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Prediction of post-intervention fractional flow reserve in diffuse or sequential coronary stenosis considering the residual trans-stent pressure gradient

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KEYWORDS

- diffused disease
- fractional flow reserve
- stable angina

Abstract

Aims: Prediction of post-intervention fractional flow reserve (FFR) in a diffuse or sequential coronary lesion is difficult due to complex haemodynamic interactions between individual stenoses. Furthermore, the existence of a residual intra-stent pressure gradient makes the prediction difficult. We developed an equation predicting the post-intervention FFR in a diffuse/sequential lesion by considering intra-stent FFR gradient. The present study aims to validate the equation in an *in vitro* model and in clinical data.

Methods and results: In the *in vitro* experiment, three sequential coronary stenoses were made with a collateral flow. The correlation coefficient of the predicted FFR and the actual post-intervention FFR was 0.99, and the absolute difference was 0.008±0.006 (n=50). In the clinical data analysis, the correlation coefficient was 0.41, and the absolute difference was 0.06±0.05 (n=67). We applied a fixed value of intra-stent FFR gradient and a collateral flow index so that the equation can be used in clinical practice. The correlation coefficient became 0.28 and the absolute difference became 0.06±0.06.

Conclusions: In clinical practice, prediction of post-intervention FFR in a diffuse/sequential lesion is difficult even when residual intra-stent pressure gradient is considered.

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Abbreviations

CFI	collateral flow index
dPR	diastolic pressure ratio
FFR	fractional flow reserve
iFR	instantaneous wave free ratio
IVUS	intravascular ultrasound
LAD	left anterior descending artery
LCX	left circumflex artery
NSTEMI	non-ST segment elevation myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
RCA	right coronary artery
RFR	resting full-cycle ratio
STEMI	ST-segment elevation myocardial infarction

Introduction

Fractional flow reserve-guided percutaneous coronary intervention (PCI) is associated with a favourable outcome compared to angiography-guided PCI[1,2]. Fractional flow reserve (FFR) measurement is conducted under maximum hyperaemic conditions induced by intracoronary or intravenous administration of a vasodilator, which may cause side effects including vomiting, hypotension, and arrhythmia[3,4]. Recently, resting non-hyperaemic indices, including the instantaneous wave free ratio (iFR), have been developed to assess the functional severity of coronary stenosis[5]. iFR and other resting indices do not require the induction of hyperaemia, and thus hyperaemia-related complications are avoidable[3,4]. Another important advantage of iFR is that post-intervention iFR is predictable in a sequential or diffuse coronary lesion by the following simple equation[6,7]: $iFR_{post}=iFR_{pre}+\Delta iFR$. Prediction of post-intervention FFR is usually considered difficult in FFR due to complex haemodynamic interactions between the individual stenoses under maximum hyperaemia[8,9]. Therefore, the current recommendation for a sequential or diffuse coronary lesions is to measure FFR distally, and perform a pressure pullback under maximum hyperaemia. Treatment of the most severely narrowed lesion is then determined by which of the lesions produces the largest ΔFFR[10-12].

We consider that another factor that makes post-intervention FFR prediction in a diffuse/sequential lesion difficult is the existence of an intra-stent pressure gradient after intervention. The post-intervention intra-stent pressure gradient inevitably affects the post-intervention FFR[13-16]. We hypothesised that post-intervention FFR, in a diffuse/sequential coronary lesion, is predictable if the post-intervention intra-stent FFR is considered. Thus we developed a mathematical equation to predict post-intervention FFR in diffuse/sequential lesions by considering the intra-stent FFR gradient. The main purpose of the present study is to validate the equation in an *in vitro* circuit model and in clinical data.

Methods

DERIVATION OF THE EQUATION

De Bruyne et al described theoretic equations to predict the FFR of each stenosis in a tandem lesion[8], but their application is limited to tandem lesions. We mathematically generalised the equations to be applicable to a diffuse/sequential coronary lesion in a previous study (Equation A)[9].

$$FFR_{post}=\frac{P_d-P_w}{P_a-\Delta P-P_w}+\frac{P_w(P_a-\Delta P-P_d)}{P_a(P_a-\Delta P-P_w)}=\frac{FFR_{pre}(1-CFI)-CFI\Delta FFR}{1-\Delta FFR-CFI} \quad (A)$$

We wanted to formulate a novel equation in which post-intervention trans-stent FFR is considered. Consider a coronary circulation model simulating the diffuse/sequential coronary lesion with a collateral circulation **(Figure 1)**. The abbreviations were

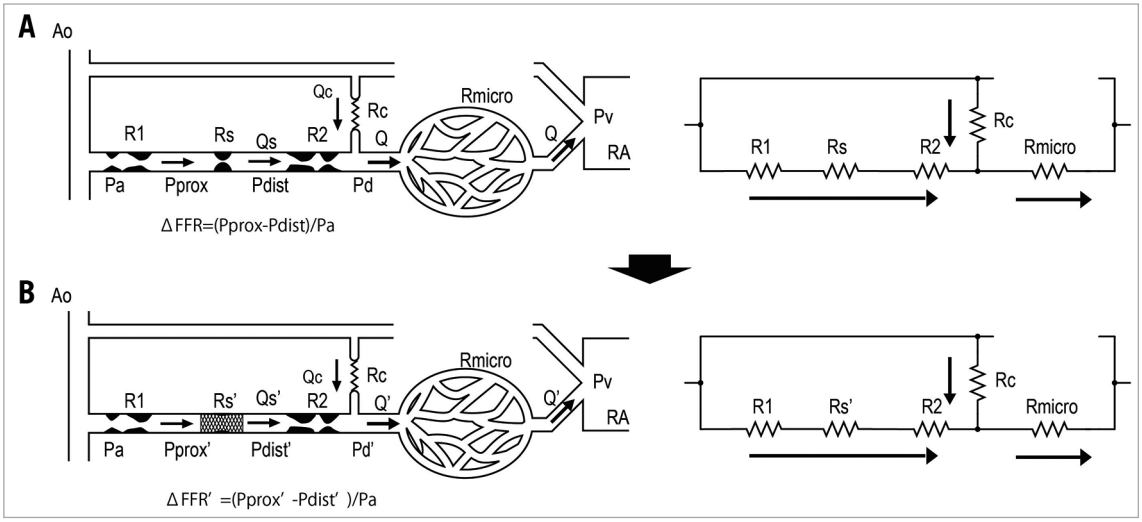

Figure 1. *Schematic model representing the coronary circulation with a sequential lesion and a collateral circulation. (A) Before coronary intervention. The resistance of the target lesion is expressed as R_s. (B) After coronary intervention. The resistance of target lesion changes to R_s'.*

defined as follows: R_s, resistance of the target coronary stenosis; R_1, summed resistance of the proximal stenoses; R_2, summed resistance of the distal stenoses; R_{micro}, hyperaemic microcirculatory resistance; R_c, resistance of the collateral circulation; P_a, aortic pressure; P_{prox}, pressure proximal to R_s; P_{dist}, pressure distal to R_s; P_d, the most distal coronary pressure; P_w, coronary wedge pressure; and P_v, central venous pressure. The pre-intervention FFR was defined as $FFR_{pre}=(P_d-P_v)/(P_a-P_v)\fallingdotseq P_d/P_a$ because P_v was usually considered to be zero while deriving the FFR indices. Pre-intervention FFR gradient across the target lesion was defined as $\Delta FFR=(P_{prox}-P_{dist})/P_a$. The parameter calculated from $(P_w-P_v)/(P_a-P_v)\fallingdotseq P_w/P_a$ was originally named "fractional flow reserve of the collateral artery (FFR_{coll})". Later, the name "pressure derived collateral flow index (CFI)" was used for this parameter[17]. Because the collateral flow reserve of the collateral artery is usually called "pressure derived CFI" in other studies, we adopted this terminology to avoid confusion. All the post-intervention parameters have been expressed by adding a prime to the pre-intervention parameters; thus, R's indicates the resistance of the target coronary lesion after PCI and $FFR_{post}=P'_d/P_a$ and $\Delta FFR'=(P'_{prox}-P'_{dist})/P_a$ are obtained. The pressure gradient across the stenosis was proportional to the flow because the flow was assumed to be the Hagen-Poiseuille flow in this model. Thus, the coronary circulation model can be considered analogous to an electric circuit. **Figure 1** also describes the electric circuit that corresponds to the coronary circulation model. Under this assumption, the FFR indices can be expressed in terms of resistance as follows:

$$CFI = \frac{R_{micro}}{R_c + R_{micro}} \quad (1)$$

$$FFR_{pre} = \frac{R_{micro}}{\left(\frac{1}{\frac{1}{R_1 + R_x + R_2} + \frac{1}{R_c}}\right) + R_{micro}} \quad (2)$$

$$\Delta FFR = (1 - FFR_{pre})\frac{R_x}{R_1 + R_x + R_2} \quad (3)$$

$$FFR_{post} = \frac{R_{micro}}{\left(\frac{1}{\frac{1}{R_1 + R'_x + R_2} + \frac{1}{R_c}}\right) + R_{micro}} \quad (4)$$

$$\Delta FFR' = (1 - FFR_{post})\frac{R'_x}{R_1 + R'_x + R_2} \quad (5)$$

By solving the above equations (1) to (5), the following Equation (B) is obtained:

$$\boldsymbol{FFR_{post} = \frac{FFR_{pre}(1 - CFI) - CFI\Delta FFR - \Delta FFR'(FFR_{pre} - CFI)}{1 - \Delta FFR - CFI}} \quad \boldsymbol{(B)}$$

The detailed process of derivations of Equation B is given in **Appendix 1**.

IN VITRO EXPERIMENT

The experimental system was similar to that described in our previous studies **(Figure 2)**. It consisted of a pump, systemic circulation, coronary circulation, and 5 constrictors placed in the coronary circulation. The pump produced a pulsatile flow at 60 rpm. 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. The circulating fluid was a 33% glycerine and 67% water a mixture comparable to the viscosity of blood. 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 constrictors made variable stenoses in the coronary artery by a screw rotation movement. The constrictor names correspond to the names of the resistances in the schematic model in **Figure 1**. FFR measurements were conducted using three 0.014 inch pressure wires (Abbott Vascular, Santa Clara, CA, USA), one placed in the proximity of R_s, another placed distally to R_s, and one placed distally to R_2.

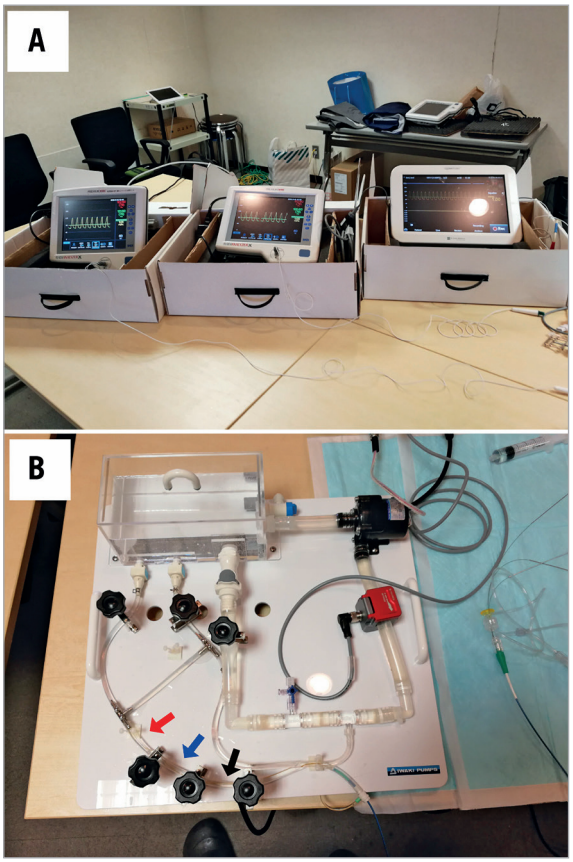

Figure 2. *In vitro experimental system. (A) The simulation system comprising a pump as well as systemic and coronary circulation. (B) Three pressure wires are placed in the coronary circulation: one placed proximally to the target stenosis (black arrow), another placed distally to the target stenosis (blue arrow), and the last one placed in the most distal point of the coronary circulation (red arrow).*

The experiment was conducted in the following sequence. Variable degrees of coronary microcirculation and collateral circulation were randomly created by the constrictors. Variable degrees of three sequential coronary stenoses were randomly generated. Then, P_a, P_{prox}, P_{dist}, and P_d were recorded by using three pressure wires, and FFR_{pre} and ΔFFR were calculated. P_w was obtained during a temporary occlusion of the distal part of the coronary artery, and pressure derived CFI was calculated. After partially releasing the stenosis of the target stenosis (R_s), P'_{prox}, P'_{dist}, and P'_d were recorded, and then FFR_{post} and ΔFFR were calculated. The apparent FFR after partially releasing the target stenosis ($FFR_{apparent}$) was defined as $FFR_{apparent}=FFR_{pre}+\Delta FFR$, and the predicted value of FFR ($FFR_{predicted}$) was calculated using Equation A. The adjusted value of FFR considering the residual pressure gradient across the target stenosis ($FFR_{adjusted}$) was calculated using Equation B. $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ were compared with FFR_{post}.

CLINICAL DATA ANALYSIS

Consecutive patients who underwent elective coronary intervention for diffuse/sequential coronary lesions in Gifu Heart Center between March 2017 and March 2018 were included in the study. The inclusion criteria required all physiological parameters including FFR_{pre}, ΔFFR, CFI, FFR_{post}, and ΔFFR' to be obtained. The data in this study consisted of 67 coronary diffuse/sequential lesions from 67 patients. As all data were retrospectively collected from the patients' records, the requirement of written informed consents was waived. The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee.

Coronary angiography and pressure wire assessments of coronary stenoses were conducted using the conventional approach. Briefly, the patients were instructed not to consume caffeine for 12 hours before the procedure, and PCI was performed through the radial approach using a 6 or 7 Fr system. Intracoronary nitrates (300 ug) were administered to all patients before pressure wires (OptoWire™; Opsens Medical, Quebec, Canada) were introduced. Equalisation was performed 1 to 2 mm distal to the guiding catheter. The distal position of the pressure wire was documented by angiography. Angioplasty was performed using second-generation drug-eluting stents, which were all optimised using imaging devices such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Maximum hyperaemia was induced by intravenous administration of adenosine. The pull-back recordings were conducted during maximum hyperaemia before and after PCI, and FFR_{pre}, ΔFFR, FFR_{post}, and ΔFFR' were obtained. Wedge pressure was recorded as the coronary pressure distal to the occluding balloon at 30s after the balloon occlusion, and pressure derived CFI was also obtained for all patients. Like in the *in vitro* experiment, $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ were calculated from FFR_{pre}, CFI, ΔFFR, and ΔFFR', and compared with FFR_{post}. It is well-known that ΔFFR' is obtained after PCI, and the coronary wedge pressure is not usually measured in real-world clinical practice. Equation B cannot be applied in clinical practice in this form. Thus, we calculated ΔFFR'/mm defined as ΔFFR' by total stent length (mm) and estimated ΔFFR' calculated as ΔFFR'/mm multiplied by the implanted stent length ($\Delta FFR'_{estimated}$). The estimated value of CFI ($CFI_{estimated}$) was obtained using the average value of CFI from this study. $FFR_{fixed\text{-}adjusted}$ was calculated by using $\Delta FFR'_{estimated}$ and $CFI_{estimated}$ in Equation B. $FFR_{fixed\text{-}adjusted}$ was compared with $FFR_{adjusted}$.

STATISTICS

$FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ were compared with FFR_{post} using linear regression analysis and the Bland-Altman plot in the *in vitro* experiment and the clinical data analysis. The absolute differences of $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ to FFR_{post} were compared using a paired t-test for the *in vitro* experiment and in the clinical data analysis. The correlation coefficient and Bland-Altman plot of $FFR_{fixed\text{-}adjusted}$ to FFR_{post} were calculated, and the absolute difference of $FFR_{fixed\text{-}adjusted}$ to FFR_{post} was compared with that of $FFR_{adjusted}$ to FFR_{post} in the clinical data analysis. All continuous variables are presented as mean±standard deviation unless otherwise stated. A two-sided p-value<0.05 was considered statistically significant in this study.

Results

IN VITRO EXPERIMENT

In the *in vitro* experiment, the procedures were repeated 50 times with changing degrees of each stenosis. Fifty different sets of pressure data were obtained in the *in vitro* experiment. FFR_{pre}, CFI, and ΔFFR were 0.60±0.08, 0.29±0.08, 0.17±0.06, respectively. After partially releasing the target stenosis, ΔFFR' and FFR_{post} were 0.05±0.02 and 0.67±0.08. $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ were 0.78±0.08, 0.71±0.10, and 0.68±0.09. The correlation coefficients of $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ were 0.94, 0.99, and 0.99 **(Figure 3)**. The absolute differences of $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ to FFR_{post} were 0.11± 0.03, 0.04±0.02, and 0.008±0.006, respectively (p<0.001, paired t-test). Equation B predicted the post-intervention FFR with a 1.3±1.0% error. The results indicated that Equation B perfectly predicted post-intervention FFR of diffuse/sequential coronary lesions when considering the residual FFR gradient in the *in vitro* experiment.

CLINICAL DATA ANALYSIS

Sixty-seven coronary diffuse/sequential lesions from 67 patients were analysed. Patients' demographics are summarised in **Table 1**. Briefly, the average age was 69.1±9.0 years old, and 48 patients (71.8%) were of male gender. Clinical presentations included 64 patients (95.5%) with stable angina and 3 patients (4.5%) with unstable angina. Non-ST segment elevation myocardial infarction (NSTEMI) and STEMI patients were not included in the study. Lesions and procedure characteristics are listed in **Table 2**. The locations of the lesions were 48 lesions (71.6%) in the left anterior descending artery (LAD), 7 lesions (10.4%) in the left circumflex artery (LCX), and 12 lesions (17.9%) in the right coronary artery (RCA). All lesions were *de novo* coronary

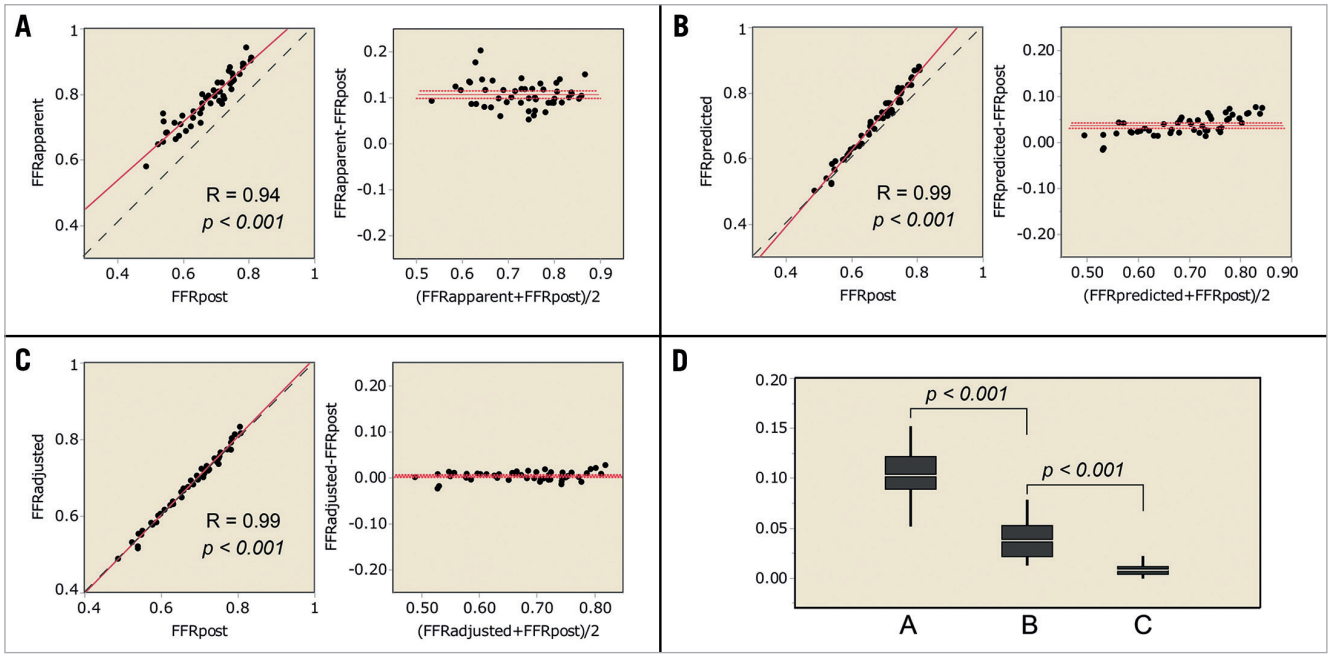

Figure 3. *Results of the in vitro experiment. (A-C) Linear regression and Bland-Altman plots. The dotted line is the line of identity. (A) $FFR_{apparent}$ compared with FFR_{post}. (B) $FFR_{predicted}$ compared with FFR_{post}. (C) $FFR_{adjusted}$ compared with FFR_{post}. D) The absolute differences to FFR_{post}. A, the absolute difference of $FFR_{apparent}$ to FFR_{post}. B, the absolute difference of $FFR_{predicted}$ to FFR_{post}. C, the absolute difference of $FFR_{adjusted}$ to FFR_{post}.*

Table 1. Baseline clinical characteristics of 67 patients.

Variables	Value
Age (years)	69.1±9.0
Male gender, n (%)	48 (71.6%)
Height (cm)	160.8±10.3
Body weight (kg)	66.2±15.1
Diabetes mellitus, n (%)	34 (51.5%)
Hypertension, n (%)	46 (70.0%)
Dyslipidaemia, n (%)	40 (61%)
Smoker, n (%)	9 (13.6%)
Haemodialysis, n (%)	5 (7.5%)
Previous myocardial infarction, n (%)	13 (19.4%)
Left ventricular ejection fraction, %	62.5±10.7
Stable angina, n (%)	64 (95.5%)
Unstable angina, n (%)	3 (4.5%)

Table 2. Procedural data in 67 sequential coronary lesions.

Variable	Value
Lesion location	
LAD	48 (71.6%)
LCX	7 (10.4%)
RCA	12 (17.9%)
Pre-FFR data	
Pre-FFR	0.68±0.11
Collateral flow index (=P_w/Pa)	0.17±0.10
ΔFFR of the target lesion	0.23±0.11
Pre-QCA data	
Lesion length, mm	23.4±9.0
Pre-reference diameter, mm	2.91±0.52
Pre-minimum lumen diameter, mm	1.30±0.35
Pre-%DS, %	54.9±12.2
Procedural data	
Implanted stent number	1.2±0.4
Total stent length, mm	29.9±13.0
Procedure time, min	92.9±31.1
Contrast volume, cc	99.9±40.6
Post-FFR data	
Post-FFR	0.81±0.07
Post-ΔFFR of the target lesion	0.04±0.03
ΔFFR/mm, mm	0.0015±0.0013
Post-QCA data	
Post-reference diameter, mm	3.15±0.45
Pre-minimum lumen diameter, mm	3.00±0.45
Post-%DS, %	5.8±9.9

lesions. Stenosis diameter of the target lesion was 54.9±12.2%, reference vessel diameter was 2.91±0.52 mm, lesion length was 23.4±9.0 mm, and the minimum lumen diameter was 1.30±0.35 mm obtained by quantitative coronary angiography (QCA). The preprocedural intravenous adenosine induced FFR (FFR_{pre}), ΔFFR of the target lesion, and CFI were 0.68±0.11, 0.17±0.10, and 0.23±0.11, respectively. All target lesions were treated by implanting a second-generation drug-eluting stent without any complications. The procedure time was 92.9±31.1 min and the contrast volume was 99.9±40.6 cm^3. The total number of implanted stents was 1.2±0.4, and the total stent

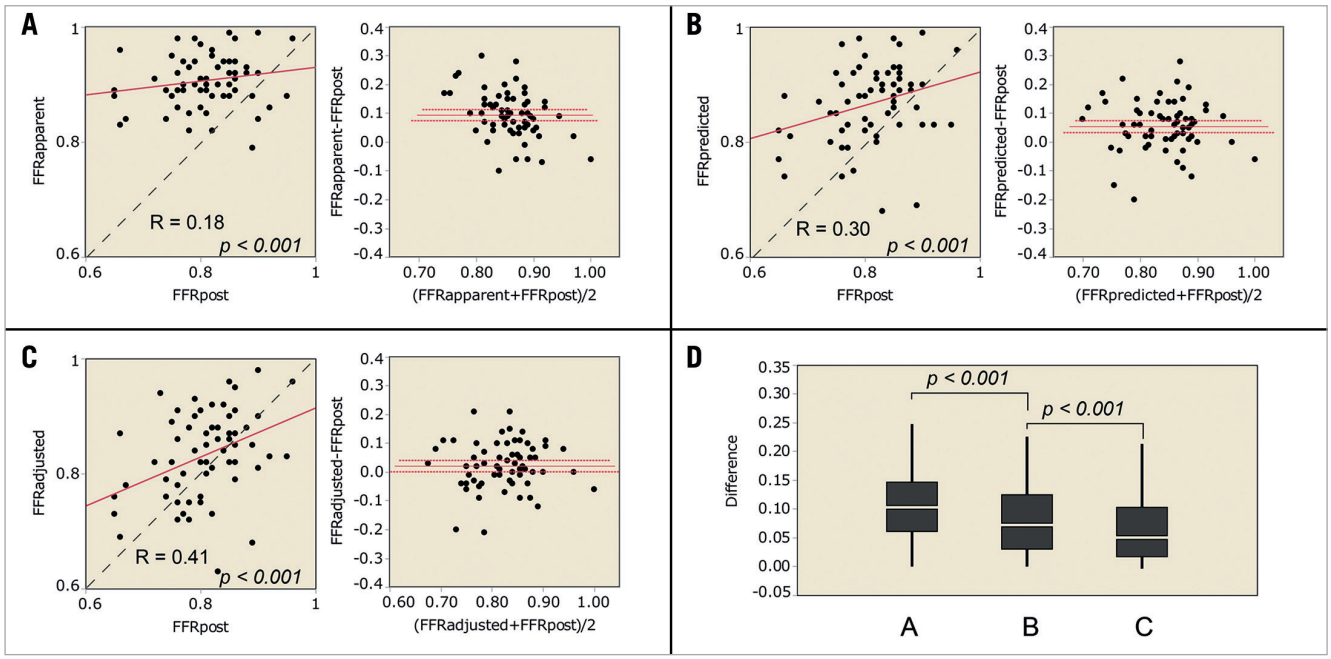

Figure 4. *Results of the clinical data analyses. (A-C) Linear regression and Bland-Altman plots. The dotted line is the line of identity. (A) $FFR_{apparent}$ compared with FFR_{post}. (B) $FFR_{predicted}$ compared with FFR_{post}. (C) $FFR_{adjusted}$ compared with FFR_{post}. D) The absolute differences to FFR_{post}. A, the absolute difference of $FFR_{apparent}$ to FFR_{post}. B, the absolute difference of $FFR_{predicted}$ to FFR_{post}. C, the absolute difference of $FFR_{adjusted}$ to FFR_{post}.*

length was 29.9±13.0 mm. In post-procedural QCA, the reference diameter was 3.15±0.45 mm, the minimum stent diameter was 3.00±0.45 mm, and the diameter stenosis was 5.8±9.9%. The postprocedural adenosine induced FFR (FFR_{post}) was 0.81±0.07, ΔFFR of the stented lesion (ΔFFR') was 0.04±0.03, ΔFFR'/mm was 0.0015±0.0013. $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ were calculated from the obtained data and were 0.91±0.05, 0.87±0.07, and 0.83±0.08, respectively. The correlation coefficients of $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ were 0.18, 0.30, and 0.41, ($p<0.001$, **Figure 4**). The absolute differences of $FFR_{apparent}$, $FFR_{predicted}$, and $FFR_{adjusted}$ to FFR_{post} were 0.11±0.06, 0.08±0.06, and 0.06±0.05, respectively ($p<0.001$, paired t-test). Equation B was used to calculate the post-intervention FFR with an 8.0±7.0% error.

When the average value of CFI of 0.17 and ΔFFR'/mm of 0.0015 were applied to Equation B, $FFR_{fixed\text{-}adjusted}$ was obtained. $FFR_{fixed\text{-}adjusted}$ was 0.83±0.07, and the correlation coefficient of $FFR_{fixed\text{-}adjusted}$ to FFR_{post} was 0.28 ($p<0.001$, **Figure 5**). The absolute difference of $FFR_{fixed\text{-}adjusted}$ to FFR_{post} was 0.06±0.06, which was not significantly different from $FFR_{adjusted}$ to FFR_{post} ($p=0.6420$, paired t-test). Equation B predicted the post-intervention FFR with an 8.0±7.2% error.

These results indicated that the accuracy of postprocedural FFR improved by taking the residual intra-stent FFR gradient into account, and the application of a fixed value of CFI and intra-stent FFR gradient did not significantly lower the accuracy of the post-procedural FFR prediction. However, the prediction error of approximately 8% is considered too large for clinical practice use.

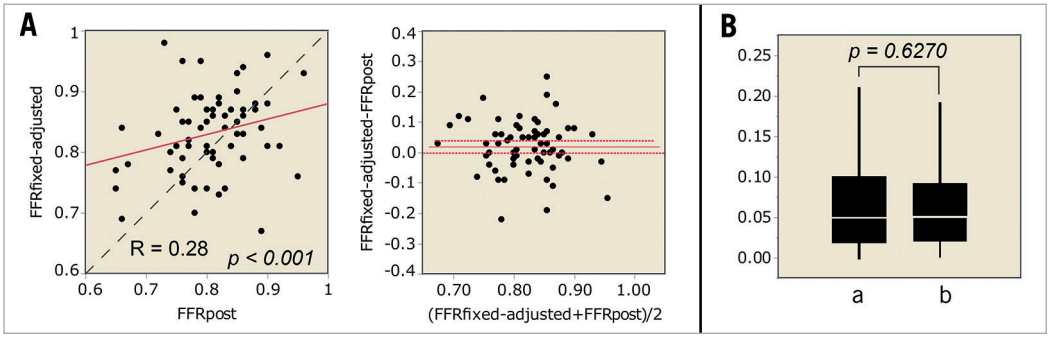

Figure 5. *Estimated FFR value using fixed value of CFI and ΔFFR in clinical data analyses. A) Linear regression and Bland-Altman plots. B) The absolute differences. a - the absolute difference of $FFR_{adjusted}$ to FFR_{post}. b - the absolute difference of $FFR_{fixed\text{-}adjusted}$ to FFR_{post}.*

Discussion

The main findings of the present study, which included the development of a novel equation which predicts the post-intervention FFR in diffuse/sequential coronary lesions, were that: the novel equation perfectly predicted post-intervention FFR of diffuse/sequential coronary lesions in the *in vitro* model of coronary circulation; in the clinical data analysis, prediction accuracy of post-intervention FFR in diffuse/sequential coronary lesions improved by taking the residual intra-stent FFR gradient into account and; the application of a fixed value of CFI and intra-stent FFR gradient did not significantly lower the accuracy of post-procedural FFR prediction. However, the prediction error in post-procedural FFR is considered too large to be used in clinical practice.

Previous studies have shown that PCI for stable angina is only beneficial in patients with significant myocardial ischaemia[18,19]. Although FFR has been regarded as the gold standard index for the invasive assessment of the physiological severity of coronary stenosis, the worldwide use of FFR remains low at around 5-10% of all PCIs[20]. The reasons for the low utilisation of FFR include the need for administration of hyperaemic agents, which is time consuming and may cause unpleasant complications[3,4]. Recently, resting indices including iFR have been developed to assess the functional severity of coronary stenosis. iFR is calculated by dividing the distal coronary pressure by the aortic pressure during the wave-free period under resting conditions. During the wave-free period, resistance in the cardiac cycle is considered to be minimal and constant. Following the results of two large randomised trials[3,4], the current European guideline has updated iFR-guided revascularisation for stable angina to class I [21]. With the success of iFR, other resting indices, including the resting full-cycle ratio (RFR) and the diastolic pressure ratio (dPR) have been introduced[21,22]. The main advantage of these resting indices over FFR is that they do not require the induction of hyperaemia, thus hyperaemia-related complications are avoidable. Another advantage is that post-intervention indices are predictable because resting coronary flow is maintained constant due to autoregulation of the coronary circulation. Kikuta et al described that iFR pullback predicted the physiological outcome of PCI with a high degree of accuracy[6,7].

On the other hand, predicting post-intervention FFR is considered difficult in diffuse/sequential coronary stenoses because complicated haemodynamic interactions exist between individual coronary stenoses. De Bruyne et al described theoretical equations to predict the FFR of each stenosis in a tandem lesion[8], but its application was limited to tandem lesions. Thus we developed an equation which can be used in a diffuse/sequential coronary lesion (Equation A)[9]. However, the calculation requires coronary wedge pressure measurements, which makes the application of the equation in clinical practice difficult. Therefore, when using FFR to evaluate a sequential or diffuse coronary lesion, the pullback curve of the pressure wire under maximum hyperaemia is used to detect the target lesion with the largest ΔFFR. After stenting the target lesion, a repeat measurement of pullback recordings of FFR is conducted[10-12]. The concept of this strategy was named "the rule of big delta" by Park et al[11].

We consider that the existence of an intra-stent pressure gradient after intervention makes the prediction even more difficult[13-16]. In the present study, we developed an equation which predicts the post-intervention FFR in the diffuse/sequential coronary lesion by considering the residual intra-stent FFR gradient (Equation B). Equation B predicted the post-intervention FFR with a 1.3±1.0% error in the *in vitro* experiment. The study results indicate that the equation was almost perfect for predicting the post-intervention FFR in *in vitro* coronary circulation. However, the prediction error was 8.0±7.2% in the clinical data analysis, which was considered too large to be used in clinical practice. The results indicate that physicians need to conduct multiple pullback recordings of FFR in the treatment of a diffuse/sequential lesion based on "the rule of big delta".

Several reasons are proposed for the large prediction error which was observed in the clinical data analysis while the error was minimal in the *in vitro* study. First, keeping a steady state of maximal hyperaemia is mandatory during a pressure wire pullback for the assessment of diffuse/serial coronary lesions, while the FFR value is usually fluctuating during continuous infusion of intravenous adenosine[23,24]. Thus, the FFR pullback curve is inevitably affected by the fluctuation of maximal hyperaemia, which causes a considerable error in predicting the post-intervention FFR in a diffuse/sequential coronary lesion. Second, the pressure wire was visually co-registered with angiography in this analysis. The operators were required to observe the pressure wire pullback curve and angiographic information at the same time and visually co-register the two pieces of information, which could represent the cause of prediction error. Third, Equation B includes 4 independent variables. All these variables are influenced by many factors *in vivo*, including the nervous system, the cardiovascular humoral factor, and stimuli during the procedure. Even small errors of each variable eventually become large errors in Equation B. In post-intervention iFR prediction, the equation includes only two variables, which is considered the great advantage of iFR.

Limitations

Several limitations exist in the present study. First, the *in vitro* coronary circulation model differed from the complex human coronary circulation in many ways. The model had no side branches between stenoses, and a single large collateral artery connected the donor and recipient arteries. Coronary arteries are not uniformly smooth like silicone tubes. These differences limit the direct applicability of an *in vitro* model to real world coronary physiology. Second, the clinical data analysis was retrospectively conducted; therefore the accuracy of data acquisition might be inferior to a prospective study. Third, the sample size of the present study was relatively small for both *in vitro* and clinical data sets. Fourth, coronary wedge pressure measurements were conducted during balloon dilatation without the continuous infusion of adenosine. Several studies reported that maximal hyperaemia can be induced

by balloon occlusion of the coronary artery[17,25], but the coronary occlusive hyperaemia might make a small difference that could affect the prediction of post-intervention FFR in diffuse/sequential coronary stenosis.

Conclusions

Prediction of post-intervention FFR in a diffuse/sequential lesion is only possible in an *in vitro* model of coronary circulation. In clinical practice, prediction is difficult due to considerable errors even when the residual intra-stent pressure gradient is considered. Physicians need to conduct multiple pullback recordings of FFR in the treatment of a diffuse/sequential lesion if they prefer to use FFR over resting indices.

Impact on daily practice

Prediction of post-intervention fractional flow reserve (FFR) in a diffuse/sequential lesion is only possible in an *in vitro* model. In clinical practice, prediction is difficult due to considerable errors even when residual intra-stent pressure gradient is considered. Physicians need to conduct multiple pullback recordings of FFR in the treatment of a diffuse/sequential lesion to obtain post-intervention FFR.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Derivation of equations A and B.

The supplementary data are published online at: www.asiaintervention.org

Supplementary data

Supplementary Appendix 1. Derivation of equations A and B.

In this appendix, the derivations of equations (A) and (B) are presented. Consider a coronary circulation model that has sequential coronary stenosis (**Figure 1** in the main text). All of the terminology is the same as that in the main text. When P_v is considered 0, the following equations are obtained: $FFR_{pre} = P_d/P_a$, $FFR_{post} = P'_d/P_a$, $CFI = P_w/P_a$, $\Delta FFR = (P_{prox} - P_{dist})/P_a$, and $\Delta FFR' = (P'_{prox} - P'_{dist})/P_a$. All calculations are made under the assumption that the pressure drop across a stenosis is proportional to the flow. Under this assumption, the electric circuit can be considered an analogue of the fluid circulation and the pressure ratio can be expressed in terms of resistance. Note that the inverse of the equivalent resistance of two or more resistors connected in parallel is the algebraic sum of the inverses of the individual resistances. The following equations are obtained:

$$\mathrm{CFI} = \frac{R_{micro}}{R_c + R_{micro}} \quad (1)$$

$$FFR_{pre} = \frac{R_{micro}}{\left(\frac{1}{\frac{1}{R_1 + R_x + R_2} + \frac{1}{R_c}}\right) + R_{micro}} \quad (2)$$

$$\Delta\mathrm{FFR} = (1 - \mathrm{FFR}_{pre})\frac{R_x}{R_1 + R_x + R_2} \quad (3)$$

$$FFR_{post} = \frac{R_{micro}}{\left(\frac{1}{\frac{1}{R_1 + R'_x + R_2} + \frac{1}{R_c}}\right) + R_{micro}} \quad (4)$$

$$\Delta\mathrm{FFR}' = (1 - \mathrm{FFR}_{post})\frac{R'_x}{R_1 + R'_x + R_2} \quad (5)$$

By solving the above equations (1) to (4), R_{micro}, R_c, R_x and R'_x are presented using CFI, FFR_{pre}, ΔFFR, $\Delta FFR'$, R_1 and R_2:

$$R_{micro} = \frac{(R_1 + R_2)\left(FFR_{pre} - CFI\right)}{(1 - CFI)\left(1 - (FFR_{pre} + \Delta FFR)\right)} \quad (6)$$

$$R_x = \frac{(R_1 + R_2)\Delta FFR}{\left(1 - (FFR_{pre} + \Delta FFR)\right)} \quad (7)$$

$$R_c = \frac{(R_1 + R_2)\left(FFR_{pre} - CFI\right)}{CFI\left(1 - (FFR_{pre} + \Delta FFR)\right)} \quad (8)$$

$$R'_x = \frac{(R_1 + R_2)\Delta FFR'}{\left(1 - (FFR_{post} + \Delta FFR')\right)} \quad (9)$$

By substituting equations (6) to (9) into equation (5), the following equation (B) is obtained:

$$FFR_{post} = \frac{FFR_{pre}(1 - CFI) - CFI\Delta FFR - \Delta FFR'(FFR_{pre} - CFI)}{1 - \Delta FFR - CFI} \quad (B)$$

Equation B calculates the post-intervention FFR with residual pressure gradient across the stent. When there is no residual pressure gradients across the stent, ΔFFR' equals to 0, then the following equation (A) is obtained:

$$FFR_{post} = \frac{FFR_{pre}(1 - CFI) - CFI\Delta FFR}{1 - \Delta FFR - CFI} \quad (A)$$

Equation A calculates the post-intervention FFR when no residual intra-stent pressure gradients are existed.