

Nitroglycerin-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions

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ABSTRACT: Objectives. To assess the predictive value of Pd/Pa after nitroglycerin administration [Pd/Pa(N)] as compared with standard fractional flow reserve [FFR]. **Methods.** Consecutive patients with intermediate coronary lesions assessed by FFR between January 2014 and October 2015 were included. We measured Pd/Pa at baseline, Pd/Pa [N], and Pd/Pa after incremental doses of intracoronary adenosine. **Results.** A total of 134 patients [27% females; mean age, 65 years] were included. The diagnostic performance of Pd/Pa[N] and identification of cut-off value for Pd/Pa [N] compared with FFR threshold of 0.8 using receiver-operating characteristic [ROC] area under the curve analysis was between 0.98 [95% confidence interval, 0.95-1.00; $P<.05$] for 48 μg and 0.86 [95% confidence interval, 0.79-0.94; $P<.05$] for 240 μg adenosine. Pd/Pa[N] ≤ 0.8 had 100% positive predictive value. Pd/Pa[N] ≥ 0.94 provided 100% negative predictive value with a high sensitivity ($>92\%$). Optimal diagnostic accuracy of Pd/Pa[N] was achieved for values ≤ 0.84 . The Pearson's correlation between Pd/Pa[N] and FFR varied between 0.89 for 24 μg adenosine and 0.77 for 240 μg [$P<.01$]. **Conclusion.** Pd/Pa[N] values can be used for diagnosis of hemodynamically significant lesions. Pd/Pa[N] correlates well with standard FFR. Pd/Pa[N] cut-off of ≤ 0.8 can be considered significant without need for adenosine injection. The value of using adenosine whenever Pd/Pa[N] is >0.94 is limited.

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Fractional flow reserve (FFR), defined as the ratio of maximal blood flow in a stenotic artery to maximum blood flow in the absence of stenosis, emerged as an important tool in clinical decision making and is recommended by current guidelines.^{1,2} FFR is calculated based on the assumption that there is a linear relationship between driving pressure and myocardial blood flow during maximal hyperemia. Therefore, since its introduction, the standard method for FFR measurement is achieving maximal hyperemia.

The achievement of maximal vasodilation of the two components of coronary circulation (epicardial and microvascular arteries), is enhanced by various stimuli.^{3,4} A bolus of intracoronary (IC) nitrate aims to prevent any vasospasm in the epicardial vessels and is recommended as a standard³ prior to the administration of adenosine, which is used for microvascular dilatation and can be administered intravenously (IV) or IC. IV adenosine was initially recommended and is used by many laboratories, but requires a large venous access and a larger amount of adenosine compared to the IC dose, resulting in higher cost. Its short-term effect, ease of use, and safety made IC adenosine the drug of choice in many laboratories.⁵

There is no widely accepted IC adenosine dose, although recent data suggest that administration of 100 μg for the right coronary artery and 200 μg for the left might be sufficient.⁶ Often, incremental doses are used to avoid side effects that are more common with higher doses. A failure

to produce maximal hyperemia was reported in 10%-15% of the initial FFR studies when low doses of adenosine were used (8-12 μg for the right coronary and 15-18 μg for the left).⁷ Submaximal hyperemia may lead to an underestimation of the lesion's hemodynamic significance. A dose-response relationship for IC adenosine doses as high as 100 μg has been demonstrated in animals and humans.^{5,8,9} More recently, experience with the administration of very high adenosine doses (up to 720 μg) has been reported with mixed results.¹⁰⁻¹²

Although injecting incremental doses of IC adenosine is feasible, it is also time and resource consuming. Furthermore, positive FFR values are often obtained with lower adenosine dose or with administration of other vasodilators.

Based on our experience with FFR studies, we noticed that post-nitroglycerin Pd/Pa (Pd/Pa[N]) could predict the hemodynamic significance of coronary lesions prior to IC adenosine injection. Therefore, the aim of this study is to assess the predictive value of Pd/Pa(N), as compared with standard IC-FFR and the impact of incremental doses of IC adenosine.

Methods

The study protocol was approved by the Western University Research Ethics Board. The authors have conformed to institutional guidelines and those of the American Physiological Society. Due to the nature of this study, informed consent was not required. As part of a quality improvement

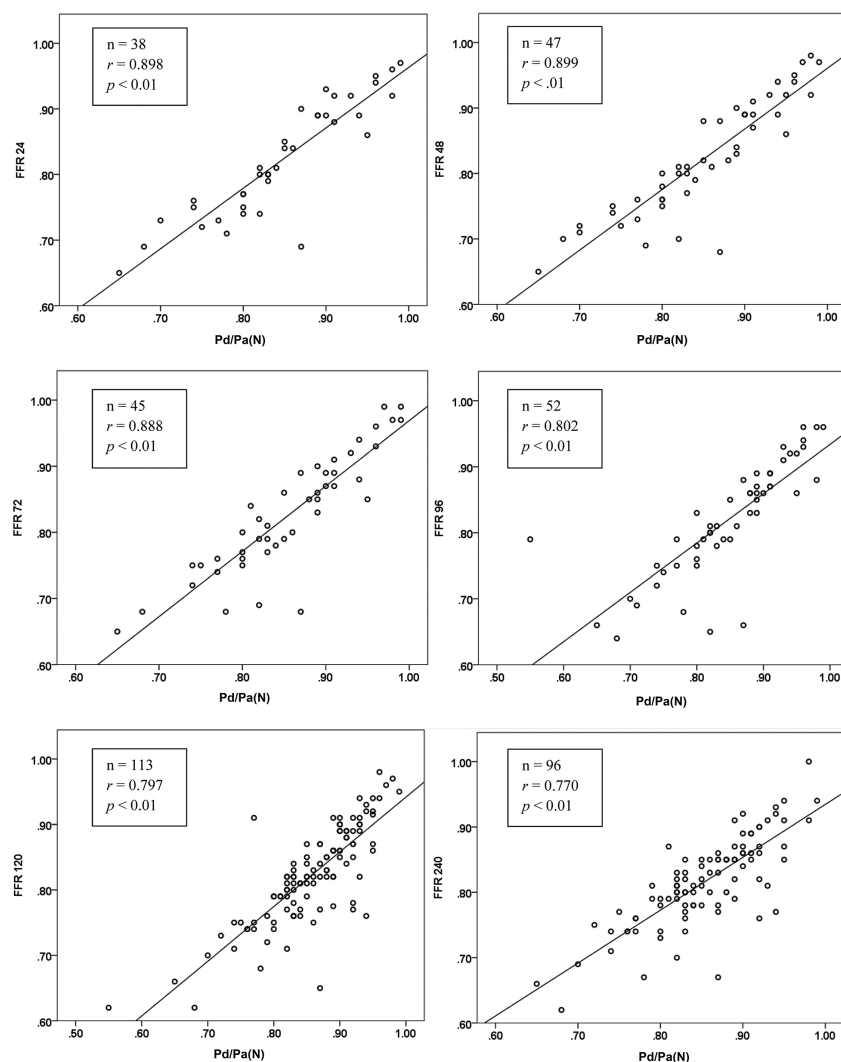


FIGURE 1. Pd/Pa(N) and fractional flow reserve [FFR] correlation. Scatter plots and Pearson's correlation coefficients between Pd/Pa readings post nitroglycerin and FFR readings taken after various dosages of adenosine.

project, data were collected from all FFR studies performed at London Health Sciences Center between January 2014 and October 2015. Incremental doses of adenosine for IC injection ranging from 24 μg to 360 μg were recommended but not mandatory for the operators. Exclusion criteria for this study were either lack of nitroglycerin injection prior to adenosine administration or injection of a single adenosine dose.

The FFR measurement protocol at our center after coronary angiography includes a 0.014" high-fidelity pressure-recording PrimeWire Prestige Plus guidewire (Philips Volcano Corporation) or PressureWire Aeris (Abbott Vascular) introduced through a 5 or 6 Fr guiding catheter into the coronary artery. The guidewire was calibrated and then advanced to the distal tip of the catheter, followed by equalization. The pressure wire was subsequently advanced into the coronary artery with the

pressure sensor placed beyond the lesion site. Pressure distal to the stenotic lesion (Pd) and aortic pressure (Pa) were recorded. A single dose of IC nitroglycerin was given (50–200 μg depending on patient blood pressure, mean dose of 113 μg) followed by a saline flush. Pd/Pa(N) corresponds to the lowest Pd/Pa determination post nitroglycerin administration, usually within 10 seconds. Incremental doses of adenosine ranging from 24 to 360 μg were given. Baseline Pd/Pa values, post Pd/Pa(N) values, and post-adenosine FFR values were recorded.

Each dose was given only after the effect of the previous dose wore off and Pd/Pa returned to baseline value. Drift was excluded at the end of each FFR study by pulling back the pressure wire to the distal tip of the catheter. Maximal drift of 0.02 was accepted.

Statistical analysis. Descriptive statistics for the study population are presented as mean ± standard deviation for continuous variables and number (%) for categorical variables. For the assessment of the relationship between Pd/Pa(N) and standard FFR, Pearson's correlation coefficient (*r*) was used. Estimation of the diagnostic performance of Pd/Pa(N) and identification of cut-off value for Pd/Pa(N) compared with FFR threshold of 0.8 was conducted using receiver-operating characteristic (ROC) and area under the curve (AUC) analysis. Sensitivity, specificity, and negative and positive predictive values with corresponding 95% confidence intervals (CIs) were calculated. All statistical tests were

considered statistically significant when a *P*-value was <.05. Data analyses were performed using Statistical Package for Social Sciences (SPSS) v. 20 (IBM, Inc).

Results

Baseline patient characteristics are described in Table 1. A total of 310 FFR studies were performed during the above-mentioned time frame; 134 studies met the inclusion criteria. Table 2 provides a list of the studied lesions and their locations. Procedural success for advancing the pressure wire distal to the stenosis was 100%.

The Pearson's correlation between Pd/Pa(N) and FFR was studied for all administered doses and was overall good, with superior correlation for the lower doses – varying between 0.89 for 24 μg and 36 μg adenosine and 0.77 for 240 μg (*P*<.01). Figure 1 shows scatter plots and positive Pearson's

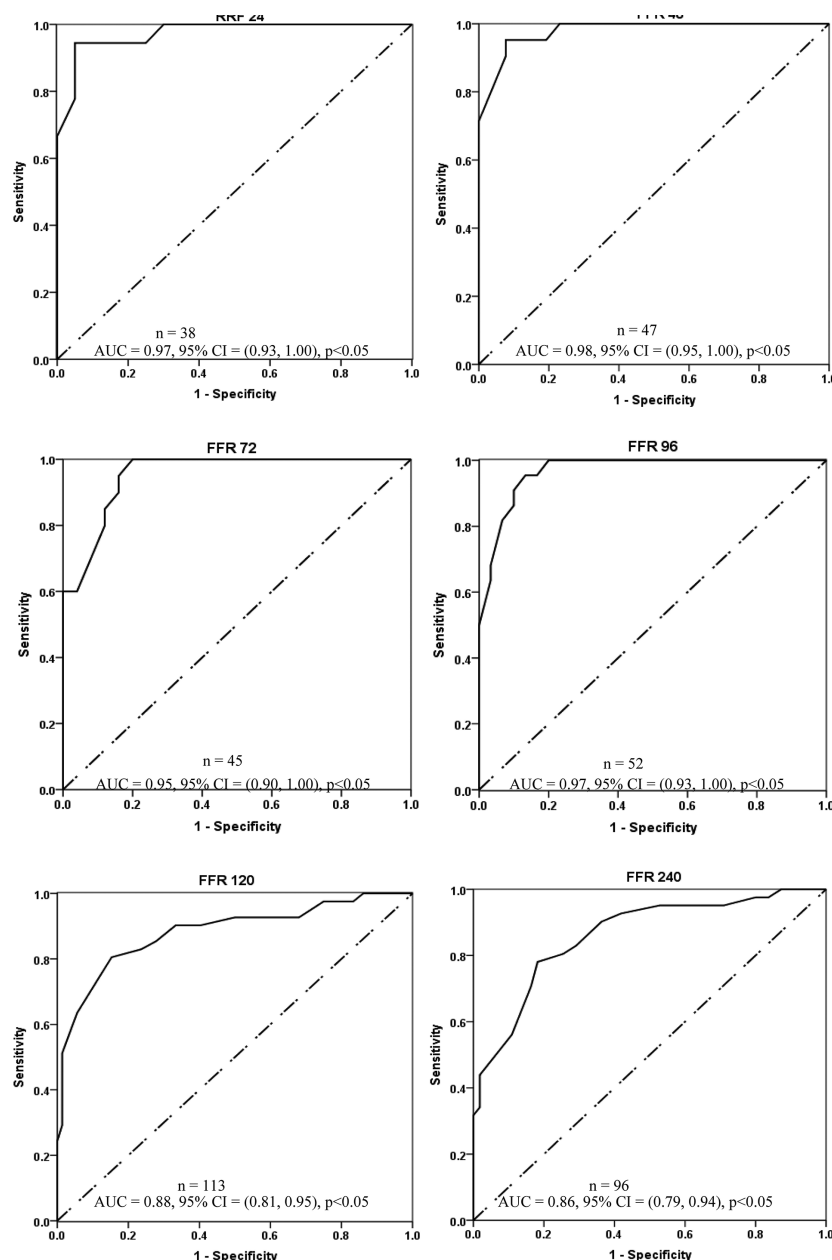


FIGURE 2. Pd/Pa(N) receiver operating characteristic curves and area under the curve [AUC] for each dosage of adenosine. A classification cut-off of 0.80 was used for each adenosine dosage. The test variable was post-nitroglycerin Pd/Pa readings. CI = confidence interval.

correlation for each adenosine dose. Figure 2 shows ROC curves for the Pd/Pa(N) using a FFR value of 0.8 as the reference (standard) variable. AUC was between 0.98 (95% CI, 0.95–1.00; $P<.05$) for 48 μ g adenosine and 0.86 (95% CI, 0.79–0.94; $P<.05$) for 240 μ g adenosine. Table 3 summarizes the cases and demonstrates the number of available values for each of the adenosine doses.

According to available and missing values and to avoid potential bias, the Pd/Pa(N), FFR 120, and FFR 240 values were

used in the subsequent analysis. Tables 4 and 5 demonstrate the classification accuracy for the two selected doses, respectively. For both, Pd/Pa(N) ≥ 0.94 provided 100% negative predictive value (NPV) with a high sensitivity ($>92\%$). The optimal diagnostic accuracy of Pd/Pa(N) was achieved for values ≥ 0.84 , which resulted in accuracy of 83.2% and 68.1% for 120 μ g adenosine and 240 μ g adenosine, respectively.

Pd/Pa (N) values as predictor of final FFR values and clinical decision.

Pd/Pa (N) ≥ 0.8 . Twenty-four patients (18%) had a Pd/Pa(N) ≥ 0.8 . For these studies, adenosine injections, regardless of dose administered or number of injections, FFR remained positive and therefore would not have changed the operator's treatment strategy.

Pd/Pa (N) >0.8 . Seventy-five patients (54%) with a Pd/Pa(N) >0.8 were further evaluated with adenosine doses of 120 μ g and 240 μ g. Of these, 55 studies were negative for the 120 μ g. Only 4 out of 55 studies turned out positive when tested with increasing dose of 240 μ g.

Discussion

The results of this study suggest that Pd/Pa(N) can be used for diagnosis of hemodynamically significant lesions. Pd/Pa(N) correlates well with FFR. Pd/Pa(N) cutoff of ≤ 0.8 can be considered significant with no need for adenosine injection. The value of using adenosine whenever Pd/Pa(N) is above 0.94 is limited.

Our findings extend recent observations,¹³ which indicate a good correlation of Pd/Pa(N) with FFR results. Moreover, a high negative predictive value for Pd/Pa(N) >0.88 to exclude lesion significance was established, potentially reducing the need for adenosine in a significant number of patients.¹³ Baseline Pd/Pa values prior to hyperemia were also studied¹⁴ and showed good correlation to FFR. However, Pd/Pa(N) was shown to correlate better with FFR than baseline Pd/Pa.¹³

The administration of IV adenosine as a means of achieving maximal hyperemia is considered by some the gold standard, but its widespread use in the catheterization laboratory is limited by some drawbacks, including length of time during drug application to achieve a steady-state and the

Table 1. Baseline demographics.

Characteristic	[N = 134]
Female	37 [27.6%]
Mean age [years]	65 ± 10.2
Baseline hemodynamic data	
Heart rate [beats/min]	66.5 ± 13.0
Blood pressure - systole [mm Hg]	125 ± 23.2
Blood pressure - diastole [mm Hg]	66 ± 10.4
Associated medical conditions	
History of coronary artery disease	62 [50.6%]
Hypertension	98 [71.7%]
Hyperlipidemia	99 [74.3%]
Smoking	
Never	83 [62.0%]
Current	15 [11.2%]
Former	36 [26.8%]
Diabetes	35 [26.1%]
Clinical indication for the study	
Angina, chest pain, or equivalent	84 [62.7%]
Non-ST elevation acute coronary syndrome	32 [23.8%]
ST-elevation MI (non-culprit vessel)	9 [6.7%]
Congestive heart failure	3 [2.2%]
Other [syncope, arrhythmia, positive stress test, valvular heart disease]	6 [4.6%]

Data presented as number (%) or mean ± standard deviation.
MI = myocardial infarction.

Table 3. Summary of cases.

FFR Score*	Number of Cases [n = 134]	Missing Cases
Pd/Pa[B]	134	0 [0%]
Pd/Pa[N]	134	0 [0%]
FFR 24	38	96 [71.6%]
FFR 36	2	132 [98.5%]
FFR 48	47	87 [64.9%]
FFR 60	17	117 [87.3%]
FFR 72	45	89 [66.4%]
FFR 96	52	82 [61.2%]
FFR 120	113	21 [15.7%]
FFR 144	2	132 [98.5%]
FFR 180	8	126 [94.0%]
FFR 192	3	131 [97.8%]
FFR 240	96	38 [28.4%]
FFR 360	1	133 [99.3%]

Data presented as number or number (%).
*Pd/Pa was measured at baseline [B], post nitroglycerin [N], or at various increasing adenosine doses from 24 µg to 360 µg.

Table 2. Studied vessels.

Vessel	Number of Cases
LMCA to LAD	3
LAD	95
Proximal	34
Middle	57
Distal	4
Diagonal	4
RCA [†]	14
Proximal	1
Middle	9
Distal	4
PRL	1
PDA	1
LCX	11
Proximal	4
Middle	7
Marginal	3
Ramus	2

LAD = left anterior descending; LMCA = left main coronary artery; RCA = right coronary artery; PRL = posterolateral branch; PDA = posterior descending artery; LCX = left circumflex.

higher occurrence of systemic adverse reactions,^{15,16} making the IC adenosine injection a more appealing alternative.

However, even the use of IC adenosine is time and resource consuming, and therefore FFR is often underused. Current data from the United States CathPCI registry indicates that only 6.1% of patients with moderate coronary lesions were assessed with FFR prior to PCI.¹⁷ Data from a Swedish registry¹⁸ showed utilization of FFR in 0.2% and 10% of patients in Iceland and Sweden, respectively.

For these reasons, the search for a simplified, quicker, and even adenosine-free alternative is ongoing. Instantaneous wave-free ratio (iFR) has been proposed as an index of stenosis severity that is independent of hyperemia and can be measured without the need for adenosine.¹⁹ The diagnostic accuracy of iFR and resting Pd/Pa compared with standard FFR was studied and found to be

80% for both indices.²⁰ Others demonstrated a lower diagnostic accuracy for iFR when compared with FFR.²¹

Recently, the effect of IC contrast injection on Pd/Pa was reported.^{22,23} It showed higher diagnostic accuracy of contrast as compared with resting Pd/Pa or iFR.²⁴ However, earlier works demonstrated that contrast-induced hyperemia is inferior compared with hyperemia achieved by other means²⁵ and the excessive use of contrast for that purpose must be balanced with the potential low risk of contrast-induced acute kidney injury.

When Pd/Pa(N) values are near normal (defined in this study by values ≥0.94), Pd/Pa(N) has an excellent NPV and a very high sensitivity. Therefore, based on our findings, the physician might opt to skip any adenosine injection since the chances of a positive FFR are very low.

Alternatively, injection of very high adenosine doses (and foregoing any doses lower than 240 µg that were tested in the current study) may be considered to rule out an FFR-positive lesion. It is likely that such negative Pd/Pa(N)-positive standard FFR results will be in the gray zone. The clinical significance of gray-zone FFR (0.8 > FFR ≥ 0.75) is not yet clear. In patients with stable coronary artery disease and gray-zone FFR followed for approximately 2 years, medically treated

Table 4. Classification accuracy based on increasing cut-off values for post-nitroglycerin Pd/Pa, using post adenosine 120 µg fractional flow reserve with 0.80 cut-off as reference.

Criterion for Pd/Pa(N)	Positive Cases [n]	Negative Cases [n]	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Diagnostic Accuracy [%]	Youden's Index
≤0.80	20	93	46.3	98.6	95.0	76.3	79.6	0.45
≤0.81	22	91	51.2	98.6	95.5	78.0	81.4	0.50
≤0.82	30	83	63.4	94.4	86.7	81.9	83.2	0.58
≤0.83	40	73	75.6	87.5	77.5	86.3	83.2	0.63
≤0.84 ^a	44	69	80.5	84.7	75.0	88.4	83.2	0.65
≤0.85	51	62	82.9	76.4	66.7	88.7	78.8	0.59
≤0.86	55	58	85.4	72.2	63.6	89.7	77.0	0.58
≤0.87	61	52	90.2	66.7	60.7	92.3	75.2	0.57
≤0.88	66	47	90.2	59.7	56.1	91.5	70.8	0.50
≤0.89	74	39	92.7	50.0	51.4	92.3	65.5	0.43
≤0.90	82	31	92.7	38.9	46.3	90.3	58.4	0.32
≤0.91	87	26	92.7	31.9	43.7	88.5	54.0	0.25
≤0.92	94	19	97.6	25.0	42.6	94.7	51.3	0.23
≤0.93	100	13	97.6	16.7	40.0	92.3	46.0	0.14
≤0.94	103	10	92.7	13.9	39.8	100.0	45.1	0.07
≤0.95	108	5	100.0	6.9	38.0	100.0	40.7	0.07
≤0.96	110	3	100.0	4.2	37.3	100.0	38.9	0.04
≤0.97	111	2	100.0	2.8	36.9	100.0	38.1	0.03
≤0.98	112	1	100.0	0.0	36.6	100.0	37.2	0.00
≤0.99	113	0	100.0	0.0	36.3	–	36.3	0.00
≤1.00	113	0	100.0	0.0	36.3	–	36.3	0.00

Data presented as number or percentage. PPV = positive predictive value; NPV = negative predictive value. ^aPost-nitroglycerin Pd/Pa was associated with the highest diagnostic accuracy when compared to a 0.80 cut-off for fractional flow reserve after 120 µg adenosine dosage.

patients had a lower event rate and no difference in presence of angina when compared with patients who were revascularized.²⁶ When followed for 4.5 ± 2.1 years, patients with deferred revascularization had similar need for intervention whether their FFR was 0.75 to 0.80 or 0.81 to 0.85.²⁷ The DEFER trial did not show clinical benefit for revascularization for lesions with FFR > 0.75 as compared with medical therapy.²⁸ A threshold of 0.8 was subsequently adopted.²⁹ It seems that a true cut-off for FFR lesions does not exist and a gradual relation between degree of ischemia and outcome is more likely.^{30,31} Taken together, the clinical benefit of using high-dose adenosine to rule out true positive lesions is currently unknown. Further studies are needed to determine if an FFR-negative lesion that turned out to be positive only after high-dose adenosine should be revascularized.

Study limitations. The present study has several limitations. The main one lies within the small number of patients and the non-randomized nature, which may introduce selection bias. Moreover, the lack of protocol-driven nitroglycerin dosage might limit the reproducibility of our findings. The absence of comparator group for IV adenosine infusion and the low number of non-left anterior descending coronary artery FFR studies

are other important limitations. Yet, we have demonstrated good correlation between Pd/Pa(N) and a wide spectrum of IC adenosine doses and the clinical importance of lesions diagnosed by very high-dose adenosine is unclear.

Conclusion

We demonstrated that Pd/Pa(N) correlates well with FFR results. When Pd/Pa(N) is ≤0.8, there is no need for adenosine injection. When Pd/Pa(N) is ≥0.94, there is a high probability of an FFR-negative lesion. Pd/Pa(N)-based strategy may be integrated into the hemodynamic assessment of borderline lesion.

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Table 5. Classification accuracy based on increasing cut-off values for post-nitroglycerin Pd/Pa, using post-adenosine 240 µg fractional flow reserve with 0.80 cut-off as reference.

Criterion for Pd/Pa(N)	Positive Cases (n)	Negative Cases (n)	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Diagnostic Accuracy [%]	Youden's Index
≤0.80	19	77	43.9	98.2	94.7	70.1	63.7	0.42
≤0.81	21	75	46.3	96.4	90.5	70.7	63.7	0.43
≤0.82	29	67	56.1	89.1	79.3	73.1	63.7	0.45
≤0.83	38	58	70.7	83.6	76.3	79.3	66.4	0.54
≤0.84 ^a	42	54	78.0	81.8	76.2	83.3	68.1	0.60
≤0.85	47	49	80.5	74.5	70.2	83.7	65.5	0.55
≤0.86	50	46	82.9	70.9	68.0	84.8	64.6	0.54
≤0.87	57	39	90.2	63.6	64.9	89.7	63.7	0.54
≤0.88	61	35	92.7	58.2	62.3	91.4	61.9	0.51
≤0.89	68	28	95.1	47.3	57.4	92.9	57.5	0.42
≤0.90	74	22	95.1	36.4	52.7	90.9	52.2	0.31
≤0.91	78	18	95.1	29.1	50.0	88.9	48.7	0.24
≤0.92	84	12	97.6	20.0	47.6	91.7	45.1	0.18
≤0.93	86	10	97.6	16.4	46.5	90.0	43.4	0.14
≤0.94	89	7	95.1	12.7	46.1	100.0	42.5	0.08
≤0.95	93	3	100.0	5.5	44.1	100.0	38.9	0.05
≤0.96	93	3	100.0	5.5	44.1	100.0	38.9	0.05
≤0.97	93	3	100.0	5.5	44.1	100.0	38.9	0.05
≤0.98	95	1	100.0	0.0	43.2	100.0	37.2	0.00
≤0.99	96	0	100.0	0.0	42.7	–	36.3	0.00
≤1.00	96	0	100.0	0.0	42.7	–	36.3	0.00

Data presented as number or percentage. PPV = positive predictive value; NPV = negative predictive value. ^aPost-nitroglycerin Pd/Pa was associated with the highest diagnostic accuracy when compared to a 0.80 cut-off for fractional flow reserve after 120 µg adenosine dosage.

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