Diagnostic Performance of Resting Distal to Aortic Coronary Pressure Using Instantaneous Wave-Free Ratio as a Reference Standard

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Abstract

Background: Recently, two randomized controlled trials suggested that the instantaneous wave-free ratio (iFR), a resting coronary physiologic index is non-inferior to fractional flow reserve for guiding revascularization. The distal to aortic coronary pressure (Pd/Pa) measured at rest is another adenosine-free index widely available in the cardiac catheterization laboratory; however, little is known about the diagnostic performance of Pd/Pa using iFR as a reference standard.

Objective: To investigate the diagnostic performance of Pd/Pa against iFR.

Methods: A total of 763 patients were prospectively enrolled from 12 institutions. iFR and Pd/Pa were measured under resting conditions. Using iFR≤0.89 as a reference standard, the diagnostic performance of Pd/Pa and its best cutoff value were assessed.

Results: By independent core laboratory analysis, iFR and Pd/Pa were analyzable in 627 and 733 patients (82.2% vs. 96.1%, p<0.001), respectively. The median iFR and Pd/Pa were 0.90 (interquartile range 0.85-0.94) and 0.92 (0.88-0.95) and the two indices were highly correlated (R^2=0.93, p<0.001, iFR=1.31*Pd/Pa-0.31). By receiver operating characteristics curve analysis, Pd/Pa showed excellent diagnostic performance (area under the curve=0.98, 95% confidence interval 0.97 to 0.99, p<0.001) with a best cutoff value of Pd/Pa≤0.91. The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 93.0%, 91.4%, 94.4%, 93.3%, and 92.7%, respectively. The above results were similar in patients with acute coronary syndrome and stable angina.

Conclusion: Pd/Pa was analyzable in a significantly higher number of patients than iFR. Pd/Pa showed excellent diagnostic performance against iFR and would likely result in similar outcomes as iFR if used to guide revascularization.

Condensed Abstract

No head-to-head comparison has been reported between the instantaneous wave-free ratio (iFR) and the distal to aortic coronary pressure (Pd/Pa), both resting coronary physiologic indices. In 763 patients, the diagnostic performance of Pd/Pa was assessed using iFR≤0.89 as a reference standard. By independent core laboratory analysis, Pd/Pa was analyzable in a higher percentage of patients than iFR (82.2% vs. 96.1%, p<0.001). The two indices were highly correlated (R^2=0.93, p<0.001). Pd/Pa showed excellent diagnostic performance (AUC=0.98, p<0.001) with the diagnostic accuracy=93.0%. Pd/Pa showed excellent diagnostic performance against iFR and it likely results in similar outcome as iFR when used to guide revascularization.

Key Words

fractional flow reserve, instantaneous wave-free ratio, resting distal to aortic coronary pressure

Abbreviations and Acronyms

FFR=fractional flow reserve

iFR=instantaneous wave-free ratio

Pd/Pa=resting distal to aortic coronary pressure

ROC=receiver operating characteristic

Based on pivotal outcome trials, fractional flow reserve (FFR) is the reference standard for invasively assessing the physiologic significance of a coronary artery stenosis (1-7). Although FFR-guided percutaneous coronary intervention has been shown to be cost-saving compared to angiography-guided revascularization and cost-effective compared to medical therapy (8,9), the drugs used to induce maximal hyperemia may be expensive in some healthcare systems (10,11), and may rarely result in significant side effects (12). As such, coronary physiologic measurements with submaximal hyperemia or at rest could streamline physiologic lesion assessment in the cardiac catheterization laboratory, albeit with reduced diagnostic accuracy (13-20).

Two randomized controlled trials recently used the instantaneous wave-free ratio (iFR) to guide revascularization (10,11). However, iFR requires software from a specific vendor, preventing its use with other pressure wire systems or free-standing hemodynamic platforms. Several studies report an equivalent diagnostic performance of iFR and the resting distal to aortic coronary pressure (Pd/Pa) against FFR (15-18,21-23) or positron emission tomography (24). Therefore, Pd/Pa appears to offer a universal resting physiologic metric with equivalent diagnostic performance to iFR. Because no study to date has examined Pd/Pa using iFR as a reference standard, the primary goal of the present study was to perform this comparison.

Methods

Study design and patient population

The current study was a post-hoc analysis of the already published CONTRAST (Can contrast injection better approximate FFR compared to pure resting physiology?) trial (18). In brief, CONTRAST (clinicaltrials.gov NCT02184117) was a multi-center, prospective,

investigator-initiated, diagnostic accuracy study of contrast FFR, resting distal to aortic coronary pressure (Pd/Pa), and the instantaneous wave-free ratio (iFR) to predict adenosine FFR. In adult subjects undergoing invasive FFR assessment of a coronary artery lesion for standard clinical indications, comprehensive coronary physiologic assessment was performed including adenosine-free indices in duplicate. Subjects were excluded if they had previous coronary artery bypass surgery, an extremely tortuous or calcified coronary artery, known severe left ventricular hypertrophy, left ventricular ejection fraction <30%, inability to receive adenosine, renal insufficiency such that additional contrast would pose unwarranted risk, or recent (within 3 weeks prior to cardiac catheterization) ST-segment elevation myocardial infarction. Culprit lesions for either ST-segment or non-ST-segment elevation myocardial infarction were also excluded. Subjects were further excluded from the present substudy if the iFR and/or Pd/Pa value was deemed inaccurate based on an independent and blinded core labortatory. The original CONTRAST study was approved by an institutional review committee from each participating site and informed consent was obtained from all participants.

Invasive coronary physiologic measurements and core laboratory assessments

All coronary physiologic parameters were measured using a 0.014-inch pressure sensor guidewire and console (PressureWire and QUANTIEN system, then St Jude Medical). After equalization to the guide catheter pressure with the sensor positioned at the ostium of the coronary artery, the pressure guidewire was advanced down the target coronary artery. First, simultaneous recording of the aortic pressure with the guide catheter and the distal coronary pressure with the pressure guidewire was performed for at least 1 minute to record resting physiology. In addition to contrast and adenosine hyperemic measurements not relevant to this

substudy, but described previously (18), a second assessment of resting physiology took place before starting intravenous adenosine hyperemia. After all lesion assessments, an optional but encouraged drift check was performed by returning the pressure sensor to the position during equalization.

All physiologic tracings were anonymized and sent to an independent and blinded core laboratory at the Cardiovascular Research Foundation (CRF) in New York for off-line analysis. Each resting tracing received a binary decision regarding its signal quality. Whole-cycle Pd/Pa was determined by the core lab based on review of the tracing. iFR was automatically calculated at the core laboratory using HARVEST software version 1.0.0.127 (then Volcano Corporation). Note that the iFR algorithm applied its own quality criteria to the pressure waveforms and electrocardiographic signal, resulting in rejection of some tracings by the software that had been accepted by the core lab itself. When repeated iFR and Pd/Pa values were available, the average value of 2 measurements rounded to 2 decimal places was used for analysis.

End points

In the current reanalysis, iFR and Pd/Pa were the indices of interest. The primary endpoint was the diagnostic performance of Pd/Pa using binary iFR≤0.89 as the reference standard, the cut-off value used in recent randomized controlled trials. (25,26) By receiver operating characteristic (ROC) curve analysis, the best cutoff value of Pd/Pa was obtained; thereafter diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Because repeated iFR and Pd/Pa measurements have been shown to differ by 0.004±0.033 and 0.001±0.023 respectively (18), lesions near the diagnostic cutoff value (± 1 standard deviation) can be classified as either positive or negative. Therefore,

we repeated the above analyses excluding lesions with 0.86<iFR<0.92 and/or 0.89<Pd/Pa<0.93. Furthermore, sensitivity analyses were performed in the subset of patients presenting with acute coronary syndrome, stable angina, and patients whose pressure tracings had been checked for drift and the drift was ≤0.03. Secondary endpoints included: 1) linear regression model and the agreement between iFR and Pd/Pa; and 2) a logistic regression model to explore the contributing factors for iFR and transformed Pd/Pa discordance.

Statistical analysis

Categorical variables are presented as counts and percentages. The McNemar test was used for paired comparisons of categorical variables. Continuous variables are presented as median and interquartile range. The Wilcoxon signed rank test was used for paired comparisons of continuous variables. A linear regression model was used to compare iFR and Pd/Pa. If no whole-cycle gradient exists, then no diastolic gradient can exist either, implying Pd/Pa=1 when iFR=1. Therefore, the linear relationship between the two variables takes the form iFR=(1+k)*Pd/Pa–k, where k was derived using a 1-parameter regression. This equation "transforms" Pd/Pa into iFR by a linear model, as has been reported in several prior studies given the highly linear relationship between Pd/Pa and iFR (16,18,22). Deviations of mean differences between iFR and transformed Pd/Pa were tested with a one-sample *t*-test. An ROC curve analysis was performed to examine the diagnostic performance of Pd/Pa using iFR≤0.89 as a reference standard. Diagnostic agreement between iFR and Pd/Pa was tested using kappa analysis. For key clinical variables (parameters listed in Table 1) and hemodynamic parameters at the time of resting coronary physiology measurement (Pa=aortic pressure, Pd=distal coronary pressure, and heart rate), a univariate logistic regression model was used to explore the factors contributing to

discordance between iFR and Pd/Pa. Variables with $p<0.10$ by univariate analysis were entered into the multivariate logistic regression model. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS® version 21.

Results

A total of 763 subjects with 1 lesion each were included from 12 institutions. By independent core laboratory analysis, iFR was analyzable in 627 patients (82.2%) and Pd/Pa was analyzable in 733 patients (96.1%, $p<0.001$ versus iFR). Pd/Pa was analyzable in all 627 patients with analyzable iFR; therefore, the following analyses were performed on the 627 patients and lesions with paired iFR and Pd/Pa measurements. Table 1 provides baseline characteristics. The median and interquartile range of iFR and Pd/Pa were 0.90 (0.85-0.94) and 0.92 (0.88-0.95) as shown in Figure 1.

Figure 2A depicts a highly correlated iFR and Pd/Pa with $R^2=0.93$ and $p<0.001$ (iFR=1.31*Pd/Pa-0.31). By Bland-Altman analysis (Figure 2B), the iFR and transformed Pd/Pa values showed no bias (mean difference=0.00±0.03, p=0.71, 95% limits of agreement: -0.06 to 0.06), with a scatter similar to repeated iFR measurements (standard deviation of iFR minus transformed Pd/Pa difference 0.03, standard deviation of two iFR measurements 0.03).

Diagnostic performance of Pd/Pa against iFR

Using the binary cutoff of iFR≤0.89 as a reference standard, Pd/Pa showed excellent diagnostic performance by ROC curve analysis (area under the curve=0.98, 95% confidence interval 0.97 to 0.99, $p<0.001$) and the best cutoff value of Pd/Pa was ≤0.91 (Figure 3A). Using the binary cutoff of Pd/Pa ≤0.91 obtained by ROC curve analysis, diagnostic accuracy, sensitivity,

specificity, positive predictive value, and negative predictive value were 93.0%, 91.4%, 94.4%, 93.3%, and 92.7%, respectively (Figure 3B). iFR and Pd/Pa were highly concordant in detecting physiologically significant stenosis (kappa=0.86, $p<0.001$).

When the above analyses were repeated in the 417 remaining subjects after allowing for iFR and Pd/Pa values to disagree within 1SD of their respective thresholds, the diagnostic accuracy improved to 100%. Therefore, sensitivity, specificity, positive predictive value, and negative predictive value were also 100% and all lesions were concordant (kappa=1.00, $p<0.001$).

When a sensitivity analysis was performed in the 131 subjects presenting with acute coronary syndrome, the diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 93.9%, 93.8%, 93.9%, 93.8%, and 93.9%, respectively. iFR and Pd/Pa were highly concordant in detecting physiologically significant stenosis (kappa=0.88, $p<0.001$). In the remaining 496 subjects presenting with stable angina, the diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 92.7%, 90.7%, 94.5%, 93.2%, and 92.4%, respectively. iFR and Pd/Pa were again highly concordant in detecting physiologically significant stenosis (kappa=0.85, $p<0.001$).

When a sensitivity analysis was performed in the 410 subjects whose pressure tracings had been checked for drift and the drift was ≤ 0.03, the diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 93.7%, 89.0%, 96.7%, 94.8%, and 93.0%, respectively. iFR and Pd/Pa were highly concordant in detecting physiologically significant stenosis (kappa=0.87, $p<0.001$).

<u>iFR guided and Pd/Pa guided revascularization strategy</u>

Using their respective cut-off values, iFR and Pd/Pa identified a similar number of physiologically significant lesions (290 (46.3%) vs. 284 lesions (45.3%), p=0.45). If one used Pd/Pa instead of iFR to guide revascularization, diagnostic discordance between the two indices would occur only when Pd/Pa is between 0.89 and 0.95 (254 out of 627 lesions, 40.5%). However, even within this range of Pd/Pa values, iFR and Pd/Pa were concordant in 94% of lesions when iFR≤0.86 and in 100% of lesions when iFR≥0.92. All except one discordance occurred when 0.86<iFR<0.92, which is the gray zone of iFR (Figure 4) as used in prior work (19).

As shown in Table 2, by univariate logistic regression analysis, the use of a β-blocker, statin, or aspirin were predictors of a lower chance of discordance and the use of insulin was a predictor of a higher chance of discordance with p<0.10. Although hemodynamics at the time of resting physiology measurements including Pa, Pd, and heart rate were significantly lower in subjects taking a β-blocker compared to subjects who are not taking a β-blocker (all p<0.001), none of them were significant predictors of discordance when entered into the model as continuous variables or categorical variables using median values. Lesion locations such as left coronary artery vs. right coronary artery, or coronary artery dominance were not predictors of discordance. By multivariate logistic regression analysis, the use of a β-blocker (odds ratio 0.43, p=0.009) or insulin (odds ratio 3.43, p=0.003) were the only independent predictors of diagnostic discordance.

Discussion

The principal finding of this study is that Pd/Pa has an excellent diagnostic performance compared with iFR and the results were similar irrespective of presentation (i.e. acute coronary

syndrome and stable angina). Given the high level of agreement between the two indices, coupled with existing evidence of their equivalent performance versus FFR (15-18,21-23,27) and cardiac positron emission tomography,(24) this study demonstrates that either resting physiologic index can be selected based on local preference and availability. These results further broaden the application of invasive coronary physiologic assessment when an operator decides not to induce hyperemia.

iFR is an index based on resting coronary pressure measurement during diastole. The highly linear relationship between Pd/Pa and iFR seen in many studies (16,18,21,22) emphasizes their similarity and common underlying signal, explaining the excellent diagnostic performance of Pd/Pa seen in our study when using iFR as the reference. While not numerically identical, one index can be linearly transformed into the other, much like the conversion of units of temperature. Therefore a 0.01 change in Pd/Pa is not equivalent to a 0.01 change in iFR, invalidating the use of the same axis for their comparison during pullbacks, but explaining the larger imprecision for iFR (0.033) than Pd/Pa (0.023) seen in the CONTRAST study (18).

Both iFR and Pd/Pa do not require hyperemia and thus share the same advantages, such as a shorter procedural time, fewer procedure-related symptoms (25,26), and lower cost compared with FFR. On the other hand, these two indices share the same disadvantages, such as worse repeatability and a physiologic disconnect from stress conditions when patients experience angina (18,28). Pd/Pa is more broadly applicable than iFR, as it can be measured with any coronary pressure monitoring system, including stand-alone hemodynamic systems that obviate the need for a separate physiology console. Further, Pd/Pa is displayed continuously in real-time and does not require activation of an algorithm for measurement, unlike iFR, which is then displayed as a segmented retrospective measurement. Pd/Pa may also be more broadly applicable

because significantly fewer measurements were deemed unacceptable by an independent core laboratory when compared with iFR.

By ROC curve analysis, the area under the curve of Pd/Pa using an iFR≤0.89 as a reference standard was 0.98, suggesting almost identical diagnostic values between the two indices. The cutoff value obtained by ROC curve analysis (Pd/Pa≤0.91) is identical to what was observed in previous studies comparing Pd/Pa with FFR used as a reference standard (Pd/Pa<0.92) (16,22). Although the two indices are highly correlated, the use of a β-blocker was an independent predictor of higher concordance. Hemodynamics at the time of resting coronary physiology measurements were not predictors of discordance; nevertheless, the decreased myocardial oxygen demand and resulting lower coronary flow may explain this result. The presence of insulin dependent diabetes was an independent predictor of lower concordance between the two indices. This may be a result of increased resting coronary flow leading to a greater pressure gradient during diastole (29).

iFR and Pd/Pa have a highly linear relationship as seen in previous studies (16,18,21,22). Results of the linear regression analysis from these 4 studies are summarized in Figure 5. The relationship between iFR and Pd/Pa can be expressed as iFR=(1+x)*Pd/Pa-x, confirming the extremely linear relationship along a wide range of physiologic severity.

Limitations of this study include its retrospective and unplanned, post-hoc design. Newer iterations of the iFR algorithm have eliminated the reliance on the electrocardiogram (30), whereas our core lab used the original software. A lower rate of iFR tracing rejections might be anticipated when using the pressure signals alone. Our use of a core lab does not reflect real world practice, and the elimination of artifacts and noise would be expected to provide the best agreement between the two metrics. Unlike the randomized trials (10), we did not mandate a

minimum threshold for drift or require its routine assessment at the end of the protocol. However, a sensitivity analysis found similar results when confining the analysis to lesions with measured and minimal drift.

Conclusion

Pd/Pa was analyzable in a significantly higher number of patients than iFR. Pd/Pa showed excellent diagnostic performance against iFR and it likely results in similar outcome as iFR when used to guide revascularization.

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Table 1: Subject demographics and lesion characteristics.

	n=627
Clinical characteristics	
Age, years	67 (58-73)
Male, n (%)	450 (71.8)
Diabetes, n (%)	147 (23.4)
Hypertension, n (%)	454 (72.4)
Hypercholesterolemia, n (%)	430 (68.6)
Family history, n (%)	153 (24.4)
Current or past smoker, n (%)	299 (47.7)
Previous myocardial infarction, n (%)	165 (26.3)
Previous percutaneous coronary intervention, n (%)	98 (15.6)
Stable angina, n (%)	496 (79.1)
Medication	
Insulin, n (%)	50 (8.0)
Antidiabetics, n (%)	126 (20.1)
β-blocker, n (%)	390 (62.2)
RAAS blocker, n (%)	356 (56.8)
Calcium channel blocker, n (%)	161 (25.7)
Nitrate, n (%)	134 (21.4)
Diuretics, n (%)	89 (14.2)
Statin, n (%)	520 (82.9)
Aspirin, n (%)	541 (86.3)
Other antiplatelet drugs, n (%)	380 (60.5)
Ticagrelor, n (%)	104 (16.6)
Angiogram	
LM/LAD/LCx/RCA, n (%)	18/383/109/117 (2.9/61.1/17.4/18.7)
% diameter stenosis, %	51 (43-61)

Values are median (interquartile range) or n (%).

LM/LAD/LCx/RCA=left main/left anterior descending artery/left circumflex artery/right coronary artery; RAAS= renin-angiotensin-aldosterone system.

Table 2: Univariate and multivariate predictors of iFR and Pd/Pa discordance by logistic regression models.

	*Univariate			Multivariate		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
β-blocker	0.39	0.21 to 0.73	0.003	0.43	0.22 to 0.81	0.009
Insulin	3.40	1.53 to 7.55	0.003	3.43	1.52 to 7.75	0.003
Statin	0.52	0.26 to 1.04	0.07	0.61	0.28 to 1.23	0.20
Aspirin	0.51	0.24 to 1.07	0.08	0.74	0.33 to 1.69	0.48

*Variables with $p<0.10$ by univariate logistic regression analysis were shown. CI=confidence interval.

Figure Legend

Figure 1: Distribution of iFR and Pd/Pa.

Panel A and B represent the distribution of iFR and Pd/Pa in the 627 lesions where both indices were analyzable. iFR=instantaneous wave-free ratio; Pd/Pa=resting distal to aortic coronary pressure.

Figure 2: Linear regression and Bland-Altman plot between iFR and transformed Pd/Pa.

Panel A, Correlation between iFR and Pd/Pa Panel B, Bland-Altman plot between iFR and transformed Pd/Pa, showing their equivalence. iFR=instantaneous wave-free ratio; LOA=limits of agreement; Pd/Pa=resting distal to aortic coronary pressure; SD=standard deviation.

Figure 3: ROC curve analysis and diagnostic performance of Pd/Pa against iFR.

As shown in Panel A, Pd/Pa showed excellent diagnostic performance against iFR≤0.89 using ROC curve analysis with BCV of Pd/Pa≤0.91. As shown in Panel B, Pd/Pa≤0.91 had high diagnostic accuracy, sensitivity, specificity, PPV, and NPV. AUC=area under the curve; BCV=best cutoff value; iFR=instantaneous wave-free ratio; NPV=negative predictive value; Pd/Pa=resting distal to aortic coronary pressure; PPV=positive predictive value; ROC=receiver operating characteristics.

Figure 4: Flow-chart of Pd/Pa-guided revascularization strategy and resulting discordant cases.

Diagnostic discordance between iFR and Pd/Pa occurred only in lesions with Pd/Pa from 0.89 to 0.95. Even within the Pd/Pa value between 0.89 to 0.95, all except one discordance occurred

when iFR is in the gray zone (defined as within 1 standard deviation of repeatability from the iFR cutoff value). iFR=instantaneous wave-free ratio; Pd/Pa=resting distal to aortic coronary pressure.

Figure 5: Summarized linear regression curves from the four studies.

Results from the four studies demonstrate extremely linear relationship between iFR and Pd/Pa along the wide range of physiologic severity. Note all formula was expressed as iFR=(1+x)*Pd/Pa-x. Formula may be transformed from the original data to facilitate the visibility. iFR=instantaneous wave-free ratio; Pd/Pa=resting distal to aortic coronary pressure.