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

Yuetsu Kikuta, MD,[a,b,*] Christopher M. Cook, MBBS,[a,*] Andrew S.P. Sharp, MD,[c] Pablo Salinas, MD,[d]
Yoshiaki Kawase, MD,[e] Yasutsugu Shiono, MD, PhD,[a] Alessandra Giavarini, MD,[f] Masafumi Nakayama, MD, PhD,[g]
Salvatore De Rosa, MD, PhD,[h] Sayan Sen, MBBS, PhD,[a] Sukhjinder S. Nijjer, MBChB, PhD,[a] Rasha Al-Lamee, MD,[a]
Ricardo Petraco, MD, PhD,[a] Iqbal S. Malik, MBBS, PhD,[a] Ghada W. Mikhail, MBBS,[a] Raffi R. Kaprielian, MBBS, MD,[a]
Gilbert W.M. Wijntjens, MD,[i] Shinsuke Mori, MD,[j] Arata Hagikura, MD,[b] Martin Mates, MD,[k] Atsushi Mizuno, MD,[l]
Farrel Hellig, MD,[m] Kelvin Lee, MD,[n] Luc Janssens, MD,[o] Kazunori Horie, MD,[p] Shah Mohdnazri, MBBS,[q]
Raul Herrera, MD,[d] Florian Krackhardt, MD,[r] Masahiro Yamawaki, MD,[j] John Davies, MBBS, PhD,[q]
Hideo Takebayashi, MD, PhD,[b] Thomas Keeble, MD,[q] Seiichi Haruta, MD, PhD,[b] Flavio Ribichini, MD, PhD,[s]
Ciro Indolfi, MD, PhD,[h] Jamil Mayet, MBChB, MD,[a] Darrel P. Francis, MB BChir, MA, MD,[a] Jan J. Piek, MD, PhD,[i]
Carlo Di Mario, MD, PhD,[f] Javier Escaned, MD, PhD,[d] Hitoshi Matsuo, MD, PhD,[e,*] Justin E. Davies, MBBS, PhD[a,*]

ABSTRACT

OBJECTIVES The authors sought to evaluate the accuracy of instantaneous wave-Free Ratio (iFR) pullback measurements to predict post-percutaneous coronary intervention (PCI) physiological outcomes, and to quantify how often iFR pullback alters PCI strategy in real-world clinical settings.

BACKGROUND In tandem and diffuse disease, offline analysis of continuous iFR pullback measurement has previously been demonstrated to accurately predict the physiological outcome of revascularization. However, the accuracy of the online analysis approach (iFR pullback) remains untested.

METHODS Angiographically intermediate tandem and/or diffuse lesions were entered into the international, multicenter iFR GRADIENT (Single instantaneous wave-Free Ratio Pullback Pre-Angioplasty Predicts Hemodynamic Outcome Without Wedge Pressure in Human Coronary Artery Disease) registry. Operators were asked to submit their procedural strategy after angiography alone and then after iFR-pullback measurement incorporating virtual PCI and post-PCI iFR prediction. PCI was performed according to standard clinical practice. Following PCI, repeat iFR assessment was performed and the actual versus predicted post-PCI iFR values compared.

RESULTS Mean age was 67 ± 12 years (81% male). Paired pre- and post-PCI iFR were measured in 128 patients (134 vessels). The predicted post-PCI iFR calculated online was 0.93 ± 0.05; observed actual iFR was 0.92 ± 0.06. iFR pullback predicted the post-PCI iFR outcome with $1.4 \pm 0.5\%$ error. In comparison to angiography-based decision making, after iFR pullback, decision making was changed in 52 (31%) of vessels; with a reduction in lesion number (-0.18 ± 0.05 lesion/vessel; $p = 0.0001$) and length (-4.4 ± 1.0 mm/vessel; $p < 0.0001$).

CONCLUSIONS In tandem and diffuse coronary disease, iFR pullback predicted the physiological outcome of PCI with a high degree of accuracy. Compared with angiography alone, availability of iFR pullback altered revascularization procedural planning in nearly one-third of patients. (J Am Coll Cardiol Intv 2018;11:757–67) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CABG = coronary artery bypass grafting

FFR = fractional flow reserve

iFR = instantaneous wave-Free Ratio

LAD = left anterior descending coronary artery

LCx = left circumflex coronary artery

NSTEMI = non–ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

RCA = right coronary artery

STEMI = ST-segment elevation myocardial infarction

Coronary physiology-guided revascularization is recommended by international guidelines and is increasingly used to aid clinical decision making in the cardiac catheterization laboratory (1-4). Aside from simply the identification of ischemia, there has been significant interest in post-percutaneous coronary intervention (PCI) physiology measurements as a means of quantifying the physiological gain from stenting. Performance of post-PCI physiology in itself permits the further assessment of residual lesions of functional significance. Furthermore, post-PCI physiological values have been demonstrated as important predictors of long-term clinical outcomes (5,6). Therefore, an accurate means of predicting the physiological outcome of revascularization at the pre-PCI stage may be beneficial in planning for optimal results.

In tandem or diffuse disease, fluid dynamic interaction occurs between lesions during maximal hyperemia such that the fractional flow reserve (FFR) of a proximal stenosis is influenced by the presence of a distal stenosis and vice versa (7). This interaction complicates the determination of FFR for each stenosis in isolation and makes accurate prediction of post-PCI FFR values in tandem or diffuse disease problematic (7). Although equations that include

measurement of coronary occlusive pressure have been formulated to circumvent the issue of hyperemic interaction between serial stenoses, FFR-based predictions of post-PCI physiology remain underused. Other considerations such as additional time and pressure-wire handling may further have an impact on the low adoption of post-PCI FFR use.

The instantaneous wave-Free Ratio (iFR) is an alternative pressure-based coronary physiological index that does not require pharmacological hyperemia (8). Because of the stability of resting coronary flow across a wide range of lesion severities (9,10), in tandem or diffuse disease, the determination of iFR for each stenosis in isolation is theoretically permissible (11). Therefore, an iFR pullback recording provides a physiological map of lesion severity along the length of a vessel and can be used to predict the physiological outcome post virtual PCI with a high degree of accuracy (11). However, until recently, the ability to generate an iFR pullback recording was only possible using offline computer algorithms that limited real-world clinical applicability.

In this study, we report the findings of the first-in-man global multicenter study using online-generated iFR-pullback curves to predict physiological outcomes post-PCI; and assess the impact of the availability of these data on procedural decision making.

METHODS

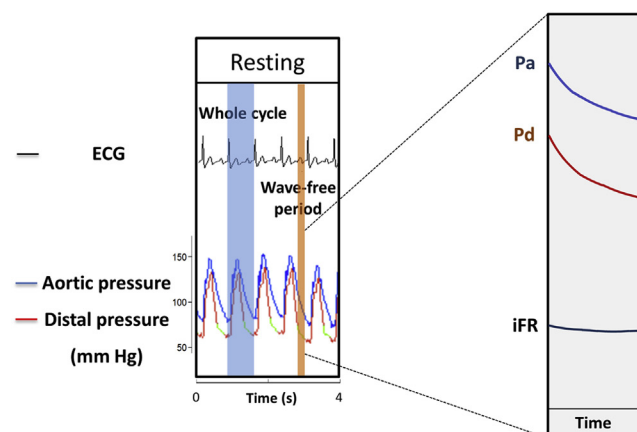**STUDY POPULATION.** Across 19 international centers, patients with a clinical indication for elective or
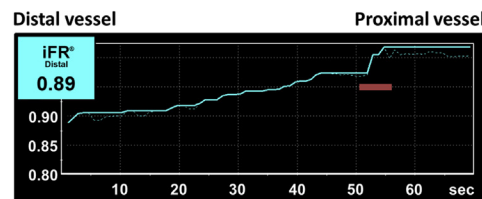
FIGURE 1 iFR Pullback Performed Pre-PCI for the Assessment of Physiological Lesion Severity and Prediction of Physiological Outcome

A **iFR is Calculated as the Ratio of Pd to Pa on a Beat-by-beat Basis**

B **iFR Pullback for Quantification of Lesion Severity**

C **Procedural Planning and the Prediction of Post-PCI iFR Outcome**
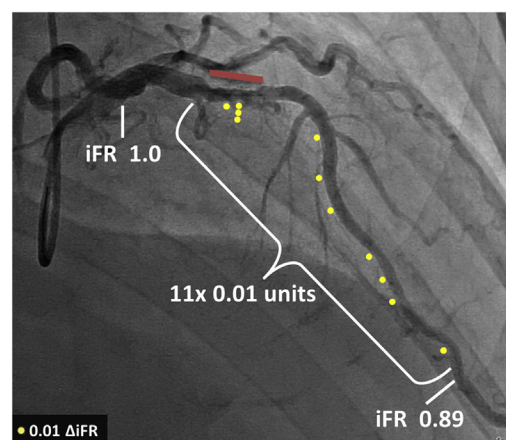
Using iFR pullback data, the operators planned the procedure and predicted and registered iFR outcome into an electronic case report form before starting PCI. iFR was predicted by summation of iFR gradient and iFR measured at the distal coronary artery before treatment procedure (**B**, **C**: red bar).

(A) After coronary angiography, iFR pullback data were calculated from the instantaneous ratio of distal coronary pressure to aortic pressure during the diastolic wave-free period on a beat-by-beat basis. (B) Using the iFR pullback recording, the iFR gradient of the lesion of interest was quantified and used for the prediction of post-procedural iFR outcome. (C) Before actual PCI, iFR was predicted by summation of the iFR gradient with the iFR measured in the distal portion of the coronary artery. Online coregistration system of iFR pullback and angiogram was not available in this study. In order to calculate the iFR gradient, operators read iFR at the proximal and distal side of each lesion from an online iFR screen during continuous fluoroscopy of the pressure wire. iFR = instantaneous wave-Free Ratio; Pa = aortic pressure; PCI = percutaneous coronary intervention; Pd = distal (coronary) pressure.

urgent PCI of a major native epicardial coronary artery with tandem or diffuse atheroma were prospectively enrolled into the iFR GRADIENT (Single instantaneous wave-Free Ratio Pullback Pre-Angioplasty Predicts Hemodynamic Outcome Without Wedge Pressure in Human Coronary Artery Disease) registry.

An iFR pullback recording was constructed from the instantaneous ratio of distal to aortic pressure during diastolic wave-free period on a beat-by-beat basis during pressure wire pullback (**Figure 1**). Vessels protected by a graft with a history of previous coronary artery bypass grafting (CABG) and culprit

vessels in patients with ST-segment elevation myocardial infarction (STEMI), TIMI (Thrombolysis In Myocardial Infarction) flow grade <3, presence of clot, or lesion severity >90% by visual assessment were excluded. All patients provided written consent, and this study had ethical approval from the local committees at each participating center.

STUDY PROTOCOL. Angiographic decision making. Coronary angiography was performed using conventional approaches. Patients underwent a diagnostic coronary angiogram according to the routine clinical practice of the participating center. Angiographic

FIGURE 2   Angiographic Lesion Detection Followed by iFR Pullback Physiological Lesion Significance Evaluation

A   Angiographic assessment
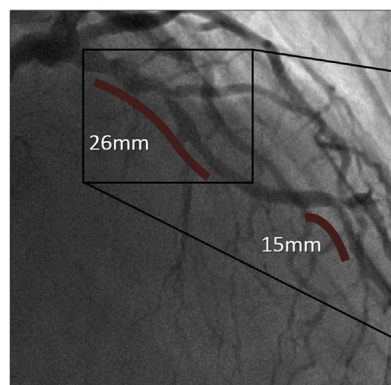
The operators detected angiographically intermediate epicardial lesions. According to the angiographic information, the operators made procedural planning and registered the treatment strategy to clinical report form, prior to physiological assessment.

Angiographic detection of epicardial stenoses
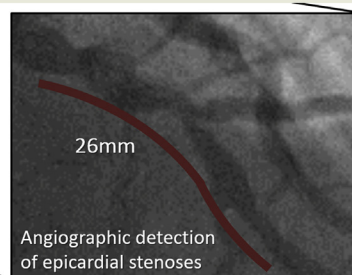
Clinical Report Form – Angiographic guidance
- Is the artery flow-limiting?   *Yes*
- The number of lesions to be stented   *2*
- Total length of lesions estimated from angiography   *41*

B   iFR pullback assessment

iFR® Distal
0.71

iFR pullback gradient overlaid onto angiogram
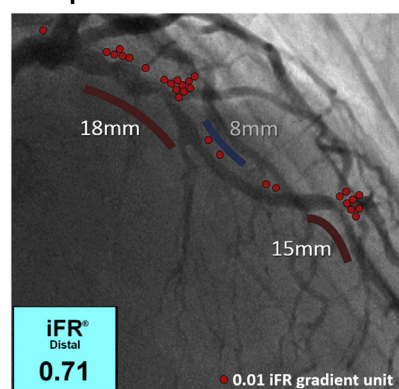
iFR pullback was performed to evaluate physiological lesion severity throughout a vessel. According to iFR gradient quantification, the operators made procedural planning using predicted iFR outcome.

iFR pullback gradient at each vessel location
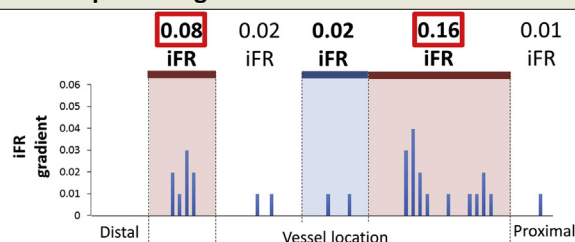
Procedural planning using iFR outcome prediction

Predicted iFR
0.95
Pre-PCI iFR
0.71

Lesions selected for PCI
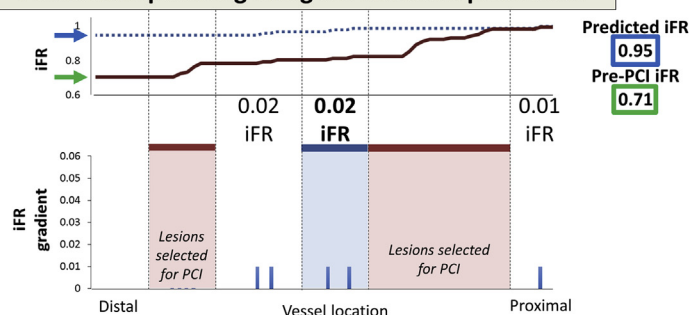
Post-PCI iFR outcome was predicted by summation of iFR gradient and distal pre-PCI iFR measured at the distal coronary artery.

Predicted iFR   =   Pre-PCI iFR   +   iFR gradient(s)
0.95   =   0.71   +   0.08 + 0.16

Clinical Report Form – iFR pullback guidance
- Is the artery flow-limiting?   *Yes*
- The number of lesions to be stented   *2*
- Total length of lesions estimated from iFR gradient significance   *33*

inclusion criteria included the presence of a ≥40% stenosis by visual estimate in any major epicardial vessels or any major branch. After angiography, the angiographic images were reviewed, and operators were asked to prospectively document their plans for angioplasty on an electronic case report form (Figure 2). Specifically, operators were required to record the number of angiographically significant lesions and the total lesion length(s) requiring stenting for each patient. This planning phase, based on visual assessment of angiographic data, was completed before any physiological measurements with iFR pullback.

iFR pullback measurement. Intracoronary nitrates (300 μg) were administered in all cases before pressure wires were introduced. Pressure wire (Prestige guide wire PLUS/Verrata guide wire; Philips/Volcano, Amsterdam, the Netherlands) normalization was performed at the coronary ostia before each recording and before resting pressure wire pullback was performed. iFR was measured in the distal position of the target vessel, followed by an iFR pullback recording along the length of the vessel under resting conditions. Pressure wire pullback was performed in a manual (96.4%) or mechanized manner (3.6%) using Volcano pullback device R100. Pullback speed was ∼0.5 to 1.0 mm/s and was continued until the pressure sensor reached the left main stem ostium or right coronary ostium. During the pressure wire pullback, regular fluoroscopic recordings of the wire position were performed with accompanying bookmarks on the iFR pullback trace. This allowed operators to determine the trans-stenotic pressure gradient (in iFR units) for each lesion of interest along the entire length of the diseased vessel. In this study, automatic coregistration of the iFR pullback curve with the angiogram was not yet available and thus was not performed.

Post-PCI iFR prediction. According to the aforementioned technique, iFR pullback was used to quantify the iFR gradient at each lesion location of interest along the length of the vessel. The predicted post-PCI iFR (iFR_{pred}) was calculated by summation of the iFR gradient(s) with the distal vessel iFR value as depicted schematically in Figure 2.

In line with the threshold value used in recent iFR clinical outcome trials (3,4), a post-PCI iFR value ≤0.89 was considered suboptimal. Accordingly, operators tailored their PCI approach to achieve a post-PCI iFR value >0.89. At this stage, operators were once more asked to record their interventional strategy with respect to the number and length of lesions to stent based on the addition of iFR pullback to angiogram data (Figure 2).

Post-PCI iFR measurement. Angioplasty was performed as per usual clinical practice using third-generation drug-eluting stents, which were all angiographically optimized. Following successful PCI, measurement of the observed post-angioplasty iFR (iFR_{obs}) was performed with the pressure sensor positioned at an identical coronary location as before.

STATISTICAL ANALYSIS. Categorical data are presented as numbers and percentages, and compared with the chi-square test. Continuous data are presented as mean ± SD. Association between continuous values was assessed by paired or Welch's t test or analysis of variance with correction for repeated measures by Bonferroni methods. Continuous agreement between iFR_{obs} and iFR_{pred} was analyzed using the Bland-Altman method. Linear regression analyses were used to investigate the difference between iFR_{obs} and iFR_{pred}. Multiple linear regression analysis was performed to identify the determinants of the difference between iFR_{obs} and iFR_{pred}, in which age, sex, and significant variables ($p < 0.05$) among patient and lesion characteristics in univariate analysis were entered as independent variables. A 2-sided α level of 0.05 was considered statistically significant. All statistical analyses were performed using Stata 14.1 (StataCorp, College Station, Texas).

RESULTS

STUDY DEMOGRAPHICS. A total of 159 patients (81% male, 67 ± 12 years of age) with 168 coronary vessels eligible for PCI were prospectively enrolled (Table 1). Clinical presentations included stable angina (83%), unstable angina (8%), non–ST-segment elevation

---

FIGURE 2 Continued

(A) Angiographic images were analyzed to detect epicardial lesions and landing zones. Operators were asked to prospectively document their plans for PCI based on angiographic image assessment. This planning phase was completed before any physiological measurements and was documented prospectively on the case report form. **(B)** iFR was measured in the distal portion of the coronary artery and followed by a resting iFR pullback recording. During the pressure wire pullback, regular fluoroscopic recordings of the wire position were made, and the iFR gradient was calculated across each angiographically-detected epicardial lesion. Abbreviations as in Figure 1.

TABLE 1 Demographic Data

Patients	159
Age, yrs	67 ± 12
Male	128 (81)
Hypertension	121 (76)
Hyperlipidemia	119 (75)
Current smoker	37 (23)
Diabetes mellitus	64 (40)
Renal failure on dialysis	0 (0)
Previous myocardial infarction	9 (6)
Impaired LV function, EF <30%	1 (0.6)
Prior CABG	1 (0.6)
Stable angina	132 (83)
Unstable angina	12 (8)
NSTEMI	10 (6)
STEMI	5 (3)
Single vessel disease	92 (58)
Multivessel disease	67 (42)
Vessels	168
Left anterior descending	119 (71)
Left circumflex	20 (12)
Right coronary artery	26 (15)
Left main and LAD	3 (2)
Left main and LCx	0 (0)
Proximal/mid or distal	75 (45)

Values are n, mean ± SD, or n (%).

CABG = coronary artery bypass graft; EF = ejection fraction; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; NSTEMI = non-ST-segment myocardial infarction; STEMI = ST-segment myocardial infarction.

myocardial infarction (NSTEMI) (6%), and STEMI (3%). Culprit vessels were assessed in unstable angina or NSTEMI in 3% of cases, respectively. Interrogated vessels were left anterior descending coronary artery (LAD) (71%), left circumflex coronary artery (LCx) (12%), right coronary artery (RCA) (15%), or left main stem plus LAD (2%).

THE ACCURACY OF PREDICTED POST-PROCEDURAL iFR OUTCOME USING iFR PULLBACK. Predicted iFR was compared with post-procedural observed iFR in 128 patients (134 vessels) (**Figure 3**). A strong linear relationship was found between the iFR_{pred} and iFR_{obs} ($r = 0.73$, $p < 0.001$) (Online Figure 1). The mean iFR_{pred} was 0.93 ± 0.05, whereas the mean iFR_{obs} was 0.92 ± 0.06 (mean ± SD). The mean difference between iFR_{pred} and iFR_{obs} was 0.011 ± 0.004. iFR pullback predicted the post-PCI iFR outcome with $1.4 \pm 0.5\%$ error.

ALTERATIONS IN CLINICAL DECISION MAKING FOLLOWING THE AVAILABILITY OF iFR PULLBACK DATA.
1. The number of lesions identified for revascularization

Table 2 displays the number of coronary lesions determined as hemodynamically significant according to angiographic appearance versus iFR pullback. In 47 of 159 patients (30%) and in 52 of 168 vessels (31%), the number of lesions to treat was changed

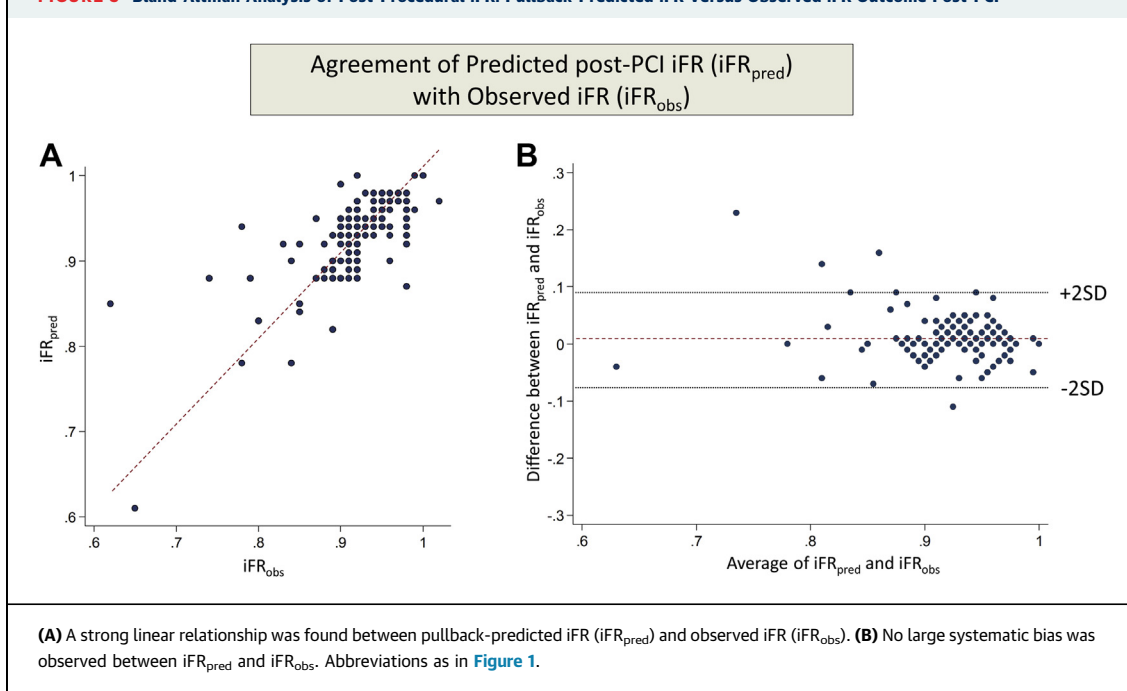**FIGURE 3** Bland-Altman Analysis of Post-Procedural iFR: Pullback-Predicted iFR Versus Observed iFR Outcome Post-PCI

(A) A strong linear relationship was found between pullback-predicted iFR (iFR_{pred}) and observed iFR (iFR_{obs}). **(B)** No large systematic bias was observed between iFR_{pred} and iFR_{obs}. Abbreviations as in **Figure 1**.

TABLE 2 Distribution of Flow-Limiting Coronary Lesions According to Angiographic or iFR Pullback Data

Post-Angiography Decision	Post-iFR Decision						
	0	1	2	3	4	LM	Total
0	**0**	1	0	0	0	0	1
1	7	**82**	4	0	0	0	93
2	2	17	**27**	3	2	1	52
3	0	3	6	**0**	0	0	9
4	1	0	0	0	**1**	0	2
LM	0	0	0	0	0	**2**	2
Total	10	103	37	3	3	3	159

Numbers indicate the number of coronary lesions; 0 indicates no significant flow-limiting epicardial lesions in an interrogated patient. In cases with a **bold** number, angio-guided percutaneous coronary intervention strategy was the same as iFR pullback-guided strategy in terms of the lesion number. In the other cases, iFR pullback changed procedural strategy from a strategy based on angiographic data only.

iFR = instantaneous wave-Free Ratio; LM = left main stem coronary artery.

after iFR pullback measurement. On a per-patient basis, the addition of iFR pullback data decreased the number of lesions identified for revascularization from 1.42 ± 0.05 following angiographic assessment

alone to 1.23 ± 0.05 (p = 0.0001 for difference) (**Figures 2 and 4A**). At the coronary artery level, disagreement on the hemodynamic significance of a vessel between angiography and iFR pullback occurred in 31 of 122 (25%), 10 of 20 (50%), and 11 of 26 (42%) in the LAD, LCx, and RCA, respectively (**Figure 4B**).

2. Length of lesions identified for revascularization

The availability of iFR pullback data decreased the total lesion length identified for revascularization from 31.3 ± 1.3 mm after angiography alone to 26.9 ± 1.3 mm after iFR pullback (p < 0.0001 for difference) (**Figures 2 and 5A**). Disagreement between total lesion length identified by angiography alone and iFR pullback occurred in 118 patients (74%) in 121 vessels (72%). The agreement in length of targets for revascularization based on angiography and iFR pullback for LAD, LCx, and RCA vessels are displayed in **Figure 5B**. Disagreement between angiography and iFR pullback was significantly higher in the RCA than LAD: 24 of 26 (92%) versus 83 of 122 (68%), respectively; p = 0.041.

FIGURE 4 Agreement in Lesion Number Appropriate for Revascularization Based on Angiography and iFR Pullback
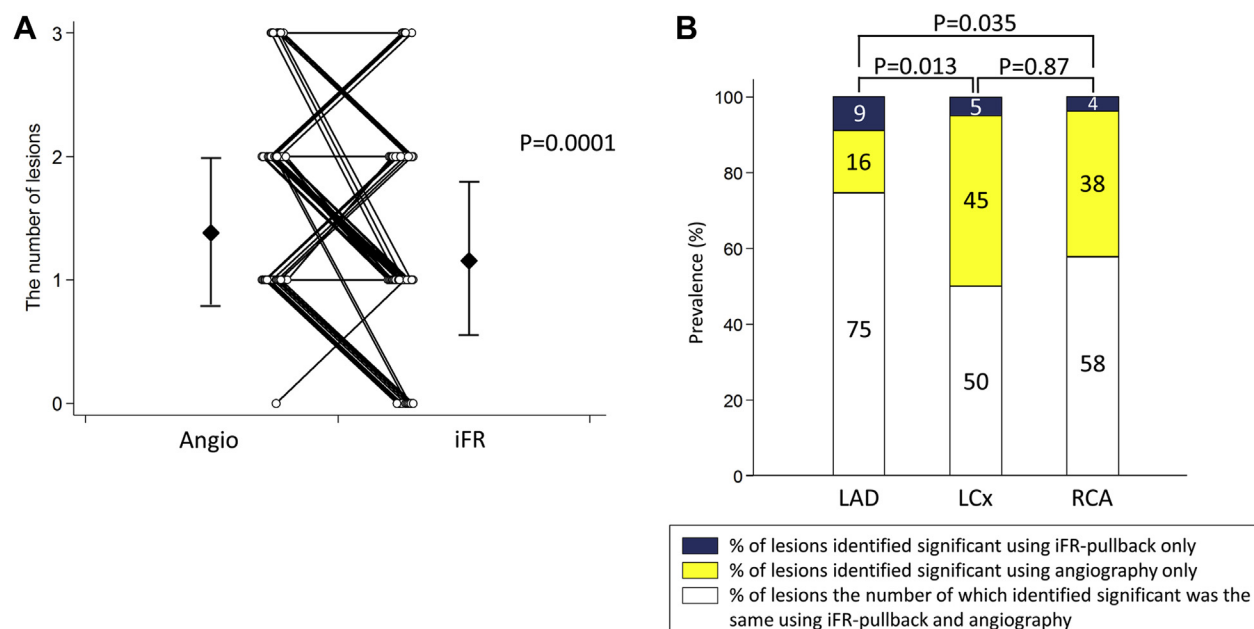
(A) The number of lesions identified as hemodynamically significant using angiography versus iFR pullback across the population. (B) The agreement in number of lesions identified as hemodynamically significant based on angiography and iFR pullback for LAD, LCx, and RCA vessels. In 16% of 122 LAD arteries, operators decided that the lesions were significant using angiography alone (**blue box, left column**). Angio = angiography; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; other abbreviations as in **Figure 1**.

FIGURE 5   Agreement in Total Lesion Length for Revascularization Based on Angiography and iFR Pullback
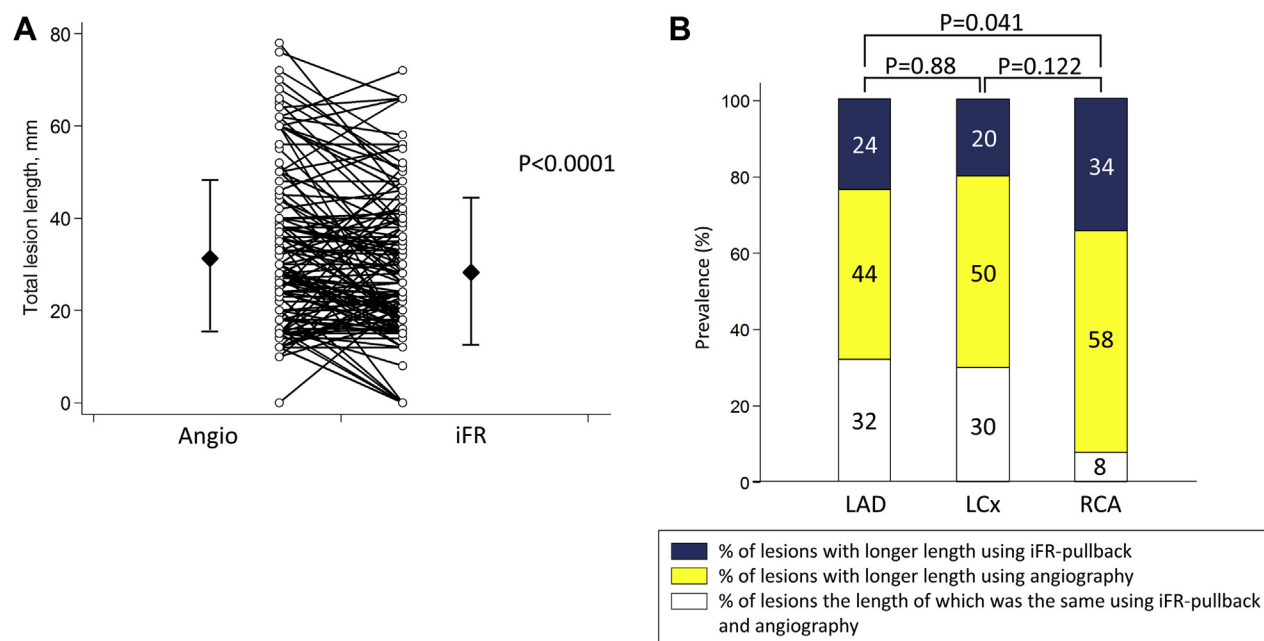
(A) The total lesion length identified for stenting using angiography versus iFR pullback across the population. **(B)** The agreement in length of targets for revascularization based on angiography and iFR pullback for LAD, LCx, and RCA vessels. Abbreviations as in **Figures 1 and 4**.

UNIVARIATE AND MULTIVARIABLE PREDICTORS OF THE DIFFERENCE BETWEEN iFR$_{pred}$ AND iFR$_{obs}$. The only univariate and multivariate predictor identified for the difference between iFR$_{pred}$ and iFR$_{obs}$ was iFR pullback measurement in culprit vessels in patients with acute coronary syndrome (ACS) (unstable angina or NSTEMI) ($\beta = 0.03$, 95% confidence interval: 0.002 to 0.058; p = 0.033 for univariate analysis; $\beta = 0.031$, 95% confidence interval: 0.003 to 0.058; p = 0.030 for multivariable analysis). Age (p = 0.75), sex (p = 0.64), diabetes mellitus (p = 0.97), hypertension (p = 0.31), hyperlipidemia (p = 0.95), creatinine (p = 0.75), smoker (p = 0.54), pre-PCI iFR (p = 0.5), number of lesions (p = 0.84), and total stent length (p = 0.28) were not significant predictors of the difference between iFR$_{pred}$ and iFR$_{obs}$.

DISCUSSION

This prospectively designed multicenter registry demonstrated that online iFR pullback predicted the physiological outcome of PCI with a high degree of accuracy. Compared with angiography alone, the addition of online iFR pullback data altered revascularization procedural planning in nearly one-third of patients.

PREDICTION OF PHYSIOLOGICAL OUTCOME USING iFR PULLBACK. iFR pullback accurately predicted post-PCI iFR physiological gains (virtual PCI), as demonstrated by the close correlation between predicted and measured post-PCI iFR values and the small absolute difference in iFR values. The mean difference between predicted iFR and observed iFR in the present study was 0.01 ± 0.004. This compares favorably to coronary occlusive pressure FFR models that report a mean difference of 0.03 ± 0.04 and 0.04 ± 0.066 for a varying proximal and a varying distal lesion, respectively (7).

Important for the realistic clinical application of virtual PCI planning, iFR pullback can be rapidly performed in the presence of diffuse and tandem coronary disease using online tools, and the data contained within can be easily used to predict the post-PCI physiological result (**Figure 2**). Furthermore, physiological mapping of the vessel using iFR pullback allows the pressure tracing itself to identify the lesions with the greatest hemodynamic impact upon flow. This marks an important distinction from an FFR pullback approach, which remains dependent on operator identification of angiographic lesions of interest.

PRE-PCI PROCEDURAL PLANNING TO OBTAIN A PHYSIOLOGICALLY FAVORABLE RESULT. Before physical PCI is commenced, iFR pullback data can inform the clinician whether their proposed strategy will improve coronary physiology sufficiently to achieve a physiologically favorable outcome. Conversely, with an FFR strategy, operators must commit to performing an initial PCI of the lesion before subsequent stent placement can be determined. Current recommended FFR practice mandates treating the lesion with the largest pressure drop first, followed by repeated remeasurement and subsequent stenting of the next largest pressure drop and so on (12,13). On occasion, this approach can require stenting of the proximal part of the vessel, followed by subsequent distal lesion intervention. Accordingly, procedural difficulty can be encountered in stent delivery across the proximal stented segment (12). This iterative approach is comparatively time consuming and involves prolonged infusions of adenosine, which are associated with a high incidence of unpleasant patient side effects (3,4). The findings of the current study support that resting iFR pullback assessment provides a simpler and easier prediction of physiological gain in tandem and diffuse disease.

iFR PULLBACK DATA ALTER OPERATOR REVASCULARIZATION DECISION MAKING. In comparison with angiography alone, the availability of iFR pullback data altered the number of hemodynamically significant lesions and total lesion length to treat by 52 (31%) and 121 (72%) of 168 vessels, respectively. Although it is not yet possible to ascertain whether this translates into different clinical outcomes, these results suggest that even within a single coronary artery, selection of the lesion(s) initially planned for PCI are altered upon receiving iFR pullback data. This study finding provides additive information to the previously reported FFR RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) study, where alterations in revascularization decision making following the addition of FFR to angiographic assessment alone were limited to the vessel rather than lesion level (14). By adopting a lesion-level approach to revascularization planning, treatment modalities such as PCI, CABG, or optimal medical therapy can be considered in light of the physiological characteristics of the entire coronary vessel. In such circumstances, the heart team may be more inclined to recommend CABG or optimal medical therapy for a

FIGURE 6 Schematic Representation of the Effect of PCI on Coronary Flow and its Implication for Post-PCI FFR and iFR Measurements

(A) Hyperemic coronary flow increases variably post stenting, thereby altering the hyperemic trans-stenotic pressure gradients in remaining lesions unpredictably. **(B)** Resting flow velocity remains stable post stenting, leaving trans-stenotic pressure gradients in remaining lesions unchanged. FFR = fractional flow reserve; other abbreviations as in **Figure 1**.

patient with physiologically diffuse disease so as to avoid very long segments of stent. Conversely, physiologically focal disease may be adequately treated with a minimum of stents, thereby potentially avoiding the need for CABG or a more extensive PCI strategy.

THE DIFFERENCE IN PREDICTION OF PHYSIOLOGICAL OUTCOME BETWEEN USING RESTING iFR AND HYPEREMIC FFR. The present study demonstrated that in tandem or diffuse disease, the difference between predicted iFR outcome and observed measured iFR values was 1.4%. This is lower than the previously reported 4% error for FFR measurements performed with coronary occlusive pressure correction and the 11% error for FFR measurements performed without coronary occlusive pressure

correction (7,15). Such comparatively large discrepancies occur with FFR because hyperemic flow increases variably post-stenting, thereby altering the trans-stenotic pressure gradient in remaining lesions unpredictably. By contrast, resting flow velocity remains stable after successful dilatation of an epicardial lesion, leaving trans-stenotic pressure gradients in remaining lesions largely unchanged (Figure 6) (5,9). Moreover, hyperemic microvascular resistance can reduce after stenting, which will alter hyperemic flow velocity yet further (16). Hyperemic flow velocity is more widely distributed in the assessment of intermediate lesions in a coronary artery, whereas resting flow velocity is narrowly distributed (5,9). This feature of resting flow permits more accurate post-PCI prediction of physiological outcome with iFR, as compared with predictions made with hyperemic FFR (11).

PREDICTION OF PHYSIOLOGICAL OUTCOME IN PATIENTS WITH ACS. Univariate and multivariable regression analysis identified that the only variable to influence the predictive power of iFR pullback was whether the iFR measurement was performed in culprit vessels in patients presenting with unstable angina and NSTEMI. This finding is entirely expected due to alterations in microcirculatory function that are known to characterize ACS states (17,18). Our results suggest prediction of post-PCI iFR values in the context of ACS could be higher by approximately 3%.

STUDY LIMITATIONS. Unmeasured intraobserver and interobserver error may have influenced the findings of our study. Potential sources of operator error include differences in the mental coregistration of the angiographic position of the pressure gradient on the iFR pullback curve. In this study, operators were required to observe physiological pullback data and angiographic information at the same time and mentally coregister the 2 pieces of information. Furthermore, visual angiographic grading of lesion length is likely to have varied between operators, but this practice remains representative of routine clinical care.

Unlike FFR, the relationship between post-PCI iFR values and patient outcomes is not yet known. Accordingly, this analysis does not extend to any predictions regarding clinical outcomes, and should be considered primarily as physiologically descriptive, as well as an assessment of the accuracy of virtual PCI using the iFR in a clinically representative patient cohort. However, with the recent reporting of the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome) randomized clinical trials, future analyses determining the relationship between post-PCI iFR values and patient outcomes will be forthcoming. Furthermore, the present study cannot demonstrate that the change in interventional procedural strategy as a result of iFR pullback translates into a more favorable clinical course for the patient. Although the use of fewer stents may be hypothesized to reduce future stent-related complications (and cost), dedicated studies that prospectively randomize patients to either an iFR pullback–guided treatment strategy versus an angiography-guided treatment strategy are required to determine whether an iFR pullback strategy is prognostically superior.

The iFR-based virtual PCI prediction model assumes a physiologically perfect result from any stents placed. Because stent optimization was only performed angiographically, it is possible that the small margin of error demonstrated within this study may be even further reduced with the adjunctive use of intracoronary imaging techniques.

Decision making after angiography alone and after iFR pullback were compared, but these operators' decision was not blinded in this study. This reflects the source of the data of this analysis being obtained from a clinical registry. Although the lack of blinding of the operator to the iFR pullback data may be considered a limitation, it is reflective of real-world clinical practice, in so much that operators are able to review all available clinical information before determining the pattern of disease and deciding on a definitive revascularization strategy. Indeed, in only 1 situation (0.6%) did an operator appear to change their clinical decision regarding the presence of disease from 0 (indicating no significant flow-limiting epicardial lesion) to 1 (indicating a coronary lesion was present) following the review of the iFR pullback data in an unblinded fashion (Table 2).

CLINICAL IMPLICATIONS. In this study, online iFR pullback was used to quantify the hemodynamic impact of individual lesions in tandem or diffuse disease and predict the improvement in iFR units post-PCI. In the planning of revascularization, online iFR pullback may be useful to evaluate whether a particular proposed PCI strategy might be expected to achieve a physiologically favorable result, even when single or multiple lesions within diffusely diseased vessels are observed.

CONCLUSIONS

This multicenter registry study demonstrates that on-line iFR pullback performed under resting conditions predicted the physiological outcome of PCI with a high degree of accuracy. Compared with angiography alone, availability of online iFR pullback data significantly decreased the number and length of hemodynamically significant lesions identified for revascularization. Overall, revascularization procedural planning was altered in nearly one-third of patients.

ADDRESS FOR CORRESPONDENCE: Dr. Justin E. Davies, Department of Cardiology, Imperial College London, The Hammersmith Hospital, B block South, 2nd Floor, NHLI-Cardiovascular Science, Du Cane Road, London W12 0NN, United Kingdom. E-mail: justindavies@heart123.com.

PERSPECTIVES

WHAT IS KNOWN? In a previous single-center, small, patient cohort study, offline computation and analysis of iFR pullback data accurately predicted the physiological outcome of revascularization in patients with diffuse or tandem disease.

WHAT IS NEW? In this prospectively designed, multicenter registry, online computation and analysis of iFR pullback data predicted physiological outcomes from virtual PCI with a high degree of accuracy. Compared with angiography alone, availability of online iFR pullback data significantly decreased the number and length of hemodynamically significant lesions identified for revascularization. Overall, revascularization procedural planning was altered in nearly one-third of patients.

WHAT IS NEXT? Further studies are required to assess whether iFR pullback guidance confers any clinical outcome and/or cost benefit over and above iFR or FFR alone guided revascularization strategies.

REFERENCES

1. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949–3003.

2. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:2212–41.

3. Davies JE, Sen S, Dehbi H-M, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med 2017;376:1824–34.

4. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med 2017; 376:1813–23.

5. Nijjer SS, Petraco R, van de Hoef TP, et al. Change in coronary blood flow after percutaneous coronary intervention in relation to baseline lesion physiology: results of the JUSTIFY-PCI study. Circ Cardiovasc Interv 2015;8:e001715.

6. Pijls NHJ, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation 2002;105:2950–4.

7. De Bruyne B, Pijls NH, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and animal validation. Circulation 2000;101:1840–7.

8. 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;59:1392–402.

9. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. Circ Res 1978;43: 242–53.

10. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med 1994;330: 1782–8.

11. Nijjer SS, Sen S, Petraco R, et al. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. J Am Coll Cardiol Intv 2014;7:1386–96.

12. Kim H-L, Koo B-K, Nam C-W, et al. Clinical and physiological outcomes of fractional flow reserve-guided percutaneous coronary intervention in patients with serial stenoses within one coronary artery. J Am Coll Cardiol Intv 2012;5:1013–8.

13. Park S-J, Ahn J-M, Pijls NHJ, et al. Validation of functional state of coronary tandem lesions using computational flow dynamics. Am J Cardiol 2012; 110:1578–84.

14. Curzen N, Rana O, Nicholas Z, et al. Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain? The RIPCORD study. Circ Cardiovasc Interv 2014;7: 248–55.

15. 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; 102:2371–7.

16. Verhoeff B-J, Siebes M, Meuwissen M, et al. Influence of percutaneous coronary intervention on coronary microvascular resistance index. Circulation 2005;111:76–82.

17. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. N Engl J Med 1994;331: 222–7.

18. Cuculi F, De Maria GL, Meier P, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64: 1894–904.

KEY WORDS coronary artery disease, instantaneous wave-Free Ratio, physiological lesion assessment, stenosis

APPENDIX For a supplemental figure, please see the online version of this paper.