Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Validation of Resting Diastolic Pressure Ratio Calculated by a Novel Algorithm and Its Correlation With Distal Coronary Artery Pressure to Aortic Pressure, Instantaneous Wave–Free Ratio, and Fractional Flow Reserve

The dPR Study

See Editorial by Kern and Seto

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BACKGROUND: Instantaneous wave–free ratio (iFR) offers a reliable non–hyperemic assessment of coronary physiology but requires dedicated proprietary software with a fully automated algorithm. We hypothesized that dPR (diastolic pressure ratio), calculated with novel universal software, has a strong correlation with iFR, similar diagnostic accuracy relative to resting distal coronary artery pressure/aortic pressure and fractional flow reserve (FFR).

METHODS AND RESULTS: The dPR study is an observational, retrospective, single-center cohort study including patients who underwent iFR or FFR. Dedicated software was used to calculate the dPR from Digital Imaging and Communications in Medicine (DICOM) pressure waveforms. The flat period on the pressure difference between sample (dP) to the time difference between the same sample points (dt) signal was used to detect automatically the period, where the resistance is low and constant, and to calculate the dPR, which is an average over 5 consecutive heartbeats. The software was validated by correlating iFR results with dPR. Software validation was done by comparing 78 iFR measurements in 44 patients who underwent iFR. Mean iFR and dPR were 0.91±0.10 and 0.92±0.10, respectively, with a significant linear correlation (R=0.997; P<0.001). Diagnostic accuracy was tested in 100 patients who underwent FFR. Mean FFR, resting distal coronary artery pressure/aortic pressure, and dPR were 0.85±0.09, 0.94±0.05, and 0.93±0.07, respectively. There was a significant linear correlation between dPR and FFR (R=0.77; P<0.001). Both distal coronary artery pressure/aortic pressure and dPR had good diagnostic accuracy in the identification of lesions with an FFR ≤0.80 (area under the curve, 0.84; 95% CI, 0.76–0.92 and 0.86; 95% CI, 0.78–0.93, respectively).

CONCLUSIONS: dPR, calculated by a novel validated software tool, showed a strong linear correlation with iFR. dPR correlated well with FFR with a good diagnostic accuracy to identify positive FFR.

*J. Ligthart and Dr Masdjedi contributed equally to this paper.

Key Words: catheter ■ methods ■ physiology ■ software ■ software validation

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WHAT IS KNOWN

- Instantaneous wave-free ratio offers a reliable non–hyperemic assessment of coronary physiology but requires dedicated proprietary software with a fully automated algorithm of a single vendor.

WHAT THE STUDY ADDS

- Diastolic pressure ratio, calculated by a novel validated software tool, showed an almost perfect linear correlation with instantaneous wave–free ratio by using pressure waveforms from any type of pressure wire or microcatheter.

When compared with angiography-guided percutaneous coronary intervention (PCI), fractional flow reserve (FFR)–guided PCI has been shown to significantly improve patient outcomes and cost-effectiveness and is currently considered the gold standard to identify the hemodynamic severity of coronary artery stenosis.[1–6] However, the concept of FFR is based on maximum hyperemic conditions requiring intracoronary or intravenous hyperemic agents with potential side effects like dyspnea, chest pain, and arrhythmias.[7]

In recent years, non–hyperemic pressure ratios, such as the instantaneous wave–free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (Pd/Pa), were introduced as alternative invasive indices to assess the severity of coronary artery stenosis.[8,9] Although Pd/Pa presents the ratio from the mean resting distal pressure to aortic coronary pressure during the whole cardiac cycle, iFR is based on the same ratio measured during the so-called wave-free period, a period during diastole in which the microvascular resistance is low and constant. When compared with FFR, the diagnostic accuracy of iFR has been assumed to be slightly better than Pd/Pa.[10]

Although Pd/Pa can be calculated from any type of pressure wire or microcatheter, the algorithm of iFR belongs to the iFR core laboratory (Imperial College, London, UK) and its use is restricted to the proprietary software of a single vendor (Philips Volcano).

The aim of this study was to validate the diastolic pressure ratio (dPR), calculated using novel software applicable to any type of pressure wire or microcatheter, to assess the correlation of dPR with iFR and to assess the diagnostic accuracy of dPR when compared with FFR and resting Pd/Pa.

METHODS

Study Design and Patient Population

Dedicated software was developed in the Erasmus Medical Center (Erasmus MC) (F.M., J.L., K.W.). The software was designed to calculate a dPR from DICOM pressure tracings generated by any type of pressure wire or catheter using either electrical (Piezo-Resistive) or optical sensors and from spreadsheet data (comma-separated values file), provided by the S5i console (Volcano Corporation, Rancho Cordova, CA; FFR software version 2.4.1.2723) offline. The dPR study consisted of 2 parts: (1) validation of the dPR software with original iFR results and (2) assessment of the correlation of dPR with FFR and its diagnostic accuracy for identification of positive FFR.

For the purpose of this retrospective study, patients were not subjected to study interventions, neither was any mode of behavior imposed, otherwise than as part of their regular treatment. Therefore, according to Dutch law, no formal approval was required. This study was conducted according to the privacy policy of the Erasmus MC and to the Erasmus MC regulations for the appropriate use of data in patient-orientated research, which are based on international regulations, including the declaration of Helsinki. All patients consented to the use of their data for scientific research.

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Coronary Angiography and Calculation of dPR

All procedures were performed according to standard local clinical practice. Pressure measurements were performed after administration of an intracoronary bolus of nitrates (100–200 μg), in case there was doubt on the hemodynamic significance of intermediate coronary artery lesions. Pd/Pa was defined as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state during the whole cardiac cycle. FFR was defined as lowest ratio of mean distal coronary artery pressure divided by mean aortic pressure during maximum hyperemia achieved by continuous intravenous infusion of adenosine at a rate of 140 μg kg^{-1} min^{-1} through an antecubital vein. The dPR was defined by the ratio between the mean diastolic pressure distal to the stenosis and the mean diastolic aortic pressure in resting conditions. The diastolic period used to calculate the dPR was automatically delineated based on the pressure difference between sample (dP)/time difference between the same sample points (dt) curve of the aortic pressure at the point at which the resistance was low, constant, and stable. The dP/dt curve represents the increase and decrease of the pressure over time during the heart cycle. dP is the pressure difference between sample points, and dt is the time difference between the same sample points. The flat line of the dP/dt tracing was used as trigger for the software to detect the wave-free period within the range of 60% to 80% of the cardiac phase as a first default. Because of this range, the wave-free period detected by dP/dt tracing can be shorter than the wave-free period detected by original iFR. Both original iFR and calculated dPR values were stored in a spreadsheet, created by the dPR software, and from each measurement, a graphic representation was provided in PDF format (Figure 1), showing the pressure and dP/dt tracings together with the triggered regions and region of interest to calculate dPR.

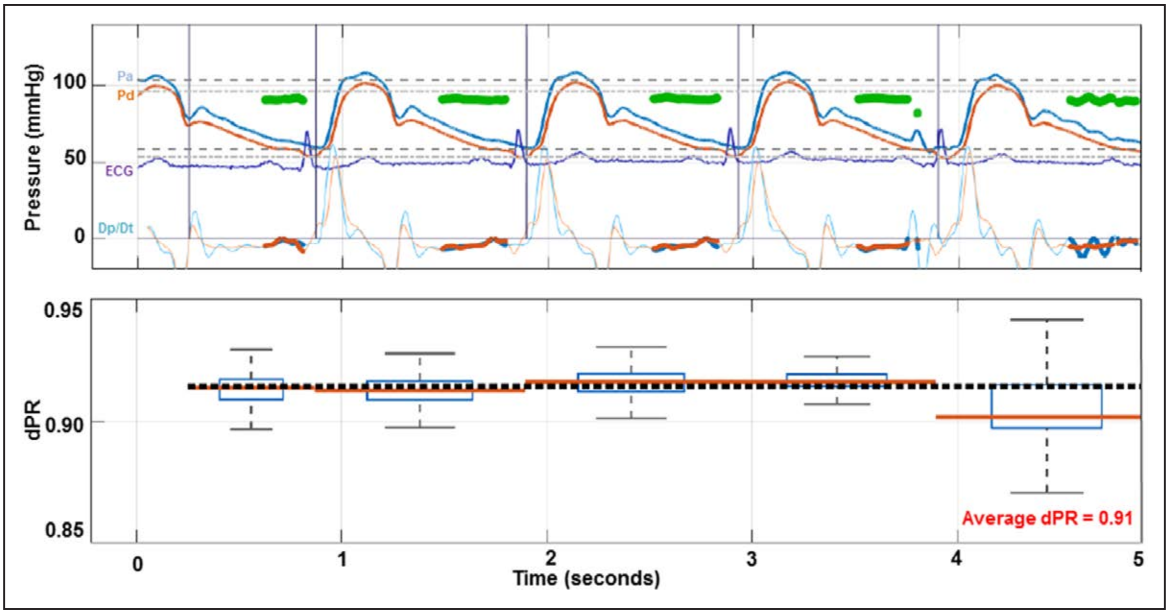

Figure 1. Sample tracing of the ECG, aortic pressure, and dP/dt with the effect of different periods in the heart cycle.
Calculation of the index (dPR [diastolic pressure ratio]) during diastole by automatically indicating the flat period of the dP/dt signal in 5 consecutive heartbeats. dP indicates the pressure difference between the sample; and dt, the time difference between the same sample points.

Validation With iFR

A total of 78 iFR measurements from 44 patients were used for the validation step. iFR measurements were performed using the Verrata pressure wire along with the original proprietary software (Philips Volcano). The comma-separated values spreadsheet files were imported in the software. The spreadsheet values of the reference aortic pressure and the wire pressure signals were used by the software to automatically analyze the dP/dt tracing and calculate the corresponding dPR based on 5 consecutive heart beats.

Validation With FFR

From April 2017 through September 2017, patients referred for coronary angiography for stable or unstable coronary artery disease and an indication to perform FFR were included. A consecutive cohort of 100 patients with adequate pressure tracings was enrolled. DICOM-recorded tracings derived from either a Pressure Wire (Pressure Wire X; Abbott Vascular, Santa Clara, CA) or microcatheter (Navvus; ACIST Medical Systems, Eden Prairie, MN) were eligible. Pressure waveforms were automatically exported to Siemens Sensis, converted to DICOM, and stored in a local hospital database.

Statistical Analysis

Continuous variables are presented as mean±SD. All continuous variables were normally distributed. Categorical variables are expressed as frequencies (n) and percentages (%). All statistical tests are 2-tailed. Pearson correlation coefficient (*R*) was used to assess the relationship between the several indices. Agreement between the indices and the interobserver variability was assessed by Bland-Altman plots with corresponding 95% limits of agreement. Receiver-operating characteristic area under the curve (AUC) analysis was used to estimate the diagnostic accuracy of dPR when compared with FFR with a threshold of ≤0.80. Statistical analysis was performed using the SPSS statistical package version 21 (IBM, Armonk, North Castle, NY).

RESULTS

Validation With iFR

A total of 44 patients (age 70±10, 70% male) presenting with stable or unstable coronary artery disease underwent iFR measurements in 78 vessels (left anterior descendending artery, n=38; left circumflex artery, n=22; right coronary artery, n=18). Baseline characteristics of the iFR cohort are summarized in Table 1. Mean iFR and dPR were 0.91±0.10 and 0.92±0.10, respectively. An excellent correlation was found between both indices (R=0.997; P<0.001; mean bias, 0.0016±0.084; Figure 2).

Patient Demographics and Procedural Data of the FFR Cohort

Baseline and procedural characteristics of the FFR cohort are summarized in Table 2. Mean age was 66 years, and the majority of patients were male (80%). Clinical presentation was stable angina (56%), unstable angina (11%), and non–ST-segment–elevation myocardial infarction (33%). Diabetes mellitus was present in 22% of the cases. The majority of the FFR measurements were performed in the left anterior descending artery (67%). The left circumflex artery and the right coronary artery were measured in 14% and 19% of the cases, respectively.

Table 1. Baseline Characteristics iFR Cohort

	Total (N=48)
Age, y mean (±SD)	70 (10)
Male sex, n (%)	31 (70)
Clinical indication procedure, n (%)	
Stable angina	32 (67)
Unstable angina	2 (4)
Non–ST-segment–elevation MI	14 (29)
Cardiovascular risk factors, n (%)	
Hypertension	23 (52)
Hyperlipidemia	17 (38)
Diabetes mellitus	14 (32)
Smoker	8 (18)
Family history of CVD	16 (36)
Comorbidity, mean (±SD)	
Creatinine, µmol/L	111 (46)
Hemoglobin E, mmol/L	8.1 (1.2)
BMI	27 (4)
Measured vessel lesions, n (%)	
Left anterior descending artery	38 (49)
Left circumflex artery	22 (28)
Right coronary artery	18 (23)
Indices, mean (±SD)	
iFR	0.91 (0.10)
dPR	0.92 (0.10)

Values are n, mean±SD of n (%). BMI indicates body mass index; CVD, cardiovascular disease; dPR, diastolic pressure ratio; iFR, instantaneous wave–free ratio; and MI, myocardial infarction.

Relationship Between dPR, Pd/Pa, and FFR

Mean FFR, resting Pd/Pa, and dPR were 0.85±0.09, 0.94±0.05, and 0.93±0.07, respectively (Table 2). A good linear correlation was found between dPR and FFR (R=0.77; P<0.001; Figure 3). The linear correlation between FFR and Pd/Pa was 0.81 (P<0.001). dPR showed to have good diagnostic accuracy in the identification of patients with FFR values ≤0.80 (AUC, 0.86; 95% CI, 0.78–0.93). Comparable results applies to Pd/Pa as well (AUC, 0.84; 95% CI, 0.76–0.92; Figure 4). The optimal cutoff value for an FFR ≤0.80 derived from the receiver-operating characteristic analyses was 0.91 for dPR and 0.92 for Pd/Pa.

DISCUSSION

In the present study, we demonstrated the feasibility of using a non–hyperemic pressure ratio, the dPR, calculated using novel software applicable to any type of pressure wire or microcatheter. dPR had an excellent linear correlation with iFR and a strong diagnostic accuracy in identifying lesions with an FFR ≤0.80.

FFR has become the gold standard to determine the severity of epicardial coronary stenoses and myocardial ischemia based on studies demonstrating significantly better outcomes with FFR-guided PCI when compared with angiography-guided PCI.[4–6,11,12] Nevertheless, despite strong guideline recommendations and increasing evidence on its cost-effectiveness, the adoption of FFR in routine clinical practice remains low.[13–16] The latter has been linked to reimbursement issues and the need for hyperemic agents. Hyperemic agents like intravenous adenosine might provoke transient dyspnea, chest pain, vomiting, rhythm disturbances, and hypotension in up to 37.5% of the cases.[8,9] For these reasons, the search for cheaper, faster, and more patient-friendly methods remains relevant and several studies assessed the concept of the adenosine-independent index iFR as an alternative method to assess lesion severity. As mentioned, the concept of FFR is based on maximum hyperemic conditions

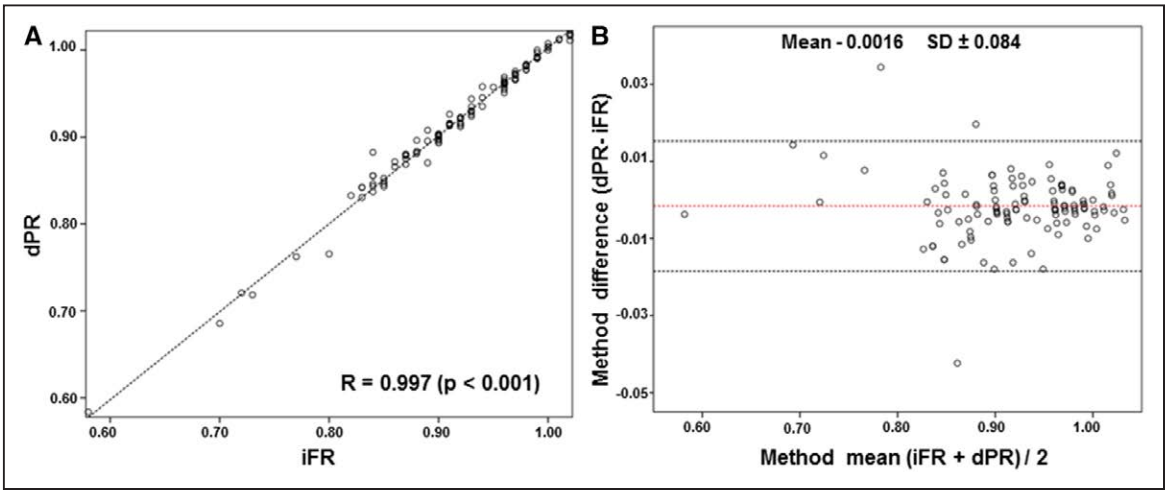

Figure 2. Scatter plot showing the relationship between the instantaneous wave–free ratio (iFR) and diastolic pressure ratio (dPR) (A) and Bland-Altman plots of difference against the mean (B).
The mean bias is represented by the solid red line and the 95% CI is represented by the dashed lines.

Table 2. Baseline Characteristics of FFR Cohort

	Total Cohort	FFR_{MC} (N=50)	FFR_{PW} (N=50)	*P* Value
Age, y mean (±SD)	66 (11)	67 (13)	66 (8)	0.94
Male sex, n (%)	80 (80)	39 (78)	41 (82)	0.62
Clinical indication procedure, n (%)				
Stable angina	56 (56)	20 (40)	36 (72)	0.001
Unstable angina	11 (11)	7 (14)	4 (8)	0.34
Non–ST-segment–elevation MI	33 (33)	23 (46)	10 (20)	0.01
Cardiovascular risk factors, n (%)				
Hypertension	65 (65)	34 (68)	31 (62)	0.53
Hyperlipidemia	55 (55)	26 (52)	29 (58)	0.55
Diabetes mellitus	22 (22)	12 (24)	10 (20)	0.63
Smoker	18 (18)	11 (22)	7 (14)	0.30
Family history of CVD	27 (27)	17 (34)	10 (20)	0.12
Comorbidity, mean (±SD)				
Creatinine, µmol/L	96 (46)	96 (40)	97 (50)	0.94
Hemoglobin E, mmol/L	8.5 (1.1)	8.6 (1.0)	8.3 (1.1)	0.27
BMI	28 (4)	28 (5)	27 (4)	0.25
Measured vessel lesions, n (%)				
Left anterior descending artery	67 (67)	34 (68)	33 (66)	0.83
Left circumflex artery	14 (14)	6 (12)	8 (16)	0.57
Right coronary artery	19 (19)	10 (20)	9 (18)	0.80
Indices, mean (±SD)				
Pd/Pa	0.94 (0.05)	0.94 (0.05)	0.94 (0.05)	0.73
FFR	0.85 (0.09)	0.85 (0.08)	0.85 (0.09)	1.00
dPR	0.93 (0.07)	0.93 (0.06)	0.92 (0.07)	0.87

Values are n, mean±SD of n (%). BMI indicates body mass index; CVD, cardiovascular disease; dPR, diastolic pressure ratio; FFR, fractional flow reserve; FFR_{MC}, FFR measured by the Acist FFR wire system; FFR_{PW}, FFR measured by pressure wire system; MI, myocardial infarction; and Pd/Pa, resting distal to aortic coronary pressure.

necessitating the use of intravenous hyperemic agents. Nevertheless, even during hyperemia, intracoronary resistance is not static but instead fluctuates in a phasic pattern throughout the cardiac cycle with the lowest resistance during diastole because of decompression of the microvasculature and because of the lowest difference in pressure between the aorta and the coronary artery during diastole.[17] The iFR concept relies on the theory that intracoronary resistance is naturally low, constant, and stable during the wave-free period precluding the need for hyperemic agents.[18] iFR had a high diagnostic accuracy to predict positive or negative FFR values. More recently, iFR-guided PCI demonstrated to be noninferior to FFR in reducing a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 12 months.[8,9] However, in a pooled meta-analysis of this 2 trials, a numeric excess in the incidence of death and myocardial infarction was found in the iFR group.[19] Although no large-scale randomized outcome studies are available on the efficacy of Pd/Pa when compared with FFR-guided revascularization, iFR appeared more sensitive than Pd/Pa to differentiate stenosis severity and showed a lower maximum difference in estimated major adverse cardiac event risk influenced by the measurement variability compared with resting Pd/Pa.[10] The latter supports the concept of applying the diastolic period to calculate pressure gradients when refraining from the use of hyperemic agents. At present, the use of iFR is restricted to the use of a single device and software (Philips Volcano), whereas a large variety of pressure wires and microcatheters are available to measure Pd/Pa and FFR. In the current study, we demonstrated the feasibility of a fast, simple, and reproducible method of measuring a dPR based on non–hyperemic DICOM pressure waveforms derived from either PW or microcatheter devices which could open up the field for a more widespread use of diastolic pressure gradients in real-world clinical practice. By using a simple software tool to automatically detect the flat period in the dP/dt curve that indicates the so-called wave-free period, we found that the resultant dPR correlated nearly perfect with the original iFR output of Phillips Volcano

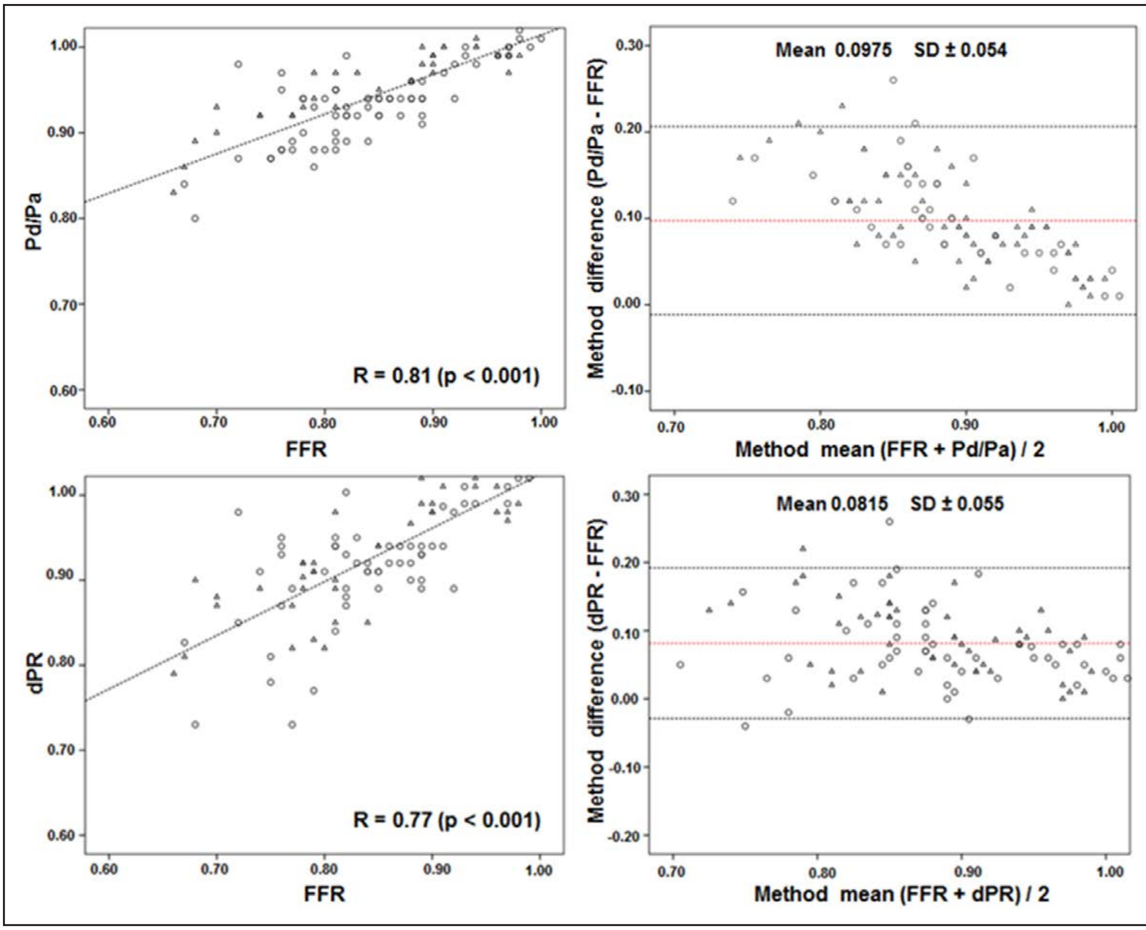

Figure 3. Scatter plot showing the relationship between fractional flow reserve (FFR) and 2 different resting indices (distal coronary artery pressure/aortic pressure [Pd/Pa] and diastolic pressure ratio [dPR]) and Bland-Altman plots of difference against the mean.
The mean bias is represented by the solid red line, and the 95% CI is represented by the dashed lines. Δ represents FFR measurements as measured using the Navvus system (FFR_{MC}), and O represents pressure wire–based FFR measurements (FFR_{PW}).

(*r*=0.997; *P*<0.001). Subsequently, our results showed a correlation between dPR and FFR (*r*=0.77) in line with previous results from the VERIFY study (Verification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in Everyday Practice) demonstrating a correlation coefficient *r* of 0.789 between iFR and FFR.[20] In addition, dPR showed a high diagnostic accuracy in the identification of patients with FFR values ≤0.80 (AUC, 0.86; 95% CI, 0.78–0.93), whereas the AUC was 0.84 (95% CI, 0.76–0.92) for Pd/Pa. Also these results are in line with previous findings as published in the RESOLVE study (Multicenter Core Laboratory Comparison of the Instantaneous Wave-Free Ratio and Resting Pd/Pa With Fractional Flow Reserve) in which the AUC was 0.81 and 0.82 for iFR and Pd/Pa, respectively.[21] In the present study, we used the flat period of the dP/dt signal to identify the wave-free period. Although during this period in diastole there is the least amount of pressure variation between aortic and distal pressures, it allowed us to develop software using the same methodology in any pressure wire or microcatheter. It is likely that using either period during diastole to compute the dPR would result in equal results. Van't Veer et al[22] looked at the correlation between iFR and resting indices during different parts of the diastole by using a simple Matlab algorithm and concluded that all diastolic resting indices were identical to iFR. Therefore, any diastolic resting index can be used with the same advantages and disadvantages inherent within iFR. However, in our validation cohort of 78 iFR measurements, we found 2 cases with a bias beyond the 95% CI. Analysis of these cases (Figure 5) showed that the dP/dt triggered a shorter wave-free period, resulting in a shorter region of interest: in 1 case positioned earlier in the heart sequence, resulting in a lower dPR ratio compared with iFR, in the other case positioned later in the heart sequence, resulting in a higher dPR when compared with iFR. In conclusion, the length of the interval used in the present algorithm depends on the length of the flat line on dP/dt waveform which might slightly differ per cardiac cycle. Conclusions about accuracy of iFR versus dPR and correlation to FFR cannot be drawn based on these 2 cases but warrant further research.

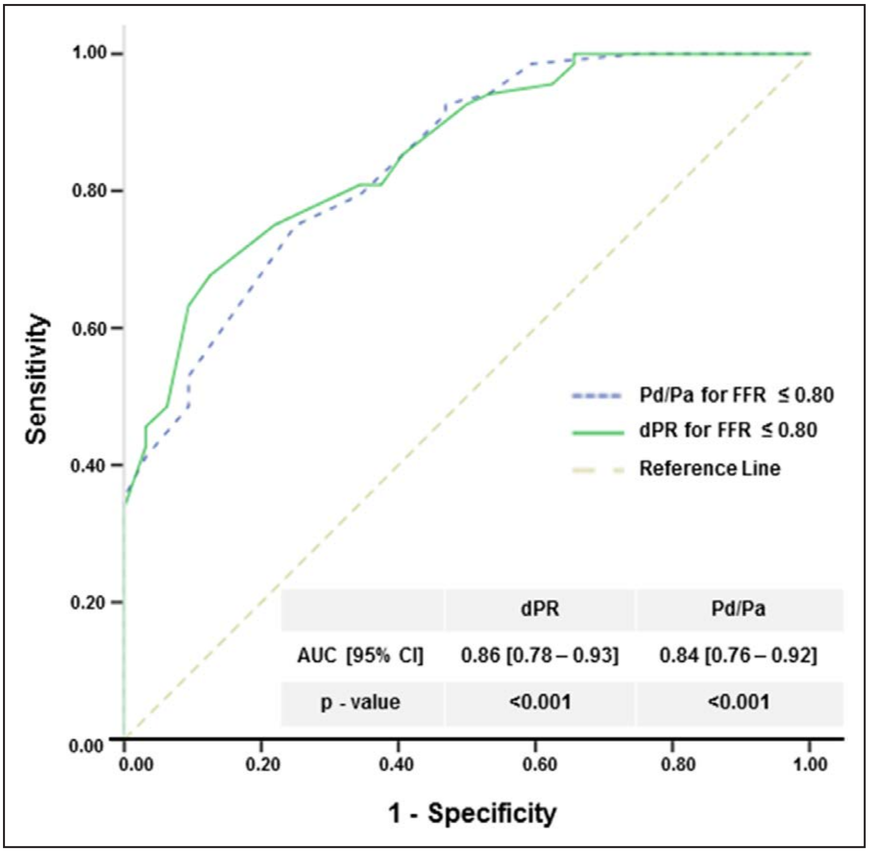

Figure 4. Receiver operating characteristic (ROC) curves for diastolic pressure ratio (dPR) and distal coronary artery pressure/aortic pressure (Pd/Pa).
Comparisons are made with a fractional flow reserve (FFR) at a cut point of 0.80. AUC indicates area under the curve.

Kobayashi et al[23] looked at the influence of lesion location on the diagnostic accuracy of resting indices contrast FFR, iFR, and Pd/Pa and found that this 3 resting indices are less accurate in left main and proximal ramus descendens artery lesions when compared with other lesion locations. The authors in the VERIFY 2 study hypothesized that in comparison with FFR, revascularization decisions based on either binary cutoff values for iFR and Pd/Pa or hybrid strategies incorporating iFR or Pd/Pa will result in similar levels of disagreement. They found that binary cutoff values for iFR and Pd/Pa result in misclassification of 1 in 5 lesions.[24] We know that perfusion of the left coronary artery is predominantly diastolic, whereas the perfusion of right coronary artery is both systolic and diastolic, because of lower pressure in the right ventricle when compared with the left ventricle.

Although the diagnostic accuracy of non–hyperemic pressure ratio in predicting positive FFR in general might differ between left- and right-sided assessments, we do not see any reason to think that any difference might be expected in the diagnostic accuracy of dPR when compared with iFR.

Thereby, our study population is too small to analyze the differences between different lesion locations and between right (19%) versus left coronary artery (81%; Table 2). However, we think that there is no reason to think that the dPR calculated based on dP/dt has superior diagnostic accuracy as any of the other resting indices.

Limitations

The present results are based on a single-center experience in which we restricted our analyses to those recordings with undamped pressure wave forms. The latter could have artificially influenced our results because recent core laboratory study data, assessing the prevalence of erroneous or suboptimal FFR measurements in clinical practice, demonstrated that in up to 30% of the recordings, pressure signals were inadequate.[25] In order not to be biased by measurements and results based on dampening pressure waveforms which might have biased the final FFR, iFR, or Pd/Pa, we scrutinized the pressure waveforms from tracings in the cases selected. To be able to mitigate to amount of bias caused by dampened pressure waveforms, we only selected cases in which pressure tracings and waveforms were adequate. Furthermore, Navvus microcatheter may confound the relationship with stenosis severity in case of small vessels (<2.5 mm), which may be relevant when considering relationships between Pd/Pa and FFR. However, all included vessels in the present study were >2.5 mm and that makes the comparison more reliable.

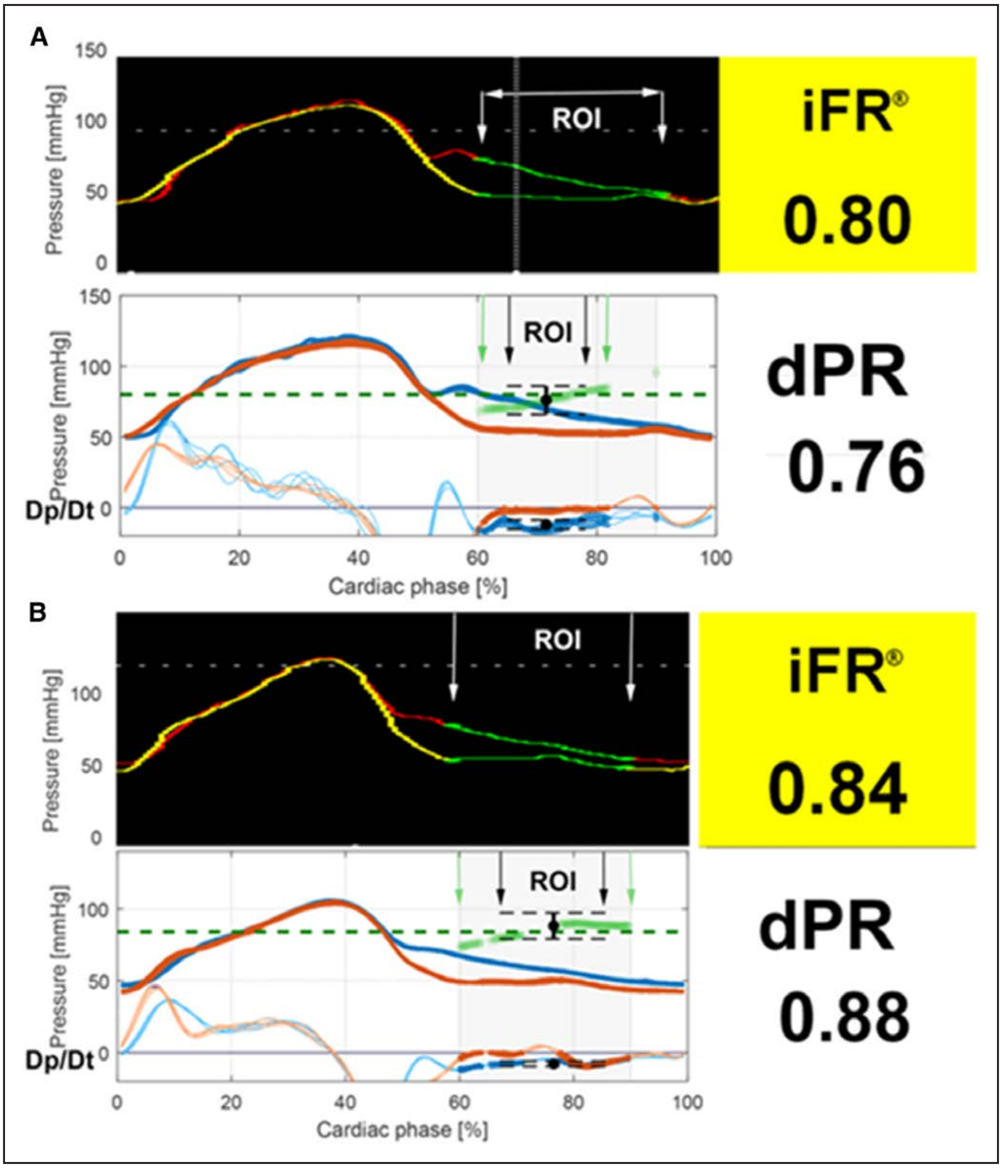

Figure 5. Explanation of discrepancy between instantaneous wave–free ratio (iFR) and dPR (diastolic pressure ratio): 2 cases with a bias beyond the 95% CI.

Compared with iFR, dPR software triggers a shorter region of interest (ROI). Depending on the position of the ROI in the sequence, this may result in a higher or lower distal coronary artery pressure/aortic pressure (Pd/Pa) ratio compared with iFR. Case A: iFR includes a region with a lump in the distal pressure, dPR detected a lump in pressure difference between sample/time difference between the same sample points (dP/dt) and did not include the region beyond this lump, positioned the ROI earlier in the sequence, resulting in a lower ratio. Case B: dPR ignored a steeper region in the dP/dt signal, positioned the ROI later in middle of the sequence, resulting in a higher Pd/Pa ratio compared with iFR.

Conclusions

Resting diastolic pressure ratio (dPR), calculated by a novel algorithm, had an excellent correlation with iFR, a high linear correlation to both Pd/Pa and FFR and a better diagnostic accuracy when compared with Pd/Pa.

ARTICLE INFORMATION

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Disclosures

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