# Fractional flow reserve assessment to determine the indications for myocardial revascularisation in patients with borderline stenosis of the left main coronary artery

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## Abstract

**Introduction:** Reliable assessment of clinical significance of borderline angiographic lesions found within the left main coronary artery (LM) is often impossible. Measurement of fractional flow reserve (FFR) is commonly used to verify borderline stenoses of the coronary arteries. However, the usefulness of FFR measurements has been validated only for arteries other than the LM.

Aim: Evaluation of the measured FFR value in determination of the indications for myocardial revascularisation in borderline LM stenosis.

**Methods:** The study involved 38 patients aged 55±9 years (range 41-74 years) with isolated borderline LM stenosis. Each patient had the measurement of FFR performed during intravenous adenosine infusion at a dose of 140  $\mu$ g/kg/min. Patients were referred for revascularisation if FFR was <0.75.

**Results:** The mean LM stenosis in quantitative coronary angiography (QCA) was  $45\pm10\%$ . FFR<0.75 was found in 18 (47%) patients, whereas 20 (53%) subjects had FFR  $\geq$ 0.75. In subjects with FFR <0.75 QCA showed significantly lower minimal lumen diameters (MLD) at the site of stenosis (1.84 $\pm$ 0.45 vs 2.24 $\pm$ 0.49, p=0.014). Additionally, a significant correlation was found between FFR and MLD (r=0.59, p<0.001). The mean clinical follow-up was 2 years (range 1-3 years). There were two (11%) fatal events in patients with FFR  $\leq$ 0.75 who underwent CABG. One (5%) patient with FFR >0.75 underwent elective CABG due to progression of LMN stenosis. Moreover, one (5%) patient experienced myocardial infarction not related to borderline stenosis of the LM.

**Conclusions:** The measurement of FFR confirms the clinical significance of stenosis only in half of the patients with borderline isolated lesion of the left main coronary artery. Withdrawal from intervention in patients with FFR  $\geq$ 0.75 is safe and is associated with favourable clinical outcomes in two-year follow-up.

Key words: fractional flow reserve, revascularisation, coronary heart disease

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## Introduction

Critical stenosis of the left main coronary artery (LM) is a major indication for myocardial revascularisation due to bad prognosis in patients with the lesion if treated with pharmacotherapy alone [1]. Surgical revascularisation improves clinical outcomes by reducing long-term mortality [2]. Percutaneous coronary

intervention (PCI) has been shown in the last few years to be a potential alternative for surgical revascularisation [3, 4] in selected subjects with critical LM stenosis.

Reliable assessment of the severity of LM stenosis based on angiography alone is often impossible, even for very experienced operators. Not uncommonly in patients diagnosed as having critical LM stenosis on

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coronary angiography, only mild atherosclerotic lesions are found in post-mortem examinations and on intracoronary ultrasonography (ICUS) [5]. Importantly, however, an accurate assessment of LM stenosis severity plays a key role in making important therapeutic decisions. Therefore, more reliable methods of clinical significance determination of borderline LM stenoses are being sought.

Measurement of fractional flow reserve (FFR) using an angioplasty guide wire with poststenotic pressure transducer is commonly applied for evaluation of the clinical significance of coronary artery stenosis excluding the LM [6]. It has been proven that abandoning the intervention at FFR  $\geq$ 0.75 is safe and is associated with a lack of considerable clinical complaints and good long-term prognosis [7]. The aim of the study was the evaluation of measured FFR value in determination of the indications for myocardial revascularisation in borderline LM stenosis.

## Methods

## Patients

The study involved patients with stable coronary heart disease and isolated, borderline stenosis of the LM on angiography. Stenosis of the LM was considered borderline if the degree of lumen diameter reduction at the site of stenosis compared with the reference artery diameter (DS) ranged from 30% to 60% on visual assessment. Patients with concomitant critical stenosis of the left anterior descending coronary artery (LAD) or the circumflex branch (CX) of the left coronary artery, with prior myocardial infarction (MI) within the area supplied by the left coronary artery, left ventricular hypertrophy on echocardiography or with contraindications to intravenous adenosine infusion were excluded from the study.

#### Angiography

All patients received aspirin 75 mg daily prior to the procedure. Procedures were performed via the Seldinger approach through puncture of the left or right femoral artery. After insertion of the 7F sheath into the femoral artery and the 6F sheath into the femoral vein, unfractionated heparin was given at a dose of 5,000 U. Routinely, 7F guiding catheters were used. Coronary angiography of the LM was performed using several opposite projections and the low-osmolar contrast agent. Prior to contrast agent injection, nitroglycerine was administered intracoronarily at a dose of 250-500  $\mu$ g, in order to produce maximum artery dilation and prevent possible spasms.

The analysis of quantitative coronary angiography (QCA) was performed by an independent angiography

analysis lab (KCRI, Kraków), using dedicated specialist computer software (New Quant 32, QCA Plus, Sanders Data Systems, Palo Alto, CA, USA). Calibration of the calculation system was carried out with the 7F guiding catheter. After manual marking of proximal and distal reference segments on the outline of the LM, computer software automatically drew contours of the artery lumen and atherosclerotic plaque. The principle of minimising the manual corrections in the automatic vessel tracing was implemented and this was applied only when obvious errors occurred due to the overlapping of vessel shade and chest anatomy. The baseline QCA was performed in several reciprocal views and the artery was analysed at the end-diastolic phase of the heart cycle. The view including the lowest minimum lumen diameter (MLD) at stenosis was chosen. The following parameters were assessed with QCA: MLD (mm), DS (%), averaged reference diameter of the vessel (Ref. D, mm) and lesion length (LL, mm).

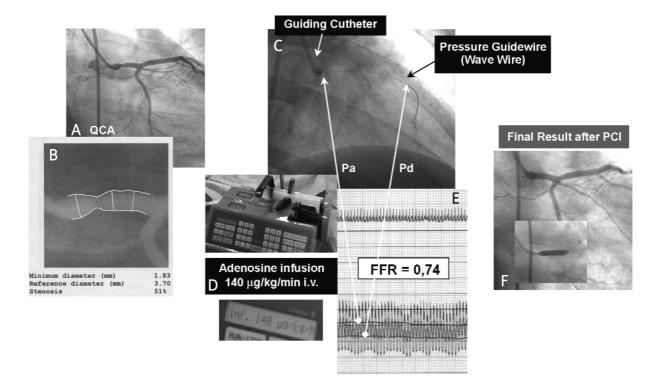
## Measurement of fractional flow reserve

FFR was measured using angioplasty guide wires with the WaveWire intracoronary pressure transducer (Volcano Therapeutics) and WaveMap system (Volcano Therapeutics). After automatic system callibration the guide wire was introduced into the middle segment of the left anterior descending coronary artery to measure the mean poststenotic pressure (Pd). The mean prestenotic pressure (Pa) was measured with the guiding catheter removed from the ostium of the LM trunk during measurement to obtain maximum accuracy. The measurement of FFR (Pd/Pa) was performed at rest and at maximum hyperaemia induced by intravenous infusion of adenosine at a dose of 140  $\mu g/kg/\text{min}$  over 5 min via the femoral vein sheath. Stenosis was recognised clinically significant at FFR<0.75. Such patients were referred to surgical or percutaneous myocardial revascularisation. The remaining patients with FFR  $\geq 0.75$  were referred for further pharmacological treatment (Figure 1).

All patients were regularly followed for the assessment of clinical symptoms, recording of deaths, MI and need for CABG or PCI procedures.

#### Statistical analysis

Constant variables were presented as a mean  $\pm$  standard deviation. The differences in parameters MLD, Ref. D, DS and LL between patient groups divided with respect to FFR values ( $\geq$ 0.75 or <0.75) were compared using Student's t-test for nonparametric variables. Categorical variables were compared using the chi-square test, and Fisher's test was used for comparison of incidence of coronary events over long-term follow-up. Analysis of the correlation matrix between FFR and



**Figure 1.** A patient with borderline stenosis in the left main coronary artery (A). Quantitative coronary angiography (QCA) showed stenosis of 51% (B). The fractional flow reserve was measured with a WaveWire guide wire (C) during intravenous adenosine infusion at a dose of 140  $\mu$ q/kg/min (D) and FFR=0.74 was obtained (E). The patient underwent PCI and stent implantation within the LM (F)

individual QCA parameters was performed. The cumulative risk of major cardiac events was estimated with the Kaplan-Meier method and the differences between the treated groups were evaluated with the log-rank test. The results were found statistically significant when the p value was less than 0.05.

## Results

The study involved 38 patients aged  $55\pm9$  years (ranging from 41 to 74 years) enrolled into the study between 5.10.2001 and 31.12.2003. The group included 29 (76%) males and 9 (24%) females. On QCA, the mean stenosis (DS) of LM was  $45\pm10\%$ , the minimal lumen diameter (MLD) of the LM was  $2.05\pm0.51$  mm, the reference lumen diameter (Ref. D) of the LM was  $3.73\pm0.67$  mm, and the mean lesion length (LL) in the LM was  $9.0\pm4.1$  mm. The location of the stenosis was the proximal segment of the LM in 14 (37%) patients, the middle segment of the LM in 4 (11%) patients and the distal segment of the LM in 15 (39%) patients. Moreover, in 5 (13%) cases the entire LM was involved.

During intravenous adenosine infusion at 140 mg/kg/min FFR <0.75 (critical stenosis) was found in 18

(47%) patients, whereas in 20 (53%) of them FFR was  $\geq$ 0.75 (borderline stenosis). The comparison of clinical characteristics between the groups of patients with FFR  $\geq$ 0.75 and FFR <0.75 is shown in Table I.

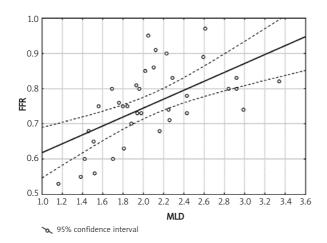
In patients with FFR <0.75 (critical stenosis), 12 (67%) were referred for surgical treatment, PCI with stent implantation was performed in 5 (28%) patients, and 1 (5%) female patient who refused CABG was qualified for pharmacotherapy alone. Patients with FFR  $\geq$ 0.75 were selected for pharmacotherapy.

The comparison of localisation of stenosis and the results of QCA between the groups of patients with FFR <0.75 and FFR  $\ge$ 0.75 is shown in Table II. No significant differences between the groups were found with respect to DS, LL and Ref. D. However, MLDs were significantly lower in patients with FFR <0.75. Moreover, a significant correlation between FFR and MLD was observed (Figure 2) and poor correlations between FFR and Ref. D (r=0.34, p<0.05) and between FFR and DS were found (r=0.37, p<0.05).

The mean long-term follow-up was 2 years (ranging from 1 to 3 years). There were two deaths in the group with FFR  $\leq$ 0.75 (patients referred for CABG). No deaths

**Table I.** Comparison of demographic parameters, history of coronary heart disease, and atherosclerotic risk factors in patients with normal (FFR  $\geq$ 0.75) and impaired fractional flow reserve (FFR <0.75)

	FFR ≥0.75 n=20	FFR <0.75 n=18	P=
Age (years)	56.5±9.4	53.4±7.6	NS
Males	16/20 (80%)	13/18 (72%)	NS
Prior myocardial infarction	6/20 (30%)	9/18 (50%)	NS
Left ventricular [%] ejection fraction	60±10	62±13	NS
Prior PCI	4/20 (20%)	5/18 (28%)	NS
Prior CABG	0	0	NS
Arterial hypertension	11/20 (55%)	15/18 (83%)	NS
Diabetes mellitus	2/20 (10%)	2/18 (11%)	NS
Smoking	9/20 (45%)	9/18 (50%)	NS
Positive family history	8/20 (40%)	10/18 (55%)	NS
Hypercholesterolemia	15/20 (75%)	14/18 (78%)	NS



**Figure 2.** Correlation between fractional flow reserve (FFR) and minimum lumen diameter (MLD) on quantitative coronary angiography (QCA). (Pearson linear correlation coefficient r=0.59, p<0.001)

occurred in the group with FFR >0.75; one patient underwent elective CABG due to significant progression of LM stenosis, and one patient experienced MI of the inferolateral wall. Kaplan-Meier curves of freedom from coronary events are shown in Figures 3 and 4. Detailed data on ischaemic events are presented in Table III. **Table II.** Comparison of baseline angiographic characteristics and mean fractional flow reserve (FFR) values in patients with normal (FFR  $\geq$ 0.75) and impaired fractional flow reserve (FFR <0.75)

	FFR ≥0.75 n=20	FFR <0.75 n=18	Ρ
Proximal LM	9/20 (45%)	5/18 (28%)	NS
Middle LM	1/20 (5%)	3/18 (17%)	NS
Distal LM	7/20 (35%)	8/18 (44%)	NS
Entire length LM stenosis	3/20 (15%)	2/18 (11%)	NS
MLD	2.24±0.49	1.84±0.45	0.014
Ref. D	3.89±0.62	3.54±0.7	NS
%DS	43±7	46±13	NS
LL	9.75±4.56	8.06±3.48	NS
FFR	0.84±0.06	0.66±0.07	<0.0001

Abbreviations: see Methods section

## Discussion

The present study has shown that in patients with angiographically isolated borderline LM stenosis, the clinical significance of this stenosis is confirmed in only half of them. Very good clinical outcomes in the long-term follow-up of patients disqualified from revascularisation following the FFR measurements suggest that such a strategy is safe and allows unnecessary cardiac surgery or PCI to be avoided.

The evaluation of LM stenosis severity with coronary angiography alone is often difficult, even for experienced interventional cardiologists and cardiac surgeons. According to the results of the CASS study, assessment of the severity of LM stenosis, even using QCA, is associated with higher variability of the results for all coronary arteries assessed both by the same investigator and by different investigators [8]. This phenomenon may result from various causes. Contrasting of the aortic bulb may make assessment of the LM ostium difficult. Furthermore, evaluation of the distal segment of the LM is often difficult due to the overlapping of contours of its main branches (bifurcation, trifurcation). In the event of diffuse narrowing including the entire LM there is no normal reference segment available for the evaluation of stenosis severity. Another common clinical problem is vasospasm of the LM after advancement of the diagnostic or guiding catheter into the LM ostium [9, 10].

The use of non-invasive methods for the evaluation of fractional flow reserve in patients with borderline stenosis of the LM is not always reliable. On the one hand, each method may produce false positive results. In patients with concomitant critical stenosis in the

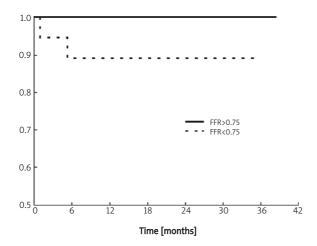


Figure 3. Comparison of Kaplan-Meier survival curves in groups with FFR  $\geq$ 0.75 (continuous line) and FFR <0.75 (dashed line). P=NS (log-rank test)

right coronary artery the resultant ischaemia appears earlier and may mask the ischaemia resulting from the borderline stenosis of the LM.

An accurate assessment of the clinical significance of borderline LM stenosis plays an important clinical role. It ensures an adequate qualification for CABG of patients only with critical stenosis with the absolute indication for revascularisation due to the unfavourable long-term prognosis with pharmacotherapy alone. Lately, a growing number of patients with LM stenosis, in particular with stenosis in the proximal or middle segment of the LM, are successfully treated with PCI

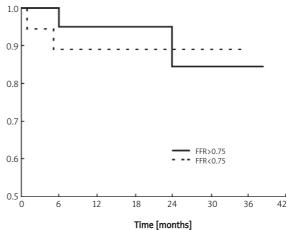


Figure 4. Comparison of Kaplan-Meier survival curves of freedom from major coronary events (death, myocardial infarction, revascularization procedures (PCI, CABG)) in groups with FFR  $\geq$ 0.75 (continuous line) and FFR <0.75 (dashed line). P=NS (log-rank test)

including stent implantation [3, 4]. On the other hand, the preclusion of significant stenosis allows avoidance of unnecessary surgical and percutaneous procedures, which are always associated with a high risk in patients with LM stenosis. This is extremely important, because CABG in patients with non-critical stenosis is associated with a risk of premature occlusion of the implanted grafts and/or native arteries, unjustified

**Table III.** Detailed characteristics of severe coronary events in patients with normal (FFR  $\geq$ 0.75) and impaired fractional flow reserve (FFR <0.75).

Initials	Age [years]	MLD ] [mm]	Ref. D [mm]	DS [%]	LL [mm]	FFR	Treatment	Event description, time from randomisation
FFR ≥0.75								
J.A.	54	2,29	4,29	47	8,69	0,83	pharmacotherapy	Angina worsening to CCS III, on control coronary angiography LM stenosis progression to 80% (with reference to %DS). Patient was qualified to CABG. Time to event – 179 days
Z.G.	68	2,61	4,49	42	6,97	0,97	pharmacotherapy	STEACS, inferolateral wall, treated in local hospital, no complications. Time to event – 728 days
FFR < 0.75	FFR <0.75							
Z.F.	42	2,26	3,23	31	6,46	0,71	CABG	CABG 2 months after diagnosis. Death in the $2^{nd}$ day following surgery with signs of low output syndrome. Time to event – 63 days
J.L.	63	1,17	3,11	62	15,2	0,61	CABG	CABG performed 4 months after LM stenosis diagnosis, no complications. 2 months after surgery recurrence of angina, treated in regional hospital, sudden cardiac death without invasive diagnostics. Time to event – 180 days

wasting of arterial and venous graft suitable material and, in the event of a competitive flow, it may cause periprocedural death or MI [11]. Premature PCI of non-critical stenosis also exposes patients to a risk of restenosis or in-stent thrombosis, which may lead to sudden cardiac death [12].

In the present study the FFR was ≤0.75 in 47% patients with borderline LM stenosis (DS 30-60%). This shows that critical stenosis was not confirmed in over 50% of patients. These results remain consistent with the findings of Bech et al. [13]. They performed FFR measurement during an intravenous adenosine infusion for the evaluation of clinical significance of borderline LM stenoses in 54 patients. FFR <0.75 was found in 30 (56%) subjects. In the study of Jimenez-Navarro et al. the presence of critical stenosis was confirmed in 7 (26%) of 27 consecutive patients with borderline stenosis of the LM on angiography [14]. However, their study involved patients with DS ranging from 30% to 50%. In another study, Jasti et al. estimated FFR in 55 patients using intracoronary injection of adenosine at a dose of 42-56  $\mu$ g. FFR <0.75 was observed in only 14 (25%) subjects [15].

Of note, there are significant limitations of intracoronary injections of adenosine for the evaluation of LM stenosis. The presence of stenosis in the ostium of the LM (in the study of Jasti et al. [15] 20 (36%) subjects) forces the operator to withdraw the guiding catheter directly after adenosine injection, which makes the measurements more difficult and less reliable. Moreover, comparative studies have shown no maximum dilation of microcirculation in some patients comparing the intracoronary adenosine injection and intravenous infusion [16, 17]. Additionally, the study of Jasti et al. [15] showed that in some patients LM stenosis occurred together with critical (DS >70%) stenosis of LAD or Cx, which also influences the results of FFR measurements within the LM, especially with intracoronary adenosine. For this reason, the method of FFR measurement might lead to overestimation of the results in the above-mentioned study. This is also shown indirectly by the fact that the ICUS minimum lumen cross-sectional area (L-CSA<sub>min</sub>) of 5.9 mm<sup>2</sup> corresponded to FFR=0.75 when comparing FFR and ICUS values [15]. In our other studies with intravenous adenosine used for the assessment of FFR in patients with borderline stenoses of the LM, FFR=0.75 corresponded to ICUS L-CSA<sub>min</sub> of 8.0 mm<sup>2</sup> [18].

In the present study, a significant correlation between FFR and LM minimum lumen diameter on QCA was observed. However, an accurate MLD that could be used as the cut-off point for the therapeutic decisions was impossible to determine due to the distribution of obtained results. Similar results were also reported in other studies [13, 15].

All above-mentioned studies acknowledge that in cases of FFR ≥0.75 intervention withdrawal is safe and associated with good long-term outcomes. In the present study, in the group of 20 patients with FFR  $\geq 0.75$  during long-term follow-up the clinically significant progression of LM stenosis was observed in only 1 (5%) female patient, who underwent elective cardiac surgery, and curves of freedom from coronary events did not differ between the groups. In the study of Bech et al. the progression of LM stenosis was reported in 2 (8%) of 24 patients qualified for pharmacotherapy alone based on FFR measurements [13]. In the studies of Jasti et al. [15] and Jimenez-Navarro et al. [14] no progression of LM stenosis that required revascularization was observed. Additionally, none of the papers, including the present one, reported any fatal cardiovascular events in the groups of patients qualified for pharmacotherapy alone.

Recently it has been shown that aggressive treatment with atorvastatin at a dose of 80 mg reduces the cardiovascular event rate [19] and stops the progression of atherosclerosis as assessed with ICUS [20] in comparison to standard therapy with pravastatin 40 mg. These findings may also be important for patients with borderline lesions in LM. This has been confirmed by the results of the study of Von Brigelen et al. [21]. They showed, based on serial measurements with ICUS, that in patients with LDL-cholesterol level below 75 mg% no increase of atherosclerotic plaque volume was observed during long-term follow-up. Thus, patients with borderline LM stenosis qualifying for pharmacotherapy alone based on the FFR measurements should have aggressive statin therapy administered with target LDL-cholesterol levels of <70 mg% [21]. This applies particularly to diabetic patients who remain at the highest risk of rapid progression of atherosclerosis when not adequately treated [22].

In conclusion, it should be emphasised that FFR measurement in patients with borderline LM stenoses has many practical advantages. It may be performed as early as at the baseline diagnostics, thus shortening the time to accurate diagnosis and eliminating the necessity for additional non-invasive tests. At the same time, the measurement of FFR is simple and repeatable, and extensive operator training is not necessary for correct interpretation of the results. On the other hand, the measurement of FFR is most reliable in patients with isolated LM stenosis. In the event of concomitant critical stenoses of other branches of the left coronary artery (LAD, CX), ICUS may be a better method for the evaluation of clinical

significance of borderline LM stenoses [10, 18, 22]. One must keep in mind that there is still no unambiguous sonographic criterion of critical LM stenosis. Data reported in literature suggested minimum lumen cross-section area values range between 6-9 mm<sup>2</sup> [10, 15, 18]. Additionally, correct interpretation of ICUS results requires extensive operator experience in performing procedures under ICUS control [10].

## Conclusion

Confirmation of significant impairment of fractional flow reserve succeeds in only half of patients with borderline LM stenosis found on angiography. The use of FFR measurements in patients with isolated borderline LM stenoses allows for reliable identification of those requiring acute cardiac revascularisation. Withdrawal from intervention in patients with FFR over 0.75 is safe and is associated with good clinical outcomes in two-year follow-up. Therefore, invasive assessment of the clinical significance of borderline stenosis of the LM should be done in each questionable case before making any therapeutic decision.

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## Zastosowanie pomiaru cząstkowej rezerwy wieńcowej dla ustalania wskazań do rewaskularyzacji serca u chorych z granicznym zwężeniem pnia lewej tętnicy wieńcowej

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## Streszczenie

**Wstęp:** Wiarygodna ocena istotności klinicznej angiograficznie granicznych zwężeń pnia lewej tętnicy wieńcowej (LTW) jest często niemożliwa. Pomiar cząstkowej rezerwy wieńcowej (FFR) jest powszechnie stosowany do weryfikacji granicznych zwężeń tętnic wieńcowych. Jednak przydatność pomiarów FFR została w pełni potwierdzona jedynie w przypadku zwężeń zlokalizowanych poza pniem LTW.

**Cel pracy:** Ocena przydatności pomiarów FFR dla ustalania wskazań do rewaskularyzacji serca w przypadku granicznych zwężeń pnia LTW.

**Metodyka:** Do badania włączono 38 pacjentów w wieku 55±9 lat (od 41 do 74 lat) z izolowanym, granicznym zwężeniem pnia LTW. U wszystkich chorych wykonano pomiar FFR w trakcie dożylnego wlewu adenozyny w dawce 140 μg/kg/min. Do zabiegów rewaskularyzacji kierowano chorych z FFR<0,75.

**Wyniki:** Średni procent zwężenia pnia LTW wynosił 45±10% w (ilościowa koronarografia – QCA). Wartość FFR<0,75 stwierdzono u 18 (47%) pacjentów, natomiast u 20 (53%) wartość FFR wynosiła  $\geq$ 0,75. W grupie z FFR<0,75 w QCA stwierdzono istotnie niższe wartości najmniejszego minimalnego wymiaru światła naczynia (MLD) w miejscu zwężenia (1,84±0,45 vs 2,24±0,49, p=0,014). Ponadto stwierdzono obecność istotnej korelacji pomiędzy FFR i MLD (r=0,59, p<0,001). Średni okres obserwacji klinicznej wyniósł 2 lata (1–3 lat). W grupie z FFR  $\leq$ 0,75 stwierdzono 2 (11%) zgony u pacjentów poddanych CABG. Natomiast w grupie z FFR >0,75 u 1 (5%) pacjentki wykonano planowy zabieg CABG z powodu progresji zwężenia pnia LTW. Ponadto u 1 (5%) pacjenta wystąpił zawał serca niezwiązany z obecnością granicznego zwężeniem pnia LTW.

Wnioski: W grupie pacjentów z angiograficznie granicznym, izolowanym zwężeniem pnia głównego lewej tętnicy wieńcowej, pomiar FFR tylko w połowie przypadków potwierdza istotność kliniczną zwężenia. Zaniechanie interwencji w przypadku FFR ≥0,75 jest bezpieczne i wiąże się z uzyskiwaniem dobrych wyników leczenia w obserwacji dwuletniej.

Słowa kluczowe: cząstkowa rezerwa przepływu wieńcowego, rewaskularyzacja, choroba wieńcowa

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