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EXPERIMENTAL

Alex Dyson
Florian Simon
Andrea Seifritz
Olga Zimmerling
José Matallo
Enrico Calzia
Peter Radermacher
Mervyn Singer

Bladder tissue oxygen tension monitoring in pigs subjected to a range of cardiorespiratory and pharmacological challenges

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A. Dyson and F. Simon contributed equally to this study. P. Radermacher and M. Singer are joint senior authors.

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A. Dyson · M. Singer (✉)
Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, Cruciform Building, Gower St, London WC1E 6BT, UK
e-mail: m.singer@ucl.ac.uk

A. Dyson
e-mail: a.dyson@ucl.ac.uk

F. Simon · A. Seifritz · O. Zimmerling · J. Matallo · E. Calzia · P. Radermacher
Sektion Anästhesiologische Pathophysiologie und Verfahrensentwicklung, Klinik für Anästhesiologie, Universitätsklinikum Ulm, Ulm, Germany

F. Simon
Department of Vascular and Endovascular Surgery, Universitätsklinikum Düsseldorf, Düsseldorf, Germany

Abstract *Purpose:* A fall in tissue oxygen tension (tPO_2) is an early indicator of organ hypoxia in both patients and animal models. We previously demonstrated the utility of bladder tPO_2 in various rodent shock models. As a prelude to clinical testing, we aimed to provide further validation of bladder tPO_2 monitoring in a large animal model undergoing a range of cardiorespiratory insults and vasoactive drug interventions. *Methods:* Anaesthetized, mechanically ventilated, instrumented female pigs ($n = 8$) were subjected to a range of short-term cardiorespiratory (changes in inspired oxygen concentration (FiO_2), haemorrhage, positive end-expiratory pressure) and pharmacologic (inotrope, pressor) challenges. Global haemodynamics, arterial and pulmonary blood gases and bladder tPO_2 were measured before and after each challenge. *Results:* Bladder tPO_2 values fell in line with increasing degrees of hypoxaemia and haemorrhage, and were restored during resuscitation. These changes often preceded those seen in global haemodynamics, arterial base excess and lactate. The rise in bladder tPO_2 with hyperoxia, performed as an oxygen challenge test, was incrementally blunted by progressive haemorrhage. Dobutamine and norepinephrine both increased cardiac output and global O_2 delivery, but had no effect on bladder tPO_2 or lactataemia in these healthy pigs. *Conclusions:* In this pig model bladder tPO_2 provides a sensitive indicator of organ hypoxia compared to traditional biochemical markers during various cardiorespiratory challenges. This technique offers a potentially useful tool for clinical monitoring.

Keywords Tissue oxygenation · Haemorrhage · Hypoxaemia · Oxygen challenge test · Catecholamines · Organ perfusion

Introduction

Tissue oxygen tension (tPO_2) measures the partial pressure of oxygen within the interstitial space. tPO_2 increases if oxygen delivery rises in excess of consumption, and falls if local oxygen requirements cannot be met [1]. tPO_2 thus represents the local oxygen supply/demand balance. In both patients and lab models, tPO_2 decreases are reported across numerous organ beds (e.g. bladder, conjunctiva, muscle, liver, kidney) during low oxygen transport states (hypoxaemia, haemorrhage, heart failure) [2–10].

We previously reported changes in tPO_2 in peripheral/accessible (bladder, muscle) and deep (liver, renal cortex) organ beds in various rat shock models [2, 3, 11]. Some inter-organ differences were noted, depending on intrinsic compensatory mechanisms [3]. However, the rise in tPO_2 following an increase in FiO_2 was uniformly diminished during haemorrhage, with the increment progressively falling with shock severity [2]. This 'oxygen challenge test' thus provides additional sensitive interrogation of the adequacy of tissue perfusion [1].

Prior to commencing clinical investigations, we sought to provide further validation in a large animal (pig) model subjected to a range of cardiorespiratory and pharmacologic challenges. We hypothesized that bladder tPO_2 would be a sensitive indicator of organ hypoxia in comparison to traditional global markers.

Materials and methods

Experiments were performed according to the National Institutes of Health Guidelines on the use of laboratory animals and after protocol approval by the University Animal Care Committee and German Federal Authorities for Animal Research. Multiple studies were requested on the same animal; permission was granted to use eight female domestic German land pigs.

Instrumentation

After 12 h of fasting with free access to water, pigs received intramuscular premedication (atropine 2.5 mg and azaperone 150–200 mg). Anaesthesia was induced with intravenous (i.v.) atropine (0.5 mg), propofol (2–3 mg/kg/h) and ketamine (1–2 mg/kg/h). After endotracheal intubation, anaesthesia, analgesia and muscle paralysis were achieved with i.v. pentobarbitone (0.14 mg/kg/h), intermittent buprenorphine (30 μg/kg/h), and i.v. alcuronium (0.28 mg/kg/h). Ventilator settings for mechanical ventilation were fraction of inspired O_2 (FiO_2) 0.21, positive end-expiratory pressure (PEEP) 5 cmH_2O, tidal volume 8 ml/kg, respiratory rate 10–12 breaths/min adjusted to maintain an arterial PCO_2 of 35–40 mmHg; inspiratory (*I*)/expiratory (*E*) ratio 1:1.5, peak airway pressure less than 40 cmH_2O. A jugular venous catheter and a 7.5-F pulmonary artery flotation catheter (744HF75-Swan-Ganz CCOmbo; Edwards Life Sciences, Irvine, USA) were inserted for drug and fluid infusions, and for measurement of central venous, pulmonary arterial and pulmonary artery occlusion pressures, respectively. A 5-F thermistor-tipped pulse contour analysis catheter (PV2015L20-Pulsiocath; Pulsion Medical Systems, Munich, Germany) and a 9-F catheter were placed in carotid and femoral arteries for blood sampling, measurement of blood pressure and cardiac output, and blood removal during haemorrhage. Ringer's solution (10 ml/kg/h) was infused as maintenance fluid, while 6 % hydroxyethyl starch (130/0.42) in a balanced electrolyte solution (Vifusal; Serumwerke, Bernburg, Germany) was given during surgery to maintain cardiac filling pressures between 6 and 10 mmHg.

Large area surface (LAS)^{TM} oxygen-sensing optodes (0.7 mm diameter; 8 mm^2 in contact with tissue; Oxford Optronix, Oxford, UK) were placed into the bladder for continuous monitoring of tissue PO_2. These luminescent optodes send short pulses of light along a fibre-optic cable to a luminophore (platinum) situated at the tip of the probe. Upon excitation, the luminophore emits light that is carried back along the optical fibre to a monitoring system that computes the signal [12]. The luminescence decay is inversely proportional to the local PO_2 within the tissue, as described by the Stern–Volmer relationship: $1/\tau = (1/\tau_0) + k_q\,[O_2]$ where τ_0 is the decay time at zero oxygen, τ is the decay time at a specific oxygen concentration $[O_2]$ and k_q is a diffusion-controlled quenching constant that denotes the probability of a singlet-state phosphor and ground-state oxygen molecule colliding [13]. The LAS^{TM} oxygen-sensing optodes are pre-calibrated by the manufacturer and automatically correct for changes in temperature.

Owing to difficulties in per-urethral catheterization in the pig, we opted for direct insertion of a modified (three-channel) Foley catheter into the bladder through a limited laparotomy. Briefly, a small vertical skin incision was made in the supra-pubic region and, subsequently, in the peritoneum to expose the bladder. The less vascularized part of the bladder was identified, a purse string suture was made, and the Foley catheter inserted and fixed by closing the "purse string". Thereafter, the bladder was repositioned to its original position and the peritoneum closed. The catheter balloon was then inflated with 10 ml n-saline. Tissue PO_2 probes were advanced through the catheter until resistance was sensed; a limited post-mortem showed the measurement area of the tPO_2 probe was contained in a pocket of tissue and thus in contact with the epithelium in the drained bladder (Supplementary Fig. 1). No macroscopic evidence of tissue damage or bleeding was observed.

Protocol

Following surgery, animals received 10 ml/kg/h Ringer's solution and were allowed to stabilize for 1 h before intervention. The protocol (Fig. 1) was designed to place each challenge in order of increasing severity. All interventions were performed at 20-min intervals; a further 10 min was permitted if continuously monitored variables (BP, tPO_2) failed to reach steady state for at least 5 min.

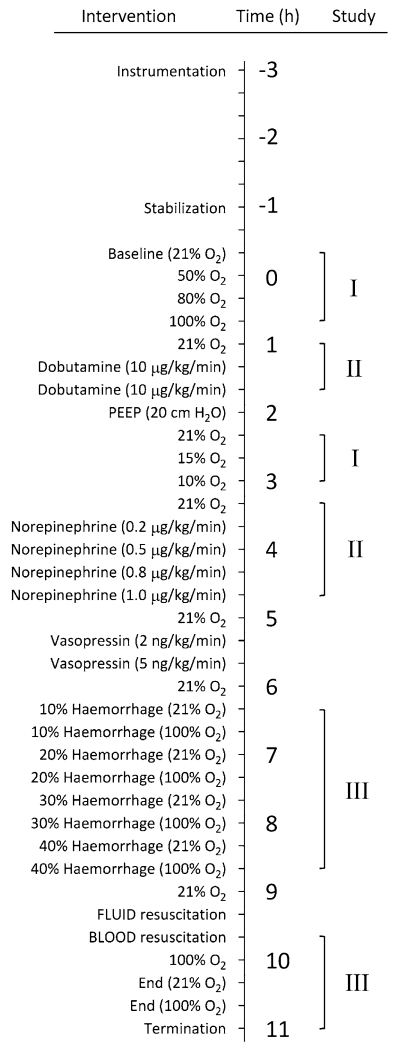

Fig. 1 Experimental protocol: each intervention lasted 20 min with measurements recorded at the end of each 20-min period. Fluid resuscitation comprised 2 l hydroxyethyl starch. Blood resuscitation denotes administration of shed blood approximating 40 % estimated circulating blood volume. End-experiment measurements were performed after exsanguination to a mean arterial pressure of 25 mmHg. *Roman numerals* signify the study number within which each data set is presented: *I* the impact of inspired oxygen concentration, *II* effects of catecholamines, *III* haemorrhage, resuscitation and oxygen challenge. *PEEP* positive end-expiratory pressure

The protocol lasted approximately 11 h, excluding instrumentation ($\sim$2 h) and stabilization.

Changes in FiO_2 (study I) were achieved by blending O_2 and N_2 and adjusted using the O_2 cell of an indirect calorimeter (QuarkRMR® Calorimeter; COSMED, Rome, Italy). This also enabled continuous measurement of global O_2 uptake (VO_2, paramagnetic O_2 cell) and CO_2 production (VCO_2, digital infrared CO_2 cell) except at high FiO_2 (0.8 and 1.0). Hyperoxia was induced by increasing FiO_2 to 0.5, 0.8 and 1.0, and hypoxaemia by decreasing FiO_2 to 0.15 and 0.1.

Study II investigated vasopressor and inotropic drugs (dobutamine, 10 and 20 μg/kg/min; norepinephrine, 0.2–1.0 μg/kg/min; vasopressin, 2 and 5 ng/kg/min). After drug infusion was ceased, ventilator settings were adjusted to PEEP from 5 to 20 cmH_2O for a 20-min period.

Progressive haemorrhage (study III) comprised removal of 10 % estimated circulating blood volume (70 ml/kg) from the arterial line at 40-min intervals. For the first 20 min after blood removal, the animal was monitored breathing 21 % O_2. A dynamic oxygen challenge test (FiO_2 increased to 1.0) was performed during the last 20 min. This process was repeated until 40 % estimated blood volume had been removed. To mimic a clinical scenario, initial resuscitation comprised 2 l hydroxyethyl starch solution, followed 20 min later by administration of blood (removed during haemorrhage). Measurements following resuscitation were made after both administration of colloid and shed blood. An oxygen challenge test was re-performed post-resuscitation. At the end of the study, animals were bled to a mean BP of 25 mmHg; a final oxygen challenge test performed 20 min later.

At baseline (end-stabilization) and following each 20-min period, measurements were taken including global haemodynamics (mean, systolic and diastolic arterial pressures, mean pulmonary artery pressure, stroke volume, heart rate, thermodilution cardiac output, and stroke volume variation), arterial and pulmonary artery blood gas analysis [PaO_2, $PaCO_2$, haemoglobin (Hb) levels and oxyhaemoglobin saturation, pH, lactate and base excess]. Global O_2 consumption (VO_2; except during hyperoxia), CO_2 production (VCO_2) and core temperature were monitored continuously.

Global oxygen delivery was calculated as the product of cardiac output and arterial oxygen content [CaO_2; $(Hb \times SaO_2 \times 1.39) + (PaO_2 \times 0.023)$]. Respiratory quotient (RQ) was calculated as the ratio of CO_2 production to O_2 consumption.

All data are presented as median, IQR and range unless otherwise stated. Statistics were performed using one-way ANOVA (non-parametric Kruskal–Wallis test) followed by Dunn's multiple comparison test. Differences between PEEPs were analysed using a Wilcoxon signed rank test. Differences between normoxia and hyperoxia during haemorrhage were analysed using repeated measures two-way ANOVA followed by Dunnett's test. All data were analysed using Prism 5.0 (GraphPad Software; San Diego, CA). $p < 0.05$ was considered statistically significant.

Results

All animals (median [IQR], weight 56 [54–59] kg) survived until the end of the experiment. Temperature rose significantly over the course of the experiment ($p < 0.05$;

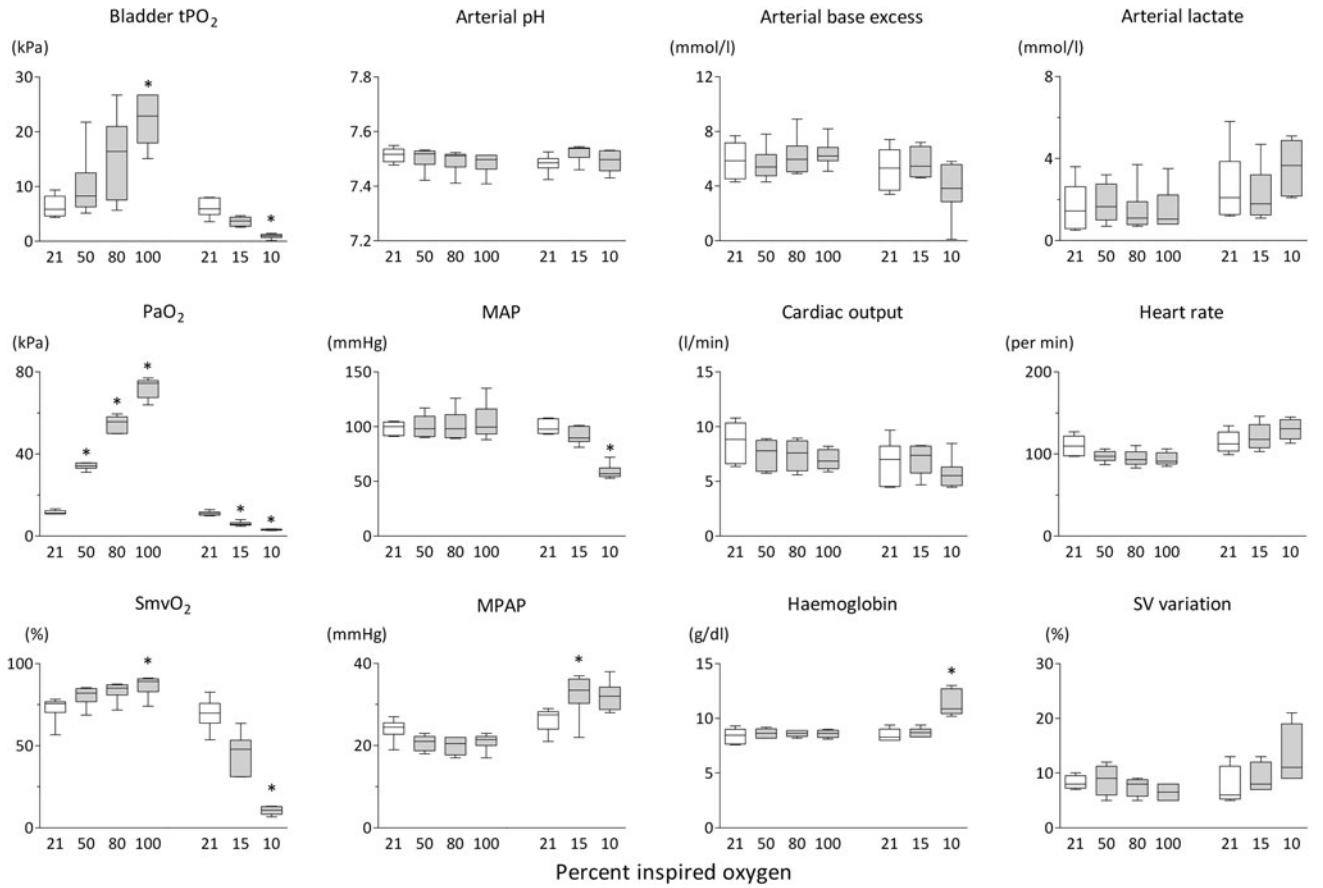

Fig. 2 Effects of hyperoxia and hypoxaemia, $*p < 0.05$ versus baseline ($FiO_2 = 0.21$). Kruskal–Wallis test followed by Dunn's multiple comparison test. *MAP* mean arterial pressure, *MPAP* mean pulmonary arterial pressure, PaO_2 partial pressure of arterial oxygen, $SmvO_2$ mixed venous (pulmonary arterial) haemoglobin oxygen saturation, *SV variation* stroke volume variation, tPO_2 tissue oxygen tension

overall ANOVA) from 37.0 [36.0–37.4] °C at baseline to 38.5 [36.8–8.8] °C following haemorrhage.

Two animals were excluded from final analysis. The first pig studied was used to assess the effectiveness and suitability of the initial protocol design, and ensure relative stability over the ~11-h study duration. Subsequently, the protocol was amended from the order (hyperoxia–hypoxaemia–PEEP–vasopressin–dobutamine–norepinephrine–haemorrhage) to that shown in Fig. 1. The second animal excluded was considered an outlier as it was essentially resistant to most of the circulatory challenges performed (Supplementary Fig. 2).

The impact of changing FiO_2 (study I) is shown in Fig. 2. Baseline values of arterial and bladder tPO_2 were 11.2 [10.8–12.3] and 5.7 [4.7–8.3] kPa, respectively. The oxygen challenge test ($FiO_2 = 1.0$) significantly increased PaO_2 (6.7-fold rise) and bladder tPO_2 (3.9-fold rise). Mixed venous (pulmonary arterial) haemoglobin oxygen saturation ($SmvO_2$) also increased with 100 % O_2 ($p < 0.05$; Fig. 2). All other measured and calculated variables remained constant during hyperoxia, notably BP and cardiac output (Fig. 2). Decreasing FiO_2 produced dose-dependent effects on PaO_2, SaO_2, $SmvO_2$ and bladder tPO_2 (Fig. 2). At 10 % FiO_2, these values fell to 3.1 [2.9–3.5] kPa, 32 [26–36] %, 11 [8–13] % and 0.9 [0.7–1.2] kPa, respectively ($p < 0.05$). BP fell and arterial haemoglobin increased with hypoxaemia. Stroke volume variation rose, albeit non-significantly ($p = 0.14$; Fig. 2). Despite maintenance of cardiac output, global oxygen delivery fell significantly owing to the reduced arterial oxygen content. This led to a significant fall in global O_2 consumption (global O_2 delivery, VO_2, VCO_2 and RQ for all three studies presented in Fig. 5). As the drop in VO_2 was not matched by a proportional fall in CO_2 production, the calculated RQ rose ($p < 0.05$). Induction of hypoxaemia did not significantly affect arterial base excess ($p = 0.19$) or lactate ($p = 0.16$) (Fig. 2).

The effects of dobutamine and norepinephrine (study II) are shown in Fig. 3. The β-adrenoreceptor agonist dobutamine increased heart rate ($p < 0.05$) with a near-significant fall in BP ($p = 0.07$; Fig. 3). The mixed α/β-agonist norepinephrine increased mean BP from 88

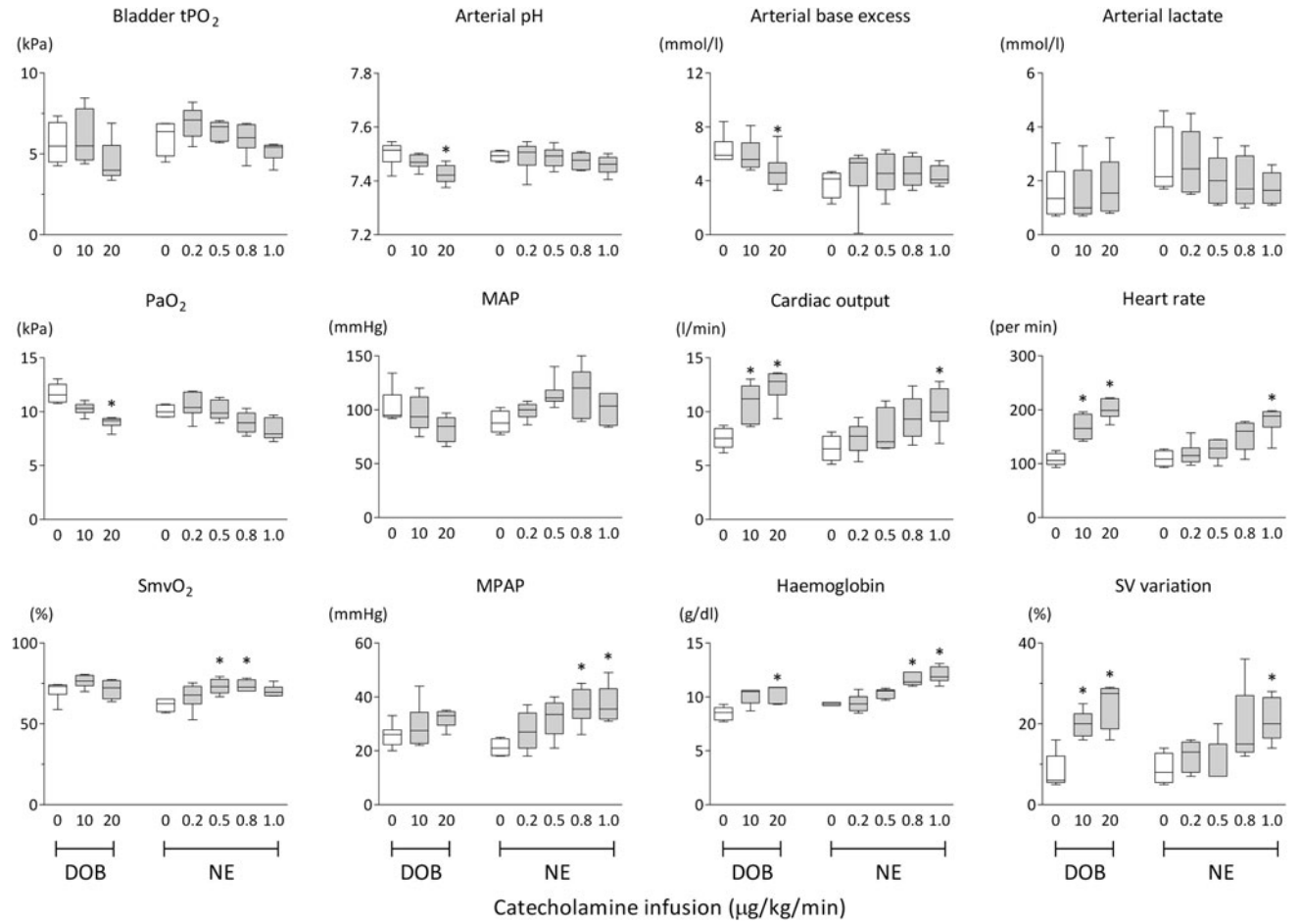

Fig. 3 Effects of dobutamine (*DOB*) and norepinephrine (*NE*), $*p < 0.05$ versus baseline (0 µg/kg/min). Kruskal–Wallis test followed by Dunn's multiple comparison test. *MAP* mean arterial pressure, *MPAP* mean pulmonary arterial pressure, PaO_2 partial pressure of arterial oxygen, $SmvO_2$ mixed venous (pulmonary arterial) haemoglobin oxygen saturation, *SV variation* stroke volume variation, tPO_2, tissue oxygen tension

[79–99] mmHg at baseline to 120 [92–135] mmHg on 0.8 µg/kg/min ($p = 0.06$; Fig. 3). Mean pulmonary artery pressure and $SmvO_2$ also rose ($p < 0.05$), while at the highest infusion rate (1 µg/kg/min) norepinephrine induced a significant tachycardia ($p < 0.05$; Fig. 3). Both catecholamines increased cardiac output (Fig. 3) and global oxygen delivery.

Despite the two-fold increase in global oxygen delivery, bladder tPO_2 and lactate levels (Fig. 3) were both unaffected by either drug. High-dose dobutamine, but not norepinephrine, generated falls in base excess and PaO_2 ($p < 0.05$; Fig. 3), while $PaCO_2$ rose (data not shown). Haemoglobin levels and stroke volume variation (Fig. 3) increased with both dobutamine and norepinephrine though rapidly normalized after drug cessation. Vasopressin (5 ng/kg/min) increased mean BP from 86 [80–87] to 101 [90–104] mmHg ($p < 0.05$) with corresponding though non-significant falls in cardiac output and bladder tPO_2 ($p = 0.08$; data not shown).

Pre-PEEP values were recorded while the animal was still receiving dobutamine. Consequently, PEEP data are shown as on-PEEP (20 cmH_2O) then off-PEEP (5 cmH_2O) (Supplementary Fig. 3). Bladder tPO_2, arterial pH, blood pressure and $SmvO_2$ rose ($p < 0.05$), while arterial base excess and lactate remained constant.

Figure 4 shows the impact of progressive haemorrhage and resuscitation, before and after short-term administration of 100 % O_2 (study III). Progressive haemorrhage (10–40 % blood volume removal) caused a significant fall in bladder tPO_2 (from 5.7 [4.7–6.7] to 4.0 [3.3–5.2] kPa; $p < 0.05$; Fig. 4). Oxygen challenge (100 % O_2) caused an equivalent rise in arterial PO_2 regardless of circulating blood volume status, yet the incremental rise in bladder tPO_2 fell with progressive blood removal ($p < 0.05$). Significant increases in bladder tPO_2 with 100 % O_2 were not seen from 20 % haemorrhage onwards. Following volume resuscitation (2 l of colloid plus administration of shed blood), bladder tPO_2 values at normoxia and during

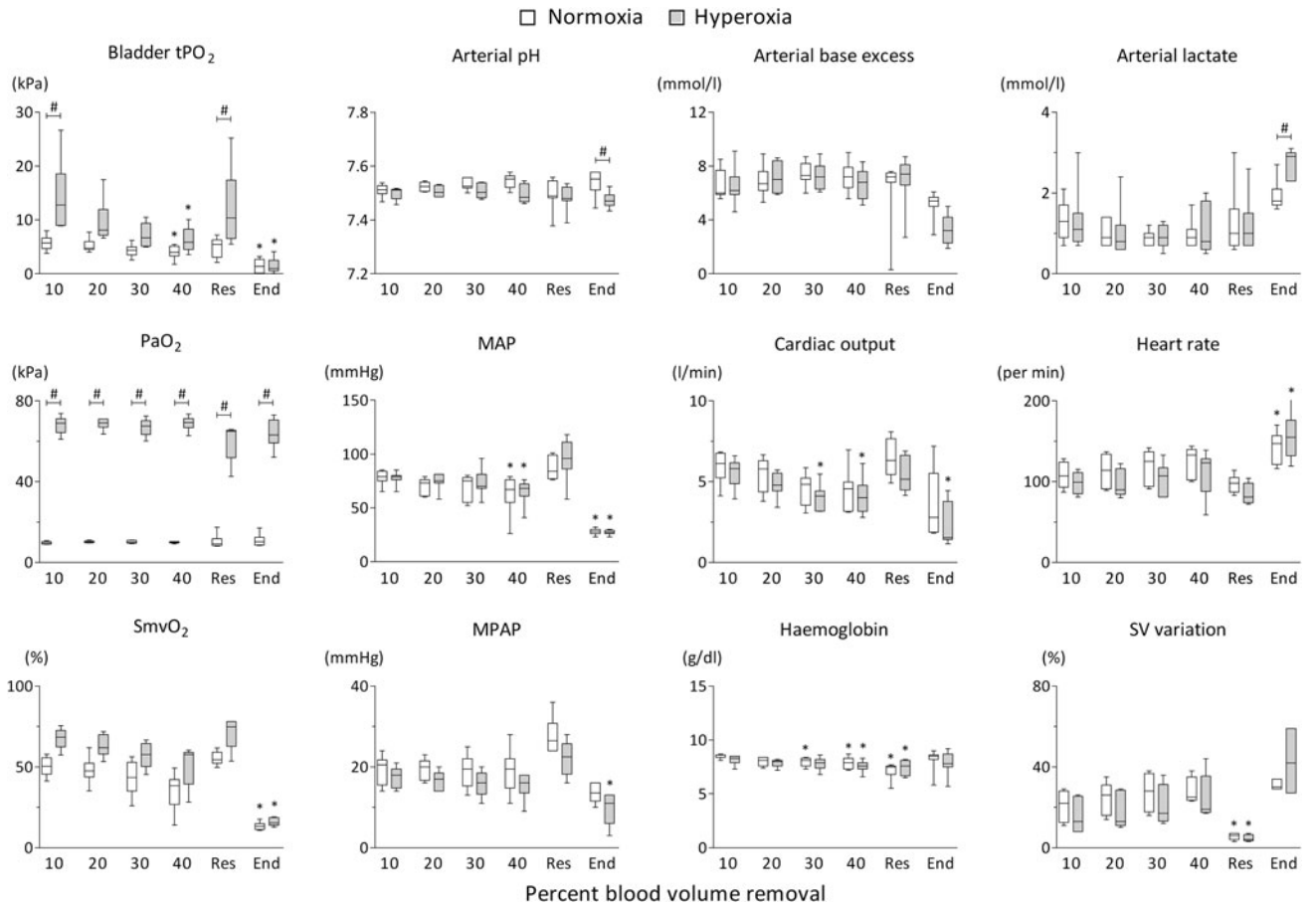

Fig. 4 Responses to normoxia and hyperoxia during progressive haemorrhage, resuscitation and at the end of the experiment (MAP 25 mmHg), $^{*}p < 0.05$ versus 10 % haemorrhage; Kruskal–Wallis test followed by Dunn's multiple comparison test. $^{\#}p < 0.05$ comparing normoxia and hyperoxia; repeated measures two-way ANOVA followed by Dunnett's test. '*Res*' denotes measurements taken post-resuscitation with fluids and shed blood. '*End*' represents the end of each experiment where mean arterial pressure was 25 mmHg, *MAP* mean arterial pressure, *MPAP* mean pulmonary arterial pressure, PaO_2 partial pressure of arterial oxygen, $SmvO_2$ mixed venous (pulmonary arterial) haemoglobin oxygen saturation, *SV variation* stroke volume variation, tPO_2 tissue oxygen tension

oxygen challenge were similar to baseline (Fig. 4). At the end of the experiment (a mean BP of 25 mmHg), bladder tPO_2 fell to 1.3 [0.1–2.7] kPa and did not change with 100 % oxygen (0.9 [0.5–2.5] kPa).

Mean BP and haemoglobin fell significantly after 40 % and 30 % blood volume removal, respectively (Fig. 4). Heart rate (increase) and global oxygen consumption (decrease) only responded significantly at the end of the study (Figs. 4 and 5, respectively), while arterial base excess, lactate and cardiac output remained unchanged throughout normoxic haemorrhage (Fig. 4).

Discussion

We hypothesized that bladder tPO_2 would provide a more sensitive indicator of organ hypoxia compared to traditional markers (base excess, lactate) in a large animal model subjected to various cardiorespiratory/pharmacologic challenges. Indeed, bladder tPO_2 values fell in line with increasing degrees of hypoxaemia and haemorrhage and were restored during resuscitation. These changes often preceded those seen in global haemodynamics, arterial base deficit and lactate. The rise in bladder tPO_2 with 100 % O_2 was incrementally blunted by progressive haemorrhage. Importantly, both static (normoxic) and dynamic (response to hyperoxia) components of bladder tPO_2 were restored following resuscitation. Dobutamine and norepinephrine both increased cardiac output and global O_2 delivery, but had no effect on bladder tPO_2 or lactataemia in these healthy pigs, implying a lack of tissue compromise. These data support our hypothesis and provide further encouragement that bladder tPO_2 monitoring may be potentially useful in man.

Bladder tPO_2 in rats is affected early following various cardiorespiratory insults [2, 3, 5, 6, 14]. Here we

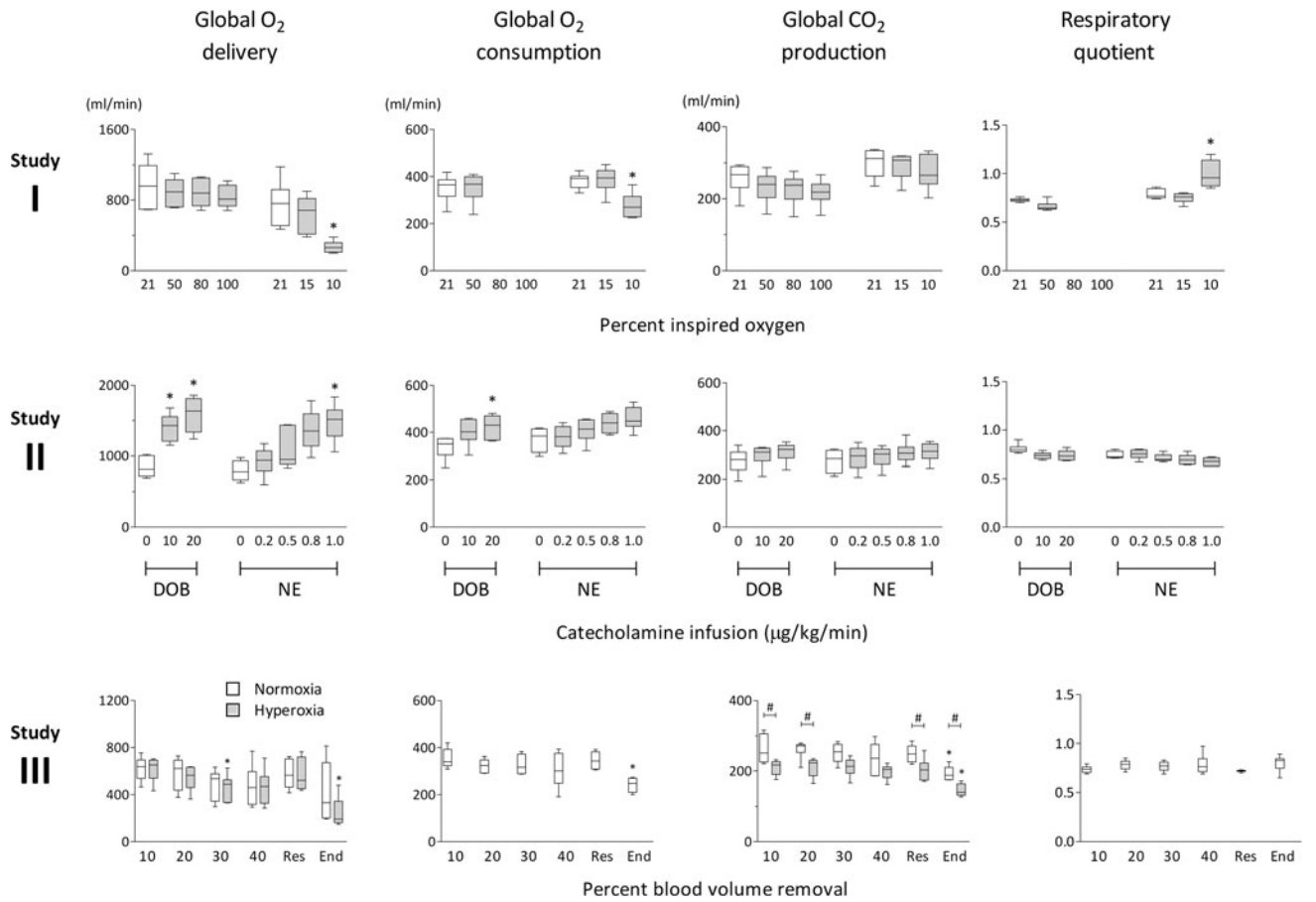

Fig. 5 Oxygen delivery and consumption following **a** changes in inspired oxygen concentration (study I), **b** dobutamine and norepinephrine administration (study II), and **c** progressive haemorrhage and resuscitation (study III), $^{*}p < 0.05$ versus baseline. **a** $FiO_2 = 0.21$, **b** 0 μg/kg/min, **c** 10 % haemorrhage. Kruskal–Wallis test followed by Dunn's multiple comparison test. $^{\#}p < 0.05$ comparing normoxia and hyperoxia (**c**); repeated measures two-way ANOVA followed by Dunnett's test. '*Res*' denotes measurements taken post-resuscitation with fluids and shed blood. '*End*' represents the end of each experiment where mean arterial pressure was 25 mmHg. Global O_2 consumption could not be measured at high inspired O_2 concentrations ($FiO_2 = 0.8$, 1.0)

demonstrate that integrating tPO_2 sensing technology into a Foley catheter delivery system is achievable in a large animal model; this has clear relevance to major surgical and critically ill patients who routinely undergo bladder catheterization. Difficulties in per-urethral catheterization in the pig necessitated direct surgical insertion of the Foley catheter into the bladder, but its principal purpose (urine drainage) was maintained along with continuous bladder tPO_2 monitoring. Studies are needed in man to confirm the stability and suitability of a per-urethral approach. It is noteworthy that although not encountered in our pig model with direct insertion, there are some instances where urethral catheterization in man may be difficult. These include bladder or pelvic trauma and specific pathologies such as cancer, fibrosis, interstitial cystitis or urinary tract infection where catheterization may be contraindicated.

Baseline (resting) tPO_2 values vary between organs, being higher in tissues with low metabolic rates such as the bladder [6, 14–16], and lower in more metabolically active tissues such as brain [17], liver [7], gut [18], renal cortex and medulla [4]. The baseline values observed in the pig bladder are similar to that measured in rats [2, 3, 6, 14–16].

Hyperoxia in pigs increased tPO_2 in subcutaneous tissue [19] and bladder detrusor muscle [20]. We found similar results in rats in peripheral (bladder, muscle) and deep (liver, kidney) organs [2]. Although absolute change in tPO_2 in each organ depended on its baseline value, proportionality was well maintained between organs with a 3.0- to 4.5-fold increase in tPO_2 while breathing 100 % O_2 compared to room air [2]. In the current study, 100 % O_2 increased bladder tPO_2 by 3.9-fold, thus demonstrating consistency between both studies and species.

With hypoxaemia, equivalent falls in tPO_2 were seen when more than one organ bed was monitored [3, 21–23]. In the present study, bladder tPO_2 fell by 83 % while breathing 10 % O_2. Concurrent falls in $SmvO_2$ and global O_2 consumption indicate oxygen supply-dependency. The decrease in tPO_2 during hypoxaemia confirms an inability

of regional oxygen supply to match continued (albeit decreased) metabolic demand.

The fall in O_2 consumption during hypoxaemia was not accompanied by a parallel fall in CO_2 production. This is consistent with a greater dependence on anaerobic glucose metabolism to generate adenosine triphosphate (ATP). However, anticipated hyperlactataemia was not observed. Blood lactate levels represent the balance between cellular production (from glycolysis) and metabolism (including mitochondrial uptake of pyruvate). As lactate is an important energy substrate for vital organs [24], the absence of hyperlactataemia could reflect an increase in consumption. This study of short-term hypoxaemia demonstrates that bladder tPO_2 monitoring is more sensitive at detecting tissue hypoxia compared to traditional global markers (arterial lactate and base excess).

We found that short-term catecholamine infusions had no effect on bladder tPO_2 or lactataemia. We reported similar findings with dobutamine in healthy rats where cardiac output was also enhanced, whereas norepinephrine produced dose-related falls in cardiac output, bladder tPO_2 and arterial base excess [15]. Bladder tPO_2 monitoring thus appears to detect compromised organ perfusion from pressor agents. The lack of a rise in bladder tPO_2 despite catecholamine-driven increases in cardiac output and oxygen delivery may indicate redistribution of regional blood flow away from the bladder. Another alternative is continued matching of local oxygen supply and demand related to catecholamine-induced increases in cellular metabolic rate and uncoupling (heat generation).

Studies in both patients and animal models report decreases in peripheral and/or central organ tPO_2 with haemorrhage [4, 7, 25–32]. In rats the increase in tPO_2 following 100 % O_2 administration progressively diminished during sequential haemorrhage, despite maintenance of PaO_2 and SaO_2 [2]. Notwithstanding inherent inter-organ variability, the consistent response seen across organs suggests a degree of similarity that could be gainfully utilized when monitoring the adequacy of organ perfusion. Notably, a lower increment in transcutaneous tPO_2 on breathing 100 % O_2 was an early prognosticator of poor outcome in human sepsis [33, 34]. In the current study, oxygen challenge during haemorrhage highlights the disconnect between vascular and tissue oxygenation. We show that progressive haemorrhage blunts the increment in tissue PO_2 observed with administration of 100 % oxygen. By contrast, PaO_2 and SaO_2 rose to the same level regardless of circulating blood volume status. This demonstrates better sensitivity with measurements of 'tissue' oxygenation over current non-invasive monitors of vascular oxygenation e.g. pulse oximetry.

Despite changes in bladder tPO_2 with haemorrhage, the current pig model was highly resistant to biochemical change; arterial lactate and base excess remained unaltered, even after removal of 40 % estimated circulating blood volume over 160 min. As pigs have the capacity to auto-transfuse from their splenic vascular bed [35], this may account for their tolerance to major blood loss.

Though not the intended purpose of this study, we noted several interesting physiological observations that warrant description. Discussion of these observations is provided in Supplementary Text 1.

Summary and conclusion

Measurement of bladder tPO_2 and the dynamic response to an oxygen challenge provide useful indicators of organ hypoxia and perfusion status and are more sensitive than arterial base excess and lactate. This technique could be gainfully utilized for early detection and prompt intervention in clinical conditions where compromised tissue vitality leads to organ dysfunction and failure. This is especially pertinent as current monitoring techniques and biochemical markers of organ perfusion are generally global, non-specific and comparatively insensitive. Clearly, any monitor of organ perfusion cannot precisely reflect every organ system but should act as a reliable surrogate for detecting changes in deeper, vital organs. Our results in this large animal model show greater sensitivity in comparison to traditional markers and provide encouragement to proceed to clinical testing.

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