Effect of Coronary Artery Bifurcation Angle on Atherosclerotic Lesion Localization Distance to the Bifurcation Site

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Abstract

Objectives: Although percutaneous coronary interventions become a common treatment modality for coronary artery diseases, lesion localization make these procedures more complex. As the lesion localizes near to the bifurcation site, more complex PCI procedures, overqualified equipments are needed and complication risk increases. Previous studies have demonstrated the strong correlation between wide angulation and significant coronary stenosis. However, a paucity of data exists about the association between bifurcation angle and lesion localization distance. In this study we analysed the effect of coronary bifurcation angle and left main coronary artery length on the atherosclerotic lesion localization.

Methods: Patients, who underwent coronary angiography between 01.01.2017- 31.12.2019 were scanned. Patients having atherosclerotic lesions causing more than 50% luminal narrowing and Medina classification score (0,0,0) were evaluated. After exclusion, 467 patients were included. 5 bifurcation subgroups (LAD-CX, LAD-Dx, CX-OM, RCA-RV, RPD-RPL) were formed. Distance of lesion to the bifurcation site, bifurcation angle and left main coronary artery length were analysed by 2 experienced cardiologists with invasive quantitaive coronary angiography (QCA) by using "extreme angio and cardiac pacs" software system.

Results: There was a strong inverse correlation between bifurcation angle and lesion localization distance to the bifurcation site (r = −0.706; p < 0.0001). There was a nonsignificant negative correlation between Left-main coronary artery length and lesion localization. Regression analysis revealed that bifurcation angle is an independent risk factor for predicting the localization of an atheroslerotic lesion in 5 mm length from the point of bifurcation site (β = −0.074, p < 0.0001). A cut-off value of 80.5° coronary bifurcation angle was found to have 84.1% sensitivity and 81.3% specificity in prediction of atherosclerotic lesion localization in 5 mm length from the point of bifurcation site.

Conclusion: In this study we showed that as the bifurcation angle increases, atherosclerotic lesions tend to approach to the bifurcation site. Since invertentions encompassing bifurcation sites are more complex, lesions with increased angulation may need extra care as they are more likely to present with further complications. Furthermore, bifurcation angle is an independent risk factor for lesion localization.

Keywords: Bifurcation angle, Atherosclerosis, Left main coronary artery, Coronary geometry

1. Introduction

Atherosclerosis is a chronic inflammatory disease of vascular intima which has a potential effect on the vascular tree as a whole. It is characterized by the imbalance between inflammatory response and lipid metabolism [1].

Due to the common pathological pathways leading to the development of cardiovascular and cerebrovascular disorders, atherosclerosis has become the leading cause of morbidity and mortality worldwide [2,3]. With the help of growing data, we may define predisposing factors and different development phases of atherosclerosis.

However, factors associated with the localization and progression rate of atherosclerotic plaques are still poorly understood.

Shear stress, defined as the frictional force acting on vascular endothelial cells, is crucial for endothelial homeostasis under normal physiological conditions. It plays a major role in generation, progression, and destabilization of atherosclerotic plaques [4]. When the laminar blood flow distrupted especially at the bifurcation sites of the vascular tree, an atheroprone milliue is generated. For this reason, the effect of vascular geometry on localization site and the progression of atherosclerotic plaques is a challenging issue. Since the first study of Caro et al [5], a substantial number of studies have been conducted to elucidate the relationship between vascular geometry and atherosclerosis. In a review study, Chiu and Chien demonstrated that most of the atherosclerotic plaques form close to the bifurcation sites of the vessels [6].

One of the major limitations of percutaneous coronary interventions (PCI) is the localization of the culprit lesions. As the coronary lesion localizes near to the bifurcation sites, more complex PCI procedures, overqualified equipment are needed, and complication risk increases. Therefore, detection of predictive factors for atherosclerotic coronary lesions localized near to the bifurcation sites becomes essential. In this study, we investigated the effect of bifurcation angle on coronary atherosclerotic lesion localization and distance of the culprit lesion from the bifurcation site.

2. Material and methods

2.1. Study design and population

In this retrospective study, subjects were selected from the 5641 patients who underwent coronary angiography between 01.01.2017-31.12.2019. Patients having Medina class (0,0,0) atherosclerotic lesions causing more than 50% luminal narrowing were scanned. Patients who had; acute coronary syndrome, normal coronary arteries, LMCA lesion, osteal left anterior descending (LAD) coronary artery lesion, osteal circumflex (CX) coronary artery lesion, atherosclerotic lesions other than Medina class (0,0,0), any kind of coronary artery arising anomalies, critical atherosclerotic lesions proximal to the investigated bifurcation sites, inadequate visualization for bifurcation angle were excluded. After exclusion 467 patients (242 male and 225 female) were included.

Abbreviation List	
PCI	Percutaneous coronary interventions
LMCA	Left main coronary artery
LAD	Left anterior descending
CX	Circumflex
PA	posteroanterior
RAO	Right anterior oblique
RPL	Right posterolateral
RPD	Right posterior descending
LAO	Left anterior oblique
ROC	Receiver operator curve
SE	Standard error

2.2. Study protocol

Detailed medical histories, clinical-demographic features and biochemical data of the included patients were recorded from patient files. Subsequently, bifurcation type, the distance of lesion to the bifurcation site, bifurcation angle, and LMCA length of included patients were measured by 2 experienced cardiologists.

2.3. Coronary angiographic evaluation

The coronary angiographies were performed and interpreted by interventional cardiologists who had more than ten years of working experience. Angiographic data were analyzed by 2 experienced cardiologists. 4 bifurcation subgroups (LAD-CX, LAD-Dx, CX-OM, RPD-RPL) were defined. LAD-CX bifurcation angle and LMCA length were measured at left anterior oblique (LAO)-50° projection with 30° caudal angulation, LAD-Dx bifurcation angle was measured at postero-anterior (PA) projection with 40° cranial angulation, CX-OM bifurcation angle was measured at right anterior oblique (RAO)-30° projection with 20° caudal angulation, right posterolateral (RPL)- right posterior descending (RPD) bifurcation angle was measured at LAO projection with invasive quantitaive coronary angiography (QCA) by using "extreme angio and cardiac pacs" software system (Beytepe-Ankara, Turkey) (Fig. 1). A mean of 3 consecutive measurements was taken. Results were expressed in millimeters. Approval of the study was obtained from the local ethics committee (Konya Education and Research Hospital Konya/Turkey-TUEK 48929119/774).

3. Statistical analysis

Statistical analyses were conducted with a commercially available software package (SPSS version 16.0, SPSS, Chicago, IL). In this study, data
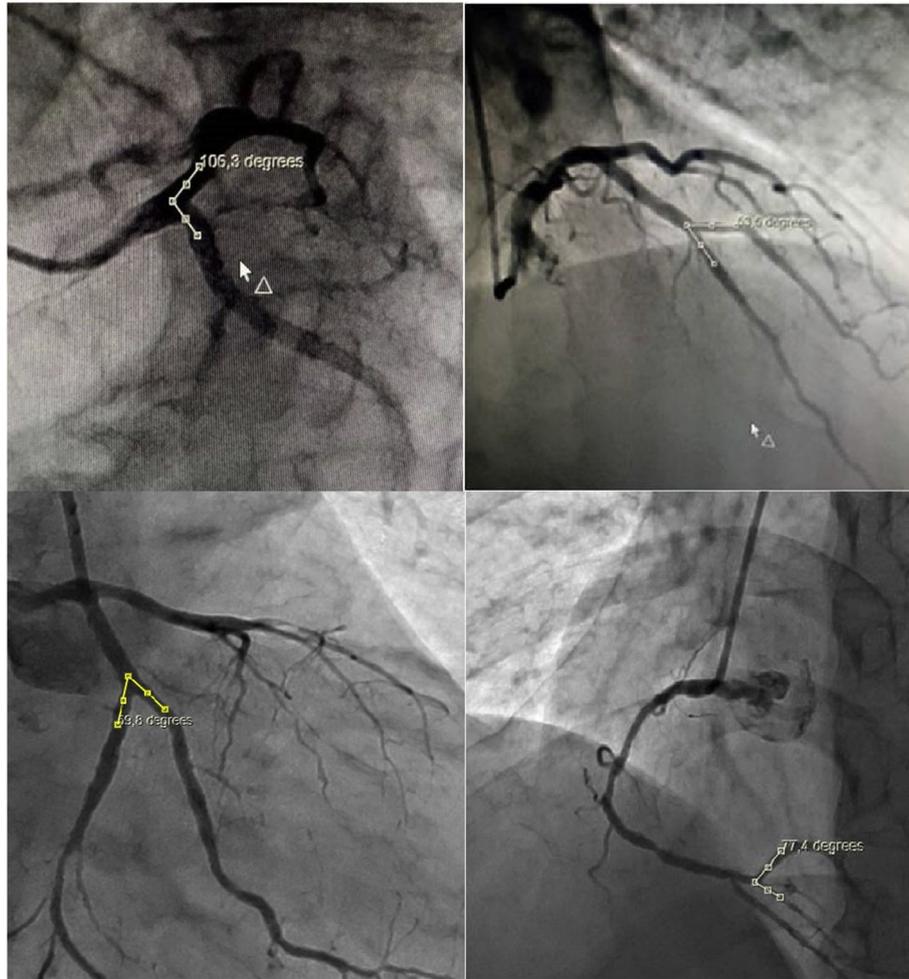
Fig. 1. Showing the measurement of bifurcation angles. Upper-left: Measurement of LAD-CX bifurcation at left anterior oblique-50° projection with 30° caudal angulation, Upper-right: Measurement of LAD-Dx bifurcation angle at postero-anterior PA projection with 40° cranial angulation, Lower-left: Measurement of CX-OM bifurcation angle at right anterior oblique-30° projection with 20° caudal angulation. Lower-right: Measurement of right posterolateral-right posterior descending bifurcation angle at left anterior oblique projection.

are expressed as mean ± SD for continuous variables and as counts and percentages for categorical variables. Differences were considered statistically significant at $p < 0,05$. Fitness to the normal distribution was analyzed with the Kolmogorov-Smirnov test. Intergroup differences were compared with the one-way analysis of variance (one-way ANOVA) in continuous variables and multiple chi-square tests in categorical variables. When it was significant, pairwise posthoc tests were performed with either Tukey HSD or Games-Howell tests for further analyzing of significant results between groups. The Kruskal-Wallis test was conducted to compare the groups for parameters that were not distributed normally and for ordinal variables. Post-hoc analysis was performed with Bonferroni test. Correlations of continuous variables were evaluated using Pearson correlation analysis or its nonparametric counterpart Spearman's correlation analysis. Values 0-0.3 indicated weakly, 0.3-0.7 indicated intermediate, and 0.7-1.0 indicated a strong correlation. In order to analyze independent risk factors associated with the atherosclerotic lesion localization in 5 mm length from the point of bifurcation site multivariate logistic regression analyses were performed. Receiver operator curve (ROC) analysis was used to determine the diagnostic accuracy of the bifurcation angle for the prediction of atherosclerotic lesion localization in 5 mm length from the point of bifurcation site.

4. Results

A total of 467 patients were enrolled. 138 patients (60 female, 78 male) formed LAD-CX group, 124 patients (56 female, 68 male) formed LAD-Dx group, 118 patients (50 female, 68 male) formed CX-OM

group, 87 patients (41 female, 46 male) formed RPL-RPD group. The demographic and biochemical characteristics of all 4 groups are presented in Table 1. There were no significant inter-group differences with regard to age, gender, smoking history, hypertension, diabetes mellitus, hyperlipidemia and heredity. Mean bifurcation angles of all groups and mean LMCA length are shown in Table 2. Although bifurcation angle was significantly higher in males (70.14 ± 22.9 vs. 63.10 ± 21.15; $p = 0.046$), there was no significant difference in terms of lesion distance to bifurcation site between males and females (9.00 ± 3.58 vs 9.13 ± 4.05; $p = 0.830$ respectively).

Correlation analysis showed that there was a strong inverse correlation between bifurcation angle and lesion distance to the bifurcation site in overall patients. ($r = -0.706$; $p < 0.0001$) (Fig. 2). When we analyze all 4 groups separately, there were also statistically significant inverse correlations between bifurcation angle and lesion localization distances in all 4 groups. (LAD-CX: $r = -0.677$, $p < 0.0001$; LAD-DX: $r = -0.654$, $p < 0.0001$; CX-OM: $r = -0.834$, $p < 0.0001$; RPL-RPD: $r = -0.522$, $p = 0.026$). Although there was a strong inverse correlation in CX-OM group, other groups had intermediate inverse correlations. On the other hand, there was no statistically significant correlation between LMCA length and lesion localization distance and bifurcation angle in the left coronary system bifurcation subgroup patients. ($r = 0.118$; $p = 0.671$ and $r = -0.130$; $p = 0.435$ respectively).

A Multivariate logistic regression analysis was used to predict independent risk factors for lesion localization in the first 5 mm from the bifurcation site. Only the coronary bifurcation angle was found to be an independent risk factor for predicting the localization of an atherosclerotic lesion in 5 mm length from the point of bifurcation site (Beta = -0.074, SE = 0.012, OR = 0.928, 95% CI = 0.906-0.951, $p < 0.0001$).

Table 2. Mean values of angiographic parameters.

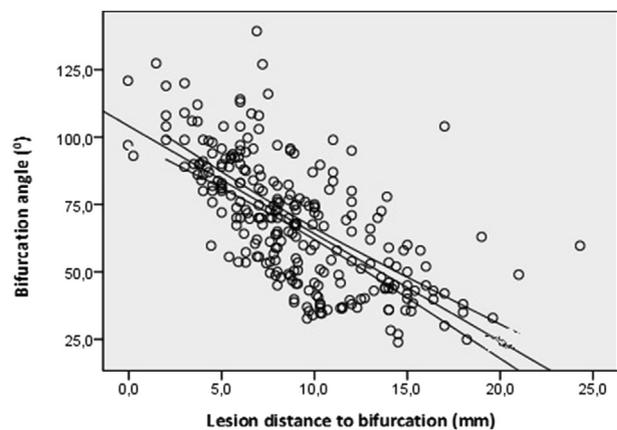| Parameter	Mean value
LMCA length (mm)	14.36 ± 4.13
LAD-CX bifurcation angle (^{0})	71.19 ± 23.29
LAD-DX bifurcation angle (^{0})	67.16 ± 21.58
CX-OM bifurcation angle (^{0})	59.63 ± 19.66
RPL-RPD bifurcation angle (^{0})	61.30 ± 21.17

Fig. 2. Correlation graph showing the strong inverse correlation between bifurcation angle and lesion distance to bifurcation site.

Table 1. Demographic and biochemical characteristics of all 4 groups (DM: Diabetes mellitus, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BUN: Blood urea nitrogen, AST: Aspartate amino transferase, ALT: Alanine amino transferase, WBC: White blood cell, PLT: Platelet).

Variables	LAD-CX group	LAD-Dx group	CX-OM group	RPL-RPD group	p
Age (years)	67.6 ± 10.76	66.1 ± 15.92	67.2 ± 9.07	65.7 ± 12.97	0.342
Male/Female (n)	78/60	68/56	68/50	46/41	0.390
Smoking (n)	57	61	54	45	0.671
DM (n)	64	57	54	47	0.325
Hypertension (n)	83	78	69	51	0.279
Heredity (n)	37	34	27	25	0.072
Fasting blood glucose (mg/dl)	150.2 ± 74.24	164.9 ± 61.35	169.5 ± 78.25	158.6 ± 77.55	0.894
LDL (mg/dl)	122.6 ± 34.47	133.1 ± 34.23	124.0 ± 39.42	112.5 ± 23.06	0.445
HDL (mg/dl)	41.8 ± 24.10	40.0 ± 9.18	42.7 ± 18.85	41.0 ± 14.05	0.638
Triglyceride (mg/dl)	156.8 ± 69.98	152.6 ± 56.65	161.4 ± 43.49	164.2 ± 53.06	0.237
Total cholesterol (mg/dl)	194.5 ± 44.26	203.3 ± 35.94	189.8 ± 43.83	186.0 ± 45.14	0.223
BUN (mg/dl)	40.7 ± 20.93	39.5 ± 19.93	37.9 ± 14.95	36.8 ± 16.53	0.732
Creatinine (mg/dl)	1.0 ± 0.34	1.03 ± 0.31	0.9 ± 0.18	0.9 ± 0.27	0.154
Sodium (mEq/L)	137.9 ± 3.17	135.8 ± 1.69	137.6 ± 4.19	137.6 ± 2.75	0.684
Potasium (mEq/L)	4.7 ± 0.71	4.3 ± 0.54	4.5 ± 0.65	4.3 ± 0.38	0.090
AST (mg/dl)	25.7 ± 9.87	26.0 ± 8.01	25.0 ± 6.18	20.2 ± 7.12	0.756
ALT (mg/dl)	20.8 ± 8.59	22.8 ± 13.39	17.2 ± 6.19	18.7 ± 6.63	0.208
Hemoglobin (g/dl)	13.5 ± 1.77	14.4 ± 1.99	13.7 ± 1.65	14.1 ± 1.68	0.063
WBC (10^9/l)	8.9 ± 2.94	9.8 ± 2.80	10.0 ± 3.13	9.0 ± 2.18	0.080
PLT (10^9/l)	260.2 ± 56.41	255.5 ± 34.11	261.7 ± 45.90	270.4 ± 27.89	0.536
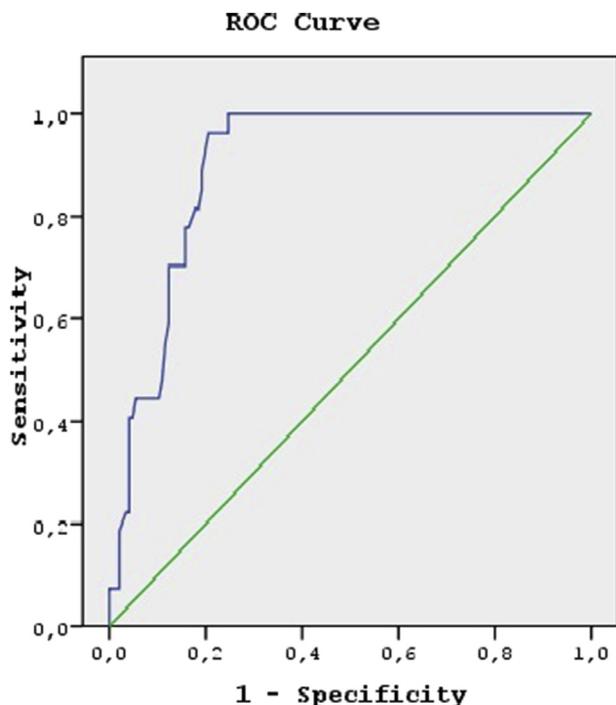
ROC Curve

Diagonal segments are produced by ties.

Fig. 3. ROC curve analysis of the performance of bifurcation angle for predicting atherosclerotic lesion localization in 5 mm length from the point of bifurcation site.

The ROC analysis for the accuracy of coronary bifurcation angle for predicting atherosclerotic lesion localization is shown in Fig. 3. The area under the curve for the coronary bifurcation angle was 0.873 [95% CI 0.841-0.968]. A cut-off value of 80.5° coronary bifurcation angle has 84.1% sensitivity and 81.3% specificity in prediction of atherosclerotic lesion localization in 5 mm length from the point of bifurcation site.

5. Discussion

Atherosclerosis is a chronic inflammatory condition characterized by hyperlipidemia and lipid oxidation and remains the main cause of death in developed countries. Although it is a disease of vascular intima in which all the vascular tree involved, there are preferred sites of lesion formation within the arteries due to differences in blood flow hemodynamics [7—9]. The early lesions of atherosclerosis arise from the subendothelial accumulation of cholesterol-rich macrophages, called 'foam cells'. Thereafter, fatty streaks lesions which are the precursors of more advanced lesions characterized by the accumulation of lipid-rich necrotic debris and smooth muscle cells (SMCs) appear.

Those fibrous lesions enlarge with the proliferation of fibrous tissues and the surrounding smooth muscle and protrude inside the arteries and consequently decrease the bloodstream. Connective tissue production by fibroblasts and deposition of calcium in the lesions lead to vascular sclerosis. Thanks to erosion at the luminal surface, and hemorrhage from small vessels that grow into the lesion from the media of the blood vessel wall, plaques become vulnerable and complex [10].

Apart from the above-mentioned complex multifactorial process which induces atherosclerosis, blood flow-induced shear stress defined as force/wall area (e.g. dyn/cm^2) plays a major role in atherogenesis. Recent studies have shown that hemodynamic forces acting on the blood vessel wall affect both endothelial cells and neighboring smooth muscle cells. These hemodynamic forces trigger complex and multiple signaling cascades via potential sensors and initiate mechanotransduction. This mechanotransduction process generates biochemical signals which result in changes in vascular behavior [11—13].

The geometric structure of the vascular tree comprises straight, curved, branched, converged, and diverged features which make the hemodynamic environment in the vascular tree complicated. In the straight part of an artery, the hemodynamic flow pattern is typically laminar and wall shear stress is high and directed. However, in the curved, branched, and diverged regions of the arterial tree the hemodynamic flow becomes disturbed with nonlaminar and irregular distribution of low wall shear stress [14]. In vivo studies demonstrated that irregular flow pattern induces transcription of pro-atherogenic genes and promote atherosclerosis, whereas regular flow pattern induces activation and regulation of anti-inflammation and anti-atherogenic genes. Disturbed shear stress near arterial bifurcations, branch ostia and curvatures are also influence the site selectivity of atherosclerotic plaque formation [15]. Not only the regulation of vascular caliber but inhibition of proliferation, thrombosis, and inflammation of the vessel wall is regulated by laminar shear stress. Thus, shear stress is critically important in regulating the atheroprotective state. In addition, reactive oxygen species (ROS) generated in response to altered flow or cyclic strain are well known for their role in mediating vascular homeostasis [16—18]. Apart from ROS, reactive nitrogen species (RNS) including nitric oxide (NO), nitrogen dioxide (NO_2-), peroxynitrite (OONO-), dinitrogen trioxide (N_2O_3), nitrous acid (HNO_2) also play a key role in endothelial function. Nitric oxide (NO) released

from the endothelium as a result of increased shear stress, regulates the vascular homeostasis via inhibiting the activity of proinflammatory cytokines. Shear stress alters mechanotransduction processes on vascular endothelial cells which induce signaling pathways. These signaling pathways as a result of altered flow conditions modulate the interactions between ROS and NO and these interactions alter redox signalings that give rise to anti-atherogenic or pro-atherogenic responses in the vascular wall [19,20]. Protective role of laminar shear stress on the vascular endothelium mediated by inhibition of endothelial proliferation, prevention of apoptosis of endothelial cells, and an increase in antioxidant enzyme activity has been demonstrated in several studies. According to those studies, reduced wall shear stress plays an important role in oxidation and lipid accumulation of the vascular intima and this adverse effect is evident in arterial bifurcation sites [21,22]. There is a higher incidence of atheroma plaques at the level of the bifurcation of the common carotid artery and in the coronary arteries compared to other parts of the vascular system which support this phenomenon. Furthermore, those atheroma plaques in segments with bifurcations tends to develop and progress rapidly independent of systemic factors [23−25]. The association between wide angulation and coronary atherosclerosis demonstrated in various studies. According to those studies, there is a statistically significant inverse correlation between coronary angulation and the degree of coronary stenosis as a result of local hemodynamic changes [26−28]. Although most studies in literature rely on the data derived from two-dimesional projection imaging techniques, Medrano et al built a three-dimensional atlas of vessel bifurcations with the help of computed tomographic coronary angiographic data by using computer aided design model [29]. A cut-off value of 80° is used to describe the physiological significance of coronary stenosis in those studies. According to a study conducted by Park et al. decreased wall pressure in coronary arteries with wide angulation is associated with significant coronary stenosis based on coronary computed tomography angiography models. They also demonstrated wall shear stress is more accurate than lumen assessment not only in determining plaque features but differentiating high-risk plaques from stable ones [30]. Although association between wide angulation and degree of coronary stenosis has been investiagated in several studies, there is a lack of

detailed analysis of hemodynamic changes in relation to the wide angulation and culprit atherosclerotic lesion distance from bifurcation site. To the best of our knowledge, no report is available on the investigation of the relationship between bifurcation angle and culprit atherosclerotic lesion distance from the bifurcation site and corresponding hemodynamics. According to our study, coronary bifurcation angle over 80.5° was associated with significant coronary stenosis and culprit lesions located within the first 5 mm from the bifurcation site. The results of our study further confirm the use of bifurcation angle as a diagnostic parameter in order to predict significant coronary stenosis with regard to its association with local hemodynamic alterations. It is well known, bifurcation lesions constitute a technically challenging area in interventional cardiology and remain complex anatomical lesion subset to treat for the interventional cardiologist. Compared to simpler lesions, bifurcation interventions are associated with more complex procedures, lower procedural success rates, higher contrast volumes, and higher rates of procedure-related complications [31−33]. Due to those factors, using the bifurcation angle as a diagnostic tool is noteworthy in terms of predicting atherosclerosis in the vascular tree with curved or bifurcation sites where more complex PCI procedures, overqualified equipment are needed. We also analyzed the association between atherosclerotic lesion localization site and LMCA length. Although we aimed to use LMCA length as another criterion in predicting atherosclerotic lesion localization site, no significant correlation was found.

6. Conclusion

In conclusion, local hemodynamic parameters influence the distribution and progression of different atherosclerotic plaques. Because of its protective effect on the vascular endothelium, decreased wall shear stress may contribute to the generation and destabilization of vulnerable plaques and those changes tend to occur in bifurcation sites. The main finding of our study which is considered to contribute to the current literature; coronary bifurcation angle over 80.5° is associated with significant coronary stenosis with subsequent hemodynamic changes and these lesions located within the first 5 mm from the bifurcation site. In addition to assessments of coronary lumen stenosis with regard to its distance from bifurcation site and bifurcation angle, we analyzed another parameter in

this study, namely, the length of LMCA in relation to the atherosclerotic lesion localization. Although there was a positive correlation between bifurcation angle, lesion localization site, and LMCA length, the diagnostic value is still low and statistically nonsignificant.

7. Limitations

There are some limitations to this study that should be acknowledged. First, the number of cases with significant stenosis confirmed by coronary angiography is relatively small. Second, we only focused on plaques associated with bifurcation sites in this study, while excluding other types of plaques. In addition, the results of this study need to be interpreted with caution with regard to the diagnostic value of invasive coronary angiography using bifurcation angle measurements. Although functional significance of coronary artery stenosis with regard to luminal narrowing is widely assessed by conventional two-dimensional QCA in cardiovascular practice, fractional flow reserve (FFR) is considered the gold standart methot for the physiological assessment of coronary artery stenosis with a cut-off FFR value of ≤ 0.80 [34—36]. In addition, not only visual estimation on angiography, but measurement using QCA cannot accurately assess the physiological severity of coronary stenosis [37]. Therefore,intravascular ultrasound (IVUS) is the most accurate intracoronary imaging modality in terms of providing quantitative assessment of vessel geometry and lesion severity [38]. Previous studies demonstrated the efficiency of IVUS in determining the functional status of coronary lesions and these studies revealed the positive correlation between the minimum lumen area (MLA) obtained by IVUS and ischemic FFR values [39]. On the other hand, IVUS is more invasive, costly, and time-consuming than conventional coronary angiography. There is also a inverse correlation between heavy superficial calcium barriers and IVUS results due to inadequate peneration of ultrasound signals. Moreover, IVUS examination is more convenient than QCA with regard to assessment of coronary lumen but this superiority is not definite for measurement of the external elastic membrane and bifurcation angles. Finally, in our study the functional severity of coronary stenosis determined by the anatomical severity of the stenosis itself. We did not take into account other factors including vessel size, trifurcation lessions which is not so rare or mass of viable myocardium distal to the bifurcation angle during angiographic assessment. Further studies with the inclusion of more cases with the inclusion of all types of lesions are desirable.

Disclosure of Funding

Conflict of interest

Author declared no conflict of interests

Author contribution

Conception and design of study: Murat Ziyrek, Ahmet L. Sertdemir. Literature review: Murat Ziyrek, Mustafa Duran. Acquisition of data: Murat Ziyrek, Ahmet L. Sertdemir. Analysis and interpretation of data: Murat Ziyrek, Ahmet L. Sertdemir. Research investigation and analysis: Murat Ziyrek, Mustafa Duran. Data collection: Murat Ziyrek, Ahmet L. Sertdemir. Drafting of manuscript: Murat Ziyrek, Mustafa Duran. Revising and editing the manuscript critically for important intellectual contents: Murat Ziyrek, Mustafa Duran. Data preparation and presentation: Murat Ziyrek, Ahmet L. Sertdemir, Mustafa Duran. Supervision of the research: Murat Ziyrek, Ahmet L. Sertdemir. Research coordination and management: Murat Ziyrek, Mustafa Duran. Funding for the research: Murat Ziyrek, Ahmet L. Sertdemir, Mustafa Duran.

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