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Brain metabolism and oxygenation in healthy pigs receiving hypoventilation and hyperoxia

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ABSTRACT

Modulation in ventilatory settings is one of the approaches and interventions used to treat and prevent secondary brain damage after traumatic brain injury (TBI). Here we investigate the effect of hyperoxia in combination with hypoventilation on brain oxygenation, metabolism and intracranial pressure. Twelve pigs were divided into three groups; *group*1–100% hyperoxia ($n=4$), *group* 2–100% hyperoxia and 20% decrease in minute volume (MV) ($n=4$) and *group* 3–100% hyperoxia and 50% decrease in MV ($n=4$). Neither of the ventilator settings affected the lactate/pyruvate ratio significantly. However, there was a significant decrease of brain lactate (2.6 ± 1.7 to 1.8 ± 1.6 mM) and a rapid and marked increase in brain oxygenation (7.9 ± 0.7 to 61.3 ± 17.6 mmHg) in group 3. Intracranial pressure (ICP) was not significantly affected in this group, however, the ICP increased significantly in group 2 with 100% hyperoxia plus 20% reduction in minute volume. We conclude that hyperoxia in combination with 50% decrease in MV showed pronounced increase in partial brain oxygen tension ($pbrO_2$) and decrease in brain lactate. The ventilatory modification, used in this study should be considered for further investigation as a possible therapeutic intervention for TBI patients.

1. Introduction

Traumatic brain injury (TBI) is a major public health problem throughout the world and is the leading cause of death and chronic disabilities in young adults in industrialized countries (Ghajar, 2000). The pathology of TBI is highly heterogeneous with various manifestation caused by a primary impact such as focal impact, acceleration–deceleration and blast waves. The primary injury in TBI is followed by secondary events such as ischemia, hypoxia and edema that can develop over hours to weeks and even become a chronic state (Masel and DeWitt, 2010; McIntosh et al., 1996). Cerebral ischemia, which is caused by arterial hypoxia and/or reduced cerebral blood flow (CBF), is one of the major secondary insults that influence the prognosis and outcome of the patients with severe head injury (Graham et al., 1989). Secondary events are a significant cause of increased mortality and morbidity following TBI (Doberstein et al., 1993, McHugh et al., 2007). Therefore, the treatment and prevention of such secondary injuries may contribute to improved outcome after TBI. Modulation in ventilator settings is one of the interventions used to treat and prevent secondary brain injury.

Previously, chronic prophylactic hyperventilation was a core in the treatment of traumatic brain injury. This was based on the knowledge that hyperventilation induces cerebral vasoconstriction, leading to a reduction of cerebral blood volume (Raichle and Plum, 1972). The resultant decrease in intracranial pressure (ICP) was suggested to improve cerebral perfusion pressure and thereby delivery of oxygen and glucose. However, surprisingly, worse outcome was observed in a randomized clinical trial studying hyperventilated TBI patients (Muizelaar et al., 1991). In another study using positron emission tomography (PET), hypocapnia ($PaCO_2 < 34$ mmHg) in TBI patients reduced the global CBF and resulted in an increase in the volume of injured and already hypoperfused brain tissue (Coles et al., 2002). Using microdialysis in patients with severe TBI, it was shown that hypocapnia decreases brain glucose and increases brain lactate concentration, indicating anaerobic metabolism (Marion et al., 2002). In patients with cardiac arrest hypocapnia was associated with decrease in cerebral

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perfusion while hypercapnia showed a decrease in brain lactate and increased cerebral perfusion (Pynnonen et al., 2011). Microdialysis can be used to monitor the metabolic state of almost any tissue (Rostami and Bondi, 2012; Ungerstedt, 1991) and is a widely used technique for monitoring brain energy metabolism during neurointensive care (Rostami and Bellander, 2011; Ungerstedt and Rostami, 2004). The most common metabolites measured are glucose, lactate, pyruvate, glycerol and glutamate. The lactate/pyruvate (L/P) ratio is a known marker of the cellular redox state and represents alterations of mitochondrial function, where values above 25 have been suggested as an indicator of anaerobic metabolism and ischemia in brain (Enblad et al., 2001).

Current guidelines recommend that prophylactic hyperventilation during the first 24 h after severe TBI should be avoided since it can compromise cerebral perfusion when CBF is already reduced (Foundation Brain Trauma, 2000). Establishment of better monitoring methods and increased knowledge about the substrate delivery and metabolic status of injured brain has led to a debate concerning ventilation strategies. In order to prevent ischemia and improve tissue oxygenation, normobaric hyperoxia has been used in TBI patients, as two previous studies have shown increased brain tissue oxygen tension by hypoventilation in injured and non-injured animals (Manley et al., 2000; van Hulst et al., 2002). Our hypothesis was that in order to increase brain oxygenation and counteract the vasoconstrictive effect of hyperoxia alone, hypercapnia could be used in parallel. Hypercapnia would generate increased levels of brain $PaCO_2$, a potent vasodilatory factor (Kontos et al., 1977b).

We investigated the effect of hyperoxia in combination with hypoventilation on brain oxygenation, metabolism and intracranial pressure. The metabolic parameters were used to reflect the effect of this ventilatory setting on brain tissue and provide information about its potentially deleterious or beneficial outcomes. We used a Clark type polarographic PaO_2 probe and microdialysis to investigate the effect of normobaric hyperoxia with and without hypoventilation on brain PaO_2 and metabolism in non-injured pigs. The rationale for using non-injured pigs in this pilot study was to evaluate normal physiological responses to hyperoxia and varying levels of controlled hypoventilation in a homogeneous group without compromised brain perfusion and metabolism. Furthermore, due to ethical reasons, our plan was to evaluate the effects in this study before including injured animals in a larger follow-up study.

2. Material and methods

2.1. Surgical preparation

Crossbred (Swedish Landrace. Estuna, Sweden) littermate, male pigs ($n = 12$) weighing 22 ± 2 kg (10–12 weeks) were used. Our opinion was that four animals in each group were enough at this phase in order to show the proof of concept. All experiments were conducted in accordance to an experimental protocol approved by the local ethical committee.

The animals were sedated with an intramuscular premedication of 12 mg/kg Ketamine hydrochloride (Ketaminol Vet®, Veterinaria AG, Zurich, Switzerland), and 0.05 mg/kg atropine sulfate (Atropin® NM Pharma AB, Stockholm, Sweden). Before intubation 4 mg/kg of Propofol (Lipuro®, Braun, Germany) was given through an ear vein via a 20G venflon cannula. The animals were then intubated and ventilated by a volume-controlled respirator (servo900C, Siemens, Germany) with the following setting: pressure regulated volume control mode 198 ml/kg, 20 breaths/min, inspired oxygen fraction of 24%, positive end-expiration pressure (PEEP) 5. The ventilation and oxygenation were monitored via a SpO_2 sensor placed over the tail artery and also by repetitive blood gas analysis (i-STAT, Abbott, USA, EG7+ cartridges) from samples obtained through an arterial line placed in the right femoral artery. This line was also used for continuous measurement of arterial blood pressure.

Anesthesia was maintained with intravenous infusion of Propofol (Lipuro®, Braun, Germany) (10 mg/kg/h) and Fentanyl (Braun®, Braun, Germany) (12 mg/kg/h) in a peripheral abdominal vein and an ear vein. The pig received 7.5–10 ml/kg/h of Ringer–Acetate (Ringer–Acetate Braun®, Braun) through the abdominal vein. Urinary output and fluid infusion were checked and calculated each hour. After a midline incision, a urinary catheter was placed in the urinary bladder by a small cystotomy. Through the same incision the temperature probe was placed in the abdominal cavity. The ECG, heart rate, blood pressure, peripheral saturation, body temperature and respiratory settings were registered during the whole experiment via the Datex/ICU Pilot device (CMA/Microdialysis AB, Sweden). At the end of the experiment the animals were injected with a high dose of potassium chloride that produced immediate cardiac arrest.

2.2. Microdialysis

The animals were in the prone position and the head was secured. After a midline incision the bregma was exposed and two burr holes were drilled 0.8 cm frontally on the sagittal suture and 1 cm laterally respectively on each side. Bolts (GSM Licox, Germany) were screwed in the holes and the dura mater was opened by diathermy. Through the bolts a three-channel brain access (GSM LICOX, Germany) was inserted. An intracranial pressure (ICP) sensor (Codman® ICP monitoring System) was placed in the left bolt. A $PbrO_2$ Clark polarographic probe (GSM LICOX, Germany) and a CMA 70 microdialysis bolt catheter with membrane length of 10 mm (CMA/Microdialysis AB, Stockholm, Sweden) were inserted in the right bolt, to the same depth. The brain catheters were eluted with a perfusion fluid (Perfusion Fluid CNS, CMA/Microdialysis AB) pumped at a rate of 0.3 μl/min using a CMA 106 pump (CMA/Microdialysis AB).

Microdialysis samples were taken every 20 min. The samples were analyzed in CMA 600 (CMA/Microdialysis AB, Sweden) for glucose, lactate and pyruvate. We monitored for at least 3 h to obtain stable values from microdialysis before modifying ventilator settings.

CMA 600 and Licox values were continuously recorded through ICU (Lab) pilot program in a computer. The Licox probes were calibrated in distilled water before and after experiment, according to the manufacture's specifications.

At the end of the experiment placement of the probes was evaluated. The brain catheter was replaced by brain markers shaft 10 mm (CMA/Microdialysis AB, Stockholm, Sweden). After 24 h of fixation in 3% formaldehyde solution the brain was sectioned and the placement of the markers evaluated.

2.3. Ventilation

All animals were initially normoventilated with normoxia and normocapnia with the respiratory settings of pressure regulated volume control mode 198 ml/kg, 20 breaths/min, inspired oxygen fraction 24%, PEEP 5. After obtaining baseline values we modified the settings and created three different groups:

Group 1 (FIO2 100% during 1 h), group 2 (FIO2 100% and 20% of minute volume (MV) during 1 h), group 3 (FIO2 100% and 50% of MV during 1 h hour), MV in groups 2 and 3 were modified by decreasing the tidal volume by 20 and 50% respectively. All groups were returned to original respiratory setting after 1 h.