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CLINICAL RESEARCH
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Diastolic pressure ratio: new approach and validation vs. the instantaneous wave-free ratio

Nils P. Johnson[1], Wenguang Li[2], Xi Chen[2], Barry Hennigan[3,4], Stuart Watkins[3,4], Colin Berry[3,4], William F. Fearon[5], Keith G. Oldroyd[3,4,*]

[1]Weatherhead PET Center, Division of Cardiology, Department of Medicine, McGovern Medical School at UTHealth and Memorial Hermann Hospital, Houston, TX, USA; [2]Boston Scientific Corporation, CA, USA; [3]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [4]West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, Agamemnon Street, Glasgow G81 4DY, UK; and [5]Division of Cardiology, Stanford University, Stanford, CA, USA

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Aims The instantaneous wave-free ratio (iFR) and whole-cycle Pd/Pa investigate coronary physiology during non-hyperaemic conditions. To test for unique physiologic properties of the wave-free period when making resting coronary pressure measurements, we compared *post hoc* a diastolic pressure ratio (dPR) and Pd/Pa against iFR for numerical similarity and test/retest repeatability.

Methods and results Eight hundred and ninety-three lesions from 833 subjects were included from the VERIFY 2 and CONTRAST studies. Diastolic pressure ratio and a linear transform of Pd/Pa were compared against iFR for diagnostic performance. Mean difference between dPR and iFR [Δ = -0.006 ± 0.011, r^2 = 0.993, area under receiver operating characteristic (ROC) curve (AUC) = 0.997] mirrored the difference of two iFR measurements repeated immediately (Δ = <0.001 ± 0.004, r^2 = 0.998, AUC = 1.00). Minor variations in the definition of dPR changed its value by <1–2% over a broad range of the cardiac cycle. A linear transform of Pd/Pa showed very good diagnostic performance (Δ = -0.012 ± 0.031, r^2 = 0.927, AUC = 0.979). *Post hoc* iFR values were validated against real-time iFR values and matched almost exactly (average Δ = <0.001 ± 0.004, 99.6% within ±0.01).

Conclusions Our dPR offers numerical equivalency to iFR. Despite different technical approaches for identifying the relevant period of diastole, the agreement between dPR and iFR and the insensitivity of dPR to minor variations in its definition further confirm numerical equivalency among resting metrics.

Keywords Instantaneous wave-free ratio • Coronary physiology

Introduction

Resting coronary physiology to guide revascularization procedures dates to the very advent of percutaneous coronary intervention (PCI). In the first reported series of coronary balloon angioplasties in 1979, Andreas Grüntzig measured the pressure drop across the stenosis (ΔP) at baseline and again after dilation, although biased by the acknowledged iatrogenic gradient generated by the device itself.[1] Pressure gradient assessment was a routine component of interventional procedures in the initial years, until catheters became too small to obtain reliable signals through the central channel. In some early clinical cases at Emory University, measurement of resting ΔP was used to help decide for or against angioplasty when angiography showed a borderline lesion (H. Vernon Anderson, personal communication, University of Texas Health Science Center at Houston).

By 1985, investigators were normalizing ΔP to the aortic pressure (Pa) in order to adjust for loading conditions.[2] While the terminology 'Pd/Pa' (referring to the ratio of the distal coronary pressure to proximal aortic pressure) was not yet used, a threshold of Pd/Pa = 0.7 (equivalent to ΔP/Pa = 0.3 using the notation of that manuscript) was shown to predict abnormal perfusion imaging and exercise testing with good diagnostic performance.[2] The resting gradient and its change after angioplasty in almost 5000 lesions was demonstrated in 1986 to associate with procedural success.[3]

*Corresponding author. Tel: +44-141-951 5180, Email: keith.oldroyd@nhs.net

The development of practical vasodilators such as intracoronary papaverine in 1986[4] and intravenous adenosine in 1990,[5] coupled with the superior agreement of exercise ST-segment changes with hyperaemia vs. resting gradients demonstrated in 1995,[6] moved the field toward fractional flow reserve.[7] However, interest in resting physiology returned with the explicit mention of the term 'resting Pd/Pa' in 2010.[8] A subsequent publication in 2012 proposed a diastolic version of resting whole-cycle Pd/Pa called the instantaneous wave-free ratio (iFR),[9] analogous in concept to a diastolic metric during hyperaemia from 2000.[10] Although the initial hypothesis regarding equivalence of myocardial resistance between the wave-free period and full hyperaemia[9] was subsequently disproven,[11] recent randomized trials have used iFR to guide treatment.[12,13]

The introduction of the resting, diastolic wave-free period[9] led to both physiologic and practical controversy. Physiologically, does the wave-free period possess unique properties when making pressure-only measurements in the coronary arteries? Practically, do existing clinical trial results[12,13] and clinical guidelines[14] apply narrowly to the wave-free period, or more generally to a broad range of diastolic metrics as suggested recently?[15] Our study hypothesized that resting metrics would demonstrate numerical equivalency despite differing physiologic and technical details, thereby making resting physiology more universally accessible.

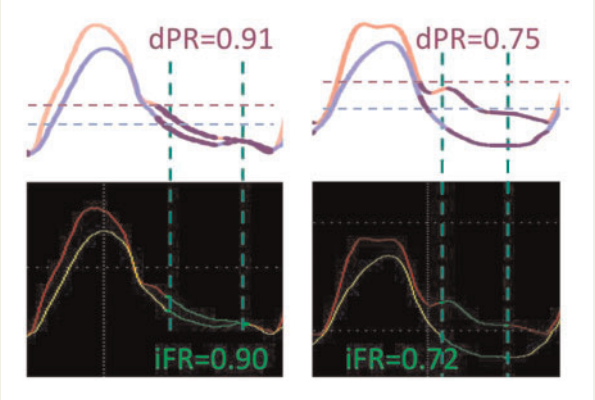

Figure 1 Diastolic pressure ratio. Because of higher coronary flow later during the cardiac cycle, pressure gradients tend to be higher and pressure ratios lower. Diastolic pressure ratio uses a pragmatic definition by including areas below the average aortic pressure (dashed horizontal purple lines in top row) with negative slope. Two example tracings show single beats comparing the diastolic pressure ratio samples (purple dots in the top row) with the instantaneous wave-free ratio window (green portion in the bottom row, taken from console screenshots). For the example on the left side, the diastolic pressure ratio and instantaneous wave-free ratio values are nearly identical despite a more narrow instantaneous wave-free ratio window. For the outlier example on the right side, the instantaneous wave-free ratio window is more centred in diastole. dPR, diastolic pressure ratio; iFR, instantaneous wave-free ratio.

Methods

Diastolic pressure ratio

Figure 1 depicts the concept behind the diastolic pressure ratio (dPR) metric as well as some example tracings. Identification of the diastolic period can be technically challenging from pressure recordings in cases with a blunted or damped dicrotic notch, although prior literature suggests that such cases may be a small minority.[16] Although the T-wave of the electrocardiogram (ECG) can also guide recognition of diastole, a substantial number of ECG signals do not meet rigorous quality criteria even during dedicated, research protocols,[17,18] and current ECG-based approaches can be converted to use only the pressure tracings.[19] Therefore, a simple yet robust method to select diastole from clinical tracings is needed to permit subcycle Pd/Pa assessment during periods of higher coronary flow.

To solve these issues, dPR applies two straightforward criteria independent of the dicrotic notch and ECG to identify a portion of the cardiac cycle that approximates diastole. The first criterion includes portions of the tracing below the mean of the aortic pressure (Pa). The second criterion selects samples with a negative slope (each sample with a pressure lower than its predecessor). These criteria apply only to the aortic pressure tracing, and only samples that meet both criteria are included in the dPR calculation. Note that samples need not be contiguous.

After identification of qualifying samples, the algorithm averages together the values from aortic (Pa) and coronary (Pd) tracings over five consecutive cardiac cycles. The Pd/Pa ratio of these subset averages equals dPR.

Virtual catheterization laboratory

Figure 2 shows a schematic concept and photos from the virtual catheterization laboratory. The purpose is to send pre-recorded pressure tracings to a Philips Volcano S5i console for *post hoc* analysis by its iFR algorithm. Via an arbitrary waveform generator (AWG 3252, Tektronix, Oregon), any ECG and aortic pressure signal can be fed into the Pa and ECG inputs. The corresponding coronary pressure signal can be sent via a second AWG to a Philips Volcano Primewire Prestige and then into the Pd input. After an initial calibration process to match pressure readings between waveform input and display, the console can be operated in iFR mode as during clinical routine.

VERIFY 2 and CONTRAST

We used the previously published VERIFY 2[20] and CONTRAST[18] diagnostic accuracy studies as sources of pre-recorded pressure tracings. We sought no additional institutional board review for this analysis because each subject had already provided written informed consent and the pressure tracings contained no confidential identifiers. The primary publications for each trial provide protocol details. Resting tracings available in duplicate for individual lesions from VERIFY 2 and CONTRAST were analysed retrospectively using the dPR algorithm as well as whole-cycle resting Pd/Pa.

In brief, VERIFY 2 (clinicaltrials.gov NCT02377310) was a prospective, single-centre study that included 197 nearly consecutive subjects and 257 coronary lesions. Resting pressure signals in the coronary artery were obtained using either the Philips Volcano Prestige or Verrata wire as per standard practice, with simultaneous recordings of the aortic pressure and surface ECG using a Philips Volcano s5 console. Two assessments of iFR were acquired in rapid, back-to-back sequence before the administration of any hyperaemic stimulus. Tracings and their associated real-time iFR values from the console were securely archived. These data were anonymized and made available for the current dPR analysis.

In brief, CONTRAST (clinicaltrials.gov NCT02184117) was a prospective, international study that included 763 subjects from 12 centres with 1 lesion/subject. Standard, commercial coronary pressure wires and acquisition unit (PressureWire Certus or Aeris wire and the

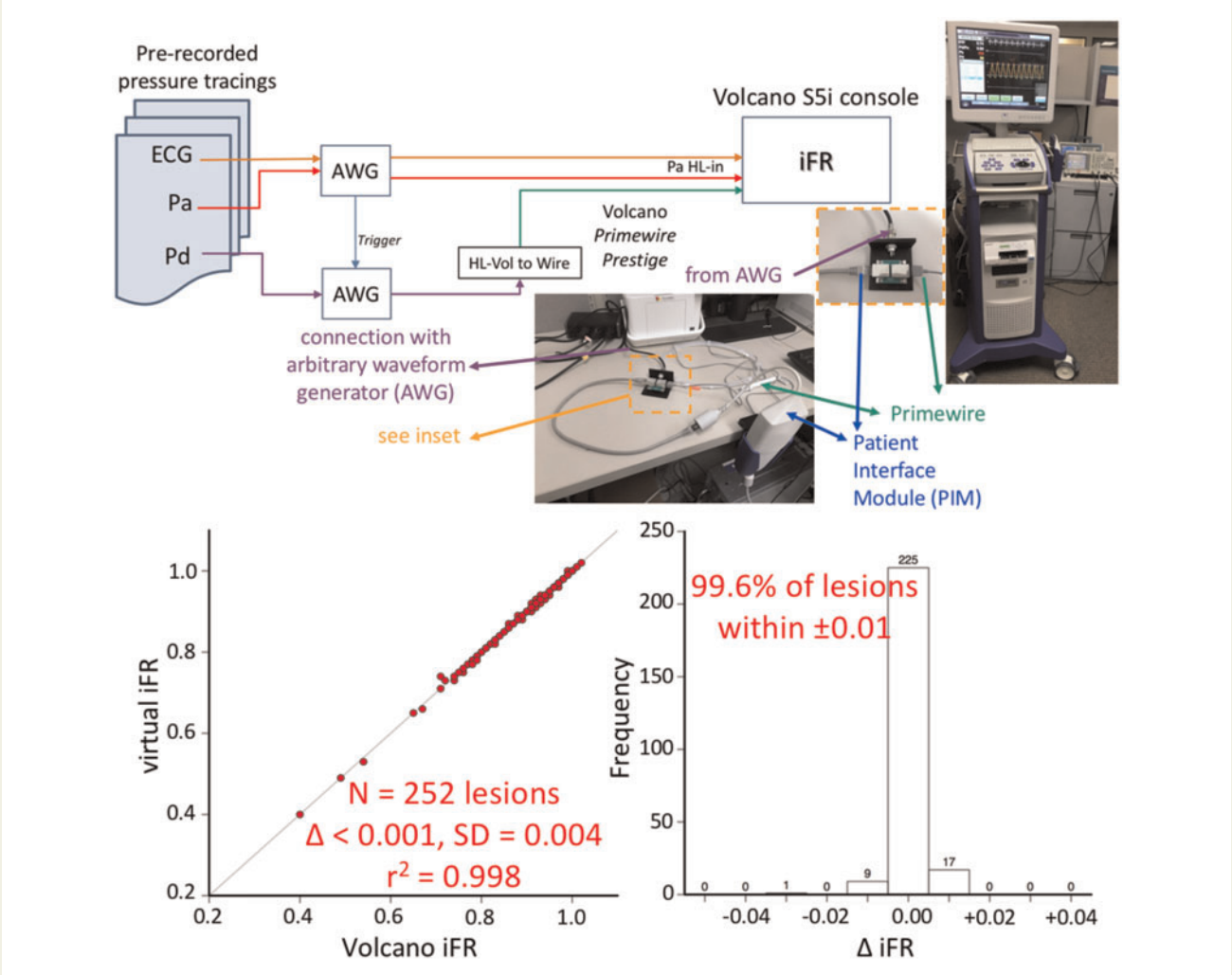

Figure 2 Virtual instantaneous wave-free ratio. A 'virtual' catheterization laboratory was created by feeding pre-recorded pressure tracings into a Philips Volcano S5i console. The electrocardiogram and aortic pressure signal (Pa) passed through an arbitrary waveform generator (AWG) into the console, while the distal coronary pressure signal (Pd) passed through an AWG first into a Philips Volcano Primewire Prestige and finally into the console. In this way pressure tracings could be analysed *post hoc* for instantaneous wave-free ratio then compared against diastolic pressure ratio. Comparing the 'virtual' instantaneous wave-free ratio value to the number saved by the console during live recording demonstrated excellent agreement between real-time and *post hoc* instantaneous wave-free ratio analyses, thereby validating the technique. dPR, diastolic pressure ratio; iFR, instantaneous wave-free ratio.

QUANTIEN system from St. Jude Medical) recorded a simultaneous ECG in addition to aortic and coronary pressure signals. Two resting assessments of iFR were performed but separated by hyperaemic stimuli of intracoronary contrast and intracoronary and/or intravenous adenosine. Anonymous tracings from CONTRAST have already been made publicly available and were used for the current dPR analysis without any of the core lab review or feedback that was part of the original publication. Specifically, iFR was recalculated using the described virtual catheterization laboratory method instead of off-line application of the HARVEST software as for the original CONTRAST publication.

Statistical methods

Analyses were performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). We employed standard statistical techniques. Applicable tests were two-tailed, and $P < 0.05$ was considered statistically significant.

To validate the virtual catheterization laboratory, its virtual, *post hoc* iFR values from VERIFY 2 were compared against the corresponding real-time iFR values using a Bland–Altman analysis and Pearson correlation. All subsequent analyses used the virtual iFR value. For lesions with valid, duplicate measurements, the first vs. second values of iFR and dPR were compared against each other in VERIFY 2 (immediate test/retest) and CONTRAST (short-term test/retest) using Bland–Altman analysis, Pearson correlation, and area under the receiver operating characteristic (ROC) curve (AUC) using a consistent threshold of ≤0.89 for each metric. An optimal binary threshold for dPR was determined using ROC analysis vs. binary iFR ≤ 0.89 by maximizing sensitivity plus specificity (peak Youden index).

For lesions that had valid, duplicate measurements of iFR and dPR, the average value was computed; for lesions with only a single, valid

Table 1 Baseline and procedural characteristics

	Total	VERIFY 2	CONTRAST
Subjects	833 (100%)	195 (100%)	638 (100%)
Age (years)	NA	NA	66 ± 10
Male	636 (76%)	183 (94%)	453 (71%)
Smoking	374 (45%)	67 (34%)	307 (48%)
Hypertension	617 (74%)	160 (82%)	457 (72%)
Dyslipidaemia	605 (73%)	175 (90%)	430 (67%)
Diabetes mellitus	224 (27%)	43 (22%)	181 (28%)
Family history of CAD	327 (39%)	164 (84%)	163 (26%)
Prior PCI	170 (20%)	76 (39%)	94 (15%)
Prior MI	263 (32%)	99 (51%)	164 (26%)
Vessels	893 (100%)	255 (100%)	638 (100%)
Stable presentation	653 (73%)	152 (60%)	501 (79%)
Acute presentation	240 (27%)	103 (40%)	137 (21%)
Left main	26 (3%)	8 (3%)	18 (3%)
LAD	539 (60%)	153 (60%)	386 (61%)
LCx	163 (18%)	49 (19%)	114 (18%)
RCA	165 (18%)	45 (18%)	120 (19%)
iFR	0.91 (IQR 0.85–0.94)	0.91 (IQR 0.87–0.95)	0.90 (IQR 0.83–0.94)

Summary values represent number (%), mean ± standard deviation, or median (IQR).
CAD, coronary artery disease; iFR, instantaneous wave-free ratio; IQR, interquartile range; LAD, left anterior descending; LCx, left circumflex; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; RCA, right coronary artery.

measurement of iFR and dPR, no average was performed. Values of dPR in VERIFY 2 and CONTRAST were compared against iFR using Bland–Altman analysis, Pearson correlation, and ROC AUC using iFR ≤ 0.89 as the reference standard.[12,13] The agreement between binary iFR and dPR using a ≤0.89 threshold was computed for each observed iFR value from the merged cohort in those lesions with duplicate measurements by dividing the number of discordances by the number of observed iFR values, and a similar method was used to quantify iFR agreement with itself upon repeat assessment.

Given prior work demonstrating an extremely linear relationship between whole-cycle resting Pd/Pa and iFR, a simple transformation might demonstrate sufficient numerical equivalence. Therefore, we computed a 'transformed Pd/Pa' using the equation from *Figure* 4A of that manuscript: (whole-cycle Pd/Pa - 0.32)/0.67.[21] All dPR vs. iFR analyses were repeated but comparing transformed Pd/Pa to iFR, as well as test/retest of transformed Pd/Pa against itself. A paired McNemar test compared binary dPR and transformed Pd/Pa against binary iFR for diagnostic performance.

To examine the sensitivity of the dPR algorithm to details of its definition, the criterion of using the mean aortic pressure was varied from 0.80*mean to 1.20*mean in increments of 0.05 for the VERIFY 2 tracings. Decreasing the threshold to 0.80*mean produces a shorter dPR window, whereas increasing the threshold to 1.20*mean produces a wider dPR window. In all scenarios, the criterion for a negative slope remained intact. Using the 1.00*mean as the reference, the relative change for each variation was computed and averaged. In a small minority of cases, analyses could not be performed since 0.80*mean and 0.85*mean thresholds were below the lowest Pa values due to narrow pulse pressures.

Role of academic and industry authors

Both VERIFY 2 and CONTRAST were investigator-initiated studies. While VERIFY 2 had no industry support, CONTRAST received financial support from St. Jude Medical. For this manuscript, dPR and the virtual catheterization laboratory were developed and implemented by employees of Boston Scientific. The academic authors had full access to the original tracings and dPR values, performed the statistical analysis, and wrote the manuscript independent of industry. However, Boston Scientific reviewed the manuscript for confidential or proprietary information as well as accuracy when describing their methods for dPR (for which a patent has been filed and commercial distribution is intended after appropriate regulatory approval) and virtual iFR. Anonymous pressure tracings for all subjects plus the associated virtual iFR values have been made publicly available.[22]

Results

A total of 255 lesions from 195 subjects (252 with valid, duplicate measurements) were included from VERIFY 2 plus a total of 638 lesions from 638 subjects (629 with valid, duplicate measurements) from CONTRAST for a grand total of 893 lesions from 833 subjects. Reasons for exclusion were inability to recover the archived tracing from VERIFY 2 (2 lesions from 2 subjects) or rejection of a CONTRAST tracing by the Philips Volcano console for inadequate ECG (125 lesions from 125 subjects). *Table 1* summarizes the clinical cohorts. *Table 2* provides details on diagnostic performance from the combined cohort. A small minority of subjects had more than one vessel assessed (60 of 893, or <7%), and it had no influence on the results as detailed in the Supplementary material online.

Virtual catheterization laboratory

Figure 2 quantifies the agreement between real-time iFR values from the console and their *post hoc* reprocessing using the virtual catheterization laboratory. Bland–Altman analysis showed a mean difference

Table 2 Diagnostic performance

	dPR	Transformed Pd/Pa	iFR
Difference with iFR	–0.006 ± 0.011	–0.012 ± 0.031	NA
Pearson r^2	0.993	0.927	
Area under ROC curve[a]	0.997	0.979	
Sensitivity[a]	95.8% (95% CI 93.4–97.5%)	87.7% (95% CI 84.0–90.7%)	
Specificity[a]	99.2% (95% CI 97.9–99.8%)	95.9% (95% CI 93.7–97.5%)	
Accuracy[a]	97.6% (95% CI 96.4–98.5%)	92.2% (95% CI 90.2–93.8%)	
True positives	388	355	
True negatives	484	468	
False positives	4	20	
False negatives	17	50	
Immediate test/retest difference	0.001 ± 0.009	0.001 ± 0.010	<0.001 ± 0.004
Immediate Pearson r^2	0.988	0.984	0.998
Immediate area under ROC curve	0.994	0.991	1.000
Short-term test/retest difference	0.003 ± 0.033	0.003 ± 0.036	0.004 ± 0.033
Short-term Pearson r^2	0.926	0.920	0.931
Short-term area under ROC curve	0.950	0.953	0.955

Summary values represent mean ± standard deviation, or median (IQR).
CI, confidence interval; dPR, diastolic pressure ratio; iFR, instantaneous wave-free ratio; IQR, interquartile range; NA, not applicable; Pa, aortic pressure; Pd, distal coronary pressure; ROC, receiver operating characteristic.
[a]Using iFR ≤ 0.89 as the reference standard.

of <0.001 ± 0.004 with a Pearson correlation coefficient $r^2 = 0.998$. A total of 99.6% virtual iFR values were within ±0.01 of the real-time iFR values and the vast majority (225 of 252, 89.3%) matched exactly. A single lesion with a 0.03 difference had atrial fibrillation and very irregular cycle lengths such that the iFR and dPR values were sensitive to the analysed portion of the tracing.

Test/retest stability

Figure 3 displays scatter plots for duplicate measurements of iFR and dPR in each cohort. The combined immediate test/retest difference was 0.001 ± 0.009 for dPR, <0.001 ± 0.004 for iFR, and 0.001 ± 0.010 for transformed Pd/Pa. The combined short-term test/retest difference was 0.003 ± 0.033 for dPR, 0.004 ± 0.033 for iFR, and 0.003 ± 0.036 for transformed Pd/Pa.

Diagnostic performance

The combined difference with iFR for dPR was -0.006 ± 0.011 with Pearson $r^2 = 0.993$ and ROC AUC 0.997 as shown in *Figure 4*, larger for more severe lesions but improving to -0.003 ± 0.007 when confined to the iFR ≥ 0.86 range where a large majority of lesions occur. Receiver operating characteristic analysis determined that a dPR binary threshold of 0.89 provided the optimal cut-off to predict binary iFR ≤ 0.89. For transformed Pd/Pa vs. iFR the combined difference was -0.012 ± 0.031 with Pearson $r^2 = 0.927$ and ROC AUC = 0.979. The accuracy of dPR to predict binary iFR was 97.6% with a sensitivity of 95.8% and specificity 99.2%. The accuracy of transformed Pd/Pa to predict binary iFR was 92.2% with a sensitivity of 87.7% and specificity of 95.9%. When binary dPR and transformed Pd/Pa disagreed with each other, dPR was more likely to agree with iFR ≤ 0.89 (odds ratio 4.0, 95% confidence interval 2.2–7.8, paired McNemar $P < 0.001$).

Figure 5 depicts the agreement between binary iFR and dPR for each value of iFR in the combined cohort, as well as iFR's agreement with itself upon repeat assessment. Of 255 lesions in one cohort, only 12 (4.7%) showed any evidence of binary iFR vs. dPR discordance (≤0.89 vs. >0.89 or vice versa) and of these only 3 (1.2%) showed it on both test and retest. All of these lesions were clustered right around the iFR 'grey zone' of 0.86–0.93,[23] with average iFR vs. dPR of 0.89 and 0.90, 0.89 and 0.915, and 0.89 and 0.90. Of 638 lesions from the other cohort, only 24 (3.8%) showed any binary iFR vs. dPR discordance and only 2 (0.3%) showed it on both test and retest. Both of these lesions were clustered right around the grey zone (average iFR vs. dPR of 0.90 and 0.89, 0.865 and 0.925).

Sensitivity of diastolic pressure ratio algorithm

Figure 6 shows how varying the definition of the dPR threshold in *Figure 1* changes the resulting values when using 100% of mean aortic pressure as the reference level. From 90% to 120% of mean the dPR values generally changed by <1–2%, although larger changes were observed for 80% of mean (1.5*interquartile range from -2.2% to +4.2%, median +0.9%) and 85% of mean (1.5*interquartile range from -1.4% to +2.8%, median +0.5%).

Discussion

Our dPR metric displays numerical equivalence to existing iFR. First, the difference between dPR and iFR mirrored the difference between 2 iFR measurements taken immediately after each other. Second, the diagnostic performance and correlation of dPR vs. iFR paralleled the same metrics for an immediately repeated iFR assessment.

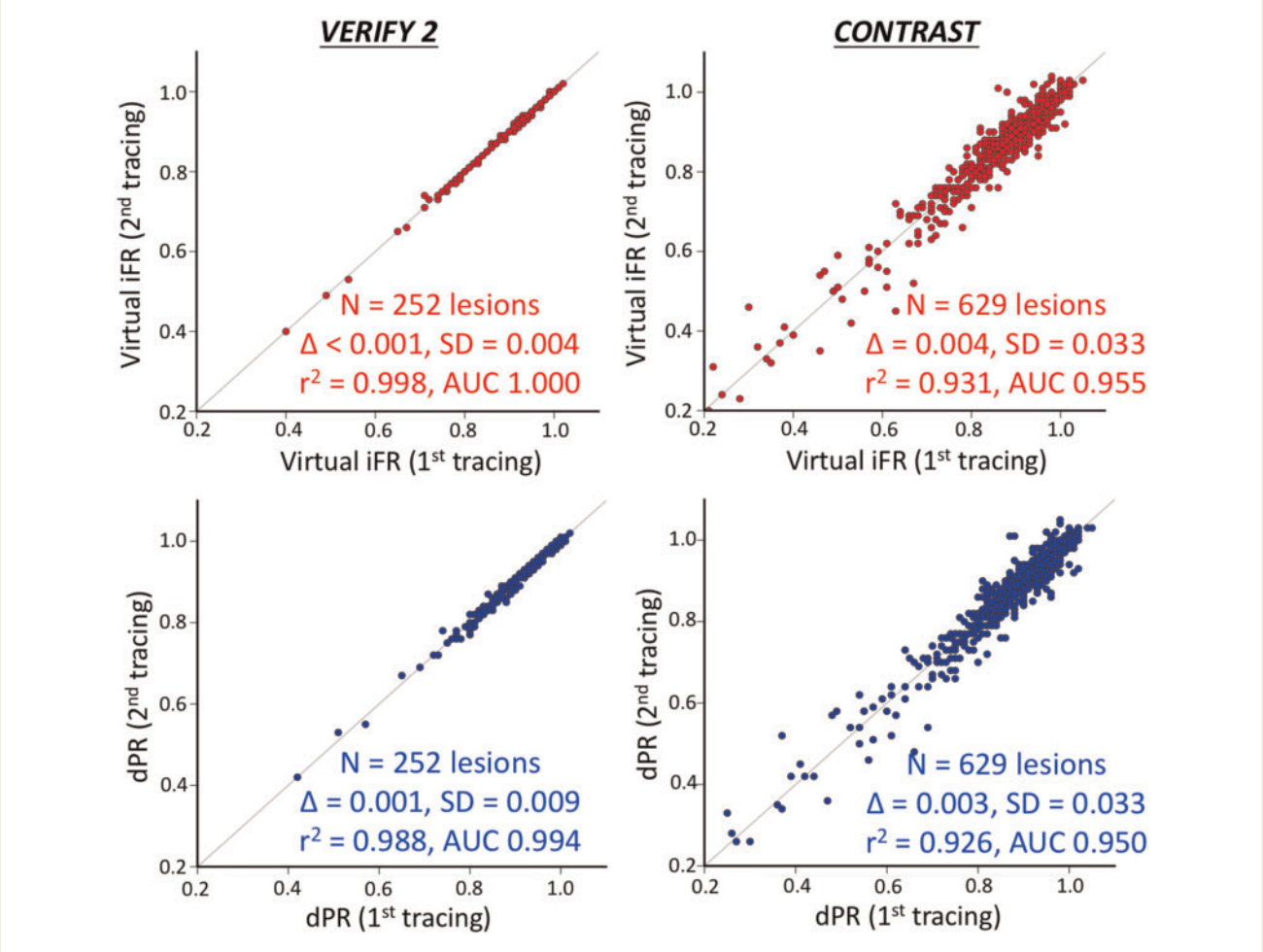

Figure 3 Repeatability of instantaneous wave-free ratio and diastolic pressure ratio. While immediate repetition (in the VERIFY 2 study) demonstrated less variation than short-term repetition (in the CONTRAST study), as expected physiologically, both instantaneous wave-free ratio and diastolic pressure ratio had similar test/retest performance. dPR, diastolic pressure ratio; iFR, instantaneous wave-free ratio.

Therefore, dPR agrees with iFR to the same degree that iFR agrees with itself a few seconds later under stable conditions.

When two tests agree as closely as dPR and iFR, performing clinical outcomes studies becomes both impossible and unnecessary. While a small minority of lesions demonstrated some binary discordance between dPR and iFR, <1% were consistent between both test and retest. Furthermore, only 2 lesions (0.2%) had a consistent difference >0.01 around the binary threshold and all occurred in the iFR 'grey zone' of 0.86–0.93.[23] The same 'grey zone' concept applies to dPR as well. Unlike resting Pd/Pa that requires a linear transformation to iFR units,[21] dPR has the same numeric value and binary threshold as iFR, thereby simplifying portability.

The fact that dPR provides the same numerical value as iFR despite a different definition of the diastolic measurement period provides additional indirect evidence against unique properties of the so-called 'wave-free period' although our study did not perform wave intensity analysis directly. Not only does this subcycle of diastole have questionable theoretical foundations,[24] but the hypothesis of its providing equivalent resistance to whole-cycle hyperaemia[9] was subsequently overturned by the original investigators.[11] Indeed, recent work showed numerical equivalence between iFR and the minimum Pd/Pa value at any point in the cardiac cycle.[25] In approximately 12% of cases, this minimum value was found outside of diastole. Therefore, despite the theoretical debate, both pragmatic and empiric evidence argues against a unique subset of diastole.

The small variation in dPR seen in *Figure 6* over wide changes in its definition implies that many different 'dPR' metrics could be proposed, all with nearly identical diagnostic performance. *Figure 6* provides a conceptual explanation for this observation. Namely, while the aortic pressure always has a triangular shape during diastole, the coronary pressure either appears triangular too (for a mild lesion) or flat (for a severe, 'ventricularized' lesion). Therefore, the average values for Pa and Pd remain constant for symmetrically wider or narrower diastolic windows, producing a constant Pd/Pa ratio.

Comparison to existing literature

Recent work proposed several different versions of dPR—all technically distinct from our definition although functionally similar—that also demonstrated numerically equivalent results to iFR using the VERIFY 2 tracings.[15] Their dPR using all of diastole beginning at the

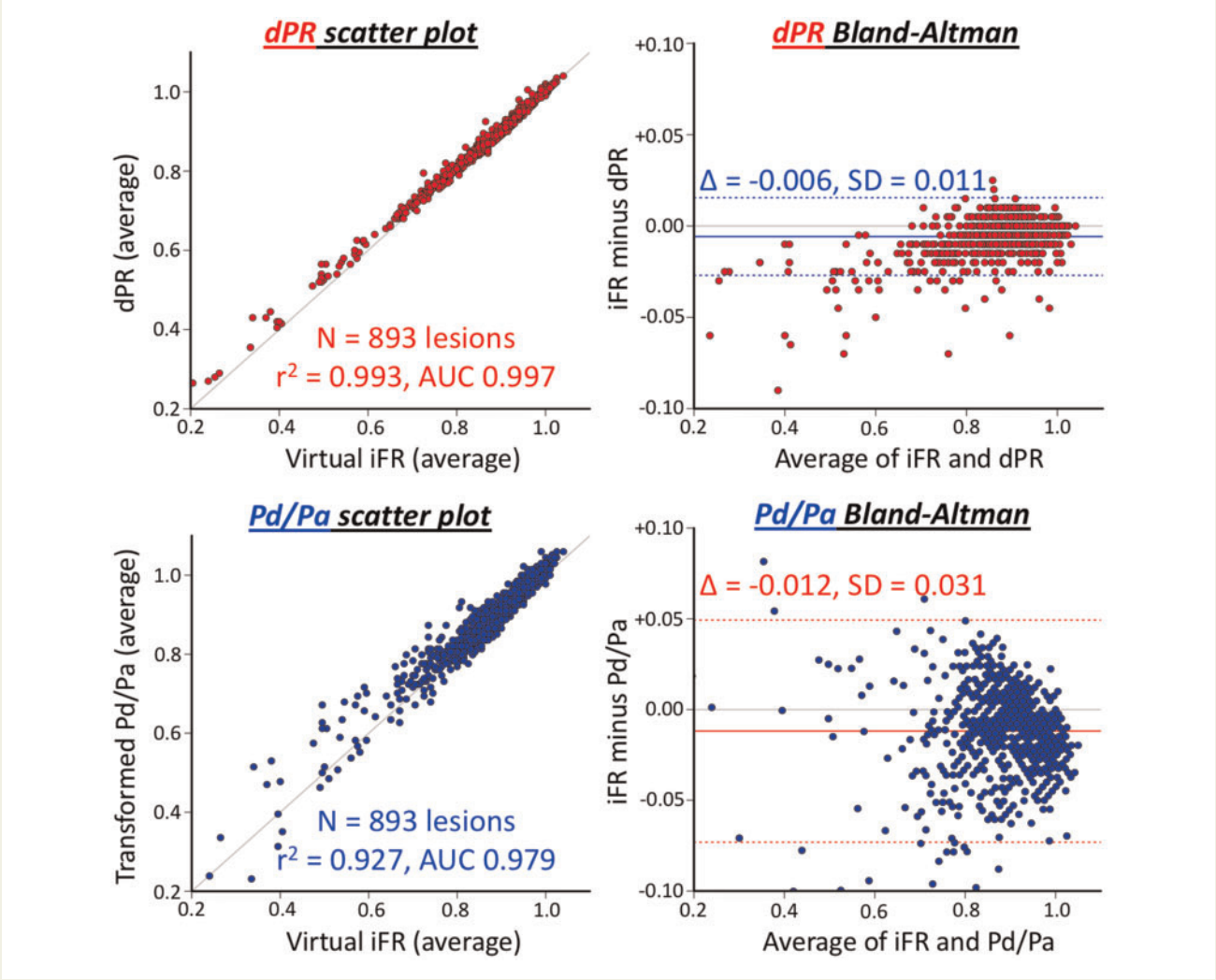

Figure 4 Numerical equivalence of diastolic pressure ratio and instantaneous wave-free ratio. In the upper row, a highly linear relationship existed between diastolic pressure ratio and the virtual instantaneous wave-free ratio value. The scatter plot revealed an excellent correlation and area under the receiver operator characteristic curve to predict instantaneous wave-free ratio ≤ 0.89, while the Bland–Altman plot demonstrated almost no average difference (solid blue line) and tight 95% confidence intervals (dashed blue lines). In the lower row, transformed Pd/Pa (using the RESOLVE relationship as detailed in the methods) showed a strong linear relationship with the virtual instantaneous wave-free ratio value with a high correlation and area under the receiver operator characteristic curve; the Bland–Altman plot demonstrated a modest average difference (solid red line) and reasonable 95% confidence intervals (dashed red lines).

dicrotic notch showed a similarity to iFR (difference 0.006 ± 0.011, r^2 = 0.984, AUC = 0.997) almost identical to our dPR and iFR (difference 0.006 ± 0.011, r^2 = 0.993, AUC = 0.997). Our dPR algorithm confirms that adherence to the original wave-free period does not matter, and extends prior findings by demonstrating that identification of a dicrotic notch is also unnecessary. Furthermore, the improved agreement between dPR and iFR when compared to a linear transformation of Pd/Pa indicates an augmentation of diagnostic performance by moving away from whole-cycle physiology. Practically, our study extends and simplifies dPR by eliminating the need for dicrotic notch detection. Finally, our dPR algorithm underwent *post hoc* validation in a large number of lesions drawn from numerous sites around the world[18,20] vs. a modestly sized, single-centre cohort.[15,20]

The functionally identical performance of several different techniques suggests a universal 'non-hyperaemic pressure ratio' with at least four different realizations: original iFR,[9] entire diastole dPR,[15] minimum Pd/Pa value at any point in the cardiac cycle,[25] and our current dPR based on mean and downsloping aortic pressure. Choosing among these implementations should be pragmatic given their numeric similarity and in practice will depend on the specific pressure wire console. Both proposed dPR techniques[15] and the revised iFR algorithm[19] avoid reliance on the ECG, since 10–15% of research tracings have insufficient ECG's.[17,18]

An extensive literature supports our finding of a high diagnostic performance of resting Pd/Pa measured over the entire cardiac cycle to predict iFR. A total of 5 studies with over 3500 subjects has demonstrated equivalent diagnostic performance between iFR and resting

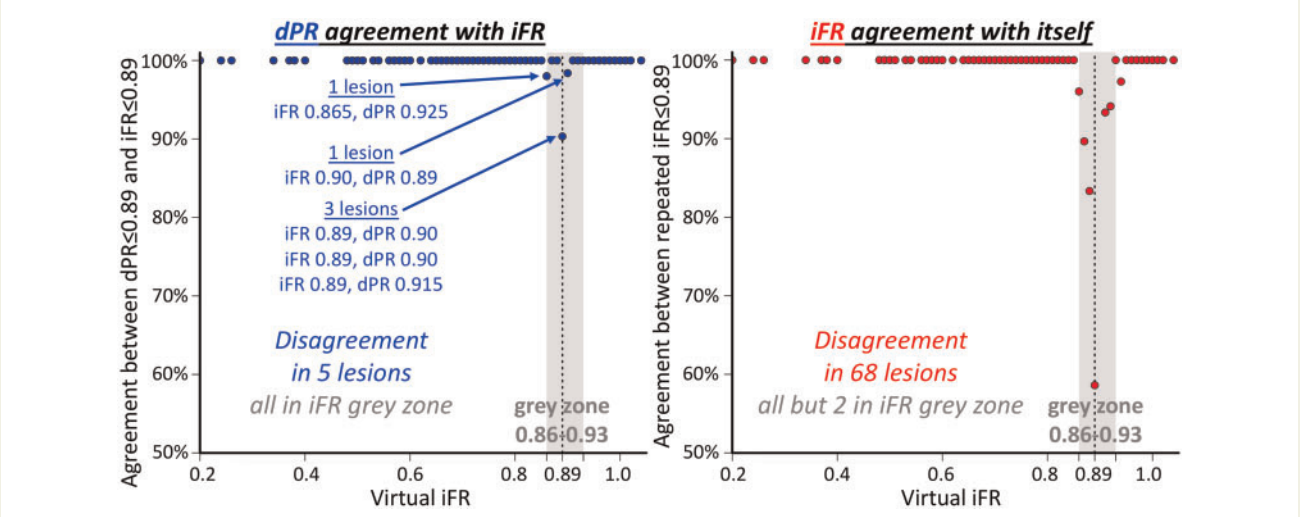

Figure 5 Agreement between binary instantaneous wave-free ratio and diastolic pressure ratio. As shown in the left panel, for the merged cohort of 893 lesions, only five lesions with valid, duplicate measurements of instantaneous wave-free ratio and diastolic pressure ratio showed consistent binary disagreement when using a ≤0.89 threshold. As detailed, all of these lesions occurred in the instantaneous wave-free ratio grey zone from 0.86 to 0.93, and three of the five differed about the binary threshold by only 0.01 instantaneous wave-free ratio units. All disagreements occurred within the grey zone and remained >90% within the grey zone, supporting the numerical equivalency demonstrated in *Figure 4* using a continuous comparison. As shown in the right panel, for lesions with valid, duplicate measurements of instantaneous wave-free ratio, all but 2 of 68 binary disagreements using instantaneous wave-free ratio ≤ 0.89 occurred within the grey zone. Agreement fell to <60% for instantaneous wave-free ratio values at the 0.89 threshold.

Pd/Pa.[17,18,20,23,26] Also, a study using cardiac positron emission tomography as the reference standard showed 'no significant differences in diagnostic accuracies' between 'iFR, and resting Pd/Pa against [coronary flow reserve] and [relative flow reserve]'.[27] Together, these results support the regulatory decision regarding resting Pd/Pa to be used 'along with knowledge of patient history, medical expertise, and clinical judgement' to decide between additional hyperaemia or immediate revascularization.[28] Additionally, whole-cycle Pd/Pa and a previous dPR algorithm[15] provide universal tools independent of a specific pressure wire system or proprietary software.

Limitations

We did not use a human core lab for tracing analysis, unlike some prior studies.[17,18,21] However, the iFR algorithm itself imposes a degree of quality control and reflects real-world implementation. Additionally, a substudy of CONTRAST demonstrated a 'close correlation between site-reported and [core lab]-analysed' physiologic values.[29] Any drift or artefact would affect both dPR and iFR equally. Therefore, we anticipate identical results had a human core lab carried out the analysis.

By design, all tracings had been collected already and their analysis was retrospective. While the clinical implementation of dPR will be real time—like iFR—the speed of our algorithm and existing quality control of pressure tracings should offer equivalent performance and results. Furthermore, a minority of tracings contained atrial fibrillation, although the dPR algorithm averages five consecutive cardiac cycles to minimize the effects of beat-to-beat variation during arrhythmia.

Although no systematic, clinical follow-up was obtained for the lesions in VERIFY 2 or CONTRAST, only 0.2% had a consistent difference between dPR and iFR >0.01 about the binary decision threshold. All of these lesions occurred in the iFR 'grey zone' of 0.86–0.93[23] that underwent subsequent hyperaemia testing to determine treatment in the SYNTAX II trial,[30] implying clinical uncertainty regarding these small, rare discordances. While 80% of lesions display binary concordance between iFR and fractional flow reserve,[17,18,21] implying an opportunity to reduce routine hyperaemia, existing studies have not addressed the 20% of discordant lesions[31] where fractional flow reserve remains the reference standard based on the totality of clinical evidence.

We did not compare our dPR results to fractional flow reserve, but given the numerical equivalency between dPR and iFR, these results would be expected to mirror prior literature.[17,18,21]

Conclusions

Our dPR offers numerical equivalency to iFR. Despite a different technical approach, the agreement between dPR and iFR and the insensitivity of dPR to minor variations in its definition further confirm numerical equivalency among resting metrics.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: N.P.J. received internal funding from the Weatherhead PET Center for Preventing and Reversing

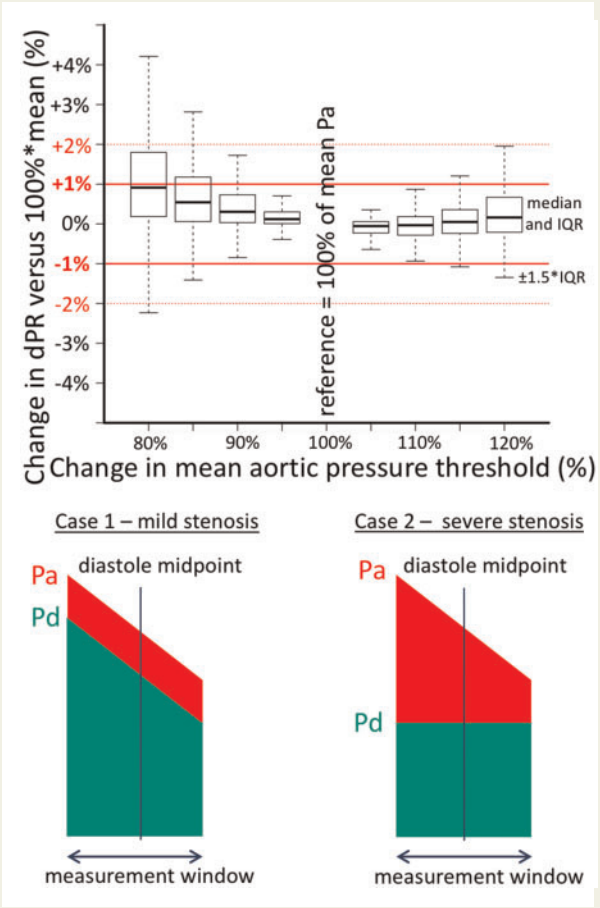

Figure 6 Stability of diastolic pressure ratio despite minor changes to its definition. Instead of using mean aortic pressure as in *Figure 1*, minor variations to diastolic pressure ratio can be created by changing the threshold from 80% to 120% of mean. Using 100% of mean as the reference, diastolic pressure ratio varied by <1–2% in relative terms, except for 80% and 85% of mean. The explanation for this stability of diastolic pressure ratio can be seen by considering schematic representations of pressure tracings. Because aortic pressure generally has a linear shape later in the cardiac cycle, its average value does not vary much when the measurement window expands or contracts around the centre point. Similarly, the average coronary pressure remains similar for a more mild stenosis that also has a linear form or for a severe stenosis that has a flat, 'ventricularized' shape. Therefore, the diastolic pressure ratio is insensitive to minor changes in its definition.

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