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Original Contribution

Low levels of urinary liver-type fatty acid-binding protein may indicate a lack of kidney protection during aortic arch surgery requiring hypothermic circulatory arrest☆

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Abstract
Study Objective: To examine the change in liver-type fatty acid-binding protein (L-FABP) levels in patients undergoing aortic arch surgery and the correlation between L-FABP and postoperative acute kidney injury.
Design: Prospective observational study.
Setting: Operating room of a general hospital.
Patients: 36 adult patients.
Interventions and Measurements: Urine samples were obtained to measure urinary L-FABP at initiation of cardiopulmonary bypass (CPB) and 5 minutes after termination of hypothermic circulatory arrest.
Main Results: 22 (61.1%) patients developed acute kidney injury within a 48-hour period. L-FABP increases more than a thousand-fold were found. In patients who subsequently developed acute kidney injury, significant increases in L-FABP were noted from 2.9 (3.6) ng/mg of creatinine before CPB to 62.1 (995.6) ng/mg of creatinine 5 minutes after termination of circulatory arrest. Values in patients who did not develop acute kidney injury increased from 1.1 (5.7) ng/mg before CPB to 1133.0 (6358.8) ng/mg of creatinine showing a significant mean difference ($P = 0.011$). The area under the L-FABP receiver operating characteristic curve at 5 minutes after termination of circulatory arrest was 0.758. A cutoff value of 75.13 ng/mg of creatinine yielded both good sensitivity (1.000) and specificity (0.546) for detecting non-acute kidney injury. Patients who developed acute kidney injury after aortic arch surgery demonstrated lower levels of urinary L-FABP.
Conclusions: Low levels of urinary L-FABP may indicate kidney injury and lack of renal protection.

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1. Introduction

Acute kidney injury is a serious disorder with consensus definitions published by the Acute Dialysis Quality Initiative and the Acute Kidney Injury Network [1,2]. Acute kidney injury typically is diagnosed by an increase in serum creatinine concentration, a reduction in glomerular filtration rate (GFR), and a reduction in urine output. Unfortunately, creatinine has a wide normal range and its levels are affected by age and gender, rendering it a poor biomarker. Serum creatinine levels increase several days after kidney insult, and increases occur only after the disease has progressed [3]. An early and sensitive biomarker for acute kidney injury is needed for early diagnosis and timely treatment.

Several biomarkers have been investigated to enable earlier diagnosis in human populations [3–6]. Liver-type fatty acid-binding protein (L-FABP) is normally expressed in the proximal convoluted and straight tubules. In a rodent model of cisplatin-induced acute kidney injury, an increased expression of urinary L-FABP by the renal tubules was noted within the first 24 hours, whereas an increase in serum creatinine was not detectable until after 72 hours of treatment with cisplatin [7]. In a prospective study of children undergoing cardiac surgery, urinary L-FABP measured within 4 hours of the procedure was a powerful early predictor of acute kidney injury, with an accuracy of 81% [3]. Another report demonstrated earlier detection of acute kidney injury after cardiac surgery in adults [8]. Urinary L-FABP levels can predict acute renal histological injuries in two different animal acute kidney injury models of cisplatin injection and ischemia reperfusion injury [9]. Urinary L-FABP also may reflect a functional decline in glomerular filtration [9]. Levels were significantly higher in patients with poor outcomes, defined as the requirement for renal replacement therapy or the composite endpoint of death or renal replacement therapy [10]. Urinary L-FABP is recognized as one of the most useful biomarkers of acute kidney injury.

Urinary excretion of L-FABP has been investigated in a number of basic and clinical investigations; it reflects stress such as urinary protein overload on the proximal tubules causing tubulointerstitial damage [11]. Renal L-FABP is likely to have an effective endogenous antioxidant function [11] and attenuates acute tubulointerstitial damage via antioxidative functions [12]. L-FABP serves as an early indicator of ischemic conditions and as an important protective cellular antioxidant molecule that inactivates reactive lipids [13]. Urinary L-FABP has been recognized as both a useful clinical marker for kidney disease and a valuable kidney protective agent [14].

Hypothermic circulatory arrest (HCA), first described in 1975 [15], is a method of cerebral and organ protection used during aortic surgery. Interruption of cerebral circulation with full recovery of neurologic function is possible since brain metabolic rate decreases with declining temperature. This technique allows the surgeon to work in a quiet and bloodless field. However, aortic arch surgery requiring hypothermic circulatory arrest results in acute kidney injury in approximately 40% to 50% of patients [16–18]. There has been no investigation of intraoperative changes in urinary L-FABP levels to date. Changes in urinary L-FABP levels in adult patients during aortic arch surgery requiring hypothermic circulatory arrest and the correlation between urinary L-FABP and postoperative acute kidney injury were examined.

2. Materials and methods

The Human Ethics Committee of Kawasaki Saiwai Hospital approved this study, and written, informed consent was obtained from each patient. Urine samples were obtained from 36 patients who underwent aortic arch surgery requiring HCA at Kawasaki Saiwai Hospital. Patients with abnormal kidney function (preoperative serum creatinine > 1.2 mg/dL) were excluded from the study.

Patients underwent general endotracheal anesthesia; propofol, thiopental sodium, sevoflurane, midazolam, fentanyl, and vecuronium bromide were given to maintain anesthesia. Patients were hemodynamically monitored with indwelling arterial and pulmonary arterial catheters. Rectal, urinary bladder, and tympanic membrane temperatures also were monitored. Transesophageal echocardiography (TEE) was used to confirm the surgical diagnosis and to assess cardiovascular management and the surgical intervention. No patient received aprotinin. Anticoagulation for CPB was performed using bolus heparin titrated to maintain activated coagulation time at more than 400 seconds.

Arterial cannulation was typically in the ascending aorta. Venous cannulations were bicaval. For cerebral protection during HCA, antegrade selective cerebral perfusion via the brachiocephalic trunk, left common carotid artery, and left subclavian artery or retrograde cerebral perfusion (RCP) via a snared superior vena cava cannula was performed. The left ventricle was vented through the right superior pulmonary vein. Hypothermic circulatory arrest was initiated after confirming that there was no cerebral activity on the electroencephalogram with target temperature.

The target temperature was under 20° C at the tympanic membrane and under 25° C in the rectum and urinary bladder. After circulatory arrest was achieved, open distal anastomosis was performed, CPB was re-established through a branch graft attached to the main tube graft, and a proximal anastomosis was performed during rewarming. Standard antegrade and retrograde cold blood cardioplegia was used for cardiac protection. No additional perfusion was performed for additional organ protection during HCA. Arterial blood gas analysis was performed every 30 minutes. During CPB, the following metabolic goals were met: pH 7.35 to 7.45, PaO_2 greater than 100 mmHg, $PaCO_2$ 30–40 mmHg, and hematocrit greater than 20%. Retrograde