Prediction of the true fractional flow reserve of left main coronary artery stenosis with concomitant downstream stenoses: *in vitro* and *in vivo* experiments

Erika Yamamoto¹, MD; Naritatsu Saito¹*, MD; Hitoshi Matsuo², MD; Yoshiaki Kawase², MD; Shin Watanabe¹, MD; Bingyuan Bao¹, MD; Hiroki Watanabe¹, MD; Hirooki Higami¹, MD; Kenji Nakatsuma¹, MD; Takeshi Kimura¹, MD

Abstract

**Aims:** The functional impact of downstream coronary stenoses on left main coronary artery (LMCA) stenosis has not been fully elucidated. This study therefore aimed to use *in vitro* and *in vivo* experiments to assess two novel equations that predict the true fractional flow reserve (FFR) of a left main coronary artery (LMCA) stenosis with concomitant downstream stenoses.

**Methods and results:** Two novel equations were derived. One equation predicts the true fractional flow reserve (FFR) of an LMCA stenosis with a downstream stenosis (Equation A), and the other predicts the true FFR of an LMCA stenosis with downstream stenoses in both the left anterior descending and left circumflex arteries (Equation B). The equations were validated in both *in vitro* and *in vivo* models of the coronary circulation. The agreements between the apparent FFR (FFR\textsubscript{app}), the predicted FFR (FFR\textsubscript{pred}) and the true FFR (FFR\textsubscript{true}) were assessed by Passing-Bablok regression analysis. Passing-Bablok regression analysis revealed that there were fixed proportional errors between FFR\textsubscript{app} and FFR\textsubscript{true}, though a very small fixed error and no proportional errors between FFR\textsubscript{pred} and FFR\textsubscript{true}. The absolute differences between FFR\textsubscript{pred} and FFR\textsubscript{true} were significantly lower as compared to those between FFR\textsubscript{app} and FFR\textsubscript{true} in all experiments.

**Conclusions:** Two novel equations which predict the true FFR of LMCA stenosis were demonstrated to be correct. The study also revealed that the functional impact of downstream stenoses on the LMCA stenosis became stronger when the downstream stenoses became more severe.

**Keywords**

- bifurcation lesion
- downstream stenosis
- fractional flow reserve
- left main coronary stenosis
- serial stenosis

*Corresponding author: Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan. E-mail: naritatsu@kuhp.kyoto-u.ac.jp
Background

Left main coronary artery (LMCA) stenosis is a relatively infrequent but serious finding. Coronary artery bypass grafting is recommended as the first-line treatment in the current guidelines. A precise evaluation of the severity of LMCA stenosis is crucial, since revascularisation of a non-significant LMCA stenosis may lead to early occlusion of the grafts and disease progression in the grafted native artery. The accurate assessment of FFR in an LMCA stenosis has still not been fully elucidated and discussion continues since revascularisation of a non-significant LMCA stenosis may only be recommended as the first-line treatment in the current guidelines.

These studies provide an important guide for the management of moderate LMCA stenosis. However, the theoretical background has still not been fully elucidated and discussion continues. The equation employed by previous investigators to predict the true FFR of LMCA stenosis was expressed in terms of resistance and could not be used without a flow meter. Furthermore, the application of the equation was limited to an LMCA stenosis with a single downstream coronary stenosis. However, LMCA stenosis accompanied by both LAD and LCX artery stenoses is not rare.

In this study, two novel equations which predict the true FFR of an LMCA stenosis with concomitant downstream stenoses were derived. One equation predicts the true FFR of an LMCA stenosis with a single downstream stenosis, and the other predicts the true FFR of an LMCA stenosis with downstream stenoses in both the LAD and LCX arteries. The equations were validated in both in vitro and in vivo models of the coronary circulation. The equations clarify the relationship between the main body stenosis and the downstream stenoses in an LMCA bifurcation lesion.

Derivation of the equations

DESCRIPTING THE RESISTANCES USING PRESSURE DATA

Figure 1A depicts a coronary model simulating an LMCA stenosis with concomitant downstream LAD and LCX artery stenoses. Collateral flow is excluded from the model. The pressure gradient across the stenosis is proportional to the flow, since the coronary flow conforms to the Hagen-Poiseuille law – the equivalent of Ohm’s law in an electrical circuit. The coronary model can be described using an analogous electrical circuit (Figure 1B). Artery 1 represents the LAD artery and Artery 2 represents the LCX artery in the model. The abbreviations are given in the Figure 1A legend.

All the pressure data in the present study are considered as the mean pressure obtained under maximum hyperaemia. Myocardial FFR is calculated as follows: $\text{FFR}_{m} = \frac{P_{a}}{Q P_{m}}$, $\text{FFR}_{1} = \frac{P_{1d}}{P_{a}}$, and $\text{FFR}_{2} = \frac{P_{2d}}{P_{a}}$. Composite FFR refers to the LMCA stenosis plus the downstream LAD/LCX artery stenosis. $\text{FFR}_{2}$ denotes the composite FFR of the LMCA plus the LAD artery. $\text{FFR}_{1}$ denotes the composite FFR of the LMCA plus the LCX artery. $n$ is defined as the ratio of $R_{2}$ to $R_{1}$. It corresponds to the LAD/LCX artery flow ratio when there are no stenoses in the LAD and LCX arteries.

PREDICTING THE TRUE FFR OF AN LMCA STENOSIS WITH ONE STENOSIS IN ONE OF THE DOWNSTREAM BRANCHES

Suppose an intervention to release $R_{1}$ is performed. $P'$a and $P'$m indicate the corresponding pressures after the intervention that release $R_{1}$. FFR$_{pred-m}$ is expressed as follows:

$$\text{FFR}_{pred-m} = \frac{P'_{a}}{Q P'_{m}} = \frac{P_{1d} P_{2d}}{P_{a} (P_{1w} - P_{m} + P_{1d})} = \frac{n \text{FFR}_{1} + \text{FFR}_{2}}{1 + n(1 - (\text{FFR}_{m} - \text{FFR}_{1}))}$$

Figure 1. Schematic model and the corresponding electric circuit. A) Schematic model representing the coronary circulation with stenoses in the LMCA and downstream LAD and LCX arteries. The systemic circulation is omitted to simplify the model. Artery 1 represents the LAD artery and Artery 2 represents the LCX artery. $R_{m}$ is the stenosis resistance in the LMCA, $R_{1}$ is the stenosis resistance in Artery 1, and $R_{2}$ is the stenosis resistance in Artery 2. $P_{a}$, $P_{m}$, and $P_{v}$ represent the aortic pressure, pressure distal to $R_{m}$ when Artery 1 is temporarily occluded, and venous pressure; $P_{1w}$ is pressure distal to $R_{1}$ when Artery 1 is temporarily occluded. Note that the definition of $P_{1w}$ is different from the original definition of the coronary wedge pressure. B) The corresponding electrical circuit. All abbreviations are the same as in Figure 1A.
Equation A calculates the true FFR of an LMCA stenosis with a single downstream stenosis. FFR_{pred-m} is the predicted true FFR of LMCA stenosis after the downstream stenosis in Artery 1 is released. The derivation of Equation A is described in the Appendix.

PREDICTING THE TRUE FFR OF AN LMCA STENOSIS WITH STENOSES IN BOTH DOWNSTREAM BRANCHES

Suppose an intervention to release both \( R_1 \) and \( R_2 \) is performed. \( P_m' \) and \( P_m'' \) indicate the corresponding pressures after both \( R_1 \) and \( R_2 \) are released. FFR_{pred-m} is expressed as follows:

\[
\text{FFR}_{\text{pred-m}} = \frac{P_m'}{P_m''} = \frac{P_{1d} P_{2d} (P_{1w} - P_m') + P_{1d} (P_{2w} - P_m'')}{1 - (\text{FFR}_m - \text{FFR}_1)} + \frac{n (1 - (\text{FFR}_m - \text{FFR}_1))}{n} \]

Equation B calculates the true FFR of an LMCA stenosis with downstream stenoses in both the LAD and LCX arteries. The derivation of Equation B is also described in detail in the Appendix.

In vitro experiment

EXPERIMENTAL PROTOCOL

The experimental system was similar to that described in our previous study (Figure 2). The correctness of Equation A and Equation B was validated in this experimental system. It consisted of a pump, systemic circulation, coronary circulation, and up to five constrictors placed in the coronary artery. The pump created a pulsatile flow at 60 beats/min. The total output of the pump was approximately 2 L/min. The pressure and flow in the coronary artery could be adjusted by a valve placed in the aorta and constrictors placed in the coronary circulation. The coronary flow was approximately 300 to 500 mL/min. Distilled water was used as the perfusate. The systemic and coronary circulations were made of silicone rubber tubes that mimic the human arterial system. The inner diameter of the coronary artery was 4 mm and the inner diameter of the aorta was 12 mm. The main artery was divided into Artery 1 and Artery 2. Artery 1 corresponded to the LAD artery and Artery 2 to the LCX artery. The constrictors were originally developed to create variable stenoses using a rotating screw. The naming of the constrictors corresponded to the names of the resistances in the mathematical model. \( R_m \), \( R_1 \), and \( R_2 \) were epicardial coronary stenoses. \( R_1 \) and \( R_2 \) represented microcirculatory resistance in Artery 1 and Artery 2. FFR measurements were conducted using two 0.014 inch pressure wires (St. Jude Medical, St. Paul, MN, USA), one placed in Artery 1 and the other placed in Artery 2. We conducted two experiments: Experiment 1 assessed Equation A, whereas Experiment 2 assessed Equation B.

EXPERIMENT 1

Experiment 1 was conducted to validate Equation A, which predicts the true FFR of the main artery stenosis after releasing the stenosis in Artery 1, when no epicardial stenosis exists in Artery 2. Four constrictors were placed in the coronary artery. The apparent FFR value of the main artery stenosis (FFR_{app-m}) was defined as \( P_m/P_a \) or \( P_{2d}/P_a \). Note that \( P_m \) is equal to \( P_{2d} \) in Experiment 1, since there were no stenoses in Artery 2. The predicted FFR value of the main artery stenosis (FFR_{pred-m}) was calculated from Equation A. The true value of the main artery stenosis (FFR_{true-m}) was measured after \( R_1 \) was released. The severity of the coronary stenoses (\( R_m \), \( R_1 \), and \( R_2 \)) and microvascular resistances (\( R_1 \) and \( R_2 \)) was changed randomly each time. Experiment 1 was conducted 50 times to obtain 50 different data sets.

EXPERIMENT 2

Experiment 2 was conducted to validate Equation B, which predicts the true FFR of the main artery stenosis after the stenoses in both Artery 1 and Artery 2 are released. Five constrictors were employed in Experiment 2. FFR_{app-m} was defined as \( P_m/P_a \). FFR_{pred-m} was calculated from Equation B. FFR_{true-m} was measured after both \( R_1 \) and \( R_2 \) were released. Experiment 2 was also conducted 50 times to obtain 50 different data sets. Various degrees of coronary stenosis with different microvascular resistances were created randomly by adjusting the five constrictors.

Figure 2. In vitro experimental system. A) The constrictor creating a variable degree of stenosis in the coronary artery by rotating the screw. B) The entire simulation system. The system consists of a pump, systemic and coronary circulation, and five constrictors. A 6 Fr introducer sheath is placed in the systemic circulation, and a guiding catheter is advanced proximal to the main artery through the 6 Fr sheath. Two pressure wires are placed in the coronary circulation, one in Artery 1, the other in Artery 2. C) Magnified view of the coronary circulation, simulating an LMCA stenosis (black arrow) and concomitant LAD and LCX artery stenoses (white arrows). The other two constrictors are placed in the distal parts of Artery 1 and Artery 2 to simulate microcirculatory resistance (arrowheads).
In vivo experiment

EXPERIMENTAL PROTOCOL

The correctness of Equations A and B was also examined using in vivo experiments. One female pig weighing 40 kg was studied in accordance with the Guide for the Care and Use of Laboratory Animals proposed by the Institute of Laboratory Animal Resources. The in vivo experimental protocol was approved by the institutional animal care and use committee at the Medical School of Kyoto University.

Anaesthesia was induced using xylazine (1 mg/kg) and ketamine (30 mg/kg) and, after intubation, anaesthesia was maintained with inhaled isoflurane 2%. One 6 Fr introducer sheath was surgically inserted into the right femoral artery and another was surgically inserted into the right femoral vein. Coronary angiography performed via the right femoral artery revealed that the LAD artery was relatively small, but the LCX artery was relatively large. The LCX artery bifurcation was used in the present study. The LCX artery main branch was the substitute for the LAD, and the LCX artery side branch was the substitute for the LCX artery. The difference between the LMCA bifurcation and the LCX artery bifurcation is the main branch/side branch flow ratio. The functional relationship between the main branch stenosis and downstream stenoses is essentially the same as that between the LMCA bifurcation and the LCX artery bifurcation. Three vascular occluders (Intermedics Co., Kyoto, Japan) were deployed to create variable degrees of coronary stenosis: one was placed in the LCX main artery proximal to the bifurcation, one in the LCX main artery distal to the bifurcation, and the other in the LCX artery side branch. FFR measurements were conducted during maximal hyperaemia induced by continuous administration of adenosine via the right femoral vein (140 μg/kg/min). We conducted two in vivo experiments. Experiment 3 assessed Equation A, whereas Experiment 4 assessed Equation B. The experimental system and procedure are described in Figure 3.

EXPERIMENT 3

Experiment 3 was conducted to validate Equation A. The experimental procedure was similar to that of Experiment 1. Two vascular occluders were placed in the LCX artery bifurcation, one in the LCX main artery proximal to the bifurcation, and the other in the LCX main artery distal to the bifurcation. FFR measurements were conducted during maximal hyperaemia induced by continuous administration of adenosine via the right femoral vein. The absolute difference between FFR app-m and FFR true-m was calculated from Equation A based on the pressure data obtained before releasing R1s. FFR true-m was obtained from the pressure data after releasing R1s. Experiment 3 was conducted 50 times to obtain 50 different data sets. Various degrees of coronary stenosis were created randomly by adjusting the three vascular occluders.

Statistics

The absolute difference between FFR app-m and FFR true-m was compared with the absolute difference between FFR pred-m and FFR true-m using a paired t-test. The agreements between FFR app-m and FFR pred-m were assessed using Passing-Bablok regression analysis. Passing-Bablok regression calculated the confidence intervals were used to assess fixed and proportional error. If 95% CI for intercept includes zero, there is no fixed error. Similarly, if 95% CI for slope includes value one, there is no proportional bias. In a Bland-Altman plot, the difference between the measurements was plotted against the mean. The Bland-Altman analysis was also used to assess fixed and proportional error. If 95% CI for the average difference includes zero, there is no fixed error. If 95% CI for regression slope includes zero, there is no proportional bias. All continuous variables were presented as mean ± standard deviation, unless otherwise stated. A two-sided p-value <0.05 was considered statistically significant.

Results

Fifty different combinations of the main artery and one or two downstream stenoses were created randomly in each experiment. FFR app-m were 0.66±0.17, 0.68±0.15, 0.77±0.13, and 0.70±0.12...
in Experiment 1 to 4, respectively. First, the impact of downstream stenoses on the LMCA stenosis assessment was analysed by comparing the difference of FFR\textsubscript{app-m} and FFR\textsubscript{true-m} with FFR\textsubscript{r} (Experiments 1-4), as well as by comparing the difference of FFR\textsubscript{app-m} and FFR\textsubscript{true-m} with FFR\textsubscript{r} (Experiments 2 and 4). In all analyses, the smaller FFR\textsubscript{r} or FFR\textsubscript{r} became, the larger the difference between FFR\textsubscript{app-m} and FFR\textsubscript{true-m} became (Figure 4).

The experimental results of Passing-Bablok regression and Bland-Altman analyses are presented in Figure 5 and Table 1. Passing-Bablok regression analysis revealed that there were fixed proportional errors between FFR\textsubscript{app-m} and FFR\textsubscript{true-m} in all experiments. Bland-Altman analysis also revealed that the difference between FFR\textsubscript{app-m} and FFR\textsubscript{true-m} was always significantly larger than zero and the regression slope was always smaller than zero. The analysis indicated that FFR\textsubscript{app-m} was always larger than FFR\textsubscript{true-m}, and the difference became larger when the mean of FFR\textsubscript{true-m} and FFR\textsubscript{app-m} became smaller. Meanwhile, Passing-Bablok regression analysis showed a very small fixed error in Experiments 1 to 4, while there were no proportional errors in Experiments 1 to 4. Bland-Altman analysis also showed that the difference between FFR\textsubscript{pred-m} and FFR\textsubscript{true-m} was slightly smaller than zero in Experiments 1 and 2, and was larger than zero in Experiments 3 and 4. The regression slopes in Bland-Altman plots when comparing FFR\textsubscript{pred-m} and FFR\textsubscript{true-m} were not significantly different from zero in all experiments, which indicated that there were no significant proportional errors between FFR\textsubscript{pred-m} and FFR\textsubscript{true-m}.

The absolute difference between FFR\textsubscript{app-m} and FFR\textsubscript{true-m} was significantly larger than the absolute difference between FFR\textsubscript{pred-m} and FFR\textsubscript{true-m} in all experiments (Figure 6). These analyses indicated that the agreements between FFR\textsubscript{pred-m} and FFR\textsubscript{true-m} were better than those between FFR\textsubscript{app-m} and FFR\textsubscript{true-m} in all experiments.

**Discussion**

Downstream stenosis affects the FFR of the LMCA stenosis. The more severe the downstream stenosis is, the larger the impact of downstream stenosis is. Two novel equations were derived to predict the true FFR of the LMCA stenosis in case of one downstream stenosis (Equation A) or two downstream stenoses (Equation B). Both Equation A and Equation B were proved to be accurate in predicting the true FFR of the LMCA stenosis.

A previous in vitro study reported that, when the composite FFR of the LMCA and a single downstream stenosis is >0.65, the apparent FFR of the LMCA stenosis does not differ greatly from its true value. The same group conducted a similar experiment and concluded that, when the apparent FFR of the LMCA is >0.80 and epicardial FFR (combined FFR of the LMCA and a downstream stenosed vessel) is >0.50, the true FFR of the LMCA stenosis is always >0.75. We consider that the theoretical backgrounds of these study results were not fully elucidated. These results are completely explained mathematically by Equation A. The mathematical proof is fully described in the Appendix. FFR\textsubscript{pred-m} is monotonically increasing in FFR\textsubscript{r}, FFR\textsubscript{m}, and n. Thus, when FFR\textsubscript{r} is <0.65 and FFR\textsubscript{m} is >0.80, FFR\textsubscript{true-m} can become <0.75. This consideration suggests that the cut-off line for the apparent LMCA FFR of 0.80 will potentially cause a false negative misinterpretation of the functional severity of an LMCA stenosis when downstream stenosis is severe. However, when the cut-off line is set to 0.85, FFR\textsubscript{pred-m} never becomes <0.75 when FFR\textsubscript{r} is >0.5. Thus, we propose that the apparent LMCA FFR between 0.80 and 0.85 is in a grey zone when a downstream LAD/LCX stenosis exists. When the apparent FFR of the LMCA stenosis is in the grey zone, the true FFR of the LMCA stenosis should be assessed after treating the downstream stenosis. Another option to determine the true functional severity of the LMCA stenosis is to apply Equation A to predict the true FFR of the LMCA stenosis.

![Figure 4](image-url) - *Plots of the difference between FFR\textsubscript{app-m} and FFR\textsubscript{true-m} against composite FFR. In all analyses, the difference between FFR\textsubscript{app-m} and FFR\textsubscript{true-m} is negatively correlated with the composite FFR in the linear regression analysis.*
FFR. However, Equation A is not practical since it requires coronary occlusion to obtain “n” in the present form. Thus, we propose applying the assumption of the LAD/LCX flow ratio as 2:1, then Equation A becomes as follows.

\[
FFR_{\text{pred-m}} = \frac{2FFR_1 + FFR_m}{3 + 2FFR_1 - 2FFR_m} \text{ (A')} 
\]

Equation A' can be applied without occluding the coronary artery. The mathematical proof of all these considerations is given in the Appendix.

Similar considerations apply in Equation B, which is a more general form of Equation A. Equation B predicts the true FFR of an LMCA stenosis with both LAD and LCX artery stenoses. An LMCA stenosis accompanied by both LAD and LCX artery stenoses is not rare in daily clinical practice\(^6\). An FFR of >0.85 would almost certainly indicate that the LMCA stenosis is not functionally significant, despite the presence of downstream LAD/LCX artery stenoses. When the composite FFR of the LMCA plus epicardial stenoses in the LAD and LCX arteries are both >0.65 and the apparent FFR of the LMCA stenosis is >0.80, the true FFR

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**Figure 5.** Passing-Bablok regressions and Bland-Altman plots of Experiments 1 to 4. A) FFR\(_{\text{app-m}}\) compared with FFR\(_{\text{true-m}}\) by Passing-Bablok regression (solid line) with 95% CI (grey zone). B) Corresponding Bland-Altman plot. The solid line denotes the mean of the difference and the dashed line denotes the 95% CI. C) FFT\(_{\text{pred-m}}\) compared with FFR\(_{\text{true-m}}\). D) Corresponding Bland-Altman plot.
True FFR of the LMCA stenosis

An apparent FFR of an LMCA stenosis between 0.80 and 0.85 is in a grey zone when either downstream LAD or LCX stenosis is <0.65. When the apparent FFR of an LMCA stenosis is in the grey zone, the true FFR of the LMCA stenosis should be assessed after treating both the LAD and LCX downstream stenoses, or the following Equation B’, which is obtained on the assumption that LAD/LCX flow ratio is 2:1, should be applied. The mathematical proof of all these considerations is given in the Appendix.

\[
\text{FFR}_{\text{pred-m}} = \frac{2\text{FFR}_1 + \text{FFR}_2}{3 + 2\text{FFR}_1 + \text{FFR}_2 - 3\text{FFR}_m} \quad (B')
\]

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<th>Experiment</th>
<th>Comparison</th>
<th>Intercept (95% CI)</th>
<th>Slope (95% CI)</th>
<th>Difference (95% CI)</th>
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<td>1</td>
<td>FFR\text{app-m} vs. FFR\text{true-m}</td>
<td>0.13 (0.09-0.20)*</td>
<td>0.90 (0.80-0.96)*</td>
<td>0.09 (0.07-0.11)*</td>
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<tr>
<td>1</td>
<td>FFR\text{pred-m} vs. FFR\text{true-m}</td>
<td>-0.03 (-0.05--0.00)*</td>
<td>1.02 (0.99-1.06)</td>
<td>-0.02 (-0.02--0.00)*</td>
<td>0.02 (-0.01-0.05)</td>
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<td>2</td>
<td>FFR\text{app-m} vs. FFR\text{true-m}</td>
<td>0.16 (0.10-0.23)*</td>
<td>0.87 (0.77-0.94)*</td>
<td>0.07 (0.06-0.09)*</td>
<td>-0.15 (-0.24--0.06)*</td>
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<tr>
<td>2</td>
<td>FFR\text{pred-m} vs. FFR\text{true-m}</td>
<td>-0.03 (-0.07-0.01)</td>
<td>1.03 (0.97-1.09)</td>
<td>-0.00 (-0.02--0.00)*</td>
<td>0.00 (-0.05-0.05)</td>
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<tr>
<td>3</td>
<td>FFR\text{app-m} vs. FFR\text{true-m}</td>
<td>0.38 (0.25-0.50)*</td>
<td>0.67 (0.52-0.82)*</td>
<td>0.12 (0.10-0.14)*</td>
<td>-0.30 (-0.45--0.15)*</td>
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<tr>
<td>3</td>
<td>FFR\text{pred-m} vs. FFR\text{true-m}</td>
<td>-0.30 (-0.00-0.20)*</td>
<td>0.95 (0.82-1.08)</td>
<td>0.06 (0.05-0.07)*</td>
<td>0.03 (-0.07-0.12)</td>
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<td>4</td>
<td>FFR\text{app-m} vs. FFR\text{true-m}</td>
<td>0.62 (0.53-0.67)*</td>
<td>0.36 (0.29-0.47)*</td>
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<td>FFR\text{pred-m} vs. FFR\text{true-m}</td>
<td>0.10 (0.01-0.20)*</td>
<td>0.95 (0.82-1.07)</td>
<td>0.07 (0.06-0.08)*</td>
<td>0.00 (-0.10-0.10)</td>
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</table>

*Statistically significant (p<0.05).

Table 1. Passing-Bablok regression and Bland-Altman analysis results.

**Figure 6.** The absolute difference between FFR\text{app-m} and FFR\text{true-m} compared with the absolute difference between FFR\text{pred-m} and FFR\text{true-m} in Experiments 1 to 4. The absolute difference between FFR\text{app-m} and FFR\text{true-m} was significantly greater than the absolute difference between FFR\text{pred-m} and FFR\text{true-m} in all experiments.

**Limitations**

The present study had several important limitations. First, the in vitro model of coronary circulation was different from the complex human coronary circulation in many ways. In the present study, distilled water was used as the perfusate. The viscosity of water is lower than that of blood, which might have influenced the study results. Most importantly, the experimental system lacked any collateral circulation, which certainly exists in humans. However, the legitimacy of the equation was also proven by the in vivo experiments which included collateral circulation. Second, a stenosis is not uniform as in the experiment, and the locations of stenoses are sometimes close to each other. If the LAD and LCX stenoses are both very proximal and the LMCA stenosis is very distal, it is very hard to obtain FFR\text{true}. In this scenario, it is not possible to calculate FFR\text{pred}. Third, the LCX artery bifurcation was employed as a substitute for the LMCA bifurcation in the in vivo experiments. The blood flow ratio between the main branch and side branch of the LCX artery bifurcation was different from that of the LMCA bifurcation. However, the difference between the LCX artery bifurcation and the LMCA bifurcation is only the blood flow ratio of the downstream artery. Equations A and B are applicable not only to the LMCA bifurcation, but to any bifurcation. Fourth, one may consider that the equations in the present study are not practical, since Equations A and B in the present study require temporary coronary occlusion of the downstream artery to measure \(P_{iw}\). However, with the assumption of an LAD/LCX artery flow ratio of 2:1, Equations A and B can be applied in clinical practice. More importantly, a better understanding of the background theory helps to improve the performance of daily practice. Finally, the present study included severe LMCA lesions with an FFR <0.50, which usually do not require FFR assessment in clinical practice. The study aimed to assess the legitimacy of Equations A and B in many settings and the study results showed that both Equation A and Equation B strongly predict the true FFR of the LMCA stenosis, even when the LMCA stenosis is very severe.

**Conclusions**

Novel equations to predict the true FFR of an LMCA stenosis in the presence of concomitant downstream LAD/LCX artery...
Impact on daily practice

FFR is an important tool to guide the decision for revascularisation of an intermediate LMCA stenosis. However, the functional impact of downstream coronary stenoses on the LMCA stenosis has not been fully elucidated. The two novel equations described in the present paper revealed that 1) the more severe the downstream stenosis, the larger the functional impact of downstream stenosis, and 2) an apparent LMCA FFR between 0.80 and 0.85 is in a grey zone when downstream LAD/LCX stenoses exist and are severe.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References


Supplementary data

Appendix. Derivation of Equations A and B.
Supplementary data

Appendix. Derivation of Equations A and B

First, the derivations of Equations A and B are presented. Then the minimum values of the true FFR of LMCA stenoses are calculated in some specific settings.

The terminology is consistent with the main text and Figure 1. Consider a model of coronary circulation simulating an LMCA stenosis with downstream LAD and LCX artery stenoses (Figure 1). Collateral flow is excluded from the model in the present study. Artery 1 represents the LAD artery and Artery 2 represents the LCX artery in the model. The LMCA is denoted as the main artery. The abbreviations are defined as follows: \( R_m \) = stenosis resistance in the main artery, \( R_{is} \) = stenosis resistance in Artery 1, \( R_{is} \) = stenosis resistance in Artery 2, \( R_{is} \) = microcirculatory resistance in Artery 1, \( R_{is} \) = microcirculatory resistance in Artery 2, \( P_a \) = aortic pressure, \( P_m \) = pressure distal to \( R_m \), \( P_{1d} \) = pressure distal to \( R_{is} \), \( P_{2d} \) = pressure distal to \( R_{is} \), when Artery 1 is totally occluded, \( P_v \) = central venous pressure, \( Q \) = total coronary flow, \( Q_{1} \) = coronary flow in Artery 1, \( Q_{2} \) = coronary flow in Artery 2. \( P_v \) approximates to zero in the model. All the pressure data employed in the present study refer to the mean pressure obtained under maximum hyperaemia. One should note that the definition of \( P_{1w} \) is different from the original article. The pressure gradient across the stenosis is proportional to the flow, which is assumed to be Hagen-Poiseuille flow in the model. The concept of a voltage divider can be applied by analogy to fluids. Myocardial FFR is calculated as follows: \( FFR_m = P_m/P_a \), \( FFR_{1} = P_{1d}/P_a \), and \( FFR_{2} = P_{2d}/P_a \). Composite FFR is defined as the LMCA stenosis plus the downstream LAD/LCX artery stenosis. \( FFR_m \) indicates the composite FFR of the LMCA plus the LAD artery, whereas \( FFR_{1} \) indicates the composite FFR of the LMCA plus the LCX artery. \( FFR_m \), \( FFR_{1} \), and \( FFR_{2} \) can be described in terms of resistance, as presented previously.

\[
FFR_m = \frac{P_m}{P_a} = \frac{1}{R_m + \frac{1}{\frac{R_1 + R_{1s}}{1}} + \frac{1}{\frac{R_2 + R_{2s}}{1}}} \quad (1)
\]

\[
\frac{P_{1d}}{P_m} = \frac{R_1}{R_1 + R_{1s}} \quad (2)
\]

\[
\frac{P_{2d}}{P_m} = \frac{R_2}{R_2 + R_{2s}} \quad (3)
\]

\[
\frac{P_{1w}}{P_a} = \frac{R_2 + R_{2s}}{R_m + R_2 + R_{2s}} \quad (4)
\]

\( P_{1w} \) is measured at the point just distal to \( R_{is} \) when Artery 1 is totally occluded. Artery 1 \( P_{1w} \) needs to be adjusted according to the change in \( P_v \).

Calculation of resistance using the pressure

\( \frac{R_2}{R_m}, \frac{R_3}{R_m}, \frac{R_2}{R_m}, \frac{R_3}{R_m} \) and \( \frac{R_2 + R_{2s}}{R_m} \) can be expressed using the pressure by solving Equations 1 to 4, as follows.

First, transform Equation 4 as follows:

\[
R_2 + R_{2s} = R_m \cdot \frac{P_{1w}}{P_a - P_{1w}} \quad (4')
\]

Substituting Equation 4’ into Equation 3 gives,

\[
\frac{P_{2d}}{P_m} = \frac{R_2}{R_m \cdot \frac{P_{1w}}{P_a - P_{1w}}}
\]

or

\[
\frac{R_2}{R_m} = \frac{P_{1w}P_{2d}}{P_m(P_a - P_{1w})}
\]
Substituting into Equation 4' we have
\[
\frac{R_{2s}}{R_m} + \frac{P_{1w}P_{2d}}{P_m(P_a - P_{1w})} = \frac{P_{1w}}{P_a \cdot P_{1w}}
\]
or
\[
\frac{R_{2s}}{R_m} = \frac{P_{1w}(P_m - P_{2d})}{P_m(P_a - P_{1w})}
\]

Equation 1 is transformed as follows:
\[
\frac{P_m}{P_a} = \frac{(R_1 + R_{1s})(R_2 + R_{2s})}{R_m + (R_1 + R_{1s})(R_2 + R_{2s})}
\]
or
\[
\frac{P_m}{P_a} = \frac{(R_1 + R_{1s})(R_2 + R_{2s})}{(R_1 + R_{1s})(R_2 + R_{2s}) + R_m(R_1 + R_{1s} + R_2 + R_{2s})}
\] (1')

Substituting Equation 4' into Equation 1' gives:
\[
\frac{P_m}{P_a} = \frac{(R_1 + R_{1s})R_m \cdot P_{1w}}{(R_1 + R_{1s})R_m \cdot P_{1w} + R_m(R_1 + R_{1s} + R_{2s} + R_{2s})}
\]
or
\[
\frac{P_m}{P_a} = \frac{R_1 + R_{1s} \cdot P_{1w}}{R_m \cdot P_{1w} + R_1 + R_{1s} + \frac{P_{1w}}{P_a \cdot P_{1w}}}
\]
or
\[
\frac{R_1 + R_{1s}}{R_m} \cdot \frac{P_{1w}}{P_a \cdot P_{1w}} (1'')
\]

FFR₁ is expressed as follows:
\[
FFR_1 = \frac{P_{1d}}{P_{1w}} = \frac{P_m}{P_a} \cdot \frac{P_{1d}}{P_{1w}}
\]

Substituting Equation 1' and Equation 2 into the above formula gives:
\[
\frac{P_{1d}}{P_a} = \frac{(R_1 + R_{1s})(R_2 + R_{2s})}{(R_1 + R_{1s})(R_2 + R_{2s}) + R_m(R_1 + R_{1s} + R_2 + R_{2s})} \cdot \frac{R_1}{R_1 + R_{1s}}
\]
\[
= \left(\frac{R_1 + R_{1s}}{R_1 + R_{1s}}\right)\left(\frac{R_2 + R_{2s}}{R_m \cdot \frac{R_2 + R_{2s}}{R_m}}\right) + R_m\left(\frac{R_1 + R_{1s} + R_2 + R_{2s}}{R_m \cdot \frac{R_1 + R_{1s} + R_2 + R_{2s}}{R_m}}\right)
\]
\[
= \frac{R_1 + R_{1s}}{R_m} \cdot \frac{R_2 + R_{2s}}{R_m} + \frac{R_1 + R_{1s}}{R_m} + \frac{R_2 + R_{2s}}{R_m}
\]

Substituting Equation 4' into the above formula gives:
\[
\frac{P_{1d}}{P_a} = \frac{R_1 + R_{1s}}{R_m} \cdot \frac{P_{1w}}{P_a \cdot P_{1w}} + \frac{R_1 + R_{1s}}{R_m} + \frac{P_{1w}}{P_a \cdot P_{1w}}
\]
True FFR of the LMCA stenosis

or

\[
\frac{P_{1d}}{P_a} \left( \frac{R_1 + R_{1s}}{R_m} \cdot \frac{P_{1w}}{P_a \cdot P_{1w}} + \frac{R_1 + R_{1s}}{R_m} \right) = \frac{R_1}{R_m} \cdot \frac{P_{1w}}{P_a \cdot P_{1w}}
\]

Substituting Equation 1' into the above formula, we get

\[
\frac{P_{1d}}{P_a} \left( \frac{P_m P_{1w}}{P_a (P_{1w} - P_m)} \cdot \frac{P_{1w}}{P_a \cdot P_{1w}} + \frac{P_m P_{1w}}{P_a (P_{1w} - P_m)} + \frac{P_{1w}}{P_a \cdot P_{1w}} \right) = \frac{R_1}{R_m} \cdot \frac{P_{1w}}{P_a \cdot P_{1w}}
\]

or

\[
\frac{R_1}{R_m} = \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m)}
\]

Substituting this equation into Equation 1' :

\[
\frac{R_{1s}}{R_m} = \frac{P_{1w} (P_m - P_{1d})}{P_a (P_{1w} - P_m)}
\]

All the resistances, including \( R_{1s}, R_1, R_{2s}, \) and \( R_2 \), are now expressed as a fraction of \( R_m \), as follows:

\[
\frac{R_{1s}}{R_m} = \frac{P_{1w} (P_m - P_{1d})}{P_a (P_{1w} - P_m)} = \frac{P_m}{P_a} \cdot \frac{P_{1d}}{P_{1w}} \cdot \frac{P_{1w}}{P_m} = \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m)}
\]

(5)

\[
\frac{R_1}{R_m} = \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m)} = \frac{P_{1d} P_{1w}}{P_a P_m} \cdot \frac{P_{1w}}{P_m}
\]

(6)

\[
\frac{R_{2s}}{R_m} = \frac{P_{1w} (P_m - P_{2d})}{P_m (P_a - P_{1w})} = \frac{P_m}{P_a} \cdot \frac{P_{2d}}{P_{1w}} \cdot \frac{P_{1w}}{1 - P_{1w}}
\]

(7)

\[
\frac{R_2}{R_m} = \frac{P_{1w} P_{2d}}{P_m (P_a - P_{1w})} = \frac{P_{1w} P_{2d}}{P_m (1 - P_{1w})}
\]

(8)

When \( n \) is defined as the ratio of \( R_2 \) to \( R_1 \), \( n \) corresponds to the Artery 1/Artery 2 flow ratio.

\[
n = \frac{R_2}{R_1} = \frac{P_{2d} P_a (P_{1w} - P_m)}{P_{1d} P_m (P_a - P_{1w})}
\]

(9)

**Derivation of Equation A**

Equation A calculates the true FFR of a main artery stenosis with a concomitant downstream stenosis in Artery 1. When there are no stenoses in Artery 2, \( P_{1d} = P_m \). Suppose an intervention is conducted in \( R_{1s} \) and \( R_{1s} \) is completely released. \( P'_m, P'_m \), and \( P'_{1d} \) indicate the corresponding pressures after the intervention. One should note that \( P'_m = P_{1d}' \) when \( R_{1s} \) is released. \( FFR'_m = P'_m/P'_a \) and \( FFR'_1 = P'_{1w}/P'_a \) are the corresponding FFR after releasing \( R_{1s} \). \( FFR'_m \) is equal to \( FFR'_1 \) after releasing \( R_{1s} \).
Under these conditions, using the resistance data, $FFR_m'$ is expressed as follows:

$$FFR_m' = \frac{P_m'}{P_a'} = \frac{\frac{1}{R_1} + \frac{1}{R_2}}{R_m + \frac{1}{R_1} + \frac{1}{R_2}} = \frac{\frac{R_1}{R_m} \cdot \frac{R_2}{R_1 + R_2}}{\frac{R_1}{R_m} \cdot \frac{R_2}{R_m} + \frac{R_1}{R_m} + \frac{R_2}{R_m}}$$

Substitute Equations 6 and 8 into the above equation:

$$FFR_m' = \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m)} \cdot \frac{P_{1w} P_{2d}}{P_m (P_a - P_{1w})} + \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m)} + \frac{P_{1w} P_{2d}}{P_m (P_a - P_{1w})} = \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m + P_{1d})} \quad (A0)$$

$P_a = P_c$ is applied to Equation 9, and transformed:

$$P_{1w} = \frac{P_a (nP_{1d} + P_m)}{P_a + nP_{1d}} \quad (9')$$

Putting Equation 9' into Equation A0 gives Equation A:

$$FFR_{pred-m} = FFR_m' = \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m + P_{1d})} = \frac{nFFR_1 + FFR_m}{1 + n(1 - (FFR_m - FFR_1))} \quad (A)$$

**Derivation of Equation B**

$P_m$, $P_m''$, $P_m'''$, and $P_m''''$ indicate the corresponding pressures after both $R_1$ and $R_2$ are released. $R_1 = 0$, $R_2 = 0$, and $P_m'' = P_m''' = P_m''''$ are all true under these conditions. $FFR_m''$ is expressed in terms of the pressure in the following form:

$$P_m'' = \frac{1}{R_1} + \frac{1}{R_2} = \frac{\frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m)} \cdot \frac{P_{1w} P_{2d}}{P_m (P_a - P_{1w})} + \frac{P_{1d} P_{1w}}{P_a (P_{1w} - P_m)} + \frac{P_{1w} P_{2d}}{P_m (P_a - P_{1w})}}{1 + \frac{P_{1w} P_{2d}}{P_m (P_a - P_{1w})} + \frac{P_{1w} P_{2d}}{P_m (P_a - P_{1w})}} \quad (B0)$$

Equation 9 is transformed:

$$P_{1w} = \frac{P_a P_m (nP_{1d} + P_{2d})}{P_a P_{2d} + nP_m P_{1d}} \quad (9'')$$

Substituting Equation 9'' into Equation B0 gives Equation B:

$$FFR_{pred-m} = \frac{P_m''}{P_a} = \frac{P_{1d} P_{2d} P_{1w}}{P_{1d} P_{2d} P_{1w} + P_a P_{2d} (P_{1w} - P_m) + P_m P_{1d} (P_a - P_{1w})}$$

$$= \frac{nFFR_1 + FFR_2}{1 - (FFR_m - FFR_2) + n(1 - (FFR_m - FFR_1))} \quad (B)$$

Note that, when $FFR_2 = FFR_m''$, Equation B is the same as Equation A.
The predicted FFR of an LMCA stenosis with a downstream LAD artery stenosis under various conditions

The predicted FFR of an LMCA stenosis with a downstream stenosis is calculated from Equation A.

\[
 FFR_{pred-m} = \frac{nFFR_1 + FFR_m}{1 + n(1-(FFR_m - FFR_1))} \quad (A)
\]

The partial derivative of \( FFR_{pred-m} \) with respect to \( FFR_1 \) and its range are calculated as:

\[
 \frac{\partial FFR_{pred-m}}{\partial FFR_1} = \frac{n(n + 1)(1 - FFR_m)}{(1 + n(1-(FFR_m - FFR_1)))^2} > 0
\]

The above inequality shows that \( FFR_{pred-m} \) increases with \( FFR_1 \). The partial derivatives of \( FFR_{pred-m} \) with respect to \( FFR_m \) and \( n \) are also calculated as:

\[
 \frac{\partial FFR_{pred-m}}{\partial FFR_m} = \frac{(n+1)(nFFR_1+1)}{(1+n(1-(FFR_m - FFR_1)))^2} > 0
\]

\[
 \frac{\partial FFR_{pred-m}}{\partial n} = \frac{(1-FFR_m)(FFR_1-FFR_m)}{(1+n(1-(FFR_m - FFR_1)))^2} < 0
\]

Thus, \( FFR_{pred-m} \) increases with \( FFR_1 \) and \( FFR_m \), but decreases with an increase in \( n \).

When \( FFR_1 \) is >0.50 and \( FFR_m \) is >0.85, the following inequality is obtained from Equation A:

\[
 FFR_{pred-m} > 0.77
\]

Note that, \( FFR_{pred-m} = 0.77 \), when \( FFR_1 = 0.50 \), \( FFR_m = 0.85 \) and \( n = \infty \).

Thus, when the apparent FFR of LMCA is >0.85 and the composite FFR is >0.50, the predicted FFR of an LMCA stenosis with a downstream stenosis is always >0.77. This is true independently of the LAD/LCX artery flow ratio.

When \( FFR_1 \) is >0.50 and \( FFR_m \) is >0.80, the following inequality is obtained from Equation A:

\[
 FFR_{pred-m} > 0.71
\]

The predicted FFR of an LMCA stenosis can be <0.75. The cut-off line of the apparent LMCA FFR of 0.80 could potentially cause a false-negative misinterpretation of the functional severity of the LMCA stenosis. However, when the LAD/LCX artery flow rate is two, the following inequality is obtained:

\[
 FFR_{pred-m} > 0.75
\]

The predicted FFR of an LMCA stenosis with a downstream stenosis is always >0.75 when the LAD/LCX artery blood flow is two, \( FFR_m > 0.85 \), and \( FFR_1 > 0.50 \). This is the mathematical proof of previously published study results.

The predicted FFR of an LMCA stenosis with downstream stenoses in both LAD and LCX arteries

Equation B predicts the true FFR of an LMCA stenosis with downstream stenoses in both the LAD and LCX arteries.

\[
 FFR_{pred-m} = \frac{nFFR_1 + FFR_2}{1 - (FFR_m - FFR_2) + n(1 - (FFR_m - FFR_1))} \quad (B)
\]

Similar calculations are also made. The partial derivatives of \( FFR_{pred-m} \) with respect to \( FFR_1 \), \( FFR_2 \), \( FFR_m \), and \( n \) are calculated:
FFR_{pred-m} increases with FFR_1, FFR_2, and FFR_m. When FFR_1 is >FFR_2, FFR_{pred-m} increases with n, but when FFR_1 is <FFR_2, FFR_{pred-m} decreases with an increase in n. When FFR_1 is >0.50, FFR_2 is >0.50, and FFR_m is >0.85, the following inequality is obtained from Equation B:

FFR_{pred-m} > 0.77

Note that, when FFR_1=0.50, FFR_2=0.50 and FFR_m=0.85, FFR_{pred-m}=0.77, which is independent of the value of n.

When the composite FFR of the LMCA plus epicardial stenoses in the LAD and LCX arteries are both >0.50 and the apparent FFR of the LMCA stenosis is >0.85, the true FFR value of the LMCA stenosis calculated from Equation B is always >0.75, independently of the LAD/LCX artery flow ratio.

**Derivation of Equation A’ and B’**

One may consider that the equations in the present study are not practical, since Equations A and B in the present study require temporary coronary occlusion of the downstream artery to measure P_1w. However, with the assumption of an LAD/LCX artery flow ratio of 2:1, Equations A and B can be applied in clinical practice. Equations A and B become as follows when n=2 is applied.

\[
FFR_{pred-m} = \frac{2FFR_1 + FFR_m}{3+2FFR_1·2FFR_m} \quad (A')
\]

\[
FFR_{pred-m} = \frac{2FFR_1 + FFR_2}{3+2FFR_1·2FFR_2·3FFR_m} \quad (B')
\]

Equations A’ and B’ can be applicable without measuring P_w. Needless to say, the true applicability of these equations should be assessed in a future clinical study.