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PROJECT REPORT
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DECLARATION

I , Dr. AJEET ARULKUMAR S J, hereby declare that the project in this book were undertaken by me under the supervision of the faculty, Department of Cardiology,Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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Application of fractional flow reserve in Intermediate lesions

INTRODUCTION

Introduction

Patients with coronary artery disease (CAD) and myocardial ischemia refractory to medical therapy frequently undergo revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). When revascularization is based mainly on angiographic guidance, it is unavoidable that a number of hemodynamically non-significant stenoses will be revascularized, whereas a number of stenoses deemed non-significant will be deferred inappropriately.[1,2,3] Visualization of coronary lesions is often limited by patient morphological features, and is plagued by abundant evidence of poor correlation with pathological findings[4] and considerable interobserver variability with regard to the severity of coronary arterial narrowings[5] and their morphology[6]

Fractional flow reserve (FFR) is a well-validated method to quantify the impact of a coronary stenosis on myocardial perfusion.[7,8] It is based on coronary pressure measurements obtained during maximal hyperemia. FFR can be obtained in a few minutes in the catheterization laboratory, allowing an "on the spot" decision about the appropriateness of revascularization.[9,10] Integrating invasive coronary physiology with angiography has become routine in many but not all cath labs.

The rationale for physiologic lesion assessment is based on 2 facts: 1) the decision to revascularize relies primarily on the hemodynamic significance of a lesion; and 2) coronary angiography frequently fails to identify the accurate hemodynamic significance of coronary stenoses, particularly those between 50% and 80% diameter stenosis. Coronary angiography produces 2-dimensional silhouette images of the 3-dimensional vascular lumen. Because angiographic stenosis severity is reported as a ratio of the stenosis' minimal lumen diameter to the adjacent "normal" reference segment, accuracy is limited by the inability to identify both "diseased" and "normal" vessel segments, particularly in the setting of diffuse CAD.

There are many studies evaluating the comparison of FFR and QCA in the west, but none from our country. This study was done to compare the patient characteristics in 2 groups of patients with intermediate lesions – Those with FFR positive and those with FFR Negative

REVIEW OF THE LITERATURE

Review of the Literature

The coronary circulation should be viewed as a two-compartment model. The first consists of large epicardial vessels (> 400 microns), which are the 'conductance vessels' because they have minimal resistance to blood flow. So, the pressure in the distal part of a healthy human coronary artery will be similar to central aortic pressure. The second compartment consists of vessels smaller than 400 microns, that is 'resistive vessels' (Fig.). Resistance to myocardial flow is predominantly by resistive vessels.

Physiological indices of the coronary circulation

There are many ways to identify the physiological significance of a lesion. FFR is the best validated of the physiological indices.

Coronary flow reserve

CFR is defined as the ratio of hyperaemic blood flow (Q max) to resting myocardial blood flow (Q rest) (i. e. CFR = Q max/Q rest). The normal value for CFR is still not well defined and normal values differ from study to study[11],[12]. However, generally a value > 4 is considered as normal, which means that microvascular resistance can decrease by a factor of 4[13]. Absolute myocardial flow is not easy to determine, hence surrogate markers of flow are usually used, such as flow velocities assessed by the Doppler Wire (FloWire, Volcano Inc., Rancho Cordova, CA, USA) or assessed by the Pressure Wire (St. Jude Medical Systems Inc., Uppsala, Sweden). Regardless of the method used to measure CFR, this technique has several limitations: resting flow is highly variable; there is considerable heterogeneity of flow velocity distal to an epicardial stenosis; hyperemic flow is directly dependent on systemic blood pressure; the hyperemic and resting measurements are performed simultaneously not successively; and CFR is not specific for an epicardial stenosis, as the CFR value depends on both epicardial vessels and microcirculation. When CFR is low, it is impossible to distinguish

whether this value is related to an epicardial artery stenosis alone, microcirculatory dysfunction alone or a combination of both. Owing to these limitations, CFR is not used routinely in clinical practice to assess the haemodynamic significance of a coronary stenosis and has limited value in clinical decision-making.

Fractional flow reserve

FFR is the ratio of maximal myocardial blood flow depending on a stenotic artery to maximal myocardial blood flow if that same artery had no stenosis. In other words, it is a fraction of the maximal normal flow, assuming that these measurements are obtained when the microvasculature resistance is minimal and constant (maximal hyperemia)[14,15].

FFR is the extent to which maximal myocardial blood flow is limited by the presence of an epicardial stenosis. FFR also excludes the confounding influence of the microcirculation, changes in hemodynamics or contractility[16].

As FFR is a ratio of two flows and this ratio can be derived from two pressures (distal coronary pressure and aortic pressure), provided they are both measured during maximal hyperemia. The theoretical explanation of this relationship between hyperaemic flows and hyperaemic pressures is displayed in Fig.

Procedure

It has been shown that the use of diagnostic catheters is technically feasible[17] . However, due to the higher levels of friction hampering wire manipulation, the smaller internal calibre prejudicing pressure measurements and the inability to perform ad hoc PCI using diagnostic catheters, the use of guiding catheters is recommended.

Two pressure wire systems are currently available on the market for measuring intracoronary pressure, namely the Pressure Wire (St. Jude Medical Systems Inc., Uppsala, Sweden) and

the Volcano Wave Wire (Volcano Inc., Rancho Cordova, CA, USA). The sensor is located 30 mm from the tip, at the junction between the radiopaque and radiolucent portions. The last generations of these 0.014 inch wires have similar handling characteristics to most standard angioplasty guide wires. As soon as a device is advanced into the coronary tree, the use of the same anticoagulation regimens as employed during a PCI procedure are recommended: heparin adjusted to weight, validated by a monitored activated coagulation time of at least 250 s.

Hyperemia

While FFR is performed, it is absolutely imperative to achieve maximal vasodilatation of the two vascular compartments of the coronary circulation, namely the conductance arteries (epicardial) and the resistance arteries (microvasculature). The pharmacological agents most often used to induce hyperemia are listed in the Table[18,19,20]. A bolus of 200 mg isosorbide dinitrate (or any other form of intracoronary nitrate) usually resolves any form of vasoconstriction of epicardial arteries. The pharmacological agents most often used to induce hyperemia in resistance arteries are adenosine (via the intracoronary or intravenous routes) and papaverine. An adenosine dose of 50 µg as an intracoronary bolus or 140 µg/kg/min as an intravenous infusion has been demonstrated to induce hyperemia similar to intracoronary papaverine[19].

Drug	Delivery
Epicardial vasodilation	
Isosorbide dinitrate	≥ 200 µg intracoronary bolus, ≥ 30 s before the first measurements
Microvascular vasodilation	
Adenosine or adenosine triphosphate	140 µg/kg/min intravenously (preferably through a central venous line)
Adenosine or adenosine triphosphate	50 µg (to 150 µg) intracoronary bolus
Papaverine	Intracoronary delivery: 12–16 mg in the right coronary artery; 16–20 mg in the left coronary artery
Nitroprusside	0.6 µg/kg intracoronary bolus

Clinical applications of FFR

The potential of angiography to evaluate the haemodynamic severity of an intermediate lesion is limited. Moreover, angiographic assessment is often the only decision-making modality for performance of angioplasty, especially in the absence of functional evaluation[21]. FFR measurements correlate well with non-invasive assessment of coronary artery disease. In patients with angiographically equivocal stenoses, it has been shown that FFR is more accurate than exercise electrocardiography, myocardial perfusion scintigraphy and stress echocardiography for assessing haemodynamic significance[22]. In addition, the clinical outcome of patients in whom PCI has been deferred, because the FFR indicated no hemodynamically significant stenosis, is very favourable. In this population, the risk of death or myocardial infarction is approximately 1% per year and this risk is not further decreased by PCI (DEFER STUDY)[23]. These results strongly support the use of FFR measurements as a guide for decision-making about the need for revascularization in 'intermediate' lesions.

Left main stem disease

The presence of a significant stenosis in the LMCA is of critical prognostic importance and often determines the type of treatment[14]. Therefore, the evaluation of haemodynamic severity is essential and non-invasive testing is often non contributive[24].The potential of coronary angiography to evaluate the haemodynamic severity of a stenosis is limited, especially in the LMCA[25]. In addition, there are significant interobserver variations in the assessment of LMCA lesions[26]. There may be several reasons for the discrepancy between angiographic and haemodynamic assessments of LMCA stenoses: the catheter may overlap with the origin of the left anterior descending and the left circumflex arteries, and

spill over of contrast medium and incomplete mixing of blood and contrast medium in the proximal part of the LMCA may render the evaluation of an ostial lesion difficult; the LMCA is generally short and, when present, atherosclerosis is often distributed diffusely, so that a normal segment is lacking, which leads to an underestimation of the 'reference' segment and thus to an underestimation of LMCA stenoses by both visual estimation and quantitative coronary angiography; the myocardial mass that depends on the LMCA is large, so the amount of blood that flows through it is great, and substantial trans-stenotic flow, in turn, induces large pressure gradients, especially during hyperaemia[27]. Finally, revascularization strategies based solely upon an angiogram are often inappropriate in patients with an LMCA stenosis.

FFR can identify LMCA stenosis responsible for ischemia. Several studies showed that an FFR-guided strategy for equivocal LMCA lesions is safe and related to a favourable clinical outcome[28]. Hamilos et al. assessed the long-term clinical outcome of 213 patients with an angiographically equivocal LMCA stenosis in whom the revascularization strategy was based on FFR. When FFR was ≥ 0.80, patients were treated medically (n = 138) and when FFR was < 0.80, a CABG was performed (n = 75). The 5-year survival and event-free survival rates were similar in both groups, supporting the use of FFR in patients with LMCA disease[27].

Multivessel disease

Patients with 'multivessel disease' actually represent a very heterogeneous population. In these patients, FFR measurement has a major implication for the mode of revascularization strategy (PCI vs CABG). Furthermore, determining which lesion(s) warrant stenting and which do not can be difficult in these patients, when using non-invasive imaging modalities. For example, myocardial perfusion scintigraphy is limited in its ability to

accurately localize lesions responsible for ischemia in these patients[29]. Preliminary FFR-guided revascularization strategies in patients with multi vessel disease were very encouraging[24]. A recent randomized multicentre study (FAME: FFR versus Angiography for Multi vessel Evaluation) in 1000 patients showed that routine measurement of FFR during PCI with drug-eluting stents in patients with multi vessel disease reduced the rate of the composite endpoint of death, myocardial infarction, re-PCI and CABG at 1 year by approximately 30% and reduced mortality and myocardial infarction at 1 year by approximately 35%, compared with current angiography-guided strategy. Moreover, the FFR-guided strategy reduces the number of stents used, decreases the amount of contrast agent used, does not prolong the procedure and is cost saving[30,31].

Myocardial infarction

After a myocardial infarction, previously viable tissue is partially replaced by scar tissue. Therefore, the total mass of functional myocardium supplied by a given stenosis in an infarct-related artery will tend to decrease[32]. By definition, hyperaemic flow and thus hyperaemic gradient will both decrease as well. Assuming that the morphology of the stenosis remains identical, FFR must therefore increase. This does not mean that FFR underestimates lesion severity after myocardial infarction. It simply illustrates the relationship that exists between flow, pressure gradient and myocardial mass, and, conversely, illustrates that the mere morphology of a stenotic segment does not necessarily reflect its functional importance. Recent data have confirmed that the hyperaemic myocardial resistance in viable myocardium within the infarcted area remains normal[33]. This further supports the application of the established FFR cut-off value in the setting of partially infarcted territories. Earlier data had suggested that microvascular function was abnormal in regions remote from a recent myocardial infarction[34,35]. However, more recent work, taking into account distal coronary pressure, indicates that hyperaemic resistance is normal in these

remote segments[36]. These data support the use of FFR to evaluate stenoses remote from a recent myocardial infarction

Bifurcation lesions

Bifurcation lesions are particularly difficult to assess angiographically because of the overlap orientation relative to parent branch and radiological artefacts. Data supporting the use of FFR in guiding PCI for bifurcation lesions are limited. Two recent studies by Koo et al. demonstrated: that after stenting, the ostium of the side branch often looks 'pinched' but is often overestimated by angiography (measurement of FFR identifies a minority of lesions that are functionally significant)[37]; and a favourable outcome for FFR-guided side branch PCI strategy for bifurcation lesions. Indeed, when kissing balloon dilation was performed only in ostial stenoses with an FFR < 0.75, the FFR at 6 months was > 0.75 in 95% of all cases[38].

Coronary artery bypass graft lesions

In theory, the assessment of stenosis severity in CABGs by FFR should not be different from FFR assessment of native vessels. At present, there are no clinical outcome data available regarding the use of FFR in graft stenosis. Therefore, FFR should be used with caution in bypass graft stenosis. Nevertheless, in patients requiring CABG for multi vessel revascularization, angiographic lesions of uncertain significance would benefit from FFR, providing prognostic information regarding potential of future bypass graft patency. Botman et al. showed that the rate of occlusion was approximately three times higher when the bypass was placed on a native artery with a hemodynamically non-significant stenosis[39]. This study suggested that FFR could have serious implications for best long-term CABG outcomes.

Post stenting

Angiography alone is not a precise technique for detecting local areas of incomplete stent expansion[40]. In 40–70% of stents that appear well deployed by angiography, intravascular ultrasound imaging reveals a region of the stent that is under expanded compared with the remainder of the stent and with the reference segments[41]. Intravascular ultrasound is the gold standard for assessing optimum stent deployment and its results are well correlated with the FFR. FFR has the advantage of being easier to use but its results are more controversial. In a small single-centre study evaluating coil stents, an FFR $\geq$ 0.94 was identified as the appropriate threshold defining optimal stent deployment[42]. This finding has not been evaluated in a broader trial with current generation stents.

AIMS OF THE STUDY

Aim of the study

The aim of the current study was to analyse the clinical and angiographic parameters in patients who underwent Fractional Flow reserve in SCTIMST during the period from January 2012 to November 2012 for patients with intermediate lesions

METHODS AND MATERIALS

Methods and Materials

All consecutive patients who underwent FFR for intermediate lesions from January 2012 to November 2012 in our hospital were taken for the study. 62 patients underwent FFR during this period and were included in the study. Their clinical and angiographic parameters were compared. In 5 patients FFR was done for 2 vessels and for a single patient FFR was done for all 3 vessels (Total of 69 lesions) Patients were divided into 2 groups based on their FFR. Those with FFR < 0.75 were considered to have hemodynamically significant stenosis, whereas those with FFR >0.75 were considered to have physiologically non obstructive CAD and managed conservatively.

FFR was performed using the RadiAnalyzer™ Xpress Measurement System (St. Jude Medical Systems Inc., Uppsala, Sweden). The Radi pressure wire was introduced into the coronary artery with help of a guiding catheter after anticoagulation. Hyperemia of the large conductance vessels was produced by intracoronary NTG in all cases. Both intracoronary(between 50 to 150 mcg bolus) and intravenous adenosine (at a dose of 140 mcg/kg/min) was used for producing vasodilation of the resistive vessels.

Statistically analysis was done using SPSS 14 software. P value of less than 0.05 was taken to be significant.

RESULTS

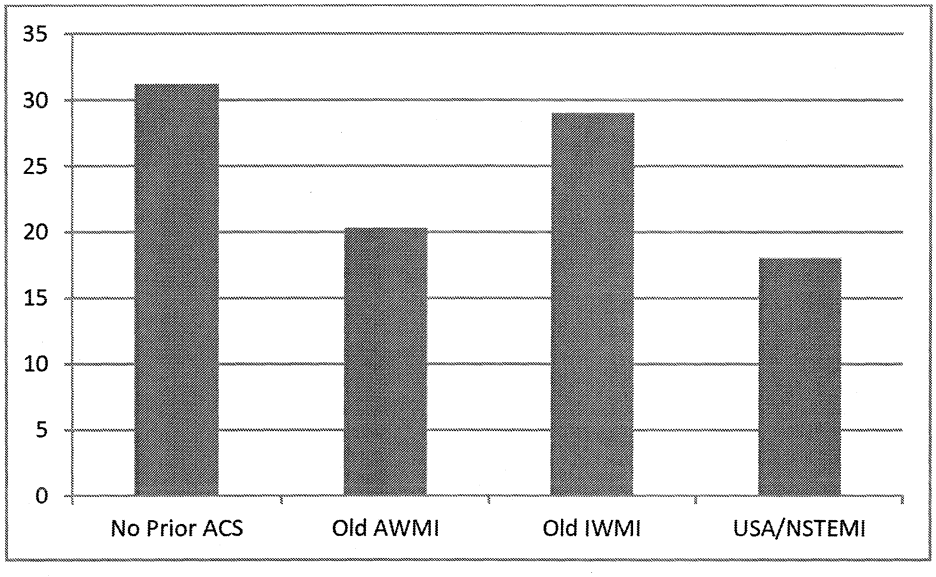
Results

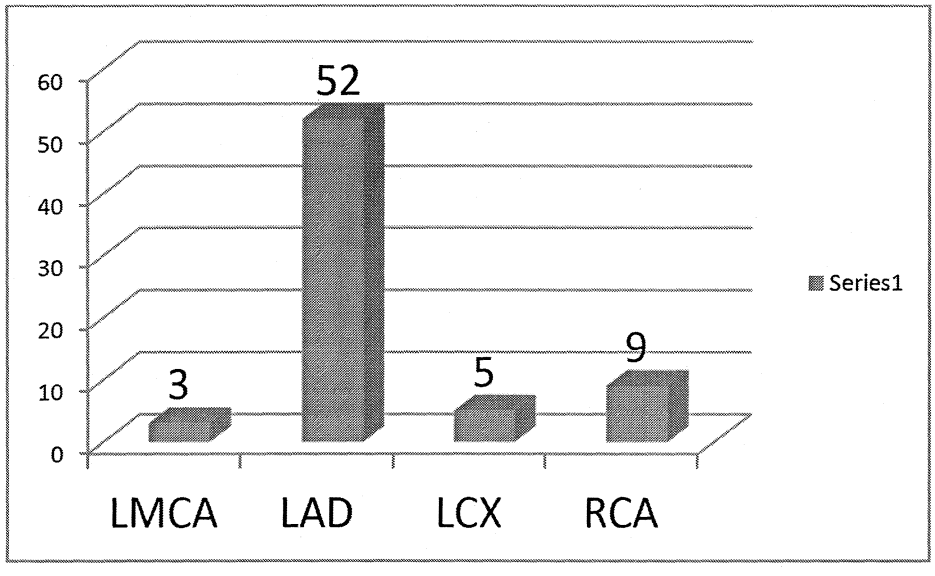
FFR was done on a total of 62 patients (69 lesions). During the same study period 673 Angioplasties were performed. Baselines characteristics are shown Figure below. 85% of the patients were male.

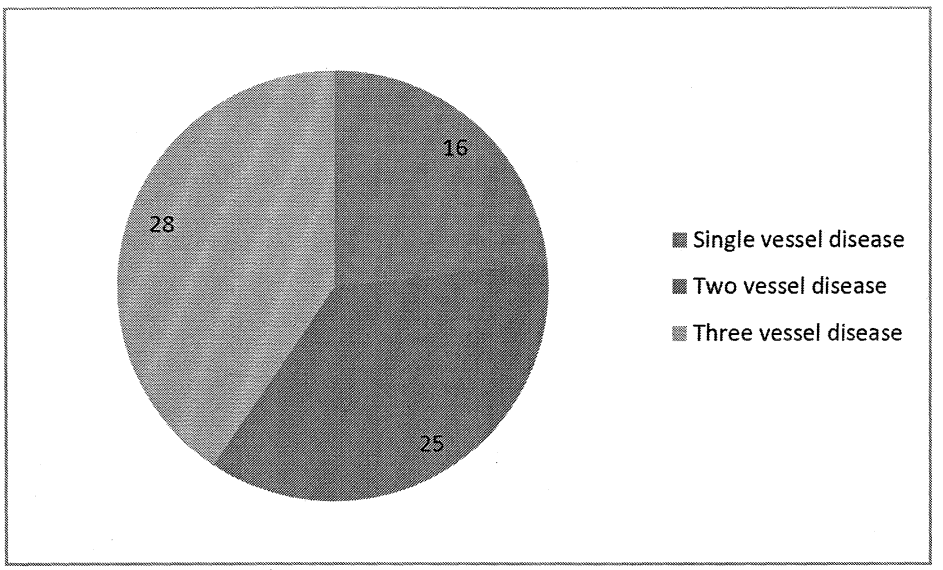
	n	Percent
Age (mean/ SD)	55.23	9.49
Male	59	85
Diabetes	33	47.8
DM Duration (years/SD)	3.17	4.9
Hypertension	35	50.7
SHT Duration (years/SD)	3.04	4.23
Smoker	40	58
Prior ACS	47	68.1
Old AWMI	14	20.3
Old IWMI	20	29
USA/NSTEMI	13	18
EF (mean/ SD)	62.2	12.2
Angina Class 1	5	7.2
Angina Class 2	59	85.5
Angina Class 3	5	7.2
TMT Not done	36	52.2
TMT Positive	30	43.5
TMT Negative	3	4.3
Single vessel disease	16	23.2
Two vessel disease	25	36.2
Three vessel disease	28	40.6
FFR positive	26	37.7
FFR (% / SD)	0.78	0.07
Ref diameter (mm/ SD)	2.38	0.62
Length (mm/ SD)	9.55	3.72
2d QCA (% SD)	49.3	9.8

Almost half the patients had diabetes (47.8%) and/or hypertension (50.7%). 58% of the patients were smokers. Two thirds had a prior ACS. Majority of the patients presented with Class II angina (85%). TMT was not done in more than half the patients (52%). Overall 40% had 3VD. 68% of the study patients had an ACS in the past which was most commonly

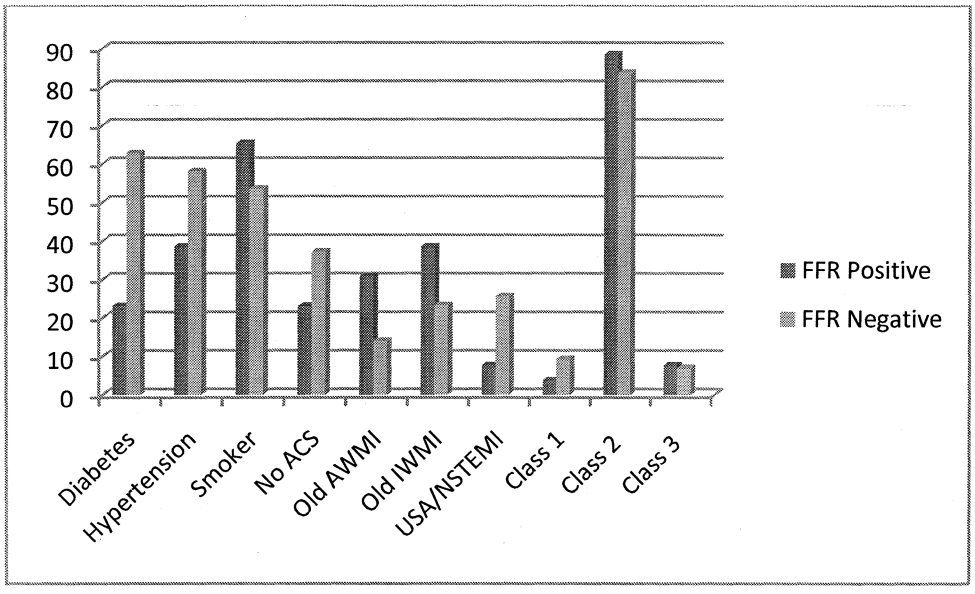
due to either AWMI or IWMI. Overall FFR was positive in 37.7 % of the patients. The 2d QCA was 49.3% (±9.8) in the entire study population. The length of the lesion was 9.55 ± 3.72 mm and the reference diameter was 2.38 ± 0.62 mm.







When patients were divided into 2 groups based on FFR, those with positive FFR were younger (51.5± 8.3 years vs 57.4± 9.5 years) and lower incidence of DM (23.1% vs 62.8%). Both were statistically significant. They also had a trend towards lower incidence of SHT (38.5% vs 58.1%). Those who had significant lesions (FFR positive) had a higher incidence of prior ACS (37.2% vs 23.1%). There were no significant differences between the groups with respect to LVEF (60.1% vs 63.4%) and presenting angina class. The time for TMT positivity was also similar between the groups(7.58 METS vs 7.05 METS). 2D QCA was 50.1 ± 11.9% in the FFR positive group compared to 48.9 ± 8.5% in the FFR negative group(p=0.62) . The length of the lesion also was not significantly different between the 2 groups. However the FFR positive group had smaller reference diameters (2.17 ± 0.7 vs 2.5±0.5; p= 0.028).



	FFR Positive		FFR Negative		
	Number	Percent	Number	Percent	P value
Age (years/SD)	51.5	8.3	57.4	9.5	0.01
Male	23	88.5	36	83.7	0.7
Diabetes	6	23.1	27	62.8	0,03
Duration(years/SD)	1.27	2.3	4.3	5.6	0.01
Hypertension	10	38.5	25	58.1	0.14
Duration(years/SD)	1.67	2.3	3.86	4.8	0.03
Smoker	17	65.4	23	53.5	0.45
EF (mean/SD)	60.1	12.6	63.4	12	0.28
Class 1	1	3.8	4	9.3	0.52
Class 2	23	88.5	36	83.7	0.52
Class 3	2	7.7	3	7	0.52
TMT (METS/SD)	7.58	1.8	7.05	3.2	0.6
No of vessels (mean/SD)	2.19	0.69	2.16	0.84	0.8
Ref diameter(mm/SD	2.17	0.7	2.5	0.5	0.028
Length (mm/SD)	9.5	3.8	9.5	3.6	0.998
2d QCA (mean / SD)	50.1	11.9	48.9	8.5	0.621

DISCUSSION

DISCUSSION

This was a study analysing the clinical and angiographic parameters between patients with FFR positive lesions and those with Negative FFR lesions. FFR was done on a total of 62 patients (69 lesions). During the same study period 661 Angioplasties were performed and 1595 Diagnostic coronary angiograms were performed. FFR was performed only one tenth as frequently as the number of PCIs. FFR in our centre was done only in cases where the lesions were intermediate. Of all the patients for whom FFR was done it was positive in only 37.7% of patients. Hence almost two thirds of patient with intermediate lesions were proven to have physiologically insignificant lesions. These patients were kept on optimal medical follow up. Patients with FFR positive lesions were surprisingly younger. This may be explained because older patients tend to have more severe disease, and the incidence of intermediate lesions may be higher in younger patients. The overall incidence of DM and SHT in our population was very high (47.8% and 50.7% respectively). In the DEFER study the incidence of DM was only 15% and SHT was 36%. In the FAME study DM and SHT were present in 25 and 63% respectively. Thus our study had a high representation of diabetics. This may reflect the larger burden of diabetics in India .However when compared to FFR negative patients, the FFR positive patients had a lower incidence and duration of DM. This is probably because patients with DM usually have multi vessel disease. Hence intermediate lesions even if present were not subjected to FFR in view of significant lesions elsewhere and directly sent for CABG. Non Diabetic patients have lesser incidence of multi vessel disease and even if they had multiple lesions they were often planned for multivessel PCI. They therefore were more often planned for FFR. Systemic hypertension was also less

prevalent in the FFR positive group but this was not statistically significant. The LV Ejection Fraction and Angina Class were all evenly matched in both the groups. Almost 85% of the patients enrolled had NYHA class II angina. Hence patients who had more severe angina Class III and Class IV probably had more than intermediate lesions not requiring FFR. Exercise ECG testing by TMT was done in 50% of the study population. It did show statistical significance between the 2 groups. However TMT tracing could not be directly inspected in every case and METS achieved was taken from the case records. Perhaps if TMT was done in all cases and if the TMT was inspected directed to check when ST segment changes started, then TMT may have been a discriminating factor. Other non-invasive evaluation for risk stratification including radionuclide studies were not done in any patient.

There was no significant difference in the 2D QCA between the 2 groups. In fact even in the FFR positive group the mean QCA was only 50.1 ± 11.9%. In our study 2D QCA did not correlate with the FFR and under assessed the stenosis even in a physiologically significant lesion. That 2D QCA is not useful has been confirmed in other studies like FAME also. Similarly the length of the lesions as assessed by 2D QCA was also not significantly different between the 2 groups. In the DEFER study however there was no difference in the reference diameter or the lesion length but significant differences in the Diameter stenosis (48 ± 9% in the FFR positive vs 52% ± 12% in the FFR negative group). A larger number in the study population may have made the trend (in Diameter Stenosis) significant in our study also.

This study confirms that physiological assessment of a lesion by non invasive methods is not practical. Even exercise treadmill test was not able to discriminate between the 2 groups. Angiographic assessment of a lesion is limited because it is a 2

dimensional depiction of a 3 dimensional – structure. It is also a lumenogram and in diffuse lesions may never have a normal segment for comparision. Some studies have shown that 3D QCA may be slightly more effective than 2D QCA in identifying significant lesions.

LIMITATION

Limitations

This was a single centre study. However this is a large tertiary care centre which caters to different all kinds of patient population. Another limitation was the small number of patients (62 patients/69 lesions) and that no randomisation was done. But all consecutive patients were included and this would remove any bias in the inclusion or exclusion criteria. TMT was not available in all patients. This was because many patients had other co morbid illness like osteoarthritis which precluded TMT in these patients.

CONCLUSION

Conclusion

FFR as a tool is underutilised in our centre. Majority of patients with intermediate lesions have physiologically insignificant stenosis. Clinical features, risk factors and non invasive tools like exercise ECG do not help in predicting the functional significance of a single lesion. 2D QCA (diameter stenosis) is not useful in identifying functionally significant stenosis. 2D QCA significantly underestimates the severity of the lesion. Similarly length of the lesion also cannot be used to determine if it if functionally significant. In case of intermediate lesions, a smaller reference vessel diameter may be predictive of a functionally significant lesion. Larger randomised trials which specifically compare the relation of 2D QCA, TMT and FFR may be done to further clarify the issue.

BIBLIOGRAPHY

1. Wijns W, De Bruyne B, Vanhoenacker PK. What does the clinical cardiologist need from noninvasive cardiac imaging: is it time to adjust practices to meet evolving demands? J Nucl Cardiol 2007;14:366 –70
2. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
3. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007;49:2105–11
4. Arnett EN, Isner JM, Redwood DR, et al. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and nec-ropsy findings. Ann Intern Med 1979;91:350 – 6
5. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. Circulation 1976;53:627–32
6. Kleiman NS, Rodriguez AR, Raizner AE. Interobserver variability in grading of coronary arterial narrowings using the American College of Cardiology/American Heart Association grading criteria. Am J Car-diol 1992;69:413–5.
7. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993;87:1354 – 67
8. De Bruyne B, Baudhuin T, Melin JA, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation 1994;89:1013–22.
9. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
10. Ntalianis A, Trana C, Muller O, et al. Effective radiation dose, time, and contrast medium to measure fractional flow reserve. J Am Coll Cardiol Intv 2010;3:821–7.
11. R. Erbel, J. Ge, A. Bockisch et al. Value of intracoronary ultrasound and Doppler in the differentiation of angiographically normal coronary arteries: a prospective study in patients with angina pectoris Eur Heart J, 17 (1996), pp. 880–889
12. A.L. McGinn, R.F. Wilson, M.T. Olivari et al. Coronary vasodilator reserve after human orthotopic cardiac transplantation Circulation, 78 (1988), pp. 1200–1209
13. K.L. Gould, R.L. Kirkeeide, M. Buchi Coronary flow reserve as a physiologic measure of stenosis severity J Am Coll Cardiol, 15 (1990), pp. 459–474
14. B. De Bruyne, T. Baudhuin, J.A. Melin et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography
15. N.H. Pijls, J.A. van Son, R.L. Kirkeeide et al. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty
16. B. de Bruyne, J. Bartunek, S.U. Sys et al. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of

coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve Circulation, 94 (1996), pp. 1842–1849
17. P. Legalery, M.F. Seronde, N. Meneveau et al. Measuring pressure-derived fractional flow reserve through four French diagnostic catheters Am J Cardiol, 91 (2003), pp. 1075–1078
18. B. De Bruyne, N.H. Pijls, E. Barbato et al. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. Circulation, 107 (2003), pp. 1877–1883
19. R.J. McGeoch, K.G. Oldroyd Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology Catheter Cardiovasc Interv, 71 (2008), pp. 198–204
20. W.A. Parham, A. Bouhasin, J.P. Ciaramita et al. Coronary hyperemic dose responses of intracoronary sodium nitroprusside Circulation, 109 (2004), pp. 1236–1243
21. W. Wijns, B. De Bruyne, P.K. Vanhoenacker What does the clinical cardiologist need from noninvasive cardiac imaging: is it time to adjust practices to meet evolving demands? J Nucl Cardiol, 14 (2007), pp. 366–370
22. N.H. Pijls, B. De Bruyne, K. Peels et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses N Engl J Med, 334 (1996), pp. 1703–1708
23. .H. Pijls, P. van Schaardenburgh, G. Manoharan et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study J Am Coll Cardiol, 49 (2007), pp. 2105–2111
24. B. De Bruyne, J. Sarma Fractional flow reserve: a review: invasive imaging Heart, 94 (2008), pp. 949–959
25. M. Ragosta, A.H. Bishop, L.C. Lipson et al. Comparison between angiography and fractional flow reserve versus single-photon emission computed tomographic myocardial perfusion imaging for determining lesion significance in patients with multivessel coronary disease Am J Cardiol, 99 (2007), pp. 896–902
26. M. Lindstaedt, M. Spiecker, C. Perings et al.How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? Int J Cardiol, 120 (2007), pp. 254–261
27. M. Hamilos, O. Muller, T. Cuisset et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis Circulation, 120 (2009), pp. 1505–1512
28. G.J. Bech, H. Droste, N.H. Pijls et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease Heart, 86 (2001), pp. 547–552
29. R.S. Lima, D.D. Watson, A.R. Goode et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease J Am Coll Cardiol, 42 (2003), pp. 64–70
30. W.F. Fearon, P.A. Tonino, B. De Bruyne et al. Rationale and design of the fractional flow reserve versus angiography for multivessel evaluation (FAME) study Am Heart J, 154 (2007), pp. 632–636
31. P.A. Tonino, B. De Bruyne, N.H. Pijls et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention N Engl J Med, 360 (2009), pp. 213–224
32. B. De Bruyne, N.H. Pijls, J. Bartunek et al. Fractional flow reserve in patients with prior myocardial infarction Circulation, 104 (2001), pp. 157–162

33. K.M. Marques, P. Knaapen, R. Boellaard et al. Microvascular function in viable myocardium after chronic infarction does not influence fractional flow reserve measurements J Nucl Med, 48 (2007), pp. 1987–1992
34. M.J. Claeys, C.J. Vrints, J. Bosmans et al. Coronary flow reserve during coronary angioplasty in patients with a recent myocardial infarction: relation to stenosis and myocardial viability J Am Coll Cardiol, 28 (1996), pp. 1712–1719
35. N.G. Uren, T. Crake, D.C. Lefroy et al. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction N Engl J Med, 331 (1994), pp. 222–227
36. K.M. Marques, P. Knaapen, R. Boellaard et al. Hyperaemic microvascular resistance is not increased in viable myocardium after chronic myocardial infarction Eur Heart J, 28 (2007), pp. 2320–2325
37. B.K. Koo, H.J. Kang, T.J. Youn et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve J Am Coll Cardiol, 46 (2005), pp. 633–637
38. B.K. Koo, K.W. Park, H.J. Kang et al. Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve Eur Heart J, 29 (2008), pp. 726–732
39. C.J. Botman, J. Schonberger, S. Koolen et al. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. Ann Thorac Surg, 83 (2007), pp. 2093–2097
40. G.W. Stone, F.G. St Goar, J.M. Hodgson et al. Analysis of the relation between stent implantation pressure and expansion. Optimal Stent Implantation (OSTI) Investigators Am J Cardiol, 83 (1999), pp. 1397–1400
41. Colombo, P. Hall, S. Nakamura et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance Circulation, 91 (1995), pp. 1676–1688
42. C.E. Hanekamp, J.J. Koolen, N.H. Pijls et al. Comparison of quantitative coronary angiography, intravascular ultrasound, and coronary pressure measurement to assess optimum stent deployment Circulation, 99 (1999), pp. 1015–1021