ACTA MEDICA TRANSILVANICA March 26(1):21-24
DOI: 10.2478/amtsb-2021-0006
Online ISSN 2285-7079

LOWER EXTREMITY ARTERY DISEASE AS A PREDICTOR OF CORONARY ARTERY DISEASE

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Keywords: *lower extremity artery disease, coronary artery disease, predictor*

Abstract: *Coronary artery disease (CAD) is an important determinant of long-term outcome in patients with lower extremity artery disease (LEAD). In this study we evaluated the CAD prevalence among LEAD patients and the association of LEAD lesions location with the CAD presence and severity. 203 patients with LEAD, referred for peripheral and simultaneous coronary angiography, were evaluated. LEAD and CAD were considered angiographically significant for stenosis higher than 50% of arterial lumen. More than two-thirds of LEAD patients had significant CAD, half of them having multi-vessel CAD and a quarter single CAD. Infrapoplitheal arterial lesions seemed to be the strongest predictor of CAD being associated with significant and multi-vessel CAD and also with the presence of left main (LM) lesions. Femoral artery lesions were highly associated with multi-vessel CAD, but there was no association with significant CAD and LM lesions. No association was found between iliac artery lesions and CAD.*

INTRODUCTION

Atherosclerosis is the main cause of lower extremity artery disease (LEAD) and coronary artery disease (CAD). Previous studies have shown that peripheral artery disease, which includes LEAD, is a CAD risk equivalent.(1,2)

High prevalence of CAD in peripheral artery disease patients was noted, ranging from 46 to 71%.(3,4,5) LEAD is highly associated with CAD, one-third of patients having a history and/or electrocardiographic signs of CAD, two-thirds presents changes in stress tests and up to 70% have at least single-CAD.(6,7,8) Studies have shown that patients with stable atherosclerotic disease, but without previous ischemic events, have more cardiovascular events in context of multi-arterial disease.(9) Moreover, mortality and long term prognosis in LEAD patients is directly correlated with CAD coexistence.(5,10,11,12) Not only the presence, but also the LEAD severity is correlated with CAD association: a high percentage of patients (up to 90%) that present in medical units with chronic limb-threatening ischemia also have CAD.(6)

The predictive value of LEAD lesion location for CAD was evaluated in several studies. Sung Woo et al demonstrated that the prevalence of proximal disease, defined as aortic-iliac and femoral-popliteal arteries stenosis, was higher in the normal or single CAD group, whereas that of involvement of both levels (proximal and distal, the last one being defined as below knee arteries) was higher in the multivessel CAD group.(5)

Multisystemic involvement of vascular disease is demonstrated in day by day practice. Association of CAD with peripheral artery disease, including LEAD, is clinically important, being well known that outcome of LEAD patients is influenced by the presence and severity of CAD. In this context, Current European guideline for peripheral artery disease (2017) recommends CAD screening in LEAD patients for risk stratification.(6)

AIM

The aim of this study was to see if there is any association between significant LEAD and CAD, if higher than 50% arterial stenosis in different segments of lower extremity arterial bed correlates with significant vs non-significant CAD, with single- vs multivessel-CAD and with left main lesions.

MATERIALS AND METHODS

We retrospectively reviewed 203 patients with symptomatic LEAD (intermittent claudication or critical limb ischemia) which underwent simultaneously digital subtraction angiography for LEAD evaluation and coronary angiography for CAD evaluation in Sibiu Emergency County Clinical Hospital, CVASIC research centre. There were excluded patients with embolic or non-atherosclerotic lower extremity artery lesions, being included only patients with chronic atherosclerotic lesions.

Significant LEAD and CAD were defined as at least one lesion with ≥ 50% lumen diameter stenosis. Lower extremity arteries were divided into three segments: iliac (common iliac artery, external iliac artery, internal iliac artery), femoral (common and superficial femoral artery and popliteal artery) and infrapopliteal (tibioperonier trunk, anterior tibial artery, posterior tibial artery, fibular artery). CAD was classified as significant-CAD (any coronary artery stenosis ≥ 50% lumen diameter in left main (LM) artery or left anterior descending (LAD) artery or circumflex artery (CxA) or right coronary artery (RCA)) or non-significant-CAD (without coronary artery stenosis ≥ 50% lumen) and as single-CAD (only one of LAD or CxA or RCA with lesion above 50%) or multivessel-CAD (LM stenosis ≥ 50%, or any of two arteries from LAD, CxA, RCA with arterial stenosis ≥ 50%).

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Article received on 18.02.2021 and accepted for publication on 02.03.2021

Cardiovascular risk factors – hypertension, dyslipidaemia and diabetes mellitus – were defined according to current guidelines. The patients were considered positive for smoking if they were active smokers or former smokers - but not more than 1 year abstinence. Normal values for C reactive-protein in our laboratory were 0-5 mg/dl. Chronic kidney disease was classified form grade I to V according to KDOQI classification, and creatinine clearance was calculated with Cockcroft-Gault formula.

Statistical analysis was performed using IBM SPSS Statistic software. Categorical variables are expressed as the number (percentages) and continuous variables were first analysed for data normality. The Shapiro-Willk test was used to analyse data normality. Normally distributed continuous variables were expressed as the mean±SD, and non-normally distributed continuous variables were expressed as the median value. Pearson Chi-Square tests was used to evaluate LEAD association with CAD. As a measure of association, we used the gamma- γ coefficient (Kendall's tau-c). Statistical significance was considered at a P value <0.05 (two-tailed).

RESULTS

Patient's characteristics

Of the 203 patients with symptomatic LEAD, 166 (81.8%) were male, 37 (18.2%) were female; the mean age was 65.31±8.616 (range 39-85years). Hypertension had the higher prevalence in our study group (79.8%) followed by smoking (76.84%), CKD (581%), hypercholesterolemia (54.7%), hypertriglyceridemia (48.3%) and diabetes mellitus (34.5%). The majority of patients were with stage II Leriche-Fontaine LEAD - 135 (64.5%) patients in stage II Leriche-Fontaine, 40 (19.7%) in stage III Leriche-Fontaine, 28 (13.8%) in stage IV Leriche Fontaine - with a mean claudication index of 144±24 m and a mean ankle-brachial index of 0.62±0.24.

Patient's demographic, clinical and biological characteristics are summarised in table no. 1 and table no. 2.

Table no. 1. Patients' demographic and clinical characteristics

Variable (N=203)	Value		
Age, years	65.31±8.6	Min: 39	Max: 85
BMI, kg/m^2	27.44±4.48	Min: 17.72	Max: 43.21
	Underweight		2 (1%)
	Normal weight		67 (33%)
	Overweight		82 (40.4%)
	Grade I obesity		40 (19.7%)
	Grade II obesity		10 (4.9%)
	Grade III obesity		2 (1%)
Gender	Male		166(81.8%)
	Female		37 (18.2%)
Smoking	Yes		156 (76.84%)
	No		47 (23.16%)
Diabetes mellitus (DM)	Yes		70 (34.5%)
	No		133 (65.5%)
Hypertension	Yes		162 (79.8%)
	Grade I		0 (0%)
	Grade II		76 (37.4%)
	Grade III		85 (41.9%)
	No		41 (20.2%)
Hypercholesterolemia	Yes		111 (54.7%)
	No		92 (45.3%)
Hypertriglyceridemia	Yes		98 (48.3%)
	No		105 (51.7%)
CKD	Yes (Creatinine clearance <90ml/min/1.73m^2)		118 (58.1%)
	Grade II		85 (41.9%)
	Grade IIIa		28 (13.8%)
	IIIb		3 (1.5%)
	Grade IV		2 (0%)
	Grade V		3 (1%)
	No (Creatinine Clearence > 90 ml/min/1.73m^2)		85 (41.9%)
Leriche-Fontaine classification	**I** : Asymptomatic		0 (0%)
	IIa: intermittent claudication at more than 200 m walk		17 (8.4%)
	IIb: intermittent claudication in less than 200 m walk		118 (58.1%)
	III: limb rest pain		40 (19.7%)
	IV: ischemic lesions – necrosis, gangrene		28 (13.8%)
Claudication index, m	144±24	Min: 0	Max: 1000
Ankle-Brachial index	0.62±0.24	Min: 0	Max: 1

Table no. 2. Patients' biological characteristics

Parameter (N=203)	Mean±SD	Minimum	Maximum
Total cholesterol, mg/dl	207.60±55.86	107	357
LDL-cholesterol, mg/dl	117.57±43.76	31	290
HDL – cholesterol, mg/dl	44.91±10.93	27	86
Triglycerides, mg/dl	185.78±148.4	44	1356
Creatinine, mg/dl	1.02±0.59	0.55	6.88
Clearance Creatinine, ml/min/1.73m^2	85.75±25.59	8.32	166.99
C reactive-protein, mg/dl	8.07±12.79	0.57	127.62

Coronary angiography characteristics of patients

In our study group 175 (86.2%) patients had right coronary dominance. The prevalence of CAD in LEAD patients was 75.4 % (153/203). Among these patients, 49.8% (101/203) had multivessel-CAD and 25.6% (52/203) had had single-CAD. LM lesions were found in 34% (69/203) of patients, including 32% (65/203) of patients with <50% stenosis, 0.5% (1/203) of patients with 50-75% stenosis and 1.5% (3/203) of patients with >75% stenosis. 57.6% (117/203) patients had significant LAD stenosis, 39.5% (80/203) patients had significant CxA stenosis and 44.82% (91/203) patients had significant RCA stenosis (table no. 3).

Table no. 3. Coronary angiography characteristics of patients

Characteristic N = 203 patients		Frequency	Percent (%)
Dominance	Right	175	86.2
	Left	22	10.8
	Co-dominance	6	3
Significant/non-significant CAD	Non-significant CAD	50	24.6
	Significant CAD	153	75.4
Non-significant/single/multivessel- CAD	Non-significant CAD	50	24.6
	Single-CAD	52	25.6
	Multivessel-CAD	101	49.8
Lesion severity	0-50%	50-75%	75-100%
LM	199 (98%)	1 (0.5%)	3 (1.5%)
LM - no (no stenosis): 134 (66%) LM - yes (stenosis of any severity): 69 (34%)			
LAD	86 (42.4%)	77 (37.9%)	40 (19.7%)
CxA	123 (60.6%)	33 (16.3%)	47 (23.2%)
RCA	112 (55,17%)	21 (10.34%)	70 (34.48%)

Association of LEAD with non-significant/single -/multivessel-CAD

In our study group, significant lesions >50% in iliac segment were not associated with multivessel-CAD (p 0.271) (table no. 5).

Instead, in patients with significant arterial stenosis (>50%) in femoral segment, the percentage of multivessel-CAD was higher than the percentage of single-CAD and non-significant CAD, respectively (94% versus 78.8% versus 86%, respectively). The difference was statistically significant (χ^2=11.8, df 4 p=0.019) (table no. 5). As a measure of association, it was used the gamma- γ coefficient, indicating a proportion of 30.2% of the association of multivessel-CAD with significant femoral lesions, but without statistical significance (p 0.157).

Similar result was found for infrapopliteal segment: in

patients with significant arterial stenosis (>50%) in infrapopliteal segment, the percentage of multivessel-CAD was higher than the percentage of single-CAD and non-significant CAD, respectively (90.1% versus 88.5% versus 72%, respectively). The difference was statistically significant (χ^2=9.9, df=4 p=0.041) (table no. 5). As a measure of association, it was used the gamma- γ coefficient, indicating a proportion of 27.8% of the association of multivessel-CAD with significant infrapopliteal lesions, but without statistical significance (p 0.59).

Table no. 5. Association of LEAD with non-significant/single -/multivessel-CAD

CAD	Iliac segment – lesion severity (%)			Chi-Square test	
	0-50	50-75	75-100	χ^2	p
Non-significant CAD	26 (52%)	4 (8%)	20 (40%)	5.165	0.271
Single-CAD	22 (42.3%)	11 (21.2%)	19 (36.5%)		
Multivessel-CAD	44 (43.6%)	23 (22.8%)	34 (33.7%)		
CAD	**Femoral segment – lesion severity (%)**			**Chi-Square test**	
	0-50	50-75	75-100	χ^2	p
Non-significant CAD	7 (14%)	1 (2%)	42 (84%)	11.803	0.019
Single-CAD	11 (21.2%)	1 (1.9%)	40 (76.9%)		
Multivessel-CAD	6 (5.9%)	9 (8.9%)	86 (85.1%)		
CAD	**Infrapopliteal segment – lesion severity (%)**			**Chi-Square test**	
	0-50	50-75	75-100	χ^2	p
Non-significant CAD	14 (28%)	1 (2%)	35 (70%)	9.950	0.041
Single-CAD	6 (11.5%)	3 (5.8%)	43 (82.7%)		
Multivessel-CAD	10 (9.9%)	6 (5.9%)	85 (84.2%)		

Association of LEAD with significant/non-significant CAD

The association of significant arterial lesions >50% in iliac and femoral segments with significant CAD (>50%) was not statistically significant with a p value of 0.134 for iliac segment and 0.394 for femoral segment.

On the other hand, in the present study, 133 (89.2%) patients with significant infrapopliteal lesions (>50%) had significant-CAD (>50%), compared with 16 (10.7%) cases with infrapopliteal lesions below 50% that had significant-CAD. The association was statistically significant (χ^2=8.1, df=2, p=0.017).

Association of LEAD with LM lesions

The association of significant arterial lesions >50% in iliac and femoral segments with the presence of LM lesion was not statistically significant with a p value of 0.278 for iliac segment and 0.091 for femoral segment.

Significant infrapopliteal lesions (>50%) were significantly associated with LM lesions (p 0.043), as shown in table no. 7.

Table no. 7. Association of significant infrapoplileal lesions (>50%) with LM lesions

LM lesion	Infrapopliteal segment – lesion severity (%)			Chi-Square test	
	0-50	50-75	75-100	χ^2	p
No (no stenosis)	19 (14.3%)	2 (1.5%)	112 (84.2%)	6.294	0.043
Yes (stenosis of any severity)	11 (15.9%)	8 (11.6%)	50 (72.5%)		

The presence of significant infrapopliteal lesions (>50%) is associated with LM lesion in proportion of 84.1% versus 15.9% in the case of nonsignificant lesions (χ^2=6.2, df=2, p=0.043), the chance that the association is verified being 4.7 times higher (p 0.05).

DISCUSSIONS

LEAD and CAD affect more frequently males than females. Age greater than 45 years for men and greater than 55 for women is associated with risk of CAD and LEAD developing.(14,15) In our study group, male gender predominance was observed and the mean age correspond to literature information.

The increased incidence of smoking, hypertension and hypercholesterolemia among studied patients coincides with literature data.(4,5)

Multisite artery disease is common for patients with atherosclerotic lesions ranging from 60 to 70% in patients with severe LEAD (6) - with CAD ranging from 46-71%.(3,4,5) Significant CAD was found in more than two-thirds of patients evaluated in this study, half of patients having multivessel-CAD and one quarter having single-CAD. The interest for CAD association with LEAD is explained by the fact that the main cause of late death in patients with peripheral artery disease is ischemic heart disease (up to 50% of deaths in patients with peripheral artery disease).(16) CONFIRM registry showed that in LEAD patients, obstructive CAD was associated with annual mortality rate of 1.6% versus 0.7% in the absence of severe CAD.(6,17)

Proximal lesions defined as iliac, femoral, popliteal artery stenosis are more likely associated with normal or single CAD. Involvement of lower extremities proximal and distal arteries has a high chance of association with multi-vessel CAD.(5) Our study results were concordant with data mentioned above: infrapopliteal lesions were associated with both the presence and severity of CAD (defined as multi-vessel CAD and LM lesions), femoral lesions were associated with multi-vessel CAD, while iliac lesions were not significantly associated with the presence of CAD.

Prognosis of peripheral artery disease patients is different according to lesion location.(5) Chan, et al demonstrated that the presence of lower extremity distal arterial disease is associated with a poorer prognosis compared with patients without distal disease. In contrast for patients with proximal disease there were no prognosis differences.(13) Multilevel LEAD disease determined a poorer prognosis in LEAD patients.(18) This prognosis differences may be explained by the higher association of distal and multilevel LEAD with multivessel-CAD, compared with proximal LEAD.

CONCLUSIONS

Significant CAD has a high prevalence among symptomatic LEAD patients.

Significant lesions in different segments of lower extremity arterial bed are differently associated with significant CAD.

Infrapopliteal significant lesions seems to be the strongest predictor of CAD, being associated with significant CAD, multivessel-CAD and with the presence of LM lesions of any severity. Thus, infrapopliteal significant lesions correlates with the presence of significant CAD and also with CAD severity quantified by the number of vessels affected (multivessel-CAD) and by LM involvement.

Significant lesions in femoral segments were highly associated with multivessel CAD, but there was no association with significant CAD and with LM lesions.

Finally, there was no significant association between iliac segment lesions and significant, multivessel-CAD and LM

lesions.

The study results suggest that CAD evaluation should be performed in symptomatic LEAD patients, with increased attention for patients with significant lesions in femoral and infrapopliteal segments. In addition, reduced daily activity in symptomatic LEAD patients can reduce angina symptoms in CAD patients; therefore, screening for "asymptomatic" CAD might be an option for LEAD patients.

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