VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 4, 310–321
DOI: 10.5603/CJ.a2019.0067
Copyright © 2019 Via Medica
ISSN 1897–5593

A simplified formula to calculate fractional flow reserve in sequential lesions circumventing the measurement of coronary wedge pressure: The APIS-S pilot study

Juan Luis Gutiérrez-Chico[1, 2, 3], Carlos Cortés[1, 4], Miłosz Jaguszewski[1, 2, 5], Michele Schincariol[2], Ignacio J. Amat-Santos[4], Juan A. Franco-Peláez[6], Grzegorz Żuk[5], Dariusz Ciećwierz[5], Wojciech Wojakowski[7], Felipe Navarro[6, 8], Shengxian Tu[9], Borja Ibáñez[6, 8, 10]

[1]Klinikum Frankfurt (Oder), Interventional Cardiology, Germany
[2]Institute of Cardiovascular Translational Research of Atlantic (ICTRA), Berlin, Germany
[3]DRK-Klinikum Westend, Berlin, Germany
[4]CIBERCV Hospital Clínico Universitario de Valladolid, ICICOR, Spain
[5]First Department of Cardiology, Medical University of Gdansk, Poland
[6]IIS-Fundación Jiménez Díaz University Hospital, Madrid, Spain
[7]University of Katowice, Poland
[8]CIBERCV, Madrid, Spain
[9]Biomedical Instrument Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China
[10]Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain

This paper was guest edited by Prof. Bon-Kwon Koo

Abstract

Background: *A simplified formula to calculate the predicted fractional flow reserve (FFR) in sequential coronary stenosis without balloon inflation is hereby proposed.*

Methods: *In patients with an indication for FFR and sequential coronary stenosis, FFR was recorded distally and between the lesions. The predicted FFR for each stenosis was calculated with a novel formula. While treating one of the lesions, wedge pressure was measured during balloon inflation to calculate Pijls' formula. FFR of the remaining lesion was finally recorded (measured FFR).*

Results: *Forty patients were enrolled in the study, 4 (10.0%) had a distal FFR > 0.80 and were excluded from the main analysis. In the remaining 36 patients, the novel formula and Pijls' formula showed virtually absolute agreement (ICCa 0.999, R^2 = 0.997 for the proximal lesion, R^2 = 0.999 for the distal lesion, kappa 1.000, Se 100%, Sp 100%). The agreement between predicted and measured FFR was good (ICCa 0.820; 0.640–0.909, R^2 = 0.717, intercept = 0.05, slope = 0.92, kappa 0.748, Se 75%, Sp 96%). In 19 (47.5%) cases the use of the formula enabled the operator to freely decide which lesion should be treated first, an option not available if the percutaneous coronary intervention (PCI) were guided by the largest pressure drop across each lesion.*

Conclusions: *The predicted FFR for each lesion in sequential coronary stenosis can be accurately calculated by a simplified formula circumventing the need for balloon inflation. This approach provides the operator upfront, with detailed information on physiology, thus having a potentially high impact on the corresponding PCI strategy.* (Cardiol J 2019; 26, 4: 310–321)

Key words: fractional flow reserve, myocardial, coronary stenosis, coronary circulation, percutaneous coronary intervention

Editorial p. 307

Address for correspondence: Prof. Juan Luis Gutiérrez-Chico, MD, PhD, FESC, FACC, DRK-Klinikum Westend, Spandauer Damm 130, 14050 – Berlin, Germany, tel: +49 (0) 176 30585019, +34 615 319370, e-mail: juanluis.gutierrezchico@ictra.es

Received: 18.11.2018 Accepted: 24.06.2019

Introduction

Fractional flow reverse (FFR) is the most extensively validated test of intracoronary physiology to assess the hemodynamic relevance of coronary stenosis in patients with stable coronary artery disease (CAD) [1]. The utility and safety of FFR--guided percutaneous coronary intervention (PCI) have been proved in several large randomized trials and different clinical scenarios [2–4]. The cut-off-value of ≤ 0.80 is currently recommended to guide PCI of coronary lesions [5].

Sequential coronary stenosis is a common finding [6] and the objective assessment of their individual severity is challenging for both the coronary angiogram and FFR, because the fluid dynamic interaction between stenosis alters their relative severity and obscures the determination of FFR for each stenosis separately [7]. De Bruyne and Pijls [7, 8] developed a formula for sequential coronary stenosis which is able to predict the FFR corresponding to each lesion. Nonetheless this method requires the measurement of coronary wedge pressure (Pw), which is available only after balloon inflation during PCI [7, 8]. This limitation together with the relative complexity of the calculation has prevented wide adoption of Pijls' formula [9]. Simpler alternatives have been proposed, like guiding the decision of treatment according to the delta of pressured drop measured in a pullback along each lesion (ΔP) [10], however this simplification reduces accurate quantitative physiologic assessment to a mere qualitative comparison (most severe lesion of the tandem), thus neglecting a considerable amount of information recorded during the study.

Gutiérrez-Chico et al. have recently proposed a simplified formula to calculate FFR in sequential lesions circumventing the measurement of Pw [11], based on the mathematical relations between the corrected FFR as function of Pw in Pijls' formula: this is a J-shaped function, with minimal curvature, in which the straight part of the J corresponds to the physiologic range of Pw, i.e. below 30 mmHg (Fig. 1). Therefore, the change in FFR calculation for both the proximal and distal stenosis is negligible within the whole Pw range that can be found in clinical practice. Gutiérrez-Chico et al. proposed using Pijls' formula with a standard central Pw value of 12 mmHg [11], thus obviating the need for balloon inflation to measure Pw (Fig. 2). The APIS-S pilot study (**A**ssessment of **P**hysiology **I**n **S**equential **S**tenosis) aims at validating the novel formula vs. the standard Pijls' formula.

Methods

Study design

This is a prospective, observational, multicentre study aimed at appraising agreement between the novel simplified formula and Pijls' formula, taken the latter as reference and at the physiologic validation of the novel formula, comparing the predicted FFR of the untreated lesion vs. the measured FFR after PCI of one lesion.

Study population

Patients from six different centres in Germany, Poland and Spain, meeting the following inclusion criteria were enrolled in the study: 1) two sequential lesions with ≥ 50% diameter stenosis by visual estimation in the same or in adjacent vessels, with a reference vessel diameter (RVD) ≥ 2.25 mm and separated by an apparently normal segment ≥ 10 mm, 2) a clinical indication for FFR, and 3) a distal FFR measurement ≤ 0.80 beyond both lesions. Main exclusion criteria were: 1) proximal lesion in the left main, with an overall SYNTAX score ≥ 33; 2) contraindication for intravenous adenosine; 3) contraindication for dual antiplatelet therapy; 4) indication for conservative/surgical treatment; 5) hemodynamic or electrical instability.

The study was conducted according to the Declaration of Helsinki and to the principles and standards of good clinical practice. The protocol was approved by the local Ethics Committee in each center and all patients signed specific informed consent for their participation.

Study protocol

Coronary angiography was obtained through femoral, radial or cubital approaches, preferably with a ≥ 6 French catheter. After administration of heparin (70–100 UI/kg), the guiding catheter was engaged into the ostium of the target vessel. The pressure line monitored through the guiding catheter was zeroed and intracoronary nitroglycerin was administered. The pressure wire was zeroed within the wire sheath and then advanced until the pressure transducer (located in the transition between the radiopaque and radiolucent segments of the wire) reached the tip of the guiding catheter. The introducer needle of the guidewire was then removed, saline was flushed into the guiding catheter and both pressure recordings were equalized. Then the pressure transducer was advanced distally to both lesions and basal Pd/Pa distal was recorded. A continuous intravenous infusion of 140 μg/kg/min adenosine was started and maintained

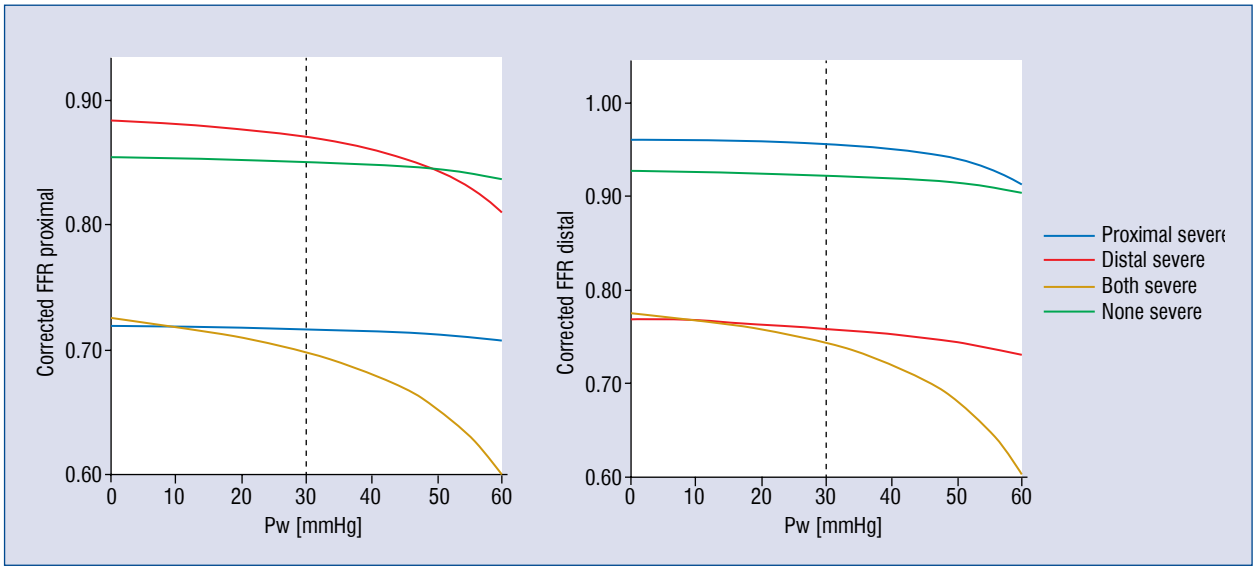

Figure 1. J-shape of Pijls' formula to calculate fractional flow reserve (FFR) in sequential lesions as a function of coronary wedge pressure (Pw). Corrected FFR for the proximal (left) and distal (right) lesions as a function of Pw. The function has been represented in four different combinations of Pa/Pd measured distally and between the lesions: 1) Pa/Pd combination in which only the proximal lesion is severe (blue), 2) in which only the distal lesion is severe (red); 3) both lesions are severe (beige) and 4) no lesion is severe (green). The change in FFR estimation is minimal within the whole physiologic range of Pw (< 30 mmHg).

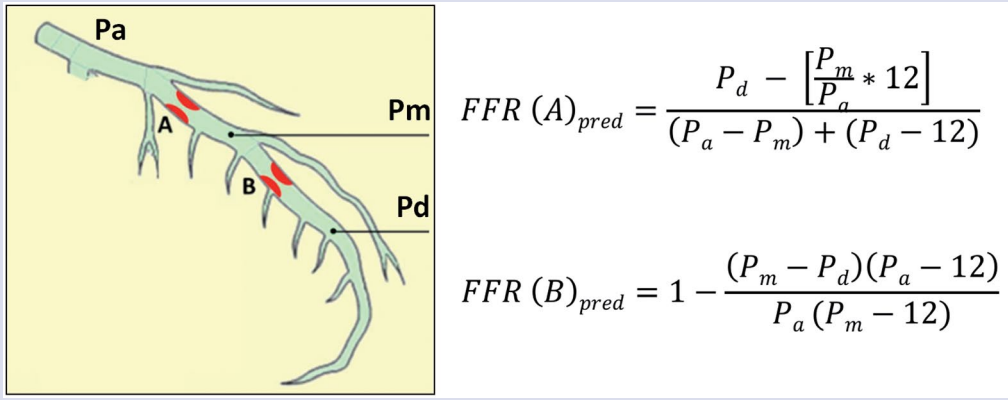

Figure 2. Simplified formula to calculate the predicted fractional flow reserve (FFR) for each lesion in sequential coronary stenosis. FFR $(A)_{pred}$ — predicted fractional flow reserve for the proximal lesion (A); FFR $(B)_{pred}$ — predicted fractional flow reserve for the distal lesion (B); P_a — pressure in the aorta; P_d — pressure distal to both lesions; P_m — pressure between lesions.

until maximal stable hyperaemia was reached. Then distal FFR was recorded distally to both lesions (d), registering the corresponding Pa(d) and Pd(d) values. Then the pressure transducer was pulled back to the segment between both lesions (m), and a second FFR measurement was recorded, registering the corresponding Pa(m) and Pd(m) values. Finally, the transducer was pulled back to the tip of the guiding catheter to check whether the pressures remain equalised proximal to the stenosis. A pressure drift of ± 3 mmHg was considered acceptable and adenosine could hence be stopped; otherwise the measurements should be repeated from the beginning.

Pd and Pa obtained distally (d) and between the lesions (m) were entered in the online calculator implemented for the study (https://journals.viamedica.pl/cardiology_journal/pages/view/calc) to calculate the predicted FFR corresponding to each lesion according to the novel formula (Figs. 2, 3).

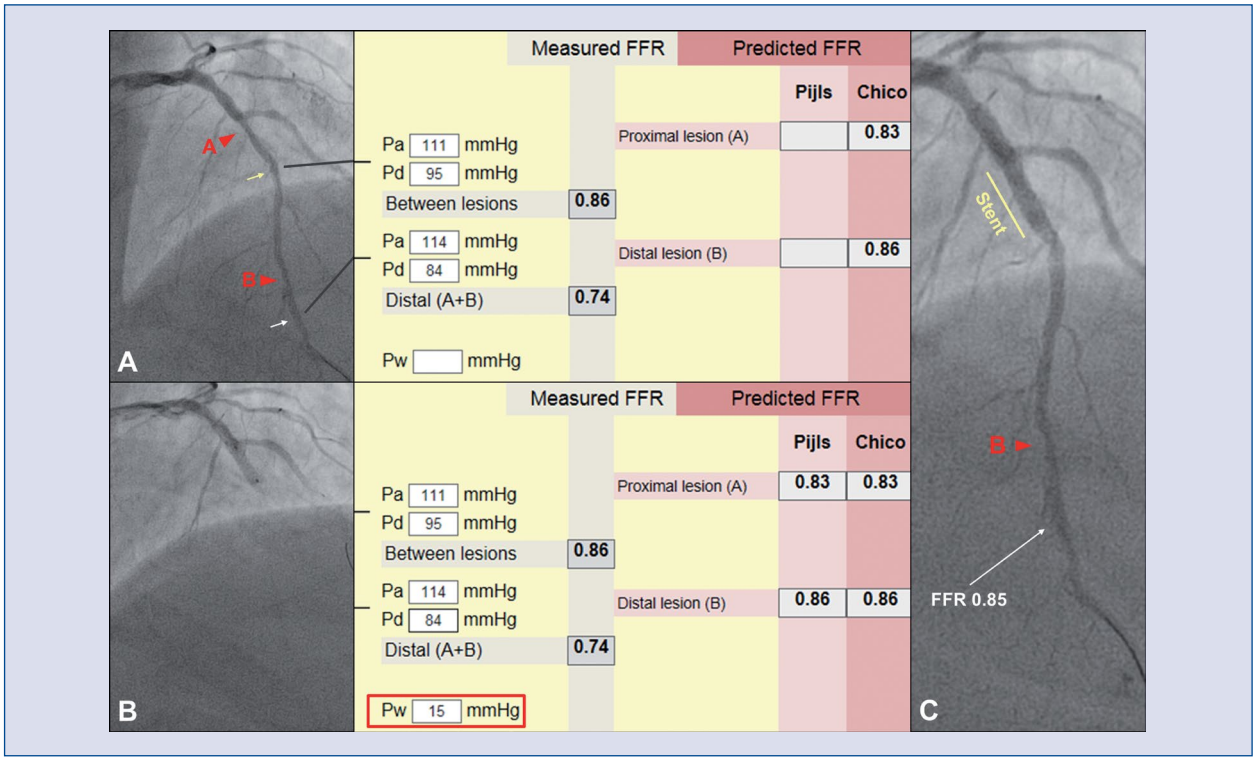

Figure 3. Interface of the online calculator implemented for the study: example of calculation; **A.** Sequential lesions in the mid left anterior descending (LAD) (red arrowhead A) and in the distal LAD (red arrowhead B). Under maximal vasodilation with adenosine, the pressure wire measured Pa = 114 mmHg and Pd = 84 mmHg, distally to both lesions (white arrow), corresponding to a measured fractional flow reserve (FFR) = 0.74. After pulling the transducer back to a position between the lesions A and B (yellow arrow), the measurements were Pa = 111 mmHg and Pd = 95 mmHg, corresponding to a measured FFR = 0.86 between the lesions. At this point Gutiérrez-Chico's novel formula estimated the predicted FFR for each lesion, without need of the coronary wedge pressure (Pw). Since the lesion in the mid LAD had the most significant FFR (0.83), this lesion was stented (**B**). During balloon inflation, Pw was obtained (Pw = 15 mmHg) and the predicted FFR values for each lesion after Pijls' formula are automatically displayed by the calculator. Notice the perfect agreement between both formulas. After optimal stent deployment in the mid LAD (**C**), FFR was measured distally to lesion B (white arrow), resulting in an FFR = 0.85, this is very similar to the values predicted by both Pijls' and Chico's formulas (0.86); Pa — pressure in the aorta; Pd — distal pressure measured at the transducer of the wire distally [https://journals.viamedica.pl/cardiology_journal/pages/view/calc].

Pa and Pd values in the formula corresponded to the values registered distally to both lesions: Pa(d) and Pd(d), respectively. In order to adjust for small fluctuations in aortic pressure, the calculator estimated Pm = Pd(m) × Pa(d) / Pa(m).

Therapeutic decision tree and PCI protocol

If FFR measured distally to both lesions > 0.80, then no stenosis was treated and the patient was excluded from the head-to-head comparison (Fig. 4). Conversely, if the FFR measured distally to both lesions ≤ 0.80, at least one lesion had to be treated depending on the FFR predicted by the novel formula for each lesion, namely:

1. If both lesions had a predicted FFR > 0.80, but the combination of both was distally ≤ 0.80, one lesion had to be treated. The decision about which lesion to treat was left at the operator's discretion. As a general rule, it was recommended to treat the lesion with the lowest predicted FFR, but operational factors, the technical feasibility or the anatomic complexity could also be considered by the operator to change the decision about which lesion to treat;
2. If only one lesion had a predicted FFR ≤ 0.80, then only that lesion had to be treated;
3. If both lesions had a predicted FFR ≤ 0.80, then both lesions had to be treated. The operator could decide which lesion to treat first based on operational factors (Fig. 4).

During the treatment of the first lesion, Pw was measured as the distal pressure registered by

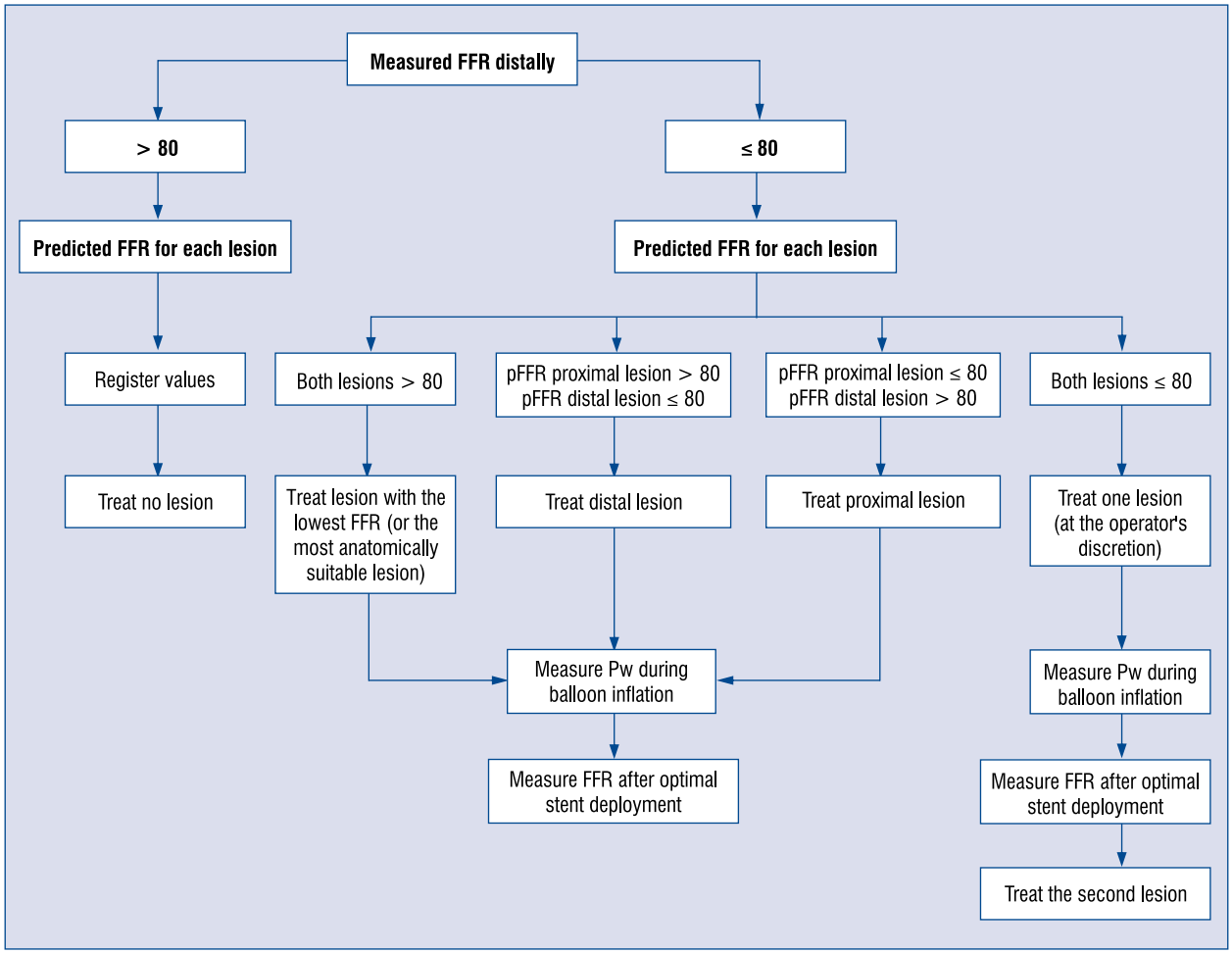

Figure 4. Flow chart for data acquisition in the APIS-S study: fractional flow reserve (FFR)-based decision tree; pFFR — predicted FFR; Pw — coronary wedge pressure.

the pressure wire whilst the balloon was inflated. PCI optimization was left at the operator's discretion and was based on angiographic standards. Once an optimal angiographic result had been achieved, a final FFR measurement was recorded, as previously described, placing the transducer at the same position as with the initial recording.

Statistical analysis

Continuous variables following a Gaussian distribution were reported as mean ± standard deviation, whilst they were reported as median (Q1–Q3) whenever a normal distribution could not be assumed. Nominal variables were reported as count (percent). The FFR predicted by the novel formula and by Pijls' formula for each lesion were contrasted, considering the latter as a gold standard, by means of linear regression, Bland-Altman analysis and intraclass correlation coefficient for the absolute agreement (ICCa). The predicted FFR values were categorised as severe (≤ 0.80) or non-severe (> 0.80) and the agreement between the novel formula and Pijls' formula was assessed as kappa coefficient, calculating the sensitivity (Se) and specificity (Sp) of the former by the corresponding cross-tabulation. The same methodology was used to assess the agreement between the predicted FFR by both formulas and the measured FFR after treatment of the first lesion.

In order to estimate the impact of using the formula on PCI strategy, as compared with the common practice of using the largest pressure drop across each lesion (ΔP), the following categories were defined for each method: 1) no PCI (if FFR measured distally > 0.80), 2) PCI of 1 lesion, 3) PCI of both lesions. The agreement between both methods was assessed by means of weighted kappa, taking into account that the ΔP cannot predict a priori the need of intervening for both lesions. Likewise, the agreement between both approaches in choosing which lesion to treat first was tested with weighted kappa, after categorising the

Table 1. Descriptive statistics of patients, intervention and lesions.

Patient level	N = 40
Male	31 (77.5%)
Age [years]	67.1 ± 9.8
BMI	28.7 ± 4.4
CV risk factors:	
Hypertension	34 (85.0%)
Hypercholesterolemia	23 (57.5%)
Diabetes mellitus:	
Type 2 on OAD	9 (22.5%)
Type 2 insulin-requiring	3 (7.5%)
Smoking:	
Previous smoker	10 (25.0%)
Current smoker	6 (15.0%)
Family history of CHD	4 (10.0%)
Previous MI	16 (40.0%)
Previous revascularization:	
PCI	21 (52.5%)
CABG	1 (2.5%)
GFR (Cockroft-Gault) [mL/min]	78.4 ± 30.9
Serum hemoglobin [g/dL]	13.0 ± 1.4
LVEF [%]	63 ± 6
Procedural variables	
SYNTAX score	13.6 ± 7.2
Contrast volume [mL]	179 ± 79
Fluoroscopy time [min]	18.1 ± 9.7
Proximal lesion	
Prox RCA	5 (12.5%)
Mid RCA	3 (7.5%)
Distal RCA	1 (2.5%)
Left main	3 (7.5%)
Prox LAD	16 (40.0%)
Mid LAD	7 (17.5%)
Prox LCx	5 (12.5%)
Calcification:	
None to little	36 (90.0%)
Moderate to severe	4 (10.0%)
Diameter stenosis [%]	62.4 ± 12.7
Distal lesion	
Mid RCA	4 (10.0%)
Distal RCA	3 (7.5%)
Right PDA	1 (2.5%)
Right PAV	1 (2.5%)
Prox LAD	1 (2.5%)
Mid LAD	14 (35.0%)
Dist LAD	11 (27.5%)
Dist LCx	2 (5.0%)
Obtuse marginal	3 (7.5%)
Calcification:	
None to little	37 (92.5%)
Moderate to severe	3 (7.5%)
Diameter stenosis [%]	64.4 ± 13.3
FFR	
FFR measured between lesions	0.85 ± 0.05
FFR measured distally	0.73 ± 0.07
Pw [mmHg]:	
Average	14 ± 6
Range	1–26
First lesion treated:	
Proximal	22 (55.0%)
Distal	14 (35%)
No lesion treated	4 (10.0%)
Both lesions treated	6 (15.0%)
FFR after treatment of first lesion	0.86 ± 0.07

Data presented as counts (percent) or as mean ± standard deviation. BMI — body mass index; CABG — coronary artery bypass graft; CHD — coronary heart disease; CV — cardiovascular; FFR — fractional flow reserve; GFR — glomerular filtration rate; LAD — left anterior descending; LCx — left circumflex; LVEF — left ventricular ejection fraction; MI — myocardial infarction; OAD — oral antidiabetics; PAV — posteroatrioventricular; PDA — posterior descending artery; PCI — percutaneous coronary intervention; Pw — coronary wedge pressure; RCA — right coronary artery

decision in: 1) proximal first, 2) operator's choice (FFR ≤ 0.80 measured distally to both lesions and predicted FFR by the formula were either > 0.80 for both lesions or ≤ 0.80 for both lesions), 3) distal first. All statistical analyses were performed using the IBM SPSS 20.0 (IBM Corp, Armonk, NY, USA) software package.

Results

Between July 2016 and January 2018 forty patients with sequential coronary lesions were included in the study in six participating centres. Table 1 summarises the clinical characteristics of the patients and anatomical description of the lesions. The average SYNTAX score was relatively low (13.6) and left anterior descending was the most frequent location for the studied lesions (57.5% of the proximal lesions, 65.0% of the distal lesions), although all main vessels were represented. In 4 (10.0%) patients FFR measured distally to both lesions was > 0.80, so they were excluded from the main analysis of the study, but

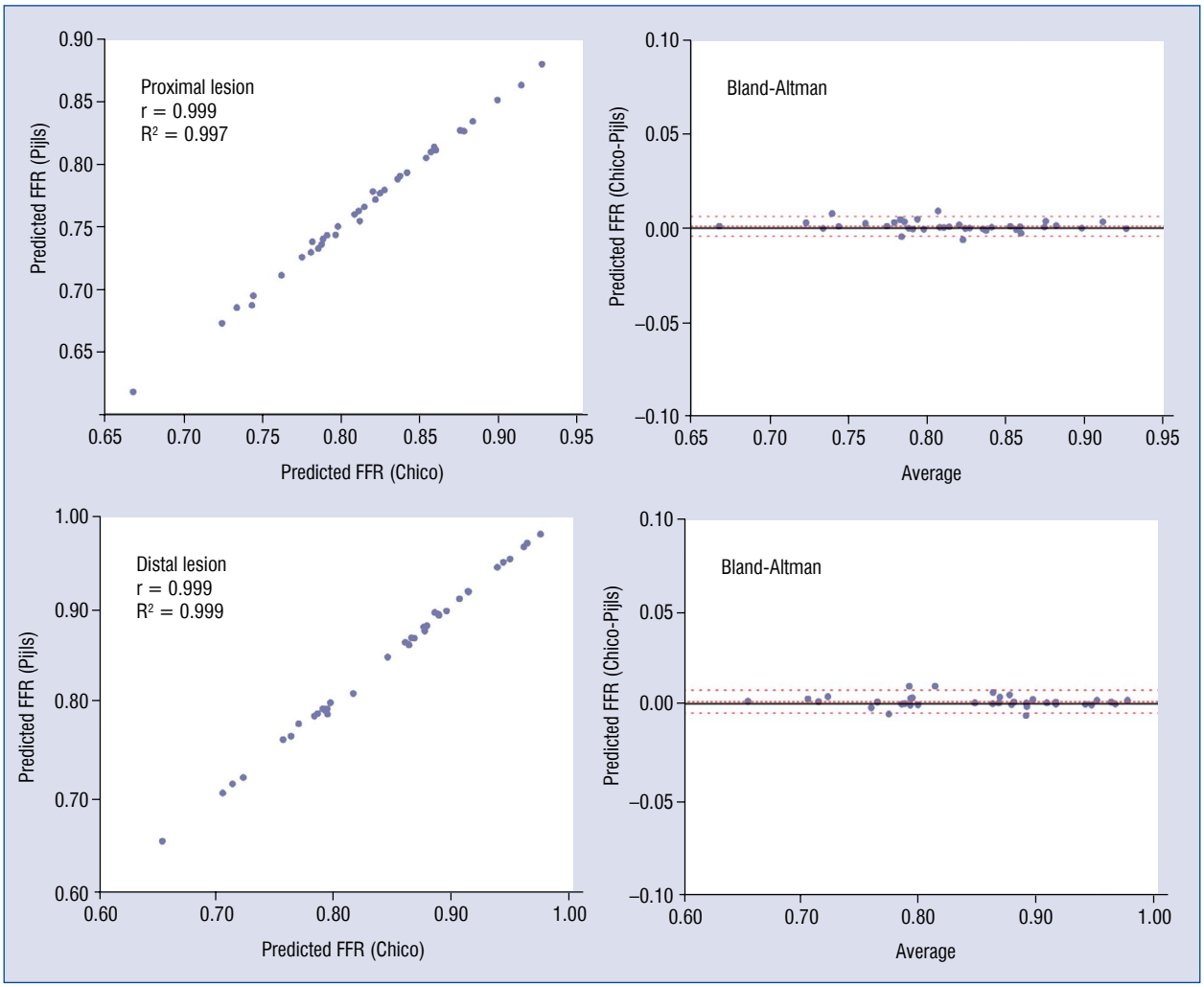

Figure 5. Agreement between Gutiérrez-Chico's novel formula and Pijls' formula; **Upper panels:** Agreement for the proximal lesion; **Lower panels:** Agreement for the distal lesion. Linear regression (left) with Pijls' formula as reference; Bland-Altman analysis (right); FFR — fractional flow reserve.

their data were registered for analysis of impact on the strategy. In 30 (75.0%) patients only one lesion was hemodynamically significant, whilst in the remaining 6 (15.0%) cases both lesions were found to be significant according to the predicted FFR. The average Pw was 14 mmHg, ranging from a minimum of 1 mmHg to a maximum of 26 mmHg.

Agreement between the novel formula and Pijls' formula was excellent: ICCa 0.999 for the predicted FFR of both the proximal and distal lesions (Fig. 5, Table 2). The predicted FFR calculated by the novel formula had a perfect linear relation with predicted FFR calculated by Pijls' formula ($r = 0.999$, Fig. 5) and the latter could accurately be predicted by the former in a model of linear regression ($R^2 = 0.997$ for the proximal lesion, $R^2 = 0.999$ for the distal lesion). The agreement between both formulas for the categorization as hemodynamically relevant (predicted FFR ≤ 0.80) vs. non-relevant (predicted FFR > 0.80) was perfect for both the proximal and the distal lesions (kappa 1.000, Se 100%, Sp 100%).

The agreement between FFR predicted by the novel formula and the FFR measured after PCI of the first lesion was good: ICCa 0.820 (0.640–0.909), $R^2 = 0.717$, intercept 0.05 (statistically non-significant), slope 0.92. For the categorization as hemodynamically relevant vs. non-relevant the agreement between predicted and measured FFR was also good (kappa 0.748). The formula resulted in one false positive (2.5%) and two false negatives (5.0%), corresponding to a Se of 75%, Sp of 96%, positive predictive value 86%, negative predictive value 93%. This level of agreement was almost identical to the one showed by the FFR predicted by Pijls' formula (Fig. 6, Table 3).

Table 2. Agreement between Pijls' formula and Gutiérrez-Chico's simplified formula.

	Pijls' formula	Chico's formula	r	R^2	P	ICCa
Predicted FFR for proximal lesion	0.82 ± 0.06	0.82 ± 0.06	0.999	0.997	< 0.0001	0.999 (0.997–0.999)
Predicted FFR for distal lesion	0.85 ± 0.08	0.85 ± 0.08	0.999	0.999	< 0.0001	0.999 (0.998–1.000)
	Pijls' formula	**Chico's formula**	**Kappa**	**P**	**Se (%)**	**Sp (%)**
Proximal lesion:						
Severe	15	15	1.000	< 0.0001	100	100
Non-severe	21	21				
Distal lesion:						
Severe	14	14	1.000	< 0.0001	100	100
Non-severe	22	22				

Data presented as counts, percent, median ± standard deviation or as coefficient (95% confidence interval). ICCa — intraclass correlation coefficient for the absolute agreement; FFR — fractional flow reserve; Se — sensitivity; Sp — specificity

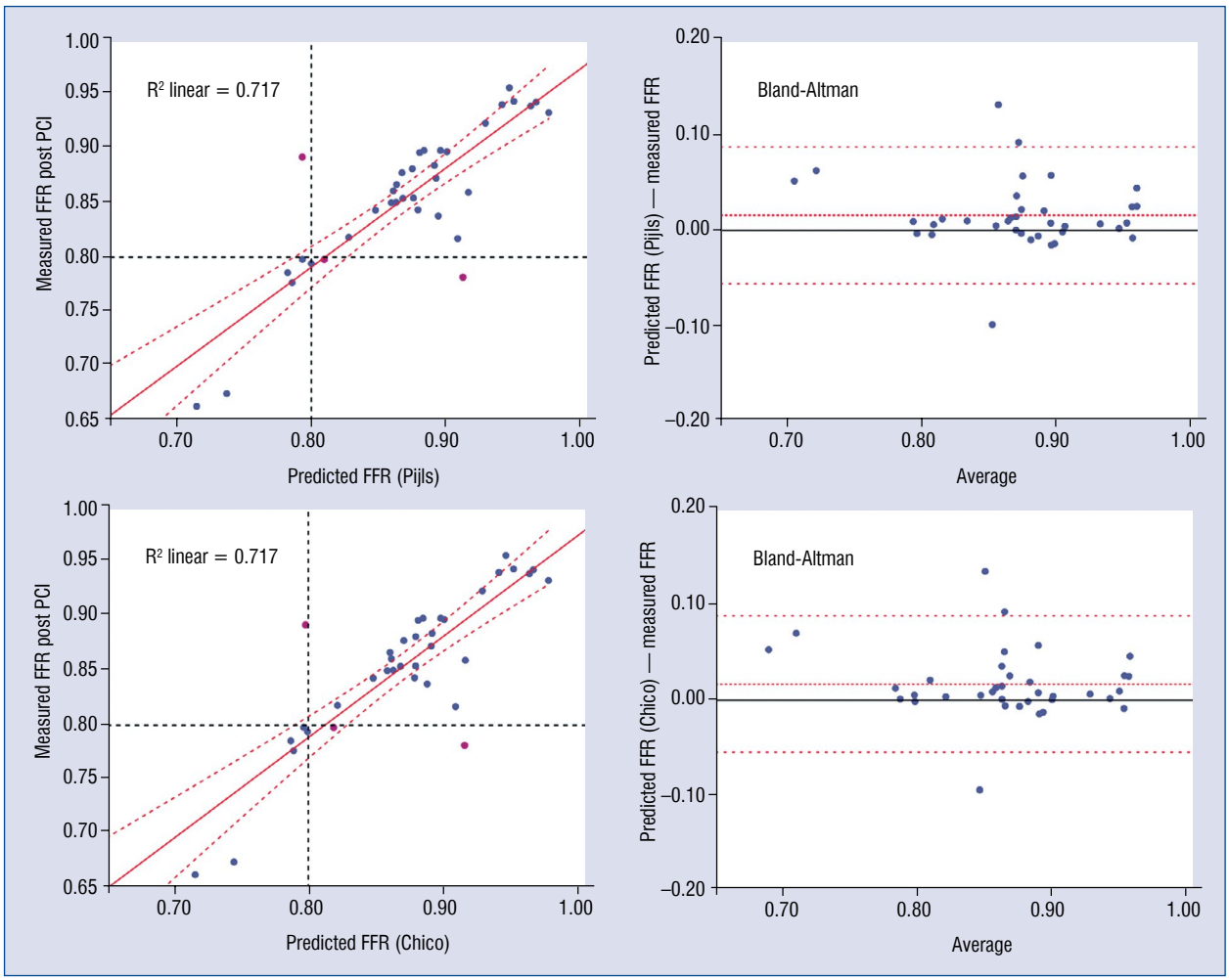

Figure 6. Agreement between predicted fractional flow reserve (FFR) and measured FFR after treatment of one of the lesions; **Upper panels:** FFR predicted by Pijls' formula; **Lower panels:** FFR predicted by Gutiérrez-Chico's simplified formula. Linear regression (left) with the measured FFR after treatment of one lesion as reference; Bland-Altman analysis (right); PCI — percutaneous coronary intervention.

Table 3. Agreement between predicted fractional flow reserve (FFR) and FFR after treatment.

	Pijls' formula	Chico's formula
Predicted FFR	0.87 ± 0.06)	0.87 ± 0.06
Measured FFR after treatment of 1st lesion	0.86 ± 0.07	
r	0.847	0.847
R^2	0.717	0.717
P	< 0.0001	< 0.0001
Intercept	0.06*	0.05*
Slope	0.91	0.92
ICCa	0.825 (0.658–0.910)	0.820 (0.640–0.909)
Kappa	0.748	0.748
False positives	1 (2.5%)	1 (2.5%)
False negatives	2 (5.0%)	2 (5.0%)
Se (%)	75	75
Sp (%)	96	96
PV (+)	86	86
PV (–)	93	93

*Statistically non-significant. Data presented as mean ± standard deviation, coefficient (95% confidence interval) or as count (percent). ICCa — intraclass correlation coefficient for the absolute agreement; Se — sensitivity; Sp — specificity; PV (+) — positive predictive value; PV (–) — negative predictive value

Calculating predicted FFR for each lesion resulted in an indication for single-lesion PCI in 30 (75.0%) cases, double-lesion PCI in 6 (15.0%) cases and no indication for PCI in 4 (10.0%) cases (Table 4). Since the approach of guiding the PCI by the largest ΔP does not enable to do an upfront indication for double-lesion PCI, the weighted kappa for the initial PCI strategy was 0.55 (0.25–0.84). Regarding which lesion that should be stented first, calculating the predicted FFR pointed to the proximal lesion in 9 (25.0%) cases, the distal lesion in 8 (22.2%) cases, whilst it was left up to the operator in 19 (52.8%) of the cases: in 6 (16.7%) of them because both lesions were significant and in 13 (36.1%) of them because both lesions had a predicted FFR > 0.80 separately, although the combination had a significant result (Table 4). Since guiding the intervention by ΔP does not permit the facultative decision on which lesion stenting is first, these results corresponded to a weighted kappa of 0.47 (0.30–0.64).

Discussion

The key messages of this study can be summarised as follows: 1) predicted FFR for each lesion in sequential coronary stenosis can be accurately calculated by a novel simplified formula, obviating the measurement of coronary wedge pressure, thus circumventing the need for balloon inflation; 2) the novel simplified formula is close to the absolute agreement with Pijls' formula, previously validated, but requiring balloon inflation; 3) the FFR predicted by the novel simplified formula has good agreement with the FFR measured after treatment of one of the lesions, identical to the level of agreement of the FFR predicted by Pijls' formula; 4) the approach of calculating predicted FFR for each individual lesion may have a substantial impact on PCI strategy in treating patients.

In the year 2000 Bernard de Bruyne and Nico Pijls proposed a formula to calculate the predicted FFR for each lesion in sequential coronary stenosis [7, 8]. By means of a sophisticated but elegant rationale, they demonstrated that the change in flow occurring if any of the lesions were removed could be estimated with just the pressure recordings obtained under maximal hyperemia before the

Table 4. Agreement between gradient of pressure drop (ΔP) and the formula to plan percutaneous coronary intervention (PCI) strategy in sequential lesions: weighted kappa.

PCI strategy (n = 12)		Formula			
		No PCI	1 lesion PCI	Both lesions PCI	Weighted kappa
ΔP	No PCI	4	0	0	0.55 (0.25–0.84)
	1 lesion PCI	0	30	6	
	Both lesions PCI	0	0	0	
		Proximal first	Operator's choice	Distal first	Weighted kappa
ΔP	Proximal first	9	15	0	0.47 (0.30–0.64)
	Operator's choice	0	0	0	
	Distal first	0	4	8	

intervention. This formula was validated in both an experimental animal model [7] and in a clinical setting [8]. Nonetheless, their formula entailed a practical drawback that ultimately prevented its widespread generalization for clinical use: it required the calculation of coronary wedge pressure (Pw) and this could be only measured while inflating a balloon in one of the lesions. That meant that PCI should start before predicted FFR values were available. That was the main reason why FFR-guided PCI in sequential stenosis has rather followed the so called "delta approach": the lesion through which the largest pressure drop occurs (ΔP) was considered the most functionally severe and it was hence treated first. The delta approach is easier to implement in the cath-lab routine, but it has some intrinsic limitations, because it neglects the accurate depiction of coronary physiology that de Bruyne and Pijls unravelled. The delta approach can only decide which lesion is most severe, in dichotomous terms, but it cannot unveil upfront whether both lesions are functionally relevant or whether no lesion is functionally relevant itself but the combination of both is. These situations are not seldom (54.3% in the present series) and their identification might be useful for operators to plan PCI accordingly.

A chance to incorporate the accuracy of Pijls' formula into clinical practice came from a pragmatic observation that predicted FFR, expressed as a function of Pw, followed a J-shaped curve, with the straight part of the J corresponding to the physiologic and pathologic range of Pw (< 30 mmHg). Rephrased in clinical terms, the predicted FFR values remained stable and practically unchanged along the whole clinical range of Pw. Ironically the parameter precluding adoption of Pijls' formula for so many years (Pw) ended up not playing such an instrumental role. Based on this observation, Gutiérrez-Chico et al. proposed to using a central Pw value for cases in which estimation of refined physiology might be deemed important [11]. The current study is a clinical validation of this approach, taking a central value of Pw = 12 mmHg (Fig. 2). The series confirms the initial premise for the application of the simplified formula: in an unselected sample of 35 patients Pw was < 30 mmHg in all cases (minimal and maximal values 1 and 26 mmHg, respectively). Under these conditions, Gutiérrez-Chico's simplified approach obviating the need for balloon inflation resulted in practically identical values of predicted FFR to the ones obtained by the classical Pijls' formula. As predicted by the mathematical model, both approaches were close to absolute agreement whenever compared as continuous (predicted FFR) or as dichotomous variables (relevant vs. non-relevant).

Agreement between predicted and measured FFR

The agreement between the FFR predicted by the novel formula and the real FFR measured after treatment of one of the lesions was also good and similar to the agreement reported by Pijls in his original article [8]: as a continuous variable, ICCa was 0.820, whilst as a dichotomous variable (relevant vs. non-relevant) the kappa coefficient was 0.748, both considered as indicative of good agreement. As observed in the Bland-Altman and in the lineal regression analysis, the predicted FFR did not incur any proportional bias (slope = 0.92), although it tended to be a subtle but non-significant constant bias (intercept = 0.05), inclined to slightly underestimate severity of the lesion. This observation had been already described by de Bruyne and Pijls in their original articles [7, 8] and might be most likely explained by a slight underestimation of the increase in coronary flow through the remaining stenosis after treatment of the first one, or because a residual pressure drop is often detected after PCI [12, 13]. Interestingly, whilst in the original animal model the predicted FFR never overestimated the true severity [7], the clinical validation reported however, some cases of overestimation [8]. The present results are in line with the original clinical study, finding a subtle non-significant trend to constant underestimation of severity, but with some cases of slight overestimation that might correspond to cases with side branches taking-off between lesions. This could explain the higher specificity than sensitivity of the method. In light of the overall good diagnostic accuracy and of the existence of some cases of overestimation, further attempts to refine the calculation by adding some constant correction factor are not justified.

Impact of the formula on planning the PCI strategy

This novel simplified approach to calculate FFR in sequential lesions provides the interventional cardiologist with precise information about physiology along the diseased vessel before exerting any insult against the coronary endothelium, other than inserting the pressure wire. This information can have important logistic advantages, when compared with the current practice of guiding intervention by ΔP. In 52.7% of the cases the decision about which lesion should be treated first could be left up to the operator, who might thus consider other anatomic

or interventional parameters in the decision. In 6 (16.7%) cases the decision was absolutely left to the operator's choice, because both lesions were significant, whilst in 13 (36.1%) of cases the decision was only partially facultative, because each lesion had a predicted FFR > 0.80 separately and only the combination of them was significant: in this scenario the operator should try to revascularize the lesion with the lowest predicted FFR, but he could change his target after considering other operational variables. Therefore, knowing this information upfront could be instrumental for the operator in order to properly plan the corresponding PCI. The poor agreement in different interventional variables between the delta approach and the calculation of predicted FFR for each lesion indicates indirectly the high potential impact of the current formula on planning the interventional strategy.

Consequence on alternative methods to estimate physiology

Intracoronary physiology is living an unprecedented blossom over the last years, with the development of a myriad of alternative methods to conventional FFR with quite good clinical performance [14–21]. Some of them, like the instant wave-free ratio (iFR) or quantitative flow ratio (QFR) offer a possibility of estimating the pressure drop along the coronary segment. Although these methods do not take into account the modification of the coronary flow after treatment of one of the lesions, their rationale might make sense, because they are not calculated under hyperaemic flow conditions and the change in flow might be hence negligible, unless any of the lesions were so severe as to impede even the resting flow. Recent studies have successfully validated the usefulness of iFR in predicting FFR in sequential stenosis using a combination of iFR pullback and virtual PCI tool [22]. These approaches show similar accuracy to the hereby described method with the advantage of also applying the diffuse disease with > 2 focal stenosis.

Limitations of the study

The current study had a low inclusion rate (40 patients in 6 participating centres over 19 months). This was exclusively due to the unusually slow regulatory processes in the corresponding countries, to logistic problems and to the incorporation at different time points of the participating centres (4 of them were actively recruiting for < 6 months). No patient has been excluded after signing the informed consent, irrespective of FFR results, to minimize the risk of selection bias. Indeed 4 patients coming for scheduled PCI based on a previous angiography, who had signed the informed consent, did not properly meet the inclusion criteria because the distal FFR > 0.80. Even these patients are hereby reported, although excluded from the main analysis, to approximate the estimation of the impact on the PCI strategy to a real-world scenario. The sample size of the study is modest as it was calculated for a general pilot study of validation. Larger studies must be performed to answer to the many questions raised by this approach, like an eventual differential accuracy in the different coronary vessels or the influence of potential sources of inaccuracy that might explain the poor agreement in a few outliers.

The use of this formula is limited to the presence of two clearly discernible stenosis. For > 2 sequential lesions or for diffuse coronary disease, the predicted FFR for each potential target lesion cannot be performed as hereby described. Likewise, Pijls' original article excluded patients with a large side branch taking off between the lesions [7, 8]. This was herein, intentionally skipped as exclusion criterion because the current study aimed at assessing the clinical performance of the simplified formula in a real-world scenario, although this decision might have hampered the accuracy of the approach in some cases.

The current study used intravenous adenosine to create a stable frame of maximal vasodilation that enabled reliable measurement of all the required parameters. It is uncertain how this formula can perform if the vasodilation were differently induced, e.g. by means of intracoronary adenosine [23, 24] or by contrast injection [25].

Conclusions

The predicted FFR for each lesion in sequential coronary stenosis can be accurately calculated by a novel simplified formula circumventing the need for balloon inflation. This approach can provide the operator upfront with detailed information of the coronary physiology, thus having a potentially high impact on planning the corresponding PCI strategy.

Conflict of interest: None declared

References

1. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med. 1996; 334(26): 1703–1708, doi: 10.1056/NEJM199606273342604, indexed in Pubmed: 8637515.

2. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation. 2001; 103(24): 2928–2934, indexed in Pubmed: 11413082.
3. 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(3): 213–224, doi: 10.1056/NEJMoa0807611, indexed in Pubmed: 19144937.
4. De Bruyne B, Pijls NHJ, Kalesan B, et al. FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012; 367(11): 991–1001, doi: 10.1056/NEJMoa1205361, indexed in Pubmed: 22924638.
5. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014; 35(37): 2541–2619, doi: 10.1093/eurheartj/ehu278, indexed in Pubmed: 25173339.
6. Mintz GS, Painter JA, Pichard AD, et al. Atherosclerosis in angiographically „normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol. 1995; 25(7): 1479–1485, indexed in Pubmed: 7759694.
7. De Bruyne B, Pijls N, Heyndrickx G, et al. Pressure-Derived fractional flow reserve to assess serial epicardial stenoses. Circulation. 2000; 101(15): 1840–1847, doi: 10.1161/01.cir.101.15.1840.
8. Pijls NH, De Bruyne B, Bech GJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. Circulation. 2000; 102(19): 2371–2377, indexed in Pubmed: 11067791.
9. Kern MJ, Lerman A, Bech JW, et al. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. Circulation. 2006; 114(12): 1321–1341, doi: 10.1161/CIRCULATIONAHA.106.177276, indexed in Pubmed: 16940193.
10. Park SJ, Ahn JM, Pijls NHJ, et al. Validation of functional state of coronary tandem lesions using computational flow dynamics. Am J Cardiol. 2012; 110(11): 1578–1584, doi: 10.1016/j.amjcard.2012.07.023, indexed in Pubmed: 22921996.
11. Jaguszewski M, Zabalza Cerdeiriña M, Alushi B, et al. How should I treat recurrent chest pain and systolic dysfunction after chemotherapy with anthracyclines? EuroIntervention. 2017; 12(13): 1674–1677, doi: 10.4244/EIJV12I13A274, indexed in Pubmed: 28106002.
12. Pijls N, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up. Circulation. 2002; 105(25): 2950–2954, doi: 10.1161/01.cir.0000020547.92091.76.
13. Piroth Z, Toth GG, Tonino PAL, et al. Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. Circ Cardiovasc Interv. 2017; 10(8), doi: 10.1161/CIRCINTERVENTIONS.116.005233, indexed in Pubmed: 28790165.
14. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol. 2012; 59(15): 1392–1402, doi: 10.1016/j.jacc.2011.11.003, indexed in Pubmed: 22154731.
15. Sen S, Asrress K, Nijjer S, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. J Am Coll Cardiol. 2013; 61(13): 1409–1420, doi: 10.1016/j.jacc.2013.01.034.
16. Petraco R, van de Hoef TP, Nijjer S, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). Circ Cardiovasc Interv. 2014; 7(4): 492–502, doi: 10.1161/CIRCINTERVENTIONS.113.000926, indexed in Pubmed: 24987048.
17. Escaned J, Echavarría-Pinto M, Garcia-Garcia H, et al. Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance. JACC: Cardiovascular Interventions. 2015; 8(6): 824–833, doi: 10.1016/j.jcin.2015.01.029.
18. Davies JE, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017 ; 376(19): 1824–34.
19. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med. 2017; 376(19): 1813–1823, doi: 10.1056/NEJMoa1616540, indexed in Pubmed: 28317438.
20. Tu S, Barbato E, Köszegi Z, et al. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. JACC Cardiovasc Interv. 2014; 7(7): 768–777, doi: 10.1016/j.jcin.2014.03.004, indexed in Pubmed: 25060020.
21. Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. JACC Cardiovasc Interv. 2016; 9(19): 2024–2035, doi: 10.1016/j.jcin.2016.07.013, indexed in Pubmed: 27712739.
22. Kikuta Y, Cook CM, Sharp ASP, et al. Pre-Angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT Registry. JACC Cardiovasc Interv. 2018; 11(8): 757–767, doi: 10.1016/j.jcin.2018.03.005, indexed in Pubmed: 29673507.
23. Jeremias A, Whitbourn RJ, Filardo SD, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. Am Heart J. 2000; 140(4): 651–657, doi: 10.1067/mhj.2000.109920, indexed in Pubmed: 11011341.
24. Rigattieri S, Biondi Zoccai G, Sciahbasi A, et al. Meta-Analysis of head-to-head comparison of intracoronary versus intravenous adenosine for the assessment of fractional flow reserve. Am J Cardiol. 2017; 120(4): 563–568, doi: 10.1016/j.amjcard.2017.05.024, indexed in Pubmed: 28651849.
25. Leone AM, Scalone G, De Maria GL, et al. Efficacy of contrast medium induced Pd/Pa ratio in predicting functional significance of intermediate coronary artery stenosis assessed by fractional flow reserve: insights from the RINASCI study. EuroIntervention. 2015; 11(4): 421–427, doi: 10.4244/EIJY14M07_02, indexed in Pubmed: 25007836.