

**Cerebral air embolism and brain metabolism:
effects of ventilation and hyperbaric oxygen in healthy and
brain-traumatised animals**

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**Cerebral air embolism and brain metabolism:
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traumatised animals**

Cerebrale luchtembolieën en brein metabolisme: effecten van beademing en
hyperbare zuurstof in gezonde en cerebraal beschadigde dieren

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Aan: Fockje en Arnoud

*Het leven is
dat wat gebeurt
als we met andere dingen
bezig zijn*

(John Lennon)

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Chapter 1

Gas embolism; pathophysiology and treatment

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In: Clinical Physiology and Functional Imaging (in press)

Abstract

Based on a literature search, an overview is presented of the pathophysiology of venous and arterial gas embolism in the experimental and clinical environment, as well as the relevance and aims of diagnostics and treatment of gas embolism.

The review starts with a few historical observations and then addresses venous air embolism by discussing pulmonary vascular filtration, entrapment, and the clinical occurrence of venous air emboli. The section on arterial gas embolism deals with the main mechanisms involved, coronary and cerebral air embolism, and the effects of bubbles on the blood-brain barrier. The diagnosis of cerebral air embolism uses various techniques including ultrasound, perioperative monitoring, computed tomography, brain magnetic resonance imaging and other modalities. The section on therapy starts by addressing the primary treatment goals and the roles of adequate oxygenation and ventilation. Then the rationale for hyperbaric oxygen as a therapy for cerebral air embolism based on its physiological mode of action is discussed, as well as some aspects of adjuvant drug therapy. A few animal studies are presented which emphasize the importance of the timing of therapy, and the outcome of patients with air embolism, (including clinical patients, divers and submariners) is described.

Introduction

Air embolism, the entry of gas into the vascular structures, is a mainly iatrogenic problem that can result in serious morbidity and even death.¹⁰⁷ The first known account of arterial embolism was by Morgagni, whose personal observations and postmortem findings were recorded in his treatise published in 1769, which was cited in the 1950s by Fries and colleagues.⁴¹ The first clinical report dates back to 1821 when Magendie described a case of venous air embolism resulting in death.⁴⁸

Diving

Air embolism due to pulmonary barotrauma is an ongoing cause of concern in all types of diving operations.³² In diving, pulmonary conditions associated with bronchial obstruction are hazardous, particularly during ascent, even when all usual precautions are taken.⁸² Air embolism is the clinical manifestation of Boyle's law as it affects the lung and is the result of overdistention and rupture of the alveoli by expanding gases during ascent. Normally, intrapulmonary and environmental pressures are equalized by exhalation during ascent. A change in pressure of approximately 70 mm Hg is sufficient to cause pulmonary barotrauma,^{92,125} thus a full inspiration with compressed air at 1 meter under water could, theoretically, lead to pulmonary barotrauma.

Threat to organs

In most cases "gas" embolism is in fact air embolism, although the medical use of other gases such as carbon dioxide, nitrous oxide, nitrogen and helium can also result in embolism.^{97,101,137} In an experimental setting, the effects of air emboli differ greatly depending on whether they are venous or arterial and on the organ(s) where the emboli finally lodge.⁴⁶ Although air bubbles can reach any organ, occlusion of the cerebral and cardiac circulation is particularly deleterious because these systems are highly vulnerable for hypoxia. Cerebral arterial air embolism is a severe complication which is known to occur during neurosurgical and cardiothoracic surgery as well as during many other diagnostic and therapeutic procedures.¹⁰⁵

This article presents an overview of venous and arterial gas embolism in the experimental and clinical environment and also discusses the relevance of diagnostics and therapy.

Venous gas embolism

Filtration

Venous air embolism occurs when gas enters the systemic venous system and is transported to the lungs via the pulmonary arteries. Studies on venous air embolism have shown that filtering by the pulmonary vessels protects the systemic and coronary circulation from air emboli originating in the venous circulation.²⁰ Animals studies have shown that when the lung filter is overloaded, the gas

bubbles will break through the filter: air doses ranging from 0.05 to 0.40 ml/kg/min were infused in dogs during ultrasonic Doppler monitoring of the arterial vessels. The pulmonary vascular filtration of venous air infusion was complete for air doses up to 0.30 ml/kg. When the air dose was increased to 0.35 ml/kg/min the filtration threshold was exceeded leading to arterial spillover of bubbles in 50% of the animals and increasing to 71% of the animals for an air dose of 0.40 ml/kg/min.^{21,22} A similar study in pigs resulted in a 130% increase of pulmonary arterial pressure to 40 mmHg: the breakdown incidence of bubbles was 67% with an air flow of 0.10 ml/kg/min.¹⁴⁰ Comparison of these data suggest that the threshold value for the breakthrough of air bubbles in pigs is less than in dogs. This difference was explained hemodynamically, whereby the rise in pulmonary pressure accompanied by a dramatic drop on the arterial side of the circulation may improve shunting via arteriovenous anastomosis.¹⁴⁰

Entrapment

Venous air embolism may lead to trapping of air bubbles in the pulmonary capillary bed, which can lead to decreased gas exchange,¹⁶ cardiac arrhythmia,^{13,35} pulmonary hypertension,³⁵ right ventricular strain,^{11,12,28} cardiac failure²⁸ and arterial gas embolism due to shunting to the left systemic vascular system.²¹

Entrapment of venous bubbles in the pulmonary microcirculation may also lead to cellular injury and lung edema resulting from the release of vasoactive mediators following pulmonary vascular obstruction.^{1,36,37,112,141} This type of lung injury is thought to be mediated by activated neutrophils sequestered in the pulmonary capillary bed during air embolism. The activated neutrophils release thromboxane and leukotrienes that increase alveolo-capillary permeability resulting in edema. The capillary leakage will result in a dose-dependent inactivation of endogenous surfactant⁷⁸ leading to alveolar collapse, formation of atelectasis, impaired gas exchange and, thus, the need for mechanical ventilation.

Clinical occurrence

Venous air emboli most often occur in patients during the insertion, maintenance or removal of a central venous catheter.^{50,113} In a review of the literature, Heckmann and colleagues discussed 26 cases in which most venous air emboli occurred during a subclavian or jugular vein catheterization procedure.⁵³ Embolism can also occur as a result of lung trauma induced by mechanical ventilation.^{60,94} Bricker and colleagues used transesophageal echocardiography in patients who required mechanical ventilation with positive end-expiratory pressure (PEEP) and found continuous venous air embolism in 5 of the 8 lung trauma patients;¹⁸ they concluded that there is a relatively high occurrence of venous air embolism in patients with pulmonary barotrauma associated with increased ventilatory pressures, and that venous emboli may contribute to cardiovascular instability

and may exacerbate lung injury in critically ill patients. In gynecologic surgical and diagnostic procedures, venous air embolism is a rare and unexpected complication.^{106,145} Laparoscopy using carbon dioxide can also lead to a venous CO₂ embolism.⁹⁷ Finally, during neurosurgery air may enter the veins, especially when patients are in the sitting position.¹¹⁹

Paradoxical emboli

In principle, every venous gas embolism has the potential to develop into an arterial gas embolism; when this happens it is called a paradoxical embolism.⁹ A paradoxical embolism occurs when the filter capacity for air bubbles of the pulmonary capillary bed is exceeded and gas bubbles shunt from the venous side to the arterial side of the circulation. Transcardiac passage of venous gas bubbles can also occur in the presence of any right to left shunt, including a patent foramen ovale.³⁸ The application of PEEP during mechanical ventilation,⁷¹ Valsalva maneuvers²³ and coughing²⁷ can increase the interatrial movement of bubbles in patients with atrial shunts.

Arterial gas embolism

Mechanisms

Arterial gas embolism causes ischemia in the organ in which the air bubbles are trapped. Van Allen and colleagues (1929) investigated arterial gas embolism of the pulmonary vein as a complication of lung surgery.² They recognised two mechanisms for arterial gas embolism: direct infusion into the pulmonary vein, and arterialisation of venous bubbles via a patent foramen ovale. The authors cited two classic key references: Bichat (1808) caused a pulmonary venous air embolism by blowing air into the lungs of a living animal at a sustained pressure greater than maximal respiratory effort; Ewald and Kobert (1883) claimed that such an embolism arose through distended normal stoma and not through ruptured alveolar septa.^{2,48}

Coronary air embolism

A key article on coronary air embolism was published in 1949 by Durant and colleagues who noted the main symptoms: temporary ischemia of the myo-cardium, short periods (< 5 min) of hypertensive crisis and ventricular fibrillation.²⁸ Coronary air embolism has been studied by intracoronary injection of a bolus of air which led to a serious depression of heart function.¹¹ In a study on dogs a 28% mortality rate was reported for an air dose of 0.02 ml/kg, whereas surviving animals showed recovery of heart function within 15 minutes. Other studies on coronary air embolism showed that depression of regional myocardial function could pass unnoticed on the basis of hemodynamic measurements. Air bubbles with a volume of 2 µl/kg injected in the

coronary artery did not change systemic hemodynamics, whereas significant changes were found in systolic segment shortening, suggesting depressed myocardial function with silent ischemia.^{11,12} For the clinician, pathognomic signs were described, including detection of air in the retinal vessels by ophthalmoscopic examination and the occurrence of sharply-defined areas of pallor on the tongue. Marbling of the skin may also occur, presumably due to embolism of the skin vessels and especially noted in superiorly located parts of the body because the distribution of air within the circulation is determined by the principle of air buoyancy.²⁸

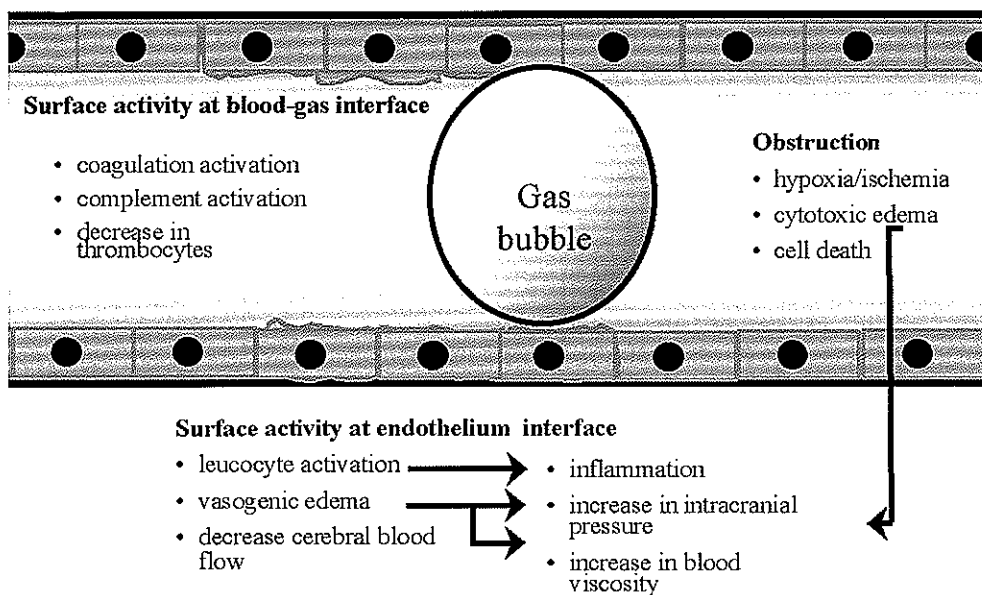


Figure 1. Bubble obstruction in a cerebral vessel. Three levels of interaction are present. First, the bubble interacts with the blood, second, there is a reaction with the endothelium and third, the obstruction leads to distal hypoxia and ischemia finally resulting in neuronal cell death.

Cerebral air embolism

Cerebral air embolism (CAE) is a serious hazard: when bubbles occlude the brain vasculature (Figure 1), intracranial pressure (ICP) increases¹³⁷ and an extremely inhomogenous distribution of blood flow in the brain causes hyperemia and ischemia.^{42,62,63,147} The pathophysiology of CAE mainly depends on the air bubble size. Microbubbles ‘irritate’ the vascular wall leading to an instantaneous breakdown of the blood-brain barrier;⁷² on the other hand, these tiny bubbles are rapidly absorbed and may only briefly interrupt cerebral arteriolar flow.⁴⁷ A good correlation has

been found between cerebral blood flow and brain function after gas embolism by small bubbles at a maximum size of 250 μm .^{29,55,62} The passage of an air bubble will obstruct local blood flow, but flow will normalise after disappearance of the bubbles. However, normalisation is often only temporary and blood flow may subsequently decrease to levels below those required to maintain neuronal function and survival.^{54,55,98}

An explanation for this mechanism was suggested by Dexter and colleagues who calculated that the absorption of large air emboli may take several hours, which is long enough to cause primary ischemic injury with diffuse brain edema leading to raised ICP.²⁶ This latter finding was recently confirmed by our group in an experimental study showing that after a large air embolism ICP increased from 12 to 52 mm Hg within 2 hours after embolization with severe detrimental effects on brain oxygenation and glucose metabolism.⁶⁵

Effects on blood-brain barrier

The presence of bubbles and their contact with endothelium of the blood-brain barrier leads to activation and adhesion of polymorphonuclear leukocytes in the damaged area of the brain.¹⁰² Brain swelling and inflammation may therefore play a stronger role in the occurrence of infarction by air emboli than they do in other forms of cerebral ischemia.⁵⁸ Leukocytes have been implicated in the progressive fall in cerebral blood flow and decreased cerebral function in animal models of gas embolism.^{29,56} Various plasma proteins including the coagulation system, complement and kinins are also activated by bubbles^{118,142,143,144} and coagulopathies are common in animal models of air embolism but are extremely rare in humans.⁴⁰

Diagnosis of cerebral air embolism

The greatest risks for a cerebral arterial gas embolism are cardiac surgery with cardiopulmonary bypass,^{5,132} hip replacements,^{35,110} craniotomy performed with the patient in sitting position,^{44,119} and cesarean section.¹⁴⁵ All these procedures have an incised vascular bed and a hydrostatic gradient favoring the intravascular entry of gas.¹⁰⁷ In most of these patients the diagnosis of CAE is made during recovery from anesthesia when neurological symptoms become manifest. Air embolism can manifest in many ways depending on the patient's position, the volume and type of gas, the size of the bubbles and the rapidity of gas entry into the arteries. Neurological symptoms and signs include: dizziness, chest pain, paresthesias, convulsions, paralysis, nausea, visual disturbances and headache. Sporadic or continued seizure activity may also occur. About 50% of the patient's will have some history of unconsciousness at some time.^{10,45,116} Anesthesia and/or analgesics alter the symptomatology and may complicate evaluation of the patients clinical status.

In addition to neurological signs there may be circulatory collapse, evidence of lung rupture and a variety of pain syndromes.¹¹⁶

The diagnosis of cerebral air embolism should be made when there are central neurological changes and the circumstances were such that a gas embolism could have occurred. However, because a definite confirmation of the diagnosis is not always easy, anesthetists and surgeons should be aware of the risk of an embolic event during medical procedures. Ultrasound techniques such as transthoracic and transesophageal echocardiography during surgery can visualize intravenous or intracardiac bubbles.^{14,93} Direct perioperative monitoring of cardiorespiratory parameters by the anesthetist may also detect emboli; e.g. a sudden decrease in end tidal CO₂ by capnography or a sudden increase in pulmonary artery pressure may be a sign of air embolism during surgery.⁷

Radiographic techniques

Animal studies^{3,4} and several clinical case reports have used computed tomography (CT) to demonstrate the presence of CAE.^{52,59,68,69,124,129,135} On the other hand, Hodgson and colleagues studied 47 divers with neurologic/pulmonary symptoms by CT scanning and were unable to show any evidence of CAE in any of the divers.⁶¹

Brain magnetic resonance imaging (MRI) in CAE may show local edema, but in two such cases even the MRI was normal.⁸⁸ A review of the studies using CT, MRI and single-photon emission computer tomography (SPECT) allows to conclude that, at present, no imaging technique alone has sufficient accuracy to warrant its use for diagnostic purposes; therefore, clinical evaluation is still preferred for the assessment of cerebral air embolism.³³ Although radiographic investigations may support or confirm the diagnosis of CAE, they can not be used to definitively rule it out.

Therapy

Immediate treatment aims to interrupt the intervention that caused the embolic event. If indicated, in a comatose patient cardiopulmonary resuscitation and endotracheal intubation should also be performed as quickly as possible to maintain adequate oxygenation and ventilation.¹⁰

Administration of oxygen is important, not only to treat hypoxia and hypoxemia, but also to decrease air bubble size by establishing a diffusion gradient that favors the elimination of gas from the bubbles.^{77,107} Although hyperventilation is recommended,¹³⁸ our group recently demonstrated in pigs that hypocapnia and hyperoxygenation do not improve cerebral functional parameters as characterised by, for example, ICP and brain lactate.⁶⁶ Systemic hypertension for a short period following bubble entrapment in the cerebral circulation is usual.^{28,34} A short period of hypertension is therapeutic because it facilitates bubble redistribution through the arterioles to the capillaries and

into the veins. Although supranormal blood pressure has been promoted,¹³⁸ in some animal models prolonged hypertension leading to increased ICP may compromise the neurological outcome as characterised by EEG and other neurophysiological parameters.²⁹ Far worse is progressive hypotension: a fall in blood pressure results in both increased bubble entrapment and (given that the autoregulation is lost)⁵⁴ causes cerebral blood flow to fall to levels below that required for normal neuronal function; therefore, the primary treatment goal is to maintain normal blood pressure.¹⁰⁷ See Figure 2 for an overview.

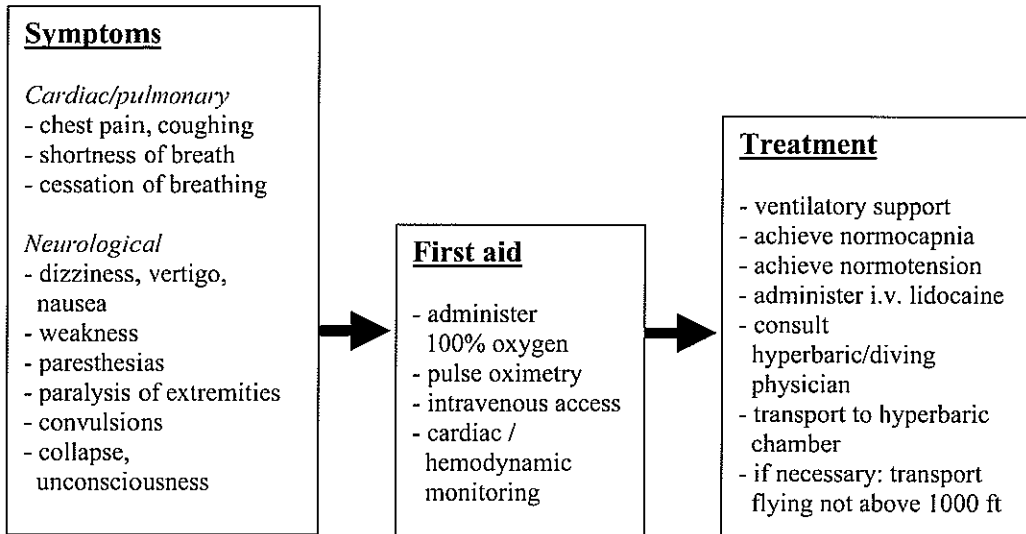


Figure 2. Diagram showing the main symptoms, first aid and treatment of gas embolism

Hyperbaric oxygen therapy

Hyperbaric oxygen (HBO) has been advocated as a therapy for cerebral air embolism.^{51,117,136} HBO diminishes the volume of intravascular bubbles by enhancing the ambient pressure, the increase in the partial pressure of oxygen favors denitrogenation of the cerebral tissue and diminishes the cerebral edema, and HBO increases the partial pressure of dissolved oxygen in the blood allowing better oxygenation of ischemic tissue.⁸⁷ These physiological modes of action seem entirely sufficient to warrant the application of HBO in CAE, despite the lack of prospective studies in humans confirming its efficacy;⁴³ this also implies that in a clinical study on CAE, the inclusion of an untreated patient control group would be unethical.¹⁰ On the other hand, the main criticism about the use of HBO, is that no prospective randomized trials have been conducted to prove its utility^{43,81} and only a few animal studies have shown the benefits of HBO therapy in CAE.^{83-86,133} However, our group recently showed in a pig model of CAE that HBO treatment after 3 minutes

Table 1
Articles on air embolism in a clinical (C) or diving (D) population undergoing hyperbaric oxygen therapy

Authors	No. of patients	C/D	Mean delay/range	Assessment	Outcome			
					Fully recovered	Minor sequelae	Severe sequelae	Dead
Pearson & Goad, 1982	5	D	20 min / 5-60 min	Neurological examination EEG	80% EEG normal			20%
Murphy et al., 1985	16	C	8 h / 0.2-25 h	Neurological examination	50%	31%	6%	12%
Leitch & Green, 1986	89	D	< 10 min*	Neurological examination	65%	18%	16%	1%
Takahashi et al., 1987	34	C	13 h / 0.5-40 h	Neurological examination	62%	15%		24%
Neuman & Hallenbeck, 1987	4	D	9 h / 1-15 h	Neurological examination CT scan	75% CT scan normal	25% CT scan normal		
Bitterman & Melamed, 1988	6	C	24 h / 11-60 h	Neurological examination CT scan	33% CT scan normal	33% CT scan normal		33%

										<i>Cerebral air embolism</i>	
										14%	22%
Massey et al., 1990	14	C	17.5 h / 1-48 h	Neurological examination	50%	14%				14%	22%
Kol et al., 1993	6	C	3 h / 2-20 h	Neurological examination	50%					17%	33%
Muskat et al., 1995	4	C	26 h / 3-48 h	Neurological examination CT scan	75%			CT scan normal			25%
Ziser et al., 1999	17	C	9.6 h / 1-20 h	Neurological examination	47%					35%	18%
Blanc et al., 2002	86	C	3.5 h / 2-8 h	Neurological examination	58%	24%				9%	8%

The authors used different classifications for the neurological outcome after completion of the HBO therapy: in general “minor neurological sequelae” or “major improvement” means only sensory deficits left while “severe neurological sequelae” or “partially recovered” means motor deficits are still present.

* divers and submariners during “free ascent” or “escape training” where the recompression chamber is on location.

and after 60 minutes improved brain parameters, characterized by ICP, brain oxygenation and brain lactate, compared with the natural progression of severe CAE.⁶⁷

Clinical reports

Table 1 presents an overview of studies which have described reports of patients with air embolism; these studies included divers, submariners and clinical patients. Although a wide variety of iatrogenic types of gas embolism have been treated by HBO, the numbers of patients are still small. A general conclusion is that the results are better when the time to treatment was as short as possible, although some patients were treated after a delay of as long as 48 hours.^{8,95,146} Murphy and colleagues reported that after HBO therapy in 16 patients, 8 had complete relief of CAE symptoms, 5 patients had partial relief and 3 had no benefit.¹⁰⁴ In a study of 34 patients by Takahashi et al., 62% had a good recovery.¹³⁴ Recently, Blanc et al. reported a significantly better outcome in patients with venous air embolism with a delay in treatment of less than 6 hours (84%) versus more than 6 hours (53%); in contrast, with arterial air embolism there were no differences between groups with less or more than 6 hours delay.¹⁰ Ziser and colleagues¹⁴⁸ studying 17 patients with CAE due to extracorporeal circulation, reported a total recovery in 47% compared with 58% in the study by Blanc et al.;¹⁰ however, the time elapsed before HBO treatment was 9.6 hours compared with 3.5 hours in the study by Blanc et al.¹⁰

Although the recovery rates in these very heterogenous groups of patients vary widely, it seems that early application of HBO therapy plays an important role in the management and treatment of iatrogenic cerebral air embolism.

Adjuvant drug therapy

Bove stated in the 1980s that the use of drugs in the treatment of cerebral air embolism is often empirical, controversial and varies between different centers and countries;¹⁷ 20 years later, this statement is still valid.¹⁰³

Intravenous fluids: Hemoconcentration has been reported in CAE^{19,127,128} and post-treatment residual symptoms have been correlated with the degree of hemoconcentration;¹⁴ therefore, fluid administration is advantageous in patients with CAE in order to achieve normovolemia. For hemodilution, colloid solutions are preferred because crystalloids may promote cerebral edema. In animals, even a moderate hemodilution to a hematocrit of 30% has been shown to reduce neurological damage.¹²²

Glucose: Neurological traumas can be worsened by hyperglycemia,^{79,120} probably due to an increased production of lactate leading to intracellular acidosis. Because a small amount of glucose

(e.g. 5% dextrose solution) even in the absence of significant hyperglycemia, may worsen the neurological outcome,⁸⁰ it is advised to avoid use of glucose-containing solutions in the acute phase of CAE.¹⁰³ Electrolyte solutions containing lactate are not recommended because they may contribute to acidosis in the presence of significant tissue hypoxia and when lactate is being produced internally.

Dextran: Dextran solutions were used earlier⁸⁹ and although they may offer some advantages (e.g. improvement of the microcirculation, anti-sludging)⁹⁹, these advantages are small compared with the potential risks of creating an acute volume overload, lung congestion and anaphylaxis.^{17,103} Therefore dextran solutions are no longer routinely used.

Barbiturates: Cerebral air embolism often causes generalized seizures which may not respond to benzodiazepines;¹³⁸ in this case it is recommended to use barbiturates. Barbiturates have the advantage of reducing cerebral oxygen consumption and lowering ICP as well as inhibiting the release of endogenous catecholamines resulting in cerebral protection after ischemia.^{62,114} Phenytoin (intravenously) is also recommended because it protects against further convulsions during hyperbaric treatment.³¹

Aminophylline is, theoretically, a useful drug for pulmonary symptoms such as chest pain, tachypnea and dyspnea in venous air embolism, but is contraindicated because it leads to dilatation of the pulmonary vasculature, resulting in an increased release of trapped bubbles into the systemic circulation.²¹

Heparin is advocated because of its protective effect against platelet clumping but reports on its use are not consistent. For example, a single case report of heparin given to a patient with neurological symptoms indicated neither adverse nor beneficial effects.⁷⁴ In animal studies, administration of heparin alone showed no benefit in CAE¹⁰³ whereas a combined therapy of indomethacin, PGI₂ and heparin resulted in a better neurophysiological outcome in rabbits.⁴⁹ However, it has been demonstrated that, given prophylactically, heparin decreases neurological impairment in an animal model of severe CAE.¹²³

Steroids: CAE initially induces increased transudation of fluid across a damaged blood-brain barrier ('vasogenic edema') and later swelling of cells that no longer have sufficient energy to maintain osmotic integrity ('cytotoxic edema').^{70,111} Earlier, cerebral edema in CAE was treated with corticosteroids^{75,115} but because later studies showed that corticosteroids increase ischemic injury^{30,39} their use is no longer recommended.

Lidocaine: McDermott and colleagues⁹⁶ demonstrated in cats that lidocaine may depress the rise of blood pressure and ICP and may improve recovery of the somatosensory evoked potential following CAE. Other animal studies reported that lidocaine reduces infarct size,¹²⁶ preserves

cerebral blood flow,^{30,108,121} reduces cerebral edema¹⁰⁸ and preserves neuro-electrical function.^{6,30,121,126} These results in brain-injured animals showed that lidocaine improves cerebral function. This was later confirmed in the clinical situation by Mitchell and colleagues, who reported significantly less postoperative cognitive deficits in valve replacement patients receiving lidocaine for 48 hours from the beginning of surgery.¹⁰⁰

Fluorocarbons are carbon-fluorine compounds characterized by a high gas dissolving capacity (O₂, CO₂, inert gases), low viscosity and chemical and biological inertness.¹³⁰ Thus, intravenous administration of these agents in doses sufficient to increase the transport of these gases should on the one hand increase tissue oxygen delivery and on the other hand the shrinking of gas bubbles due to higher diffusion gradient. Animal studies demonstrated a reduction in mortality in gas embolism,^{90,91,131} a reduction in brain infarct size,²⁴ an improvement in cardiovascular function after air embolisation¹³⁹ and less vascular damage in the retina.⁵⁷ More studies on perfluorocarbons are needed to prove their efficacy and safety in humans, particularly with regard to oxygen toxicity.¹⁰³

Conclusions

Air embolism, the entry of gas into the vascular structures, is a mainly iatrogenic clinical problem that can result in serious morbidity and even death. In most cases, 'gas' embolism is air embolism, although the medical use of other gases such as carbon dioxide, nitrous oxide, nitrogen and helium can also result in embolism. There is a significant amount of in vivo data to demonstrate that cerebral damage is caused by even small volumes of arterial gas. However, the exact relevance of these data for the clinical situation has not yet been fully elucidated. Although data on the morbidity and mortality of air embolism in humans are scarce, many case reports and retrospective studies on small numbers of patients suffering from cerebral air embolism have shown that HBO is the treatment of choice for this complication.

In any case, all practical steps should be taken to minimize venous and arterial bubbles and also to develop techniques to better detect air emboli in the arterial circulation. Clinicians must be aware that air embolism can occur during surgical procedures and should know how to quickly treat this problem. HBO therapy is indicated in the presence of neurological deficits. The physiological mode of action of hyperbaric oxygen seems to support hyperbaric therapy for cerebral air embolism.

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Chapter 2

Intracranial pressure, brain PCO₂, PO₂ and pH during hypo- and hyperventilation at constant mean airway pressure in pigs

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Abstract

Objective: To evaluate in healthy non brain traumatised animals the effects of hypo- and hyperventilation on intracranial pressure (ICP) and brain carbon dioxide, oxygen and pH during the use of a ventilatory mode at constant mean airway pressure (MAwP).

Design: Prospective animal study.

Setting: University laboratory

Subjects: Eight crossbred Landrace/Yorkshire pigs.

Interventions: The animals were ventilated in a pressure-controlled mode according to the “Open Lung Concept” with an inspired oxygen fraction (FiO_2) of 1.0. Started at normoventilation, a stepwise hypo- and hyperventilation was performed to $PaCO_2$ values of 90.4 ± 10.4 and 26.9 ± 4.1 mm Hg, respectively. The ICP and brain parenchyma values ($PbrCO_2$, $PbrO_2$, $brpH$) measured by multiparameter sensors were recorded continuously during these manoeuvres.

Results: During hypoventilation, there was a significant increase in $PbrCO_2$ tension ($p < 0.05$), a significant increase in $PbrO_2$ tension ($p < 0.05$) and a significant increase in ICP ($p < 0.05$). During hyperventilation, there was a significant decrease in $PbrCO_2$ tension ($p < 0.05$) and a significant decrease in ICP ($p < 0.05$) whereas the change in $PbrO_2$ was not significant. The values of MAwP were kept stable during the stepwise hypo- and hyperventilation and this resulted in a constant mean arterial pressure.

Conclusions: Controlled hypo- and hyperventilation at constant MAwP in non brain traumatised pigs, appears to induce changes in ICP and cerebral perfusion pressure which, however, do not necessarily lead to cerebral ischemia. To achieve adequate cerebral perfusion at an increased ICP level due to hypoventilation, one has to maintain sufficient arterial blood pressure. Hypercapnia resulted in a significant increase of brain oxygenation; however, this does not allow to conclude that permissive hypercapnia is neuroprotective.

Introduction

Patients with acute lung injury are currently often treated with ventilatory modes that limit minute ventilation by the use of low tidal volumes. The rationale behind this mode of mechanical ventilation is that limitation of the tidal volumes reduces ventilatory-induced lung injury. This in turn leads to a reduction in shear forces during inspiration/expiration thus preventing further structural damage to the alveolar walls and pulmonary surfactant system, which would otherwise aggravate the already detrimental pulmonary condition of the patient.¹ One of the main side-effects of this mode of ventilation is an increase in arterial carbon dioxide partial pressure (PaCO_2), therefore this mode is called 'permissive hypercapnia' but is well accepted in intensive care.^{2,3} However, there is no consensus on the rate of increase and the upper limit of arterial carbon dioxide tension.^{4,5}

Hypercapnia has different interrelated effects on the brain which are not all beneficial. First, hypercapnia augments cerebral blood flow: due to the increase of blood volume in the brain secondary to vasodilation, intracranial pressure (ICP) will rise.⁶ Subsequently, cerebral perfusion pressure (CPP) may decrease, as this is defined as the blood pressure gradient across the brain and represents the difference between mean arterial pressure (MAP) and ICP.

Second, there are changes in acid base status. Animal studies have shown that a five-fold increase in hydrogen ion concentration in plasma results in a two-fold increase in brain tissue and a corresponding decrease in brain pH.⁷ These effects may aggravate the brain metabolism in patients in whom modes of artificial ventilation are applied which result in high PaCO_2 levels.

There are no data available about the effects on PaCO_2 and ICP during use of ventilation modes at constant mean airway pressure (MAwP). The latter is important because induction of hypoventilation and hyperventilation could change MAwP with consequent changes of the pulmonary and systemic circulation.

Therefore, the aim of this study was to investigate these effects in healthy non brain traumatized pigs during ventilation at constant MAwP by measuring brain carbon dioxide (PbrCO_2), brain oxygen (PbrO_2), brain pH (brpH) and ICP at different PaCO_2 levels.

Methods

Animal care

The study protocol was approved by the University's animal committee and the care and handling of the animals were in accordance with the European Community guidelines (86/609/EC). Subjects were eight crossbred Landrace/Yorkshire pigs of either sex (21-25 kg).

Surgical and analytical procedures

Anesthesia was induced with 0.1 ml/kg i.m. ketamine (Ketalin 100 mg/ml, Apharmo, Arnhem, the Netherlands) and i.m. midazolam 0.1 mg/kg (Dormicum 5.0 mg/ml, Roche Ned., Mijdrecht, the Netherlands). Muscle relaxation was induced by 0.2 mg/kg i.v. pancuronium bromide (Pavulon, Organon Teknika, Boxtel, the Netherlands). Following intubation, animals were connected to a ventilator (Servo Ventilator 300, Siemens-Elcoma, Sweden). To ensure a maximum PaO₂, the animals were ventilated in a pressure-controlled (PC) mode according to the 'Open Lung Concept'⁸ with a PEEP level of 6 cm H₂O, peak pressure of 15/16 ± 2/3 cm H₂O, an I/E ratio of 1:2 and an inspired oxygen concentration (FiO₂) of 1.0. The driving pressure of 10 cmH₂O resulted in a tidal volume of approximately 10 ml/kg; frequency was set to maintain normocapnia (PaCO₂: 35-40 mm Hg).

Anesthesia was maintained with i.v. ketamine 10 mg/kg/h and midazolam 1 mg/kg/h, and muscle relaxation with i.v. pancuronium bromide 0.2 mg/kg/h.

Body temperature was kept within the normal range (37-38°C) by means of a heating mattress. Subsequently, two arterial catheters were inserted in both femoral vessels. In the left femoral artery a multiparameter sensor (Paratrend/Trendcare, Agilent, Böblingen, Germany) was inserted for continuous measurements of PaO₂, PaCO₂, pH and blood temperature and calibrated with conventional blood gas analyses (ABL 505, Radiometer, Copenhagen, Denmark). The mean systemic arterial blood pressure was measured in the right femoral artery using a transducer (Statham P23XL, Spectramed, Oxnard, CA, USA) and recorded (Siemens Sirecust 404-1, Danvers, MA, USA).

After surgical exposure of the skull, a 6-mm burr hole was made 1.5 cm to the left of the sagittal suture, 4 cm caudal of the upper margin of the orbita. Through a cut in the dura mater a calibrated intracranial pressure sensor (Codman Neuromonitor, Johnson & Johnson, Berkshire, UK) was inserted to a depth of 20 mm into the brain parenchyma and a multiparameter sensor (Paratrend/Trendcare, Agilent, Böblingen, Germany) was inserted to a depth of 25 mm. This latter device comprises of two optical fibres for measurements of PbrCO₂ and brpH, a miniaturised Clark electrode for PbrO₂ measurements and a thermocouple for the determination of temperature; the sensor has been validated both *in vitro* and *in vivo*.^{9,10}

After completion of the surgical procedures, a 60-minute stabilisation period was allowed before starting baseline recording of all measured parameters in blood and brain: i.e. MAP, blood gases, ICP and brain parenchyma values (PbrCO₂, PbrO₂, brpH).

The pigs were initially ventilated to maintain an end-tidal PaCO₂ of 35 to 40 mm Hg based on the values of the arterial transducer. After a stable period of at least 10 minutes (change in PaCO₂ ≤ 2

mm Hg) small stepwise changes of the ventilatory frequency were applied, using the online blood gas monitoring, to increase the PaCO₂ during hypercapnia by about 10 mm Hg at each step, or to decrease the PaCO₂ during hypocapnia by about 5 mmHg at each step; each PaCO₂ level lasted for about 15 minutes. If end expiratory flow was not zero, intrinsic PEEP was measured by pressing the end expiratory hold knob at the ventilator and compensated by a reduction in static PEEP to keep MAwP constant.

For each animal, from normocapnia there were 3 steps to hyperventilation and 5 steps to hypoventilation; at each step we measured PaCO₂ values and the corresponding values of PbrCO₂, PbrO₂, brpH, ICP and CPP. At the end of the experiments the sensors were calibrated again to assess any drift in the measured values. The animals were then killed by an i.v. overdose of pentobarbital (Euthesate 200 mg/ml, Apharmo, Arnhem, the Netherlands).

Statistical analysis

The statistical analysis of data was performed using the InStat 2.0 biostatistics package (GraphPad Software, San Diego, USA). Data during normoventilation, hypoventilation and hyperventilation are presented as mean ± standard deviation (SD). Comparison was performed between normoventilation values and maximum achieved hypoventilation/hyperventilation values by means of a paired t-test. Statistical significance was accepted at a p-value < 0.05. The relationship between PaCO₂, PbrCO₂ and ICP is given in a linear regression with the correlation coefficient.

Results

All animals survived the study period. Values of MAwP were kept stable during the ventilatory maneuvers and this (together with the anesthesia procedures) resulted in stable cardiocirculatory conditions. The results of the blood gas analyses with corresponding values of brain parameters measured during normoventilation, hypoventilation and hyperventilation are presented in Table 1. During hypoventilation, there were significant changes in PbrCO₂, brpH and ICP. PbrCO₂ increased by 69% and ICP increased by 38%; there was a nonsignificant 11% decrease in CPP. During hyperventilation there was a significant decrease in PbrCO₂ and ICP. PbrCO₂ decreased by 34% and ICP decreased by 27%. There was a slight 3.4% increase in CPP, which was not statistically significant.

Table 1

Data on blood and brain parameters in normoventilatio, hypoventilation and hyperventilation.
Values are mean \pm SD. N = 8 animals.

	Normoventilation	Hypoventilation	Hyperventilation
Blood gases			
PaO ₂	568 \pm 15	487 \pm 27.6 *	608 \pm 51
PaCO ₂	42.8 \pm 4.6	90.4 \pm 10.4 *	26.9 \pm 4.1 *
pH	7.39 \pm 0.08	7.13 \pm 0.10 *	7.55 \pm 0.05 *
Brain			
PbrCO ₂	68.9 \pm 11.4	116.1 \pm 21.3 *	45.7 \pm 11.8
BrpH	7.04 \pm 0.13	6.81 \pm 0.18 *	7.11 \pm 0.12
ICP	22 \pm 4	30.3 \pm 5.9 *	16 \pm 2.4 *
CPP	73.8 \pm 14.7	65.5 \pm 17.4	76.3 \pm 16.6
Brain temp	37.8 \pm 0.4	38.1 \pm 0.6	38.1 \pm 0.4
Rectal temp	37.6 \pm 0.6	37.8 \pm 0.2	37.9 \pm 0.7
MAP	95 \pm 13	94 \pm 16	94 \pm 9
MAwP	9.2 \pm 1.8	8.9 \pm 1.9	9.2 \pm 2

PaO₂, PaCO₂, PbrCO₂ (mm Hg)

ICP Intracranial pressure (mm Hg)

CPP Cerebral perfusion pressure (mm Hg)

MAP Mean arterial pressure (mm Hg)

MAwP Mean airway pressure (cm H₂O)

Brain and rectal temperature (°C)

* p < 0.05 : vs normoventilation

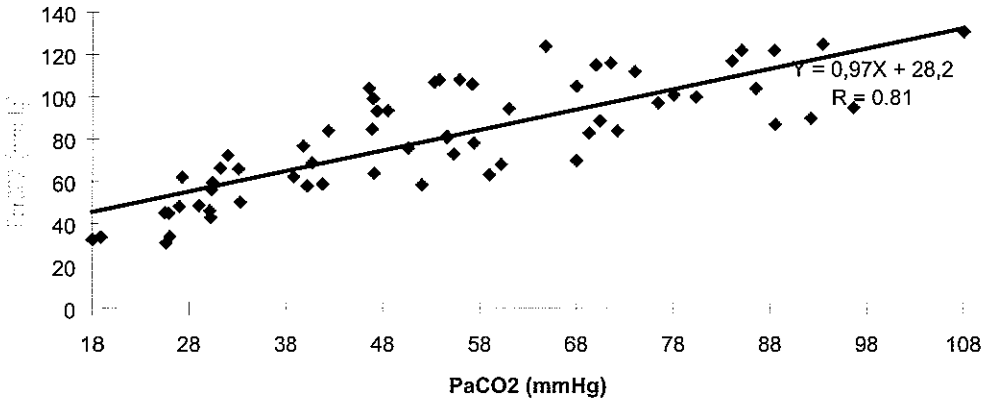


Figure 1.

Effect of PaCO_2 on the PbrCO_2 during hypo- and hyperventilation in non brain traumatized pigs during ventilation at constant mean airway pressure. A linear relationship was observed between PaCO_2 and PbrCO_2 .

Figure 1 shows the PbrCO_2 values plotted in relation to the PaCO_2 values. The line of regression fits the equation: $Y = 0.97X + 28.2$ with a correlation coefficient of 0.81.

Figure 2 shows the relation between ICP and PaCO_2 . The equation of the regression line is: $Y = 0.17X + 14.5$ with a correlation coefficient of 0.58. Table 2 gives the PbrO_2 values in relation to the arterial blood gas values in different phases of hypoventilation and hyperventilation.

Two animals had PbrO_2 values of zero (one animal due to hemorrhage/edema and the other due to technical failure) whereas PbrCO_2 and brpH were appropriate for the conditions; for analysis, therefore, PbrO_2 values from only 6 of the 8 animals were used. During hypoventilation there was a significant 84% increase in PbrO_2 , whereas during hyperventilation there was a nonsignificant 8% decrease in PbrO_2 .

Table 2

Data on blood and brain oxygenation during normoventilation, hypoventilation and hyperventilation. Values are mean \pm SD. N=6 animals

	PaCO ₂	PaO ₂	δ PaO ₂	PbrO ₂	δ PbrO ₂
Normoventilation	39.3 \pm 1.4	537 \pm 28.6	0	78 \pm 40.3	0
Hypoventilation	94.1 \pm 8.2	460 \pm 38.5*	-14 \pm 8	144 \pm 48.1*	84 \pm 45
Hyperventilation	23.9 \pm 3.4	554 \pm 57.4	3 \pm 10	72 \pm 41.1	-8 \pm 5

δ values: are percentual differences from normoventilation (%)

PaCO₂, PaO₂, PbrO₂ (mm Hg)

* p < 0.05: vs normoventilation

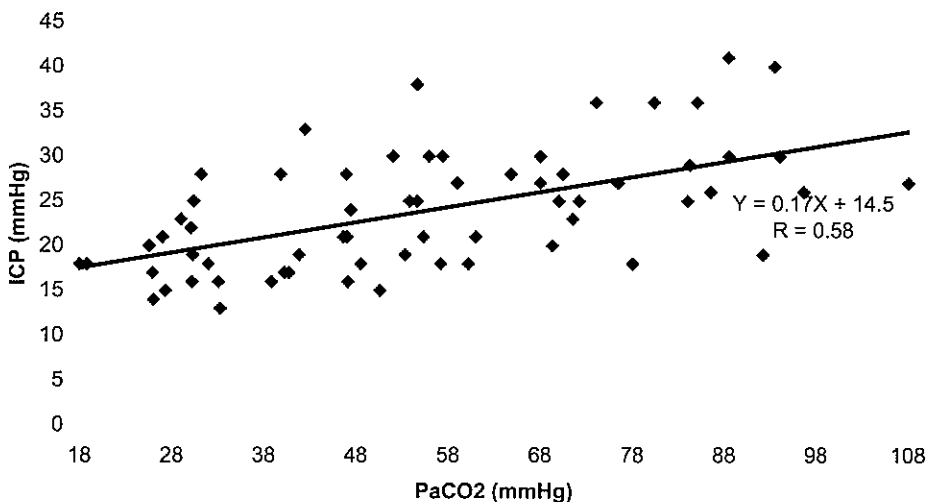


Figure 2.

Effect of PaCO₂ on the ICP during hypo- and hyperventilation in non brain traumatised pigs during ventilation at constant mean airway pressure. A linear relationship was observed between PaCO₂ and ICP.

Discussion

The technique used in the present study to measure brain tissue values with the multiparameter sensor has already been extensively described in different studies.¹⁰⁻¹² The baseline intracerebral data for brain parenchyma of PbrCO₂, brpH and ICP in normoventilated pigs in our study were comparable with data from other studies in cats, dogs and piglets which measured PbrCO₂ and brain pH, using the same multiparameter sensor.¹¹⁻¹³

It is known that an increase in MAwP results in overdilatation of alveoli, compressing the pulmonary capillary bed resulting in an impairment of the pulmonary circulation.^{8,14} In the present study, to eliminate these effects, MAwP was kept stable during the whole study period (Table 1). We used the model of stepwise decrease in ventilatory frequency with stable MAwP to obtain a gradual increase in PaCO₂ values. In hyperventilation, the ventilator frequency was adjusted with small steps to prevent changes in MAwP; the rationale for this is that if one either increases the I/E ratio at constant frequency or increases the frequency at constant I/E ratio to establish an expiratory time, which will be too short to empty the lung to ambient pressure, an intrinsic PEEP will be created.⁸ In this study, if end expiratory flow was not zero, intrinsic PEEP was measured by pressing the expiratory hold knob at the ventilator and compensated by a reduction in static PEEP to keep MAwP constant.

Increased PaCO₂ produces a rightward shift of the oxygen dissociation curve and this led to a decreased affinity of hemoglobin for oxygen which may compromise oxygen loading in alveolar capillaries. In the presence of hypoxia, severe hypercapnia may produce a dramatic decline in arterial oxygen saturation. Therefore, permissive hypercapnia requires the use of hyperoxic-inspired gas where inspired oxygen should be provided to maintain arterial saturation no lower than 85-90%.² In our study we chose an FiO₂ of 1.0 to prevent brain hypoxemia in the severe hypercapnic situation with accompanying metabolic changes; for that reason higher baseline values for PbrO₂ were recorded in our animals (78 ± 40.3 mm Hg). In two earlier studies in dogs, use of an FiO₂ of 0.25 and 0.21, resulted in PbrO₂ values of 28 ± 8 mm Hg and 27 ± 7 mm Hg, respectively.^{11,15} Data from experiments in pigs ventilated with 40% oxygen resulted in PbrO₂ values of 29.4 ± 13.3 mm Hg.¹² Assuming that an increase of the inspiratory oxygen fraction in a steady state under constant metabolic conditions, from 0.4 to 1.0 is by factor 2.5 and that the increase in the brain oxygen tissue will be the same ratio, our baseline data are comparable with previous studies. Recently, Menzel et al. reported PbrO₂ values in humans of 82.7 ± 44.1 mm Hg at 100% FiO₂,¹⁶ which confirm our experimental data. Although the global cerebral oxygen consumption is a stable value under constant metabolic conditions, it is well known that oxygen is heterogeneously distributed to

the brain.¹² Experimental physiological studies exploring brain oxygen distribution suggested that there are different oxygen pressure “layers” in the brain and even rhythmical variations in time.^{17,18} In our experiments, the heterogeneity of the brain tissue oxygen values in normoventilation is reflected in a SD of 40.3 mm Hg for P_{brO_2} ; therefore, we present these data both as absolute values and the percentual difference. In our study hypercapnia results in a significant increase in P_{brO_2} despite that PaO_2 decreases significantly. This could result from a combination of shifting the oxygen dissociation curve plus increasing flow to the brain due to hypercapnic cerebrovascular dilatation. Although it is not clear whether oxygen consumption was decreased¹⁹ or oxygen delivery increased to the hypercapnic brain, Laffey et al. even consider that hypercapnic acidosis may exert brain protection.²⁰ Acute hypercapnia, at least to a $PaCO_2$ level of 80-100 mm Hg appears to have no harmful effects provided that oxygenation is preserved.^{2,21}

It is known that hypercapnia increases ICP. The main mechanism whereby hypercapnia influences ICP is the increase of cerebral blood volume secondary to diminished vascular tone during maintained or raised vascular pressure.^{6,21} In the absence of pre-existing intracranial abnormalities, however, diffuse intracranial hypertension is relatively well tolerated due to intact compensatory mechanisms. The mechanism of autoregulation enables brain perfusion to remain stable when blood pressure or ICP changes, and is controlled mainly through myogenic control of arteriolar resistance.^{21,22} In our study, the stepwise induced hypercapnia resulted in a significant increase in ICP; however, the maximum achieved value of 30.3 ± 5.9 mm Hg does not necessarily lead to cerebral ischemia. The small decrease of CPP (65.5 ± 17.4 mm Hg) suggests that the cerebral circulation is still adequate under these conditions. In normal humans the CPP ranges from 70 to 100 mm Hg. Clinical experience has demonstrated the safety of CPP in the range 50 to 60 mm Hg undergoing induced hypotension under general anesthesia; in laboratory conditions, ischemia is not seen until CPP falls below 40 mm Hg.^{5,21,23}

The cellular compartments of the brain are well buffered and have a buffer capacity almost similar to that of blood.^{7,24} In the normoxic hypercapnic situation in the brain, the $PaCO_2$ primarily determines the cellular and extracellular pH in the absence of non physiological levels of lactate. In our study, during hypoventilation $PaCO_2$ increased 111%, the arterial pH decreased from 7.39 to 7.13 whereas P_{brCO_2} increased 68% and the brain pH decreased from 7.04 to 6.81.

In the present study, during hyperventilation P_{brCO_2} and ICP values significantly decreased, whereas brain pH and CPP increased only slightly. It is known that hypocapnia can lead to vasoconstriction thus reducing cerebral blood flow. In addition to reduced cerebral blood flow, marked alkalosis shifts the oxyhemoglobin dissociation curve to the left, further limiting oxygen delivery to the brain. The values of the P_{brO_2} and CPP during hypocapnia up to a $PaCO_2$ of $26.9 \pm$

4 mm Hg in our study, suggest that there was still adequate oxygen delivery and perfusion of the brain.

We found a correlation between PaCO₂, PbrCO₂ and ICP which is applicable in the acute situation of hypercapnia in healthy brain. During prolonged hypercapnia with continued elevated PaCO₂ levels, however, the cerebral circulation adapts with a correction of brain extracellular pH, returning towards normal blood flow with restoration of a normal ICP within less than 24 hours.^{6,25}

In conclusion, controlled hypoventilation with constant MAwP, as used in healthy non brain traumatized pigs, severely affects the brain CO₂ and ICP. However, in our study, the ICP and CPP related to the maximum achieved values, indicate that the cerebral circulation is probably not impaired. Hypercapnia resulted in a significant increase of brain oxygenation; however, this does not allow to conclude that permissive hypercapnia is neuroprotective. In addition, hypocapnia appeared to cause changes within the normal clinical ranges for ICP and CPP.

Future studies should investigate the interrelations between continuously monitored brain parameters, ventilator settings and other information such as blood lactate levels or brain tissue microdialysis.

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Chapter 3

Brain glucose and lactate levels during ventilator-induced hypo- and hypercapnia

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Submitted

Abstract

Objective: Levels of glucose and lactate were measured in the brain by means of microdialysis in order to evaluate the effects of ventilator-induced hypocapnia and hypercapnia on brain metabolism in healthy non-brain-traumatized animals.

Design and setting: Prospective animal study in a university laboratory.

Subjects: Eight adult Landrace/Yorkshire pigs.

Interventions: The microdialysis probe was inserted in the brain along with a multiparameter sensor and intracranial pressure (ICP) probe. The animals were ventilated in a pressure-controlled mode according to the open lung concept with an inspired oxygen fraction of 0.4/1.0. Starting at normoventilation ($\text{PaCO}_2 \pm 40$ mm Hg) two steps of both hypercapnia ($\text{PaCO}_2 \pm 70$ and 100 mm Hg) and hypocapnia ($\text{PaCO}_2 \pm 20$ and 30 mm Hg) were performed. Under these conditions, brain glucose and lactate levels as well as brain oxygen (PbrO_2), brain carbon dioxide (PbrCO_2), brain pH (brpH), brain temperature and ICP were measured.

Results: At hypercapnia ($\text{PaCO}_2 = 102.7$ mm Hg) there were no significant changes in brain glucose and lactate but there was a significant increase in PbrCO_2 , PbrO_2 and ICP. In contrast, at hypocapnia ($\text{PCO}_2 = 19.8$ mm Hg) there was a significant increase in brain lactate and a significant decrease in both brain glucose and PbrCO_2 .

Conclusions: Hypocapnia decreases brain glucose and increases brain lactate concentration, indicating anaerobic metabolism, whereas hypercapnia has no influence on levels of brain glucose and brain lactate.

Introduction

In intensive care medicine both hypoventilation and hyperventilation are accepted as ventilatory modes for treatment of different categories of patients but it still debated whether hyperventilation should be used to treat patients with brain injury and increased intracranial pressure (ICP).¹ The rationale behind hyperventilation-induced hypocapnia is to decrease ICP by reducing cerebral blood flow (CBF) through cerebral vasoconstriction.² However, the problem with hypocapnia is that CBF may be reduced to such an extent that hypoxia may occur.³

On the other hand, patients with acute lung injury are often ventilated with a low tidal volume in order to reduce or to avoid ventilatory-induced lung injury. This ventilation mode always results in increased arterial carbon dioxide partial pressure (PaCO₂); this increase in PaCO₂ is called 'permissive hypercapnia'.⁴ Although this technique is commonly used, there is no consensus on the upper limit of PaCO₂.⁵

In a pig model, our group recently demonstrated that brain oxygen tension (PbrO₂) significantly increases during hypoventilation and decreases during hyperventilation.⁶

Aerobic metabolism is the major energy source to normal brain; however, during hypoxia and ischemia, lactate accumulation may occur, indicating anaerobic glycolysis. Previous studies on PbrO₂ have mostly involved human subjects or animals with brain injury.⁷⁻¹⁰ Because brain trauma, hemorrhage or global cerebral ischemia can themselves impair cerebral circulation and oxygenation, these studies have limited value when determining the levels of brain oxygenation and metabolism during different ventilatory modes. Therefore, monitoring of brain glucose/lactate in a non-brain-traumatized animal model is an important requirement in order to elucidate the pathophysiological mechanisms of hypo- and hypercapnia. Advances in brain monitoring technology currently enable simultaneous measurement of brain glucose/lactate metabolism by means of microdialysis^{11,12} as well as PbrO₂, brain carbon dioxide (PbrCO₂), brain pH (brpH) and brain temperature by means of a multiparameter sensor.^{13,14} The rationale to combine these two methods was to acquire data on the above-mentioned parameters in case of ventilation-induced hypocapnia and hypercapnia.

Methods

Animal Care

This study was approved by the Animal Committee of the Erasmus Medical Centre Rotterdam. Care and handling were in accordance with the European Community guidelines.

Surgical and analytical procedures

In eight adult crossbred Landrace/Yorkshire pigs of either sex (30-35 kg) anesthesia was induced with 0.1 ml/kg ketamine i.m. (Ketalin 100 mg/ml, Apharmo, Arnhem, the Netherlands) and midazolam 0.1 mg/kg i.m. (Dormicum, Roche Ned., Mijdrecht, the Netherlands). Muscle relaxation was induced by 0.2 mg/kg pancuronium bromide (Pavulon, Organon Teknika, Boxtel, the Netherlands).

After intubation, animals were connected to a ventilator (Servo Ventilator 300, Siemens-Elema, Solna, Sweden) and ventilated in a pressure-controlled mode according to the 'Open Lung Concept'.¹⁵ After the initial recruitment maneuver with a pressure of 40 cm H₂O, animals were ventilated with a positive end-expiratory pressure (PEEP) of 6 cm H₂O, peak pressure of 15 ± 3 cm H₂O, an inspiratory/expiratory (I/E) ratio of 1:2 and an inspired oxygen fraction (FiO₂) of 0.4. Tidal volume was 8-10 ml/kg bodyweight and frequency was set to maintain normocapnia (PaCO₂ 35-40 mm Hg). Arterial blood gases were measured using conventional methods (ABL 505, Radiometer, Copenhagen, Denmark).

Anesthesia was maintained with i.v. ketamine (10 mg/kg/h) and midazolam (1 mg/kg/h) and muscle relaxation with i.v. pancuronium bromide (starting with 0.2 mg/kg/h and adapted as required) while body temperature (measured rectally) was kept within normal range (37.5-38.5 °C) by means of a heating mattress.

Two arterial catheters were then inserted in both femoral arteries. A multiparameter sensor (Paratrend/Trendcare, Philips Medical, Böblingen, Germany) was inserted for continuous measurement of PaO₂, PaCO₂, pH and brain temperature, and calibrated with conventional blood gas analyses (ABL 505, Radiometer, Copenhagen, Denmark). The systemic arterial blood pressure and heart rate were measured with a transducer (Statham P23XL, Spectramed, Oxnard, CA, USA) connected to the other femoral artery catheter and recorded (Hewlett Packard, Merli 68S, Philips, Böblingen, Germany).

After surgical exposure of the skull, two 6-mm burr holes were made: one was 4 cm to the left and the other 4 cm to the right of the sagittal suture, both 4 cm caudal of the upper margin of the orbita. Through a cut in the dura mater a calibrated intracranial pressure probe (Codman Neuromonitor, Johnson & Johnson, Berkshire, UK) was inserted in the left burr hole to a depth of 20 mm and a multiparameter sensor catheter in the right burr hole to a depth of 25 mm. Into the same right burr hole a microdialysis probe (CMA/20, Carnegie Medicine AB, Solna, Sweden) was inserted by means of a steel guiding needle. The membrane of the microdialysis probe has a cut-off value of 20 kDa.

In order to control the metabolic stability of the animals during anesthesia, a second probe was placed in the muscle of the thigh of the lower limb as a control for glucose and lactate values.¹⁶ Probes were perfused with an artificial cerebrospinal fluid (manufacturer's guide; Carnegie Medicine AB, Solna, Sweden) at a rate of 2 μ l/min with a micro-injection pump (CMA100, Carnegie Medicine AB, Solna, Sweden). Dialysate volumes of 20 μ l (sampling time 10 min) were collected in microvials and stored at -80°C until analysis. Analysis of the microdialysis samples for glucose and lactate levels was performed with an analyser (CMA 600, Carnegie Medicine AB, Solna, Sweden).

Experimental protocol

After completion of all surgical procedures, there was a 1-hour stabilization period at an FiO_2 of 0.4 before baseline measurements were made. Subsequently, an "oxygen test" was conducted to ensure correct placement of the multiparameter sensor in the brain tissue.⁷ In short, FiO_2 was increased from 0.4 to 1.0 for 15 min and the PbrO_2 had to increase sharply; if the PbrO_2 did not increase by at least 15 mm Hg, the sensor was advanced a further 3-5 mm into the brain. FiO_2 was left at 1.0 for the remainder of the experiment.

Initially, the pigs were normoventilated to maintain an end tidal PaCO_2 of 35-40 mm Hg based on the values from the arterial sensor. After a stable period of at least 30 min, hypoventilation was started to obtain a PaCO_2 of 70 mm Hg. Hypoventilation was achieved by stepwise decrease in the ventilatory frequency, which was controlled by the online blood gas sensor. After a stable period of 30 min (change in $\text{PaCO}_2 < 2$ mm Hg/10 min), arterial blood gas values and data on all parameters were recorded. The ventilatory frequency was then further decreased to obtain a PaCO_2 of approximately 100 mm Hg, whereas mean airway pressure (MAWP) remained unchanged. After 30 min arterial blood gas values and all brain parameters were measured again. After hypoventilation the ventilator was reset to normoventilation and blood gas values and brain parameters were again measured.

Subsequently, hyperventilation was started to obtain two PaCO_2 levels: 30 mm Hg and 20 mm Hg. Between each step there was a stable period of 30 min followed by measurement of blood gas values and brain parameters. Finally, animals were again normoventilated, followed by a final measurement of arterial blood gas values and brain parameters. The entire protocol lasted approximately four hours. At the end of the experiment, the sensors were calibrated to assess any drift in the measured parameters. The animals were killed by an i.v. overdose of pentobarbital (Euthesate 200 mg/ml, Apharmo, Arnhem, the Netherlands).

Statistical analysis

Analysis of data was performed using the InStat 2.0 Biostatistics Package (GraphPad Software 93-98, San Diego, CA, USA). One-way analysis of variance for repeated measures with Dunnett's multiple comparison test as post-hoc test were used. Statistical significance was accepted at a p-value < 0.05. Results are expressed as mean \pm SD. The relationship between PaCO₂, PbrCO₂, PbrO₂ and brain lactate is presented in a linear regression with the correlation coefficient.

Results

All animals were maintained under stable circulatory conditions and all survived the 4-h study period. Table 1 gives data on heart rate, mean arterial pressure (MAP), rectal temperature, ICP, cerebral perfusion pressure (CPP) and brain temperature, measured at baseline, at hypoventilation and hyperventilation, and at the end of the experiment (normoventilation).

During the entire protocol the levels of muscle glucose/lactate remained stable (data not shown). The correlations between PaCO₂, PbrCO₂, PbrO₂ and brain lactate are shown in Figures 1 to 3; we found linear relationships with correlation coefficients of 0.80, 0.80 and 0.62, respectively.

Brain glucose/lactate

Table 2 gives data on brain glucose and lactate in relation to PaCO₂ at different stages of hypo- and hypercapnia. At moderate hypercapnia (PaCO₂ = 71.4 mm Hg), there was a nonsignificant increase in brain glucose and a decrease in lactate. At extreme hypercapnia (PaCO₂ = 102.7 mm Hg) there was a non-significant decrease in both brain glucose and lactate.

At moderate and at maximum hypocapnia (PaCO₂ = 28.9 and 19.8 mm Hg), there was a significant decrease in brain glucose and a significant increase in lactate.

Brain oxygen (PbrO₂) brain carbon dioxide (PbrCO₂) and brain pH (brpH)

Data on arterial blood gases and brain parameters at different stages of hypo- and hyperventilation compared with baseline are presented in Table 3. At moderate hypercapnia (PaCO₂ = 71.4 mm Hg) there was a significant increase in PbrCO₂. At extreme hypercapnia (PaCO₂ = 102.7 mm Hg) although there was a significant decrease in PaO₂, there was a significant increase in PbrO₂. There was also a significant increase in both PbrCO₂ and ICP (Table 1).

At moderate hypocapnia (PaCO₂ = 28.9 mm Hg) there was a significant decrease in PbrCO₂ and a significant increase in brpH. At maximum hypocapnia (PaCO₂ = 19.8 mm Hg) there was a significant decrease in PbrCO₂ and a significant increase in brpH.

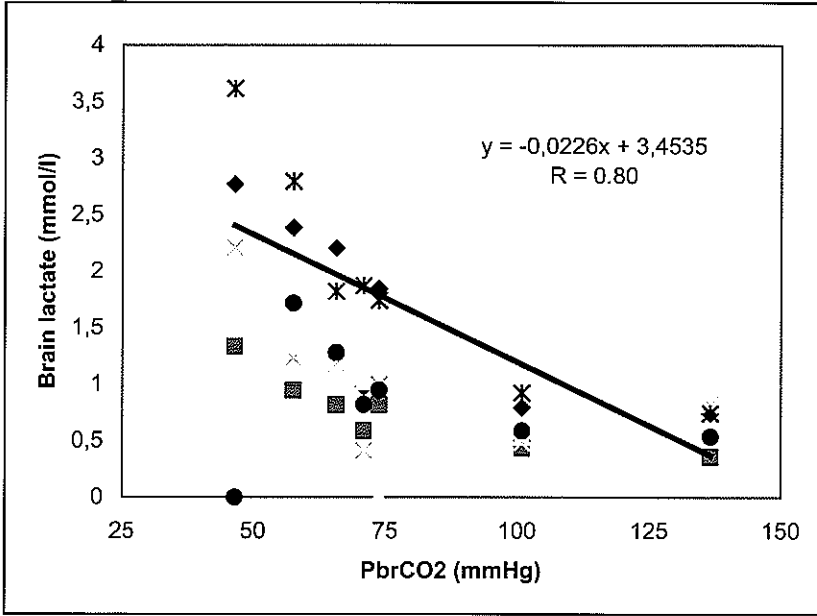


Figure 1. Effect of PbrCO₂ and brain lactate during ventilator-induced hypo- and hypercapnia. A linear relationship was observed between PbrCO₂ and brain lactate.

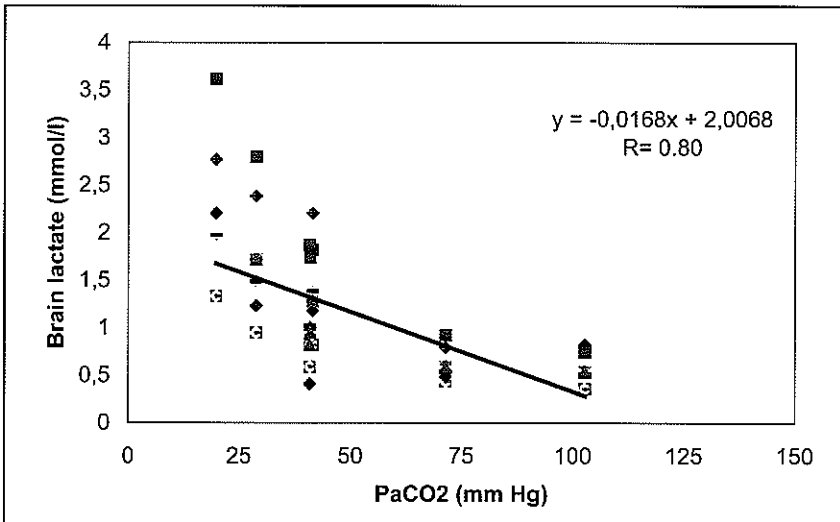


Figure 2. Effect of PaCO₂ and brain lactate during ventilator-induced hypo- and hypercapnia. A linear relationship was observed between PaCO₂ and brain lactate.

Table 1

Data on heart rate, mean arterial pressure, rectal temperature, intracranial pressure, cerebral perfusion pressure and brain temperature at baseline and at maximum hypoventilation, hyperventilation and at normoventilation (n=8 pigs)

	Baseline	Hypoventilation	Hyperventilation	Normoventilation
Heart rate	125 ± 26	130 ± 14	120 ± 28	108 ± 26
Mean arterial pressure	105 ± 9	101 ± 9	98 ± 16	100 ± 15
Rectal temperature	38.3 ± 0.4	38.4 ± 0.5	38.5 ± 0.4	38.6 ± 0.3
Brain				
Intracranial pressure	11 ± 4	20 ± 5*	13 ± 5	14 ± 3
Cerebral perfusion pressure	93 ± 12	83 ± 12	85 ± 21	85 ± 19
Brain temperature	38.7 ± 0.5	38.6 ± 0.4	38.8 ± 0.5	38.7 ± 0.6

Values are mean ± SD
 MAP, ICP and CPP (mm Hg)
 Rectal and brain temp (°C)
 * p < 0.05, vs baseline

Table 2

Data on PaCO₂, brain glucose and brain lactate in different stages of hypo-, normo- and hyperventilation (n = 8 pigs)

	PaCO ₂	Glucose	Lactate
Normoventilation (baseline)	40.8 ± 2.6	3.25 ± 1.05	0.95 ± 0.51
Hypoventilation	71.4 ± 6.3	3.14 ± 0.91	0.64 ± 0.18
Hypoventilation	102.7 ± 7.6	3.14 ± 0.77	0.62 ± 0.18
Normoventilation	41.0 ± 3.6	2.45 ± 0.91	1.08 ± 0.49
Hyperventilation	28.9 ± 3.0	2.18 ± 0.91*	1.77 ± 0.69*
Hyperventilation	19.8 ± 3.0	1.91 ± 0.91 *	2.38 ± 0.87*
Normoventilation	41.6 ± 3.5	2.15 ± 0.95	1.26 ± 0.49

Values are mean ± SD
 PaCO₂ (mm Hg)
 Glucose, Lactate (mmol/l)
 * p < 0.05 versus baseline

Table 3

Data on arterial blood gases and brain oxygen in different stages of hypo-, normo- and hyperventilation (n = 8 pigs)
Values are mean \pm SD

	PaCO ₂	PaO ₂	pH	PbrCO ₂	PbrO ₂	brpH
Baseline	40.8 \pm 2.6	543 \pm 31	7.44 \pm 0.03	70.9 \pm 9.0	55.3 \pm 34.6	7.15 \pm 0.05
Hypoventilation	71.4 \pm 6.3**	507 \pm 47	7.23 \pm 0.07**	100.9 \pm 9.6**	89.1 \pm 44.6	7.04 \pm 0.04**
Hypoventilation	102.7 \pm 7.6**	467 \pm 39**	7.11 \pm 0.03**	136.6 \pm 9.2**	116 \pm 63.3*	6.93 \pm 0.03**
Normoventilation	41.0 \pm 3.6	551 \pm 46	7.47 \pm 0.03	73.8 \pm 7.7	58.6 \pm 33.8	7.20 \pm 0.03
Hyperventilation	28.9 \pm 3.0**	556 \pm 27	7.56 \pm 0.05**	57.6 \pm 7.8*	51.6 \pm 21.6	7.24 \pm 0.06**
Hyperventilation	19.8 \pm 3.0**	585 \pm 31	7.69 \pm 0.06**	46.5 \pm 7.9**	37.0 \pm 18.7	7.28 \pm 0.04**
Normoventilation	41.6 \pm 3.5	564 \pm 34	7.45 \pm 0.02	65.7 \pm 6.9	51.1 \pm 25.0	7.20 \pm 0.04

PaCO₂, PaO₂, PbrCO₂, PbrO₂ (mm Hg)

* P < 0.05 vs normoventilation (baseline)

** P < 0.01 vs normoventilation (baseline)

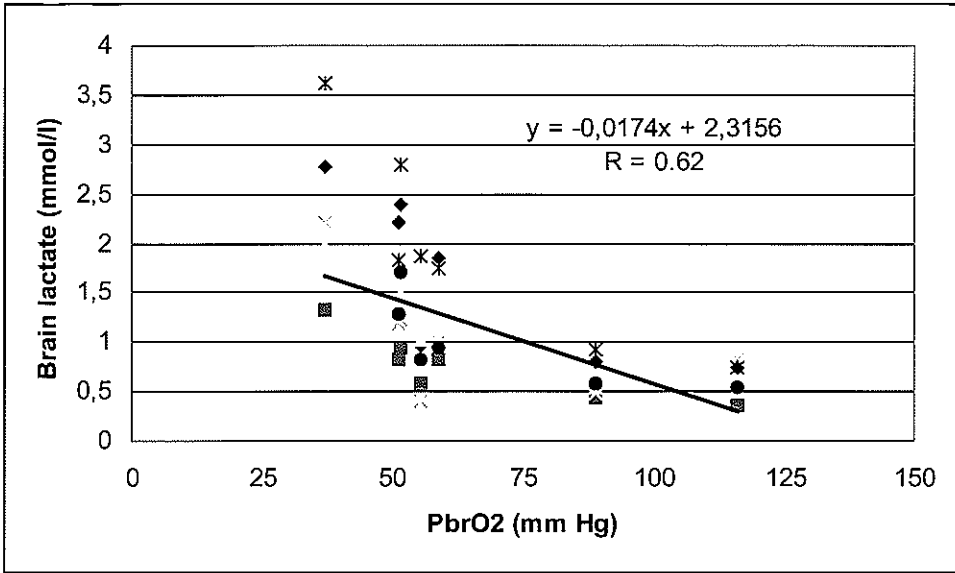


Figure 3. Effect of PbrO₂ and brain lactate during ventilator-induced hypo- and hypercapnia. A linear relationship was observed between PbrO₂ and brain lactate.

Discussion

The present study investigated brain metabolism in healthy non-brain-traumatized pigs during hypo- and hyperventilation with an FiO₂ of 1.0 by measuring brain glucose and lactate, as well as PbrO₂, PbrCO₂, brpH and ICP. The main findings are that, during hypercapnia, brain glucose and lactate were unchanged and PbrO₂ even increased. In contrast, during hypocapnia there was a significant decrease in both PbrO₂ and in brain glucose, and a significant increase in brain lactate. The fact that even at quite high PbrO₂ we have a close correlation with the brain lactate is difficult to explain but may be due to our experimental conditions using 100% oxygen (see Figure 3).

It is well known that cerebral oxygenation is a crucial factor to maintain the normal physiology of brain metabolic function.^{17,18} The development of microsensor and microdialysis technology allows to measure PbrO₂ together with PbrCO₂ and brpH, thus enabling estimation of acidosis, and glucose and lactate levels in the brain. However, one has to be aware that a limitation of this technology is that values derived from the sensor/probe represent data from a very local area only and do not represent the entire brain. In addition, for the microdialysis, one has to consider that the total recovered amount of glucose and lactate depends on the membrane length and the flow rate used. Applying our experimental set-up, we could recover in vitro 22% and 39%, respectively, from

known concentrations of glucose and lactate. These in vitro percentages were then used to correct the values of glucose and lactate measured in the brain, as recommended by Hillered et al.¹¹

Our findings of decreased glucose and increased lactate during hypocapnia would indicate a poor outcome for our animals if one compares our experimental results with data from neuro-surgical patients with poor outcome in which the brain lactate concentration was only ± 1.6 mmol/l.⁸

However, if one compares our results with other data from healthy awake humans in which the lactate concentrations were higher (2-4 mmol/l)¹⁹ this would mean that our increased lactate concentrations during hypocapnia have no deleterious effect. In the light of these contradictory results one can conclude that it is more important to have one's own reference values rather than only discussing the harmfulness of increased/decreased brain glucose/lactate levels. For example, when applying the results of these two human studies to our animals, according to one study⁸ our animals should have died whereas according to the other¹⁹ our animals would not suffer any deleterious effects.

Studies on the effect of hypercapnia on cerebral metabolism in animal models have also produced conflicting results. For example, some groups show no changes²⁰ another shows a decrease²¹ and another even demonstrated an increase²² in the oxygen consumption of the brain. In an editorial, Siesjö concluded that it may be difficult to interpret contradictory results between studies due to differences in the experimental animals, techniques used to measure²³ or calculate cerebral metabolic rate, and the use of anesthetics.²⁴ The influence of anesthetic agents on CBF was studied by Yang and colleagues who found that anesthetic agents may impair the cerebral vasodilatory response to CO₂ and that under anesthesia higher PaCO₂ levels are required to elicit the same level of vasodilatation compared with awake subjects.²⁵

Studies in humans^{26,27} and animals^{28,29} have shown that hypocapnia resulting from hyperventilation has adverse effects on brain metabolism, which is confirmed by our results. Hypocapnia may lead to an ischemic cerebral hypoxia, which could explain the increase in lactate and the decrease in glucose found in the present study. There is also evidence that hypocapnia may even worsen hypoxic-ischemic brain injury in animals²⁸ and may be the cause of the development of cerebral lesions in preterm human neonates.²⁷

In a review, Dexter describes the effect of PaCO₂ on head injured-patients: hypocapnic patients had no better neurological outcome than normocapnic patients.³⁰ In the guidelines for the management of severe head injury, it is stated that prolonged hypocapnia should be avoided in the absence of increased ICP.¹ Although hypocapnia may be beneficial in reducing ICP in case of increased ICP, there is a risk that hypocapnia may still induce ischemic damage.

In the present study, the baseline values for PbrCO_2 and brpH were comparable to those obtained in other animal studies using the same multiparameter sensor.^{7,13,14} However, compared with our previous study,⁶ baseline values for ICP and PbrO_2 were slightly lower in the present study. These differences may be due to differences in the experimental conditions and in the body weight of the animals used.

Two other studies used non-brain-injured pigs; in a hemorrhagic shock model, Manley et al, showed that increased PaCO_2 resulted in increased PbrO_2 and that decreased PaCO_2 resulted in decreased PbrO_2 .³¹ Similarly, Hemphill et al. reported an increase in PbrO_2 in hypercapnia and a decrease in hypocapnia.³² These two studies and the present one underline the need to use a non-injured-brain model in order to describe brain metabolism during hypo- and hypercapnia.

The results of our study confirm results of the above two studies, but we were the first to measure brain oxygenation and brain glucose/lactate showing that hypocapnia leads to a significant decrease in glucose and increase in lactate, suggesting anaerobic metabolism.

From these results in healthy non-brain-traumatized pigs one may speculate that hypercapnia may be less harmful for the brain than hypocapnia breathing 100% oxygen. However, further studies are needed to elucidate the exact mechanisms involved and the therapeutic consequences for the brain-injured model in both normoxic and hyperoxic conditions.

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Chapter 4

Oxygen tension under hyperbaric conditions in healthy pig brain

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Abstract

Objective: To investigate the effect of hyperbaric conditions on brain oxygenation, intracranial pressure and brain glucose/lactate levels in healthy non-brain-traumatized animals.

Design and setting: Prospective animal study in a hyperbaric chamber.

Subjects: Twelve adult Landrace/Yorkshire pigs.

Interventions: The animals were normoventilated in a pressure-controlled mode according to the open lung concept first at normobaric pressures (FiO₂ of 0.4 and 1.0) and subsequently in the hyperbaric chamber at 1.9 bar and 2.8 bar (both at an FiO₂ of 1.0). Under these conditions brain oxygen tension and intracranial pressure were recorded and brain glucose/lactate levels were measured by microdialysis.

Results: At normobaric conditions, increasing the FiO₂ from 0.4 (baseline) to 1.0 resulted in a significant increase in brain oxygen tension from 33 ± 14 to 63 ± 28 mm Hg (p < 0.05). Compared with baseline, both hyperbaric conditions (at an FiO₂ of 1.0) led to a significant increase in brain oxygen tension to 151 ± 65 mm Hg (p < 0.001) at 1.9 bar and to 294 ± 134 mm Hg (p < 0.001) at 2.8 bar.

Conclusions: If there is a need for increased oxygenation in the brain, one way to achieve this is to apply hyperbaric conditions at 100% oxygen. Compared with an atmospheric pressure with an FiO₂ of 0.4, a 9-fold increase (900%) in PbrO₂ values can be reached by increasing the FiO₂ to 1.0 and the pressure to 2.8 bar. In this study hyperbaric oxygen pressure in the brain did not lead to changes in intracranial pressure or in brain glucose/lactate levels.

Introduction

One hundred percent oxygen at three times the atmospheric pressure at sea level can result in arterial oxygen tensions in excess of 1500 mm Hg and oxygen tension in tissue of almost 500 mm Hg.^{1,2} Such high oxygen tensions have a number of both beneficial and deleterious effects on different tissues. Especially in neurology there is a growing interest in hyperbaric oxygen (HBO) therapy.³⁻⁵ In the brain, hyperbaric oxygen acts directly on the autoregulated small blood vessels resulting in vasoconstriction leading to a decrease in cerebral blood flow⁶⁻⁸ and consequently to a reduction in intracranial volume which, in turn, results in a reduction of increased intracranial pressure (ICP).⁹⁻¹¹ Cerebral vasoconstrictive effects of HBO have been demonstrated in both clinical and experimental studies. HBO was shown to induce a reduction of cerebral blood flow followed by a decrease in the elevated ICP which is beneficial under pathological conditions in the presence of ischemia and brain edema e.g. in stroke or brain trauma.¹²⁻¹⁴ Moreover, in an important group of patients (e.g. head injured) oxygenation of the brain is essential.^{15,16}

However, the extent to which one may be able to increase brain oxygen tension (PbrO₂) under HBO is unknown. Therefore, we investigated PbrO₂ in healthy non-brain-traumatized pigs during two clinically used hyperbaric oxygen pressures. On the other hand, HBO can also have acute toxic effects on the brain.^{17,18} Thus, the beneficial effects of HBO therapy must be balanced against negative effects and toxicity. Therefore, under the same conditions we also studied whether HBO has any deleterious effects on ICP or on brain metabolism.

Methods

Animal Care

All experiments were performed in accordance with the Guiding Principles for Research Involving Animals and Human Beings as approved by the Council of the American Physiological Society and with the regulations of the Animal Care Committee of the Erasmus University Rotterdam and European Community guidelines (86/609/EC).

All experiments were performed in the hyperbaric chamber (Haux, Karlsbad-Ittersbach, Germany) of the Diving Technical Center of the Royal Netherlands Navy, Den Helder.

Surgical and analytical procedures

In 12 crossbred Landrace/Yorkshire pigs of either sex (30-35 kg) anesthesia was induced with 0.1 ml/kg i.m. ketamine (Ketalin 100 mg/ml, Apharmo, Arnhem, the Netherlands) and 0.1 mg/kg i.m. midazolam (Dormicum, Roche Ned., Mijdrecht, the Netherlands). Muscle

relaxation was induced by 0.2 mg/kg i.v. pancuronium bromide (Pavulon, Organon Teknika, Boxtel, the Netherlands).

After intubation, animals were connected to a ventilator (Servo Ventilator 300, Siemens- Elema, Solna, Sweden) and ventilated in a pressure controlled mode according to the 'Open Lung Concept'.¹⁹ After the initial recruitment maneuver, animals were ventilated with a PEEP of 8 cm H₂O, peak pressure of 18 ± 3 cm H₂O, an I/E ratio 1:2 and an inspired oxygen fraction (FiO₂) of 0.4. Tidal volume was 6-8 ml/kg bodyweight and frequency was set to maintain normocapnia (PaCO₂ of 35 - 45 mm Hg). Arterial blood gases (PaO₂, PaCO₂, pH) and blood glucose/lactate levels were measured using conventional methods (GEM Premier 3000, Instrumentation Laboratory Company, Lexington, Mass., USA).

Under hyperbaric conditions we could not measure PaO₂ because these values were then beyond the measuring range of the blood gas recording device. Anesthesia was maintained with i.v. ketamine (10 mg/kg/h) and midazolam (1 mg/kg/h) and muscle relaxation with i.v. pancuronium bromide (starting with 0.2 mg/kg/h and adapted as required) while body temperature (measured rectally) was kept within normal range (37-38 °C) by means of a heating lamp. The systemic arterial blood pressure and heart rate were measured using a transducer (Statham P23XL, Spectramed, Oxnard, CA, USA) and continuously recorded on a Siemens monitor (9000 S, Siemens Elema, Solna, Sweden).

After surgical exposure of the skull, three 6-mm burr holes were made: two at 1.5 cm left and right of the sagittal suture, 4 cm caudal of the upper margin of the orbita, and the third burr hole 1 cm frontal of the coronalis suture left of the sagittal suture. Through a cut in the dura mater a calibrated intracranial pressure sensor (Codman Neuromonitor, Johnson & Johnson, Berkshire, UK) was inserted in the frontal left burr hole to a depth of 20 mm into the brain parenchyma, and two brain oxygen sensors (Licox, Revoxode CC1.SB, GMS mbH, Kiel-Mielkendorf, Germany) were inserted in both caudal burr holes to a depth of 15 mm; these latter sensors were placed at this depth to target temporal white matter. Brain temperature was measured concurrently using a Licox temperature probe. PbrO₂ was then corrected for temperature using the Licox computer (Licox, GMS mbH, Kiel-Mielkendorf, Germany). The mean values of PbrO₂ from both hemispheres were used for the statistical analysis (24 measurements grouped into 12) at each FiO₂ and at each pressure condition.

Into the same caudal burr holes two microdialysis probes (CMA/20, Carnegie Medicine AB, Solna, Sweden) were inserted by means of a steel guiding needle. The membrane of the microdialysis probe has a cut-off value of 20 kDa. Probes were perfused with an artificial cerebrospinal fluid at a rate of 2 µl/min using a microinjection pump (CMA100, Carnegie

Medicine AB, Solna, Sweden). Dialysate volumes of 20 μ l (sampling time 10 min) were collected in microvials and stored at -80°C until analysis. Analysis of the microdialysis samples for glucose and lactate levels was performed with an analyser (CMA 600, Carnegie Medicine AB, Solna, Sweden).

Licox measurements

The two brain oxygen sensors used were flexible polarographic Clark-type probes (identical to those used in clinical neurosurgery) with a polyethylene surface.

For hyperbaric measurements the oxygen sensor cable (a coax cable approx. 1.5 m long) was cut and connected with cable sockets and connectors to the hyperbaric chamber wall. Inside the chamber a coax cable (approx. 1.5 m long) was connected from the chamber wall to the oxygen sensors. The temperature cable (a regular cable) was connected in the same way with sockets and connectors. Before the experiment, we calibrated the oxygen probe in air in the hyperbaric chamber at 1.0, 1.9 and 2.8 bar and found a highly significant correlation between PO_2 and barometric pressure of $y = 98.1 x + 26$ ($r^2 = 99.4$); there were no abnormal values nor any damage to the sensor. The calibration procedure for zero drift (zero display error) and at room air level was performed according to the manufacturer's guide and repeated for each hyperbaric session.

Experimental protocol

After instrumentation of the animals there was a 1-h stabilization period at FiO_2 of 0.4 (baseline measurement) before conducting an "oxygen test"²⁰ which was performed to ensure correct placement of the oxygen sensors in the brain tissue: FiO_2 was increased from 0.4 to 1.0 and remained at 1.0 for the remainder of the experiment. PbrO_2 had to increase sharply: if the PbrO_2 did not increase by at least 15 mm Hg, the sensor was advanced a further 3-5 mm into the brain. Thirty minutes after PbrO_2 had stabilized, all parameters were recorded.

Table 1
Data on hemodynamics, temperature, blood gases, blood/brain glucose/lactate and intracranial pressure (n = 12 pigs).

FiO ₂	0.4	1.0	1.0	1.0	1.0
Pressure	1.0	1.0	2.8	1.9	1.0
Hemodynamics					
Heart rate	102 ± 12	102 ± 16	94 ± 14	97 ± 13	99 ± 14
Mean arterial pressure	116 ± 17	119 ± 10	114 ± 10	117 ± 10	121 ± 10
Temperature					
Body temperature	37.0 ± 0.7	37.1 ± 0.7	37.2 ± 0.7	37.2 ± 0.7	37.2 ± 0.7
Brain temperature	37.1 ± 0.6	37.3 ± 0.6	37.4 ± 0.6	37.5 ± 0.5	37.5 ± 0.5
Blood					
PaO ₂	193 ± 17	536 ± 39	NR	NR	532 ± 27
PaCO ₂	39 ± 4	38 ± 5	41 ± 4	41 ± 5	43 ± 4
pH	7.49 ± 0.04	7.50 ± 0.05	7.47 ± 0.04	7.45 ± 0.05	7.43 ± 0.05
Blood glucose	5.7 ± 0.6	5.4 ± 0.7	5.4 ± 0.6	5.7 ± 0.9	5.8 ± 0.8
Blood lactate	1.1 ± 0.6	1.0 ± 0.4	0.9 ± 0.4	1.0 ± 0.4	0.9 ± 0.4
Brain					
Intracranial pressure	13 ± 6	13 ± 6	14 ± 6	14 ± 6	15 ± 6
Brain glucose	3.86 ± 1.1	4.27 ± 1.6	3.95 ± 1.1	3.77 ± 1.1	3.68 ± 1.1
Brain lactate	1.03 ± 0.3	1.02 ± 0.6	0.95 ± 0.3	0.97 ± 0.3	1.08 ± 0.4

Values are mean ± SD

NR: not recorded (outside range of measurement device)

MAP, ICP, PaO₂, PaCO₂ (mm Hg)

Body and brain temp (°C)

Blood glucose and lactate, brain glucose and lactate (mmol/l)

Heart rate (bpm)

Our preliminary experiments in the hyperbaric chamber have shown that PbrO_2 stabilizes within 7-10 min after changing the pressure (data not shown). The pressure level of 2.8 bar was reached within 2 min, was maintained for 10 min, was reduced again within 1 min to 1.9 bar which was again maintained for 10 min, and was then returned to normobaric pressure within 1 min: this schedule and all time points of measurements of the parameters are shown in Figure 1. The measurements were taken 10 min after each change in FiO_2 /pressure.

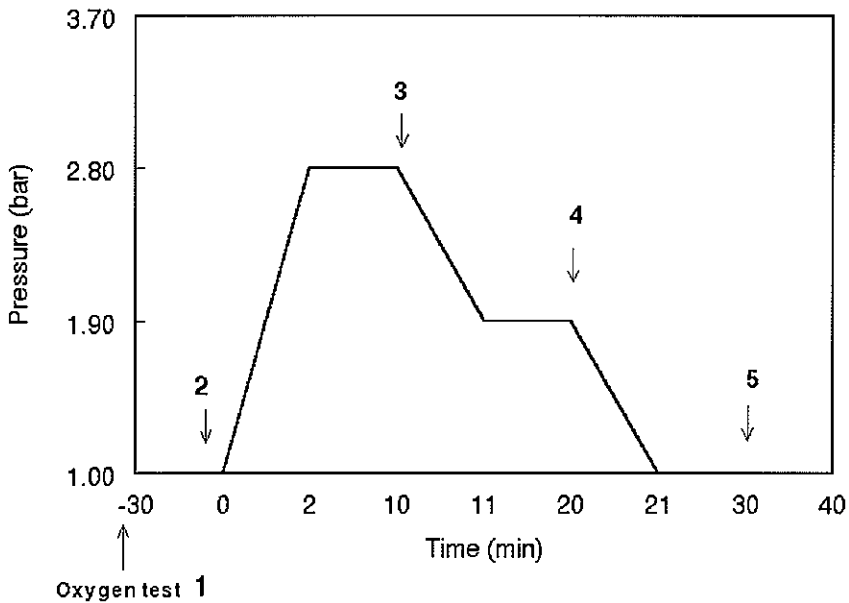


Figure 1. Overview of the experimental protocol showing the five measurement times (arrows). For details of the oxygen test see the text (Experimental protocol); the oxygen test entailed a change in FiO_2 from 0.4 to 1.0 and all subsequent measurements were made with an FiO_2 of 1.0. Each measurement was taken 10 min after each change in FiO_2 /pressure.

Statistical Analysis

For statistical analysis Kruskal-Wallis non-parametric ANOVA test with Dunnet's multiple comparison test as post-hoc test and Student's *t* test were used as appropriate. Statistical significance was accepted at a *p*-value < 0.05. Results are expressed as mean \pm SD.

The relationship between FiO_2 /pressure and PbrO_2 is presented in a linear regression.

Results

All animals survived the study period in a stable cardiocirculatory condition.

At an FiO_2 of 0.4 the value for PbrO_2 was 33 ± 14 mm Hg. Increasing the FiO_2 to 1.0 resulted in a significant increase in PbrO_2 to 63 ± 28 mm Hg ($p < 0.05$). Under hyperbaric conditions, 2.8 bar at an FiO_2 of 1.0 led to a further significant increase in PbrO_2 to 294 ± 134 mm Hg ($p < 0.001$) compared to baseline, and 1.9 bar at the same FiO_2 resulted in PbrO_2 of 151 ± 65 mm Hg ($p < 0.001$) which was still significantly increased compared to baseline. Finally, at normobaric pressure with an FiO_2 of 1.0, PbrO_2 returned to 70 ± 27 mm Hg ($p < 0.01$). Under hyperbaric conditions there was no significant change in any of the other measured parameters (Table 1). Figure 2 shows PbrO_2 in relation to FiO_2 /pressure. The regression line fits the equation $y = 111.5x - 34.4$ with a correlation coefficient of 0.98.

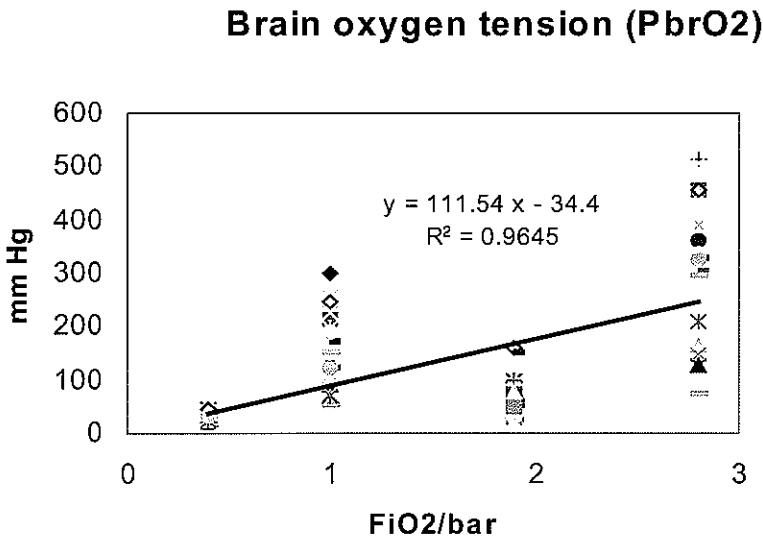


Figure 2. Effect of FiO_2 /pressure on the PbrO_2 . A linear relationship was observed between FiO_2 /pressure and PbrO_2 .

Discussion

The results of this study show that under hyperbaric conditions it is possible to increase oxygen tension within minutes in brain tissue of non-brain-traumatized pigs. Compared with an atmospheric pressure with an FiO_2 of 0.4, a 9-fold increase (900%) in PbrO_2 values can be reached by increasing the FiO_2 to 1.0 and the pressure to 2.8 bar. Moreover, when HBO is applied according to our time schedule this does not lead to any deleterious effect on brain

metabolism as measured by the techniques used in this study. In theory, increased hyperbaric pressure itself could also lead to an opposition of anesthesia and activate NMDA (N-methyl-D-aspartate) receptors with a negative effect on the brain.²¹

In these experiments, we chose to investigate conditions at 1.9 and 2.8 bar because these are standard clinically applied pressures to treat neurological symptoms of decompression illness in e.g. divers, pilots and caisson workers.²² In these patient groups, the symptoms are clinically treated by applying periods of 100% oxygen at 2.8 bar or lower. However, during this therapy (maximum 20 min at 2.8 bar and 20-60 min at 1.9 bar) short periods of 'air breaks' (5 min and 15 min, respectively) are applied to minimize cerebral oxygen toxicity.²² In the present study at both 2.8 bar and 1.9 bar the pressure was maintained for only 10 min to avoid the effects of any oxygen toxicity; therefore, in these experiments there was no need to apply 'air breaks'.

Although global cerebral oxygen consumption is stable under constant metabolic conditions, oxygen distribution in the brain is heterogenous.^{23,24} The diffusion distance in the brain is approx. 50-150 μm .²⁵ Studies on brain oxygen distribution have also indicated different "layers" of oxygen pressure in the brain.^{25,26} Similarly, in the present study the heterogeneity of brain oxygenation is reflected in large standard deviations in our PbrO_2 measurements.

The data from the present study are of clinical relevance. For example, brain injured patients could have an inhomogenous cerebral blood flow (CBF) and increased ICP both of which lead to a situation of local hypoxia. Recent studies in rats with normobaric hyperoxia showed that infarct lesions significantly reduced in size and neurological outcome improved in comparison with normoxia at normobaric pressure.^{27,28} Under hyperbaric conditions, on the one hand one is able to increase the arterial oxygen tension to almost 1500 mm Hg^{1,2} and on the other hand to increase the brain tissue oxygen tension to 300 mm Hg (authors unpublished data); this means that independent of the perfusion and/or hemoglobin (Hb) content of the blood, oxygenation of the brain can almost be guaranteed. In others words, even in the absence of Hb the physically dissolved amount of oxygen in blood will be high enough to supply sufficient oxygen to tissue.²⁹ On the other hand, if perfusion is disturbed, sufficient oxygen can be supplied to the cells by diffusion from the surrounding tissue.³⁰

When considering clinical application of hyperbaric oxygen therapy, the potential benefit must be balanced against its potential toxicity. In neurology, potential benefits of HBO in the treatment of brain injury have been reported. For example, HBO increases the amount of oxygen dissolved in the plasma depending on the absolute pressure used. The dissolved oxygen can reach the hypoperfused brain areas due to the greater pressure gradient and HBO

can also increase the deformability of the red blood cells both of which improve oxygenation in hypoxic brain areas.³⁰ Moreover HBO, has been shown to improve glucose metabolism in the injured brain, suggesting a better recovery of tissue which can persist for at least 24 h after the HBO session.³¹

A negative aspect of HBO is that it may cause a reduction in CBF by constriction of cerebral vessels due to hyperoxia in humans and animals.^{32,33} This is supported by a recent study in an animal model which showed that HBO interferes with the autoregulation of brain perfusion: the decrease of CBF is associated with a decrease in nitric oxide (NO) and the inactivation of NO antagonized the relaxation of cerebral vessels during HBO.³⁴ However, with a prolonged hyperbaric exposure, the regional vasoconstrictive control decreases, resulting in an increase of CBF.³⁵ Cerebral autoregulation is maintained by mean arterial pressures in the range of 50-160 mm Hg.³⁶ When cerebral autoregulation is disturbed due to hypotension or severe acidosis in local ischemic brain tissue, CBF no longer decreases with the administration of oxygen.³⁶ In surrounding areas where the autoregulation still exists, vasoconstriction due to hyperbaric oxygen reduces flow in the collateral circulation to the ischemic penumbra and opposes the goal of improving flow in the ischemic region; however, this could also shunt blood into the infarct, which is non responsive to stimuli for dilatation and constriction. Again, the beneficial effects of reducing the elevated ICP must be balanced against diminishing blood flow in compromised brain tissue.

Animal studies have shown positive results after global brain ischemia, with increased survival rates in the HBO-treated group.^{4,37} Sixty minutes after global brain ischemia HBO was effective in reducing ICP, whereas there was no significant change in CBF. Thus, the decrease in ICP might be caused by attenuation of cerebral cytotoxic edema, rather than by reduction of CBF.¹⁴

Whereas in a first clinical trial HBO therapy improved the outcome of stroke patients³ a later clinical study⁵ could not confirm these beneficial effects or the positive results reported in most experimental studies. Therefore, more investigations are needed to elucidate the complex mechanisms involved in the application of hyperbaric oxygen therapy in stroke, brain-injured and other patient groups.

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Chapter 5

Effects of cerebral air embolism on brain metabolism in pigs

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Abstract

Objectives: Cerebral air embolism was induced in pigs and changes in intracranial pressure (ICP), brain oxygen (PbrO₂), brain carbon dioxide (PbrCO₂), brain pH (brpH) and glucose, lactate and pyruvate levels were used to characterize this model.

Methods: In 7 anesthetized pigs, ICP, PbrO₂, PbrCO₂ and brpH were measured continuously with multiparameter sensors and brain glucose metabolism by microdialysis. After injection of air into the internal carotid artery, these parameters were recorded for 2 h. *Results:* ICP increased (433%) to 52 ± 8 mm Hg ($p < 0.05$). PbrO₂ decreased to 11.9 ± 5.2 mm Hg. PbrCO₂ increased by 109% to 120.4 ± 21.5 mm Hg ($p < 0.05$). Brain glucose decreased (38%) to 2.32 ± 0.91 mmol, while brain lactate increased (364%) to 5.22 ± 0.53 mmol/l ($p < 0.05$).

Conclusions: Cerebral air embolism has a deleterious effect on ICP and brain metabolism. Therefore, this model may be suitable for testing therapeutic regimens in cerebral air embolism.

Introduction

The well-known syndrome of air embolism results when air enters the vasculature and can lead to serious morbidity and even death.¹ Air bubbles may reach any organ and result in local hypoxemia; however, occlusion of the cerebral circulation is particularly deleterious because this organ is highly vulnerable for hypoxia.² Cerebral air embolism (CAE) is a serious hazard during various clinical interventions and in diving medicine.^{2,3} When bubbles occlude the brain vasculature, intracranial pressure (ICP) increases and an extremely inhomogenous distribution of blood flow in the brain causes hyperemia and ischemia.^{4,5}

Monitoring of brain metabolic function under these conditions would be an important requirement for a better understanding of the pathophysiology of CAE. New advances in microsensor technology enable simultaneous measurement of brain oxygen (PbrO₂), brain carbon dioxide (PbrCO₂) and brain pH (brpH)^{6,7,8} as well as brain metabolism (glucose, lactate and pyruvate) by means of microdialysis.^{9,10} The rationale to combine these two latter techniques was to establish the physiological relationship between the data obtained from both techniques in case of cerebral air embolism.

To create cerebral air embolism we injected air into the internal carotid artery and measured ICP, PbrO₂, PbrCO₂ and brpH using microsensor technology, and brain metabolism by microdialysis to characterize the effects of air embolism on the brain. To our knowledge, no previous data have been derived using these two combined techniques in a model of CAE.

Methods

Animal Care

All experiments were performed in accordance with the Guiding Principles for Research Involving Animals and Human Beings as approved by the Council of the American Physiological Society and with the regulations of the Animal Care Committee of the Erasmus University Rotterdam and European Community guidelines (86/609/EC).

Surgical and analytical procedures

In seven crossbred Landrace/Yorkshire pigs of either sex (30-35 kg) anesthesia was induced with 0.1 ml/kg i.m. ketamine (Ketalin 100 mg/ml, Apharmo, Arnhem, the Netherlands) and 0.1 mg/kg i.m. midazolam (Dormicum, Roche Ned., Mijdrecht, the Netherlands). Muscle relaxation was induced by 0.2 mg/kg i.v. pancuronium bromide (Pavulon, Organon Teknika, Boxtel, the Netherlands).

After intubation, animals were connected to a ventilator (Servo Ventilator 300, Siemens-Elema, Sweden) and ventilated in a pressure controlled mode according to the 'Open Lung Concept'.¹¹ After the initial recruitment maneuver, animals were ventilated with a PEEP of 6 cm H₂O, peak pressure of 15 ± 3 cm H₂O, an I/E ratio 1:2 and an inspired oxygen fraction (FiO₂) of 0.4. Tidal volume was 10-12 ml/kg and frequency was set to maintain normocapnia (PaCO₂ of 35 - 40 mm Hg). Arterial blood gases were measured using conventional methods (ABL 505, Radiometer, Copenhagen, Denmark).

Anesthesia was maintained with i.v. ketamine (10 mg/kg/h) and midazolam (1 mg/kg/h) and muscle relaxation with i.v. pancuronium bromide (starting with 0.2 mg/kg/h and adapted as required) while body temperature was kept within the normal range (37-38 °C) by means of a heating mattress.

Subsequently, arterial catheters were inserted in both femoral vessels. A multiparameter sensor (Paratrend/Trendcare, Philips, Böblingen, Germany) was inserted for continuous measurements of arterial PaO₂, PaCO₂, pH and body temperature and calibrated with conventional blood gas analyses (ABL 505). The systemic arterial blood pressure was measured using a transducer (Statham P23XL, Spectramed, Oxnard, CA, USA) and continuously recorded on a Hewlett Packard monitor (Merli 68S, Philips, Böblingen, Germany).

Through a 5 F sheath in the femoral artery, the angiocatheter (Biocompatibles Ltd., Farnham, Surrey, UK) was introduced by means of a guidewire into the internal carotid artery. After introduction, the position of the catheter was controlled by arteriography; the diameter of the catheter was small enough to allow blood flow in the internal carotid artery.

After surgical exposure of the skull, four 6-mm bore holes were made, two at 1.5 cm left and right of the sagittal suture, 4 cm caudal of the upper margin of the orbita, the other two bore holes 1 cm frontal of the coronalis suture both also left and right of the sagittal suture. Through a cut in the dura mater a calibrated intracranial pressure sensor (Codman Neuromonitor, Johnson & Johnson, Berkshire, UK) was inserted in the frontal left bore hole to a depth of 20 mm into the brain, and two multiparameter sensors (Paratrend/Trendcare, Philips, Böblingen, Germany) were inserted in both caudal bore holes to a depth of 25 mm into the white brain tissue.

Into the same caudal bore holes two microdialysis probes (CMA/20, Carnegie Medicine AB, Solna, Sweden) were inserted by means of a steel guiding needle. The membrane of the microdialysis probe has a cut-off value of 20 kDa, a length of 10 mm and a diameter of 0.5 mm. Probes were perfused with an artificial cerebral spinal fluid at a rate of 2 µl/min with a microinjection pump (CMA 100, Carnegie Medicine AB, Solna, Sweden). Dialysate volumes of 20 µl (sampling time 10 min) were collected in microvials and stored at -80 °C until analysis. Analysis of the microdialysis

samples for glucose, lactate and pyruvate levels was performed with an analyser (CMA 600, Carnegie Medicine AB, Solna, Sweden). Dialysate concentrations for glucose, lactate and pyruvate were corrected for probe recovery.

Experimental protocol

After completion of all surgical procedures, a 1-h stabilization period was allowed. Subsequently, an "oxygen test"⁷ was performed to ensure that placement of the multiparameter sensors in the brain parenchyma was correct: FiO_2 was increased to 1.0 for 15 min and then returned to 0.4. $PbrO_2$ had to increase sharply and then return to baseline after the FiO_2 was returned to 0.4. If the $PbrO_2$ did not increase by at least 15 mmHg, the sensor was advanced 3-5 mm into the brain. Thirty minutes after $PbrO_2$ had returned to baseline, all values were then recorded for brain parenchyma and microdialysis parameters at 10-min intervals, for a 30-min period. Then, 0.5 ml/kg of air was injected through the catheter in the internal carotid artery at 1 ml air/sec, followed by 3 ml saline at 1 ml/sec. After embolization, for the subsequent 2 h, 20 μ l dialysate was collected at 10-min intervals. Similarly, at the same time intervals, multiparameter sensor data and ICP data were recorded. At 2-h min after embolization, measurements were stopped and the sensors were calibrated again to assess any drift in the measured values. The animals were killed by an overdose of pentobarbital (Euthesate 200 mg/ml, Apharmo, Arnhem, the Netherlands).

Statistical Analysis

For statistical analysis two-way analysis of variance, one-way analysis of variance for repeated measures with Dunnett's multiple comparison test as post-hoc test and Student's *t* test were used as appropriate. Statistical significance was accepted at a *p*-value < 0.05. Results are expressed as mean \pm SEM.

Table 1

Data on heart rate, mean arterial pressure and body temperature at baseline and at 60 and 120 min after embolization (*n* = 7 pigs).

	Baseline	60 min	120 min
Heart rate	126 \pm 6	134 \pm 10	130 \pm 4
Mean arterial pressure	107 \pm 6	114 \pm 5	108 \pm 6
Body temperature	37.4 \pm 0.3	37.5 \pm 0.3	37.6 \pm 0.2

Values are mean \pm SEM
Heart rate (bpm)

MAP (mm Hg)
Body temp.(°C)

Results

All animals survived the 2-h study period in a stable cardiocirculatory condition.

Data on heart rate, mean arterial pressure and rectal temperature at baseline and at 60 and 120 min after embolization are given in Table 1.

After embolization, there was an immediate hypertensive period with tachycardia, both of which stabilized to baseline values within 10 min; there was a significant increase in mean arterial pressure from 107 ± 6 mm Hg to 160 ± 6 mm Hg and a significant increase in the heart rate from 126 ± 6 to 172 ± 8 min⁻¹ (Figure 1).

At baseline the ICP was 12 ± 1 mm Hg before the injection of air. After embolization the ICP increased continuously, was significantly increased at 70 min and continue to increase to 52 ± 8 mm Hg (433%) at the end of the 2-h study period. The cerebral perfusion pressure (CPP) decreased significantly from 100 ± 4 to 53 ± 7 mm Hg during the 2-h study period (Figure 2).

Data on PbrO₂ and PbrCO₂ every 10 min for 2 h are given in Figure 3. There was a non-significant decrease (54%) in PbrO₂ from 25.7 ± 6.2 to 11.9 ± 5.2 mm Hg at the affected side whereas at the contralateral side there was a 31% decrease from 19.3 ± 4.7 to 13.3 ± 4.9 mm Hg. There was a significant increase (109%) in PbrCO₂ from 57.7 ± 2.7 to 120.4 ± 21.5 mm Hg within 10 min after embolization at the affected side which almost returned to baseline values within 50 min; the contralateral side increased significantly (45%) from 56.4 ± 2.5 to 81.8 ± 10.5 mm Hg. Brain pH at the affected side showed a significant decrease within 20 min from 7.20 ± 0.02 to 6.83 ± 0.12 ; there was a slow improvement thereafter but brpH did not return to baseline values within the 2-h post-embolization period (Figure 4).

Brain glucose metabolism

Table 2 gives data on brain glucose, pyruvate and lactate/pyruvate (L/P) ratio during the 2-h study period. After embolization, within 10 min there was a 38% decrease in brain glucose, while at the contralateral side there was a 36% decrease in glucose; both sides returned to baseline values within 30 min.

Lactate reached a maximum level at 20 min, with a significant increase (364%) at the affected side. Thereafter, there was a slow decrease in lactate until the end of the study period; however, in spite of this decrease, at 2 h the values were still three times those at baseline (Figure 4). The contralateral side had a significant increase (310%) in lactate.

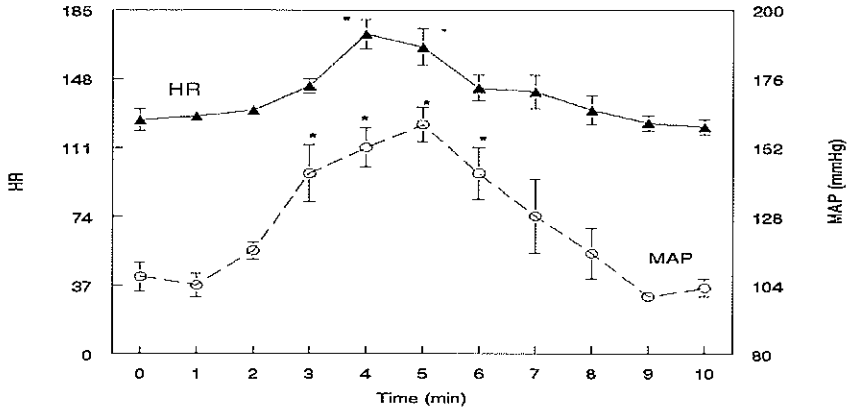


Figure 1. Heart rate (HR) and mean arterial pressure (MAP) in the first 10 min after embolization in cerebral air embolism. Values are mean \pm SEM; * $p < 0.05$ versus baseline

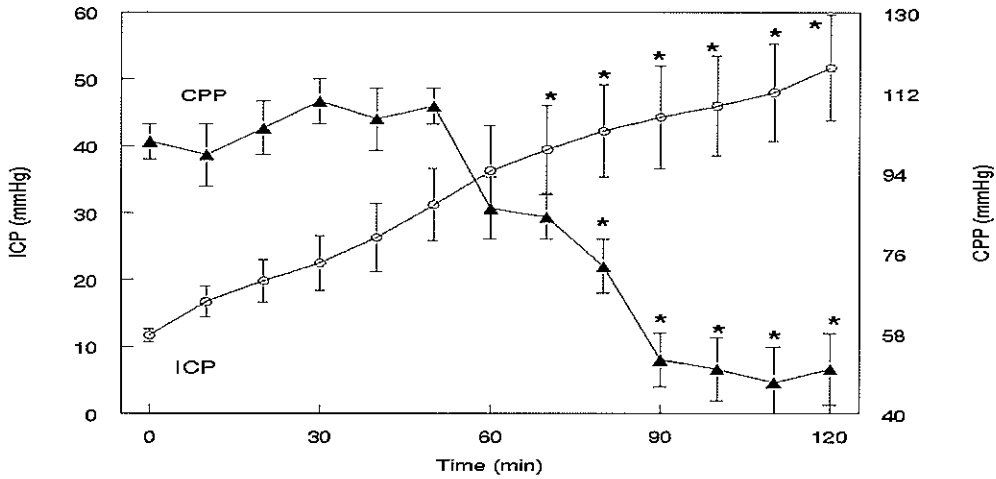


Figure 2. Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in cerebral air embolism over 2 hours. Values are mean \pm SEM; * $p < 0.05$ versus baseline

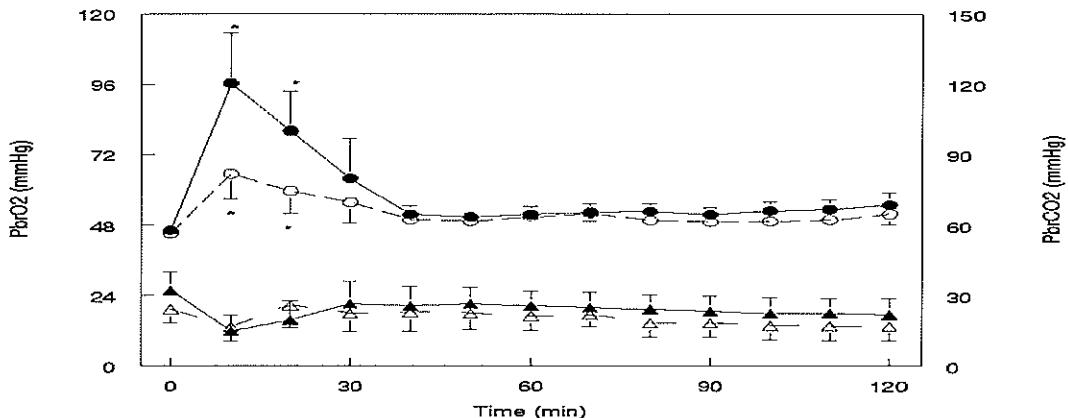


Figure 3. Data on brain oxygen (PbrO₂) and brain carbon dioxide (PbrCO₂) in cerebral air embolism over 2 hours. Values are mean ± SEM; * p < 0.05 versus baseline.
 PbrO₂: triangles (closed: affected side, open: contralateral side)
 PbrCO₂: circles (closed: affected side, open: contralateral side)

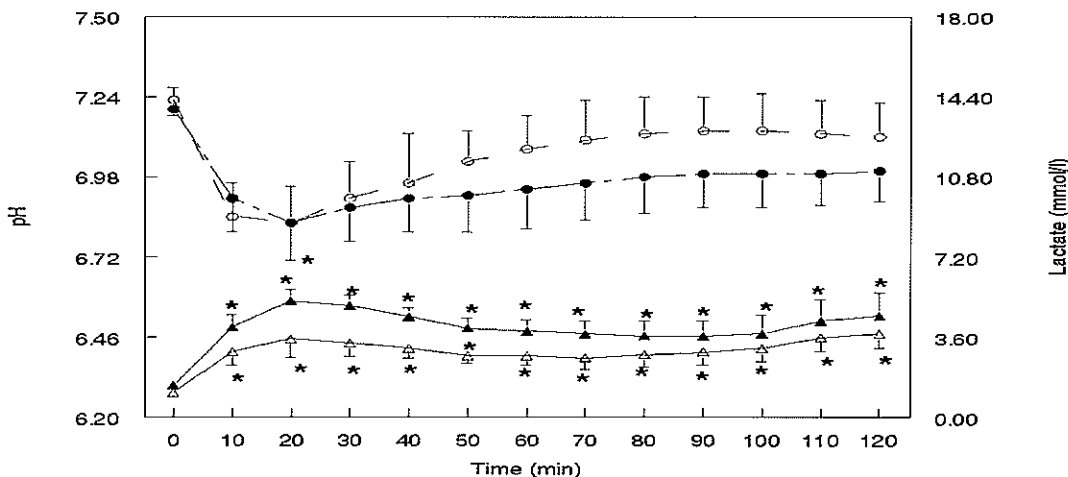


Figure 4. Data on brain pH (brpH) and lactate in cerebral air embolism over 2 hours. Values are mean ± SEM; * p < 0.05 versus baseline
 brpH: circles (closed: affected side, open: contralateral side)
 brain lactate: triangles (closed: affected side, open: contralateral side)

Table 2

Data on glucose, pyruvate and lactate/pyruvate (L/P) ratio in the brain at baseline and at every 10 minutes thereafter for 2 hours. (n=7 pigs)

Time (min.)	Glucose		Pyruvate		L/P ratio
	Affected	Contralateral	Affected	Contralateral	
0	3.05 ± 0.91	2.05 ± 0.50	119.6 ± 14.9	113.4 ± 41.8	12.1
10	1.91 ± 0.55	1.32 ± 0.36	125.4 ± 12.2	112.0 ± 33.5	32.3
20	2.73 ± 0.86	1.96 ± 0.59	167.9 ± 18.3	143.4 ± 39.1	31.0
30	3.09 ± 0.96	2.41 ± 0.77	204.3 ± 18.0	167.8 ± 42.9	24.6
40	3.37 ± 1.05	2.55 ± 0.82	207.9 ± 25.3	178.4 ± 45.1	21.7
50	3.37 ± 1.05	2.37 ± 0.68	211.5 ± 35.7	175.9 ± 47.0	18.8
60	3.37 ± 1.05	2.09 ± 0.68	205.9 ± 42.7	177.0 ± 48.3	18.8
70	3.37 ± 1.05	1.82 ± 0.46	209.6 ± 47.6	162.6 ± 50.0	17.8
80	3.23 ± 1.00	2.14 ± 0.59	206.8 ± 49.8	165.0 ± 48.2	17.7
90	3.09 ± 0.96	2.09 ± 0.55	202.8 ± 45.4	167.1 ± 48.4	17.9
100	2.78 ± 0.87	2.14 ± 0.64	200.5 ± 44.1	167.5 ± 47.2	18.7
110	2.32 ± 0.86	2.00 ± 0.73	216.2 ± 48.7	182.7 ± 50.1	19.9
120	2.32 ± 0.91	1.87 ± 0.68	220.3 ± 45.6	181.6 ± 48.6	20.7

Values are mean ± SEM (n=7)
L/P ratio for lactate and pyruvate at affected side
Glucose (mmol/l)
Pyruvate (µmol/l)

Pyruvate concentration increased by 79% and 58% at the affected and contralateral side, respectively, reaching a maximum 50 min after embolization and remaining at that level for the remainder of the 2-h study period. The L/P ratio at the affected side increased from 12.1 to 32.3 within 10 min after embolization followed by a slow decrease to 20 after 50 min.

Discussion

The results of this study show that cerebral air embolism (CAE) is associated with a significant increase in ICP, a significant increase in brain lactate and PbrCO_2 as well as a significant decrease in brpH .

To develop an animal model of CAE, it is not precisely known how much air is needed in the cerebral circulation to induce maximal but not fatal brain damage. Clearly one would strive for the most severe situation, but it is unknown what volume of air might be optimal. Our preliminary experiments with 10 pigs (unpublished data) have shown that 1-1.5 ml/kg bodyweight of air given as a bolus into the internal carotid artery was lethal; these data are in agreement with Fries et al. who showed in dogs that 1-1.25 ml/kg of air resulted in a mortality of 50% and 0.5 ml/kg air was sufficient to cause permanent brain damage.¹² In contrast, Gomes et al.¹³ reported lethal volumes of at least 2 ml/kg of air in dogs; in the latter study, however, because air was introduced into the common carotid artery shunting of air into extracerebral vessels via the external carotid artery is the likely explanation for these differences.¹⁴ These data formed the rationale for our choice of 0.5 ml/kg in the present study. The pathophysiology of CAE is largely dependent on the size of the air bubbles.⁵ Micro bubbles "irritate" the vascular wall leading to an instantaneous breakdown of the blood-brain barrier; on the other hand, these bubbles are rapidly absorbed and therefore only briefly interrupt cerebral arteriolar flow.¹⁵ In contrast, Dexter et al.¹⁶ calculated that the absorption of large air emboli might take more than several hours, which is long enough to cause primary ischemic injury with diffuse brain edema resulting in an increase in ICP.

It has also been shown that multifocal reactive hyperemia develops in the vicinity of occluded vessels which leads to local swelling of the brain regions and results in an extremely inhomogenous perfusion.^{4,5}

Some limitations of the microdialysis technique used in our study must be acknowledged. First, microdialysis is a local measurement of extracellular concentrations of glucose, lactate and pyruvate. The experimental event described in the present study is a global insult that should have affected all regions of the brain, including the areas monitored by the

microdialysis probe. Second, the microdialysis values of extracellular substrates are qualitative and must be related to the absolute concentrations by the 'in vitro' recovery rates. The recovery rates varied depending on membrane length and flow rate of the microdialysis probe and different percentages have been reported in various studies.¹⁷⁻²¹ In our study, based on the probes and flow used,^{18,19} the in vitro recovery for glucose, lactate and pyruvate are 22%, 39% and 45%, respectively. Third, because there are no data on the use of microdialysis in CAE, comparison between our findings and those of experimental studies on brain ischemia and clinical studies with neurosurgical patients needs some caution.

In the present study the baseline values for ICP were comparable with data from other animal studies.^{6,7,8} After embolization of our animals, ICP rose progressively (more than fourfold) over the 2-h study period. This rise in ICP after cerebral air embolism tends to confirm clinical observations where the patient's condition deteriorates within 1-2 h after suffering the embolic hit.^{22,23} Similarly, Fries et al.¹² reported that both the volume of injected air and the rise in ICP were correlated with morbidity and mortality and, moreover, that this relationship was dose-dependent.

Generally, when the ICP increases, the cerebral perfusion pressure (CPP) decreases, because the relationship is defined as the blood pressure gradient across the brain and represents the difference between the MAP and ICP.²⁴ In our experiments, a temporary hypertensive response occurred within 2 min of embolization of the cerebral circulation. The peak response of both heart rate and blood pressure occurred 4-5 min after beginning air infusion and stabilized to baseline values within 10 min, which confirm data from earlier studies.^{25,26} Subsequently, in our animals the progressive increase in ICP with a stable MAP results in a decrease of CPP during the study period. At the end of the 2-h measurement period, the CPP reaches values suggesting ischemia which is supported by data (acquired by different techniques) from other animal studies on CAE.^{27,28}

In animal studies, Maas and colleagues²⁹ found a close correlation between the decrease in CPP (induced by the increase in ICP) and PO₂ measurements in brain tissue. In a feline model, Zauner et al. found that a CPP less than 50 mm Hg is correlated with a significant decrease in brain tissue oxygen.⁶ In our study, after embolization, there was a decrease in PbrO₂ for 20 min, which almost recovered to baseline values after 50 min and was followed by a slow decrease again during the remainder of the 2-h study period; after 2 h CPP was 53 ± 7 mm Hg and the average PbrO₂ had reached the ischemic level of 10-15 mm Hg.

Although our baseline values for both PbrCO₂ and brpH agree with those obtained with the same multiparameter sensor in other animal studies,^{6,7,8} the PbrO₂ values were comparable

with some ^{7,8} but about 10 mm Hg lower than others.⁶ This difference may be explained by differences in experimental conditions and the species investigated. Moreover, brain tissue oximetry by multiparameter sensors is a local measurement e.g. PbrO₂ measures pO₂ in a small area of the brain.⁸

In the present study the changes in brain oxygen parameters occurred immediately after embolization, but the response of each parameter differed over time. The maximum value for PbrCO₂ in our study (120.4 ± 21.5 mm Hg) is higher than in a study on brain insult for 45 min in dogs using ligatures of both carotid arteries (PbrCO₂: 105 ± 44 mm Hg).⁷ Studies on focal ischemia in cats resulted in a maximum PbrCO₂ value of 71 ± 23 mm Hg,⁶ whereas a clinical study on arterial occlusion during aneurysm surgery reported a maximum PbrCO₂ value of 67 ± 26 mm Hg.³⁰ We believe that the increase in PbrCO₂ in our study reflects local compromised cerebral perfusion due to bubbles in the brain vascular bed, which reduced the “wash out”, in contrast with arterial occlusion in which metabolic substrates as oxygen and glucose are diminished.

The brain pH level was lowest 20 min after embolization and did not recover during the 2-h study period. To investigate whether this slow recovery of brpH may be an indicator of metabolic anaerobic metabolism, we also monitored brain concentrations of glucose, lactate and pyruvate using the microdialysis technique. Under normal circumstances, brain lactate output is low in the presence of sufficient oxygen. Lactate accumulation occurs when oxidative energy metabolism is rendered inoperative, either through substrate (O₂) unavailability (ischemia), or damage to mitochondria.¹⁷ If oxygen is lacking or the transport mechanisms or the mitochondria are damaged, pyruvate undergoes anaerobic conversion to lactate by the enzyme lactate dehydrogenase. In the present study, glucose decreased (38%) within 10 min after embolization but returned to baseline values within 30 min; there was a fourfold increase in lactate to 5.22 mmol/l at the affected side followed by a slow decrease, which (at the end of the study) was still three times that of baseline value. The recovery of the brain glucose values suggest that in the area where the probes are placed, the brain bloodflow is locally restored by the clearance of bubbles in the obstructed vessels. The temporary increase of the PbrO₂ supports this mechanism. At the embolized side the pyruvate concentration increased by 79% to a maximum after 50 min and remained at that level until the end of the 2-h study period. A high level of lactate in the brain has been shown to be a prognostic factor after head injury.³¹ Microdialysis data from 20 patients with severe head injury, demonstrated that a lactate level > 1.0 mmol/l was generally observed in patients with a poor prognosis after such injury.³² Valadka et al.³³ reported on six patients suffering from

incurable ICP elevation after severe head injury; the patient's clinical deterioration was accompanied by a significant increase in brain tissue lactate level.

The lactate/pyruvate (L/P) ratio is a well-known marker of cell ischemia.³⁴ During ischemia there is an increased production of lactate whereas pyruvate decreases, i.e. the L/P ratio increases. An increase of lactate alone is not a good marker of ischemia, because an increase may be due to hypoxia or ischemia as well as hypermetabolism. In our study, a baseline L/P ratio of 12.1 (normal range is 10-18), confirmed a normal and stable condition; after embolization the L/P ratio increased to 32.3, indicating ischemia. There is no recovery to normal values for either lactate or pyruvate, suggesting diminishing clearance by decreasing blood flow or brain cell damage due to ischemia. Although we were not able to demonstrate this, the increase of ICP and decrease of CPP suggest an alteration of blood flow.

The present data show that the rise of ICP in CAE is not related to an elevated level of $P_{br}CO_2$. High interstitial levels of lactate and an increased L/P ratio in the brain due to hypoxic/ischemic conditions and a decreasing CPP may be an indicator of serious cellular metabolism derangement and edema of the brain.

In conclusion, this study has shown that CAE has a severe effect on the ICP, glucose and oxygen delivery and metabolism as measured with multiparameter sensors and microdialysis techniques. Our model of cerebral air embolism appears therefore to be suitable for the testing of therapeutic regimens.

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Chapter 6

Hyperventilation impairs brain function in acute cerebral air embolism in pigs

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Submitted

Abstract

Objective: To evaluate in a model of cerebral air embolism (CAE) the effects of ventilation-induced hypocapnia and hyperoxemia on intracranial pressure (ICP), cerebral perfusion pressure (CPP), brain oxygen (PbrO₂), brain carbon dioxide (PbrCO₂), brain pH (brpH) and brain glucose and lactate.

Design and setting: Prospective animal study in a university medical center.

Subjects: Fifteen Landrace/Yorkshire pigs.

Interventions: In 15 anesthetized pigs ICP, PbrO₂, PbrCO₂ and brpH were measured with multiparameter sensors, and brain glucose and lactate by microdialysis. All these parameters were recorded for 2 h after injection of air into the internal carotid artery. Nine animals were hyperventilated (PaCO₂ ± 25 mm Hg) and hyperoxygenated (FiO₂ 1.0) and six animals were normoventilated (PaCO₂ ± 40 mm Hg with an FiO₂ 0.4) and served as controls.

Results: In the hypocapnic group the ICP raised from 8 ± 1 to 52 ± 6 mm Hg, which was similar to that in the control group (12 ± 1 to 57 ± 8 mm Hg). At the end of the 2-h study period, there were no significant differences in PbrO₂, PbrCO₂ and brpH between the two groups. The decreased brain glucose and increased brain lactate reached severe pathological values by the end of the 2-h study period.

Conclusions: Hypocapnia and hyperoxemia in acute CAE can not improve pathological functional brain parameters compared with normoventilated controls. Similarly, the pathological changes in brain glucose/lactate could also not be improved by hypocapnia and hyperoxemia. These results in animals indicate that this combined therapeutic approach may not be suitable for humans.

Introduction

Cerebral air embolism (CAE) is a potential life-threatening result of many medical and surgical procedures.^{1,2} It may also occur as a result of various diagnostic and surgical procedures when air is accidentally infused into the systemic circulation.³ Air bubbles which occlude the brain vasculature may cause acute neurological events such as coma, desorientation, focal sensory deficits or motor deficits.⁴ Another problem faced by clinicians is CAE occurring in divers due to rapid ascent.⁵ In addition, arterial air embolism can lead to various cardiovascular symptoms, regardless of the underlying cause.^{1,6}

The acute therapy for CAE consists of administration of 100% oxygen in combination with hyperventilation.^{7,8} The rationale for this combined intervention is twofold: first, the increase in FiO_2 will improve the 'off-gassing' of the bubbles and also improve oxygenation in occluded brain tissue by diffusion, and second, the hyperventilation-induced hypocapnia should induce a reduction in ICP to keep the cerebral perfusion pressure (CPP) at the required level.⁸ However, there is no proof as to whether this treatment does lead to functional improvement of brain parameters. Therefore, in the current study we wanted to investigate whether it would be rational to use hyperventilation in combination with hyperoxemia to improve the functional state of the brain after air embolization.

For this purpose, intracranial pressure (ICP), CPP, brain oxygen (PbrO_2), brain carbon dioxide (PbrCO_2) and brain pH (brpH) were measured using the microsensor technology,^{9,10} and brain metabolism of glucose and lactate by microdialysis.^{11,12} We hypothesized that after air embolization, hypocapnia combined with hyperoxemia will improve the functional state of the brain.

Methods

Animal Care

This study was approved by the Animal Committee of the Erasmus Medical Centre Rotterdam. Care and handling were in accordance with the European Community guidelines.

Instrumentation and microdialysis analyses

In 15 crossbred Landrace/Yorkshire pigs (30-35 kg) of either sex anesthesia was induced with 10 mg/kg i.m. ketamine (Ketalin 100 mg/ml, Apharmo, Arnhem, the Netherlands) and 0.1 mg/kg i.m. midazolam (Dormicum, Roche Ned., Mijdrecht, the Netherlands). Muscle relaxation was induced by 0.2 mg/kg i.v. pancuronium bromide (Pavulon, Organon Teknika, Boxtel, the Netherlands).

After intubation, animals were connected to a ventilator (Servo Ventilator 300, Siemens-Elrema, Sweden) and ventilated in a pressure controlled mode according to the 'Open Lung Concept'.¹³ After the initial recruitment maneuver (2-3 breaths up to a pressure of 40 cm H₂O) all the animals were ventilated with a PEEP of 6 cm H₂O, peak pressure of 15 ± 3 cm H₂O, an I/E ratio 1:2 and an inspired oxygen fraction (FiO₂) of 0.4. The applied pressure differences resulted in tidal volumes of 10-12 ml/kg and the frequency was set to maintain normocapnia (PaCO₂ of 35 - 40 mm Hg). Arterial blood gases were measured by the ABL 505 (Radiometer, Copenhagen, Denmark).

Anesthesia was maintained with i.v ketamine (10 mg/kg/h) and midazolam (1 mg/kg/h) and muscle relaxation with i.v pancuronium bromide (starting with 0.2 mg/kg/h and adapted as required) while body temperature (measured rectally) was kept within the normal range (37-38 °C) by means of a heating mattress.

Subsequently, arterial catheters were inserted in both femoral arteries. A multiparameter sensor (Paratrend/Trendcare, Philips Medical, Böblingen, Germany) was inserted through one of the catheters for continuous measurements of PaO₂, PaCO₂, pH and temperature and calibrated with conventional blood gas analyses (ABL 505). The arterial blood pressure and heart rate were measured using a transducer (Statham P23XL, Spectramed, Oxnard, CA, USA) and continuously recorded on a Hewlett Packard monitor (Merli 68S, Agilent, Böblingen, Germany). The CPP is calculated as the difference between the mean arterial pressure (MAP) and ICP.

Through the other catheter, a 5 F sheath was inserted in the femoral artery and the angiocatheter (Biocompatibles Ltd, Farnham, Surrey, UK) was introduced by means of a guidewire into the internal carotid artery (left or right side). After introduction, the position of the catheter was controlled by arteriography; the diameter of the catheter was small enough to allow blood flow through the internal carotid artery.

After surgical exposure of the skull, four 6 mm burr holes were made: two at 1.5 cm left and right of the sagittal suture, 4 cm caudal of the upper margin of the orbita, the other two burr holes 1 cm frontal of the coronalis suture both also left and right of the sagittal suture.

Through a cut in the dura mater a calibrated ICP sensor (Codman, Neuro monitor, Johnson & Johnson, Berkshire, UK) was inserted in the frontal left burr hole to a depth of 20 mm into the brain parenchyma, and two multiparameter sensors (Paratrend/ Trendcare, Agilent, Böblingen, Germany) were inserted in both caudal burr holes to a depth of 25 mm into the white brain tissue. Into the same caudal burr holes two microdialysis probes (CMA/20, Carnegie Medicine AB, Solna, Sweden) were inserted by means of a steel guiding needle. The

membrane of the microdialysis probe has a cut-off value of 20 kDa. Probes were perfused with an artificial cerebrospinal fluid (manufacturers guide; Carnegie Medicine AB, Solna, Sweden) at a rate of 2 $\mu\text{l}/\text{min}$ with a microinjection pump (CMA100, Carnegie Medicine AB, Solna, Sweden). Dialysate volumes of 20 μl (sampling time 10 min) were collected in microvials and stored at -80°C until analysis. Analysis of the microdialysis samples for glucose and lactate levels was performed with a CMA600 analyser (CMA, Carnegie Medicine AB, Solna, Sweden).

Experimental protocol

After completion of all surgical procedures, there was a 1-hour stabilization period at an FiO_2 of 0.4 before baseline measurements were made. Subsequently, an "oxygen test"¹⁴ was conducted to ensure correct placement of the multiparameter sensor in the brain tissue. In short, FiO_2 was increased from 0.4 to 1.0 for 15 min and the PbrO_2 had to increase sharply; if the PbrO_2 did not increase by at least 15 mm Hg, the sensor was advanced a further 3-5 mm into the brain. PbrO_2 had to return to baseline values after the FiO_2 was returned to 0.4.

Thirty minutes after PbrO_2 had returned to baseline, the baseline values were recorded for all brain parameters and microdialysis parameters. Then, 0.5 ml/kg of air was injected through the catheter in the internal carotid artery at about 1 ml air/sec, followed by 3 ml saline at about 1 ml/sec. After embolization, for the subsequent 2 h, 20 μl dialysates was collected at 10-min intervals. Similarly, at the same time intervals, multiparameter sensor data of the brain and ICP were recorded. Data on heart rate, MAP, rectal/brain temperature, and blood gases were recorded continuously and are presented at baseline and at 60 min and 120 min after embolization for both groups of animals.

Hypocapnic group: In 9 animals, 3 min after embolization, hyperventilation was started by increasing the frequency and increasing the FiO_2 from 0.4 to 1.0. The frequency was set to maintain hypocapnia ($\text{PaCO}_2 \pm 25$ mm Hg). This ventilator setting and the FiO_2 level of 1.0 were maintained for the 2-h measuring period.

Control group: In 6 animals, 3 min after embolization, normoventilation ($\text{PaCO}_2 \pm 40$ mm Hg with FiO_2 0.4) was applied; these animals served as control group.

At 2-h after embolization, measurements were stopped and the sensors were again calibrated to assess any drift in the measured values. All animals were killed by an overdose of pentobarbital (Euthesate 200 mg/ml, Apharmo, Arnhem, the Netherlands).

Statistical analysis

Data were analyzed using the InStat 2.0 Biostatistics Package (GraphPad Software 93-98, San Diego, USA). Inter- and intra-group comparisons were analyzed with repeated measures ANOVA with Dunnett's multiple comparison test as post-hoc test. Statistical significance was accepted at a p -value < 0.05 . Results are expressed as mean \pm SD.

Table 1

Data on heart rate, mean arterial pressure, temperature and blood gases at baseline, and at 60 and 120 min after air embolization for the hypocapnic ($n=9$) and control group ($n=6$)

	Baseline	60 min	120 min
Heart rate			
Hypocapnic	102 \pm 3	100 \pm 4	111 \pm 9
Control	98 \pm 8	96 \pm 8	102 \pm 6
Mean arterial pressure			
Hypocapnic	106 \pm 2	97 \pm 2	93 \pm 6
Control	111 \pm 4	118 \pm 8	108 \pm 8
Rectal temperature			
Hypocapnic	37.5 \pm 0.1	37.4 \pm 0.1	37.3 \pm 0.2
Control	37.3 \pm 0.2	37.4 \pm 0.2	37.4 \pm 0.1
Brain temperature			
Hypocapnic	37.4 \pm 0.2	37.2 \pm 0.2	36.8 \pm 0.3
Control	37.4 \pm 0.2	37.3 \pm 0.2	37.2 \pm 0.2
Blood Gases			
<i>PaO₂</i>			
Hypocapnic	199 \pm 4	515 \pm 13*#	521 \pm 14*#
Control	189 \pm 5	192 \pm 5	191 \pm 4
<i>PaCO₂</i>			
Hypocapnic	39 \pm 1	24 \pm 1*#	23 \pm 1*#
Control	40 \pm 2	43 \pm 2	42 \pm 1
<i>pH</i>			
Hypocapnic	7.47 \pm 0.01	7.60 \pm 0.01*#	7.60 \pm 0.01*#
Control	7.42 \pm 0.02	7.39 \pm 0.02	7.43 \pm 0.01

Values are mean \pm SD

* $p < 0.05$ intragroup versus baseline

$p < 0.05$ intergroup

MAP, PaO₂, PaCO₂ (mm Hg)

Rectal and brain temperature in °C

Heart rate (bpm)

Results

All animals were in stable cardiocirculatory conditions at baseline and survived the 2-h study period. Table 1 gives data on heart rate, MAP, rectal/brain temperature, and blood gases at baseline and at 60 min and 120 min after air embolization for both groups of animals.

Compared to baseline, the ICP increased significantly over time in both groups during the 2-h study period (Figure 1a) but there were no significant differences between the two groups. In the hypocapnic group the ICP increased significantly over time from 8 ± 1 (at baseline) to 52 ± 6 mm Hg; in the control group ICP increased significantly over time from 12 ± 1 (at baseline) to 57 ± 8 mm Hg. There was a significant difference in CPP between the two groups at 20 to 70 min after embolization (Figure 1b).

Compared with baseline, after air embolization in both groups there was an immediate and significant increase in $P_{br}CO_2$, which after 40 min decreased to almost baseline values and remained stable for the rest of the study (Figure 2). In the hypocapnic group $P_{br}O_2$ rose immediately when switching FiO_2 from 0.4 to 1.0, then decreased again and finally reached the same levels as the normocapnic group ventilated with an FiO_2 of 0.4 (Figure 2). In both groups, $brpH$ decreased immediately after air embolization, then slowly improved, but did not return to baseline values during the 2-h study period (Figure 3).

Figure 4 presents data on brain glucose and lactate during the 2-h study period. Ten minutes after air embolization, in the hypocapnic group there was a decrease in brain glucose which continued to decrease until the end of the study period. In the control group, after an initial decrease there was a slight increase during the subsequent 60 min followed by another slight decrease at the end of the study. After embolization, lactate sharply increased in both groups and remained high in the hypocapnic group and slightly decreased in the normoventilated group (Figure 4).

Discussion

The hypothesis of this study was that hypocapnia combined with hyperoxemia would improve the functional state of the brain in CAE. However, the results clearly show that there was no improvement in measured brain parameters and, therefore, the hypothesis can not be supported.

It is well known that cerebral oxygenation is a crucial factor to maintain the normal physiology of brain metabolic function. The development of microsensor and microdialysis technology permits measuring of $P_{br}O_2$ together with $P_{br}CO_2$ and $brpH$ thus enabling estimation

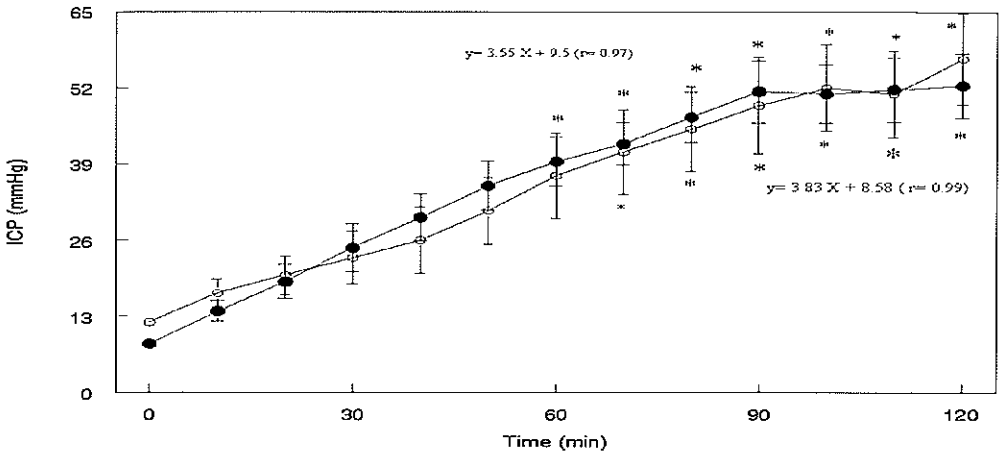


Figure 1. Intracranial pressure (ICP) over 2 hours. Values are mean \pm SD.

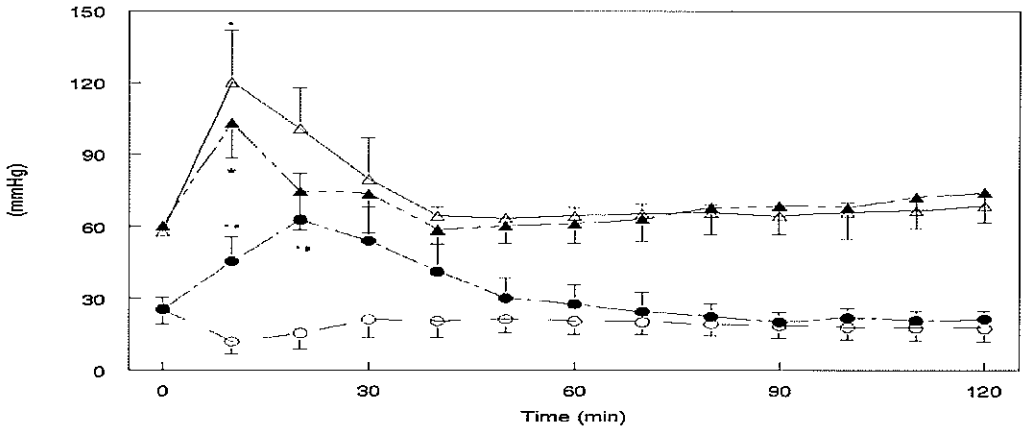


Figure 2. Data on brain oxygen (PbrO₂) and brain carbon dioxide (PbrCO₂) in cerebral air embolism over 2 hours. Values are mean \pm SD. * p<0.05 intragroup versus baseline, # p<0.05 intergroup
Brain oxygen: circles (open: controls; closed: treated)
Brain carbon dioxide: triangles (open: controls; closed: treated)

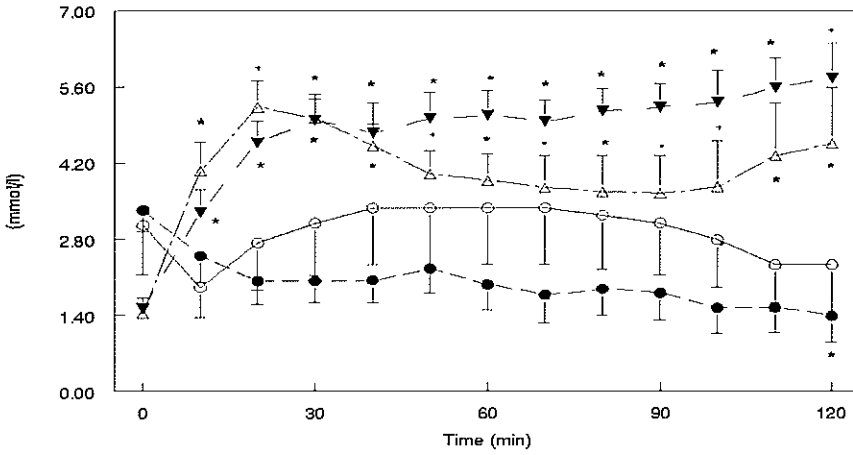


Figure 3. Data on brain glucose and brain lactate in cerebral air embolism over 2 hours. Values are mean \pm SD
 Brain glucose: circles (open controls, closed treated)
 Brain lactate: triangles (open controls, closed treated)

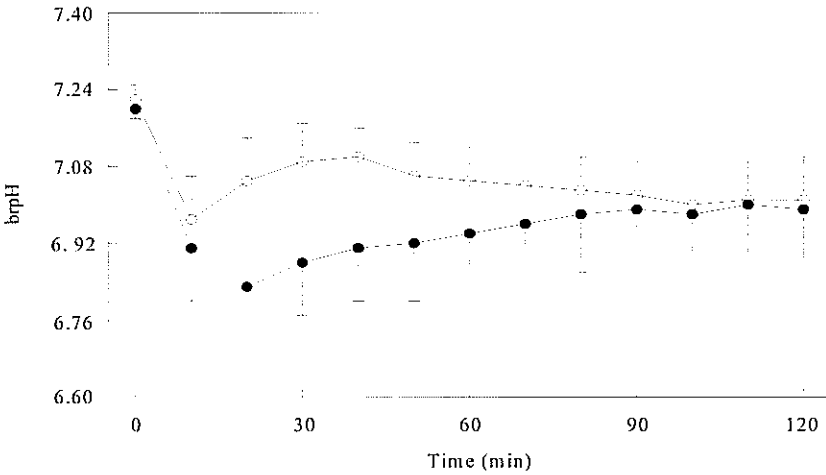


Figure 4. Data on brain pH in cerebral air embolism over 2 hours
 Values are mean \pm SD
 Brain pH: circles (open: treated, closed: controls)

of acidosis, and glucose/lactate levels in the brain. However, one has to be aware that a limitation of this technology is that values derived from the sensor/probe represent data from a very local area only and do not represent the entire brain. The experimental event described in the present study is more or less a global insult that should have affected almost all regions of the brain (even the contralateral side by shunting), but predominantly the areas monitored by the sensors/probes. In addition, for the microdialysis, one has to consider that the total recovered amount of glucose/lactate depends on the membrane length of the probe and the flow rate used. Applying our experimental set-up, we could recover *in vitro* 22% and 39%, respectively, from known concentrations of glucose and lactate. These *in vitro* percentages were then used to correct the values of glucose and lactate measured in the brain, as recommended by Hillered et al.¹⁵

CAE is an iatrogenic complication of numerous invasive medical procedures in anesthesia and intensive care.^{2,4} Intensive care physicians are often confronted with this severe complication during high-risk interventions, e.g. in cardiovascular surgery using extracorporeal circulation, in neurosurgery, and in routine procedures involving placement of central venous catheters.^{3,4} Air bubbles in the cerebral arteries cause an abrupt occlusion of blood flow in the areas supplied by these vessels, leading to ischemic damage if arterial obstruction continues.¹⁶ In fact, bubbles have a natural tendency to dissolve¹⁷ and several interventions can be used to accelerate this process.⁸ Otherwise they can remain in the intravascular space for more than 24 h¹⁸; for bubbles with a diameter of 4 mm it can take up to 560 min before they disappear.¹⁹ Moreover, the pathophysiology of CAE is complex and involves more than vessel occlusion alone; CAE can damage cerebral endothelium, initiating a complex inflammatory response that causes secondary injury and cerebral edema resulting in an increase in ICP.^{16,20}

A high FiO_2 increases oxygen content in the blood and leads to blood denitrogenation; this increases the pressure gradient of nitrogen between the air bubbles and blood, and thus improves the diffusion of nitrogen from the bubble into blood leading to disappearance of the bubble.²¹ Rat studies have shown that, with increasing oxygen concentration, bubbles resolve more rapidly than with normal air breathing.^{22,23} In a mathematical model it was calculated that the time needed for a bubble to disappear is 12 h with at an FiO_2 of 1.0 and up to 40 h with an FiO_2 of 0.4.^{24,25} When comparing these theoretical data with *in vivo* data (using computer tomography to measure the bubble clearance) the absorption time was also 3 times faster when switching FiO_2 from 0.4 to 1.0.²⁶

In the present study, the baseline values for ICP were comparable with data from other animal studies.^{10, 14} After air embolization in our animals, ICP rose progressively over the study period to very high pathological values independent of hypocapnia and hyperoxemia.

In the current study, all the detrimental changes in all the other measured parameters can be explained by the following two mechanisms. On the one hand by occlusion (leading to hypoxia) and, on the other hand, by the increase in ICP. There was a significant decrease in MAP in the hyperventilated group resulting in a significant decrease in CPP in the hypocapnic group (at 20-70 min) which probably caused the deterioration of the $P_{br}O_2$ after the initial increase. In both groups, end values of brain glucose and lactate were at levels of compromised brain tissue in severe head injuries.^{27, 28}

In our study, compared with the normoventilated group, hyperventilation resulted in a smaller increase in $P_{br}CO_2$ within 10 min after air embolization; surprisingly after 30 min $P_{br}CO_2$ values in the hypocapnic were almost the same as controls, despite continuous hyperventilation. It has been discussed whether or not hyperventilation has a detrimental effect on the brain^{29,30}: reducing the $PaCO_2$ to 25 mm Hg decreases the global cerebral blood flow by 30-40% which is a level associated with mild cerebral ischemia²⁹ and in some pathological conditions hyperventilation can even be detrimental e.g. in stroke,³⁰ permanent focal cerebral ischemia³⁰ during neonatal extracorporeal-membrane oxygenation³¹ and in infants with perinatal anoxia.³² Similarly, a study in humans reported that slowing down of the EEG induced by hyperventilation could be reversed by hyperbaric oxygen, which indicates that hyperventilation reduces oxygen delivery and limits cerebral metabolism.³³ Finally, brain lactate concentrations increase during severe hypocapnia and are inversely proportional to $PaCO_2$, which suggests insufficient oxygen to maintain oxidative metabolism.^{27,28}

In conclusion, in the present study hypocapnia combined with hyperoxemia (FiO_2 of 1.0) in CAE does not improve the functional state of the brain as compared with normocapnia (FiO_2 of 0.4). These results in animals indicate that this combined therapeutic approach may not be suitable for humans with CAE. Further studies should investigate whether even hypercapnia may have beneficial effects on the functional state of the brain.

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Chapter 7

Effects of hyperbaric treatment in cerebral air embolism on intracranial pressure, brain oxygenation and brain glucose metabolism in the pig

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Submitted

Abstract

Objective: To evaluate the effects of hyperbaric oxygen (HBO) treatment after cerebral air embolism (CAE) on intracranial pressure (ICP), brain oxygenation (PbrO₂), brain glucose/lactate metabolism and EEG.

Design and setting: Prospective animal study in a hyperbaric chamber.

Subjects: Eleven Landrace/Yorkshire pigs.

Interventions: In 11 anesthetized pigs, ICP and PbrO₂ were measured with microsensor technology, brain glucose/lactate by microdialysis, and EEG by conventional methods. After injection of air into the internal carotid artery, animals were treated immediately (at 3 min; t=3) or at 60 min (t=60) with standard HBO therapy for 5 h.

Results: At the end of HBO treatment, ICP in the t=60 group (39 ± 8 mm Hg) was significantly higher than in the t=3 group (27 ± 6 mm Hg), PbrO₂ values for group t=3 and t=60 were 66 ± 14 and 52 ± 15 mmHg, respectively (no significant difference from baseline), and there were no pathological scores in the visually assessed EEG. However, there was a significant decrease in brain glucose and a significant increase in brain lactate in both groups at the end of the 5-h study period.

Conclusions: In this study, hyperbaric oxygen treatment initiated at both 3 and 60 min after embolization decreased the deleterious effects of CAE on ICP and brain metabolism. Therefore, this model appears suitable to test the application of HBO treatment with a delay longer than 60 min after embolization, as is often the case in the clinical situation.

Introduction

Arterial air embolism is a serious hazard because air bubbles may reach any organ and result in local hypoxemia. However, cerebral air embolism (CAE) is particularly dangerous because the brain is highly vulnerable for hypoxia. CAE is thus a severe and potentially life-threatening complication that is known to occur during neurosurgery/cardiothoracic surgery and during various diagnostic and therapeutic procedures and in diving medicine.^{1,2}

Hyperbaric oxygen (HBO) therapy has been advocated as a therapy for CAE, whereby the patient breathes 100% oxygen at a pressure above that of the atmosphere at sea level.^{3,4} The increased ambient pressure (decreases the size of the gas bubbles) and the resulting systemic hyperoxia improves oxygenation of hypoxic tissue.

Questions have been raised about the effect of HBO therapy in relation to timing of treatment. Most investigators agree, however, that early, rather than late, treatment is most appropriate for an air embolism.^{5,6} Unfortunately, data supporting this statement are more anecdotal than scientific.^{7,8}

We have developed a pig model for CAE measuring intracranial pressure (ICP) and brain oxygenation (P_{brO_2}) with microsensor technology, and brain glucose/lactate metabolism by microdialysis, to characterize the effects of air embolism on the brain. The results of that study showed that CAE has a deleterious effect on both ICP and brain metabolism.⁹

Therefore, in the present study, HBO treatment was applied to treat CAE at two different time periods after embolization. We added electroencephalograph (EEG) monitoring in this study to further characterize the model, since the EEG can detect cerebral ischemia almost immediately¹⁰ and because it is a non-invasive technique and easy to apply in a clinical situation (in contrast with the other measured parameters using sensors in the brain tissue, which are more suitable in an experimental setting).

We hypothesized that immediate HBO treatment of CAE will result in less brain impairment (as characterized by the measured parameters) than delayed treatment. Therefore, in this study, HBO treatment was started immediately at 3 min (ideally, when the hyperbaric chamber is on location e.g. during diving) or after a delay of 60 min (more realistic in a clinical situation) after inducing a cerebral air embolism.

Methods

Animal Care

This study was approved by the Animal Committee of the Erasmus Medical Center Rotterdam. Care and handling were in accordance with the European Community guidelines. All experiments were performed in the hyperbaric chamber (Haux, Karlsbad-Ittersbach, Germany) of the Diving Technical Center of the Royal Netherlands Navy in Den Helder.

Surgical and anesthetic procedures

In 11 crossbred Landrace/Yorkshire pigs of either sex (30-35 kg) anesthesia was induced with 0.1 ml/kg i.m. ketamine (Ketalin 100 mg/ml, Apharmo, Arnhem, the Netherlands) and 0.1 mg/kg i.m. midazolam (Dormicum, Roche Ned., Mijdrecht, the Netherlands). Muscle relaxation was induced by 0.2 mg/kg i.v. pancuronium bromide (Pavulon, Organon Teknika, Boxtel, the Netherlands).

After intubation, animals were connected to a ventilator (Servo Ventilator 900C, Siemens-Eléma, Sweden) and ventilated in a pressure controlled mode according to the 'Open Lung Concept'.¹¹ After the initial recruitment maneuver, animals were ventilated with a positive end-expiratory pressure (PEEP) of 6 cm H₂O, peak pressure of 15 ± 3 cm H₂O, an inspiratory/expiratory (I/E) ratio 1:2 and an inspired oxygen fraction (FiO₂) of 0.4. Tidal volume was 10-12 ml/kg and frequency was set to maintain normocapnia (PaCO₂ of 35 - 40 mm Hg). Anesthesia was maintained with i.v. ketamine (10 mg/kg/h) and midazolam (1 mg/kg/h) and muscle relaxation with i.v. pancuronium bromide (starting with 0.2 mg/kg/h and adapted as required), while body temperature (measured rectally) was kept within the normal range (37-38 °C) by means of a heating lamp.

Subsequently, arterial catheters were inserted in both femoral vessels. In the right femoral artery, the mean arterial blood pressure and heart rate was measured using a transducer (Statham P23XL, Spectramed, Oxnard, CA, USA) and continuously recorded on a Siemens 9000C Monitor (Siemens, Voorburg, the Netherlands). Arterial blood gases, blood glucose/lactate and hematocrit levels were measured using conventional methods (GEM, Premier 3000, Instrumentation Laboratory, Breda, the Netherlands). The cerebral perfusion pressure (CPP) was calculated as the difference between mean arterial pressure (MAP) and ICP. Through a 5 F sheath in the left femoral artery, the angiocatheter (Biocompatibles Ltd., Farnham, Surrey, UK) was introduced by means of a guidewire into the internal carotid artery (left or right). After introduction, the position of the catheter was controlled by arteriography;

the diameter of the catheter was small enough to allow blood flow in the internal carotid artery.

After surgical exposure of the skull, three 6-mm burr holes were made: two at 1.5 cm left and right of the sagittal suture and 4 cm caudal of the upper margin of the orbita, the other burr hole 1 cm frontal of the coronalis suture also right of the sagittal suture. Through a cut in the dura mater a calibrated intracranial pressure sensor (Codman Neuromonitor, Johnson & Johnson, Berkshire, UK) was inserted in the frontal right burr hole to a depth of 20 mm into the brain parenchyma, and two oxygen sensors (Licox, GMS mbH, Kiel-Mielkendorf, Germany) were inserted in both caudal burr holes to a depth of 15 mm. Probes were placed at a tip depth to target temporal white matter. Brain temperature was measured concurrently using a companion Licox temperature probe. $P_{br}O_2$ was then corrected for brain temperature using the Licox computer. Into the same caudal burr holes two microdialysis probes (CMA/20, Carnegie Medicine AB, Solna, Sweden) were inserted by means of a steel guiding needle. The membrane of the microdialysis probe has a cut-off value of 20 kDa, a length of 10 mm and a diameter of 0.5 mm. Probes were perfused with an artificial cerebrospinal fluid at a rate of 2 μ l/min with a microinjection pump (CMA100, Carnegie Medicine AB, Solna, Sweden). Dialysate volumes of 20 μ l (sampling time 10 min) were collected in microvials and stored at $-80^{\circ}C$ until analysis. Analysis of the microdialysis samples for glucose, lactate, pyruvate and glycerol was performed with an analyser (CMA 600, Carnegie Medicine AB, Solna, Sweden).

Licox measurements

The two brain oxygen sensors used were flexible polarographic Clark-type probes (identical to those used in clinical neurosurgery) with a polyethylene surface. For hyperbaric measurements the oxygen sensor cable (a coax cable approx. 1.5 m long) was cut and connected with cable sockets and connectors to the hyperbaric chamber wall. Inside the chamber a coax cable (approx. 1.5 m long) was connected from the chamber wall to the oxygen sensors. The temperature cable (a regular cable) was connected in the same way with sockets and connectors. The calibration procedure for hyperbaric conditions has been published earlier by our group.¹²

EEG recording

The EEG was recorded on a PC system with Schwarzer Handy Brain 11 (OSG, Rumst, Belgium), sample frequency 250 Hz and bandpass 0.13-70 Hz (-3 dB) and an average reference. Stainless steel needle electrodes were inserted in the skin and were positioned with reference to a line connecting both medial eye borders. The most frontal pair of electrodes

were inserted 1 cm behind the reference line and 3 cm lateral left and right of the midline, a second and third pair 4 cm left and right of the midline and 2.5 cm and 4 cm behind the reference line respectively. Two more electrodes were positioned 2 cm in front of the reference line and 1 cm left (M1) and right (M2) of the midline to enable montage with a common midline reference.

Experimental protocol

After instrumentation of the animals there was a 1-h stabilization period at an FiO_2 of 0.4 (baseline measurement) before conducting an “oxygen test”¹³ which was performed to ensure correct placement of the oxygen sensors in the brain tissue: briefly, FiO_2 was increased from 0.4 to 1.0 and remained at 1.0 during the remainder of the experiment. PbrO_2 had to increase by at least 15 mmHg, if not, the sensor was advanced a further 3-5 mm into the brain. Then, in each animal a hyperbaric exposure was performed for 10 min at 2.8 bar and for 10 min at 1.9 bar at an FiO_2 of 1.0 to record baseline data for PbrO_2 at these two pressures. After the pressure had returned to values recorded in the oxygen test, values for brain tissue and microdialysis parameters were recorded. Then, 0.5 ml/kg of air was injected through the catheter in the internal carotid artery at 1 ml air/s and (to allow for catheter dead space) immediately followed by 3 ml saline at 1 ml/s. One group of animals (group A, 6 animals) was treated with HBO starting within 3 min after embolization. The second group (group B, 5 animals) was treated with HBO 60 min after embolization. In the time between embolization and treatment, this latter group of animals was hyperventilated to get a $\text{PaCO}_2 \pm 30$ mm Hg at an FiO_2 of 1.0.

Hyperbaric treatment was initiated in accordance with the US Navy Treatment Table 6 (4.48 h) (Figure 1, see also Discussion) for arterial gas embolism.^{4,14}

Treatment was done in a hyperbaric chamber in which a technician or nurse set the ventilator, took blood gases and microdialysis sampling. During the study period, from each animal 20 μl microdialysate was collected at 10-min intervals. At the same time intervals, all other data were recorded. Ten minutes after HBO treatment ended, measurements were stopped and the sensors were calibrated again to assess any drift in the measured values. The animals were killed by an overdose of pentobarbital (Euthesate 200 mg/ml, Apharmo, Arnhem, the Netherlands).

Hyperbaric treatment table USN 6

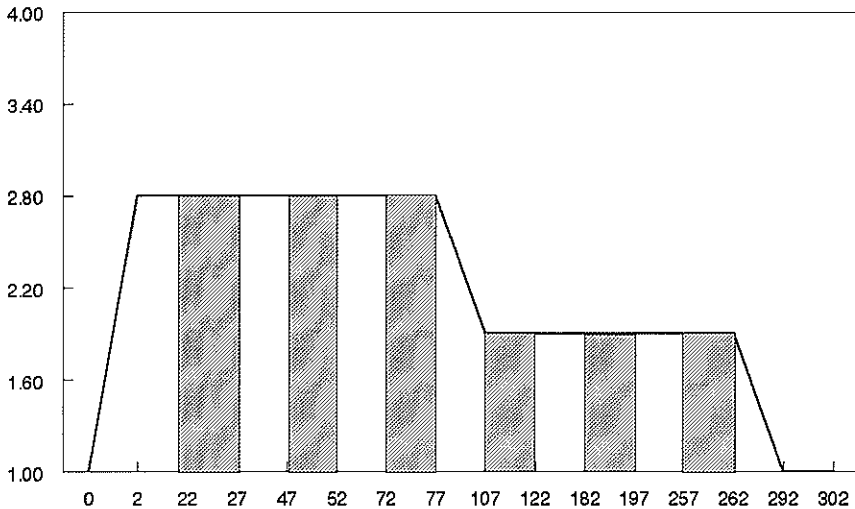


Figure 1. Hyperbaric Oxygen Treatment table Table 6. United States Navy.

According to this protocol, one starts initial compression to 2.8 bar (18 m equivalent depth) breathing 100% oxygen for 20 min and continues for two periods of 20 min oxygen breathing with 5 min air breathing, then over a 30-min period, there is a decrease pressure from 2.8 bar to 1.9 bar breathing 100% oxygen. At 1.9 bar, there are two periods of 60 min oxygen breathing with 15 min air breathing, followed by a decrease to 1.0 bar on 100% oxygen during a 30 min period.

EEG analysis

EEG was recorded at the same time as the other variables. EEG recordings were visually assessed and scored as follows: 1 = no cerebral activity; 2 = burst suppression; 3 to 6 = predominantly delta, theta, alpha or beta activity. In addition, after embolization, the time to the first changes in EEG were recorded, as well as the time to complete disappearance of EEG activity, and the total time of iso-electric EEG. Quantitative analysis of the changes in EEG will be published elsewhere.

Statistical analysis

Two-way and one-way analysis of variance for repeated measures with Dunnett's multiple comparison test as post-hoc test and the Student's *t*-test were used as appropriate. Statistical significance was accepted at a *p*-value < 0.05. Results are expressed as mean ± SD.

Results

Table 1 presents data on all measured parameters before embolization (baseline) and after HBO treatment. There were no significant differences between the two groups at baseline. All animals survived the study period in group A, in group B one pig died during HBO treatment due to increased ICP and herniation (Table 3, animal 5). This latter animal had a baseline ICP of 17 mm Hg which, after embolization, increased to 39 mm Hg after 60 min and continued to increase to 70 mm Hg (with a CPP of 35 mm Hg) in spite of HBO treatment. After 3 h, there was an iso-electric EEG and after waiting for 15 min we decided to stop HBO treatment in this pig. Subsequently, severe pathological values were found in this animal: brain lactate values of 4.13 $\mu\text{mol/l}$ and brain glucose 0.87 $\mu\text{mol/l}$.

In both groups of animals ICP increased continuously during the study period. However, the increase in ICP was greater in the group treated after 60 min. Intergroup differences in ICP were significant at 5 h only (Figure 2).

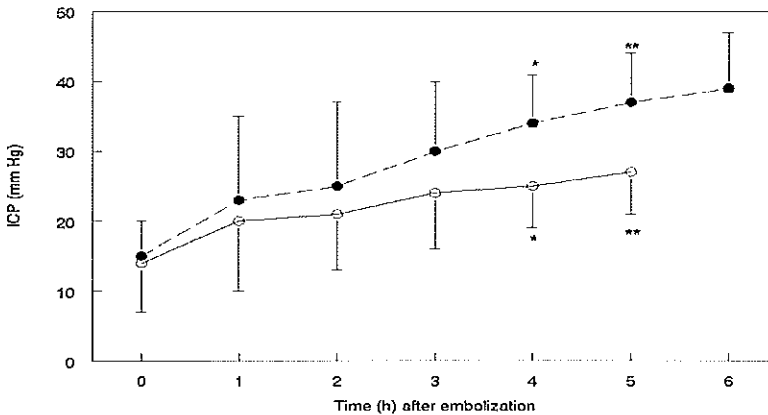


Figure 2. Intracranial pressure (ICP) for group A (t = 3) and group B (t = 60). Values are mean \pm SD. Open circles t = 3 min, closed circles t = 60 min. * p < 0.05 intragroup versus baseline ** p < 0.05 intergroup

Table 1

Data on measured parameters in the two study groups.

	Baseline		End	
	Group A	Group B	Group A	Group B
	t = 3 min	t = 60 min	t = 3 min	t = 60 min
Heart rate	98 ± 14	94 ± 6	90 ± 6	93 ± 8
MAP	112 ± 11	120 ± 6	111 ± 6	114 ± 10
Body temperature	37.3 ± 0.5	37.1 ± 0.8	37.7 ± 0.8	37.8 ± 0.7
Blood				
PaO ₂	540 ± 43	528 ± 35	532 ± 33	515 ± 33
PaCO ₂	42 ± 5	41 ± 3	42 ± 6	37 ± 2
pH	7.44 ± 0.05	7.48 ± 0.03	7.46 ± 0.05	7.49 ± 0.04
Glucose	5.9 ± 0.6	5.5 ± 0.9	5.0 ± 0.5	4.8 ± 0.9
Lactate	1.1 ± 0.7	0.7 ± 0.2	0.6 ± 0.2	0.8 ± 0.1
Hematocrit	0.26 ± 0.02	0.27 ± 0.03	0.25 ± 0.02	0.26 ± 0.02
Brain				
Intracranial pressure	14 ± 7	15 ± 5	27 ± 6* [#]	39 ± 8* [#]
Brain temperature	37.7 ± 0.7	37.6 ± 0.8	38.4 ± 0.8	38.1 ± 0.6
Brain glucose	3.23 ± 0.64	3.73 ± 0.68	2.25 ± 0.98*	1.41 ± 0.82*
Brain lactate	0.77 ± 0.18	0.85 ± 0.26	2.31 ± 1.46*	3.00 ± 1.33*
Brain pyruvate	109.5 ± 98.6	108 ± 39.3	131.1 ± 62	134 ± 49.3
Brain glycerol	94.6 ± 59.9	133.5 ± 77.7	64.0 ± 54.2	101.9 ± 72.4

Values are mean ± SD

* p < 0.05 versus baseline

p < 0.05 intergroup differences

Body and brain temperature (°C)

Heart rate (bpm)

MAP, PaO₂, PaCO₂, ICP (mm Hg)

Blood and brain glucose and lactate (mmol/l)

Brain pyruvate and glycerol (μmol/l)

Table 2
Data on brain oxygen, brain glucose and brain lactate from the beginning of hyperbaric treatment for group A and group B

Time (min)	FIO ₂	Bar	PbrO ₂		Brain glucose		Brain lactate	
			A	B	A	B	A	B
0	1.0	1.0	76 ± 25	58 ± 28	4.00 ± 1.50	3.73 ± 0.91	0.82 ± 0.31	3.23 ± 2.14 [#]
22	1.0	2.8	284 ± 112	222 ± 113	3.36 ± 1.81	3.82 ± 0.95	3.03 ± 0.82*	2.64 ± 2.21
27	0.2	2.8	63 ± 5	53 ± 20	4.68 ± 1.77	3.45 ± 0.82	3.08 ± 1.28*	2.39 ± 1.67
47	1.0	2.8	225 ± 112	178 ± 98	4.91 ± 1.36	2.23 ± 1.50 [#]	1.66 ± 0.72*	2.97 ± 2.08
52	0.2	2.8	55 ± 9	46 ± 18	4.86 ± 2.00	2.05 ± 1.41 [#]	1.28 ± 0.56	3.23 ± 2.14
72	1.0	2.8	201 ± 89	159 ± 94	4.36 ± 1.72	2.36 ± 1.00	1.41 ± 0.59	2.54 ± 1.26
77	0.2	2.8	51 ± 9	44 ± 18	4.32 ± 2.02	2.18 ± 1.05*	1.51 ± 0.64*	2.72 ± 1.36
107	1.0	1.9	95 ± 41	93 ± 62	3.20 ± 1.45	1.76 ± 0.95*	1.82 ± 1.02*	3.03 ± 1.15
122	0.2	1.9	35 ± 9	29 ± 9	3.00 ± 1.45	1.55 ± 0.86*	2.00 ± 1.20*	3.13 ± 1.00
182	1.0	1.9	110 ± 35	84 ± 57	2.55 ± 1.68	1.23 ± 0.73*	2.51 ± 1.74*	2.90 ± 1.26
197	0.2	1.9	36 ± 9	29 ± 12	2.68 ± 2.00	1.27 ± 0.73*	2.85 ± 1.46*	3.00 ± 1.44
257	1.0	1.9	130 ± 46	80 ± 65	2.36 ± 1.86	1.59 ± 0.95*	2.62 ± 1.69*	2.84 ± 1.69
262	0.2	1.9	43 ± 5	41 ± 11	2.27 ± 1.50	1.59 ± 1.00*	2.62 ± 1.64*	2.74 ± 1.69
292	1.0	1.0	67 ± 17	57 ± 33	2.27 ± 1.42*	1.51 ± 0.91*	2.53 ± 1.59*	2.88 ± 1.58
302	1.0	1.0	66 ± 14	52 ± 15	2.23 ± 1.28*	1.48 ± 0.92*	2.47 ± 1.56*	3.00 ± 1.33

Values are mean ± SD

Brain glucose and lactate (mmol/l)

PbrO₂ (mm Hg)

* p < 0.05 intragroup versus baseline

p < 0.05 intergroup

Brain oxygenation

Figure 3 shows data on PbrO_2 during the first 10 min after embolization. In group A, PbrO_2 decreased within 3 min after embolization and then increased within 7 min after starting HBO treatment at 2.8 bar. Thereafter, PbrO_2 decreased at 1.9 bar and then remained stable for the rest of the experiment.

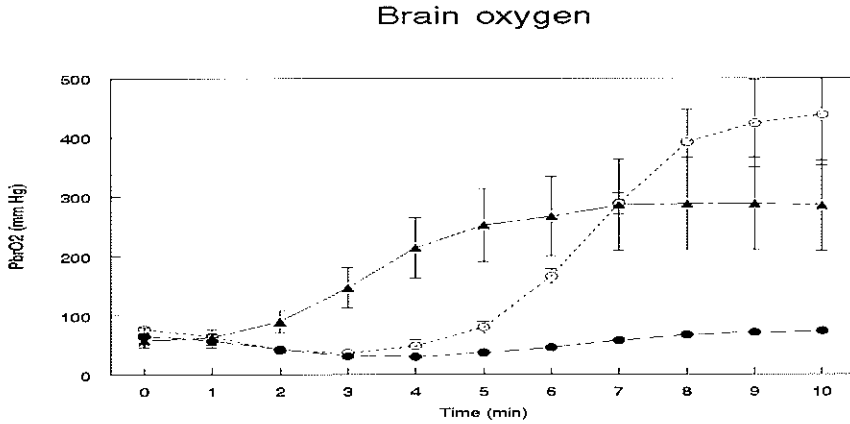


Figure 3. Data on brain oxygenation (PbrO_2) during the first 10 min after air embolization for group A ($t = 3$ min) and group B ($t = 60$ min). Values are mean \pm SD. Open circles $t = 3$ min, closed circles $t = 60$ min, closed triangles first 10 min after starting HBO treatment (60 min after embolization).

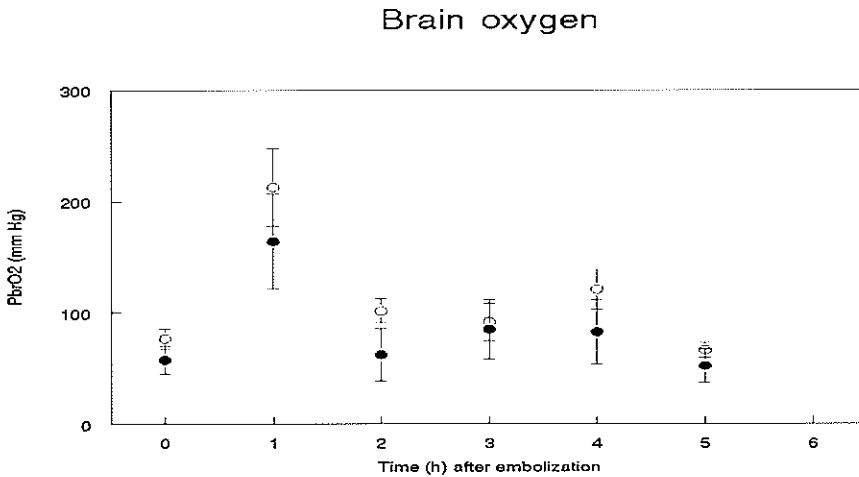


Figure 4. Data on brain oxygenation (PbrO_2) hourly for group A ($t = 3$ min) and group B ($t = 60$ min) during hyperbaric oxygen treatment. Values are mean \pm SD. Open circles $t = 3$ min, closed circles $t = 60$ min.

In group B, PbrO_2 stayed relatively low during the first hour after embolization and then also increased during the first 10 min of the HBO treatment (Figure 2).

Table 2 presents data on brain oxygen during each change in FiO_2 or pressure during HBO treatment according Table 6 USN.

Figure 4 shows data on PbrO_2 for both groups for each hour up to the end of the hyperbaric treatment (5 h). At the end of treatment, PbrO_2 values for group A and B were 66 ± 14 and 52 ± 15 mm Hg, respectively.

Microdialysis

Table 2 gives data on brain glucose and brain lactate during the study period. At the end of the experiment, both groups had a significant decrease in glucose compared with intragroup baseline values. Whereas at 1 bar, lactate showed a trend in both groups to increase over time, the early treatment group had a lower lactate level over time than the later treatment group (Table 2). After treatment there was a significant increase in lactate versus baseline for both groups. There were small, non-significant and non-consistent changes in brain pyruvate and glycerol.

EEG results

EEG values are given in Tables 3 and 4. Table 3 gives data for each animal at different time points. Table 4 shows that there was no correlation between the length of the iso-electric period and the final EEG scores. In both groups there was no difference in recovery time and normalisation of the EEG after embolization.

Discussion

The results of this study demonstrate that HBO therapy within 3 min of CAE leads to a greater reduction in ICP than treatment after 60 min. Moreover, compared with untreated animals in our previous study using the same CAE model,⁹ both the 3 and 60 min groups had a lower ICP throughout the study period. In the current study there were no differences in PbrO_2 either before embolism or after 5 h of HBO treatment. The PbrO_2 values at the end of the experiments (not different from baseline values before embolisation) suggest that HBO was able to prevent very damaging effects due to CAE, at least in this study. The effectiveness of HBO therapy is also confirmed by the EEG results in this study. However, there was a continuous increase in brain lactate levels and lower brain glucose levels over the study period.

Table 3

Data on EEG scores

Scores: 1 Iso-electric
 2 Burst suppression
 3 Predominantly delta
 4 Predominantly theta
 5 Predominantly alpha
 6 Predominantly beta (normal)

Time period	Animal (and group t = 3 or t = 60)										
	1	2	3	4	5	6	7	8	9	10	11
Animal	3	3	3	60	60	60	3	3	60	60	3
Delay	6	6	6	5	6	6	6	6	5	6	6
Baseline	5	6	5	2	4	4	5	4	5	6	4
10 min	6	6	6	4	4	6	6	5	5	6	6
60 min	5	6	6	4	4	6	5	5	5	6	6
70 min	6	5	6	5	4	6	6	5	6	6	6
2 h	4	6	5	5	4	5	5	5	5	6	6
3 h	6	5	6	5	^b	6	5	4	5	6	6
4 h				5	^b	6			4	6	
5 h									4	6	
6 h											
End ^a	6	6	6	5	1	6	4	4	5	6	6
Time(s) to first EEG changes	10	4	21	22	7	12	13	12	12	16	18
Time(s) to iso-electric EEG	15	15	30	28	20	34	19	23	^c	24	29
Duration(s) of iso-electric EEG	65	45	90	102	70	54	62	280	^c	24	135

^a End is last recording after surfacing^b Missing values due to earlier ending of experiment (animal 5 developed a persisting iso-electric EEG for at least 15 minutes)^c No development of iso-electric EEG**Table 4**

Data on EEG: Time to first EEG changes after embolization, time to iso-electric EEG and duration of iso-electric EEG in both groups.

	Group A (t=3, 6 animals)	Group B (t=60, 5 animals)
Time to first EEG changes (s)	13.0 ± 6.0	13.8 ± 5.6
Time to iso-electric EEG (s)	21.8 ± 6.6	26.5 ± 6.0
Duration of iso-electric EEG (s)	112.8 ± 62.5	87.7 ± 32.5

Values are mean ± SD

It is well established that cerebral oxygenation is crucial for the maintenance of normal brain metabolic function. Advancements in microsensor and microdialysis technology allow to measure PbrO₂ together with brain glucose/lactate, thus enabling estimation of acidosis and glucose/lactate levels in the brain. However, one limitation of this technology is that values derived from the sensor/probe represent data from a very local area only and do not represent the entire brain. The experimental event described in the present study is more or less a global insult that should have affected almost all regions of the brain (even the contralateral side by shunting), but predominantly the areas monitored by the sensors/probes. In addition, for the microdialysis, one has to consider that the total recovered amount of glucose/lactate depends on the membrane length of the probe and the flow rate used. Applying our experimental set-up, we could recover *in vitro* 22% and 39%, respectively, from known concentrations of glucose and lactate. These *in vitro* percentages were then used to correct the values of glucose and lactate measured in the brain, as recommended by Hillered et al.¹⁵

At the end of the study period there were no significant changes in PbrO₂; however, the lactate values increased over time suggesting anaerobic metabolism. Whether these data can be attributed to the temporary low PbrO₂ during air breathing during HBO treatment, or due to the occlusion of brain vessels by air embolism, is difficult to determine. The significantly lower glucose levels in both groups at the end of the study suggest decreased perfusion. On the other hand, the PbrO₂ and EEG data indicate that brain metabolism was within “normal” range throughout the study period. Hosmann and colleagues, who combined EEG, cerebral blood flow and cerebral metabolism in a CAE model, found that, with a depressed EEG (in contrast to our results) there was a pronounced reactive hyperemia and concluded that there was a transient uncoupling of blood flow, electrophysiological function and metabolism.¹⁶ Cerebral air embolism is known to lead to a progressive increase in ICP.^{17,18} In the present study, after embolization HBO treatment was able to prevent a further increase in ICP. Furthermore, CPP values of 84 and 75 mm Hg for group A and B, respectively, at the end of the treatment does not indicate general brain ischemia, which is also supported by the visually assessed normal EEG scores.

One study has shown that intracarotid injection of air caused reversible suppression of the EEG which can be divided into immediate effects (generalized, transient and ischemic), and secondary effects beginning 1-12 h after the embolism which are of a focal irritative nature and may lead to status epilepticus.¹⁶ Meldrum et al. reported that, after embolization, the EEG has an isoelectric period after 15-30 s which lasts 84-100 s. Our results were similar: time to the iso-electric EEG period was \pm 22-27 s which lasted for 88-113 s.¹⁹ In the present study,

one of our 11 animals failed to show any EEG changes immediately after CAE compared with 2 of 21 animals in the study by Meldrum et al.¹⁹

HBO treatment is the primary therapy for CAE. However, one of the main criticisms about the application of HBO therapy is that no prospective randomised trials have been performed to prove its benefit.^{7,20} Furthermore, only a few animal studies have demonstrated the benefits of HBO therapy in CAE.^{21,22} On the other hand, a review of patients treated with HBO clearly indicates improved outcome (as characterized e.g. by neurological examination, neuro-physiological techniques such as EEG, somato-sensory evoked potentials and neuro-psychometric tests) compared to non-recompression treatment.⁴ Our HBO treatment was based on the US Navy (USN) protocol (designated as Table 6 USN, Figure 1), used for treatment of patients suffering from CAE.¹⁴

The rationale for HBO treatment is;

1. compression to 2.8 bar reduces the diameter of the air bubbles. Using a dog model, Leitch et al. evaluated the efficacy of HBO treatment of arterial gas embolism at pressures ranging from 2.8 bar to 10.0 bar breathing air and at 2.8 bar oxygen: there were no significant differences in the recovery rates of the neurophysiological parameters (e.g. somatosensory evoked potentials) and none of the treatments was more effective than oxygen administration at 2.8 bar (i.e. Table 6 USN).²¹
2. a high FiO_2 increases oxygen pressure in the blood which improves the diffusion of nitrogen from the bubble into blood, enhancing the disappearance of the bubble.²³ In a mathematical model it was calculated that the time needed for bubbles to disappear is 15 h with an FiO_2 of 1.0 and up to 40 h with an FiO_2 of 0.4.²⁴
3. the high arterial oxygen pressure provides an increased oxygen diffusion gradient which improves oxygenation of hypoxic tissue.²⁵
4. hyperbaric oxygen may help to prevent cerebral edema by vasoconstriction and diminishes the adherence of leukocytes to "bubble-damaged" endothelium.^{26,27}

There is no consensus about how long the delay may be between embolization and HBO treatment.^{4,7} However, most investigators agree that earlier, rather than later, treatment is most appropriate for an air embolus,^{3,5} Davis and colleagues noted that the best results of treatment for CAE is therapy within minutes after the event.⁵ This apparently comes from cases in a military or commercial diving environment, where the diagnosis was quickly made and treatment facilities were available. Although prompt HBO intervention is likely to lead to better neurological recovery, successful treatment has been reported in patients even after a delay of 6-24 h.²⁸⁻³¹

In a clinical situation of CAE, a delay of one hour or longer is more realistic. Two retrospective studies on iatrogenic CAE had a mean delay of 8 and 17 h, respectively, before initiation of hyperbaric treatment.^{2,29} In both studies, 50% of the patients recovered from all neurological symptoms, but in the group with a 17 h delay in treatment 35% had severe neurological sequelae or deaths compared with 18% in the group treated with an 8 h delay. In addition, it was recently demonstrated that patients treated with HBO within 6 h had a better outcome (68% complete recovery of all neurological deficits by neurological examination) than those treated later (40% recovery).⁸

In conclusion, our study shows that oxygen breathing increases $PbrO_2$ which can be further increased by HBO therapy which reduces the risk of severe brain hypoxia. Future studies should investigate the progress of the measured parameters in the individual animals after the end of the 5-h study period (for, say, 5-12 h); this is particularly interesting because some of our values were within “normal” range ($PbrO_2$, EEG) or were aberrant (ICP, brain glucose/lactate). The results also suggest that this CAE model is suitable to elucidate the consequences of different delay periods between the onset of hyperbaric oxygen treatment after embolization.

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Chapter 8

Quantitative EEG monitoring during cerebral air embolism and hyperbaric oxygen treatment in a pig model.

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Submitted

Abstract

The purpose of this study was to evaluate the contribution of quantitative EEG (qEEG) to an animal model of cerebral air embolism (CAE). In twelve anesthetized pigs, air was injected into the internal carotid artery, and HBO treatment was started after either 3 min or 60 min (US Navy treatment table 6). Off-line spectral analysis was used to determine the frequency content of the EEG signal and factor analysis was performed to determine the frequency ranges that optimally showed the changes in the power spectrum.

Factor analysis revealed two factors that represented different and independent spectral changes during embolization, 0.5-7.3 Hz (band 1) and 26.4-30.3 Hz (band 2). Shortly after embolization, the power in both bands decreased to an minimum, representing an isoelectric EEG in 11 out of the 12 animals. EEG differences between animals were considerable, despite standardized doses of injected air, and qEEG can objectively assess and quantify these differences in immediate impact of air embolism on brain function. Also, qEEG enabled monitoring of the recovery from the initial embolic event and the response on treatment. The initial recovery was much more protracted in band 2 than in band 1, but even after completing HBO treatment, qEEG values did not return to baseline values in all animals. In addition, two animals did not survive until the end of the HBO treatment and qEEG proved to be superior to the other measured hemodynamic variables to detect and assure a deterioration of brain function.

In conclusion, this study showed that qEEG monitoring has significant additional value to monitoring hyperbaric oxygen treatment.

Introduction

Various medical situations can introduce air in the arterial blood vessels, leading to air embolism.¹ Air embolism is especially dangerous when it affects the cerebral circulation, because the brain is highly vulnerable to hypoxia. In the clinical setting, cerebral air embolism (CAE) can occur, for example, as a complication of cardio-aortic surgery or carotid endarterectomy, which often leads to permanent residual neurological deficits.

In diving, CAE is a feared complication of pulmonary barotrauma and is the major cause of lethal diving accidents.² In diving medicine, hyperbaric oxygen (HBO) treatment is a well-established therapy for CAE.³ Largely based on clinical experience, its beneficial effect can be impressive and may lead to complete recovery from severe neurological deficits in divers. Although HBO treatment is also regarded as the therapy of choice in iatrogenic CAE, its use remains controversial.⁴

Recently, Van Hulst et al.⁵ developed an animal model of severe CAE to study its pathophysiological impact on brain hemodynamics and metabolism, as well as the effects of normobaric and hyperbaric oxygen. To provide a direct measure of brain function, visually assessed EEG was added.

The present study extends the model with quantitative EEG (qEEG) which allows a more objective and quantitative evaluation of changes in brain function. Moreover, trend lines can be calculated to detect changes over time during on-line monitoring.⁶⁻⁸ The contribution of qEEG monitoring to the previously described animal model of CAE during HBO therapy was evaluated.

Methods

Animal Care

This study was approved by the Animal Committee of the Erasmus Medical Center Rotterdam. Care and handling were in accordance with the latest European Community guidelines.

Surgical and analytical procedures

A detailed description of the surgical and analytical procedures of the used pig model have recently been published by Van Hulst et al.⁵

In brief: in twelve cross-bred Landrace/Yorkshire pigs of either sex (32-36 kg), anesthesia was induced with ketamine and intramuscular midazolam, and maintained with ketamine (10 mg/kg/h) and midazolam (1 mg/kg/h). Pancuronium was used for neuromuscular relaxation.

Body temperature was kept within the normal range (37-38 °C) by means of a heating mattress.

The animals were ventilated in a pressure-controlled mode according to the 'Open Lung Concept' with a positive end-expiratory pressure of 6 cm H₂O.⁹ Ventilation frequency was set to maintain normocapnia (PaCO₂ 35-40 mm Hg). An angiocatheter was positioned into the internal carotid artery to enable air injection. Intra-arterial blood pressure was continuously monitored and arterial blood gases were measured using conventional methods.

Three bore holes in the skull were made and a calibrated intracranial pressure sensor (Codman Neuromonitor, Johnson & Johnson, Berkshire, UK), two oxygen sensors (Licox, GMS mbH, Kiel-Mielkendorf, Germany) and two microdialysis probes (CMA/20, Carnegie Medicine AB, Solna, Sweden) were inserted and positioned.

EEG recording method

The EEG was recorded on a PC system with a Schwarzer HandyBrain 11 (OSG, Rumst, Belgium), with a sample frequency of 250 Hz and a bandpass filter of 0.13-70 Hz (-3 dB). The EEG device was positioned within the hyperbaric chamber (see below). Stainless steel needle electrodes were inserted in the skin and positioned with reference to a line connecting both medial eye borders: the most frontal pair of electrodes was inserted 1 cm behind this reference line and 3 cm left and right of the midline, a second and third pair 4 cm left and right of the midline and 2.5 cm and 4 cm behind the reference line, respectively. Two more electrodes were positioned 2 cm in front of the reference line and 1 cm left (M1) and right (M2) of the midline. A common midline reference montage was used with a connection of M1 and M2 as reference. The EEG was recorded continuously during the 6-h experiment. For analysis, smaller EEG periods were selected (see Figure 1).

Experimental protocol

The experiments were performed in a multiplace hyperbaric unit (Haux Medusa, Karlsbad-Ittersbach, Germany). A hyperbaric technician/nurse performed the bloodgas and microdialysis sampling and controlled the ventilation settings.

After completion of all surgical procedures, EEG recording was started and a 1-h stabilization period was allowed. Then, a normobaric 100% oxygen test was performed and, subsequently, a compression test was performed for 10 min at 18 meters of seawater (msw; 2.8 bar) and 10 min at 9 msw (1.9 bar) on 100% oxygen, to provide adequate baseline measurements at these treatment depths.

Next, 0.5 ml/kg of air was injected through the catheter into the internal carotid artery at 1 ml air/s, followed by 3 ml of saline at 1 ml/s. This procedure, accounted for catheter dead space.

The animals were randomly assigned to two groups. In group A (n=7), the HBO treatment was started 3 min after embolization and in group B (n=5) after 60 min. Meanwhile, group B animals were hyperventilated ($\text{PaCO}_2 \pm 30$ mm Hg) on 100% oxygen. HBO treatment was initiated in accordance with the US Navy Treatment Table 6 for arterial gas embolism.¹⁰ Although all variables were recorded continuously, for EEG analyses attention was focused on selected measurement segments (see Figure 1).

At the end of the experiment, the animals were killed by an overdose of pentobarbital.

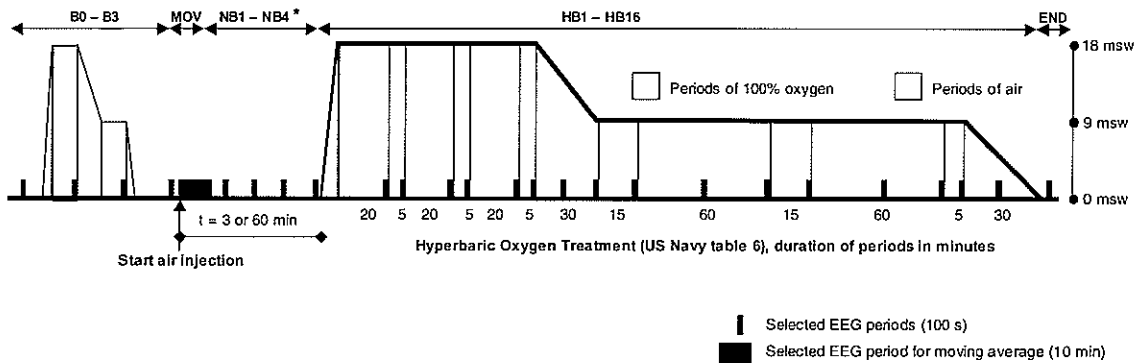


Figure 1

Experimental protocol of the hyperbaric oxygen treatment. The delay before treatment was 3 minutes for group A and 60 minutes for group B (* = additionally selected segments for group B, during the 60 minutes before HBO treatment; for group A, the MOV period extends into the hyperbaric period). B=Baseline, MOV=Moving Average, NB=Normobaric, HB=Hyperbaric, END=end of experiment.

qEEG analysis

During the experiments, the animals were monitored by visual EEG assessment. The development and persistence for 15 min or more of an isoelectric EEG in combination with markedly increased ICP values (>50 mm Hg) during the HBO treatment was considered an end-point. After the experiments, off-line quantitative EEG analysis was performed. For this purpose, EEG segments were selected, starting from the measurement periods indicated in Figure 1. This resulted in 22 segments for group A and 26 segments for group B. All segments had a duration of 100 sec except for the segment immediately following air injection, which lasted 10 min.

The selected EEG signals were high-pass filtered (4th order Bessel; cut-off frequency 0.5 Hz). Large-amplitude baseline drifts were removed by subtracting the first-order (straight line) approximation of the signal over the entire segment. A Hanning window was applied before

Fast Fourier Transformation of the 100 sec EEG segments and calculation of the spectral power density. Finally, the spectral changes relative to the baseline spectrum (from segment B3, see Figure 1) were computed for all constructed channels and per frequency band (see next paragraph). For this purpose, the mean spectral power density (MSPD) was calculated over all frequency resolution points in each band, for the baseline and for each selected segment separately. For each of the channels, the MSPD changes of segment s relative to baseline segment B3 and per band b were then expressed as

$$10 \cdot \log[\text{MSPD}(b,s) / \text{MSPD}(b,B3)].$$

In the 10-min period following air injection, rapid EEG changes could be expected. For that reason, a method was used to calculate spectral changes in this segment with a high time resolution. Spectra were first computed for epochs of 2 sec, following the procedure described above, with each epoch overlapping the preceding one by 50%. Next, moving average spectra were computed by averaging over three successive epochs, resulting in a 3-sec time shift between spectra and a spectral resolution of approximately 0.5 Hz. Analogous to the procedure per segment, the log spectral changes relative to the baseline spectrum were computed for all 3-epoch averages, all frequency bands and all channels. In addition, the spectral power density changes were determined per frequency resolution point (instead of averaging over bands) to allow subsequent factor analysis. Moving averages that contained artefacts were treated as missing values.

Factor analysis

Factor analysis was performed to identify those frequency bands in which spectral changes were most pronounced. For this purpose, the logarithms of the relative changes in the spectral points between 0.5 and 30 Hz in the 10 min directly following air injection were used as variables. Since all animals showed a sequence of clearly ischemia-related EEG changes, evolving into an isoelectric EEG in 11 out of 12 cases, the results for all animals were pooled into one data set.

In a preliminary study, factor analysis was applied to data sets in which spectra were calculated with 0.25 Hz, 0.5 and 1.0 Hz resolution (epoch lengths of 4, 2 and 1 sec, respectively). Thus, the effects of a higher time resolution (shorter epoch length) could be weighed against those of a higher signal-to-noise ratio (longer epoch length). To maintain an adequate ratio between variables and cases, various subsets of spectral points were analysed separately. Because this preliminary analysis did not reveal relevant differences in the resulting factors, in the final factor analysis the log spectral changes at 0.5 Hz resolution were used.

A varimax rotation was employed to identify those independent frequency ranges in which the spectral changes optimally reflected the EEG changes. The factor analysis was performed for all channels separately. Frequency ranges were considered to represent significant changes if the rotated factors had factor loadings above 0.71. The mean spectral changes within these frequency ranges were used to study the time course of spectral EEG changes, as described previously.

Statistical analysis

The Statistical Package for the Social Sciences was used for data analysis and to create lines and boxplots of the selected segments. Unless otherwise specified, the non-parametric Mann-Whitney test was used to analyse group differences and the Wilcoxon rank test was used to analyse changes in time. Given values represent median value and ranges. A significance level of at least $p < 0.05$ was used.

Results

All 12 animals were in stable cardiocirculatory conditions at baseline and 10 survived the study period. Table 1 gives data on heart rate, MAP, CPP and ICP at baseline, 10 min after air injection and at the end of the study period.

The hyperbaric chamber did not affect the quality of the recorded EEG signals, which was generally good. Compression and decompression had no influence on this quality. The EEG of the pigs at the start of each experiment (before the compression test) showed no significant differences compared to the signal during and after the compression test prior to air injection. In one animal, external sources caused artefacts during a period of approximately 25 min after air injection, and this period had to be excluded from the analysis.

Table 1. Changes in hemodynamic variables at baseline, 10 min after air injection and at the end of the study period.

	Baseline		10 min after air injection		Final measurement	
	median	range	median	range	median	range
HR	96	86-143	95	89-178	96	78-140
MAP	126	92-144	114 *	70-132	112 *	76-137
CPP	108	80-121	94 *	43-116	84 *	10-162
ICP	14.0	8-24	15.5 **	9-30	27.5 **	14-66

*** = significantly different from baseline with * $p < 0.05$ or ** $p < 0.005$

HR = Heart Rate (/min); MAP = Mean Arterial Pressure (mmHg); CPP = Cerebral Perfusion Pressure (mmHg); ICP = Intracranial Pressure (mmHg).

Factor analysis

Factor analysis of the moving average changes during the first 10 min after air injection revealed two different factors, one in the low frequency range, 0.5-7.3 Hz (band 1), and one in the higher beta frequency range, 26.4-30.3 Hz (band 2). For each animal, no relevant topographical differences were apparent in the shape and magnitude of the spectral changes between the six EEG channels. Therefore, one channel was selected (the right middle electrode vs. the common reference) for further analysis. The two factors derived from factor analysis were used to study the time course of spectral EEG changes in this selected channel.

qEEG during the initial 10 min after air injection

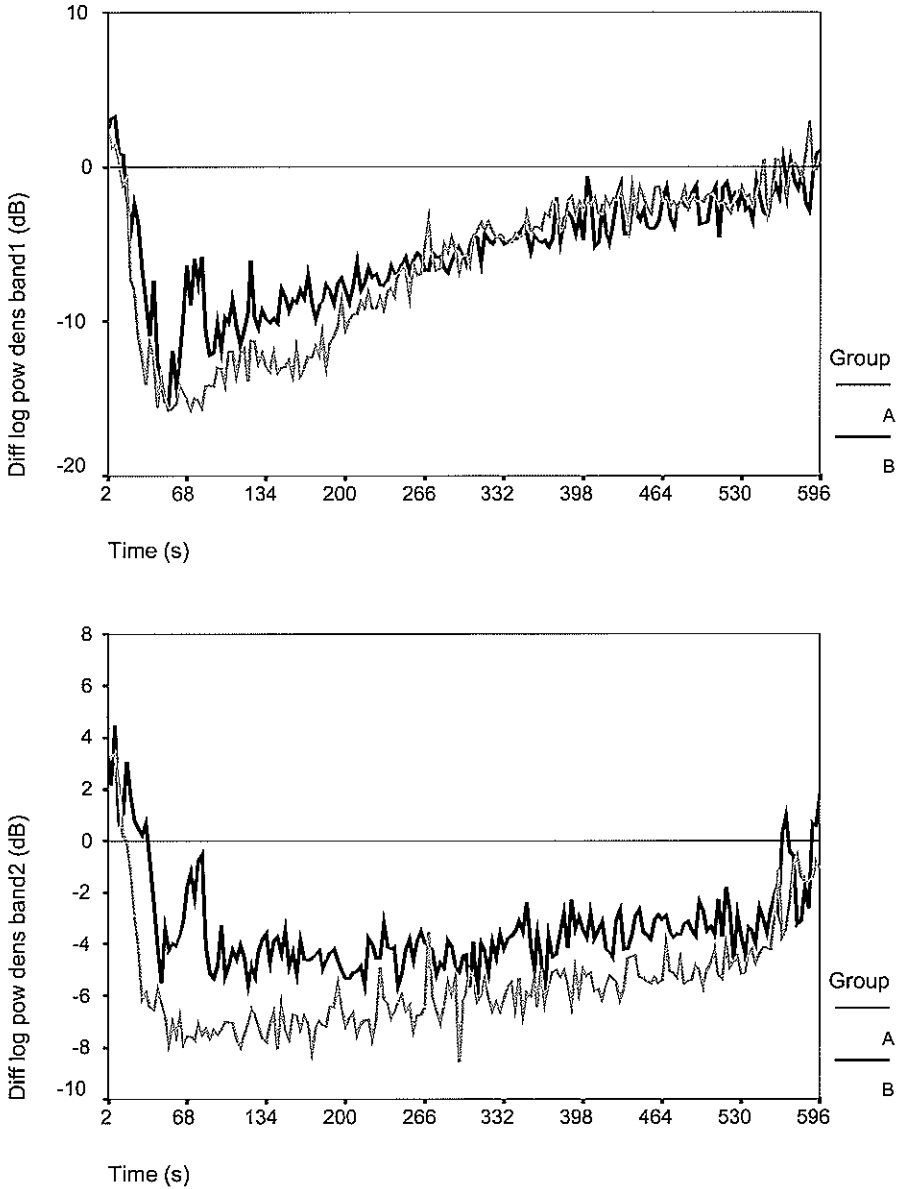
The visually assessed baseline EEG of all animals showed activity at all frequencies, with dominance in the alpha and beta frequency ranges. Figure 2 shows the time course of the changes in the mean spectral power density in the two frequency bands for the two groups. The differences between the two independent factors representing the EEG changes can be clearly recognized. The power in band 1 shows a faster recovery after the initial changes due to embolization than the power in band 2.

In all animals, the first changes after air injection consisted of a slight increase in power in both frequency bands during a few seconds. Next, the power in the two bands decreased simultaneously to a minimum. The median decrease was 19 dB (range 12-22) in band 1 and 8 dB (range 3.5-12) in band 2. The pigs in group A showed a significantly ($p < 0.05$) larger power decrease in both bands than the pigs in group B. For band 1, the decrease in groups A and B was 20 dB (range 17.5-22) and 16 dB (range 12-19), respectively. For band 2, this was 9 dB (range 7.5-12) and 6 dB (range 3.5-9). The maximal power decrease represented an isoelectric EEG in 11 of the 12 animals. In one animal, however, the maximum decrease in both bands (12 and 3.5 dB) occurred without the development of an isoelectric EEG.

Two different patterns of recovery could be recognized based on changes in band 1. A group of 7 animals (3 in group A, 4 in group B) showed an evident return of the power in this band within 1.5 min after air injection. In a second group of more slowly recovering animals, this increase in power started after 3 min or more. Within 6.5 minutes, all animals showed a certain degree of recovery in band 1. Compared to band 1, the power in band 2 showed a much more protracted recovery in all animals. In fact, in two animals (1 in group A, 1 in group B), there were no signs of recovery at all for the first 10 min. At the end of the 10-min period after air injection, the power in band 1 had returned to baseline values in 6 animals (3 in group A, 3 in group B). By contrast, the power in band 2 had recovered completely in only two animals (1 in group A and 1 in group B).

Figure 2

Time course of changes in the mean spectral power density of the EEG during the first 10 minutes after air injection for groups A and B, relative to baseline (B3, see Figure 1). Results are shown for frequency bands 1 (0.5-7.3 Hz) and 2 (26.4-30.3 Hz).



During the initial 10 min, in most animals the ICP increased gradually, and the CPP and MAP decreased. The values of these variables after 10 min differed significantly from the baseline values (Table 1). However, there was no significant inter-group difference. This was somewhat surprising, since (a) there was a significant difference between the two groups in the maximal power decrease in both bands, and (b) group A animals started with HBO treatment after 3 min.

qEEG monitoring during HBO treatment

To study the time course of spectral changes during the entire experiment, the selected EEG segments of 100 s (see Figure 1) were used. Again, no relevant differences in spectral changes were found between the EEG channels. For each of the animals, the development and time course of the changes in the two frequency bands were analysed visually. As mentioned above, the return to baseline power values did not occur in all animals in the first 10 min after embolization. Figure 3 shows a continuing restoration toward baseline during the remainder of the experiment, as occurred in most animals. However, even at the end of the experiment this recovery was not always complete. Two animals developed an isoelectric EEG during the course of the HBO treatment and died before the end of the experiment (1 in group A and 1 in group B). These two registrations will be discussed separately.

Of the remaining 10 animals, 8 (4 in group A, 4 in group B) showed complete recovery of power in band 1 at the end of the experiment, two (both in group A) did not. Over the first few segments, band 2 showed a sharp increase in power, but after about 15 min the recovery rate decreased in both groups (see Figure 3). Band 2 recovered completely in 7 animals (4 in group A and 3 in group B).

At the end of the experiment, there was a significant decrease of CPP and MAP and increase of ICP. No inter-group differences were found (see Table 1).

qEEG changes in the two animals that died during the HBO treatment

Two animals did not survive until the end of the HBO treatment. In the first animal (number 4 in Figure 4; group A), although the power in band 1 showed an initial increase a few minutes after air injection, there was no complete recovery to baseline values at any time. In band 2, only a slight initial increase in power occurred. For about the first 1.5 h after embolization, corresponding to the period of treatment at 18 msw, there was a steady-state situation. During the subsequent gradual decompression to 9 meters, the EEG suddenly deteriorated and developed into an isoelectric EEG, from which the pig did not recover. In this animal, the ICP increased steadily from 15.7 mm Hg at air injection to 82 mmHg. Heart rate and blood pressure were stable during the entire experiment; consequently, the CPP decreased gradually.

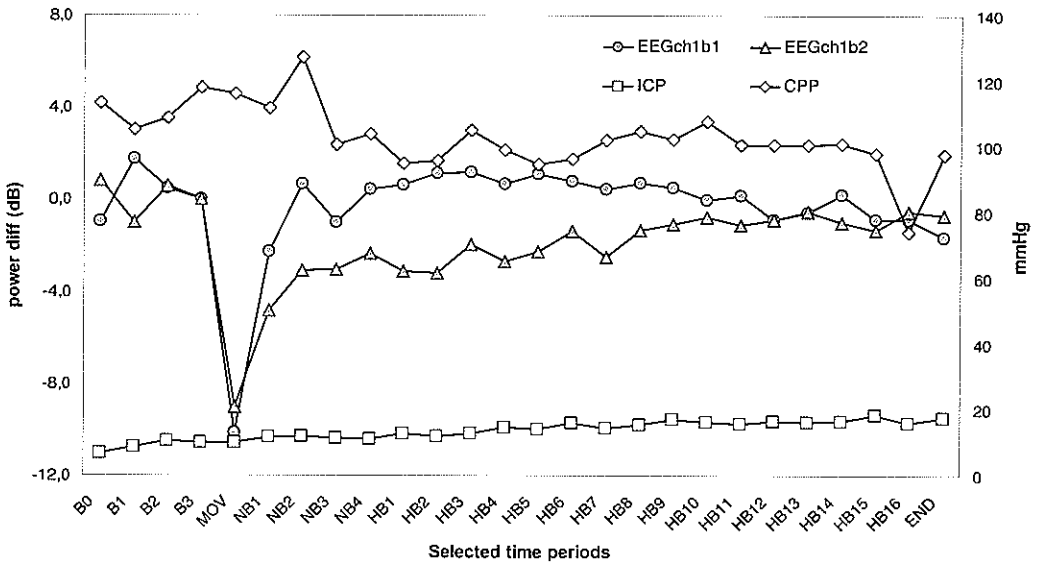


Figure 3
Time course of EEG changes and changes in ICP and CPP in a representative animal.

For the second animal (number 5 in Figure 4; group B) no EEG data are available for the first 25 min after embolization due to severe artefacts caused by an external source. However, at 25 min after air injection, the power in band 1 corresponded to the baseline level (because of the artefacts, for this animal, segment B0 was used as baseline recording). The power in band 2 never returned to the baseline value and remained at a constant, low level during the entire experiment. Again, a steady-state situation occurred during the compression phase at 18 msw. Subsequently, during decompression to 9 msw, the power in band 1 gradually decreased. After about 75 min at 9 msw, the rate of power decline suddenly increased and power decreased to a value corresponding to an isoelectric EEG, from which the animal did not recover. In this animal, the ICP increased steadily after air injection, reaching a maximum value of 73 mm Hg. Simultaneously with the onset of EEG deterioration, the MAP and CPP began to drop. The lowest level of the CPP reached was 10 mm Hg.

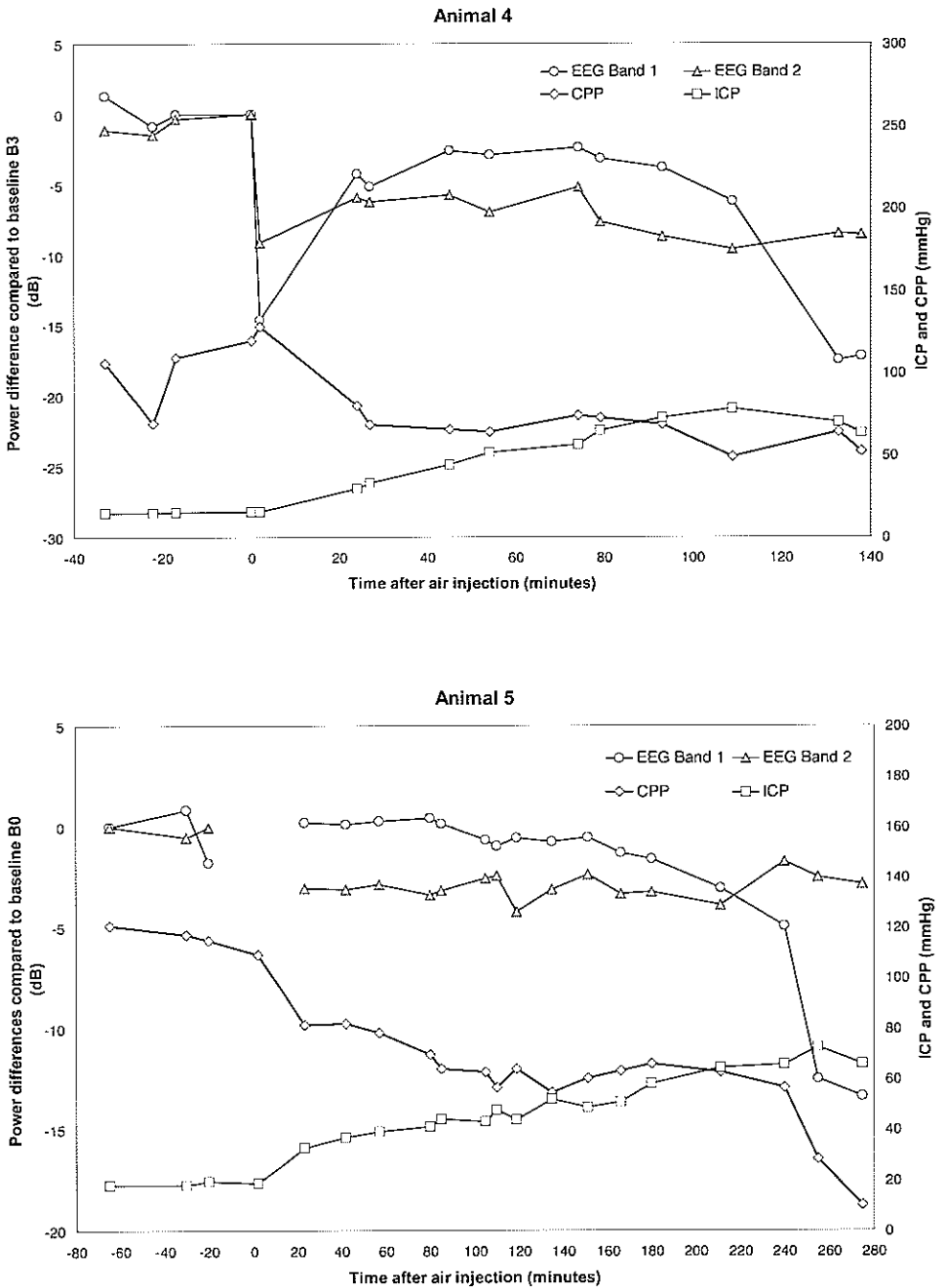


Figure 4

Time course of EEG changes in the 2 frequency bands and ICP and CPP of the 2 animals that developed an isoelectric EEG during the HBO treatment. Because of artefacts, in animal 5 the first EEG period after air injection is missing and the period B0 was used as baseline.

Discussion

Twelve pigs that underwent HBO treatment according to the US Navy Treatment Table 6 after injection of intracarotid air were monitored with EEG. Factor analysis of the spectral power density of this EEG revealed two factors that showed marked spectral changes, one in the slow frequency range (0.5-7.3 Hz) and the other in the fast beta frequency range (26.4-30.3 Hz).

No relevant topographical differences were found either in these factors or in the time course of the EEG changes in the two frequency bands. This was not an unexpected finding. Since pigs have a very extensive collateral cerebral blood vessel system, the injected volume of 10-15 ml of air is likely to obstruct cerebral blood flow for a short period of time in both hemispheres equally. Although future registrations could, therefore, be limited to one electrode position, we recommend using more electrodes for practical reasons. Wound fluids and leaking blood can cause hard-to-control artefacts in signals from electrodes in the surgical wound area. If those artefacts cannot be corrected for, monitoring can easily be continued using one of the other attached electrodes.

The two factors representing ischemic changes as found in the present study are somewhat different from those found in a previous study during global⁸ or focal cerebral ischemia.¹¹ In their study of spectral EEG changes during short periods of circulatory arrest in humans under anesthesia, four factors were found: two in the delta frequency range, one in the alpha and one in the beta range.⁸ In the other study by Visser et al.¹¹, factor analysis of ischemic spectral EEG changes caused by carotid clamping during carotid endarterectomy revealed two factors, one in the delta range and one in the alpha/beta frequency range. Despite differences in frequency band position and width, the findings of the present study essentially confirm their concept of two major components that describe ischemic EEG changes.¹¹ In this concept, the higher frequency bands (alpha and beta range) are particularly sensitive to the initial changes in the EEG, and power changes in this band can be used to determine whether complete recovery is reached. The low frequency bands (delta range) appear to be more important in assessing the extent of ischemic damage to the brain. First, an increase in slow frequencies can be found, but a subsequent disappearance occurs when progressing to an isoelectric curve. Also in the present study, power in the beta frequency range (band 2) was the last to reach baseline levels (see Figures 2 and 3). However, in the two animals that died during the HBO treatment, ischemic brain dysfunction was mainly detected by the decline of power in

frequency band 1, as was illustrated in Figure 4. This might be due to the fast development of severe ischemic changes.

The different behavior of the slow and fast EEG activity has also been described in other animal models for cerebral ischemia.¹² This converging evidence implies that cerebral function monitoring (CFM), an EEG derivate, is inadequate as a monitoring tool. CFM, which is sometimes used as an alternative for visual assessment in animal models for cerebral hypoxia¹³, is an amplitude-integrated trend registration of the EEG signal in one broad frequency band of 2-15 Hz. The use of a single band implies that CFM misses the independent changes in the low and higher frequencies. In addition, because of the width of the band, the sensitivity to detect minor ischemic changes will be lower than with the narrow bands based on factor analysis.

Our results show that qEEG monitoring is useful both during periods of fast EEG changes resulting from air embolism, as discussed above, and as a follow-up tool during subsequent HBO treatment. During HBO treatment, the restoration to baseline power levels can be monitored. In addition, the qEEG proved to be sensitive to detect the secondary development of brain dysfunction during the HBO treatment, most clearly demonstrated in the two animals that did not survive until the end of the treatment. To this end, qEEG monitoring appeared to be superior to detect and assure a deterioration of brain function, compared to CPP and ICP (see Fig. 4). However, these variables are of course complementary. The ICP/ CPP monitoring provides information about the cause of a disturbed brain function, while the EEG measures the actual effect brain function itself.

An interesting finding was that in both animals that died the EEG started to deteriorate during decompression from 18 to 9 msw. This suggests that decompression is a critical phase in the treatment schedule. Also during HBO treatment of patients with CAE, clinical deterioration during decompression is a well known problem. Our findings illustrate that qEEG is an appropriate method to detect whether such a deterioration occurs.

Somewhat surprisingly, after the HBO treatment no intergroup differences were found in the measured hemodynamic variables. Furthermore, there were no relevant differences in EEG outcome between the two groups. If anything, there was a slight trend to a better EEG of the group B animals, thus not confirming our expectations of a better result in group A where HBO treatment was started with a very short latency of 3 min after air embolism. This discrepancy may be explained by coincidental differences in group composition with respect to the initial impact of the air embolism. The drop of power in both frequency bands directly following air injection was significantly larger for group A. This difference might be caused

by the one animal in group B that did not develop an isoelectric EEG. In addition, there was a trend to a longer duration of the isoelectric period in the group A animals.

More generally, EEG differences between animals were considerable. The longest isoelectric period observed was almost 5 min, while in one animal the EEG did not develop into an isoelectric curve. This considerable variability in EEG changes, despite standardized doses of injected air, was also described by Meldrum et al.¹² This implies that to enable reliable comparison of studied groups, it is essential to quantify the effect of the given embolic stimulus in a particular animal. In our opinion, qEEG analysis will outperform visually analysed EEG in this respect, because of its quantitative nature.

Although not the topic of this study, an interesting finding is that during HBO treatment the brain glucose concentration steadily declines and the brain lactate level increases, despite the fact that the cerebral circulation is restored and a high dose of oxygen is delivered. This suggests that the neuronal metabolism continues to be (partly) anaerobic, which is likely to affect normal neuronal function. This phenomenon has been described before. It is thought to be the result of a disturbed mitochondrial membrane function, which hinders oxygen uptake and utilisation.^{14, 15} This conception of an ongoing deterioration in brain function may find additional support in our observation that the EEG often did not completely return to baseline. In conclusion, we believe to have shown that qEEG monitoring is of significant additional value to the air embolism pig model. First, using qEEG, the immediate impact of the air embolism on brain function can be objectively assessed and quantified. Second, the time course of the recovery from this initial event can be reliably followed. Third, secondary deterioration of brain function after initial recovery can be promptly detected. Finally, brain function, as represented by the EEG, can be objectively assessed after completing HBO treatment as end-point, and the effect of different treatment schedules can be compared. Since EEG actually measures brain function, it can be regarded as an outcome measure superior to hemodynamic variables. This is especially relevant when clinical evaluation is obscured, as in anesthetized animals. Moreover, qEEG monitoring can also be used for monitoring patients with CAE during HBO treatment.

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Summary and conclusions

Chapter 1. Gas embolism: pathophysiology and treatment

This chapter presents a review on gas embolism. Gas embolism, defined as the entry of gas into vascular structures, can occur in many clinical environments as an iatrogenic complication. In most cases gas embolism is in fact an air embolism, although the medical use of other gases (such as carbon dioxide) can also result in this condition. Air bubbles may reach any organ, but their effect on the cerebral and cardiac circulation is particularly deleterious because these organs are highly vulnerable for hypoxia.

Animal studies investigating venous air embolism have shown that the lung capillary bed filters the bubbles to some extent, thereby protecting the systemic circulation from gas emboli. In a clinical situation most venous gas emboli occur in patients in whom a central venous catheter has been placed. The greatest risks for arterial gas embolism occur with cardiac surgery with cardiopulmonary bypass, craniotomy performed with the patients in the sitting position, and hip replacement procedures.

We briefly describe the neurological symptoms and signs of air embolism and the therapy available in the acute situation. Also emphasized is the importance of clinicians recognizing this complication and the related need to develop better techniques to detect air emboli in the circulation. In addition, the use of adjuvant drug therapy is discussed, including the use of fluorocarbons. Although prospective randomized trials on the use of hyperbaric oxygen therapy in humans are lacking, numerous case reports and a few retrospective patient studies, allow to conclude that hyperbaric oxygen therapy is indicated in patients with neurological deficits due to cerebral air embolism.

Chapter 2. Intracranial pressure, brain PCO_2 , PO_2 and pH during hypo- and hyperventilation at constant mean airway pressure in pigs

Patients with acute lung injury are often treated with a ventilation strategy that aims to limit or reduce ventilation-induced lung injury by the use of low tidal volumes. However, the main side effect of this mode of (hypo)ventilation is an increase in arterial carbon dioxide partial pressure. Although this mode (also called “permissive hypercapnia”) is well accepted in intensive care, there is no consensus on the acceptable upper limit of arterial carbon dioxide.

Hypercapnia also augments cerebral blood flow which can cause intracranial pressure to rise and, subsequently, cerebral perfusion pressure to decrease. On the other hand, hyperventilation results in hypocapnia which, in turn, can lead to vasoconstriction and thus reduce cerebral blood flow. In addition, the respiratory alkalosis shifts the oxyhemoglobin dissociation curve to the left, further limiting oxygen delivery to the brain.

Therefore, this study investigated the effects of hypoventilation and hyperventilation on brain parameters – characterized by measurement of intracranial pressure, brain carbon dioxide, brain oxygen and brain pH in healthy non-brain-traumatized pigs during ventilation at constant mean airway pressure. It was important to maintain constant mean airway pressure because induction of both hypoventilation and hyperventilation may require changes in mean airway pressure with subsequent changes in the pulmonary and systemic circulation.

Our main findings were that hypoventilation (hypercapnia) leads to a significant increase in intracranial pressure, brain carbon dioxide and brain oxygenation, and to a decrease in cerebral perfusion pressure. In contrast, during hyperventilation there was a significant decrease in intracranial pressure and brain carbon dioxide, and a slight increase in brain oxygenation and in cerebral perfusion pressure.

The next step was to investigate the interrelations between continuously monitored brain parameters (i.e. brain oxygen, brain carbon dioxide, brain pH and intracranial pressure), ventilator settings, and brain metabolism as characterized by glucose and lactate concentrations with the same experimental conditions as described above.

Chapter 3. Brain glucose and lactate levels during ventilator-induced hypo- and hypercapnia

We extended the study described in Chapter 2 by introducing the specialized microdialysis technique to provide the most direct assessment possible of the effects of hypocapnia and hypercapnia on brain glucose and lactate levels and, again, on brain oxygen, brain carbon dioxide, brain pH and intracranial pressure. Most studies on brain oxygenation and microdialysis have involved human subjects or animals with brain injury. Because brain injury itself can impair cerebral circulation and oxygenation, these studies have limited value when investigating the effects of different ventilation modes on functional brain parameters. Thus the monitoring of brain glucose and brain lactate levels in a non-brain-traumatized animal model is an important prerequisite in order to elucidate the pathophysiological mechanisms of hypocapnia and hypercapnia.

Therefore, in this study - starting at normoventilation - two steps of hypoventilation and hyperventilation were performed and under these conditions the above-mentioned brain parameters were measured. At hypercapnia, there were no significant changes in brain glucose and lactate levels, and the changes in brain oxygen, carbon dioxide and pH were similar to those observed in the study in Chapter 2. In contrast, at hypocapnia there was a significant increase in brain lactate and a decrease in brain glucose, indicating anaerobic metabolism.

This results of this study show that hypocapnia decreases brain glucose and increases brain lactate concentrations whereas hypercapnia has no influence on levels of brain glucose and no significant effect on brain lactate. Subsequently, in the same non-brain-traumatized animal model, we investigate the effects of two clinically used hyperbaric oxygen pressures on brain oxygen tension.

Chapter 4. *Oxygen tension under hyperbaric conditions in healthy pig brain*

There is a growing interest in hyperbaric oxygen therapy in neurology, because an increase in brain oxygen tension may have beneficial effects in ischemic brain injuries. Because it is unknown to what extent it is advisable to increase brain oxygen tension under hyperbaric conditions, we investigated brain oxygen tension in non-brain-traumatized animals at two clinically used hyperbaric oxygen pressures (1.9 and 2.8 bar, both at an FiO_2 of 1.0). The results show that, compared with baseline, both hyperbaric conditions led to a significant increase in brain oxygen tension. At a pressure of 2.8 bar there was a nine-fold increase in brain oxygenation compared with normobaric pressure at an FiO_2 of 0.4.

On the other hand, increased brain oxygen tension can also lead to acute toxic reactions such as convulsions and an increase in oxygen radicals. Thus the beneficial effects of hyperbaric oxygen therapy must be balanced against negative effects and toxicity. Therefore, under the same conditions, we also studied whether hyperbaric oxygen therapy has any deleterious effects. It was shown that hyperbaric oxygen pressure in the brain did not lead to changes in intracranial pressure or in brain glucose/lactate levels.

After having elucidated the effects of commonly applied ventilatory modes and hyperbaric oxygen treatment on brain functional parameters and brain metabolism in healthy pig brain, we wanted to extend the studies by exploring some pathological conditions. Therefore, we first developed and validated a model of acute cerebral air embolism in pigs in order to investigate the effects of this acute trauma on functional brain parameters and brain metabolism. Then, using the same model, we looked at the effects of normobaric and hyperbaric oxygen on the

same brain parameters and also explored the additional value of quantitative EEG monitoring under these conditions.

Chapter 5. *Effects of air embolism on brain metabolism in pigs*

Air embolism results when air enters the vasculature and this can lead to serious morbidity or death. This hazard can occur during various clinical interventions as well as in diving medicine. Monitoring of brain metabolic function under these conditions would enable a better understanding of the pathophysiology of cerebral air embolism.

Therefore, this study describes the validation and technical aspects of an animal model of cerebral air embolism. We used microsensor technology to measure brain oxygenation, brain carbon dioxide, brain pH and intracranial pressure combined with a microdialysis technique to measure brain glucose and lactate levels. Both techniques are well established in neurosurgery but have not yet been applied in a model of cerebral air embolism. After injection of air into the internal carotid artery changes in brain metabolism were measured for two hours.

The data show an initial decrease in brain oxygenation and in glucose levels followed by a partial recovery of these values, suggesting a partial clearance of the bubbles in the brain. During the two-hour study period there was a fourfold increase in intracranial pressure and, as a consequence, a decrease in cerebral perfusion pressure at a level indicating brain ischemia. High interstitial levels of lactate and the increased lactate/pyruvate ratio in the brain also indicate brain ischemia.

These data show that cerebral air embolism has a severe deleterious effect on intracranial pressure and brain metabolism. Therefore, this model may be suitable to test therapeutic regimens with the aim to develop an appropriate therapy for cerebral air embolism for use in the clinical setting.

Chapter 6. *Hyperventilation impairs brain function in acute cerebral air embolism in pigs*

The acute therapy for cerebral air embolism consists of administration of 100% oxygen in combination with hyperventilation. The rationale for this is twofold: first, to promote the “off-gassing” of bubbles and to improve oxygenation in occluded brain tissue and, secondly, to induce a reduction in intracranial pressure and maintain cerebral perfusion pressure at the required level. However, it is unclear whether this treatment leads to functional improvement of brain parameters. Therefore, this study investigated the effect of ventilation-induced hyperventilation with 100% oxygen in the model of cerebral air embolism described in

Chapter 5. This therapy is commonly applied in the clinical environment when an arterial embolism occurs.

The data show that hyperventilation does not improve cerebral function in air embolized animals compared with the control animals that were normoventilated with 40% oxygen. These results in animals indicate that there is no rationale to treat patients suffering from cerebral air embolism with this combined therapy of hyperventilation and hyperoxygenation.

Chapter 7. Effects of hyperbaric treatment in cerebral air embolism on intracranial pressure, brain oxygenation and glucose metabolism in the pig

In this study we applied hyperbaric oxygen treatment in our model of cerebral air embolism (described in Chapter 5) in order to evaluate the effects on brain functional parameters characterised by intracranial pressure, brain oxygenation, and brain glucose/lactate metabolism. Two groups of animals were treated with hyperbaric oxygen therapy, either 3 minutes after embolization (immediate treatment group) or 60 minutes after embolization. The rationale for the 60-minute delay before initiating hyperbaric treatment was based on the fact that in the clinical situation a delay of one hour – or often even longer - is the more realistic scenario.

In this study we added conventional EEG monitoring to further characterize the model. The reason for this is that EEG monitoring is a non-invasive technique that is easy to apply in a clinical situation. This is in contrast to the other brain functional parameters that were measured by placing sensors in brain tissue, which is a method more suited to the experimental setting.

The results of this study demonstrate that hyperbaric oxygen therapy within 3 minutes of embolization leads to a greater reduction in intracranial pressure than treatment after 60 minutes. Moreover, compared with the untreated animals in our previous study using the same model of cerebral air embolism (Chapter 5), both groups had a significantly lower intracranial pressure throughout the study period. In the current study there were no differences in brain oxygenation either before embolization or before hyperbaric treatment. This may explain, in part, why there were no “pathological scores” on the EEG at the end of the study. The brain oxygenation values at the end of the experiments (not different from baseline values before embolization) suggest that hyperbaric treatment was able to prevent the very damaging effects associated with cerebral air embolism - at least in the model used in this study. The effectiveness of hyperbaric oxygen therapy is also confirmed by the EEG results obtained in

this study. When translated to the clinical setting, this means that hyperbaric oxygen can be applied to treat cerebral air embolism even after a delay of one hour.

Chapter 8. *Quantitative EEG monitoring during cerebral air embolism and hyperbaric oxygen treatment in a pig model*

Having studied the effects of normobaric and hyperbaric oxygen on cerebral air embolism we then extended the model by investigating the contribution of quantitative EEG (qEEG) monitoring. The rationale for applying this technique was that qEEG provides a more direct measure of global changes in brain function.

Using the same model of cerebral air embolism, in this study qEEG monitoring showed the immediate changes resulting from embolization. Moreover, the response to treatment over time could be reliably followed, qEEG was superior to the other measured variables in following the fast deterioration in brain function and, finally, brain function - as represented by the qEEG - can be objectively assessed after completion of hyperbaric oxygen therapy. The results of this experiment showed that qEEG monitoring offers significant additional value in the assessment of the effects of hyperbaric oxygen treatment initiated after 3 minutes and after 60 minutes in our model of cerebral air embolism in pigs.

In conclusion, the studies described in this thesis contribute to the general knowledge on the use of hypoventilation and hyperventilation in non-brain-traumatized animals and offer more insight into the mechanisms involved in and therapy of cerebral air embolism. Both hypoventilation and hyperventilation are commonly applied ventilatory modes in which the limits of arterial carbon dioxide are still under discussion. During hypoventilation we found no deleterious effects on glucose metabolism and an increase in brain oxygen tension, whereas the application of hyperventilation resulted in anaerobic metabolism. The results also show that, in our model of cerebral air embolism, hyperventilation has no additional value as a treatment modality. Furthermore, hyperbaric treatment resulted in a significant increase in brain oxygen tension and improved the outcome of functional brain parameters in cerebral air embolism.

More studies are needed, on the one hand to further elucidate the role of hypoventilation on brain oxygenation and, on the other, to explore the consequences of longer delays before hyperbaric treatment is initiated in case of cerebral air embolism.

Samenvatting en conclusies

In **Hoofdstuk 1** wordt een overzicht gegeven over gasembolieën. Gasembolieën worden gedefiniëerd als het op een onnatuurlijke wijze binnentreden van gas in de bloedbaan en kunnen tijdens diverse klinische omstandigheden optreden als iatrogene complicatie. In de meeste gevallen betreft het “lucht”embolieën, echter er kunnen zich situaties voordoen waarbij andere gassen zoals kooldioxide of helium een rol spelen. Luchtbellen kunnen via de bloedbaan in allerlei organen terechtkomen, maar met name de hersenen en het hart zijn kwetsbaar omdat deze organen het meest gevoelig zijn voor hypoxie. Uitgebreide dierstudies hebben aangetoond dat het longvaatbed een goede filter is voor gasbelletjes die vanuit de veneuze circulatie worden aangevoerd en op deze manier voorkomt dat de bellen in de arteriële circulatie terechtkomen. In de klinische situatie treden de meeste veneuze luchtbellen op bij patiënten met een veneuze lijn. De grootste kans op het ontstaan van arteriële luchtembolieën is tijdens operaties zoals open-hart chirurgie en neurochirurgische ingrepen bij patiënten in een zittende operatie houding. In het artikel worden de cardiale en neurologische symptomen beschreven die kunnen optreden in de acute klinische situatie. We benadrukken dat het belangrijk is dat klinici zich bewust moeten zijn van luchtembolieën als complicatie bij een ingreep en dat moderne technieken als trans-oesofageale en trans-thoracale echografie gebruikt moeten worden voor de detectie van intravasale bellen. De medicamenteuze therapie en het gebruik van fluorocarbonen is beschreven. De toepassing van hyperbare zuurstoftherapie wordt tenslotte geadviseerd bij alle patiënten die neurologische klachten hebben en verdacht worden van een cerebrale luchtembolie. Ofschoon gerandomiseerde prospectieve studies ontbreken zijn er voldoende case reports en een beperkt aantal retrospectieve onderzoeken die aantonen dat de mortaliteit en morbiditeit verbeteren bij patiënten die met hyperbare zuurstof behandeld zijn.

Patiënten met ARDS worden vaak beademd met een strategie die als doel heeft verdere longbeschadiging ten gevolge van beademing te beperken, met als nadeel dat dit kan leiden tot hypoventilatie. Deze zogenaamde “permissive hypercapnia” is een geaccepteerde beademingsstrategie, waarbij echter over de maximale arteriële kooldioxide-spanning geen consensus bestaat. Hypercapnie leidt tot vasodilatatie in de hersenen met een toename van de

intracranieële druk, wat schadelijk kan zijn voor de patient. Aan de andere kant kan hyperventilatie leiden tot vasoconstrictie in de hersenen en leiden tot ischemie.

In **Hoofdstuk 2** worden de effecten van hyper- en hypoventilatie op de hersenen bestudeerd door middel van metingen van de intracranieële druk en elektroden die zuurstof, kooldioxide en pH in de hersenen meten. De beademingsstrategie is het "Open long" concept met een constante mean airway pressure (MAwP). Dit laatste is belangrijk omdat verschillen in MAwP kunnen leiden tot veranderingen in longvaatbed en veneuze return, met consequenties voor de centraal veneuze en intracranieële druk. Hypoventilatie resulteerde in een stijging van de intracranieële druk en brein zuurstof waarden, terwijl hyperventilatie een daling liet zien van de breinoxygenatie en cerebrale perfusie druk.

De volgende stap was om te onderzoeken of hyper- en hypoventilatie effect hadden op de brein stofwisseling van glucose en lactaat. De meeste studies over breinoxygenatie en glucose stofwisseling zijn uitgevoerd bij hersentrauma's en hebben slechts beperkte waarde bij het bestuderen van de effecten van beademing op de hersenen. In **Hoofdstuk 3** wordt brein glucose en lactaat gemeten door middel van microdialyse tijdens verschillende stappen van hypo- en hyperventilatie met een constante MAwP. In deze studie wordt stapsgewijs geventileerd vanaf normoventilatie naar twee niveaus van hypoventilatie en twee van hyperventilatie. Tijdens maximale hypoventilatie werden geen veranderingen gevonden in brein glucose en lactaat en dezelfde veranderingen als beschreven in Hoofdstuk 2 voor brein zuurstof, kooldioxide, pH en intracranieële druk. Daarentegen trad er een significante daling op van brein glucose en een stijging van het brein lactaat bij maximale hyperventilatie, wijzend op een anaeroob metabolisme.

Vervolgens hebben we, op basis van dit model, brein zuurstof gemeten onder hyperbare omstandigheden op dieptes (drukken) die veel worden gebruikt in klinische omstandigheden. In de neurologie is namelijk een toenemende interesse in de toepassing van hyperbare zuurstoftherapie bij ischemische aandoeningen. Het gebruik van 100% zuurstof tot drukken van 3 bar kan leiden tot zuurstofwaarden in het arterieële bloed en de weefsels die een veelvoud zijn van de waarden die onder normale atmosferische omstandigheden verkregen worden. In de hersenen geeft hyperbare zuurstof een vasoconstrictie die kan leiden tot een daling van een verhoogde intracranieële druk. Anderzijds heeft hyperbare zuurstof ook toxische effecten, zoals een toename van zuurstofradicalen en het optreden van convulsies. Bij de indicatiestelling van hyperbare zuurstof dient daarom een goede afweging gemaakt te worden van de potentiële therapeutische effecten en bijwerkingen. In **Hoofdstuk 4** meten we de maximale waarden van zuurstof in de hersenen op twee dieptes (9 mt/1.9 bar en 18 mt/2.8

bar) die vaak gebruikt worden bij hyperbare zuurstoftherapie. Op een diepte van 18 meter (druk 2.8 bar) wordt een toename met een factor 9 van de zuurstofspanning in de hersenen gemeten. De tegelijkertijd gemeten waarden van glucose en lactaat in de hersenen en de intracranieële druk blijven constant. We concluderen dat de toepassing van hyperbare zuurstoftherapie bij ischemische aandoeningen fysiologisch zinvol kan zijn, maar dat de praktische problemen verdere studies noodzakelijk maken, alvorens een definitief oordeel gegeven kan worden.

In de voorgaande studies hebben we de effecten onderzocht van beademingsstrategieën en hyperbare zuurstof op het metabolisme van gezonde hersenen. Aansluitend hebben we een model van cerebrale luchtembolieën ontwikkeld en gevalideerd, waarna de eerder onderzochte beademingsstrategieën en hyperbare zuurstof hierop zijn toegepast als therapie.

In **Hoofdstuk 5** wordt het diernodel beschreven van een cerebrale arteriële luchtembolie. Op een gestandaardiseerde wijze wordt lucht ingespoten in de arteria carotis interna; de intracranieële druk, brein zuurstof, kooldioxide, pH en de glucose stofwisseling (door middel van microdialyse) zijn de parameters die gebruikt worden om het pathofysiologisch mechanisme te beschrijven tijdens een meetperiode van 2 uur.

Na een initiële daling van de brein zuurstof en glucose trad een gedeeltelijk herstel op gedurende de meetperiode, wat verklaarbaar is door het deels oplossen en uitwassen van de bellen in de hersencirculatie. Er trad een viervoudige toename van de intracranieële druk op en er was een forse daling van de cerebrale perfusie druk tot een waarde, die leidt tot hersenischemie. Hoge lactaat waarden en een stijging van de lactaat/pyruvaat ratio bevestigen de hypoxische/ischemische condities van het brein in dit model.

Op basis van deze bevindingen concluderen we dat cerebrale luchtembolieën ernstige schade geven aan de hersenen en dat het model geschikt is voor het testen van medicamenteuze en therapeutische interventies.

Hoofdstuk 6. De acute therapie voor cerebrale luchtembolieën bestaat uit hyperventilatie met 100% zuurstof, zoals wordt gepropageerd in de handboeken voor "intensive care". De ratio is tweeledig, te weten enerzijds versnelt de oxygenatie het uitwassen van de luchtbellen en verhoogt het de zuurstofconcentratie in hypoxisch weefsel, anderzijds kan hyperventilatie een toegenomen intracranieële druk doen afnemen. Op basis van het model van cerebrale luchtembolieën zoals is beschreven in Hoofdstuk 5, is hyperventilatie met 100% zuurstof als gecombineerde therapie bestudeerd tijdens een meetperiode van 2 uur.

De resultaten toonden aan dat er geen verbeteringen waren van de gemeten brein parameters zoals intracranieële druk, brein zuurstof en glucose metabolisme. Op basis van deze

bevindingen concluderen wij dat er geen redenen zijn om deze therapie van hyperventilatie met 100% zuurstof bij patiënten met een cerebrale luchtembolie toe te passen.

Een andere voor de hand liggende therapie is hyperbare behandeling.

In **Hoofdstuk 7** onderzoeken we de effecten van hyperbare zuurstoftherapie op het model, zoals is beschreven in Hoofdstuk 5, toegepast direct (3 minuten) na het toedienen van de luchtembolie en na een tijdsperiode van 60 minuten. Een directe behandeling betreft meer de situatie bij het duiken waar veelal een recompressiekamer aanwezig is op de duiklocatie, terwijl het in een klinische situatie realistischer is dat een patiënt na een cerebrale luchtembolie met een vertraging van één tot enkele uren pas behandeld kan worden met hyperbare zuurstoftherapie. In deze studie is EEG toegevoegd om het model verder te verfijnen, daar het EEG een directe en snellere detectie geeft van hersenischemie en omdat het een niet-invasieve meting betreft die ook eenvoudig kan worden toegepast in de klinische situatie. De resultaten tonen aan dat hyperbare zuurstoftherapie toegepast na drie minuten leidt tot een significant betere waarde van de intracraniale druk ten opzichte van de groep die na 60 minuten wordt behandeld. Echter, beide groepen laten ook zien dat de waarden van de intracraniale druk, na 5 uur hyperbare behandeling, significant lager zijn dan het natuurlijk verloop (stijging van de intracraniale druk met een factor 4) zoals is beschreven in Hoofdstuk 4. De zuurstofwaarden in de hersenen en de EEG's vertonen normale waarden aan het eind van de behandeling. De brein glucose en lactaat laten wel afwijkende waarden zien. We concluderen hieruit dat hyperbare zuurstoftherapie na een cerebrale luchtembolie zinvol is om de cerebrale schade te beperken, gezien de waarden van de intracraniale druk, brein zuurstof en de EEG scores. Het is van belang om bij volgende studies te onderzoeken wat het verloop is van de gemeten parameters na de hyperbare therapie, gezien enerzijds de goede resultaten en anderzijds de afwijkende waarden van brein glucose en lactaat. Tenslotte concluderen we op basis van onze bevindingen, dat het behandelen van patiënten met een cerebrale luchtembolie met hyperbare zuurstof, ook met een uitstel van 1 uur of langer na het incident, nog zinvol is.

In de studie beschreven in **Hoofdstuk 8** worden de EEG's uit een eerdere studie nader bekeken. In Hoofdstuk 7 werden de EEG's visueel gescoord terwijl nu een kwantitatieve analyse (qEEG) wordt uitgevoerd. We tonen aan dat qEEG in staat is de impact van de toediening van de lucht te meten en kwantificeren gedurende de eerste 10 minuten na de toediening van de lucht. Tijdens de hyperbare behandeling waren door middel van qEEG de ischemische veranderingen snel en on-line te meten en tenslotte kon worden aangetoond dat de qEEG's van sommige dieren niet volledig hersteld waren na de hyperbare behandeling. De

resultaten van deze studie tonen aan dat qEEG analyse een substantiële bijdrage levert aan de evaluatie van de hersenschade door een luchtembolie na een hyperbare behandeling.

Samengevat dragen de studies bij aan de kennis over de toepassing van hypo- en hyperventilatie op de hersenen in proefdieren zonder cerebrale beschadiging. Zowel hypo- als hyperventilatie zijn veel toegepaste applicaties bij verschillende aandoeningen. We tonen aan dat hypoventilatie geen nadelige effecten heeft op de glucose stofwisseling en leidt tot een toename van de zuurstof in de hersenen, terwijl hyperventilatie resulteert in een anaeroob metabolisme in het brein.

De resultaten van de studies geven meer inzicht in de therapie en pathofysiologie bij cerebrale luchtembolieën, laten zien dat cerebrale luchtembolieën een forse impact hebben op het brein en dat hyperbare zuurstoftherapie een gunstig effect heeft op de intracranieële druk en andere brein parameters. Daarnaast tonen we eveneens aan dat hyperventilatie met een hoge inspiratoire zuurstofwaarde geen effect heeft op de gemeten parameters.

Tenslotte pleiten we voor meer studies naar het effect van hypoventilatie op de hersenen en het therapeutisch effect van hyperbare zuurstofbehandelingen op cerebrale luchtembolieën na langere tijd.

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Prof. dr. H. Örnhagen. Dear Hans, we have had a very good collaboration on diving and submarine medicine since 1990, which has been of benefit to both the Swedish and Dutch Navy. It is an honour for me that you, as one of the founders of the European Undersea and Baromedical Society, will be a member of the scientific committee.

Prof. dr. S. Grond. Thank you very much for participating in the scientific committee. Your expertise in hyperbaric medicine will lead to fruitful discussions.

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Curriculum vitae

Robert André van Hulst was born on 3rd September 1957 in Culemborg, The Netherlands. He finished High School in Leeuwarden in 1976. After one year of study in Chemistry at the University of Groningen, he started medical studies in 1977 and graduated as a physician in January 1985. He joined the Navy in May 1985.

- 1985 Surgeon lieutenant in the Royal Netherlands Navy
- 1986 Ship's physician on board HMS Tydeman, Royal Naval Oceanographic Ship
- 1987-89 Training diving and submarine medical officer
- 1990 Diving medical officer Special Amphibious Forces, Royal Marines
- 1990 Head Diving Medical Centre, Den Helder
- 1992 Naval Staff School; management training. Promotion: surgeon commander
- 1993 Commanding Officer Field Dressing Station, Senior Medical Officer, Royal Netherlands Marines. UNTAC Cambodia
- 1994-98 Degree in Occupational Medicine
- 1998 PhD research (part-time) on cerebral air embolism and oxygenation, Department of Experimental Anesthesiology, Erasmus MC Rotterdam (Prof. Dr. B. Lachmann)
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Medical representative for the Royal Netherlands Navy on diving and submarine medicine in NATO workgroups

Medical representative for the Netherlands government in the European Diving Technology Committee (EDTC) and Diving Medical Advisory Committee (DMAC)

Consultant Medical Committee, Dutch Sportsdiving Association (NOB)

International sports diving-instructor CMAS 2 stars

List of abbreviations

ATP	adenosine triphosphate
brpH	brain pH
CAE	cerebral air embolism
CBF	cerebral blood flow
CBV	cerebral blood volume
CSF	cerebrospinal fluid
CPP	cerebral perfusion pressure
DAP	diastolic arterial pressure
FiO ₂	fraction of inspired oxygen
HBO	hyperbaric oxygen
ICP	intracranial pressure
I/E	inspiratory/expiratory ratio
MAP	mean arterial pressure
MAwP	mean airway pressure
PaO ₂	arterial oxygen pressure
PaCO ₂	arterial carbon dioxide pressure
PbrO ₂	brain oxygen pressure
PbrCO ₂	brain carbon dioxide pressure
PEEP	positive end-expiratory pressure
SAP	systolic arterial pressure
VAE	venous air embolism

Stellingen behorende bij het proefschrift:

Cerebral air embolism and brain metabolism

R.A. van Hulst, september 2003

1. Hyperventilatie met een hoge inspiratoire zuurstof concentratie bij cerebrale luchtembolieën heeft geen therapeutische waarde (dit proefschrift)
2. De praktische nadelen verhinderen de toepassing van hyperbare zuurstof bij ischemische hersenaandoeningen ondanks de vele theoretische en fysiologische voordelen (dit proefschrift)
3. Hyperbare zuurstof is de enige behandeling die aantoonbaar de door cerebrale luchtembolieën veroorzaakte schade beperkt (dit proefschrift)
4. Intracranieële druk is een goede maat voor de effectiviteit van de behandeling van cerebrale luchtembolieën, met name gedurende hyperbare therapie (dit proefschrift)
5. Kwantitatieve EEG analyse (qEEG) dient te worden toegepast bij elke patiënt die verdacht wordt van cerebrale luchtembolieën (dit proefschrift)
6. Duiken kan een beroep, hobby of medisch experiment zijn.
7. Ook een atheïst kan leven als een god in Frankrijk.
8. In tegenstelling tot wat men vaak denkt is de gemiddelde hartfrequentie bijna 1: op enkele hartclozen na heeft iedereen EEN hart (H.A.M. Daanen)
9. Duikgeneeskunde is iets anders dan geneeskunde bij duikers en moet worden uitgeoefend door specialisten.
10. De technologische ontwikkelingen in de geneeskunde staan haaks op het expeditionair karakter van de militaire geneeskunde en komt de operationale inzetbaarheid niet ten goede.
11. Gezien de bereikbaarheid van Den Helder als gevolg van de infrastructuur in Noord-Holland dient overwogen te worden de Marinehaven te verplaatsen naar Rotterdam.