ORIGINAL ARTICLE

The association between left ventricular mass index and coronary collateral circulation in patients with chronic total occlusion

Kronik tam tıkanmalı hastalarda sol ventrikül kitle indeksi ile koroner kollateral dolaşımının ilişkisi

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ABSTRACT

Objective: Left ventricular (LV) hypertrophy predisposes the myocardium to ischemia through several mechanisms. The LV mass index (LVMI) is used as a readily available and reliable measurement of LV hypertrophy. The LVMI can also be used to evaluate LV remodeling. The hypothesis of this study was that LV hypertrophy might augment coronary collateralization in patients with chronic total occlusion (CTO) and the aim was to research any association between LVMI and collateral formation in CTO. As a secondary goal, specific LV geometric types that might be associated with collateral presence were also investigated.

Methods: A total of 305 patients with CTO were included and categorized into 4 groups based on Rentrop grade.

Results: The LVMI demonstrated an incremental linear trend as the Rentrop grade increased. In the receiver operating characteristic curve, the likelihood that a cut-off value of 100.1 g/m^2 would accurately differentiate patients with collaterals from those without collaterals was 75.8%, with 68.5% sensitivity and 68.6% specificity. A 1 gram/m^2 increase in LVMI was associated with a 7.5% greater likelihood of collateral development. In addition, compared with normal geometry, the presence of eccentric hypertrophy was associated with 6.7 times higher odds of the presence of coronary collaterals.

Conclusion: The results of this study indicated that a greater LVMI predicted coronary collateral presence. Furthermore, having an eccentric geometric type of hypertrophy increased the likelihood of coronary collaterals more than other geometries. This finding signified that in addition to LV wall thickness, the type of hypertrophy was also decisive in predicting collateral presence.

ÖZET

Amaç: Sol ventrikül hipertrofisi, çeşitli mekanizmalar aracılığıyla miyokardı iskemiye yatkınlaştırır. Sol ventrikül kitle indeksi (SVKİ), sol ventrikül hipertrofisinin kolayca elde edilebilen ve güvenilir bir ölçümü olarak kullanılmaktadır. Ayrıca, sol ventrikül yeniden şekillenmesi bu parametre ile kategorize edilebilir. Bu çalışmada, kronik tam tıkanmalı (KTO) hastalarda sol ventrikül hipertrofisinin koroner kollateralizasyonu artırabileceği hipotezinde bulunduk ve SVKİ ile KTO'daki kollateral gelişimi arasındaki ilişkiyi araştırmayı amaçladık. İkincil hedef olarak, hangi spesifik sol ventrikül geometrik tipinin kollateral varlığı ile ilişkili olabileceğini belirlemeyi amaçladık.

Yöntemler: Kronik tam tıkanmalı saptanan 305 hastayı dahil ettik ve dört Rentrop Grade grubuna sınıflandırdık.

Bulgular: Sol ventrikül kitle indeksi, artan Rentrop gruplarına doğru doğrusal bir artış gösterdi. ROC eğrisinde, SVKİ için 100.1 g/m^2'lik bir kestirim değerinin, kollateralleri bulunan hastaları bulunmayanlardan %68.5 duyarlılık ve %68.6 özgüllük ile doğru bir şekilde ayırdetme ihtimali %75.8'di. SVKİ'nİn bir gram/m^2'lik artışı, %7.5'lik artmış kollateral gelişme olasılığı ile ilişkiliydi. Normal geometriye kıyasla, eksantrik hipertrofi varlığı 6.7 kat daha fazla koroner kollateral varlığı ihtimali ile ilişkiliydi.

Sonuç: Bu çalışmada KTO'lu hastalarda artmış SVKİ'nın koroner kollateral varlığını öngördürdüğünü gösterdik. Ayrıca, geometrik tipte bir eksantrik hipertrofi geometrisine sahip olmak koroner kollateralleri diğer geometrilere göre daha fazla artırmaktadır. Bu bulgu, sol ventrikül duvar kalınlığının yanı sıra, hipertrofi tipinin de, kollateral varlığını öngörmede belirleyici olduğunu göstermektedir.

Received: June 11, 2018 *Accepted:* September 18, 2018

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Coronary collaterals are natural anastomoses between coronary arteries that are distinguishable angiographically when the receiving artery fails to provide sufficient blood supply.[1] These anastomoses are frequently present in patients with chronic total occlusion (CTO) and prevent myocardial necrosis.[2] Numerous factors may trigger collateral formation, including ischemia, pressure gradients, and several growth factors.[1,3]

Left ventricular (LV) hypertrophy predisposes the myocardium to ischemia as a result of increasing the epicardial-endocardial distance, causing inadequate coronary growth relative to muscle mass and decreasing capillary density.[1] However, the relationship between ischemia secondary to LV hypertrophy and coronary collateralization has been poorly understood.[4,5] Methodological differences in assessing LV hypertrophy and geometry likely contributed to this situation. In contemporary practice, the LV mass index (LVMI) is used as a readily-available and reliable measurement of LV hypertrophy. Furthermore, the LVMI can also be used to categorize LV remodeling.

It has been hypothesized that LV hypertrophy might augment collateralization in patients with CTO. The objective of this study was to investigate any association between the LVMI and collateral formation in CTO. A secondary goal was to determine which specific LV geometric type or types might be associated with collateral presence. LV hypertrophy was quantified by calculating the LVMI and using 4 LV remodeling types recommended by contemporary echocardiography guidelines to classify the geometry.

METHODS

Patient population

The angiographic data of 2870 consecutive patients who underwent coronary angiography between January 2012 and January 2014 were screened. Patients with stable angina pectoris with at least 1 major CTO were included. A total of 305 patients were included after eliminating those who met the exclusion criteria: patients with acute coronary syndromes (within 6 months), severe valvular disease, acute decompensated heart failure, LV ejection fraction <40%, previous revascularization procedures (percutaneous coronary intervention and/or coronary artery bypass grafting surgery), renal or hepatic insufficiency, and severe thyroid disorders. This study was approved by the institutional committee.

Abbreviations:

CI	*Confidence interval*
CRP	*C-reactive protein*
CTO	*Chronic total occlusion*
LDL	*Low-density lipoprotein*
LV	*Left ventricle*
LVMI	*Left ventricular mass index*
OR	*Odds ratio*
ROC	*Receiver operating characteristic*

Study design

In this retrospective, cross-sectional study, the objective was to investigate a potential association between angiographically visible collateralization, which was classified according to Rentrop grade, and the LVMI, an index of LV hypertrophy, in CTO patients. As a secondary objective, LV remodeling according to the LVMI and relative wall thickness was investigated to determine specific remodeling types associated with good collateralization.

Echocardiography and left ventricular mass index determination

The LVMI was calculated using a well-validated formula that uses the end-diastolic left ventricular diameter and wall thicknesses.[6] The LVMI and relative wall thickness were also used to classify 4 types of left ventricular remodeling: normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy.[6]

Coronary angiography and coronary collateral grading

All of the patients underwent elective coronary angiography with an experienced cardiologist using the standard Judkins technique with a femoral or radial approach. The evaluation of coronary angiograms, determination of the Rentrop grade of the collaterals, and calculation of the SYNTAX score were performed by 2 interventional cardiologists who were blinded to the laboratory and clinical data.[7] CTO was defined as ≥99% epicardial coronary artery stenosis of presumed duration exceeding 3 months (based on the onset of ischemic symptoms, the history of myocardial infarction and previous coronary angiography) leading to a decreased blood flow that was clinically significant (Thrombolysis in Myocardial Infarction 0).[8] The Rentrop classification of 0 to 3 was used: No visible filling of collaterals was considered grade 0, filling of side branches but not epicardial segments was classified as grade 1, grade 2 reflected partial filling of epicardial segments, and complete filling of epicardial segments was considered grade 3.[9] In patients

who had more than 1 collateral vessel with different grades, the researchers calculated the mean collateral score and accepted this value as the collateral score.

Statistical analysis

Continuous variables were presented as mean±SD and categorical variables as number and percentage (%). One-way analysis of variance was used to determine differences between Rentrop grade groups. Post-hoc pairwise comparisons between groups were adjusted with the Bonferroni correction (all pairwise p values were adjusted at the 0.05 level). A chi-square test was used to compare categorical variables. Pearson's r coefficient was used for linear relationships between continuous variables, and point-biserial correlation analysis was used to examine the relationship between Rentrop grades and LVMI. P values derived from point-biserial correlation analysis were used to evaluate the Rentrop grade groups and the continuous variables, and a "p for trends" was calculated. Receiver operating characteristic (ROC) analysis was conducted to evaluate the relationship between LVMI and the presence of collaterals. Youden's index was used to distinguish the outcome with a cut-off of maximum sensitivity and specificity. Logistic regression was used to determine predictors of the presence of collaterals. For this approach, Rentrop grade groups were separated into grade 0 vs. other grades (1, 2, and 3). Parameters with unadjusted p values of <0.15 were included in the multivariate analysis. For issues of multicollinearity, as in the case of a cholesterol panel, the parameter that provided the most variance with the dependent variable was included. Because the LVMI and LV remodeling types were highly correlated (r=0.688), 3 multivariate models were developed: Model 1 included LVMI g/m^2, Model 2 included dichotomized variable LVMI ≥100.1 g/m^2 (which was derived from ROC analysis for discriminating coronary collateral circulation presence), and Model 3 included LV remodeling types (instead of LVMI parameters). The backward likelihood ratio method was used in the selection of variables in multivariate analysis, and for parameters excluded from the analysis, the most recent p values before exclusion were recorded. For increased stability, bootstrapping (sampling with replacement) was applied and bootstrapped parameter estimates were recorded. Nagelkerke R-squared values and the overall classification success of each model were calculated. To interpret it simply, the adjusted risk ratio of LVMI ≥100.1 g/m^2 was calculated using the formula of Zhang et al.,[10] in which the frequency of the outcome in the reference (control) group and an adjusted odds ratio (OR) of outcome were used. Wilk's lambda distribution was employed for stepwise discriminant analysis. Standardized canonical discriminant function coefficients were calculated. The eigenvalue of the discriminant function, the value of the canonical correlation R squared (to assess the accounted variance), and the correct classification accuracy of the function were recorded. All of the statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Statistical power was calculated for the study of Harrison et al. using G*Power version 3.1.9.2 (G*power, Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany).

RESULTS

The overall patient population was male predominant and overweight (Table 1). There was a decremental linear trend in age, C-reactive protein (CRP), low-density lipoprotein (LDL), and SYNTAX score with an ascending Rentrop grade. Diabetes was 2.5-times more prevalent in the Rentrop 0 group compared with the Rentrop 3 group. The LVMI showed an incremental linear trend as the Rentrop grade increased. LV remodeling types differed in favor of hypertrophy patterns (concentric and eccentric hypertrophy) in the higher Rentrop grades.

The LVMI was 25% higher in males than females (Table 2). The presence of hypertension doubled the LVMI. Also, in diabetics, LVMI was approximately 10% higher than in patients without. The LVMI had a positive and moderate correlation with the Rentrop grade. Furthermore, the LVMI showed a negative weak to moderate correlation with the SYNTAX score. The LVMI had trivial correlations with age, body mass index, and CRP.

In the ROC curve analysis, a cut-off of 100.1 g/m^2 for LVMI suggested a 75.8% chance that this parameter alone correctly distinguished patients with collaterals from patients without, with a sensitivity of 68.5% and a specificity of 68.6% (area under the curve: 0.758, 95% confidence interval: 0.699–0.817; p<0.001) (Fig. 1).

Table 1. Baseline characteristics of the study population

Variables	Rentrop 0 (n=58)	Rentrop 1 (n=65)	Rentrop 2 (n=77)	Rentrop 3 (n=105)	p¶
Age, years, n (%)	57.7±9.3	54.2±10.0	54.9±12.3	53.8±10.3	0.050*
Male, n (%)	35 (60.3)	35 (53.8)	44 (57.1)	60 (57.1)	0.778
Body mass index (kg/m^2)	26.6±2.9	26.7±2.9	26.4±2.7	27.4±2.9	0.877
Hypertension, n (%)	30 (51.7)	37 (56.9)	39 (50.6)	51 (48.5)	0.893
Diabetes mellitus, n (%)	32 (55.2)	26 (40.0)	25 (32.4)	24 (22.8)	0.001
Hyperlipidemia, n (%)	41 (70.6)	45 (69.2)	50 (64.9)	63 (60.0)	0.535
Smoking, n (%)	16 (27.6)	17 (26.1)	21 (27.2)	32 (30.4)	0.978
Glucose (mg/dL), Mean±SD	128.0±49.0	114.5±53.2	121.9±50.5	118.0±48.3	0.315
Creatinine (mg/dL), Mean±SD	1.1±0.2	1.1±0.2	1.0±0.2	1.0±0.2	0.420
Hemoglobin (g/L), Mean±SD	13.6±1.9	13.7±1.9	13.5±1.7	13.9±2.2	0.145
C-reactive protein (mg/dL), Mean±SD	5.8±2.2	5.5±1.8	3.3±1.9	2.7±1.5	<0.001†
Total cholesterol (mg/dL), Mean±SD	199.4±41.0	210.6±53.3	214.4±47.6	203.7±55.7	0.231
High-density lipoprotein (mg/dL), Mean±SD	37.7±7.2	38.6±8.4	39.1±9.0	40.2±9.2	0.471
Low-density lipoprotein (mg/dL), Mean±SD	131.4±44.5	121.3±38.7	112.7±36.8	112.6±37.5	0.007*
Triglycerides (mg/dL), Mean±SD	160.0±92.7	145.1±88.4	153.8±95.5	152.8±85.2	0.724
Ejection fraction (%), Mean±SD	48.9±8.6	49.7±8.9	50.4±8.8	50.9±8.3	0.500
Left ventricular mass index (g/m^2), Mean±SD	91.8±15.7	103.1±18.6	109.2±16.5	112.6±18.4	<0.001‡
Left ventricular remodeling					
Normal geometry, n (%)	31 (53.3)	18 (27.6)	24 (31.1)	14 (13.3)	
Concentric remodeling, n (%)	14 (24.1)	23 (35.3)	16 (20.7)	24 (22.8)	
Concentric hypertrophy, n (%)	11 (19.0)	17 (26.1)	24 (31.1)	41 (39.0)	
Eccentric hypertrophy, n (%)	2 (3.4)	7 (10.7)	13 (16.8)	26 (24.7)	<0.001
LAD occlusion, n (%)	35 (60.3)	37 (56.9)	41 (53.2)	47 (44.7)	0.209
Circumflex coronary artery occlusion, n (%)	13 (22.4)	14 (21.5)	19 (24.6)	16 (15.2)	0.640
Right coronary artery occlusion, n (%)	29 (50.0)	30 (46.1)	39 (50.6)	60 (57.1)	0.683
SYNTAX score, Mean±SD	18.9±7.0	17.7±7.5	15.9±5.0	15.0±5.0	0.001*

*p<0.05 for comparisons between Rentrop 0 and 2; Rentrop 0 and 3. †p<0.05 for comparisons between Rentrop 0 and 2, 3; Rentrop 1 and 2, 3.
‡All p values <0.05 except comparisons between Rentrop 1 and 2; Rentrop 2 and 3. ¶"P for trend" was also calculated for the variables that were significantly different between Rentrop groups. P for trend was the point biserial correlation of variables with Rentrop grades. P for trend for age: =0.021; for CRP: <0.001; for LDL: =0.001; for LVMI: <0.001; for SYNTAX ccore: <0.001.
LAD: Left anterior descending coronary artery; CRP: C-reactive protein; LDL: Low-density lipoprotein; LVMI: Left ventricular mass index; SD: Standard deviation.

Younger age, CRP, LDL, SYNTAX score, the absence of diabetes mellitus, and a greater LVMI were determined to be independent predictors of the presence of collaterals (Table 3). Adjusted with other parameters, a 1 gram/m^2 increase in LVMI was associated with a 7.5% increased likelihood of collateral development (Model 1). Model 2 demonstrated that the group with a greater LVMI (LVMI ≥100.1 g/m^2) had a 2.1 times greater probability of collateral development (OR: 3.650, corresponding risk ratio: 2.1) than those without. In Model 3, the odds of collateral presence in patients with eccentric hypertrophy was 6.7 times higher, concentric hypertrophy was 3 times higher, and concentric remodeling was 2.4 times higher than in patients with normal geometry.

Stepwise discriminant analysis selected the same variables (except diabetes mellitus). The discriminant function correctly classified 76.7% of the population (Similarly, the classification success of logistic regression was 75.5%). LVMI contributed most to the discriminant function (standardized coefficient: -0.636) (Table 4). Therefore, we confirmed the results.

Table 2. Relationship between left ventricular mass index and other variables, Pearson correlation coefficient or mean±SD between groups

Variables	Left ventricular mass index (g/m^2)	*p*
Age (years)	0.158	0.031
Male vs female	122.2±20.9 vs 98.5±16.3	<0.001
Body mass index (kg/m^2)	0.212	0.013
Hypertension (yes vs no)	115.4±20.1 vs 68.3±17.1	<0.001
Diabetes mellitus (yes vs no)	103.2±18.7 vs 89.9±18.0	0.056
Hyperlipidemia (yes vs no)	104.8±19.5 vs 101.2±17.8	0.214
Glucose (mg/dL)	0.097	0.147
Hemoglobin (g/L)	0.012	0.345
C-reactive protein (mg/dL)	0.132	0.032
Total cholesterol (mg/dL)	0.019	0.315
High-density lipoprotein (mg/dL)	0.058	0.213
Low-density lipoprotein (mg/dL)	0.102	0.067
Triglycerides (mg/dL)	0.007	0.687
Ejection fraction (%)	0.068	0.197
SYNTAX score	-0.264	0.001
Rentrop grades*	0.453	<0.001

*Point biserial correlation.

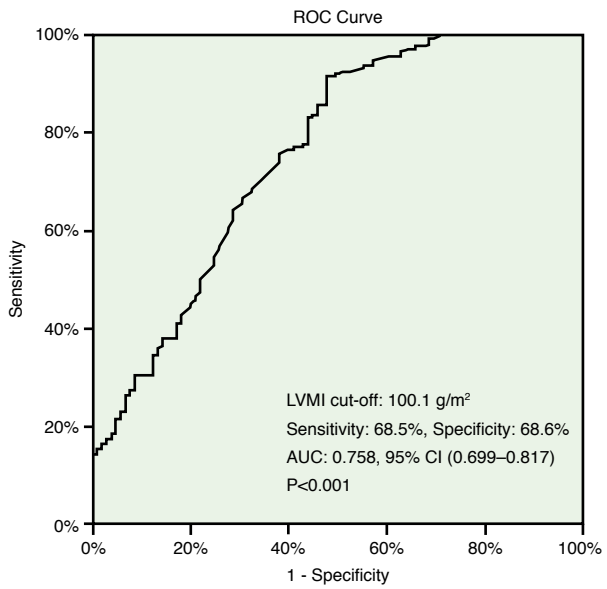

Figure 1. Receiver operating characteristic (ROC) curve demonstrating the accuracy of the left ventricular mass index (LVMI) in predicting coronary collateral presence. Youden's index was used to determine the sensitivity and specificity values of LVMI. The area under the ROC curve (AUC), a measure of how well the model distinguishes patients with collaterals than patients without, was 0.758 (p<0.001). CI: Confidence interval.

DISCUSSION

Our results indicated that LV hypertrophy augmented coronary collateralization in patients with CTO. The evidence revealed that increased LVMI, which is an indicator of LV hypertrophy, was strongly correlated with ascending Rentrop grades and was also an individual predictor after adjustment with other potential predictors (Tables 1 and 3). In addition to the close relationship with Rentrop grade, LVMI distinguished the patients who had collaterals (Fig. 1).

We also determined that having a geometric pattern of eccentric hypertrophy followed by concentric hypertrophy was associated with collateral presence. This finding indicated that rather than LV wall thickness, hypertrophy itself was more decisive in predicting the presence of collaterals (Tables 1 and 3).

Coronary collaterals have been considered an inborn bypass process supporting a myocardium jeopardized by ischemia. Coronary collateral circulation has been associated with reductions in infarct size, morbidity, and mortality in cases of myocardial infarction. Coronary collateral formation may be triggered by numerous factors, including ischemia, pressure gradi-

Table 3. Logistic regression analysis of potential coronary collateral circulation predictors

	Unadjusted		Adjusted**	
Variables	OR (95% CI)	*p**	OR (95% CI)	*p*††
Age (years)	0.968 (0.946–0.991)	0.007	0.963 (0.935–0.991)	0.011
Male (yes)	0.799 (0.494–1.293)	0.361		
Body mass index (kg/m^2)	1.007 (0.928–1.093)	0.861		
Hypertension (yes)	1.023 (0.609–1.720)	0.931		
Diabetes mellitus (yes)	0.412 (0.251–0.676)	<0.001	0.455 (0.250–0.857)	0.010
Creatinine (mg/dL)	1.509 (0.761–2.994)	0.239		
Hemoglobin (g/L)	0.892 (0.788–1.010)	0.072	0.849 (0.698–1.010)	0.098
CRP (mg/dL)	0.693 (0.614–0.782)	<0.001	0.771 (0.673–0.883)	<0.001
Total cholesterol (mg/dL†)	1.005 (0.999–1.010)	0.092		
HDL (mg/dL†)	1.024 (0.924–1.055)	0.116		
LDL (mg/dL†)	0.990 (0.984–0.997)	0.002	0.990 (0.983–0.997)	0.008
Triglycerides (mg/dL†)	0.999 (0.996–1.001)	0.313		
Ejection fraction (%)	1.018 (0.991–1.047)	0.194		
SYNTAX score	0.941 (0.906–0.976)	0.001	0.935 (0.895–0.976)	0.002
LVMI, g/m^2‡	1.103 (1.058–1.125)	<0.001	1.075 (1.053–1.098)	<0.001
LVMI (≥100.1 g/m^2¶)	4.867 (2.902–8.163)	<0.001	3.645 (2.014–6.595)‡‡	<0.001
Left ventricular remodeling#				
Normal geometry	Reference		Reference	
Concentric remodeling	2.520 (1.368–4.643)	0.003	2.393 (1.184–4.837)	0.015
Concentric hypertrophy	3.733 (1.982–7.031)	<0.001	3.002 (1.455–6.193)	0.003
Eccentric hypertrophy	9.917 (3.283–29.954)	<0.001	6.683 (1.992–22.426)	0.002

*Parameters with unadjusted p values <0.15 were included in the multivariate analysis. †Between the correlated variables total cholesterol, HDL, and LDL, the LDL parameter demonstrated the most variance, so it was included in the multivariate analysis. ‡LVMI was included in Model 1 with other significant predictors (age, DM, CRP, LDL, and SYNTAX score). ¶LVMI cut-off was derived from receiver operating characteristic analysis to discriminate coronary collateral circulation presence. Dichotomized variable LVMI ≥100.1 g/m^2 was included in Model 2 (instead of continuous variable LVMI g/m^2) with other significant predictors (age, DM, CRP, LDL, and SYNTAX score). #As a result of the high correlation (r=0.688) with LVMI, left ventricular remodeling was included in Model 3 with other significant predictors (age, DM, CRP, LDL, and SYNTAX score). **Nagelkerke R square of Model 1 was 42.3%, overall classification success of model was 75.5%. Nagelkerke R square of Model 2 was 35.6%, overall classification success of model was 75.3%. Nagelkerke R square of Model 3 was 35.0%, overall classification success of model was 73.1%. ††Backward likelihood ratio method was used in the selection of variables in multivariate analysis, and for parameters excluded from the analysis, the most recent p values before exclusion were recorded. ‡‡Adjusted risk ratio for LVMI ≥100.1 g/m^2 was 2.1 (accounted from adjusted OR and 27.6% prevalence of LVMI ≥100.1 g/m^2 in the Rentrop grade 0 group).
CI: Confidence interval; CRP: C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LVMI: Left ventricular mass index; OR: Odds ratio.

ents, and growth factors.[1,3] LV hypertrophy promotes ischemia by increasing the epicardial-endocardial distance, leading to greater transmural loss of subendocardial perfusion pressure and also causing an inadequate coronary growth relative to muscle mass, resulting in decreased capillary density.[1] Therefore, we speculated that as a trigger of ischemia, LV hypertrophy might enhance the coronary collateralization process.

Our results are consistent with previous studies that have demonstrated good collateral development in hypertensive subjects, approximately two-fifths of whom exhibit LV hypertrophy.[5,11–13] Karpanou et al.[11] reported that collaterals were more prevalent in hypertensives (70.6% vs. 57.1%). They also found that "good" collaterals were nearly 2 times more prevalent in hypertensive patients with coronary artery disease. In a 2013 paper, Shu et al.[12] stated that patients with a high diastolic blood pressure (≥90 mm Hg) had more "good" collaterals than those with a low diastolic blood pressure. They proposed that fluid shear stress may have had a role in developing "good" collater-

Table 4. Stepwise discriminant analysis and linear discriminant analysis with left ventricular mass index

Variables retained by the model	Standardized coefficients*	Wilk's lambda	*p*†
Age (years)	0.261	0.976	0.018
C-reactive protein (mg/dL)	0.533	0.857	<0.001
Low-density lipoprotein (mg/dL)	0.345	0.967	0.006
SYNTAX score	0.416	0.953	0.001
LVMI (g/m^2)	-0.636	0.847	<0.001
Overall model‡		0.681	<0.001

*Standardized canonical discriminant function coefficients. †p value is associated with the Wilk's lambda test.
‡Eigenvalue is 0.469, canonical correlation R squared is 31.9%, the correct classification of the function is 76.7%.

als. Kyriakides et al.[5] showed that hypertension was more prevalent in Rentrop 2 and 3 collateral grades, and that LV wall thickness was greater.

In contrast to our study, Harrison et al.[4] found no difference between LV hypertrophy and collateralization in animal and human studies. In the animal study, they compared 9 dogs with renal hypertension and LV hypertrophy with 17 controls. They evaluated coronary collaterals with radioactive microspheres. "Collateral resistance" and "normal zone resistance" were not different between groups (Standardized effect size for difference in these parameters was 0.5 and 0.25, respectively, and the study power for the difference in mean was 11.5% and 9%, respectively). In the human study, they categorized patients with aortic valve disease who were candidates for surgery into 2 groups according to the presence of LV hypertrophy. They considered alterations in echocardiography-guided posterior wall thickening during transient occlusion of the left anterior descending artery a surrogate of collateral presence. They found nonsignificant differences between groups (Standardized effect size for the difference was 0.5, and the study power for difference in mean was 8.9%). The small sample size in both the animal and human studies may have led to false negative results.

Another finding that is slightly different from our study was the association of collaterals with an increased ventricular wall thickness in the study performed by Kyriakides et al.[5] In our research, the overall LVMI was a better predictor of collateral presence than wall thickness. However, Kyriakides et al. reported only wall thickness, LV end-diastolic dimensions, and the anthropometric measures of the participants as complementary information to assess ventricular hypertrophy. From this point of view, we can speculate that in their study, increased wall thickness might be a marker of LV hypertrophy.

One major limitation of our study is that we couldn't quantify ischemia, which was a preliminary assumption. But, previous reports have demonstrated the high prevalence of coronary microvascular dysfunction that plays a key role in ischemia in LV hypertrophy.[14,15] However, the greater ischemic burden may correlate with increased collateralization. Another limitation is that we could not assess coronary microcirculation. Epicardial coronary arteries represent only the tip of the iceberg. The third limitation of our study is that, as an innate problem in all cross-sectional studies, we cannot demonstrate a cause and effect relationship. However, considering it in reverse, good collateralization may facilitate the ventricular hypertrophication process.

Despite these limitations, our study has advantages when compared with previous studies on the subject. For example, we used the standardized formula to quantify LV hypertrophy and identified cases according to individual remodeling categories.[6] These standardizations eliminated methodological ambiguities.

In summary, we have demonstrated that LV hypertrophy augmented coronary collateralization in patients with CTO. As a secondary goal, we found that the presence of a geometric pattern of eccentric hypertrophy followed by concentric hypertrophy was associated with collateral presence. This finding suggested that rather than LV wall thickness, hypertrophy itself was more decisive in predicting collateral presence. Based on these findings, we can speculate that defining the molecular, physiological, and hemodynamic background of collateralization in the setting

of LV hypertrophy may prompt researchers to investigate the driving force of these natural bypasses.

Acknowledgments

None

Funding

This research received no grant from any funding agency in public, commercial or not-for-profit sectors.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

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Keywords: Coronary collateral circulation; left ventricular hypertrophy; left ventricular mass index.

Anahtar sözcükler: Koroner kollateral dolaşım, sol ventrikül hipertrofisi, sol ventrikül kitle indeksi.