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RESEARCH ARTICLE | *Cardiovascular and Renal Integration*

Renal hemodynamics and oxygenation during experimental cardiopulmonary bypass in sheep under total intravenous anesthesia

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Evans RG, Iguchi N, Cochrane AD, Marino B, Hood SG, Bellomo R, McCall PR, May CN, Lankadeva YR. Renal hemodynamics and oxygenation during experimental cardiopulmonary bypass in sheep under total intravenous anesthesia. *Am J Physiol Regul Integr Comp Physiol* 318: R206–R213, 2020. First published December 11, 2019; doi:10.1152/ajpregu.00290.2019.—Renal medullary hypoxia may contribute to the pathophysiology of acute kidney injury, including that associated with cardiac surgery requiring cardiopulmonary bypass (CPB). When performed under volatile (isoflurane) anesthesia in sheep, CPB causes renal medullary hypoxia. There is evidence that total intravenous anesthesia (TIVA) may preserve renal perfusion and renal oxygen delivery better than volatile anesthesia. Therefore, we assessed the effects of CPB on renal perfusion and oxygenation in sheep under propofol/fentanyl-based TIVA. Sheep (n = 5) were chronically instrumented for measurement of whole renal blood flow and cortical and medullary perfusion and oxygenation. Five days later, these variables were monitored under TIVA using propofol and fentanyl and then on CPB at a pump flow of 80 mL·kg^{-1}·min^{-1} and target mean arterial pressure of 70 mmHg. Under anesthesia, before CPB, renal blood flow was preserved under TIVA (mean difference ± SD from conscious state: −16 ± 14%). However, during CPB renal blood flow was reduced (−55 ± 13%) and renal medullary tissue became hypoxic (−20 ± 13 mmHg versus conscious sheep). We conclude that renal perfusion and medullary oxygenation are well preserved during TIVA before CPB. However, CPB under TIVA leads to renal medullary hypoxia, of a similar magnitude to that we observed previously under volatile (isoflurane) anesthesia. Thus use of propofol/fentanyl-based TIVA may not be a useful strategy to avoid renal medullary hypoxia during CPB.

acute kidney injury; cardiac surgery; hypoxia; renal circulation

INTRODUCTION

Acute kidney injury (AKI) is a common postoperative complication of cardiac surgery requiring cardiopulmonary bypass (CPB), with an estimated global incidence of 20–30% (11). Hypoxia in the renal medulla has been proposed as a critical pathophysiological event in AKI of diverse etiology (27), including that which occurs after cardiac surgery (6). Renal medullary hypoxia during experimental CPB has previously been observed in rats (4) and in a pilot study in pigs (32). We recently demonstrated the development of medullary hypoxia in a clinically relevant ovine model of CPB when volatile anesthesia (VA) with isoflurane was used (16). However, choice of anesthetic regimen may have important implications for renal hemodynamics and oxygenation during surgery and thus risk of postoperative AKI (22, 23). Indeed, recent experimental evidence indicates that total intravenous anesthesia (TIVA) with propofol and fentanyl better preserves renal perfusion, and thus renal oxygen delivery (D_{O_2}), than volatile anesthesia (VA) with isoflurane (12). Therefore, in the current study we aimed to assess whole kidney and regional renal hemodynamics and oxygenation in an ovine model of CPB, under identical experimental conditions as our previous study using VA (16) but instead using TIVA. Thus we tested the hypothesis that kidney hypoperfusion and hypoxia during CPB can be ameliorated by use of propofol/fentanyl-based TIVA rather than isoflurane-based VA.

METHODS

Ethics. These experimental studies received prior approval from the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health under guidelines of the National Health and Medical Research Council of Australia. For the current study of the effects of TIVA and CPB, five Merino ewes (35–43 kg body wt) were studied. The sample size was based on our recent findings in sheep during CPB under VA with isoflurane, showing that biologically significant changes in renal oxygen consumption ($\dot{V}_{O_2}$) could be detected with n = 5 (16). We chose renal $\dot{V}_{O_2}$ for our power calculation because it is derived from six individual measurements [blood hemoglobin concentration, renal blood flow (RBF), and arterial and renal venous blood P_{O_2} and saturation], and so is attended by considerable random variation. In that previous study, the renal venous catheter, required for measurement of renal venous oxygen content and thus renal $\dot{V}_{O_2}$, remained patent in only 5 of 12 sheep we studied. In our current experiment the renal venous catheter remained patent in all five sheep, so the experiment was terminated once these five animals had been studied. Other than the anesthetic regimen, the conditions for this experiment were identical to those of our previous study performed under VA with isoflurane (16). All studies fulfilled the Animal Research: Reporting of In Vivo Experiments (ARRIVE) criteria.

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Before experimentation, sheep were housed in individual metabolic cages with free access to water and 800 g of oaten chaff daily.

Surgical preparation. Sheep underwent preliminary surgery under general anesthesia, induced with sodium thiopental (15 mg/kg; Jurox, Rutherford, Australia) and maintained with isoflurane (2.0–2.5%; Isoflo, Zoetis, Rhodes, Australia). Via a left retroperitoneal approach, a transit-time flow probe was placed around the renal artery, a catheter was inserted in the renal vein, and fiber-optic probes (CP-026-001; Oxford Optronix, Abingdon, UK) were implanted in the renal cortex and medulla for measurement of tissue oxygen tension (P_{O_2}), tissue perfusion, and tissue temperature (2). The carotid artery and jugular vein were cannulated, and a bladder catheter (Foley size 14 French, 30 mL; Euromedical, Malaysia) was inserted. Flunixin meglumine (50 mg; Norbrook, Tullamarine, Australia) and procaine penicillin (900 mg; Ilium, Troy Laboratories, Glendinning, Australia) were administered just before surgery and then 24 and 48 h postoperatively. The experiment was then performed 5 days later. For a detailed description of this experimental model, see Refs. 2, 17. Each sheep received an infusion of compound sodium lactate (1 $mL \cdot kg^{-1} \cdot h^{-}1$, Baxter, Old Toongabbie, NSW, Australia) given intravenously from 6.00 PM the night before the experiment until induction of anesthesia on the day of the experiment. None of the sheep showed signs of systemic infection, inflammation, or other illness on the day of the experiment.

Experimental measurements. Analog signals of arterial pressure [AP, mmHg; averaged over each experimental period to derive mean AP (MAP)], RBF (mL/min), and cortical and medullary perfusion (arbitrary units), tissue P_{O_2} (mmHg), and temperature (°C) were digitized as previously described (2). Samples of arterial, mixed venous, and renal venous blood were collected, at the midpoint of each experimental period, for oximetry and blood chemistry (ABL Systems 625, Copenhagen, Denmark). Urine flow during each experimental period was measured volumetrically. Concentrations of creatinine and sodium were measured in arterial plasma and urine using standard assays in a hospital pathology laboratory.

Experimental protocol. For the first experimental period (30 min), each animal was studied while conscious and unrestrained in its home cage. Anesthesia was then induced with propofol (5 mg/kg in 0.5 mL/kg; AFT Pharmaceuticals, Burwood, NSW, Australia) and fentanyl (2.5 μg/kg in 50 μL/kg; Hameln Pharmaceuticals, Hameln, Germany). After endotracheal intubation and commencement of artificial ventilation ($F_{I_{O_2}} = 60\%$), continuous infusions of propofol (40 $mg \cdot kg^{-1} \cdot h^{-1}$; 4 $mL \cdot kg^{-1} \cdot h^{-1}$) and fentanyl (5 $\mu g \cdot kg^{-1} \cdot h^{-1}$; 100 $\mu L \cdot kg^{-1} \cdot h^{-1}$) commenced, which continued for the duration of the experiment. Once anesthesia was established, each sheep received 10 mL/kg of compound sodium lactate over a 20-min period and then 2 $mL \cdot kg^{-1} \cdot h^{-1}$ throughout the experiment. Once MAP and RBF were stable, the second (20 min) experimental period began (anesthetized).

CPB was then established (details below) at a flow rate of 80 $mL \cdot kg^{-1} \cdot min^{-1}$. This is equivalent to 3.16 $L \cdot min^{-1} \cdot m^{-2}$ in an adult human and is the same flow rate used in our previous study under isoflurane-based VA (16). This pump flow rate is considerably greater than standard practice for normothermic CPB (2.2–2.5 $min^{-1} \cdot m^{-2}$) at our associated clinical service (36) and internationally (24). Thus it would be considered more than adequate in a clinical setting. If required, metaraminol (10 mg/mL, diluted to 0.5 mg/mL. Montrose Life Sciences, NSW, Australia) was given intravenously in boluses of ~0.1 mg to maintain a target MAP of 70 mmHg (65–75 mmHg). This vasopressor and its mode of administration, as well as the target arterial pressure of 70 mmHg, were chosen to mimic standard clinical practice at our associated clinical center (36). Once MAP and RBF were stable, the third (20 min) experimental period began (on bypass).

Neuromuscular blockade was not used. Depth of anesthesia, as determined by muscular relaxation, the absence of a swallowing reflex, toleration of mechanical ventilation, and the absence of withdrawal or corneal reflexes, was adequate. Additional doses of propofol and fentanyl were given at the discretion of the anesthetist. For example, additional doses of propofol (2.5 mg/kg) and fentanyl (7.5 μg/kg) were given just before the first skin incision for establishing CPB.

Cardiopulmonary bypass. An incision was made on the right-hand side above the fourth rib, the periosteum was opened, and the rib was removed. Heparin (300 IU/kg, heparin Injection, Pfizer, NSW, Australia) was administered before CPB. An elongated one-piece arterial cannula (22 or 24 French, EOPA77424, Medtronic, MN) and a single stage venous cannula (32 French, DPL66132, Medtronic) were deployed, along with a left ventricular drainage vent.

The perfusion circuit was primed with 300–500 mL blood from a donor animal, 1 g cefazolin (AFT Pharmaceuticals, NSW, Australia), 50 mL mannitol (20% wt/vol Osmitrol, Baxter, NSW, Australia), and 10,000 IU heparin, with the volume made up to 1.3 liters with compound sodium lactate. A tubing pack specifically designed for sheep was employed (cat no. 06634900, LivaNova, Dandenong, Victoria, Australia). CPB was initiated at a nonpulsatile flow of 80 $mL \cdot kg^{-1} \cdot min^{-1}$ using a Stockert SIII heart-lung machine and a hollow fiber membrane oxygenator with integrated arterial filter (Sorin 6F, LivaNova). Once CPB was established, the heart was fibrillated with a 9-V DC pulse across the ventricle. Target body temperature was set at 36°C using a cooler/heater (Hemotherm, Cincinatti Subzero, Cincinatti, OH). Gas flow through the oxygenator was 800 mL/min (50:50 air and oxygen), achieving an arterial P_{O_2} of 250 mmHg or more, as is standard practice in our associated clinical center (36). This gas flow rate also promotes hypercapnia during CPB (arterial $P_{CO_2} = 50.9 \pm 4.6$ mmHg), promoting renal vasodilatation and so optimizing renal perfusion and thus oxygenation (5).

At the completion of the experimental protocol, sheep were killed with an intravenous overdose of sodium pentobarbital (100 mg/kg, Lethobarb, Virbac, Wetherill Park, Australia).

Statistical analysis. Data are expressed as between-sheep means ± SD. They were subjected to repeated measures ANOVA with a Greenhouse-Geisser correction (21). Within-subject pairwise comparisons were assessed using Tukey's test (34). Analyses were performed using SYSTAT (Version 13, Systat, San Jose, CA). Two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

Variables in conscious sheep. In conscious sheep, all systemic and renal hemodynamic variables (Table 1 and Fig. 1) and variables related to systemic and renal oxygenation (Tables 2 and 3 and Figs. 1 and 2) were similar to those observed in conscious sheep in our previous study of renal oxygenation during CPB in sheep under VA (16). Core body temperature of conscious sheep (39.1 ± 0.2°C) was similar to that observed previously by ourselves (16) and others (13).

Effects of anesthesia before initiation of cardiopulmonary bypass. Under propofol/fentanyl anesthesia (TIVA), core body temperature fell by 1.0 ± 0.2°C during the 30–60 min required to achieve stable anesthesia, to 38.1 ± 0.2°C ($P_{Tukey} < 0.001$). Neither MAP nor RBF differed significantly from that in conscious sheep ($P_{Tukey} \geq 0.084$; Fig. 1). Renal D_{O_2} was reduced by 34 ± 13% ($P_{Tukey} = 0.001$; Fig. 2), due mainly to reduced arterial blood oxygen concentration (−22 ± 5%; $P_{Tukey} = 0.001$), secondary to reduced arterial hemoglobin concentration (−26 ± 5%; $P_{Tukey} = 0.001$), in association with volume loading given after induction of anesthesia (Table 2). Renal $\dot{V}_{O_2}$ was also reduced under TIVA (−25 ± 15%; $P_{Tukey} = 0.011$; Fig. 2), despite the absence of significant changes in creatinine clearance or calculated sodium reabsorption ($P_{Tukey} \geq 0.357$; Table 1). Thus renal fractional oxygen extraction was similar to that in the conscious sheep ($P_{Tukey} = 0.818$), despite the fact that whole body fractional

Table 1. *Renal hemodynamics, oxygenation and function*

Variable	*n*	Conscious	Anesthetized	On Bypass	P_{Time}
Renal vascular conductance, $\mu L \cdot kg^{-1} \cdot min^{-1} \cdot mmHg^{-1}$	5	66.7 ± 6.1	61.0 ± 15.7	37.8 ± 12.3**†	0.014
Cortical perfusion, units	4	2,199 ± 916	2,921 ± 821	1,407 ± 719†	0.053
Medullary perfusion, units	4	1,658 ± 1168	1,856 ± 987	585 ± 369	0.168
Urine flow, $\mu L \cdot kg^{-1} \cdot min^{-1}$	5	33.0 ± 21.8	33.2 ± 40.4	19.2 ± 12.8	0.599
Sodium excretion, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	5	4.36 ± 4.24	2.92 ± 2.74	1.30 ± 1.10	0.359
CrCl, $mL \cdot kg^{-1} \cdot min^{-1}$	5	2.19 ± 1.10	2.08 ± 1.71	1.14 ± 1.22	0.350
T_{Na}^{+}, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	5	308 ± 155	291 ± 237	155 ± 167	0.328
Fraction excretion of sodium, %	5	1.22 ± 0.82	1.45 ± 1.13	1.19 ± 0.59	0.739
T_{Na}^{+}/renal $\dot{V}O_2$, mol/mol	5	87.5 ± 49.9	115.7 ± 111.6	77.2 ± 82.2	0.637

Data are expressed as means ± SD. Renal vascular conductance is renal blood flow divided by the product of body weight and mean arterial pressure. Creatinine clearance (CrCl) is the product of urine flow and urinary creatinine concentration divided by plasma creatinine concentration. Sodium reabsorption (T_{Na}^{+}) is the product of CrCl and plasma sodium concentration minus sodium excretion. *P* values are the outcomes of repeated measures ANOVA for the main effect of "time." $^{**}P \leq 0.01$, for within-group comparison with the conscious state (Tukey's test). †$P \leq 0.05$, for within-group comparison of bypass with the anesthetized state (Tukey's test).

oxygen extraction fell from 37.8 ± 3.6% to 19.3 ± 5.2% ($P_{Tukey} = 0.001$; Fig. 2).

Neither renal cortical nor medullary perfusion were significantly affected by TIVA ($P_{Tukey} \geq 0.230$; Table 1). Cortical tissue P_{O_2} increased markedly (by 84.6 ± 45.7 mmHg; $P_{Tukey} = 0.009$), but medullary tissue P_{O_2} was not significantly altered ($P_{Tukey} = 0.996$; Fig. 1).

Effects of transition to cardiopulmonary bypass. Core body temperature was intentionally reduced to 36.5 ± 0.1°C on bypass, consistent with the reduction in core temperature of 2–3°C employed during coronary artery bypass graft and valve procedures performed at our associated clinical center (36). At a pump flow of 80 $mL \cdot kg^{-1} \cdot min^{-1}$ and target arterial pressure of 70 mmHg (72.7 ± 7.9 mmHg achieved), systemic vascular conductance was 1.11 ± 0.13 $mL \cdot kg^{-1} \cdot min^{-1} \cdot mmHg^{-1}$, systemic D_{O_2} was 8.7 ± 0.8 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, and systemic $\dot{V}O_2$ was 2.98 ± 0.23 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. Thus systemic fractional oxygen extraction increased to 34.7 ± 5.6% ($P_{Tukey} = 0.003$ for comparison with the anesthetized state), similar to the value when sheep were conscious ($P_{Tukey} = 0.606$; Fig. 2). By deploying a relatively low gas flow through the oxygenator, the sheep were rendered hypercapnic during CPB (Table 2). The hypercapnia, along with the small increase in plasma lactate concentration during CPB (by 1.38 ± 0.52 mM compared with the anesthetized state; $P_{Tukey} = 0.001$), likely explains the fall in arterial pH during CPB (by 0.20 ± 0.03 pH units compared with the anesthetized state; $P_{Tukey} < 0.001$; Table 2).

During CPB there were reductions in MAP (−19.9 ± 9.4 mmHg; $P_{Tukey} = 0.012$; Fig. 1), RBF (−55 ± 13%; $P_{Tukey} < 0.001$), renal vascular conductance (−43 ± 7%; $P_{Tukey} = 0.005$), renal D_{O_2} (−65 ± 12%; $P_{Tukey} < 0.001$), and renal $\dot{V}O_2$ (−42 ± 16%; ($P_{Tukey} < 0.001$), compared with conscious sheep (Table 1 and Figs. 1 and 2). The renal fractional extraction of oxygen was significantly greater on CPB than in both the conscious state ($P_{Tukey} = 0.017$) and under TIVA before CPB ($P_{Tukey} = 0.041$) (Fig. 2). In all four sheep with working cortical laser Doppler probes, there were decreases in cortical perfusion (−51 ± 22% versus anesthetized; $P_{Tukey} = 0.019$) and medullary perfusion (−58 ± 36%). However, the apparent change in medullary perfusion was not statistically significant (Table 1). Cortical tissue P_{O_2} fell during CPB ($P_{Tukey} = 0.028$) but did not differ significantly from its level in conscious sheep ($P_{Tukey} = 0.713$) (Fig. 1). Medullary tissue P_{O_2} during CPB was 10.2 ± 13.4 mmHg, 19.1 ± 11.6 mmHg less than under TIVA alone ($P_{Tukey} = 0.011$) and 19.5 ± 13.5 mmHg less than in the conscious sheep ($P_{Tukey} = 0.010$).

Metaraminol was required to achieve the target MAP during the experimental period on CPB in two of the five sheep, at total doses of 1.2 and 0.8 mg (12 and 8 boluses, respectively). Each bolus of metaraminol was accompanied by an increase in MAP of 5–20 mmHg, which was sustained for 2–5 min, with transient mild renal vasoconstriction followed by a rapid return of RBF to levels at or greater than pretreatment levels. These observations are consistent with our previous observation of selective vasoconstriction in extrarenal vascular beds during infusion of metaraminol in sheep during CPB (16).

DISCUSSION

In a model of ovine experimental CPB performed under propofol/fentanyl-based TIVA, the renal medulla became hypoxic. Critically, the effects of CPB on renal oxygenation in sheep during TIVA were very similar to those we observed previously in sheep under VA with isoflurane (16). In both cases, we found RBF and renal D_{O_2} to be markedly reduced during CPB, even though systemic oxygen extraction was similar to that in the conscious sheep. Thus our current findings provide no support for the proposition that renal medullary oxygenation is better preserved during CPB under propofol/fentanyl based TIVA than isoflurane-based VA. Indeed, they indicate that the kidney, particularly the renal medulla, is susceptible to hypoxia during CPB.

The major impetus for our current study was the recent findings from a direct comparison of the effects on renal oxygenation of propofol/fentanyl-based TIVA and isoflurane-based VA in healthy sheep during abdominal surgery (12). In that study, systemic hemodynamics were similar under the two anesthetic regimens, but RBF, renal vascular conductance, renal D_{O_2}, and cortical and medullary perfusion were greater under TIVA than VA. This difference could at least in part be due to differences in renal sympathetic vasomotor drive, since renal sympathetic nerve activity was not elevated under TIVA but was increased under VA (12). Similarly, in the current study RBF was relatively well preserved under TIVA, but it fell when VA was used under the same experimental conditions (16). However, TIVA was still associated with reduced renal D_{O_2}. This can be explained by volume loading after induction of anesthesia, resulting in dilutional anemia, and thus

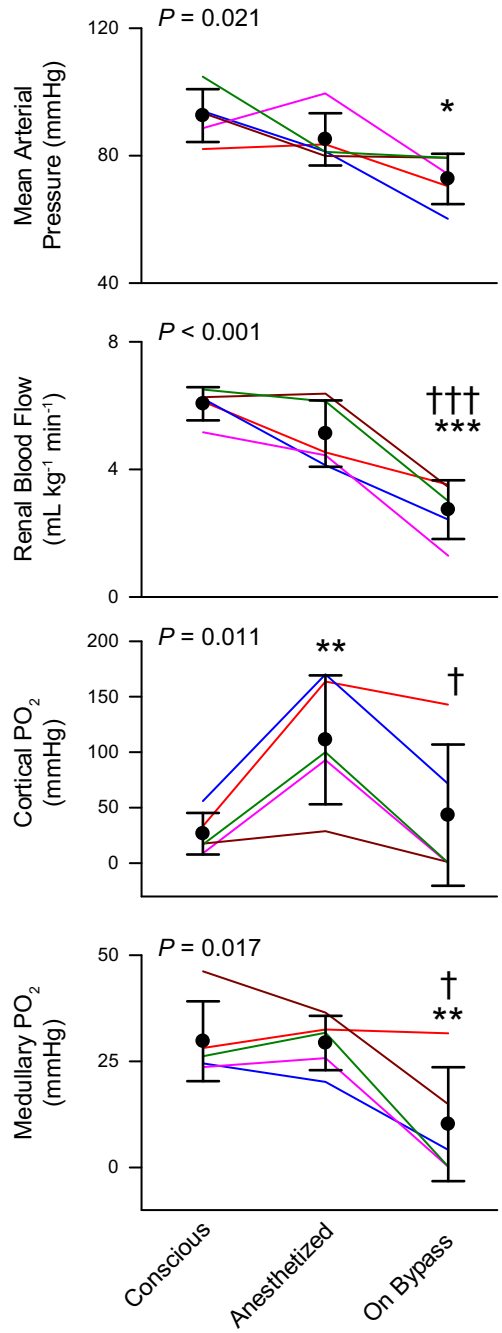

Fig. 1. Renal hemodynamics and renal tissue oxygen tension. Black circles and error bars represent the means ± SD of each variable across each of the 3 experimental periods (n = 5 for all variables). Colored lines show data for individual animals. P values were derived repeated measures ANOVA. *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, for comparison with "Conscious"; †$P \leq 0.05$, †††$P \leq 0.001$, for comparison of "On Bypass" with "Anesthetized" (Tukey's test).

reduced arterial oxygen concentration, despite markedly increased arterial P_{O_2} at an $F_{I_{O_2}}$ of 0.6. Nevertheless, renal cortical and medullary tissue P_{O_2} was well maintained under both TIVA (current study) and VA (16), presumably as a result of the hyperoxemic experimental conditions. Indeed, at an $F_{I_{O_2}}$ of 0.6, cortical P_{O_2} under TIVA was greater than its level in the conscious animal breathing room air. A similar trend was observed under VA, although this apparent effect was not statistically significant (P_{Tukey} = 0.06) (16). Thus, in the absence of the challenge of CPB, RBF is better preserved in sheep under propofol/fentanyl-based TIVA than isoflurane-based VA, but in both cases renal tissue hypoxia can be averted by hyperoxemia.

Renal medullary hypoxia during CPB was accompanied by reduced RBF and moderate hemodilution, so reduced renal D_{O_2}, both in sheep under TIVA (current study) and in sheep under VA (16). Oxygenation of the renal medulla during CPB appears to be strongly dependent on renal D_{O_2} (16). In our previous study using VA, when we progressively increased renal D_{O_2} by altering pump flow (from 60, to 80, to 100 $mL \cdot kg^{-1} \cdot min^{-1}$), or increasing arterial pressure (from ~65 to ~90 mmHg) with the vasopressor metaraminol, renal medullary tissue P_{O_2} increased (16). Thus renal medullary hypoxia during CPB in our ovine model appears to be attributable to an altered balance between renal oxygen supply and demand. In this respect, it is notable that in the current study systemic fractional oxygen extraction during CPB was similar to that in conscious sheep, but renal fractional oxygen extraction was markedly increased. A similar observation has recently been made in human patients during CPB (19). Thus our findings add to the growing evidence from experimental models of CPB (16), computational models of CPB (20, 29, 30), and observations from human patients undergoing CPB (18, 19), indicating that standard perfusion conditions deployed during CPB in clinical practice do not adequately protect the kidney, and in particular the renal medulla, from hypoxia. This concept is also consistent with indirect evidence of renal medullary hypoxia during CPB in human patients, obtained through measurement of urinary P_{O_2} (25, 36). The presence of renal hypoxia during CPB is also supported by the observation of elevated plasma erythropoietin concentration in patients on admission to the intensive care unit after cardiac surgery requiring CPB (9).

The major strength of our study was the use of a large animal model of CPB in which we can both closely mimic clinical practice and quantify global and regional renal hemodynamics and oxygenation. We chose perfusion conditions that would be considered more than adequate in adult cardiac surgery (see METHODS). The adequacy of systemic oxygenation is evidenced by the fact that systemic oxygen extraction during CPB was similar to that in conscious sheep. Arterial lactate concentration did increase modestly during CPB, as is observed in human patients during CPB (10, 31, 33). This increase in lactate concentration is likely due, at least in part, to the use of compound sodium lactate as the major component of the solution used for priming the CPB circuit (10). We should also emphasize that the hypercapnia and consequent mild acidosis experienced by the sheep we studied during CPB are not signs of inadequate systemic circulatory function. Rather, they were deliberately induced, through use of a relatively low gas flow through the oxygenator, to promote renal vasodilatation and thus renal oxygenation. However, despite apparently adequate systemic oxygenation, renal medullary hypoxia developed during CPB. This regional hypoxia was not reflected in measures of whole body oxygenation, so would not be detected by standard intraoperative monitoring systems used the clinical situation, such as in-line monitoring of arterial and venous blood gases, and thus whole body D_{O_2} and $\dot{V}_{O_2}$. Thus there is a need for development of methods to monitor renal oxygen-

Table 2. *Arterial blood oximetry and chemistry*

Variable	Conscious	Anesthetized	On Bypass	P_{Time}
P_{O_2}, mmHg	92.9 ± 9.2	278.5 ± 46.4***	270.9 ± 44.9***	<0.001
S_{O_2}, %	96.6 ± 0.7	99.2 ± 0.4***	98.6 ± 0.5***	<0.001
Hb, g/dL	9.96 ± 0.24	7.63 ± 0.53***	7.58 ± 0.70***††	<0.001
Oxygen content, mL O_2/dL	13.90 ± 0.61	10.88 ± 0.80***	10.85 ± 1.01***	0.005
P_{CO_2}, mmHg	35.1 ± 1.3	32.1 ± 2.3	50.9 ± 4.6***†††	<0.001
pH	7.50 ± 0.04	7.55 ± 0.04*	7.35 ± 0.02***†††	<0.001
Lactate, mM	0.47 ± 0.23	1.10 ± 0.33	2.48 ± 0.76***†††	0.002
Sodium, mM	138.8 ± 5.4	134.0 ± 5.7	135.8 ± 1.1	0.313
Potassium, mM	3.91 ± 0.09	3.06 ± 0.19***	3.02 ± 0.25***	<0.001
Chloride, mM	103.5 ± 5.9	102.0 ± 6.2	102.2 ± 2.7	0.771
Calcium, mM	1.11 ± 0.10	1.03 ± 0.07	1.13 ± 0.03	0.236
Bicarbonate, mM	27.3 ± 2.0	28.0 ± 2.4	27.6 ± 2.3	0.397
Base-excess, mM	4.45 ± 1.92	5.42 ± 2.59	2.28 ± 2.15**†††	0.002

Data are expressed as means ± SD; $n = 5$ for all variables. Hb, hemoglobin; P_{O_2}, oxygen tension; P_{CO_2}, partial pressure of carbon dioxide; S_{O_2}, saturation of hemoglobin with oxygen. Blood oxygen content was calculated as $(0.0139 \times [Hb] \times S_{O_2}) + (0.003 \times P_{O_2})$. *P* values are the outcomes of repeated measures analysis of variance for the main effect of "time." *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ for within-group comparison with the conscious state (Tukey's test). ††$P \leq 0.01$, †††$P \leq 0.001$, for within-group comparison of bypass with the anesthetized state (Tukey's test).

ation in patients undergoing major surgery requiring CPB. Candidate methods include continuous measurement of urinary oxygen tension (7, 14, 25, 36) and use of near infrared spectroscopy (3).

The fact that we studied young and otherwise healthy animals is both a strength and a weakness. It is a strength because we would expect the kidneys of elderly patients with multiple comorbidities to be even more susceptible to hypoxia than those of young healthy sheep. Nevertheless, care should be taken in extrapolating our findings to the general population of older patients who undergo cardiac surgery. Other limitations of our study should be acknowledged. First, we relied to an extent on a historical comparison between the current study using TIVA and our previous study using VA (16). These two studies were conducted in the same laboratory, by the same personnel, and apart from the difference in anesthetic regimen, with an identical protocol. Nevertheless, these studies were conducted sequentially rather than in parallel and without randomization of the anesthetic regimens or blinding of the outcome assessors. Thus direct comparison of these data sets using tests of statistical significance would not be valid. Second, the volume of fluid in which the TIVA was administered was an important difference between the two anesthetic regimens. Across the period from induction of anesthesia to the end of CPB (~150 min), we estimate that a 40-kg sheep anesthetized with TIVA would have received ~410 mL more fluid than a sheep of the same weight anesthetized with VA, in the form of the vehicles for the anesthetic agents. This may account for the 15% lesser arterial hemoglobin concentration and 16% lesser arterial oxygen concentration during CPB on TIVA (current study) compared with VA (16), resulting in a 16% lesser systemic D_{O_2} during CPB at a flow rate of 80 $mL \cdot kg^{-1} \cdot min^{-1}$. Although in clinical practice a higher fluid volume would be given during TIVA than during VA, a direct comparison of these two anesthetic regimens should include stringent control of fluid input. Nevertheless, renal medullary hypoxia was observed during CPB under TIVA despite a pump flow equivalent to 3.16 $L \cdot min^{-1} \cdot m^{-2}$ in an adult human (16), considerably greater than standard practice for normothermic

Table 3. *Venous blood oximetry and chemistry*

Variable	Conscious	Anesthetized	On Bypass	P_{Time}
Mixed venous blood				
P_{O_2}, mmHg	39.6 ± 4.3	58.7 ± 9.7***	50.5 ± 6.2*	0.012
S_{O_2}, %	60.5 ± 3.7	85.0 ± 6.1***	68.2 ± 5.9††	0.002
Hb, g/dL	10.16 ± 0.67	7.16 ± 0.69***	7.32 ± 0.99**	0.006
Oxygen content, mL O_2/dL	8.65 ± 0.83	8.77 ± 0.66	7.13 ± 1.19	0.115
P_{CO_2}, mmHg	41.2 ± 1.7	35.9 ± 2.5	55.3 ± 4.2***†††	<0.001
pH	7.47 ± 0.05	7.50 ± 0.04	7.32 ± 0.02***†††	<0.001
Lactate, mM	0.48 ± 0.27	1.14 ± 0.30	3.28 ± 1.58**††	0.014
Renal venous blood				
P_{O_2}, mmHg	59.7 ± 5.9	76.1 ± 3.1	73.2 ± 15.4	0.115
S_{O_2}, %	87.9 ± 1.5	93.7 ± 1.6	86.6 ± 6.8†	0.082
Hb, g/dL	10.30 ± 0.64	7.34 ± 0.75***	7.08 ± 0.87***	0.002
Oxygen content, mL O_2/dL	12.57 ± 0.56	9.71 ± 0.74**	9.05 ± 1.29***	0.006
P_{CO_2}, mmHg	33.4 ± 4.4	34.1 ± 3.2	51.6 ± 6.3***†††	<0.001
pH	7.52 ± 0.02	7.53 ± 0.04	7.35 ± 0.02***†††	0.001
Lactate, mM	0.46 ± 0.30	1.12 ± 0.33	2.43 ± 0.77***††	0.011

Data are expressed as means ± SD; $n = 5$ for all variables. Hb, hemoglobin; P_{O_2}, oxygen tension; P_{CO_2}, partial pressure of carbon dioxide; S_{O_2}, saturation of hemoglobin with oxygen. Blood oxygen content was calculated as $(0.0139 \times [Hb] \times S_{O_2}) + (0.003 \times P_{O_2})$. *P* values are the outcomes of repeated measures ANOVA for the main effect of "time." *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ for within-group comparison with the conscious state (Tukey's test). †$P \leq 0.05$, ††$P \leq 0.01$, †††$P \leq 0.001$, for within-group comparison of bypass with the anesthetized state (Tukey's test).

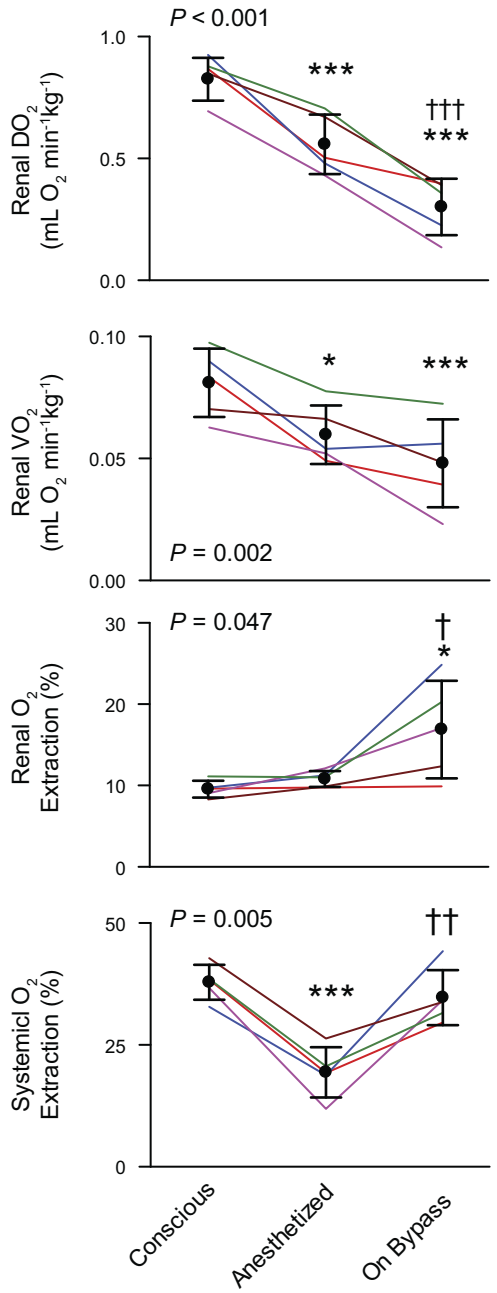

Fig. 2. Whole kidney and systemic oxygenation. Black circles and error bars represent the means ± SD of each variable across each of the 3 experimental periods (n = 5 for all variables). Colored lines show data for individual animals. P values were derived repeated measures ANOVA. *$P \leq 0.05$, ***$P \leq 0.001$, for comparison with "Conscious"; †$P \leq 0.05$, ††$P \leq 0.01$, †††$P \leq 0.001$, for comparison of "On Bypass" with "Anesthetized" (Tukey's test).

CPB (2.2–2.5 $min^{-1} \cdot m^{-2}$) at our associated clinical service (36) and internationally (24).

We are also unable to provide significant insights into the mechanisms underlying the renal vasoconstriction observed during CPB. Increased circulating concentrations of neurohormonal factors such as epinephrine, norepinephrine, arginine vasopressin, and angiotensin II likely make a significant contribution (26). Loss of renal autoregulation during nonpulsatile CPB in a state of hemodilution likely also contributes. Hemodilution, on its own, is known to blunt renal autoregulation (8). Furthermore, renal autoregulation appears to be blunted in humans during CPB (1). Our use of metaraminol to meet target MAP during CPB in two of the sheep may also have contributed to the observed vasoconstriction, although this is unlikely to have had a major impact, since this vasoconstrictor appears to have selectivity toward extrarenal vascular beds (16). We also must acknowledge the possibility that our failure to detect a significant reduction in medullary perfusion during CPB could be a type 2 statistical error. In one sheep, the laser Doppler probe in the renal cortex was dysfunctional, while in another sheep, the probe in the renal medulla was dysfunctional. Both cortical and medullary perfusion fell during CPB in all sheep with functional laser Doppler probes. However, while the apparent change in cortical perfusion was statistically significant, the apparent change in medullary perfusion was not. Finally, our current experimental protocol did not include any observations of postoperative outcome, as the sheep were humanely killed while still on CPB.

Perspectives and Significance

There is emerging evidence that renal medullary hypoxia during cardiac surgery performed on CPB is associated with development of AKI. For example, low urinary P_{O_2} during (25) or after (14) CPB, or at any time during the surgical procedure (36), was found to be associated with later development of AKI. Similarly, in both adult (3) and pediatric (28) patients, intraoperative renal hypoxia detected by near infrared spectroscopy predicted later development of AKI. Thus any refinement of protocols employed by the surgical team that could ameliorate medullary hypoxia has the potential to mitigate risk of postoperative AKI. This includes choice of anesthetic regimen.

The effects of CPB on renal oxygenation during propofol/fentanyl-based TIVA were remarkably similar to those we observed previously during isoflurane-based VA (16). Thus, regardless of the anesthetic regimen, RBF, renal vascular conductance, renal D_{O_2}, and medullary tissue P_{O_2} were reduced. Consequently, our findings provide no evidence that TIVA provides a strategy to avoid renal medullary hypoxia during CPB. This conclusion is consistent with the outcome of a recent large-scale (5,400 patients) multicenter clinical trial, which failed to detect a difference in the incidence or severity of AKI between the use of TIVA and VA for elective coronary artery bypass surgery (15). However, the results of a small-scale (112 patients), single center clinical trial provided evidence that use of propofol rather than sevoflurane might reduce the risk of AKI after valvular surgery performed on CPB (35). Thus the relative renal benefits of TIVA and VA for surgery requiring CPB merit further experimental and clinical investigation. Nevertheless, our current findings show that the renal medulla is susceptible to hypoxia during CPB under TIVA, as it is during CPB under VA. Thus TIVA may not be sufficient to avoid or attenuate renal medullary hypoxia during CPB.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.G.E., N.I., A.D.C., R.B., C.N.M., and Y.R.L. conceived and designed research; R.G.E., N.I., A.D.C., B.M., S.G.H., P.R.M., C.N.M., and Y.R.L. performed experiments; R.G.E. and S.G.H. analyzed data; R.G.E., N.I., A.D.C., R.B., C.N.M., and Y.R.L. interpreted results of experiments; R.G.E. prepared figures; R.G.E. drafted manuscript; R.G.E., N.I., A.D.C., B.M., S.G.H., R.B., C.N.M., and Y.R.L. edited and revised manuscript; R.G.E., N.I., A.D.C., B.M., S.G.H., R.B., P.R.M., C.N.M., and Y.R.L. approved final version of manuscript.

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