Original Article

Use of Urinary Biomarkers for Early Diagnosis of Acute Kidney Injury After Descending Thoracic Aorta Surgery

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ABSTRACT

Background: Acute kidney injury (AKI) is a common complication after cardiovascular surgery. The incidence of AKI after cardiovascular surgery is high, which worsens outcomes. We examined the incidence of AKI after aortic surgery without circulatory arrest and the effectiveness of AKI urinary biomarkers, including liver-type fatty acid-binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL).

Methods: The participants were 60 adults who underwent surgery for a descending thoracic aortic aneurysm with left heart bypass technique under general anesthesia. Urinary L-FABP and NGAL levels were measured immediately and 24 hours after surgery and compared between patients with and without AKI.

Results: Twenty-one patients (35%) developed AKI. Urinary L-FABP level significantly differed between the AKI group and non-AKI group at 24 hours after surgery. In contrast, urinary NGAL was not associated with AKI.

Conclusions: After replacement of the descending aorta, which can cause mild reperfusion injury, L-FABP was better than NGAL in predicting postoperative AKI.

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Acute kidney injury (AKI) is a serious complication after cardiovascular surgery and is associated with worse postoperative outcomes.[1, 2] Postoperative AKI increases the mortality rate after cardiovascular surgery, the rate of hemodialysis, and lengths of stay in the intensive care unit (ICU) and hospital.[1, 3–6]

We previously reported that the incidence of AKI after aortic arch surgery with circulatory arrest is high, 52%.[2] This high incidence of AKI is likely attributable to renal ischemia during aortic surgery with circulatory arrest.

Therefore, strategies to prevent and treat postoperative AKI must be developed. Serum creatinine (Cr) level is usually used when diagnosing AKI. However, it takes a number of days after ischemic injury before serum Cr level substantially increases; thus, it is not rapid enough to implement necessary preventive measures. Therefore, new, more rapid, biomarkers are needed in order to improve postoperative outcomes.

We investigated the usefulness of urinary liver-type fatty acid-binding protein (L-FABP) as a rapid biomarker

of oxidative stress associated with ischemia. Our previous report noted an association between L-FABP and onset of AKI associated with aortic surgery with circulatory arrest and that L-FABP rapidly changed after ischemia.[7] However, we observed that L-FABP also had a neutralizing effect on oxidative stress associated with ischemia. Therefore, although it reflects the degree of oxidative stress, it does not always reflect patient outcome. In other words, AKI can develop in patients without L-FABP elevation in response to oxidative stress. We thus hypothesized that L-FABP could be a biomarker reflecting the renoprotective function of the body.[7]

In the present study, we investigated whether urinary L-FABP exhibited a similar response after descending thoracic aortic surgery, in which renal ischemia was milder and thus did not require circulatory arrest. In addition, we simultaneously investigated the usefulness of neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker of AKI.

Methods

Participants

This study protocol was approved by the ethical review board of the Kawasaki Saiwai Hospital (receipt number 25-4; July 26, 2013; Ethical Review Board Chair: Riki Okeda). The protocol was also registered with the UMIN Clinical Trials Registry (registered study protocol number: UMIN study ID 000011558). The authors have no conflicts of interest in relation to this research.

The study enrolled adults (age $\geq$20 years) scheduled for surgical repair of descending thoracic aortic aneurysms at the Kawasaki Saiwai Hospital during the period from August 2013 until August 2015. The study was explained to the patients before surgery, and written consent was obtained from all participants. Patients were excluded if they had a preoperative serum Cr level of 1.5 mg/dl or higher, if they required circulatory arrest during surgery, or if the surgical procedure was changed during surgery.

Surgery and anesthesia management

General anesthesia with differential lung ventilation was performed with double-lumen intubation, and anesthesia was maintained with sevoflurane, propofol, fentanyl, and remifentanil. Patients were monitored by electrocardiography and SpO_2. A direct arterial line was placed by using the radial artery (FloTrac System, Edwards Lifesciences Corp., Irvine, CA, USA), right foot dorsal artery, or right posterior tibial artery. Circulation was managed with a pulmonary artery catheter inserted from the right internal jugular vein (Swan-Ganz Catheter, Edwards Lifesciences Corp.) and a central venous catheter (PreSep Oximetry Catheter, Edwards Lifesciences Corp.). The cardiac index (CI) with the indices of cardiac function and intravascular volume, stroke volume variation (SVV), and stroke volume index (SVI) were measured, and circulation was managed to maintain a CI of 2.2 L/min/m² or higher, an SVV less than 13%, and an SVI of 40 − 75 ml/m². When these thresholds were not satisfied, catecholamines were used as needed during infusion loading. Decisions regarding catecholamines and infusions were made by the anesthesiologist, as was the decision to use the diuretic furosemide. hANP 0.0125 µg/kg/min was administered for renal protection. We previously reported that hANP has an AKI prophylactic effect for aortic surgery with circulatory arrest.[8] Red blood cell products were transfused to ensure a hemoglobin concentration of 10 g/dl or higher upon completion of surgery. Transesophageal echocardiography was used for anesthesia management and evaluation of cardiac function during surgery.

Surgery was performed with the patient in the right half-lateral recumbent position. After left thoracotomy, the site of the descending aorta to be replaced with an artificial blood vessel was exposed, and the blood vessel was replaced with an artificial blood vessel after cardiopulmonary bypass (CPB) had been established. Extracorporeal circulation was used for cardiopulmonary bypass and was managed with left heart bypass. The blood delivery site was the left femoral artery, and the blood removal site was the descending aorta or left pulmonary vein. After CPB was established, the central side of the descending aorta at the site of artificial blood vessel replacement was first cross-clamped. Then, an incision was made in the descending aorta, and an anastomosis was grafted from the central side to the artificial blood vessel. The cross-clamping site was switched to the peripheral side of the site of artificial blood vessel replacement, and an anastomosis was grafted from the peripheral side to the artificial blood vessel. The patient was then taken off CPB. During CPB, circulation was managed with an off-pump bypass, and 100 units/kg of heparin sodium was drip-infused before starting CPB. Activated clotting time (ACT) was confirmed to be 250 seconds or longer. During CPB, additional heparin sodium was administered to ensure that ACT was 250 seconds or longer. After completion of surgery, the patient was moved to the ICU under sedation and put on an artificial

Table 1　Classification/staging system for acute kidney injury[9]

Stage	Serum creatinine criteria	Urinary output criteria
1	Increase in serum creatinine of ≥0.3 mg/dl or ≥150% to 200% (1.5- to 2-fold) from baseline	<0.5 ml/kg per hour for >6 hours
2	Increase in serum creatinine of >200% to 300% (>2- to 3-fold) from baseline	<0.5 ml/kg per hour for >12 hours
3	Increase in serum creatinine of >300% (>3-fold) from baseline (or serum creatinine of ≥4.0 mg/dl with an acute increase of ≥0.5 mg/dl)	<0.3 ml/kg per hour for 24 hours or anuria for 12 hours

respirator. Sedation was stopped after confirming that patient hemodynamics were stable. The patient was taken off the artificial respirator after confirming that he/she was awake and responsive to commands.

Variables investigated

The following items were investigated as background and perioperative factors: age, sex, body mass index (kg/m²), history of hypertension, history of diabetes, history of cerebrovascular disease, history of chronic pulmonary obstructive disorder, preoperative hemoglobin concentration (Hb) (g/dl), estimated glomerular filtration rate (eGFR) (ml/min/1.73 m²), duration of surgery (min), duration of anesthesia (min), duration of CPB perfusion (min), perioperative blood loss (ml), perioperative transfusion volume (ml), perioperative red blood cell transfusion volume (ml), perioperative urinary output (ml), perioperative use of furosemide, and perioperative use of carperitide.

Postoperative data collected included number of days in the ICU (days), number of days on an artificial respirator (days), and mortality rate. This information was collected from medical records and anesthesia records. For urinary biomarker measurements, urine samples were collected at completion of surgery and 24 hours after surgery; 5 ml was collected from the urethral catheter for each urine test and then placed in frozen storage at −80℃. At a later date, urine samples to be tested for urinary L-FABP and NGAL were transferred to SRL Inc. (Tokyo, Japan), and the biomarkers were measured. L-FABP was measured with an enzyme-linked immunosorbent assay (ELISA) or a chemiluminescent enzyme-linked immunosorbent assay (CLEIA). For the final analysis, samples measured with ELISA were converted to units similar to those used for CLEIA. To adjust for changes in urinary concentration, L-FABP is expressed as the ratio of L-FABP (in ng/mg) to urinary Cr.

AKI diagnosis

The diagnostic criteria of the Acute Kidney Injury Network (AKIN) (Table 1) were used to diagnose AKI.[9] The severity classification of AKIN also includes criteria for urinary output, as shown in Table 1. However, in our hospital, we have a protocol that defines the time to the start of hemodialysis, which is based on a urinary output less than 0.5 ml/kg/h over 4 hours. This explains why we did not include urinary output in the AKIN diagnostic criteria to diagnose AKI.

Statistical analysis

The Student unpaired t-test and chi-square test were used to compare patient background information, preoperative factors, and postoperative factors between the AKI and non-AKI groups. The results are presented as mean ± standard deviation or number (%) of subjects. Because the Kolmogorov-Smirnov test showed that urinary L-FABP and urinary NGAL were not normally distributed, the Mann-Whitney U-test was used. The results are presented as median (interquartile range). A p value of less than 5% was considered to indicate statistical significance. The GraphPad Prism 6 statistical software package (GraphPad Software Inc., La Jolla, CA, USA) was used all analysis.

Results

We measured urinary L-FABP and NGAL in 60 patients who underwent descending aorta replacement surgery. The background and perioperative characteristics of these patients are shown in Table 2. Mean age was 66.4 years (range 36 − 86 years), and there were 41 men (68.3%) and 19 women (31.7%). Mean preoperative eGFR was 60.2 ± 15.5 ml/min/1.73 m², mean duration of surgery was 306.4 ± 84.1 min, and mean duration of CPB was 90.4 ± 30.8 min. There was a significant difference between groups in sex (higher risk for men: AKI group, 18 [85.7%] vs non-AKI group, 23 [59.0%]; p = 0.034). No significant difference was seen for preoperative eGFR (58.7 ± 3.2 ml/min/1.73 m² in AKI group vs 61.0 ± 2.6 ml/min/1.73 m² in non-AKI group; p = 0.593), duration of surgery (302.9 ± 18.0 min vs 308.3 ± 13.8 min, respectively; p = 0.816), or duration of CPB (89.3 ±

Table 2 Baseline clinical and intraoperative characteristics in patients with and without acute kidney injury (AKI)

	AKI group (n = 21)	Non-AKI group (n = 39)	P value
Age (yrs)	67.9 ± 2.8	65.5 ± 2.0	0.497
Men	18 (85.7%)	23 (59.0%)	0.034
BMI (kg/m²)	24.5 ± 0.9	25.7 ± 0.7	0.353
HT	11 (52.4%)	29 (74.4%)	0.856
DM	3 (14.3%)	4 (10.3%)	0.876
CVD	0 (0.0%)	2 (5.1%)	0.299
COPD	1 (4.8%)	2 (5.1%)	0.952
Preoperative Hemoglobin (g/dl)	13.1 ± 0.3	13.2 ± 0.3	0.088
Preoperative eGFR (ml/min/1.73 m²)	58.7 ± 3.2	61.0 ± 2.6	0.593
Surgery time (min)	302.9 ± 18.0	308.3 ± 13.8	0.816
Anesthesia time (min)	409.7 ± 17.3	418.4 ± 14.3	0.71
CPB duration (min)	89.3 ± 7.0	91.03 ± 4.9	0.841
Volume of bleeding during surgery (ml)	1268 ± 260.1	1215 ± 89.4	0.815
Volume of infusion during surgery (ml)	2710 ± 231.6	3141 ± 150.6	0.11
Volume of RBC during surgery (ml)	906.7 ± 117.4	897.4 ± 94.9	0.953
Urine output during surgery (ml)	941.4 ± 196.5	1059 ± 126.7	0.603
Furosemide during surgery	11 (52.4%)	18 (46.2%)	0.652
Carperitide during surgery	9 (42.9%)	24 (61.5%)	0.171

Values are means ± standard deviation or numbers (percentages). Liver-type fatty acid-binding protein (L-FABP) values are medians (interquartile ranges).
BMI: body mass index, HT: hypertension history, DM: diabetes mellitus history, CVD: cerebrovascular disease history, COPD: chronic obstructive pulmonary disease history, eGFR: estimated glomerular filtration rate, CPB: cardiopulmonary bypass, RBC: red blood cells

Table 3 Postoperative outcomes in patients with and without acute kidney injury (AKI)

	AKI (n = 21)	Non-AKI (n = 39)	P value
AKI stage 1	19 (90.5%)	−	
AKI stage 2	2 (9.5%)	−	
AKI stage 3	0	−	
End of surgery L-FABP (ng/mg Cr)	52.1 (267.8)	58.9 (166.6)	0.201
24 h after surgery L-FABP 24 (ng/mg Cr)	88.6 (126.2)	28.6 (31.0)	0.016
End of surgery NGAL (ng/ml)	7.3 (25.1)	6.9 (19.8)	0.322
24 h after surgery NGAL 24 (ng/ml)	25 (20)	15 (20)	0.437
Postoperative ventilation period (days)	1.0 ± 0.0	1.2 ± 0.1	0.304
Postoperative ICU stay (days)	4.6 ± 0.33	5.0 ± 0.4	0.521
Mortality	0	0	−

Values are means ± standard deviation or numbers (percentages), except those for urinary liver-type fatty acid-binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL), which are medians (interquartile ranges). ng/mg Cr, ratio of L-FABP in ng/mg to urinary creatinine (to adjust for changes in urinary concentration).
Cr: creatinine, ICU: intensive care unit

7.0 min vs 91.03 ± 4.9 min, respectively; p = 0.841). There was no significant difference for any other background or perioperative factors.

Changes in urinary L-FABP and NGAL and postoperative factors are shown in Table 3 and Fig. 1－4. Overall, 21 patients (35%) developed postoperative AKI: 19 (90.5%) with stage 1 AKI, 2 (9.5%) with stage 2 AKI, and 0 (0%) with stage 3 AKI. Comparisons of urinary L-FABP and NGAL immediately after surgery and 24 hours after surgery in the AKI group and non-AKI group are shown in
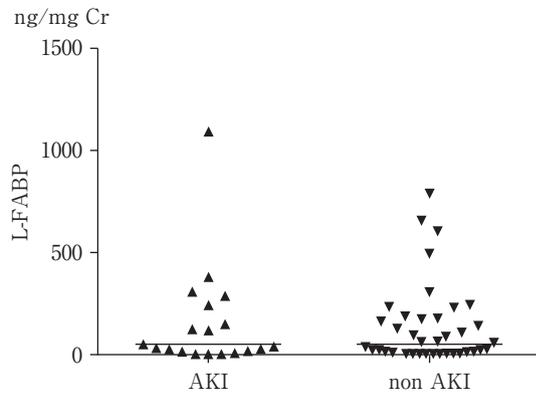
Fig. 1　End of surgery AKI vs non AKI
ng/mg creatinine (Cr), ratio of L-FABP in ng/mg to urinary creatinine (used to adjust for changes in urinary concentration).
AKI: acute kidney injury, L-FABP: urinary liver-type fatty acid-binding protein

Fig. 2　Twenty-four hours after surgery AKI vs non AKI
ng/mg creatinine (Cr), ratio of L-FABP in ng/mg to urinary creatinine (used to adjust for changes in urinary concentration).
*$p < 0.05$, AKI group vs non-AKI group
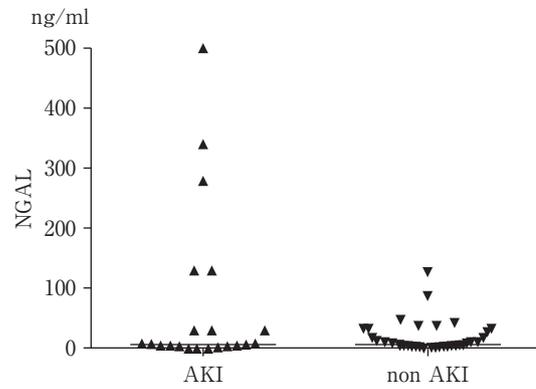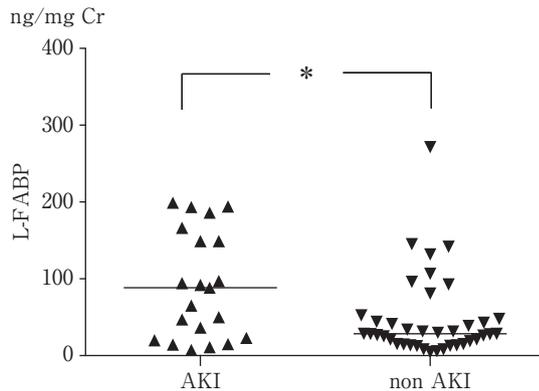AKI: acute kidney injury, L-FABP: urinary liver-type fatty acid-binding protein

Fig. 3　End of surgery AKI vs non AKI
mg/g creatinine (Cr), ratio of NGAL in mg/g to urinary creatinine (used to adjust for changes in urinary concentration).
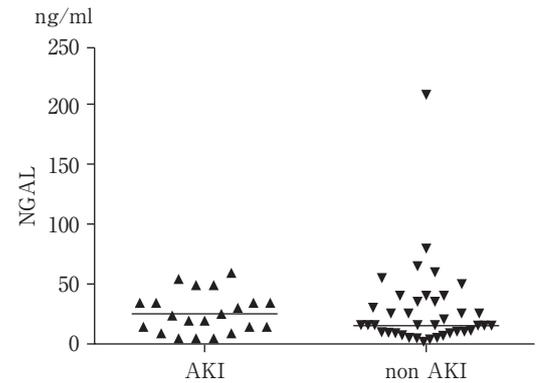AKI: acute kidney injury, NGAL: neutrophil gelatinase-associated lipocalin

Fig. 4　Twenty-four hours after surgery AKI vs non AKI
mg/g creatinine (Cr), ratio of NGAL in mg/g to urinary creatinine (used to adjust for changes in urinary concentration).
AKI: acute kidney injury, NGAL: neutrophil gelatinase-associated lipocalin

Fig. 1 – 4. The change in urinary L-FABP at completion of surgery was 52.12 (267.8) ng/mg Cr in the AKI group and 58.90 (166.6) ng/mg Cr in the non-AKI group ($p = 0.210$), a nonsignificant difference. However, the difference was significant at 24 hours after surgery: 88.58 (126.2) ng/mg Cr in the AKI group and 28.60 (31.0) ng/mg Cr in the non-AKI group ($p = 0.016$). Analysis of the change in L-FABP from immediately after surgery to 24 hours after surgery showed an increasing trend in the AKI group and a decreasing trend in the non-AKI group. As shown in Fig. 3

and 4, at completion of surgery urinary, NGAL was 7.30 (25.1) ng/ml in the AKI group and 6.90 (19.8) ng/ml in the non-AKI group ($p = 0.322$), a nonsignificant difference. In addition, there was no significant difference at 24 hours after surgery, when the levels were 25.00 (20) ng/ml in the AKI group and 15.00 (20) ng/ml in the non-AKI group ($p = 0.437$). There was a slight increasing trend when we compared levels immediately after and 24 hours after surgery.

Discussion

L-FABP is an intracytoplasmic protein with a molecular

weight of 14 to 15 kDa. It reversibly binds with hydrophobic ligands such as saturated fatty acids, unsaturated fatty acids, and eicosanoids. The function of FABP is transporting bound fats to organelles that perform β-oxidation of fatty acids, such as the mitochondria and peroxisome, and transporting fatty acids to liganded transcription factors (peroxisome proliferator-activated receptor). These functions are thought to contribute to homeostasis of intracellular fatty acid levels.[10, 11] L-FABP expression increases in proximal tubules during renal injury, and ischemia and oxidative stress in proximal tubules increase secretion of L-FABP into urine.[10–12]

Urinary L-FABP was found to be a promising biomarker for early diagnosis of AKI.[13–16] In a study of pediatric cardiac patients, urinary L-FABP significantly increased in an AKI group at 4 hours after surgery.[13] In adult cardiac patients, urinary L-FABP increased in an AKI group from immediately after surgery until 48 hours after surgery.[14] Furthermore, urinary L-FABP was significantly elevated in an AKI group after completion of cardiac surgery performed under CPB.[15]

In the present study, urinary L-FABP was significantly elevated in the AKI group at 24 hours after surgery, but there was no significant difference between the AKI and non-AKI groups at completion of surgery. In this study, we used left heart bypass, and the descending aorta was blocked during replacement of the artificial blood vessel, so renal perfusion consisted of non-pulsatile blood flow during CPB, which is the same condition as renal perfusion with CPB during general cardiac arrest. However, the duration of CPB in the present AKI group was 89.3 minutes, which is considerably shorter than in other studies, which reported CPB times of 145[13] and 157 minutes[15] and an increase in L-FABP immediately after surgery. Furthermore, the present aortic cross-clamping time was even shorter, so the period of renal perfusion with non-pulsatile blood flow was short, which may have resulted in better perioperative renal perfusion conditions than in previous reports. These factors may explain why urinary L-FABP did not increase immediately after surgery in our study. However, in previous reports, measurements were taken every few hours after reperfusion, so the investigators were able to develop a detailed picture of changes in biomarkers, whereas in this study biomarkers were only measured twice, at completion of surgery and 24 hours after surgery. Thus, we were unable to identify peak elevation times. In future studies, when conducting descending

aortic surgery with left heart bypass, detailed changes in urinary L-FABP must be investigated in order to clarify measurement timing and identify the optimal timing for AKI prognostication and medical intervention.

Urinary L-FABP may have renoprotective effects.[7, 17–19] In genetically modified animals that express urinary L-FABP, accumulation of fatty acid peroxide is inhibited, and it has been reported that urinary L-FABP has antioxidant action, which may protect the kidneys.[17] In kidney injury induced by aristolochic acid, urinary L-FABP reduces oxidative stress, mitigates damage to tubules, and may have renoprotective effects.[19] We also found that urinary L-FABP levels in the postoperative AKI group after thoracic aortic arch surgery with circulatory arrest were lower than those in the non-AKI group and have described the renoprotective effects of urinary L-FABP.[7]

We hypothesized that when urinary L-FABP is not induced during times of extreme stress, such as during circulatory arrest, kidney injury develops.[7] However, in this study, urinary L-FABP was elevated in the AKI group, which does not support this hypothesis. The discrepancy may be attributable to the different level of kidney injury associated with complete ischemia under hypothermic circulatory arrest and renal ischemia associated with short-term non-pulsatile perfusion. Future studies should investigate patients with complete ischemia, including those with kidney transplants.

NGAL is a protein secreted from activated neutrophils. It has a molecular weight of 25 kDa and belongs to the lipocalin family.[10, 20–23] NGAL is expressed at extremely low levels in several human tissues, including kidney, trachea, lung, and colon.[20, 21] Furthermore, NGAL secretion rapidly increases in proximal tubules during renal ischemia/reperfusion injury.[20, 22–24] The present results showed no significant difference in urinary NGAL after aortic surgery using left heart bypass, regardless of whether the patient developed AKI. A previous study reported that urinary NGAL elevation after surgery preceded that of serum Cr, which made it effective for early diagnosis of AKI, and it has been described as a promising biomarker for AKI.[15, 20, 21, 25–28] A study of adult cardiac patients found that urinary NGAL was elevated in an AKI group at all time points, from completion of surgery to 24 hours after surgery.[20] Furthermore, after pediatric cardiac surgery, urinary NGAL was elevated from 2 hours after surgery in an AKI group. Therefore, as compared with serum Cr, which becomes elevated 24 hours after surgery, urinary NGAL is

believed to be a more promising biomarker for early detection of AKI.[21]

Among reports claiming that urinary NGAL is effective as an AKI biomarker for cardiovascular surgery, the procedures were performed with temporary cardiac arrest using CPB, which means that renal blood flow would have been reduced because of the non-pulsatile flow of renal perfusion.[15, 20, 21, 25–27]

Increased secretion of urinary NGAL in response to renal ischemia/reperfusion injury may explain why urinary NGAL increases in response to reduced renal blood flow after CPB. Renal perfusion is non-pulsatile during left heart bypass, so renal perfusion is temporarily reduced during CPB. However, in this study, duration of CPB was short, as was the duration of reduced renal perfusion, which may explain why urinary NGAL did not increase. In addition, 90.5% of the patients who developed AKI (35%) had stage 1 AKI. This proportion is higher than that in a previous report of cases of elevated urinary NGAL, where the incidence of stage 1 AKI was 55%, and indicates that our patients had less kidney damage.[15] Furthermore, studies of cardiac surgery patients with elevated urinary NGAL also included patients with severe disease, as 33% of an AKI group required postoperative dialysis.[22]

The main mechanism responsible for organ damage is reduced organ blood flow, namely ischemia/reperfusion injury, but it is important to consider organ damage caused by hypercytokinemia, which causes multiorgan failure from sepsis. Duration of CPB and body temperature are important factors in hypercytokinemia during cardiac surgery with CPB.[29] Therefore, cytokine levels during circulatory arrest associated with aortic arch replacement may differ significantly from those induced by left heart bypass. Thus, a multifaceted approach must be used to evaluate the possibility that multiorgan failure resulting from a systemic inflammatory response may differ from changes associated with reperfusion.

Conclusion

We investigated changes in postoperative urinary L-FABP and NGAL and found that the incidence of AKI was 35% after descending aorta aneurysm surgery using left heart bypass without circulatory arrest. While this value was lower than the AKI incidence of 61% we previously reported after aortic surgery with circulatory arrest, it is still high and adversely affects patient outcomes. Urinary L-FABP was elevated in the AKI group 24 hours after surgery, which confirmed that L-FABP was an effective biomarker for early diagnosis of AKI. In contrast, there was no elevation in urinary NGAL, irrespective of AKI onset, for reasons that are unclear.

When considering treatment strategies for AKI after cardiovascular surgery, unnecessary confusion can be avoided by identifying biomarkers that are effective, in the context of a full understanding of diagnostic and surgical procedures. Furthermore, most existing studies bundled all cardiac surgery procedures together, and no study assessed the relationship between AKI and urinary biomarkers after aortic surgery performed with off-pump left heart bypass. The present data are therefore important. Future research in this field should attempt to clarify the relationship between urinary biomarkers and kidney injury.

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