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Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery

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Catalytic iron, the chemical form of iron capable of participating in redox cycling, is a key mediator of acute kidney injury (AKI) in multiple animal models, but its role in human AKI has not been studied. Here we tested in a prospective cohort of 250 patients undergoing cardiac surgery whether plasma catalytic iron levels are elevated and associated with the composite outcome of AKI requiring renal replacement therapy or in-hospital mortality. Plasma catalytic iron, free hemoglobin, and other iron parameters were measured preoperatively, at the end of cardiopulmonary bypass, and on postoperative days 1 and 3. Plasma catalytic iron levels, but not other iron parameters, rose significantly at the end of cardiopulmonary bypass and were directly associated with bypass time and number of packed red blood cell transfusions. In multivariate analyses adjusting for age and preoperative eGFR, patients in the highest compared with the lowest quartile of catalytic iron on postoperative day 1 had a 6.71 greater odds of experiencing the primary outcome, and also had greater odds of AKI, hospital mortality, and postoperative myocardial injury. Thus, our data are consistent with and expand on findings from animal models demonstrating a pathologic role of catalytic iron in mediating adverse postoperative outcomes. Interventions aimed at reducing plasma catalytic iron levels as a strategy for preventing AKI in humans are warranted.

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Catalytic iron is the chemical form of iron that is neither transferrin nor protein bound and is therefore capable of catalyzing the Fenton and Haber–Weiss reactions, generating hydroxyl radicals, and causing cellular oxidative damage.[1,2] Under conditions of tissue injury[2] or hemolysis,[3] sudden release of intracellular stores of iron may result in elevated circulating levels of catalytic iron that may have a pathologic role in a variety of disease states including acute coronary syndrome[4,5] and acute kidney injury (AKI). In animal models of AKI, catalytic iron has been implicated in nephrotoxicity resulting from ischemia/reperfusion,[6] aminoglycosides,[7] cisplatin,[8] rhabdomyolysis,[9] hemoglobinuria,[10] and iodinated radiocontrast.[11] In many of these models, treatment with an iron chelator is protective.[7,8,12,13] The generalizability of these findings to humans is unknown.

In humans undergoing cardiac surgery, postoperative AKI is common and is associated with a several-fold increased risk of death.[14] Although the mechanisms of AKI following cardiac surgery are incompletely understood, release of free heme and iron during cardiopulmonary bypass (CPB) is likely to play a key role.[15] During CPB, extracorporeally circulated blood is exposed to nonphysiologic surfaces and shear forces that may injure red blood cells, leading to the release of free hemoglobin and catalytic iron.[16–19] We hypothesized that plasma catalytic iron levels increase after cardiac surgery and are associated with an increased risk of AKI requiring renal replacement therapy or in-hospital mortality (RRT/death).

RESULTS

Baseline characteristics

We enrolled and collected plasma and urine samples from 250 patients who underwent cardiac surgery (248 with CPB; 2 without CPB). Baseline and operative characteristics are shown in Table 1.

Iron markers before and after cardiac surgery

Figure 1 shows pre- and postoperative plasma catalytic iron levels in patients who did or did not reach the composite end

Table 1 | Baseline characteristics of the patients

Characteristic	$N = 250$
Demographics	
Age (years)	79 (72–83)
Female	107 (43)
White	242 (97)
Preoperative renal function	
Plasma creatinine (mg/dl)	1.2 (1.0–1.5)
eGFR (ml/min per 1.73 m^2)	49.9 (41.0–66.1)
CKD (eGFR <60 ml/min per 1.73 m^2)	170 (68)
Comorbidities	
Hypertension	205 (82)
Congestive heart failure	103 (41)
Diabetes mellitus	93 (40)
Chronic lung disease	56 (22)
Malignancy	52 (21)
Chronic liver disease	8 (3)
Preoperative iron marker levels	
Catalytic iron (μmol/l)	0.35 (0.29–0.44)
Free hemoglobin (mg/dl)	14.5 (8.9–24.1)
Total iron (μg/dl)	97 (81–106)
Transferrin (mg/dl)	211 (167–244)
Transferrin saturation (%)	33 (26–42)
Ferritin (ng/ml)	86 (46–156)
Urinary NGAL (ng)/creatinine (mg)	18.9 (7.5–68.8)
Operative characteristics	
Type of procedure	
CABG	31 (12)
Valve	111 (44)
CABG and valve	78 (31)
Status of procedure	
Elective	152 (61)
Urgent	98 (39)
First or reoperative	
First cardiovascular surgery	172 (69)
Reoperative cardiovascular surgery	78 (31)
Cardiopulmonary bypass time (min)	140 (100–196)
Cross-clamp time (min)	93 (66–126)

Abbreviations: CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin.
Data are presented as *n* (%) or median (interquartile range IQR, 25–75th percentile). Estimated GFR was determined using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

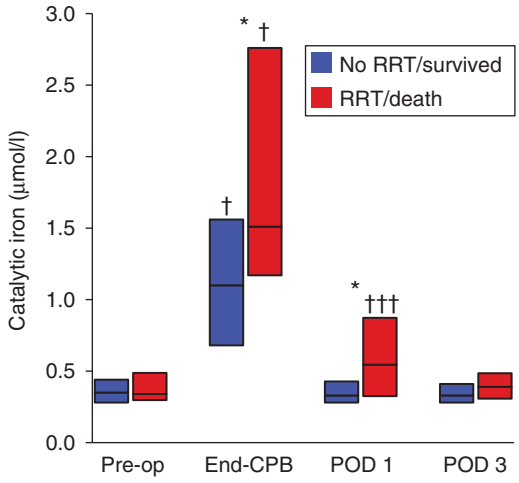

Figure 1 | Plasma catalytic iron levels—no RRT/survived versus RRT/death. $^{\dagger}P<0.001$, $^{\dagger\dagger\dagger}P<0.05$ for within-group comparisons to preoperative (Pre-op) levels; $^{*}P<0.01$ for between-group comparisons at individual time points. $N = 228$ (no RRT/survived); $N = 22$ (RRT/death). Bars represent median (25–75th interquartile range (IQR)). CPB, cardiopulmonary bypass; POD, postoperative day; RRT/death, renal replacement therapy or in-hospital mortality.

point of RRT/death. In both groups, plasma catalytic iron levels peaked at end-CPB, reaching levels ~2–3-fold higher than preoperative levels, and subsequently returned to baseline by postoperative day 3 (POD 3). At the first postoperative time point (end of CPB), plasma catalytic iron levels were significantly higher among patients who did versus who did not experience RRT/death, and remained significantly higher on POD 1 (Figure 1).

Figure 2 shows levels of pre- and postoperative plasma and urinary iron markers in patients who did or did not experience RRT/death. Similar to plasma catalytic iron, plasma free hemoglobin and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels peaked at end-CPB in both groups. In addition, plasma ferritin and urinary NGAL levels were significantly higher on POD 1 among patients who did versus who did not experience RRT/death. In contrast to plasma catalytic iron, no other plasma or urinary iron markers were significantly different between groups at end-CPB (Figure 2).

Catalytic iron and adverse postoperative outcomes

Among the 250 patients, 64 developed AKI and 22 reached the primary composite end point of RRT/death (3 required RRT and survived, 13 died without RRT, and 6 required RRT and died). The causes of death were septic shock ($N = 9$), myocardial infarction ($N = 3$), respiratory failure ($N = 2$), mesenteric ischemia ($N = 1$), gastrointestinal bleed ($N = 1$), cerebrovascular accident ($N = 1$), cardiogenic shock ($N = 1$), and ventricular fibrillation ($N = 1$).

Univariate analyses between iron markers from each time point, baseline/operative characteristics, and RRT/death are shown in Table 2. Univariate analyses between change in iron markers over time and RRT/death are shown in Supplementary Table S1 online. Plasma catalytic iron and plasma ferritin levels measured at end-CPB and POD 1 and urinary NGAL levels measured on POD 1 were directly associated with RRT/death (Table 2). CPB time was directly associated, whereas age and estimated glomerular filtration rate (eGFR) were inversely associated, with RRT/death (Table 2). Additional univariate associations are shown in Table 2. As the strongest associations were observed on POD 1, subsequent analyses on adverse postoperative outcomes focused on iron markers at this time point.

Figure 3 shows the association between quartiles of catalytic iron on POD 1 and adverse outcomes. After adjusting for age and preoperative eGFR, patients with