Tissue oxygen monitoring in rodent models of shock

Alex Dyson, Ray Stidwill, Val Taylor, and Mervyn Singer
Bloomsbury Institute of Intensive Care Medicine, Department of Medicine, and Wolfson Institute for Biomedical Research, University College London, London, United Kingdom

Submitted 15 January 2007; accepted in final form 19 March 2007

Dyson A, Stidwill R, Taylor V, Singer M. Tissue oxygen monitoring in rodent models of shock. Am J Physiol Heart Circ Physiol 293: H526–H533, 2007. First published March 23, 2007; doi:10.1152/ajpheart.00052.2007.—Tissue PO2 (tPO2) reflects the balance between local O2 supply and demand and, thus, could be a useful monitoring modality. However, the consistency and amplitude of the tPO2 response in different organs during different cardiorespiratory insults is unknown. Therefore, we investigated the effects of endotoxemia, hemorrhage, and hypoxemia on tPO2 measured in deep and peripheral organ beds. We compared arterial pressure, blood gas and lactate levels, descending aortic and renal blood flow, and tPO2 in skeletal muscle, bladder epithelium, liver, and renal cortex during 1) LPS infusion (10 mg/kg), 2) sequential removal of 10% of circulating blood volume, and 3) reductions in inspired O2 concentration in an anesthetized Wistar rat model with values measured in sham-operated animals. Different patterns were seen in each of the shock states, with condition-specific variations in the degree of acidemia, lactatemia, and tissue O2 responses between organs. Endotoxemia resulted in a rise in bladder tPO2 and an early fall in liver tPO2 but no significant change in muscle and renal cortical tPO2. Progressive hemorrhage, however, produced proportional declines in liver, muscle, and bladder tPO2, but renal cortical tPO2 was maintained until profound blood loss had occurred. By contrast, progressive hypoxemia resulted in proportional decreases in tPO2 in all organ beds. This study highlights the heterogeneity of responses in different organ beds during different shock states that are likely related to local changes in O2 supply and utilization. Whole body monitoring is not generally reflective of these changes.

Tissue oxygen tension; hemodynamics; rat; endotoxemia; hemorrhage; hypoxemia

Tissue oxygen tension (tPO2) represents the balance between local O2 supply and demand. Under resting conditions, the level will vary between and within organs; it will be higher in tissues with low metabolic rates, such as the bladder (35, 36), and lower in more metabolically active tissues, such as the brain (20), liver (48), gut (45), and renal cortex and medulla (51).

Decreases in tPO2 across numerous organ beds during low O2 transport states, such as hemorrhage, hypoxemia, and heart failure, imply an inability of the regional O2 supply to match continuing metabolic demands. These beds range from conjunctiva (18, 42), subcutaneous tissue (15), bladder (44), and muscle (6, 28) to deeper organs, such as the liver (33, 48) and kidney (51). The fall from baseline levels generally corresponds to the severity of the insult (27, 44). By contrast, sepsis, the systemic inflammatory response to infection, results in elevated tPO2. This suggests mitochondrial dysfunction and/or a metabolic shutdown and, consequently, reduction in O2 utilization, despite local availability. This phenomenon has been witnessed in organs as diverse as the bladder and skeletal muscle in septic patients (4, 30, 38) and animal models (35, 36). Furthermore, a rise in tPO2 is still seen in low-cardiac output sepsis if fluid resuscitation is adequate (35, 36).

Measurement of tPO2 clearly offers a potentially useful diagnostic/monitoring tool for the critically ill patient, in whom current monitoring techniques are generally global, nonspecific, and often insensitive. However, because only a small number of studies have simultaneously assessed tPO2 in more than one organ bed (28, 33, 45), interorgan differences are largely unknown. This is particularly pertinent when accessible peripheral tissues, such as the bladder and muscle, are considered as a surrogate for monitoring changes in deeper, more vital organs, such as the liver and kidney. Accordingly, we sought to determine hemodynamic and tissue O2 responses to endotoxemia, hemorrhage, and hypoxemia in a short-term anesthetized rat model in peripheral (muscle and bladder) and deep (liver and renal cortex) organ beds.

METHODS

Male Wistar rats (~300 g body wt) were used in all experiments. Before instrumentation, animals were housed in cages of six on a 12:12-h light-dark cycle with free access to food and water. All experiments were performed according to local University College London ethics committee approval and Home Office (United Kingdom) guidelines under the 1986 Scientific Procedures Act.

Spontaneously breathing animals were anesthetized with 5% isoflurane in room air and placed on a heated mat to maintain rectal temperature at 36.5–37.5°C. Under 2% isoflurane anesthesia, the left common carotid artery and right internal jugular vein were cannulated using 0.96-mm-OD polyvinylchloride tubing (Biocorp, Huntingdale, Australia). The arterial line was connected to a pressure transducer (Powerlab, AD Instruments, Chalgrove, UK) for continuous monitoring of mean arterial pressure. A tracheostomy was performed, and 2.08-mm-OD polyethylene tubing (Portex, Hythe, UK) was used to secure and suction the airway; the tubing was connected to a T-piece to maintain anesthesia. A midline laparotomy was performed, and the bladder was cannulated using 1.57-mm-OD polyethylene tubing (Portex) inserted through a small incision at the apex. The isoflurane level was then reduced to 1.2% for the remainder of the experiment. To allow access to the abdominal vasculature, the cecum and small intestine were wrapped in clear plastic wrap and placed outside the abdominal cavity. The left renal artery and descending aorta were isolated from surrounding tissue by careful blunt dissection. Ultrasonic 1- and 2-mm-diameter flow probes (Transonics Systems, Ithaca, NY) were coated with a water-soluble lubricant and placed around the left renal artery and descending aorta, respectively, for measurement of blood flow. Insertion of large-area-surface (LAS) O2 sensors (0.7 mm diameter) connected to a tissue-monitoring system (Oxylite, Oxford Optronix, Oxford, UK) allowed continuous monitoring of tPO2 in muscle, bladder, liver, and renal cortex. The LAS sensor is a new, the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: M. Singer, Bloomsbury Institute of Intensive Care Medicine, Univ. College London, Cruciform Bldg., Gower St., London WC1E 6BT, UK (e-mail: m.singer@ucl.ac.uk).
large-area sensing device that measures oxygenation along the shaft of
the catheter, i.e., away from the tip and site of maximal tissue trauma.

The relatively large sensing area of the LAS sensor averages spatial
microenvironmental tPO2 fluctuations and, thereby, is less sensitive to
tissue movement and placement. The sensor sends short pulses of light
(475 nm) along a fiber-optic cable to a platinum-complex fluorophore
located 2 mm from the tip of the probe and provides a total
measurement tPO2 surface area of 8 mm² in contact with the tissue.

On interaction with O2, the fluorophore emits light (600 nm) back
to the detection unit, the lifetime of which is inversely proportional to the
local Po2 within the tissue of interest. Inasmuch as the fluorescence
decay is longer at a lower Po2, accurate measurements can be made
within the physiological range (0–60 mmHg). In contrast to polaro-
graphic techniques, O2 is not consumed during the measurement
process.

For measurement of muscle tPO2, a small incision was made at
midhigh level, and an 18-gauge guidance cannula was used to insert
the sensor into the vastus intermedius muscle to a depth of 10 mm.
The left kidney was punctured using a 22-gauge needle and the O2
probe was inserted to a depth of 2 mm and later withdrawn by 1 mm
to prevent anomalous measurements resulting from local hemotoma.

An insertion depth of 1 mm enables measurement of tPO2 within the
renal cortex, as previously described (51). The bladder O2 probe was
sited within the bladder lumen via the bladder catheter, which con-
tinually drained the bladder, thus ensuring good sensor contact with
the epithelial surface. For measurement of liver tPO2, the probe was
placed directly into the airtight space between two of the liver lobes.
Pilot studies showed data comparable to those obtained from direct
puncture, but without induction of trauma.

Mean arterial pressure, blood flow in the left renal artery and
descending aorta, and all tPO2 measurements were continuously moni-
tored and recorded on a computer using a 16-channel Powerlab
system and Chart 4.2 acquisition software (AD Instruments).

After instrumentation, intravascular volume optimization was
achieved by repeated 1.5-mI intravenous fluid challenges given over
10 s every 5 min until blood pressure or aortic blood flow failed to
increase >10%. This ensured adequate filling at baseline. A continu-
ous fluid infusion of normal saline was then administered at a rate of
20 ml·kg⁻¹·h⁻¹ for the duration of the experiment to ensure adequate
filling throughout the experiment. Clear plastic wrap was placed over
the abdomen to minimize evaporative fluid and convective heat loss.
Rectal temperature was recorded at baseline and at 15-min intervals
for the duration of the experiment using a thermometer (model 1319,
TES Electrical Electronic, Taipei, Taiwan) inserted to a depth of 3 cm.

Animals were allowed to stabilize for >30 min to achieve stable
baseline physiological variables. Sham-operated controls were moni-
tored for an additional 3 h before they were killed. Arterial blood
samples (~0.2 ml) were collected in heparinized capillary tubes for
blood gas analysis (ABL-70 analyzer, Radiometer, Copenhagen, Den-
mark), which included measurement of arterial base excess, lactate,
and Po2. In separate studies, the animals were subjected to a variety
of cardiorespiratory insults. 1) Endotoxemia was induced by intrave-
nous infusion of endotoxin (10 mg/kg; Escherichia coli LPS, serotype
0127:B8, Sigma, Poole, UK) over 5 min. 2) Controlled hemorrhage
was achieved by removal of 10% of estimated circulating blood
volume (based on a total of 70 ml/kg) from the arterial line into a
heparinized syringe. The exsanguinated blood was kept at 37°C on a
heated mat and reinfused into the animal 15 min later, and the effects
of retransfusion were observed. Every 15 min thereafter, 10% of
circulating blood volume was removed until death occurred. 3) Hyper-
oxemia was achieved by varying the percentage of inspired O2 (FiO2).
A blend of pure O2 and N2 was delivered through a flowmeter via the
isoflurane vaporizer while the animal remained anesthetized: 15% O2
for 30 min followed by normoxia for 30 min, 12.5% O2 for 30 min
followed by 30 min of normoxia, and 10% O2 for the final hour or
until death occurred. The O2 content of the gas mixture was assessed
before delivery by passage of a sample through the blood gas ana-
lyzer.

In control and endotoxin-treated animals, arterial blood gas analy-
ysis was performed at 0 (baseline), 0.5, 1, and 3 h. In hemorrhagic
shock, analysis was performed at baseline and at 30-min intervals
thereafter using the exsanguinated blood. In hypoxemic rats, blood
gas analysis was performed at baseline and at the end of each period
of altered FiO2, i.e., at 30-min intervals. Inasmuch as some animals
subjected to consecutive hemorrhage or hypoxemia died before the
3-h time point, efforts were made to obtain a perterminal sample.

Values are means ± SE (n = 6–10 per group). Statistics were
performed on raw data using a repeated-measures two-way ANOVA
followed by Tukey’s post hoc test (SigmaStat, Systat Software, San
Jose, CA) to compare multiple groups at multiple time points.

RESULTS

Before instrumentation, the body weight of each study group
of rats was similar (305.6 ± 4.3 g). All animals in the control
(n = 10) and endotoxin-treated (n = 9) groups survived for the
3-h duration of the experiment. All animals (n = 6) subjected
to sequential hemorrhage died before 3 h: time of death
127.3 ± 10.8 min. In the hypoxemia group, four of six animals
died before 3 h: time of death 149.8 ± 10.2 min.

At baseline, i.e., after volume optimization and a stabiliza-
tion period, none of the groups showed statistically sig-
nificant differences from one another for any cardiorespiratory
variable measured. Baseline values of tPO2 were highest
in the bladder, followed by muscle, liver, and renal cortex
(Figs. 1–3).

All measurements in control animals remained constant for
the duration of the experiment, with the exception of aortic
blood flow and bladder tPO2, which progressively fell, and
kidney cortical tPO2, which gradually rose (P < 0.05; Figs.
1–3). Core temperature in the hemorhage and hypoxemia
groups did not differ from that in time-matched controls at any
duration during the experiment. Endotoxin significantly increased
core temperature to a maximum of 39.5 ± 0.3°C at 3 h
compared with 37.5 ± 0.3°C in time-matched controls (P <
0.001). Arterial Pco2 remained constant in control animals
throughout the experiment: 38.7 ± 2.4 and 31.7 ± 2.6 mmHg
at baseline and 3 h, respectively (P = 0.1).

The effects of endotoxin on hemodynamic, tPO2, and arterial
blood gas variables are shown in Fig. 1. The predictable early
fall in blood pressure and aortic and renal blood flow was
followed by recovery within 1 h. In this model, flows subse-
quently fell (P < 0.05 vs. control), but blood pressure re-
mained unchanged, and hemoglobin was elevated compared
with baseline (P < 0.01; Fig. 4). This suggests that normovol-
emia was not maintained, likely because of increased capillary
leak, despite the concurrent high-volume resuscitation. Calcu-
lated O2 delivery was decreased at 3 h compared with baseline
(P < 0.05; Fig. 4). Arterial lactate and base excess became
progressively deranged (P < 0.001 vs. control), with signifi-
cance achieved as early as 1 h after injection. Arterial Po2 and
percent saturation (HbO2) remained unchanged in control and
LPS-treated rats, whereas different patterns were observed in
tPO2 in the four organ beds. Although bladder tPO2 increased
compared with controls from as early as 1 h (P < 0.01 by
overall ANOVA), renal cortical tPO2 (P = 0.68) and muscle
tPO2 (P = 0.14) showed no significant change, whereas liver
tPO2 fell significantly (P < 0.05) from 2 h. Arterial Po2
remained constant throughout the experimental period (76.5 ±
6.5 and 73.4 ± 9.8 mmHg at baseline and 3 h, respectively $P = 0.8$), whereas arterial $P\text{CO}_2$ decreased (34.8 ± 1.6 and 21.5 ± 3.4 mmHg at baseline and 3 h, respectively, $P < 0.01$).

Figure 2 shows the effects of sequential hemorrhage. Initial removal of 10% of blood volume significantly affected only mean arterial pressure, which fell from 92.7 ± 2.5 to 78.2 ± 1.6 mmHg at 15 min ($P < 0.05$) and recovered on reinfusion of the shed blood. Subsequent exsanguination caused a progressive decrease in mean arterial pressure, with preterminal values averaging 44.2 ± 4.9 mmHg ($P < 0.001$). Similar changes were seen in aortic and renal blood flow ($P < 0.01$). Arterial base excess and lactate were maintained within normal limits until 40% of blood volume had been removed, at which point rapid and progressive deterioration was noted for both variables ($P < 0.01$; Fig. 2, see Fig. 6). Arterial PO2 remained constant for 1 h and then increased to a maximum of 107.9 ± 6.9 mmHg from a baseline of 80.9 ± 2.4 mmHg ($P < 0.001$). This rise in arterial PO2 is related to hypocapnia secondary to metabolic acidosis-induced hyperventilation. Accordingly, arterial $P\text{CO}_2$ decreased from 39.6 ± 1.5 mmHg at baseline to preterminal values of 14.5 ± 1.6 mmHg ($P < 0.001$). tPO2 in muscle, bladder, and liver were reduced by a similar proportion after progressive hemorrhage ($P < 0.001$ vs. control) and fell along with $O_2$ delivery (Fig. 4) fell later (12.5% $O_2$), and arterial base excess decreased only at the preterminal phase (10% $O_2$). Arterial PO2 initially fell along with the degree of hypoxemia but rose at 10% $O_2$ because of hyperventilation-induced hypocapnia related to the profound metabolic acidosis. Similarly, the oxyhemoglobin level initially fell along with FiO2 but remained unchanged at 10% O2 (Fig. 4). Arterial PO2 was reduced during hypoxemia but was not significantly different from baseline: 36.6 ± 0.8 and 23.4 ± 9.3 mmHg at baseline and preterminal ($P < 0.1$). During normoxemia, tPO2 returned to control values in all beds (except bladder after 12.5% O2), whereas blood pressure and blood flows showed no evidence of recovery. Arterial lactate showed only a nonsignificant ($P = 0.12$) rise, even with marked acidemia (Figs. 3 and 6).

The relationship between global $O_2$ delivery and tPO2 in the different organs is illustrated in Fig. 5. Despite the different baseline values, the proportionality in terms of fall in tPO2 was often maintained across the organ beds. Muscle tPO2 showed the most consistency across the different insults, followed by the liver, although the fall in hepatic tPO2 occurred sooner with endotoxin. Renal cortical and bladder tPO2 showed less consistency.

Fig. 1. Effects of endotoxemia on hemodynamic, tissue PO2 (tPO2), and blood gas biochemical variables. MAP, mean arterial pressure; ABF, aortic blood flow; RBF, renal blood flow; ABE, arterial base excess. Values are means ± SE. *$P < 0.05$ vs. control; †$P < 0.05$ vs. endotoxemia baseline; ‡$P < 0.05$ vs. control baseline (2-way ANOVA with repeated measures followed by Tukey’s test).
DISCUSSION

tPO2 represents the balance between local O2 supply and demand. It has been used in clinical studies of heart failure, sepsis, blood loss, and the adequacy of resuscitation from a variety of sites, including conjunctiva (42), subcutaneous tissue (18), and skeletal muscle (4). However, the relevance of changes in these more peripheral beds with regard to deeper, “vital” organs, such as the liver and kidney, has not been previously addressed. We set out to answer this question by constructing models of three pathophysiologically distinct shock states (hemorrhage, hypoxemia, and early sepsis) that share common features of severe cardiorespiratory and biochemical derangement.

We achieved reasonable hemodynamic stability in our sham-operated model over the time course of the experiment. In terms of macrocardiorespiratory variables, only aortic blood flow fell from baseline. However, hematocrit was maintained, suggesting maintenance of intravascular filling, and there was no significant change in O2 delivery. Renal cortical tPO2 increased over the course of the experiment, despite no change in macrovascular renal blood flow. Because renal blood flow predominantly supplies the cortex, an impairment of cortical O2 utilization and/or a relative decrease in microvascular shunting is implied, inasmuch as renal venous PO2 is usually very high (49). This could be related to surgical stress and/or trauma from direct puncture, resulting in release of inflammatory mediators, including nitric oxide, or to a potential metabolic effect of isoflurane anesthesia on the kidney.

Our study demonstrates heterogeneous tPO2 responses to the different cardiorespiratory insults in the four organ beds. These responses vary between organs during the course of the same insult and in the same organ during different shock states. Alterations in peripheral (bladder and skeletal muscle) tPO2 mirrored those in central organ (liver and renal cortex) tPO2 during hypoxemia in terms of direction and magnitude. In contrast, the renal cortical tPO2 response to hemorrhage was considerably delayed compared with the response of the other organ beds, whereas endotoxemia resulted in a much wider variation, ranging from an early rise in bladder tPO2 to an early fall in hepatic tPO2.

Our results challenge the traditional paradigm that a fall in O2 delivery by whatever means, i.e., a reduction in cardiac output, hemoglobin, or O2 saturation, will produce a similar response at the organ level. They also highlight increased sensitivity and/or adaptation of individual organs to specific insults. For example, we previously argued that sepsis-induced organ failure represents a state of metabolic shutdown as a consequence of impaired mitochondrial energy generation (7, 8). This line of thought was initiated by our finding of elevated bladder epithelial tPO2 in high- and low-cardiac output short-term endotoxemic rat models (35, 36), indicative of a reduced O2 demand relative to supply. Similar findings were reported in gut mucosa (46) and human skeletal muscle (4, 38). Inasmuch as >90% of total body O2 consumption is directed toward mitochondrial respiration, an elevated tPO2 is highly suggestive of decreased mitochondrial utilization and/or a metabolic shutdown with a consequent reduction in O2 demand.

In the present study, we replicated our earlier finding of a rise in bladder epithelial tPO2 during short-term endotoxemic sepsis (35, 36). However, this did not translate to muscle or...
renal cortex, where no significant change in tPO₂ from control values was noted, despite a fall in aortic and renal blood flow, or in the liver, where an early and marked fall was observed. This is likely to reflect early specific organ responses to endotoxin, ranging from a metabolic shutdown in the bladder to an increase in hepatic O₂ demand. Fry et al. (17) reported a decline of ~90% in hepatic tPO₂ in a 6-h endotoxemic rat model, although these animals maintained normal systemic oxygenation and blood pressure. Ince (21) described a “microcirculatory and mitochondrial distress syndrome,” where microcirculatory and mitochondrial dysfunction persists, despite apparent restoration of the macrocirculation. Our results support this concept, although individual responses are seen in different organ beds, at least in this short-term model.

There are several potential explanations for an early fall in liver tPO₂. 1) Dahn et al. (12) reported increases in hepatic blood flow (72%) and splanchnic O₂ consumption (60%) in septic patients, yet they suggested from modeling data that intrahepatic flow redistribution would significantly reduce central lobular O₂. 2) Microcirculatory heterogeneity may lead to increases in local hypoxic regions and, consequently, could limit O₂ availability in septic (5, 14, 21, 39), as well as hemorrhagic (50), shock states. 3) Hepatic metabolic activity is augmented during early sepsis as part of the acute-phase response.

Fig. 3. Effects of hypoxemia [10–21% inspired O₂ (FIO₂)] on hemodynamic, tPO₂, and blood gas biochemical variables. *P < 0.05 vs. control; †P < 0.05 vs. hypoxemia baseline; ‡P < 0.05 vs. control baseline (2-way ANOVA with repeated measures followed by Tukey’s test).

Fig. 4. Effects of endotoxemia, hemorrhage, and hypoxemia on O₂ delivery, hemoglobin, and oxyhemoglobin (HbO₂). O₂ delivery was calculated as the product of descending aortic blood flow, hemoglobin, and arterial O₂ (%) and 1.34. *P < 0.05 vs. control baseline (2-way ANOVA with repeated measures followed by Tukey’s test).
response (11), and this may continue, despite a fall in O₂ delivery. Activation of Kupffer cells, which constitute 15% of liver mass, would greatly increase O₂ consumption as a result of hypermetabolism and free radical generation within these macrophages. This may represent a considerable component of the increased liver O₂ utilization during sepsis.

4) Portal venous O₂ saturation may be considerably lower because of decreased gut flow and/or any increase in gut metabolic activity. In a recent short-term septic dog study, Rahal et al. (34) reported a decrease in portal venous O₂ saturation from 91.7 ± 1.4% to 59.8 ± 6.1% at 150 min in conjunction with a fall in cardiac output. This is particularly pertinent, inasmuch as the portal vein contributes 75% of hepatic blood flow (25).

It is important to stress the severe, short-term (3-h) nature of the endotoxin challenge we applied. It was designed to match the time courses of the other lethal insults, but it will engender a different physiological response to a more protracted septic insult. In a mouse model of endotoxic sepsis, liver tPO₂ also decreased by ~75% at 6 h (25). Liver O₂ extraction fell concurrently from 41% in control animals to 15% after endotoxin, implying a significant fall in utilization over and above the decrease in tissue oxygenation. In a separate study, the same group reported recovery of liver tPO₂ toward normal values if the animals survived for 6 h after endotoxin exposure (26). Using a 15-h murine septic shock model, Albuszies et al. (1) reported impaired hepatic metabolic capacity, despite well-maintained hepatosplanchnic oxygenation and microvascular perfusion, whereas MacMicking et al. (31) reported oxidative damage to the liver only 10–11 h after an endotoxin challenge. This may be related to the high antioxidant capacity of the liver, in particular glutathione, which protects mitochondria against oxidant and nitrosative damage (9). As a consequence, effects of sepsis on mitochondrial activity in the liver may be delayed with respect to other organs. Kozlov and colleagues (29) found a decrease in mitochondrial respiratory activity in cardiomyocytes but a concurrent rise in liver mitochondria. We previously demonstrated mitochondrial dysfunction in liver and muscle in a long-term (72-h) awake, fluid-resuscitated rat model of fecal peritonitis (8). Only muscle ATP-to-ADP ratios were significantly reduced at 4 h, whereas mitochondrial function was more affected in the liver than in muscle at 24 and 48 h.

In contrast to endotoxemia, we observed decreased liver, muscle, and bladder tPO₂ in hemorrhagic shock and hypoxemia. These observations are consistent with a fall in O₂ delivery related to decreases in cardiac output and arterial O₂ content. Decreases in tissue oxygenation following hemorrhage have been reported by other groups in peripheral tissues, such as skeletal muscle (6) and conjunctiva, (6, 18, 42), and in deeper tissues, such as the liver and gut (28, 33, 48).

The renal cortical tPO₂ response to hemorrhage did not follow that seen in other organ beds until the preterminal stage. This may be related to regional flow autoregulation, which, as we and others previously showed (32, 51), is better maintained in the cortex than in the medulla during hemorrhage. In contrast to other organ beds, renal O₂ consumption varies directly according to O₂ delivery in the normal physiological range and during hemorrhagic shock, as shown by Schlötig and colleagues (41). In the liver, however, the same group found that metabolic demands exceeded O₂ delivery during hemorrhage (40). This could explain the maintained renal cortical tPO₂ and the early decrease in hepatic tPO₂ we observed during hemorrhage (and endotoxemia). Tubular sodium reabsorption is traditionally considered to account for 70–90% of renal O₂ consumption (41). Because renal O₂ consumption depends on delivery, a fall in O₂ supply should result in decreased sodium and water reabsorption and, thus, polyuria. This clearly does not happen in shock states; thus the reduction in O₂ consumption must be secondary to reduced glomerular filtration.

Fig. 5. Relationship between global O₂ delivery (DO₂) and tPO₂ in response to continued endotoxemia, progressive hemorrhage, and increasing hypoxemia. Values are means.

AJP-Heart Circ Physiol • VOL 293 • JULY 2007 • www.ajpheart.org

Fig. 6. Comparison of continued endotoxemia, progressive hemorrhage, and increasing hypoxemia on arterial base excess and lactate. Values are means ± SE.
There was a fourfold variation in baseline tPO2 in the four organ beds. Comparable data cited by us (35, 43, 44, 51) and others (2, 23, 37, 48) reflect differences in their individual metabolic activity and O2 supply. The platinum optode used in this study calculates PO2 over a relatively large area using the principle of fluorescence quenching. This is related directly to the local tPO2 according to the Stern-Volmer equation. Inasmuch as the fluorescence lifetime is longest at low tPO2 values, these probes are most sensitive in the physiological range of 0–60 mmHg. The probe also samples from a relatively large volume of tissue compared with many other probes and, thus, may be less susceptible to small variations in probe position in proximity to blood vessels.

Consistent with our previous findings in this spontaneously breathing, anesthetized rat model (35, 36), arterial PO2 increases and Pco2 falls (data not shown) as a result of compensatory hyperventilation for severe metabolic acidosis. This hyperventilation could even increase arterial PO2 at 10% O2 above that measured at 12.5% O2. However, this was not reflected in tPO2 in any of the organ beds monitored, inasmuch as blood flow was also significantly reduced with lower FIO2. Acute derangements in arterial base excess and lactate are used clinically as indicators of poor organ perfusion. These indexes correlate well with severity of illness and mortality (3, 13, 16). Although hyperlactatemia is traditionally considered a marker of tissue hypoxia, it is clear that it can be elevated in critical illness by nonanaerobic mechanisms, including increased activity of the Na+-K+-ATPase pump in skeletal muscle related to increased catecholamine levels (19, 22) and accelerated glycolysis (24). Other causes include an inability to metabolize pyruvate to acetyl CoA due to decreased activity of pyruvate dehydrogenase (47) and a decrease in mitochondrial respiration that may be due to direct inhibition (3, 13, 16) or substrate (O2) limitation (24). Figure 6 shows the relationship between arterial base deficit and lactate. Accordingly, hemorrhage produced equivalent increases in blood levels of both variables, although, with preterminal hypoxemia, there was considerable deterioration in the base deficit with little change in lactate. With endotoxin, the blood lactate and base deficit levels were equivalent to those observed in hemorrhage and mild-to-moderate hypoxemia. We did not measure blood pyruvate levels or blood cations and anions to draw comparisons between the different shock states in terms of calculated anion gap and strong ion difference. Precise mechanisms remain to be determined to explain the disparity during late hypoxemia, although one component may be increased consumption of lactate by the liver, heart, and other organs as a fuel substrate. Alternatively, hypoxia has been shown to inhibit the Na+-K+-ATPase pump (10), which could account for the absence of hyperlactatemia coupled with a severe metabolic acidosis in late hypoxemia.

In summary, we demonstrate heterogeneous responses in tPO2 in different organ beds to a variety of short-term cardiorespiratory insults. Only hypoxemia produced comparable, severity-dependent changes across all organs. The renal cortex appears to initially protect itself by decreasing its O2 consumption during hemorrhage, in contrast to the liver, which is more compromised than the other organs during endotoxemia. The arterial lactate and base deficit responses also varied between insults and did not necessarily reflect major deterioration or protection in any individual organ. This study highlights the utility of assessing organ hypoperfusion from global markers such as lactate or from tPO2 in surrogate organ beds such as the bladder. However, it also demonstrates the limitations of these techniques, in that specific organs may be differentially affected by different conditions that may not be apparent from markers monitored globally or in other tissues.

REFERENCES


