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Original Paper

Heme Oxygenase-1 and Acute Kidney Injury following Cardiac Surgery

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Key Words
Acute kidney injury · Cardiac surgery · Cardiopulmonary bypass · Hemolysis · Interleukin · Hemoglobin · Heme oxygenase-1 · Angiotensin-converting enzyme inhibitor

Abstract
Background: Intraoperative hemolysis and inflammation are associated with acute kidney injury (AKI) following cardiac surgery. Plasma-free hemoglobin induces heme oxygenase-1 (HO-1) expression. HO-1 degrades heme but increases in experimental models of AKI. This study tested the hypothesis that plasma HO-1 concentrations are associated with intraoperative hemolysis and are increased in patients that develop AKI following cardiac surgery. ***Methods:*** We measured plasma HO-1, free hemoglobin, and inflammatory markers in 74 patients undergoing cardiopulmonary bypass (CPB). AKI was defined as an increase in serum creatinine concentration of 50% or 0.3 mg/dl within 72 h of surgery. ***Results:*** Twenty-eight percent of patients developed AKI. HO-1 concentrations increased from 4.2 ± 0.2 ng/ml at baseline to 6.6 ± 0.5 ng/ml on postoperative day (POD) 1 ($p < 0.001$). POD1 HO-1 concentrations were 3.1 ng/ml higher (95% CI 1.1–5.1) in AKI patients, as was the change in HO-1 from baseline to POD1 (4.4 ± 1.3 ng/ml in AKI patients vs. 1.5 ± 0.3 ng/ml in no-AKI patients, $p = 0.006$). HO-1 concentrations remained elevated in AKI patients even after controlling for AKI risk factors and preoperative drug therapy. Peak-free hemoglobin concentrations correlated with peak HO-1 concentrations on POD1 in patients that developed AKI ($p = 0.02$). Duration of CPB and post-CPB IL-6 and IL-10 concentrations were also associated with increased HO-1 on POD1. ***Conclusion:*** Plasma HO-1 is increased in patients that develop AKI, and CPB duration, hemolysis, and inflammation are associated with increased HO-1 concentrations following cardiac surgery. Strategies that alter hemolysis and HO-1 expression during cardiac surgery may affect risk for AKI.

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Introduction

Acute kidney injury (AKI) frequently occurs after cardiac surgery and increases postoperative morbidity and death [1]. The mechanisms underlying postoperative AKI are not well defined but are associated with intraoperative hemolysis, hypotension, altered autoregulation of renal perfusion, inflammation, and oxidative stress [2–4]. Cardiopulmonary bypass (CPB) hemolyzes erythrocytes, increasing plasma concentrations of free hemoglobin [3]. Circulating hemeproteins damage the kidney by scavenging nitric oxide and increasing lipid peroxidation [5]. We previously demonstrated that postoperative AKI is associated with enhanced intraoperative hemeprotein release and enhanced lipid peroxidation in patients undergoing CPB [3]. Heme oxygenase-1 (HO-1), the inducible isoform of heme oxygenase, catalyzes the degradation of heme. HO-1 has protective anti-inflammatory and anti-oxidant effects and is increased in renal tissue, plasma, and urine during AKI [6]. A recent study demonstrated that plasma and urine HO-1 concentrations are increased in an animal model of hemeprotein-mediated AKI and in medical intensive care unit (ICU) patients with AKI [7]. HO-1 expression is associated with acute systemic inflammation, and an enhanced inflammatory response has been associated with an increased risk of postoperative kidney injury [8], atrial fibrillation [9], and myocardial injury [10].

The contributions of hemolysis during CPB, subsequent changes in HO-1 concentrations and inflammation to the development of AKI following cardiac surgery are not known. This study tested the hypothesis that plasma HO-1 concentrations are associated with hemolysis and inflammation during cardiac surgery and are increased in patients that develop AKI.

Methods

Plasma-free hemoglobin, HO-1 concentrations, and kidney injury were measured in patients that participated in a clinical trial testing the hypothesis that perioperative angiotensin-converting enzyme (ACE) inhibition enhances fibrinolysis and inflammation more than angiotensin receptor blockade (ARB) (ClinicalTrials.gov: NCT00607672) [11]. In the parent trial, 1 week to 5 days prior to cardiac surgery, patients were randomized to treatment with placebo, ramipril (2.5 mg the first 3 days followed by 5 mg/day), or candesartan (16 mg/day). Exclusion criteria included left ventricular ejection fraction less than 30%, serum potassium greater than 5.0 mEq/l, serum creatinine greater than 1.6 mg/dl, and inability to discontinue preexisting ACE inhibitor or ARB treatment. The study was approved by the Vanderbilt University Human Research Protection Program and the TN Valley Healthcare System Institutional Review Board and conducted according to the Declaration of Helsinki. All patients provided written informed consent. Seventy-four patients completed the study and comprise the study cohort.

Standardized Patient Treatment and AKI Diagnosis

Anesthetic and surgical management was conducted according to institutional protocols, as previously described [11]. AKI was defined according to the Acute Kidney Injury Network (AKIN) criteria [12]. Accordingly, AKI was defined as an increase in a patients' serum creatinine concentration of 50% or 0.3 mg/dl (26.5 μmol/l) within 72 h of surgery (stage I). Stage II AKI was defined as a 100% increase in serum creatinine and stage III AKI as a 200% increase in serum creatinine within 72 h of surgery. The AKIN urine output criteria for AKI diagnosis were not used due to confounding by intravascular hypovolemia and diuretic use [13], both of which are common among cardiac surgery patients. Baseline creatinine was determined during the preoperative anesthesiology assessment clinic visit for outpatients and on the morning of surgery for inpatients. AKI risk was calculated for all patients using the Acute Kidney Injury in Cardiac Surgery (AKICS) score [14]. The AKICS score predicts AKI following cardiac surgery based on baseline creatinine, age, congestive heart failure, preoperative blood glucose, combined coronary artery bypass and valve surgery, duration of CPB, postoperative central venous pressure, and postoperative vasoactive infusion and mechanical (intra-aortic balloon pump) hemodynamic support.

Measurement of HO-1, Hemolysis and Inflammation

Blood was sampled at anesthetic induction (baseline), at the conclusion of CPB (post-CPB), and on postoperative day 1 (POD1), immediately placed on ice, centrifuged for 20 min, and plasma frozen at –80°C. Plasma HO-1 concentrations were measured with a commercially available immunoassay (Enzo Life Sciences, Ann Arbor, Mich., USA). Plasma-free hemoglobin was measured using the two-wavelength method as previously described [15]. IL-6, IL-8, and IL-10 plasma concentrations were simultaneously measured using the Human Inflammation Cytokine Cytometric Bead array kit (BD Biosciences Pharmingen, San Diego, Calif., USA) by the Vanderbilt University Immunology Core laboratory.

Statistical Analysis

Discrete variables were compared between groups using χ^2 test or Fisher's exact test depending on the number of events for pairwise comparisons. Continuous variables were compared between groups using an independent samples t test or Mann-Whitney U test depending on whether data were normally distributed. Correlations were assessed by linear regression after log transformation of variables that were not normally distributed. Repeated measures of HO-1, free hemoglobin, and interleukins were analyzed using mixed effects models with fixed effects of disease (AKI vs. no AKI) and time. We included a random subject effect and a first-order autoregressive process [AR(1)] to adjust for any errors in the mixed effects model. A two-tailed p value less than 0.05 was considered statistically significant, and data are presented as means ± SEM unless otherwise indicated. Statistical analyses were performed with the statistical package IBM SPSS for Windows (Version 21.0, IBM, New York, N.Y., USA) and SAS for Windows (Version 9, Cary, N.C., USA).

Results

Acute Kidney Injury

Twenty-eight percent of patients (21 of 74) developed postoperative AKI. Patient characteristics are presented in table 1. Of the 21 patients that developed AKI, 19 developed AKIN stage 1, 1 AKIN stage 2, and 1 AKIN stage 3. No patient required renal replacement therapy. The peak change in creatinine within the first three postoperative days was 0.57 ± 0.11 mg/dl in the AKI group compared to 0.04 ± 0.02 mg/dl in the no-AKI group ($p < 0.001$). The AKICS score, as expected, was higher in patients that developed AKI compared to those that did not (8.3 ± 1.0 vs. 4.4 ± 0.5, $p = 0.001$). In addition, postoperative AKI was associated with a longer duration of hospitalization following surgery (9.0 ± 1.0 vs. 6.7 ± 0.4 days, $p = 0.01$), and postoperative AKI tended to lead to long-term renal dysfunction, defined as persistent serum creatinine elevation greater than 1.6 mg/dl. Sixty-one percent (45 of 74) of the patients returned to the Vanderbilt University Medical Center for postoperative medical care and had follow-up creatinine data available at a median follow-up of 220 days after hospital discharge. The prevalence of creatinine concentrations greater than 1.6 mg/dl was 33.3% (4 of 12) in AKI patients compared to 9.1% (3 of 33) in no-AKI patients ($p = 0.07$) demonstrating the long-term renal consequence of AKI after cardiac surgery in this cohort.

Heme Oxygenase-1

Plasma HO-1 concentrations had a biphasic response to cardiac surgery, decreasing from 4.2 ± 0.2 ng/ml at baseline to 3.9 ± 0.2 ng/ml post-CPB ($p = 0.002$ vs. baseline) before rising to 6.6 ± 0.5 ng/ml on POD1 ($p < 0.001$ vs. baseline). Baseline HO-1 concentrations were not associated with baseline subject characteristics including age, gender, diabetes, heart failure, BMI, and preoperative renal function. Interestingly, HO-1 concentrations were increased in patients randomized to ACE inhibitor therapy (5–7 days of study drug prior to surgery). At anesthetic induction, HO-1 concentrations were 25% higher in patients randomized to an ACE inhibitor [5.1 ± 0.4 vs. 3.8 ± 0.3 ng/ml in placebo patients ($p = 0.006$) and 4.0 ± 0.3 in ARB patients ($p = 0.04$)], and following CPB, HO-1 concentrations remained increased in patients randomized to an ACE inhibitor [4.3 ± 0.3 vs. 3.6 ± 0.3 ng/ml in placebo patients ($p = 0.03$)].

Table 1. Patient characteristics

Characteristics	n = 74
Age, years	65.8±1.2
Female gender, n	43 (58.1)
White ethnicity, n	71 (98.6)
BMI	29.8±0.9
Baseline hematocrit, %	40.8±0.5
Baseline creatinine, mg/dl	1.01±0.03
Baseline eGFR, ml/min/m^2	70.4±2.0
Blood glucose, mg/dl	128.4±7.5
Baseline LVEF, %	56.1±1.4
Medical history, n	
Diabetes	22 (29.7)
Hypertension	56 (75.7)
Congestive heart failure	24 (32.4)
COPD	10 (13.5)
Prior cardiac surgery	14 (18.9)
Atrial fibrillation	33 (44.6)
Preoperative medications, n	
β-Blocker	41 (55.4)
Statins	40 (54.1)
NSAID	9 (12.3)
Type of surgery, n	
Valvular surgery only	57 (77.0)
CABG surgery only	4 (5.4)
CABG plus valvular surgery	12 (16.2)
ASD repair	1 (1.4)
CPB time, min	137.3±6.0
Aortic cross-clamp use, n	42 (56.8)
Aortic cross-clamp time, min[1]	97.8±6.4
Lowest hematocrit during CPB, %	25.7±0.6
Total OR time, min	313.4±11.0
OR vasopressor/inotrope requirements	
Norepinephrine, μg/min	6.1±0.6
Milrinone, μg/kg/min	0.12±0.03
Dobutamine, μg/kg/min	1.3±0.2
Epinephrine, μg/min	1.0±0.5
CVP at ICU arrival, mmHg	11.9±0.6
AKICS score	5.5±0.5
Length of hospital stay, days	7.3±0.3

Figures in parentheses are percentages. BMI = Body mass index; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease; NSAID = non-steroidal anti-inflammatory drug; CABG = coronary artery bypass grafting; ASD = atrial septal defect; CVP = central venous pressure.

[1] Among patients receiving aortic cross-clamp.

On POD1, HO-1 concentrations were not different between patients randomized to placebo, ACE inhibitor, or ARB therapy (p = 0.26).

Postoperative HO-1 concentrations were increased in patients subsequently diagnosed with AKI despite similar concentrations prior to and during surgery. On POD1, HO-1 concentrations were 3.1 ng/ml higher (95% CI 1.1–5.1) in AKI patients, as was the change in HO-1 from baseline to POD1 (4.4 ± 1.3 ng/ml in AKI patients vs. 1.5 ± 0.3 ng/ml in no-AKI patients,

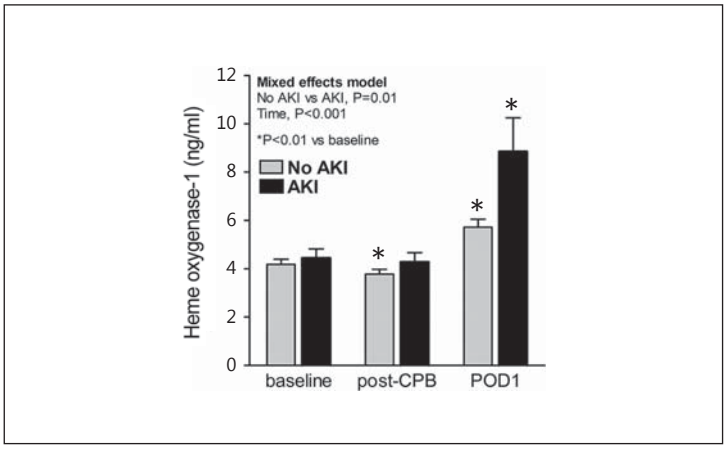

Fig. 1. HO-1 concentrations in patients undergoing CPB. HO-1 concentrations were higher in patients that developed AKI compared to those that did not.

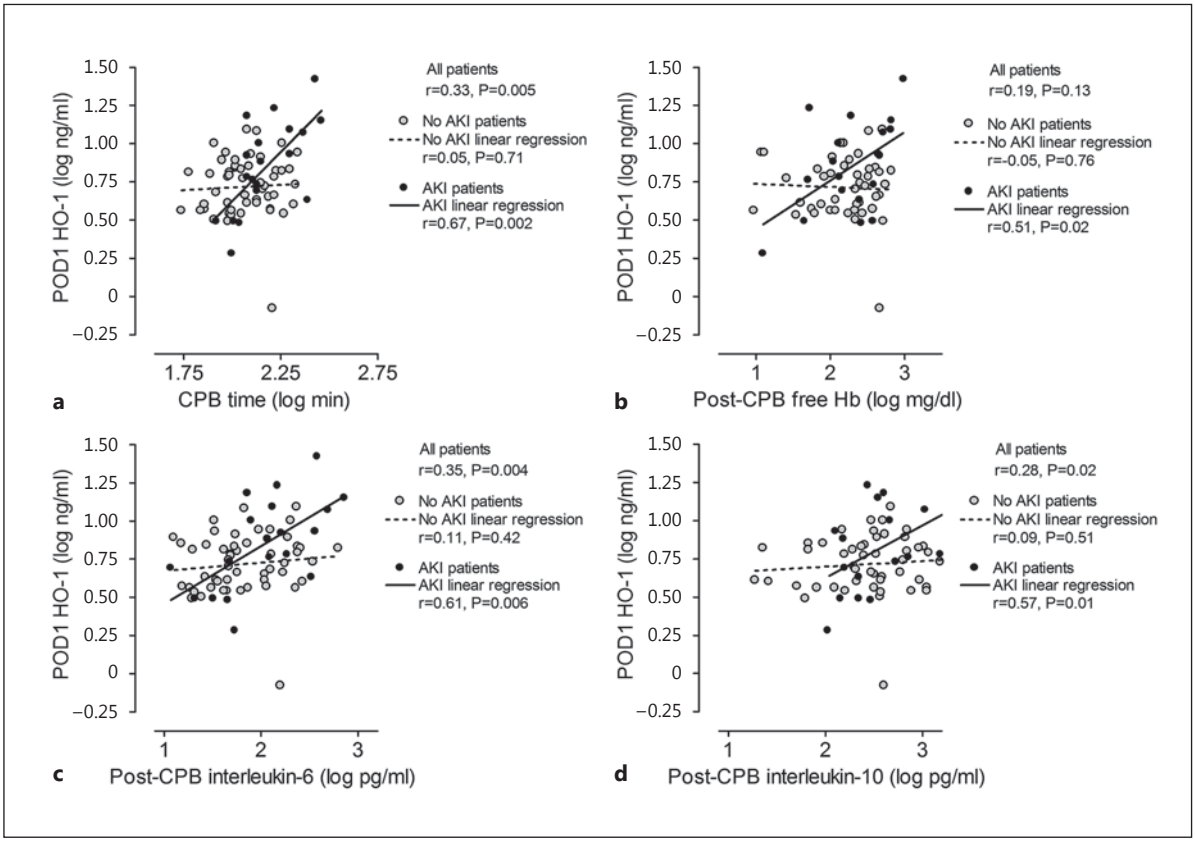

Fig. 2. Correlations between POD1 HO-1 and duration of CPB (**a**), post-CPB free hemoglobin (**b**), post-CPB IL-6 (**c**), and post-CPB IL-10 (**d**) in patients that did and did not develop AKI.

p = 0.006), and HO-1 concentrations in AKI patients over the course of study (p = 0.01, fig. 1). Because of the effect of the ACE inhibitor on HO-1 concentrations and to adjust for differences in AKI risk factors between patients that did and did not develop AKI, we measured the association of HO-1 concentrations on AKI adjusting for the effects of study drug and AKICS score using a mixed effects model. Increased perioperative HO-1 concentrations remained independently associated with postoperative AKI (p = 0.046).

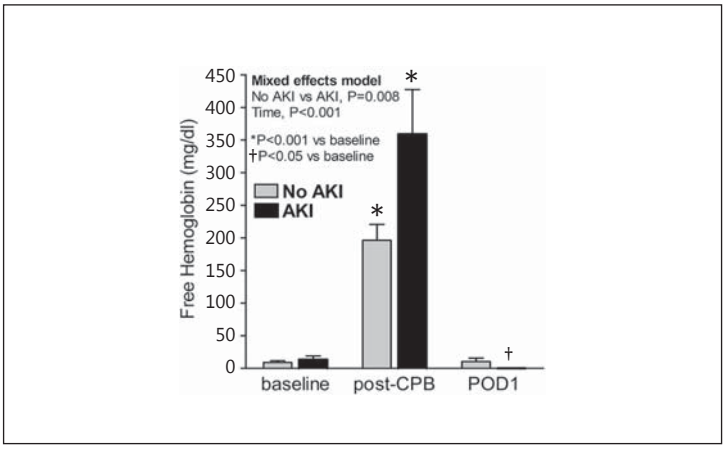

Fig. 3. Plasma-free hemoglobin concentrations in patients undergoing CPB. Free hemoglobin concentrations were higher in patients that developed AKI compared to those that did not.

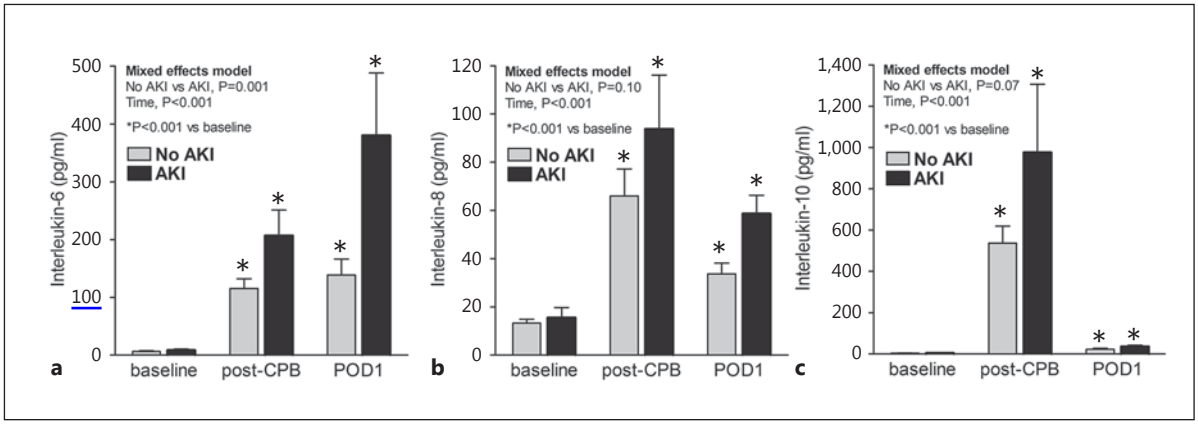

Fig. 4. Inflammatory response to CPB as measured by IL-6 (**a**), IL-8 (**b**), and IL-10 (**c**). IL-6 concentrations were significantly higher in patients that developed AKI compared to those that did not.

Duration of CPB (p = 0.005, fig. 2a), post-CPB IL-6 concentrations (p = 0.004, fig. 2c), and post-CPB IL-10 concentrations (p = 0.02, fig. 2d) were also each associated with increased HO-1 concentrations on POD1.

Hemolysis

CPB was associated with a significant increase in plasma-free hemoglobin. Free hemoglobin concentrations increased from 10.2 ± 2.5 mg/dl at baseline to 242.5 ± 27.2 mg/dl following CPB (p < 0.001) before falling to 7.6 ± 3.7 mg/dl by POD1. Baseline free hemoglobin concentrations were similar between AKI and no-AKI groups (p = 0.48). The increase in free hemoglobin concentrations was 158.2 mg/dl greater in patients that developed AKI (345.6 ± 66.3 vs. 187.4 ± 23.5 mg/dl, p = 0.03), and free hemoglobin concentrations were higher in the AKI group over the course of study (p = 0.008, fig. 3). In patients that developed AKI, but not in those that did not, increased post-CPB free hemoglobin concentrations were associated with increased POD1 HO-1 concentrations (p = 0.02, fig. 2b). Since CPB time and total operating room (OR) time strongly correlated (r = 0.87, p < 0.001), it is not surprising that total OR time also correlated with post-CPB free hemoglobin (r = 0.45, p < 0.001), post-CPB IL-6 (r = 0.80, p < 0.001) and HO-1 on POD1 (r = 0.39, p = 0.001).

Inflammatory Cytokines

The pro-inflammatory markers IL-6 and IL-8 and the anti-inflammatory marker IL-10 increased significantly during and following surgery (all p values <0.001, effect of time), with IL-8 and IL-10 peaking post-CPB and IL-6 on POD1. IL-6 concentrations were higher (p = 0.001, fig. 4a), while IL-8 (p = 0.10, fig. 4b) and IL-10 (p = 0.07, fig. 4c) concentrations tended to be higher in patients that developed AKI compared to those that did not. Patients that underwent aortic cross-clamping had higher free hemoglobin (318.1 ± 40.7 vs. 143.2 ± 24.4 mg/dl, p = 0.003) and IL-6 (189.8 ± 28.2 vs. 77.6 ± 11.8 pg/ml, p = 0.003) concentrations post-CPB but similar HO-1 concentrations (6.9 ± 0.7 vs. 6.1 ± 0.6 ng/ml, p = 0.44) compared to patients that did not undergo surgery with aortic cross-clamping. In separate mixed effects model analyses, the association between postoperative AKI and perioperative changes in free hemoglobin, HO-1 and IL-6 concentrations remained significant even after adjusting for the effect of aortic cross-clamping.

Discussion

This study measured the changes in plasma HO-1 concentrations during cardiac surgery, the associations between intraoperative hemolysis and HO-1 and inflammation, and the ability of HO-1, free hemoglobin, and markers of inflammation to discriminate between patients that develop postoperative AKI from those that do not. HO-1 concentrations increased significantly following cardiac surgery. Intraoperative concentrations of free hemoglobin, IL-6, and IL-10 were associated with HO-1 expression in the plasma, and postoperative AKI was associated with increased HO-1, free hemoglobin, and IL-6.

HO-1 may be a marker of AKI but has been shown to attenuate renal injury in an experimental model of rhabdomyolysis [16]. Free hemoglobin induces HO-1 expression, and HO-1 degrades heme into carbon monoxide, iron, and biliverdin [6]. HO-1 attenuates inflammation and oxidative stress [6, 17], and the product of HO-1 degradation, carbon monoxide, has been shown to reduce CPB-induced kidney injury in pigs [18]. HO-1 activity is not only upregulated by heme but also by ischemia-reperfusion injury and IL-10 [6], supporting the rationale that HO-1 expression may be important in cardiac surgery-induced AKI. Although induction of HO-1 seems to be protective in hemeprotein-mediated AKI, it is important to note that induction of HO-1 may induce renal injury in certain settings and that inhibition of HO activity may actually be protective [6, 19]. Future studies will determine if plasma HO-1 is increased in patients that develop AKI because HO-1 is a marker of injury associated with AKI or because HO-1 contributes to AKI following cardiac surgery. The time course of HO-1, free hemoglobin, IL-6 and IL-10 concentrations during cardiac surgery suggests that CPB-associated hemolysis and inflammation precede HO-1 upregulation and subsequent kidney injury. In the study by Zager et al. [7], HO-1 was upregulated in animal models of rhabdomyolysis and septic AKI. Plasma and urine HO-1 concentrations were associated with intrarenal HO-1 expression, but HO-1 concentrations in liver, lung, and spleen tissue were not elevated during AKI. In the 10 medical ICU patients with AKI, plasma and urine HO-1 concentrations were higher compared to matched controls, but the collection of blood and urine in these patients occurred after AKI had been diagnosed. CPB surgery provides an excellent model of AKI in humans because a clear onset of injury associated with CPB provides the opportunity to assess and sample patients prior to, during, and after injury. Our finding of increased plasma HO-1 concentrations in cardiac surgery patients with AKI supports the results observed by Zager et al. [7] but also demonstrates for the first time that increased plasma HO-1 may precede AKI.

Preoperative treatment with an ACE inhibitor was associated with a significant increase in plasma HO-1 concentrations. These differences were most notable before the onset of CPB.

ACE inhibition also increases HO-1 expression in rat kidney [20]. The mechanism of ACE inhibition-mediated HO-1 expression is not known, but the absence of effect by ARB suggests that ACE inhibition may affect HO-1 expression through bradykinin rather than angiotensin II (Ang II). Both ACE inhibition and ARB decrease the effect of Ang II (either by decreasing the formation of Ang II or blocking the Ang II type 1 receptor), whereas only ACE inhibition enhances the effect of endogenous bradykinin by blocking its hydrolysis and inhibiting desensitization of its receptor [21]. Bradykinin stimulates the release of nitric oxide through the bradykinin B2 receptor [22], and nitric oxide induces HO-1 expression [23]. This might explain the observed effect of ACE inhibition on HO-1 concentrations in our study population.

The release of both hemoglobin and myoglobin during CPB surgery has been associated with AKI in prior studies [3, 24]. However, the dominant hemeprotein released during CPB surgery is hemoglobin [3]. Hemeproteins, when released from cells, cause kidney injury through various mechanism including lipid peroxidation and vasoconstriction [5]. The increased free hemoglobin concentrations following CPB observed in AKI patients from the current study support these earlier studies. This suggests that free hemoglobin, measured immediately after CPB, may be an early biomarker of postoperative AKI. In addition, therapies targeting hemolysis reduction, free hemoglobin scavenging, or attenuation of hemeprotein-induced lipid peroxidation might reduce the risk of postoperative AKI. Avoiding CPB by performing off-pump coronary artery bypass surgery, for example, reduces hemolysis and the risk of postoperative AKI [25].

Techniques aimed to reduce the inflammatory surge associated with cardiac surgery have also been developed, since acute inflammation has been implicated in the development of postoperative kidney injury in some studies [8, 26]. Consistent with these studies, we found that perioperative plasma concentrations of IL-6 and to a lesser extent IL-8 or IL-10 are associated with AKI. In addition, we found that intraoperative concentrations of IL-6 and IL-10 highly correlated with plasma HO-1 concentrations on POD1, but only in patients that were subsequently diagnosed with AKI. This observation might be explained by the higher degree of hemolysis and inflammation in AKI patients and suggests that HO-1 may play an important role in the development of AKI following cardiac surgery. On the contrary, increased inflammation in AKI patients may be due to mechanisms separate from hemolysis and HO-1 induction. Pharmacological inhibition of the inflammatory response in cardiac surgery patients has been shown to decrease some adverse postoperative outcomes. Administration of steroids in the immediate postoperative period, for example, reduces the incidence of postoperative atrial fibrillation [27]. However, the effect of anti-inflammatory drugs on postoperative kidney function has been disappointing. The administration of dexamethasone before CPB does not appear to protect the kidney, as measured by changes in creatinine clearance or N-acetyl-b-D-glucosaminidase [28].

Limitations

Although plasma concentrations of HO-1 were different between the AKI and no-AKI groups on POD1, concentrations measured immediately after CPB were not significantly different between groups, limiting enthusiasm for HO-1 as an early biomarker of postcardiac surgery-induced AKI. This similarity in HO-1 concentrations between the AKI and no-AKI groups immediately after CPB might be explained by the effect of free hemoglobin on HO-1 induction. The time point of the post-CPB sample collection coincided with maximum free hemoglobin concentrations, and in cell cultures, induction of HO-1 occurs 4 h after injury [7]. Furthermore, the differences in HO-1 concentrations observed on POD1 may point to a potential mechanistic role of CPB-induced hemolysis in the development of AKI following cardiac surgery. In further support of the role HO-1 may play in the development of AKI, the anti-inflammatory immune modulator bardoxolone methyl increases HO-1 expression, atten-

uates kidney injury in an animal model of ischemic AKI [29], and improves kidney function in patients with diabetic nephropathy [30]. In addition, statins, aspirin, and resveratrol can also increase HO-1 protein expression, and the effect of these drugs remains to be studied in patients at risk for postoperative AKI [31]. Amplification of the HO-1 pathway can also be achieved by administering one of the products of HO-1 metabolism (CO), which induces IL-10 expression, further increasing the production of HO-1 [32]. It will be important to assess the effect of HO-1 independent of free hemoglobin to determine if HO-1 is protective against AKI in cardiac surgery patients with similar degrees of hemolysis. Lastly, we were unable to perform multivariate regression to determine if HO-1 is an independent risk factor for postoperative AKI because of the limited number of patients that developed AKI. Nonetheless, the identification of elevated HO-1 concentrations in patients that develop AKI following cardiac surgery provides the rationale for targeting the hemolysis HO-1 pathway in order to reduce postoperative AKI and long-term renal dysfunction.

In conclusion, this study has demonstrated that postoperative AKI is associated with increased plasma HO-1, free hemoglobin, and IL-6 concentrations, and that intraoperative hemolysis and inflammation are associated with postoperative plasma HO-1 concentrations in patients undergoing cardiac surgery. Hemolysis is a modifiable risk factor of postoperative AKI, and manipulation of HO-1 expression and other effects of free hemoglobin during cardiac surgery warrant further investigation.

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Disclosure Statement

None of the authors has a conflict of interest or disclosure.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Erratum

In the article by Billings FT, Yu C, Byrne JG, Petracek MR and Pretorius M, entitled 'Heme oxygenase-1 and acute kidney injury following cardiac surgery' [Cardiorenal Med 2014;4:12–21], Frederic T. Billings should read Frederic T. Billings IV.