Discordance Between Resting and Hyperemic Indices of Coronary Stenosis Severity: The VERIFY 2 Study

Barry Hennigan[1,2] MBBChBAO, BMedSci, Keith G Oldroyd[1,2] MBChB, MD (Hons), Colin Berry[1,2] MBChB, MD, PhD, Nils Johnson[3] MD, MS John McClure[2] Ph.D., Peter McCartney[1] MBChB , Margaret B McEntegart[1] MBChB, PhD, Hany Eteiba[1] MBChB, BSc, Mark C Petrie[1] MBChB, BSc, Paul Rocchiccioli[1] MBChB, MD, Richard Good[1] MBBS, MD, Martin M Lindsay[1] MBChB, MD , Stuart Hood[1] MBChB, MD, Stuart Watkins[1] MBChB, MD.

1= University of Glasgow 2=Golden Jubilee National Hospital, Clydebank, Glasgow 3= The Weatherhead PET Imaging Center, Houston, Texas, U.S.A.

Disclosures: There was no industry involvement in any aspect of this study. Professor Berry has undertaken research, consulting and lectures for St Jude Medical based on contracts with The University of Glasgow. Professor Oldroyd has received honoraria for consultancy and lectures from St Jude Medical and Volcano Corporation. NPJ receives internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis; and significant institutional research support from St. Jude Medical (for NCT02184117) and Volcano/Philips Corporation (for NCT02328820), makers of intracoronary pressure and flow sensors.

Corresponding author: Dr Barry Hennigan @ barryhennigan@physicians.ie,

Phone: 00441419515000 extension 5331

Word count= 5348

Subject Codes:

Percutaneous Coronary Intervention

Revascularisation

Coronary Revascularisation

Fractional Flow Reserve

Abstract

Background: Distal coronary to aortic pressure ratio (Pd/Pa) and instantaneous wave-free ratio (iFR®) are indices of functional significance of a coronary stenosis measured without hyperemia. It has been suggested that iFR® has superior diagnostic accuracy to Pd/Pa when compared to Fractional Flow Reserve (FFR).

Hypotheses: In comparison to FFR, revascularization decisions based on either binary cut-off values for iFR and Pd/Pa or hybrid strategies incorporating iFR® or Pd/Pa will result in similar levels of disagreement.

Methods and Results: A prospective study in consecutive patients undergoing FFR for clinical indications using proprietary software to calculate iFR®. We measured Pd/Pa, iFR®, FFR and hyperemic iFR (HiFR). Diagnostic accuracy vs FFR <0.80 was calculated using binary cut-off values of ≤0.90 for iFR® and ≤0.92 for Pd/Pa and adenosine zones for iFR® of 0.86-0.93 and Pd/Pa of 0.87-0.94 in the hybrid strategy.

197 patients with 257 stenoses (mean DS 48%) were studied. Using binary cut-offs diagnostic accuracy was similar for iFR and resting Pd/Pa with misclassification rates of 21% vs 20.2%, p= 0.85. In the hybrid analysis, 54% of iFR cases and 53% of Pd/Pa cases were outside the adenosine zone and rates of misclassification were 9.4% vs 11.9%, p=0.55.

Conclusions: Binary cut-off values for iFR and Pd/Pa result in misclassification of 1 in 5 lesions. Using a hybrid strategy approximately half of the patients do not receive adenosine but 1 in 10 lesions are still misclassified. The use of non-

hyperaemic indices of stenosis severity cannot be recommended for decision making in the cath lab.

Clinical Trial Registration: NCT02377310

https://clinicaltrials.gov/ct2/show/NCT02377310

Keywords

FFR

iFR

Coronary Physiology

Introduction

Fractional flow reserve (FFR) is the ratio of distal coronary pressure to aortic pressure (Pd/Pa) across a stenosis measured during maximal hyperemia, most commonly achieved by the intra-coronary or intra-venous administration of adenosine. Multiple studies have demonstrated that FFR guided revascularization improves clinical outcomes compared to angiographic guidance alone (1-3). This has resulted in a Class 1 recommendation from the ESC and a Class 2a recommendation from the ACC/AHA for the use of FFR (4, 5). Despite this, there has only been limited adoption of FFR into routine clinical practice (6). Some observers have suggested that this is due to the need to induce maximal hyperemia to measure FFR and have consequently studied and promoted the use of resting (non-hyperemic) indices of stenosis severity including Pd/Pa (7,8) and the instantaneous wave free ratio (iFR®) which through utilization of a patented algorithm measures the trans-stenotic pressure ratio in the so called “wave free period” of diastole (9). Initially it was proposed that iFR® could be utilized for decision making using a dichotomous cut-off value in a similar fashion to FFR. In the ADVISE registry (n=339 stenoses) an iFR® value of ≤0.89 provided 80% agreement with the widely used FFR cut-off value of ≤0.80 (10).

At present, there are several ongoing clinical studies utilizing iFR for decision making in the catheter laboratory. In the DEFINE FLAIR (NCT02053038) and iFR SWEDEHEART (NCT02166736) trials patients are randomized to iFR (no

adenosine) or FFR-guided management using a binary cut-off for iFR of <0.90 and the usual FFR cut-off value of ≤0.80. In the SYNTAX II study (NCT02015832), in an effort to improve agreement with FFR, a hybrid decision making strategy is employed in which if the iFR is between 0.86 to 0.93, adenosine is administered and Percutaneous Coronary Intervention (PCI) performed if the FFR is ≤0.80. If the iFR is < 0.86, PCI is performed anyway without any FFR measurement and if the iFR is > 0.93, no PCI is performed.

Compared to standard of care FFR guided decision-making, this study sought to quantify the rates of inappropriate and/or incomplete revascularization with strategies utilising resting indices of stenosis severity. Specifically, we compared the levels of agreement between iFR and Pd/Pa based algorithms using the previously described optimal cut-off values of ≤0.90 for iFR® and ≤0.92 for Pd/Pa (binary strategy) and the previously described adenosine zones for iFR® of 0.86-0.93 and Pd/Pa of 0.87-0.94. We hypothesized that rates of diagnostic accuracy would be similar with both resting indices and both strategies.

Methods

This is a single center prospective study in near consecutive patients undergoing pressure wire studies for standard indications. The project was based on approval from the UK National Research Ethics Service, and

management approval in the Golden Jubilee National Hospital, Glasgow. All patients were required to provide written informed consent for their data to be recorded and analyzed. Patients aged 18 to 90 years old with angiographically intermediate coronary stenoses in which FFR measurement was clinically indicated were eligible to be included. Standard exclusion criteria for pressure wire studies applied and included the following; severe calcific coronary disease, severe tortuosity rendering pressure wire studies difficult or impossible, recent myocardial infarction within the previous 72 hours, ongoing unstable chest pain, known intolerance of adenosine or severe asthma.

Prior to being admitted to the cardiac catheterization laboratory patients had a large bore cannula inserted in an antecubital fossa vein for the administration of intravenous (IV) adenosine (140 mcg/kg/min) as per standard institutional practice. Following diagnostic angiography, the Volcano Prestige® or Verrata® Wire (Volcano Corporation, Rancho Cordova, CA) was inserted into the guide catheter, calibrated and passed to the distal third of the coronary artery beyond the lesion of interest. Once in position and following the administration of intra-coronary isosorbide dinitrate (200mcg), resting Pd/Pa was recorded followed by iFR®. Then IV adenosine was administered until conditions of stable maximal hyperemia had been established. Both minimum and steady state FFR were noted and finally HiFR was measured again in duplicate. Care was taken to ensure FFR was recorded during stable haemodynamic conditions with a consistent FFR reading for ≥ 5 beats denoting steady state values. The adenosine was then stopped and the wire withdrawn to the guide catheter to

check for “pressure drift”. If pressure drift of > 0.03 was detected the data acquisition was repeated. The data was stored on the Volcano s5® Console HDD with intermittent anonymized data backup to an encrypted hard disk drive for archiving and external core lab analysis. The results were recorded on a standardized case report form by the operating cardiologist and further patient demographics and risk factor data were extracted from the online electronic patient record and tabulated for analysis. All vessels were analyzed for QCA data by an interventional cardiologist (BH and PM) blinded to the pressure wire data on a Centricity CA 1000 Cardiac Review 1.0 workstation. Syntax scores were calculated before and after PCI using version 2.11 of the online Syntax Score Calculator. The well validated Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) (11) score was used to describe the percentage of myocardium at risk based on visual and QCA estimation of stenosis ≥50%. Multiple QCA parameters were analyzed to explore variation in rates of misclassification versus FFR ≤0.80.

Statistics

The statistical analysis for the main study hypothesis was performed by a biostatistician (JM) who was independent of the clinical research team. The null hypothesis was that there would be no difference in the level of agreement with FFR between iFR and resting Pd/Pa. To ensure that the limits of a two-sided 95% confidence interval would exclude a difference in agreement of at least 5%

with 80% power we determined that 254 vessels would have to be studied. Data was anonymized, transferred and analysed according to the predetermined statistical plan without any further consultation between the chief investigator and statistician. Pearson Chi square tests, Fisher's exact test and the McNemar test were performed where appropriate to assess for statistical significance. We analyzed the data and produced summary statistics using SPSS statistics package Version 21.0. Armonk, NY: IBM Corp. We compared iFR®, HiFR and Pd/Pa with FFR using correlation coefficients and generated Receiver-Operating Characteristic (ROC) curves to determine the discriminatory power of iFR® and Pd/Pa outside the pre-specified adenosine ranges for Pd/Pa of 0.87-0.94 inclusive and for iFR of 0.86-0.93 inclusive as well as for the binary cut-off values of ≤0.92 for Pd/Pa and ≤0.90 for iFR®. ROC curves were compared with DeLong's test (12) using the pROC package (13) in R (http://www.R-project.org/). We calculated rates of inappropriate and incomplete revascularization associated with each of the treatment strategies involving Pd/Pa and iFR® and compared these to an FFR only guided strategy. Segment location and QCA parameters were analyzed to determine whether they affected the diagnostic accuracy of the non-hyperemic indices. The primary endpoint was the level of agreement of iFR® versus Pd/Pa using binary cut-off values in reference to FFR ≤0.80.

Results

Study Population We studied 197 patients with 257 moderate coronary stenoses. The clinical characteristics of these patients are shown in Table 1. The vessels studied had mean (SD) diameter stenosis of 48 (13)% and a mean (SD) area stenosis of 71 (14)%. Mean (SD) lesion length was 16.4 (10.3) mm. The mean FFR in our study was 0.81 +/- 0.09 (Figure 1) as compared to a mean of 0.83 +/- 0.11 in ADVISE 2 (14). The mean (SD) APPROACH score was 21.6 (16.6)%. The resting pressure measurements were recorded before the FFR measurements, therefore the operator was unaware of the FFR results at the time of the iFR® and Pd/Pa recordings. Of the 257 lesions, 84 (33%) were classified as complex on the basis of exhibiting two or more of the following: thrombus, ulceration, irregularity, moderate to severe calcification or bifurcation location.

Agreement with FFR using Binary Cut-Off Values for iFR and Pd/Pa

Correlation coefficients (Spearman's rho values) for Pd/Pa vs FFR and iFR® vs FFR were similar at 0.752 and 0.733 respectively (Table 2). Using the

RESOLVE study (15) cut-off values for iFR® at ≤0.90 and Pd/Pa ≤0.92 (Figure 2) the level of misclassification compared to FFR ≤0.80 was similar: 21% versus 20.2% p= 0.85 (Table 3). The area under the ROC curve for iFR® and Pd/Pa were 0.853 vs 0.858, p=0.79 (Figure 3). As previously reported the relationship between Pd/Pa and iFR® was highly linear: iFR® = 1.502 * Pd/Pa - 0.503 (r=0.98).

Agreement with FFR using Hybrid Algorithms (iFR-FFR and Pd/Pa-FFR)

In the hybrid analysis, 54% of cases were outside the pre-specified adenosine zone of 0.86-0.93 for iFR® and 53% of cases were out with pre-specified adenosine zone of 0.87-0.94 for Pd/Pa. In all vessels the rates of misclassification were 9.4% for iFR and 11.9% for Pd/Pa, p=0.55 (Table 4). Sensitivities and specificities (%) are shown in table 5 according to index and cut-off value.

Levels of Incomplete Revascularization and Inappropriate PCI

Using binary cut-off values (versus the gold standard of FFR≤0.80 for ischemia), the numbers of inappropriate PCI were 26/257(10%) for iFR and 25/257(9.7%) for Pd/Pa, p=1.00 and the numbers of incomplete revascularization were 28/257(11%) for iFR and 27/257(10.5%) for Pd/Pa, p=1.00. Using the hybrid strategy, the rates of inappropriate PCI were 2/139(1.4%) for iFR and 0/135(0%) for Pd/Pa, p=0.16 and the rates of incomplete revascularization were 11/139(8%) for iFR and 16/135(11.9%) for Pd/Pa, p=0.10.

Proximal vs non-proximal coronary segments

We analysed iFR and Pd/Pa based decision making strategies in stenoses in proximal coronary vessels (Syntax segments 1, 5, 6 and 11) compared to all other lesions.

Binary strategy: Using iFR® the levels of misclassification were 27.7% in proximal stenoses vs 15.2% in non-proximal stenoses, p=0.014 (Table 6). Using Pd/Pa the levels of misclassification were 24.4% in proximal stenoses vs 16.7% in non-proximal stenoses, p=0.12.

Hybrid strategy: Using iFR the levels of misclassification were 8.3% in proximal stenoses vs 10.1% in non-proximal stenoses, p=0.77. Using Pd/Pa the levels of misclassification were 14.1% in proximal stenoses vs 9.9% in non-proximal stenoses, p=0.60. (Table 7).

Levels of Agreement Excluding vessels with Grey Zone FFR Values

When all vessels with an FFR 0.75-0.80 are excluded the rates of misclassification were 16.8% for iFR and 15.3% for Pd/Pa (p=0.66) using the binary cut-off values as per the primary study analysis. When using the hybrid strategy cut-off values the rates of misclassification were 3.4% for iFR and 4.2% for Pd/Pa, p=1.00.

Discussion

The RESOLVE study was the first multi-centre, core-lab adjudicated independent comparative analysis of iFR and resting Pd/Pa using the proprietary Volcano Corporation Harvest™ software to calculate iFR® (n=1768 patients). RESOLVE confirmed 80% agreement between iFR® and FFR with an optimal cut-off value for iFR® of 0.90 (15). The level of agreement between Pd/Pa and FFR was 81% with an optimal cut off value of 0.92, confirming the results of the previously published VERIFY study (16) and the subsequent ADVISE II study (14). Although first described as an 'adenosine-independent index', in fact, the value of iFR® falls significantly with adenosine as first demonstrated in the VERIFY study, confirming that myocardial resistance during the wave free period is neither minimal nor equivalent to mean whole cardiac cycle resistance during hyperemia (16).

Our results indicate that there is no diagnostic advantage to utilizing a vendor-specific iFR® guided revascularization strategy beyond that which is already available on all pressure sensing guidewire/microcatheter systems utilizing Pd/Pa. The results also indicate that operators who routinely utilize resting indices for decision making can anticipate a 1 in 5 level of misclassification compared to FFR (Figure 4) with the binary cut-off strategy and a 1 in 10 level of misclassification compared to FFR utilizing a hybrid strategy regardless of whether Pd/Pa or iFR® is used, again in line with previous published studies. As a result of this we cannot recommend the use of resting indices in clinical practice at present. Beyond that, the multicenter CONTRAST Study which involved 763 subjects enrolled in 12 international centres, has shown that simple

contrast hyperemia has a superior diagnostic ability than resting indices and therefore institutions with limited access to hyperemic agents could consider contrast hyperemia as a superior alternative (17). Notably, and in contrast to Pd/Pa, iFR® was associated with a higher rate of misclassification in proximal vs. non-proximal lesions. This observation relates to the fact that proximal stenoses generally subtend larger myocardial territories and manifest higher increases in coronary blood flow when vasodilators are administered (18). Accordingly a small "negative" resting gradient may develop into a clinically significant FFR value during hyperaemia (Figure 4). At least in our estimation, a decision making strategy based on resting pressures represents a sub-optimal and currently non-evidence based approach. There are two ongoing non-inferiority studies comparing the clinical outcomes of patients undergoing iFR vs FFR guided PCI using binary cut-off values and therefore no hyperaemia at all in the patients allocated to iFR guidance (19). Although these studies will provide important data on clinical outcomes using iFR guidance a potentially more appropriate study design to test would require randomization to revascularisation or not of patients in whom iFR and FFR provide divergent treatment decisions.

Strengths and Weaknesses of this Study

Although we conducted a single center study, the results are nonetheless clinically relevant. Our data were obtained during routine clinical care, represent a contemporary, real world experience of prospectively collected data and were analyzed using proprietary software. None of the recordings were excluded. The

mean FFR value in our population was very close to the cut-off value of 0.80 used for decision making confirming that FFR assessment was appropriately used and that the comparative analyses between resting and hyperemic indices conducted were not skewed by a preponderance of extreme values.

The global adoption of coronary physiology guided management is increasing with up to 30% usage in the U.S.A. following the recent publication of appropriate use criteria (20). As uptake increases, so education and training becomes increasingly important, especially for clinicians who may be less familiar with the differential accuracy of resting and hyperaemic indices of stenosis severity. The hybrid decision making strategies may in fact add to the complexity of interpretation of results and in doing so paradoxically increase operator reluctance to utilise pressure wire technology. A further concern with the hybrid strategy is that the value of FFR will remain unknown up to half of the patients, precluding any clinically relevant assessment of the recently demonstrated relationship between FFR and prognosis which may be a questionable trade off for many cardiologists (21).

Acknowledgements

We thank our patients, medical, nursing and cardiac physiology staff who supported this study.

Dr. Hennigan was supported by British Heart Foundation Project Grant

PG/14/97/31263 and an institutional grant from the British Heart Foundation **RE/13/5/30177** to the University of Glasgow.

References

1. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–224.

2. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N,Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional Flow Reserve–Guided PCI for Stable Coronary Artery Disease. N Engl J Med 2014;371:1208–1217.

3. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bär F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis. Journal of the American College of Cardiology 2007;49:2105–2111.

4. Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A; European Society of Cardiology Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol Ç, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; EACTS Clinical Guidelines Committee, Sousa Uva M, Achenbach S, Pepper J, Anyanwu A, Badimon L, Bauersachs J, Baumbach A, Beygui F, Bonaros N, De Carlo M, Deaton C, Dobrev D, Dunning J, Eeckhout E, Gielen S, Hasdai D, Kirchhof P, Luckraz H,

Mahrholdt H, Montalescot G, Paparella D, Rastan AJ, Sanmartin M, Sergeant P, Silber S, Tamargo J, ten Berg J, Thiele H, van Geuns RJ, Wagner HO, Wassmann S, Wendler O, Zamorano JL; Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery; European Association of Percutaneous Cardiovascular Interventions.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;35:2541–2619.

5. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS,Foody JM, Gerber TC, Hinderliter AL, King SB 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation. ACCF/AHA/ACP/AATS/PCNA/SCAI/ STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2012;126:3097–3137.

6. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary Patterns of Fractional Flow Reserve and Intravascular Ultrasound Use Among Patients Undergoing Percutaneous Coronary Intervention in the United States. Journal of the American College of Cardiology 2012;60:2337–2339.

7. Mamas MA, Horner S, Welch E, Ashworth A, Millington S, Fraser D, Fath-Ordoubadi F, Neyses L, El-Omar M. Resting Pd/Pa measured with intracoronary pressure wire strongly predicts fractional flow reserve. J Invasive Cardiol 2010;22:260–265.

8. Kwon TG, Matsuzawa Y, Li J, Aoki T, Guddeti RR, Widmer RJ, Cilluffo RR, Lennon RJ, Lerman LO, Lerman A. Clinical usefulness of nonhyperemic baseline Pd/Pa as a hybrid baseline Pd/Pa-fractional flow reserve strategy. Coron Artery Dis 2015;26:49–55.

9. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE.Development and Validation of a New Adenosine-Independent Index

of Stenosis Severity From Coronary Wave–Intensity Analysis. Journal of the American College of Cardiology 2012;59:1392–1402.

10. Petraco R, Escaned J, Sen S, Nijjer S, Asrress KN, Echavarria-Pinto M, Lockie T, Khawaja MZ, Cuevas C, Foin N, Broyd C, Foale RA, Hadjiloizou N, Malik IS, Mikhail GW, Sethi A, Kaprielian R, Baker CS, Lefroy D, Bellamy M, Al-Bustami M, Khan MA, Hughes AD, Francis DP, Mayet J, Di Mario C, Redwood S, Davies JE. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical pop- ulation of intermediate coronary stenoses: results of the ADVISE registry. EuroIntervention 2013;9: 91–101.

11. Ortiz-Pérez JT, Meyers SN, Lee DC, Kansal P, Klocke FJ, Holly TA, Davidson CJ, Bonow RO, Wu E., Angiographic estimates of myocardium at risk during acute myocardial infarction: validation study using cardiac magnetic resonance imaging. Eur Heart J. 2007 Jul;28(14):1750-8.

12. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988 Sep;44(3):837-45.

13. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, Müller M. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics. 2011 Mar 17;12:77.

14. Escaned J, Echavarría-Pinto M, Garcia-Garcia HM, van de Hoef TP, de Vries T, Kaul P, Raveendran G, Altman JD, Kurz HI, Brechtken J, Tulli M, Von Birgelen C, Schneider JE, Khashaba AA, Jeremias A, Baucum J, Moreno R, Meuwissen M, Mishkel G, van Geuns RJ, Levite H, Lopez-Palop R, Mayhew M, Serruys PW, Samady H, Piek JJ, Lerman A; ADVISE II Study Group. ADVISE II Study Group. Prospective Assessment of the.Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance : Results of ADVISE II International, Multicenter Study (ADenosine Vasodilator Independent Stenosis Evaluation II) JACC Cardiovasc Interventions. 2015 May;8(6):824-33.

15. Jeremias A, Maehara A, Généreux P, Asrress KN, Berry C, De Bruyne B, Davies JE, Escaned J, Fearon WF, Gould KL, Johnson NP, Kirtane AJ, Koo BK, Marques KM, Nijjer S, Oldroyd KG, Petraco R, Piek JJ, Pijls NH, Redwood S, Siebes M, Spaan JA, van 't Veer M, Mintz GS, Stone GW.Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. J Am Coll Cardiol. 2014 Apr 8;63(13):1253-61.

16. Berry C, van 't Veer M, Witt N, Kala P, Bocek O, Pyxaras SA, McClure JD, Fearon WF, Barbato E, Tonino PA, De Bruyne B, Pijls NH, Oldroyd KG.VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice):

a multicenter study in consecutive patients. Journal of the American College of Cardiology 2013;61:1421–1427.

17. Johnson NP, Jeremias A, Zimmermann FM, Adjedj J, Witt N, Hennigan B, Koo BK, Maehara A, Matsumura M, Barbato E, Esposito G, Trimarco B, Rioufol G, Park SJ, Yang HM, Baptista SB, Chrysant GS, Leone AM, Berry C, De Bruyne B, Gould KL, Kirkeeide RL, Oldroyd KG, Pijls NH, Fearon WF. Continuum of Vasodilator Stress From Rest to Contrast Medium to Adenosine Hyperemia for Fractional Flow Reserve Assessment. J Am Coll Cardiol Intv. 2016;9(8):757-767.

18. De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, Van Crombrugge P, Heyndrickx GR, Wijns W. Fractional flow reserve in patients with prior myocardial infarction.Circulation 2001;104:157–162.

19. Götberg M, Christiansen EH, Gudmundsdottir I, Sandhall L, Omerovic E, James SK, Erlinge D, Fröbert O. Instantaneous Wave-Free Ratio versus Fractional Flow Reserve guided intervention (iFR-SWEDEHEART): Rationale and design of a multicenter, prospective,registry-based randomized clinical trial.Am Heart J. 2015 Nov;170(5):945-50.

20. Desai NR, Bradley SM, Parzynski CS, Nallamothu BK, Chan PS, Spertus JA, Patel MR, Ader J, Soufer A, Krumholz HM, Curtis JP. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary Intervention. JAMA 2015;314:2045.

21. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Domínguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jiménez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, López-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodés-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol. 2014 Oct 21;64(16):1641-54.

Figure Legends

Figure 1 Frequency Histogram of vessel number (where n=257) versus Steady state FFR value (Steady state FFR is conventional fractional flow reserve at the most stable point in hyperemia as observed by the operating cardiologist) with a y-axis reference line at the mean FFR value of 0.812.

Figure 2. Scatterplot demonstrating the relationship between FFR and iFR with a 0.90 cutoff for iFR (y-axis reference line) and 0.80 cut-off for FFR (x-axis reference line). (a)= false negative iFRs (b)= True negative iFRs (c)= True positive iFRs (d)= False positive iFRs.

Figure 3. Scatterplot demonstrating the relationship between Pd/Pa and FFR with a 0.92 cutoff for Pd/Pa (y-axis reference line) and 0.80 cut-off for FFR (x-axis reference line). (a)= false negative Pd/Pas (b)= True negative Pd/Pas (c)= True positive Pd/Pas (d)= False positive Pd/Pas.

Figure 4. Receiver Operator Characteristic Curves demonstrating diagnostic accuracy of iFR, Pd/Pa and HiFR in reference to FFR ≤0.80.
Delong's test p-values for 2 correlated ROC curves: iFR vs Pd/Pa: 0.793 HiFR vs iFR: 0.0001, HiFR vs Pd/Pa : 0.0003

Figure 5. 57 year old man who underwent coronary physiology 16 days post NSTEMI with troponin I of 0.2 ug/L. Moderate mid LAD disease with a QCA Diameter stenosis 50.25% with area stenosis of 75.25% . Pd/Pa= 0.95, iFR=0.94, FFR=0.80. Managed medically with no recurrence of angina reported at 2 years post MI.

Table 1 Clinical characteristics of study population (n=197)

	n	%
Male	136	69
Family History CAD	122	61.9
Diabetic	31	15.7
Hypertension	123	62.4
Smoking	48	24.4
Hyperlipidemia	133	67.5
Previous MI	73	37.1
Previous PCI	55	27.9
Vessels (n=257)		
LAD	148	57.6
RCA	45	17.5
LCX	37	14.4
OM	12	4.7
LMS	9	3.5
Diagonal	6	2.3

Clinical presentation	N=257	%
Stable Angina	129	50.1
NSTEMI	79	30.1
Unstable Angina	18	7.0
Atypical Chest Pain	13	5.1
Convalescent STEMI	8	3.0
CCF	5	2.0
Arrhythmia	3	1.2
Pre-Valve Surgery	2	1.0

Convalescent STEMI Patients (n=5) were as follows;

1. Non culprit LAD FFR within 24 hours of spontaneously resolved transient inferior ST elevation due to RCA culprit.
2. FFR of LAD and LPDA in a patient with a >48 hours late presenting Q wave MI due to an OM Culprit
3. FFR of LCX and RCA in a patient 19 days post late anterior STEMI
4. FFR LAD culprit vessel 2 months post successful thrombolysis with moderate residual plaque
5. FFR LCX and LAD in a patient with a late inferior STEMI > 4 days due to an RCA culprit.

CAD: coronary artery disease; MI: myocardial Infarction; PCI: Percutaneous coronary intervention; LAD: left anterior descending artery; LCx: left circumflex artery; RCA=Right coronary artery; OM=Obtuse marginal artery LMS= Left main stem artery; NSTEMI= Non ST elevation myocardial infarction; STEMI= ST elevation myocardial infarction; CCF= Congestive cardiac failure; LPDA= Left posterior descending artery

Table 2. Correlation coefficients between resting and hyperaemic indices

			Pd/Pa	iFR 1	Minimal FFR	Steady State FFR Value
Spearman's rho	Pd/Pa	Correlation Coefficient	1.000 N/A	.889 (P=0.001)	.743 (P=0.001)	.752 (P=0.001)
	iFR	Correlation Coefficient	.889 (P=0.001)	1.000 N/A	.720 (P=0.001)	.733 (P=0.001)
	Minimal FFR	Correlation Coefficient	.743 (P=0.001)	.720 (P=0.001)	1.000 N/A	.981 (P=0.001)
	Steady State FFR Value	Correlation Coefficient	.752 (P=0.001)	.733 (P=0.001)	.981 (P=0.001)	1.000 N/A
	H-iFR 1	Correlation Coefficient	.697 (P=0.001)	.727 (P=0.001)	.904 (P=0.001)	.913 (P=0.001)

Pd/Pa is resting whole cycle mean pressure ratio, iFR is the instantaneous wave-free ratio, Minimal FFR is conventional fractional flow reserve at the minimal observed ratio, Steady state FFR is conventional fractional flow reserve at the most stable point in hyperemia as observed by the operating cardiologist and Hyperemic iFR (H-iFR) is iFR analysis performed during steady state hyperemic conditions. NA= Not Applicable. P values indicated in parentheses below correlation coefficients.

Table 3. Sensitivity Analyses for iFR and Pd/Pa Using Defined Binary Cut-Off Compared with FFR.

	Value	FFR≤0.8	FFR>0.8	Misclassification (%)
iFR	≤0.9	81	26	21
	≥0.9	28	122	
Pd/Pa	≤0.92	82	25	20.2
	>0.92	27	123	

iFR vs Pd/Pa – McNemar's chi-squared = 0.03, df = 1, p-value = 0.85

Table 4. Sensitivity Analyses for iFR and Pd/Pa Using Defined adenosine zones Compared with FFR ≤0.80.

Modality	Value	Number (n)	Concordant (n)	Discordant (n)	Misclassification (%)
iFR*	<0.86	49	47	2	9.4
	>0.93	90	79	11	
Pd/Pa**	<0.87	27	27	0	11.9
	>0.94	108	92	16	

McNemar's chi-squared* = 0.3636, df = 1, p-value = 0.5465
*Lesions out with the iFR adenosine zone (0.86-0.93) 54.1% of vessels.
**Lesions out with the Pd/Pa adenosine zone (0.87-0.94) 52.5% of vessels.

Table 5. demonstrating the sensitivity, specificity, positive predictive value and negative predictive value (%) according to both binary and hybrid cut-offs for iFR and Pd/Pa.

Parameter and cut-off	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
iFR ≤0.90 Binary Cut-off	74.3	82.4	75.7	81.3
Pd/Pa ≤0.92 Binary cut-off	75.2	83.1	76.6	82
iFR 0.86-0.93 Adenosine Zone Hybrid Analysis	89.9	98.6	95.9	87.8
Pd/Pa 0.87-0.94 Adenosine Zone Hybrid Analysis	85.3	100	100	85.1

Table 6. Sensitivity Analyses for iFR in Proximal vs Distal segments Using ≤0.9 Cut-Off Compared with FFR .

Modality	Value	FFR≤0.8	FFR>0.8	Misclassification (%)
iFR proximal	≤0.9	33	15	27.7
	>0.9	18	53	
iFR distal	≤0.9	48	11	15.2
	>0.9	10	63	

Proximal (Syntax segments 1,11,5,6) vs Distal (Syntax segments ≠ 1,11,5,6) – Comparison of 2 proportions: 95% CI=(0.0248, 0.225), Pearson Chi-square test of association: p=0.014 Fisher's exact test: p=0.021

Table 7. Sensitivity Analyses for Pd/Pa in Proximal vs Distal segments Using ≤0.92 Cut-Off Compared with FFR .

	Value	FFR ≤ 0.8 (n)	FFR > 0.8 (n)	Misclassification (%)
Pd/Pa Proximal Segments	≤0.92	35	13	24.4*
	>0.92	16	55	
Pd/Pa Distal Segments	≤0.92	47	12	16.7
	>0.92	11	68	

Sensitivity Analyses for Pd/Pa in Proximal (Syntax segments 1,11,5,6) vs Distal (Syntax segments ≠ 1,11,5,6)
*: Chi-square test of association: p=0.125. Fisher's exact test: p=0.161

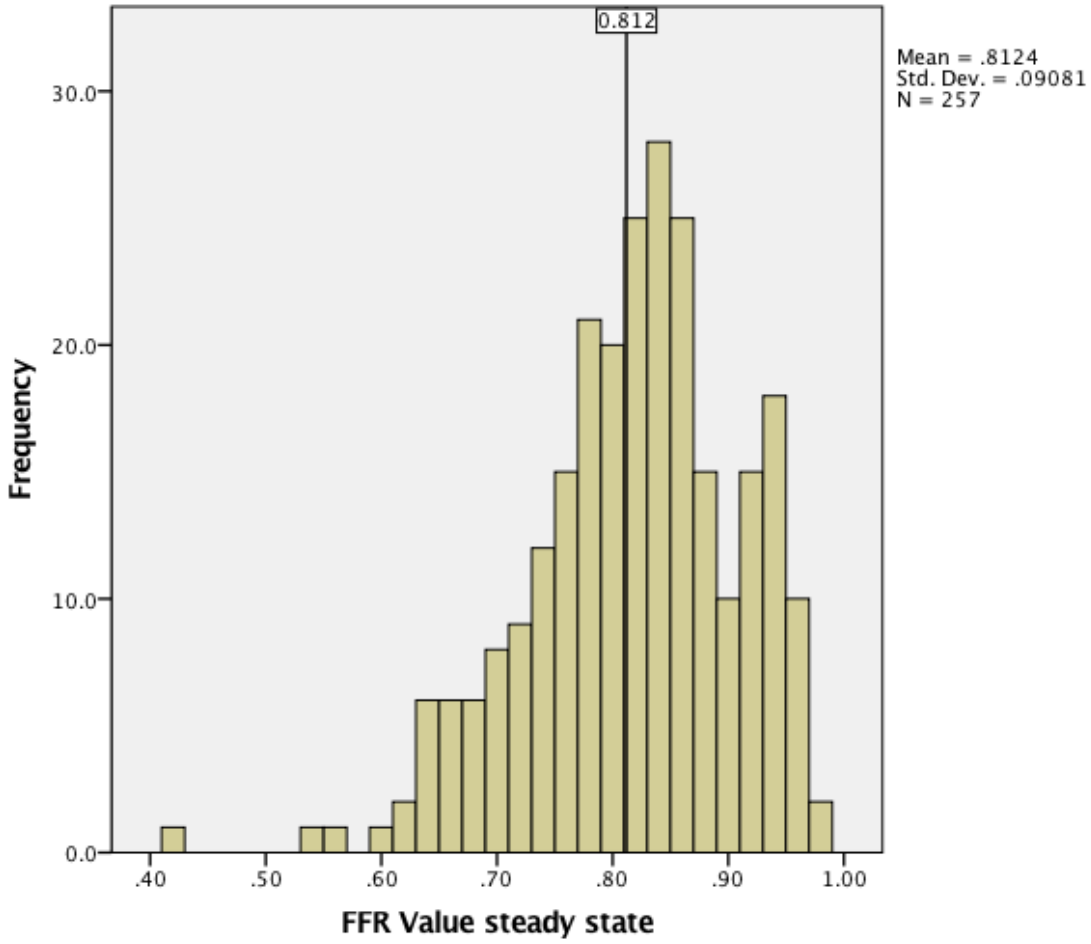
0.812
Mean = .8124
Std. Dev. = .09081
N = 257
30.0
20.0
10.0
0.0
Frequency
.40
.50
.60
.70
.80
.90
1.00
FFR Value steady state

Figure 1.

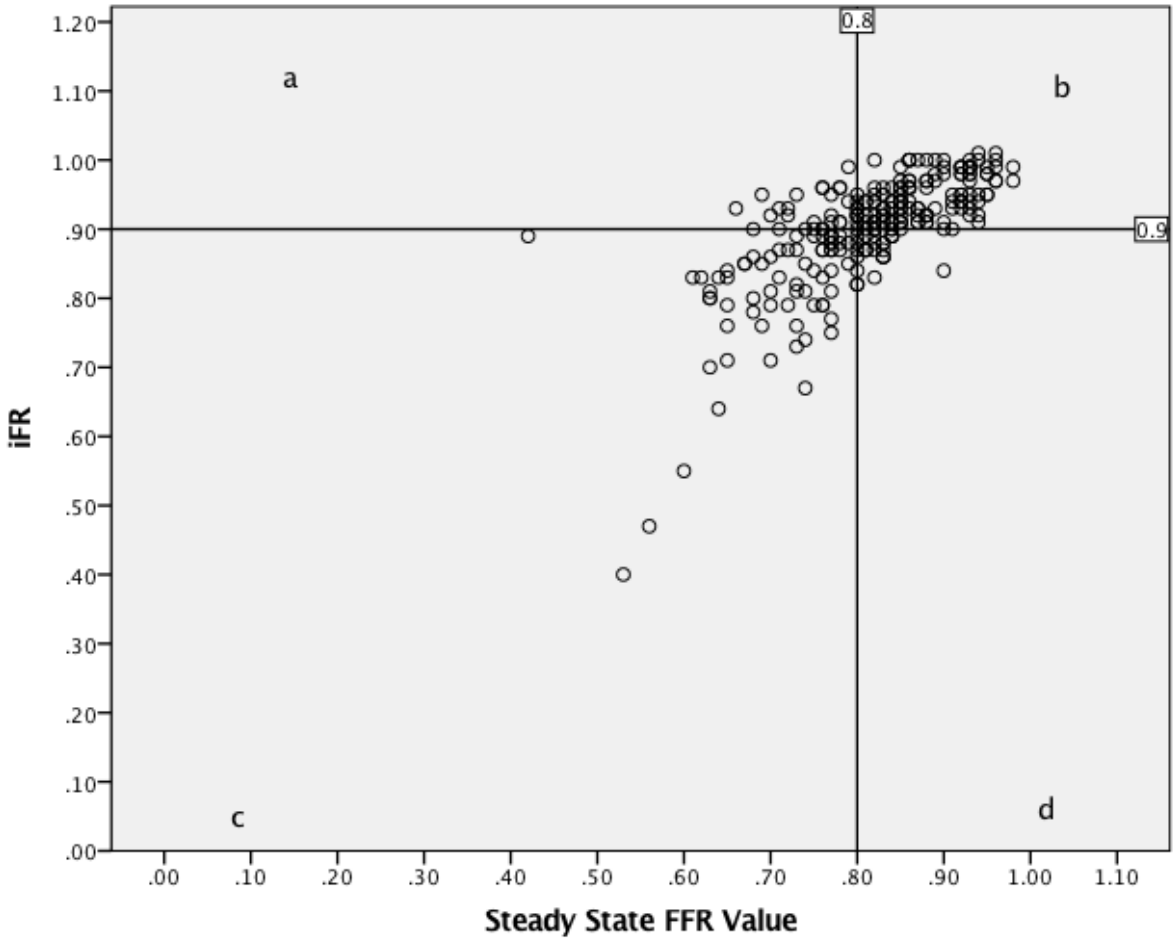
a
b
c
d
0.8
0.9
iFR
Steady State FFR Value
1.20
1.10
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
.00
.00
.10
.20
.30
.40
.50
.60
.70
.80
.90
1.00
1.10

Figure 2.

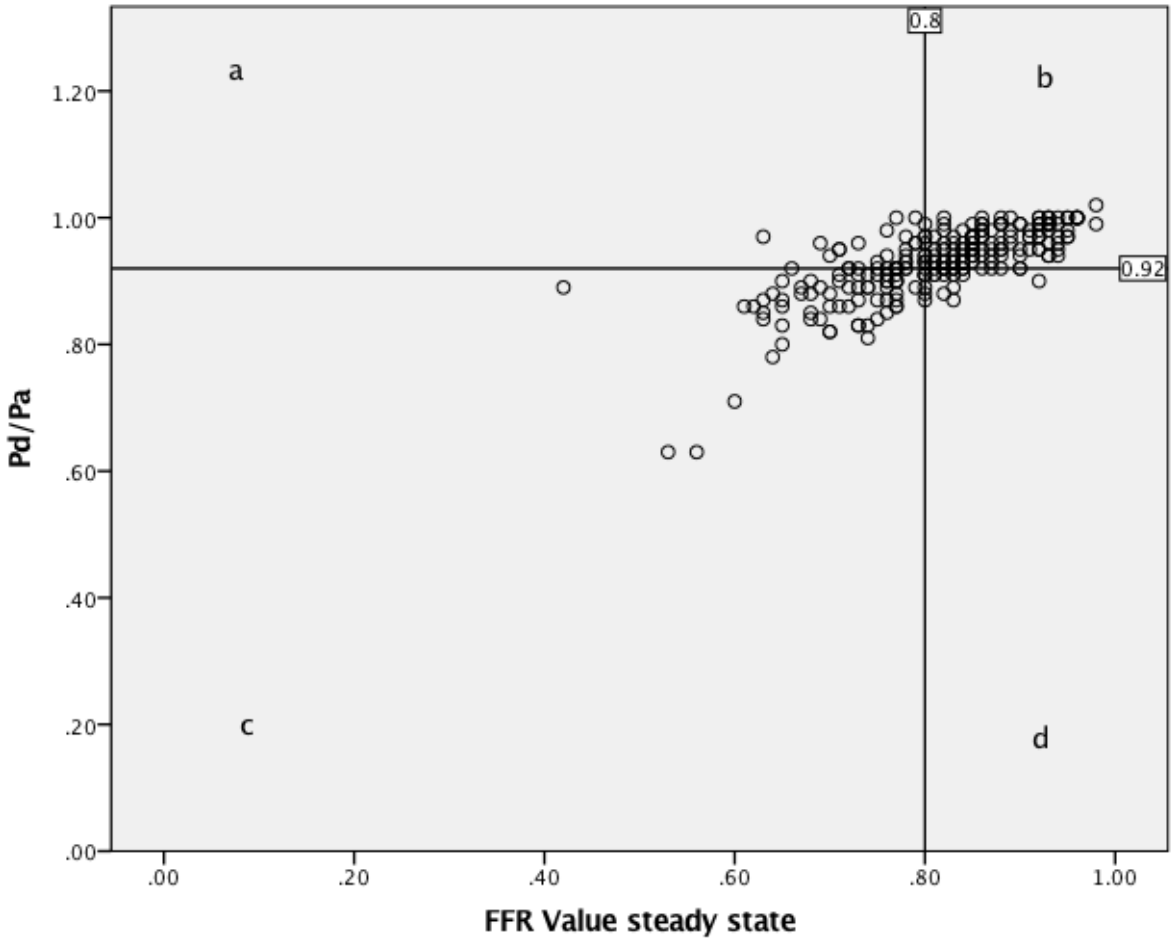
a
b
c
d
0.8
0.92
1.20
1.00
.80
.60
.40
.20
.00
Pd/Pa
.00
.20
.40
.60
.80
1.00
FFR Value steady state

Figure 3.

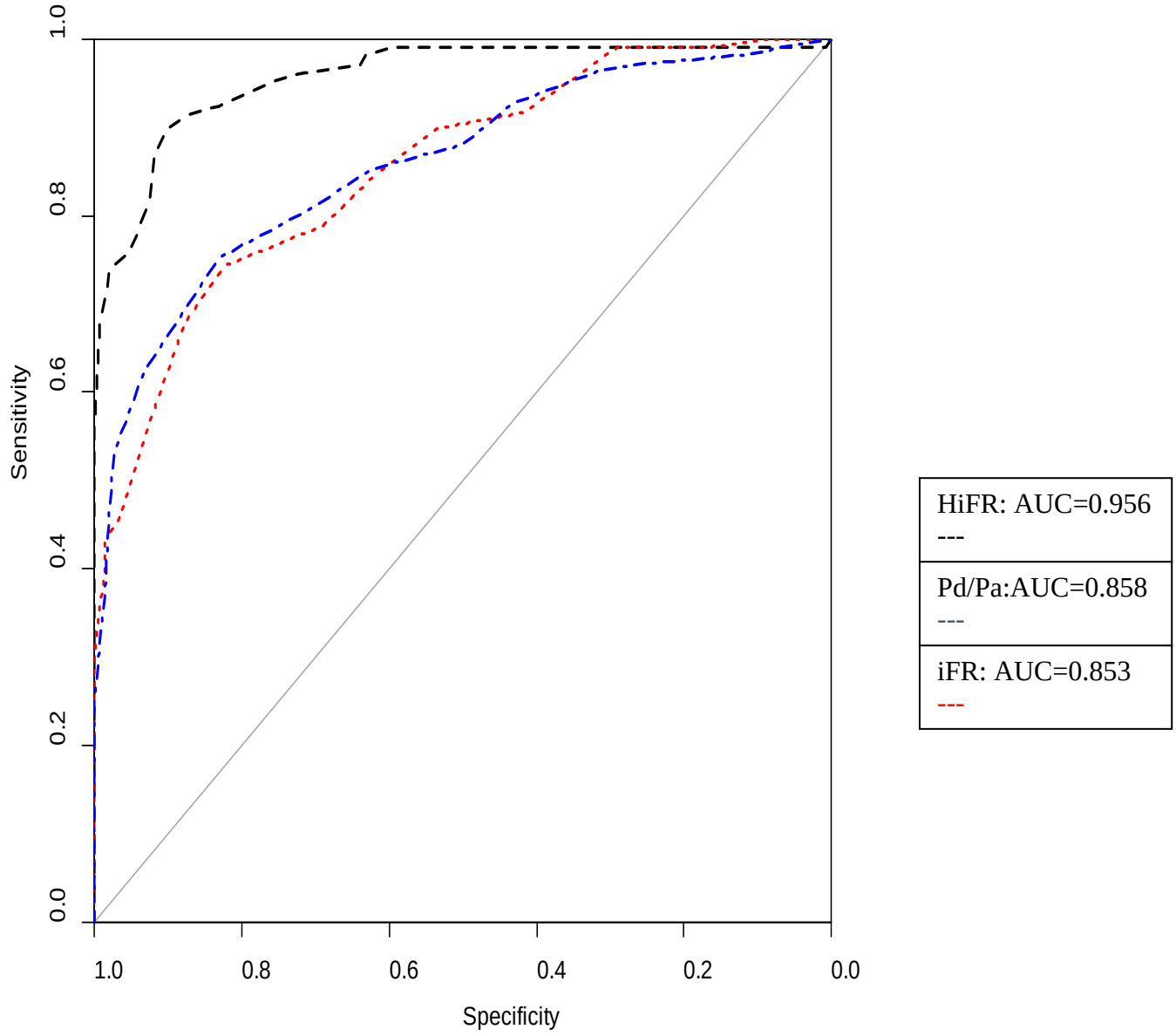
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
1.0
0.8
0.6
0.4
0.2
0.0
Specificity
HiFR: AUC=0.956
Pd/Pa:AUC=0.858
iFR: AUC=0.853

Figure 4.

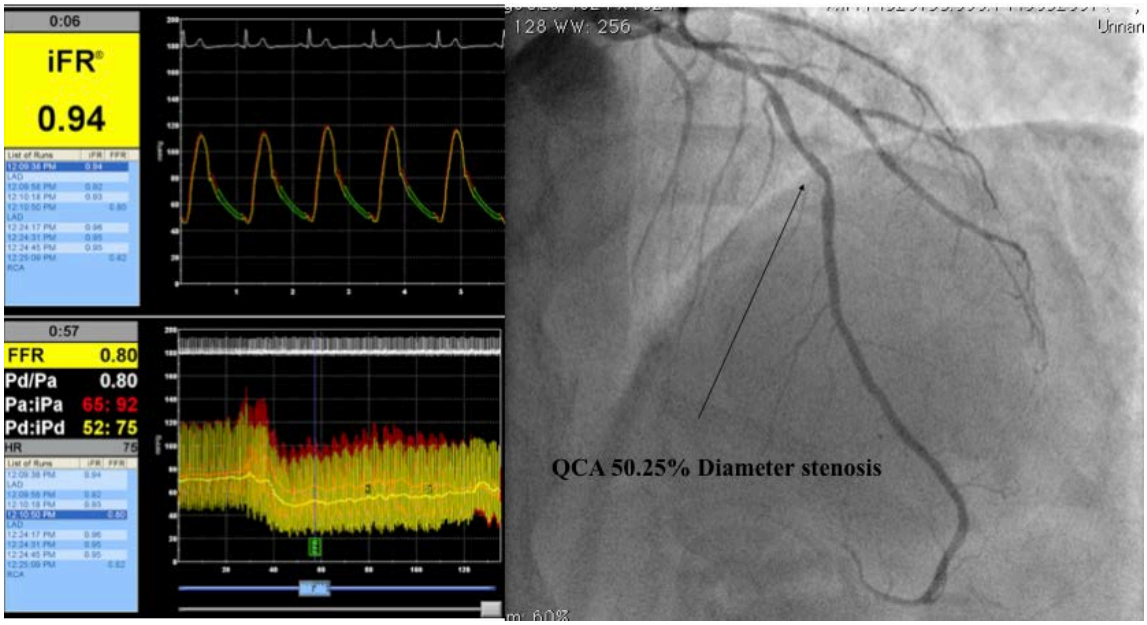
0:06
iFR®
0.94
0:57
FFR 0.80
Pd/Pa 0.80
Pa:iPa 65: 92
Pd:iPd 52: 75
HR 75
128 WW: 256
QCA 50.25% Diameter stenosis

Figure 5.