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# Effects of changes in inspired oxygen fraction on urinary oxygen tension measurements

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## Abstract

**Background:** Continuous measurement of urinary $PO_2$ ($PuO_2$) is being applied to indirectly monitor renal medullary $PO_2$. However, when applied to critically ill patients with shock, its measurement may be affected by changes in $FiO_2$ and $PaO_2$ and potential associated $O_2$ diffusion between urine and ureteric or bladder tissue. We aimed to investigate $PuO_2$ measurements in septic shock patients with a fiberoptic luminescence optode inserted into the urinary catheter lumen in relation to episodes of $FiO_2$ change. We also evaluated medullary and urinary oxygen tension values in Merino ewes at two different $FiO_2$ levels.

**Results:** In 10 human patients, there were 32 $FiO_2$ decreases and 31 increases in $FiO_2$. Median pre-decrease $FiO_2$ was 0.36 [0.30, 0.39] and median post-decrease $FiO_2$ was 0.30 [0.23, 0.30], $p = 0.006$. $PaO_2$ levels decreased from 83 mmHg [77, 94] to 72 [62, 80] mmHg, $p = 0.009$. However, $PuO_2$ was 23.2 mmHg [20.5, 29.0] before and 24.2 mmHg [20.6, 26.3] after the intervention ($p = 0.56$). The median pre-increase $FiO_2$ was 0.30 [0.21, 0.30] and median post-increase $FiO_2$ was 0.35 [0.30, 0.40], $p = 0.008$. $PaO_2$ levels increased from 64 mmHg [58, 72 mmHg] to 71 mmHg [70, 100], $p = 0.04$. However, $PuO_2$ was 25.0 mmHg [IQR: 20.7, 26.8] before and 24.3 mmHg [IQR: 20.7, 26.3] after the intervention ($p = 0.65$). A mixed linear regression model showed a weak correlation between the variation in $PaO_2$ and the variation in $PuO_2$ values. In 9 Merino ewes, when comparing oxygen tension levels between $FiO_2$ of 0.21 and 0.40, medullary values did not differ (25.1 ± 13.4 mmHg vs. 27.9 ± 15.4 mmHg, respectively, $p = 0.6766$) and this was similar to urinary oxygen values (27.1 ± 6.17 mmHg vs. 29.7 ± 4.41 mmHg, respectively, $p = 0.3192$).

**Conclusions:** Changes in $FiO_2$ and $PaO_2$ within the context of usual care did not affect $PuO_2$. Our findings were supported by experimental data and suggest that $PuO_2$ can be used as biomarker of medullary oxygenation irrespective of $FiO_2$.

**Keywords:** Inspired oxygen fraction, Sepsis, Septic shock, Urinary oxygen tension, Urinary oxygenation

## Background

Critically ill patients with sepsis develop acute kidney injury (AKI) in 20 to 50% of cases [1]. Despite its clinical importance, available methods for early detection of kidney damage have major limitations. One of the mechanisms implicated in the pathophysiology of this condition is hypoxia of renal tissue, particularly in the renal medulla [2]. Selective hypoxia in the renal medulla was observed in an ovine model of sepsis, despite the presence of global renal hyperemia [3]. In clinical practice, it is not feasible to measure renal medullary tissue oxygen tension in the intensive care unit (ICU). Nevertheless, it is possible to measure oxygen tension of bladder urine ($PuO_2$) by the introduction of a fiber-optic probe in the bladder catheter [4, 5]. A number of experimental investigations have been performed to evaluate this technique and have documented a robust correlation between urinary $PO_2$ and medullary $PO_2$ [6].

One of the caveats for the understanding of relationship between urinary and medullary $PO_2$ is that it may be cofounded by several factors. A concern arising from experimental and computational models is that systemic arterial oxygen tension ($PaO_2$) may affect ureteric and bladder wall oxygenation which, in turn, may influence $PuO_2$ [7–10]. Experimental observations in anesthetized rabbits suggested that oxygen exchange within the urinary tract is slow and is unlikely to be a major confounder of the relationship between renal medullary tissue $PO_2$ and $PuO_2$ [7]. Nevertheless, the potential for such confounding in human sepsis, where $PuO_2$ measurement might be applied to guide management of risk of AKI and therapeutic interventions, remains unknown. Therefore, to assess whether systemic oxygenation has a potentially confounding impact on urinary oxygenation, we aimed to evaluate $PuO_2$ in critically ill patients with sepsis during the periods before and after changes in fractional inspired oxygen ($FiO_2$) instituted to manage $PaO_2$ within clinically acceptable levels. Also, to support our clinical findings, we investigated the medullary and urinary oxygen tension levels in a sheep experiment within a similar range of $FiO_2$ variation.

## Methods

### Observational study in septic patients

#### *Study design*

We performed a prospective observational cohort study in the ICU of a tertiary care hospital located in Melbourne, Australia, from January 2017 to March 2018. The protocol was approved by the Human Research Ethics Committee of the Austin Hospital (HREC/16/Austin/26). Written informed consent was obtained from all participants or their legal representatives.

#### *Participants*

A convenience sample of adult patients (18 years old or older) with suspected or confirmed septic shock was enrolled in the study. We excluded patients who were anuric, on chronic dialysis, pregnant, or who were kidney transplant recipients.

### *Measurement of PuO2*

For each patient, a fiberoptic luminescence optode (NX-LAS-1/O/E-5 m, Oxford Optronix, Abingdon, UK) was inserted into the lumen of the urinary catheter via a sterile procedure, as described in detail previously [11]. In brief, the sensing tip of the probe was advanced to the distal tip of the catheter so that the probe was placed inside the bladder. The fiberoptic probe was connected to a luminescence lifetime oximeter (Oxylite Pro, Oxford Optronix, UK) interfaced with a laptop computer running LabChart software (Version 8, ADInstruments, Bella Vista, NSW, Australia). $PuO_2$ was recorded every minute from the time of the probe insertion until the removal of the urinary catheter by the treating medical team or at ICU discharge, whichever occurred first.

### *FiO2 settings and measurement of PaO2 and PuO2*

$FiO_2$ was modified at the discretion of bedside clinicians to maintain a peripheral oxygen saturation level greater than 90%. Episodes of $FiO_2$ change were documented in the laptop computer software by the bedside nurse at the moment the intervention took place and were verified against observation charts. To describe arterial oxygen levels, we identified arterial blood gases (ABG) that were collected before and after $FiO_2$ modification (Fig. 1). To make before and after periods distinctive, we restricted the analysis to ABG samples that were obtained within a time difference from $FiO_2$ change of 30 min or more. For each $PaO_2$ measurement, we obtained the mean value of 30 $PuO_2$ measurements centerd around the exact time when the ABG was collected (15 min before and 15 min after the blood was drawn). Blood gas analysis was performed with an ABL800 FLEX blood gas machine (Radiometer, Copenhagen, Denmark). No specific method was used to ascertain the ABG stability for the purposes of the study. However, the unit where the study was conducted is a world-class intensive

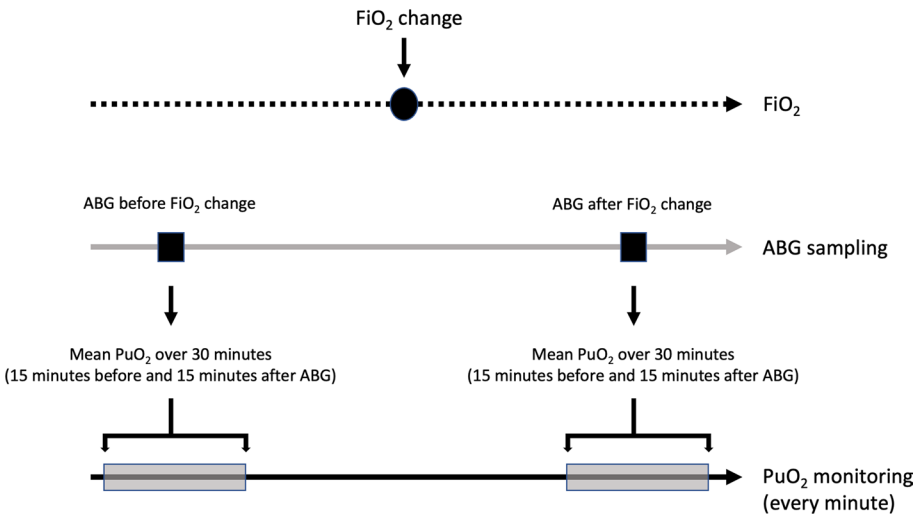


**Fig. 1** Schematic representation of the procedure used to obtain $PaO_2$ and $PuO_2$ measurements before and after an episode of $FiO_2$ change during the observation period. ABG: arterial blood gas; $FiO_2$: fraction of inspired oxygen; $PuO_2$: urinary oxygen tension

care with a 1:1 nurse-to-patient ratio. The ABG analyzer is located inside the unit and the team is trained to obtain reliable measurements according to the institutional protocol.

#### *Data extraction*

Aside from the abovementioned variables, we collected information on age, gender, baseline creatinine, infection source, comorbidities and ICU severity scores. We also recorded data on duration of mechanical ventilation, number of hours in mandatory and spontaneous modes, mechanical ventilation parameters, end-tidal partial pressure of carbon dioxide ($EtCO_2$), ICU and hospital length of stay, and hospital mortality.

### Experimental study using healthy adult sheep

#### *Animal preparation*

We obtained data from 9 healthy adult Merino ewes included in an experimental study of sheep undergoing aseptic surgical procedures under general anesthesia [18]. The study was 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. A similar fiberoptic luminescence optode (Oxford Optronix, Abingdon, UK) used in human patients was inserted into the lumen of the urinary catheter and surgically inserted into the renal medulla. The tissue oxygen tension was continuously recorded at 100 Hz on a computer using a CED micro 1401 interface with Spike 2 software (Cambridge Electronic Design, Cambridge, United Kingdom).

#### *Experimental protocol for the variation of FiO2*

The protocol had 4 components of 20-min duration: a 10-min period to allow oxygen levels to stabilize followed by a 10-min experimental period. Our primary experimental stabilization criteria included renal medullary $PO_2$ and urinary $PO_2$. This timing was determined by assessing the medullary and urinary $PO_2$ values over time. A block randomization was used to set $FiO_2$ at 0.21, 0.40, 0.60 and 1.0. The total gas flow on the mechanical ventilator was maintained at a constant rate of 1.5 L/min, whilst the ratio of the individual oxygen-to-air gas volumes was altered to achieve the target $FiO_2$. For the current analysis, we obtained data from the periods when $FiO_2$ levels were 0.21 and 0.40.

### Statistical analyses

Continuous variables are reported as median (quartile 1, quartile 3) and categorical variables are reported as number (%). An aggregate measure was calculated per patient and the paired-sample Wilcoxon test was used to compare median values between the two time periods (before and after $FiO_2$ change). Proportions were compared using Fisher's exact test. To account for multiple episodes of $FiO_2$ change per patient, we performed a mixed linear regression model to assess the relationship between the variation of $PaO_2$ ($\Delta PaO_2$) and the variation of $PuO_2$ ($\Delta PuO_2$).

In the sheep experiment, values for each $FiO_2$ setting were calculated and a comparison between groups was performed by using Kruskal–Wallis test.

Statistical analysis was performed using R version 4.0.5. Two-tailed $p \leq 0.05$ was considered statistically significant.

## Results

### Human septic patients

We studied 10 patients, whose clinical characteristics are reported in Table 1. During the study period, patients were mechanically ventilated for 733 h (88.9% of total duration), of which 459 h were in spontaneous mode (55.6%). The mechanical ventilation parameters during the study period are described in Table 2. Arterial blood gases were obtained in 233 occasions. Across the cohort of 10 patients there was a weak but statistically significant positive association between $PaO_2$ and $PuO_2$ (Fig. 2, $r^2 = 0.022$, $p = 0.004$). This relationship was plotted for each patient (Additional file 1: Fig. S1).

We observed 63 episodes of changes in the $FiO_2$ setting: on 32 occasions $FiO_2$ was decreased and on 31 $FiO_2$ was increased. In the episodes where $FiO_2$ decreased, the median [Q1, Q3] pre-intervention $FiO_2$ was 0.36 [0.30, 0.39] and the median post-intervention $FiO_2$ was 0.30 [0.23, 0.30] ($p = 0.006$). When $FiO_2$ increased, the median $FiO_2$ before the intervention was 0.30 [0.21, 0.30] and the median $FiO_2$ after the intervention was 0.35 [0.30, 0.40], $p = 0.008$. There were 14 episodes of successive increase/decrease in the same patient. Such episodes were successive and conditional on the presence of a $PaO_2$ measurement and the time difference between these episodes was 4.29 [2.49, 5.38] hours.

In the episodes when $FiO_2$ was decreased, $PaO_2$ fell from 83 [77, 94] mmHg to 72 [62, 80] mmHg ($p = 0.009$, Fig. 3). Nevertheless, $PuO_2$ did not vary significantly across the two time points, being 23.2 [20.5, 29.0] mmHg before the intervention and 24.2 [20.6, 26.3] mmHg after the intervention ($p = 0.557$, Fig. 4). In such episodes, $\Delta PaO_2$ was $-14$ [$-22.2$, $-3.0$] mmHg and $\Delta PuO_2$ was $-0.02$ [$-4.3$, 2.9] mmHg.

When $FiO_2$ was increased, $PaO_2$ increased from 64 [58, 72] mmHg to 71 [70, 100] mmHg ($p = 0.038$, Fig. 3). The corresponding $PuO_2$ measurements were 25.0 [20.7, 26.8] mmHg before the intervention and 24.3 [20.7, 26.3] mmHg after the intervention ($p = 0.652$, Fig. 4). $\Delta PaO_2$ was 8 [$-5.5$, 14.0] mmHg and $\Delta PuO_2$ was 0.5 [$-2.6$, 4.1] mmHg. A mixed linear regression model showed a weak relationship between the change in $PaO_2$ and the change in $PuO_2$ ($r^2 = 0.003$, $p = 0.652$, Fig. 5) Also, we obtained of an aggregated measure per patient and observed that $\Delta PuO_2$ was $-0.532$ [$-1.410$, 0.331] mmHg and $\Delta PaO_2$ was $-3.25$ [$-8.880$, $-0.125$] mmHg, $p = 0.1431$.

Other laboratory parameters measured before and after $FiO_2$ change were similar between the two time points (Table 3). The urine output before $FiO_2$ change was 63.8 [32.5, 95.0] ml and 70.5 [30.6, 95.0] after $FiO_2$ change, $p = 0.9396$ (Additional file 2: Fig. S2).

### Experimental study

In the sheep experiment, we evaluated urinary and medullary tissue oxygen measurements in four $FiO_2$ levels: 0.21, 0.40, 0.60 and 1.00 (Table 4). For each variable, a total of 36 measurements were obtained. The median $PaO_2$ value at 0.21 FiO2 was 54.5 [51.3, 74.4] mmHg, 209 [181, 223] mmHg at 0.40 FiO2, $p < 0.001$. When comparing 0.21 and 0.40 $FiO_2$, we found no statistically significant difference in oxygen tension measurements. The medullary oxygen tension was 25.3 [15.3, 30.5] mmHg at 0.21 $FiO_2$ and 28.3 [15.9, 43.4] mmHg at 0.40 $FiO_2$, $p = 0.6766$; and the urinary oxygen

**Table 1** Baseline characteristics of study patients

| Patient number | Age | Gender | Baseline creatinine | Infection source | Comorbidities | APACHE II | APACHE III | Death | ICU LOS (days) | Hospital LOS (days) | Episodes of $FiO_2$ increase | Episodes of $FiO_2$ decrease |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 45 | Male | 67 | Unknown | None | 10 | 28 | No | 12 | 18 | 1 | 1 |
| 2 | 80 | Female | 159 | Ventilator-associated pneumonia | Post emergent left artery embolectomy for ischemic lower limb | 19 | 71 | No | 8 | 18 | 10 | 8 |
| 3 | 53 | Female | 88 | Ischemic ileal perforation | Post-laparotomy, hepatitis C cirrhosis | 16 | 41 | No | 4 | 28 | 3 | 3 |
| 4 | 74 | Male | 335 | Biliary | Cirrhosis, IHD, AF, AS, gout | 33 | 113 | Yes | 4 | 4 | 1 | 1 |
| 5 | 68 | Female | 64 | Pneumonia | Diabetes, alcohol abuse, depression | 31 | 111 | Yes | 18 | 18 | 5 | 3 |
| 6 | 55 | Female | 47 | Pneumonia | Diabetes, smoking | 16 | 37 | No | 5 | 26 | 1 | 2 |
| 7 | 76 | Female | 68 | Pneumonia | Diabetes, AF, hypertension | 25 | 105 | No | 8 | 22 | 0 | 2 |
| 8 | 50 | Female | 76 | Viral pneumonia | Oesophageal reflux | 10 | 39 | No | 4 | 9 | 1 | 3 |
| 9 | 56 | Female | 47 | Necrotizing pneumonia with empyema | Wegener's granulomatosis, COPD, leg necrotic ulcer | 27 | 74 | No | 7 | 22 | 1 | 2 |
| 10 | 69 | Male | 88 | Influenza A | COPD, peripheral vascular disease, OSA | 22 | 44 | No | 25 | 31 | 8 | 7 |

APACHE: Acute and Chronic Health Evaluation; LOS: length of stay; IHD: ischemic heart disease; AF: atrial fibrillation; AS: aortic stenosis; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea

**Table 2** Mechanical ventilation parameters of human patients

| Parameter | |
|---|---|
| Number of hours in mandatory MV mode, *n* (%) | 274 (33.2%) |
| Number of hours in spontaneous MV mode, *n* (%) | 459 (55.6%) |
| Number of hours not in MV, *n* (%) | 92 (11.2%) |
| Tidal volume, ml | 450 (400, 550) |
| Inspiratory pressure, $cmH_2O$, median (IQR) | 18 (15, 22) |
| Respiratory rate, breaths per minute, median (IQR) | 17 (13, 21) |
| Pressure support, $cmH_2O$, median (IQR) | 10 (10, 14) |
| PEEP, $cmH_2O$, median (IQR) | 5 (5, 8) |
| Minute-volume, L/min, median (IQR) | 7.7 (6.7, 9.5) |
| EtCO2, mmHg, median (IQR) | 39 (34, 50) |

EtCO2: end-tidal carbon dioxide; MV: mechanical ventilation

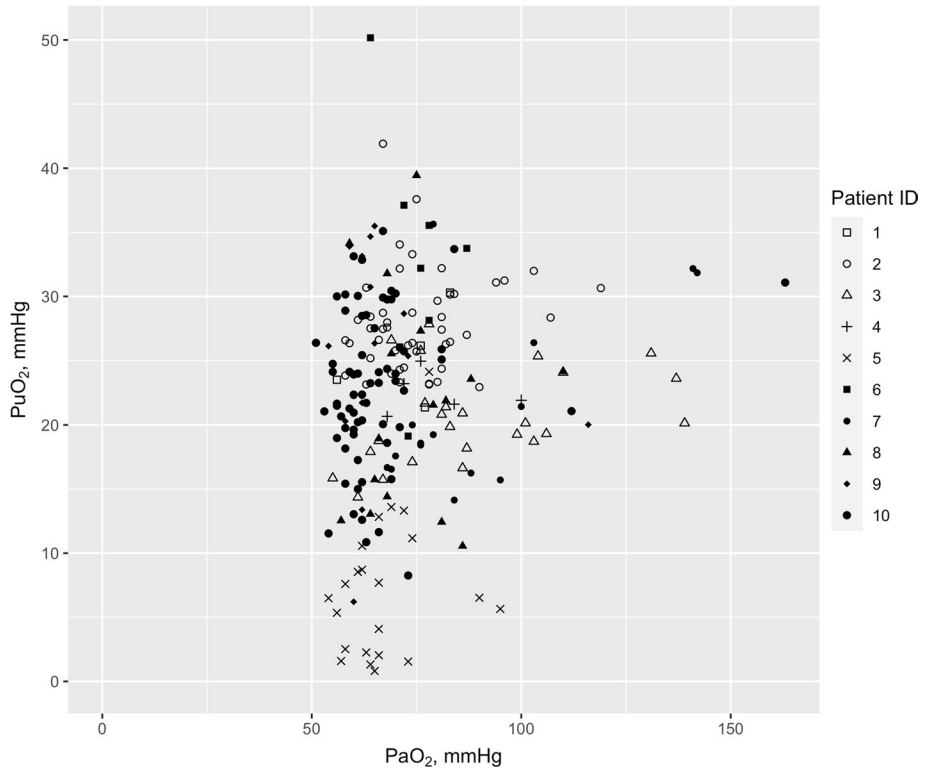


**Fig. 2** Scatterplot of arterial and urinary oxygen tension measured in the ten patients enrolled in the study. $PuO_2$: urinary oxygen tension; $PaO_2$: arterial blood oxygen tension

tension was 25.5 [21.6, 32.6] mmHg at 0.21 $FiO_2$ and 30.0 [27.4, 33.6] mmHg at 0.40 $FiO_2$, $p = 0.3192$.

At higher $FiO_2$ levels, $PaO_2$ values increased (303 [282, 306] mmHg at 0.60 FiO2 and 510 [499, 525] mmHg at 1.00 $FiO_2$. Furthermore, medullary oxygen tension tended to increase at these levels (33.4 [22.6, 45.0] mmHg at 0.60 $FiO_2$ and 40.0 [34.0, 46.8] mmHg at 1.00 $FiO_2$ ($p = 0.087$) while urinary oxygen tension values significantly increased (59.4 [36.5, 66.0] mmHg at 0.60 $FiO_2$ and 87.9 [66.1, 99.8] mmHg at 1.00 $FiO_2$ ($p < 0.001$).

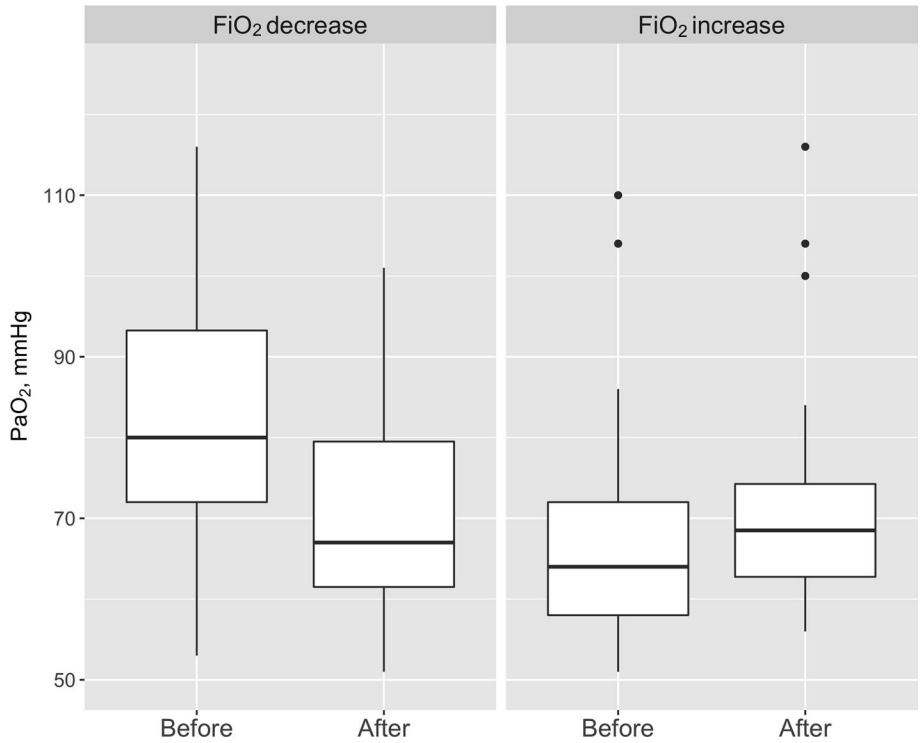


**Fig. 3** Box plot representation of arterial blood oxygen tension before and after changes in fractional inspired oxygen. $FiO_2$: fractional inspired oxygen; $PaO_2$: arterial blood oxygen tension

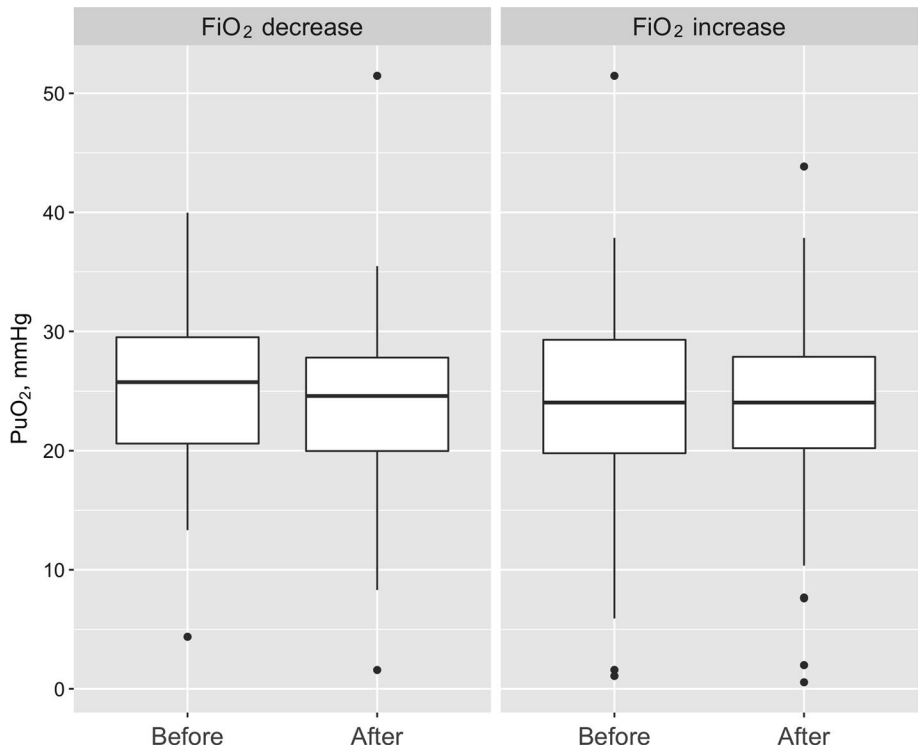


**Fig. 4** Box plot representation of urinary oxygen tension before and after changes in fractional inspired oxygen. $FiO_2$: fractional inspired oxygen; $PuO_2$: urinary oxygen tension

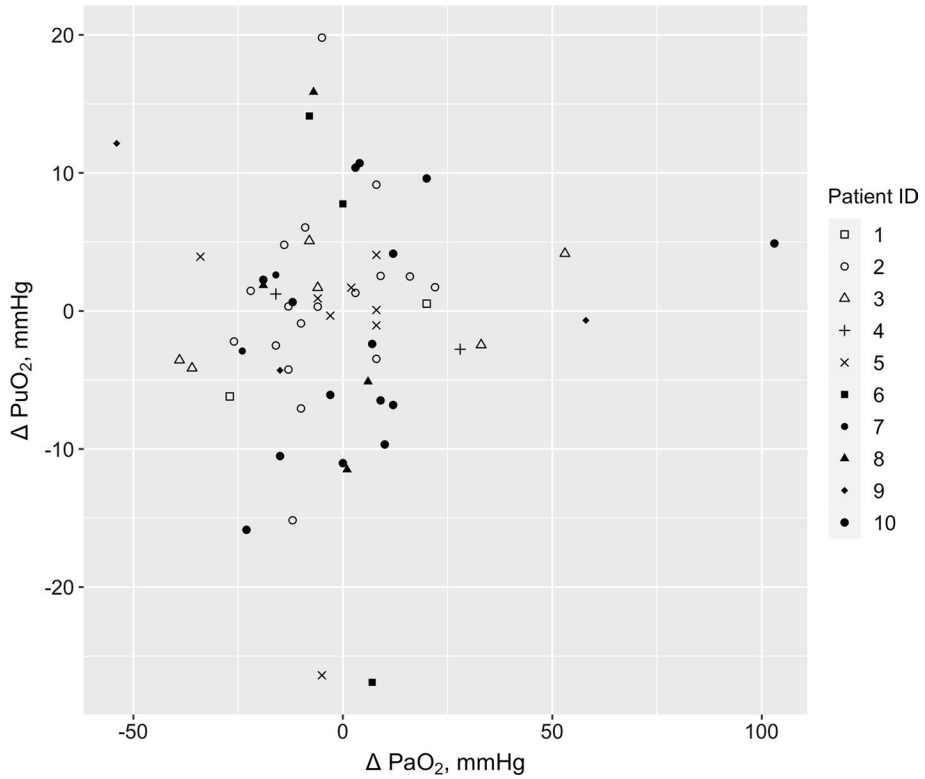


**Fig. 5** Relationship between the changes in arterial oxygen tension (Δ $PaO_2$) and urinary oxygen tension (Δ $PuO_2$)

**Table 3** Laboratory values before and after FiO2 change in human patients

| | Before | After | *p* value |
|---|---|---|---|
| FiO2 decrease | | | |
| pH | 7.41 [7.38, 7.46] | 7.41 [7.39, 7.45] | 0.722 |
| pCO2 | 41.50 [36.75, 46.5] | 42.75 [36.5, 45.63] | 0.734 |
| Bicarbonate | 27.00 [22.88, 29.88] | 27.00 [23.25, 30.25] | 0.098 |
| Base excess | 3.00 [0, 5.00] | 2.50 [− 0.75, 5.75] | 0.335 |
| Chloride | 103.50 [102.00,106.88] | 103.50 [101.63, 106.88] | 1.000 |
| Lactate | 1.28 [1.03, 1.88] | 1.35 [1.01, 2.01] | 1.000 |
| Creatinine | 67.00 [59.00, 80.00] | 70.50 [58.13, 80.88] | 1.000 |
| Hemoglobin | 92.50 [79.80, 119.00] | 94.25 [78.25, 118.13] | 0.888 |
| Glucose | 9.65 [6.38, 11.55] | 10.25 [7.53, 11.05] | 0.529 |
| $FiO_2$ increase | | | |
| pH | 7.41 [7.39, 7.45] | 7.42 [7.36, 7.43] | 1.000 |
| $pCO_2$ | 43.00 [35.00, 44.50] | 44.00 [34.00, 45.50] | 1.000 |
| Bicarbonate | 26.00 [24.00, 27.00] | 27.00 [22.00, 28.00] | 0.583 |
| Base excess | 2.00 [0, 3.00] | 2.00 [0, 4.00] | 0.684 |
| Chloride | 106.00 [103.00, 109.00] | 107.00 [103.00, 107.00] | 0.833 |
| Lactate | 1.60 [1.00, 1.90] | 1.60 [1.10, 3.00] | 0.176 |
| Creatinine | 65.50 [58.88, 70.75] | 66.50 [62.75, 75.25] | 0.178 |
| Hemoglobin | 103.00 [79.00, 117.00] | 102.00 [80.00, 127.00] | 0.344 |
| Glucose | 9.90 [8.50, 10.90] | 10.30 [7.80, 11.70] | 0.910 |

**Table 4** Measurements of $PaO_2$, medullary oxygen tension and urinary oxygen tension under different $FiO_2$ settings obtained in the experimental study using healthy adult sheep

| Variable | 0.21 $FiO_2$ | 0.40 $FiO_2$ | 0.60 $FiO_2$ | 1.00 $FiO_2$ | *p*-value |
|---|---|---|---|---|---|
| Medullary oxygen tension, mmHg | 25.3 [15.3, 30.5] | 28.3 [15.9, 43.4] | 33.4 [22.6, 45.0] | 40.0 [34.9, 46.8] | 0.087 |
| Urinary oxygen tension, mmHg | 25.5 [21.6, 32.6] | 30.0 [27.4, 33.6] | 59.4 [36.5, 66.0] | 87.9 [66.1, 99.8] | < 0.001 |
| $PaO_2$, mmHg | 54.5 [51.3, 74.4] | 209 [181, 223] | 303 [282, 306] | 510 [499, 525] | < 0.001 |

$PaO_2$: end-tidal carbon dioxide; MV: mechanical ventilation

For a larger change in $FiO_2$ (from 0.21 to 0.60), medullary oxygen tension values were similar (25.3 [15.3, 30.5] mmHg vs. 33.4 [22.6, 45.0] mmHg, $p = 0.2224$) but urinary oxygen tension values increased (25.5 [21.6, 32.6] mmHg vs. 59.4 [36.5, 66.0] mmHg, $p = 0.001$).

## Discussion

### Key findings

We conducted an observational study in human septic patients to determine whether $PuO_2$ is affected by changes in systemic oxygenation during routine care of patients with septic shock. As expected, changes of $FiO_2$ resulted in significant changes in $PaO_2$. However, we found no significant differences between $PuO_2$ measured before and after the interventions occurred. We supported our clinical findings with data from an experimental sheep experiment showing that medullary and urinary oxygen tension measurements did not differ within a similar range of $FiO_2$ variation.

### Relationship to previous studies

To our knowledge, there have been no previous investigations of the relationship between systemic and urinary oxygenation in human patients with septic shock. Ngo et al. addressed this issue in a group of patients undergoing cardiac surgery, finding no significant relationship between $PaO_2$ and $PuO_2$ during cardiopulmonary bypass [6]. Importantly, however, these observations were obtained in a unique physiological state with non-pulsatile flow, an extracorporeal circuit and mild hypothermia. Our current observations are likely more generally applicable to patients in a critical care setting. They are also very consistent with the outcomes of a retrospective analysis of three 3 studies involving a total of 28 adult Merino ewes during experimental sepsis [4, 12, 13], in which only a weak linear relationship was found between $PaO_2$ and $PuO_2$, accounting for $\leq 6\%$ of the variation of $PuO_2$ [6].

The absence of detectable changes in $PuO_2$ in response to modest but clinically significant changes in $FiO_2$ and thus $PaO_2$ indicate that renal medullary tissue $PO_2$ was not markedly affected by these clinical maneuvers. Experimental evidence supports the concept that extreme variations in $FiO_2$ and/or $PaO_2$ lead to corresponding changes in the oxygen tension of renal tissue. For example, in anesthetized rats a reduction in $FiO_2$ from 1.0 to 0.1 resulted in a decline in cortical and medullary microvascular $PO_2$ as assessed by dual-wavelength phosphorimetry [14]. Likewise, studies using fluorescence optodes in anesthetized rabbits demonstrated variations in both cortical and medullary tissue $PO_2$ with variations in $FiO_2$ [7, 15–17]. These findings provide support to

our experimental findings that greater $FiO_2$ variation is associated with greater $PuO_2$ response, in particular at 0.60 and 1.00 $FiO_2$.

Our ovine study sample derived from a larger experiment comprising 18 healthy sheep undergoing abdominal surgery under total intravenous or volatile anesthesia. In this study, increasing $FiO_2$ from 0.21 to 1.00 increased cortical and medullary tissue $PO_2$ [18]. However, it is also well-established that renal medullary tissue $PO_2$ is less responsive to changes in $PaO_2$ than the renal cortical tissue $PO_2$ [16, 18, 19]. This appears to be a consequence of counter-current diffusive shunting of oxygen between descending and ascending vasa recta, which acts to reduce delivery of oxygen to renal medullary tissue [20]. Consequently, small but physiologically (and clinically) significant changes in $FiO_2$ and/or $PaO_2$ may not appreciably alter renal medullary tissue $PO_2$. In support of this concept, no appreciable difference was observed in medullary tissue $PO_2$ in our group's preceding experiment when $FiO_2$ was varied from 0.4 to 0.6 [18]. Similarly, in anesthetized rats outer medullary microvascular $PO_2$ did not vary significantly when $FiO_2$ was varied from 0.21 and 0.30 [21]. We cannot directly measure renal medullary tissue $PO_2$ in patients and can only draw indirect inferences from measurement of $PuO_2$ and consideration of available experimental evidence. However, the most parsimonious interpretation of our current findings is that modest changes in $FiO_2$ and thus $PaO_2$ neither markedly alter renal medullary tissue $PO_2$ in patients with sepsis nor confounded the relationship between medullary tissue $PO_2$ and $PuO_2$.

#### Study implications

Our findings suggest that commonly performed adjustments to $FiO_2$ settings in patients with sepsis do not result in significant changes in $PuO_2$. In consonance of these findings, we observed that variations of $FiO_2$ between 0.21 and 0.40 did not alter either medullary or urinary oxygen tension measurements in a sheep experiment. Thus, variations of systemic oxygenation seem unlikely to confound or affect the utility of urinary oxygenation as a biomarker for risk of AKI. Nevertheless, at higher $FiO_2$ (0.60 and 1.00), significantly increased $PuO_2$ values were obtained. One possible explanation is that in our septic patients, the $FiO_2$ gap was far smaller in comparison to the experimental study. Also, one could argue that a type 2 error was present in the observational study which may have been controlled for during the experimental protocol.

Additional investigation is needed to explore whether the lack of $PuO_2$ variation in face of $PaO_2$ changes derives from the presence of confounding factors affecting medullary oxygen values. Also, further studies in critically ill patients are needed to elucidate whether sustained differences in oxygen exposure [22, 23] influence renal related outcomes. Thus, changes in $PaO_2$, as a consequence of altered $FiO_2$ in routine care of patients with septic shock, is unlikely to be a major confounder of the relationship between renal medullary tissue $PO_2$ and $PuO_2$. In the current study, $PaO_2$ was used as a measure of systemic oxygenation because it reflects the balance between oxygen delivery and consumption. Had $SpO_2$ been used, the accuracy would have been affected by peripheral tissue perfusion, use of vasoactive agents and altered cardiac output. Finally, continuous measurement of $PuO_2$ might be useful for monitoring the impact on renal medullary oxygenation.

### Strengths and limitations

We evaluated systemic and urinary oxygenation in human septic patients and assisted our proposition with experimental data. Our findings are consistent with previous observations in sepsis [6] and provide additional evidence that the relationship between renal medullary tissue $PO_2$ and $PuO_2$ is unlikely to be confounded by changes in $FiO_2$ or $PaO_2$ in the range commonly encountered in the ICU. As such, they provide further support for the use of $PuO_2$ as a clinical surrogate of renal medullary $PO_2$.

Our study has several limitations. First, the clinical component was an observation designed to assess the effects on $PuO_2$ where the observed intervention (change of $FiO_2$) was not protocolized. Moreover, controlling for variables such as creatinine or urine output was not feasible due to technical limitations and the limited number of patients. However, we aimed to undertake an exploratory analysis to generate a preliminary hypothesis to guide advanced studies. Moreover, we added data from a sheep experiment where $FiO_2$ variation was protocolized. Also, due to the lower number of measurements in the experimental study, greater heterogeneity was observed. Second, the inclusion of septic patients in our clinical study did not occur in the early stage of resuscitation. On the other hand, the instances of $FiO_2$ change we captured took place in a stable state with lower propensity for $PuO_2$ to be affected by additional confounding effects of interventions intended to optimize oxygen delivery to the tissues. Furthermore, changes in $FiO_2$ performed under stable conditions might have reduced the likelihood of reverse causation or provided mitigation of any potential effect of other interventions. Third, the observational nature of the study may have led to confounding by indication. For instance, the reasons motivating the clinician to change $FiO_2$ settings could have affected the relationship between $FiO_2$ and $PuO_2$. However, a larger degree of $FiO_2$ change would be expected if optimization measures capable of affecting such relationship were in place. Our patients were enrolled in the stabilization phase of sepsis, a time when, in general, only limited interventions are performed to achieve physiologic parameters aiming to prevent organ dysfunction. Finally, we addressed only the variation of systemic oxygenation within the normoxemic range. However, such a normoxemic range is typical in the care of patients in the ICU.

## Conclusions

Changes in $FiO_2$ and $PaO_2$ within the context of usual care did not appreciably affect $PuO_2$. Our findings suggest that, within the values reported, $PuO_2$ measured in a clinical and experimental setting is not confounded by changes in inspired oxygen fraction or arterial oxygen tension and that PuO2 can be used as biomarker of medullary oxygenation irrespective of FiO2.

**Abbreviations**

| | |
|---|---|
| ABG | Arterial blood gas test |
| AKI | Acute kidney injury |
| $EtCO_2$ | End-tidal partial pressure of carbon dioxide |
| $FiO_2$ | Fraction of inspired oxygen. |
| ICU | Intensive Care Unit |
| $PaO_2$ | Arterial oxygen tension |
| $PuO_2$ | Urinary oxygen tension |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40635-022-00479-y.

**Additional file 1.** Relationship between $PaO_2$ and $PuO_2$ values in each individual study patient.

**Additional file 2.** Box plot illustrating the hourly urinary output before and after a change in $FiO_2$.

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**Author contributions**
RB, GME, EAO and SLC: conception or design of the work. EAO, SLC, FY, NI and LB: acquisition, analysis and interpretation of data. EAO, SLC and ATM: drafting of the manuscript. YRL, CNM, RGE, GME and RB: critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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**Availability of data and materials**
Data are available by contacting the corresponding author.

## Declarations

**Ethics approval and consent to participate**
The protocol conducted in human patients was approved by the Human Research Ethics Committee of the Austin Hospital (HREC/16/Austin/26) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal representatives. The protocol conducted in Merino ewes was 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.

**Consent for publication**
Not applicable.

**Competing interests**
The authors have no conflicts of interest to declare.

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## Publisher's Note