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ASSESSMENT OF FRACTIONAL FLOW RESERVE FOR INTERMEDIATE CORONARY LESIONS IN PATIENTS WITH CORONARY ARTERY DISEASE (FFRICO STUDY)

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Abstract
Background of the study: Fractional flow reserve (FFR) is an invasive index that state the functional significance of severity of coronary stenosis which can be applied for simple as well as complex lesion assessment along with coronary angiography. This FFRICO study was designed to evaluate the utility of FFR for intermediate coronary lesions (50-70% diameter stenosis) in patients with coronary artery disease (CAD) and their clinical outcome in Indian patients. It also compares the clinical outcomes among patients who underwent revascularization versus those kept under medical follow-up based on FFR assessment.
Methods: FFRICO study was a single-center, retrospective study which included 100 patients who underwent coronary angiography followed by FFR for intermediate coronary lesions during the period, January 2016 to January 2018. Study populations were divided into three groups:i) Group-1–FFR>0.8 with medical follow-up;ii) Group-2–FFR ≤0.8 and under went revascularization; and iii) Group-3–FFR≤0.8 and did not undergo revascularization. FFR was measured in lesions with intermediate coronary stenosis. The endpoint was major adverse cardiac events (MACE), defined as composite of cardiac death, non-fatal acute coronary syndrome, and any repeat revascularization.
Results: The mean age of 100 patients was 59.79 years. About62% patients had multi-vessel disease. Majority 60 (82.2%) of the patients had unstable angina ingroup-1,while12(52.3%) in group-2 and all the 4 (100%) in group-3 had unstable angina. Mean FFR was0.87 in group-1,0.76 in group-2 and group-3. MACE was reported in 3(4.1%) patients in group-1, 1(4.3%) in group-2 and 2(50%)in group-3.MACE rate was significantly high in group-3 compared to group-1 and group-2 ($p<0.001$).
Conclusion: This study helps in reassuring the utility of FFR-based clinical decisions in patients with CAD in Indian patients.
Keywords: fractional flow reserve; percutaneous coronary intervention; revascularization; coronary angiography; coronary artery disease

Introduction

Coronary angiography continues to be used as the standard method for quantifying the severity of coronary stenosis. However, many studies and daily clinical experience consistently showed that the accuracy of coronary angiography frequently fails to identify the hemodynamic significance of coronary stenosis, particularly between 30% and 90% diameter stenosis.(1) Functional severity of coronary narrowing is the most prominent prognostic factor among the individuals with documented coronary artery disease (CAD).(2)Hence, in guiding and deciding the treatment strategy for patients with known or suspected CAD, combined assessment of anatomical and physiological/functional information with high accuracy become very important, particularly in those with intermediate degree of stenosis (50-70%).(3)
Fractional flow reserve (FFR) is an invasive technique developed in 1990s for the assessment

of functional significance of severity of coronary stenosis with a diagnostic precision of myocardial scintigraphy, although with a better spatial resolution.(2) FFR is calculated as the ratio of the distal coronary pressure of the stenosis divided by the aortic pressure during maximal hyperemia.(2,4) Since flow is proportional to pressure, if resistance is minimum and constant, pressure can be used as a substitute off low during maximum hyperemia. Therefore, FFR in combination with conventional angiography is evolving rapidly as an accurate approach of combining anatomy and physiology.(5)

Role of FFR in determining the need for coronary stenting has been studied in various trials and has been recommended to assess the significance of intermediate coronary lesions.(6-8) However, in India, clinical use of FFR is more or less limited to tertiary care centers and its utilization is probably confined to a small group of patients with CAD. Demographic, risk profile and natural history of CAD among Indian/Asian patients are affected by some unique factors such as younger age group, pre dominant metabolic syndrome, exposure to lipid-rich

Diet and increasingly common sedentary life style and there is data which discuss about smaller coronary artery diameters in Indian patients undergoing angiography.(9-12)Thus, it is speculative that many Indian patients with border line lesions endure unwarranted revascularization without much clinical improvement. Therefore, this FFRICO study was designed to evaluate the utility of FFR for intermediate coronary lesions (50-70% diameter stenosis) in patients with CAD and their clinical outcome in Indian patients. It also compares the clinical outcomes among patients who underwent revascularization versus those kept under medical follow-up based on FFR assessment.

Materials and Methods

Study design and population

FFRICO study was a single-center, retrospective study which included 100 patients who underwent coronary angiography along with FFR guidance during the period, January 2016 to January2018. All patients with stable ischemic heart disease or those who had acute coronary event a week or more prior to the procedure were included. The present study was approved by the institutional ethics committee. Study populations were divided into three groups: i) Group-1–FFR > 0.8 and on optimal medical therapy (OMT) follow-up) Group-2–FFR

≤0.8 and underwent revascularization by per cutaneous coronary intervention(PCI) or coronary artery bypass grafting (CABG) and iii) Group-3 – FFR ≤0.8 and did not undergo revascularization as per patient's preference.

Patients with culprit coronary vessel responsible for acute coronary syndrome within 7 days (however, if the FFR was studied in non-culprit coronary arteries in the same patient it was included). Left main coronary artery lesion, previous CABG, contraindication to adenosine, conditions for which FFR has not been validated such as tortuous coronary arteries, left ventricular hypertrophy and with life-threatening co-morbidity were excluded. The coronary arteries supplying collaterals to the vascular bed subtended by a totally occluded artery were also excluded.

Coronary Pressure Measurement and Calculation of FFR

FFR was measured in lesions with intermediate coronary stenosis for the assessment of hemodynamic significance. Intracoronary pressure measurements were performed with a 0.014-inch pressure guide wire (Pressure Wire Aeris from St. Jude Medical or Prime wire PRESTIGE from Volcano Inc , Rancho Cordova, California, USA) introduced through a guide catheter. Hyperemia was induced by intravenous adenosine(140μg/kg/min until a steady state was obtained or for at least 6minutes)after a bolus dose of intracoronary

nitroglycerin of 200 µm. The FFR was estimated from the ratio of mean hyperemic distal coronary pressure measured by the pressure-wire and the mean aortic pressure obtained by the coronary guide catheter. As per the departmental protocol, FFR valueof>0.8was considered as a criterion to defer revascularization at the time of procedure and the decision to revascularize was based on the cut-off value of FFR ≤0.8. Pressure gradient of>10mmHg was considered significant if there were serial stenotic lesions. After the procedure, aspirin and clopidogrel was recommended for at least 12 months to those patients who underwent revascularization. The patients who received only medical therapy received antiplatelet, statins and beta-blockers.

Clinical End Point and Follow-Up

The endpoint during the follow-up was major adverse cardiac events (MACE), defined as composite of cardiovascular death, non-fatal acute coronary syndrome, and any repeat revascularization of the vessel in which FFR was studied. A repeat angiogram was performed only when indicated clinically. The culprit artery responsible for the recurrence of symptoms is based on the correlation of electrocardiographic changes, echo cardiographic data, and the diagnostic angiogram.

All patients were evaluated at the outpatient intervention clinic for drug compliance, new/ persistent/worsening symptoms, ECG changes and any MACE events including repeat coronary angiogram and coronary revascularization, if done.

Statistical Analysis

The data was analyzed using commercially available SPSS Software (version20.,SPSS,Inc., Chicago, IL, USA) to study the percentage of patients who had clinical event, MACE, repeat angiogram and revascularization – PCI/CABG. Continuous variables are expressed as mean and standard deviations and discrete variables as counts and percentage. For categorical variables, chi-square test and Fisher exact t-test were used, and for continuous variables, student t-test was used. A p-value <0.05 was considered statistically significant.

Results

The mean age of 100 patients was 59.79 years with 49 (49%) patients between 41–60 years of age. Majority 76 (76%) of the patients had unstable angina and 8 (8%) had non-ST-elevation myocardial infarction. Around 36 (36%) patients had primary ST-T changes, 33 (33%) had reginal wall motion abnormality, 25 (25%) had a history of revascularization, 11(11%) had in- stent restenosis /graft occlusion. About 62 (62%) patients had multi-vessel disease. Total 58 (58%) patients stayed in hospital for < 3days. Exceptional angina was present in 96(96%) of the study participants. Table 1 describes the baseline demographic and clinical characteristics of all patients.

Comparison of groups- Mean age was 60.36 ±8.22 years in group-1, 57.52 ±9.92 years in group-2 and 60.75 years in group-3. Males were more in all the three groups compared to females. Majority 60 (82.2%) of the patients had unstable angina in group-1, while 12 (52.3%) in group-2 and all the 4(100%) in group-3 had unstable angina. **Table 2** outlined comparison of variables among three groups. Mean FFR was 0.87 in group-1, 0.76 in group-2 and group-3. Procedural findings and clinical out comes of patients in all three groups are depicted in **Table3**. MACE occurred in 3(4.1%) patients in group-1, 1(4.3%) in group-2 and 2 (50%) in group-3. MACE rate was significantly high in group-3 compared to group-1 and group-2 (Chisquare value-14.3; p<0.001). However, MACE rates among group-1 and group-2 showed no statistically significant difference (Chi square value = 0.3008; p = 0.5834). Total3

(4.1%) patients with MACE in group-1 underwent revascularization.

Table1: Baseline demography and clinical characteristics of all patients

Variables	**N=100**
Mean Age, years	59.79
Age Distribution, n(%)	
31 – 40 years	01 (1%)
41 – 50 years	16 (16%)
51 – 60 years	33 (33%)
61 – 70 years	36 (36%)
71 – 80 years	14 (14%)
Gender, n(%)	
Male	70 (70%)
Female	30 (30%)
Risk Factors, n (%)	
Diabetesmellitus	58 (58%)
Hypertension	69 (69%)
Dyslipidemia	29 (29%)
Smoking	20 (20%)
Family history of CAD	08 (8%)
Renal dysfunction	00
History of ACS	34 (34%)
Prior revascularization	25 (25%)
ISR/Graft Occlusion	11 (11%)
CHF Recovered	01 (1%)
CRHD	01 (1%)
Clinical presentation, n(%)	
Unstableangina	76 (76%)
OldIWMI	01 (1%)
Recent IWMI	09 (9%)
Recent AWMI	04 (4%)
RWMA	33 (33%)
NSTEMI	08 (8%)
Primary ST-T changes	36 (36%)
Number of diseased vessels, n(%)	
Single vessel disease	38 (38%)
Double vessel disease	40 (40%)
Triple vessel disease	22 (22%)
Duration of AOE, n(%)	
<1week	41 (41%)
1-2 weeks	19 (19%)

2weeks to1month	26 (26%)
1-2 months	03 (3%)
2-3 months	02 (2%)
3-6 months	05 (5%)
Duration of hospital-stay, n(%)	
<3 days	58 (58%)
3to5 days	23 (23%)
5to7 days	11 (11%)
7to14 days	06 (6%)
14to30 days	02 (2%)

CAD: coronary artery disease; ACS: acute coronary syndrome; ISR: in-stent restenosis; CHF: congestive heart failure; CRHD: chronic rheumatic heart disease IWMI: inferior wall myocardial infarction; AWMI: anterior wall myocardial infarction; RWMA: regional wall motion abnormality; NSTEMI: non-ST elevation myocardial infarction; AOE: angina of exertion

Table2: Comparison of various parameters among three groups

	FFR>0.8	**FFR<0.8**	
Variables	**Group1 OMT(n =73)**	**Group 2 PCI/CABG (Revascularized) (n=23)**	**Group3 (Not revascularized) (n=04)**
Age, years(mean± SD)	60.36±8.22	57.52±9.92	60.75
Age Distribution, n(%)			
31 – 40 years	00	1 (4.3%)	00
41 – 50 years	9 (12.3%)	6 (26%)	1 (25%)
51 – 60 years	24 (32.9%)	8 (34.8%)	1 (25%)
61 – 70 years	29 (37.7%)	6 (26%)	1 (25%)
71 – 80 years	11 (15%)	2 (8.7%)	1 (25%)
Gender, n(%)			
Male	52 (71.2%)	14 (60.9%)	4 (100%)
Female	21 (18.8%)	9 (39.1%)	00
Male: Female	2.47:1	1.6:1	4:0
Clinical presentation, n(%)			
Unstable angina	60 (82.2%)	12 (52.3%)	4 (100%)
Old IWMI	1 (1.4%)	00	00
Recent IWMI	6 (8.3%)	3 (13.1%)	00
Recent AWMI	2 (2.8%)	2 (8.6%)	00
NSTEMI	4 (5.4%)	4 (17.4%)	00
CHFRecovered	00	1 (4.3%)	00
CRHD	00	1 (4.3%)	00

Number of diseased vessels, n (%)			
Single vessel disease	31 (42.4%)	6 (26.1%)	1 (25%)
Double vessel disease	28 (38.4%)	12 (52.2%)	00
Triple vessel disease	14 (19.2%)	5 (21.7%)	3 (75%)
Proximal LAD>50%	23 (31.5%)	14 (60.9%)	2 (50%)
Proximal RCA>50%	11 (15.1%)	11 (47.8%)	2 (50%)
>2CAD risk factors	45 (61.6%)	16 (69.6%)	2 (50%)
Prior revascularization	19 (26%)	5 (21.7%)	1 (25%)
ISR/Graft occlusion	8 (11%)	3 (13%)	00
FFR: fractional flow reserve; OMT: optimal medical therapy; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; IWMI: inferior wall myocardial infarction; AWMI: anterior wall myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; CHF: congestive heart failure; CRHD: chronic rheumatic heart disease;LAD:leftanteriordescending;RCA:rightcoronaryartery;CAD:coronaryartery disease; ISR: in- stentrestenosis			

Table3: Procedural findings and clinical outcomes among three groups

Profile characteristic	**FFR>0.8**	**FFR<0.8**	
	Group1 OMT(n =73)	**Group 2 PCI/CABG (Revascularized) (n=23)**	**Group3 (Not-Revascularized) (n = 04)**
Mean ejection fraction,% (mean± SD)	55.68±6.78	50.65±8.56	56.25±7.5
Mean minimum stenosis diameter, mm	1.32	1.18	1.06
Mean FFR,(mean ±SD)	0.8725±0.0297	0.7609±0.021	0.765±0.030
Median follow-up, months (range)	22.8(6to 52)	17(4to 48)	13.6(2to 42)
MACE, n (%)	3 (04.1%)	1 (04.3 %)	2 (50 %)
Revascularized (PCI/CABG),n(%)	3 (4.1%)	00	1 (25%)
Death, n(%)	00	1 (04.3%)	1 (25%)
Doing well, n(%)	70 (95.9%)	22 (95.7%)	2 (50%)
OMT: optimal medical therapy; FFR: fractional flow reserve; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting			

Discussion

This study attempted to compare the clinical outcomes of FFR assessment based coronary revascularization. The strategy of OMT for stenosis with FFR >0.8 and treating only stenosis that are hemodynamically significant (<0.8) with revascularization appears safe as evidenced by the similar MACE rates in both the cases. Those patients who had coronary stenosis with FFR<0.8 and refused to undergo revascularization had higher MACE rates (50%). These results strongly support the importance of FFR in clinical decision making in Indian patients

with intermediate single or multi-vessel disease.

MACE occurred in 3(4.1%) patients in group-1,1(4.3%) in group-2 and 2(50%) in group-3; and was significantly high in group-3 compared to other two groups (p=0.000). In a study by Srinivas Prasad et al., 3 (3.4%) patients in group-1 had MACE, 4 (2.3%) in group-2, and 7 (41.17%)in group-3 which was similar as reported in our study.(13) As MACE was significantly higher (50%) in patients with FFR <0.8 and did not undergo revascularization, FFR based revascularization decision appears to be a safe strategy in Indian patients. Consistent with the present results, IRIS-FFR also showed that with FFR ≤0 .75 ,the risk of MACE was significantly lower in revascularized lesions than in deferred lesions.(14)

The present study results prove that there is no difference in the outcome of functionally insignificant stenosis (i.e., not responsible for reversible ischemia, indicated by an FFR>0.8) treated medically and functionally significant stenosis (i.e., causing reversible ischemia, FFR<0.8) treated surgically. In addition, it also proves that deferring revascularization for a functionally significant stenosis is associated with significant adverse outcomes with detrimental effects as reported in previous study.15

Similar results were reported by Pijls NHJ et al.,8who concluded that PCI of a functionally insignificant stenosis was not of benefit for the patient, neither from a prognostic nor from a symptomatic point of view. Therefore, PCI of such stenosis should be discouraged. The lesions, at highest risk of causing cardiac death or acute myocardial infarction, are those that are functionally significant. The chance of dying or experiencing an acute myocardial infarction related to such a stenosis in the next five years is five times higher even when treated by PCI than for a stenosis of similar angiographic severity (anatomical/structural) but not associated with reversible ischemia (functional) and treated medically.(8)

In the present study, prevalence of positive FFR among patients was 27%, which is comparably lower than that found in the DEFER study (55%), where enrollment was primarily based on angiography cases of patients with negative stress test or without a stress test.4 However, in the all-comers FAME-2 study, which included consecutive patients who underwent angiography for their symptoms and were found to have at least 50% stenosis in coronary angiogram, 72% patients who were eligible were found to have FFR <0.8.16,17 Further more, in DEFER trial,4,8which randomized patients with FFR≥ 0.75 in to deferred group and PCI group showed that the five years event-free survival rates were statistically comparable among both groups (80% vs 73%, p = 0.52), and demonstrated that functionally insignificant coronary stenosis could be safely deferred for up to five years, regardless of angiographic stenosis.

In the present study, MACE among patients with FFR > 0.8 was found to be 4.1%, comparable to the patients who had FFR>0.8 in the FAME-2 study (registry group), where in, the occurrence of MACE was 3% over one year.18 There was remarkable difference in the MACE rates between patients who underwent revascularization and those who refused it initially (4.3% vs 50%) in the present study. The higher event rates could be explained by higher risk profile such as diabetes, multi-vessel disease, and 96% exertional angina. In FFR negative lesions, OMT alone resulted in excellent outcomes, regardless of the angiographic appearance of the stenosis as reported in various other studies.19-21

Study Limitations

The single center, retrospective and non-randomized study design, and the small sample size (n=100) may not generalize the results. The smaller sample size in the third group might have inflated the event rates; and lack of quantitative assessment might affect the study results.

Conclusion

Despite the differences in clinical profile of patients when compared with those in randomized clinical trials, the data from this study reflects real-world practice. Hence, this study, being probably the second of its kind in India, helps in reassuring the utility of FFR-based clinical decisions in patients with CAD in this part of the world.

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