

# Effects of ventilation with 100% oxygen during early hyperdynamic porcine fecal peritonitis\*

Eberhard Barth, MD; Gabriele Bassi, MD; Dirk M. Maybauer, MD, PhD; Florian Simon, MD; Michael Gröger, MA; Sükrü Öter, MD, PhD; Günter Speit, PhD; Cuong D. Nguyen, MD; Cornelia Hasel, MD; Peter Möller, MD, PhD; Ulrich Wachter, MA; Josef A. Vogt, PhD; Martin Matejovic, MD, PhD; Peter Radermacher, MD, PhD; Enrico Calzia, MD, PhD

**Objective:** Early goal-directed therapy aims at balancing tissue oxygen delivery and demand. Hyperoxia (i.e., pure oxygen breathing) has not been studied in this context, since sepsis increases oxygen radical production, which is believed to be directly related to the oxygen tension. On the other hand, oxygen breathing improved survival in various shock models. Therefore, we hypothesized that hyperoxia may be beneficial during early septic shock.

**Design:** Laboratory animal experiments.

**Setting:** Animal research laboratory at university medical school.

**Subjects:** Twenty domestic pigs of either gender.

**Interventions:** After induction of fecal peritonitis, anesthetized and instrumented pigs were ventilated with either 100% oxygen or supplemental oxygen as needed to maintain arterial hemoglobin oxygen saturation  $\geq 90\%$ . Normotensive and hyperdynamic hemodynamics were achieved using hydroxyethyl starch and norepinephrine infusion.

**Measurements and Main Results:** Before and at 12, 18, and 24 hrs of peritonitis, we measured lung compliance; systemic, pulmonary, and hepatosplanchnic hemodynamics; gas exchange;

acid-base status; blood isoprostanes; nitrates; DNA strand breaks; and organ function. Gluconeogenesis and glucose oxidation were calculated from blood isotope and expiratory  $^{13}\text{CO}_2$  enrichments during continuous intravenous 1,2,3,4,5,6- $^{13}\text{C}_6$ -glucose. Apoptosis in lung and liver was assessed postmortem (TUNEL staining). Hyperoxia did not affect lung mechanics or gas exchange but redistributed cardiac output to the hepatosplanchnic region, attenuated regional venous metabolic acidosis, increased glucose oxidation, improved renal function, and markedly reduced the apoptotic death rate in liver and lung.

**Conclusions:** During early hyperdynamic porcine septic shock, 100% oxygen improved organ function and attenuated tissue apoptosis without affecting lung function and oxidative or nitrosative stress. Therefore, it might be considered as an additional measure in the first phase of early goal-directed therapy. (Crit Care Med 2008; 36:495–503)

**KEY WORDS:** lactate; lactate/pyruvate ratio; gluconeogenesis; glucose oxidation; stable isotope; creatinine clearance; isoprostane; nitrate; apoptosis

Early goal-directed therapy for septic shock attempts to balance oxygen delivery and demand, mainly by optimizing cardiac function and hemoglobin concentration. In contrast, hyperoxia (i.e., ventilation with 100% oxygen) has not been studied in this context (1). Hyperoxia may theoretically aggravate tissue injury:

Septic shock is associated with oxidative stress resulting from enhanced formation of reactive oxygen species (ROS) and nitrogen species (2, 3), and ROS production is directly related to oxygen tension (4, 5). Nevertheless, hyperoxia has benefits: Oxygen has antibiotic activity (6), and, in fact, perioperative hyperoxia reduced wound infections after abdominal surgery

(7, 8). Furthermore, ventilation with 100% oxygen improved survival in various shock models characterized by depressed oxygen delivery (9, 10). In rats undergoing ischemia/reperfusion and hemorrhage, hyperoxia increased blood pressure, redistributed cardiac output to the hepatosplanchnic organs and the kidney, improved microcirculatory perfusion, and reduced the systemic inflammatory response (11, 12). These data, however, originate from short-term hypodynamic rodent models characterized by hypotension and low cardiac output, which is in contrast to the hyperdynamic circulation commonly seen in patients with septic shock. Furthermore, rodents markedly differ from humans with respect to their immune response to sepsis (13) and their tissue antioxidative capacity and susceptibility to oxidative stress (14, 15). Therefore, we tested whether

**\*See also p. 637.**

From Sektion Anästhesiologische Pathophysiologie und Verfahrensentwicklung (EB, GB, DMM, FS, MG, SO, CDN, UW, JAV, MM, PR, EC), Abteilung Thorax- und Gefäßchirurgie (FS), Abteilung Humangenetik (GS), and Abteilung Pathologie (CH, PM), Universitätsklinikum, Ulm, Germany; Istituto di Anestesiologia e Rianimazione dell'Università degli Studi di Milano, Azienda Ospedaliera, Polo Universitario San Paolo, Milano, Italy (GB); Fizyoloji Anabilim Dalı, Gülhane Askeri Tıp Akademisi, Ankara, Turkey (SO); and I. interní klinika, Karlova Univerzita, Lékařská fakulta a Fakultní nemocnice, Plzeň (MM). Drs. Barth, Bassi, and Maybauer equally contributed to this study.

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For information regarding this article, E-mail: peter.radermacher@uni-ulm.de

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early hyperoxia is beneficial during porcine normotensive, hyperdynamic fecal peritonitis-induced septic shock.

## MATERIALS AND METHODS

The experiments were performed in adherence with the National Institutes of Health Guidelines on the Use of Laboratory Animals. The study protocol was approved by the University Animal Care Committee and the Federal Authorities for Animal Research (Regierungspräsidium Tübingen, Germany).

**Animals and Preparation.** Before surgery, 20 domestic pigs of either gender were fasted for 24 hrs with free access to water. Preanesthesia consisted of intramuscular atropine (2.5 mg) and azaperone (150–200 mg). Anesthesia was induced with intravenous atropine (0.5 mg), propofol (1–2 mg·kg<sup>-1</sup>), and ketamine (1.5–2.0 mg·kg<sup>-1</sup>). Animals were mechanically ventilated (Fio<sub>2</sub> 0.21, positive end-expiratory pressure [PEEP] 8 cm H<sub>2</sub>O, tidal volume 8 mL·kg<sup>-1</sup>, respiratory rate 10–12 breaths·min<sup>-1</sup> adjusted to maintain arterial Pco<sub>2</sub> at 35–45 mm Hg). Anesthesia and analgesia were achieved with continuous intravenous pentobarbitone (0.14 mg·kg<sup>-1</sup>·hr<sup>-1</sup>) and intermittent buprenorphine (30 µg·kg<sup>-1</sup>) and muscle paralysis with continuous intravenous alcuronium (0.28 mg·kg<sup>-1</sup>·hr<sup>-1</sup>). Depth of anesthesia was continuously controlled by electroencephalographic analysis over the total 36 hrs of the experiment. The spectral edge frequency was always <15 Hz, and the median power frequency was 5–10 Hz (16–18). A gastric tube with an inflatable esophageal balloon was placed so that cardiac oscillations were detected on the balloon pressure tracing. Both jugular veins and femoral arteries were exposed. A catheter was inserted into the superior vena cava; a balloon-tipped thermodilution pulmonary artery catheter was placed to measure central venous, pulmonary arterial, and pulmonary artery occluded pressures and cardiac output. One femoral arterial catheter was placed for blood pressure recording and blood sampling, a fiberoptic one for thermal-dye double-indicator dilution measurements. Precalibrated ultrasonic flow probes were placed around the portal vein and the hepatic artery via a midline laparotomy. The ileal serosal microcirculation was monitored after fixation of tissue oxygen tension and laser Doppler flowmetry probes into the gut wall via two incisions in the visceral peritoneum. A fiberoptic Pco<sub>2</sub> sensor was inserted into a loop ileostomy. Two tubes were placed through the abdominal wall for peritonitis induction and ascites drainage. Catheters were introduced into the portal vein and into a hepatic vein under ultrasound guidance. A catheter in the bladder allowed urine collection. After surgery, animals recovered for 6 hrs before baseline measurements were recorded. Ringer's solution was continuously infused as maintenance fluid (10 and 7.5 mL·kg<sup>-1</sup>·hr<sup>-1</sup> during

and after surgery, respectively). As needed, animals received hydroxyethyl starch to maintain cardiac filling pressures during surgery and glucose to keep glycemia at 4–6 mmol·L<sup>-1</sup> (controls n = 7, median [quartiles] infusion rate 2.5 [1.2; 3.2], hyperoxia n = 8, 3.4 [2.0–4.5] mg·kg<sup>-1</sup>·min<sup>-1</sup>). Simultaneously with anesthesia induction, 0.5 g·kg<sup>-1</sup> of autologous feces were suspended in 100 mL of saline and cultivated at 38°C until the induction of peritonitis. Body temperature was kept constant within ±1°C of the value before induction of peritonitis (i.e., 37–39°C) with heating pads or cooling.

**Measurements and Calculations.** Systemic, pulmonary, intestinal, and hepatic (ultrasound flow probes on the portal vein and the hepatic artery) hemodynamics and gas exchange (arterial, portal, hepatic, and mixed venous blood gases and oximetry); intrathoracic blood volume and extravascular lung water (thermal green dye double indicator dilution); ileal mucosal-arterial Pco<sub>2</sub> gap (fiberoptic sensor in the ileostomy); nitrate + nitrite (NO<sub>2</sub><sup>-</sup> + NO<sub>3</sub><sup>-</sup>) concentrations (chemoluminescence); blood glucose, lactate, pyruvate, bilirubin, creatinine, tumor necrosis factor (TNF)-α, and 8-isoprostane concentrations; whole blood cell DNA strand breaks (tail moment in the comet assay); and alanine- and aspartate-aminotransferase activities were determined as described previously (17–19). Bladder pressure was measured as a surrogate for intra-abdominal pressure (20). Systemic and regional oxygen transport values were calculated using standard formulas. Blood norepinephrine concentrations were assessed with high-performance liquid chromatography (21). Superoxide dismutase and catalase activities in lung and liver were measured using commercial kits (19). Systemic CO<sub>2</sub> production was measured using indirect calorimetry; systemic oxygen uptake was calculated using the Fick principle and corrected for conditions of standard temperature and pressure, dry, and ambient temperature and pressure, saturated, because the direct measurement of oxygen consumption using the calorimetry device is impossible during hyperoxia (22). Lung compliance was derived from gas flow and airway and pleural (i.e., esophageal) pressures using an occlusion technique (23) adopted for pigs (24). The alanine- and aspartate-aminotransferase activities and bilirubin, creatinine, 8-isoprostane, TNF-α, and NO<sub>2</sub><sup>-</sup> + NO<sub>3</sub><sup>-</sup> concentrations are normalized per gram of plasma protein to correct for dilution by intravenous fluids (25). Using a steady-state approach, endogenous glucose production was calculated as the difference between the rate of appearance of stable, nonradioactively labeled 1,2,3,4,5,6-<sup>13</sup>C<sub>6</sub>-glucose during continuous intravenous isotope infusion minus the exogenous glucose infusion rate after gas chromatography-mass spectrometry assessment of plasma isotope enrichment (26). Direct, aerobic glucose oxidation was derived from the mixed expiratory <sup>13</sup>CO<sub>2</sub> isotope enrichment

measured using nondispersive infrared spectrometry (27) and corrected for the plasma isotope ratio and CO<sub>2</sub> production (26).

The amount of apoptotic nuclei was determined in lung and liver tissue sections using the TUNEL (terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling) assay (19). Slides were evaluated by an experienced pathologist (CH) blinded for the sample grouping. Only nuclear staining was considered positive.

**Experimental Protocol.** After surgery, the ventilator settings were as follows: tidal volume 8 mL·kg<sup>-1</sup>, PEEP 10 cm H<sub>2</sub>O, inspiratory/expiratory ratio 1:1.5, peak airway pressure ≤40 cm H<sub>2</sub>O. If the Pao<sub>2</sub>/Fio<sub>2</sub> was <300 mm Hg or <200 mm Hg, inspiratory/expiratory ratio was increased to 1:1 and PEEP to 12 or 15 cm H<sub>2</sub>O, respectively. The respiratory rate was adjusted to maintain arterial Pco<sub>2</sub> at 35–45 mm Hg until a maximum of 40 breaths/min. In addition to the Ringer's solution, hydroxyethyl starch (15 mL·kg<sup>-1</sup>·hr<sup>-1</sup>; 10 mL·kg<sup>-1</sup>·hr<sup>-1</sup> if central venous pressure or pulmonary artery occlusion pressure was ≥18 mm Hg) was infused to maintain cardiac filling pressures ≥15 mm Hg and intrathoracic blood volume ≥25 mL·kg<sup>-1</sup>. Continuous intravenous norepinephrine was adjusted (increments of 0.05 µg·kg<sup>-1</sup>·min<sup>-1</sup>; no further increase if heart rate ≥160 beats/min to avoid tachycardia-induced myocardial ischemia) to maintain mean blood pressure at the baseline levels. Continuous intravenous glucose was added if necessary to maintain glycemia at 4–6 mmol·L<sup>-1</sup>. Immediately after baseline data collection, peritonitis was induced, and simultaneously animals were randomly assigned either to Fio<sub>2</sub> = 0.21 (control group, n = 10, 7 males/3 females, median body weight 51 [range 46–59] kg), which was only modified thereafter to maintain arterial hemoglobin oxygen saturation ≥90%, or to 100% oxygen (hyperoxia group, n = 10, 4 males/6 females, median body weight 51 [range 46–58] kg), which was maintained until the end of the experiment. In accordance with literature reports (28, 29) and pilot experiments, fecal peritonitis was induced by inoculating the autologous feces into the abdominal cavity through the drainage tubes, which were subsequently kept clamped for the following 12 hrs. Additional measurements were recorded at 12, 18, and 24 hrs of peritonitis. Then the animals were euthanized under deep anesthesia by KCl injection. Immediately thereafter, blood and ascites samples from the abdominal cavity were collected for microbiology, and liver and lung biopsies were taken for TUNEL staining.

**Statistical Analysis.** All data are presented as median (quartiles). After exclusion of normal data distribution with the Kolmogorov-Smirnov test, differences within each group before and after induction of peritonitis were tested using a Friedman analysis of variance on ranks and, subsequently, a Dunn's test for multiple comparisons with Bonferroni correc-

Table 1. Microbiology results in blood cultures and ascites fluid. Numbers in brackets refer to the frequency of the individual germ

	Control	Hyperoxia
Blood	Escherichia Coli (7) Acinetobacter jejunii (2) Klebsiella pneumoniae (1) Proteus mirabilis (1) Streptococcus faecalis (1) Stenotrophomonas maltophilia (1)	Escherichia Coli (7) Sporae producer spp (2) Sterile (2)
Ascites	Escherichia Coli (9) Pseudomonas aeruginosa (4) Proteus mirabilis (2) Streptococcus faecalis (2) Streptococcus spp (2) Staphylococcus spp (2) Klebsiella pneumoniae (1) Clostridium perfringens (1) Sporae producer spp (1)	Escherichia Coli (9) Staphylococcus spp (6) Sporae producer spp (6) Streptococcus spp (5) Streptococcus faecalis (2) Bacillus firmus (2) Klebsiella pneumoniae (1) Pseudomonas aeruginosa (1)

tion. Differences between groups were analyzed by the Mann-Whitney rank-sum test for unpaired samples. Because of the multiple statistical testing resulting from the numerous variables measured, all results have to be interpreted in an exploratory rather than confirmatory manner.

## RESULTS

One control animal died from refractory hypotension after data collection at 18 hrs of peritonitis. Therefore, statistical analysis at 24 hrs included only nine control pigs. Table 1 shows the results of the microbiology cultures (ascites, 24 cultures of nine different germs in the controls vs. 32 cultures of eight different germs in the hyperoxic animals; blood, 13 cultures of six different germs in the controls vs. nine cultures of three different germs in the hyperoxia group). Two hyperoxic animals had sterile blood cultures. Both the hydroxyethyl starch infusion rate (median [quartiles], controls 15 [15; 15], hyperoxia 15 [13; 15] mL·kg<sup>-1</sup>·hr<sup>-1</sup>) and the ascites production over 24 hrs (controls 5 [3; 8], hyperoxia 4 [2; 6] mL·kg<sup>-1</sup>) were similar. While urine production rate was higher in the hyperoxia group (9 [8; 11] vs. 7 [5; 8] mL·kg<sup>-1</sup>·hr<sup>-1</sup>,  $p < .05$ ), the norepinephrine infusion rate needed to maintain blood pressure did not significantly differ (hyperoxia 0.10 [0.00; 0.40], controls 0.45 [0.20; 0.60] μg·kg<sup>-1</sup>·min<sup>-1</sup>).

Table 2 and Figures 1 and 2 summarize the systemic and pulmonary hemodynamics, gas exchange, acid-base data, and metabolism. According to the protocol, blood pressure was well maintained, whereas heart rate, cardiac output, and filling pressures significantly increased. Pulmonary hypertension and deteriora-

tion of pulmonary compliance, PaO<sub>2</sub>/Fio<sub>2</sub> ratio, and venous admixture were present in all animals but less pronounced in the hyperoxia group ( $p < .05$  at 12 hrs). Despite fluid resuscitation and blood sampling, hemoglobin concentrations and, consequently, oxygen transport significantly increased. While oxygen uptake was not significantly affected, CO<sub>2</sub> production increased significantly in the hyperoxia group. The progressive fall of arterial pH and base excess was less pronounced in the hyperoxia group ( $p < .05$  at 12 and 18 hrs, Fig. 1). While endogenous glucose production significantly increased in both groups, direct aerobic glucose oxidation was significantly higher in the hyperoxic animals at the end of the experiment. Hence, these pigs showed a near-complete (vs. approximately two thirds only in the controls) oxidation of the endogenous substrate formation (Fig. 2).

Table 3 and Figure 3 summarize the regional hemodynamics, gas exchange, acid-base, and organ function. Despite the increased intra-abdominal pressure, portal venous flow increased as well. The contribution of portal venous and total liver blood flow to cardiac output significantly increased in the hyperoxic animals ( $p < .05$  at 24 hrs, Fig. 3), which was associated with a lower oxygen extraction of the portal-drained viscera and a higher liver oxygen transport. Neither microvascular perfusion nor the ileal serosal Po<sub>2</sub> was significantly affected. While portal venous lactate/pyruvate ratios significantly increased, liver oxygen and lactate uptake were not affected. By contrast, hepatic venous lactate/pyruvate ratios were significantly lower in the hy-

peroxia-treated animals. The arterial-ileal mucosal Pco<sub>2</sub> gap significantly increased, and portal and hepatic venous pH and base decreased. The regional venous metabolic acidosis was less pronounced in the hyperoxia group ( $p < .05$  at 12 and 18 hrs, Fig. 1). Transaminase activities and bilirubin and creatinine concentrations significantly increased, but creatinine clearance was significantly higher in the hyperoxia group in the second half of the experiment.

Table 4 and Figure 4 summarize the blood norepinephrine concentrations; the variables of the inflammatory response, oxidative stress, and antioxidant activity; and the apoptotic events. TNF-α, NO<sub>2</sub><sup>-</sup> + NO<sub>3</sub><sup>-</sup>, and 8-isoprostane concentrations and the tail moment in the comet assay significantly increased. Post-mortem lung and liver tissue activities of superoxide dismutase and catalase were similar. However, hyperoxia markedly reduced the number of apoptotic cells in lung and liver (Fig. 4).

## DISCUSSION

In the present study, we investigated the effects of hyperoxia during long-term normotensive, hyperdynamic porcine septic shock. The key findings were that hyperoxia a) did not affect lung mechanics or pulmonary gas exchange; b) did not aggravate oxidative or nitrosative stress; c) redistributed cardiac output in favor of the hepatosplanchnic organs; d) improved direct, aerobic glucose oxidation rate and renal function; e) attenuated metabolic acidosis; and f) reduced apoptosis in liver and lung.

According to the experimental protocol, both groups presented with comparable systemic hemodynamics. The reduced norepinephrine requirements, which did not reach statistical significance due to the large interindividual variation, confirm the systemic vasoconstrictor properties of oxygen ventilation described in animals (11, 12, 30) and patients (31, 32). Within the limitations of our methodology we could not confirm, however, the hyperoxia-related impairment of left ventricular function described by others (33): While intrathoracic blood volume, a well-accepted surrogate of cardiac preload, and cardiac output were comparable, pulmonary artery and cardiac filling pressures were lower in the hyperoxic animals.

Sepsis increased portal venous and total hepatic blood flow. The fractional con-

Table 2. Systemic and pulmonary hemodynamics, gas exchange, acid-base data, and metabolism

	Before Peritonitis	12 Hrs Peritonitis	18 Hrs Peritonitis	24 Hrs Peritonitis
HR, beats·min <sup>-1</sup>				
Control	96 (83–113)	125 (113–140)	131 (113–150) <sup>b</sup>	143 (136–152) <sup>b</sup>
Hyperoxia	87 (81–94)	120 (103–122)	129 (107–144) <sup>b</sup>	143 (122–154) <sup>b</sup>
MAP, mm Hg				
Control	94 (88–97)	102 (93–116)	91 (84–95)	95 (87–100)
Hyperoxia	90 (86–93)	101 (95–113)	94 (87–105)	92 (84–93)
MPAP, mm Hg				
Control	28 (26–32)	41 (36–45) <sup>a,b</sup>	44 (39–46) <sup>b</sup>	48 (39–54) <sup>b</sup>
Hyperoxia	30 (25–30)	33 (29–36)	34 (30–37)	36 (32–41) <sup>b</sup>
CVP, mm Hg				
Control	10 (8–14)	13 (12–16)	16 (13–18)	19 (14–21) <sup>b</sup>
Hyperoxia	10 (6–13)	9 (7–15)	11 (9–15)	12 (10–16)
PAOP, mm Hg				
Control	12 (10–14)	17 (12–18) <sup>a</sup>	17 (14–19)	19 (15–23) <sup>b</sup>
Hyperoxia	10 (8–14)	11 (8–14)	14 (11–17)	14 (11–20)
CO, mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	111 (105–122)	138 (123–160)	168 (128–210) <sup>b</sup>	191 (149–248) <sup>b</sup>
Hyperoxia	110 (99–128)	129 (118–144)	134 (126–174)	161 (125–174) <sup>b</sup>
ITBV, mL·kg <sup>-1</sup>				
Control	26 (24–27)	27 (26–31)	28 (26–30)	30 (28–33)
Hyperoxia	27 (24–30)	27 (24–34)	28 (26–29)	28 (26–30)
EVLW, mL·kg <sup>-1</sup>				
Control	2 (1–3)	3 (1–5)	5 (4–6) <sup>b</sup>	5 (4–6) <sup>b</sup>
Hyperoxia	3 (2–4)	4 (3–6)	5 (1–6)	4 (2–6)
Arterial PO <sub>2</sub> , mm Hg				
Control	90 (89–93)	80 (73–83) <sup>a</sup>	74 (64–81) <sup>a,b</sup>	71 (57–83) <sup>a,b</sup>
Hyperoxia	92 (91–99)	490 (470–521)	337 (262–450)	286 (149–390)
Arterial PCO <sub>2</sub> , mm Hg				
Control	37 (36–40)	37 (36–40) <sup>a</sup>	43 (42–45)	44 (36–81)
Hyperoxia	38 (37–42)	42 (41–44)	43 (40–46)	41 (38–45)
Mixed venous PO <sub>2</sub> , mm Hg				
Control	41 (38–43)	46 (44–51) <sup>a,b</sup>	44 (43–55) <sup>a,b</sup>	48 (44–52) <sup>a,b</sup>
Hyperoxia	42 (40–44)	63 (61–66)	62 (59–69)	58 (54–67)
PaO <sub>2</sub> /FiO <sub>2</sub>				
Control	430 (421–440)	380 (349–397) <sup>a</sup>	295 (217–345) <sup>b</sup>	205 (68–289) <sup>b</sup>
Hyperoxia	439 (433–477)	490 (465–526)	336 (257–463) <sup>b</sup>	285 (147–394) <sup>b</sup>
Qs/Qt, %				
Control	11 (9–12)	23 (19–27) <sup>a,b</sup>	36 (32–38) <sup>b</sup>	47 (29–74) <sup>b</sup>
Hyperoxia	10 (8–13)	16 (14–19)	30 (23–32) <sup>b</sup>	34 (25–45) <sup>b</sup>
Cpl, mL·cmH <sub>2</sub> O <sup>-1</sup>				
Control	61 (55–80)	33 (20–36) <sup>a,b</sup>	31 (25–33) <sup>b</sup>	19 (17–32) <sup>b</sup>
Hyperoxia	71 (58–118)	50 (42–68)	37 (25–65) <sup>b</sup>	28 (26–40) <sup>b</sup>
DO <sub>2</sub> , mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	11 (10–11)	17 (15–21) <sup>b</sup>	17 (10–28) <sup>b</sup>	19 (16–21) <sup>b</sup>
Hyperoxia	10 (9–11)	16 (17–18) <sup>b</sup>	16 (14–20) <sup>b</sup>	17 (15–22) <sup>b</sup>
VO <sub>2</sub> , mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	3.8 (3.6–4.0)	4.4 (3.7–4.8)	4.2 (3.6–4.8)	5.0 (4.7–5.1)
Hyperoxia	4.1 (3.8–4.4)	3.8 (3.7–4.5)	4.0 (3.6–4.7)	4.2 (3.9–5.1)
VCO <sub>2</sub> , mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	3.0 (2.9–3.3)	3.3 (2.9–3.8)	3.5 (3.2–3.8)	3.5 (3.3–4.2)
Hyperoxia	2.8 (2.7–3.0)	3.3 (3.1–3.7)	3.8 (3.3–4.4) <sup>b</sup>	4.2 (3.6–4.9) <sup>b</sup>
Arterial pH				
Control	7.50 (7.47–7.53)	7.45 (7.40–7.47)	7.38 (7.33–7.39) <sup>b</sup>	7.29 (7.07–7.43) <sup>b</sup>
Hyperoxia	7.50 (7.47–7.51)	7.45 (7.43–7.48)	7.44 (7.38–7.47)	7.43 (7.38–7.47)
Arterial lactate, mmol·L <sup>-1</sup>				
Control	0.7 (0.6–0.8)	0.8 (0.8–0.9)	1.1 (0.9–1.5) <sup>b</sup>	1.2 (0.9–3.3) <sup>b</sup>
Hyperoxia	0.7 (0.7–0.8)	0.8 (0.7–1.1)	1.0 (0.7–1.1)	1.3 (0.9–1.6) <sup>b</sup>
Arterial L/P ratio				
Control	8 (7–8)	11 (10–11) <sup>b</sup>	14 (11–17) <sup>b</sup>	14 (11–21) <sup>b</sup>
Hyperoxia	8 (7–8)	9 (9–11)	11 (8–14) <sup>b</sup>	13 (10–17) <sup>b</sup>
Hemoglobin, g·L <sup>-1</sup>				
Control	76 (70–81)	10.2 (82–107) <sup>b</sup>	93 (88–103)	100 (90–105) <sup>b</sup>
Hyperoxia	73 (67–78)	80 (76–87)	81 (77–92) <sup>b</sup>	89 (77–98) <sup>b</sup>

CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; ITBV, intrathoracic blood volume; EVLW, extra vascular lung water; PaO<sub>2</sub>/FiO<sub>2</sub>, Horowitz oxygenation index; Qs/Qt, venous admixture; Cpl, total respiratory system compliance; VO<sub>2</sub>, systemic oxygen uptake; DO<sub>2</sub>, systemic oxygen delivery; L/P ratio, lactate/pyruvate ratio.

<sup>a</sup>Significant difference between control and hyperoxia at the same time ( $p < .05$ ); <sup>b</sup>Significant difference within each group vs before peritonitis ( $p < .05$ ).

Data are median and 25°–75° percentile (Control, n = 10; Hyperoxia, n = 10).

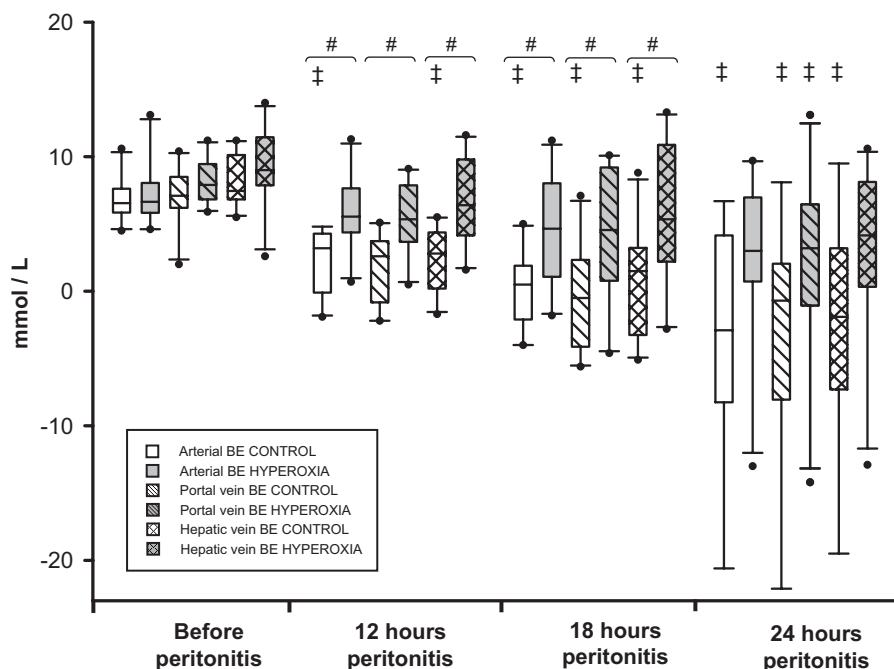


Figure 1. Arterial (*open whiskers*), portal (*hatched whiskers*) and hepatic (*cross-hatched whiskers*) venous base excess (BE) in the control (*white symbols*, n = 10) and hyperoxic (*gray symbols*, n = 10) animals. Data are median (quartiles/range), ‡Significant difference within groups vs. baseline; #p < .05 between groups.

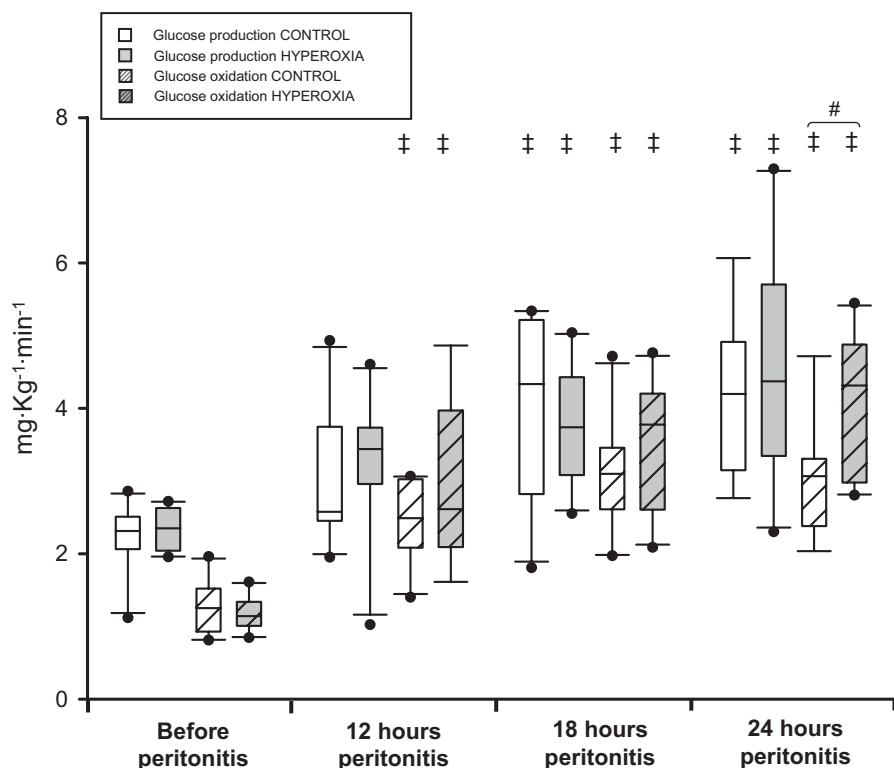


Figure 2. Rates of endogenous glucose production (*open whiskers*) and direct, aerobic glucose oxidation (*hatched whiskers*) in the control (*white symbols*, n = 10) and hyperoxic (*gray symbols*, n = 10) animals. Data are median (quartiles/range), ‡Significant difference within groups vs. baseline; #p < .05 between groups. Before induction of peritonitis, glucose oxidation accounted for approximately 50% of the endogenous production rate in both groups. At the end of the experiment, hyperoxia resulted in a near-complete oxidation of the endogenous substrate formation, whereas glucose oxidation in the control group accounted for approximately only two thirds of the endogenous substrate release.

tribution to cardiac output, however, was significantly higher in the hyperoxic animals at the end of the experiment. This redistribution of cardiac output in favor of the hepatosplanchnic organs, which confirms previous findings in rodents (11, 30), may assume particular importance: Up to now, no vasoactive drug had increased hepatosplanchnic blood flow beyond its effect on cardiac output (34). Using laser Doppler flowmetry, we did not observe any change in microvascular blood flow during oxygen ventilation, which is in contrast to findings in healthy, anesthetized pigs using microsphere techniques (35). Since tissue  $P_{O_2}$  values were also comparable, it is unlikely that we missed major microvascular effects. Hence, the attenuated regional venous acidosis and the lower hepatic venous lactate/pyruvate ratios are probably due to restored cellular energy metabolism rather than improved microcirculatory perfusion. In fact, the higher  $CO_2$  production indicates that hyperoxia caused a preferential use of glucose for energy metabolism. Such a switch in fuel utilization is associated with improved energy balance: The ratio of reduced nicotinamide adenine dinucleotide to reduced flavin adenine dinucleotide and, consequently, the stoichiometry of adenosine triphosphate synthesis to oxygen consumption (i.e., the yield of oxidative phosphorylation) are higher for glycolysis than for  $\beta$ -oxidation because reduced nicotinamide adenine dinucleotide as an electron donor provides three coupling sites rather than two only from reduced flavin adenine dinucleotide (36). This metabolic adaptation ameliorates organ function: In pigs, glucose oxidation enhanced left heart contractility and improved the pressure-volume relationship (37).

In our experiment, 100% oxygen over 24 hrs did not affect pulmonary gas exchange or lung mechanics. Ample literature is available that indicates breathing 100% oxygen may impair pulmonary gas exchange due to inhibition of hypoxic pulmonary vasoconstriction (38) and re-sorption atelectasis (38, 39) in lung regions with low ventilation/perfusion ratios (40). Moreover, hyperoxic ventilation combined with high tidal volumes caused lung injury (41), similar to the damage induced by prolonged hyperoxia (>48 hrs) (42). This striking discrepancy may be due to our ventilator protocol, that is, application of PEEP levels of 12–15 cm  $H_2O$ , prolonged inspiration time, and low tidal volumes (8 mL·kg<sup>-1</sup>): An open lung

Table 3. Regional hemodynamics, gas exchange, acid-base, and organ function data

	Before Peritonitis	12 Hrs Peritonitis	18 Hrs Peritonitis	24 Hrs Peritonitis
IAP, mm Hg				
Control	3 (2–7)	18 (14–20) <sup>b</sup>	18 (14–22) <sup>b</sup>	18 (17–22) <sup>b</sup>
Hyperoxia	3 (1–9)	14 (13–20)	21 (17–22) <sup>b</sup>	19 (17–23) <sup>b</sup>
Qpv, mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	18 (16–20)	30 (22–34) <sup>b</sup>	34 (31–36) <sup>b</sup>	36 (24–42) <sup>b</sup>
Hyperoxia	15 (13–17)	29 (25–35)	36 (30–37) <sup>b</sup>	36 (29–44) <sup>b</sup>
Qha, mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	1.1 (0.4–1.7)	2.0 (0.8–5.5)	2.7 (1.1–3.7)	2.3 (1.3–4.5)
Hyperoxia	0.7 (0.3–3.2)	1.3 (0.8–3.0)	2.7 (0.8–3.9)	2.2 (0.8–6.7)
Liver flow, mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	19 (18–21)	34 (24–39) <sup>b</sup>	36 (32–38) <sup>b</sup>	39 (28–44) <sup>b</sup>
Hyperoxia	16 (15–19)	32 (26–37) <sup>b</sup>	39 (32–40) <sup>b</sup>	40 (30–46) <sup>b</sup>
Ileal mucosal P <sub>O</sub> <sub>2</sub> , mm Hg				
Control	25 (6–51)	17 (11–18)	21 (18–47)	6 (5–7)
Hyperoxia	34 (15–68)	32 (8–56)	4 (1–93)	13 (1–99)
Ileal mucosal perfusion, units				
Control	293 (275–831)	266 (108–424)	257 (237–419)	260 (219–326)
Hyperoxia	481 (343–716)	466 (293–682)	405 (309–586)	587 (267–859)
Gut O <sub>2</sub> extraction, %				
Control	35 (29–41)	15 (13–18) <sup>a,b</sup>	18 (15–21) <sup>a,b</sup>	17 (14–22) <sup>a,b</sup>
Hyperoxia	34 (32–39)	12 (11–13) <sup>b</sup>	11 (10–12) <sup>b</sup>	13 (10–14) <sup>b</sup>
Ileal mucosal-arterial P <sub>CO</sub> <sub>2</sub> gap, mm Hg				
Control	18 (12–22)	32 (26–49) <sup>b</sup>	33 (28–38) <sup>b</sup>	27 (14–41)
Hyperoxia	19 (17–25)	21 (17–39)	29 (21–32)	36 (18–54) <sup>b</sup>
pv L/P ratio				
Control	9 (8–9)	12 (11–12)	14 (12–17) <sup>a,b</sup>	15 (12–19) <sup>b</sup>
Hyperoxia	8 (8–9)	11 (9–13)	12 (9–15)	13 (9–16) <sup>b</sup>
hDO <sub>2</sub> mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	1.3 (1.1–1.6)	3.7 (2.9–4) <sup>b</sup>	3.2 (2.4–3.7) <sup>a,b</sup>	3.0 (2.6–4.1) <sup>b</sup>
Hyperoxia	1.2 (0.9–1.3)	3.5 (3.1–4.2) <sup>b</sup>	4.4 (3.9–4.6) <sup>b</sup>	4.1 (3.4–4.6) <sup>b</sup>
hVO <sub>2</sub> mL·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	0.7 (0.4–0.8)	0.6 (0.5–0.7)	0.6 (0.4–0.8)	0.7 (0.4–0.8)
Hyperoxia	0.6 (0.6–0.7)	0.6 (0.4–0.9)	0.7 (0.7–1.1)	0.9 (0.7–1.2)
Liver lactate balance, μmol·kg <sup>-1</sup> ·min <sup>-1</sup>				
Control	12 (7–13)	15 (13–18)	12 (9–18)	11 (7–21)
Hyperoxia	12 (8–12)	12 (8–15)	17 (11–23)	21 (6–29)
hv L/P ratio				
Control	8 (6–9)	10 (10–13) <sup>a,b</sup>	14 (9–20) <sup>a,b</sup>	14 (9–32) <sup>a,b</sup>
Hyperoxia	5 (5–7)	8 (6–10)	9 (6–10)	9 (8–11)
hv ASAT, IU·g <sub>protein</sub> <sup>-1</sup>				
Control	1.1 (0.7–1.2)	2.9 (2.5–3.3) <sup>a</sup>	3.5 (3.0–3.9) <sup>a</sup>	3.5 (3.0–4.8) <sup>a,b</sup>
Hyperoxia	0.8 (0.7–1.0)	2.1 (1.7–2.7) <sup>a</sup>	2.8 (2.2–3.5) <sup>a</sup>	3.5 (2.8–4.0) <sup>b</sup>
hv ALAT, IU·g <sub>protein</sub> <sup>-1</sup>				
Control	0.5 (0.5–0.6)	0.7 (0.6–0.8)	0.8 (0.7–1.0) <sup>a</sup>	0.8 (0.7–0.9) <sup>b</sup>
Hyperoxia	0.5 (0.5–0.6)	0.7 (0.6–0.8)	0.7 (0.7–0.9) <sup>a</sup>	0.9 (0.8–1.0) <sup>b</sup>
Creatinine, μmol·g <sub>protein</sub> <sup>-1</sup>				
Control	5 (4–6)	13 (8–15) <sup>a</sup>	14 (10–18) <sup>a</sup>	14 (11–19) <sup>b</sup>
Hyperoxia	4 (4–5)	9 (7–11) <sup>a</sup>	11 (8–13) <sup>a</sup>	10 (8–15) <sup>b</sup>
Creatinine clearance, mL·min <sup>-1</sup>				
Control		91 (65–113)		61 (44–112) <sup>a,c</sup>
Hyperoxia		101 (86–125)		109 (90–122)

IAP, intra-abdominal pressure; Qpv, portal vein flow; Qha, hepatic artery flow; L/P ratio, lactate pyruvate ratio; pv, portal venous; hDO<sub>2</sub>, liver oxygen delivery; hVO<sub>2</sub>, liver oxygen uptake; hv, hepatic venous; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase.

<sup>a</sup>Significant difference between control and hyperoxia at the same time ( $p < .05$ ); <sup>b</sup>Significant difference within each group vs before peritonitis ( $p < .05$ ); <sup>c</sup>Significant difference within each group between the first and second half of the experiment for creatinine clearance.

Data are median and quartiles (Control, n = 10; Hyperoxia, n = 10).

concept during general anesthesia, mainly consisting of stepwise increases of PEEP until 15 cm H<sub>2</sub>O, prevented the formation of atelectasis (43, 44). Moreover, low tidal volume ventilation was lung-protective within 20 hrs of ovine fecal peritonitis (45) and in patients with acute respiratory distress syndrome despite increased Fio<sub>2</sub> levels (46). Further-

more, Aboab et al. (47) recently demonstrated in patients with acute lung injury that high PEEP levels (about 15 cm H<sub>2</sub>O) together with low tidal volumes prevented alveolar derecruitment induced by 100% oxygen. Finally, the peritonitis *per se* may have attenuated any putative toxicity of 100% oxygen: Both reduced and increased sensitivities to hyperoxia were

reported in animals challenged with lipopolysaccharide, oleic acid, and gastric juice aspiration (48–50).

Hyperoxia reduced the amount of TUNEL-positive cells in lung and liver. It is generally assumed that ROS formation causes lung damage with alveolar cell death (51). We can only speculate on this discrepancy. In rats, hyperoxia before car-

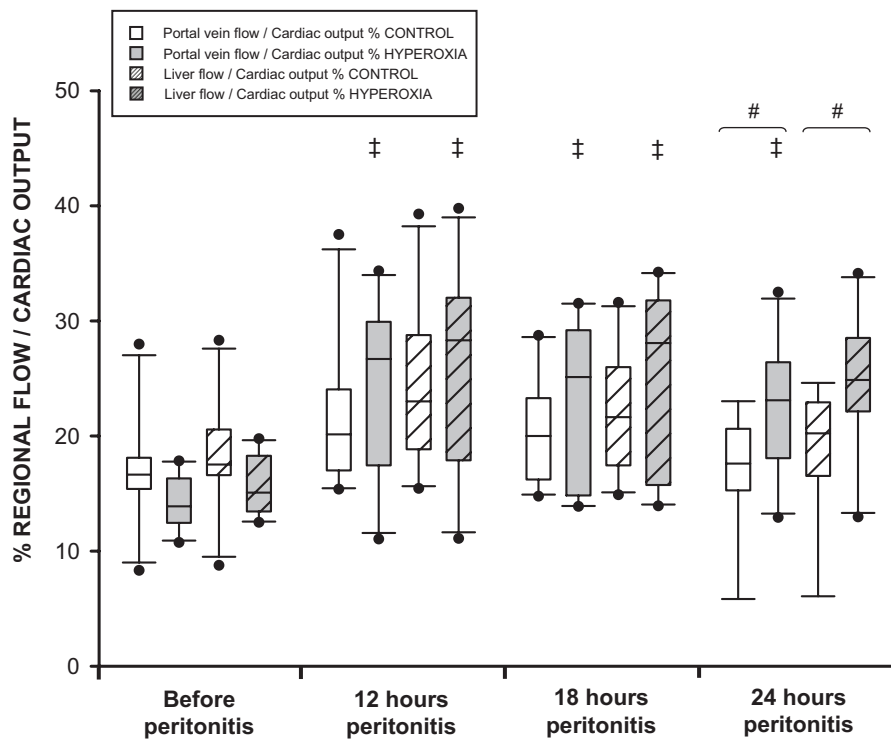


Figure 3. Portal venous (*open whiskers*) and total liver blood flow (*hatched whiskers*) in percentage of cardiac output in the control (*white symbols*, n = 10) and hyperoxic (*gray symbols*, n = 10) animals. Data are median (quartiles/range). ‡Significant difference within groups vs. baseline; #p < .05 between groups.

diac ischemia significantly reduced myocardial infarct size, cytochrome c release, DNA fragmentation, and nuclear TUNEL staining (52). We can exclude such “hyperoxic preconditioning,” since tissue superoxide dismutase and catalase activities were similar. We cannot judge either on a putative antibiotic effect of hyperoxia (6): While the number and dispersal of germs in the ascites fluid did not differ, less positive blood cultures were found in the hyperoxia group, including the only two sterile cultures. However, markers of inflammation, oxidative, and nitrosative stress (i.e., TNF- $\alpha$ , NO $_2^-$  + NO $_3^-$ , and 8-isoprostane blood levels and blood cell DNA strand breaks) were comparable. Finally, although these differences did not reach statistical significance, hyperoxia reduced the norepinephrine needs and plasma levels (Table 4). After major surgery, norepinephrine decreased the mitochondrial membrane potential of peripheral blood lymphocytes (53), and thus energy metabolism, and increased the rate of apoptosis (54, 55). Furthermore, norepinephrine itself can generate ROS (56) and may thus aggravate apoptosis.

*Limitations of the Study.* A major limitation of our study is that it lasted only

Table 4. Parameters of inflammatory response, oxidative stress, and antioxidant activity as well as plasma noradrenaline concentrations

	Before Peritonitis	12 Hrs Peritonitis	18 Hrs Peritonitis	24 Hrs Peritonitis
TNF $\alpha$ , pg $\cdot$ g $_{\text{protein}}^{-1}$				
Control	1,617 (1,449–2,945)	6,821 (5,711–9,443) <sup>b</sup>	8,785 (6,309–20,853) <sup>b</sup>	15,276 (6,322–29,948) <sup>b</sup>
Hyperoxia	1,511 (1,179–1,740)	4,800 (3,699–6,160)	8,843 (6,530–13,950) <sup>b</sup>	10,674 (7,415–18,508) <sup>b</sup>
NO $_2^-$ + NO $_3^-$ , $\mu$ M $\cdot$ g $_{\text{protein}}^{-1}$				
Control	0.6 (0.5–0.7)	1.6 (1.2–3.0) <sup>b</sup>	1.7 (1.4–2.3) <sup>b</sup>	1.8 (1.4–2.3) <sup>b</sup>
Hyperoxia	0.7 (0.5–1.2)	1.4 (0.8–1.9)	1.9 (1.0–3.0)	1.6 (1.0–3.3) <sup>b</sup>
8 isoprostane, pg $\cdot$ g $_{\text{protein}}^{-1}$				
Control	1,182 (1,040–3,591)	4,442 (3,532–15,032)	5,916 (5,239–20,762) <sup>b</sup>	20,296 (4,630–35,723) <sup>b</sup>
Hyperoxia	2,415 (1,429–2,913)	4,878 (3,933–7,712)	8,226 (7,203–10,730) <sup>b</sup>	10,740 (4,953–15,732) <sup>b</sup>
DNA strand breaks, tail moment				
Control	0.13 (0.11–0.21)	0.20 (0.12–0.28) <sup>b</sup>	n.d.	0.37 (0.19–0.43) <sup>b</sup>
Hyperoxia	0.15 (0.11–0.18)	0.27 (0.21–0.60) <sup>b</sup>	n.d.	0.23 (0.16–0.59) <sup>b</sup>
SOD activity (lung) IU $\cdot$ g $_{\text{protein}}^{-1}$				
Control	n.d.	n.d.	n.d.	3,583 (3,353–4,103)
Hyperoxia	n.d.	n.d.	n.d.	3,900 (2,475–4,466)
Catalase activity (lung) IU $\cdot$ g $_{\text{protein}}^{-1}$				
Control	n.d.	n.d.	n.d.	77 (73–86)
Hyperoxia	n.d.	n.d.	n.d.	71 (61–78)
SOD activity (liver) IU $\cdot$ g $_{\text{protein}}^{-1}$				
Control	n.d.	n.d.	n.d.	17,548 (11,921–27,318)
Hyperoxia	n.d.	n.d.	n.d.	11,516 (9,251–12,345)
Catalase activity (liver) IU $\cdot$ g $_{\text{protein}}^{-1}$				
Control	n.d.	n.d.	n.d.	536 (464–734)
Hyperoxia	n.d.	n.d.	n.d.	552 (364–660)
Norepinephrine, pg $\cdot$ mL $^{-1}$				
Control	0 (0–21)	215 (126–529)	3,897 (272–10,488) <sup>b</sup>	6,183 (3,648–62,474) <sup>b</sup>
Hyperoxia	0 (0–0)	62 (37–203)	321 (117–1,553) <sup>b</sup>	1,411 (436–3,143) <sup>b</sup>

TNF $\alpha$ , Tumor necrosis factor  $\alpha$ ; n.d. not determined; SOD, superoxide dismutase.

<sup>a</sup>Significant difference between control and hyperoxia at the same time ( $p < .05$ ); <sup>b</sup>Significant difference within each group vs before peritonitis ( $p < .05$ ).

Data are median and 25°–75° percentile (Control, n = 10; Hyperoxia, n = 10).

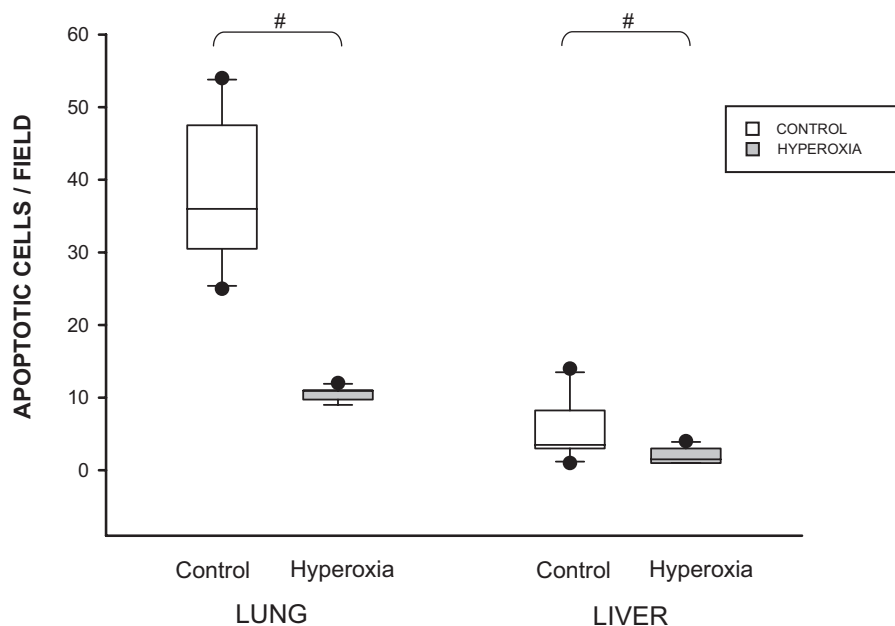


Figure 4. Total number of TUNEL-positive apoptotic cells per field of vision in postmortem lung (left panel) and liver (right panel) specimens in the control (white symbols, n = 10) and hyperoxic (gray symbols, n = 10) animals. Data are median (quartiles/range). #p < .05 between groups.

24 hrs. This limited duration precludes any conclusion whether hyperoxia is beneficial later or may even result in subsequent deterioration. Nevertheless, in our porcine model of normotensive, hyperdynamic polymicrobial septic shock, hyperoxia did not affect lung mechanics and pulmonary gas exchange, redistributed cardiac output in favor of the hepatosplanchnic organs, and shifted whole body metabolism to the preferential use of glucose. Since glucose oxidation provides the best ratio of adenosine triphosphate synthesis and oxygen consumption, oxygen ventilation may be affiliated with improved yield of energy metabolism in early septic shock.

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