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SUBCLINICAL KIDNEY INJURY AFTER EXPOSURE TO CARDIOPULMONARY BYPASS: COMPARISON OF MILD AND MODERATE HEMODILUTION

Subklinička ozljeda bubrega nakon izloženosti izvantjelesnoj cirkulaciji: usporedba blage i umjerene hemodilucije

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Abstract

Introduction: Frequency of clinically manifesting kidney injury after all types of heart surgery involving cardiopulmonary bypass ranges between 1 % and 5 % and frequency of subclinical kidney injury is even higher but can be almost impossible to detect in the early postoperative period by using traditional biomarkers. Alpha-1-microglobulin (A1M) and lipocalin associated with neutrophil gelatinase (NGAL) are potential early urine biomarkers of subclinical kidney injury. We hypothesized that moderate hemodilution with priming solution during cardiopulmonary bypass reduces kidney injury, which was determined by using A1M and NGAL, together with traditional serum biomarkers urea and creatinine.

Methods: Total of 158 participants scheduled for elective heart surgery involving cardiopulmonary bypass were included in the study and divided into two groups by the degree of hemodilution during surgery, which was defined by ratio of intraoperative and postoperative hematocrite: mild hemodilution group (ratio ≥ 60 %) and moderate hemodilution group (ratio < 60 %).

Results: Biomarkers of kidney injury, A1M and NGAL, increased in all patients that underwent elective heart surgery involving cardiopulmonary bypass. Mild and moderate hemodilution group showed significant differences in absolute values of A1M at five hours after surgery (p = 0.029), as well as in the ratio of A1M (A1M 24 hours after surgery/A1M before surgery) (p =

0.023). No differences between the two groups were found for biomarkers NGAL, urea and creatinine. The transfusion dose of blood products did not correlate with markers of kidney injury during the first 24 hours after cardiopulmonary bypass, unlike the length of cardiopulmonary bypass, cardiac ischemia, as well as temperature which significantly correlated with the ratios (24 hours after surgery/before surgery) of creatinine, A1M and NGAL in not consistent direction.
Conclusion: Moderate hemodilution had a protective effect on subclinical kidney injury in the early period after cardiopulmonary bypass, as seen from differences between the groups for biomarker A1M. Urea and creatinine were not sensitive enough in detecting subclinical kidney injury shortly after cardiopulmonary bypass, while NGAL increased, but similar in both groups.

Sažetak

Ključne riječi:
hemodilucija, izvantjelesna cirkulacija, alfa-1-mikroglobulin (A1M), lipokalin povezan s neutrofilnom želatinazom (NGAL), subkliničko bubrežno oštećenje

Uvod: Učestalost akutnog bubrežnog oštećenja nakon kardiokirurških zahvata s izvantjelesnom cirkulacijom kreće se između 1 % i 5 %, a učestalost subkliničkog bubrežnog oštećenja smatra se češćom, premda je takvo oštećenje značajno teže dokazivo u ranom poslijeoperacijskom razdoblju s pomoću tradicijskih biljega. Alfa-1-mikroglobulin (A1M) i lipokalin povezan s neutrofilnom želatinazom (NGAL) potencijalni su rani biobiljezi subkliničkog bubrežnog oštećenja. Hipoteza ovog istraživanja jest kako umjerena hemodilucija tijekom izvantjelesne cirkulacije smanjuje učestalost akutnog bubrežnog oštećenja, određivanoga s pomoću mokraćnih biobiljega A1M i NGAL, zajedno s tradicijskim biobiljezima, urejom i kreatininom.
Postupci: U istraživanje je uključeno 158 bolesnika podvrgnutih kardiokirurškom zahvatu s izvantjelesnom cirkulacijom koji su podijeljeni u dvije skupine s obzirom na stupanj hemodilucije tijekom zahvata, koji je definiran omjerom intraoperacijskog i poslijeoperacijskog hematokrita: blaga hemodilucija (omjer ≥ 60 %) i umjerena hemodilucija (omjer < 60 %).
Rezultati: Biobiljezi bubrežnog oštećenja, A1M i NGAL, povećali su se u svih bolesnika podvrgnutih kardiokirurškom zahvatu s izvantjelesnom cirkulacijom. Skupine s blagom i umjerenom hemodilucijom pokazale su značajne razlike u apsolutnim vrijednostima A1M pet sati nakon kirurškog zahvata ($p = 0.029$), kao i u omjeru A1M (A1M 24 sata nakon zahvata/A1M prije zahvata) ($p = 0.023$). Nisu pronađene razlike između dviju skupina u koncentracijama NGAL, ureje i kreatinina. Transfuzijska doza krvnih pripravaka nije bila povezana s biljezima bubrežnog oštećenja tijekom prvih 24 sata nakon izvantjelesne cirkulacije, za razliku od čimbenika poput trajanja izvantjelesne cirkulacije, ishemije miokarda, te niže tjelesne temperature, koji su korelirali s omjerom (24 sata nakon zahvata/prije zahvata) kreatinina, A1M i NGAL u nekonzistentnim smjerovima.
Zaključak: Umjerena hemodilucija imala je zaštitni učinak na subkliničko bubrežno oštećenje u ranom razdoblju nakon izvantjelesne cirkulacije, što je vidljivo iz razlike između skupina za biobiljeg A1M. Ureja i kreatinin nisu bili dovoljno osjetljivi za otkrivanje subkliničkog bubrežnog oštećenja u ranom razdoblju nakon izvantjelesne cirkulacije, dok se NGAL povećao, ali slično u obje skupine.

INTRODUCTION

Cardiopulmonary bypass during heart surgery implies a potential for perioperative kidney injury.[1-6] The incidence of acute kidney injury after heart surgery involving cardiopulmonary bypass ranges between 1 % and 5 %.[7,8] The incidence of mild, subclinical kidney injury is reported to be even higher, but is difficult to diagnose by using traditional clinical and laboratory parameters, such as serum urea and creatinine, creatinine clearance and urinary sediment analysis.[9-12] Subclinical kidney injury, especially tubular injury, can be identified in urine by using highly specific early biomarkers, such as alpha-1-microglobulin (A1M) and neutrophil gelatinase associated lipocalin (NGAL).[13-24] We hypothesized that moderate hemodilution with priming solution during cardiopulmonary bypass reduced kidney injury, which was determined by using urinary biomarkers A1M and NGAL, together with traditional serum biomarkers urea and creatinine. Hemodilution was categorized as mild or moderate according to the ratio of intraoperative and postoperative hematocrit. A part of the data from this study was previously published in a paper that described only aggregated changes of biomarkers in the entire sample.[25] This paper presents a new analysis that investigates impact of hemodilution on the dynamics of renal biomarkers in the same sample of the participants.

METHODS

The study was approved by the Ethical Committee of University of Zagreb School of Medicine (approval number: 251-59-10106-25-111/8). All of the participants read and signed an informed consent for participation in the study. The study was conducted from November 2012 to June 2013 and a total of 158 patients scheduled for elective heart surgery requiring cardiopulmonary bypass, were included in the study. All of the participants were retrospectively divided into two groups according to the degree of hemodilution during cardiopulmonary bypass.

Other inclusion criteria were as follows: normal kidney function, normal ejection fraction of the left ventricle and no recent exposure to nephrotoxic substances (i.e. radiocontrast agents, antibiotics, etc.). Exclusion criteria were diabetes mellitus, significant postoperative hemodynamic instability and the need for inotropic support.

Anesthesia technique and perioperative management

All of the patients were premedicated with 5-10 mg of intramuscular morphine. After placing standard monitoring and bispectral index monitor, the patients were preoxygenated and general endotracheal anesthesia was induced by administering fentanyl 3-4 mcg/kg, etomidate 0.2-0.3 mg/kg and rocuronium 0.6 mg/kg. After endotracheal intubation, the patients were mechanically ventilated by using volume controlled mechanical ventilation on Datex-Ohmeda S/5 Avance anesthesia machine. Radial or cubital artery was cannulated for continuous invasive blood pressure monitoring, while central venous cathether and Swan-Ganz thermodilution cathether were placed in the internal jugular or subclavian vein to monitor central venous pressure, pulmonary artery pressure and pulmonary artery wedge pressure. Urine output was monitored after the catheterisation of the urinary bladder.

Anesthesia and analgesia were maintained by using sufentanil in continuous infusion (0.25-0.75 mcg/kg/h), inhalational sevoflurane which was titrated to maintain the bispectral index between 40 and 60, and rocuronium which was applied in additional boluses of 0.1-0.2 mg/kg throughout the procedure. The patients were anticoagulated with 300-400 IU/kg of unfractionated heparin before cannulation of the aorta and caval veins or right atrium. Arterial cannulas size 24 Fr and venous cannulas size 31-51 Fr were used. Activated clotting time above 480 s five minutes after administering heparin was used as a measure of adequate anticoagulation before initiating extracorporal circulation.

The following equipment was used for extracorporal circulation: Stockert S III Console and Terumo Sarns Perfusion System 9000 with non-pulsatile

pump, Medtronic Affinity and Euroset Admiral set of venous pumps and membrane oxygenators, Dideco 38 μm arterial microfilter and Medtronic and Edwards sets of pipes. Priming solution in total volume of 1700 mL consisted of: 500 mL of Ringer solution, 500 mL of Hartmann solution, 500 mL of 6 % hydroxyethyl starch solution, 200 mL of 20 % mannitol solution, and 10000 IU of unfractionated heparin. After ensuring an adequate flow of extracorporal circulation, as well as adequate oxygenation, mechanical ventilation via anesthesia, the machine was stopped and subsequently, sevoflurane was administered via vaporiser in the system of extracorporal circuit. The body temperature, monitored by the probes placed in esophagus and rectum, was maintained around 31 ˚C throughout the procedure and was also monitored via Swan-Ganz cathether. The mean perfusion pressure was maintained on 73 mmHg on average and any deviations in mean perfusion pressure were corrected by applying noradrenaline or nitroglycerin. Anterograde and retrograde cardioplegia was applied for myocardial protection.

After the end of the surgical procedure and ensuring adequate heart function, hemodynamic stability and increasing body temperature to 37 ˚C, extracorporal circulation was stopped and mechanical ventilation via anesthesia machine was resumed. 1 mg of protamine per 100 units of initially applied heparin required to produce the desired activated clotting time was administered to diminish the effect of anticoagulation, after which arterial and venous cannulas were removed. At the end of the surgery, the administration of sevoflurane via anesthesia machine was stopped, as well as the administration of rocuronium. Continuous analgosedation with sufentanil was continued while intubated and mechanically ventilated patients were transferred to the Intensive Care Unit.[25]

Table 1 Distribution of participants by the type of surgical procedure (N=158)
Tablica 1. *Raspodjela ispitanika prema vrsti kirurškog zahvata (N=158)*

Surgical procedure/*kirurški zahvat*	**n**
CABG	70
AVR	36
CABG + AVR	14
MVR	3
MVP	6
CABG + MVP	5
CABG + MVR	1
AVR + MVR	2
TVR	2
TVP	1
Combined valve surgery/other surgery ***Kombinirani kirurški zahvat zaliska/drugi zahvati***	
AVR + MVR + TVR	2
MVR + TVP	2
MVP + TVP	1
AVR + TVP	1
AVR + MVP + TVP	1
ASD	4
PVR	1
Bentall	4
Bentall + MVP + TVP + ASD	1
Exc. myxoma LA	1

CABG, coronary artery bypass grafting; AVR, aortic valve repair; MVR, mitral valve repair; MVP, mitral valve reconstructive plastic; TVR, tricuspid valve repair; TVP, tricuspid valve reconstructive plastic; PVR, pulmonary artery valve replacement; ASD, atrial septal defect repair; Bentall, surgical replacement of ascendent aorta and aortical valve with artificial implant; Exc. myxoma LA, surgical excision of left atrial myxoma
CABG, koronarni bypass; AVR, popravak aortnog zaliska; MVR, popravak mitralnog zaliska; MVP, rekonstruktivna plastika mitralnog zaliska; TVR, popravak trikuspidalnog zaliska; TVP, rekonstruktivna plastika trikuspidalnog zaliska; PVR, zamjena zaliska plućne arterije; ASD, popravak defekta atrijskog septuma; Bentall, kirurška zamjena ascendentne aorte i aortnog zaliska umjetnim implantatom; Isključen miksom LA, kirurška ekscizija miksoma lijevog atrija

Biomarkers of kidney injury

The biomarkers of kidney injury were determined in different timepoints during the perioperative period: immediately before the initiation of extracorporal circulation (basal value), 5 hours and 24 hours after the discontinuation of extracorporal circulation for A1M and NGAL and immediately before extracorporal circulation initiation (basal value) and 24 and 48 hours after extracorporal circulation discontiunuation for urea and creatinine.

Serum urea and creatinine were determined in all 158 participants. A1M was determined in a total of

150 participants due to incorrect sampling in 8 participants, while NGAL was determined in only 66 participants due to the unavailabilty of sets which were too expensive to cover for all participants. Urinary concentration of A1M was measured by using immunonephelometric assay (Behring Werke, Marburg, Germany) and urinary concentration of NGAL was measured by using chemiluminescent immunometric assay (Abbott Diagnostic, Wiesbaden, Germany). The normal values of A1M and NGAL in urine of healthy individuals are considered below 14 mg/g creatinine or 3.5 – 8 mg/L (< 15 mg/L) for A1M and below 132 ng/mL, or 104 – 107 ng/mL for NGAL.[25-28]

Statistical analysis

The Kolmogorov-Smirnov test was used to analyse the normality of data distribution. In accordance to the results, nonparametric tests were used in further analysis. The Friedman test was used to analyse the differences in dependent measurements and the Mann-Whitney U test was used to determine the differences in two different hemodilution groups. The ratio of intraoperative and postoperative hematocrit was used to determine the degree of hemodilution: ratio ≥ 60 % being mild hemodilution and ratio < 60 % being moderate hemodilution. Correlations between individual parameters and the ratio of hematocrit were analysed by using Spearman coefficients of correlation. All P-values below 0.05 were considered significant. The Statistica version 10.0 was used as a statistical programme support.

RESULTS

The study included a total of 104 male and 54 female patients, aged between 19 and 83 years, with mean age being 63±14 years. Table 1 shows the distribution of cardiosurgical procedures. Most of the procedures included a coronary bypass (44 %), followed by heart valves surgery (37 %) and combined coronary bypass and heart valves surgery (13 %).

Table 2 presents the changes in parameters for the entire sample of participants. The median duration of extracorporal circulation was 93 minutes (interquartile range (IQR) 70-135 minutes), with median duration of heart ischemia of 62 minutes (IQR 46-90 minutes), median body temperature of 32 °C (IQR 30-32 °C) and median perfusion pressure of 75 mmHg (IQR 70-75 mmHg). Some of the participants were not exposed to cardiac ischemia due to surgical technique without stopping cardiac function. The median hematocrit was 41 % before extracorporal circulation (IQR 38-44 %) and 22 % during extracorporal circulation (IQR 21-26 %). The decrease in hematocrit ratio is explained by hemodilution during extracorporal circulation. The median hemoglobin level was 129 g/L before extracorporal circulation (IQR 118-140 g/L) and 70 g/L during extracorporal circulation (IQR 64-81 g/L).

Table 2 also shows the number of participants who required transfusion of blood products, expressed as the number of doses transfused for each blood product: during extracorporal circulation 58 participants (36.71 %) received the transfusion of packed red blood cells (median number of doses 2, IQR 1-2)

Table 2 Duration of extracorporal circulation, changes in hemoglobin/hematocrit, blood transfusions and changes in measured parameters of kidney function (N=158)
Tablica 2. *Trajanje izvantjelesne cirkulacije, promjene hemoglobina/hematokrita, transfuzija krvnih pripravaka i promjene biobiljega bubrežnog oštećenja (N=158)*

	Median, IQR
ECC	
Duration (min)/*trajanje*	93, 70-135
Duration of heart ischemia (min) *Trajanje srčane ishemije*	62, 46-90
Temperature during ECC (°C) *Temperatura za vrijeme ECC (°C)*	32, 30-32
Mean perfusion pressure (mmHg) *Srednji perfuzijski tlak (mmHg)*	75, 70-75

	Median, IQR
Htc	
Before ECC (%)/ *prije*	41, 38-44
During ECC (%)/*tijekom*	22, 21-26
Ratio of Htc (during ECC/before ECC) *Omjer Htc (tijekom ECC-a/prije ECC-a)*	0.56, 0.5-0.63
Hgb	
Before ECC (g/L)/*prije*	129, 118-140
During ECC (g/L)/*tijekom*	70, 64-81
Ratio of Hgb (during ECC/before ECC) *Omjer Hgb (tijekom ECC-a/prije ECC-a)*	0.55, 0.51-0.62
pRBCs	
During ECC (number of doses) *Tijekom ECC-a (broj doza)*	2, 1-2
After ECC (number of doses) *Nakon ECC-a (broj doza)*	2, 1-3
Other blood products/ *Ostali krvni proizvodi*	
FFP after ECC (number of doses) *FFP nakon ECC-a (broj doza)*	3, 2-4
Fibrinogen after ECC (number of doses) *Fibrinogen nakon ECC-a (broj doza)*	2, 2-4
PLT after ECC (number of doses) *PLT nakon ECC-a (broj doza)*	7, 4-8
A1M* (mg/L)	
Before surgery/*prije kirurškog zahvata*	18, 9-26
5 hours after surgery *5 sati nakon kirurškog zahvata*	15, 5-32
24 hours after surgery *24 sata nakon kirurškog zahvata*	31, 20-45
Ratio of A1M (24 hours after surgery/before surgery) *Omjer A1M (24 sata nakon operacije/prije kirurškog zahvata)*	2, 1-2
NGAL† (ng/mL)	
Before surgery/*prije kirurškog zahvata*	11, 7-18
5 hours after surgery *5 sati nakon kirurškog zahvata*	6, 2-15
24 hours after surgery *24 sata nakon kirurškog zahvata*	23, 14-46
Ratio of NGAL (24 hours after surgery/before surgery) *Omjer NGAL (24 sata nakon operacije/prije kirurškog zahvata)*	2, 1-2
Creatinine‡ (μmol/L)	
Before surgery/*prije kirurškog zahvata*	103, 89-113
24 hours after surgery *24 sati nakon kirurškog zahvata*	105, 90-124
48 hours after surgery *48 sati nakon kirurškog zahvata*	105, 88-123
Ratio of creatinine (48 hours after surgery/before surgery) *Omjer kreatinina (48 sati nakon operacije/prije operacije)*	1, 1-1
Urea‡ (mmol/L)	
Before surgery/*prije kirurškog zahvata*	6, 5-8

	Median, IQR
24 hours after surgery *24 sati nakon kirurškog zahvata*	5, 4-7
48 hours after surgery *48 sati nakon kirurškog zahvata*	6, 4-7
Ratio of urea (48 hours after surgery/before surgery) *Omjer uree (48 sati nakon kirurškog zahvata/ prije zahvata)*	1, 1-1

ECC, extracorporal circulation; Hct, hematocrit; Hgb, hemoglobin; pRBCs, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet concentrate; A1M – alfa-1-microglobulin; NGAL, neutrophil gelatinase-associated lipocalin
*A1M was determined in 150 participants
†NGAL was determined in 66 participants
‡urea and creatinine were determined in all participants
Omjer uree (48 sati nakon operacije/prije operacije)
Mjera uree (48 sati nakon kirurškog zahvata/prije zahvata) 1, 1-1
ECC, ekstrakorporalna cirkulacija; Hct, hematokrit; Hgb, hemoglobin; pRBC, koncentrirane crvene krvne stanice; FFP, svježe smrznuta plazma; PLT, koncentrat trombocita; A1M – alfa-1-mikroglobulin; NGAL, lipokalin povezan s neutrofilnom želatinazom
**A1M je određen kod 150 sudionika*
†NGAL je određen kod 66 sudionika
‡urea i kreatinin određeni su kod svih sudionika

and 91 participants (57.59 %) received the transfusion of packed red blood cells after extracorporal circulation (median number of doses 2, IQR 1-3).

After extracorporal circulation, 61 participants (38.61 %) received fresh frozen plasma (median number of doses 3, IQR 2-4), 26 participants (16.46 %) received fibrinogen (median number of doses 2, IQR 2-4) and 14 participants (8.86 %) received platelet concentrate (median number of doses 7, IQR 4-8).

Regarding changes in parameters of kidney function, the results show a slight decrease of early parameters of kidney damage (A1M and NGAL) 5 hours after surgery with double increase of both A1M and NGAL 24 hours after surgery compared to the preoperative values: median 2 (IQR 1-2) for the ratio of A1M and median 2 (IQR 1-2) for the ratio of NGAL. The values of urea and creatinine did not significantly change 24 hours after the procedure.

Table 3 shows the differences of all measured biomarkers of kidney injury during the early postoperative period depending on the degree of hemodilution. Significant differences between the two groups were found for urine biomarker A1M 5 hours after surgery: median 26 (IQR 5-49) mg/L in mild hemodilution group versus median 11 (IQR 5-29) mg/L in moderate hemodilution group, as well as for the difference in the ratio of A1M (24 hours after surgery/before surgery) which was also greater in the mild hemodilution group.

Table 3 Differences in urine and serum biomarkers of kidney injury before and after extracorporal circulation depending on the degree of hemodilution: Mann-Whitney U test (N=158)
Tablica 3. *Razlike mokraćnih i serumskih biobiljega bubrežnog oštećenja prije i poslije izvantjelesne cirkulacije ovisno o stupnju hemodilucije: Mann-Whitney U test (N=158)*

	Median, IQR		z	P
	Mild hemodilution (Htc during/Htc before surgery ≥60 %)	Moderate hemodilution (Htc during/Htc before surgery <60 %)		
A1M*				
Before surgery/*prije kirurškog zahvata*	14, 7-25	19, 9-26	-1.19	0.235
5 hours after surgery *5 sati nakon kirurškog zahvata*	26, 5-49	11, 5-29	-2.18	0.029

	Median, IQR		z	P
	Mild hemodilution (Htc during/Htc before surgery ≥60 %)	Moderate hemodilution (Htc during/Htc before surgery <60 %)		
24 hours after surgery *24 satia nakon kirurškog zahvata*	32, 19-48	31, 21-45	-0.23	0.821
Ratio (24 hours after surgery/before surgery) *Omjer (24 sati nakon kirurškog zahvata/ prije zahvata)*	2, 2-3	2, 1-2	-2.28	0.023
NGAL†				
Before surgery/*prije kirurškog zahvata*	12, 7-18	11, 8-18	-0.15	0.883
5 hours after surgery *5 sati nakon kirurškog zahvata*	6, 3-233	6, 2-12	-0.71	0.477
24 hours after surgery *24 sata nakon kirurškog zahvata*	24, 14-48	23, 14-47	-0.18	0.86
Ratio (24 hours after surgery/before surgery) *Omjer (24 sata nakon kirurškog zahvata/ prije zahvata)*	2, 2-3	2, 1-2	-0.44	0.66
Urea‡				
Before surgery/*prije kirurškog zahvata*	6, 5-8	6, 5-8	-0.37	0.712
24 hours after surgery *24 sati nakon kirurškog zahvata*	5, 4-7	5, 4-6	-0.78	0.434
48 hours after surgery *48 sati nakon kirurškog zahvata*	6, 4-8-	6, 4-7	-0.85	0.396
Ratio (48 hours after surgery/before surgery) *Omjer (48 sati nakon kirurškog zahvata/ prije zahvata)*	1, 1-2	1, 1-1	-0.98	0.327
Creatinine‡				
Before surgery/*prije kirurškog zahvata*	107, 94-112	102, 87-114	-1.26	0.207
24 hours after surgery *24 sati nakon kirurškog zahvata*	111, 95-130	104, 88-123	-1.78	0.075
48 hours after surgery *48 sati nakon kirurškog zahvata*	107, 93-129	105, 85-121	-1.67	0.096
Ratio (48 hours after surgery/before surgery) *Omjer (48 sati nakon kirurškog zahvata/ prije zahvata)*	1, 1-1	1, 1-1	-0.29	0.775

A1M, alfa-1-microglobulin; NGAL, neutrophil gelatinase-associated lipocalin
*A1M was determined in 150 participants
†NGAL was determined in 66 participants
‡urea and creatinine were determined in all participants
A1M, alfa-1-mikroglobulin; NGAL, lipokalin povezan s neutrofilnom želatinazom
**A1M je određen kod 150 sudionika*
†NGAL je određen kod 66 sudionika
‡urea i kreatinin su određeni kod svih sudionika

The results presented in Table 4 show a weak positive correlation, in a total sample of participants, between a higher ratio of intraoperative and postoperative hematocrit (less hemodilution) and the concentration of A1M 5 hours after extracorporal circulation (rho = 0.241, P = 0.003). Furthermore, the results presented in Table 4 also show a weak positive correlation between a higher ratio of intraoperative and postoperative hematocrit (less hemodilution) and the ratio of A1M (24 hours af-

Table 4 Correlation of hematocrit ratio (during surgery/after surgery) with biomarkers of kidney injury (N=158)
Tablica 4. *Korelacija omjera hematokrita (tijekom operacije/nakon operacije) i biobiljega bubrežnog oštećenja (N=158)*

	Spearman correlation coefficient rho	P
A1M *		
Before surgery/*prije kirurškog zahvata*	-0.094	0.251
5 hours after surgery *5 sati nakon kirurškog zahvata*	0.241	0.003
24 hours after surgery *24 sata nakon kirurškog zahvata*	0.029	0.722
Ratio (24 hours after surgery/before surgery) *Omjer (24 sata nakon kirurškog zahvata/ prije zahvata)*	0.220	0.007
NGAL †		
Before surgery/*prije kirurškog zahvata*	-0.050	0.691
5 hours after surgery *5 sati nakon kirurškog zahvata*	0.100	0.423
24 hours after surgery *24 sata nakon kirurškog zahvata*	0.068	0.588
Ratio (24 hours after surgery/before surgery) *Omjer (24 sata nakon kirurškog zahvata/ prije zahvata)*	0.164	0.188
Urea ‡		
Before surgery/*prije kirurškog zahvata*	0.037	0.647
24 hours after surgery *24 sati nakon kirurškog zahvata*	0.115	0.150
48 hours after surgery *48 sati nakon kirurškog zahvata*	0.076	0.345
Ratio (48 hours after surgery/before surgery) *Omjer (48 sati nakon kirurškog zahvata/ prije zahvata)*	0.035	0.662
Creatinine ‡		
Before surgery/*prije kirurškog zahvata*	0.162	0.042
24 hours after surgery *24 sati nakon kirurškog zahvata*	0.173	0.029
48 hours after surgery *48 sati nakon kirurškog zahvata*	0.150	0.060
Ratio (48 hours after surgery/before surgery) *Omjer (48 sati nakon kirurškog zahvata/ prije zahvata)*	-0.024	0.764

A1M, alfa-1-microglobulin; NGAL, neutrophil gelatinase-associated lipocalin; Htc, hematocrit
*A1M was determined in 150 participants
† NGAL was determined in 66 participants
‡ urea and creatinine were determined in all participants
A1M, alfa-1-mikroglobulin; NGAL, lipokalin povezan s neutrofilnom želatinazom; Htc, hematokrit
**A1M je određen kod 150 sudionika*
† NGAL je određen kod 66 sudionika
‡ Urea i kreatinin su određeni kod svih sudionika

ter surgery/before surgery) (rho = 0.22, P = 0.007). It is also to mention a positive correlation of intraoperative and postoperative hematocrit with creatinine levels before (rho = 0.162, P = 0.042) and 24 hours (rho = 0.173, P = 0.029) after extracorporal circulation.

As seen from Table 5, there was a significant correlation between the duration of extracorporal circulation, as well as the duration of heart ischemia and temperature during extracorporal circulation, with certain biomarkers of kidney injury.

Table 5 Correlation of ratios (24 hours after surgery/before surgery) of parameters of kidney injury with other measured perioperative parameters (N=158)
Tablica 5. *Korelacija omjera (24 sata nakon operacije/prije operacije) biobiljega bubrežnog oštećenja s ostalim mjerenim parametrima (N=158)*

	Spearman correlation coefficient rho/ P *Spearmanov koeficijent korelacije rho/P*			
	Creatinine ratio ‡ *omjer*	A1M ratio * *omjer*	NGAL ratio † *omjer*	Urea ratio ‡ *omjer*
Duration of ECC *Trajanje ECC*	-0.325 / <0.001	0.944 / <0.001	0.072 / 0.563	0.279 / <0.001
Duration of heart ischemia during ECC *Trajanje srčane ishemije tijekom ECC-a*	-0.270 / 0.001	0.839 / <0.001	0.054 / 0.668	0.264 / 0.001
Temperature during ECC *Temperatura tijekom ECC-a*	0.206 / 0.009	-0.623 / <0.001	-0.050 / 0.692	-0.192 / 0.016
Pressure during ECC *Tlak tijekom ECC-a*	-0.123 / 0.123	0.227 / 0.005	0.140 / 0.261	0.117 / 0.143
Hct before ECC *Hct prije ECC-a*	-0.092 / 0.249	-0.030 / 0.716	-0.021 / 0.866	-0.075 / 0.347
Hb before ECC *Hb prije ECC-a*	-0.084 / 0.295	-0.024 / 0.775	-0.032 / 0.799	-0.085 / 0.289
Hct during ECC *Hct tijekom ECC-a*	-0.089 / 0.267	0.132 / 0.107	0.118 / 0.345	-0.068 / 0.398
Hb during ECC *Hb tijekom ECC-a*	-0.076 / 0.345	0.138 / 0.093	0.174 / 0.162	-0.049 / 0.540
pRBCs during ECC *pRBC-i tijekom ECC-a*	0.087 / 0.517	0.212 / 0.113	-0.348 / 0.103	0.054 / 0.687
pRBCs after ECC *pRBC-i nakon ECC-a*	-0.147 / 0.165	0.103 / 0.341	-0.344 / 0.046	0.098 / 0.355
FFP after ECC *FFP nakon ECC-a*	-0.184 / 0.157	0.167 / 0.206	-0.405 / 0.085	0.075 / 0.565
Fibrinogen after ECC *Fibrinogen nakon ECC-a*	-0.321 / 0.110	0.136 / 0.518	-0.304 / 0.558	-0.214 / 0.294
PLT after ECC *PLT nakon ECC-a*	-0.015 / 0.960	0.261 / 0.367	0.866 / 0.333	0.278 / 0.336

A1M, alfa-1-microglobulin; NGAL, neutrophil gelatinase-associated lipocalin; Htc, hematocrit; Hb, hemoglobin; ECC, extracorporal circulation; pRBCs, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet concentrate
* A1M was determined in 150 participants
† NGAL was determined in 66 participants
‡ urea and creatinine were determined in all participants
A1M, alfa-1-mikroglobulin; NGAL, lipokalin povezan s neutrofilnom želatinazom; Htc, hematokrit; Hb, hemoglobin; ECC, ekstrakorporalna cirkulacija; pRBC, koncentrirani eritrociti; FFP, svježe smrznuta plazma; PLT, koncentrat trombocita
** A1M je određen kod 150 sudionika*
† NGAL je određen kod 66 sudionika
‡ Urea i kreatinin su određeni kod svih sudionika

The duration of extracorporal circulation significantly correlated with the ratios of A1M (rho/P = 0.944/<0.001), creatinine (rho/P = -0.325/<0.001) and urea (rho/P = 0.279/<0.001). The duration of heart ischemia during extracorporal circulation significantly correlated with the ratios of A1M (rho/P = 0.839/<0.001), creatinine (rho/P = -0.270/0.001) and urea (rho/P = 0.264/0.001), as well as the temperature during extracorporal circulation (rho/P = -0.623/<0.001 for A1M; rho/P = 0.206/0.009 for creatinine and rho/P = -0.192/0.016 for urea).

The results presented in Table 5 show no significant correlations between the absolute preoperative and intraoperative values of hemoglobin and hema-

tocrit with the ratios of kidney injury biomarkers and no significant correlation between the perioperative number of transfused doses of blood products and the ratios of kidney injury biomarkers, with an exception for the correlation between the postoperative number of transfused packed red blood cells doses and the ratio of NGAL (24 hours after surgery/before surgery) (rho/P = -0.344/0.046).

DISCUSSION

Our results show that a moderate hemodilution had a protective effect on subclinical kidney injury, which is mostly evident from the difference in A1M concentrations 24 hours after cardiopulmonary bypass, as well as the ratio of A1M concentrations (24 hours after cardiopulmonary bypass/before surgery) between the mild and moderate hemodilution group. The measured biomarkers of early kidney injury (A1M and NGAL) increased over time in all patients, which is seen from the double increase of both biomarkers, expressed as the ratio of concentrations after and before extracorporal circulation: twice for A1M and twice for NGAL 24 hours after the procedure. Conversely, some of the researches found in literature did not find any difference in the incidence of perioperative kidney injury between the groups of patients with mild and moderate hemodilution.[29,30,31]

However, the concentrations of both urinary biomarkers (A1M and NGAL) decreased slightly at 5 hours after extracorporeal circulation. This decline is likely attributable to the dilution of urine caused by increased urine output in the early postoperative period.[32]

A1M and NGAL are low molecular weight proteins of which concentrations increase after the damage of the tubular epithelial cells and as such, can be used as early noninvasive biomarkers of kidney injury.[18,20,22,23,33] The degree of hemodilution due to the administration of priming solution in the system of extracorporal circulation is unavoidable and depends upon several factors, such as: preoperative hematocrit, total blood volume, body mass, age and gender. An optimal degree of hemodilution is difficult to determine, as well as its impact on renal function.[34] Furthermore, the degree of hemodilution during the cardiopulmonary bypass is inconsistently defined across published studies.[35,36] We classified hemodilution as mild or moderate for the purposes of our analysis based on the ratio of intraoperative and postoperative hematocrit.

Hypo-oncotic hemodilution can have negative consequences on renal function, such as increased capillary permeability and consequently tissue edema and impaired oxygen delivery, as well as impaired hormonal regulation of the renal blood flow.[37-41] On the contrary, moderate hemodilution can have a positive impact on renal function but it is difficult to define for the purpose of optimal clinical performance. Despite contradictory opinions found in literature, it is generally accepted that the level of hematocrit of around 24 % represents moderate hemodilution.[41] Several mechanisms by which moderate hemodilution can improve renal function are described in literature: decreased blood viscosity by dilution of plasma, improved blood flow through renal cortex and medulla, improved glomerular filtration, as well as overall increased tissue perfusion and a potential for the reduction of ischemia/reperfusion injury.[38,42-46] Karkouti et al. found the lowest risk of postoperative acute kidney injury requiring dialysis in a group of patients with moderate hemodilution.[29] Despite extensive discussion on the correlation between hemodilution and perioperative morbidity and mortality across the literature, there is still an overall conflicting evidence regarding the impact of hemodilution on renal function.[31,47-53] Most of the studies on the optimal degree of perioperative hemodilution, recommend perioperative hematocrite between 22 % and 24 %, with the lowest safest value to be 19%.[47,52,54]

Despite the observed changes in concentrations of early urine biomarkers, the results from our research did not show any change in the levels of traditional serum biomarkers of kidney injury 24 and 48 hours after extracorporal circulation, which also falls within the limitations of our study, because observation over a longer period of time might be necessary to observe the potential changes in urea and creatinine.

More than a few studies found a strong correlation between hemodilution related kidney injury and consequently worse perioperative outcomes, with various risk factors such as: older age, female gender, lower body mass index, lower preoperative hematocrite levels, increased perioperative transfusion rate, etc.[36,49,55-62] Data from our results did not show an increased risk of kidney injury due to the number of doses of blood products transfused perioperatively, with the exception of a slight correlation between NGAL ratio and the number of packed red blood cells doses transfused postoperatively. However, no correlation was observed between all the other biomarkers of kidney injury and the measured parameters of perioperative transfusion: number of intraoperatively and postoperatively transfused doses of packed red blood cells and the number of postoperatively transfused doses of fresh frozen plasma, fibrinogen and platelet concentrate. It is also to highlight limitation of our study in the context of perioperative transfusion, because kidney function was observed in a relatively short time interval of only 48 hours after the cardiopulmonary bypass. Although prior studies have suggested that low preoperative or intraoperative hemoglobin and hematocrit were associated with the risk of kidney injury, our analysis did not show any significant correlation between these variables and kidney injury in a total sample of participants.[36,49,55-57,59]

The duration of cardiopulmonary bypass and heart ischemia, as well as temperature are well known risk factors for perioperative kidney injury. Our results also confirmed the correlation of the mentioned parameters and ratios of biomarkers of kidney injury (A1M, urea and creatinine) but in a non-consistent direction which is hard to explain.[63,64]

CONCLUSION

Kidney injury is detected in all patients undergoing cardiopulmonary bypass. Moderate hemodilution demonstrates a protective effect on the kidney function, as indicated by the changes in A1M levels. This protective effect is not observed with NGAL. Traditional serum biomarkers are not useful in the detection of subclinical kidney injury early after the cardiopulmonary bypass. Perioperative transfusion of blood products was not associated with the increase of kidney injury markers during the first 24 hours after the cardiopulmonary bypass. The duration of the cardiopulmonary bypass, heart ischemia and temperature significantly correlated with the kidney injury markers, however, in a non-consistent direction.

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