BJA

British Journal of Anaesthesia, 115 (5): 736–42 (2015)

doi: 10.1093/bja/aev346
Clinical Practice

Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: a randomized study on crystalloid *vs* colloid

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Abstract

Background: In the present randomized study, we evaluated the differential effects of a colloid and a crystalloid fluid on renal oxygen delivery (RD_{O_2}), glomerular filtration (GFR), renal oxygen consumption ($R\dot{V}O_2$), and the renal oxygen supply–demand relationship (i.e. renal oxygenation) after cardiac surgery with cardiopulmonary bypass.

Methods: Thirty patients with normal preoperative renal function, undergoing uncomplicated cardiac surgery, were studied in the intensive care unit in the early postoperative period. Patients were randomized to receive a bolus dose of either a crystalloid (Ringers-acetate® 20 ml kg^{-1}, *n*=15) or a colloid solution (Venofundin® 10 ml kg^{-1}, *n*=15). Systemic haemodynamics were measured via a pulmonary artery catheter. Renal blood flow and GFR were measured by the renal vein retrograde thermodilution technique and by renal extraction of ^{51}Cr-EDTA (=filtration fraction). Arterial and renal vein blood samples were obtained for measurements of renal oxygen delivery (RD_{O_2}) and $R\dot{V}O_2$. Renal oxygenation was estimated from the renal oxygen extraction.

Results: Despite an increase in cardiac index and renal blood flow with both fluids, neither of the fluids improved RD_{O_2}, because they both induced haemodilution. The GFR increased in the crystalloid (28%) but not in the colloid group. The crystalloid increased the filtration fraction (24%) and renal oxygen extraction (23%), indicating that the increase in GFR, the major determinant of $R\dot{V}O_2$, was not matched by a proportional increase in RD_{O_2}.

Conclusions: Neither the colloid nor the crystalloid improved RD_{O_2} when used for postoperative plasma volume expansion. The crystalloid-induced increase in GFR was associated with impaired renal oxygenation, which was not seen with the colloid.

Clinical trial registration: NCT01729364.

Key words: colloids; crystalloids; glomerular filtration rate; plasma volume expansion; postoperative treatment; renal blood flow; renal oxygen consumption and oxygenation

Acute kidney injury (AKI) after cardiac surgery with cardiopulmonary bypass continues to be a significant cause for morbidity and mortality. Depending on the complexity of the procedure, the incidence of postoperative AKI, defined as an increase of serum creatinine by >50%, ranges between 15 and 30%.[1–4] Dialysis-dependent AKI, occurring in 2–5% of cardiac surgery patients,

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Accepted: August 31, 2015

Editor's key points

- Acute kidney injury is one major postoperative complication after cardiac surgery with cardiopulmonary bypass, and it is not known whether or not there are differences in renal oxygen delivery between plasma volume expansion with crystalloid and colloid.
- In a randomized design, effects on renal oxygen delivery and other renal factors were compared between plasma volume expansion with crystalloid and colloid.
- Neither colloid nor crystalloid improved renal oxygen delivery, but crystalloid, but not colloid, increased the GFR with impaired renal oxygenation.

carries a mortality between 50 and 80% and is associated with high hospital costs.[5–7] Furthermore, increasing evidence suggests that a minor elevation in serum creatinine after cardiac surgery is an independent risk factor for increased mortality and for prolonged stay in the intensive care unit and in hospital.[6 8 9]

The pathogenesis of cardiac surgery-associated AKI involves a variety of pathways.[10] Impaired renal oxygen delivery (RD_{O_2}), causing ischaemic tubular cell injury, has been considered to be one of the main mechanisms underlying postcardiac surgery AKI.[11] A decreased oxygen delivery may be caused by haemodilution-induced anaemia and intraoperative hypotension together with low postoperative cardiac output, in turn caused by heart failure or hypovolaemia.[3 12–14] The renal medulla, particularly the outer portion, is on the verge of hypoxia even in normal conditions. This is caused by the high utilization of oxygen of the medullary thick ascending limb and a relative medullary hypoperfusion, when compared with the cortex. The outer portion of the renal medulla is therefore particularly sensitive to impaired RD_{O_2}.[15]

I.V. fluids, such as colloids or crystalloids, are commonly used for treatment of postoperative hypovolaemia after cardiac or other major surgery, to prevent or ameliorate early AKI.[16] However, even though i.v. fluids may increase cardiac output and renal blood flow (RBF), they will also decrease arterial oxygen content by haemodilution, with potentially no or minor beneficial net effects on RD_{O_2}. Indeed, recent animal studies have shown that colloids or crystalloids do not increase RD_{O_2} despite increases in cardiac output and that crystalloids, in contrast to colloids, may impair regional renal microvascular oxygenation.[17 18]

To our knowledge, the effects of i.v. fluids on RD_{O_2} and renal oxygenation have not been studied in postoperative patients after major surgery. Furthermore, perioperative data on the differential effects of crystalloids *vs* colloids with respect to RBF, RD_{O_2}, glomerular filtration rate (GFR), renal oxygen consumption ($R\dot{V}O_2$), and renal oxygenation, defined as the renal oxygen supply–demand relationship, are lacking. We therefore performed a randomized study to evaluate the differential renal effects of bolus doses of a crystalloid and a colloid. In the present study, we tested the null hypothesis that there is no difference between a crystalloid and a colloid with respect to changes in RD_{O_2} and renal oxygenation after major surgery.

Methods

Patients

The study protocol was approved by the Gothenburg Regional Ethics Committee (www.epn.se). Written informed consent was obtained from each patient before the operation. The study was registered in ClinicalTrials.gov, identifier: NCT01729364. The inclusion criteria were as follows: (i) age >18 yr; (ii) elective coronary artery bypass surgery with cardiopulmonary bypass; (iii) preoperative normal serum creatinine; (iv) left ventricular ejection ≥40%; and (v) attainment of target levels of central venous pressure (5–10 mm Hg), mean arterial pressure (MAP; >70 mm Hg), and mixed venous oxygen saturation (Sv_{O_2}; >60%) before randomization, according to our local clinical treatment protocol. The exclusion criteria were as follows: (i) combined cardiac surgery procedures; (ii) excessive postoperative bleeding (>100 ml h^{-1}); (iii) intra- or postoperative need for inotropic or vasoactive support or diuretics (furosemide, mannitol); or (iv) hypotension because of arrhythmias.

Premedication consisted of oxazepam (10 mg) and oxycodone (10 mg). Anaesthesia was induced by fentanyl (5–10 μg kg^{-1}) and propofol (1–1.5 mg kg^{-1}). Before and after cardiopulmonary bypass, anaesthesia was maintained with sevoflurane (0.5–2.5%) in a 50% O_2–air mixture. During cardiopulmonary bypass, anaesthesia was maintained with an i.v. infusion of propofol (2–4 mg kg^{-1} h^{-1}). The pump was primed with acetated Ringer's solution (1300 ml) without mannitol. Normothermic, non-pulsatile cardiopulmonary bypass was performed at a flow of 2.4 litres min^{-1} m^{-2} and a target haematocrit of 20–25%. In the intensive care unit, the patients were sedated with propofol (1.5–3.6 mg kg^{-1} h^{-1}) and morphine (0.5–1 mg h^{-1}) and mechanically ventilated.

Systemic haemodynamics

Arterial blood pressure was measured continuously via a radial or femoral artery catheter. A pulmonary artery thermodilution catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was used for measurements of central venous pressure, pulmonary artery and wedge pressures and cardiac output. Bolus measurements of thermodilution cardiac output were performed in triplicate and indexed to the body surface area for cardiac index (CI). Systemic vascular resistance index, pulmonary vascular resistance index, and stroke volume index (SVI) were calculated according to standard formulae.

Measurements of renal variables

An 8 Fr catheter (Webster laboratories, Baldwin Park, CA, USA) was introduced into the left or right renal vein, via the right femoral vein under fluoroscopic guidance. The catheter was placed in the central portion of the renal vein, with the position being confirmed by venography using ultra-low doses of iohexol, 5–15 mg I kg^{-1} (Omnipaque 300 mg I ml^{-1}; GE Healthcare, Stockholm, Sweden). Renal blood flow was measured in duplicate by the continuous retrograde thermodilution technique.[19–22] At the end of each urine collection period, the bladder was rinsed with 100 ml of sterile water. After the collection of blood and urine blanks, an i.v. priming dose of chromium ethylenediaminetetraacetic acid (^{51}Cr-EDTA; GE Healthcare, Amersham, UK) was given, followed by an infusion at a constant rate, individualized to body surface area and preoperative serum creatinine. Serum ^{51}Cr-EDTA activity from arterial and renal vein blood was measured using a well counter (Wizard 3', 1480, Automatic gamma counter; Perkin Elma LAS, Turkuu, Finland).

Experimental procedure

The experimental procedure was performed 4–6 h after the end of cardiopulmonary bypass when the patients had a stable body

temperature >36°C. The patients were sedated and mechanically ventilated during the whole experimental procedure and were randomized to receive either a crystalloid (20 ml kg^{-1}, Ringer-acetate®; Fresenius Kabi, Uppsala, Sweden) or a colloid solution (10 ml kg^{-1}, hydroxyethylstarch 60 mg ml^{-1}, 130/0.62, Venofundin®; B. B. Braun, Melsungen, Germany). After an equilibration period of at least 60 min, two 30 min urine collection control periods (periods C1 and C2) were started. The investigational fluid was then administered during 20–30 min. Thermodilution measurements of RBF and CI were conducted, and blood and urine samples were obtained at 20, 40 and 60 min after the end of the fluid administration. Formulae for calculation of the various renal variables are shown in Table 1. All renal data were normalized to a body surface area of 1.73 m^2.

Statistical analysis

To detect a relative difference of 25% in RD_{O_2} or renal oxygen extraction with a power of 80% and a two-sided significance level of 0.05, at a standard deviation of 24 ml min^{-1} and 0.024, respectively, 30 patients would be required (15 patients in each group), based on data from a previous study.[23] To compensate for drop-outs, we aimed to include ~40 patients. Intragroup effects of the colloid and crystalloid solutions, respectively, were determined by one-way ANOVA for repeated measurements. Differences between groups were compared using an analysis of covariance (ANCOVA) for repeated mesurements, using the mean of the two baseline measurements (C1 and C2) as a covariate. This statistical approach adjusts for baseline differences between groups. Categorical data were compared using Fisher's exact test. A *P*-value <0.05 was considered significant. PASWStatistics 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Data are presented as mean and standard deviation (SD) of the mean.

Results

Informed consent was obtained from 39 patients the day before surgery. The clinical trial profile is shown in Figure 1. Thirty patients were randomized after renal vein catheterization to receive either a colloid (*n*=15) or a crystalloid solution (*n*=15). There were no significant differences between the two groups with respect to preoperative characteristics, as presented in Table 2. There were no significant differences between the groups at baseline (C1 and C2), before fluid administration, in any of the measured or calculated variables (Tables 3 and 4).

Table 1 Formulae for calculation of renal variables. Ca_{O_2} and Crv_{O_2}, arterial and renal vein oxygen contents; CVP, central venous pressure; MAP, mean arterial pressure; $[Na^+]_s$, serum sodium concentration; $[Na^+]_u$, urine sodium concentration

Variable	Formula
Renal blood flow (RBF)	(unilateral renal vein blood flow×2)+urine flow
Renal plasma flow (RPF)	RBF×(1−haematocrit)
Filtration fraction (FF)	{RPF×[^{51}Cr-EDTA arterial]−(RPF−urine flow)×[^{51}Cr-EDTA renal vein]}/(RPF×[^{51}Cr-EDTA arterial])
Glomerular filtration rate (GFR)	FF×RPF
Renal vascular resistance (RVR)	(MAP−CVP)/RBF
Arterial–renal vein (rv) oxygen content difference ($RAVO_2$-diff)	$(Ca_{O_2} - Crv_{O_2})$
Renal oxygen consumption ($R\dot{V}O_2$)	RBF×$(Ca_{O_2} - Crv_{O_2})$
Renal oxygen extraction	$(Ca_{O_2} - Crv_{O_2}/Ca_{O_2})$
Renal sodium filtration	GFR×$[Na^+]_s$
Renal sodium excretion	Urine flow×$[Na^+]_s$
Renal sodium reabsorption	(GFR×$[Na^+]_s$)−(Urine flow×$[Na^+]_u$)

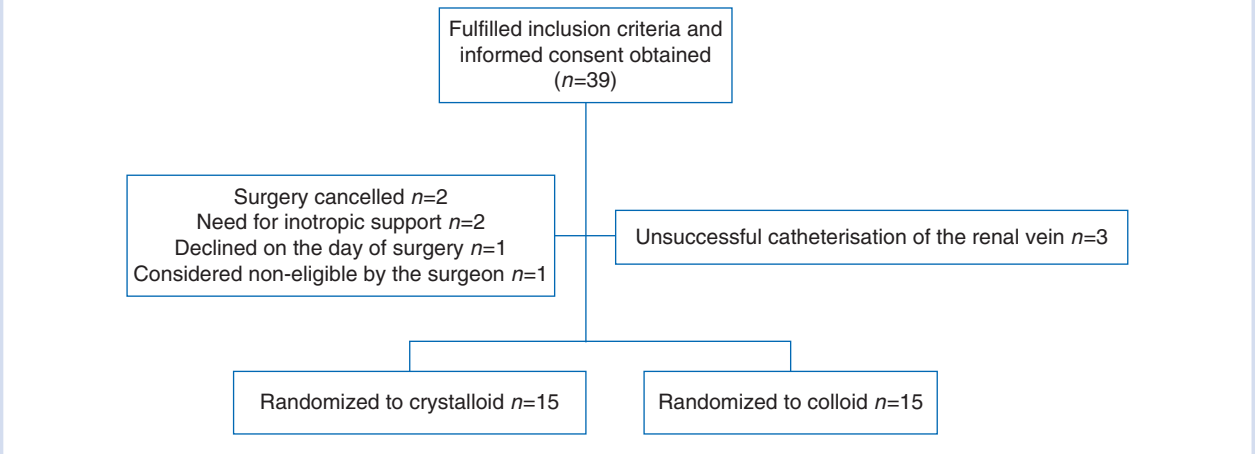

Fig 1 Clinical trial profile.

Table 2 Patient characteristics. Values are means (SD). ACE inhibitor, angiotensin-converting enzyme inhibitor; CPB, cardiopulmonary bypass

Characteristic	Crystalloid	Colloid
Number of patients (*n*)	15	15
Female [*n* (%)]	3 (14)	1 (7)
Age (yr)	68 (43–80)	66 (48–83)
Weight (kg)	78.8 (11.2)	78.3 (9.4)
Body surface area (m^2)	2.08 (0.47)	1.94 (0.14)
Left ventricular ejection fraction (%)	57 (8)	57 (6)
Hypertension [*n* (%)]	6 (39)	11 (73)
Preoperative serum creatinine (μmol $litre^{-1}$)	80 (10)	81 (12)
Postoperative serum creatinine (μmol $litre^{-1}$)	72 (13)	76 (15)
β-Adrenergic blocker [*n* (%)]	11 (73)	14 (93)
ACE inhibitor [*n* (%)]	7 (47)	5 (33)
Calcium antagonist [*n* (%)]	4 (27)	3 (21)
Diuretics [*n* (%)]	2 (13)	2 (13)
CPB time (min)	66 (17)	75 (19)
Aortic cross-clamp time (min)	40 (17)	48 (15)

Effects of i.v. fluids on systemic haemodynamics, arterial oxygen content, and systemic oxygen delivery (Table 3)

As expected, both fluids induced haemodilution, with significant decreases in haematocrit and Ca_{O_2}. There was a peak 9% increase in MAP at 20 min after the end of fluid infusion in the crystalloid group, after which MAP declined towards baseline. In the colloid group, there was a consistent 12–15% increase in MAP. A 16–18% peak increase in CI and SVI were seen after 20 min in the crystalloid group, followed by a decline towards baseline. In the colloid group, there was a consistent 18–23% increase in CI and SVI. An increase in CI of >10% was seen in 12 of 15 patients in the crystalloid group and 13 of 15 patients and colloid group, and 11 of 15 patients in both groups increased their CI by >15%. Left- and right-sided filling pressures increased, systemic vascular resistance index decreased, and heart rate was unaffected by the two fluids. There was a transient 10% increase in systemic oxygen delivery index in the crystalloid group at 40 min, whereas systemic oxygen delivery index was not affected in the colloid group.

Crystalloid *vs* colloid

The decrease in haematocrit and arterial oxygen content was significantly greater after the fluid bolus administration in the colloid group. The increase in MAP was not significantly different between groups. The increase in CI was significantly higher in the colloid group, while changes in SVI or heart rate did not differ between groups. The increases in left- and right-sided filling pressures and mean pulmonary artery pressure were significantly higher in the colloid group during the experimental procedure. Increases in systemic oxygen delivery index and decreases in systemic vascular resistance index after fluid administration did not differ significantly between groups.

Effects of i.v. fluids on renal variables (Table 4)

There was a transient 9% increase in RBF at 20 min in the crystalloid group, whreas there was a more consistent 11–17% increase in RBF in the colloid group. The ratio between RBF and CI (RBF/CI)

Table 3 Systemic variables. Values are mean (SD). ANCOVA, between-groups analysis of variance with baseline as a covariate; ANOVA, within-group analysis of variance; Ca_{O_2}, arterial oxygen content; CI, cardiac index; CVP, central venous pressure; DO_2I, systemic oxygen delivery index; Hct, arterial haematocrit; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index (in dyn s cm^{-5} m^{-2})

Variable	Crystalloid				One-way ANOVA	Colloid				One-way ANOVA	ANCOVA crystalloid *vs* colloid
	Baseline	20 min	40 min	60 min	P-value	Baseline	20 min	40 min	60 min	P-value	P-value
MAP (mm Hg)	77.5 (10.1)	84.8 (13.0)	80.7 (10.7)	80.0 (10.3)	0.015	74.1 (13.2)	85.4 (12.0)	83.1 (14.2)	83.7 (14.3)	<0.001	0.112
CI (litres min^{-1} m^{2-1})	2.49 (0.53)	2.88 (0.64)	2.85 (0.67)	2.65 (0.61)	<0.001	2.63 (0.59)	3.24 (0.45)	3.21 (0.47)	3.17 (0.47)	<0.001	0.010
HR (beats min^{-1})	74.5 (10.5)	73.8 (10.6)	75.0 (10.9)	73.5 (10.3)	0.286	75.3 (11.8)	77.7 (9.5)	77.5 (9.1)	77.1 (10.0)	0.065	0.067
SVI (ml $beat^{-1}$ m^{-2})	33.6 (6.6)	39.5 (8.7)	38.3 (8.5)	36.3 (8.1)	<0.001	35.3 (7.5)	42.1 (6.5)	41.7 (5.6)	41.5 (5.8)	<0.001	0.103
SVRI (units)	2346 (759)	2189 (820)	2135 (841)	2246 (747)	0.028	2154 (741)	1875 (463)	1850 (513)	1892 (490)	<0.001	0.139
PCWP (mm Hg)	9.8 (2.8)	12.7 (3.2)	11.1 (3.4)	11.1 (2.9)	<0.001	9.5 (2.9)	14.9 (3.4)	14.3 (3.0)	13.9 (3.1)	<0.001	0.001
CVP (mm Hg)	8.7 (3.1)	11.0 (3.9)	10.3 (3.9)	10.2 (3.5)	<0.001	7.1 (2.1)	11.4 (2.5)	10.8 (2.4)	10.6 (2.3)	<0.001	0.001
MPAP (mm Hg)	18.1 (3.4)	20.9 (5.1)	21.2 (5.4)	19.8 (4.7)	<0.001	17.7 (3.1)	24.1 (4.1)	22.9 (4.0)	22.5 (3.8)	<0.001	0.001
Hct	0.337 (0.045)	0.314 (0.046)	0.325 (0.044)	0.321 (0.046)	<0.001	0.332 (0.041)	0.288 (0.039)	0.288 (0.039)	0.291 (0.039)	<0.001	0.000
Ca_{O_2} (ml $litre^{-1}$)	148 (21)	137 (22)	142 (22)	141 (22)	<0.001	147.6 (19)	127.3 (17)	126.8 (17)	128.5 (17)	<0.001	<0.001
DO_2I (ml min^{-1} m^{-2})	365 (73)	390 (82)	400 (89)	367 (84)	<0.001	387 (92)	411 (74)	406 (77)	405 (62)	0.144	0.786

Table 4 Renal variables. Values are mean (SD). ANCOVA, between-groups analysis of variance with baseline as a covariate; ANOVA, within-group analysis of variance; GFR, glomerular filtartion rate; $RAVO_2$-diff, arterial–renal vein oxygen content difference; RBF/CI, relationship between RBF and cardiac index; RD_{O_2}, renal oxygen delivery; RBF, renal blood flow; RO_2Ex, renal oxygen extraction; RV_{O_2}, renal oxygen consumption; RVR, renal vascular resistance; SrV_{O_2}, renal vein oxygen saturation. All renal data were normalized to a body surface area of 1.73 m^2

Variable	Crystalloid				One-way ANOVA	Colloid				One-way ANOVA	ANCOVA crystalloid vs colloid
	Baseline	20 min	40 min	60 min	P-value	Baseline	20 min	40 min	60 min	P-value	P-value
RBF (ml min^{-1})	674 (170)	738 (178)	688 (226)	673 (201)	0.025	706 (199)	827 (164)	787 (207)	792 (184)	0.019	0.089
RVR (mm Hg ml^{-1} min^{-1})	0.108 (0.03)	0.107 (0.03)	0.112 (0.04)	0.112 (0.03)	0.625	0.104 (0.04)	0.093 (0.02)	0.098 (0.03)	0.098 (0.03)	0.394	0.165
RD_{O_2} (ml min^{-1})	99.2 (25.0)	99.7 (23.0)	95.9 (26.7)	93.1 (25.0)	0.176	102.5 (24.9)	105.4 (27.4)	99.7 (30.6)	101.6 (27.7)	0.750	0.582
GFR (ml min^{-1})	68.6 (14.3)	79.5 (21.1)	87.5 (22.7)	76.4 (16.0)	<0.001	70.9 (15.3)	85.7 (23.5)	78.3 (29.0)	83.9 (38.8)	0.291	0.989
Sodium filtration (mmol min^{-1})	9.42 (2.02)	10.88 (2.97)	12.00 (3.28)	10.44 (2.25)	<0.001	9.69 (2.03)	11.72 (3.27)	10.73 (4.05)	11.52 (5.41)	0.288	1.000
Sodium reabsorption (mmol min^{-1})	9.10 (2.01)	9.63 (3.00)	11.18 (3.21)	9.89 (2.14)	0.002	9.30 (2.05)	11.33 (3.22)	10.19 (4.01)	11.26 (5.20)	0.235	0.573
Fitration fraction	0.157 (0.031)	0.161 (0.046)	0.194 (0.052)	0.174 (0.045)	<0.001	0.154 (0.050)	0.148 (0.043)	0.142 (0.050)	0.146 (0.050)	0.773	0.030
Urine flow (ml min^{-1})	2.7 (1.2)	8.7 (4.9)	6.5 (4.3)	4.1 (1.9)	<0.001	2.5 (1.2)	2.4 (1.3)	3.5 (2.0)	3.9 (2.3)	0.003	0.002
$R\dot{V}O_2$ (ml min^{-1})	9.5 (2.4)	11.1 (2.3)	11.5 (2.9)	11.0 (3.4)	<0.001	10.1 (3.3)	10.6 (4.7)	10.1 (3.0)	10.3 (3.0)	0.964	0.085
SrV_{O_2} (%)	88.9 (3.2)	87.2 (3.3)	86.2 (3.6)	86.5 (3.9)	<0.001	88.4 (4.0)	88.0 (4.2)	87.5 (4.1)	87.8 (3.8)	0.452	0.019
RO_2Ex	0.099 (0.031)	0.113 (0.030)	0.121 (0.033)	0.120 (0.039)	<0.001	0.104 (0.039)	0.106 (0.043)	0.111 (0.039)	0.109 (0.039)	0.653	0.032
$RAVO_2$-diff (ml $litre^{-1}$)	14.3 (3.2)	15.4 (3.3)	17.3 (4.3)	16.8 (5.3)	0.004	15.3 (5.4)	13.4 (5.1)	13.8 (4.6)	13.8 (4.1)	0.169	0.002
RBF/CI	0.274 (0.054)	0.261 (0.056)	0.243 (0.055)	0.257 (0.055)	0.012	0.278 (0.090)	0.258 (0.055)	0.250 (0.073)	0.254 (0.069)	0.210	0.904

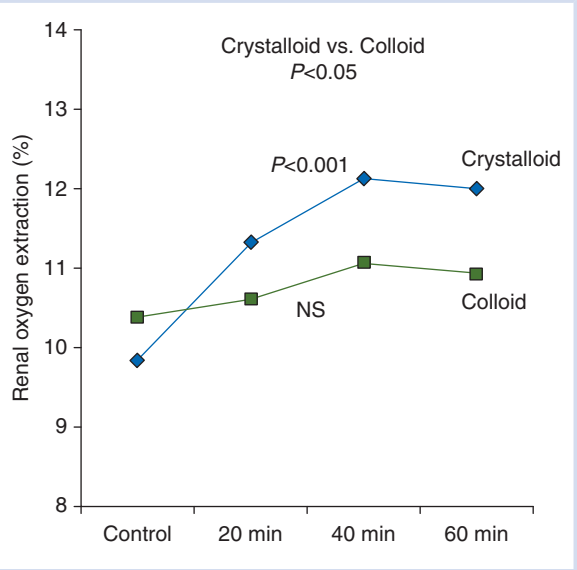

Fig 2 Effects of a crystalloid (10 ml kg^{-1}) and a colloid (20 ml kg^{-1}) bolus on renal oxygen extraction after cardiac surgery. The crystalloid increased renal oxygen extraction ($P<0.001$) 20, 40 and 60 min after the bolus, in contrast to the colloid (NS), suggesting impairment of renal oxygenation. The change in renal oxygen extraction was significantly ($P<0.05$) more pronounced in the crystalloid group compared with the colloid group.

decreased with the crystalloid but not with the colloid. Renal vascular resistance was not affected in any of the groups. Bolus fluid administration did not affect RD_{O_2} in any of the groups. The GFR and sodium filtration increased transiently with the crystalloid, with a peak 28% increase at 40 min. In the colloid group, GFR and sodium filtration were not significantly changed from baseline after fluid administration. In the crystalloid group, tubular sodium reabsorption increased transiently, with a peak increase of 23% at 40 min, whereas in the colloid group tubular sodium reabsorption did not change significantly from baseline. The filtration fraction (FF) increased transiently in the crystalloid group (24% at 40 min), with no changes in the colloid group. Urine flow increased in both groups. The $R\dot{V}O_2$ increased (by 16–21%) in the crystalloid group, with no changes in the colloid group. Renal vein oxygen saturation decreased and arterial–renal vein oxygen content difference increased in the crystalloid group, whereas these variables were not affected in the colloid group. Renal oxygen extraction, a direct measure of the renal oxygen supply–demand relationship, increased by 23% in the crystalloid group, whereas the colloid bolus did not affect renal oxygen extraction Figure 2.

Crystalloid *vs* colloid

The increase in urine flow was significantly higher in the crystalloid group. The increase in FF in the crystalloid group differed significantly from the change in the colloid group. In the crystalloid group, changes in renal vein oxygen saturation, renal oxygen extraction, and arterial–renal vein oxygen content difference were significantly higher than in the colloid group. There was a trend for a higher increase in $R\dot{V}O_2$ in the crystalloid group ($P=0.085$) and a higher increase in RBF in the colloid group ($P=0.089$). There were no significant intergroup differences in RD_{O_2}, GFR, renal vascular resistance, RBF/CI, sodium filtration, or sodium reabsorption.

Discussion

We studied the renal effects of acute plasma volume expansion with artificial solutions early after cardiac surgery. The main findings were that, despite apparent increases in cardiac index and RBF with both fluids, neither of the fluids increased RD_{O_2}. Furthermore, plasma volume expansion with the crystalloid impaired the renal oxygen supply–demand relationship, expressed as a more pronounced increase in renal oxygen extraction compared with the colloid.

The lack of effect on RD_{O_2}, despite the increase in RBF with both fluids, is explained by the fact that the arterial oxygen content decreased in both groups as a result of plasma volume expansion and haemodilution. In addition, the crystalloid bolus seemed to redistribute blood flow away from the kidneys, as reflected by the reduction in the RBF/CI ratio. Thus, the increase in RBF was not in proportion to the increase in CI with the crystalloid.

One important difference between the two fluids was their differential effects on the renal oxygen supply–demand relationship. The $R\dot{V}O_2$ increased in the crystalloid group, which was not matched by a proportional increase in RD_{O_2}, as indicated by the increase in renal oxygen extraction. In contrast, $R\dot{V}O_2$, RD_{O_2}, and renal oxygen extraction were not affected by the colloid. Our group has repeatedly shown in postoperative patients that the major determinant of $R\dot{V}O_2$ is GFR. An increase in glomerular sodium filtration will increase the sodium reabsorption, which, in turn, will increase $R\dot{V}O_2$.[19 20 24] Also in the present study, the increase in glomerular sodium filtration was associated with increases in sodium reabsorption and $R\dot{V}O_2$ in the crystalloid group. In the colloid group, however, this chain of events was not observed, as the colloid did not affect GFR.

Infusion of a bolus dose of an isotonic crystalloid, such as the acetated Ringer's solution used in the present study, redistributes within 20–30 min to the interstitial fluid space because of the short (8–10 min) distribution half-life.[25 26] Thus, a bolus dose of a crystalloid induces only a transient increase in plasma volume, as also demonstrated by a return towards baseline of haematocrit, cardiac filling pressures, and CI within 60 min in the present study, in contrast to the colloid group. Thus, to maintain the plasma volume in an expanded state in the treatment of postoperative hypovolaemia, repeated bolus doses of a crystalloid are required, with a potential for each of the crystalloid boluses to impair renal oxygenation in a hypovolaemic patient already subjected to impaired RD_{O_2} and potentially also renal medullary ischaemia.

In the present study, we measured the renal extraction of ^{51}Cr-EDTA, which is a direct measure of the renal FF (i.e. the GFR/RPF ratio). The FF increased with the crystalloid, suggesting that the increase in GFR (and $R\dot{V}O_2$) was not matched by a proportional increase in renal blood flow. We have previously shown in postoperative cardiac surgery patients that there is a close positive correlation (r^2>0.81) between the renal FF and renal oxygen extraction.[19 20] Thus, the crystalloid-induced increase in FF supports our finding of a renal oxygen supply–demand impairment with a crystalloid.[19 20 27]

Our data are in line with previous animal studies. Thus, in an experimental study on Merino cross-ewes, it was shown that both a crystalloid and a colloid infusion, if anything, reduced RD_{O_2}, because of haemodilution, despite increased cardiac output.[17] Furthermore, in a rat hypovolaemic shock model, saline for treatment of hypovolaemia did not improve RD_{O_2} or renal microvascular P_{O_2}.[28] In a recent experimental study, it was shown that acute normovolaemic haemodilution with a crystalloid decreased renal microvascular oxygenation in the cortex and outer medulla, in contrast to a colloid (hydroxethyl starch 6% 130/0.4), which maintained regional renal microvascular oxygenation.[18] Haemodilution with the crystalloid was also associated with highest formation of tissue oedema and highest expression of hypoxia-inducible factor-1α, in their study.

In the present study, both fluids increased cardiac index. In the colloid group, the increase in CI was more pronounced and consistent during the experimental procedure. One could therefore argue that a larger bolus dose of the crystalloid, e.g. 30 ml kg^{-1}, would have induced a more pronounced increase in CI, RBF, and renal oxygen delivery, with less or no impairment of the renal oxygen demand–supply relationship. On the contrary, a higher dose of the crystalloid would have induced a more pronounced haemodilution, which would have counteracted a beneficial increase in RBF, with potentially no net increase in RD_{O_2}. Furthermore, a higher dose of the crystalloid would decrease the oncotic pressure further, potentially increasing GFR and $R\dot{V}O_2$ to a greater extent than with a lower dose of crystalloid. Thus, it is not immediately evident that a higher dose (e.g. 30 ml kg^{-1}) of a crystalloid than the one used in the present study would have had a less negative effect on the renal oxygen demand–supply relationship.

One limitation of the present study was that we included patients who were considered haemodynamically stable, according to our local postoperative treatment protocol. Thus, we did not measure arterial pulse pressure or stroke volume variation to assess fluid responsiveness.[28 29] The reason for this approach is that we considered it unethical to include patients with obvious haemodynamic signs of hypovolaemia, defined by our clinical protocol, without treating this condition during the preparation for the experimental procedure, including time to reach a body temperature >36°C, time needed for serum ^{51}Cr-EDTA to reach steady state (at least 60 min), and baseline measurements (60 min) before start of the plasma volume expansion. However, 80–90% of the patients in both groups responded to the plasma volume by an increase in CI.[29 30] We therefore strongly believe that our results on the renal effects of colloid and crystalloid solutions are valid for a group of patients undergoing major surgery, responding to plasma volume expansion with an increase in CI in the early postoperative period.

In conclusion, we evaluated the differential renal effects of a colloid and a crystalloid early after cardiac surgery. Although both fluids increased CI and RBF, neither of the fluids improved renal oxygen delivery. The crystalloid-induced increase in GFR was associated with impaired renal oxygen demand–supply relationship, not seen with the colloid. Treatment of hypovolaemia with a bolus dose of a crystalloid therefore has the potential to impair renal oxygenation in postoperative patients.

Authors' contributions

Planned and designed the study: B.R., J.S., S.-E.R.
Conducted the experiments: J.S.L., G.B., V.K.
Analysed data: J.S.L., G.B.
Carried out statistical analysis: J.S.L.
Interpreted data: G.B., B.R., J.S., S.-E.R.
Wrote up the first draft: J.S.L.
Revised the manuscript: G.B., B.R., S.-E.R.
All authors gave final approval of the submitted version.

Declaration of interests

None declared.

Funding

Swedish State Support for Clinical Research (ALFGBG-70000); The Gothenburg Medical Society.

References

1. Englberger L, Suri RM, Li Z, *et al*. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. *Critical Care* 2011; **15**: R16
2. Heringlake M, Knappe M, Vargas Hein O, *et al*. Renal dysfunction according to the ADQI-RIFLE system and clinical practice patterns after cardiac surgery in Germany. *Minerva Anestesiol* 2006; **72**: 645–54
3. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med* 1998; **128**: 194–203
4. Robert AM, Kramer RS, Dacey LJ, *et al*. Cardiac surgery-associated acute kidney injury: a comparison of two consensus criteria. *Ann Thorac Surg* 2010; **90**: 1939–43
5. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med* 1998; **104**: 343–8
6. Lassnigg A, Schmidlin D, Mouhieddine M, *et al*. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol* 2004; **15**: 1597–605
7. Swaminathan M, Phillips-Bute BG, Patel UD, *et al*. Increasing healthcare resource utilization after coronary artery bypass graft surgery in the United States. *Circulation* 2009; **2**: 305–12
8. Liotta M, Olsson D, Sartipy U, Holzmann MJ. Minimal changes in postoperative creatinine values and early and late mortality and cardiovascular events after coronary artery bypass grafting. *Am J Cardiol* 2014; **113**: 70–5
9. Ryckwaert F, Boccara G, Frappier JM, Colson PH. Incidence, risk factors, and prognosis of a moderate increase in plasma creatinine early after cardiac surgery. *Crit Care Med* 2002; **30**: 1495–8
10. Rosner MH, Portilla D, Okusa MD. Cardiac surgery as a cause of acute kidney injury: pathogenesis and potential therapies. *J Intensive Care Med* 2008; **23**: 3–18
11. Parida S, Badhe AS. Cardiac surgery-associated acute kidney injury. *J Anesth* 2013; **27**: 433–46
12. Habib RH, Zacharias A, Schwann TA, *et al*. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome. *Crit Care Med* 2005; **33**: 1749–56
13. Kanji HD, Schulze CJ, Hervas-Malo M, *et al*. Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. *J Cardiothorac Surg* 2010; **5**: 71
14. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. *Ann Thorac Surg* 2003; **76**: 784–91; discussion 92
15. Brezis M, Rosen S. Hypoxia of the renal medulla — its implications for disease. *N Engl J Med* 1995; **332**: 647–55
16. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009; **37**: 2079–90
17. Wan L, Bellomo R, May CN. A comparison of 4% succinylated gelatin solution versus normal saline in stable normovolaemic sheep: global haemodynamic, regional blood flow and oxygen delivery effects. *Anaesth Intensive Care* 2007; **35**: 924–31
18. Konrad FM, Mik EG, Bodmer SI, *et al*. Acute normovolemic hemodilution in the pig is associated with renal tissue edema, impaired renal microvascular oxygenation, and functional loss. *Anesthesiology* 2013; **119**: 256–69
19. Bragadottir G, Redfors B, Nygren A, Sellgren J, Ricksten SE. Low-dose vasopressin increases glomerular filtration rate, but impairs renal oxygenation in post-cardiac surgery patients. *Acta Anaesthesiol Scand* 2009; **53**: 1052–9
20. Redfors B, Sward K, Sellgren J, Ricksten SE. Effects of mannitol alone and mannitol plus furosemide on renal oxygen consumption, blood flow and glomerular filtration after cardiac surgery. *Intensive Care Med* 2009; **35**: 115–22
21. Sward K, Valsson F, Sellgren J, Ricksten SE. Bedside estimation of absolute renal blood flow and glomerular filtration rate in the intensive care unit. A validation of two independent methods. *Intensive Care Med* 2004; **30**: 1776–82
22. Tidgren B, Brodin U. Plasma renin activity and oxygen content along the renal veins in hypertensive patients. *Clin Physiol* 1988; **8**: 407–16
23. Redfors B, Bragadottir G, Sellgren J, Swärd K, Ricksten SE. Acute renal failure is NOT an 'acute renal success'—a clinical study on the renal oxygen supply/demand relationship in acute kidney injury. *Crit Care Med* 2010; **38**: 1695–701
24. Swärd K, Valsson F, Sellgren J, Ricksten SE. Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. *Intensive Care Med* 2005; **31**: 79–85
25. Drobin D, Hahn RG. Kinetics of isotonic and hypertonic plasma volume expanders. *Anesthesiology* 2002; **96**: 1371–80
26. Ewaldsson CA, Hahn RG. Kinetics and extravascular retention of acetated Ringer's solution during isoflurane or propofol anesthesia for thyroid surgery. *Anesthesiology* 2005; **103**: 460–9
27. Ricksten SE, Bragadottir G, Redfors B. Renal oxygenation in clinical acute kidney injury. *Crit Care* 2013; **17**: 221
28. Legrand M, Mik EG, Balestra GM, *et al*. Fluid resuscitation does not improve renal oxygenation during hemorrhagic shock in rats. *Anesthesiology* 2010; **112**: 119–27
29. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**: 2642–7
30. Marik PE, Lemson J. Fluid responsiveness: an evolution of our understanding. *Br J Anaesth* 2014; **112**: 617–20

Handling editor: T. Asai