Relationship between left main trifurcation angulation, calcium score, and the onset of plaque formation

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ABSTRACT

Background: It has been suggested that a wider left main (LM) bifurcation angle is associated with the development of atherosclerosis. However, the relationship between LM trifurcation angulation and atherosclerosis has not been investigated.

Aims: We aimed to investigate the relationship between LM trifurcation angulation and the presence of calcifications in the left coronary artery (LCA) using coronary computed tomography angiography (CCTA). Furthermore, we assessed the relationship between LM trifurcation angulation and the age at which calcification originated.

Methods: The LM trifurcation angle and coronary artery calcium (CAC) score in the LCA were measured. Based on observational studies, we assumed that CAC progression is 25% per year on average. Then, we calculated the age at which LCA CAC scores were lower than 0.1 Agatston units.

Results: Of 266 patients, 52 patients (mean age of [standard deviation, SD] 61 [6] years; 28 men) with LM trifurcation were included in the study. Calcified plaques occurred in the LCA in 36 patients (69.2%). The mean LM trifurcation angle in patients with a diseased LCA was wider than that in patients with a normal LCA (108° [33°] vs. 91° [28°]; $P = 0.04$). Pearson correlation coefficient showed that the wider the LM trifurcation angle was, the earlier the calcification in the LCA may be expected ($r = -0.34$; $P = 0.04$ with outliers; $r = -0.43$; $P = 0.009$ without outliers).

Conclusions: A wider LM trifurcation angle is associated with a higher LCA CAC score. Moreover, the LM trifurcation angle has a significant impact on the earlier onset of atherosclerosis.

Key words: coronary atherosclerosis, coronary computed tomography angiography, calcium score, left main trifurcation angulation

INTRODUCTION

Despite the exposure of the coronary arteries to systemic risk factors, the distribution of atherosclerotic plaques is focal and forms at specific precisely defined risk points. Typical locations are proximal segments of coronary artery branches and inner curvatures, areas of flow recirculation and flow reversal where wall shear stress is on average low and fluctuates during the cardiac cycle [1–4].

Computed tomography allows visualization of coronary artery plaque distribution and assessment of a coronary calcium score. Coronary artery calcium (CAC) score is an independent and powerful predictor of coronary artery diseases [5]. It has been shown that a wider bifurcation angle between the left anterior descending (LAD) and left circumflex branch (LCx) is associated with the development of coronary atherosclerosis [6–13].

However, the relationship between left main (LM) trifurcation angulation and atherosclerosis is unknown. This study aimed to investigate the relationship between LM trifurcation angulation, plaque burden reflected by the CAC score, and the onset of plaque formation.

WHAT'S NEW?

For the first time, the relationship between left main (LM) trifurcation angulation and atherosclerosis was investigated. In our study, a wider left coronary artery trifurcation angle was associated with a higher coronary calcium score in the left coronary artery. We also found that the LM trifurcation angle is a geometric risk factor for atherosclerosis and has a significant impact on the onset of coronary calcification. Local hemodynamic factors may be the major determinants of atherosclerotic plaque localization and progression.

METHODS

Study population

The Bioethics Committee granted an exemption from ethics approval for this study. In addition, the need for informed consent from study participants was waived. This study was an observational retrospective registry of individuals who underwent CAC scoring as part of health check-ups in a self-referral setting.

Of the 266 consecutive patients with suspected chronic coronary syndrome with an intermediate or a low probability of coronary artery disease undergoing coronary computed tomography angiography (CCTA) at the Silesian Center for Heart Diseases over a period of one year, 52 patients 61 (6) years; 28 men with LM trifurcation were included in the study. Patients included in the study had no other vascular abnormalities on CCTA. Patients with stents and pacemakers and those who had myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary bypass surgery were excluded.

The evaluated risk factors for coronary artery disease were hypertension (systolic blood pressure values of at least 140 mm Hg and/or diastolic blood pressure values of at least 90 mm Hg or taking antihypertensive drugs), diabetes mellitus (fasting plasma glucose level ≥7.0 mmol/l, 2-hour plasma glucose ≥11.1 mmol/l, random plasma glucose ≥11.1 mmol/l with symptoms or use of oral antidiabetic therapy and insulin), smoking (active smokers), positive family history of coronary artery diseases (in first-degree male relatives before 55 years of age or female relatives before 65 years of age), body mass index and hypercholesterolemia (low-density lipoprotein cholesterol level of at least 3 mmol/l).

CCTA protocol

CCTA scans were performed using a 128-slice dual-source computed tomography scanner (SOMATOM Definition Flash, Siemens Healthineers, Forchheim, Germany). First, non-contrast computed tomography scans were performed to evaluate the CAC score. Then, the nonionic low osmolar contrast agent Omnipaque 350 mgI/ml (Iohexol, GE Healthcare, Chicago, IL, US) was injected to visualize the coronary arteries (average 55 ml of contrast per patient with a flow of 5–5.5 ml/sec). The scanning parameters were beam collimation 2 × 64 mm × 0.6 mm with a z-axis flying spot, slice thickness of 1.5 mm, tube voltage ranging from 100 to 120 kV (depending on body mass index [BMI]), tube current of 300–450 mA, and reconstruction interval of 0.5 mm with electrocardiogram gating. All patients were given a 0.8 mg dose of nitroglycerin lingual spray, and patients with a heart rate above 75 beats per minute were given 2.5–5 mg intravenous metoprolol.

Measurement of calcium score and left main trifurcation angle

The CAC score was calculated by the Agatston method. The presence of a lesion with an area greater than 1 mm^2 and a peak intensity greater than 130 Hounsfield units was automatically identified and color-coded by the software (Syngo.via). Calcium scores of the LM, LAD, intermediate artery (IM), and LCx were summed to calculate the total left coronary artery (LCA) calcium score.

The LM trifurcation angle was calculated after identifying the centerline vectors along the course of the LAD and LCx. The LM trifurcation angles were measured in diastole based on multiplanar reconstructions (MPR) views.

Figure 1 shows a schematic measurement of the LM trifurcation angle. The angle between the LAD and LCx was measured independently by two readers with over 15 years of clinical and research experience in cardiac computed

Figure 1. Measurement of the left main (LM) trifurcation angle. The angle between the left anterior descending artery (LAD) and left circumflex (LCx) branch is 95°. Calcified plaques are present at the LM, LAD, and LCx

Table 1. Baseline characteristics of the study population

Risk factors	Whole population (n = 52)	CAC = 0 (n = 16)	CAC >0 (n = 36)	*P*-value
Age, years, mean (SD)	61 (6)	58 (9)	63 (8)	0.07
Male sex, n (%)	28 (54)	7 (44)	21 (58)	0.33
Body mass index, kg/m², mean (SD)	27.7 (3)	27 (3)	28 (3)	0.32
Hypertension, n (%)	28 (54)	9 (56)	19 (53)	0.82
Type 2 diabetes mellitus, n (%)	5 (9.6)	2 (12)	3 (8)	0.64
Current smoker, n (%)	9 (17.3)	4 (25)	5 (14)	0.33
Family history of CAD, n (%)	16 (30.8)	7 (44)	9 (25)	0.18
Hypercholesterolemia, n (%)	15 (28.8)	7 (44)	8 (22)	0.11
eGFR (Cockcroft-Gault), ml/min/1.73 m², median (IQR)	95 (84–95)	95 (84–96)	94 (84–95)	0.07

Abbreviations: CAD, coronary artery disease; eGFR, estimated glomerular filtration rate

tomography. Three measurements were obtained, and the average values were analyzed.

Statistical analysis

Quantitative data are reported as mean (standard deviation [SD]) or median with interquartile ranges (IQR). Qualitative data are expressed as counts and frequencies. Qualitative variables were compared using the χ^2 test. The Mann-Whitney U-test was used to compare continuous variables with a distribution other than normal. Depending on the value of the calcification score, patients were divided into two groups: with calcifications (CAC >0) and without calcifications (CAC = 0) in the LCA. The Shapiro-Wilk test was used to check the normality of the data in a given group. Homoscedasticity was assessed by the mean-based Levene test. The differences between LM angles in the groups were tested using a one-tailed t-test.

In addition, the likelihood of calcification occurrence with increasing LM trifurcation angle was calculated. To assess the exact change in the odds, univariable logistic regression was performed.

Furthermore, we investigated the influence of the LM trifurcation angulation on the onset of calcification in relation to age using Pearson correlation. To do so, for each patient, we estimated the age at which the disease originated. According to the literature, we assumed that CAC is progressing at an average of 25% per year [14–16], and then we calculated the age at which the CAC score in the LCA was less than 0.1 Agatston units in each patient.

P-values <0.05 were considered statistically significant. Statistical analysis was performed using the Python package (numPy, sciPy, statsmodels, scikit-learn).

RESULTS

The final study group consisted of 52 patients. The median age of the study population was 61 (6) years; 54% of the patients were male. A similar proportion of patients in the subgroup had hypertension and type 2 diabetes mellitus. All patients suffering from hypercholesterolemia had been taking statins. The demographic and clinical characteristics of the patients are presented in Table 1. Calcifications were found in the LCA in 36 patients (69.2%) in the study group. Patients with CAC >0 had, on average, a wider LM trifurcation angle than patients without calcifications ($P = 0.04$). The mean LM trifurcation angle was 108° (33°) in patients with CAC >0, which was considerably wider than the angle measured in patients with CAC of 0, which was 91° (28°) (Supplementary material, *Figure S1*).

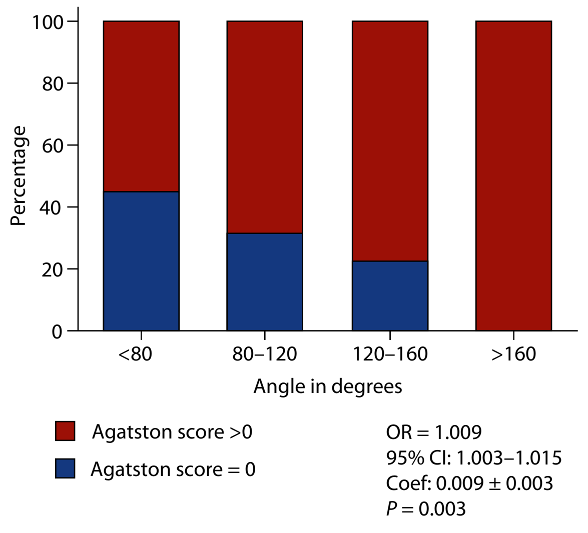

Figure 2. Logistic regression results. The histogram presents that a wider left main trifurcation angle is associated with an increase in the odds of calcifications in the left coronary artery

Abbreviations: CI, confidence interval; OR, odds ratio

We also assessed changes in the likelihood of calcification occurrence with an increase in the LM trifurcation angle. The histogram plotted in Figure 2 shows that wider angulation is associated with an increase in the odds of LCA calcification. In the logistic regression analysis, LM trifurcation angles were predictors of occurrence of lesions in the LCA, and each degree of increase in the LM angle comes with approximately 1% greater odds of occurrence of calcification in the LCA (odds ratio [OR], 1.009; 95% confidence interval [CI], 1.003–1.015; $P = 0.003$).

Then, the age at which calcifications originated was correlated with LM trifurcation angulation (Figure 3). Among the plotted points, one subject was assessed as an outlier and marked with a red color. This was an extreme obser-

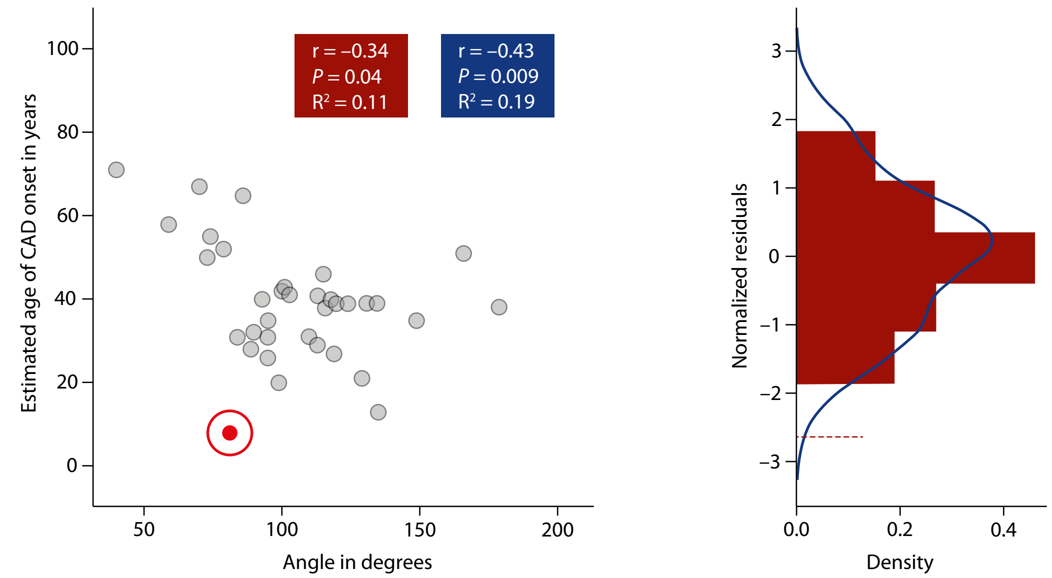

Figure 3. Pearson correlation results. On the left side, the relationship between the left main trifurcation angle and the age at which the left coronary artery calcium score was lower than 0.1 Agatston units in each patient. One subject was assessed as an outlier and marked with a red color. Two correlation coefficients were calculated: one considering the outlier (the red color) and one excluding the outlier (blue color). Both results were statistically significant. On the right side, the plot of normalized residuals. The residual calculated for the outlier differs by nearly 3 standard deviations from the expected value of this distribution, so we decided to treat this point as a potential outlier

Abbreviations: see Table 1

vation, possibly disrupted by additional risk factors. Two correlation coefficients were calculated: one considering the outlier (red color) and one excluding the outlier (blue color). Both results were statistically significant (r = −0.34; $P = 0.04$ vs. r = −0.43; $P = 0.009$, respectively) and indicate that the wider the LM trifurcation angle is, the earlier calcification may be expected in a given patient.

The diameters and lengths of each main branch artery did not influence the distribution and severity of coronary artery calcification (results were not included in the publication).

DISCUSSION

Approximately 20%–38% of the population has LM trifurcation [17–20]; however, the relation between LM trifurcation angulation and atherosclerosis is unknown. For the first time, the relationship between LM trifurcation angulation and atherosclerosis was investigated in this study. We found that the LM trifurcation angle is a geometric risk factor for atherosclerosis and has a significant impact on the onset of coronary calcification. The patients with trifurcation of the LM and a CAC score above 0 had a wider LAD and LCx angle than the patients with CAC of 0. Moreover, a larger angle between side branches is associated with an increase in the odds of calcification occurrence. Finally, we demonstrated for the first time that the wider the LM trifurcation angle is, the earlier the onset of calcification is expected. This observation suggests that plaque formation and coronary artery calcification are related to arterial geometry features and local shear stress distribution. The presence of an intermediate branch requires a wider LM angle. This geometry of arteries promotes secondary disturbed flows that generate regions of low and/or oscillatory wall shear stress at the lateral wall of the LM divider [21]. Low and/or oscillatory endothelial shear stress induced by mechanotransduction changes the proatherogenic phenotype of endothelial cells [22]. We believe that measuring the LM trifurcation angle in patients without lesions in the LCA may be prognostic.

Our results are in line with observations focused on LM bifurcation [6–13, 23]. All of them demonstrated that LAD-LCx bifurcation angulation is a potential geometric risk factor for atherosclerosis. For instance, Cui et al. [6] suggested that a wider bifurcation angle between the LAD and LCx is associated with noncalcified lesions and might predict significant left coronary stenosis. Interestingly, Sun et al. [7, 13, 24] demonstrated that the measurement of the LM bifurcation angle improves the diagnosis of calcified plaques. According to Ziyrk et al. [25], the bifurcation angle has an impact on the localization of lesions.

Another study focuses on LM-LAD angulation. Moon et al. [8] showed that a wider LM-LAD angle could be used to identify patients at higher risk for coronary artery disease. Konishi et al. [26] studied the relationship between LM and LAD angulation in a population with chronic kidney disease and reported that a wider LM-LAD bifurcation angle was associated with a high CAC score. Furthermore, Konishi et al. [27], in another study, postulated that a wide LM-LAD angle was a predictor of restenosis after stent implantation in proximal LAD disease. Malvè et al. [20], using computational fluid dynamics simulations, showed that the tortuosity of the LM-LAD coronary branches is associated with low wall shear stress and could be used as a surrogate marker for the onset of atherosclerosis. Other authors also postulated that a wide angle between side branches intensifies disturbed blood flow, magnitude of reversed flow, and flow separation, increasing the spatial wall shear stress variations that are important in atherogenesis [28–30].

The present study has some limitations that should be pointed out. First, we considered only calcified plaques. Notably, the CAC score represents the progression of both the noncalcified and calcified plaque burdens in patients without statin use [31]. Second, there was no correlation with invasive coronary angiography. Notably, however, according to Sun and Chaichan, there is no difference between angle measurements on CCTA and invasive angiography [32]. Third, we did not adjust for confounding risk factors for CAC. In our study, the patient populations with CAC of 0 and CAC greater than 0 were homogeneous. In addition, patients with high CAC scores without traditional risk factors have an increased incidence of coronary heart disease events, whereas patients without CAC with multiple risk factors have a low event rate [32]. Information on former smokers was not collected. Another limitation is the small sample size, so multicenter studies are needed. One limitation may be the lack of detailed information on the treatment, but there is no scientific evidence or large multicenter trials that show that cardiovascular drugs can significantly prevent occurrence of coronary calcification or significantly limit progression or reduce calcium score [33, 34].

CONCLUSIONS

Our findings suggest that the geometric features of LM trifurcation are related to the risk of atherosclerosis. Wider LM trifurcation angulation is closely correlated with LCA disease and earlier calcified plaque onset. Measurement of the LM trifurcation angle may be used to identify patients at higher risk of coronary artery disease. The prognostic value of our observations warrants further research and observational studies.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

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