Case Series

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Renal dysfunction in adults following cardiopulmonary bypass is linked to declines in S-nitroso hemoglobin: a case series

Andrew Moyal, BS, MD[a], Ryan Nazemian, MD, PhD[a,b], Edwin Pacheco Colon, MS, MBA[a,b], Lin Zhu, MD, PhD[a,b], Ruth Benzar, MD[a,b], Nicole R. Palmer, BA, MPH[a], Martha Craycroft, RN[c], Alfred Hausladen, PhD[a,b], Richard T. Premont, PhD[a,c,d], Jonathan S. Stamler, MD[a,c,d], John Klick, MD[b], James D. Reynolds, PhD[a,b,d,*]

Background: Impaired kidney function is frequently observed in patients following cardiopulmonary bypass (CPB). Our group has previously linked blood transfusion to acute declines in S-nitroso haemoglobin (SNO-Hb; the main regulator of tissue oxygen delivery), reductions in intraoperative renal blood flow, and postoperative kidney dysfunction. While not all CPB patients receive blood, kidney injury is still common. We hypothesized that the CPB procedure itself may negatively impact SNO-Hb levels leading to renal dysfunction.

Materials and methods: After obtaining written informed consent, blood samples were procured immediately before and after CPB, and on postoperative day (POD) 1. SNO-Hb levels, renal function (estimated glomerular filtration rate; eGFR), and plasma erythropoietin (EPO) concentrations were quantified. Additional outcome data were extracted from the patients' medical records.

Results: Twenty-seven patients were enroled, three withdrew consent, and one was excluded after developing bacteremia. SNO-Hb levels declined after surgery and were directly correlated with declines in eGFR ($R = 0.48$). Conversely, plasma EPO concentrations were elevated and inversely correlated with SNO-Hb ($R = -0.53$) and eGFR ($R = -0.55$). Finally, ICU stay negatively correlated with SNO-Hb concentration ($R = -0.32$).

Conclusion: SNO-Hb levels are reduced following CPB in the absence of allogenic blood transfusion and are predictive of decreased renal function and prolonged ICU stay. Thus, therapies directed at maintaining or increasing SNO-Hb levels may improve outcomes in adult patients undergoing cardiac surgery.

Keywords: Cardiopulmonary bypass, kidney injury, nitric oxide, S-nitroso, S-nitroso haemoglobin

Introduction

Each year in the United States, hundreds of thousands of patients undergo cardiopulmonary bypass (CPB)[1,2]; coronary artery bypass grafting (CABG) alone accounts for ~400 000 of these procedures[3]. Developed in the 1960s, use of CPB is now viewed as routine by the lay public. And yet, despite significant advances in surgical techniques, extra-corporeal circulation technology and related perioperative care algorithms, going "on pump" is not a benign event. Instead, CPB has the potential to induce a myriad of adverse postoperative sequelae, independent of the cardiac condition that prompted the surgical intervention[4–6].

One of the most common detrimental consequences of CPB is acute kidney injury (AKI), which may be severe enough to require renal replacement therapy[5,7]. The reported rates of postoperative kidney injury vary widely, mainly as a result of changing diagnostic criteria[8]. Yet even at the low end (estimated at 5–10% of all patients undergoing CPB), kidney injury remains a major contributor to poor postoperative outcomes including significant increases in 30-day mortality[9]. Equally important is the growing recognition that an episode of AKI may confer long-term risk. A large meta-analysis focused on prolonged survival after discharge determined that in-hospital AKI significantly

HIGHLIGHTS

- S-nitroso haemoglobin (SNO-Hb) within red blood cells is a major regulator of micro-vascular oxygen deliver. We found that SNO-Hb decreased during adult bypass and that this decline was directly linked to declines in kidney function and increases in length of hospital stay. Thus SNO-Hb can serve as novel biomarker of early post-operative dysfunction and could also be a drugable target to improve surgical outcomes.

[a]Institute for Transformative Molecular Medicine, Departments of [b]Anesthesiology & Perioperative Medicine, [c]Cardiology, School of Medicine Case Western Reserve University and [d]Harrington Discovery Institute, University Hospitals-Cleveland Medical Center, Cleveland, OH

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*Corresponding author. Address: Institute for Transformative Molecular Medicine, Department of Anesthesiology and Perioperative Medicine, Case Western Reserve University, Harrington Discovery Institute University Hospitals-Cleveland Medical Center 4-128 Wolstein Research Building 2103 Cornell Road Cleveland, OH 44106. Tel.: +21 636 857 27; fax: +21 636 829 68. E-mail: jxr343@case.edu (J D. Reynolds).

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increased mortality rates from 4.3 to 8.9 per 100 person-years (relative risk 2.59; 95% CI between 1.97 and 3.42)[7]. Similarly, it was determined that 15% of patients who experienced an in-hospital episode of AKI progressed to Stage 3 chronic kidney disease (CKD) within 2.5 years; the incidence rate was only 3% in a matched patient group without AKI[10]. A particularly notable finding from this latter study was that the AKI patients were identified at the time of discharge as "*completely recovered*", defined as having a serum creatinine less than 1.1 times their baseline (admission) value.

AKI frequently occurs following CPB because the procedure and surgical manipulations can reduce or interrupt kidney blood flow[11,12]. Systemic regulators of oxygen delivery can be interrupted by renal hypo-perfusion that decreases local production of endogenous vasodilators while stimulating the build-up of vasoconstrictive inflammatory agents. Consequently, the period of oxygen deficiency in the renal microvasculature may be prolonged, with blood flow (and potential delivery of protective agents) being impaired even after restoration of large vessel flow[13–15]. Despite the primacy of AKI to negatively impact coronary patient outcomes, there are no accepted therapies to prevent injury or rapidly restore renal function, a consequence of the poor understanding of the events that initiate and/or propagate kidney damage.

Based on a robust combination of data from pre-clinical interventional experiments[16–19] and observational clinical studies[20], we postulate that renal injury results (at least in part) from CPB-mediated disruptions in S-nitrosothiol (SNO) homoeostasis. Protein S-nitrosylation is a major mechanism through which the cellular influences of nitric oxide (NO) are exerted[21,22]. Haemoglobin (Hb) is the prototypical S-nitrosylated protein[23,24], with SNO-Hb deploying vasodilatory NO bioactivity as red blood cells (RBCs) transit the circulatory system. Low oxygen tension in the periphery promotes the graded-release of SNO-based vasodilatory activity from the beta-Cys 93 thiol within RBCs—oxygen delivery is thus linked to local metabolic demand[25]. Blood flow, inflammation, and cell signalling are all impacted by surgical interventions[26–30]. This inter-connection suggests CPB may induce a combination of systemic and focal (e.g. kidney) impairments in S-nitrosylation. As a first proof of concept test of this hypothesis, we monitored SNO-Hb levels in a cohort of adult heart surgery patients to determine if changes in NO/SNO bioactivity could be linked to subsequent kidney dysfunction and outcome. Reporting of the results of this case series follows the SCARE[31] and PROCESS Guidelines[32].

Patients and methods

Population

This single-site investigation was a prospective observational case series conducted at University Hospitals-Cleveland Medical Center, a tertiary care and research institution. The protocol was approved by the hospital's institutional review board and the trial was registered with a public database in accordance with the Declaration of Helsinki. Inclusion criteria were patients over the age of 18 undergoing CPB. Patients were excluded if it was a repeat CPB procedure, they had any blood-borne infection, pre-existing kidney disease, they received an intraoperative or postoperative allogenic RBC transfusion, or if they were enroled in an interventional study. Written informed consent to participate was obtained from each patient prior to surgery. Subjects consented to offline analysis of blood samples and review of their medical records along with the plan to publish aggregate de-identified results.

Surgery

A standard perioperative routine was followed: premedication with iv midazolam; surgical anaesthesia with inhaled isoflurane and iv fentanyl; and iv rocuronium for neuromuscular relaxation. Autologous RBCs and crystalloid pump prime were employed to maintain haematocrit at greater than 18%. Vasodilators, vasoconstrictors, and inotropes were employed as clinically indicated. The CPB system consisted of a Terumo oxygenator (Terumo Medical), and Sorin S5 roller pump (Sorin Medical). Blood cardioplegia using the Quest MPS system (Quest Medical) was utilized on all cases. CPB used non-pulsatile perfusion at 2.4 l/min/m^2. Nasopharyngeal temperature was maintained at 32°C during CPB; rewarming to 36°C occurred at bypass conclusion.

Arterial blood samples were obtained from an indwelling catheter prior to going on CPB (T1), immediately after discontinuation of the CPB circuit (T2), and on postoperative day one (POD 1; T3)—arterial access typically ended on POD 1 or 2 with catheter removal. Samples were transported on ice to the research laboratory for quantification of SNO-Hb levels. Postoperative patient management was directed by the ICU staff who were unaware of the study goals. RBC SNO-Hb levels were quantified offline; the resultant values were not used to direct anyone's clinical care. Additional blood chemistry values were extracted from the subjects' medical records.

Blood samples analysis

RBC SNO-Hb concentrations were determined using a validated photolysis/chemiluminescence method[33]. Hb was isolated from the RBCs and then stored at −80°C for batch analysis. Measurements of plasma erythropoietin (EPO) were performed using an ELISA kit according to the manufacturer's protocol. Estimated glomerular filtration rate (eGFR) was calculated for each individual, based on levels of serum creatinine, serum

Table 1

Demographic data

Parameter	Value
Population	
Age (years)	71 ± 10
Sex (M/F)	19/8
Ethnicity	
White	23
African American	2
Undeclared	2
BMI (kg/m^2)	31 ± 6
eGFR (arbitrary units)	76.7 ± 24.3
Hb (g/dl)	11.9 ± 1.5
HbA1c (%)	5.7 ± 0.5

eGFR, estimated glomerular filtration rate; F, female; Hb, haemoglobin; M, male.

Table 2
General surgical data

Parameter		Value
Procedure		
AVR		8
MVR		7
TVR		2
CABG		4
ASDC		1
AAA		1
Pump time (min)		144 ± 60
Clamp time (min)		123 ± 67
Surgery time (min)		333 ± 97
Estimated blood loss (ml)		643 ± 327
Autologous transfusion (ml)		572 ± 345
Oxygenation	Pre	Post
Arterial saturation (SaO_2; %)	99.4 ± 2.3	98.3 ± 5.1
Arterial oxygen content (CaO_2; ml/dl)	16.0 ± 2.1	12.9 ± 2.4[a]
Total haemoglobin (g/dl)	11.9 ± 1.5	9.7 ± 1.7[a]
ICU stay (h)		71 ± 61
Hospital stay (days)		11 ± 6

[a]Significantly different from the Pre value, $P < 0.05$.
AAA, abdominal aortic aneurysm; ASDC, atrial septal defect closure; AVR, atrial valve replacement; CABG, coronary artery bypass grafting; MVR, mitral valve replacement; TVR, tricuspid valve replacement.

albumin, blood urea nitrogen (BUN), sex, and demographics, using the following equation:[34]

$$\text{eGFR} = 170 \times (P_{cr})^{-.999} \times [\text{Age}]^{-.176} \times [.762 \text{ if patient is female}] \times [1.180 \text{if patient is black}] \times [\text{BUN}]^{-.170} \times [\text{Alb}]^{+.31834}$$

Statistics

Analyses were conducted using R-statistical analysis software, Version 4.1.2. Standard parametric methods were used to assess for change in specific parameters over time. After confirming the assumption of normality and sphericity, paired *t*-tests were used for comparing before/after differences while repeated-measures analysis of variance was employed for the longitudinal data comparisons. Linear relationships were assessed for using Pearson correlation coefficients. In all cases, *P* values less than 0.05 were considered statistically significant.

Results

Twenty-seven patients provided pre-operative written informed consent to be enroled in the study; their demographic details are presented in Table 1. Three patients withdrew their consent after enroling while one patient developed bacteremia and was therefore withdrawn. The final cohort had an average baseline eGFR of 76.7 ± 24.3 ml/min and an average total Hb level of 11.8 ± 1.5 g/dl. General surgical data for the 23 subjects are presented in Table 2. Most procedures were valve repairs yet across the group, surgical parameters were relatively consistent. Patients were well-oxygenated but experienced a decline in arterial blood oxygen content resulting from a 2 g/dl decline in Hb levels at the end of surgery; ICU time and hospital stay were comparable with historical norms. Perioperative clinical chemistry data for kidney function and NO components are presented in Table 3. Creatinine, albumin, and BUN fluctuated with only the latter parameter significantly increasing during the study period. The rise in EPO level by POD 1 was indicative of a period of decreased kidney oxygenation. Note that the inclusion of all three markers in the calculation of GFR provided a clearer picture of post-operative kidney function (Fig. 2) than creatinine alone. SNO-Hb levels declined by the end of surgery and then further declined on POD 1, which accounted for the matching decline in totalNO-Hb as the amount of FeNO-Hb stayed constant.

We next tested for correlations between SNO status, kidney function, and outcome (i.e. ICU stay). Based on Cohen[35], in our linear regression model with $n = 23$ and to see effect size of 0.5 at a significance level of 0.05, we have achieved 89% power. Figure 1A graphically-depicts the reduction in NO bioactivity. As noted, this reduction was almost entirely accounted for by the loss of SNO-Hb ($P = 0.00087$) as haem nitrosyl Hb (FeNO-Hb) levels remained constant ($P = 0.36$). Figure 1B graphically-depicts the increase in EPO ($P = 0.0024$). Strengthening the link between SNO-Hb and kidney oxygenation, there was a direct inverse correlation between change in EPO levels and SNO-Hb (Fig. 1C, $P = 0.03$), that is lower SNO-Hb was associated with higher EPO concentration.

The functional consequences of changes in SNO-Hb and EPO were reflected in worsened kidney function and increased hospitalization time. Both the magnitude of the decline in SNO-Hb and the increase in EPO correlated with declines in eGFR (Fig. 2A and Fig. 2B, respectively). Finally, as an overall measure of outcome, declines in SNO-Hb were directly correlated with increased ICU length of stay (Fig. 2C, $P = 0.03$).

Table 3
Perioperative clinical chemistries

Parameter	Start	End	POD 1	POD 2	POD 3
Creatinine (mg/dl)	0.99 ± 0.29	1.04 ± 0.32	1.01 ± 0.27	0.98 ± 0.33	0.90 ± 0.31
Albumin (g/dl)	3.3 ± 0.5	3.7 ± 1.0	3.3 ± 0.3	3.1 ± 0.4	3.4 ± 1.4
BUN (mg/dl)	18 ± 6	18 ± 5	20 ± 6	24 ± 9	25 ± 9
EPO (mU/ml)	17.8 ± 15.0	21.5 ± 21.0	47.3 ± 28.7[a]	—	—
NO components (X per Hb × 10^3)					
SNO-Hb	5.9 ± 2.1	4.8 ± 1.7	4.1 ± 1.2[a]	—	—
FeNO-Hb	2.5 ± 1.0	2.3 ± 1.3	2.2 ± 1.0[a]	—	—
totalNO-Hb	8.5 ± 2.6	7.1 ± 2.4	6.3 ± 1.8[a]	—	—

[a]Significantly different from the Start value, $P < 0.05$.
BUN, blood urea nitrogen; EPO, erythropoietin; FeNO-Hb, iron nitrosyl haemoglobin; POD, postoperative day; SNO-Hb, S-nitroso haemoglobin; totalNO-Hb, total nitric oxide bound to haemoglobin.

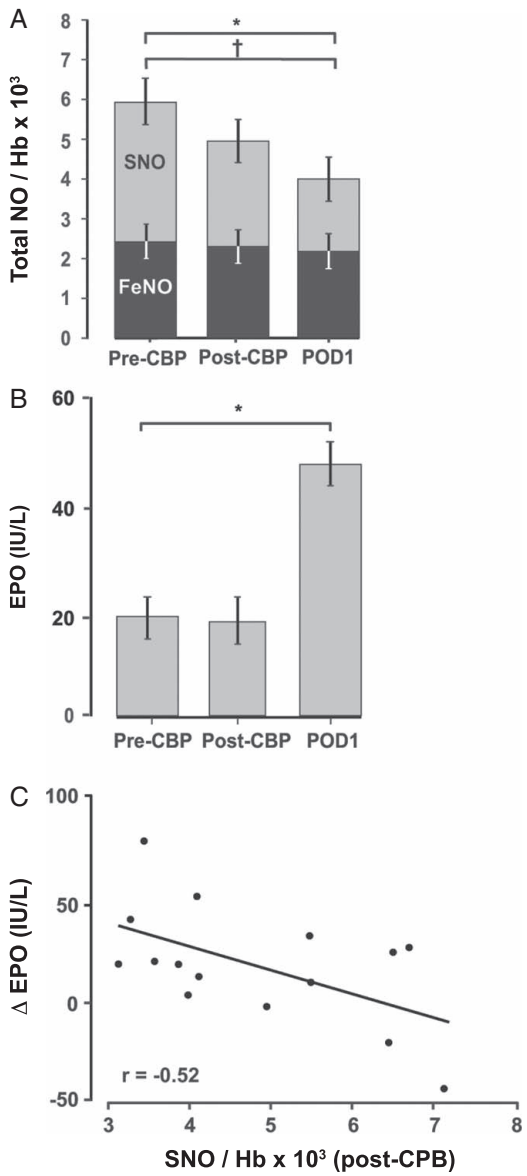

Figure 1. Change in clinical markers after cardiopulmonary bypass (CPB). (A) Amounts of FeNO, S-nitroso haemoglobin (SNO-Hb) and total nitric oxide (NO) (expressed per Hb × 10^3) in pre-CPB (T1), immediate post-CPB (T2) and postoperative day 1 (POD 1, T3) blood samples. SNO-Hb and total NO declined from pre-CPB (T1) to post-CPB (T2) and POD 1 (T3), while FeNO levels remained constant. (B) Erythropoietin (EPO) concentrations in pre-CPB, immediate post-CPB and POD 1 blood samples. EPO increased after CPB, from T1/T2 to T3. (C) Scatter plot depicting the inverse correlation between SNO-Hb level post-CPB and change in EPO (Δ EPO) from completion of CPB to POD 1 (T3-T2). The level of SNO inversely correlated with the EPO concentration ($r = -0.53$, $P = 0.037$).

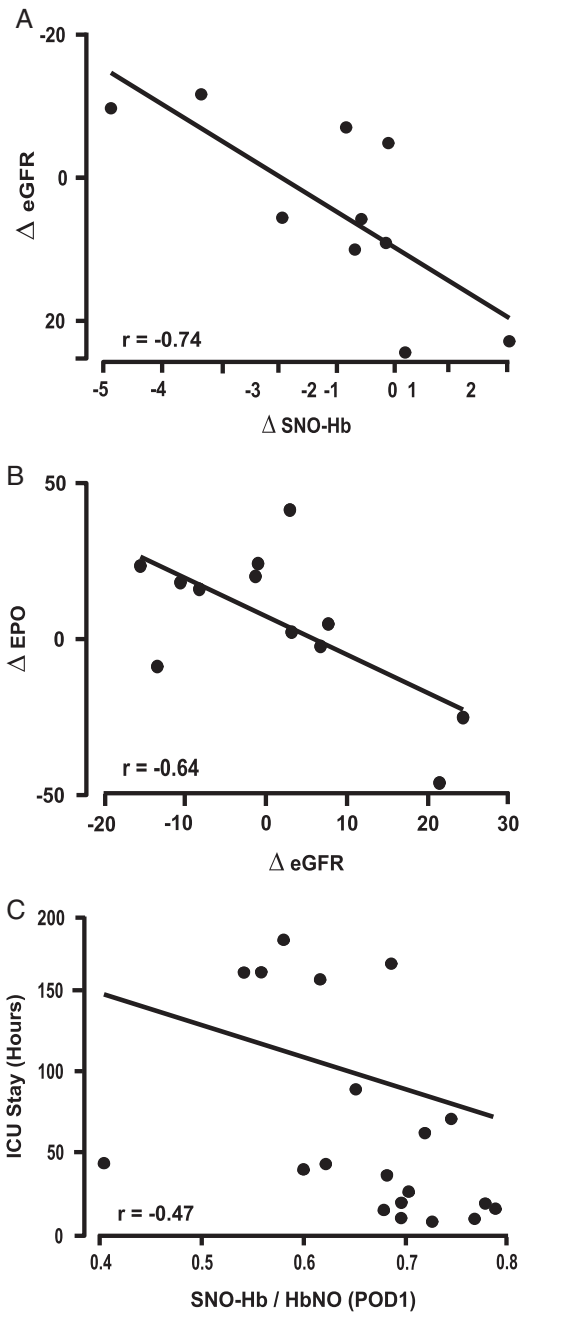

Figure 2. Relationship between clinical blood markers and outcome. (A) Change in estimated glomerular filtration rate (eGFR) from pre-cardiopulmonary bypass (CPB) (T1) to postoperative day 1 (POD 1) was plotted versus change in S-nitroso haemoglobin (SNO-Hb) during CPB (from T1 to T2). Decline in eGFR after CPB correlated with decline in SNO-Hb during CPB ($r = 0.74$, $P = 0.01$). (B) Change in serum erythropoietin (EPO) from pre-CPB to POD 1 (T3-T1) was plotted versus change in eGFR from pre-CPB (T1) to POD 1 (T3). The increase in EPO correlated with the decline in eGFR after CPB ($r = -0.65$, $P = 0.02$). (C) Length of ICU stay after CPB was plotted versus SNO-Hb level at POD 1 (T3). As an overall measure of outcome, declines in SNO-Hb at T3 (POD 1) were directly correlated with increased ICU stay.

Discussion

The results from this observational study link CPB-mediated disruptions in SNO homoeostasis to impaired kidney function and worse outcomes (defined as increased ICU stay) in adult cardiac surgical patients. These findings add to a growing appreciation that, in general, depletion of NO bioactivity can reduce tissue oxygenation and induce organ dysfunction and, specifically, that kidneys exhibit an enhanced sensitivity to conditions that reduce circulating RBC SNO-Hb levels[12,20].

The unique anatomical make-up and functional activity of the kidneys confers an enhanced susceptibility to oxygen

deprivation[14]. The kidneys receive ~20–25% of cardiac output (even though they constitute only 2% of body mass), which, along with the small difference between the arterial and venous oxygen content, would suggest significant reserve capacity. Instead, the presence of preglomerular countercurrent shunts (key for sodium resorption) entails that, even under normal conditions, the kidney functions in a hypoxic environment; the pO_2 in the cortex is between 40 and 45 mmHg, and it gets progressively lower in the internal regions of the medulla and papilla. As a result, there is little oxygen reserve, so even small reductions in blood flow, and thus oxygen delivery, can have outsized effects on renal cellular activity compared to other organs[36,37].

Various nonspecific efforts directed towards limiting the intraoperative initiating factors of AKI (*viz.* renal hypo-perfusion) have been implemented; these include modifying surgical techniques to reduce kidney ischaemia time and limiting volume depletion. However, fluid management recommendations present the dichotomy of avoiding both anaemia and blood transfusion. In addition, compliance with such efforts can be thwarted by a patient's pre-existing condition(s) and/or intraoperative changes in status (e.g. Haemorrhage, difficult dissection, etc.)[38–40].

A significant number of pharmacologic agents have been utilized in attempts to prevent or ameliorate AKI. These include dopaminergic agonists, antioxidants and free radical scavengers, atrial natriuretic peptide, anti-inflammatories, diuretics, volume expanders, statins, NO donors, etc[38,41,42]. Specific drugs in each category (alone or as combination therapy) have demonstrated benefit in pre-clinical models of AKI, but this success has not translated to clinical practice for a variety of reasons:

(1) Nonspecific vasoactive agents produce dose-limiting hypo- or hypertension;
(2) Previous lack of consensus on defining AKI with respect to both appearance and resolution;
(3) Therapy initiation curtailed due to patient status (e.g. volume expansion/fluid loading in the setting of cardiovascular or pulmonary disease); and/or
(4) Failure to improve outcome in clinical trials (e.g. diuretics)[38,41].

The mechanism(s) that precipitated the decline in RBC SNO-Hb we observed here remain to be determined. As noted previously, in other settings, surgical manipulation has been shown to reduce SNO-Hb. There is also the inflammatory response and haemolysis that occurs as the RBCs circulate through the bypass circuit. Finally, it is important to recognize the current CPB protocol involves non-pulsatile flow[43], which is a very artificial setting compared to the innate movement of blood through the vasculature. As a result, an interval without pressure cycling (and no variable sheer stress) could impact the generation of NO/SNO from endothelial nitric oxide synthase. Whatever the cause(s), our findings suggest a new contributor to AKI; aberrant S-nitrosylation.

This discovery provides for a novel putative therapeutic target —restoration of RBC NO/SNO bioactivity. Using swine, we previously determined that surgical manipulations can deplete circulating SNO-Hb levels, leading to reductions in kidney blood flow and eGFR, and increases in enzymatic markers of tissue injury, all of which were resolved by administration of an S-nitrosylating agent[17]. We have observed similar benefits following intraoperative transfusion with SNO-Hb loaded RBCs[19]. We have also determined that administration of a SNO-donor can improve tissue oxygenation in humans[44] and we are initiating a clinical trial to determine if the same agent (ethyl nitrite) can improve the efficacy of blood transfusion (NCT03999229). These previous translational and clinical findings, along with the current clinical results, strongly suggest that increasing the intraoperative circulating pool of NO/SNO bioactivity could be both prophylactic and therapeutic against AKI.

This study supports the current body of evidence that CPB can induce postoperative AKI and worsen patient outcomes, and adds to it by identifying a potential mediator of injury (reductions in SNO-Hb). We recognize that the correlative analysis of the prospectively collected data coupled with the small sample size are weaknesses of this study—additional studies in bypass patients with more significant pathologies as well contributions from other organ dysfunction on SNO-Hb and outcomes are certainly warranted. However, the matching findings regarding AKI from other adult bypass studies lessen this concern[12,45,46]. There was an insufficient number of patients to sub-divide the cohort by surgical intervention. Nonetheless, the surgical data (Table 2) indicates this was a relatively homogenous group. Moreover, as noted, identifying SNO-Hb as a determinant of renal function and, ultimately, patient outcome, is consistent with a growing body of literature connecting deficits in RBC SNO-Hb to pathologies of kidney oxygenation.

In summary, we have linked CPB-mediated dysregulated SNO homoeostasis to kidney dysfunction and worse patient outcomes. SNO-Hb levels are inversely correlated with kidney function, in terms of eGFR, EPO, and ICU stay, suggesting its utility as a target for therapeutic intervention and as a prognostic biomarker. While we focused here on CPB, we believe that reductions in RBC SNO-Hb may be the major contributor to the incidence and severity of AKI in a variety of medical settings (e.g. sepsis, blood transfusion, laparoscopic surgery, etc). As such, therapeutics that can prevent or correct reductions in the ability of RBCs to deliver oxygen would have widespread clinical applications—and are currently undergoing human testing[44]—applications that could improve patient outcomes and reduce medical care costs by reducing hospital length of stay and ameliorating progression to chronic kidney disease.

Ethical approval

Circulating S-Nitrosothiols in Human Health and Disease Study was approved by the University Hospitals-Cleveland Medical Center Institutional Review Board. Protocol Number 06-10-04.

Consent

Written informed consent was obtained from each subject prior to surgery. Subjects consented to offline analysis of blood samples and review of their medical records along with the plan to publish aggregate de-identified results. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

This was a multi-departmental effort that required coordination, input, and hands-on involvement from several individuals. With respect to specific contributions: J.D.R. conceived the study; J.D.R. designed the research studies in consultation with M.C., J.K., and J.S.S.; A.M. led the subject sampling and monitoring with assistance from R.N., E.P.C., L.Z., N.R.P., M.C., and J.K.; A.M., R.N., E.P.C., L.Z., N.R.P., and A.H. conducted the blood sample analyses; A.M., R.N., E.P.C., L.Z., R.B., N.R.P., and A.H. collated and analyzed the data; A.M., J.K., and J.D.R. wrote the manuscript with critical insights provided by R.B., R.T.P., and J.S.S.; A.H. contributed new reagents/analytical tools; and all authors provided editorial input to the final submission.

Conflicts of interest disclosure

J.S.S. and J.D.R. hold patents related to renitrosylation, some of which may be licensed for commercial development. In addition, J.S.S. has an equity interest in SNO Bio, a company developing nitrosylation-related therapeutics, and is a consultant to NNOXX, a company developing devices to measure SNO-Hb. Their institutions are aware of these potential conflicts and appropriate management plans are in place. None of the other authors have relevant conflicts to disclose.

Research registration unique identifying number (UIN)

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