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Evaluation of Resting Full Cycle Ratio (RFR) in Comparison with Fractional Flow Reserve (FFR) in Assessment of Intermediate Coronary Stenosis, A Prospective Single Center Evaluation

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Abstract

Assessment of coronary physiology in intermediate coronary lesions plays a vital role in strategic intervention. Although instantaneous free wave ratio (IFR) have been validated in coronary physiology assessment, evidence in support for novel resting full cycle ratio (RFR) is growing. In our present single center prospective study, we uniquely compared RFR with Fractional Flow Reserve (FFR) in assessment of intermediate coronary lesions and evaluated the influence of coronary hyperemia with adenosine, nitroglycerine and contrast on nonhyperemic index RFR in predicting the lesion significance. We observed RFR correlated well with FFR (agreement K:0.781) and RFR cut off of 0.89 correlated with FFR of 0.8. RFR had sensitivity of 89%, specificity of 92%, positive predictive value of 80% and negative predictive value of 96% ($p<0.001$, AUC 0.89) for delineating lesion severity. Effect of hyperemia in nonhyperemic indices were as follows: Hyperemic agents improve the diagnostic accuracy of nonhyperemic index RFR, contrast RFR with cut off of 0.875 correlated with an FFR of 0.8, adenosine RFR with cut off of 0.795 correlated with FFR of 0.8 in our study. Presence of diabetes and Smoking had no effect on RFR as observed in our study.

Keywords: Resting full cycle ratio (RFR); Intermediate; Coronary; Stenosis; Physiology.

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Introduction

Assessment of coronary physiology plays an important role in intermediate coronary lesions and adds to the individualized management strategy. FAME study established adenosine added FFR as the gold standard for delineation of coronary lesion significance. Adenosine induced bronchospasm and AV nodal conduction disturbance sometimes poses real difficulty in carrying out this physiologic procedure. Swedheart and Define Flare established an equivocal role of IFR as compared to FFR in assessing the borderline lesion. Major limitation of these study was its dependence on particular phase of cardiac cycle, so the concept of scanning the coronary physiology throughout the cardiac cycle emerged in the form of resting full cycle ratio (RFR).

RFR exhibits some unique advantage as compared to FFR as follows:[1]

- Nonhyperemic index of coronary physiology
- Represents the lowest Pd/Pa across whole cardiac cycle

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- Less probability of missing a physiologically significant lesion as it scans through full cardiac cycle
- Faster to carry out
- No extra discomfort to the patient
- No extra cost

Validate RFR[2], Revalidate and Illumien 1+ Predict study delineated the equivalence of RFR as compared to IFR in assessing the lesions with intermediate stenosis. All the studies have well delineated RFR to be having good sensitivity, specificity, positive and negative predictive value with remarked diagnostic accuracy.[3–9] But literature data is still in scarcity comparing gold standard FFR with RFR in delineating coronary lesion. Our present study will delineate the correlation between RFR and FFR in assessing intermediate coronary lesions with its sensitivity, specificity, positive and negative predictive value. We will have a novel insight of whether turning this non hyperemic index hyperemic by iodinated contrast, nitroglycerine and adenosine will add its diagnostic accuracy and prediction of significant coronary lesion. Our present study will definitely add to the paucity of evidence of RFR in treating the intermediate lesions.

Aims and Objectives

Hypothesis: RFR assessment is non-Inferior to FFR assessment in intermediate coronary stenosis.

Aims

1. To compare the efficacy of RFR with FFR in assessing lesion severity in borderline coronary lesions.
2. To assess the effect of nitroglycerine, adenosine and iodinated contrast on RFR.
3. To assess the impact of Diabetes Mellitus and smoking on RFR

Objectives

To Determine

1. Sensitivity and Specificity
2. Positive and Negative Predictive Value
3. Diagnostic accuracy of RFR and FFR in intermediate coronary lesion

Materials and Methods

After due ethical committee approval and written consent of participants, this study was conducted in SCTIMST, Department of Cardiology in patients with intermediate coronary lesions. Patients were selected based on preset inclusion and exclusion criteria. Eligible patients chosen for FFR assessment were studied for RFR based on proposed methodology.

Inclusion Criteria

- Age above 18 years
- Intermediate coronary lesions (40–70%) requiring physiological assessment
- Culprit vessels after 5 days of myocardial infarction

Exclusion Criteria

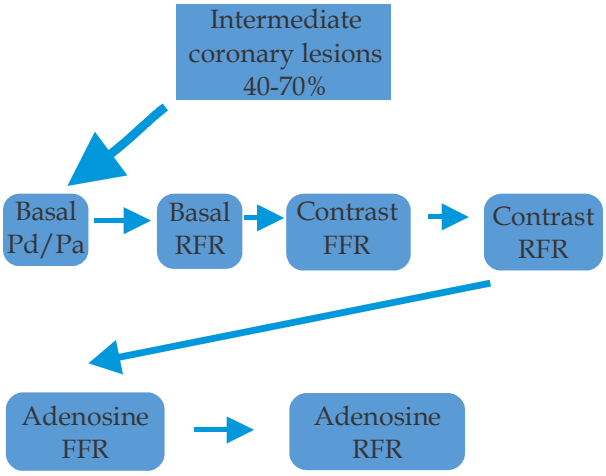
- Unwilling patient
- Contraindication to adenosine
- Graft vessel study
- Collateralized vessels
- Acute coronary syndrome with culprit vessel up to 5 days
- Patients with organ failures

Methods

After engaging the vessel of interest with guide and pressure equalization, FFR wire was placed distal to the lesion, 100 microgram intracoronary NTG was infused and baseline FFR and RFR values were noted. 10 ml of iodinated low osmolar contrast which has weak hyperemic effect was injected into the coronary after baseline FFR & RFR documentation. Values of hyperemia induced FFR & RFR were documented post contrast. After wash out period of two minutes, adenosine infusion was started at 140 mcg/kg/min, RFR with adenosine was documented and then FFR at 2 minutes of adenosine infusion was recorded. Continuous hemodynamic monitoring was done during the procedure. As part of evaluation, subgroup of diabetic and smoking subjects were assessed to evaluate the impact of smoking and diabetes on RFR. All obtained data was used for statistical analysis.

We recorded all the baseline FFR and RFR and analyzed the hyperemic response of iodinated contrast, nitroglycerine and adenosine on RFR in predicting the lesion severity and comparative efficacy of RFR with gold standard FFR. Based on baseline FFR, patient were provided the requisite modality of coronary care in the form of revascularization or medical management.

Flow Chart



40 patients were selected
32 patients were recruited
34 lesions assessed

Stastistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then nonparametric test was used. Quantitative variables were pair wise compared using Wilcoxon signed rank test (as the data sets were not normally distributed). Qualitative variables were correlated using Fisher's Exact test/*Chi* square test. Interrater kappa agreement was used to find out the strength of agreement between RFR and FFR. Receiver operating characteristic curve was used to find out cut off point of RFR taking FFR as gold standard. Diagnostic test was used to calculate sensitivity, specificity, PPV and NPV. A p value of <0.05 was considered statistically significant. The data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Table 1: Baseline Demography.

Variable	Number (%)/Mean ±SD
Age	60.25±4.02 (Years)
Males	26(76%)
Females	8 (24%)
Diabetes	20(59%)
Hypertension	27(80%)
Smoking	14(41%)
Dyslipidemia	32(94%)

Males constituted majority of our study population (76%), majority (59%) were diabetic, hypertension was prevalent in 80% of cases, smokers constituted 41% and dyslipidemia was found in 94% of study population. Most patients in our study group had multivessel disease (52.94%) out of whom triple vessel disease was more prevalent as compared to single vessel disease. We intervened right coronary more as compared to LAD and LCX.

Table 2: Demography of Coronary Lesions.

Stable Angina	26%
ACS	74%
Vessels involved	
LM	2
LAD	12
LCX	6
RCA	16
Vessel stenosis	
40–50%	0
50–60%	14%
60–70%	86%

RFR and FFR Flow Chart

Table 3: Concordant and Discordant FFR and RFR.

34 lesions	RFR + 10	FFR+ 8	CABG 1 + PCI 7
		FFR– 2	Medical Follow up
	RFR – 24	FFR– 23	Medical Follow up
		FFR+ 1	PCI 1.
Concordant	FFR+/RFR+ 8		
	FFR–/RFR– 23		
Discordant	FFR+/RFR– 1		
	FFR–/RFR+ 2		

We analyzed FFR in 34 patients based upon which 25 patients were kept on medical follow

up, 8 patients were considered for PCI and one patient was considered for CABG. We noted FFR and RFR were positively concordant in 8 patients and negatively concordant in 23 patients. In three patients FFR and IFR exhibited discordant response.

Baseline RFR was positive in 29.41% which did not change with contrast and nitroglycerine but the cut off value of RFR came down to 0.87 from 0.89 which was significant. But a major change we noted with adenosine where the cut-off value significantly came down and was different from baseline cutoff of 0.89. Adenosine had the maximum hyperemic influence on RFR as compared to contrast and nitroglycerine. We noted a baseline discordance in RFR and FFR in 3% of cases which was not significant. Value of Kappa (0.78) can be interpreted as follows, our study showed a strong association of FFR and RFR in delineating physiologically significant coronary ischemia.

Table 4: Study Results.

	Sample size	Mean ± SD	Median	Min–Max	Inter quartile Range
RFR Baseline	34	0.89 ± 0.08	0.92	0.63–0.98	0.860–0.940
RFR Nitroglycerine	34	0.87 ± 0.08	0.9	0.66–0.94	0.840–0.920
RFR Contrast	34	0.87 ± 0.07	0.9	0.68–0.95	0.840–0.900
RFR Adenosine	34	0.78 ± 0.07	0.78	0.61–0.89	0.740–0.840
FFR Adenosine	34	0.8 ± 0.07	0.82	0.63–0.94	0.790–0.850

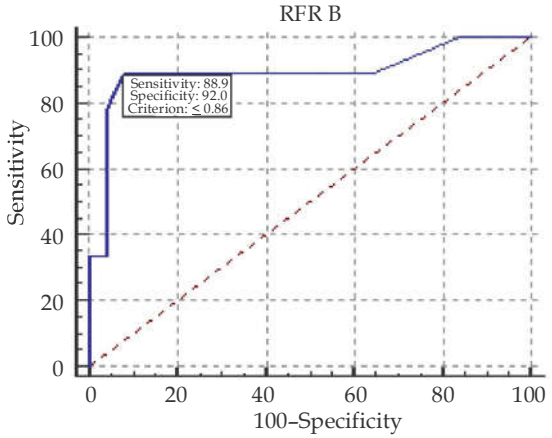


Fig. 1: RFR cut-off of 0.89.

Table 5: Comparison of baseline RFR with hyperemic FFR and baseline RFR with hyperemic FFR.

	Sample size	Mean ± SD	Median	Min/Max	Inter quartile Range	P value
RFR B	34	0.89 ± 0.08	0.92	0.63–0.98	0.860–0.940	
RFR N	34	0.87 ± 0.08	0.9	0.66–0.94	0.840–0.920	0.001
RFR C	34	0.87 ± 0.07	0.9	0.68–0.95	0.840–0.900	0.0002
RFR A	34	0.78 ± 0.07	0.78	0.61–0.89	0.740–0.840	<.0001

	Sample size	Mean ± SD	Median	Min/Max	Inter quartile Range	P value
FFR A	34	0.8 ± 0.07	0.82	0.63–0.94	0.790–0.850	
RFR N	34	0.87 ± 0.08	0.9	0.66–0.94	0.840–0.920	<.0001
RFR C	34	0.87 ± 0.07	0.9	0.68–0.95	0.840–0.900	<.0001
RFR A	34	0.78 ± 0.07	0.78	0.61–0.89	0.740–0.840	0.012

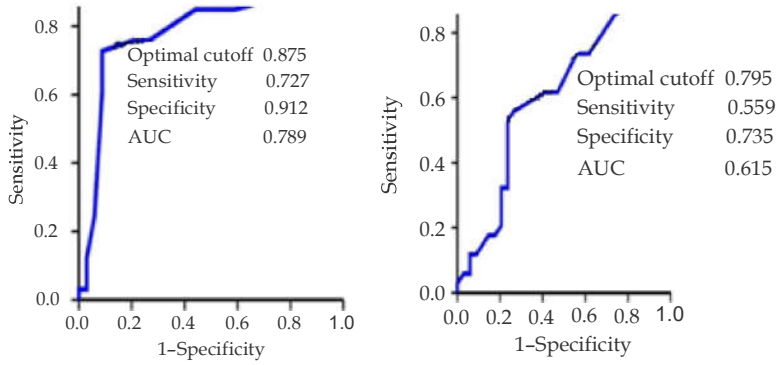


Fig. 2: RFR with contrast cut-off 0.87 and RFR with adenosine cut-off 0.87.

We analyzed the area under ROC curve to delineate the cutoff of RFR and FFR which showed RFR cut off value of 0.89 was similarly sensitive and specific with similar predictive value of FFR 0.8.

We analyzed whether smoking influenced RFR value which came out to be statistically nonsignificant ($p>0.05$). Although smoking liberates multitude of coronary vasoconstrictors, it did not influence the value of RFR in our study as noted below.

Discussion

Resting Full Cycle Ratio (RFR), a novel nonhyperemic index was compared with gold standard test Fractional Flow Reserve (FFR) as a head to head comparison in our institution over a period of one year. Role of coronary physiology assessment by FFR in intermediate coronary lesion is well established.[10-19]

We tried to analyze the hyperemic effect on nonhyperemic index like RFR. We compared the effect of nitroglycerine, adenosine and contrast on RFR and compared it with FFR which is conventionally carried out with adenosine. We noted adenosine had more influence on RFR as compared to nitroglycerine and contrast. Adding influence of hyperemia to nonhyperemic index like RFR resulted in better prediction of more physiologically significant coronary lesion as noted in ADVISE study.[20,21] We noted a baseline discordance in RFR and FFR in 3% of cases which was not significant ($p>0.05$). We observed the change in baseline RFR with contrast, adenosine and nitroglycerine was statistically significant with p value <0.05 although numerical change in RFR value with contrast and nitroglycerine was less as compared to with adenosine. RFR and FFR baseline correlate revealed strong positive correlation with sensitivity of 88% and specificity of 92% between them to predict the lesion severity. Swedheart and Define Flair and other[22,23] studies have validated iFR and its noninferiority with FFR. A value of 0.89 has been derived as an equivalent value to 0.80 of FFR. Several studies, like VALIDATE RFR, IRIS-FFR, ILUMIEN I, PREDICT analysis have retrospectively analyzed RFR with iFR and have documented equivalence of cut off value 0.89 for RFR. In our prospective comparison of RFR with FFR we got a RFR value of 0.89 is as equivalent to FFR of 0.80 from area under ROC curve as reported in VALIDATE FFR and IRIS-FFR study. VALIDATE RFR study have reported the limitation of iFR by sensitive land marking of the pressure wave form and the assumption of maximal flow and minimal resistance occur during a fixed period of diastole which lead to the emergence of concept of RFR. RFR is unique in measuring coronary physiology by being independent of ECG, land mark identification and timing within the cardiac cycle. In VALIDATE RFR was highly correlated with iFR with R^2 of 0.99 and $p<0.001$ with diagnostic accuracy of 97.4%, sensitivity 98.2%, specificity 96.9%, positive predictive value 94.5%, negative predictive value 99% with area under the ROC of 0.996 and diagnostic equivalence of 1%. iFR in right coronary artery has lowest sensitivity making RFR as a validated choice to be executed in days to come. To state in a line RFR does not miss the significant coronary stenosis not being limited by assessment of specific segments of cardiac cycle. RE –VALIDATE FFR determined the diagnostic utility of RFR in physiologic assessment of coronary artery disease as compared to iFR. Our study was unique in analyzing RFR and FFR head to head with influence of mild hyperemic drugs like contrast and nitroglycerine to strongly hyperemic response with Adenosine. RFR avoids contrast, reduce side effects, procedural time and cost of the procedure. REVALIDATE enrolled 431 patients and demonstrated equivalence of IFR and RFR with diagnostic accuracy of 97.8%. We analyzed the ROC curve to delineate the cut off value of RFR

with contrast which would be sensitive and specific as FFR, it came out to be 0.87 as compared to be 0.89 at baseline. Changing the nonhyperemic index to hyperemic especially with adenosine we turned the false negative cases to true positive which was statistically significant ($p<0.05$). Illumien I + PREDICT study compared RFR to FFR, revealed 79.2% overall accuracy of RFR compared with FFR similar to other nonhyperemic pressure ratios. RFR had sensitivity of 78.9%, specificity of 79.8% with diagnostic accuracy of 79.2% which is comparable to our series where RFR was sensitive in 88.82% with better specificity of 92%. Positive and negative predictive value of RFR across Illumen I+PREDICT study was 88.7% and 65.4% where as in our study ended up in better predictivity with positive predictive value of 80 and negative predictive value of 95.8. VALIDATE RFR study carried out with much precision yielded higher sensitivity 98.2%, specificity 96.9%, positive predictive value 94.5% and negative predictive value 99%. Older studies of RFR from which concept of Validate RFR was born like VERIFY -2 and IRIS FFR also yielded similar predictive value as compared to ours. We included ACS patients beyond five days of presentation for estimation of RFR and IFR. Delpon et al. demonstrated good correlation of RFR and FFR in MI which was 0.84 and the overall agreement was 0.82 with rates of false positive and negative 15% and 3% respectively. As ACS constituted majority of our study group, it showed the same correlation trend as produced by Delpon et al. in patients with acute MI. In their study SCD cohort had higher rate of false positive RFR.

Majority of our patients had lesion in LAD. Neiwiara et al demonstrated higher correlation between RFR and FFR in patients with non-LAD lesions as compared to LAD lesions. In spite of being a LAD dominant cohort we did not come across any odd in correlation between RFR and FFR in our study group.

Our study was unique in turning a nonhyperemic index to hyperemic one, most pronounced effect was observed with adenosine as compared to nitroglycerine and contrast which resulted in more true positive cases as observed in our study and it was statistically significant as compared to adenosine based FFR. Presence of smoking and diabetes mellitus did not influence RFR.

Conclusion

RFR correlates well with FFR (agreement K:0.781). RFR cut off of 0.89 correlated with FFR of 0.8 in our study. RFR in our study had sensitivity of 89%, specificity of 92%, positive predictive value of 80% and negative predictive value of 96% ($p<0.001$, AUC 0.89). Effect of hyperemia in non-hyperemic indices are as follows: hyperemic agents improve the diagnostic accuracy of nonhyperemic index RFR, contrast RFR with cut off of 0.875 correlated with an FFR of 0.8, adenosine RFR with cut off of 0.795 correlated with FFR of 0.8. Presence of diabetes and Smoking had no effect on RFR as observed in our study.

References

1. Jeremias A, Maehara A, Genereux P, et al. Resting fullcycle ratio (RFR): A novel physiologic index compared to Fractional Flow Reserve (FFR) in assessing the hemodynamic severity of a coronary stenosis: ILUMIEN I + PREDICT. Euro PCR 2018.
2. Svanerud J, Ahn JM, Jeremias A, et al. Validation of a novel nonhyperemic index of coronary artery stenosis severity: The Resting Fullcycle Ratio (VALIDATE RFR) study. EuroIntervention 2018; 14:806–814.
3. Ahn JM, Park DW, Shin ES, et al. IRIS FFR: prognostic performance of five resting pressure-derived indexes of coronary physiology. TCT 2018.
4. Lee J-M, Koo BK, Shin ES, et al. Physiological and clinical assessment of resting physiological indexes. Circulation 2019;139.
5. Nam CW, Koo BK. Fractional flow reserve assessment of serial lesions April 2014.
6. Hennigan B, Oldroyd KG, Berry C, et al. Discordance between resting and hyperemic indices of coronary stenosis severity: The VERIFY 2 study. Circ Cardiovasc Interv 2016;9:e004016.
7. Ahn JM, Nam CW, Doh JH, et al. Fractional flow reserve and cardiac events in coronary artery disease: Data from a prospective IRIS-FFR registry. Circulation 2017;135:2241–2251.
8. Lee J-M, Jeon KH, Hwang D, et al. Clinical implications of three-vessel fractional flow reserve measurement in patients with coronary artery disease. Eur Heart J 2018;39(11):945–951.
9. Kumar G, Desai R, Gore A, et al. RE-VALIDATE: REal world VALIDATion of the nonhyperemic InDex of coronary Artery sTEnosis severity: Resting fullcycle ratio (RFR)-RE-VALIDATE RFR. Crtonline.org
10. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984; 310:819.
11. Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. J Am Coll Cardiol 2010; 55:173.

12. Qian J, Ge J, Baumgart D, et al. Safety of intracoronary Doppler flow measurement. Am Heart J 2000;140:502.
13. Kern MJ, Donohue TJ, Aguirre FV, et al. Clinical outcome of deferring angioplasty in patients with normal translesional pressure-flow velocity measurements. J Am Coll Cardiol 1995;25:178.
14. Ofili EO, Kern MJ, Labovitz AJ et al. Analysis of coronary blood flow velocity dynamics in angiographically normal and stenosed arteries before and after endolumen enlargement by angioplasty. J Am Coll Cardiol 1993;21:308.
15. Donohue TJ, Kern MJ, Aguirre FV, et al. Assessing the hemodynamic significance of coronary artery stenoses: Analysis of translesional pressure-flow velocity relations in patients. J Am Coll Cardiol 1993;22:449.
16. Miller DD, Donohue TJ, Younis LT, et al. Correlation of pharmacological 99mTc–sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. Circulation 1994;89:2150.
17. Joye JD, Schulman DS, Lasorda D, et al. Intracoronary Doppler guide wire versus stress single-photon emission computed tomographic thallium-201 imaging in assessment of intermediate coronary stenoses. J Am Coll Cardiol 1994;24:940.
18. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703.
19. Echavarria-Pinto M, Escaned J, Macías E, et al. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve: A combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. Circulation 2013;128:2557.
20. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: Results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;59:1392.
21. Escaned J, Echavarría–Pinto M, Garcia–Garcia HM, et al. Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance: Results of ADVISE II International, Multicenter Study (ADenosine Vasodilator Independent Stenosis Evaluation II). JACC Cardiovasc Interv 2015;8:824.
22. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med 2017;376:1813.
23. Davies JE, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med 2017;376:1824.