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Personalised fractional flow reserve: a novel concept to optimise myocardial revascularisation

Rebecca C. Gosling[1,2,3]*, BSc, MRCP; Paul D. Morris[1,2,3], PhD, MRCP; Patricia V. Lawford[1,3], BSc, PhD; D. Rodney Hose[1,3,4], BSc, PhD; Julian P. Gunn[1,2,3], MD, MRCP

1. Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom; 2. Department of Cardiology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; 3. Insigneo Institute for In Silico Medicine, Sheffield, United Kingdom; 4. Department of Circulation and Medical Imaging at the Norwegian University of Science and Technology (NTNU), Trondheim, Norway

R.C. Gosling and P.D. Morris contributed equally to this manuscript.

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KEYWORDS

- fractional flow reserve
- innovation
- stable angina

Abstract

Aims: Fractional flow reserve (FFR) represents the percentage reduction in coronary flow relative to a hypothetically normal artery; however, percutaneous coronary intervention (PCI) seldom achieves physiological normality (FFR 1.00), particularly in the context of diffuse disease. In this study we describe a method for calculating the vessel-specific maximal achievable FFR (FFR_{max}) providing a personalised assessment of what PCI can achieve.

Methods and results: FFR measurements were obtained from 71 patients (100 arteries) undergoing angiography. Three-dimensional (3D) coronary anatomy was reconstructed from angiographic images. An ideal intervention, in which all stenoses are removed, was modelled, and the FFR_{max} calculated. The "personalised" FFR (FFR_{pers}) was calculated as measured FFR/FFR_{max}. PCI was performed in 52 vessels and post-PCI FFR measured in 50. FFR_{max} was compared to post-PCI measured FFRs. The mean FFR_{max} was 0.92 (±0.04). This was on average 0.04 (±0.05) higher than the corresponding post-PCI measured FFR ($p<0.001$). FFR_{pers} was significantly higher (0.06±0.04) than measured FFR ($p<0.001$), indicating that FFR overestimates flow restoration achievable with PCI.

Conclusions: A patient's maximal achievable FFR can now be determined prior to PCI. This approach provides a more realistic assessment of the physiological benefit of PCI than is implied by baseline FFR and may prevent unnecessary intervention.

**Corresponding author: Room O137, Medical School, Beech Hill Road, Sheffield, S10 2RX, United Kingdom. E-mail: r.gosling@sheffield.ac.uk*

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Abbreviations

3D	three-dimensional
CFD	computational fluid dynamics
FFR	fractional flow reserve
FFR_{max}	maximal achievable fractional flow reserve
FFR_{pers}	personalised FFR
LAD	left anterior descending
LCX	left circumflex
LMS	left main stem
PCI	percutaneous coronary intervention
RCA	right coronary artery
VCI	virtual coronary intervention

Introduction

Fractional flow reserve (FFR) is the gold standard method by which the physiological significance of epicardial coronary artery disease is determined in the cardiac catheterisation laboratory[1,2]. When FFR is used to guide percutaneous coronary intervention (PCI), clinical and economic outcomes are improved[3]. FFR represents the ratio of blood flow through a stenosed vessel relative to that in a hypothetically normal vessel. Measuring flow *in vivo* is challenging; therefore, pressure is used as a surrogate for flow. However, PCI seldom achieves a post-treatment FFR of 1.0, even when there is a satisfactory angiographic result. Therefore, by assuming that an FFR of 1.0 is achievable, the baseline FFR may suggest a greater potential benefit to be achieved by PCI than is actually possible. This is especially true in the presence of complex, diffuse disease and serial lesions. A suboptimal post-PCI FFR can lead to further unnecessary treatment with little cumulative gain in FFR. This could pose additional risk without significant clinical benefit. Knowing the maximal achievable FFR (FFR_{max}) prior to intervention would be advantageous in planning revascularisation. In this study, we aimed to introduce a method which personalises FFR assessment from the coronary angiogram by predicting the best possible physiological response that PCI can achieve at an artery-specific level.

Methods

STUDY DESIGN

This was an observational cohort study performed in the South Yorkshire Cardiothoracic Centre, Sheffield Teaching Hospitals NHS Foundation Trust, and the University of Sheffield, United Kingdom.

STUDY POPULATION

Data were collected prospectively from patients undergoing coronary angiography and pressure wire assessment between January 2014 and June 2016. Consecutive patients >18 years of age with angiographically confirmed coronary disease (30-90% stenosis by visual angiographic assessment) were recruited. Patients were excluded if they had presented acutely within the previous 60 days, had prior coronary artery bypass graft surgery, chronic total occlusions, if passage of a pressure wire would be unsafe, or if the patient was unable or unwilling to consent. All patients provided informed written consent and the study was approved by the regional ethics committee. Coronary artery segments were defined according to the American Heart Association reporting system[4]. Diffuse disease and serial lesions were defined according to SYNTAX score definitions[5].

INVASIVE ANGIOGRAPHY AND MEASURED FFR

Coronary angiograms were performed according to standard practice. Diseased arteries were assessed with a pressure wire (Philips Volcano or Abbott Vascular). Hyperaemia was induced by an intravenous infusion of adenosine at 140 µg/kg/min. The FFR measurement was taken during maximal stable hyperaemia according to the methods originally described by Pijls et al[6]. The decision to proceed to PCI was made by the operator, guided by angiographic and invasive FFR assessment. In patients who underwent PCI, FFR measurement was repeated after treatment.

3D RECONSTRUCTION

A 3D reconstruction of the arterial anatomy was created using a Philips workstation offline after the procedure. The operator performing the reconstruction was blinded to the FFR results and procedural details. Two angiographic images ≥30° apart were selected. The images were imported alongside the ECG signal data which allowed end-diastolic frames to be selected for reconstruction (segmentation). The 3D reconstruction was exported to the Sheffield VIRTUheart™ software.

VIRTUAL CORONARY INTERVENTION AND PHYSIOLOGICAL SIMULATION

The vessel geometry was represented as a set of connected circular cross-sections following points along the centreline of the vessel. Using a dedicated graphical user interface, the operator selected the location of all stenoses they wished to treat or virtually remove. The cross-sectional radius was then adjusted and the vessel trajectory smoothed using a cubic spline and virtual coronary intervention (VCI) was performed, i.e., the artery was "virtually" stented[7]. As a validation step, the actual PCI procedure that was performed *in vivo* was replicated in the model system. To compute the maximal achievable FFR, a theoretical, ideal intervention in which all discernible stenoses were treated was modelled. The virtually treated artery was then subjected to computational fluid dynamics (CFD) simulation and computation of FFR. All CFD analyses were performed using ANSYS CFX v18.2 (ANSYS Inc., Canonsburg, PA, USA). Personalised proximal and distal boundary conditions were applied on the assumption that the coronary microvascular resistance was not altered by removal of stenoses[8,9]. The result obtained was the "virtual FFR" of the normalised vessel, i.e., FFR_{max}. The distal boundary was tuned using personalised pressure measurements[10]. Because the simulation was tuned using the invasive pressure wire data, no assumptions were made about boundary condition selection. CFD simulation was used to derive and evaluate personalised FFR assessment and was

not a test of virtual FFR accuracy, which is a separate concept. To assess the reproducibility of FFR_{max} computation, ten percent of cases were reprocessed, with the operator blinded to the original results. The focus was on reproducibility of FFR_{max} computation; therefore, the baseline vessel 3D reconstruction was not repeated. FFR_{max} results were compared and the intra-class correlation coefficient calculated.

CALCULATION OF PERSONALISED FFR

Personalised FFR (FFR_{pers}) was calculated as invasively measured (m)FFR divided by FFR_{max} ($\frac{mFFR}{FFR_{max}}$). Therefore, it represents the degree of flow restoration potentially achievable on a vessel-specific basis. The mathematical derivation of this index is provided in **Supplementary Appendix 1**.

DATA ANALYSIS

Data are described as mean (±SD) and % (proportions) unless otherwise stated. FFR_{max} was compared to post-PCI FFR using a paired samples t-test and Pearson correlation. All statistical analyses were performed using SPSS, Version 24 (IBM Corp., Armonk, NY, USA).

Results

PATIENT, LESION AND PROCEDURAL CHARACTERISTICS

Seventy-one patients with angiographically confirmed disease were studied. The mean age was 65.2 (±9.9) years, 52 (73%) were male, 15 (21%) had type 2 diabetes mellitus, 46 (65%) had hypertension and 52 (73%) had hyperlipidaemia **(Table 1)**. These patients provided one hundred vessels for study – three left main stem (LMS), 52 left anterior descending (LAD), eight diagonal, four obtuse marginal, 14 left circumflex (LCX), and 19 right coronary arteries (RCA). Twelve (12%) had serial lesions and 25 (25%) had diffuse disease. The average % diameter stenosis, determined by QCA, was 54.1 (±12). The mean invasively measured baseline FFR (mFFR) was 0.76 (±0.13). Fifty-two (52%) vessels underwent PCI, and the post-PCI FFR was measured in 50. Mean stent length and diameter were 27.5 (±10.8) mm and 3.0 (±0.5) mm, respectively. All patients received second-generation drug-eluting stents.

Table 1. Baseline patient and lesion characteristics.

Patient characteristics		
Mean age (years)		65.3 (±9.9)
Sex	Male	52 (73%)
	Female	19 (27%)
Smoking status	Current	9 (13%)
	Ex	41 (58%)
	Never	21 (30%)
Prior myocardial infarction		26 (37%)
Hypertension		46 (65%)
Hyperlipidaemia		52 (73%)
Diabetes mellitus type 2		15 (21%)
Vessel characteristics		
Vessel studied	Left main stem	3 (3.0%)
	Left anterior descending	52 (52%)
	Left circumflex	14 (14%)
	Right coronary artery	19 (19%)
	Diagonal	8 (8.0%)
	Obtuse marginals	4 (4.0%)
PCI treated		52 (52%)
Diffuse disease		25 (25%)
Serial lesions		12 (12%)
QCA average diameter stenosis (%)		54.1
QCA average lesion length (mm)		19.5

PCI: percutaneous coronary intervention; QCA: quantitative coronary angiography

ACCURACY OF VCI TO PREDICT POST-PCI FFR

After PCI, the measured FFR was 0.89 (±0.05) and the virtual (v)FFR was 0.90 (±0.05). The difference between measured and modelled post-VCI FFR was 0.009 (±0.03). The average absolute error was ±0.01 (±2%). The correlation between post-PCI measured FFR and post-VCI modelled FFR was 0.88.

MAXIMAL ACHIEVABLE FFR (FFR_{max})

FFR_{max} was successfully computed in a mean time of 95 s. Segmentation time is additional to this. The entire process from loading the image to obtaining the FFR takes approximately five minutes per case. Mean FFR_{max} was 0.92 (±0.04) (range = 0.81-0.99). A vessel-specific breakdown is shown in **Table 2**. In the 50 cases with a post-PCI FFR measurement, the post-PCI mFFR was 0.89 (±0.05), on average 0.04 (±0.05) lower than the corresponding FFR_{max}, and the range of the difference was 0-0.18 (p=<0.001). A subgroup analysis of the post-PCI cases is shown in **Table 3**.

Table 2. Mean FFR_{max} stratified by vessel and vessel segment.

	N	FFR_{max}	Average pressure drop (across segment)
Left main stem	68	0.99	0.01
Left anterior descending	54	0.92	0.08
Proximal	54	0.98	0.02
Mid	54	0.94	0.04
Distal	43	0.91	0.04
Left circumflex	14	0.94	0.06
Proximal	14	0.98	0.02
Distal	14	0.94	0.04
Right coronary artery	19	0.94	0.06
Proximal	19	0.98	0.02
Mid	19	0.96	0.02
Distal	19	0.94	0.02
Diagonal	8	0.90	0.10
Obtuse marginal	4	0.95	0.05

FFR: fractional flow reserve; N: number

Table 3. Subgroup analysis of PCI-treated patients.

	N (%)	Baseline FFR (mean)	FFR_{max} (mean)	Post-PCI FFR (mean)
All PCI-treated vessels	52	0.68	0.93	0.89
Vessel treated				
Left main stem	1 (2%)	0.57	0.86	0.83
Left anterior descending	31 (60%)	0.69	0.91	0.88
Left circumflex	4 (8%)	0.57	0.96	0.96
Right coronary artery	14 (27%)	0.68	0.94	0.91
Diagonal artery	1 (2%)	0.76	0.96	0.91
Obtuse marginals	1 (2%)	0.64	0.95	0.96

FFR: fractional flow reserve; N: number; PCI: percutaneous coronary intervention

In 14 vessels, FFR_{max} was >0.05 higher than post-PCI FFR. In 13/14, this was due to uncovered disease distal to the stented segment **(Figure 1)**. In one, there was a residual pressure drop across the stented segment. The average length of "virtual stent" used to achieve the FFR_{max} was 30.7 (±9.6) mm per vessel. The per-vessel virtual stent length was on average 2.8 mm longer than the stent length deployed during PCI (p=0.18).

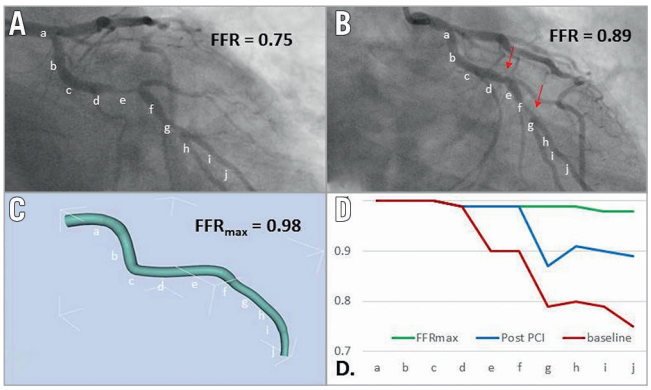

Figure 1. *Using co-registration to determine the difference between FFR_{max} and post-PCI FFR. A 55-year-old with stable angina underwent coronary angiography, revealing a lesion in the LCX. The invasively measured FFR was 0.75 (A). The patient underwent PCI and measured post-PCI FFR was 0.89 (B). The FFR_{max} was calculated as 0.98 (C). This result is significantly higher than the achieved post-PCI FFR, suggesting that further optimisation may have been possible (there are residual diseased segments distal to the stent, marked in panel B). By plotting the FFR values along the length of the vessel, a comparison between baseline, post-PCI and FFR_{max} values is made (D); a-j along the x-axis represent the 10 vessel segments identified on the angiographic images. This demonstrates a second distal lesion which accounts for the difference between the FFR_{max} and post-PCI FFR.*

REPRODUCIBILITY OF FFR_{max} COMPUTATION

The computation of FFR_{max} was highly reproducible. Of the 10 cases reprocessed, the average difference was 0.002 (±0.003). The intra-class correlation coefficient was 0.99 (p<0.001).

COMPARISON BETWEEN MEASURED FFR AND PERSONALISED FFR (FFR_{pers})

FFR_{pers} was calculated in all vessels. The mean FFR_{pers} was 0.82 (±0.14). The mean difference between FFR_{pers} and measured FFR was 0.06 (±0.04) (p=<0.001). All measured FFR and corresponding FFR_{pers} results are shown in **Figure 2**.

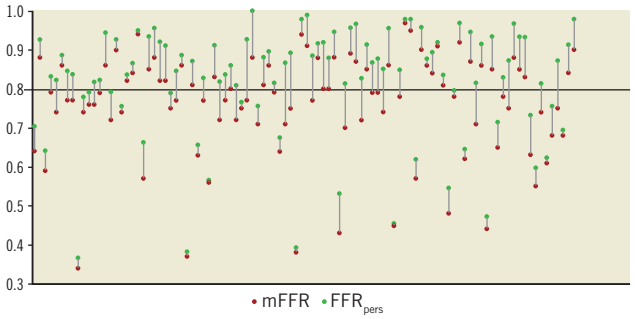

Figure 2. *Individually plotted mFFR and corresponding FFR_{pers} values for all lesions studied. The mFFR value is plotted for all 100 lesions studied (red dot). The corresponding FFR_{pers} is plotted (green dot) and joined by a grey line. The black horizontal line represents the 0.80 treatment threshold.*

Discussion

We have demonstrated a method of determining the maximal achievable FFR (FFR_{max}) prior to intervention based upon the invasive coronary angiogram and standard pressure wire data on a vessel-specific basis. This allowed personalisation of FFR assessment. In a cohort of real-world patients with stable coronary artery disease, FFR_{max} was successfully computed in all cases in a mean time of 95 s. The mean value of the FFR_{max} was 0.92.

FFR represents the percentage reduction in coronary flow relative to a hypothetically normal artery. However, it does not accurately reflect the potential flow restoration achievable with PCI in a particular patient. This is because the maximal achievable FFR on a case-by-case basis is not known prior to intervention. As such, it does not always accurately predict which patients will benefit from PCI and to what degree. Therefore, even with FFR guidance, it may still be challenging to determine which patients will benefit from revascularisation, especially when the measured FFR is close to 0.80[11]. A universal threshold of 0.80 is applied to all patients to determine when revascularisation is likely to provide benefit. Although this threshold is supported by clinical outcome data in large groups as a whole, and is probably satisfactory in most cases, an FFR of 0.78 can describe a number of different physiological situations which may respond differently to PCI.

A personalised approach to coronary physiological assessment using FFR_{max} and FFR_{pers} may help to identify patients who will gain benefit from targeted PCI **(Figure 3)**, patients who are likely to get limited physiological benefit from PCI due to underlying diffuse disease **(Figure 4)** and patients in whom further procedural optimisation may be possible **(Figure 5)**.

It is unclear what degree of flow restoration is required for the patient to gain symptomatic and/or prognostic benefit. Some limited outcome data suggest that patients with a post-PCI measured FFR >0.90 have reduced rates of major adverse cardiac events following PCI[12]. Our method will require outcome studies to determine the value of FFR_{pers} which might more accurately define the threshold for treatment.

Not only was FFR_{max} significantly lower than 1.0, but it varied considerably between cases (range 0.81-0.99). This is consistent with previous work showing that, even in the absence of an angiographic stenosis, there is a pressure drop along the length of the vessel[13]. In patients with confirmed coronary artery disease elsewhere, the average drop in pressure along an apparently normal vessel was 10 (±8) mmHg under hyperaemic conditions (FFR 0.89±0.08, range 0.69-1.00). For eight percent of these patients, the FFR value was below the threshold for treatment (≤0.80). In patients with apparently completely normal arteries, the average FFR was 0.97±0.02 (range 0.92-1.00).

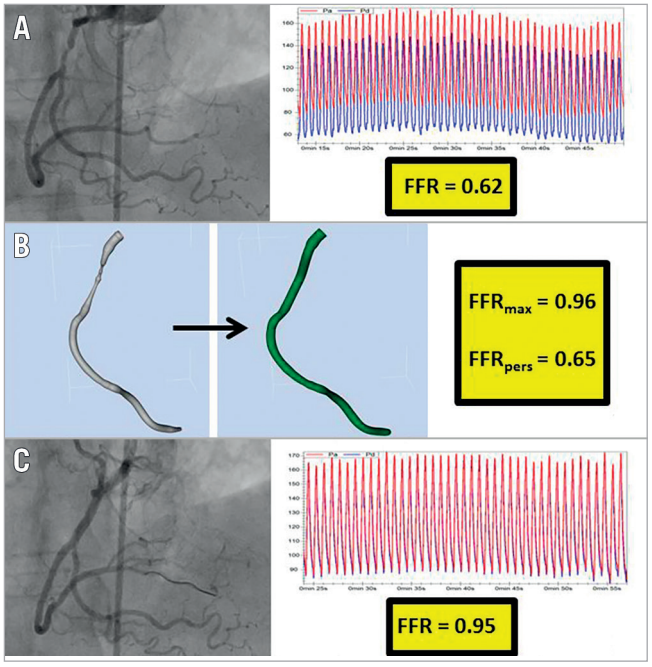

Figure 3. *Identifying a focal lesion that is likely to achieve a good physiological result from targeted PCI. An 81-year-old with stable angina underwent angiography, identifying a lesion in the RCA. Pressure wire assessment revealed an FFR of 0.62 (A). A reconstruction of the arterial geometry was created (B, left image) and the stenoses virtually removed to reveal the "normalised" geometry (B, central image). The FFR_{max} and FFR_{pers} were calculated as 0.96 and 0.65, respectively. These results advise the operator that this lesion is likely to lead to an excellent physiological result from focal PCI. PCI was performed with a good angiographic result (C, left image). Post-PCI measured FFR was 0.95 (C, right image).*

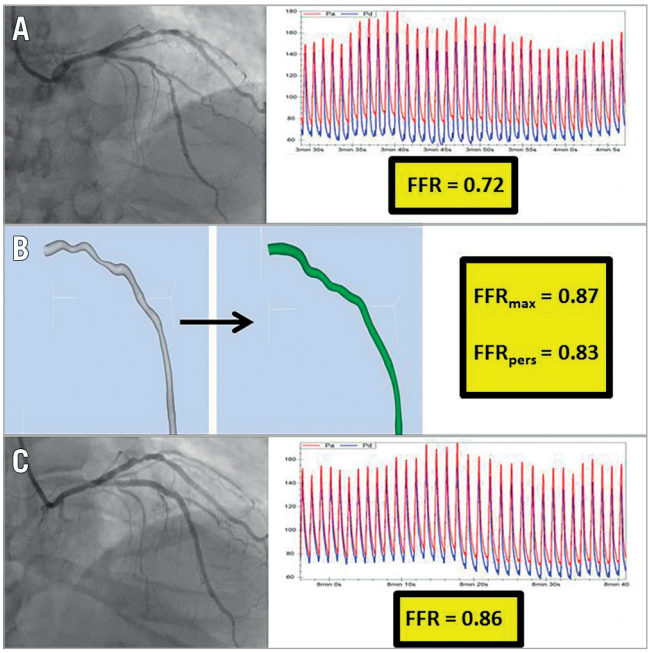

Figure 4. *Identifying a lesion that is unlikely to achieve a significant physiological improvement from focal PCI. A 61-year-old with stable angina underwent coronary angiography, revealing a lesion in the LAD. The invasive FFR measurement was 0.72 (A). A reconstruction of the arterial geometry was created (B, left image) and the stenoses virtually removed to reveal the "normalised" geometry (B, central image). The FFR_{max} and FFR_{pers} were calculated as 0.87 and 0.83, respectively. These results suggest that only a modest physiological benefit is likely to be achieved from focal PCI. This patient proceeded to PCI with a good local angiographic result (C, left image). The post-PCI FFR was, however, only 0.86 (C, right image), which is in keeping with the predicted FFR_{max}. Knowing the FFR_{max} in this case would have informed the decision to perform PCI in the first place, and would help to prevent futile attempts to improve the post-PCI FFR.*

A gradual pressure drop in the presence of diffuse disease can be associated with increased mortality, and it is usually not amenable to intervention[14]. An optimal physiological result is seldom achieved following PCI, despite the use of long (>30 mm) and ultra-long (>50 mm) drug-eluting stents[15]. In patients with a lesion length >30 mm, fewer than one third achieved a post-PCI FFR of >0.90, with only 11% >0.95. Eight (11%) vessels remained haemodynamically significant (FFR ≤0.80). In another study, 17.8% of vessels remained ischaemic (FFR <0.80) immediately after treatment, and 9.5% continued to be ischaemic despite further attempts at PCI optimisation. Diffuse disease was a predictor of a post-PCI FFR ≤0.80[16]. In our study, similar post-PCI FFR results were seen. Eighteen (36%) patients had a post-PCI FFR >0.90 and four (8%) >0.95. Three (6%) remained haemodynamically significant (FFR <0.80). Higher post-PCI

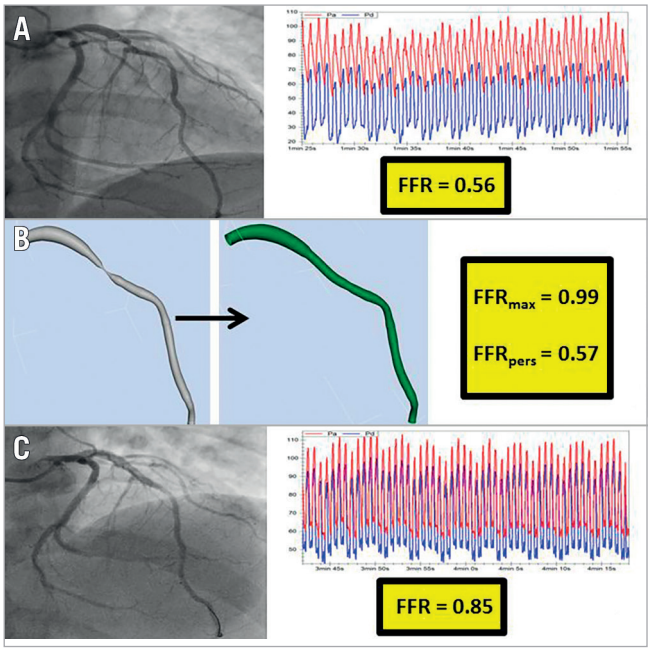

Figure 5. *Identifying a lesion that may benefit from further post-PCI optimisation. A 55-year-old with stable angina underwent coronary angiography, revealing a lesion in the LAD. The invasively measured FFR was 0.56 (A). A reconstruction of the arterial geometry was created (B, left image) and the stenoses virtually removed to reveal the "normalised" geometry (B, central image). The FFR_{max} and FFR_{pers} were calculated as 0.99 and 0.57, respectively. These results advise the operator that this lesion is likely to lead to a good physiological result from focal PCI. The patient underwent PCI and the invasively measured post-PCI FFR was 0.85 (C). This initial result is significantly lower than the FFR_{max}, suggesting that further procedural optimisation may have been possible.*

FFR results are associated with improved outcomes[12,17-19], yet in clinical practice this is not always achievable. Identifying patients likely to have a suboptimal physiological result following PCI would therefore be advantageous. FFR_{max} could provide this.

In some cases, a suboptimal post-PCI FFR is not due to the presence of untreatable diffuse disease but can be the result of a poorly optimised procedure. The FFR_{max} can help the operator to distinguish between these two scenarios, either by guiding further optimisation or conversely by preventing further treatment that is futile and potentially harmful. Procedural optimisation with post-dilatation, and in some cases further stent implantation, has previously been shown to result in modest increases in FFR. In the ILUMIEN 1 trial, a statistically non-significant increase in post-PCI FFR from 0.86 to 0.90 was achieved with OCT-driven optimisation[20]. In our study, FFR_{max} was on average 0.04 (range 0-0.18) higher than the post-PCI FFR, suggesting that a similar level of optimisation may have been possible. In 14 (28%) cases, the FFR_{max} was >0.05 higher than the post-PCI FFR. This was most frequently (in 13 out of these 14 cases) due to the presence of uncovered disease distal to the stented segment.

Limitations

Our computational model is based upon a single lumen reconstruction. This could lead to an overestimation of FFR. The accuracy of the vFFR computation is affected by the accuracy of the vessel reconstruction (segmentation). Previous studies using this approach have shown the ability to predict the FFR with high accuracy[10,21]. The accuracy of FFR_{max} cannot be fully validated as there is no method of *in vivo* measurement available. However, our results are consistent with other studies of *in vivo* post-PCI results. Furthermore, our model has previously been shown to have extremely high accuracy in predicting FFR[10] and we would expect similar accuracy to be extrapolated in the normalised geometries. Although our model can predict FFR with high accuracy, it is still subject to the same limitations (notably its reliance on minimising microvascular resistance) as invasive FFR measurement.

Conclusions

We have demonstrated the feasibility of calculating the maximal achievable FFR prior to PCI on a vessel-specific basis, allowing the personalisation of FFR assessment. Unlike standard FFR, our methods of personalising FFR reflect the potential benefit of PCI relative to patient-specific anatomy rather than an unachievable hypothetical norm. This new concept opens new horizons for treatment planning and could prevent unnecessary PCI or excessive stenting.

Impact on daily practice

PCI seldom achieves a post-treatment FFR of 1.0, even when there is a satisfactory angiographic result. Therefore, in many cases, FFR leads the operator to overestimate the potential benefit of PCI. We have developed a method of personalising FFR which reflects flow reduction relative to patient-specific anatomy rather than a hypothetical norm and therefore more accurately predicts the potential physiological benefit from PCI.

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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. Mathematical derivation of FFR_{pers}.

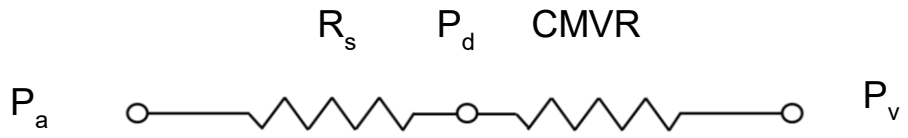
The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-00668

Supplementary data

Supplementary Appendix 1. Mathematical derivation of FFR_{pers}

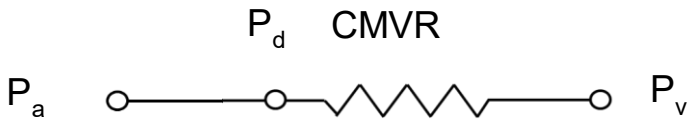
Derivation of "traditional" FFR is based upon the following electrical analogues.

Pre-intervention



Where P_a = proximal aortic pressure, R_s = stenosis resistance, P_d = distal aortic pressure, CMVR = microvascular resistance and P_v = venous pressure.

Post-intervention



This model assumes that post intervention (or in the absence of a stenosis) the only resistance is that provided by the distal microvasculature (CMVR), i.e., there is no residual resistance along the epicardial vessel.

Using this model:

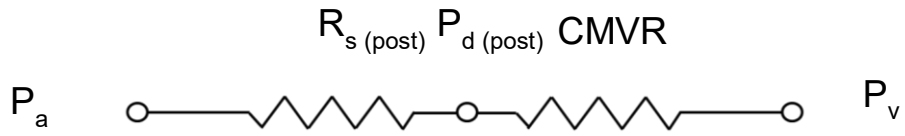
$$FFR = \frac{Qs}{Qn} \quad \text{where:} \quad Qs = \frac{Pd}{R} \quad \text{and} \quad Qn = \frac{Pa}{R}$$

as there is assumed to be no pressure drop along the length of the normalised vessel P_d=P_a.

We can therefore re-arrange the equation such that:

$$\frac{Qs}{Qn} = \frac{Pd}{Pa} = FFR$$

However, if we adjust this model to accept that a residual epicardial resistance can exist in the absence of a stenosis, then our post-intervention model is:



In this model

$$\frac{Qs}{Qn} = \frac{Pd}{CMVR} \ / \ \frac{P_{d\ (post)}}{CMVR}$$

therefore,

$$\frac{Qs}{Qn} = \frac{P_d}{CMVR} * \frac{CMVR}{P_{d\ (post)}}$$

Here CMVR cancels out leaving:

$$\frac{Qs}{Qn} = \frac{P_d}{P_{d\ (post)}}$$

$P_{d\ (post)}$ can be described as FFR_{max} x Pa.

Therefore,

$$\frac{Qs}{Qn} = \frac{P_d}{FFR_{max} * P_a} = \frac{mFFR}{FFR_{max}}$$