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The Impact of Downstream Coronary Stenosis on Fractional Flow Reserve Assessment of Intermediate Left Main Coronary Artery Disease

Human Validation

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ABSTRACT

OBJECTIVES The aim of this study was to determine the impact of downstream coronary stenosis in the left anterior descending coronary artery (LAD) or left circumflex coronary artery (LCx) on the assessment of fractional flow reserve (FFR) across an intermediate left main coronary artery (LMCA) stenosis in humans with the pressure wire positioned in the nondiseased downstream vessel.

BACKGROUND Accurate assessment of intermediate LMCA disease is critical for guiding decisions regarding revascularization. In theory, FFR across an intermediate LMCA stenosis will be affected by downstream disease, even if the pressure wire is positioned in the nondiseased downstream vessel.

METHODS After percutaneous coronary intervention of the LAD, LCx, or both, an intermediate LMCA stenosis was created with a deflated balloon catheter. FFR was measured in the LAD and LCx coronary arteries before and after creation of downstream stenosis by inflating an angioplasty balloon within the newly placed stent. The true FFR (FFR_{true}) of the LMCA, measured in the nondiseased downstream vessel in the absence of stenosis in the other vessel, was compared with the apparent FFR (FFR_{app}) measured in the presence of stenosis.

RESULTS In 25 patients, 91 pairs of measurements were made, 71 with LAD stenosis and 20 with LCx stenosis. FFR_{true} of the LMCA was significantly lower than FFR_{app} (0.81 ± 0.08 vs. 0.83 ± 0.08, $p < 0.001$), although the numerical difference was small. This difference correlated with the severity of the downstream disease ($r = 0.35$, $p < 0.001$). In all cases in which FFR_{app} was >0.85, FFR_{true} was >0.80.

CONCLUSIONS In most cases, downstream disease does not have a clinically significant impact on the assessment of FFR across an intermediate LMCA stenosis with the pressure wire positioned in the nondiseased vessel. (J Am Coll Cardiol Intv 2015;8:398–403) © 2015 by the American College of Cardiology Foundation.

Determining the significance of intermediate left main coronary artery (LMCA) disease based purely on its angiographic appearance is particularly challenging (1). Because of the prognostic importance of significant LMCA disease and because revascularization of LMCA disease often involves coronary artery bypass graft surgery, accurate evaluation of the functional importance of LMCA disease is critical.

Fractional flow reserve (FFR) is a coronary pressure wire-based index for assessing the physiological

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significance of a coronary stenosis (2,3). Results of large, prospective, multicenter, randomized trials have demonstrated that lesions with an ischemic FFR benefit from revascularization, whereas those with a nonischemic FFR can be treated safely with medical therapy alone (4–6). This has led to an increase in the role of FFR in guiding decisions regarding revascularization.

One of the assumed limitations of measuring FFR to assess the significance of LMCA disease is the presence of a significant stenosis in a downstream vessel, either the left anterior descending coronary artery (LAD) or the left circumflex coronary artery (LCx). For example, in a patient with an LAD stenosis and intermediate LMCA disease, the FFR measured with the pressure wire in the distal LAD will be affected by both the LAD and LMCA disease. Previous studies have shown that positioning the pressure sensor between the LMCA stenosis and the LAD stenosis does not allow accurate measurement of the FFR of the LMCA because the LAD stenosis distal to the sensor can decrease flow across the LMCA and artificially decrease the hyperemic gradient of the LMCA (7).

To address this limitation, one might consider placing the pressure wire in the nondiseased downstream vessel, for example, the LCx in a patient with intermediate LMCA disease and an LAD stenosis. However, in theory, the flow across the LMCA stenosis is affected by the flow down both downstream vessels (LAD and LCx), and, therefore, the flow and hyperemic gradient across the LMCA measured with the pressure wire in the LCx might be decreased in the presence of significant LAD disease, resulting in an artificially increased FFR. Determining the degree to which downstream disease affects the FFR assessment of LMCA disease in humans with the pressure wire positioned in the nondiseased downstream vessel was the goal of this study.

METHODS

Patients undergoing percutaneous coronary intervention of either an LAD or LCx lesion, or both, were eligible for this study if they provided informed written consent. After percutaneous coronary intervention of the epicardial vessel, a coronary pressure wire (St. Jude Medical, Inc., St. Paul, Minnesota) was positioned in both the LAD and the LCx. A deflated balloon catheter was positioned within the stented segment in the LAD or LCx. Over the pressure wire positioned in the other downstream vessel, a balloon that had been previously inflated and deflated (i.e., "winged") was positioned in the LMCA to create an intermediate stenosis; if necessary, the balloon was partially inflated with up to 1 mm of saline solution and contrast media. Two patients with de novo intermediate LMCA disease did not require the use of a winged balloon.

FFR, defined as mean distal coronary pressure divided by mean aortic pressure, was measured in both vessels simultaneously during the administration of intravenous adenosine at 140 μg/kg/min. A baseline (true) FFR of the LMCA (FFR_{true}) from the pressure wire in the nondiseased downstream vessel was recorded. The balloon within the stented segment of either the LAD or the LCx was then gradually inflated to create increasingly severe downstream disease. The apparent FFR (FFR_{app}) of the LMCA from the pressure wire in the nondiseased downstream vessel was recorded simultaneously (**Figures 1 and 2**). The first septal branch was used as the delineator between the proximal and mid-LAD, and the first obtuse marginal branch was used as the delineator between the proximal and mid-LCx.

STATISTICAL ANALYSIS. Each patient had 4 to 5 measurements of FFR_{app} in the nondiseased downstream vessel with variable degrees of stenosis in the other vessel, ranging from mild to complete

ABBREVIATIONS AND ACRONYMS

FFR = fractional flow reserve

FFR_{app} = apparent fractional flow reserve

FFR_{epi} = epicardial fractional flow reserve

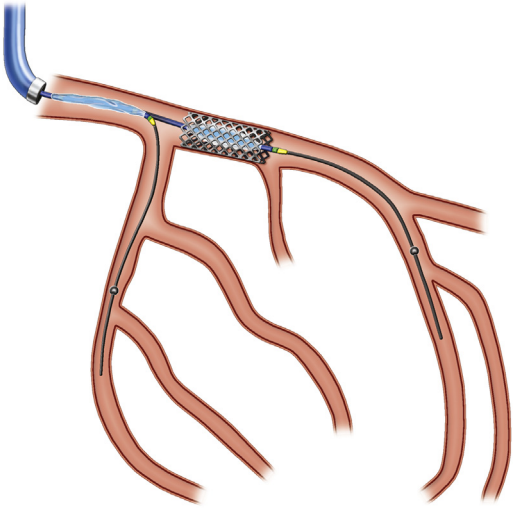
FFR_{true} = true fractional flow reserve

LAD = left anterior descending coronary artery

LCx = left circumflex coronary artery

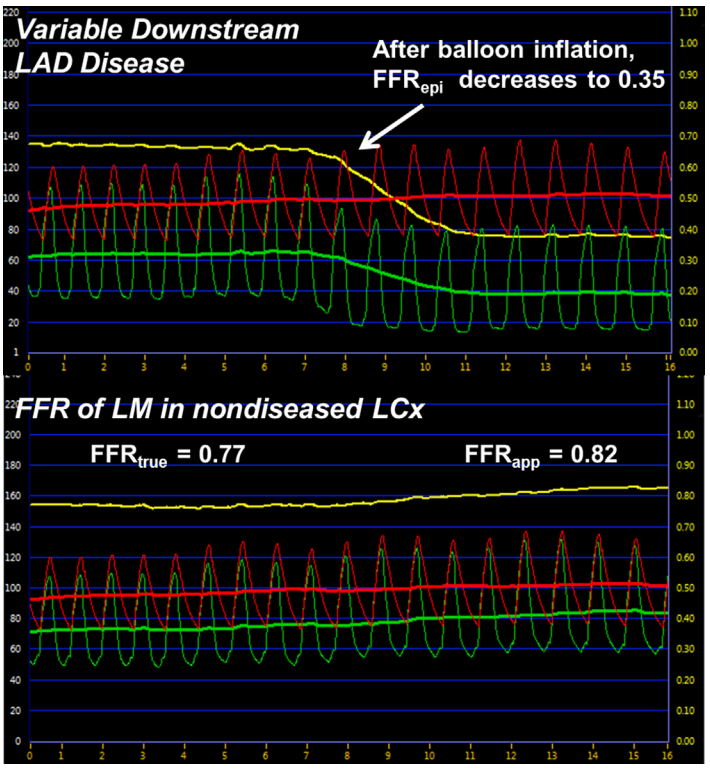
LMCA = left main coronary artery

FIGURE 1 Experimental Layout



Cartoon of experimental layout demonstrating deflated ("winged") balloon in the left main coronary artery, variably inflated balloon within the newly placed left anterior descending coronary artery (LAD) stent, and pressure wires down the LAD and the left circumflex coronary artery.

FIGURE 2 Case Example of the Effect of Complete LAD Occlusion



Images of the simultaneous coronary pressure recordings during creation of variable downstream stenosis. **(Top)** The coronary pressure recorded from the LAD pressure wire before and after balloon inflation within a newly placed LAD stent (the **green line** is distal coronary pressure, the **red line** is aortic pressure, and the **yellow line** is FFR value). **(Bottom)** The coronary pressure recorded simultaneously from the LCx pressure wire (FFR_{true} and FFR_{app}) before and after inflation of the balloon in the LAD, ultimately leading to complete occlusion (the **green line** is distal coronary pressure, the **red line** is aortic pressure, and the **yellow line** is the FFR value). FFR = fractional flow reserve; FFR_{app} = apparent fractional flow reserve; FFR_{epi} = epicardial fractional flow reserve; FFR_{true} = true fractional flow reserve; LAD = left anterior descending coronary artery; LM = left main coronary artery.

occlusion. Values are presented as the mean ± SD unless otherwise stated. Paired *t* tests were used to evaluate the difference between FFR_{true} and FFR_{app}. Paired *t* tests were also used to compare the difference between FFR_{true} and FFR_{app} in different groups including LAD versus LCx and proximal segment versus midsegment. The intraclass correlation coefficient was determined using mixed-model analysis to determine association between variables. A plot of the difference between FFR_{true} and FFR_{app} versus the epicardial FFR (FFR_{epi}) (combination of FFR of the LMCA and the downstream disease) was used to assess the effect of distal epicardial lesion severity on change in LMCA FFR. We arbitrarily assigned a change in the FFR_{true} to the FFR_{app} of the LMCA of

TABLE 1 Baseline Clinical Characteristics

Variable	
Age, mean, years	64.4 ± 8.1
Male sex	23 (95.8)
Body mass index, kg/m^2	28.8 ± 4.3
Comorbidities	
Diabetes	8 (33.3)
Hypertension	22 (91.7)
Dyslipidemia	23 (95.8)
Smoking	5 (20.8)
Family history of coronary disease	4 (16.7)
Downstream stenosis territory	
Left anterior descending	71 (78.0)
Left circumflex	20 (22.0)
Downstream stenosis segment	
Proximal	36 (39.6)
Mid	55 (60.4)

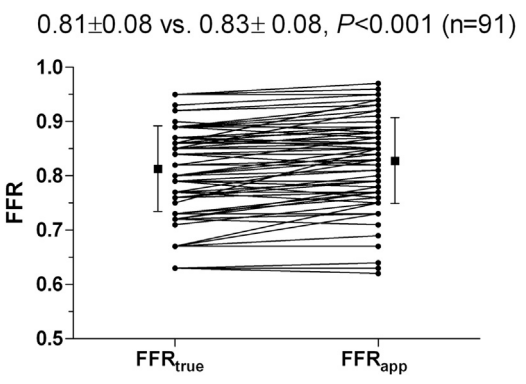
Values are mean ± SD, or n (%).

>0.05 to indicate a significant change. With an SD of 0.07, we would need at least 18 paired FFR measurements to have 80% power to detect a significant difference at a p value of 0.05. A 2-sided probability value of 0.05 was considered significant. Statistical calculations were performed using SPSS version 15 (SPSS, Chicago, Illinois), and graphs were generated using Graphpad Prism version 5.01 (Graphpad Software, La Jolla, California).

RESULTS

A total of 25 patients were included in this study. One patient had stenting of both the LCx and LAD and therefore had 2 downstream stenoses created,

FIGURE 3 Effect of Downstream Disease on Left Main Coronary Artery FFR (Entire Cohort)



Comparison of FFR_{true} and FFR_{app} of the left main coronary artery in the entire cohort. Abbreviations as in Figure 2.

TABLE 2 Average Hyperemic Pressures and FFR With and Without Downstream Stenosis

	Downstream Stenosis			
Variable	Absent	Present	Mean Difference	p Value
P_a	89.3 ± 16.1	89.9 ± 18.6	0.6 ± 7.8	0.45
P_d	72.5 ± 15.7	74.4 ± 19.1	1.9 ± 7.3	0.02
FFR	0.83 ± 0.08	0.81 ± 0.08	0.02 ± 0.02	<0.001

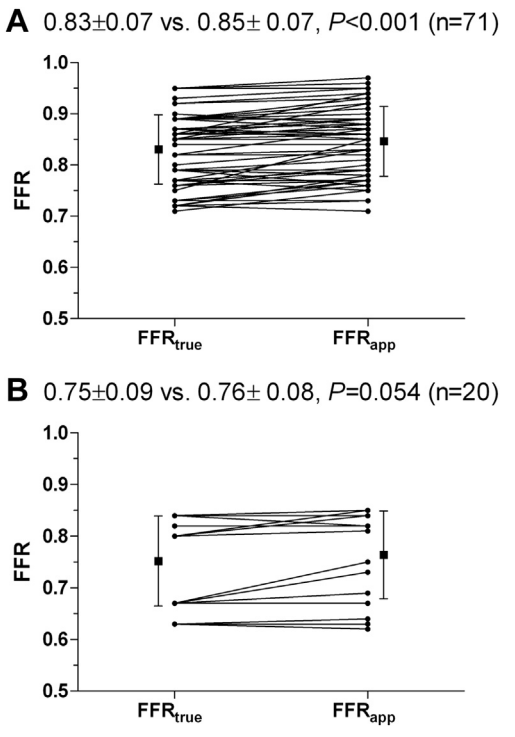
Values are mean ± SD.

FFR = fractional flow reserve; P_a = proximal or aortic pressure; P_d = distal pressure.

meaning that the effect on the FFR of the LMCA was evaluated in the presence of 26 downstream variable stenoses. A total of 91 comparisons of FFR_{true} with the FFR_{app} were made, 71 with LAD downstream disease and 20 with LCx downstream disease, whereas 36 were proximal and 55 were midvessel. Baseline clinical characteristics of the patients included in this study are shown in Table 1.

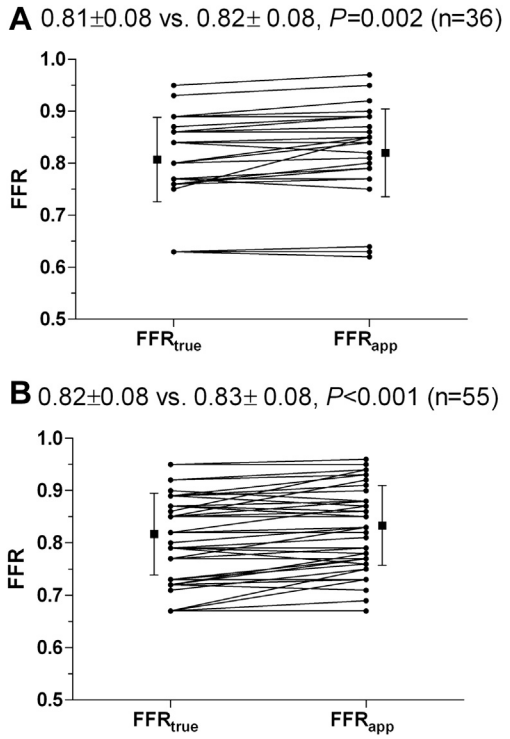
In the whole cohort, the change in FFR of the LMCA after creation of downstream disease was statistically significant but numerically small, with an absolute mean difference of 0.015 (95% confidence interval: 0.01 to 0.02) (FFR_{true} vs. FFR_{app} was 0.81 ± 0.08 to 0.83 ± 0.08, $p < 0.001$) (Figure 3, Table 2). There was a significant change in FFR_{true} to FFR_{app} due to downstream LAD disease (0.83 ± 0.07 to 0.85 ± 0.07, $p < 0.001$) (Figure 4A) and a trend due to downstream LCx disease (0.75 ± 0.09 to 0.76 ± 0.08, $p = 0.054$) (Figure 4B). FFR_{true} to FFR_{app} also changed significantly when evaluating downstream disease in the midvessel (0.82 ± 0.08 to 0.83 ± 0.08, $p < 0.001$) and the proximal vessel (0.81 ± 0.08 to 0.82 ± 0.08, $p = 0.002$) (Figures 5A and 5B). The difference between FFR_{true} and FFR_{app} correlated with the severity of the downstream disease, the composite of the FFR of the LMCA plus the downstream stenosed artery (epicardial FFR [FFR_{epi}]) (mixed-model intraclass correlation coefficient $r = 0.93$, $p < 0.001$). In all cases in which the FFR_{app} was >0.85, the FFR_{true} was >0.80. The FFR_{true} to FFR_{app} change was >0.05 in only 6 cases, and the average FFR_{epi} in these cases

FIGURE 4 Effect of Downstream Disease on LMCA FFR (LAD vs. LCx)



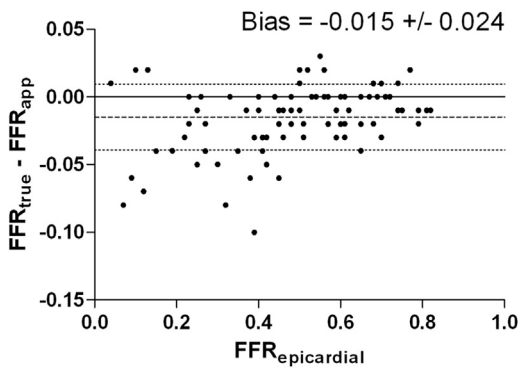
Comparison of FFR_{true} and FFR_{app} of the LMCA with the pressure wire in the LCx and in the presence and absence of downstream LAD **(A)** and LCx **(B)** disease. LMCA = left main coronary artery; other abbreviations as in Figure 2.

FIGURE 5 Effect of Downstream Disease on LMCA FFR (Proximal vs. Midvessel)



Comparison of FFR_{true} and FFR_{app} of the LMCA in the presence of proximal vessel **(A)** and midvessel **(B)** downstream disease. Abbreviations as in Figures 2.

FIGURE 6 Bland Altman Plot Comparing FFR_{true} and FFR_{app}



Bland-Altman plot demonstrating the relationship between the difference in FFR_{true} and FFR_{app} based on the severity of downstream disease as assessed by FFR of the LMCA and the downstream stenosis (FFR_{epi}). Abbreviations as in Figure 2.

was 0.24 ± 0.17 (maximum, 0.45), whereas the average FFR_{epi} in the cases in which the change from FFR_{true} to FFR_{app} was ≤0.05 was 0.51 ± 0.18. A display of the change in FFR_{true} to FFR_{app} based on the FFR_{epi} is shown in the Bland-Altman plots in Figures 6 and 7.

DISCUSSION

The main finding of this study is that downstream epicardial disease can affect the FFR assessment of intermediate LMCA disease when the pressure wire is positioned in the nondiseased epicardial vessel, but the magnitude of this effect is small and, in most cases, clinically irrelevant. This finding is consistent with the many observational studies that have demonstrated the safety of deferring revascularization on an angiographically intermediate LMCA lesion if the FFR is ≥0.75 to 0.80 (1,8–10). These studies included patients with downstream epicardial disease in which the FFR of the LMCA was assessed with the pressure wire in the least diseased epicardial vessel, and no correction was made to take into account the impact of the epicardial disease in the other vessel. The small differences between FFR_{true} and FFR_{app} in the present study explain why a non-ischemic FFR remained predictive of excellent outcome in the observational studies and support the use of FFR to assess intermediate LMCA disease, even in the presence of a diseased downstream epicardial vessel.

FIGURE 7 Minimal Effect of Downstream Disease on LMCA FFR

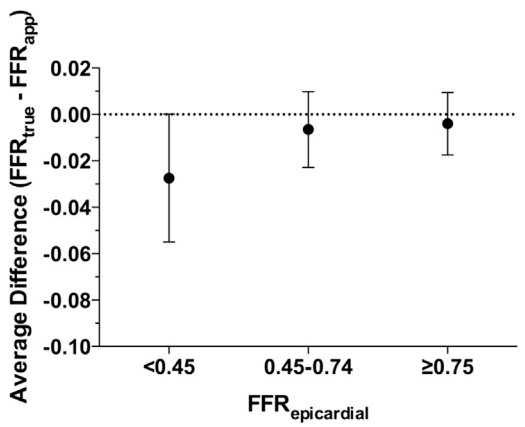


Chart demonstrating the average difference between the FFR_{true} and FFR_{app} depending on the severity of the downstream stenosis (FFR_{epi}). Abbreviations as in Figure 2.

The findings in this human validation study are similar to what we found in studies using an in vitro model and an animal model (11,12). In the in vitro model, we found that downstream LAD disease appeared to have a slightly greater impact on increasing the FFR_{app} than did downstream LCx disease and that significant changes between FFR_{true} and FFR_{app} occurred only with severe downstream disease (11). Our animal model demonstrated these findings, as well as the progressive impact of increasingly severe downstream disease on the change between FFR_{true} to FFR_{app} (12). Similar to our animal study, in this human validation, we did not see a dramatic difference between the effect of downstream LAD disease and downstream LCx disease, although the LAD did appear to have a greater impact. Because the LAD, in general, supplies more myocardium than the LCx, one would expect an LAD lesion to have a greater effect on FFR of the LMCA with the pressure wire in the LCx than vice versa. Our animal model, like the current human study, also did not show a dramatic difference between the effect of a midvessel stenosis and that of a proximal vessel stenosis, although one might expect a proximal lesion to have a greater impact.

These findings together support the conclusion that, although in theory, downstream epicardial disease affects the FFR assessment of the LMCA with the pressure wire in the nondiseased vessel, in practice, this effect is less than one might expect. In fact, in this study, we found only 6 cases in which the FFR_{app} was >0.05, higher than the FFR_{true}; in these cases, the FFR_{epi} (composite of the FFR of the LMCA and downstream stenosis) was on average 0.24, and in all

cases, it was ≤0.45, indicating that the downstream stenosis was essentially occlusive.

CLINICAL IMPLICATIONS. From a clinical standpoint, if one is interested in assessing the functional significance of an intermediate LMCA lesion in a patient with significant downstream disease in 1 vessel and finds that the FFR in the nondiseased vessel is ≤0.80, then it can be assumed that the LMCA lesion is functionally significant. If the FFR is >0.85, it can be assumed that the true FFR (in the theoretical absence of the contralateral downstream disease) will be >0.80. If the FFR is between 0.81 and 0.85 and the FFR_{epi} is ≤0.45, then it is possible that the true FFR will be ≤0.80 after revascularization of the downstream epicardial disease.

STUDY LIMITATIONS. The variable stenoses in the downstream vessel in this study were created artificially with a balloon immediately after stenting, and the intermediate LMCA disease was created artificially in most cases with a deflated balloon. This scenario may not be reflective of a more chronic setting with atherosclerotic narrowings. There were more cases with downstream LAD disease compared with LCx disease; however, because one would expect downstream LAD disease to have a greater impact than LCx disease and because we observed a trend in this direction, it is unlikely that inclusion of more LCx cases would change the results. We did not address the scenario when both downstream epicardial vessels have significant lesions. In this case, pullback of the pressure wire in both vessels during hyperemia can help to determine the contribution of the LMCA disease to an abnormal FFR, and anatomic evaluation with intravascular imaging may also prove informative.

CONCLUSIONS

Downstream epicardial disease does affect the functional assessment of intermediate LMCA disease with the pressure wire in the nondiseased downstream epicardial vessel, but the effect on FFR is small and clinically irrelevant, unless the downstream disease is severe.

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REFERENCES

1. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation 2009;120:1505–12.

2. Pijls NHJ, van Son JAM, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993;86:1354–67.

3. De Bruyne B, Bartunek J, Sys SU, Pijls NH, Heyndrickx GR, Wijns W. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. Circulation 1996;94:1842–9.

4. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007;49:2105–11.

5. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

6. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

7. Pijls NHJ, De Bruyne B, Bech GJW, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. Circulation 2000;102:2371–7.

8. Bech GJ, Droste H, Pijls NH, et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. Heart 2001;86:547–52.

9. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. Circulation 2004;110:2831–6.

10. Lindstaedt M. Patient stratification in left main coronary artery disease—rationale from a contemporary perspective. Int J Cardiol 2008;130:326–34.

11. Daniels DV, van't Veer M, Pijls NH, et al. The impact of downstream coronary stenoses on fractional flow reserve assessment of intermediate left main disease. J Am Coll Cardiol Intv 2012;5:1021–5.

12. Yong AS, Daniels D, De Bruyne B, et al. Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. Circ Cardiovasc Interv 2013;6:161–5.

KEY WORDS coronary artery disease, fractional flow reserve, left main coronary artery