Contents lists available at ScienceDirect

IJC Heart & Vasculature

Extent of the difference between microcatheter and pressure wire-derived fractional flow reserve and its relation to optical coherence tomography-derived parameters

Yoshiki Matsuo [a,1], Yasutsugu Shiono [a,1], Kuninobu Kashiyama [b,1], Yasushi Ino [a,1], Takahiro Nishi [a], Kosei Terada [a,1], Hiroki Emori [a,1], Daisuke Higashioka [a,1], Yosuke Katayama [a,1], Amir Khalifa Mahfouz [a,1], Teruaki Wada [a,1], Suwako Fujita [a,1], Masahiro Takahata [a,1], Kunihiro Shimamura [a,1], Manabu Kashiwagi [a,1], Akio Kuroi [a,1], Atsushi Tanaka [a,1], Takeshi Hozumi [a,1], Takashi Kubo [a,*,1], Takashi Akasaka [a,1]

[a] The Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama, Japan
[b] The Second Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

ARTICLE INFO

ABSTRACT

Background: Although previous studies demonstrated that microcatheter-derived fractional flow reserve (mc-FFR) tends to overestimate lesion severity compared to pressure wire-derived FFR (pw-FFR), the clinical utility of mc-FFR remains obscure. The extent of differences between the two FFR systems and its relation to a lesion-specific parameter remain unknown. In this study, we sought to compare mc-FFR with pw-FFR and determine the lower and upper mc-FFR cut-offs predicting ischemic and non-ischemic stenosis, using an *ischemic* and a *clinical* FFR threshold of 0.75 and 0.80 as references, respectively. We further explored optical coherence tomography (OCT) parameters influencing the difference in FFR between the two systems.
Methods and results: In this study, 44 target vessels with intermediate de novo coronary artery lesion in 36 patients with stable ischemic heart disease were evaluated with mc-FFR, pw-FFR and OCT. Bland-Altman plots for mc-FFR versus pw-FFR showed a bias of −0.04 for lower mc-FFR values compared to pw-FFR values. The mc-FFR cut-off values of 0.73 and 0.79 corresponded to the 0.75 *ischemic* pw-FFR and 0.80 *clinical* pw-FFR thresholds with high predictive values, respectively. The differences in the two FFR measurements (pw-FFR minus mc-FFR) were negatively correlated with OCT-derived minimum lumen area (MLA) (R = −0.359, p = 0.011). The OCT-derived MLA of 1.36 mm^2 was a cut-off value for predicting *the clinically significant difference* between the two FFR measurements defined as >0.03.
Conclusion: Mc-FFR is clinically useful when the specific cut-offs are applied. An OCT-derived MLA accounts for *the clinically significant difference* in FFR between the two systems.

1. Introduction

Fractional flow reserve (FFR) is the mainstay of functional hemodynamic assessment of coronary artery lesions, guiding decisions in percutaneous coronary interventions (PCI). Recently, a rapid exchange monorail FFR microcatheter using fiber-optic sensor technology (Navvus™; ACIST Medical Systems, Inc., Eden Prairie, MN) has been developed. The microcatheter system allows easier lesion negotiation with a coronary guidewire, maintaining guidewire position throughout the procedure and repeated measurements with less signal drift. Despite the potential advantages of the microcatheter FFR system, previous studies consistently demonstrated that microcatheter-derived FFR (mc-FFR) using an elliptically-shaped catheter comparable to a 0.022-inch diameter tends to overestimate lesion severity compared to pressure wire-derived FFR (pw-FFR) using a 0.014-inch wire [1–5]. A minimal difference between the FFR measurements closely around the cut-off point could lead to the different treatment decision when a cut-off FFR value is interpreted as a strict dichotomous value. Therefore, the utility of mc-FFR in clinical practice remains obscure due to a relatively wide limits of agreement between mc-FFR and pw-FFR

* Corresponding author at: Department of Cardiovascular Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-8510, Japan.
E-mail address: takakubo@wakayama-med.ac.jp (T. Kubo).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[1–5]. In this study, we sought to compare mc-FFR with pw-FFR and further evaluate the diagnostic performance of mc-FFR and determine the lower and upper mc-FFR thresholds predicting ischemic and non-ischemic stenosis, using *an ischemic FFR* threshold of 0.75 and a *clinical FFR* threshold of 0.80 as references, respectively. Then, we explored lesion-specific parameters influencing the difference in FFR between the two systems using optical coherence tomography (OCT).

2. Methods

2.1. Study design and patients

This study was a prospective single-center cohort study conducted in Wakayama Medical University Hospital between July 2015 and May 2017. Patients with suspected stable coronary artery disease [6] were eligible for inclusion if they had at least one intermediate de novo coronary artery lesion with 40 to 70% stenosis and reference diameter ≥ 2.25 mm assessed by visual estimation. The patients were excluded if they had prior coronary bypass surgery, left ventricular ejection fraction <30%, left ventricular hypertrophy, severe valvular heart disease, occluded coronary artery in any coronary artery, or contraindications to adenosine triphosphate. Left main coronary artery stenosis, prior treated arteries, extremely tortuous coronary arteries, or tandem lesions were excluded from this study. The study protocol was approved by the institutional review board, and all participants provided written informed consent. The study is registered on UMIN under the identifier UMIN000018618.

2.2. FFR measurements

After routine coronary angiography and the administration of therapeutic anticoagulation and intracoronary isosorbide dinitrate, FFR measurements were performed with both pressure wire and microcatheter system. First, a pw-FFR was measured using a 0.014-inch pressure sensor-tipped wire (Abbott Vascular Inc, Santa Clara, California). The pressure wire was positioned with the sensor in the distal third of the target artery and the location of the pressure sensor was documented by angiography. Subsequently, an mc-FFR was measured using a microcatheter FFR system (NavvusTM; ACIST Medical Systems) and its dedicated console (Rxi system; ACIST Medical Systems). Following advancement of a 0.014-inch conventional guide wire beyond the stenosis, the monorail microcatheter was inserted over the guidewire and the optical pressure sensor was positioned at the exact measurement site as the pw-FFR sensor recorded on angiography. Both pw-FFR and mc-FFR measurements were subjected to initial equalization and performed during administration of intravenous adenosine triphosphate 150 μg/kg/min for at least 3 min. An FFR was automatically calculated as the ratio of mean coronary blood pressure distal to the stenosis and mean aortic pressure at the time of the induced maximal hyperemia. At the completion of the measurement, the pressure wire or microcatheter was pulled back to the catheter tip to check signal drift defined as distal coronary artery pressure/aortic pressure <0.97 or >1.03 [7]. When a signal drift was detected, the measurements were repeated all over again. In this study, a pw-FFR value of 0.75 was considered as *the ischemic threshold* and a pw-FFR of 0.80 as *the clinical threshold* as references, respectively.

2.3. OCT image acquisition and analysis

An OCT imaging in a target vessel was performed with the ILU-MIEN System with a Dragonfly OCT catheter (Abbott Vascular, Inc).

After the catheter was placed distally in the target vessel, the pullback was initiated automatically by automatic injection of contrast. Pullback speed was 20 mm/s and the total pullback distance of the system was 55 mm. The offline OCT analyses were performed using proprietary software (Abbott Vascular, Inc). Minimum lumen area (MLA), reference lumen area, and lesion length were measured.

2.4. Quantitative coronary angiography

Quantitative Coronary Angiography was performed offline by an experienced interventional cardiologist blinded to the FFR and OCT results using Cardiovascular Angiography Analysis System (CAAS; Version 7.3, Pie Medical Imaging, Maastricht, The Netherlands). Reference segment and percent diameter stenosis were measured in end-diastole in the projection where maximal narrowing was observed. Reference vessel diameter was defined as the mean of diameters within the 5-mm proximal and distal non-affected segments.

2.5. Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are described as number (percentage). FFR values between the two systems were compared with a paired *t* test. Bland-Altman analysis with 95% limits of agreement (mean difference ± 1.96 SDs) was performed to assess agreement between the FFR measurement methods.

The diagnostic performance of mc-FFR was evaluated for a 0.75 *ischemic* pw-FFR threshold and a 0.80 *clinical* pw-FFR threshold, respectively. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) between pw-FFR and mc-FFR as well as area under the receiver-operating characteristic (ROC) curves were calculated for the two different pw-FFR cut-offs.

The correlation between variables including OCT parameters and the difference in the two FFR measurements were evaluated by using Spearman's rank correlation analysis. ROC curve analysis was performed to determine the cut-off values of OCT and FFR parameters predicting *a clinically significant difference* between mc-FFR and pw-FFR (defined as > 0.03). Values of p < 0.05 were considered statistically significant. All statistical analyses were performed with JMP Pro Version 13.0.0 (SAS Institute Inc, Cary, North Carolina).

3. Results

3.1. Patients and lesions

The patient and lesion characteristics are listed in Tables 1 and 2. The mean reference vessel diameter and diameter stenosis were 2.69 ± 0.49 mm and 58 ± 14%, respectively.

3.2. Comparison of mc-FFR with pw-FFR

While there was a strong correlation between mc-FFR and pw-FFR (Pearson's correlation coefficient = 0.920, p < 0.001), mc-FFR value was significantly lower than pw-FFR value (0.74 ± 0.13 vs. 0.78 ± 0.11; p < 0.001). Bland-Altman plots for mc-FFR versus pw-FFR showed a bias of −0.04 (limits of agreement: −0.14 to 0.06) for lower mc-FFR values compared to pw-FFR value (Fig. 1).

Table 1
Baseline characteristics.

	N (%)
No. of patients	36
Age, yrs	72.5 ± 8.1
Body mass index (kg/m^2)	23.5 ± 4.4
Male sex	22 (61)
Risk factors	
Hypertension	30 (8)
Dyslipidemia	25 (69)
Diabetes	22 (61)
Smoking	9 (25)
Family history	6 (17)
Left ventricular ejection fraction, %	53.9 ± 6.3
Prior myocardial infarction	9 (25)
Prior percutaneous coronary intervention	13 (36)
Prior coronary bypass graft surgery	0 (0)
CCS grading of angina	
Grade 1	20 (56)
Grade 2	7 (19)
Grade 3	6 (17)
Grade 4	3 (8)
Medications	
Aspirin	33 (92)
P2Y12 receptor inhibitors	19 (53)
ACE inhibitor/ARB	20 (56)
Beta blocker	15 (42)
Calcium channel blocker	18 (50)
Statins	31 (86)
Anti-diabetic	14 (39)
Insulin	0 (0)

ACE, Angiotensin-converting enzyme.
ACS, acute coronary syndrome.
ARB, Angiotensin receptor blockers.
CCS, Canadian Cardiovascular Society.

Table 2
Lesion characteristics.

	N (%)
Total lesions	44
Index artery	
Right coronary artery	10 (23)
Left anterior descending artery	28 (64)
left circumflex artery	6 (14)
Proximal lesion location	35 (80)
Multivessel disease	28 (64)
Angiography	
Reference vessel diameter, mm	2.69 ± 0.49
Minimum lumen diameter, mm	1.15 ± 0.50
% diameter stenosis	58 ± 14
Optical coherence tomography	
Lumen area at proximal reference, mm^2	7.12 ± 2.79
Lumen area at distal reference, mm^2	5.35 ± 2.19
Minimum lumen area, mm^2	1.70 ± 0.79
% area stenosis	29 ± 12
Lesion length, mm	19.0 ± 8.5
Fractional flow reserve (FFR)	
pw-FFR	0.78 ± 0.11
mc-FFR	0.74 ± 0.13

Values are expressed as n (%) or mean ± standard deviation. Mc-FFR indicates microcatheter-derived fractional flow reserve; Pw-FFR, pressure wire-derived fractional flow reserve.

3.3. Diagnostic performance of mc-FFR

The mc-FFR cut-off value for a 0.75 *ischemic* pw-FFR threshold was 0.73 with PPV of 95%. Likewise, the mc-FFR cut-off value for a 0.80 *clinical* FFR threshold are 0.79 with NPV of 94% (Fig. 2). There was neither lesion with an mc-FFR <0.75 and a pw-FFR >0.80, nor lesion with an mc-FFR >0.80 and a pw-FFR <0.75, indicating no clinically significant discordance between pw-FFR and mc-FFR.
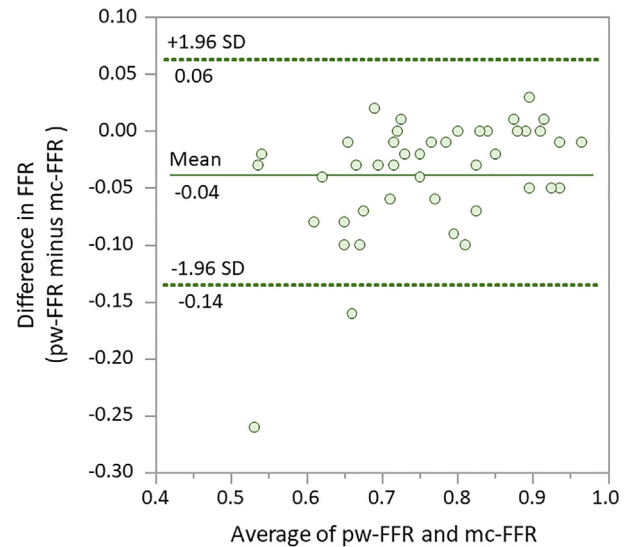

Fig. 1. Bland-Altman plot of difference in FFR (pw-FFR minus mc-FFR) against the average of the two measurements. Limits of agreement are shown as dashed lines (limits of agreement: −0.14 to 0.06), and average difference is shown as a solid line. Mc-FFR indicates microcatheter-derived fractional flow reserve; pw-FFR, pressure-wire derived FFR.

3.4. Clinically significant difference between the two FFR measurements

The differences in the two FFR measurements (pw-FFR minus mc-FFR) were significantly correlated with OCT-derived MLA (R = −0.359, p = 0.011), lesion length (R = 0.07, p = 0.042), and mc-FFR value (R = −0.603, p < 0.001), but not with OCT-derived reference lumen area (p = 0.074), % area stenosis (p = 0.465), or angiography-derived parameters including reference diameter (p = 0.355), minimum lumen diameter (p = 0.229), and % diameter stenosis (p = 0.314). In the ROC curve analyses, OCT-derived MLA of 1.36 mm^2 was a cut-off value for predicting *a clinically significant difference* between the two FFR measurements (defined as the difference in FFR > 0.03) (Supplementary Fig. 1), which was below the OCT-derived MLA cut-off point of 1.72 mm^2 for a 0.75 *ischemic* pw-FFR threshold (Supplementary Fig. 2). Likewise, mc-FFR of 0.70 was a physiological counterpart predicting for *a clinically significant difference* in the two FFR measurements (Supplementary Fig. 1).

4. Discussion

In this study, a significant correlation was found between mc-FFR and pw-FFR. The values obtained by mc-FFR fell short of those obtained by pw-FFR by an average of 0.04. The mc-FFR cut-off values of 0.73 and 0.79 corresponded to the 0.75 *ischemic* pw-FFR and the 0.80 *clinical* pw-FFR thresholds with high predictive values, respectively. The differences in the two FFR measurements (pw-FFR minus mc-FFR) were negatively correlated with OCT-derived MLA and mc-FFR value. When an OCT-derived MLA was less than 1.36 mm^2, the FFR values between the two systems significantly diverged.

4.1. Diagnostic performance of mc-FFR and clinical decision-making

Based on diagnostic accuracy assessment, revascularization based on mc-FFR ≤0.73 or deferral based on mc-FFR ≥0.79 is justified with >90% of predictive value according to the 0.75 *ischemic* or the 0.80 *clinical* pw-FFR thresholds (Fig. 2). An mc-FFR between 0.74 and 0.78 is considered as 'gray-zone' and revascular-

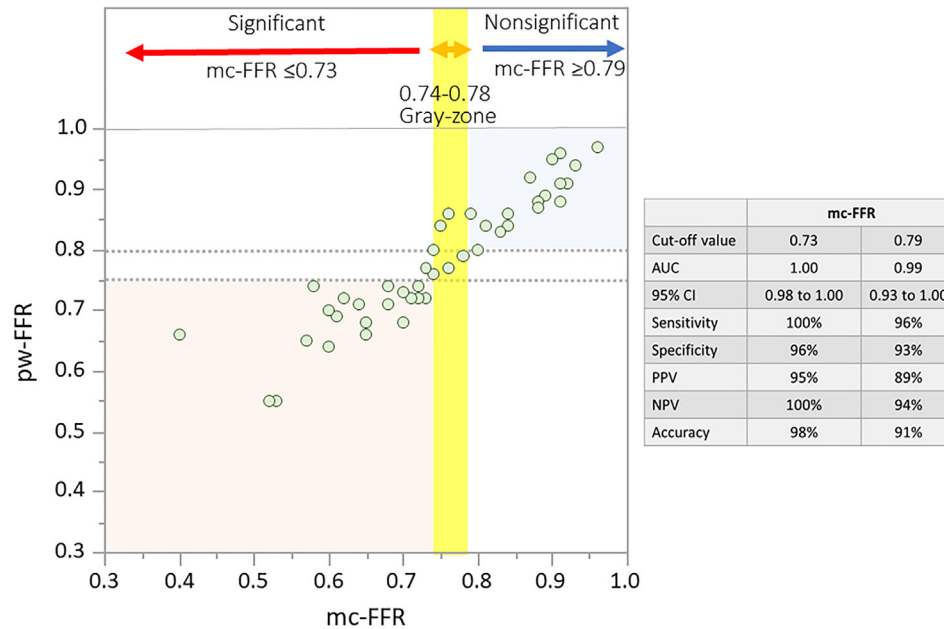|	mc-FFR	
Cut-off value	0.73	0.79
AUC	1.00	0.99
95% CI	0.98 to 1.00	0.93 to 1.00
Sensitivity	100%	96%
Specificity	96%	93%
PPV	95%	89%
NPV	100%	94%
Accuracy	98%	91%

Fig. 2. Scatterplots of mc-FFR versus pw-FFR and proposed mc-FFR cut-off values for clinical decision-making. The mc-FFR cut-off value for a 0.75 *ischemic* pw-FFR threshold was 0.73 with PPV of 95%. By contrast, the mc-FFR cut-off value for a 0.80 *clinical* FFR threshold are 0.79 with NPV of 94%. The value of mc-FFR between 0.74 and 0.78 is considered as 'gray-zone'. AUC indicates area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; other abbreviations as in Figure 1.

ization decisions need to be made based on a comprehensive evaluation including symptoms, anatomical features, other stress tests, and risk-benefit profile.

In previous reports, the mc-FFR-based decision-making according to a dichotomous cutoff value of 0.80 leads to inappropriate indication of coronary revascularization with pw-FFR in 19 to 23% of the lesions [4,5]. On the other hand, in the ACCESS-NZ trial [1], where a more lenient decision criterion was taken, no cases showed discordant lesion classification at the 0.80 cut-off value between mc-FFR and pw-FFR within measurement variability of pressure wire (±0.045). A multicenter trial of the ACIST-FFR Study [3] found that 3% of cases showed clinically meaningful diagnostic discordance with the pw-FFR >0.80 and mc-FFR <0.75.

4.2. Predictors for the differences between mc-FFR and pw-FFR

The ACIST-FFR study [3] demonstrated reference vessel diameter, lesion length and a physiological parameter of mc-FFR as predictors for the difference in FFR between mc-FFR and pw-FFR. Pouillot et al. [4] also identified a reference vessel diameter as a predictor for the difference. Ali et al. [5] identified angiographic parameters of distal reference vessel diameter and lesion length as independent predictors for the difference in multivariable analysis. The discordant findings among the above studies may be explained by differences in sample size, patient and lesion characteristics among studies, and, in particular, angiographic coronary lesion assessment with significant interobserver variability [8]. With using OCT parameters appropriate for geometric assessment with low interobserver variability [9], we demonstrated a modest correlation of the difference in FFR between the two systems with OCT-derived MLA and a weak correlation with OCT lesion length.

4.3. The extent of the differences between mc-FFR and pw-FFR

Previous studies comparing mc-FFR with pw-FFR consistently demonstrated a trend for overestimation of lesion severity with mc-FFR being significantly lower than pw-FFR with a range of

0.02–0.03 (Supplementary table) [1–4]. The present study demonstrated a difference in FFR between the two measurements of 0.04 being numerically large, as compared with the previous trials. The present study included lesions with small vessel diameter and severe stenosis compared with previous trials (Supplementary table). Given an inverse correlation of OCT-derived MLA with the difference in FFR, the relatively small lumen area in the current study may account for the large difference in FFR. In daily clinical practice, a difference in FFR of ≤0.03 is often recognized as nonsignificant and is generally overlooked in the assessment of a pressure signal drift. In our study, *a clinically significant difference in FFR of >0.03 was generated in a lesion with OCT-derived MLA of <1.36 mm^2, which was below the ischemic cut-off point of 1.72 mm^2*, as well as in a lesion with mc-FFR of <0.70, which was also below the ischemic mc-FFR cut-off point of 0.73 (Fig. 2), then falling outside of a range of clinical decision. Therefore, the difference in FFR between the two systems may have minimal impacts on clinical decision-making.

5. Limitations

This study has some limitations. First, this study included a small number of patients in a single center. The mc-FFR cut-off values generated from this study and their utility require external validation in a large cohort. Second, despite a prospective study, patients and lesions were inconsecutively selected at the discretion of treating physician, leading to potential selection bias. Third, a continuous relationship of pw-FFR with subsequent clinical outcomes established in previous studies [10,11] could not be applied in the microcatheter system, given the greater differences between mc-FFR and pw-FFR in the smaller lumen area. Forth, a minor difference in pressure sensor positions between pw-FFR and mc-FFR might have caused the difference in FFR values. Lastly, a multimodality evaluation by using mc-FFR, pw-FFR and OCT in this study cannot be applied to clinical practice in terms of cost-effectiveness.

6. Conclusions

In conclusion, the microcatheter system is clinically as useful as conventional pressure wire system when the specific thresholds are applied for ischemia (mc-FFR $\leq$0.73) and coronary revascularization (mc-FFR $\geq$0.79), respectively.

Declaration of Competing Interest

Dr. Shiono and Dr. Kubo have received lecture fees from Abbot Vascular Japan. Dr. Akasaka has received lecture fees and research funds from Abbott Vascular Japan and ACIST Japan. All other authors report that they have no relationships relevant to the contents of this paper to disclose.

CRediT authorship contribution statement

Yoshiki Matsuo: Conceptualization, Methodology, Writing - original draft. **Yasutsugu Shiono:** Writing - review & editing. **Kuninobu Kashiyama:** Writing - review & editing. **Yasushi Ino:** Investigation. **Takahiro Nishi:** Data curation. **Kosei Terada:** Investigation. **Hiroki Emori:** Visualization, Investigation. **Daisuke Higashioka:** Visualization, Investigation. **Yosuke Katayama:** Visualization, Investigation. **Amir Khalifa Mahfouz:** Investigation. **Teruaki Wada:** Investigation. **Suwako Fujita:** Software. **Masahiro Takahata:** Investigation. **Kunihiro Shimamura:** Investigation. **Manabu Kashiwagi:** Resources. **Akio Kuroi:** Resources. **Atsushi Tanaka:** Validation. **Takeshi Hozumi:** Software. **Takashi Kubo:** Conceptualization, Methodology. **Takashi Akasaka:** Supervision.

Acknowledgement

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100500.

References

[1] M. Menon, W. Jaffe, T. Watson, M. Webster, Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial, EuroIntervention: J. EuroPCR Collaboration Working Group Interventional Cardiol. Eur. Soc. Cardiol. 11 (2015) 257–263.

[2] G.W. Wijntjens, T.P. van de Hoef, R.P. Kraak, et al., The IMPACT Study (influence of sensor-equipped microcatheters on coronary hemodynamics and the accuracy of physiological indices of functional stenosis severity), Circulat. Cardiovasc. Intervent. 9 (2016).

[3] W.F. Fearon, J.W. Chambers, A.H. Seto, et al., ACIST-FFR Study (assessment of catheter-based interrogation and standard techniques for fractional flow reserve measurement), Circulat. Cardiovasc. Intervent. 10 (2017).

[4] C. Pouillot, S. Fournier, J. Glasenapp, et al., Pressure wire versus microcatheter for FFR measurement: a head-to-head comparison, EuroIntervention: J. EuroPCR Collaboration Working Group Intervent. Cardiol. Eur. Soc. Cardiol. 13 (2018) e1850–e1856.

[5] Z.A. Ali, Y. Parviz, M. Brinkman, et al., Pressure wire compared to microcatheter sensing for coronary fractional flow reserve: the PERFORM study, EuroIntervention: J. EuroPCR Collaboration Working Group Intervent. Cardiol. Eur. Soc. Cardiol. 14 (2018) e459–e466.

[6] S.D. Fihn, J.C. Blankenship, K.P. Alexander, et al., 2014 ACC/AHA/AATS/PCNA/ SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, Circulation 130 (2014) 1749–1767.

[7] M. Matsumura, N.P. Johnson, W.F. Fearon, et al., Accuracy of fractional flow reserve measurements in clinical practice: observations from a core laboratory analysis, JACC Cardiovasc. Intervent. 10 (2017) 1392–1401.

[8] C.W. White, C.B. Wright, D.B. Doty, et al., Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis?, New England J. Med. 310 (1984) 819–824.

[9] T. Kubo, T. Akasaka, J. Shite, et al., OCT compared with IVUS in a coronary lesion assessment: the OPUS-CLASS study, JACC Cardiovasc. Imaging 6 (2013) 1095–1104.

[10] N.P. Johnson, G.G. Toth, D. Lai, et al., Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes, J. Am. Coll. Cardiol. 64 (2014) 1641–1654.

[11] E. Barbato, G.G. Toth, N.P. Johnson, et al., A prospective natural history study of coronary atherosclerosis using fractional flow reserve, J. Am. Coll. Cardiol. 68 (2016) 2247–2255.