated for revascularization are shown in Table 3. Of the 8 patients for whom revascularization was indicated, only one patient underwent complete revascularization by surgical approach (CABG), while the other 7 patients underwent a PCI procedure. After the PCI procedure, the measurement of FFR values (Post PCI FFR) was repeated, which are also shown in Table 3.

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Table 3. Angiography characteristics of Lesions Assessed by Fractional Flow Reserve and Non-Hyperemic Pressure Ratios in groups with indicated and deferred revascularization

Characteristics	Fractional Flow Reserve Measurement in Deferred Lesion (N=17) (total N of lessions 23)	Fractional Flow Reserve Measurement in Revascularized Lesion (N=8) (total N of lessions 12)
Lesion territory		
Left main	6 (26%)	3 (25%)
Left anterior descending artery	9 (39%)	7 (58.3%)
Right coronary artery	2 (9%)	0 (0%)
Left circumflex artery	6 (26%)	1 (8.3%)
Diagonal	0 (0%)	1 (8.3%)
Lesion location		
Proximal	8 (35%)	5 (41.7%)
Mid	9 (39%)	4 (33.3%)
Distal	6 (26%)	3 (25%)
Angiographic vessel disease		
1 vessel	11 (64.7%)	4 (50%)
2 vessels	6 (35.3%)	4 (50%)
FFR and NHPR		
FFR mean	0.88 ± 0.06	0.74 ± 0.08
NHPR mean	0.92 ± 0.04	0.77 ± 0.1
POST PCI FFR mean	NA	0.88 ± 0.05

The average follow-up time was 15 months. Average EF after the follow-up period was 53 ± 9.4%. After the follow-up period, out of the total number of included patients, 10 patients had complaints.

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Out of 10 patients with typical anginal symptoms, exercise tests were performed in 8 patients, and all were negative for myocardial ischemia.

Not a single patient who underwent revascularization or revascularization was deferred after measuring hyperemic and non-hyperemic ratios experienced non-fatal target vessel myocardial infarction (NF-TVMI) and repeated target lesion revascularization (TLR) after long-term follow-up.

DISCUSSION

This study included 25 patients with anginal symptoms, without evidence of ischemia on stress tests, or whose stress tests were inconclusive about myocardial ischemia, or after MSCT of the coronary arteries, and who had coronary artery stenosis in the range of 30-70% on coronary angiography.

Procedural characteristics were obtained: angiographic characteristics of lesions, values of hyperemic and non-hyperemic ratios, demographic characteristics of patients and associated comorbidities, as well as composite outcomes of procedures during an average follow-up period of 15 months for 25 cases of interventions measuring hyperemic and non-hyperemic ratios performed in the Cath lab of the Cardiology Clinic of the University Clinical Center in Niš.

FFR measurements, based on an objective assessment of myocardial ischemia, allow interventional cardiologists to make decisions about the need for revascularization in patients with coronary artery disease, thereby achieving a better balance between the risks and benefits of percutaneous coronary intervention (PCI) in different clinical situations. Numerous clinical evidences indicate that the application of this targeted invasive functional method contributes to the adequate selection of patients and lesions for treatment, avoiding unnecessary interventions, reducing health costs and improving clinical outcomes. (7)

The DEFER study, after 15 years of follow-up, showed no significant differences in the mortality rate in patients with functionally insignificant lesions treated with medical therapy, and there was a lower rate of myocardial infarction (MI) in the delayed intervention group compared with the functionally insignificant lesion stented group (2.2% vs. 10.0%, p=0.03). (8)

In studies of multivessel coronary disease, the composite primary outcome of death, myocardial infarction, or repeat revascularization at 1 year was lower in the FFR-guided group than in the

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angiography-guided group (13.2% (67 patients) vs. 18.3% (91 patients), p=0.02). This difference was maintained after 2 years of follow-up. (5) After 5 years, FFR-guided PCI reduced the risk of the primary composite outcome including time to death, myocardial infarction, or emergency revascularization, mainly due to fewer emergency revascularizations. At a median follow-up of 11.2 years, the primary endpoint occurred in 150 of 447 patients (33.6%) in the FFR-guided PCI group versus 182 of 441 (41.3%) in the medical therapy group. PCI was superior in 29.2% of comparisons, medical therapy in 23.3%, and the two groups were equal in 47.5%, resulting in a success ratio of 1.25 in favor of PCI (95% confidence interval (CI) 1.01–1.56, P = 0.043). The corresponding difference in success was 5.9% (95% CI 0.2–11.6) and the number needed to treat was 17 (95% CI 9–500). Success ratios were 0.88 for all-cause death (95% CI 0.66–1.17), 1.50 for myocardial infarction (95% CI 0.98–2.31), and 4.57 for urgent revascularization (95% CI 2.53–8.24). (9)

While the RIPCORD 2 trial showed that systematic assessment of FFR compared with angiography alone did not lead to a significant reduction in costs or improvement in quality of life at one year's follow-up. (10)

ADVISE trial showed that the hyperemic response of the microcirculation to the administration of adenosine depends on age and that FFR values increase with the age of the patient, while non-hyperemic values remain constant in all age groups. These findings contribute to the explanation of the differences observed in the classification of functional stenosis with hyperemic and non-hyperemic coronary ratios and highlight the importance of simultaneous determination of NHPR. (11)

The European Society of Cardiology gives invasive functional evaluation tests a class IIb indication for the evaluation of moderate severity stenosis on non-culprit arteries during the index procedure in NSTEMI clinical presentation. (12)

Out of the total number of cases, 10 patients had two-vessel disease, so hyperemic and non-hyperemic ratios were calculated on both arteries. Only one patient had disease of the distal left main and trifurcation, but ratios were measured only through LM-LAD, due to low heart rate and the impossibility of repeating the procedure through LCx (Left circumflex artery) and RI (ramus intermedius).

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Out of the total number of patients, 9 patients had disease of the left main, and only in 3 cases revascularization was performed, since in the other cases the ratios showed hemodynamically insignificant lesions. Revascularization of all 3 cases of LM disease was performed percutaneously. Only in one case PCI LM was guided by OCT (optical coherence tomography), precisely because of the trifurcation of the left main and the impossibility of measuring hyperemic ratios due to the patient's low heart rate. All interventions on LM were started with a provisional technique, and only in one case was a 2-stent technique performed - TAP.

After the follow-up period, out of the total number of included patients, 10 patients had anginal complaints. Out of 10 patients with typical anginal symptoms, exercise tests were performed in 8 patients, and all were negative for myocardial ischemia. One patient who underwent PCI LM-LAD after measurement of hyperemic and non-hyperemic ratios due to typical anginal complaints after 3 years of the intervention underwent recoronarography and measurement of FFR and NHPR through LM-LAD. Both indices showed the insignificance of the lesion. After 10 months of recoronarography and repeated FFR measurements, the patient denied the existence of angina and angina-like complaints.

In 12 patients, FFR and non-hyperemic indices were measured after acute myocardial infarction and pPCI on the culprit lesion in an average of 1-2 months after the acute infarction, which is in accordance with current recommendations on the treatment of acute myocardial infarction. (12)

In all patients in whom revascularization procedures were deferred, FFR values were >0.80, while revascularization was indicated in all those with values ≤ 0.75. In patients in the gray zone with values ranging from 0.75 to 0.80, the decision was made depending on anginal complaints and after pullback. A total of 7 patients were in the gray zone according to FFR values. 5 patients in the gray zone had lower NHPR values, so revascularization was indicated in all of them. Revascularization was deferred in the other 2 patients. In one case, the NHPR value was >0.90, and the other patient with NHPR 0.89 had CTO RCA and FFR and NHPR were measured on donor vessel. In both patients, antianginal therapy was optimized, and the patients did not have angina complaints during follow-up.

Our results are consistent with literature data that showed that revascularization did not improve the prognosis of lesions with FFR ≥0.76, while for lesions with FFR ≤0.75 a benefit of revascularization was observed over medical treatment in terms of MACE, while a significantly

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increased risk of cardiac death or myocardial infarction was noted in revascularized lesions with FFR between 0.80 and 0.85 compared to medical treatment, which supports modern clinical guidelines that prohibit stent implantation in stenoses without objective evidence of ischemia. (12, 13).

CONCLUSION

With this research, we established favorable outcomes of coronary interventions guided by FFR and NHPR ratios. Our goal for future research will be to demonstrate favorable long-term outcomes after coronary interventions guided by FFR and NHPR compared to angiographically guided revascularization procedures: a composite outcome including cardiac mortality, non-fatal target vessel myocardial infarction (NF-TVMI) and target lesion revascularization (TLR) after a long-term follow-up of 5 years. Also, one of the future goals will be the inclusion of more patients with FFR values in the gray zone and the comparison of their outcomes depending on the indication of revascularization or optimal medical therapy alone.

Ethical approval

The study was approved by the institutional review board of University Clinical Center Niš, and written informed consent was obtained from all patients.

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