Acute renal failure is NOT an "acute renal success"—a clinical study on the renal oxygen supply/demand relationship in acute kidney injury

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Objectives: **Acute kidney injury occurs frequently after cardiac or major vascular surgery and is believed to be predominantly a consequence of impaired renal oxygenation. However, in patients with acute kidney injury, data on renal oxygen consumption (RVO_2), renal blood flow, glomerular filtration, and renal oxygenation, i.e., the renal oxygen supply/demand relationship, are lacking and current views on renal oxygenation in the clinical situation of acute kidney injury are presumptive and largely based on experimental studies.**

Design: **Prospective, two-group comparative study.**

Setting: **Cardiothoracic intensive care unit of a tertiary center.**

Patients: **Postcardiac surgery patients with (n = 12) and without (n = 37) acute kidney injury were compared with respect to renal blood flow, glomerular filtration, RVO_2, and renal oxygenation.**

Interventions: **None**

Measurements and Main Results: **Data on systemic hemodynamics (pulmonary artery catheter) and renal variables were obtained during two 30-min periods. Renal blood flow was measured using two independent techniques: the renal vein thermodilution technique and the infusion clearance of paraaminohippuric acid, corrected for renal extraction of paraaminohippuric acid. The filtration fraction was measured by the renal extraction of ^{51}Cr-EDTA and the renal sodium resorption was measured as the difference between filtered and excreted sodium. Renal oxygenation was estimated from the renal oxygen extraction. Cardiac index and mean arterial pressure did not differ between the two groups. In the acute kidney injury group, glomerular filtration (−57%), renal blood flow (−40%), filtration fraction (−26%), and sodium resorption (−59%) were lower, renal vascular resistance (52%) and renal oxygen extraction (68%) were higher, whereas there was no difference in renal oxygen consumption between groups. Renal oxygen consumption for one unit of reabsorbed sodium was 2.4 times higher in acute kidney injury.**

Conclusions: **Renal oxygenation is severely impaired in acute kidney injury after cardiac surgery, despite the decrease in glomerular filtration and tubular workload. This was caused by a combination of renal vasoconstriction and tubular sodium resorption at a high oxygen demand. (Crit Care Med 2010; 38:1695–1701)**

Key Words: kidney failure; acute; renal blood flow; glomerular filtration rate; oxygen consumption; cardiac surgery

Acute kidney injury (AKI) develops in 5–25% of patients after cardiac and major vascular surgery (1, 2). Dialysis-dependent AKI in these patients is associated with a mortality of up to 80% (3, 4) and even a minimal increase in serum creatinine after cardiac surgery is associated with a nearly three-fold increase in mortality (3). The pathogenesis of postoperative AKI is believed to be predominantly a consequence of renal ischemia (5, 6). The outer portion of the medulla is particularly sensitive to ischemia, as medullary tissue oxygen tension is low because of the high oxygen utilization of the medullary thick ascending limbs of the renal medulla (7).

It is well known that tubular sodium resorption is a major determinant of renal oxygen consumption (RVO_2) (8) and it has been shown that there is a close correlation between glomerular filtration rate (GFR), renal sodium resorption, and RVO_2 in postoperative patients (9). The filtered load of sodium is, thus, an important determinant of RVO_2 in man, and maneuvers that decrease GFR and the sodium load to the distal tubules act to decrease medullary sodium resorption and O_2 consumption, thereby increasing medullary oxygenation and vice versa (10). It has provocatively been stated that "acute renal failure is acute renal success" (11–16), as a reduction in GFR in AKI should lead to a reduction of the renal reabsorptive workload, thus preserving medullary oxygenation with a reduced risk of further aggravation of ischemia.

In patients with AKI, data on RVO_2, renal blood flow (RBF), GFR, and renal oxygenation, i.e., the renal oxygen supply-demand relationship, are lacking, and current views on renal oxygenation in the clinical situation of AKI are presumptive and largely based on experimental studies (11).

We have, therefore, studied patients with AKI after complicated cardiac surgery with respect to their RVO_2, RBF, GFR, and renal oxygenation. RBF was assessed by two independent techniques,

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the retrograde renal vein thermodilution (TD) technique and by infusion clearance (IC) of paraaminohippuric acid (PAH), with correction for renal extraction of PAH. Patients undergoing cardiac surgery with no postoperative renal impairment served as controls. Our null hypothesis was that renal oxygenation is normal in AKI due to proportional reductions in GFR, RBF, and RVO_2.

MATERIALS AND METHODS

The Human Ethics Committee of the University of Gothenburg approved the study protocol and written informed consent was obtained from the patients at the preoperative evaluation (control group) and the next of kin in the AKI group. Our aim was to compare a group of patients with AKI to a control group with no renal impairment, at a numerical ratio of 1:3. Between September 2006 and December 2009, we therefore prospectively included 53 adult postcardiac surgery patients. Fourteen of those had had a complicated coronary artery and/or valve surgery and developed AKI. The inclusion criteria for the AKI group were a) cardiac surgery with cardiopulmonary bypass, b) normal preoperative renal function (serum-creatinine $\leq$115 μmol/L), and c) development of AKI stage 1 or 2, according to the Acute Kidney Injury Network criteria, defined as a 50–200% postoperative increase in serum creatinine from baseline (17). Thirty-nine patients served as controls with the following inclusion criteria: a) elective cardiac surgery with cardiopulmonary bypass, b) preoperative left ventricular ejection fraction of $\geq$45%, and c) normal preoperative renal function (serum-creatinine $\leq$115 μmol/L). Data from some of the patients in the control group have partially been published previously (18–20). The exclusion criteria in the AKI group were as follows: a) heart transplantation, b) thoracoabdominal aortic surgery, c) aortic dissection, d) use of radiocontrast agents, and e) postoperative arrhythmias requiring treatment. In the control group the exclusion criteria were as follows: a) postoperative need for inotropic support, b) postoperative arrhythmias requiring treatment, and c) significant postoperative bleeding.

In the intensive care unit, the patients were sedated with propofol (control group: 63.8 ± 3.0 μg/kg/min, AKI group: 61.7 ± 4.2 μg/kg/min), treated with morphine or fentanyl, with no addition of nonsteroidal antiinflammatory drugs, and mechanically ventilated to normocapnia. The hemodynamic and renal management of the complicated patients with AKI were at the discretion of the attending intensive care physicians. The clinical treatment protocol includes inotropic support with milrinone and/or norepinephrine to maintain a cardiac index of $\geq$2.1 l/min/m^2, whole-body oxygen extraction of <40%, and a mean arterial pressure at 70–75 mm Hg with or without an intra-aortic balloon pump. To promote diuresis, a continuous infusion of furosemide (5–20 mg/hr) is used.

Systemic Hemodynamics. All patients were monitored by a pulmonary artery TD (Baxter Healthcare, Irvine, CA) and arterial catheters. Measurements of TD cardiac output were performed in triplicate, and indexed to body surface area to get the cardiac index. Systemic vascular resistance index, left ventricular stroke volume index, systemic oxygen delivery index (DO_2I), systemic oxygen consumption index (VO_2I), and systemic oxygen extraction (O_2Ex) were calculated according standard formulae.

Measurements of Renal Variables. An 8-Fr catheter (Webster Laboratories, Baldwin Park, CA) was introduced into the left renal vein via the right femoral vein under fluoroscopic guidance. The catheter was placed in the central portion of the renal vein and its position was verified by venography with ultralow doses of iohexol (Omnipaque 300 mg I/mL, GE Healthcare, Stockholm, Sweden) (21) (control: 30–60 mg I/kg, AKI: 5–15 mg I/kg). Using the renal vein catheter, we measured RBF by two independent techniques, continuous retrograde TD and IC of PAH (Merck, Whitehouse Station, NJ) with correction for the PAH concentration in the renal vein (22, 23). An intravenous priming dose of PAH, (8 mg/kg) and chromium ethylenediaminetetraacetic acid (^{51}Cr-EDTA) (GE Healthcare Limited, The Grove Center, Amhersham, England) (0,6 MBq/m^2 body surface area) were given, after blood and urine blanks were taken, followed by an infusion at a constant rate individualized to body weight and serum creatinine. Serum concentrations of PAH and serum ^{51}Cr-EDTA activity were measured by a spectrophotometer (Beckman DU 530, Life Science UV/Vis, Fullerton, CA) and a well counter (Wizard 3", 1480, Automatic Gamma Counter, Perkin Elma LAS, Turkuu, Finland), respectively.

Experimental Procedure. In the control group, measurements started when the patients had a stable body temperature of >36,0°C, approximately 4–6 hrs after end of cardiopulmonary bypass. The AKI group was studied 2 to 6 days after cardiac surgery. After an equilibration period of at least 60 mins, two 30-min urine collection periods ensued. At the end of each period, cardiac output and renal TD measurements were performed and blood samples were taken from radial artery, pulmonary artery, and renal vein. The inotropic medication and the fluid infusion rate were not changed during the experimental procedure. In the control group, serum creatinine was assessed on the first and second postoperative days.

Data Calculation. RBF was measured by retrograde TD of the left renal vein as follows: RBF_{TD} = (left renal vein blood flow × 2) + urine flow. RBF was also measured by the IC of PAH: RBF_{IC} = (amount PAH infused per min)/([PAH arterial] − [PAH renal vein])/(1 − hematocrit). Furthermore, for comparison we calculated effective RBF as follows: effective RBF = (amount PAH infused per min)/[PAH arterial]/0.9/(1 − hematocrit). Renal extraction of PAH was calculated as follows: renal extraction of PAH = ([PAH arterial] − [PAH renal vein])/PAH arterial]. Filtration fraction was measured as renal extraction of ^{51}Cr-EDTA: filtration fraction = (renal plasma flow [RPF] × [^{51}Cr-EDTA arterial] − (RPF−urine flow) × [^{51}Cr-EDTA renal vein] / (RPF × [^{51}Cr-EDTA arterial]), where RPF = RBF × (1 − hematocrit). GFR was filtration fraction × RPF and renal vascular resistance was (mean arterial pressure − central venous pressure)/RBF. Renal oxygen consumption, delivery, and extraction were calculated according to standard formulae. The glomerular sodium filtration was the product of GFR and serum sodium concentration and the tubular resorption of sodium was the difference between filtered and excreted sodium. All renal data were normalized to a body surface area of 1.73 m^2.

Statistical Analysis. Intragroup data on renal and hemodynamic variables from the two 30-min measurement periods were compared using paired Student's *t* test and thereafter pooled. To test difference between the groups, independent-samples *t* test assuming nonequal variances between groups were used. To detect a difference in renal oxygen extraction of 30% between the groups at an SD of 0.032 (9), 12 and 35 patients were needed at power of 78% (1-ß = 0.78), and a significance level of .05 (α = .05). Categorical baseline data were compared using a chi-square or Fisher's exact test. In both groups, linear regression analyses were performed to correlate RVO_2 to renal sodium resorption and GFR, respectively. Furthermore, in the AKI group, dose norepinephrine was correlated to renal vascular resistance and the furosemide dose was correlated to urine flow, fractional excretion of sodium, and RVO_2. A probability level (*p* value) of less than .05 was considered to indicate statistical significance. The data are presented as mean ± SEM.

RESULTS

In the control group, one patient was excluded because of significant postoperative bleeding. In the AKI group, one patient developed ventricular fibrillation during the equilibration period, which was successfully converted. This patient was excluded. Furthermore, one patient in each group was excluded because of

Table 1. Baseline characteristics

	Control Group (n = 37)	AKI Group (n = 12)	*p* Value
Preoperative characteristics			
Gender, n (% men)	34 (92)	9 (75)	ns
Age (year)	64.7 ± 1.8	68.8 ± 1.3	ns
BSA (m^2)	2.0 ± 0.03	2.1 ± 0.07	ns
Preop LVEF (%)	58.7 ± 1.2	43.1 ± 6.3	.032
Diabetes, type 1/type 2	0/6	0/2	ns
Hypertension, n (%)	19 (51)	9 (75)	ns
Preop s-creatinine (μmol/L)	83.2 ± 1.8	90.5 ± 3.9	ns
Preop treatment:			
ACE inhibitor, n (%)	18 (49)	8 (67)	ns
β-blocker, n (%)	28 (76)	10 (83)	ns
Calcium antagonists, n (%)	6 (16)	1 (8)	ns
Euroscore	2.8 ± 0.3	7.6 ± 0.9	<.001
Perioperative characteristics			
Type of surgery:			
CABG, n (%)	32 (86)	5 (42)	.004
Valve, n (%)	4 (11)	2 (17)	ns
Combined, n (%)	1 (3)	5 (42)	.002
Other, n (%)	0	0	ns
Nonelective, n (%)	0	3 (25)	.12
CPB time (min)	75.3 ± 5.5	182.7 ± 23.7	<.001
Aortic cross-clamp time (min)	45.3 ± 3.1	104.3 ± 17.0	.005
ICU Higgins	1.4 ± 0.2	12.3 ± 1.3	<.001

AKI, acute kidney injury; ns, not significant; BSA, body surface area; Preop, preoperative; LVEF, left ventricular ejection fraction; s-creatinine, serum creatinine; ACE, angiotensin-converting enzyme; CABG, coronary artery bypass surgery; Nonelective, surgery performed within 24 hrs after referral; CPB, cardiopulmonary bypass; ICU, intensive care unit.

Data are presented as means ± SEM.

unsuccessful placement of the renal vein catheter.

Patients in the AKI group had a lower preoperative ejection fraction and a higher Euroscore (24). Furthermore, isolated coronary artery surgery was less, whereas combined procedures were more common in the AKI group. Nonelective procedures were performed in 25% of patients in the AKI group. Cardiopulmonary bypass and aortic cross-clamp times, as well as the Higgins intensive care unit admission score (25), were higher in the AKI group (Table 1). Individual data of the AKI group at inclusion are shown in Table 2. Patients were studied 2–6 days after surgery at a 62–184% increase in serum creatinine. All patients were mechanically ventilated with a Sequential Organ Failure Assessment score of 7–12. All patients were treated with norepinephrine, eight patients (75%) with milrinone, ten patients (83%), with furosemide and three patients (25%) with an intra-aortic balloon pump.

Systemic Variables. Whereas there were no differences in mean arterial pressure, stroke volume index, heart rate, or cardiac index between the groups, the AKI patients had higher cardiac filling pressures and arterial lactate, whereas systemic vascular resistance index was lower (−11%) compared with the control group (Table 3). Furthermore, there were no differences in serum hemoglobin, arterial oxygen saturation, DO_2I, or systemic O_2Ex, but mixed venous oxygen saturation was lower (−7%) due to an increase in VO_2I (18%) in the AKI group. Body temperature was slightly but significantly higher in the AKI group.

Renal Variables. Measured and derived renal variables obtained from the two independent methods, renal TD and PAH IC, are presented in Table 4. The AKI patients had significantly lower RBF (TD: −37%, IC: −40%), Renal delivery of oxygen (TD: −38%, IC: −41%), GFR (TD: −57%, IC: −58%), sodium filtration (TD: −57%, IC: −58%), and sodium resorption (TD: −59%, IC: −60%) than the control patients. Renal vascular resistance was higher in the AKI group (TD: 51%, IC: 52%). Furthermore, renal oxygen extraction was 68% higher in the AKI group, whereas there was no difference in RVO_2 between the groups. PAH extraction was 20% lower in AKI group. There were no differences in urine flow between groups. In the control group, mean serum creatinine values preoperatively and on the first and second postoperative days were 83 ± 2, 78 ± 5, and 85 ± 5 μmol/l, respectively. The postoperative serum creatinine values did not differ significantly from the preoperative value. None of the patients in the AKI group died or required renal replacement therapy during their stay in the intensive care unit.

RVO_2 correlated to GFR in both controls ($p < .001$, $r^2 = 0.82$) and the AKI patients ($p = .016$, $r^2 = 0.50$), but the slope of the regression line in the AKI group was significantly steeper ($p = .04$) (Fig. 1). Furthermore, RVO_2 correlated to sodium resorption in both the control ($p < .001$, $r^2 = 0.85$) and the AKI ($p = .005$, $r^2 = 0.61$) (Fig. 2) groups. This slope, indicating oxygen consumption per sodium reabsorbed, was also significantly steeper in the AKI group ($p = .004$). Thus, the oxygen consumption/mmol sodium reabsorbed was 1.94 ± 0.36 in the AKI group and 0.82 ± 0.071 in the control group. The slope intercepts on the abscissa differed significantly from origin ($p = .002$) in both groups (control: 2.4 ± 0.65 and AKI: 3.3 ± 2.29 mL O_2/min), but the slope intercepts indicating basal renal oxygen consumption did not differ between groups.

Norepinephrine dose did not correlate to renal vascular resistance, and treatment with furosemide did not correlate to RVO_2, urine flow, or fractional excretion of sodium in the AKI group.

DISCUSSION

The major findings of the present study were that in spite of the 60% decrease in GFR and renal sodium resorption in postcardiac surgery patients with AKI, RVO_2 was not proportionally reduced and, in fact, was not significantly different from that of control patients with no renal impairment. In addition, in these hemodynamically treated high-risk cardiac surgical patients with AKI, RBF was 35–40% lower than control patients; this low level, in turn, was caused by renal vasoconstriction. Finally, the renal oxygen supply/demand relationship was severely impaired in early AKI, as demonstrated by the almost 70% increase in renal oxygen extraction.

To our knowledge, this is the first study evaluating RVO_2 and renal oxygenation in relation to tubular workload in clinical AKI. From Figure 1 it can be seen that there is a close correlation between GFR and RVO_2 in both groups of patients. According to the

Table 2. Individual data at inclusion of the AKI group

Patient no.	Study Entry (Day)	Serum Creatinine Preop (μmol/L)	Serum Creatinine Inclusion (μmol/L)	% Increase	SOFA Score	IABP	Norepinephrine (μg/kg/min)	Milrinone (μg/kg/min)	Furosemide (μg/kg/min)
1	5	65	136	109	9	No	0.25	0	2.53
2	2	107	209	95	10	Yes	0.16	0.24	1.02
3	3	112	200	79	9	Yes	0.12	0.13	0.80
4	4	91	151	66	12	No	0.14	0.18	0
5	4	102	170	67	7	No	0.09	0	0.99
6	6	78	145	86	9	No	0.43	0.43	0
7	6	101	194	92	7	No	0.22	0	2.22
8	2	90	146	62	10	Yes	0.33	0.44	3.70
9	3	81	230	184	10	No	0.11	0.52	3.06
10	6	93	210	126	7	No	0.32	0.25	1.05
11	5	84	217	158	9	No	0.27	0	0.95
12	2	82	135	65	10	No	0.33	0.26	3.21
Mean	*3.9*	*90.5*	*178.6*	*99.1*	*9.1*	*25%*	*0.23*	*0.31*[a]	*1.95*[a]
SEM	*0.5*	*3.9*	*10.1*	*11.3*	*0.4*		*0.03*	*0.05*[a]	*0.35*[a]

AKI, acute kidney injury; Preop, preoperative; SOFA, sequential organ failure assessment; IABP, intra-aortic balloon pump.
[a]Mean and SEM among treated.
Data in italics indicates means and SEM of the variables.

Table 3. Systemic variables

	Control Group (n = 37)	AKI Group (n = 12)	*p* Value
MAP (mm Hg)	73.9 ± 1.1	73.5 ± 0.7	ns
CI (L/min/m^2)	2.63 ± 0.08	2.77 ± 0.16	ns
HR (beats/min)	75.4 ± 1.7	88.7 ± 6.1	ns
SVI (ml/beat/m^2)	35.3 ± 1.1	33.1 ± 3.1	ns
CVP (mm Hg)	7.6 ± 0.3	11.4 ± 0.8	<.001
PCWP (mm Hg)	10.1 ± 0.63	15.7 ± 1.01	<.001
SVRI (dynes · sec/cm^5/m^2)	2084 ± 71	1847 ± 88	.048
DO_2I (ml/min/m^2)	378 ± 11	396 ± 25	ns
VO_2I (ml/min/m^2)	101.6 ± 2.6	120.2 ± 4.3	.002
O_2Ex (%)	27.0 ± 0.7	31.6 ± 2.0	ns
SaO_2 (%)	98.3 ± 0.1	97.7 ± 0.4	ns
SvO_2 (%)	71.7 ± 0.7	66.8 ± 1.9	.020
Serum hemoglobin (g/L)	106.5 ± 2.0	105.4 ± 3.1	ns
Arterial lactate (mmol/L)	0.88 ± 0.08	1.53 ± 0.23	.020
Body temperature (°C)	36.5 ± 0.10	37.2 ± 0.27	.046

AKI, acute kidney injury; MAP, mean arterial pressure; ns, not significant; CI, cardiac index; HR, heart rate; SVI, stroke volume index; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; DO_2I, systemic oxygen delivery index; VO_2I, systemic oxygen consumption index; O_2Ex, systemic oxygen extraction; SaO_2, systemic arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.
Values are means ± SEM.

"acute failure is a renal success" hypothesis (11–16), AKI patients should operate on the lower part of the regression line of the control patients. However, the regression line of the AKI patients is clearly shifted to the left, i.e., at a certain level of GFR, RVO_2 is higher, as also demonstrated during the recovery phase after renal ischemia/reperfusion injury in rats (26, 27). Thus, our findings do not support the hypothesis put forward by many investigators that "acute renal failure is a renal success." On the contrary, the relatively high RVO_2 in combination with a 40% decrease in renal delivery of oxygen in AKI suggests that renal hypoxia may also be present after the initiation phase of AKI.

It is well established that the rate of oxygen utilization by the kidney consists of an oxygen cost of active sodium resorption plus a basal oxygen consumption. The relative increase in RVO_2 in the AKI group could thus be due to an increase in basal renal consumption, e.g., due to renal inflammation or increased oxidative stress (28). Although one should be cautious when extrapolating regression lines, the intercepts of the regression lines in Figure 2 indicate the basal RVO_2 of the studied subjects, which was approximately 25% of total RVO_2 in both groups. Thus, this finding does not support the hypothesis that the uncoupling of RVO_2 from GFR and renal sodium resorption in AKI is caused by an increase in basal renal oxygen consumption.

In our study, RVO_2 was approximately 10–12 mL/min in the postoperative sedated, mechanically ventilated controls, a value that is slightly lower than that previously reported in conscious healthy volunteers (29, 30). The regression line in Figure 2 indicates that the control group consumed a mean of 0.82 mL of oxygen per mmol of reabsorbed sodium, which is in line with findings from previous animal studies (31). In contrast, the AKI group consumed 1.9 mL O_2/mmol reabsorbed sodium. Thus, net reabsorbing a certain amount of sodium consumed 2.4 times more oxygen in the AKI group than in the control group.

One can only speculate on the mechanism behind the increased oxygen utilization for sodium transport in the AKI patients. A potential explanation could be ischemia-induced loss of epithelial cell polarization and loss of tight junction integrity in AKI, as has been shown in experimental studies and after human renal transplantation (32, 33). The tubular cells thus lose their ability to efficiently pump in a specific direction, from one compartment to another (34, 35). Despite this loss of direction, Na^+/K^+-ATPase has been found to re-

Table 4. Renal variables obtained from the thermodilution and the infusion clearance techniques

	Control Group (n = 37)	AKI Group (n = 12)	*p* Value
RO_2Ex	0.097 ± 0.004	0.163 ± 0.009	<.001
Urine flow (ml/min)	3.73 ± 0.39	4.04 ± 0.48	ns
Thermodilution measurements			
RBF_{TD} (ml/min)	758 ± 40	477 ± 54	<.001
RVR (mm Hg/ml/min)	0.097 ± 0.005	0.146 ± 0.015	.01
GFR (ml/min)	74.7 ± 4.7	32.3 ± 3.6	<.001
FF	0.148 ± 0.006	0.109 ± 0.014	.022
Na^+ filtration (mmol/min)	10.2 ± 0.7	4.4 ± 0.4	<.001
Na^+ resorption (mmol/min)	9.7 ± 0.7	4.0 ± 0.4	<.001
FE_{Na}	0.050 ± 0.007	0.099 ± 0.019	.028
RDO_2 (ml/min)	110.0 ± 6.2	68.0 ± 7.2	<.001
RVO_2 (ml/min)	10.4 ± 0.6	11.0 ± 1.1	ns
Infusion clearance of PAH			
RBF_{IC} (ml/min)	822 ± 40	496 ± 34	<.001
ERBF (ml/min)	779 ± 37	375 ± 35	<.001
RVR (mm Hg/ml/min)	0.086 ± 0.004	0.131 ± 0.095	<.001
GFR (ml/min)	80.3 ± 4.2	33.6 ± 3.4	<.001
FF	0.148 ± 0.005	0.107 ± 0.014	.017
Na^+ filtration (mmol/min)	11.0 ± 0.6	4.6 ± 0.5	<.001
Na^+ resorption (mmol/min)	10.5 ± 0.6	4.2 ± 0.5	<.001
FE_{Na}	0.042 ± 0.004	0.093 ± 0.015	.008
RDO_2 (ml/min)	120,1 ± 6.6	70.9 ± 4.5	<.001
RVO_2 (ml/min)	11.4 ± 0.5	11.8 ± 0.8	ns
PAH extraction	0.85 ± 0.01	0.68 ± 0.04	.002

AKI, acute kidney injury; RO_2Ex, renal oxygen extraction; ns, not significant; RBF_{TD}, renal blood flow assessed by the thermodilution technique; RVR, renal vascular resistance; GFR, glomerular filtration rate; FF, filtration fraction; FE_{Na}, fractional excretion of sodium; RDO_2, renal oxygen delivery; RVO_2, renal oxygen consumption; RBF_{IC}, renal blood flow assessed by infusion clearance; ERBF, effective renal blood flow.

Values are means ± SEM.

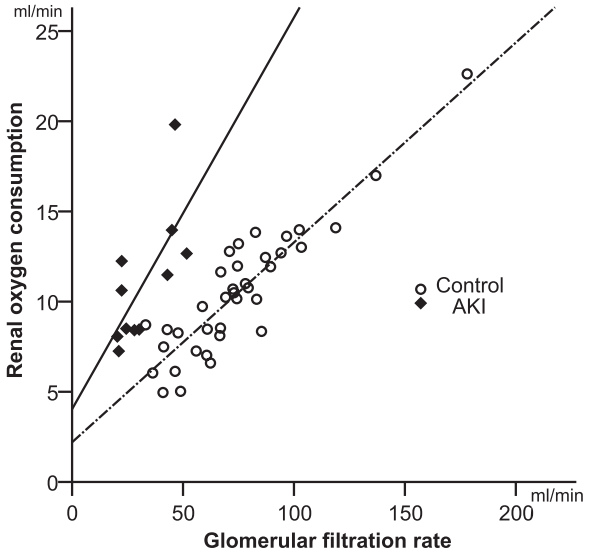

Figure 1. Shows the individual data on the relationship between renal oxygen consumption and glomerular filtration rate for the control group and patients with acute kidney injury (*AKI*). Note that the slope of the regression line was significantly ($p = .04$) higher in the AKI group compared with control.

tain its Na^+-pumping activity (35), and it has been proposed that this could result in a futile cycle, with vectorized transport of sodium uncoupled from ATP utilization (34).

Another explanation for the increased oxygen costs for sodium resorption in clinical AKI may be diminished renal generation of nitric oxide (NO) due to endothelial damage and down-regulation of endothelial nitric oxide synthase (14, 36–38). NO has been shown to directly compete with oxygen for mitochondrial respiration, suggesting a basal modulatory role for NO on oxygen consumption (14, 39). Laycock et al (39) showed that blockade of nitric oxide synthase increased RVO_2 in dogs while reducing GFR and renal sodium resorption. Indeed, inhibition of NO synthesis more than doubled the RVO_2/renal sodium resorption ratio in that study.

Previous reports on RBF in acute renal failure, particularly in the critical care setting, are scarce (40), and to our knowledge, RBF in patients with clinical AKI has not been compared with that for controls with no renal impairment in a single study. Renal vasoconstriction in various phases of experimental AKI has been attributed to afferent arteriolar vasoconstriction caused by the tubuloglomerular feedback mechanism, vasoconstrictors (catecholamines, angiotensin II, endothelin), and outer medullary congestion. Furthermore, it has been ascribed to ischemic endothelial cell injury causing an imbalance in the production of endothelin and endothelial nitric oxide or to angiotensin II-induced activation of reactive oxygen species that inactivates NO (28, 41, 42).

RBF in humans has frequently been measured as effective RBF, approximating the renal PAH extraction to 0.9, which is usually correct in subjects with healthy kidneys (43, 44). Due to the tubular damage, mean PAH extraction was only 0.68 with a range from 0.48 to 0.84 in the AKI group. Thus, without correction for renal PAH extraction, RBF will be seriously underestimated in patients with AKI, as also demonstrated by the 25% lower mean effective RBF compared with RBF_{IC} and a potential error of 7% to 47% at the most extreme deviations of PAH extraction from 0.9.

Fractional excretion of sodium was twice as high in AKI patients compared with controls. This may be explained by tubular damage or by the fact that 10/12 patients in the AKI group were treated with furosemide, which will increase fractional sodium excretion (9, 19). The use of furosemide in the majority of patients may also explain why urine flow was similar in the two groups. Furosemide also decreases RVO_2 in uncomplicated postoperative patients with no renal impairment (9, 19). Thus, despite the use of furosemide, RVO_2 was considerably elevated when related to GFR and renal sodium resorption in the AKI group. On the other hand, the dose of furosemide used

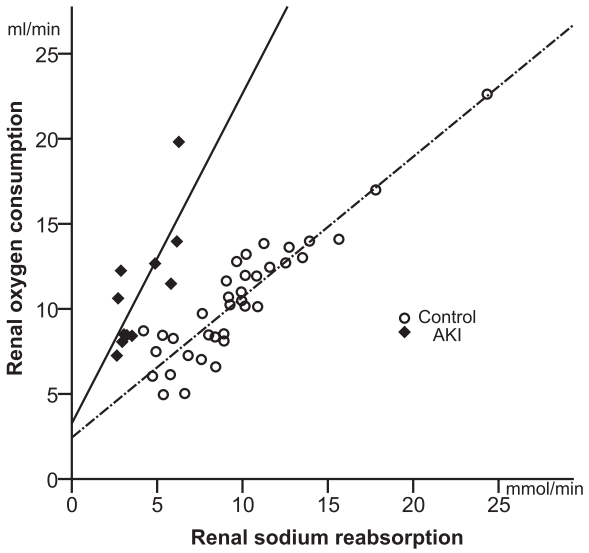

Figure 2. Shows the individual data on the relationship between renal oxygen consumption (RVO_2) and renal sodium resorption for the control group ($RVO_2 = 2.43 + 0.82 \times$ sodium resorption) and patients with acute kidney injury (*AKI*) ($RVO_2 = 3.27 + 1.94 \times$ sodium resorption). Note that the slope of the regression line was significantly ($p = .004$) higher in the AKI group compared with control, whereas the intercepts of the regression lines did not differ significantly.

did not correlate to fractional excretion of sodium, urine flow, or RVO_2.

CONCLUSIONS

In this study on hemodynamically treated high-risk patients with postoperative AKI, renal oxygenation was severely impaired. This was caused by a combination of renal vasoconstriction and a tubular sodium resorption at a high oxygen demand.

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