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Alterations in endothelial activation biomarkers ICAM-1 and VCAM-1 following mitral regurgitation surgery

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ABSTRACT

Objective: Severe chronic degenerative mitral regurgitation (MR) is characterised by altered hemodynamics and high-shear stress, which initiate left ventricular (LV) remodelling, including upregulation of various cytokines. We evaluated endothelial activation during surgical correction of chronic MR by assessing adhesion molecules ICAM-1 and VCAM-1, classic markers of inflammation, and their association with postsurgical LV dysfunction (LVD).

Material and Methods: The study included asymptomatic patients with grade 3-4 degenerative MR. Transthoracic echocardiography data and blood samples were collected before and five days after surgical correction of MR. Circulating levels of adhesion molecules were measured by ELISA.

Results: Ejection fraction, end-diastolic diameter (EDD), and volume all decreased significantly after surgery. A significant decline in ICAM-1 concentration was observed between the two periods (457.11±256.12 vs. 240.29±157.14 ng/mL; p=0.031), whereas VCAM-1 levels did not change significantly. Leukocyte count and C-reactive protein were significantly higher in the postoperative period. Early postoperative LVD (in 35.7% of patients) was not correlated with adhesion molecule levels. However, we observed significant changes in ICAM-1 levels associated with postoperative EDD >5.6 cm, which indicates LV dilatation. These patients had markedly lower preoperative and postoperative ICAM-1 values than others.

Conclusion: Serum ICAM-1 levels significantly decline following surgical correction of MR and are associated with postoperative enlargement of the LV. Our study highlights dynamic changes in endothelial activity and underscores the need for a better understanding of this process in MR.

Keywords: Mitral valve replacement, vascular cell adhesion molecule-1, left ventricular dysfunction, endothelial activation

INTRODUCTION

Mitral regurgitation (MR) is a valvular disease that is predominantly degenerative in developed countries, whereas infectious and rheumatic causes remain common in other countries (1,2). Initial cardiac structural derangements due to chronic primary MR elicit cellular responses leading to pathological wall remodelling. Specifically, end-diastolic volume (EDV) overload disrupts extracellular matrix (ECM) architecture and induces cytoskeletal alterations that, along with oxidative stress, generate inflammation, a fibrotic response, and apoptotic cell death. Pathological left ventricular (LV) remodelling includes altered matrix metalloproteinase activity and collagen isoform distribution, reduced protein degradation, cell slippage, myocyte loss, and, finally, myocardial fibrosis (2-4). The remodelling of the MR underpins the progression of cardiac dysfunction and complications, such as myocardial weakening, cardiac arrhythmias, thrombosis, and heart failure. The currently recommended therapeutic approach is surgical repair or replacement of the mitral valve in patients eligible for surgery (5,6).

Altered hemodynamics and a high-shear-stress environment in moderate-to-severe chronic MR contribute to structural and functional modifications (5,7-9). Consistent with this, endothelial cells subjected to mechanical strain or altered shear stress rapidly generate a stress response, reflected by upregulated gene and protein expression of inflammatory cytokines, chemokines, and cell adhesion molecules. Endothelial injury is considered an adverse event that maintains and aggravates LV remodelling and interferes with recovery (1,2,5-9).

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The short-term effects of surgical relief of volume overload on LV remodelling, function, and systemic hemodynamics during MR correction have not been sufficiently studied, particularly with respect to cellular events. Alterations in shear stress and inflammation increase the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which are considered biomarkers of endothelial activation and mediators of inflammation. Their induction can occur via cytokines and local peptides, such as tumour necrosis factor-α (TNF-α), transforming growth factor -β1 (TGF-β1), and bone morphogenetic protein-4 (BMP-4) (8-11). The primary role of adhesion molecules is to provide a firm attachment of leukocytes during the inflammatory response. ICAM-1 is a receptor for leukocyte β2-integrins, while VCAM-1 interacts with α4β7 integrin and is involved in leukocyte transendothelial migration to sites of inflammation (9-12). In addition, ICAM-1 is involved in wound healing and is constitutively expressed in the lung microvascular endothelium (3,10). The expression of adhesive molecules can be induced in several other cell types that do not usually express them, as observed in myogenic cells during regenerative myogenesis of skeletal muscle (10-14).

We aimed to evaluate endothelial activation during surgical correction of chronic primary MR by assessing adhesion molecules ICAM-1 and VCAM-1, along with classic markers of inflammation [white blood cell count (WBC), C-reactive protein (CRP), and fibrinogen]. The association between the adhesion molecules and postsurgical LV dysfunction (LVD) is also analysed.

MATERIAL and METHODS

Study Population

This pilot prospective cohort study included 28 consecutive patients with grade 3-4 MR, according to the 2020 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with valvular heart disease, and used appropriate validated techniques (2,5). The patients were recruited in 2025 at the Clinic for Cardiac Surgery, University Clinical Centre of Serbia, University of Belgrade.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Review Board of the University of Nis in Serbia (approval no: 12-16442-1/2-4 from December 20, 2024).

The inclusion of patients started in December 2024 and lasted until July 2025. Inclusion criteria included adult, asymptomatic patients with primary severe MR of non-ischemic and non-rheumatic causes who agreed to participate in the study and provided written informed consent. The patients underwent routine transthoracic echocardiography with quantification of MR, as well as transesophageal echocardiography (TEE), which was used to guide intraoperative decision-making. Quantitative grading of severe primary MR was based on 2D echocardiography and included: Effective regurgitant orifice area by 2D proximal is velocity surface area ≥40 mm^2, regurgitant volume ≥60 mL/beat, and regurgitant fraction ≥50%. Surgical indications for patients with asymptomatic primary MR also included ejection fraction (EF) <60%, LV end-systolic diameter >40 mm, atrial fibrillation, systolic pulmonary artery pressure (SPAP) >50 mmHg, and/or left atrial volume index >60 mL/m^2 (2,15).

The appropriate surgical approach was determined using TEE. Patients underwent either mechanical mitral valve replacement (MVR) or mitral valve prosthetic ring annuloplasty (MVA) with a restrictive prosthetic ring (downsizing by 2.7±0.8 ring sizes). MVR was commonly performed in patients with severe MR who were unsuitable for surgical repair, according to recommendations (2,15).

Exclusion criteria included ischemic cardiomyopathy, acute cardiac events, coronary artery disease, history of bypass surgery or percutaneous angioplasty, aortic valve disease, mitral stenosis, or other cardiac diseases. Patients with diabetes mellitus, malignancies, or acute or chronic inflammatory diseases were not recruited. In addition, patients who developed an infection during postoperative recovery were excluded from the study.

Data Collection

Patient data were collected before the procedure and 5 days after the procedure using transthoracic echocardiography (2D and M-mode). The obtained variables were measured or calculated (through the Teicholz method), including dimensions [end-diastolic (EDD), end-systolic (ESD)] and volumes of the LV (EDV, ESV, SV), EF, as well as derived measures of forward LVEF (100× forward stroke volume/LV EDV), right ventricle systolic pressure, and LV wall stress (WS).

Patients were divided into groups and compared based on the development of early postoperative LV systolic dysfunction, defined as LV EF <50% after mitral valve surgery.

Biomarker Measurement

A blood sample was collected from each patient before surgery and again 5 days after surgery. Assessment of inflammatory biomarkers after 5 days is often used to provide crucial information on the patient's response to treatment and to monitor early treatment effectiveness. During this period, early-induced inflammatory markers (e.g., CRP) typically decrease rapidly with effective treatment; consequently, their changes may reveal the course of the disease, progression to complications, or recovery. ICAM-1 and VCAM-1 are also part of the rapid phase of the endothelial-cell response to various stimuli (16-20).

The solid-phase sandwich ELISA was used to measure the concentrations of adhesion molecules. Human ICAM-1/CD54 Allele-specific Quantikine ELISA Kit had a sensitivity of 0.254

ng/mL and an assay range of 1.6-50 ng/mL, while the Human VCAM-1/CD106 Quantikine ELISA Kit had a sensitivity of 1.26 ng/mL and an assay range of 6.3-200 ng/mL (R&D Systems, Inc., Europe Abingdon OX14 3NB, UK). Routine laboratory examination consisted of CBC and analysis of biochemical parameters, performed using the CELL-DYN Ruby Haematology Analyser (Abbott Diagnostics, Illinois, U.S.A.). Inflammatory biomarkers (WBC, CRP, and fibrinogen) and adhesion molecules were analyzed across the two time periods.

Statistical Analysis

Results are presented as continuous or categorical variables: Continuous data are reported as mean ± standard deviation, and categorical data as percentages, as required. The distribution of the variables was assessed using the Shapiro-Wilk test. Independent and paired t-tests were used to compare measured parameters before and after the corrective procedures in patients. The Pearson correlation coefficient was used to measure linear correlation between two sets of data. The chi-square test was used to compare categorical parameters. We collected complete data for all patients. A significance threshold was set at $p<0.05$. Statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 28 included patients, 21 (75%) were male and 7 (25%) were female, with a mean age of 65.1±12.6 years. Twelve (42.8%) underwent MVA, while 16 (57.1%) underwent MVR. Gender did not influence the type of surgery ($p>0.05$). The average duration of MR was 12±11 months. Following standard preoperative preparation, all patients underwent general anesthesia. Open-heart surgery was performed via median sternotomy, with partial resection of post sternal tissue and an inverted T-shaped vertical pericardiotomy. The cardiopulmonary bypass was applied. The mean cross-clamp and cardiopulmonary bypass times were 83.76±21.41 and 115.88±38.20 minutes, respectively. All patients recovered well after surgical MR correction without complications.

Transthoracic echocardiography showed that EF, EDD, EDV, SV, and RVSP were significantly decreased after surgery compared with the preoperative period ($p<0.05$). The mean postoperative EF did not differ significantly between the MVA and MVR groups (54.5%±15.16 vs. 52.8%±5.88). The echocardiographic parameters for the two time periods are shown in Table 1.

We observed a significant difference in ICAM-1 concentrations between the two periods [457.11±256.12 vs. 240.29±157.14 ng/mL; p=0.031; 95% confidence interval (CI): 26.07-443.29]. By contrast, there was no significant change in VCAM-1 levels (1019.45±737.39 vs. 1099.07±764.59 ng/mL, $p>0.05$) in our patients (Table 2). Additionally, there was no significant correlation between preoperative and postoperative levels of ICAM-1 or VCAM-1.

The WBC and CRP levels were significantly elevated in the postoperative period, likely reflecting tissue injury caused by the surgery. However, fibrinogen concentration did not change markedly (Table 2).

Before surgery, ICAM-1 and fibrinogen concentrations were observed to be significantly and negatively correlated (p=0.020; r=-0.613). There was a weak tendency toward a negative correlation between ICAM-1 and CRP levels (p=0.090, r=-0.470). Postoperatively, ICAM-1 levels tended to correlate positively with EDD (p=0.052, r=0.435). No other significant correlations were observed between the adhesion molecules and inflammatory biomarkers or echocardiographic parameters.

Early postoperative LVD (<50% EF) was recorded in 10 patients (35.7%), with a mean EF of 44.20±5.54% compared with 58.33±5.52% in patients without LVD (p=0.001; 95% CI: 7.414-20.852). Preoperative EDD was higher in those who developed

Table 1. Echocardiography parameters in the two time periods

Parameter	Mean ± SD		p-value (CI)
	Before surgery	After surgery	
EF (mL)	62.14±8.25	53.29±8.81	0.013 (2.17-15.54)
EDD (cm)	6.06±0.57	5.29±0.49	0.001 (0.41-1.14)
ESD (cm)	3.97±0.52	3.81±0.59	NS
EDV (mL)	187.51±39.71	137.67±28.53	0.000 (30.36-69.33)
ESV (mL)	71.06±21.56	64.12±22.55	NS
SV (mL)	116.21±31.86	73.55±15.12	0.000 (24.57-60.85)
FLVEF (mL)	33.64±8.94	42.13±16.05	NS
RVSP (mmHg)	51.82±11.56	39.86±7.84	0.008 (3.68-20.25)
WS (kdynes/cm^2)	117.95±17.45	115.90±14.59	NS

EF: Ejection fraction, EDD: End-diastolic diameter, ESD: End-systolic diameter, EDV: End-diastolic volume, ESV: End-systolic volume, SV: Stroke volume, FLVEF: Forward left ventricular EF, RVSP: Right ventricular systolic pressure, WS: W all stress, SD: Standard deviation, CI: Confidence interval, NS: Not significant.

Table 2. Adhesion molecules and inflammatory biomarkers in the two time periods			
Parameter	**Mean ± SD**		**p-value (CI)**
	Before surgery	**After surgery**	
ICAM-1 (ng/mL)	457.11±256.12	240.29±157.14	0.031 (26.07-443.29)
VCAM-1 (ng/mL)	1019.45±737.39	1099.07±764.59	NS
WBC ($x10^9$)	7.32±2.76	11.61±1.96	0.000 (-6.18- -2.39)
CRP (mmol/L)	2.68±3.23	117.59±47.61	0.000 (-141.79- -8.02)
FIB (g/L)	3.25±0.56	3.31±0.35	NS

ICAM-1: Intracellular adhesion molecule-1, VCAM-1: Vascular cell adhesion molecule-1, WBC: White blood cells, CRP: C-reactive protein, FIB: Fibrinogen, SD: Standard deviation, CI: Confidence interval, NS: Not significant.

LVD, but the difference was not statistically significant (6.44±0.62 vs. 5.86±0.44; p=0.060). Of the postoperative echocardiographic parameters, ESD differed significantly, with a greater diameter in those with LVD vs. others (4.26±0.47 vs. 3.56±0.52 cm; p=0.028; 95% CI: -1.317 to -0.091).

Adhesion molecules and inflammatory biomarkers did not correlate with postoperative EF or with the development of LVD. Accordingly, both patient groups demonstrated declines in ICAM-1 levels after MR correction. VCAM-1 concentration decreased in the non-LVD group, whereas it was slightly higher in the LVD group; however, the difference was not statistically significant.

However, the results demonstrate significant changes in ICAM-1 levels in patients with postoperative EDD >5.6 cm (the upper limit of normal diastolic size), indicating LV dilatation (n=13, 46.4%). These patients had significantly lower preoperative and postoperative ICAM-1 values than patients with normal-sized EDD (preoperative ICAM-1: 276.987±191.83 vs. 592.198±216.501; p=0.015; postoperative ICAM-1: 139.65±106.86 vs. 312.173±138.097; p=0.042).

In addition, postoperative WBC count was significantly associated with EDD >5.6 cm. Lower WBC counts were observed in patients with an enlarged LV (10.250±1.477 vs. 12.625±1.675; p=0.017).

DISCUSSION

Mitral valve regurgitation is an important contributor to cardiovascular disease. Patients with severe MR undergo surgical repair, preferably before symptom onset, because studies have found better survival in this setting. Importantly, severe MR indicates that substantial ventricular remodeling has already occurred due to chronic volume overload. Despite a preoperative EF ≥60%, LV contractile dysfunction is a common complication of MR surgery. Thus, the actual state of the LV in asymptomatic MR may be masked by a normal EF. When the mitral defect is corrected, the influence of regurgitant volume disappears and afterload increases, thereby revealing the actual state of LV function (1,2,5,6,21).

A prolonged increase in WS in MR is associated with activation inflammatory and apoptotic pathways, ultimately leading to cell loss and myocardial ECM derangement with diffuse interstitial fibrosis (6,21). At the same time, the endothelium, a dynamic system that adapts in response to shear stress, undergoes functional and structural reorganization, including altered expression of molecules mediating cell-matrix and cell-cell interactions. Research on ischemic mitral valve regurgitation shows that the endothelium has an early and dynamic role in valve adaptation. Specifically, an insult to the endothelium and intimal tissue is followed by a defensive response in which signaling from injured cells initiates remodeling pathways (5,6,21).

Adhesion molecules ICAM-1 and VCAM-1 are established markers of endothelial activation. The upregulation of these molecules helps inflammatory cells adhere to and infiltrate the subendothelium. Accordingly, their concentrations have been elevated in various inflammatory conditions (9,10,22,23). Nevertheless, evidence shows that these adhesion molecules are related not only to inflammatory processes but also to degenerative processes and epithelial injury-resolution responses (10,13,23). ICAM-1, VCAM-1, and E-selectin were found to be constitutively expressed on both degenerative (mostly calcified) and inflamed valves during acute endocarditis. Moreover, aortic valvular endothelium displays an inflammatory response under shear stress conditions, including the upregulation of ICAM-1 and VCAM-1. These molecules are correlated with the occurrence of cardiac events and therefore have been proposed for the assessment of cardiovascular risk (10,22,23).

We determined that serum ICAM-1 levels changed following MR-correcting surgery. Blood ICAM-1 declined significantly five days after surgery. By contrast, VCAM-1 levels did not vary significantly in relation to MR surgery. Leukocyte counts and CRP values were elevated postoperatively, likely reflecting tissue damage, and declined gradually.

Moreover, ICAM-1 levels were markedly associated with EDD size but not with LVD occurrence, although patients who

developed LVD had higher preoperative LV diameters. LV EDD >5.6 cm indicates LV dilatation, which is often accompanied by reduced systolic function, chronic strain, or LVD. An enlarged EDD suggests structural changes and impaired contractility, which may increase the risk of heart failure (24-26). Li et al. (24) demonstrated that an enlarged LV EDD in patients with coronary artery disease is an independent predictor of all-cause mortality. Our patients with postoperative LV dilatation had significantly lower ICAM-1 levels than others.

LV dilatation alters blood flow dynamics and vortex patterns, changes wall shear stress, and consequently affects the behavior and function of the cardiovascular system. Dilatation reduces blood flow velocity during diastolic filling, likely because of a longer filling period and a reduced pressure gradient between LV pressure and left atrial pressure. In this context, endocardial cells engage in a series of signaling cascades that modify protein expression (27,28).

Moreover, our results reveal a discrepancy between inflammatory biomarkers and adhesion molecules. Preoperatively, ICAM-1 was inversely correlated with fibrinogen and CRP. VCAM-1 did not correlate with other biomarkers. These results suggest that the adhesion molecules may not be exclusively influenced by the inflammatory response, but rather by another process. Also, the changes we observed occurred relatively quickly following operative correction and appeared to be related to hemodynamic changes associated with surgery. We suppose that higher preoperative ICAM-1 levels may result from increased shear stress in the heart and increased pressure in the pulmonary vessels due to MR.

Valvular endothelial cells exhibit several distinct features in their responses to mechanical and haemodynamic stimuli. Their response to oscillatory and turbulent shear stress includes upregulation of chemokines and adhesion proteins (ICAM-1 and VCAM-1) (1). Moreover, circulating ICAM-1 is proposed to originate from proteolytic cleavage and release of cell surface-bound ICAM-1, mediated by kinases and metalloproteinases (e.g., ADAM17) (29,30). In this context, a recent in vitro study observed a profound upregulation of the endothelial iRhom1 adapter protein in response to physiological shear stress. This pseudoprotease is one of the crucial regulators of metalloproteinase ADAM17 (30).

An additional may involve MR-induced increases in left atrial and pulmonary pressures (31). As mentioned, the pulmonary microvasculature constitutively expresses high levels of ICAM-1 (5). The pressure changes in MR may injure the pulmonary vascular endothelium and disrupt its expression and release of surface molecules. Endothelial impairment in this setting is characterized by the production of nitric oxide and endothelin-1 (ET-1). Elevated ET-1 levels have been associated with left atrial dimensions and atrial fibrillation in patients with mitral valve disease (32,33). ET-1 secretion is promoted by increased wall shear stress and pressure overload, while elevated ET-1 may promote local remodeling processes, including the upregulation of ICAM-1 and VCAM-1 (34,35).

A study (36) found differences in the expression of ICAM-1 and VCAM-1 on vascular endothelial cells subjected to shear stress versus cytokine stimulation. The shear stress enhanced the TNF–α–induced expression of ICAM-1 (both transcriptional and surface expression levels) but decreased the TNF–α–induced expression of VCAM-1 and E-selectin. However, the introduction of static incubation diminished the aforementioned effects of TNF-α. The findings suggest a decisive role for shear stress in modulating the effects of TNF-α on the expression of adhesion molecule genes.

Additionally, a recent study (20) investigated endothelial cell-derived extracellular vesicle markers in acute myocardial infarction and identified a rapid and selective increase in EVs bearing VCAM-1, but not ICAM-1. The study reveals a novel vesicle-dependent mechanism for the rapid mobilization of neutrophils from a splenic reserve following ischemic injury to the myocardium.

The relevance of these two studies to our results is reflected by the presence of both changes during and after MR surgery: Alterations in shear stress and inevitable but controlled tissue injury.

Study Limitations

Limitations of our preliminary study include a single-center design and a limited number of eligible patients, due to restrictions in the randomization process. Therefore, to enhance robustness, prospective and multi-center studies are needed. In future studies, it would be informative to compare cytokine and chemokine levels and their correlations with levels of endothelial cell adhesion molecules. The study analyzed a small set of laboratory parameters, and future work should explore additional variables and their interactions, including laboratory biomarkers, demographic elements, genetic traits, and environmental factors. This would provide a more comprehensive understanding of pathophysiological developments and potentially inform risk-assessment strategies.

Our research provides new insights into mitral valve surgery, particularly regarding understudied molecular changes. In general, serum biomarkers are considered cost-effective and available tools for assessing patients' diagnoses, prognoses, and treatment options. In the future, endothelial activation biomarkers could be utilized as a reliable, easy-to-use source of information for MR patients and for post-surgical evaluation. According to our results, ICAM-1 warrants further investigation as a predictor of LV dilatation and dysfunction. Given the

importance of enlarged LV EDD in predicting patient outcomes (24-26), the decline in ICAM-1 associated with EDD enlargement could be further explored as an additional or surrogate biomarker. Our results, together with evidence of higher cardiac adverse events due to endothelial activation (5), warrant further investigation for risk assessment, monitoring, and treatment options.

CONCLUSION

We can conclude that ICAM-1 serum levels significantly decline following surgical correction of chronic primary MR and are associated with increased postsurgical EDD size. Our study highlights the dynamic changes in endothelial activity and the need for a proper understanding of both endothelial activation in MR and the interpretation of its serum indicators.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Review Board of the University of Nis in Serbia (approval no: 12-16442-1/2-4 from December 20, 2024).

Informed Consent: Informed consent was obtained.

Footnotes

Author Contributions

Concept - S.K., J.M., B.D., S.P., D.S.; Design - S.K., J.M., B.D., S.P., D.S.; Data Collection or Processing - S.K., J.M., S.P.; Analysis or Interpretation - S.K., J.M., B.D., S.P., D.S.; Literature Search - S.K., J.M., B.D., D.S.; Writing - S.K., J.M., B.D., S.P., D.S.

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