

Role of glycocalyx damage in cardiac surgery as part of the mechanism of acute kidney injury

Papel del daño del glucocálix en la cirugía cardíaca como parte del mecanismo de lesión renal aguda

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Abstract

Background: Valve replacement surgery with cardiopulmonary bypass is associated with a systemic inflammatory response that may cause endothelial injury and contribute to renal dysfunction. The endothelial glycocalyx, a key structure for vascular integrity, can be disrupted during these procedures, leading to the release of circulating biomarkers that may allow early detection of subclinical renal injury. **Objective:** To evaluate the relationship between endothelial glycocalyx injury, circulating biomarkers (syndecan-1 and hyaluronic acid), and the risk of subclinical acute kidney injury (AKI) in patients undergoing valve replacement surgery with cardiopulmonary bypass. **Material and methods:** A prospective observational study was conducted in adult patients undergoing valve replacement at a tertiary cardiovascular center ($n = 21$). Serum syndecan-1 and hyaluronic acid levels were measured before and after surgery, and renal clearance was assessed. AKI was defined according to KDIGO criteria. **Results:** Postoperative increases in syndecan-1 and hyaluronic acid indicated glycocalyx injury. Patients with aortic cross-clamp times > 60 minutes showed reduced renal clearance of syndecan-1 ($p < 0.05$), suggesting subclinical renal dysfunction. **Conclusions:** Valve replacement surgery with cardiopulmonary bypass is associated with endothelial glycocalyx injury and subclinical impairment of renal function, detectable through circulating biomarkers.

Keywords: Syndecan-1. Hyaluronic acid. Glycocalyx. Endothelial dysfunction. Acute kidney injury.

Resumen

Antecedentes: La cirugía valvular con circulación extracorpórea se asocia a una respuesta inflamatoria sistémica que puede producir daño endotelial y contribuir al desarrollo de disfunción renal. El glicocálix endotelial, estructura clave para la integridad vascular, puede verse afectado durante estos procedimientos, liberando biomarcadores circulantes potencialmente útiles para la detección temprana de lesión renal subclínica. **Objetivo:** Evaluar la relación entre el daño del glicocálix endotelial, los biomarcadores circulantes (sindecán-1 y ácido hialurónico) y el riesgo de lesión renal aguda (LRA) subclínica en pacientes sometidos a reemplazo valvular con circulación extracorpórea. **Material y métodos:** Estudio observacional prospectivo en adultos sometidos a reemplazo valvular en un centro cardiovascular terciario ($n = 21$). Se midieron niveles séricos de sindecán-1 y ácido hialurónico antes y después de la cirugía, y se evaluó su depuración renal. La LRA se definió según criterios KDIGO. **Resultados:** El aumento posoperatorio de sindecán-1 y ácido hialurónico evidenció daño del glicocálix.

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Los pacientes con tiempos de pinzamiento aórtico > 60 minutos mostraron menor depuración renal de sindecán-1 ($p < 0.05$), sugiriendo disfunción renal subclínica. **Conclusiones:** La cirugía valvular con circulación extracorpórea se asocia con lesión del glicocáliz endotelial y alteración subclínica de la función renal, detectable mediante biomarcadores circulantes.

Palabras clave: Sindecán-1. Acido hialurónico. Glicocáliz. Disfunción endotelial. Lesión renal aguda.

Introduction

Cardiac valvular disease is a condition that affects populations in both developed and developing countries. It is estimated that approximately 79% of the 15.6 to 19.6 million people with rheumatic heart disease live in developing nations. However, this epidemiological figure may be underestimated, given that its diagnosis depends on echocardiography, a technology that is often unavailable in the regions where these patients reside. Despite the various causes of valvular disease, rheumatic etiology remains predominant in developing countries, with valve replacement surgery being the treatment of choice¹.

In 2009, Dirk Bruegger and collaborators evaluated endothelial damage in patients undergoing coronary bypass. They found an increase in serum levels of endothelial damage markers, such as syndecan-1 and heparan sulfate. These are key components of the glycocalyx, an essential structure for maintaining endothelial barrier integrity².

Inflammatory processes are known to affect the glycocalyx. Chelazzi's study on sepsis and glycocalyx degradation describes that the first step of damage is characterized by increased paracellular permeability, allowing albumin and fluid leakage into the interstitial space. The loss of anionic charge alters the geometry of endothelial junctions through direct endothelial damage. Other inflammatory changes include loss of vascular tone due to heparan sulfate degradation, a procoagulant state with microthrombus formation, overexpression of adhesion molecules, increased leukocyte trafficking, and reduction of the antioxidant properties of the endothelium³.

Acute kidney injury (AKI) is a frequent and clinically relevant complication following cardiovascular surgery, with a reported incidence of 20-30%, depending on the type and complexity of the procedure⁴. However, AKI specifically associated with glycocalyx damage is less common compared to other mechanisms of renal injury during cardiac surgery.

Despite its lower frequency, renal injury related to the glycocalyx can significantly affect renal function and has been associated with alterations in specific biomarkers such as syndecan-1. Several studies have

demonstrated that renal clearance of syndecan-1 is highly variable and is directly influenced by renal function. One study reported that its clearance correlates positively with creatinine clearance and urinary volume, suggesting that renal function plays an essential role in its elimination⁵.

The clearance of hyaluronic acid (HA), on the other hand, depends on its molecular weight. Under physiological conditions, it is eliminated by both the liver and the kidneys. However, in patients with end-stage renal disease, its clearance is markedly reduced⁶.

Valve replacement surgery and subsequent hospitalization represent a considerable economic burden for public health systems and for patients. In a study published in the *Annals of Thoracic Surgery*, the median total hospital cost of aortic valve replacement surgery was approximately \$38,000 per patient, with variability depending on complications and clinical characteristics⁷. Therefore, a deeper understanding of the pathophysiological mechanisms triggered by surgery could contribute to reducing morbidity, mortality, and costs associated with these procedures. In this context, we consider it relevant to investigate whether patients with lower renal clearance of glycocalyx components – secondary to inflammation – have a higher risk of developing acute kidney injury in the immediate postoperative period.

Consequently, the objective of this study is to demonstrate that glycocalyx damage following cardiovascular surgery is reflected in the release of hyaluronic acid and syndecan-1, and that renal clearance of these biomarkers depends on aortic cross-clamp time. It is hypothesized that impaired clearance could be associated with the development of acute kidney injury.

Material and methods

This prospective observational study with serial measurements includes adult patients over 18 years of age undergoing elective cardiac surgery for valve replacement, with available preoperative albumin levels. Sampling will be non-probabilistic, and inclusion criteria comprise patients scheduled for valve replacement or re-replacement surgery. Patients with renal

insufficiency, hematological malignancies, or specific surgeries such as Bentall, Bono, or coronary revascularization will be excluded.

Twenty-four hours before surgery, routine laboratory tests will be performed, including plasma albumin, syndecan-1, hyaluronic acid, and inflammatory markers (TNF, IL-1, IL-6, IL-10). After surgery, serum will be collected to measure syndecan-1 and hyaluronic acid, which will be refrigerated until processing.

Upon admission to the postoperative care unit, the urinary catheter will be clamped, temporarily blocking urine flow. After 30 minutes, a urine sample will be taken to measure TNF, IL-1, IL-6, IL-10, and to determine renal clearance. In addition, gasometric parameters (Hb, Hct, SaO₂, PaO₂, FiO₂, SvO₂, PvO₂) and hemodynamic variables will be recorded, as well as NT-proBNP and CRP values at 24 hours.

Six ml of peripheral blood will be collected in tubes with inert gel and 10 ml of urine in centrifuge tubes. Both samples will be immediately transported to the laboratory, where they will be centrifuged at 2500 rpm for 15 minutes at 4 °C. Subsequently, 500 µl aliquots of serum and urine will be prepared and stored at -75 °C until analysis.

The ELISA technique will be used to measure syndecan-1 and hyaluronic acid levels, following the specific protocol for each assay. Data will be processed using SPSS, with descriptive and inferential analyses to evaluate associations between perioperative characteristics and postoperative complications.

Statistical analysis will include the Chi-square test for qualitative variables and Student's t-test for quantitative variables. Results will be considered significant with $p < 0.05$.

Subclinical renal dysfunction was defined as a reduction in the relative clearance of syndecan-1 and/or hyaluronic acid, estimated through the ratio between serum and urinary concentrations of the biomarker, in the absence of acute kidney injury according to KDIGO criteria. Since direct measurement of urinary flow was not available for all patients, it was not possible to calculate the classic clearance ($U \times V/P$). Therefore, an approximation based on relative concentrations was used, which represents a limitation of the study.

Ethical aspects

In accordance with Articles 16, 17, and 23 of the Regulations of the General Health Law on Health Research, this study is prospective and observational,

poses no risk, and therefore does not require informed consent.

We, the researchers, confirm that a review of the scientific literature justifies conducting this study and that we have the capacity to carry it out to high scientific standards. We are committed to protecting the confidentiality of participants' personal data, prioritizing their well-being and safety. Furthermore, we will comply with national and international ethical guidelines, such as the General Health Law, the WHO's ethical guidelines, and the Declaration of Helsinki.

Biosafety considerations

The study required special biosafety conditions. Gasometric parameters were measured on the Cobas b 221 analyzer (Roche Diagnostics), whose reliability was evaluated in a study by Hermida-Ameijeiras et al.,⁸ with acceptable coefficients of variation that meet analytical quality standards.

The analysis of glycocalyx components was performed with ELISA tests for syndecan-1 (Diacclone) and hyaluronic acid (Corgenix), following the technical specifications of the providers. ELISA was also used to determine levels of IL-6, IL-10, and TNF- α .

Results

Our study included 21 patients undergoing valve replacement, of whom 12 were women (57%) and 9 were men (43%). The average age was 56.4 years (range 23-75), with a median of 59 years. The average body weight was 65.5 kg and the average body mass index (BMI) was 24.9 kg/m², indicating that the cohort was predominantly in the overweight range, with no cases of obesity. Regarding medical history, rheumatic fever was the most frequent, followed by systemic arterial hypertension and smoking.

In preoperative laboratory studies, none of the patients showed evidence of renal insufficiency; all had controlled glucose, leukocyte counts within adequate limits, and no anemia was observed.

The preoperative albumin value was 4 g/dL, with a 25th percentile (Q25) of 3.88 and a 75th percentile (Q75) of 4.37 (Table 1).

The median cardiopulmonary bypass time was 100 minutes, within accepted parameters not associated with negative effects, such as postoperative bleeding or vasoplegia. The median aortic cross-clamp time was 71 minutes, exceeding the threshold of \approx 60 minutes considered the limit of well-tolerated

Table 1. Preoperative and postoperative laboratory values

Variables	Frequency	Median	Percentile 25 (Q1)	Percentile 75 (Q3)
Preoperative neutrophils ($10^3 \geq /\mu\text{L}$)	21	3.40	2.70	4.30
Preoperative leukocytes ($10^3 \geq /\mu\text{L}$)	21	6.20	5.10	7.85
Preoperative glucose (mg/dL)	21	91.80	86.00	97.35
Preoperative creatinine (mg/dL)	21	0.81	0.72	1.04
Preoperative lactate dehydrogenase (U/L)	20	183.25	136.88	209.58
Preoperative hemoglobin (g/dL)	21	14.40	14.05	15.50
Preoperative hematocrit (%)	21	43.50	39.30	46.25
Preoperative platelets ($10^3 \geq /\mu\text{L}$)	21	183.00	152.50	215.00
Preoperative albumin (g/dL)	21	4.00	3.88	4.37
Preoperative C-reactive protein (mg/L)	15	2.66	1.15	4.31
Preoperative uric acid (mg/dL)	20	6.51	5.57	7.32
Preoperative alkaline phosphatase (U/L)	20	81.20	69.18	107.13
Preoperative total bilirubin (mg/dL)	21	0.74	0.60	1.10
Preoperative direct bilirubin (mg/dL)	21	0.16	0.11	0.23
Preoperative indirect bilirubin (mg/dL)	21	0.58	0.50	0.86
Preoperative AST (U/L)	21	24.70	17.45	32.90
Preoperative ALT (U/L)	21	21.50	16.06	29.00
Postoperative hemoglobin (g/dL)	21	11.100	9.850	12.600
Postoperative hematocrit (%)	21	33.200	29.800	37.100
Postoperative leukocytes ($10^3 \geq /\mu\text{L}$)	21	14.800	13.050	19.600
Postoperative neutrophils ($10^3 \geq /\mu\text{L}$)	21	12.900	11.100	16.300
Postoperative platelets ($10^3 \geq /\mu\text{L}$)	21	162.00	130.00	185.50
Postoperative glucose (mg/dL)	21	173.600	130.100	192.150
Postoperative creatinine (mg/dL)	21	0.8100	0.6700	0.9900
Postoperative lactate dehydrogenase (U/L)	21	401.000	308.350	473.300
Postoperative AST (U/L)	21	55.600	42.350	64.350
Postoperative C-reactive protein (mg/L)	21	1.9100	1.0800	3.3300
Initial pH of blood gases at the beginning of CPB	21	7.4500	7.4100	7.4700
PO ₂ of blood gases at the beginning of CPB	21	75.800	68.050	107.500
PCO ₂ of blood gases at the beginning of CPB	21	32.000	30.000	35.750
HCO ₃ of blood gases at the beginning of CPB	21	23.000	22.000	24.950
Saturation at the beginning of CPB	21	95.000	94.000	98.500
Base excess at the beginning of CPB	21	-0.300	-2.600	1.250
Lactate at the beginning of CPB	21	1.600	1.150	2.050
pH of blood gases at the end of CPB	21	7.3900	7.3450	7.4050
PO ₂ of blood gases at the end of CPB	21	171.000	127.000	223.500

(Continues)

Table 1. Preoperative and postoperative laboratory values (*continued*)

Variables	Frequency	Median	Percentile 25 (Q1)	Percentile 75 (Q3)
PCO ₂ of blood gases at the end of CPB	21	35.000	33.250	38.000
HCO ₃ of blood gases at the end of CPB	21	22.000	21.000	22.400
Saturation at the end of CPB	21	99.000	98.000	99.000
Base excess at the end of CPB	21	-3.000	-3.900	-2.150
Lactate at the end of CPB	21	2.200	2.050	3.250

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CPB: cardiopulmonary bypass; PO₂: partial pressure of oxygen; PCO₂: partial pressure of carbon dioxide; HCO₃: bicarbonate.

myocardial ischemia in valve surgery. Longer times have been associated with greater myocardial injury and adverse events^{9,10} (Table 2).

Regarding sample evaluation, patients presented an average fluid balance of 206 ml, reflecting normovolemic management during surgery, and bleeding of 390 ml (Table 3).

With respect to glycocalyx endothelial damage markers, preoperative levels of hyaluronic acid and syndecan-1 were present and not decreased; in addition, they showed an almost equivalent relationship with urinary values, indicating renal clearance.

After surgery, there was a notable elevation of endothelial damage biomarkers: hyaluronic acid increased from 47 ng/mL to 48.5 ng/mL ($p = 0.028$) and syndecan-1 from 155 ng/mL to 518 ng/mL ($p = 0.000$), although postoperative urinary levels of syndecan-1 remained below the baseline median (Table 4).

A serum increase in syndecan-1 after cardiopulmonary bypass is demonstrated, accompanied by a paradoxical behavior with a decrease in urinary excretion after surgery compared to preoperative values.

An increase in serum hyaluronic acid is also observed after cardiopulmonary bypass; however, there was no significant relationship in terms of renal clearance.

Regarding cardiopulmonary bypass time and aortic cross-clamping, statistical significance was only found when correlating glycocalyx markers with cross-clamp time. It was observed that times less than 60 minutes were associated with higher urinary levels of syndecan-1, while longer times were related to lower urinary concentrations (Fig. 1).

Spearman's correlation analysis showed significance only between aortic cross-clamp time and syndecan-1 clearance (Fig. 2).

When dividing patients according to albumin levels above or below 4 g/dL, it was found that the median serum hyaluronic acid was lower when albumin was

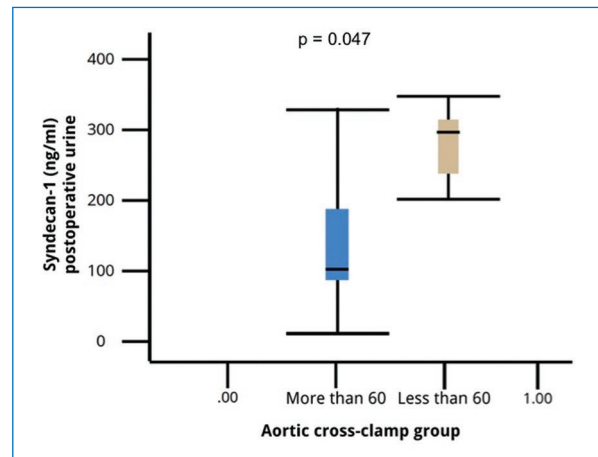


Figure 1. Bar graph with error bars. Association between aortic cross-clamp duration and postoperative urinary concentrations of Syndecan-1.

below 4 g/dL. As for serum syndecan-1, values were lower with low albumin and higher when albumin was above this value, although without statistical significance (Table 5).

In the analysis of interleukin clearance, significance was only found for interleukin-10, which increased from a median of 5.3 to 1205.5 (values are correct) pg/mL, although without significance in its urinary levels.

Discussion

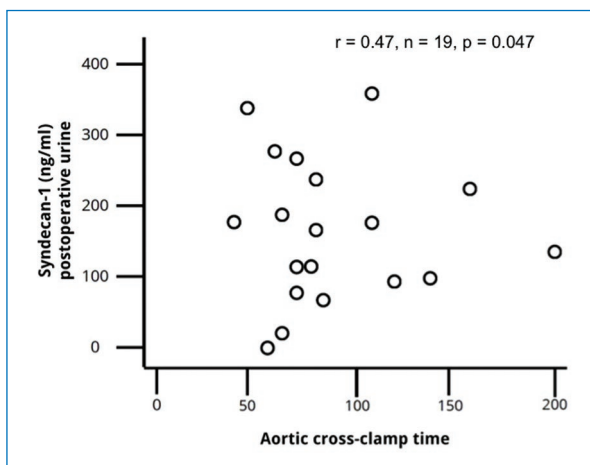
The endothelial glycocalyx plays a fundamental role in maintaining the integrity of the glomerular filtration barrier and in vascular homeostasis. Its damage has been associated with various pathological conditions, including acute kidney injury (AKI), a frequent complication following cardiac surgery with cardiopulmonary bypass. In this context, glycocalyx degradation can cause important renal consequences, such as loss of

Table 2. Cardiopulmonary bypass time and aortic cross-clamp time

Variables	Frequency	Median	Percentile 25 (Q1)	Percentile 75 (Q3)
Cardiopulmonary bypass time (minutes)	21	100	87.5	134.5
Aortic cross-clamp time (minutes)	21	71	36.5	111

Table 3. Total fluid balance and intraoperative bleeding

Variables	Total fluid balance (ml)	Intraoperative bleeding (ml)
Frequency	21	21
Median	206.00	390.00
Percentile 25	-290.50	202.50
Percentile 75	400.00	560.00

**Figure 2.** Scatter plot. Association between aortic cross-clamp duration and postoperative urinary concentrations of Syndecan-1.

cell polarity, increased apoptosis of tubular epithelial cells, and destabilization of the glomerular filtration barrier, which favors albuminuria and glomerulosclerosis.

The accumulation of hyaluronic acid in the kidney promotes inflammation and fibrosis through its interaction with the CD44 receptor, impairs renal function, and favors tubular damage. Its release after glycocalyx degradation contributes to endothelial dysfunction and the progression of glomerular deterioration¹¹. For its part, syndecan-1 (SDC-1) is essential for renal cellular integrity; its shedding compromises cell polarity, induces tubular apoptosis, and favors alteration of the

glomerular barrier, which can aggravate albuminuria and glomerulosclerosis¹².

In our study, endothelial damage biomarkers (hyaluronic acid and syndecan-1) increased significantly after surgery, confirming glycocalyx alteration induced by cardiopulmonary bypass. In addition, we observed a decrease in renal clearance of syndecan-1 in patients with aortic cross-clamp time > 60 minutes, suggesting an association between ischemia duration and renal capacity to eliminate damaged glycocalyx components.

However, these findings should be interpreted with caution. The observational design of the study prevents establishing a causal relationship, and the alteration in biomarker clearance does not necessarily equate to clinically manifest acute kidney injury. Although none of the patients developed AKI according to KDIGO criteria, the reduction in clearance of these biomarkers could represent a state of subclinical renal dysfunction, potentially reversible, that could precede the development of clinical renal damage in scenarios of greater aggression or susceptibility.

Finally, glycocalyx destabilization affects the glomerular filtration barrier and could contribute to progression toward proteinuria and glomerulosclerosis. Previous studies have demonstrated that systemic inflammation and hemodynamic stress induced by cardiac surgery favor glycocalyx degradation, which supports our findings and reinforces the hypothesis that endothelial damage could participate in the continuum of perioperative renal injury¹³.

Limitations

This study has several limitations. First, the small sample size (n = 21) decreases statistical power to detect subtle associations and limits the generalization of findings to larger populations undergoing valve surgery with cardiopulmonary bypass. As a consequence, some observed trends in biomarker behavior or in renal clearance may not have reached statistical

Table 4. Preoperative and postoperative values of hyaluronic acid and Syndecan-1

Variables	Hyaluronic acid (ng/ml) preoperative serum	Hyaluronic acid (ng/ml) postoperative serum	Hyaluronic acid (ng/ml) preoperative urine	Hyaluronic acid (ng/ml) postoperative urine	Syndecan-1 (ng/ml) preoperative serum	Syndecan-1 (ng/ml) postoperative serum	Syndecan-1 (ng/ml) preoperative urine	Syndecan-1 (ng/ml) postoperative urine
Frequency	20	20	20	20	20	20	20	20
Median	47.00	48.50	37.00	39.00	155.00	518.00	207.00	153.50
Percentile 25	41.75	45.00	32.50	36.00	110.75	278.50	131.00	101.2
Percentile 75	48.75	50.75	44.75	44.75	374.75	561.75	411.75	235.25
Significance	-	-	-	-	-	0.000*	-	0.009*

*Wilcoxon signed-rank test for related samples.

Table 5. Interleukin values

Variables	IL-1 β Preoperative serum (pg/ml)	IL-1 β Postoperative serum (pg/ml)	IL-1 β Preoperative urine (pg/ml)	IL-1 β Postoperative urine (pg/ml)	IL-10 Preoperative serum (pg/ml)	IL-10 Postoperative serum (pg/ml)	IL-10 Preoperative urine (pg/ml)	IL-10 Postoperative urine (pg/ml)
Frequency	20	20	20	20	20	20	20	20
Median	0.00	0.00	0.00	0.000	5.300	1205.500	0.000	0.000
Percentile 25	0.00	0.00	0.00	0.000	0.000	868.350	0.000	0.000
Percentile 75	0.00	0.00	0.00	3.675	12.575	1481.600	0.000	4.950
Significance	-	-	-	-	-	0.000*	-	-

*Wilcoxon signed-rank test for related samples.

significance, and identified associations should be interpreted with caution.

Second, subclinical renal dysfunction was defined through circulating biomarkers of glycocalyx damage and relative clearance estimates, which represent a surrogate marker of early renal alteration and not a direct measurement of classic renal clearance. Complete measurements of urinary flow for all patients were not available, which prevented the formal calculation of clearance using the formula $U \times V/P$, so the results should be interpreted as indirect evidence of subclinical renal dysfunction.

Finally, the study did not include patients with severe hypoalbuminemia (< 3.5 g/dL), which limits the assessment of the impact of preoperative albumin on glycocalyx damage and renal function. Multicenter studies with larger sample size and complete measurements of renal clearance are required to validate these

preliminary findings and clarify the clinical relevance of subclinical renal dysfunction in this context.

Conclusions

In the study conducted by Bruegger et al.,² endothelial damage was evaluated in patients undergoing coronary revascularization surgery with and without cardiopulmonary bypass, concluding that both groups presented elevated values of endothelial damage markers. They proposed ischemia-reperfusion injury and the inflammatory response as probable mechanisms of this phenomenon².

In our study, we obtained preoperative values of serum markers of endothelial glycocalyx damage, as well as their urinary levels to evaluate their clearance. We observed an increase in baseline levels of hyaluronic acid (from 47 ng/ml to 48.5 ng/ml, $p = 0.028$) and

syndecan-1 (from 155 ng/ml to 518 ng/ml, $p = 0.000$), findings consistent with other studies demonstrating the association between cardiopulmonary bypass and endothelial glycocalyx damage.

Our results reinforce the importance of the glycocalyx in the pathophysiology of acute kidney injury and highlight the relevance of aortic cross-clamp time in the alteration of renal clearance of endothelial biomarkers. Early detection of these alterations could allow preventive strategies aimed at minimizing renal damage in the context of cardiovascular surgery.

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The authors declare that they have not received funding for this study.

Conflicts of interests

The authors declare no conflicts of interests.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected

and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence.

The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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