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Frequency of abnormal fractional flow reserve measurements among major coronary arteries☆

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ABSTRACT

Background: Fractional flow reserve(FFR) is a validated tool for evaluating functional severity and guiding the revascularization of angiographically moderate coronary artery lesions.
Objective: To study if there is a higher frequency of positive FFR measurements in the left anterior descending(LAD) versus other major coronary arteries and also evaluate the differences in the total length of the stent placed.
Methods: A retrospective cohort study including all subjects (January 2011 to December 2015) who had fractional flow reserve (FFR) measured during coronary catheterization was conducted. Coronary catheterizations with FFR at a single tertiary care center were reviewed and FFR ≤ 0.80 post adenosine was deemed positive. The differences in the baseline characteristics and the degree of stenosis were compared between the different vessel groups.
Results: Of the 758 vessels included in the analysis, the majority were LAD(51.3%) followed by right coronary artery (RCA)(22.8%), Circumflex(22.2%), Left main(2.2%), and Ramus intermedius(1.5%). 25.1% of 758 vessels were FFR positive. The proportion of positive FFR were higher among LAD versus other vessels(33.2%vs.16.5%,$p < 0.001$), while no differences were noted between RCA and circumflex($p = 0.87$) or other vessels excluding LAD($p = 0.69$). Of 175 patients who received stents, no statistical difference was noted in the median[range] total length of the stent between LAD(22[9–64]) and the other coronary arteries (18[8–42])($p = 0.19$). In patients with an FFR <0.75, we found that the stent length(median [range]) was significantly longer in LAD(28[9–42]) than the other coronary arteries(18[8–42])($p = 0.03$).
Conclusion: In our study, FFR was almost twice as likely to be positive in the LAD when compared to other major coronary arteries. Furthermore, there was a trend towards FFR positive LAD lesions needing longer stents than other coronary arteries. This data should encourage operators to evaluate moderate, long lesions in the LAD with FFR, as they have a higher probability of functional significance.

1. Introduction

Fractional flow reserve (FFR) is a well validated method to evaluate the functional significance of angiographically moderate coronary artery lesions. FFR is calculated using the ratio of mean coronary-artery pressure, distal to the coronary lesion in question, to the mean aortic pressure in the setting of maximal hyperemia [1]. An FFR value of ≤0.80 is commonly regarded as the cutoff for defining ischemia [2]. Several studies have shown that patients with stable coronary artery disease and abnormal FFR benefit from revascularization [3,4].

FFR is affected by the degree of intraluminal reduction by coronary lesions, the magnitude of hyperemic response achieved, and the size of the myocardial territory supplied by the artery being tested [5]. Several factors have been identified as confounders of FFR including age and sex [6,7]. Other factors, such as chronic kidney disease and acute coronary syndromes, have been shown to alter coronary microcirculation through neuro-hormonal mediated mechanisms and affect FFR measurements [6]. To date, there have been few studies investigating anatomic factors affecting FFR measurements. The purpose of this study is to establish if there is a higher frequency of positive FFR measurements in the LAD compared to the other major epicardial coronary arteries.

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2. Methods

This is a retrospective cohort study including all subjects (January 2011 to December 2015) from Baylor University Medical Center (BUMC) and Jack and Jane Hamilton Heart and Vascular Hospital (BHVH), Dallas, Texas, who had fractional flow reserve (FFR) measured during coronary catheterization (with/without a PCI). FFR was conducted in accordance to the 2011 joint guidelines from The American College of Cardiology Foundation / American Heart Association / Society for Cardiovascular Angiography and Interventions (ACCF/AHA/*SCAI*) and current expert consensus [2,8]. Hyperemia was achieved using intracoronary adenosine in all but one case reviewed, with doses ranging from 30 to 140 μg. Each individual vessel was considered as a unique record for the data analysis. Data were obtained from the Baylor patients captured for the American College of Cardiology Cath PCI registry. Information on demographics, comorbidities, procedural details and FFR values were collected. We manually validated the position of the stent in relation to the FFR measurement for all the records included in this analysis. The FFR instances were grouped by primary coronary artery. Secondary coronary arteries (i.e. diagonals, obtuse marginal, posterior descending and postero-lateral branches) were included in their associated primary coronary artery. FFR of 0.80 or less (≤0.8) before or after administration was deemed a positive test result.

This study was approved by the Baylor Health Care System institutional review board with a waiver of consent.

2.1. Statistical analysis

Analyses were done using STATA 14.2. Categorical variables were presented as proportions and continuous variables as mean (SD) or median (range) where applicable. Differences in demographics, baseline characteristics were compared using Chi-square/Fischer exact tests for proportions and Kruskal-Wallis/One-way ANOVA for continuous variables as appropriate. Including those FFR positive patients with a stent, we further investigated if the length/diameter of the stents differed between the vessels. A *p*-value of <0.05 was deemed to be statistically significant.

3. Results

During the time period reviewed at our institution, there were a total of 14,892 angiograms performed and 6552 PCIs. The proportions of FFRs performed per PCI during the time period was 5.23%. There were a total of 618 instances with FFR measured during this study period. Of these 618 instances 480 had single vessel FFR, 113 had FFR on 2 vessels and 25 had FFR on 3 vessels, for a total of 780 vessels that were identified for analysis. Those with FFR performed on bypass grafts ($n = 20$) and incomplete details (n = 2) were then excluded. Of the 758 vessels included in the analysis, the majority were LAD (51.3%), followed by RCA (22.8%), Circumflex (22.2%), Left main (2.2%), and Ramus intermedius (1.5%). The baseline characteristics and demographics were similar between the various vessel groups. The median degree (%) of stenosis varied between the various vessel groups (Table 1). 25.1% of the 758 vessels were found to have a FFR ≤0.8 (Table 2). The proportion of significant FFR (≤0.8) was found to be higher among LAD lesions when compared with other vessels ($p < 0.001$), while no difference was noted when RCA was compared with circumflex ($p = 0.87$) or with other vessels excluding LAD ($p = 0.69$) (Fig. 1). Among FFR positive vessels, the median (range) degree of stenosis was 75 (10–90) in LAD compared to 80 (50–90) in the other vessels ($p = 0.001$). All of the vessels with a significant FFR were stented but for 15 patients. 6 of these patients were referred for CABG, 4 were medically treated, and we were not able to access the record of 5 patients. Of the 175 vessels that were stented, no statistical difference was noted in the median [range] total length of the stent between LAD (22 [9–64]) and the other coronary arteries (18[8–42]) ($p = 0.19$). In patients with an FFR <0.75, we found that the stent length (median [range]) was significantly longer in LAD (28[9–42]) than the other coronary arteries (18[8–42]) ($p = 0.03$) (Table 3). There was not a statistical difference in stent diameter when comparing LAD (3[2.25–4.0]) to all other

Table 1
Baseline characteristics and demographics.

	Arteries					p-Value
	Left main ($n = 17$)	LAD ($n = 389$)	Circumflex ($n = 168$)	Ramus intermedius ($n = 11$)	RCA ($n = 173$)	
Mean age ± SD (years)	63.9 ± 9.7	65.6 ± 10.1	64.3 ± 10.2	67.3 ± 7.9	63.8 ± 10.0	0.26
Gender						0.97
Female	5 (29.4%)	137 (35.2%)	59 (35.1%)	3 (27.3%)	59 (35.1%)	
Male	12 (70.6%)	252 (64.8%)	109 (64.9%)	8 (72.7%)	114 (65.9%)	
Diabetes mellitus	9 (52.9%)	143 (36.8%)	67 (39.9%)	5 (45.5%)	68 (39.3%)	0.66
Hypertension	15 (88.2%)	283 (72.8%)	133 (79.2%)	11 (100%)	120 (69.4%)	0.04
Hyperlipidemia	11 (64.7%)	137 (35.2%)	75 (44.6%)	7 (63.6%)	62 (35.8%)	0.01
Cerebrovascular accident	0	17 (4.4%)	11 (6.6%)	0	7 (4.1%)	0.57
Peripheral vascular disease	0	18 (4.6%)	15 (8.9%)	1 (9.1%)	7 (4.1%)	0.17
Chronic lung disease	0	21 (5.4%)	8 (4.8%)	1 (9.1%)	7 (4.1%)	0.74
Heart failure	2 (11.8%)	42 (10.7%)	20 (11.9%)	0	13 (7.5%)	0.55
Smoker						0.86
Never	15 (88.2%)	341 (87.7%)	144 (85.7%)	10 (90.9%)	152 (87.9%)	Ref
Yes	1 (5.9%)	34 (8.7%)	15 (8.9%)	0	15 (8.7%)	0.99
Quit	1 (5.9%)	14 (3.6%)	9 (5.4%)	1 (9.1%)	6 (3.5%)	0.48
Mean BSA ± SD (m^2)	2.1 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.2	0.59
Median BMI (range) (kg/m^2)	31.3 (24.1–47.7)	29.6 (9.5–72.1)	30.7 (15.7–48.8)	25.9 (20.5–41.7)	30 (17.4–59.9)	0.2
Median heart rate (range) (bpm)	73 (50–94)	66 (18–119)	67 (42–100)	60 (50–89)	65 (46–109)	0.33
Median systolic BP (range) (mm Hg)	133 (104–226)	133 (86–219)	134.5 (87–208)	140 (113–195)	135 (86–215)	0.88
Median diastolic BP (range) (mmHg)	77 (50–102)	76 (38–119)	75 (38–113)	76 (63–95)	76 (54–124)	0.89
Ejection fraction%						
≤40	2 (13.3%)	54 (15.3%)	25 (16.8%)	0	17 (11.5%)	Ref
41–50	2 (13.3%)	65 (18.8%)	28 (18.8%)	3 (33.3%)	30 (20.3%)	0.49
>50	11 (73.4%)	228 (65.9%)	96 (64.4%)	6 (66.7%)	101 (68.2%)	0.62
eGFR ≥ 60	12 (70.6%)	252 (66.7%)	110 (66.7%)	10 (90.9%)	114 (67.5%)	0.59
Median degree of stenosis (%) (range)	50 (20–80)	60 (10–90)	50 (10–90)	70 (50–90)	60(10–99)	0.0001
Family history of CAD	4 (28.6%)	122 (34.6%)	55 (35.3%)	1 (10%)	43 (27.9%)	0.29
Prior coronary intervention	3 (17.7%)	121 (31.1%)	63 (37.5%)	5 (45.5%)	58 (33.5%)	0.32
Prior coronary artery bypass	4 (30.8%)	18 (6.2%)	15 (11.5%)	0	15 (12.3%)	0.01

BSA: Body surface area; BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; * the percentages presented are column percentages.

Table 2
FFR measurements by Vessels.

Artery	FFR		p-Value
	Negative (>0.8)	Positive (≤0.8)	<0.001
Left main	16 (94.1%)	1 (5.9%)	
Left anterior descending	260 (66.8%)	129 (33.2%)	
Circumflex	140 (83.3%)	28 (16.7%)	
Ramus intermedius	9 (81.8%)	2 (18.2%)	
Right coronary artery	143 (82.7%)	30 (17.3%)	

*Percentages presented in this table are row percentages.

Table 3
Stent measurements by vessels.

	Other arteries ($n = 60$)	LAD ($n = 115$)	p-value
Median stent length (mm) (range)	18 (8–42)	22 (9–64)	0.19
Median stent diameter (mm) (range)	3.00 (2.25–4.00)	3.00 (2.25–4.00)	0.7
	Other Arteries except LAD ($n = 30$)	RCA($n = 30$)	p-value
Median stent length (mm) (range)	18 (8–33)	18 (12–42)	0.78
Median stent diameter (mm) (range)	2.63 (2.25–3.50)	3.00 (2.25–4.00)	0.002
	LAD (n = 115)	RCA(n = 30)	p-value
Median stent length (mm) (range)	22 (9–64)	18 (12–42)	0.44
Median stent diameter (mm) (range)	3.00 (2.25–4.00)	3.00 (2.25–4.00)	0.06

LAD: Left anterior descending; RCA: Right coronary artery.

coronary arteries (3[2.25–4.0]) ($p = 0.7$) or when comparing the LAD stent diameter (3[2.25–4.0]) to the RCA stent diameter (3[2.25–4.0]) ($p = 0.06$) (Table 3). We conducted a sensitivity analysis including only the main arteries (excluding side branches and surrogates). A total of 671 vessels were included in this analysis; the results were similar to the findings from the main analysis except that the median stent diameter of the LAD group (3[2.25–4.00]) was statistically different from that of RCA (3[2.25–4.00]) ($p = 0.02$).

4. Discussion

In 758 vessels reviewed, we found that a positive FFR result (≤0.80) was statistically more significant in the LAD when compared to the other major coronary vessels (33.2% vs 16.5%, $p < 0.001$), while no difference was noted when RCA was compared with circumflex ($p = 0.87$) or with other vessels excluding LAD ($p = 0.69$). While there have been earlier studies evaluating the relationship between FFR and major coronary arteries, our study has a larger sample and represents a more even distribution of lesions among the epicardial coronary arteries compared to most of the previously published studies. Leone et al. evaluated the relationship between the FFR value and the amount of myocardium subtended to an intermediate lesion on FFR [9]. FFR was inversely correlated with the amount of "jeopardized myocardium" based on three different validated scores. However, in that study 72% of lesions were LAD, and only 9% and 19% of lesions were in the RCA and LCx respectively. Furthermore, at baseline 18% of the patients had prior PCI and 18% had CTOs which may confound the results. Others have reported that majority of LAD lesions were found to be FFR positive (≤0.8), however, they did not specifically compare incidence of the epicardial arteries between each other [10–12]. One large, multicenter study showed a higher incidence of positive FFR in the LAD, however, in this study 76.1% of lesions studied were angiographically >75% which questions whether they were truly intermediate or not [13].

Harle et al. compared the mean FFR and instantaneous wave-free ratio (iFR) among the combined anterior and posterior coronary territories. This smaller study included 220 vessels for comparison and found a statistically significant higher mean FFR measurements in the posterior circulation compared to the anterior circulation. Furthermore, there was no difference seen between FFR and iFR, or among baseline clinical characteristics or stenosis severity [14]. While this study compared mean FFR values, it did not directly compare the incidence of positive FFR measurements which likely has higher clinical significance for operators. A more recent study demonstrated a greater discordance between FFR and iFR in the LM and proximal LAD lesions compared to other epicardial arteries [15].

In our study the median length of FFR positive lesions in the LAD was longer when compared to the median length of lesions in other major coronary arteries (22 vs 18 $p < 0.19$), however, this missed statistical significance. However, in the subset analysis of patients with lesions with FFR </= 0.75 there was a statistically significant difference of median stent lengths when the LAD was compared to the other coronary arteries (28 vs 19, $p = 0.03$) than the other coronary arteries. This evidence may be one anatomic factor why angiographically intermediate LAD lesions were more likely to be FFR positive, given that they were frequently longer, tubular lesions. Furthermore, there was not a statistical difference in stent diameter when comparing LAD to all other coronary arteries or when comparing the LAD stent diameter to the RCA stent diameter.

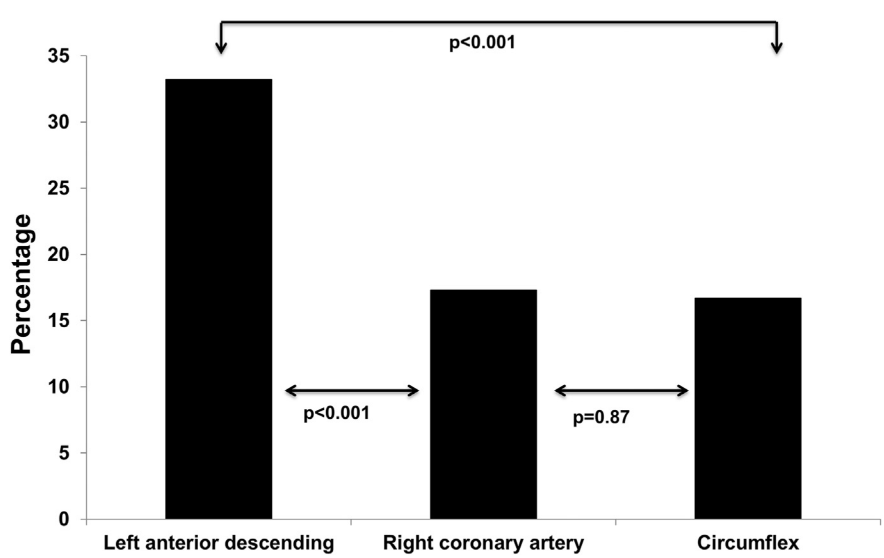

Fig. 1. Frequency of positive fractional flow measurements (FFR ≤ 0.80) in major coronary arteries.

Several mechanisms affecting coronary flow hemodynamics have been proposed and investigated which may add evidence to support our findings. Harle et al. found statistical differences in intracoronary hydrostatic pressure due to coronary tree height differences in the setting of supine positioning for coronary angiography. In this study, the LAD and the RPDA had the highest height differences and correlated to higher hydrostatic pressures [16]. Furthermore, intracoronary flow has been found to correlate to the size of myocardial area being perfused. Leone et al. found that FFR was inversely proportional to the myocardial jeopardy index (MJI), a system used to estimate the amount cardiac mass affected by a stenotic lesion, and that MJI was the strongest predictor of FFR [10]. In another study including 296 coronary lesions, Shiono et al. have reported that the length of the lesion, lumen diameter and myocardial supply distal to the stenosis were independent predictors of a positive FFR [17].

According to Poiseuille's Law, change in fluid pressure along a tube is proportional to length of the tube and inversely proportional to the radius of the tube. Therefore, epicardial length and radius will affect flow and change in pressure. Lesion length and total atherosclerotic burden may also confound fractional flow reserve measurements [18]. The average length of the LAD was previously reported to be 10–13 cm; whereas, the non-dominant LCx was 6–8 cm in length. The typical dominant RCA was 12–14 cm prior to bifurcation of PDA and PLB. The mean luminal diameters were as follows: LM- 4.0 cm, LAD- 3.6 cm, LCx- 3.0 cm, RCA- 3.2 cm [19]. Differences in coronary length and diameter may represent another physiologic mechanism contributing to the difference in FFR positive measurements that we observed.

By a detailed and systematic search of our database, we obtained a complete cohort of subjects with FFR measurements for this study. However, some bias may have been induced due to certain covariates not captured in the registry. Further, this study included only two centers with similar clinical practice guidelines. Secondary coronary arteries (i.e. diagonals, obtuse marginal, posterior descending and postero-lateral branches) were included in their associated primary coronary artery for analysis. While this was a small number of the total cases it could be a source of bias. Additionally, there was not a set protocol for administering adenosine. While the guidelines at the time were followed for conducting FFR, the dose and route of adenosine were operator dependent, and therefore, the true hyperemic response may have been variable. Further, we were not able to perform subgroup analysis based on the lesion location within the artery (1.e ostial, proximal, middle and distal). Similarly, pre-treatment with intracoronary nitroglycerin was completed in most cases, however, the dose was variable according to operator preference and hemodynamic status of the patient.

In summary, our data shows a clear increased incidence of positive FFR measurements in the LAD compared to other major coronary arteries. Our view of the data presented here is not meant to deter operators from using FFR according to the guidelines to evaluate intermediate lesions in other coronary arteries. These data should encourage operators that moderate, long lesions in the LAD should be evaluated with FFR, due to the higher probability of being functionally significant.

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