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Respiration and the Airway

Systemic haemodynamic, renal perfusion and renal oxygenation responses to changes in inspired oxygen fraction during total intravenous or volatile anaesthesia

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Abstract

Background: Anaesthesia-induced changes in renal perfusion are dependent on the choice of anaesthetic agent. However, the effects of varying inspired oxygen fraction (FiO_2) on renal perfusion and oxygenation during TIVA (propofol + fentanyl) or volatile anaesthesia (VA; isoflurane) are unknown.

Methods: In 16 Merino ewes, we surgically implanted a renal artery flow probe and laser-Doppler and oxygen-sensing probes in the renal medulla and cortex. We compared the systemic and renal effects of graded alterations in FiO_2 (0.21, 0.40, 0.60, and 1.0) during TIVA or VA and compared the changes with those in the non-anaesthetised state.

Results: Compared with the non-anaesthetised state, TIVA and VA decreased renal blood flow (−50% *vs* −75%), renal oxygen delivery (−50% *vs* −80%), and renal cortical (−40% *vs* −60%) and medullary perfusion (−50% *vs* −75%). At an FiO_2 of 0.21, both anaesthetic regimens induced similar reductions in cortical (−58 *vs* −65%) and medullary (−37% *vs* −38%) oxygenation. At higher concentrations of FiO_2, renal blood flow and renal tissue perfusion were not changed, but intrarenal oxygenation improved similarly under TIVA and VA. In particular, at an FiO_2 of ≥0.40 and ≤0.60, cortical and medullary oxygen tension were similar to the non-anaesthetised state.

Conclusions: Irrespective of FiO_2, TIVA decreased renal and intrarenal perfusion less than VA, but at low FiO_2 concentrations both led to equivalent reductions in renal cortical and medullary oxygenation. However, with FiO_2 between 0.40 and 0.60 during TIVA or VA, both cortical and medullary oxygenation was maintained at normal physiological levels.

Keywords: isoflurane; propofol; renal perfusion; renal oxygenation; systemic haemodynamics; TIVA; volatile anaesthesia

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Editor's key points

- The authors investigated the interaction between varying inspired oxygen fraction (FiO_2) with type of anaesthesia on renal perfusion and oxygenation in healthy sheep.
- TIVA and volatile anaesthesia had a similar impact on systemic haemodynamic parameters.
- Renal macro- and micro-haemodynamic parameters were better maintained under TIVA than under volatile anaesthesia.
- There was no cross effect of varying FiO_2 with the type of anaesthetic regime on haemodynamic parameters.
- Levels of renal cortical and medullary tissue oxygen tension were best maintained with FiO_2 between 0.40 and 0.60.

Acute kidney injury (AKI) can occur in 5%–13% of patients undergoing major abdominal surgery.[1,2] Development of postoperative AKI is associated with an increased short-term risk of in-hospital mortality and carries a long-term risk of chronic kidney disease.[3,4] Perioperative derangements in renal perfusion and oxygenation are likely to play a critical role in the pathogenesis of postoperative AKI.[3–5]

We recently reported that volatile anaesthesia (VA) reduces renal blood flow (RBF) and intrarenal perfusion to a greater extent than total intravenous anaesthesia (TIVA).[6,7] Adequate oxygen delivery to the kidneys is determined not just by arterial partial pressure of oxygen (P_aO_2) and total RBF, but also by the distribution of such blood flow to the cortical and medullary circulations.[8] Yet, whether the different effects of TIVA and VA on global- and regional-kidney oxygenation can be modified by changes in intraoperative inspired oxygen fraction (FiO_2) is unclear. Moreover, the optimal target FiO_2 during abdominal surgery to maintain renal oxygenation within a normal, non-anaesthetised physiological range, despite the detrimental effects of TIVA and VA on renal perfusion, remains unclear.

In this experimental study using healthy adult sheep, we assessed systemic haemodynamics, RBF, renal oxygen delivery (RDO_2) and consumption (RVO_2), and renal cortical and medullary tissue perfusion and oxygen tension (PtO_2) at various concentrations of FiO_2 during TIVA or VA after major abdominal surgery. First, we compared the effects of increasing FiO_2 on renal PtO_2 during TIVA and VA. We hypothesised that increasing FiO_2 would increase PtO_2 to a greater extent with TIVA than with VA, as a result of the greater depression of renal perfusion induced by VA. Second, we determined the concentration of FiO_2, under TIVA or VA, to maintain intrarenal PtO_2 at normal, non-anaesthetised physiological levels. We hypothesised that this would be achieved with a lower concentration of FiO_2 with TIVA than with VA.

Methods

Animal preparation

The studies on healthy adult Merino ewes (1.5–2.0 year of age) were approved by the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health under guidelines laid down by the National Health and Medical Research Council of Australia. All studies performed fulfilled the Animal Research: Reporting of In Vivo Experiments criteria.[9]

Two aseptic surgical procedures were performed in 16 sheep (body weight: 37.5 [33–44] kg) under general anaesthesia. First, under general anaesthesia, induced with sodium thiopental (15 mg kg^{-1}; Jurox, Rutherford, Australia) and maintained with isoflurane (2.0–2.5%; Isoflo, Zoetis, Rhodes, Australia), a carotid arterial loop was constructed and a 20-mm transit-time probe (Transonic Systems, Ithaca, NY, USA) was implanted on the pulmonary artery.[10] Animals were allowed 3–4 weeks to recover. The day before the second surgical procedure, cannulae were inserted into the carotid arterial loop and jugular vein.

Second, sheep were randomly allocated in a 1:1 ratio to receive either isoflurane (Isoflo, Zoetis, Rhodes, Australia) or propofol (AFT Pharmaceuticals Pty. Ltd, Burwood, NSW, Australia) and fentanyl (Hameln Pharmaceuticals, Hemeln, Germany) general anaesthesia. Via a left retroperitoneal approach, a 4-mm transit-time probe (Transonic Systems) was placed on the left renal artery and the renal vein was cannulated.[10] During the same surgical procedure, fibre-optic probes (Oxford Optronix, Abingdon, UK) were inserted into the renal cortex and medulla.[10,11]

Analog signals of mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), RBF, cortical and medullary perfusion and PtO_2 were continuously recorded at 100 Hz on a computer using a CED micro 1401 interface with Spike 2 software (Cambridge Electronic Design, Cambridge, UK). Blood samples were obtained simultaneously from the carotid arterial and renal venous catheters for blood oximetry (ABL system 625; Radiometer Medical, Copenhagen, Denmark). Total peripheral conductance (TPC), stroke volume (SV), renal vascular conductance (RVC), RDO_2, RVO_2, and renal oxygen extraction ratio were calculated.[11–13] Pain was assessed by monitoring behavioural changes including lip curling, abnormal body and ear posture, bruxism, and a lack of drinking or eating. To minimise any pain during and after surgery, pre- and post-surgical analgesia was maintained with i.m. injections of flunixin meglumine (1 mg kg^{-1}; Norbrook, Tullamarine, Australia) administered at the start of surgery, and then 4 and 24 h after operation. The morning after surgery all sheep were standing, had eaten all their food and drunk, and displayed no signs of pain.

Regimens for VA and TIVA

Animals were positioned in right lateral recumbence for the entire duration of the surgical procedure and measurement periods with VA and TIVA. In the VA group (n=8), anaesthesia was induced with i.v. sodium thiopental (12.5 mg kg^{-1}) and the animals were intubated before the return of palpebral reflex. Anaesthesia was maintained with isoflurane (2.0%–2.5%) at a concentration that kept MAP at ~70 mm Hg and HR at ~90 beats min^{-1}. In the VA group, narcotic agents were not used for analgesia, so isoflurane was used at a relatively high concentration to achieve effective antinociception.[14,15] In the TIVA group (n=8), sheep received i.v. propofol 5 mg kg^{-1} and fentanyl 2.5 μg kg^{-1} for induction and the animals were intubated before the return of palpebral reflex. Anaesthesia and analgesia were maintained with continuous infusions of propofol 37.5 mg kg^{-1} h^{-1} and fentanyl 10 μg kg^{-1} h^{-1}, which maintained MAP at ~70 mm Hg and HR at ~90 beats min^{-1}. Neuromuscular block was not used in either treatment group. Depth of anaesthesia appeared similar and satisfactory in all sheep, as judged by muscular relaxation, ability to tolerate the tracheal tube without swallowing, tolerance of mechanical ventilation, immobility, and lack of corneal and withdrawal

reflexes. In all animals, surgical procedures under VA or TIVA were completed within 120–150 min at an FiO_2 of 0.60.

Experimental protocol for the variation of FiO_2

The protocol had four components, each comprising a series of 20-min periods. FiO_2 was set at 0.21 (room air: 21%), 0.40 (40%), 0.60 (60%), and 1.0 (100%), allocated using a block randomisation design. At each concentration of FiO_2, a 10-min period was allowed for kidney oxygen concentrations to stabilise, after which a 10-min experimental period began. The total gas flow on the mechanical ventilator was maintained at a constant rate of 1.5 L min^{-1}, whilst the ratio of the individual oxygen-to-air gas volumes was altered to achieve the target FiO_2.

Systemic and renal haemodynamic measurements at postoperative day 3

After 3 days of recovery from the second surgical procedure, systemic and renal variables were monitored over a 60-minute period in non-anaesthetised sheep standing in their home metabolic cage.

Statistical analysis

Variables are reported as median (25th–75th percentile [interquartile range]). All analyses were performed using GraphPad PRISM 6.0 software (San Diego, CA, USA). Statistical analysis was performed on absolute values calculated as 10-minute averages during the second half of the 20-minute measurement period, when FiO_2 was randomly set to 0.21, 0.40, 0.60, and 1.0 during VA or TIVA. Variables in non-anaesthetised animals on postoperative Day 3 were calculated as 60-minute averages. Data generated during changes in FiO_2 were analysed using repeated measures analysis of variance (ANOVA) with factors group (P_{Group}: VA or TIVA), treatment (P_{FiO2}) and their interaction ($P_{GroupxFiO2}$). The Wilcoxon signed rank test was used for within-group comparisons of the variables during anaesthesia with the levels in non-anaesthetised sheep. The Mann–Whitney *U*-test was used to assess differences in postoperative Day 3 variables between the VA and TIVA groups. Two-sided $P \leq 0.05$ was considered statistically significant.

Results

Arterial blood gases and lactate

Graded increases in FiO_2 resulted in increases in the arterial partial pressure of oxygen (P_aO_2) that were similar during VA and TIVA ($P_{Group} \geq 0.05$; Fig. 1). When breathing room air (FiO_2 0.21) the P_aO_2 was significantly lower during TIVA and VA (~57 mm Hg) than in the non-anaesthetised state (~95 and ~94 mm Hg, respectively) (Tables 1 and 2). At all other concentrations of FiO_2 (0.4–1.0), P_aO_2 was significantly greater than in non-anaesthetised animals (Fig. 1). Graded increases in FiO_2 did not significantly influence arterial partial pressure of carbon dioxide (P_aCO_2), haemoglobin, or lactate concentrations (Tables 1 and 2). However, compared with the non-anaesthetised state, at all concentrations of FiO_2, during both TIVA and VA, P_aCO_2 and lactate concentrations were elevated, but haemoglobin was not (Tables 1 and 2).

Systemic haemodynamics

MAP, HR, CO, SV, and TPC were similar during TIVA and VA across all concentrations of FiO_2 (Fig. 1). There was a modest but significant increase in MAP when increasing FiO_2 from 0.21 to 0.60 during VA and TIVA, but no significant changes in CO, HR, SV, and TPC (Fig. 1).

Compared with the non-anaesthetised state, at all concentrations of FiO_2, during TIVA and VA, MAP (~18%), CO (~30%), and SV (~35%) were significantly reduced (all $P \leq 0.05$), but HR and TPC were unchanged (Tables 1 and 2).

Renal blood flow and renal oxygen handling

Compared with the non-anaesthetised state, there were large reductions in RBF and RVC during TIVA and VA at all FiO_2 concentrations (Tables 1 and 2). RBF (~58 *vs* ~130 ml min^{-1}) and RVC (~0.8 *vs* ~1.6 ml min^{-1} mm Hg^{-1}) declined more with VA than with TIVA, respectively (both $P_{Group}<0.01$; Fig. 2). Similarly, RDO_2 was significantly less during VA than TIVA (~7 *vs* ~17 ml O_2 min^{-1}; $P_{Group}=0.01$). With both anaesthetic regimens RDO_2 was significantly reduced compared with the non-anaesthetised state (Tables 1 and 2). However, renal oxygen extraction ratio was higher during VA than with TIVA ($P_{Group}=0.001$) (Tables 1 and 2).

Alterations in FiO_2 did not significantly change RBF or RVC during TIVA or VA (Fig. 2). However, increases in FiO_2 up to 0.60 caused progressive increases in RDO_2, although the levels were still significantly below those the non-anaesthetised state (Tables 1 and 2). In contrast, with both TIVA and VA there were similar reductions in RVO_2 and renal oxygen extraction ratio as FiO_2 was increased from 0.21–1.0 (both $P_{FiO2}<0.001$) (Fig. 3).

Intrarenal perfusion and oxygenation

Renal cortical and medullary perfusion were maintained at higher levels during TIVA than VA, irrespective of the concentration of FiO_2 (both $P_{Group}=0.001$; Fig. 2). Compared with the non-anaesthetised state, renal cortical (~956 *vs* ~475 blood perfusion units) and medullary perfusion (~454 *vs* ~221 blood perfusion units) were lower at all concentrations of FiO_2 during TIVA and VA (Tables 1 and 2). In contrast, cortical and medullary PtO_2 were similar with TIVA and VA and were only lower than the non-anaesthetised state at an FiO_2 of 0.21 (Tables 1 and 2).

Increasing FiO_2, during TIVA or VA, did not significantly change cortical or medullary perfusion, but progressively increased cortical and medullary PtO_2 (Fig. 2). At an FiO_2 of 0.40 and 0.60, cortical and medullary PtO_2 were not significantly different from the non-anaesthetised state. However, when FiO_2 was set at 1.0, there was a greater elevation in renal cortical PtO_2 with TIVA than with VA ($P_{GroupxFiO2}=0.002$; Fig. 2), an effect not observed in the medulla (Tables 1 and 2).

Systemic and renal haemodynamics in non-anaesthetised sheep on postoperative day 3

All animals in the TIVA and VA groups recovered without any respiratory complications from surgical procedures. In non-anaesthetised sheep breathing room air (0.21), at 3 days after anaesthesia systemic haemodynamics, arterial blood gases and lactate concentrations in the TIVA and VA groups were similar (Tables 1 and 2). Despite the greater decreases in RBF

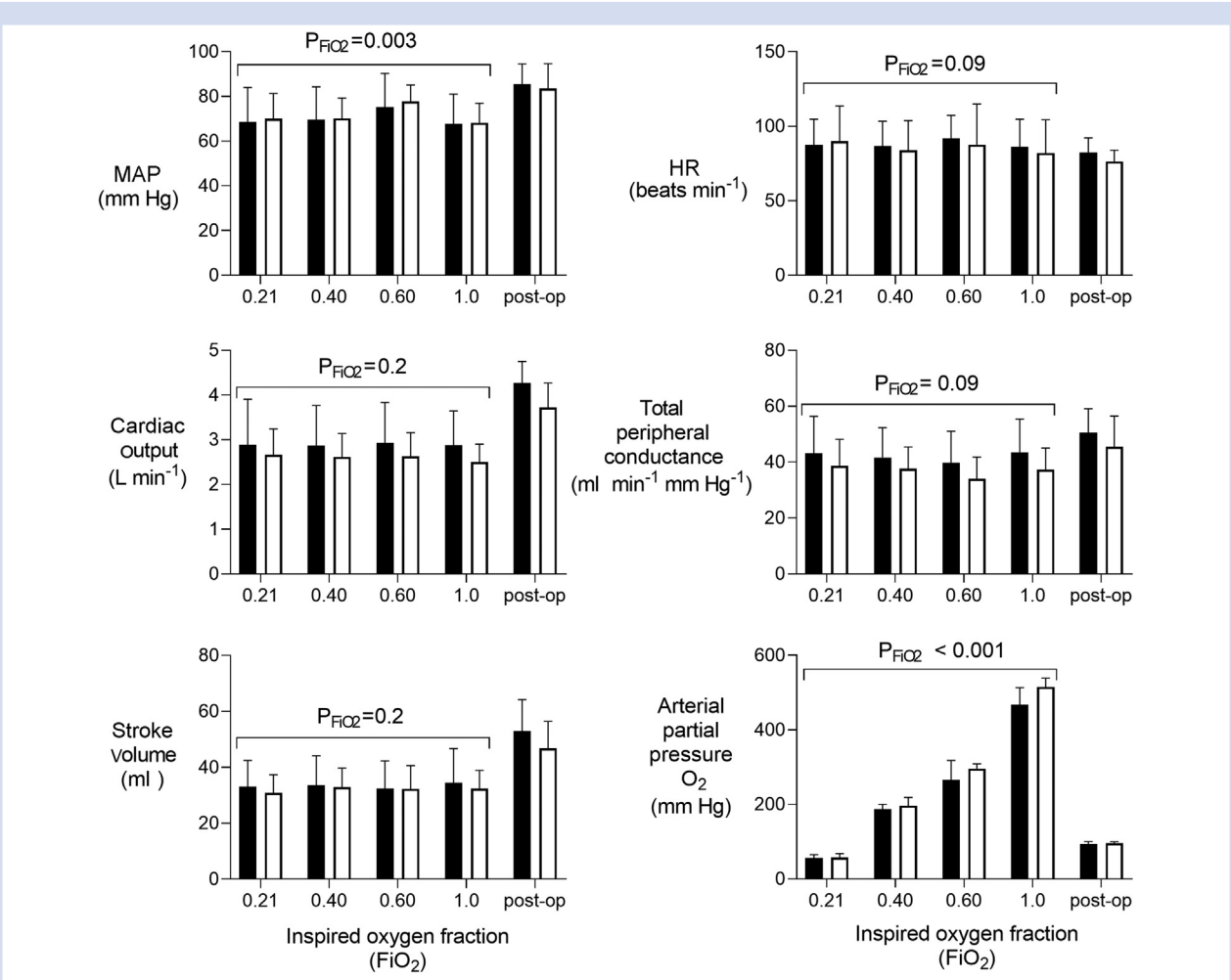

Fig 1. Systemic haemodynamics and the partial pressure of arterial oxygen at various inspired oxygen fractions under isoflurane or propofol/fentanyl anaesthesia, and the levels in the non-anaesthetised state on postoperative (post-op) Day 3. Data are expressed as median (interquartile range). *P*-values represent the outcomes of a two-way repeated measures analysis of variance (ANOVA), testing whether responses to changes in inspired oxygen fraction were significantly different during isoflurane (filled bars; $n=8$) or propofol (open bars; $n=8$) anaesthesia.

and intrarenal perfusion with VA than with TIVA, renal haemodynamics and oxygenation in these groups were not significantly different (Tables 1 and 2).

Discussion

After abdominal surgery under TIVA or VA in healthy adult sheep, we examined the effects of changes in FiO_2 on systemic and global renal haemodynamics and intrarenal perfusion and oxygenation. We found that during TIVA or VA there were similar reductions in MAP, CO, and SV, but that global RBF, RVC, RDO_2, and cortical and medullary perfusion were maintained at higher levels with TIVA than VA. Graded increases in FiO_2, from 0.21 to 1.0, did not alter systemic or renal haemodynamics during TIVA or VA, but increased cortical and medullary PtO_2 similarly with both regimens. Finally, we found that with both anaesthetic regimens, when FiO_2 was maintained between 0.40 and 0.60, the levels of cortical and medullary PtO_2 were similar to those in the non-anaesthetised state.

Relationship to previous studies

Previous studies of experimental abdominal surgery[6] and cardiopulmonary bypass[7] have demonstrated that RBF, RVC, RDO_2, and intrarenal perfusion decrease with VA, but significantly less with TIVA. Our current findings confirm these observations. These different renal responses appear to be partly attributable to an increase in renal sympathetic vasomotor drive with VA, an effect absent with TIVA.[6] However, despite their clinical relevance, renal and intrarenal perfusion and oxygenation responses to changes in intraoperative FiO_2 during TIVA or VA have not been reported previously.

Table 1 Systemic and renal haemodynamics at different inspired oxygen fractions (FiO_2) during volatile anaesthesia (VA), compared with the levels in the non-anaesthetised state on postoperative Day 3 (n=8). Variables are expressed as between-animal median (interquartile range). *P<0.05, **P<0.01, and ***P<0.001 indicates significant differences between variables at postoperative Day 3 compared with variables in response to changes in FiO_2 (0.21, 0.40, 0.60, and 1.0) during volatile anaesthesia. P-values were derived from a Wilcoxon signed rank test. A Boneferroni correction (k=4) was applied to all P-values.

Variable	VA 0.21 FiO_2	VA 0.40 FiO_2	VA 0.60 FiO_2	VA 1.0 FiO_2	Postoperative 0.21 FiO_2
MAP (mm Hg)	69 (58–83)**	70 (56–78)**	75 (65–86)*	68 (62–74)**	86 (78–92)
HR (beats min^{-1})	87 (69–99)	86 (75–99)	92 (85–101)	86 (68–103)	82 (76–88)
Cardiac output (L min^{-1})	2.0 (2.2–3.4)***	2.9 (2.3–3.3)***	2.9 (2.4–3.3)***	2.9 (2.4–3.4)***	4.3 (3.8–4.5)
Total peripheral conductance (ml min^{-1} mm Hg^{-1})	43 (36–53)	42 (38–49)	40 (32–49)	43 (35–52)	49 (41–56)
Stroke volume (ml)	33 (27–40)***	34 (26–39)***	32 (26–38)***	35 (27–39)	53 (48–56)
Renal blood flow (ml min^{-1})	57 (33–74)***	58 (34–77)***	57 (35–75)***	60 (37–79)***	232 (202–275)
Renal vascular conductance (ml min^{-1} mm Hg^{-1})	0.8 (0.6–1.1)**	0.8 (0.6–1.0)**	0.8 (0.6–0.9)**	0.9 (0.7–1.1)**	2.8 (2.2–3.7)
Renal oxygen delivery (ml O_2 min^{-1})	6 (4–7)***	8 (6–9)***	7 (6–10)***	8 (6–10)***	34 (31–36)
Renal oxygen consumption (ml O_2 min^{-1})	2.3 (1.8–2.9)	1.5 (1.0–1.8)*	1.6 (1.1–1.9)*	1.5 (1.1–1.4)*	3.0 (2.7–3.6)
Renal oxygen extraction ratio (%)	30 (26–34)**	19 (18–21)*	19 (18–20)*	16 (14–18)	10 (8–11)
Cortical tissue perfusion (blood perfusion units)	469 (395–592)***	487 (385–658)***	502 (423–571)***	440 (318–521)***	1250 (1101–1260)
Cortical tissue oxygen tension (mm Hg)	18 (15–24)***	28 (18–36)	38 (31–42)	51 (39–62)	44 (39–47)
Medullary tissue perfusion (blood perfusion units)	221 (195–235)***	231 (206–261)***	240 (177–287)***	214 (203–222)***	997 (857–1084)
Medullary tissue oxygen tension (mm Hg)	26 (20–34)**	47 (35–55)	57 (35–64)	61 (39–73)	43 (39–45)
Arterial partial pressure of oxygen (mm Hg)	57 (53–62)***	187 (181–191)***	265 (262–293)***	467 (459–497)***	94 (89–97)
Arterial partial pressure of carbon dioxide (mm Hg)	44 (39–51)**	45 (38–52)**	45 (39–54)**	46 (38–55)**	32 (32–33)
Arterial haemoglobin concentration (g dl^{-1})	9.2 (8.5–9.8)	9.2 (8.6–9.8)	9.1 (8.3–9.5)	9.3 (8.6–9.8)	9.6 (9.2–9.8)
Arterial lactate concentration (mmol L^{-1})	0.7 (0.6–0.9)*	0.7 (0.6–0.8)*	0.7 (0.6–0.8)*	0.7 (0.6–0.9)*	0.4 (0.3–0.5)

Table 2 Systemic and renal haemodynamics at different inspired oxygen fractions (FiO_2) during total intravenous anaesthesia (TIVA), compared with the levels in the non-anaesthetised state on postoperative Day 3 (n=8). Variables are expressed as between-animal median (interquartile range). *P<0.05, **P<0.01, and ***P<0.001 indicates significant differences between variables at postoperative Day 3 compared with variables in response to changes in FiO_2 (0.21, 0.40, 0.60, and 1.0) during TIVA. P-values were derived from a Wilcoxon signed rank test. A Boneferroni correction (k=4) was applied to all P-values.

Variable	TIVA 0.21 FiO_2	TIVA 0.40 FiO_2	TIVA 0.60 FiO_2	TIVA 1.0 FiO_2	Postoperative 0.21 FiO_2
MAP (mm Hg)	70 (61–73)	70 (66–74)	78 (73–80)	68 (65–71)*	84 (78–87)
HR (beats min^{-1})	90 (76–96)	84 (72–90)	88 (69–102)	82 (72–86)	76 (70–82)
Cardiac output (L min^{-1})	2.7 (2.4–2.8)**	2.6 (2.4–2.7)**	2.6 (2.4–2.7)**	2.5 (2.4–2.6)**	3.7 (3.3–4.0)
Total peripheral conductance (ml min^{-1} mm Hg^{-1})	36 (32–40)	35 (32–40)	32 (27–37)	34 (28–39)	43 (39–46)
Stroke volume (ml)	31 (27–34)**	33 (30–36)**	32 (27–38)**	32 (31–36)**	47 (42–52)
Renal blood flow (ml min^{-1})	124 (79–158)***	130 (93–165)***	141 (108–167)***	122 (91–148)***	270 (235–305)
Renal vascular conductance (ml min^{-1} mm Hg^{-1})	1.6 (1.3–1.6)***	1.7 (1.4–1.8)***	1.7 (1.4–1.8)***	1.6 (1.1–1.7)***	3.3 (2.9–3.6)
Renal oxygen delivery (ml O_2 min^{-1})	13 (9–18)***	17 (10–22)**	20 (15–24)**	17 (13–23)**	36 (32–40)
Renal oxygen consumption (ml O_2 min^{-1})	2.6 (1.7–3.1)	2.2 (1.2–2.7)	1.9 (1.5–2.1)**	1.5 (1.1–1.7)***	3.7 (3.4–4.2)
Renal oxygen extraction ratio (%)	19 (16–21)*	14 (12–17)	10 (9–10)	9 (8–10)	12 (9–14)
Cortical tissue perfusion (blood perfusion units)	950 (811–1199)**	940 (757–1065)**	1021 (808–1141)**	913 (681–1134)**	1550 (1349–1762)
Cortical tissue oxygen tension (mm Hg)	10 (2–14)*	23 (10–33)	34 (17–48)	88 (50–124)*	41 (31–57)
Medullary tissue perfusion (blood perfusion units)	481 (337–539)	442 (341–482)*	452 (337–481)*	441 (325–529)*	941 (486–1184)
Medullary tissue oxygen tension (mm Hg)	25 (21–36)**	40 (31–46)	41 (31–52)	63 (33–69)	46 (39–49)
Arterial partial pressure of oxygen (mm Hg)	57 (50–63)***	197 (179–211)***	296 (282–305)***	515 (505–531)***	96 (95–98)
Arterial partial pressure of carbon dioxide (mm Hg)	37 (34–38)**	37 (34–39)**	37 (34–38)**	37 (34–3)**	32 (31–34)
Arterial haemoglobin concentration (g dl^{-1})	9.6 (8.6–10.4)	9.8 (8.8–10.8)	9.7 (8.6–10.4)	9.6 (8.6–10.4)	9.9 (9.1–10.9)
Arterial lactate concentration (mmol L^{-1})	1.2 (0.9–1.4)***	1.1 (0.8–1.5)***	1.3 (0.9–1.5)***	1.3 (0.8–1.6)***	0.5 (0.4–0.5)

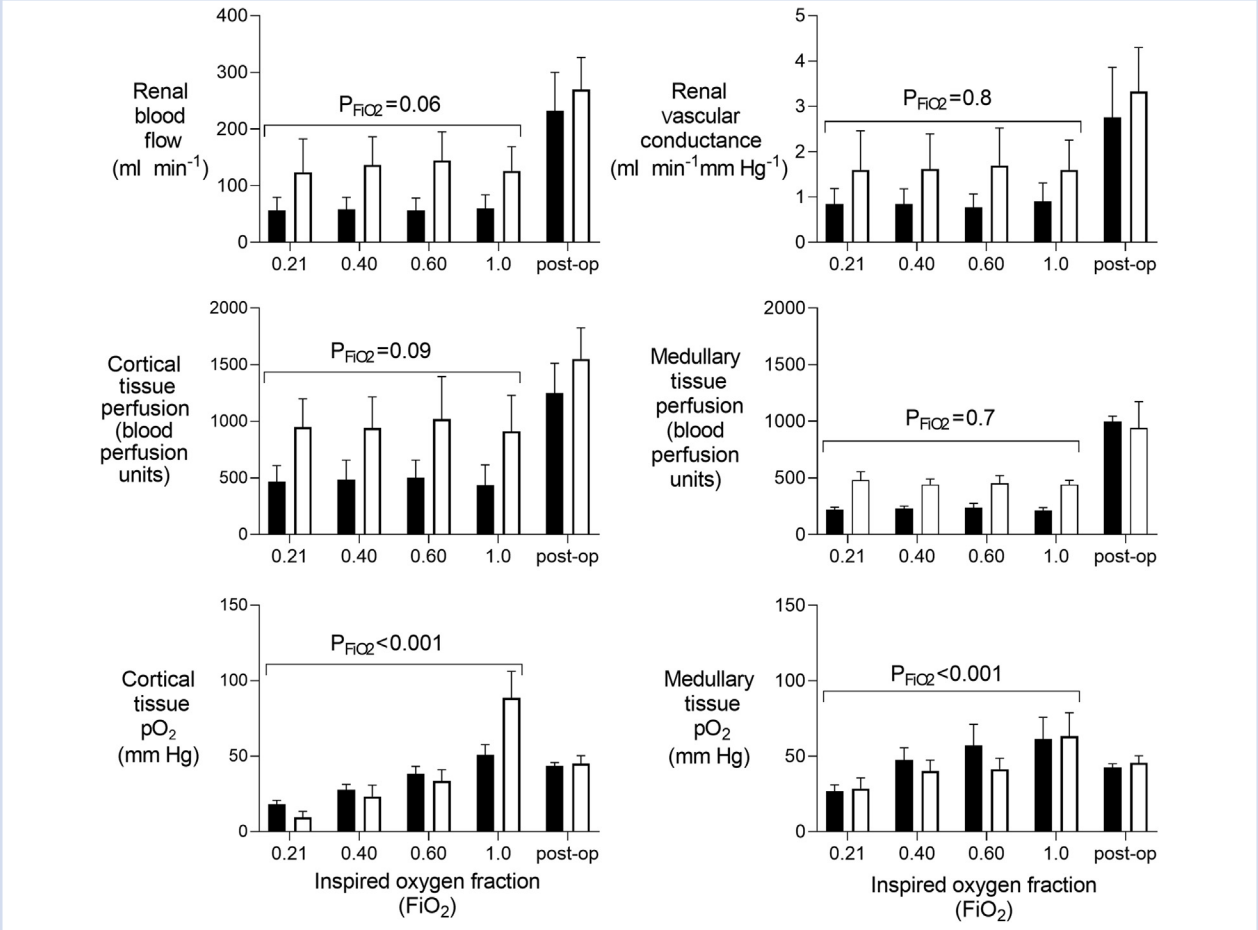

Fig 2. Renal haemodynamics and intrarenal perfusion and oxygenation at various inspired oxygen fractions under isoflurane or propofol/fentanyl anaesthesia, and the levels in the non-anaesthetised state on postoperative (post-op) Day 3. Data are expressed as median (interquartile range). *P*-values represent the outcomes of a two-way repeated measures analysis of variance (ANOVA), testing whether responses to changes in inspired oxygen fraction were significantly different during isoflurane (filled bars; $n=8$) or propofol (open bars; $n=8$) anaesthesia.

In accord with previous findings,[16,17] mild arterial hypoxaemia induced by an FiO_2 of 0.21 during anaesthesia did not induce a hyperaemic response in the renal cortex or medulla. In contrast, progressive increases in hindlimb blood flow and local biceps femoris perfusion have been found in response to graded hypoxemia.[16] This lack of a renal hyperaemic response to arterial hypoxaemia selectively within the kidneys may increase their susceptibility to tissue hypoxia, a major risk factor for AKI secondary to major surgical procedures.[3–5] Increments in intraoperative FiO_2 did not alter intrarenal perfusion, but elicited similar increases in cortical and medullary PtO_2 with TIVA or VA (apart from a difference in cortical PtO_2 at an FiO_2 of 1.0), despite renal perfusion being consistently held at a higher level with TIVA.

Renal PtO_2 is determined by oxygen supply and local renal tissue metabolic demand,[18] but the factors determining its level under anaesthesia are unclear. We found that anaesthesia decreased renal perfusion and RDO_2, which was accompanied by decreased RVO_2, likely because of reduced demand for oxygen to drive tubular sodium reabsorption.[19,20] Under both TIVA and VA, mild systemic hypoxemia induced by a low FiO_2 increased renal oxygen extraction, but despite this, renal PtO_2 remained below the level in the non-anaesthetised state. Furthermore, we show that with either anaesthetic regimen intrarenal PtO_2 is determined largely by arterial P_aO_2, which is dependent on FiO_2, and not by systemic or renal haemodynamics. Similarly, in anaesthetised rabbits, arterial P_aO_2, not RBF, appeared to be the main influence on intrarenal PtO_2 during changes in FiO_2.[16,21] These observations support the notion that, under anaesthesia, arterial P_aO_2 is a major determinant of cortical and medullary PtO_2 during changes in FiO_2 and this effect is largely independent of changes in systemic haemodynamics, RBF, intrarenal perfusion, or the type of anaesthetic agent.

The optimal target FiO_2 for the kidneys during surgical procedures remains unresolved and controversial.[22,23] A recent clinical trial in 5074 patients undergoing colorectal surgery, with FiO_2 concentrations of either 0.30 or 0.80, found

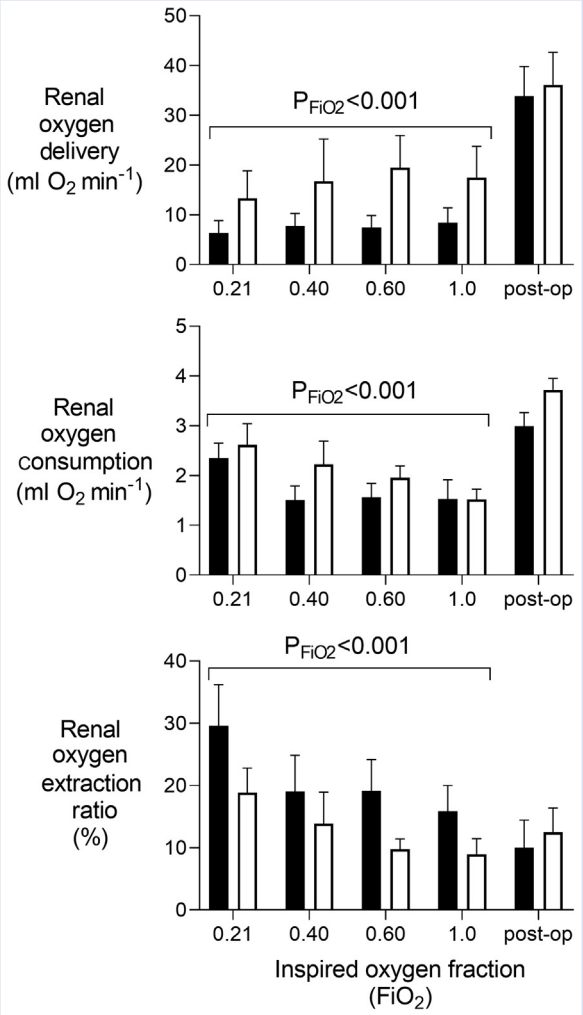

Fig 3. Global renal oxygen delivery, consumption and extraction ratio at various inspired oxygen fractions under isoflurane or propofol/fentanyl anaesthesia, and the levels in the non-anaesthetised state on postoperative (post-op) Day 3. Data are expressed as median (interquartile range). *P*-values represent the outcomes of a two-way repeated measures analysis of variance (ANOVA), testing whether responses to changes in inspired oxygen fraction were significantly different during isoflurane (filled bars; n=8) or propofol (open bars; n=8) anaesthesia.

no significant difference in the ~7% incidence of postoperative AKI.[24] Our study indicates that intrarenal PtO_2 can be maintained within the normal physiological range if FiO_2 is held $\geq$0.40 and $\leq$0.60 with both TIVA and VA, even in the presence of renal hypoperfusion. However, the maintenance of adequate intraoperative renal PtO_2 may not preclude the possibility of unresolved renal hypoperfusion increasing the risk of postoperative AKI.[3,5]

Our findings are also relevant to our understanding of renal medullary physiology. Previous studies providing evidence that the renal medulla functions on the brink of hypoxia (10–15 mm Hg) were conducted under anaesthesia.[25–28] We demonstrate that anaesthesia can profoundly reduce RBF, RDO_2, and intrarenal perfusion.[6,7,29] In accord, reductions in RBF of ~50%, as estimated by para-aminohippurate clearance, have been reported in humans anaesthetised with isoflurane.[30,31] Thus, this concept that the renal medulla functions on the edge of hypoxia may be misleading and likely represents an effect of anaesthesia. In agreement, observations in healthy non-anaesthetised sheep demonstrate that renal medullary and cortical PtO_2 are similar and range between 30 and 45 mm Hg.[6,7,29,32] Nevertheless, the renal medulla remains more susceptible to hypoxia if RBF is compromised,[11] in pathological situations such as sepsis,[33,34] and during cardiopulmonary bypass performed with either VA or TIVA.[7,29]

Study implications

Our findings imply that alterations in regional-kidney oxygenation to variations in FiO_2 occur independently of changes in systemic haemodynamics, renal perfusion, or anaesthetic regimen. They also confirm the established finding that ventilation with room air under anaesthesia reduces P_aO_2, attributable to ventilation/perfusion mismatch.[35] Finally, they imply that regional-kidney PtO_2 can be maintained at the normal physiological levels seen in the non-anaesthetised state, if FiO_2 is held $\geq$0.40 and $\leq$0.60 with TIVA and VA.

Strengths and limitations

We performed a comprehensive assessment of the impact of changing FiO_2 during TIVA or VA on systemic haemodynamics, and renal and intrarenal perfusion and PtO_2 in a healthy large animal. We maintained a similar depth of anaesthesia with both anaesthetic protocols, as judged by similar effects on systemic haemodynamics, responses to reflexes, and on arterial blood gases. The length of the abdominal surgical procedure lasting 120–150 minutes is relevant to abdominal surgery in humans. Finally, we compared the systemic and renal variables measured under general anaesthesia with those in the non-anaesthetised state on postoperative Day 3.

We acknowledge some limitations to our study. We used isoflurane for VA, which is now not commonly used in human surgical procedures. However, there is no evidence that more commonly used VA agents such as sevoflurane are more renoprotective than isoflurane.[36] Because of the short (20 minute) periods of observation, we did not measure glomerular filtration rate, a major determinant of RVO_2, however, we monitored the impact of changing FiO_2 on whole-kidney oxygen supply and demand by measuring RDO_2, RVO_2, and oxygen extraction ratio. The effects of isoflurane were examined in the absence of fentanyl, which enabled analysis of the effects of isoflurane alone without the confounding effects of fentanyl. However, the lack of fentanyl resulted in higher isoflurane requirements to maintain adequate anaesthesia and analgesia, which may have contributed to the reduction in CO, as has been reported in anaesthetised dogs.[37,38] Finally, the dose of propofol required in sheep was relatively high as a result of inherent species differences in metabolism and excretion of this drug.[39] At high doses, propofol reduces HR,[40] which in combination with a reduced SV would lower CO.

Conclusions

In healthy adult sheep, global and regional kidney perfusion decrease significantly during anaesthesia, but such decreases are less with TIVA than VA and are largely independent of FiO_2. The inability of the kidneys to mount a hyperaemic response to mild systemic hypoxaemia may increase the susceptibility to renal injury during major surgical procedures. However, renal PtO_2 can be maintained at levels similar to the non-anaesthetised state if FiO_2 is held $\geq$0.40 and $\leq$0.60 with both TIVA and VA.

Authors' contributions

Study conception: NI, CNM, YRL
Study design: NI, JK, YI, CNM, YRL
Hypothesis delineation: NI, CNM, YRL
Data acquisition: NI, JK, YI, YL
Data analysis: YRL, NI
Data interpretation: YRL, CNM, RB, RGE
Writing of manuscript: YRL, CNM, RB
Revision before submission: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

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