KARDIOLOGIA POLSKA

Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957

Online first
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ISSN 0022–9032 e-ISSN 1897–4279

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Article type: Short communication

Received: February 2, 2023

Accepted: April 29, 2023

Early publication date: May 13, 2023

Large unstained cells (LUCs) count is a useful predictor of coronary artery disease co-existence in patients with severe aortic stenosis

Short title: LUCs as co-existence CAD predictors in SA patients

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INTRODUCTION

The burden of aortic valve stenosis (SA) is growing due to demographic changes with an aging of population [1]. The appropriate diagnosis especially in patients with angina pectoris symptoms is of outmost importance due to its association with limited life expectancy.

Coronary artery disease (CAD) and aortic valve degeneration share similar pathogenetic factors including lipid accumulation and calcium deposition [2].

There is a limited utility of angina pectoris symptoms is CAD diagnosis among patients with aortic stenosis since chest pain is typical for both diseases. Previous reports demonstrated 50%

prevalence of angiographically significant coronary artery disease among patients presenting angina pectoris symptoms with already diagnosed aortic stenosis [3].

Noninvasive stress tests are characterized with low specificity and exercise tests usually performed in the assessment of coronary artery disease are contradicted in symptomatic SA patients. Several attempts for non-invasive laboratory markers inclusion in diagnostics were undertaken [4, 5].

Some simple laboratory investigations might help in the evaluation of cardiovascular patient.

The aim of the study was to find a non-invasive easily accessible marker for coronary artery disease co-exitance in patients with aortic stenosis.

METHODS

Two hundred consecutive patients with symptomatic aortic stenosis with or without coronary artery disease admitted to the cardiac surgery department between November 2017 and September 2022, were analyzed. Subjects with active endocarditis or CAD with moderate SA, and patients with history of oncological or rheumatic disorders were excluded from the study. The final study group comprised 190 patients with severe aortic stenosis divided according to absence (group 1, n = 85, 44.7%) or presence (group 2, n = 105, 55.3%) of coronary artery disease defined as the coronary artery atherosclerotic changes covering at least 50% of the artery lumen. Demographic and clinical data were analyzed. Blood samples were collected at admission, and results were related to echocardiographic findings.

All patients referred for the surgical procedure had preserved left ventricular ejection fraction. Echocardiographic intra- and inter-observer variability may be related to pre- and post-operative differences in the visualization; however, it remains low in the experienced centers. Echocardiographic methodology was presented in Supplementary material no. 2.

The study was approved by the local Institutional Ethics Committee (no. 198/2021).

Statistical analysis

Analysis was performed using MedCalc® Statistical Software version 20.027 (MedCalc/Software Ltd, Ostend, Belgium). Detailed information was presented in Supplement 3.

RESULTS AND DISCUSSION

Preoperative echocardiographic characteristics revealed a difference between groups in median (interquartile range [IQR]) transvalvular aortic gradient 58 (50–67) mm Hg vs. 54 (46–61) mm

Hg (P = 0.005) and presented in detail in Supplementary material no. 1 and *Table S1*. Patients in group 2 were older, and diabetes and atrial fibrillation occurred more often in this population. Detailed demographical and clinical data is presented in Supplementary material no. 1 and *Table S2*, and preoperative laboratory results in Supplementary material no. 1 and *Table S3*.

Large unstained cell (LUC) count was the only laboratory parameter from whole blood count excluding serum C-reactive protein analysis, which varied in both subgroups (P = 0.007).

In the multivariable logistic regression model with backward stepwise elimination method (Table 1): age (P = 0.010), diabetes mellitus (P = 0.003), and LUC count (P = 0.035) were revealed as predictors of CAD co-existence with severe SA, even despite statin therapy. For LUC cells the estimate odds ratio [OR] was found 1.737 (95% confidence interval [CI], 1.040–2.901).

The multivariable analysis and the ROC analysis established that following indicators have the highest significance for CAD co-existence: LUC count above 0.19 K/uL (OR, 1.737; 95% CI, 1.040–2.901; P = 0.035; AUC = 0.602 with a sensitivity of 68% and specificity of 51%), age (OR, 1.056; 95% CI, 1.012–2.101; P = 0.010; AUC = 0.612 with a sensitivity of 82% and specificity of 36%) and diabetes mellitus (OR, 2.765; 95% CI, 1.413–5.410; P = 0.003; AUC = 0.608, yielding sensitivity of 43% and specificity of 79%). Detailed information regarding uni- and multivariable analysis was presented in Table 1.

Our analysis presents a new approach for assessment of CAD co-existing with SA based on whole blood count analysis. This is the first, to our best knowledge, study indicating LUC obtained from whole peripheral blood analysis as simple and reliable predictor of CAD disease in SA-patients.

There is over 50% co-existence of CAD in patients with severe SA [3]. The identification of accompanying diseases is crucial for therapy planning. Established CAD in SA was related to significantly higher risk of cardiac mortality [7]. The normal results of exercise test were found in 1/5 patients with asymptomatic SA and silent CAD [8]. Such observations indicate the necessity for alternative non-invasive tests in this group of patients.

Both, degenerative SA, and CAD, share similar risk factors including male gender, arterial hypertension, diabetes mellitus, smoking, and hypercholesterolemia. In our multivariable analysis, age and diabetes mellitus were found significant for CAD prediction.

Chest pain is the most typical presentation of obstructive CAD. In SA, anginal symptoms are related to imbalance between hypertrophic myocardium oxygen demands acting in increased wall stress secondary to left ventricle compensatory afterload, and its blood flow supply [9]. Exercise test may be inconclusive, especially in asymptomatic patients. Coronary flow reserve

(CFR) in patients with SA is impaired due to reduced diastolic filling time and elevated LV pressure combined with perivascular and myocardial fibrosis [10].

In our analysis, we focused on inflammatory characteristics in both diseases. The significance of inflammatory activation as arterial hypertension trigger was postulated [11]. The results of our study point out the role of possible predictors for co-existence of CAD in SA patients available from whole blood count analysis.

The link between altered monocytic phenotype and hypertension has been already presented [12]. Our novel finding is first presenting the importance of LUC in cardiovascular disorders. The knowledge about LUC cells is scarce and its role and significance is often overlooked. LUC reflect to activated lymphocytes and peroxidase-negative cells. Though LUC cells are claimed to present the lack of specificity, they represent the group of cells including blasts, atypical lymphocytes, plasma cells, and peroxidase-negative neutrophils [13]. Our previous report showed the prognostic value of LUC in the assessment of inflammatory activation and carotid artery stenosis characteristics [14]

Our results confirm previous reports of atherosclerosis development in patients with SA characterized by chronic inflammatory activation and show that this phenomenon may rely on more advanced innate immunity response characterized by LUC.

The lack of possibility to evaluate the potential influence of anti-inflammatory effect of statins and antidiabetic treatment may be a limitation of our study.

In conclusion, LUC count above 0.19 K/uL in whole blood analysis can be regarded as possible indicator for co-exitance of coronary artery disease in patients with aortic stenosis.

Article information

Conflict of interest: None declared.

Funding: None.

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Table 1. Uni- and multivariable analysis for CAD prediction in SA patients

Parameters	**Univariable Analysis**			**Multivariable Analysis**		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age (per 1 year)	1.062	1.021–1.104	0.003	1.056	1.012–1.101	0.012
Sex (male)	1.139	0.623–2.084	0.67	—	—	—
DM	2.792	1.460–5.338	0.002	2.765	1.413–5.410	0.003
HA	1.142	0.560–2.329	0.72	—	—	—
COPD	0.634	0.165–2.437	0.507	—	—	—
PAD	1.209	0.529–2.766	0.65	—	—	—
AF	2.222	0.879–1.205	0.05	—	—	—
LUC	1.890	1.122–3.182	0.02	1.737	1.040–2.901	0.035

Abbreviations: AF, atrial fibrillation; CI, confidence interval; COPD, chronic pulmonary obstructive disease; DM, diabetes mellitus; HA, arterial hypertension; LUC, large unstained cells; OR, odds ratio; PAD, peripheral artery disease