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The impact of the extent and severity of coronary artery disease on fractional flow reserve measurements

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Abstract. – OBJECTIVE: Coronary angiography has a limitation to determine the severity of intermediate stenosis (30-70%)[1,2]. Fractional flow reserve (FFR) is a method for the assessment of the intermediate stenosis severity[3]. The effect of coronary artery disease (CAD) severity on the FFR results is not clear. In this study, we aimed to expose the effect of CAD severity calculated with Syntax and Gensini scores on FFR results.

PATIENTS AND METHODS: We scanned patients data (n=378) who had undergone fractional flow reserve measurements in our center. Patients with acute coronary syndrome in the last month, moderate or severe valvular diseases, acute heart failure, serious bradycardia, atrial fibrillation/flutter, severe left ventricular hypertrophy or patient with deficient data were excluded. 351 patients were included in the study. Syntax and Gensini scores were calculated and compared with FFR results. Hemodynamically significant result for FFR, ratio <0.80 was accepted.

RESULTS: The negative correlation between high Gensini, high Syntax scores and FFR results was statistically significant. Especially patients with Syntax scores >22 had notable more crucial lesions in FFR measurements (p<0.001). Cardiovascular disease risk factors such as age, gender, hypertension, diabetes mellitus and dyslipidemia did not correlate with the FFR results. Patients with intermediate stenosis (30-70%) and high Gensini and high Syntax scores were found to have more hemodynamically significant on FFR measurements (FFR <0.80).

CONCLUSIONS: Intermediate lesions with high Syntax score should be evaluated by hemodynamic procedures and treated more carefully with optimal medical treatment or revascularization. Revascularization method of CAD with high Syntax score should be decided with hemodynamic procedures as FFR measurements.

Key Words
Fractional flow reserve, Syntax score, Gensini score.

Introduction

Coronary angiography is accepted the gold standard for the diagnosis of coronary artery disease, but it has a limitation in evaluating the functional significance of intermediate coronary stenosis (30-70% stenosis)[1-4]. This limitation can cause an unnecessary myocardial revascularization[5,6].

Some intracoronary hemodynamical measurements can be used to assess functional severity of coronary stenosis. These are fractional flow reserve (FFR) and coronary flow velocity reserve (CFR). FFR is a lesion-specific invasive procedure to determine the functional significance of the stenosis[7]. FFR measurement is recommended to evaluate the hemodynamic significance of coronary stenosis at the last guidelines about coronary artery disease[8]. Bishop and Samady[2] have shown that the lesion severity itself is not the major and independent determinant for FFR measurements. In their review; FFR results could be affected by the presence of atherosclerosis, small vessel disease and left ventricular hypertrophy. Sahinarslan et al[9] found that overall extent and severity of coronary artery disease in a patient may affect the FFR measurement and may lead to misinterpretation of the lesion severity. The maximal hyperemic response is necessary for successful FFR measurements and maximal hyperemic response depends on the endothelial function of microvascular structure[10,11]. Atherosclerosis is a systemic disease, and there is a strong relationship between atherosclerosis and endothelial dysfunction[12-14]. Endothelial dysfunction caused by atherosclerotic coronary artery disease may affect FFR measurements.

Gensini score and Syntax score are used to determine the extent and severity of coronary artery disease[15,16]. Gensini score is older scoring system

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than Syntax score for the extent and severity of coronary artery disease. Syntax score also has a strong predictive value about outcomes after revascularization.

In this study, we aimed to investigate the possible effect of the extent and severity of coronary artery disease on FFR ratio results.

Patients and Methods

Study population

We retrospectively reviewed 378 patients who had undergone Fractional Flow Reserve measurement at our clinic. Twenty-seven patients were excluded from the study. Patients with acute coronary syndrome in the last month, moderate or severe valvular diseases, coronary revascularization performed at the left anterior descending artery (LAD), acute heart failure, serious bradycardia, atrial fibrillation/flutter, severe left ventricular hypertrophy or patient with deficient files were excluded. Three hundred fifty-one patients with an intermediate stenosis at proximal LAD who had undergone FFR procedure were eligible. All subjects provided written informed consent before FFR procedure and the protocol was approved by the local Ethics Committee.

Patients' clinical and demographic characteristics, encompassing age, gender, history of arterial hypertension, diabetes mellitus, current smoking status, family history of coronary artery disease, history of myocardial infarction and medications used, were noted. In addition, serum levels of fasting blood glucose, creatinine, hematocrit and lipid panel, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels, were also recorded.

The extent and severity of coronary artery disease were evaluated with Gensini score and Syntax score. All coronary angiographies were evaluated with *Qangio xa software v7.2* (Medis Medical Imaging Systems, Leiden The Netherlands) for the length and stenosis ratio of the coronary lesions. With this software, we minimized the inter and intra-observer variability. Gensini score grades the stenosis in the epicardial coronary arteries as 1 for 1-25% stenosis, 2 for 26-50% stenosis, 4 for 51-75% stenosis, 8 for 76-90% stenosis, 16 for 91-99% stenosis, and 32 for total occlusion; then, these numbers are multiplied by a constant number determined according to the anatomical localization of the stenosis. The Syntax scores of these patients were calculated by two interventional cardiologists from initial coronary angiographies. All coronary lesions were scored with using the Syntax Score algorithm, which is available on the website (www.syntaxscore.com). SYNTAX scores >22 was accepted as an extend and severe coronary artery disease.

FFR Measurement

A 6-to-8 French guiding catheter without side hole was used for FFR measurement. All patients were anticoagulated with an intra-arterial unfractionated heparin (at least 5,000 U). A 0.014-inch pressure monitoring guidewire (PrimeWire, Volcano, Sa Diego, CA, USA) was calibrated and advanced through the coronary artery until positioning distally to the stenosis. An intermediate proximal LAD stenosis, followed by non-significant narrowing in the case of a diffuse disease may have a FFR >0.80 when the tip of the wire is placed just beyond the lesion, while measurement at distal LAD may be <0.80. Because of that, the position of the pressure wire was in the distal LAD with all measurements. An intracoronary injection of 200 µg nitroglycerin was administered to prevent vasospasm. Baseline distal coronary pressure was recorded then intracoronary adenosine (60 to 300 µg) was given to induce maximum hyperemia. When the lowest pressure was obtained, the FFR measurement was recorded. If the first measurement was not hemodynamically significant, the recording was repeated two times with an increased dose of adenosine (over 300 µg adenosine) for receiving to hyperemia. FFR ratio was calculated as the ratio of the mean distal intracoronary pressure to the mean aortic pressure at the time of maximum hyperemia and automatically generated by the software of the pressure monitoring system. FFR value < 0.80 was accepted hemodynamically significant. We divided the patients into two groups according to this accepted ratio. Group I included 227 patients with FFR ratio of ≥ 0.80 and Group II included 124 patients with FFR ratio of < 0.80.

Statistical Analysis

Analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were defined as percentages (%). To test the distribution pattern, the Kolmogorov-Smirnov test was used. The study population was assigned into two groups on the basis of post-procedural FFR results. Continuous variables of normally disturbed variables were analyzed with an independent *t*-test, and continuous variables of non-normally disturbed variables were analyzed with Mann-Whitney U-test. Categorical variables were summarized as percentages and compared using chi-square tests. Spearman's correlation coefficient was computed to examine the association between 2 continuous variables. Effects of different variables on FFR results were calculated in univariate analysis for each. A *p-value* <0.05 was considered statistically significant.

Results

The baseline clinical and pre-procedural characteristics of the study population are summarized in Table I. A total of 351 patients (mean age 61.80 ± 9.65 years, 69.8% men) were grouped into two groups according to FFR results. Group I included 227 patients with FFR ratio of ≥ 0.80 and Group II included 124 patients with FFR ratio of <0.80. There were no significant differences regarding age, gender, lipid panels, fasting glucose levels, creatinine levels, hematocrit percentiles,

Table I.

	FFR result is insignificant (n=227)	FFR result is significant (n=124)	*p*-value
Age	61.56+10.01	62.20+9.05	0.550
Gender			
Men	155 (67.8%)	90 (73.2%)	0.470
Women	73 (32.2%)	33 (26.8%)	
Hypertension (HT)			
With HT	77 (33.9%)	47 (38.2%)	0.551
Without HT	151 (66.1%)	76 (61.8%)	
Diabetes Mellitus (DM)			
With DM	143 (63.0%)	74 (60.2%)	0.338
Without DM	85 (37.0%)	49 (39.8%)	
Smoking			
With smoking	123 (54.2%)	63 (51.8%)	0.494
Without smoking	105 (45.8%)	60 (48.2%)	
Family History (FHx) of CAD			
With FHx	119 (52.4%)	59 (48.0%)	0.435
Without FHx	109 (47.6%)	64 (52.0%)	
History of MI			
With Hx	194 (85.0%)	102 (82.9%)	0.798
Without Hx	34 (15.0%)	21 (17.1%)	
Adenosine	180.57+41.10	129.68+56.14	<0.001
FFR ratio	0.86+0.04	0.74+0.04	<0.001
SYNTAX score	15.29+6.75	23.80+9.64	<0.001
GENSINI score	25.15+18.66	41.89+24.89	<0.001
Glucose	123.93+49.24	133.24+67.84	0.142
Creatinine	1.01+0.84	0.91+0.23	0.164
Total Cholesterol	191.98+48.60	185.19+49.70	0.216
LDL	115.15+40.18	113.36+14.36	0.693
HDL	43.56+12.31	41.46+12.48	0.130
Triglyceride	164.59+115.68	152.23+81.15	0.293
Htc	42.30+4.56	41.47+6.01	0.452
Preprocedural medical treatment			
ASA	104	63	0.371
Clopidogrel	8	5	0.810
ACE-I/ARB	142	83	0.414
CCB	95	61	0.186
Betablockers	30	18	0.735
Diuretics	12	5	0.601

diabetes mellitus, hypertension, current smoking, and history of myocardial infarction between the groups (Table I). Also, there were no significant differences about preprocedural medical treatment including usage of acetylsalicylic acid, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, calcium channel blockers and diuretics (Table I). Group I had higher mean adenosine dosage than Group II (180.5±41.10 and 129.68±56.14, $p < 0.001$).

We found lower FFR ratio in patients with higher Gensini Score and higher Syntax scores (Table I). FFR ratio <0.80 is more regular in patients with Syntax score >22 than patients with Syntax score ≤22. With the univariate regression analysis, we found that age, gender, lipid panels, fasting glucose levels, creatinine levels, hematocrit percentiles, diabetes mellitus, hypertension, current smoking, and history of myocardial infarction had no effect on FFR results (Table II). These findings support the hypothesis deduced from the FFR measurement. Conversely, when we tried to evaluate the impact of extent and severity of CAD on FFR results, we found that higher Syntax score and Gensini score were associated with hemodynamically significant stenosis on FFR results in regression analysis (*p-value* <0.001) (Table III).

Discussion

We showed that FFR results of intermediate coronary stenosis can be affected by the severity and extent of the lesions which calculated Syntax Score and Gensini Score. We found a statistically significant difference in FFR results between patients had severe CAD and did not have severe CAD.

Coronary angiography is the gold standard method for the diagnosis of coronary artery disease[17]. In contrast, the hemodynamically significance of the coronary stenosis may not be determined with conventional coronary angiography, especially for the intermediate stenosis (30-70%)[3,7,11,18]. Fractional Flow Reserve measurements are the gold standard method to determine the significance of the stenosis[8]. FFR is the ratio of distal coronary artery pressure to the aortic pressure during maximum vasodilatation. This procedure accepts the microvascular resistance homogeneous at maximum hyperemia. However, this situation is not valid for every patient. The distal coronary pressure can be affected by both epicardial and microvascular resistance. Higher microvascular resistance is associated with higher FFR; lower microvascular resistance is associated with lower FFR[19,20]. Endothelial dysfunction affects microvascular resistance[20]. Hypertension, diabetes mellitus, dyslipidemia, smoking and age are the risk factors for the endothelial dysfunction and atherosclerosis[10]. Atherosclerosis systemic inflammatory disease affects endothelial function. Atherosclerosis may affect microvascular resistance, may affect measurement of distal pressure of FFR procedure so extent and severe coronary artery disease may affect FFR results. Bishop and Samady[2] have shown that the lesion severity itself is not the major and independent determinant for FFR measurements. In their review, FFR results could be affected by the presence of atherosclerosis, small vessel disease and left ventricular hypertrophy. Sahinarslan et al[9] found that overall extent and severity of coronary artery disease in a patient may affect the FFR measurement and may lead to misinterpretation of the lesion severity.

We found lower FFR results in patients with higher Gensini Score. Also, we found higher Syntax scores associated with hemodynamically significant stenosis. FFR ratio <0.80 is more regular in patients with Syntax score >22 than patients with Syntax score ≤22. In our regression analyses, we found that age, gender, lipid panels, fasting glucose levels, creatinine levels, hematocrit percentiles, diabetes mellitus, hypertension, current smoking, and history of myocardial infarction had no effect on FFR results. These data supported via the hypothesis of FFR measurements. But we found higher Syntax

Table II. Regression analysis to provide univariate data for the predictors of presence of significant FFR results.

Variable	OR (CI %95)	*p*-value
Age	1.008 (0.985-1.031)	0.514
Gender	0.765 (0.471-1.244)	0.280
Adenosine	0.975 (0.969-0.982)	<0.001
Hypertension	0.841 (0.534-1.326)	0.456
Diabetes mellitus	1.150 (0.734-1.802)	0.541
Smoking	1.145 (0.739-1.775)	0.544
Family history of CAD	1.214 (0.783-1.882)	0.386
History of MI	1.157 (0.639-2.097)	0.630
Glucose	1.003 (1.000-1.007)	0.086
Creatinine	0.693 (0.393-1.221)	0.204
Total Cholesterol	0.997 (0.993-1.002)	0.213
LDL	0.999 (0.993-1.004)	0.681
HDL	0.985 (0.967-1.004)	0.114
Triglyceride	0.999 (0.997-1.001)	0.319
Hematocrit	0.983 (0.942-1.026)	0.431

Table III. Regression analysis of Syntax and Gensini Scores to provide univariate data for the predictors of presence of significant FFR results.

Variable	OR (CI %95)	*p*-value
Syntax Score	1.136 (1.099-1.174)	<0.001
Gensini Score	1.036 (1.024-1.048)	<0.001

score and Gensini score were associated with hemodynamically significant stenosis on FFR results in regression analysis (*p-value* <0.001) as the result of the report of Sahinarslan et al[9]. These results support our hypothesis on the study protocol and also the hypothesis of Sahinaslani et al[9].

Our study had some strong parts. In our study, all coronary angiographies were evaluated with Qangio xa software v7.2 (Medis Medical Imaging Systems, Netherlands) for the length and stenosis ratio of the coronary lesions. With using this software, we minimized the inter- and intra-observer variability for evaluation the coronary stenosis. When the first measurement was not hemodynamically significant, the recording was repeated two times with increased dose of adenosine (over 300 µg adenosine) for receiving to hyperemia. With this approach we minimized the missing of hemodynamically significant coronary lesions.

In this retrospective work, microvascular resistance was not determined directly. In some study, coronary flow reserve (CFR) and FFR are used together. Calculation of CFR would demonstrate extent and severity of microvascular dysfunction in the present study. We included only patients with FFR measurements on LAD, so FFR results on Cx and/or RCA could change point of view. Also data were collected retrospectively, lack of a constant adenosine dosage for maximum hyperemia may be a limitation of our research[21].

Conclusions

"Extent and severe coronary artery disease – atherosclerosis" may affect FFR results. When an intermediate lesion is detected on a coronary angiography (especially in multivessel disease with intermediate lessons on LAD), the hemodynamic severity of intermediate stenosis should be evaluated by FFR. Then intermediate stenosis should be treated more carefully with optimal medical treatment or revascularization[22].

Conflict of Interests

None to declare.

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