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Do lipid microemboli induce acute kidney injury during cardiopulmonary bypass?

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Abstract

Background: Acute kidney injury (AKI) following cardiopulmonary bypass affects 5% of patients, representing significant postoperative morbidity and mortality. Animal models have shown an increased uptake of lipid microemboli (LME) into the renal vasculature, potentially indicating ischaemic causation. This study tested a new lipid filtration system (RemoweLL) against a conventional system with no lipid-depleting capacity to determine the efficacy of the filtration system and its effects on renal function.

Methods: Thirty consecutive patients underwent coronary artery bypass graft surgery using either the RemoweLL filtration system (15 patients) or a conventional cardiopulmonary bypass circuit (15 patients). Renal function was assessed using cystatin C concentrations as a surrogate marker of glomerular injury, as well as perioperative glomerular filtration rate (GFR) and serum creatinine concentrations. Patients were defined as having acute renal injury if there was an increase in absolute serum creatinine $\geqslant$3 mg/dL (26.4 μmol/L) or 1.5-fold increase from baseline as categorised using the AKIN criteria.

Results: Postoperative differences in LME count between the two groups were highly significant [$p<0.001$]. Analysis of peak cystatin C concentrations showed significantly lower levels in the LME filtration group on the 2nd postoperative morning [$p=0.04$]. Two-factor ANOVA revealed a trend towards interaction, but this failed to reach significance [$p=0.06$]. There were no differences throughout the study period in serum creatinine or GFR [$p>0.05$]. There were no differences in any of the serum or urinary electrolytes.

Conclusions: This study has shown a trend towards improved cystatin C removal with LME filtration; with significantly lower peak concentrations, although no further evidence of renoprotection could be demonstrated. Further research is warranted to establish possible renal benefits of LME filtration in patients undergoing cardiac surgery.

Keywords

lipid microemboli; acute kidney injury; cardiopulmonary bypass; coronary artery bypass grafting; pericardial suction blood

Introduction

Approximately 30% of all patients undergoing cardiac surgery suffer from acute kidney injury (AKI) postoperatively, which remains a major cause of morbidity and mortality.[1,2] The severity of AKI can range from subclinical injury to established renal failure requiring dialysis and is often exacerbated by other co-morbidities such as diabetes mellitus.[3] The pathophysiology of renal dysfunction is incompletely understood, but is deemed multifactorial and can be related to perioperative renal hypoperfusion and the presence of endogenous and exogenous nephrotoxins (such as free radicals, anaesthetic agents etc.), which results in glomerular and tubular injury. It is interesting to note that a study in patients undergoing coronary artery bypass grafting (CABG) surgery performed without cardiopulmonary bypass (CPB) showed that there is a smaller increase in markers of renal injury compared to those with CPB, suggesting that CPB is a major factor.[1] As a highly

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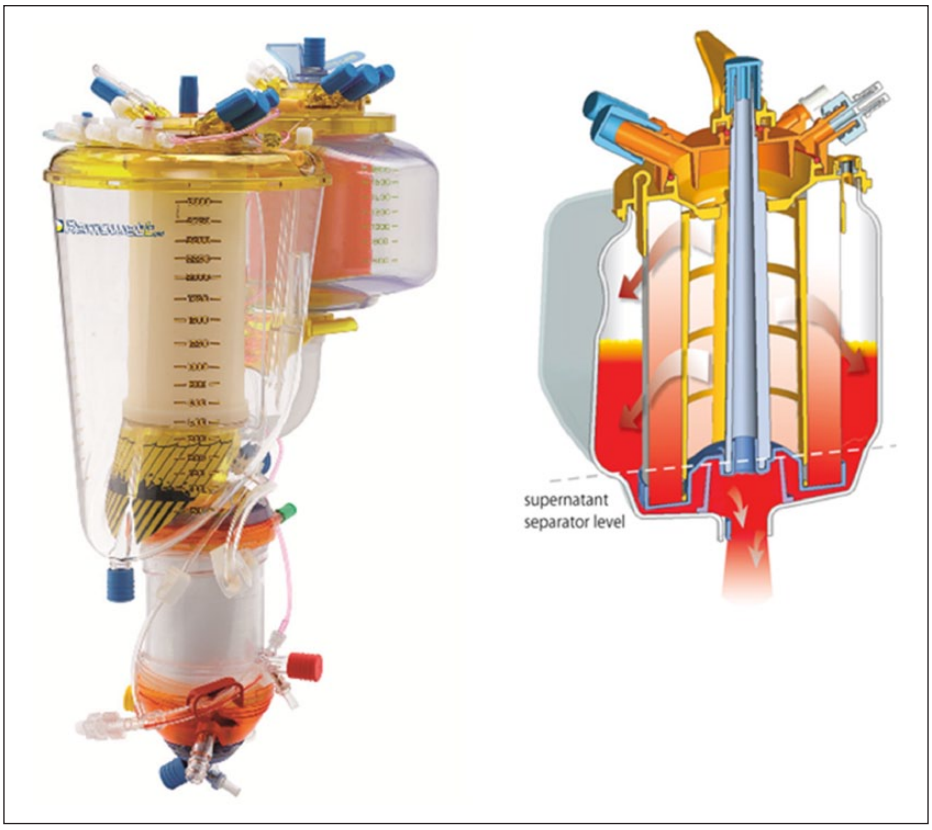

Figure 1. RemoweLL Cardiotomy Schematic. The RemoweLL® ECC system comprising a leucocyte filter and lipid microemboli siphon.

vascularised organ, the kidney is at risk from emboli, particularly lipid microemboli (LME) which have been shown in great numbers in the renal vasculature of patients undergoing CPB and might act through either a direct mechanical mechanism or through the cytotoxicity of the lipids and free fatty acids that make up LME.[4] A similar profile is observed in the cerebral vasculature of patients who have died shortly after surgery with CPB, with evidence of LME in the form of small capillary arteriolar dilatations, the numbers of which are proportional to the length of CPB.[5,6] Renal function is also dependent upon higher perfusion pressures and is, therefore, susceptible to periods of hypoperfusion during the surgical period.[2]

The measurement of renal injury has traditionally been undertaken using creatinine clearance and glomerular filtration rate (GFR). The Acute Dialysis Quality Initiative, set up in 2002, defined AKI according to the RIFLE criteria (Risk, Injury and Failure; and Loss; and End-stage kidney disease) this was further refined in 2004 by the Acute Kidney Injury Network (AKIN) to define AKI as an abrupt increase in absolute serum creatinine $\geqslant$3 mg/dL (26.4 µmol/L) or a percentage increase greater than 50% (1.5-fold from baseline). However, creatinine clearance, whilst specific, is not very sensitive; serum creatinine levels do not significantly increase until the GFR has reduced to less than 50% of its baseline[7] and is dependent upon several other factors, such as muscle mass. The assay is also susceptible to interference from various drugs and endogenous substances. Equally, GFR requires meticulous collection of urine over a fixed period of time, which is laborious and impractical in many clinical settings. A cysteine protease inhibitor, cystatin C, which is produced by all nucleated cells, is exclusively eliminated from the body by glomerular filtration and its serum concentration has been used to estimate GFR from spot serum samples rather than using serial urine collections. Additionally, the assay required is less susceptible to methodological interference which is inherent in the method of creatinine estimation and there is less inter-individual variation than serum creatinine, allowing for an earlier detection of AKI.[8] Typically, markers of renal dysfunction peak at 1-2 days postoperatively.[1]

The aim of the current study was to determine if a new cardiotomy reservoir (RemoweLL, Eurosets s.r.l, Mirandola, Italy; Figure 1) could attenuate the acute renal injury associated with CPB. The RemoweLL consists of 2 layers of 40-µm, non-woven polyester, the second treated with a polymeric coating to provide multilayer filtration for leucocytes and lipids, through which the blood is forced before entering the sedimentation chamber that

allows the separation and subsequent siphoning of a lipid-rich supernatant using a novel "U' bend at the outlet to the cardiotomy reservoir, the efficacy of which we have previously reported. [9]

Methods

Following Institutional Review Board, Research Ethics Committee approval (10/H0606/30) and written, informed consent, a prospective, single-centre, single-blind, randomised, controlled study was performed in 30 patients undergoing CABG with CPB, assigned to either a control or intervention (RemoweLL) extracorporeal circuit at University Hospital Southampton (Southampton, United Kingdom). Both intervention and control groups received the same anaesthetic regime. The patients were pre-medicated with 10 mg of morphine and 2 mg of lorazepam. Anaesthesia was induced with midazolam, fentanyl and pancuronium and maintained using intermittent positive pressure ventilation with oxygen-enriched air and isofluorane. During CPB, a propofol infusion was used to maintain anaesthesia. The CPB circuit consisted of either the Admiral (control) microporous, hollow-fibre, membrane-oxygenation system with integrated cardiotomy reservoir or the RemoweLL (intervention) microporous, hollow-fibre, membrane-oxygenation system with an integrated cardiotomy lipid/leucocyte filter (Eurosets s.r.l, Mirandola, Italy). The circuit was primed with two litres of lactated Ringer's solution that contained 5000 units of heparin. Prior to the establishment of CPB, 3 mg/kg body weight of heparin were administered and supplemented as required to maintain an activated clotting time of 480 s. Continuous, non-pulsatile blood-flow was delivered to the patient using a multi-flow roller pump (HL20, Maquet, Hirrlingen, Germany) at an indexed flow rate of 2.4 L/m^2/min. Alpha-stat pH management was used to control the acid-base balance. The mean arterial pressure was maintained between 50-60 mmHg with pharmacological manipulation, if necessary. After aortic clamping, electromechanical diastolic arrest was induced with the delivery of cold (4°C) blood cardioplegic solution. Distal anastomoses were completed during a single period of aortic clamping. Proximal anastomoses were performed with a beating heart, using an aortic partial-occluding clamp. CPB was terminated after the patient was re-warmed to a nasopharyngeal temperature of 37°C.

Hydration was achieved with the intravenous administration of dextrose 5% solution infused at 1 ml/kg/hr. Blood, Gelofusine or human albumin solution was given to maintain adequate filling and systemic perfusion pressures and haemoglobin levels above 8.5 g/dl.

Lipid analysis

Lipid emboli detection was carried out using light microscopy, as previously described.[9] A collection bottle was inserted proximal to the cardiotomy reservoir in the cardiotomy suction tubing. Following heparinisation and the initiation of scavenging by the cardiotomy suckers, pericardial suction blood (PSB) was siphoned into the collection bottle until an adequate volume was obtained for the initial baseline LME count. The PSB was then diverted back to the cardiotomy reservoir for the remainder of the operative period and the collection bottle discarded. The PSB was left to separate for as long as possible in the cardiotomy reservoir until it was either required to maintain adequate systemic volume or the period of CPB was ending. Following the reintroduction of the PSB from the cardiotomy reservoir into the systemic circulation, a sample was taken from the arterial sampling line to give a post-filtration (i.e. systemic) sample. One hundred microlitres of the sample were diluted 1/10 with saline (1000 μL) and agitated for 2-3 minutes to homogenise. Ten microlitres were placed onto a Thoma Chamber (Sigma-Aldrich Company Ltd, Gillingham, Dorset, United Kingdom) and the lipids counted under light microscopy with 40/0.65 optics. The lipids could be seen as spherical non-nucleated cells. The number of the lipids per μL was obtained by counting the average number of lipids in 4 small squares (Y) and inserted into the formula X=Yx16x100 where 16 equals the number of small squares (total volume 0.1μL) and 100 equals the dilution factor.

Renal analysis

Blood samples were taken for analysis of cystatin C and electrolytes (including urea and creatinine) pre-CPB and on the 1st, 2nd and 3rd postoperative mornings. A 10 mL urine sample was taken for analysis of urine microalbumin and osmolarity. The glomerular filtration rate (GFR) was calculated using the CKD-EPI creatinine equation (2009). Cystatin C assays were performed at the John Radcliffe Hospital, Oxford. Acute kidney injury is defined as an increase in absolute serum creatinine $\geqslant$3 mg/dL (26.4 μmol/L) or a 1.5-fold increase from baseline or urine output $\leqslant$0.5 mL/kg/hour for 6 hours. Serum and urine electrolytes were collected at all intraoperative time points (pre-CPB, 5 and 30 minutes on CPB, 5 minutes before cross-clamp removal, 5 minutes before the end of CPB and 1 and 24 hours post-CPB).

Statistics

The assessment of normal distribution was carried out using the Shapiro-Wilk Test and confirmed using a QQ

Table 1. Demographic data. Data presented as mean with standard deviations. Time of cardiotomy release is the amount of time the pericardial suction blood was left separated from the systemic circulation. There were no significant differences between the two groups of patients with regards to morbidity, preoperative drug regimens and perioperative details.

	Admiral		RemoweLL		p
	Mean	SD	Mean	SD	
Male (n)	12.00		11.00		
Diabetes (n)	2.00		3.00		
Statin (n)	8.00		8.00		
Age (years)	69.93	7.54	69.33	7.29	0.83
Height (m)	1.76	0.10	1.71	0.08	0.10
Weight (kg)	87.51	13.37	82.84	14.90	0.37
Body Mass Index	28.15	3.56	28.31	4.15	0.91
Body Surface Area	2.07	0.20	1.98	0.21	0.24
Calculated Flow (L/min)	4.96	0.47	4.74	0.50	0.24
Minimum Flow (L/min)	3.83	0.53	3.67	0.42	0.46
Maximum Flow (L/min)	5.43	0.53	5.27	0.42	0.46
Nadir Haemoglobin (g/L)	87		79		0.71
Nadir Haematocrit (%)	26.1		23.7		0.71
Mean MAP (mmHg)	57	5.5	56	7.4	0.96
Minimum MAP (mmHg)	31	3.8	29	5	0.65
Maximum MAP (mmHg)	81	11	89	5.1	0.26
Bypass Time (min)	101.40	22.01	88.47	23.51	0.13
X-Clamp Time (min)	62.67	17.67	51.20	17.11	0.08
Procedure (CABG x N)	3.33	0.49	3.13	0.83	0.43
Fluid Balance (mL)	1678.60	842.38	1562.27	867.16	0.71
Time of Cardiotomy Release (min)	74.93	19.27	67	17	0.23
Volume in Cardiotomy Reservoir (mL)	776.67	632.14	780.00	567.20	0.99

X-clamp: aortic cross-clamp; MAP: mean arterial pressure; CABG: coronary artery bypass graft.

Plot. As many of the parameters were measured at various time points, two-factor ANOVA for repeated measures was undertaken to explore differences between the groups. Normally distributed data were tested using a t-test for two independent samples whilst non-normally distributed values were LOG transformed and, if shown to be normally distributed, tested as above. If still non-normally distributed, data were tested using the Mann-Whitney test for two independent samples. A p-value $\leqslant 0.05$ was considered significant. Normally distributed data are presented as mean±standard deviation. Non-normally distributed data are presented as median (IQR) whilst graphically displayed as box and whisker plots with boxes representing 25th-75th centiles with median and whiskers as maximum and minimum values.

Results

Thirty patients successfully underwent the study assessments (15 per group). The demographics of the patients undergoing the study are given in Table 1. Both groups were equally matched in terms of male:female ratio, preoperative statin regime and number of patients with diabetes mellitus. All patients were on aspirin and clopidogrel anticoagulation therapy preoperatively. In line with hospital protocol, both treatments were stopped 10 days before surgery. There were no differences in terms of perioperative details, including CPB time, number of grafts and fluid balance. There were no differences in transfusion rates or haemoglobin levels between the 2 groups at any time point [$p>0.05$]. Fluid balances were the same between groups [1678.60±842.38 mL vs.1562.27±867.16 mL; $p=0.71$]. No patients exhibited a urine output $\leqslant 0.5$ mL/kg/hour.

Baseline LME counts (n/μL) were similar in the two groups [400 (200) vs. 400 (400); $p=0.47$], but there was a significant reduction in LME count with the RemoweLL lipid filter [100 (75); $p<0.001$] compared with a significant rise in the Admiral circuit [1,200 (200); $p<0.001$] (Table 2; Figure 2). Post-op differences between the Admiral and RemoweLL circuits were significant [1,200 (200) vs. 100 (75), respectively; $p<0.001$]. Baseline levels of cystatin C were higher in the Admiral Group compared to the RemoweLL Group although this was not

Table 2. LME Count. LME; lipid microemboli counted using light microscopy as detailed in *Lipid analysis* section. Data are presented as median (IQR). A p-value ⩽0.05 was considered significant.

	Time	Admiral	RemoweLL	p
LME Count (n/μL)	Pre-CPB	400 (200)	400 (400)	0.47
	Post CPB	1200 (200)	100 (75)	<0.001

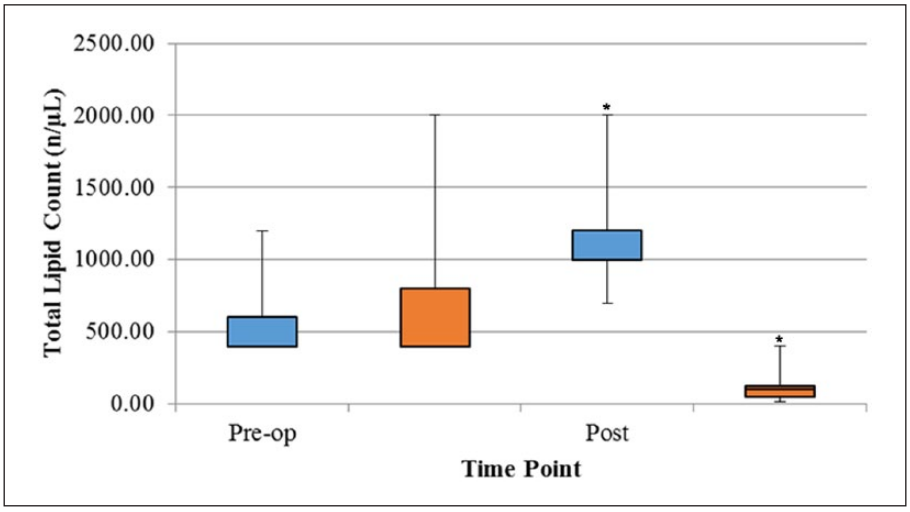

Figure 2. Lipid microemboli count pre- and post-filtration. Pre-filtration sample taken following the administration of heparin and the initiation of pericardial suckers. Post-filtration sample taken from the arterial sampling manifold following the release of PSB into the systemic circulation. Blue; control (Admiral), Orange; intervention (RemoweLL). Data presented as box and whiskers plots with boxes representing 25th-75th centiles with median and whiskers as maximum and minimum values. *p⩽0.05. PSB: pericardial suction blood.

significant [Admiral 1.14 (0.49) mg/L vs. RemoweLL 0.96 (0.22) mg/L; p=0.11; Table 3]. Two-factor ANOVA revealed a trend towards interaction, but failed to reach significance [p=0.06]. Analysis of peak concentrations showed significantly less cystatin C in the RemoweLL Group on the 2nd postoperative morning [Admiral 1.36 (0.86) mg/L vs. RemoweLL 0.85 (0.49); p=0.04]. The subsequent postoperative morning showed a trend towards lower concentrations in the RemoweLL Group, but this failed to reach significance [p=0.08], with both groups returning to baseline values (Figure 3). There were no differences throughout the study period in serum creatinine concentrations [ANOVA p=0.35]. Analysis of serum creatinine increases and reduction in GFR (according to AKIN criteria) showed eight patients, in total, who suffered some form of acute renal injury. Four patients (26% - 1 in Admiral Group, 3 in RemoweLL Group) were classed as at "Risk" whilst one was defined as having sustained "Injury" (RemoweLL Group). Three further patients (all Admiral Group) were classed as having renal "Failure". Serum creatinine concentrations were analysed using log transformed t-tests and showed no significance at any time points [p range 0.41-0.66]. Stepwise analysis of GFR showed no differences at any time point [p range 0.61-1.0]. There were no differences in any of the serum electrolytes (Table 4). No patients received renal replacement therapy.

Discussion

Acute renal injury affects approximately 1-5% of patients undergoing cardiac surgery and is a major cause of morbidity and mortality.[1] Whilst there are many factors indicated in its causation, such as perioperative renal hypoperfusion and the presence of endogenous and exogenous nephrotoxins, which result in glomerular and tubular injury, there is evidence that suggests AKI might occur as a result of ischaemic damage rather than altered blood flow profiles of CPB.[1] Brondén et al. observed an extremely high uptake of a radioactive tritium-labelled triolein shed blood phantom (to replicate LME) into the kidneys of pigs.[10] When one considers the highly vascularised nature of the kidneys, the double capillary network of the glomeruli and tubuli and the high blood flow to the organs, it is highly suggestive that LME may contribute to renal complications postoperatively. Two mechanisms have been proposed through which LME might act to facilitate renal

Table 3. Cystatin C release. Samples taken pre-CPB, 1st, 2nd and 3rd postoperative mornings. Data are presented as median (IQR). A p-value ⩽0.05 was considered significant.

	Time	Admiral	RemoweLL	p
Cystatin C (mg/L)	Pre-op	1.14 (0.49)	0.96 (0.22)	0.1
	1st Post-op morning	1.15 (0.62)	0.82 (0.52)	0.12
	2nd Post-op morning	1.36 (0.86)	0.85 (0.49)	0.04
	3rd Post-op morning	1.28 (0.92)	0.93 (0.49)	0.08

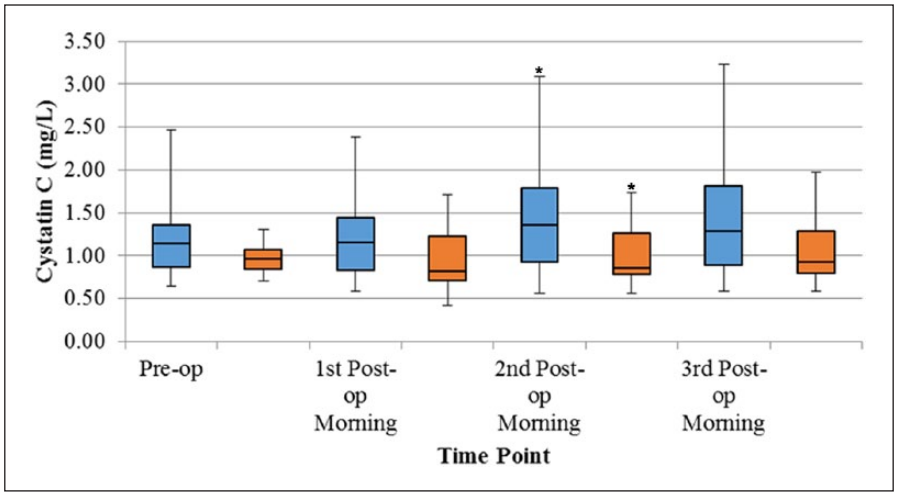

Figure 3. Cystatin C changes. Samples taken pre-CPB, 1st, 2nd and 3rd postoperative mornings. Blue; control (Admiral), Orange; intervention (RemoweLL). Data presented as box and whiskers plots with boxes representing 25th-75th centiles with median and whiskers as maximum and minimum values. *p⩽0.05.

dysfunction. The first is a mechanical obstruction; Appelblad and colleagues demonstrated the ability of mediastinal fat to impair capillary-pore blood flow.[11] The second is a possible toxic effect; oleic acid (the major component of LME) is a known initiator of neutrophil activation that induces acute respiratory distress-type clinical symptoms in animal models,[12] whilst free fatty acids and triglycerides have toxic properties, as demonstrated in a feline model where charged oleic acid caused cytotoxic cerebral oedema.[13] This implies that lipid material cannot only cause mechanical obstruction, but chemical interactions may also play a negative role in the capillaries of the organs.

There are several methods of measuring renal function. Cystatin C was chosen as a surrogate marker of renal function as it is exclusively removed by glomerular filtration and has shown good correlation with GFR without the meticulous collection of urine and is more specific and less susceptible to methodological interference than serum creatinine testing. Furthermore, its use has been validated in CABG patients.[1] The Acute Kidney Injury Network defines AKI as an abrupt increase in absolute serum creatinine ⩾3 mg/dL (26.4 μmol/L) or a percentage increase greater than 50% (1.5 fold from baseline). Therefore, in this study, both cystatin C and increases in serum creatinine were used to investigate renal dysfunction during and in the post-CPB period. Baseline measurements showed similar levels of serum cystatin C in both groups [p=0.11], with a significant increase occurring at the second postoperative morning. There was a trend towards significance between the groups overall, but this failed to reach significance [p=0.06]. The timings and indications for renal replacement therapy are not governed by fixed criteria and are subject to alterations in many factors, including potassium, creatinine, urea and acid-base status.[14] For this reason, even though eight patients exhibited acute rises in serum creatinine concentrations, no patient received any postoperative support for renal failure, which is reflected in the similarity in GFR and increases in serum creatinine between the groups. Furthermore, both groups of patients showed similar adequate urine output during the post-op period and, whilst acute oliguria is a helpful indicator of AKI (⩽0.5 mL/kg/hour for 6 hours indicates AKI), it is neither specific nor sensitive and has been shown to be common in cardiac surgery, occurring as an appropriate response to intravascular hypovolaemia.[15,16] Normal serum cystatin C is considered to be in the region of 0.6 to 1 mg/L.[17] Given that these patients, whilst being otherwise relatively fit and healthy, are being treated for atherosclerosis, it is perhaps

Table 4. Serum Electrolytes. Samples taken pre-CPB, 1st, 2nd and 3rd postoperative mornings. Data are presented as median (IQR) or mean±standard deviation. A p-value ⩽0.05 was considered significant.

	Time	Admiral	RemoweLL	p
Sodium (mmol/L)	Pre	137.33±2.35	137.6±2.06	0.74
	Day 1	137.2±3.78	136.53±3.66	0.63
	Day 2	135.53±4.29	134.27±3.15	0.36
	Day 3	136±2.93	133.67±3.66	0.06
Potassium (mmol/L)	Pre	3.88±0.36	4.31±0.64	0.03
	Day 1	4.57±0.5	4.5±0.34	0.68
	Day 2	4.43±0.51	4.37±0.3	0.74
	Day 3	4.41±0.23	4.29±0.41	0.33
Urea (mmol/L)	Pre	5.5 (2.2)	5.4 (1.5)	0.9
	Day 1	6 (3.6)	5.2 (2.1)	0.22
	Day 2	5.8 (5.8)	5.7 (3.5)	0.61
	Day 3	6.5 (4.9)	6.3 (3.8)	0.88
Creatinine (μmol/L)	Pre	75 (20.5)	75 (21.5)	0.67
	Day 1	87 (34.5)	81 (37.5)	0.43
	Day 2	82 (43.5)	87 (41)	0.83
	Day 3	78 (24.5)	85 (24.5)	0.41
Estimated GFR ($mL/min/1.73m^2$)	Pre	89 (13.5)	89 (19)	0.91
	Day 1	76 (33)	79 (30)	0.61
	Day 2	82 (38)	72 (30)	0.67
	Day 3	85 (32)	81 (24)	1

GFR: glomerular filtration rate.

unsurprising that their cystatin C levels are on the upper limits of normal at baseline (Admiral 1.14 (0.49) vs. RemoweLL 0.96 (0.22) mg/L), as it is unlikely that the coronary arteries are the only vessels that exhibit signs of narrowing. The results seen here mimic those seen in the study by Abu-Omar et al. who also saw an increase in serum cystatin C levels at post-op day 2. As patients in both groups can be considered at low risk of AKI, it is debatable whether any changes in their cystatin C levels would be similar or relevant to those patients with preoperative renal dysfunction. However, it is known that those patients with chronic renal failure are more at risk of developing an AKI on top of their already diminished renal function; therefore, it seems reasonable to suggest that the prevention of LME uptake in the renal vasculature may be of greater benefit in this particular cohort.

Summary

Kidneys have exhibited the highest uptake of LME in animal models and so the role of LME in renal dysfunction was investigated using cystatin C as a surrogate maker of AKI. There was a significantly lower concentration of cystatin C in the RemoweLL Group in the postoperative period, suggesting a renoprotective role for LME filtration although no other parameters confirmed prevention of renal injury. Further investigation is warranted to elucidate any long-term benefits of LME filtration in patients undergoing cardiac surgery.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The manufacturer of the medical device under trial funded the biochemical analysis used in this study. The authors had full control of the design of the study, methods used, outcome measurements, analysis of data and production of the written report.

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