Hypoxia

Effects of hypothermia, hypoxia, and hypercapnia on brain oxygenation and hemodynamic parameters during simulated avalanche burial: a porcine study

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Abstract

Avalanche patients who are completely buried but still able to breathe are exposed to hypothermia, hypoxia, and hypercapnia (triple H syndrome). Little is known about how these pathological changes affect brain physiology. The study aim was to investigate the effect of hypothermia, hypoxia, and hypercapnia on brain oxygenation and systemic and cerebral hemodynamics. Anesthetized pigs were surface cooled to 28°C. Fraction of inspiratory oxygen (FIO2) was reduced to 17% and hypercapnia induced. Hemodynamic parameters and blood gas values were monitored. Cerebral measurements included cerebral perfusion pressure (CPP), brain tissue oxygen tension (PbtO2), cerebral venous oxygen saturation (ScvO2), and regional cerebral oxygen saturation (rSO2). Tests were interrupted when hemodynamic instability occurred or 60 min after hypercapnia induction. ANOVA for repeated measures was used to compare values across phases. There was no clinically relevant reduction in cerebral oxygenation (PbtO2, ScvO2, rSO2) during hypothermia and initial FIO2 reduction. Hypercapnia was associated with an increase in pulmonary resistance followed by a decrease in cardiac output and CPP, resulting in hemodynamic instability and cerebral desaturation (decrease in PbtO2, ScvO2, rSO2). Hypercapnia may be the main cause of cardiovascular instability, which seems to be the major trigger for a decrease in cerebral oxygenation in triple H syndrome despite severe hypothermia.

NEW & NOTEWORTHY

Avalanche patients who are completely buried but still able to breathe are exposed to hypothermia, hypoxia, and hypercapnia (triple H syndrome). In a porcine model, there was no clinically relevant reduction in cerebral oxygenation during hypothermia and initial FIO2 reduction. Hypercapnia was associated with an increase in pulmonary resistance followed by a decrease in cardiac output and CPP, resulting in hemodynamic instability and cerebral desaturation (decrease in PbtO2, ScvO2, rSO2). Hypercapnia may be the main cause of cardiovascular instability, which seems to be the major trigger for a decrease in cerebral oxygenation in triple H syndrome despite severe hypothermia.

accidental hypothermia; avalanche; brain oxygenation; hypercapnia; hypothermia; hypoxia; near-infrared spectroscopy

INTRODUCTION

One out of four completely buried avalanche patients is expected to develop accidental hypothermia (1–3), which, in the case of cardiac arrest (CA), protects the brain from hypoxic damage due to reduced oxygen consumption (4–6). Recent studies have shown that only 12% of avalanche patients with CA admitted for extracorporeal rewarming survived, compared with 76–85% of other accidentally hypothermic patients with CA (7, 8). In addition, these survivors showed a poorer neurological outcome. Since completely buried avalanche patients experience hypothermic CA when an air pocket prevents asphyxiation (3, 9), it is reasonable to assume that the composition of respiratory gases in the air pocket significantly influences systemic and cerebral hemodynamics and thus the functional outcome of these patients. The combined effect of hypothermia with hypoxia and hypercapnia has been designated the triple H syndrome (10), in which the pathophysiological consequences (mainly cardiovascular and respiratory changes) of the combination of low oxygen (O2) and high carbon dioxide (CO2) levels were evidenced in various experimental studies with normothermic human subjects breathing into artificial air pockets in snow debris (10–12). A porcine model was employed to...
investigate the cardiovascular effects of hypothermia in combination with low O₂ and high CO₂ levels (13) and described mixed acidosis and impairment of cardiac output (CO) in hypoxic animals without sufficient delivery/removal of respiratory gases. However, no data are available regarding the effects of the triple H syndrome on cerebral oxygenation.

We therefore investigated the effects of hypothermia, hypoxia, and hypercapnia on brain oxygenation and hemodynamic parameters in a porcine model mimicking a scenario of long complete avalanche burial. Measurements included mean arterial pressure (MAP), CO, mean pulmonary artery pressure (mPAP), intracranial pressure (ICP), brain tissue oxygen tension (PbtO₂), cerebral venous oxygen saturation (ScvO₂), and regional cerebral oxygen saturation (rSO₂). We also assessed the correlation between rSO₂ and cerebral perfusion pressure (CPP), PbtO₂, and ScvO₂ to clarify whether near-infrared spectroscopy (NIRS) can be used to noninvasively monitor changes in cerebral perfusion and oxygenation in patients with triple H syndrome.

## MATERIALS AND METHODS

This study was approved by the Institutional Animal Care and Use Committee of the Medical University of Innsbruck and the Austrian Ministry of Science, Research and Economy (Protocol No. BMWF-66.011/0027-II/3b/2013). The study was conducted in the experimental research unit of the University Department of Anaesthesiology and Critical Care Medicine of Innsbruck [574 m above sea level (a.s.l.)] in accordance with the European Union regulations for animal experiments (Directive 2010/63/EU of the European Parliament and the European Council), and reporting is in accordance with current ARRIVE guidelines (14).

### Animal Anesthesia and Preparation

This study protocol was performed in 10 healthy, 12- to 16-wk-old domestic pigs weighing between 35 and 50 kg. Data from one pig were excluded because of a malfunction in the monitoring devices. Animals were fasted overnight but had free access to water. Premedication was done with a single bolus dose of ketamine (25 mg/kg im; Jansen, Vienna, Austria) 1 h before transport to the study site. Anesthesia was induced with a single bolus dose of ketamine (25 mg/kg im), propofol (1 mg/kg iv), and piritramide (30 mg im); neuromuscular blockade was achieved with a continuous infusion of suxamethonium (0.3 mg/kg/h). Normovolemia was maintained by administering lactated Ringer solution (10 mL/kg/h iv). Co2 tension in the monitoring devices. Animals were fasted overnight but had free access to water. Premedication was done with a single bolus dose of ketamine (25 mg/kg im; Jansen, Vienna, Austria) 1 h before transport to the study site. Anesthesia was induced with a single bolus dose of ketamine (25 mg/kg im), propofol (1 mg/kg iv), and piritramide (30 mg iv; Jansen, Vienna, Austria). The animals were placed in the supine position and were intubated during spontaneous ventilation with a 7.0-mm-internal diameter tracheal tube (Rüsch, Kernen, Germany). Volume-controlled ventilation (Evita 2; Draeger, Lübeck, Germany) was started with 21% inspiratory O₂, a tidal volume of 6–8 mL/kg body wt, and a ventilation rate adjusted to maintain normocapnia (35–45 mmHg); an α-stat regime was used to adjust ventilator settings and report blood gas values (15) without administration of exogenous CO₂. Anesthesia was maintained with propofol (6–8 mg/kg/h iv) and repetitive injections of piritramide (15 mg iv); neuromuscular blockade was achieved with a continuous infusion of pancuronium (0.3 mg/kg/h). Normovolemia was maintained by administering lactated Ringer solution (10 mL/kg/h iv). A standard lead II electrocardiogram (ECG) was used to monitor cardiac rhythm, and a pulse oximeter was placed on the tail. A 7.0-Fr saline-filled pulmonary artery catheter (Edwards Life Sciences, Irvine, CA) was placed in the pulmonary artery via an 8.5-Fr internal jugular vein catheter (Arrow, Reading, PA) to measure right atrial and pulmonary artery pressure, CO, and core temperature (Tcore). A 6.0-Fr saline-filled arterial catheter (Arrow, Reading, PA) was placed in the right femoral artery to measure aortic blood pressure. A pigtail catheter (MP A2; Cordis Corporation, Miami Lakes, FL) was advanced into the transverse sinus via the left femoral vein under radiological guidance to collect cerebral venous blood samples. A NIRS optode (INVOS System; Somanetics Inc., Troy, MI) was fixed on the right forehead. In the corresponding region of the left hemisphere a brain tissue oxygen catheter (Licox-Clark-type probe; Integra NeuroSciences, Ratingen, Germany) and an intracranial pressure probe (Neurovent-P; Raumedic AG, Helmbrechts, Germany) were placed in the white matter of the corresponding region of the left hemisphere through two burr holes by a neurosurgeon. The intravascular catheters were attached to pressure transducers (1290 A; Hewlett Packard, Büblingen, Germany) and calibrated at the level of the right atrium and the meatus acusticus (to calculate CPP), being at the same height in the supine position. Hemodynamic and respiratory variables were measured and analyzed with an AS/3 monitor (Datex-Ohmeda AS/3; GE Healthcare, Chalfont St Giles, UK). Blood gases were analyzed with a blood gas analyzer (ABL 800 Flex; Radiometer Medical ApS, Brønshøj, Denmark).

### Study Protocol

After instrumentation, probes were calibrated according to the manufacturer’s specifications, and the experimental protocol (Fig. 1) started with baseline measurement of hemodynamic, respiratory, and cerebral oxygenation parameters and blood gases. Thereafter, the pigs were surface cooled with crushed ice until a core temperature of 28°C was reached. After 5 min of steady state at 28°C, the fraction of inspiratory oxygen (FiO₂) was progressively lowered to 17% in ~5–10 min, and thereafter the FiO₂ level was kept constant until the end of the protocol. Levels of PaO₂ were tailored in pilot tests and according to previous data from the literature in order to simulate a triple H syndrome with sufficient O₂ delivery in the cooling phase (10–13). After 20 min with reduced inspiratory oxygen, hypercapnia was induced by reducing the ventilation rate to 6 ventilations/min and removing the CO₂ absorber of the anesthesia machine.

Tests were interrupted with hemodynamic instability (i.e., a 30% decrease in mean arterial pressure) or 60 min after hypercapnia induction. After completion of the experimental protocol, the animals were euthanized.

### Measurements

Measurements included MAP and other hemodynamic parameters including CO, heart rate (HR), mPAP, and pulmonary and systemic vascular resistance (PVR and SVR, respectively); blood gas analysis including arterial pH (pHa), arterial hemoglobin (Hb), arterial partial pressure of oxygen (PaO₂) and carbon dioxide (PaCO₂), arterial and cerebral venous lactate (Lac and Lac cv), arterial serum potassium (K⁺), arterial serum sodium (Na⁺), arterial serum bicarbonate (HCO₃⁻), arterial serum chloride (Cl⁻), arterial serum creatinine (Cr), arterial serum urea (Urea), and arterial serum lactate (Lact).
Statistical Analysis

ANOVA for repeated measures was used to compare different phases [baseline, end of hypothermia, end of FIO₂ reduction (without hypercapnia), and 20 min of hypercapnia (or 10 min of hypercapnia when the end point was before 20 min)] of MAP, CO, HR, SVR, mPAP, PVR, CPP, ICP, PbtO₂, ScvO₂, rSO₂, and difference between Laccv and Laca. ANOVA for repeated measures was also used to detect differences in Tcore between four time points (baseline, end of hypothermia, end of FIO₂ reduction, and end of hypercapnia). Pairwise comparisons were analyzed by means of Student’s t test after adjustment of P values with Bonferroni correction. A correlation coefficient for repeated observations (16) was used to determine whether changes in rSO₂ were correlated with changes in PbtO₂, CPP, and ScvO₂ during each phase and whether changes in Tcore were correlated with changes in brain temperature (Tbrain). Values are given as means ± standard deviation (SD). All given P values are two-sided, and P < 0.05 was considered statistically significant. SPSS 23 (IBM, Armonk, NY) was used for statistical analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Data from nine pigs were obtained and included in the analysis. The pigs weighed 36.9 ± 2.1 kg and were 11.1 ± 4.1 cm long. Test duration from baseline measurement to the end point of the protocol was 224 ± 17 min. Six (67%) tests were interrupted because of hemodynamic instability (i.e., a 30% decrease in MAP, all in the hypercapnia phase), and three (33%) tests were interrupted 60 min after hypercapnia induction. Baseline Tcore was 38.0 ± 0.8°C and decreased to 28.0 ± 0.1°C (P < 0.001) in 167.0 ± 24.5 min during hypothermia induction. Tcore remained at 28.1 ± 0.2°C at the end of the FIO₂ reduction phase (P = 1.000 for comparison with the end of the hypothermia phase) and increased to 28.3 ± 0.3°C at the end of the hypercapnia phase (P = 0.017 for comparison with the end of the FIO₂ reduction phase). During the test, changes in Tcore were correlated with changes in Tbrain (r = 0.997, P < 0.001). Results for blood gas analyses, etCO₂, and MAP levels at baseline, after 5-min steady state at 28°C, after 10 min and at the end of the FIO₂ reduction phase (20 min), and after 10 min, 20 min, and at the end of the hypercapnia induction are shown in Table 1.

Systemic and Pulmonary Changes in Hemodynamics

MAP decreased during all three experiment phases. CO and HR decreased during the hypothermia and the hypercapnia phase but remained unchanged during reduction of FIO₂. SVR and PVR increased with hypothermia, with PVR showing a further increase after induction of hypercapnia. In this phase, mPAP also significantly increased (Fig. 2).

CPP, ICP, and Cerebral Oxygenation Changes

CPP decreased during each of the three experiment phases (Fig. 3). ICP progressively increased during the tests, but pairwise comparisons of phases were not statistically significant after Bonferroni correction. PbtO₂ progressively decreased during the tests (Fig. 3); interestingly, the relative decrease during the first 20 min of (or 10 min if the test was interrupted before) the hypercapnia phase was greater than during the FIO₂ reduction phase (−39 ± 32%...
ScvO₂ increased during hypothermia, did not change during FIO₂ reduction, and decreased during the first 20 min of the hypercapnia phase (Fig. 3). There were no changes in the difference between Lac.cv and Lac.a.

**Correlation between rSO₂ and CPP, PbtO₂, and ScvO₂**

rSO₂ decreased only in the hypercapnia phase (Fig. 3). During hypothermia, changes in rSO₂ correlated with changes in CPP ($r = -0.399, P = 0.039$), in ScvO₂ ($r = 0.428, P = 0.023$), but not in PbtO₂. During reduced FIO₂, changes in rSO₂ correlated only with changes in CPP ($r = 0.664, P = 0.002$). After hypercapnia induction, changes in rSO₂ correlated with changes in CPP ($r = 0.930, P < 0.001$), PbtO₂ ($r = 0.667, P < 0.001$), and ScvO₂ ($r = 0.907, P < 0.001$) (Table 2).

**DISCUSSION**

This animal model mimicking a scenario of long complete avalanche burial (triple H syndrome) suggests that hypercapnia may be the main cause of cardiovascular instability on a severely hypothermic body exposed to reduction of inspiratory oxygen, which leads to a significant decrease in oxygen delivery to the brain. We observed a significant impairment of systemic and pulmonary hemodynamic parameters resulting in cerebral desaturation (decrease in PbtO₂, ScvO₂, and rSO₂) in the hypercapnia phase. Our data show that this mismatch cannot be compensated by the effect of hypothermia, which is known to decrease brain oxygen consumption. Another important finding made in this study is that no decrease in cerebral oxygenation occurs during severe hypothermia (Tcore 28°C) under normocapnic conditions.
normoxic conditions or initial reduction of inspiratory oxygen to 17%, as long as spontaneous circulation is preserved.

Survival of completely buried avalanche patients is strongly time dependent. Causes of death are reflected in the course of avalanche survival curves (1–3), showing that avalanche patients die from asphyxia within the first 35 min of burial if they are not able to breathe under the snow. In patients who are able to breathe, if delivery/removal of

**Table 2.** Correlation coefficients with *P* values for changes in *rSO₂* with changes in CPP, *PbtO₂*, and *ScvO₂* during hypothermia, *FIₐO₂* reduction, and hypercapnia phases

| Correlation of rSO₂ with | Hypothermia | | | Hypercapnia |
|-------------------------|-------------|-------------|-------------|
|                         | *r* | *P* Value | *r* | *P* Value | *r* | *P* Value |
| CPP                    | -0.399 | 0.039 | 0.664 | 0.002 | 0.930 | <0.001 |
| *PbtO₂*                | -0.062 | 0.797 | 0.388 | 0.152 | 0.667 | <0.001 |
| *ScvO₂*                | 0.428 | 0.023 | 0.184 | 0.452 | 0.907 | <0.001 |

CPP, cerebral perfusion pressure; *FIₐO₂*, fraction of inspiratory oxygen; *PbtO₂*, brain tissue oxygen tension; *rSO₂*, regional cerebral oxygen saturation; *ScvO₂*, cerebral venous oxygen saturation.
respiratory gases is sufficient patients will develop a triple H syndrome after 35–60 min. Our group previously investigated the triple H syndrome in a pilot field study under authentic avalanche conditions (13). When delivery/removal of respiratory gases was insufficient, pigs quickly developed hypoxia and hypercapnia and subsequently circulatory collapse, leading to a plateau in Tcore (between 22 and 53 min, with a Tcore between 31 and 34°C) (13). Conversely, pigs with sufficient gas exchange remained circulatory stable and continued to cool down until hypothermic cardiac arrest (which occurred between 83 and 178 min with a Tcore between 21 and 28°C in the previous pilot study) (13). In the present study we attempted to observe brain oxygenation in a scenario of long complete avalanche burial based on FIO2 and CO2 levels tailored according to pilot tests and previous data from the literature (10–13). Our results confirm that cooling Tcore to 28°C is possible with optimal delivery of O2 and removal of CO2. Cooling was accompanied by a reduction in MAP and CPP in relation to severe hypothermia; blood gas values showed an increase in arterial partial pressure of oxygen (PaO2), probably due to the shift in the oxygen dissociation curve to the left and reduced oxygen demand, which decreases by ~6–8% for each °C and drops to ~30% of the initial value at 28°C core temperature (6, 17, 18). Our data also confirm results from the in-field pilot study in relation to hemodynamic parameters and blood gas values (13). Then, we introduced in a stepwise sequence the other two factors contributing to the triple H syndrome. The reduction in FIO2 to 17% did not lead to a clinically relevant impairment in either cerebral oxygenation or hemodynamic parameters within 20 min. Conversely, in parallel to the increase in CO2 there was a progressive decrease in PaO2, an increase in pulmonary resistance, a decrease in cardiac output, and an impairment of MAP (i.e., 30% decrease), leading to premature termination of the experiment in 67% of the cases. Whether the hypoxic pulmonary vasoconstriction was primarily related to rapid constriction solely due to hypoxic hypercapnia or to a gradual development of tone due to sustained hypoxia should be subject to further investigation (19).

Impairment of CO led to a decrease in CPP, which, despite severe hypothermia, caused a decrease in cerebral tissue oxygenation. We recently showed that cerebrovascular autoregulation is disturbed even in moderate hypothermia and that cerebral oxygen supply directly depends on perfusion pressure (20). There was also a progressive decrease in PaO2, most probably due to displacement of O2 by CO2 in the alveoli (where an extremely low partial pressure of oxygen was estimated with the alveolar gas equation). Thus, the impairment of cerebral tissue oxygenation in the present study, which is reflected by a decrease in PbtO2, ScvO2, and rSO2, is most likely due to a simultaneous reduction in CPP and a decrease in arterial oxygen saturation.

Porosity of the snow surrounding the air pocket seems to favor O2 diffusion from snow into the air pocket (12). This can allow survival after even longer burials in real-life scenarios. Our data suggest that with severe hypothermia brain oxygenation could remain sufficient even with a mild reduction in FIO2. An excess of CO2, on the other hand, can lead to impairment of CPP due to acute heart failure, thus causing cerebral hypoxia even in the presence of severe hypothermia.

In this study NIRS correlated moderately well with CPP and also demonstrated cerebral desaturation in the hypercapnia phase (decrease in ScvO2). However, rSO2 is still difficult to understand in such extremely critical clinical situations because, on one hand, absolute limits indicating critical deterioration are still missing and, on the other hand, there are a number of variables that influence it. In addition to perfusion pressure, hypothermia, hypoxia, and hypercapnia, other factors such as skin perfusion and vasopressor administration also may affect rSO2, which is why the measured NIRS value should always be critically questioned (21).

There are some limitations to this study. First, the results of this experimental study may not be directly transferable to humans; for example, pigs have a higher body temperature at rest (22) and an oxygen dissociation curve that is less affected by temperature (18). However, the use of a porcine model for hypothermic studies is well established. The cerebral and cardiovascular physiology and hypothermia pathophysiology of pigs are more similar to those of humans than those of other mammalians (23). Second, propofol and piritramide reduce cerebral blood flow and cerebral metabolic rate, and ketamine increases cerebral blood flow, potentially affecting the neurovascular coupling relationship. However, for ethical reasons, the experiment could only be performed on anesthetized animals. Despite the possibility that anesthetics may have accelerated the cooling rate by shivering suppression and vasodilation (24), controlled ventilation mitigated impairment of respiration and the observed parameters are in accordance with those seen in previous animal studies (13, 25). Third, the use of a ventilator obscured some of the relevant ventilatory responses during cooling. Spontaneous respiration in cooling humans influenced cerebral hypoperfusion via hyperventilation and hypocapnia (26). However, in a study under authentic avalanche conditions pigs did not show hypocapnia despite spontaneous respiration (13). Fourth, during the tests there was an overlap between FIO2 reduction and hypercapnia phases. For this reason, we cannot completely elucidate whether the impairment of brain oxygenation and hemodynamic parameters recorded in the third phase was related only to hypercapnia or partially to the sustained FIO2 reduction. Nevertheless, this is consistent with long complete avalanche burials (9).

This animal model of triple H syndrome suggests that hypercapnia may be the main cause of cardiovascular instability, which seems to be the major trigger for a decrease in cerebral oxygenation, despite severe hypothermia. Our study suggests that steps that prevent or reduce hypercapnia in completely buried avalanche patients (11, 27, 28) could prevent impairment of hemodynamic parameters and sustain brain oxygenation for a longer period of time and therefore possibly save lives. Further studies should investigate cerebral oxygenation during spontaneous respiration and with the measurement of cerebral microcirculation and cerebral metabolism to further elucidate the underlying pathophysiological mechanisms. Such studies may allow us to better understand factors affecting NIRS values in order to evaluate
the potential use of noninvasive monitoring devices in the management of completely buried avalanche sectors.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

G.S., G.P., M. Falk, and H.B. conceived and designed research; G.S., G.P., P.B., B.G., D.P., and R.H. performed experiments; G.S., T.D., M. Falla, M. Falk, and H.B. analyzed data; G.S., G.P., M. Falla, P.B., M. Falk, R.H., and H.B. interpreted results of experiments; G.S. and T.D. prepared figures; G.S. and M. Falk drafted manuscript; G.S., G.P., T.D., M. Falla, P.B., M. Falk, B.G., D.P., R.H., and H.B. edited and revised manuscript; G.S., G.P., T.D., M. Falla, P.B., M. Falk, B.G., D.P., R.H., and H.B. approved final version of manuscript.

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