Perioperative heart-type fatty acid binding protein is associated with acute kidney injury after cardiac surgery

Jennifer A. Schaub[1], Amit X. Garg[2], Steven G. Coca[1], Jeffrey M. Testani[1], Michael G. Shlipak[3], John Eikelboom[4], Peter Kavsak[5], Eric McArthur[6], Colleen Shortt[4], Richard Whitlock[4] and Chirag R. Parikh[1] for the TRIBE-AKI Consortium

[1]*Department of Internal Medicine and Applied Translational Research, Yale University School of Medicine, New Haven, Connecticut, USA;* [2]*Division of Nephrology, Department of Medicine, Western University, London, Ontario, Canada;* [3]*Division of General Internal Medicine, University of California San Francisco School of Medicine, San Francisco, California, USA;* [4]*Division of Cardiac Surgery, Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada;* [5]*Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada and* [6]*Institute for Clinical Evaluative Sciences Western, London, Ontario, Canada*

Acute kidney injury (AKI) is a common complication after cardiac surgery and is associated with worse outcomes. Since heart fatty acid binding protein (H-FABP) is a myocardial protein that detects cardiac injury, we sought to determine whether plasma H-FABP was associated with AKI in the TRIBE-AKI cohort; a multi-center cohort of 1219 patients at high risk for AKI who underwent cardiac surgery. The primary outcomes of interest were any AKI (Acute Kidney Injury Network (AKIN) stage 1 or higher) and severe AKI (AKIN stage 2 or higher). The secondary outcome was long-term mortality after discharge. Patients who developed AKI had higher levels of H-FABP pre- and postoperatively than patients who did not have AKI. In analyses adjusted for known AKI risk factors, first postoperative log(H-FABP) was associated with severe AKI (adjusted odds ratio (OR) 5.39 (95% confidence interval (CI), 2.87–10.11) per unit increase), while preoperative log(H-FABP) was associated with any AKI (2.07 (1.48–2.89)) and mortality (1.67 (1.17–2.37)). These relationships persisted after adjustment for change in serum creatinine (for first postoperative log(H-FABP)) and biomarkers of cardiac and kidney injury, including brain natriuretic peptide, cardiac troponin-I, interleukin-18, liver fatty acid binding protein, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin. Thus, perioperative plasma H-FABP levels may be used for risk stratification of AKI and mortality following cardiac surgery.

Kidney International advance online publication, 1 April 2015; doi:10.1038/ki.2015.104

KEYWORDS: acute kidney injury; cardiac surgery; heart-type fatty acid binding protein; mortality

Correspondence: *Chirag R. Parikh, Section of Nephrology, Yale University School of Medicine, 60 Temple Street, Suite 6C, New Haven, 06510 Connecticut, USA. E-mail: chirag.parikh@yale.edu*

Received 30 October 2014; revised 9 February 2015; accepted 12 February 2015

Acute kidney injury (AKI) is a common complication of cardiac surgery and strongly predicts adverse outcomes. Identification and management of AKI remains a troublesome area of clinical practice largely for two reasons. First, the diagnosis of AKI hinges on changes in serum creatinine, which often does not change until 2–3 days after the initial insult.[1] Second, serum creatinine can rise for myriad reasons, including true tubular injury, hemodynamic alterations, or cardio-renal interactions.[1]

Recent biomarker research strives to ameliorate these clinical conundrums. Several urinary proteins have been identified as biomarkers of renal injury, including interleukin 18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid binding protein (L-FABP), and kidney injury molecule-1 (KIM-1).[1–4] These markers detect damage to the proximal and distal tubular cells, and IL-18 and NGAL detect AKI sooner than change in serum creatinine.[1] In contrast, cardiac biomarkers such as serum brain natriuretic peptide (BNP) improve risk stratification for AKI preoperatively.[5] More recent literature has explored phenotyping AKI with a combination of renal and cardiac biomarkers.[6]

Fatty acid binding proteins are a family of highly conserved proteins, which are involved in transporting free fatty acid molecules in the cytosol. There are at least 10 variants identified thus far, which are widely expressed in various tissues. One particular member of the protein family, heart fatty acid binding protein (H-FABP), is widely expressed in the cytosol of the myocardium and has limited expression in other tissues, including the distal tubular cells of the kidneys.[7,8] Both animal and human data have demonstrated that H-FABP is released less than 30 min after myocardial injury and is mostly renally excreted within 24 h.[9–12] Recent literature has demonstrated that H-FABP has utility in detecting a variety of cardiac derangements, such as myocardial infarction,[13] postoperative myocardial injury,[14,15] and ongoing ischemic damage in heart failure.[16,17] One small

study recently demonstrated that patients with elevated preoperative H-FABP undergoing elective coronary artery bypass graft surgery (CABG) were more likely to experience AKI postoperatively.[18] H-FABP is additionally strongly associated with mortality in a wide variety of settings.[19–25]

Thus, the purpose of our study was three-fold. First, we sought to establish whether elevated pre- or postoperative H-FABP levels were associated with any AKI or severe AKI. Second, we explored whether elevated H-FABP levels captured similar information as previously established kidney injury and cardiac biomarkers. Third, we examined the association of H-FABP with long-term mortality for additional risk stratification of patients with AKI.

RESULTS

Patient characteristics

Baseline characteristics between patients without AKI, any AKI (AKIN Stage 1 or higher), and severe AKI (AKIN Stage 2 or higher) are presented in Table 1. Overall, 330 patients (34.3%) experienced any AKI and 37 patients (3.9%) had severe AKI during their hospital stay. Only 1.1% of the cohort developed oliguria within the first 24 h postoperatively, and the median time to creatinine rise was 3 days. Patients who experienced any AKI were more likely to have a history of diabetes, hypertension, congestive heart failure, and lower baseline estimated glomerular filtration rate than patients without AKI (P-value, <0.01 for all comparisons). They were additionally more likely to undergo surgeries that had longer cross-clamp and perfusion time and experience a complicated postoperative course, including more extra-renal complications, longer ventilator time, and ICU stays (P-value, <0.001 for all comparisons).

Biomarker characteristics

Preoperative plasma H-FABP was associated with preoperative serum creatinine level ($r=0.50$, P-value <0.001) and preoperative estimated glomerular filtration rate ($r=-0.55$, P-value <0.001). Patients within the highest tertile of first postoperative H-FABP were more likely to undergo emergency surgery (22.6% in tertile 3 vs. 14.5% in tertile 1, P-value 0.018), have longer cross-clamp times (101 min vs. 56 min, P-value <0.001), longer perfusion times (148 min vs. 80 min, P-value <0.001) and less likely to have off-pump surgery (2.5% vs. 18.6%, P-value <0.001). The first postoperative values of all cardiac and renal biomarkers, including plasma H-FABP, serum BNP, plasma cardiac troponin-I (cTnI), urinary IL-18, urinary NGAL, urinary KIM-1, and urinary L-FABP, were significantly higher in patients who experienced any AKI than patients without AKI (Table 2).

Perioperative H-FABP levels in those without AKI, any AKI, and severe AKI

Patients who experienced any AKI had higher levels of H-FABP both pre- and postoperatively than patients who did not experience AKI, and patients with severe AKI had the highest levels among the three groups (Figure 1). The first postoperative H-FABP levels in patients who experienced severe AKI increased by about 13-fold (median 77.4 ng/ml, interquartile range (IQR) (38.5, 141.0)) (P-value <0.001), whereas they increased by about 8-fold in the patients who experienced any AKI (median 39.6 ng/ml, IQR (25.1, 62.1)) (P-value <0.001). During the subsequent postoperative days, H-FABP levels declined, but at a slower rate in patients who experienced any AKI. By postoperative day 3, the H-FABP levels had not returned to baseline in any group.

Correlation between first postoperative H-FABP and other cardiac and renal biomarkers

The first postoperative H-FABP was weakly correlated with other urinary biomarkers of kidney injury, including IL-18, KIM-1, L-FABP, and NGAL. The strongest correlation between H-FABP and a kidney injury biomarker was with L-FABP ($r=0.31$, P-value <0.001). The association was stronger with cTnI ($r=0.58$, P-value <0.001) (Table 3).

Association of log(H-FABP) with any AKI and severe AKI

Preoperatively, higher log(H-FABP) levels were associated with any AKI in univariate models, and the association persisted after adjusting for clinical covariates and logarithmically transformed individual kidney injury and cardiac biomarkers (Table 4). While preoperative log(H-FABP) was associated with severe AKI in univariate models, the significance was lost after adjusting for clinical covariates, although the effect size estimate remained similar (Table 5).

Each unit increase in first postoperative log(H-FABP) was independently associated with any AKI (adjusted OR 1.83 (95% CI, 1.41–2.36)) and severe AKI (adjusted OR 5.39 (95% CI, 2.87–10.11)) after adjustment for clinical covariates. The relationship between first postoperative log(H-FABP) and severe AKI (Table 5) persisted after adjustment for change in serum creatinine as well as logarithmically transformed renal and cardiac biomarkers, including IL-18, NGAL, KIM-1, L-FABP, BNP, and cTnI. In contrast, the relationship between first postoperative log(H-FABP) and any AKI (Table 4) was attenuated after adjusting for change in serum creatinine, logarithmically transformed renal biomarkers and serum BNP.

The ORs between postoperative days 2 and 3 log(H-FABP) and any AKI and severe AKI were all strongly statistically significant and are presented in Supplementary Tables 1 and 2.

Association of log(H-FABP) with long-term mortality

During the follow-up period (median 3 years, IQR (2.2, 3.6)), 10.8% of the entire cohort died.

Patients with elevated preoperative log(H-FABP) were significantly more likely to die, even after adjustment for multiple risk factors (adjusted hazard ratio (HR) 1.67 (95% CI, 1.17–2.37) per unit increase). This relationship persisted after adjustment for logarithmically transformed renal injury and cardiac biomarkers (Table 6).