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Improved Diagnosis through Diastolic Hyperemia-Free Ratio (DFR) over Fractional Flow Reserve (FFR) in Intermediate Coronary Lesions

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Abstract

Objectives: To compare the fractional flow reserve (FFR) and diastolic hyperemia-free ratio (DFR) measurements in a population with intermediate coronary artery stenosis and improve the diagnosis.

Background: Visual assessment of coronary artery stenosis severity, particularly in intermediate lesions, is prone to errors in decision-making. FFR provides a reliable assessment of functional severity in these cases but requires hyperemia induction by adenosine, which has side effects and increased cost. DFR is a novel hyperemia-independent index, which could be used as an alternative to adenosine-based hyperemia induction.

Methods and Results: Between September 2019 to March 2020, 25 patients with 38 intermediate coronary stenotic lesions were included in the study. All patients underwent assessment of whole cycle Pd/Pa (ratio of distal coronary pressure to proximal aortic pressure), DFR and FFR. Mean whole cycle Pd/Pa, DFR and FFR were 0.93±0.06, 0.88±0.09, and 0.85±0.08, respectively. A significant positive correlation between DFR and FFR [r = 0.74; p<0.001] was observed. Receiver operating characteristic analysis showed an area under the curve of 0.90. DFR-only strategy with a treatment cut-off of ≤0.89 showed a diagnostic agreement with the FFR-only strategy in 74% of lesions, with a sensitivity of 54%, specificity of 82%, a positive predictive value of 60%, and a negative predictive value of 79%.

Conclusions: Real-time DFR measurements show a clinically reliable correlation with FFR. Hence, using DFR is likely to avoid adenosine administration as well as reduce the cost and procedural time. Further studies with a larger sample size would be ideal to evaluate specific cut-off values and endpoints.

Keywords: Fractional Flow Reserve; Diastolic Hyperemia Free Ratio; Intermediate Coronary Artery Stenosis

Introduction

Though coronary angiography usually suffices in determining critical coronary artery stenosis (CAS), it has limitations in assessing the hemodynamic significance of intermediate coronary lesions [1]. Functional assessment in the catheterization laboratory of this subset of subjects is usually performed by fractional flow reserve (FFR), instantaneous wave-free ratio (IFR), or whole cycle Pd/Pa (ratio of distal coronary pressure to proximal

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aortic pressure). FFR has been widely reported in these patients and is a proven reliable indicator in the assessment of functional severity, aiding in planning a course of action [2, 3]. However, FFR assessment requires the administration of adenosine for inducing hyperemia, which involves additional costs and side effects [4]. The use of FFR has been limited due to these factors and others, such as greater radiation dose, longer procedural time, and physicians experience [5]. IFR is a recently developed adenosine-independent resting index used in the assessment of CAS severity, which utilizes the wave-free period in diastole during which there is minimal coronary resistance. IFR seems to correlate well with FFR and an IFR-FFR hybrid approach has demonstrated promising reproducible results [6, 7]. Two recently published large randomized control trials demonstrated non-inferiority of IFR compared to FFR-guided revascularization for major adverse cardiac events [8, 9]. Diastolic hyperemia-free ratio (DFR) is another recently emerging resting index, which has been shown to be equivalent to IFR in the absence of adenosine administration. However, this method has not been extensively applied and characterized in patients of different ethnic backgrounds. Recent reports analyzing physiologic data in benchtop modeling from the VERIFY and CONTRAST studies suggest a high correlation between IFR and diastolic Pd/Pa [10, 11], with a similar cut-off value of DFR ≤0.89 to determine hemodynamic significance. Though recent studies indicate that DFR is numerically equivalent to IFR in the physiological assessment of coronary lesions, there are limited real-world studies comparing FFR with DFR [12]. We, therefore, aimed to determine real-time FFR and DFR measurements in patients with intermediate coronary stenosis. Our specific objectives were to assess the correlation of (a) DFR with FFR pre- and post-percutaneous coronary intervention, (b) whole cycle Pd/Pa with FFR and DFR, and (c) thereby derive the best cut-off value for DFR, which offers maximum accuracy in comparison with FFR.

Methods

Study Population

This is a single-center, retrospective observational study conducted in a tertiary care hospital in Chennai, India, where 38 lesions in 25 patients with intermediate coronary stenosis were assessed using pressure indices.

Procedural Aspects

A coronary angiogram was performed using either a radial or femoral approach [13-15]. When a radial route was used, an intra-arterial cocktail (nitro-glycerine 100 mcg and verapamil 5.0mg) was administered. Patients were adequately anticoagulated using unfractionated heparin. Patients with coronary lesions ranging from 40-80% diameter stenosis in native major epicardial vessels of at least 2.0 mm in diameter were selected for physiological assessment. A 6/7 F guide catheter without a side hole was used for the study. First, the aortic pressure transducer was zeroed by positioning at the level of the heart and opening to the atmosphere. Next, a 0.014-inch FFR wire with a pressure sensor (COMET pressure wire- Boston Scientific) was connected to the Polaris multimodality guidance system (Boston Scientific). Once positioned, the pressure wire at the tip of the guiding catheter was flushed (due to the viscosity of the contrast agent), and disengaged from the coronary artery ostium as required. Pressure equalization between the wire and the aorta was achieved. This procedural step is of major importance while performing a functional assessment of the severity of stenosis. After equalizing the pressure at the tip of the catheter, the wire was advanced into the target vessel as distally as possible for pressure recordings. All patients were given intracoronary nitro-glycerine (100 - 200 micrograms) to relieve wire-induced spasm and vessel tonus. Baseline whole cycle Pd/Pa was recorded for all lesions included in the study. Then DFR measurements were automatically recorded by switching on the DFR algorithm using the Boston Scientific Polaris multimodality guidance system. After DFR measurement, FFR assessment was performed under hyperemia induction through intravenous adenosine administration at a dose of 140 mcg/Kg b.w./min for 2 minutes. This was increased up to 180 mcg/Kg/min as required. For the intracoronary route, a bolus of adenosine of 50–100 mcg for RCA and 75–150 mcg for left coronary arteries was used. During intravenous adenosine administration, the lowest ratio registered in a steady state of hyperemia was noted as the FFR value. In the case of intracoronary administration, Pd/Pa was continuously recorded until it returned to baseline. The lowest recorded value was taken as FFR (excluding artifacts). At the end of the measurement, the FFR wire was withdrawn, and when the pressure sensor reached the guide catheter, the pressure reading was checked for the presence of any pressure drift. If there was a significant drift of ± 0.02 (Pd/Pa: mm of Hg), the entire measurement was repeated. The clinical decision to intervene or keep the patient on optimal medical therapy was based entirely on the FFR measurement, except for patients with a significantly low value of baseline whole cycle Pd/Pa (Figure 1).

Statistics

We used SPSS statistical software version 25.0 (SPSS Inc., Chicago, Illinois) to perform data analysis. All data were verified for normal distribution prior to analysis. All continuous variables were reported as mean ± standard deviation or median. Categorical variables were defined as the number of observed patients (percentage). Student's t-test was used to compare normally distributed continuous variables between groups. If continuous variables did not follow a normal distribution, the Mann-Whitney U test was

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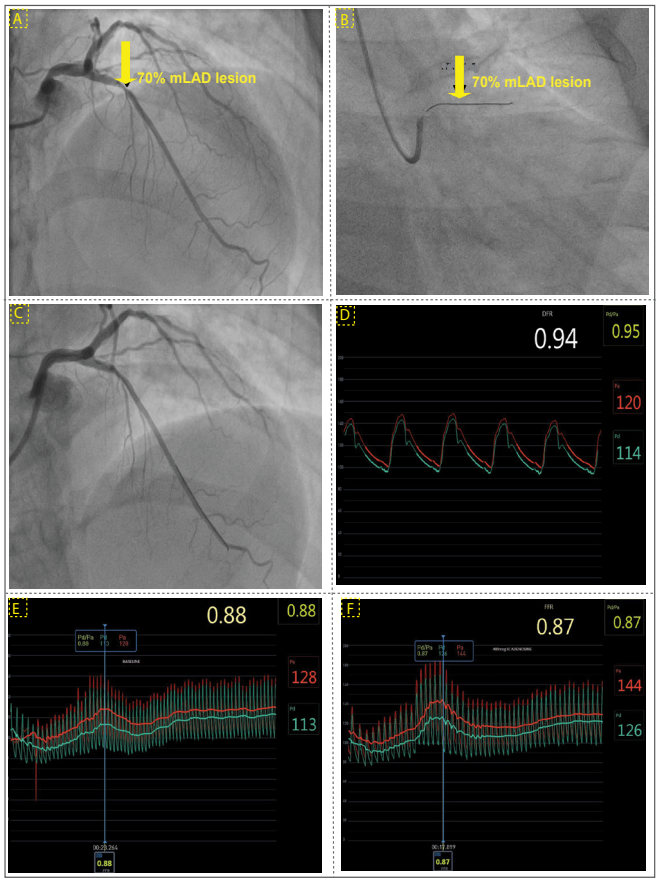

Figure 1: DFR and FFR approach followed by coronary angiography in the catheterization laboratory. (A) Step 1- CAG: Coronary Angiogram done in left coronary artery using EBU catheter showed borderline lesion of 70 % in mid Left Anterior descending (LAD) artery (B) Step 2- Equalise: COMET wire was placed prior to FFR assessment for the diseased segment of vessel and catheter was flushed with Nitroglycerin. Later pressures are equalized by the system resulting in Pd/Pa value of 1.00. (C) Step 3- Cross lesion localisation: After equalizing the pressure, the wire was placed distal to the lesion of interest. Aortic pressure (Pa) was measured from the guide catheter and distal pressure (Pd) from the pressure sensor. FFR was calculated as the ratio Pd to Pa at maximal hyperemia. (D) Step 4- DFR assessment: Diastolic Fractional Flow Reserve measured for the present patient was 0.94. (E) Step 5- FFR assessment (BASELINE): Pd/Pa in FFR. (F) FFR after adenosine treatment: Administration of vasodilator achieve smaximal hyperemia of coronary artery. FFR measured after Intra coronary injection of Adenosine 400 mcg is 0.87. Representative image from a patient undergone the procedure.

used to draw a comparison between groups. The correlation between FFR and DFR was assessed with Pearson rank correlation coefficient (r). Conventional summary statistics for diagnostic tests, compared with a patient's true disease status as indicated by FFR ≤0.80, were calculated from a 2x2 contingency table, comparing either the DFR strategy or the hybrid DFR – FFR strategy with standard FFR. The area under the receiver operating characteristic (ROC) curve was assessed through non-parametric ROC analysis.

Results

Demographics of the Study Group

Thirty-eight intermediate coronary lesions from 25 patients were included in this study. The baseline characteristics of the study population is summarised in Figure 2A. The mean age group of the patients enrolled in the study was 59.9±9.2 years. Hypertension was the most predominant risk factor at 60% (N=15), followed by diabetes at 52% (N=13) and dyslipidemia at 44% (N=11). Smoking frequency was recorded at 84% in the study group (Figure 2B). Chronic stable angina was the most common reason for patients undergoing physiological lesion assessment in the population, constituting 72% (N=18) (Figure 2C). The mean left ventricular ejection fraction (Simpson's method) of the patients was 57.88±7.67%. A predominant subset of patients had normal left ventricular (LV) function (Figure 2D). Less than 50% of the patients in the study group underwent a stress test, and it was positive in the majority of them (Figure 2E).

Co-Morbidities and Lesion Characteristics of the Study Group

In addition to hypertension, diabetes, dyslipidemia, and smoking habits, other co-morbidities assessed in the study group included chronic stable angina and altered left ventricular ejection fraction (LV-EF) (Figure 3A). Thirty-eight intermediate coronary lesions were assessed with left anterior descending coronary artery lesions being the most predominant (50%, N=19), followed by left circumflex (15.8%, N=6), right coronary artery (13.2%, N=5) and diagonal coronary arteries (13.2%, N=5). Of the total lesions assessed, 63% (N=24) were AHA type-A lesions and 37% (N=14) were AHA type-B lesions. The average mean visual estimate of coronary lesion stenosis was 64.86 ± 9.5. The characteristics of the coronary lesions are described in Figure 3B. Out of the 38 lesions, baseline Pd/Pa and DFR were assessed for all and FFR was assessed for 34 lesions. The mean Pd/Pa of the study population at baseline was 0.93±0.05. The mean baseline DFR of the study population was 0.88±0.09. The mean baseline FFR of the 34 lesions assessed was 0.85±0.07. For the assessment of FFR, intracoronary adenosine was used in 55.8% (N=19) and intravenous adenosine was used in 44.2% (N=15) of patients. The mean FFR in patients administered IV adenosine was 0.85±0.08, and the mean FFR in patients administered intracoronary adenosine was 0.85±0.07. The route of adenosine administration did not significantly affect the FFR (p=0.91).

Correlation between DFR versus FFR/Pd/Pa

In this investigation, DFR correlated well with FFR [r= 0.74; p< 0.001] (Figure 4A). Receiver operating characteristic curve (ROC) analysis identified an area under

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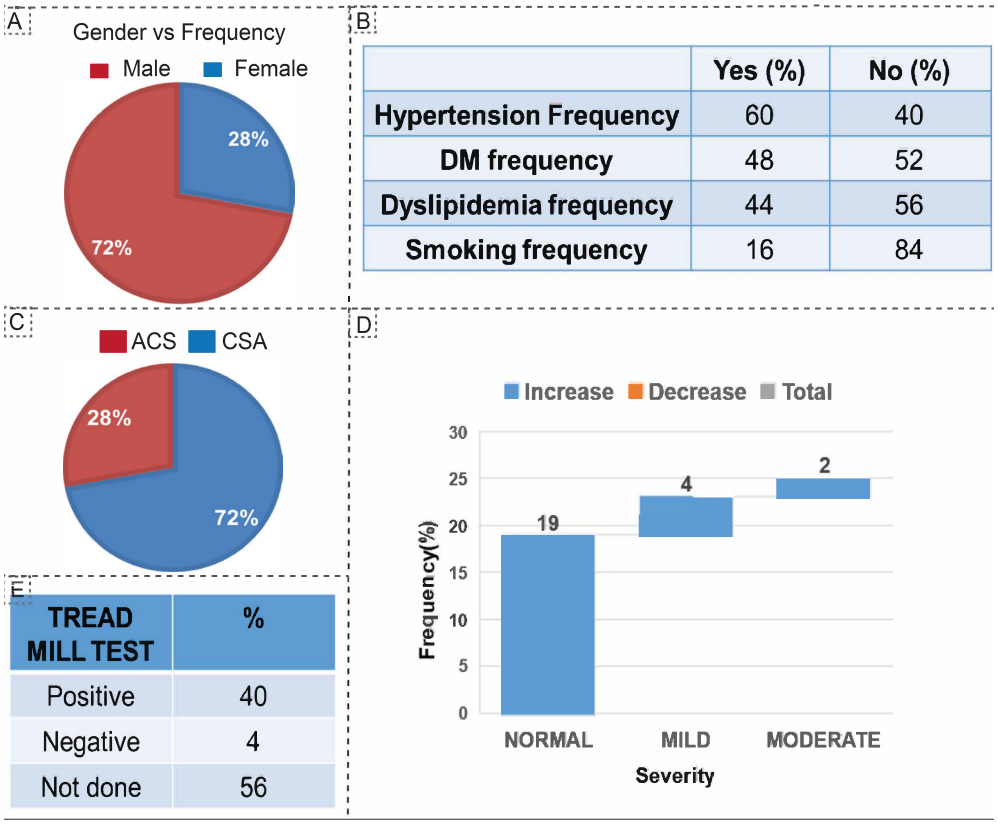

	Yes (%)	No (%)
Hypertension Frequency	60	40
DM frequency	48	52
Dyslipidemia frequency	44	56
Smoking frequency	16	84

TREAD MILL TEST	%
Positive	40
Negative	4
Not done	56

Figure 2: Demographics of the study group. (A) Pie chart depicting the gender distribution. Male (72%), Female (28%). (B) Tabular column showing the prevalence of various risk factors – Hypertension, diabetes, dyslipidemia, smoking. (C) Pie chart showing the percentage of the population presenting with either acute coronary syndrome (28%) or chronic stable angina (72%). (D) Bar chart showing the presence of LV systolic dysfunction. Normal LV function (19), Mild LV dysfunction (4), Moderate LV dysfunction (2). (E) Tabular column showing the distribution of treadmill test done. Positive (40%), Negative (4%). Not done (56%).

the curve of 0.90, which suggests the high accuracy of DFR as a diagnostic test for FFR (Figure 4B). We observed in the population that a mean DFR value of 0.87 was the best value to predict an FFR value of 0.80. A DFR-only strategy using a cut-off of 0.89 showed a diagnostic agreement with FFR in 25 (74%) lesions with a sensitivity of 54%, specificity of 82%, a positive predictive value of 60%, and a negative predictive value of 79%. For comparative studies of IFR with FFR, a hybrid IFR approach was utilized for comparison between IFR and FFR for lesions with an IFR value between 0.86 – 0.93 [16]. Comparison between DFR and FFR showed maximum true positivity at a DFR value of 0.86 and maximum true negativity at a DFR value of 0.92. Using a DFR cut-off value for revascularization of 0.86 and 0.92 for deferral resulted in a significant improvement in the diagnostic agreement between DFR and FFR. With the hybrid approach, there was diagnostic agreement in 33 (97%) lesions with a sensitivity of 100%, specificity of 95.6%, a positive predictive value of 85.7%, and a negative predictive value of 100%. Using the hybrid approach, adenosine exposure could be avoided in 18 (53%) lesions (Figure 4A). Correlation analysis of the whole cycle Pd/Pa with DFR was also performed for baseline measurements. In our study, Pd/Pa correlated well with DFR [r = 0.96, p<0.001] (Figure 4C). ROC analysis identified an area under the curve of 0.96 (Figure 4D), which suggests a high accuracy of Pd/Pa as a diagnostic test for DFR.

Correlation between FFR vs Pd/Pa

Correlation analysis of whole cycle Pd/Pa with FFR was performed for baseline measurements, which showed a good correlation between Pd/Pa with FFR [r=0.74, p<0.001] (Figure 5A). ROC analysis identified an area under the curve of 0.90 (Figure 5B), which suggests good accuracy of Pd/Pa as a diagnostic test for FFR. Of the 38 lesions revascularization was performed in 15 (39.4%) patients. PCI was the predominant form of revascularization with 14 (93.3%) out of 15 patients undergoing PCI and one patient undergoing coronary artery bypass grafting (CABG). Post-PCI Pd/Pa and DFR were performed in 8 patients and post-PCI FFR data were available for 6. Out of six patients for whom post-PCI FFR data was available, baseline FFR was not performed in two patients given significant baseline DFR. The mean post-PCI Pd/Pa was 0.96±0.01. The mean

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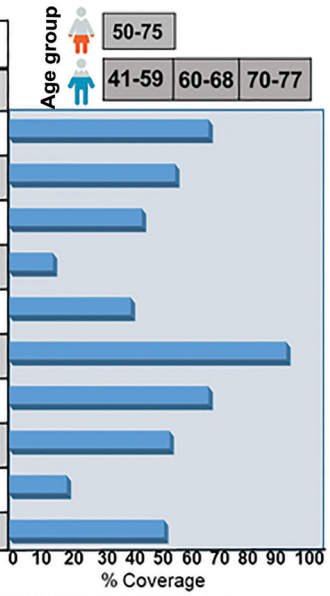
A

Comorbidities of study group

Variables	N =25 / Mean ± SD
Age	59.9 ± 9.28
Male	18
Hypertension	15
Diabetes	12
Smoker	4
Dyslipedmia	11
Sinus rhythm	25
Chronic stable angina	18
Left ventricular ejection fraction	57.8 ± 7.67
Radial route	21
Intracoronary adenosine	19



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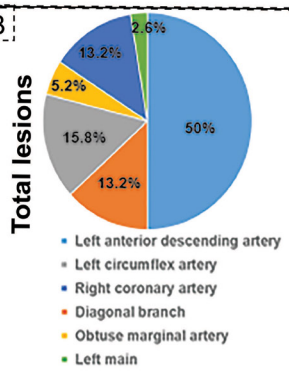

Type of lesions	Prevalence (%)
Type A	24 (63%)
Type B	14 (37%)
Visual stenosis estimate- Mean ± SD	64.8 ±9.52
Pre PCI mean Whole cycle Pd/Pa	0.93 ± 0.05
Pre PCI mean DFR	0.88 ± 0.09
Pre PCI mean FFR	0.85 ± 0.08

Figure 3: Co-morbidities and Lesion characteristics of the study group. (A) Comorbidities such as hypertension, DM, dyslipidemia and smoking habit, other co-morbidities such as variation in sinus rhythm, chronic stable angina, altered left ventricular ejection fraction. (B) Characteristics of the coronary lesions observed in the study group.

baseline Pd/Pa of these six patients was 0.90±0.02. There was a significant mean change in Pd/Pa post-PCI of 0.06±0.02 with a p-value of <0. 001. The mean post-PCI DFR was 0.93±0.02. The mean baseline DFR value of these patients was 0.82±0.04. There was a significant mean change in DFR post-PCI of 0.11±0.05, with a p-value of <0. 001. The mean FFR post-PCI was 0.86±0.02. The mean baseline FFR value of these patients was 0.74±0.05. There was a significant mean change in FFR post-PCI of 0.12±0.07, with a p-value of 0.04 (Figure 5C).

Discussion

The usage of resting coronary physiology as a guide for the revascularization of coronary arteries dates back to of percutaneous coronary intervention. Andreas Gruntzig, the father of percutaneous coronary intervention, measured the pressure drop across the stenosis at baseline and after balloon dilation with the measured value being affected by the device itself [17]. The development of vasodilators like papaverine and adenosine moved the field of physiological assessment of the severity of coronary stenosis toward fractional flow reserve (FFR). Interest in resting physiology returned with resting Pd/Pa measurement beginning in 2010 [18]. A diastolic version of the whole cycle Pd/Pa called the instantaneous wave-free ratio (IFR) was developed in the past decade [19]. The main advantage of resting physiology is that hyperemia is no longer needed to assess lesion severity. The interest in a wave-free period to assess pressure measurements led to the development of various other diastolic indices to assess lesion severity. Diastolic hyperemia-free ratio (DFR) is one such diastolic index that does not include the wave-free period to assess the hemodynamic significance of a coronary lesion. This index was proven numerically equal to IFR despite differing physiologic and technical features [10, 20].

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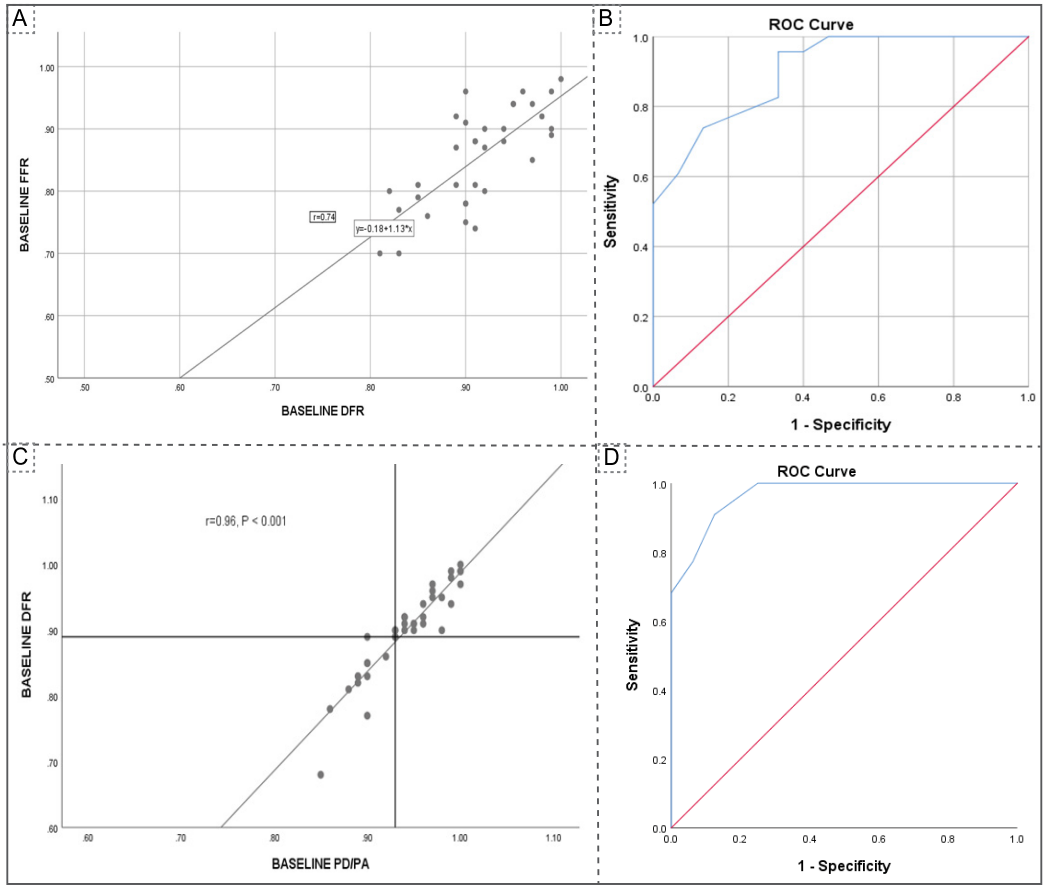

Figure 4: Accuracy of DFR as a diagnostic test for FFR. (A) DFR correlated well with FFR [r= 0.74; p< 0.001] (B) ROC analysis identified an area under the curve of 0.90 which suggests high accuracy of DFR as a diagnostic test for FFR (C) Pd/Pa correlated well with DFR [r= 0.96, p<0.001] (D) ROC analysis identified an area under the curve of 0.96 suggesting Pd/Pa as a diagnostic test for DFR.

DFR-only Approach

Our objective was to assess the role of non-hyperaemic flow indices (i.e. DFR) in the intermediate coronary lesion in comparison to hyperemic flow index (i.e. FFR). Our data suggest that DFR correlates well with FFR in the assessment of intermediate coronary stenosis. The best diagnostic accuracy (83%) for DFR to predict an FFR value of 0.80 was obtained at 0.87. Various studies have evaluated the comparison of IFR with FFR, showing a good relationship between these indices with a correlation coefficient (r) ranging from 0.75 to 0.90 [16, 19, 21]. In line with these reports, in our study, DFR correlated well with FFR with a correlation coefficient of 0.74 (p<0.001) in a relatively new South Asian ethnic population.

Hybrid Approach

The hybrid IFR-FFR approach was initially introduced in the ADVISE II study [22], which proposed that with an IFR value of ≤0.85, revascularization needs to be performed, and with a value of ≥0.94 medical management is advisable [22]. Any values falling between IFR ranges 0.86 – 0.93 required FFR for further decision making. In our study, a comparison between DFR and FFR yielded maximum true positivity at a DFR value of 0.86 and maximum true negativity at a DFR value of 0.92. Using this hybrid approach, we achieved a diagnostic agreement in 33 (97%) lesions with a sensitivity of 100%, specificity of 95.6%, a positive predictive value of 85.7%, and a negative predictive value of 100%. Using the hybrid approach, adenosine exposure could be avoided in 18 (53%) lesions. In addition, we could safely defer revascularization and FFR measurement for any DFR ≥0.93, and any lesion having a DFR value of ≤ 0.85 should be directly referred for revascularization without the need for FFR.

Discordant Measurements

The discordant measurements consisted of nine (26.4%) lesions, with five (14.7%) false negative (FFR-Positive, IFR-Negative) measurements, and four (11.7%) false positive (FFR-Negative, IFR-Positive) measurements. This discordance is comparable to that of FFR and IFR observed

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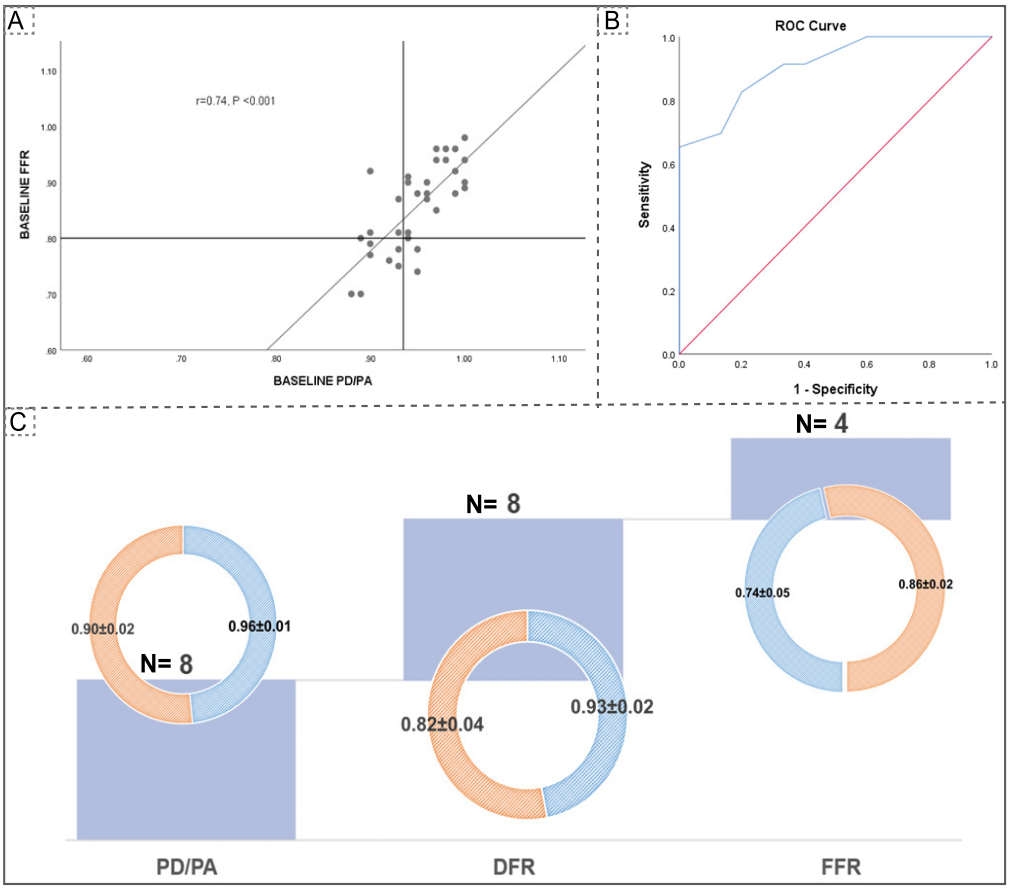

Figure 5: Accuracy of Pd/Pa as a diagnostic test for FFR. (A) Graph showing a correlation between whole cycle Pd/Pa and FFR (B) ROC analysis of the whole cycle Pd/Pa showing an area under the curve (AUC) of 0.90 suggestive of high accuracy of the whole cycle Pd/Pa as a diagnostic test for fractional flow reserve (C) Comparison of mean Pd/Pa, DFR and FFR at baseline and post PCI (square boxes - number of patients calculated for PD/PA, DFR, and FFR; Circle - baseline mean ± SD (Blue): post-PCI mean ± SD (Orange).

in previous studies, where a mismatch of up to 20% was noted [16, 23]. No statistically significant differences were noted in the baseline comorbidities and lesion characteristics between the false positive and false negative groups.

Whole Cycle Pd/Pa

There have been few studies associating the whole cycle Pd/Pa with FFR along with DFR. Our study reveals a good correlation between Pd/Pa with FFR ($r=0.74$, $p<0.001$). ROC analysis identified an area under the curve of 0.90, which suggests a reliable accuracy of Pd/Pa as a diagnostic test for FFR. Correlation analysis of the whole cycle Pd/Pa with DFR was also performed for baseline measurements. In our study, Pd/Pa also correlated well with DFR ($r = 0.96$, $p<0.001$). ROC analysis identified an area under the curve of 0.96, suggesting high accuracy of Pd/Pa as a diagnostic test for DFR. A resting whole cycle Pd/Pa cut-off value of 0.92 correlated well with an FFR value of ≤0.80 with a sensitivity of 91% and specificity of 77%, which was comparable to previous studies [16, 18]. However, a study done by Park et al showed that the discriminatory power of whole cycle Pd/Pa was low when compared to IFR and this can apply to DFR as well [24].

Post PCI Role

In our study, we were unable to perform a correlation analysis of DFR and FFR under post-PCI as there were not enough samples available for assessment. However, our study showed a statistically significant change in the mean DFR, FFR, and mean Pd/Pa post-PCI compared to pre-PCI.

Clinical Implications

Resting indices for physiological assessment of coronary stenosis eliminate the necessity for using adenosine and thereby reduce the associated side effects and related expenses. Though data are available regarding the usage of IFR for functional lesion assessment of intermediate coronary artery stenosis, to our knowledge, ours is the first real-world study to directly assess the correlation between DFR and FFR in a unique ethnic group of South Asian origin. Though our

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study displayed a good correlation between DFR and FFR, it also showed a wide grey zone between DFR values of 0.86-0.92, where FFR was required for clinical decision-making. Until large randomized controlled trials comparing FFR and DFR are performed, it is crucial to follow a hybrid DFR- FFR approach in deciding on a revascularization strategy. For any value of DFR 0.85 or less and 0.93 or more, FFR can be safely deferred.

Limitations

With this being a retrospective analysis, the level of evidence from this study will be inferior to prospective large-scale randomized control studies. Though we compared FFR and DFR, all decisions were made (even with significant values of DFR) based on FFR measurements. The small sample size is a major limiting factor of the study, but the validation of the DFR in a relatively new South Asian ethnic group is realized.

Conclusion

Real-time DFR measurements can be easily performed and have a diagnostic accuracy of 83% when compared with FFR. As with IFR, usage of DFR has the potential to reduce exposure of patients to adenosine, decrease the side effects, and reduce the procedure time and costs. DFR can also come to our aid in patients whom adenosine is contraindicated. Further prospective and randomized trials with larger sample sizes are required to evaluate its use in various clinical settings.

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Ethics Statement

This study was carried out in accordance with the approval of the institute ethics committee of SRIHER ref no: CSP-MED/20/FEB/59/53 DATED 07.03.2020. Informed consent was not necessary as it is a retrospective study.

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Author Contributions

The study was designed by Muralidharan Thoddi Ramamurthy and Vinod Kumar Balakrishnanan. DFR and FFR were interpreted by Nagendra Boopathy Senguttuvan, Vinod Kumar Balakrishnanan and Preetam Krishnamurthy. Mano Vikash Vallivedu and Namakkal-Soorappan Rajasekaran wrote the manuscript. Steven Pogwizd and John R. Hoidal reviewed and improvised the manuscript. All others were involved in interpreting the data and critical discussions. All authors read and approved the final version of this manuscript.

Data Availability

In addition, Dr. Muralidharan Thoddi Ramamurthy will be happy to share the relevant data sets through direct email communication.

Competing Interests

The authors have no competing interests to declare.

Consent for Publication

All authors verified the content and approved the final version for submission and publication.

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