Effects of Preoxygenation on Desaturation Time during Hemorrhagic Shock in Pigs

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ABSTRACT

Background: Patients in hemorrhagic shock often require emergent airway management. Clinical experience suggests that oxygen desaturation occurs rapidly in these patients; however, data are scant. The hypothesis of this study was that increasing levels of hemorrhagic shock, varying levels of fraction of inspired oxygen (F_{IO_2}) for preoxygenation, and fluid resuscitation significantly affect the duration until critical desaturation occurs.

Methods: Fifteen pigs were studied in a hemorrhagic shock model with controlled hemorrhage (15, 30, and 45 ml/kg blood loss) and randomized to standard fluid resuscitation or no fluids. At each shock level, three apnea experiments (in randomized order) were performed after 5 min of preoxygenation at 21, 50, or 100% F_{IO_2}. After preoxygenation, ventilation was discontinued and the time to peripheral oxygen saturation of 70% or less was measured.

Results: During normovolemia, peripheral oxygen desaturation to less than 70% occurred after 33 ± 7 s ($F_{IO_2} = 0.21$, mean $\pm$ SD), 89 ± 12 s ($F_{IO_2} = 0.5$), and 165 ± 22 s ($F_{IO_2} = 1.0$; $P < 0.001$). During increasing blood loss, peripheral oxygen desaturation to SpO_2 less than 70% occurred significantly ($P < 0.001$) faster compared with normovolemia, but no effect of fluid resuscitation was observed. With 45 ml/kg blood loss, peripheral oxygen desaturation to less than 70% occurred after approximately 15 ($F_{IO_2} = 0.21$) to 65 ($F_{IO_2} = 0.5$) to 140 s ($F_{IO_2} = 1.0$).

Conclusions: Findings from this swine hemorrhagic shock model confirm that F_{IO_2} and the level of hemorrhagic shock, but not fluid resuscitation, influence the rate of apneic desaturation. A five-fold increase in time until critical oxygen desaturation occurs can be achieved when preoxygenating with 100% oxygen compared with room air, underscoring the importance of adequate preoxygenation before emergent airway management.

What We Already Know about This Topic

- ❖ Critically ill patients are at risk for hypoxemia during emergency tracheal intubation.
- ❖ Determinants of the rate of oxyhemoglobin desaturation during apnea in this setting are poorly studied.

What This Article Tells Us That Is New

- ❖ In a pig hemorrhagic shock model, time to SpO_2 less than 70% during apnea decreased with lower preoxygenation F_{IO_2} and with greater level of hemorrhagic shock but was unaffected by fluid resuscitation.

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PATIENTS in hemorrhagic shock often require emergent airway management to secure the airway and to provide adequate oxygenation and ventilation. Airway management in critical patients is most commonly performed as rapid sequence induction[1] without mask ventilation after induction of anesthesia to avoid the aspiration of gastric content.[2] The rapid sequence induction technique exposes the patient to a period of apnea and subsequent oxygen desaturation before an airway can be established. As a consequence, adequate preoxygenation before rapid sequence induction is paramount to avoid critical hypoxia.[3] In a healthy patient, preoxygenation for 4 min with a fraction of inspired oxygen (F_{IO_2}) of 1.0 typically raises the arterial oxygen partial pressure (PaO_2) from 80 to 400 mmHg, allowing for a prolonged period of apnea before critical oxygen desaturation ensues. In contrast, as a recent study showed, the corresponding PaO_2 increase after 4 min of preoxygenation with a tight fitting bag-mask assembly in hemodynamically unstable intensive care unit patients was from 67 to 104 mmHg PaO_2 only.[4] Patients with critical illness and major trauma may not be

able to rapidly increase oxygenation during preoxygenation because of increased oxygen consumption, blood loss, stress, hypoventilation, and inadequate lung perfusion compared with stable patients undergoing elective surgery. It is thus probable that hemorrhagic shock causes a similar restriction of creating an adequate oxygen reserve after preoxygenation.

A second factor in emergent airway management and rapid sequence induction potentially associated with adverse outcomes is the inability to provide adequate FIO_2 for preoxygenation. Although it is fairly straightforward in the operating room to provide and achieve a FIO_2 of 1.0, this may not be possible in other settings such as the emergency department, in prehospital and austere environments.[5,6] The effects of varying levels of FIO_2 for preoxygenation on oxygen desaturation in hemorrhagic shock are unknown. Therefore, we tested, in a porcine hemorrhagic shock model, the hypothesis that increasing levels of hemorrhagic shock, varying levels of FIO_2 for preoxygenation, and fluid resuscitation significantly affect the time window until critical desaturation occurs.

Materials and Methods

This project was approved by the Austrian Federal Animal Investigational Committee (Vienna, Austria), and the animals were managed in accordance with the American Physiological Society institutional guidelines and Position of the American Heart Association on Research Animal Use. Animal care and use was performed by qualified individuals and supervised by a veterinarian, and all facilities and transportation comply with current legal requirements and guidelines according to Utstein guidelines.[7] Anesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research would have been terminated if pain or fear resulted. Our animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care.

Surgical Preparations and Measurements

This study was performed on 15 healthy, 12- to 16-week-old swine weighing 35 to 45 kg. The animals were fasted overnight, but had free access to water. The pigs were premedicated with azaperone, a neuroleptic agent, (4 mg/kg intramuscular; Janssen, Vienna, Austria) and atropine (0.1 mg/kg intramuscular) 1 h before surgery. Anesthesia was induced with a bolus dose of ketamine (20 mg/kg intramuscular), propofol (1–2 mg/kg intravenous), and piritramide (30 mg intravenous) administered *via* an ear vein. Anesthesia was maintained with propofol (6–8 mg/kg/h) and piritramide (30 mg bolus as needed). Neuromuscular blockade was achieved with 0.3 mg/kg/h pancuronium after tracheal intubation to prevent spontaneous breathing or gasping.

Each animal was placed in a supine position, and the trachea was intubated during spontaneous respiration. After intubation, pigs were ventilated with a volume-controlled ventilator (Evita 4; Dräger, Lübeck, Germany) with 21% oxygen at 14 breaths/min, an inspiratory to expiratory ratio

of 1:2, and a tidal volume adjusted to maintain normocapnia, which was defined as an end-tidal pCO_2 of 35–45 mmHg measured by continuous capnography. Furthermore, a positive end-expiratory pressure of 5 cm H_2O was applied throughout the study, except for the desaturation experiments, in which ventilation was disconnected and no positive end-expiratory pressure was being applied. Lactated Ringer's solution (10 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}, 500 ml maximum) was administered in the preparation phase.[8] A standard lead II electrocardiogram was used to monitor cardiac rhythm. Depth of anesthesia was judged clinically, and additional propofol and piritramide could be given at the sole discretion of the supervising physician. Body temperature was measured with nasopharyngeal temperature probe and maintained between 38.5 and 39.5°C by forced-air warming using a Bair-Hugger® blanket (Arizant, Eden Prairie, MN). In addition, all intravenous fluids were prewarmed to 37°C.

A 7-French saline-filled catheter was advanced *via* femoral cut-down into the inferior vena cava for measurement of central venous pressure, administration of intravenous drugs, and withdrawal of blood to induce hemorrhagic shock; another 7-French catheter was advanced *via* femoral artery into the abdominal aorta for measurement of aortic blood pressure and arterial blood samples. A 7.5-French pulmonary artery catheter was placed *via* cut-down in the neck and puncture of the internal jugular vein into the pulmonary artery to measure pulmonary artery pressures and mixed venous oxygen saturation. The intravascular catheters were attached to pressure transducers (model 1290A; Hewlett Packard, Böblingen, Germany) that were aligned at the level of the right atrium. All pressure tracings were recorded with a data acquisition system (Dewetron port 2000, Graz, Austria; and custom software, Peter Hamm, Departmental Technician, Department of Anesthesiology and Critical Care Medicine, Innsbruck Medical University, Innsbruck, Austria). Blood gases were measured with a blood gas analyzer (Chiron, Walpol, MA); end-tidal carbon dioxide was measured using an infrared absorption analyzer (Multicap; Datex, Helsinki, Finland).

Experimental Protocol

Before the experiment, animals were randomly assigned to one of two groups: (1) fluid resuscitation after each controlled hemorrhage step (n = 7 pigs) or (2) no fluid resuscitation (n = 8 pigs) (fig. 1). Randomization was performed by random numbers generated by a simple software routine. Fluid resuscitation consisted of 25 ml/kg lactated Ringer's solution and 15 ml/kg 3% gelatin solution (Gelofusine; B. Braun Melsungen AG, Melsungen, Germany). Three controlled hemorrhage steps were planned (15 ml/kg, 30 ml/kg, 45 ml/kg) and at each level, 15 ml/kg blood was withdrawn from the femoral central venous catheter over approximately 10–15 min. No fluids were given during controlled hemorrhage. For pigs in the fluid resuscitation group, fluids were infused after completion of each hemorrhage over a period of 15–20 min (a total of 3 fluid resuscitations).
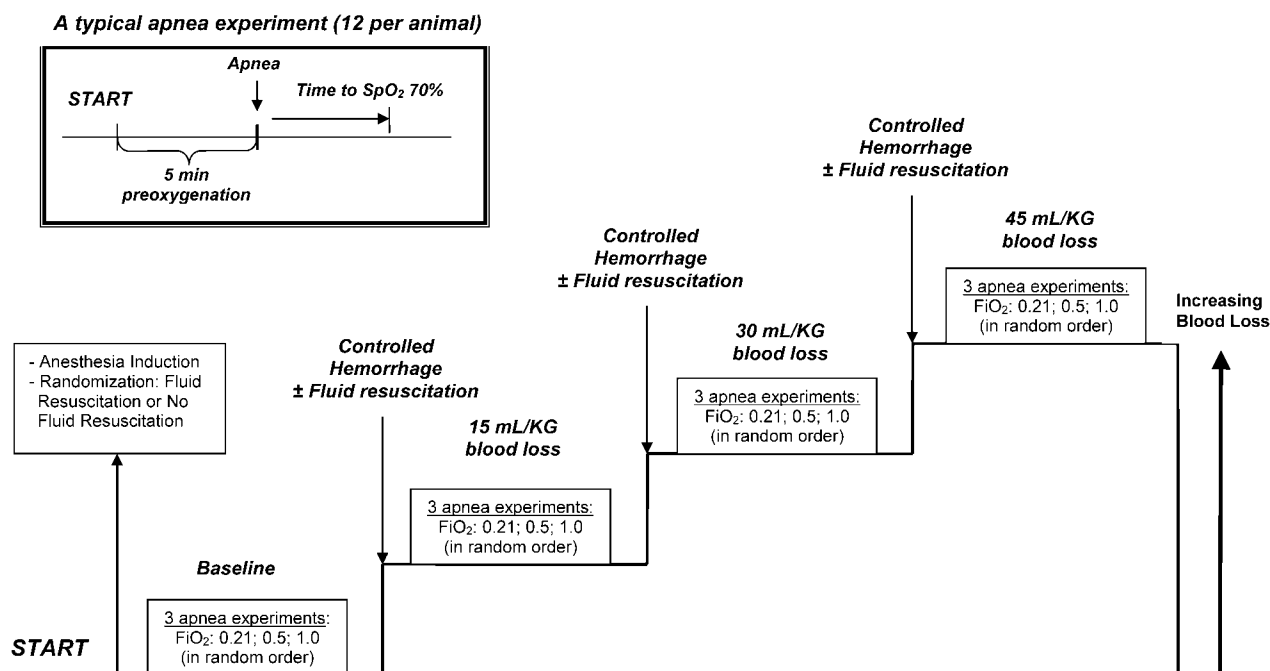
Fig. 1. Experimental protocol. The inset describes the design of a typical apnea experiment. Twelve of these were done for each animal. Fluid resuscitation was identical at each step of hemorrhage for animals in the fluid resuscitation group. It consisted of 25 ml/kg lactated Ringer's solution and 15 ml/kg 3% gelatin solution. F_{IO_2} = fraction of inspired oxygen; Sp_{O_2} = peripheral oxygen saturation.

Three desaturation experiments were performed in randomized order at baseline and at each hemorrhage level, resulting in a total of 12 desaturation experiments per pig. The three desaturation experiments performed at each level consisted of preoxygenating the pigs at three different F_{IO_2} levels: 21, 50, and 100% (in random order) for 5 min. After 5 min, pigs were disconnected from the ventilator and the time during apnea until pulse oximetry oxyhemoglobin saturation (Sp_{O_2}) reached less than 70% was measured (primary outcome variable). After each desaturation experiment, animals were then ventilated with 100% oxygen for 5 min for recovery. Before the next experiment, animals were ventilated with 21% oxygen for another 5 min to achieve a new baseline. This cycle of three desaturation experiments (21, 50, 100%) was repeated at each level of hemorrhage (total of 12 per animal). A complete experiment (from baseline to 45 ml/kg hemorrhage) would typically last 1.5–2 h per animal.

Serial arterial blood gases were measured at baseline, after 3 and 5 min of preoxygenation, and at 1, 2, and 3 min of apnea (only until an Sp_{O_2} og less than 70% was reached). At completion of all desaturation experiments, surviving animals were killed with an overdose of fentanyl, propofol, and potassium chloride.

Statistical Analysis

Data were described as mean and SD for normally distributed variables and as median and interquartile range for nonnormally distributed variables. Baseline comparison between the two groups (fluid-resuscitated animals *vs.* non–fluid-resuscitated animals) was performed with simple univariate

statistics such as two-sided, unpaired *t* test or chi-square test, where appropriate. To analyze the primary outcome variable, time interval to a peripheral oxygen desaturation of Sp_{O_2} of 70% or less, we used a mixed model with repeated measures and an unstructured variance-covariance matrix. Degrees-of-freedom adjustments were performed by the method of Kenward-Roger in case of unequal variances. Animals were nested in the two groups (fluid/no fluids). In addition, we tested interaction between the primary outcome variable and degree of shock (baseline, 15, 30, and 45 ml/kg blood loss) and the degree of preoxygenation (F_{IO_2} 0.21, 0.5, and 1.0). To achieve a normal distribution and avoid heteroscedasticity, variables were subjected to a square-root transformation where appropriate. A *P* value less than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 17.0.2 (SPSS Inc., Chicago, IL) and SAS 9.2 (SAS Institute, Cary, NC).

Results

Before starting the experimental protocol, there were no differences in hemodynamic variables, blood gases, weight, and temperature between groups at baseline. During normovolemia, peripheral oxygen desaturation to Sp_{O_2} of 70% or less occurred after 33 ± 7 s (F_{IO_2} = 0.21, mean $\pm$ SD), 89 ± 12 s (F_{IO_2} = 0.5), and 165 ± 22 s of apnea ($P < 0.001$; fig. 2). Fluid-resuscitated pigs achieved higher Pa_{O_2} levels after preoxygenation compared with non–fluid-resuscitated pigs, an effect that was consistently seen at F_{IO_2} of 0.5 and 1.0 (fig. 3). With increasing blood loss, peripheral oxygen desatura-
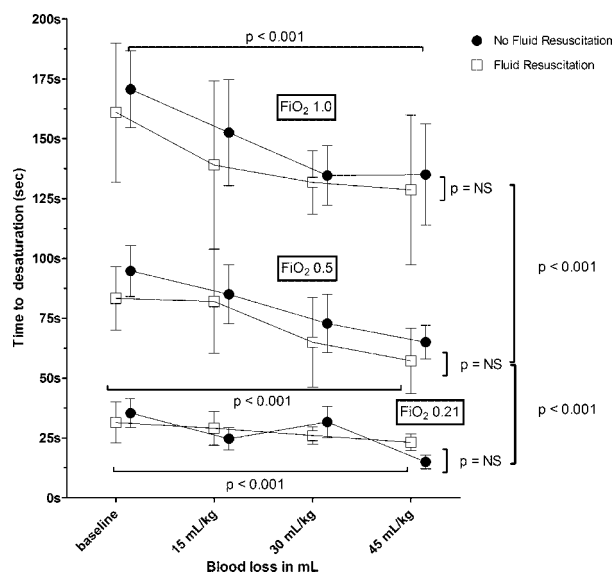
Fig. 2. Time to critical desaturation (peripheral oxygen saturation [SpO$_2$] less than 70%) after apnea at different levels of hemorrhage and fraction of inspired oxygen (FIO$_2$) for preoxygenation. The time until critical desaturation of SpO$_2$ less than 70% was measured at three different preoxygenation levels (21, 50, and 100%) and at increasing levels of controlled hemorrhage (normovolemia and 15, 30, and 45 ml/kg). Pigs were randomly allocated to receive no fluid resuscitation (●) or fluid resuscitation (□) throughout the experiment. *P* values indicate three different hypotheses tested: (1) a comparison between the three different levels of FIO$_2$ (0.21, 0.5, 1.0); (2) within each FIO$_2$ level between fluid resuscitation and no fluid resuscitation, and (3) within each FIO$_2$ level, the comparison between baseline and the highest degree of hemorrhagic shock (45 ml/kg).

tion to SpO$_2$ of 70% or less after apnea occurred significantly ($P < 0.001$) faster compared with normovolemia (fig. 2). After severe hemorrhage (45 ml/kg), we found, on average, a reduction in desaturation time after apnea of 25 s after preoxygenation with FIO$_2$ 1.0, a reduction of 24 s with FIO$_2$ 0.5, and a reduction of 18 s on room air.

Because SpO$_2$ measurements by pulse oximetry become less precise during increasing levels of hemorrhagic shock, we assessed the corresponding arterial oxyhemoglobin saturation (SaO$_2$) levels from arterial blood gas analysis measured at SpO$_2$ 70% and found no influence of the degree of hemorrhage or fluid resuscitation (fig. 4). Corresponding SaO$_2$ levels were consistently between 60 and 70% oxygen saturation. PaCO$_2$ levels averaged 34.8 ± 3.9 mmHg before each desaturation experiment and increased to 52.0 ± 7.5 mmHg after 1 min of apnea and to 58.8 ± 8.4 mmHg after 2 min of apnea. No effect of increasing levels of hemorrhage was observed, but fluid-resuscitated animals had consistently lower PaCO$_2$ levels compared with non–fluid-resuscitated animals.

With increasing levels of hemorrhage, plasma lactate concentrations increased from 3 to 8 mM, but no effect of fluid resuscitation was observed (fig. 5A). It is noteworthy that not all animals survived until the end of the experiment. Among fluid-resuscitated animals, one (of seven) died during the 30
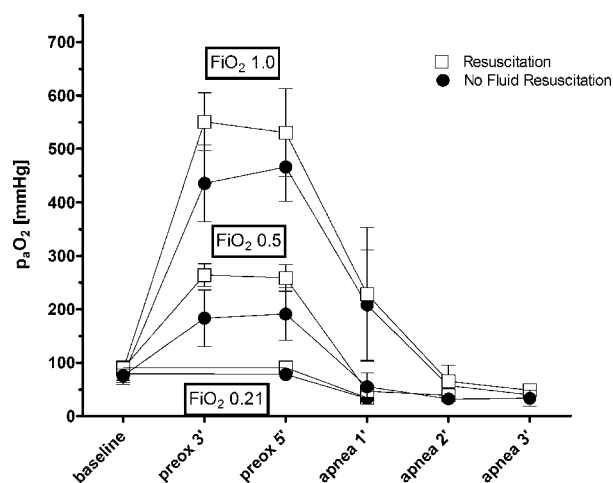

Fig. 3. Arterial partial pressure of oxygen (PaO$_2$) at different levels of inspiratory oxygen concentration. The PaO$_2$ was measured by serial arterial blood gas analyses at baseline, after 3 and 5 min of preoxygenation, and after 1, 2, and 3 min of apnea. Three levels of fraction of inspired oxygen (FIO$_2$) were compared (21, 50, and 100%—cumulative) as well as fluid resuscitation (□) *versus* no fluid resuscitation (●). preox = preoxygenation with FIO$_2$ 21, 50, or 100% after 3 and 5 min.

ml/kg hemorrhage stage, whereas six (of eight) died among animals who did not receive fluid resuscitation, three at 30 ml/kg and three at 45 ml/kg.

It is noteworthy that pH changed only minimally with increasing blood loss and did not differ between fluid-resuscitated and non–fluid-resuscitated animals. Hemoglobin concentration averaged 9 g/dl at baseline and decreased with increasing blood loss in fluid-resuscitated animals to 4 g/dl but remained basically unchanged in non–fluid-resuscitated pigs (fig. 5B). Heart rate was, on average, 75 beats/min at baseline and substantially increased in non–fluid-resuscitated animals to 200 beats/min, whereas fluid-resuscitated animals showed an increase only to 110 beats/min (fig. 5C). Mean arterial blood pressure was 60 mmHg at baseline and
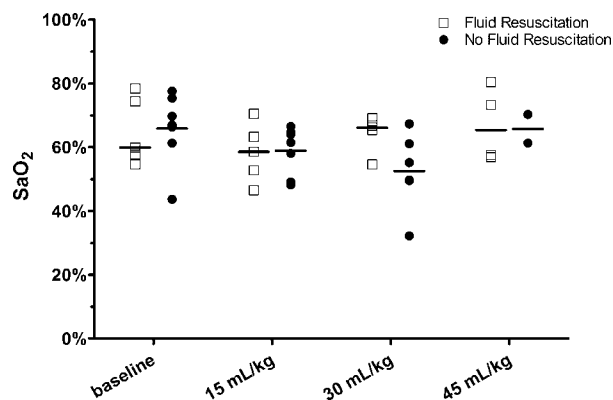

Fig. 4. Arterial hemoglobin oxygen saturation (SaO$_2$) measured at peripheral oxygen saturation (SpO$_2$) less than 70% at different levels of hemorrhage. Arterial blood gases were taken when SpO$_2$ reached 70%. Fluid resuscitated (□) *versus* non–fluid-resuscitated (●) animals.
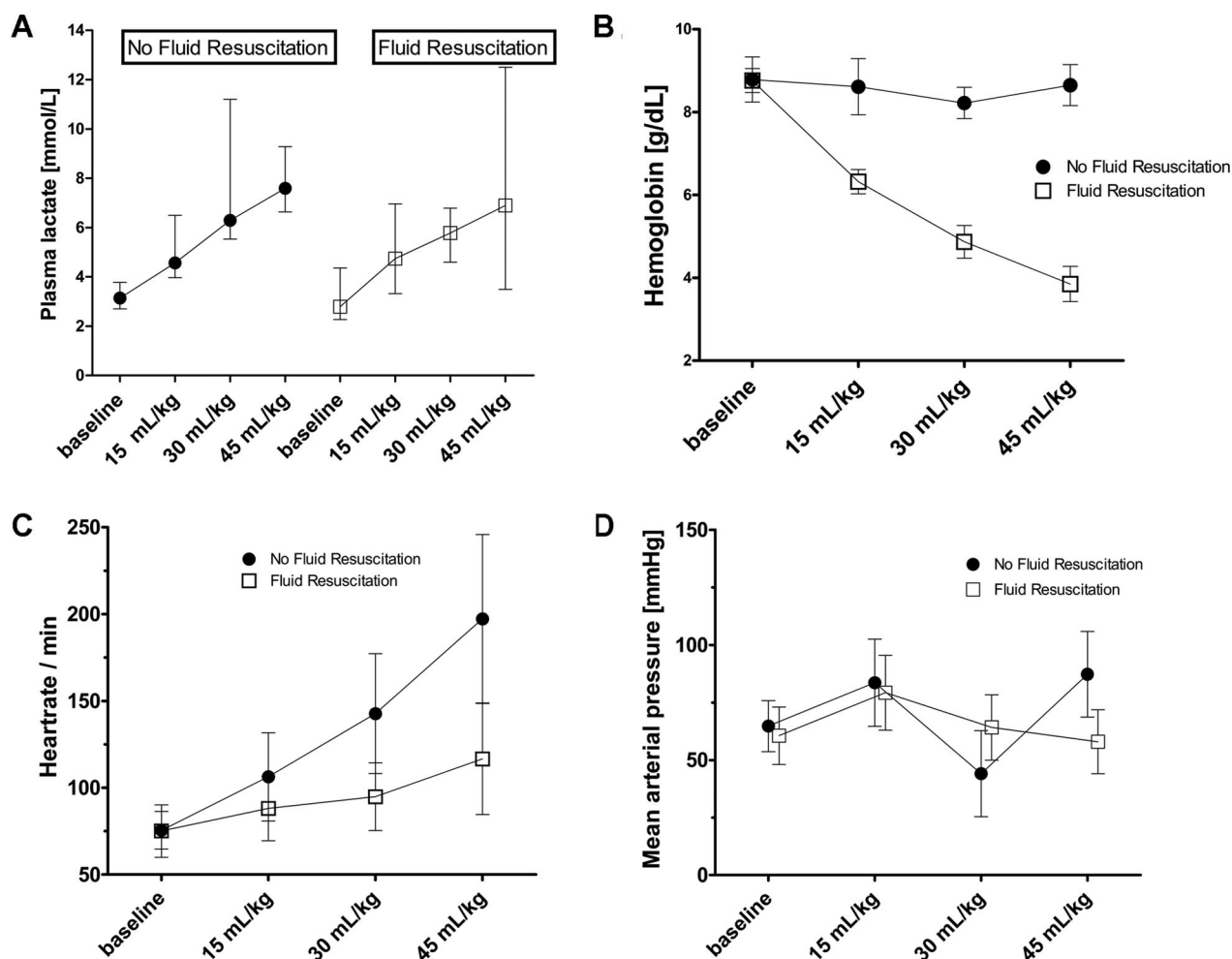
Fig. 5. Hemodynamic and metabolic parameters during the experiment. Plasma lactate (*A*) and blood hemoglobin (*B*) concentrations and heart rate (*C*) and mean arterial blood pressure (*D*). Fluid-resuscitated (□) *versus* non–fluid-resuscitated (●) animals.

remained between 50 and 80 mmHg in both groups during ongoing hemorrhage (fig. 5D).

Discussion

In this porcine model, we found that critical desaturation (SpO_2 less than 70%) after apnea occurred significantly faster with increasing levels of hemorrhage and hypovolemia, but without any effect of fluid resuscitation. Furthermore, preoxygenation with increasing FIO_2 levels increased PaO_2 values independently of the degree of blood loss and subsequent fluid resuscitation.

It is a surprising result of our study that we did not observe a difference between fluid-resuscitated and non–fluid-resuscitated animals on desaturation times after apnea, despite the fact that fluid-resuscitated animals achieved higher PaO_2 levels after 5 min of preoxygenation. Perhaps the positive effect of fluid resuscitation on PaO_2 levels is countered by the significant reduction of the hemoglobin concentration in blood (in our experiment from 9 to 4 g/dl) and the subsequent decrease in oxygen content. A simple calculation may illustrate the severe reduction in oxygen content in fluid resusci-

tated animals: oxygen delivery, the most important physiologic determinant of shock, is dependent on cardiac output and arterial oxygen content (CaO_2). At baseline, the animals in our experiment had an average CaO_2 of 12.5 ml O_2/100 ml (SaO_2, 100%; hemoglobin, 9 g/dl; PaO_2, 95 mmHg) when being ventilated with room air. At the most severe level of hemorrhage in our experiment (45 ml/kg blood loss) and after 5 min of preoxygenation with 100% oxygen, non–fluid-resuscitated animals still averaged a hemoglobin concentration of 9 g/dl and achieved a CaO_2 of 13.8 ml O_2/100 ml (SaO_2, 100%; PaO_2, 475 mmHg), whereas fluid-resuscitated animals achieved a CaO_2 of only 7.2 ml O_2/100 ml (hemoglobin, 4g /dl; SaO_2, 100%; PaO_2, 550 mmHg), which represents a reduction of more than 50% in CaO_2. This reduction in CaO_2 in fluid-resuscitated animals may be the reason why we did not observe an effect of fluid resuscitation on desaturation times after apnea.

In general, the decrease in arterial oxygen content and cardiac output during hemorrhagic shock are the cause for impaired tissue oxygenation and the switch to anaerobic metabolism represented in the observed lactic acidosis. To

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counter reduced oxygen delivery during hemorrhagic shock, tissue oxygen availability will be increased by a metabolic acidosis-induced right shift of the oxygen dissociation curve and a corresponding increase in the oxygen extraction rate.

Lactate and heart rate doubled compared with baseline values in non–fluid-resuscitated pigs, whereas mean arterial blood pressure remained stable. These observations indicate that our model reflects compensated shock; the 45 ml/kg blood loss in our laboratory animals would reflect an acute blood loss of approximately 3.2 l in a 70-kg human.

The time window of 2 min and 20 s until peripheral oxygen desaturation reached 70% in our hemorrhagic shock model is notably less than the 5 min expected after adequate preoxygenation.[9,10] A likely explanation for this observation is that the oxygen consumption of piglets aged 3–4 months (as used in our experiment) is approximately 6 ml $\cdot$ min^{-1} $\cdot$ kg^{-1},[11] which is substantially higher than in adult humans. As a consequence, desaturation times observed in our experiment may not be directly extrapolated to adult human patients. Had the animals been subjected to additional stress, hypoventilation, increased oxygen consumption, or even decompensated shock, it is likely that peripheral oxygen desaturation would have occurred even faster, despite excellent Pa_{O_2} levels after preoxygenation.

When we cautiously extrapolate the findings of this experiment to the clinical setting, it becomes apparent that our data mirror the observation of rapid oxygen desaturation in critically ill hospitalized patients in whom Mort[4] found a substantially limited oxygen reserve. Critical oxygen desaturation during airway management has profound consequences in patients: mortality doubled in patients who developed a critical peripheral oxygen desaturation before or after a prehospital intubation attempt by paramedics compared with matched controls.[12] It is noteworthy that mortality increased the most when peripheral oxygen desaturation was less than 70% or more than 120 s. Data from a critical care unit setting suggest that even brief episodes of hypoxia in patients with severe head trauma substantially increases mortality.[13]

It seems clear on the basis of our data that the time available to safely perform airway management by rapid sequence induction in patients suffering from hemorrhagic shock is much shorter than currently thought.[14,15] This is even more important when preoxygenation cannot be achieved with 100% oxygen.[3,16] Using 100% oxygen seems the most prudent choice for preoxygenation, allowing for the highest Pa_{O_2} and the longest time period of apnea before critical desaturation occurs, despite the concerns of continuously administrating 100% oxygen during hemorrhagic shock, which has been shown to increase damage from reactive oxygen species during reperfusion as well as vasoconstriction.[17]

Some limitations need to be noted. We did not measure oxygen consumption, shunt, or cardiac output, and we considered apnea to have steady-state kinetics,[18] all of which may have had an impact on the experiment. In addition, our animals were randomized in order of F_{IO_2} but not in the degree of hemorrhage; thus, the animals experienced cumulative episodes of hypoxemia that may have caused profound cellular and metabolic changes such as hypoxic preconditioning. During prolonged hemorrhagic shock, atelectasis in the lungs has likely formed, which may have had profound consequences on alveolar stability and gas exchange through the alveolar membrane. However, the fact that we observed no time-dependent effect of hemorrhagic shock on arterial oxygen saturation (fig. 4) makes it somewhat unlikely that decreased alveolar stability introduced a significant bias in our experiment. Furthermore, during the entire experiment, except the periods of apnea but including the 5-min preoxygenation period, animals were ventilated with 5 cm H_2O positive end-expiratory pressure, which may not always be done clinically.[19]

In conclusion, findings from this swine hemorrhagic shock model confirm that F_{IO_2} and the level of hemorrhagic shock, but not fluid resuscitation, influence the rate of apneic desaturation. A five-fold increase in time to peripheral oxygen desaturation less than 70% may be achieved when securing adequate preoxygenation with 100% oxygen compared with a F_{IO_2} of 0.21. With a greater degree of hemorrhagic shock, peripheral oxygen desaturation occurred significantly faster independently of fluid resuscitation and the degree of preoxygenation.

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