

Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on post-operative acute kidney injury

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Abstract

Background. Acute kidney injury (AKI) after cardiac surgery is a common and serious condition carrying significant costs. During cardiopulmonary bypass (CPB) surgery, modifiable factors may contribute to post-operative AKI. Their avoidance might be a potential target for nephroprotection.

Methods. The objective of the present study was to identify and determine whether intraoperative hypotension, anaemia, or their combination, red blood cell transfusion or vasopressor use are independent risk factors for post-operative AKI defined by the RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease) classification and other thresholds using a mixed logistic multivariate model.

Results. We analysed 381 468 mean arterial pressure (MAP) measurements from 920 consecutive on-pump cardiac surgery patients. Overall, 19.5% developed AKI which was associated with an 8.2-fold increase in-hospital mortality. Haemoglobin concentration was an independent risk factor for AKI {odds ratio [OR] 1.16 per g/dL decrease [95% confidence interval (CI) 1.05–1.31]; $P = 0.018$ } with systemic arterial oxygen saturation and pressure values not adding further strength to such an association. MAP alone or vasopressor administration was not independently associated with AKI but volume of red blood cell transfusion was, with its effect being apparent at a haemoglobin level of >8 g/dL (>5 mmol/L). In patients with severe anaemia (<25 th percentile of lowest haemoglobin), the independent effect of hypotension (>75 th percentile of area under the curve MAP <50 mmHg) on AKI was more pronounced [OR 3.36 (95% CI 1.34–8.41); $P = 0.010$].

Conclusion. Intraoperative avoidance of the extremes of anaemia, especially during severe hypotension and avoidance of transfusion in patients with haemoglobin levels >8 g/dL (>5 mmol/L) may help decrease AKI in patients undergoing cardiac surgery and represent targets for future controlled interventions.

Keywords: acute kidney injury; anaemia; blood transfusion; cardiac surgery; hypotension

Introduction

Acute kidney injury (AKI) is a common and major complication of cardiopulmonary bypass (CPB) [1–3] and is independently associated with increased morbidity [4] and mortality [5, 6]. Cardiac surgery is now the second most common cause of AKI in the critically ill [7].

Many risk factors for AKI after cardiac interventions have been identified, but only some are modifiable [8, 9]. Episodes of hypotension and decreased arterial oxygen content may be particularly important. Despite target systemic mean arterial pressure (MAP) values of >55 or 60 mmHg [10, 11] during CPB, more severe hypotensive periods occur relatively frequently and may be prolonged with MAP values below the optimal renal autoregulation threshold [12]. They may induce ischaemic kidney damage [8, 13]. Similarly, bleeding or haemodilution can decrease arterial oxygen content, impair renal oxygen delivery and contribute to AKI [14]. Transfused red cells may be unable to properly load and unload oxygen and may have negative effects on renal outcome. Red cell transfusions have a shortened lifespan; their haemolysis leads to an increase in circulating catalytic iron [15].

Intraoperative hypotension, decreased oxygen content and transfusion of red cells are modifiable and might be potential targets for kidney protection during CPB.

Until recently, MAP during CPB has been incompletely and only manually recorded making its assessment as a risk factor difficult and inaccurate [16–19]. However, MAP measurements with frequent and electronically stored recordings have now overcome such limitations. This development, together with the frequent measurement of arterial blood gases, makes it possible to more accurately assess the relationship between hypotension

and decreased arterial oxygen content during CPB and the development of AKI.

Accordingly, we conducted a study to investigate the effects of MAP and systemic arterial oxygen content on postoperative renal function. We hypothesized that, after adjustment for relevant covariates, severity and duration of hypotension, low arterial haemoglobin or transfusion of red cells in the setting of adequate haemoglobin levels would be independent risk factors for post-operative AKI.

Materials and methods

Study design and setting

In a retrospective observational cohort study from December 2004 to January 2007, we linked electronically stored intraoperative systemic MAP and blood gas data with perioperative serum creatinine concentrations in consecutive patients undergoing CPB at the Austin Hospital, Melbourne. Study approval (H2004/02452) was given and written informed consent was waived by the Ethics Committee.

Data source and collection

Consecutive patients undergoing on-pump cardiac surgery were selected. The first intra-arterial MAP value was automatically recorded on a CPB data storage machine (Stoekert S3, Munich, Germany) immediately after cannulation of the aorta and then every 20 s until the end of the CPB. Arterial blood gas analysis (Ciba Corning 865; Ciba Corning Diagnostics, Medfield, MA) was performed every 30 min during CPB. Baseline serum creatinine data was generated from the immediately pre-operative Out-patient Department visit of each patient (on average 3–7 days preoperatively). Post-operative serum creatinine was measured daily for all patients using the modified Jaffé method. We excluded patients presenting with pre-operative end-stage kidney disease requiring dialysis, AKI preceding surgery [20], patients having received contrast media within 3 days pre-operatively, patients operated off-pump or treated with post-operative extracorporeal membrane oxygenation.

For collection of relevant pre-, intra- and post-operative covariates, we used the prospectively collected institutional Cardiac Surgery Database. The definition of co-morbidities is summarized in Appendix Box 1. Post-operative data included hourly MAP recordings, length of stay in Intensive Care and in hospital, in-hospital mortality and post-operative complications. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22] were used.

Management of patients

All patients were cared for by the same team of cardiologists, surgeons, anaesthetists and intensivists. Angiotensin II-converting enzyme inhibitors, angiotensin receptor blockers and non-steroidal anti-inflammatory drugs were ceased on the day before surgery. Surgical approach was by median sternotomy. MAP was monitored via arterial catheter (Philips MP 90, North Ryde, Australia). Intra- and post-operative haemodynamic management targeted an arterial flow during non-pulsatile CPB of 2.4 L/min/m² and a post-operative cardiac index of >2.4 L/min/m² as measured by pulmonary artery catheter and a MAP >60 mmHg (or >70 mmHg in patients at increased risk for ischaemia–reperfusion injury including pre-operative chronic kidney disease, arterial hypertension or haemodynamic instability). Management of intraoperative MAP included (i) infusion of crystalloids or colloids or (ii) the use of vasopressors (metaraminol, phenylephrine exclusively at this centre). Blood was transfused when haemoglobin level was measured to be <7 g/dL (4.4 mmol/L). In case of significant bleeding, tranexamic acid was used as standard antifibrinolytic drug. The pump prime solution was made up with 2 L of crystalloid solution (Plasmalyte 148) (Baxter, Sydney, Australia). Myocardial protection was by antegrade and retrograde, intermittent, warm blood cardioplegia in all patients. The cardioplegia solution contained 50 mL of potassium chloride (1 mmol/mL) and 100 mg of lignocaine, 1 L of Plasmalyte 148 with additional 30 mmol of magnesium chloride. The cardioplegia was delivered at a blood to solution ratio of 9:1. Core body temperatures were maintained between 32 and 34°C and, for aortic surgery in deep hypothermia, at 16–22°C. Analgesia was achieved with acetaminophen and morphine or fentanyl with avoidance of non-steroidal anti-inflammatory drugs. Post-operative renal replacement therapy was initiated if at least one

of the following criteria was fulfilled [23]: oliguria (urine output <100 mL for >6 h) that has been unresponsive to fluid resuscitation measures, hyperkalaemia [(K⁺) >6.5 mmol/L], severe acidaemia (pH <7.2) or clinically significant organ oedema (e.g. lung) in the setting of renal failure.

Haemoglobin, arterial oxygen saturation and pressure, MAP and post-operative renal function

The major study outcome was AKI after cardiac surgery. We primarily defined AKI according to the serum creatinine criteria of the RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease) classification [24] as an increase in serum creatinine >50% from baseline to peak value within the first seven post-operative days [6, 25]. For sensitivity analysis, we also defined AKI as renal replacement therapy initiation or creatinine increase >0.3 mg/dL, >0.5 mg/dL, >25%, >100%, >200% or an absolute change in serum creatinine occurring within 2, 3 or 7 days post-operatively, respectively.

We obtained the lowest haemoglobin, oxygen saturation and pressure values and calculated the median values accordingly during CPB in each patient. The systemic arterial oxygen content (O₂ in mL per dL blood) was calculated according to the standard formula: (haemoglobin [g/dL] × 1.34 × oxygen saturation of arterial blood) + (arterial pressure of oxygen [PaO₂] in mmHg × 0.0031), where 1.34 = mL oxygen-binding capacity per gram of haemoglobin and 0.0031 = dissolved oxygen in plasma per mmHg (mL/dL). Arterial oxygen transport was not calculated because intraoperative cardiac index was set at 2.4 L/min/m².

We determined various MAP indices during CPB including the lowest and median MAP, the time and area under the curve (AUC) for intraoperative hypotension defined as systemic MAP <50, <60 and <70 mmHg and MAP variability. The AUC of MAP was defined as the time–pressure integral of the blood pressure <50, <60 and <70 mmHg (min × mmHg) as previously described [26]. The sum of the areas with a MAP <50, <60 or <70 mmHg every 20 s was obtained using the trapezoidal method (between first and last area <50, <60 or <70 mmHg). To evaluate relative intraoperative MAP or haemoglobin variability, the coefficient of variability (Variable_{CV} = Variable_{Standard deviation} × 100/Variable_{Mean}) was calculated for each patient.

Statistical analysis

We followed a preset statistical analysis plan according to the above a priori defined hypotheses. Data distribution was evaluated using histograms. Normally distributed data are presented as means ± SD and non-normally distributed data as medians with 25–75th percentiles. For comparison of linear variables, the *t*-test or the Mann–Whitney *U*-test were used. Fisher's exact test or the chi-square test was used for categorical values as appropriate.

We used mixed effects multivariate regression analysis to evaluate whether modifiable factors including haemoglobin, indices of arterial oxygen content or MAP or vasopressor use or dose or the volume of transfused red blood cells were independently associated with the development of AKI. After testing for interaction, we considered key variables that are known to be associated with AKI after cardiac surgery including emergency operation, atrial fibrillation, use of vasopressor and those that are summarized in 'AKI following cardiac surgery Score' (AKICS; [3]). To prevent over-fitting, models were adjusted for unmodified AKICS alone, a validated risk score of AKI after adult cardiac surgery. AKICS included age >65 years, congestive heart failure NYHA III/IV, pre-operative serum creatinine >1.2 mg/dL and capillary glucose >140 mg/dL, combined coronary revascularisation and valve surgery, CPB duration >120 min, low cardiac output (i.e. use of inotropic milrinone dose) and central venous pressure >14 cm H₂O (=Model 0, Table 3). Additionally to Model 0, the final multivariate model was fit using a stepwise selection procedure that permitted the inclusion of any additional variable with *P* < 0.10 in the model (Table 3). Logarithmic transformations were applied to non-parametric data before regression analysis was performed. Goodness of fit of each logistic regression was assessed using the Hosmer–Lemeshow test.

In a planned sensitivity analysis, we tested the influence of intraoperative MAP indices, haemoglobin, arterial oxygen content and vasopressor use or blood transfusion on post-operative renal function excluding aortic or emergency surgery cases and using several different AKI definitions (renal replacement therapy initiation, creatinine increase >0.3 mg/dL, >0.5 mg/dL, >25%, >100% or >200%). Post hoc we investigated the cumulative effect of severe hypotension and anaemia and tested whether intraoperative severe hypotension (>75th percentile of AUC MAP <50 mmHg) would be a risk factor to develop AKI in patients with severe

intraoperative anaemia (haemoglobin concentration <25th percentile) compared to patients with severe hypotension but without anaemia (haemoglobin concentration >75th percentile). In addition, we tested whether patients with severe hypotension and severe anaemia more frequently develop AKI compared to patients without hypotension (<25th percentile of AUC MAP <50 mmHg) but with severe anaemia. Statistical analysis was carried out using SPSS software package version 16.0 (SPSS Inc., Chicago, IL). A two-sided P-value <0.05 was considered to be statistically significant.

Results

We retrieved data from 1004 consecutive cardiac surgery patients with electronic data storage during CPB. Excluding 84 patients (Figure 1), we used ‘complete’ data (<10% missing data) from 920 on-pump cardiac surgery patients with 381 468 intraoperative MAP and 3681 arterial blood gas measurements.

Patient characteristics and outcomes

The majority of patients were male, elderly and underwent coronary revascularisation (Tables 1 and 2). A significant proportion of our study cohort presented with co-morbidities (Table 1).

Overall, 19.5% of patients developed post-operative AKI according to the RIFLE classification. Their median increase in serum creatinine was 83 (54–135) versus 14 (4–25) $\mu\text{mol/L}$ in patients without AKI. Patients with AKI were more likely to have chronic kidney disease, atrial fibrillation, congestive heart failure, prolonged CPB, higher scores for AKI after cardiac surgery and emergency surgery (Tables 1–3). Post-operative AKI was associated with increased length of stay in the Intensive Care Unit and in hospital (Table 1) and an unadjusted risk of in-hospital mortality of 8.2 [95% confidence interval (CI) 3.7–18.0]; $P < 0.001$ and, after adjustment for EuroScore [27], emergency operation and atrial fibrillation, of 3.9 (1.6–9.2); $P = 0.002$.

Anaemia, decreased oxygen content and red blood cell transfusion

Patients with AKI had lower haemoglobin concentration, lower oxygen content and higher variability in such content (all $P < 0.001$, Table 3). We found an inverse relationship between lowest haemoglobin concentration during CPB and the incidence of AKI with an optimal haemoglobin level approximately >9 g/dL (>5.6 mmol/L) (Figure 2). When haemoglobin was <8 g/dL (<5 mmol/L), AKI incidence increased from ~15–20 to 25–30%. In such patients, red cell transfusion did not further increase AKI incidence compared to patients with haemoglobin <8 g/dL (<5 mmol/L) not receiving transfusion. In contrast, in a subgroup of patients ($N = 15$) receiving blood transfusion in the presence of a lowest haemoglobin level >8 g/dL (>5 mmol/L), AKI incidence increased by 40–50% (Figure 2).

Volume of transfused red blood cells and low haemoglobin value were independent risk factors for AKI with systemic arterial oxygen saturation and pressure values not adding importance to this variable as both were not associated to AKI (Table 3).

Hypotension and vasopressors

Systemic MAP and use or dose of vasopressors during CPB were not independent risk factors for AKI (Table 3; all P -values >0.25). The duration of MAP <50 mmHg was similar comparing patients who developed AKI (7 min [3–13]) with those without AKI (6 min [3–10]), ($P = 0.313$, after adjustment for CPB duration). In relation to CPB duration, patients with or without AKI spent similar amounts of time with MAP <50, <60 or <70 mmHg (Figure 3). There was no difference in intraoperative MAP indices according to differential serum creatinine increase (not shown). Post-operative MAP was not independently associated with the development of subsequent AKI [odds ratio (OR) 1.001 (0.968–1.034); $P = 0.972$].

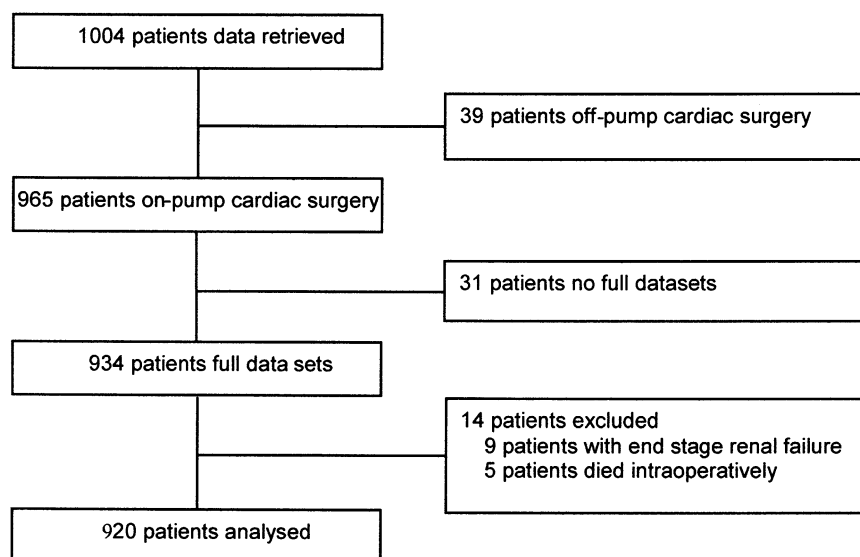


Fig. 1. Flow chart showing patients flow through the study.

Table 1. Baseline characteristics and postoperative outcome^{a,b}

	AKI (N = 741)	No AKI (N = 179)	P
Baseline			
Age, years	67.5 ± 11.3	63.4 ± 12.2	<0.001
Female, <i>n</i>	54 (30.2%)	192 (25.9%)	0.248
Chronic kidney disease [19] ^c , <i>n</i>	64 (35.8%)	186 (25.1%)	0.004
Diabetes mellitus, <i>n</i>	61 (34.1%)	224 (30.2%)	0.484
Arterial hypertension, <i>n</i>	137 (76.5%)	531 (71.7%)	0.189
Respiratory disease, <i>n</i>	28 (15.6%)	84 (11.3%)	0.114
Peripheral vascular disease, <i>n</i>	20 (11.7%)	74 (10.0%)	0.491
Myocardial infarction ^d , <i>n</i>	37 (20.7%)	159 (21.5%)	0.817
Atrial fibrillation, <i>n</i>	47 (26.3%)	69 (9.3%)	<0.001
NYHA Class III/IV, <i>n</i>	78 (43.6%)	212 (28.6%)	<0.001
Pre-operative medication			
ACE inhibitors/angiotensin II receptor blockers	120 (67.0%)	449 (60.6%)	0.111
Nitrates, <i>n</i>	18 (10.1%)	39 (5.3%)	0.017
Non-steroidal anti-inflammatory drugs, <i>n</i>	25 (14.0%)	102 (13.8%)	>0.99
EuroScore, points [24]	7.0 (5.0–9.0)	4.0 (2.0–6.5)	<0.001
Outcome			
Serum creatinine increase within 7 days, <i>n</i>			
>50%	179 (100%)	N/A	
>100%	64 (35.8%)	N/A	
>200%	20 (11.2%)	N/A	
Renal replacement therapy initiation, <i>n</i>	40 (22.3%)	8 (1.1%) ^e	<0.001
Length of stay in Intensive Care Unit, hours	69 (36–140)	23 (20–45)	<0.001
Intensive Care Unit readmission, <i>n</i>	28 (15.6%)	17 (2.3%)	<0.001
Length of stay in hospital, days	10 (7–18)	7 (6–9)	<0.001
Mortality in hospital, <i>n</i>	18 (10.1%)	10 (1.4%)	<0.001

^aN/A, not applicable.^bValues denote mean ±SD, median (25–75th percentiles) or proportion of patients in %.^cNYHA, New York Heart Association. ACE inhibitors, angiotensin II-converting enzyme inhibitors.^dWithin 90 days preoperatively.^eFor hyperkalaemia/severe acidaemia.**Table 2.** Intraoperative characteristics^a

Variable	AKI (N = 179)	No AKI (N = 741)	P
Type of cardiac surgery			
CABG, <i>n</i>	73 (40.9%)	497 (67.0%)	<0.001
No. of grafts	1.7 ± 1.6	2.3 ± 1.4	<0.001
Valve surgery, <i>n</i>	64 (35.8%)	141 (19.0%)	<0.001
Valve and coronary artery surgery, <i>n</i>	31 (17.3%)	83 (11.2%)	0.026
Aortic surgery, <i>n</i>	18 (10.1%)	44 (5.9%)	0.028
Redo cardiac surgery, <i>n</i>	15 (8.4%)	45 (6.1%)	0.262
Duration of CPB, minute	150 (107–217)	115 (92–145)	<0.001
Low cardiac output, <i>n</i>	23 (12.9%)	132 (17.8%)	0.110
Central venous pressure >14 cm H ₂ O	27 (15.1%)	96 (13.0%)	0.453
Infusion volume, mL	2400 (2000–3500)	2500 (2000–3150)	0.783
Urine output, mL	1000 (600–1815)	1000 (675–1600)	0.611
Arterial serum lactate, mmol/L	1.6 (1.2–2.3)	1.4 (1.1–1.9)	0.004

^aValues denote mean ±SD, median (25–75th percentiles) or proportion of patients in %. CABG, coronary artery bypass grafting surgery.

Cumulative effect of severe hypotension and anaemia

Patients with severe hypotension and anaemia developed AKI more frequently compared to patients with severe hypotension but without anaemia [Figure 4; OR 3.41 (95% CI 1.74–6.66); *P* < 0.001]. When testing this finding in multivariate analysis, the combination of severe hypotension with severe anaemia was an independent risk factor for AKI [OR 3.36 (95% CI 1.34–8.41); *P* = 0.010] with a greater creatinine increase than in patients without anaemia (*P* = 0.004).

There was also a trend for patients with severe hypotension and anaemia developing AKI more frequently than patients with anaemia but without hypotension [OR 2.43 (0.94–6.28); *P* = 0.06] (Figure 4).

Other risk factors for AKI and sensitivity analysis

Emergency cardiac surgery, return to operating room, atrial fibrillation and the AKI after cardiac surgery Score were independently associated with AKI (Table 3).

Table 3. Results of multivariate logistic regression modelling of risk factors for AKI^a

Variable	AKI (N = 179)	No AKI (N = 741)	P univariate (95% CI)	Adjusted OR (95% CI)	P multivariate
Model 0					
AKICS Score, points [3] ^b	5.8 (3.9–8.1)	4.3 (2.6–6.3)	<0.001	1.09 per point increase (1.04–1.15)	<0.001
Emergency ^c	25 (13.8%)	22 (3.1%)	<0.001	4.36 (2.31–8.22)	<0.001
Return to operating room, n	34 (19.0%)	52 (7.0%)	<0.001	2.74 (1.68–4.49)	<0.001
Atrial fibrillation, n	47 (26.3%)	69 (9.3%)	<0.001	2.66 (1.69–4.17)	<0.001
Intra-aortic balloon pump, n	19 (10.6%)	25 (3.4%)	<0.001	1.27 (0.61–2.66)	0.521
Intraoperative variables added to Model 0					
Haemoglobin concentration, g/dL ^d					
Median ^c	8.1 (7.4–9.3)	8.7 (7.7–9.7)	<0.001	1.18 per g/dL decrease (1.02–1.34)	0.028
Lowest ^c	7.4 (6.4–8.6)	8.2 (7.0–9.3)	<0.001	1.16 per g/dL decrease (1.03–1.31)	0.018
Variability, % ^c	1.2 (0.6–2.2)	0.9 (0.5–1.5)	<0.001	1.10 per % increase (0.94–1.28)	0.239
Arterial O ₂ content, mL/dL ^d					
Median ^c	12.2 (11.2–13.9)	13.0 (11.6–14.4)	<0.001	1.13 per mL/dL decrease (1.02–1.26)	0.027
Lowest ^c	10.9 (9.6–12.5)	12.0 (10.4–13.5)	<0.001	1.11 per mL/dL decrease (1.02–1.22)	0.018
Variability, % ^c	1.7 (0.8–3.0)	1.2 (0.7–2.1)	<0.001	1.07 per % increase (0.96–1.20)	0.241
SaO ₂ , %	99.7 (99.6–99.8)	99.7 (99.6–99.8)	0.949	N/A	N/A
PaO ₂ , mmHg	324 (274–385)	319 (272–375)	0.543	N/A	N/A
Red blood cell transfusion, mL ^d	750 (500–1000)	500 (250–750)	<0.001	1.001 per mL (1.000–1.002)	0.013
Vasopressors					
Metaraminol, mg	3.5 (1.9–6.5)	3.5 (1.5–6.0)	0.852	N/A	N/A
Phenylephrine, mg	4.9 (2.2–8.5)	2.3 (1.3–4.5)	0.007	1.05 (0.95–1.16)	0.334
MAP, mmHg					
Median ^c	68.5 (64.0–73.0)	68.0 (64.0–73.0)	0.841	N/A	N/A
Lowest ^c	31.0 (25.0–36.0)	32.0 (25.5–36.5)	0.554	N/A	N/A
Variability, % ^c	16.7 (14.1–19.7)	17.0 (14.3–19.6)	0.390	N/A	N/A
AUC MAP, min × mmHg					
<50 mmHg ^c	0.32 (0.13–0.66)	0.37 (0.17–0.69)	0.304	N/A	N/A
<60 mmHg ^c	1.49 (0.86–2.68)	1.51 (0.93–2.58)	0.673	N/A	N/A
<70 mmHg ^c	5.27 (3.55–7.46)	5.17 (3.51–7.38)	0.986	N/A	N/A

^aOR, odds ratio; N/A, not applicable. Values denote median (25–75th percentiles), SaO₂, arterial oxygen saturation; PaO₂, arterial pressure of oxygen. Hosmer–Lemeshow goodness-of-fit test results: χ^2 7.0 (P = 0.323) for Model 0.

^bIncludes risk factors for AKI such as preoperative cardiac and renal function, age, type and duration of cardiac operation.

^cOperation within 24 h after first symptoms.

^dAlternative inclusion as values are biologically linked.

^eVariables were added stepwise to Model 0.

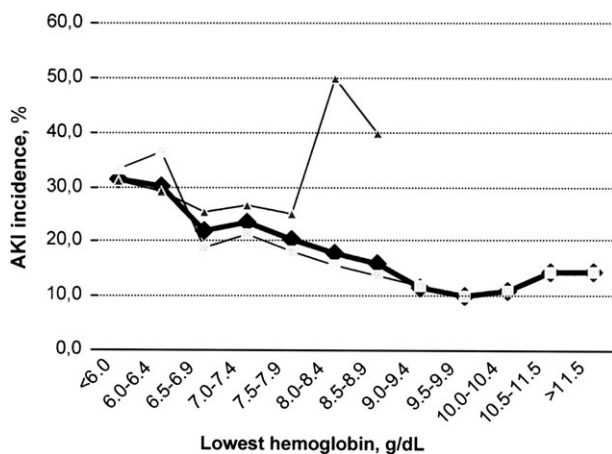


Fig. 2. Relationship between lowest haemoglobin concentration during CPB and incidence of post-operative AKI with the superimposed effect of transfusion (all patients—diamonds, patients not receiving PRBC—squares and patients receiving PRBC—triangles). The increased risk of AKI associated with transfusion seems to take effect at a haemoglobin level >8 g/dL (>5 mmol/L). PRBC, packed red blood cells.

The study findings remained essentially unchanged when aortic or emergency cases were excluded or the relative or absolute change in serum creatinine within 2, 3 or 7 days post-

operatively or different dichotomous endpoints (AKI defined as renal replacement therapy initiation, creatinine increase >0.3 mg/dL, >0.5 mg/dL, >25%, >100% or >200%) were used in multivariate regression analysis (not shown).

Discussion

In this observational study of 920 patients receiving CPB, we used extensive measurements of intraoperative MAP and arterial blood gases to investigate the association between MAP and haemoglobin concentration during CPB and AKI. We found that decreased haemoglobin concentration was an independent risk factor for AKI with an effect cut-off value of <9 g/dL (<5.6 mmol/L) and that arterial pressure of oxygen and arterial oxygen saturation did not add further strength to such an association. Systemic hypotension alone—in the setting of a target MAP >60–70 mmHg—and the use or dose of vasopressors were not independently associated with AKI. However, the combination of low haemoglobin concentration and severe hypotension acted synergistically to increase the risk of AKI. Finally, the volume of transfused red blood cells represented a specific additional risk factor in patients with a haemoglobin concentration >8 g/dL (>5 mmol/L).



Fig. 3. Time of intraoperative MAP in relation to duration of CPB separated for patients with AKI versus those without AKI.

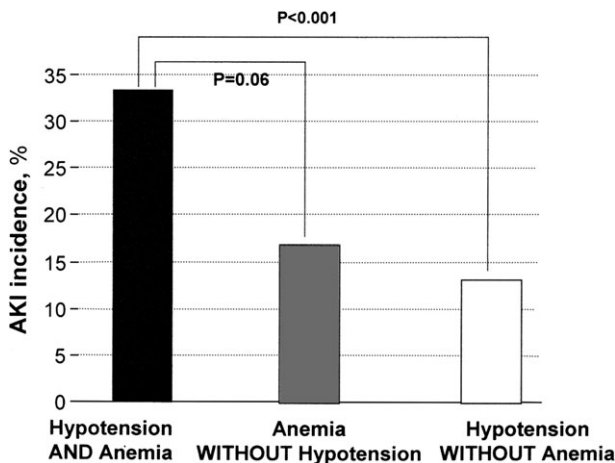


Fig. 4. Cumulative effect of severe hypotension and anaemia during CPB for AKI. Patients with severe hypotension (>75th percentile of AUC MAP <50 mmHg) AND anaemia (lowest haemoglobin concentration <25th percentile); developed more frequently AKI ($N = 24/72$) compared to patients with severe hypotension but WITHOUT anaemia (lowest haemoglobin concentration >75th percentile), ($N = 21/164$); $P < 0.001$ and to patients WITH anaemia but WITHOUT hypotension (<25th percentile of AUC MAP <50 mmHg), ($N = 7/41$); $P = 0.06$ suggesting a cumulative effect of anaemia and hypotension.

Relationship to previous studies

Several studies have investigated intraoperative risk factors for AKI after CPB with each concentrating on the independent effect of selected covariates such as MAP [15–19, 23], haemodilution [11, 28, 29] or the intraoperative transfusion of red blood cells [28]. Our findings on reduced intraoperative haematocrit values and blood transfusion as independent risk factors for AKI are in line with two previous studies [28, 29]. Also, in a large cardiac surgery cohort, the importance of post-operative anaemia for AKI was highlighted [30].

MAP values applied during CPB are often near the minimum levels necessary to maintain renal function, and any further disturbance may lead to ischaemia and cellular damage [8]. However, in small interventional studies [18, 31] comparing a higher blood pressure group (range 67–77 mmHg) [18] with a lower blood pressure group (range 39–70 mmHg) [18] and in retrospective cohort studies [16, 26], there were no deleterious effect of a low intraoperative perfusion pressure on post-operative renal function or mortality.

Due to technological limitations, previous studies used manually recorded and potentially incomplete and biased MAP values or lacked additional covariates [16–19]. Thus, they may have had limited accuracy, precision and statistical power for their interpretation within a complex pathophysiological context, making the role of these intraoperative factors or their combination as modifiable predictors of post-operative AKI uncertain. We performed our study to clarify these associations.

Pathophysiological considerations

Understanding modifiable risk factors for the development of AKI is important. Imbalance between renal oxygen delivery and renal oxygen consumption is generally assumed to play a pivotal role in AKI [31–34]. Renal oxygen delivery is determined by renal blood flow and by arterial oxygen content. Renal blood flow declines when MAP falls below the optimal autoregulation threshold [35]. However, glomerular filtration rate will decline in parallel to blood flow, and, because glomerular filtration rate determines oxygen-dependant tubular reabsorption, renal oxygen consumption will also decrease [32, 33, 36, 37].

Arterial hypoxaemia reduces renal oxygen delivery, however, in otherwise healthy subjects, it does not result in AKI, possibly because of the compensating effect of increased blood flow [13]. Thus, neither decreased arterial oxygen content nor hypotension *per se* will necessarily result in AKI. Their combination, however, may exhaust the kidneys' compensatory ability and low arterial oxygen content may compromise renal blood flow autoregulation, and by means of the arterial chemoreceptor reflex, reduce renal blood flow [13, 38, 39].

Clinical importance of study findings

In almost all patients of the present study, the MAP achieved during CPB was below physiological MAP values and, most probably, was often even below the MAP range of effective autoregulation. Although MAP indices *per se* in our study were not independently associated with the risk of AKI, we do not wish to imply that hypotension is not an important source of renal injury. When more time with a MAP <50 mmHg is spent, hypotensive AKI may arise. Hypotension is often combined with hypoxaemia not just in the present setting of CPB but also during hypovolaemic shock and cardiac arrest. In our study, two specific factors may have alleviated the effects of hypotension

alone. The first is haemodilution, which reduces blood viscosity and thus resistance and which might have resulted in higher renal blood flow at a given MAP [14, 40]. The second is hypothermia, which should have reduced renal oxygen consumption. An additional explanation would be that other mechanisms required for cellular adaptation to hypoxia and oxygen sensing might contribute to AKI independent of changes in MAP [41]. Our study demonstrates the deleterious renal effect of combined anaemia and hypotension in the clinical setting, highlighting a potential synergistic effect.

Nonetheless, conservative use of red blood cells transfusion may be advisable because—in addition to inflammation triggered by transfusion [42]—different lines of evidence point towards circulating free iron-mediated nephrotoxicity with haemolysis and free haemoglobin as likely important mechanism of AKI in patients receiving cardiac surgery with CPB [43, 44]. Our study suggests that red cell transfusion carries increased risk if given to patients with a haemoglobin concentration >8 g/dL (>5 mmol/L).

Future research should focus on the management of cardiac surgery patients applying blood loss minimising techniques, blood transfusion targeted to an 'optimal' haemoglobin value and strict avoidance of severe hypotension. The mechanism responsible for renal injury in this specific clinical situation should be further clarified.

Strengths and limitations

Our study is one of the more extensive investigations of the possible link between intraoperative MAP, haemoglobin concentration, arterial oxygen content at a set intra- and postoperative cardiac index (>2.4 L/min/m²) and other modifiable factors and AKI in patients receiving CPB surgery. It used a large data set of objective, accurate and precise observations of several salient risk factors for AKI ensuring sufficient statistical power and the ability to explore a complex pathophysiological issue. However, this is a single-centre hypothesis-generating study and the results may have been different to a centre practicing a more tolerant approach to hypotension or a less tolerant approach to anaemia. This study was observational, thus any association identified cannot carry inferences of causality. There is limited ability to interpret the 'null' effect of post-operative hypotension on AKI as this was not the primary study objective and therefore, measurements may have been too infrequent. On the other hand, it appears unlikely, given the large data set, that a clinically relevant influence of post-operative MAP went undetected.

In conclusion, our study suggests that anaemia might participate in renal injury during CPB and that its effect may be stronger with superimposed severe hypotension. We suggest that severe intraoperative anaemia, particularly in combination with hypotension should be avoided during CPB; both represent targets for future controlled interventions. Blood transfusion appears associated with further renal injury; therefore, unnecessary transfusion in patients with an adequate haemoglobin level (>8 g/dL/ >5 mmol/L) appears undesirable. Intraoperative MAP can be kept >60 – 70 mmHg allowing the use of vasopressors. Further studies

are needed to investigate if modified blood conservation strategies or restriction of red blood cell transfusion to haemoglobin levels <8 g/dL (<5 mmol/L) can improve renal outcomes.

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Appendix

Box 1. Definition of co-morbidities and complications

Chronic kidney disease	Pre-operative estimated glomerular filtration rate <60 mL/min/1.73m ² [21]
Diabetes mellitus	Fasting or casual blood glucose ≥126 or ≥200 mg/dL with polyuria or polydipsia, requiring antidiabetic medication or history of diabetes regardless of duration of disease
Arterial hypertension	Blood pressure exceeding 140/90 mmHg or a history of arterial hypertension or the need for antihypertensive medications
Hypercholesterolaemia	History of fasting cholesterol >5 mmol/L or on treatment
Respiratory disease	On chronic inhaled or oral bronchodilator therapy or oral steroids aimed at lung disease or daily cough with sputum for 3 months a year for at least 2 years and/or dyspnoea with forced expiratory volume in 1 s <75% of the inspiratory vital capacity
Peripheral vascular disease	Claudication, absent pedal pulses, previous lower extremity bypass and lower limb amputation for ischaemia
Myocardial infarction	History hospitalisation for a myocardial infarction in the medical record, with two of the following criteria needed: A) prolonged chest pain not relieved by rest/nitrates B) enzyme level elevation C) new wall motion abnormalities D) serial electrocardiogram's showing Q-waves in at least two leads
Atrial fibrillation	Documented atrial fibrillation in electrocardiogram

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