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EXPERIMENTAL

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Intracranial pressure, brain PCO_2, PO_2, 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-traumatized 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 and setting:* Prospective animal study in a 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 of 1.0. Starting at normoventilation, a stepwise hypo- and hyperventilation was performed to $PaCO_2$ values of 90.4±10.4 and 26.9±4.1 mmHg, respectively. The ICP and brain parenchyma values [carbon dioxide ($PbrCO_2$), oxygen ($PbrO_2$), and pH (brpH)] measured by multiparameter sensors were recorded continuously during these maneuvres. *Results:* During hypoventilation there was a significant increase in $PbrCO_2$ tension, $PbrO_2$ tension, and ICP. During hyperventilation there was a significant decrease in $PbrCO_2$ tension and ICP while the change in $PbrO_2$ was not significant. MAwP was 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-traumatized 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 must maintain sufficient arterial blood pressure. Hypercapnia resulted in a significant increase in brain oxygenation; however, this does not necessarily mean that permissive hypercapnia is neuroprotective.

Keywords Permissive hypercapnia · Hyperventilation · Intracranial pressure · Open lung concept · Brain oxygen · animal model

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 various interrelated effects on the brain which are not all beneficial. First, hypercapnia augments cerebral blood flow. Due to the increase in blood volume in the brain secondary to vasodilation intracranial pressure (ICP) rises [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 fivefold increase in hydrogen ion concentration in plasma results in a twofold 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.

No data are 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 can change MAwP, with consequent changes in pulmonary and systemic circulation. This study investigated 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

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). Anesthesia was induced by 0.1 ml/kg ketamine intramuscularly (Ketalin 100 mg/ml, Apharmo, Arnhem, The Netherlands) and 0.1 mg/kg midazolam intramuscularly (Dormicum 5.0 mg/ml, Roche Ned., Mijdrecht, The Netherlands). Muscle relaxation was induced by 0.2 mg/kg pancuronium bromide intravenously (Pavulon, Organon Teknika, Boxtel, The Netherlands). Following intubation the animals were connected to a ventilator (Servo Ventilator 300, Siemens-Elema, Sweden). To ensure maximum PaO_2 the animals were ventilated in a pressure-controlled (PC) mode according to the open lung concept [8] with a positive end-expiratory pressure (PEEP) level of 6 cmH_2O, peak pressure of 15/16±2/3 cmH_2O, an I/E ratio of 1:2 and an inspired oxygen concentration (FIO_2) of 1.0. The driving pressure of 10 cmH_2O resulted in a tidal volume of approximately 10 ml/kg; frequency was set to maintain normocapnia ($PaCO_2$: 35–40 mmHg).

Anesthesia was maintained with 10 mg/kg ketamine intravenously and 1 mg/kg midazolam per hour, and muscle relaxation with pancuronium bromide 0.2 mg/kg intravenously per hour. 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 PaO_2, $PaCO_2$, 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, Calif., USA) and recorded (Siemens Sirecust 404-1, Danvers, Mass., 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 two optical fibers for measurements of $PbrCO_2$ and brpH, a miniaturized Clark electrode for $PbrO_2$ 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-min stabilization 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 ($PbrCO_2$, $PbrO_2$, brpH). The pigs were initially ventilated to maintain an end-tidal $PaCO_2$ of 35–40 mmHg based on the values of the arterial transducer. After a stable period of at least 10 min (change in $PaCO_2 \leq 2$ mmHg) small stepwise changes in the ventilatory frequency were made using the online blood gas monitoring to increase $PaCO_2$ during hypercapnia by about 10 mmHg at each step, or to decrease the $PaCO_2$ during hypocapnia by about 5 mmHg at each step. Each $PaCO_2$ level lasted for about 15 min. 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. From normocapnia there were three steps to hyperventilation and five steps to hypoventilation in each animal; at each step we measured $PaCO_2$ values and the corresponding values of $PbrCO_2$, $PbrO_2$, 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 overdose of intravenous pentobarbital (Euthesate 200 mg/ml, Apharmo).

Data were analyzed statistically using the Instat 2.0 biostatistics package (GraphPad Software, San Diego, Calif., USA). Data during normoventilation, hypoventilation, and hyperventilation are presented as mean ±standard deviation. Differences in normoventilation values and maximum achieved hypoventilation/hyperventilation values were compared by means of a paired *t* test. Statistical significance was accepted at a *p* value less than 0.05. The relationship between $PaCO_2$, $PbrCO_2$, and ICP is presented in a linear regression with the correlation coefficient.

Results

All animals survived the study period. MAwP values were kept stable during the ventilatory maneuvers, and this (together with the anesthesia procedures) resulted in stable cardiocirculatory conditions. The results of 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 $PbrCO_2$, brpH, and ICP. $PbrCO_2$ increased by 69% and ICP increased by 38%; there was a nonsignificant 11% decrease in CPP. During hyperventilation there was a significant decrease in $PbrCO_2$ and ICP. $PbrCO_2$ decreased by 34% and ICP decreased by 27%. There was a slight 3.4% increase in CPP, which was not statistically significant.

Figure 1 shows $PbrCO_2$ plotted in relation to $PaCO_2$. The regression line fits the equation $y=0.97x+28.2$, with

Table 1 Data on blood and brain parameters in normoventilation, hypoventilation and hyperventilation (n=8)

	Normoventilation	Hypoventilation	Hyperventilation
Blood gases			
PaO_2 (mmHg)	568±15	487±27.6*	608±51
$PaCO_2$ (mmHg)	42.8±4.6	90.4±10.4*	26.9±4.1*
pH	7.39±0.08	7.13±0.10*	7.55±0.05*
Brain			
$PbrCO_2$ (mmHg)	68.9±11.4	116.1±21.3*	45.7±11.8*
brpH	7.04±0.13	6.81±0.18*	7.11±0.12
Intracranial pressure (mmHg)	22±4	30.3±5.9*	16±2.4*
Cerebral perfusion pressure (mmHg)	73.8±14.7	65.5±17.4	76.3±16.6
Brain temperature (°C)	37.8±0.4	38.1±0.6	38.1±0.4
Rectal temperature (°C)	37.6±0.6	37.8±0.2	37.9±0.7
Mean arterial pressure (mmHg)	95±13	94±16	94 ± 9
Mean airway pressure (cmH_2O)	9.2 ±1.8	8.9±1.9	9.2±2

*p<0.05: vs. normoventilation

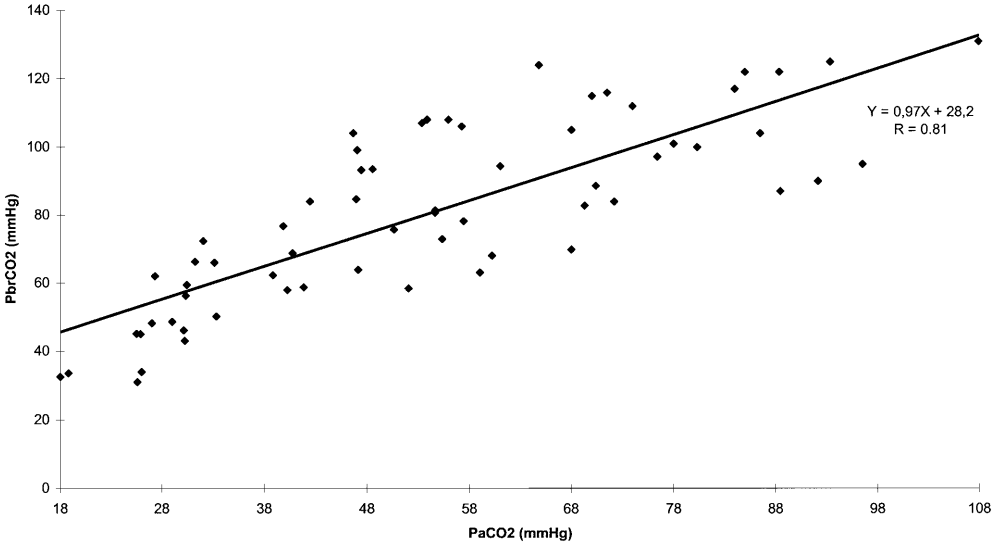

Fig. 1 Effect of $PaCO_2$ on the $PbrCO_2$ during hypo- and hyperventilation in non-brain-traumatized pigs during ventilation at constant mean airway pressure. A linear relationship was observed between $PaCO_2$ and PbrCO2

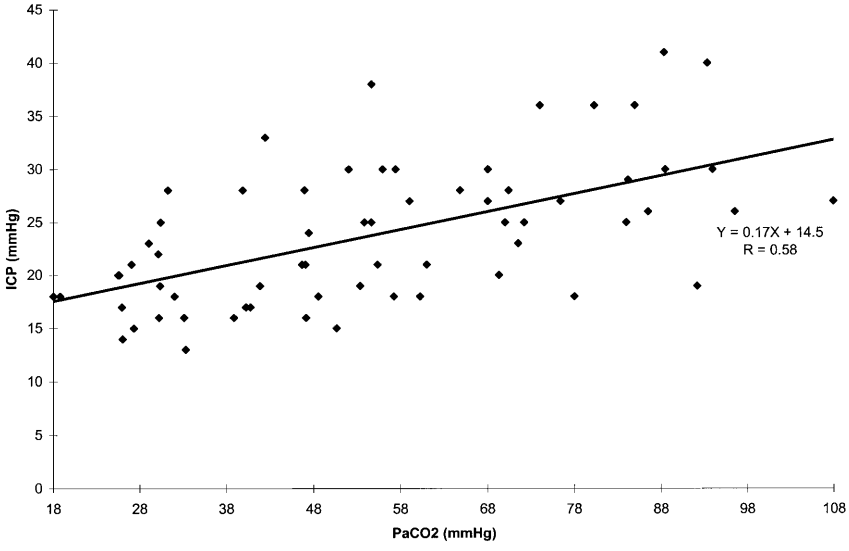

Fig. 2 Effect of $PaCO_2$ on the ICP during hypo- and hyperventilation in non-brain-traumatized pigs during ventilation at constant mean airway pressure. A linear relationship was observed between $PaCO_2$ and ICP

Table 2 Data on blood and brain oxygenation during normoventilation, hypoventilation and hyperventilation (n=6) (Δ proportional differences from normoventilation)

*p<0.05: vs. normoventilation

	Normoventilation	Hypoventilation	Hyperventilation
$PaCO_2$ (mmHg)	39.3±1.4	94.1±8.2	23.9±3.4
PaO_2 (mmHg)	537±28.6	460±38.5*	554±57.4
ΔPaO_2 (%)	0	–14±8	3±10
$PbrO_2$ (mmHg)	78±40.3	144±48.1*	72±41.1
$\Delta PbrO_2$ (%)	0	84±45	–8±5

a correlation coefficient of 0.81. Figure 2 shows the relationship between ICP and $PaCO_2$. The regression equation is y=0.17x+14.5, with a correlation coefficient of 0.58. Table 2 presents the $PbrO_2$ values in relation to 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 to technical failure) while $PbrCO_2$ and brpH were appropriate for the conditions. For analysis therefore $PbrO_2$ values from only six of the eight animals were used. During hypoventilation there was a significant 84% increase in $PbrO_2$, while during hyperventilation there was a nonsignificant 8% decrease in $PbrO_2$.

Discussion

The technique used in the present study to measure brain tissue values with the multiparameter sensor has previously been described extensively in various studies [10, 11, 12]. The baseline intracerebral data for brain parenchyma of $PbrCO_2$, brpH, and ICP in normoventilated pigs in our study were comparable with data from other studies in cats, dogs, and piglets which measured $PbrCO_2$ and brain pH using the same multiparameter sensor [11, 12, 13].

It is known that an increase in MAwP results in overdistention 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 $PaCO_2$ values. In hyperventilation the ventilator frequency was adjusted with small steps to prevent changes in MAwP. The rationale for this is that an intrinsic PEEP is created if one either increases the I/E ratio at constant frequency or increases the frequency at constant I/E ratio to establish expiratory time which is too short to empty the lung to ambient pressure [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 $PaCO_2$ 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 FIO_2 of 1.0 to prevent brain hypoxemia in the severe hypercapnic situation with accompanying metabolic changes. For this reason higher baseline values for $PbrO_2$ were recorded in our animals (78±40.3 mmHg). In two earlier studies in dogs the use of FIO_2 values of 0.25 and 0.21 resulted in $PbrO_2$ values of 28±8 mmHg and 27±7 mmHg, respectively [11, 15]. Data from experiments in pigs ventilated with 40% oxygen resulted in $PbrO_2$ values of 29.4±13.3 mmHg [12]. Assuming that an increase in 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 those of previous studies. Recently Menzel et al. [16] reported $PbrO_2$ values in humans of 82.7± 44.1 mmHg at 100% FIO_2, 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 distributed heterogeneously 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 standard deviation of 40.3 mmHg for $PbrO_2$. Therefore we present these data both as absolute values and the proportional difference. In our study hypercapnia resulted in a significant increase in $PbrO_2$ but significant decrease in PaO_2. 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 decreased [19], or oxygen delivery increased to the hypercapnic brain, Laffey et al. [20] have even suggested that hypercapnic acidosis exerts brain protection. Acute hypercapnia, at least to a $PaCO_2$ level of 80–100 mmHg, appears to have no harmful effects provided that oxygenation is preserved [2, 21].

It is known that hypercapnia increases ICP. The main mechanism by which hypercapnia affects ICP is

by the increase in cerebral blood volume secondary to diminished vascular tone during maintained or raised vascular pressure [6, 21]. In the absence of preexisting 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 by 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 mmHg does not necessarily lead to cerebral ischemia. The small decrease in CPP (65.5±17.4 mmHg) suggests that the cerebral circulation is still adequate under these conditions. In normal humans the CPP ranges from 70 to100 mmHg. Clinical experience has demonstrated the safety of CPP in the range 50–60 mmHg undergoing induced hypotension under general anesthesia; in laboratory conditions ischemia is not seen until CPP falls below 40 mmHg [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 nonphysiological levels of lactate. In our study $PaCO_2$ increased 111% during hypoventilation, arterial pH decreased from 7.39 to 7.13, $PbrCO_2$ increased 68%, and brain pH decreased from 7.04 to 6.81. In the present study $PbrCO_2$ and ICP values decreased significantly during hyperventilation while brain pH and CPP increased only slightly. It is known that hypocapnia can lead to vasoconstriction and thus reduce 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 $PbrO_2$ and CPP during hypocapnia up to a $PaCO_2$ of 26.9± 4 mmHg in our study suggest that there was still adequate oxygen delivery and perfusion of the brain. We found a correlation between $PaCO_2$, $PbrCO_2$, and ICP which reflects the acute situation of hypercapnia in healthy brain. During prolonged hypercapnia with continued elevated $PaCO_2$ 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 h [6, 25].

In conclusion, controlled hypoventilation with constant MAwP, as used in healthy non-brain-traumatized pigs, severely affects the brain CO_2 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 in brain oxygenation. However, this does not permit the conclusion 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 and brain tissue microdialysis.

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References

1. Houmes RJM, Bos JAH, Lachmann B (1994) Effect of different ventilator settings on lung mechanism: with special reference to the surfactant system. Appl Cardiopulm Pathophysiol 5:63–72
2. Dries DJ (1995) Permissive hypercapnia, clinical management update. J Trauma 39:5:984–989
3. Hickling KG, Joyce C (1995) Permissive hypercapnia in ARDS and its effect on tissue oxygenation. Acta Anaesthesiol Scand 39 [Suppl 107]:201–208
4. Feihl F, Perret C (1994) Permissive hypercapnia, how permissive should we be? Am J Respir Crit Care Med 150:1722–1737
5. Ohmura A, Sha M, Katagiri J (1995) How far can we go with permissive hypercapnia? A case presentation and some biased comments with emphasis on maintaining normal haemoglobin level. Acta Anaesthesiol Scand 39 [Suppl 107]:209–213
6. Ropper AH, Rockoff MA (1993) Physiology and clinical aspects of raised intracranial pressure. In: Ropper AH (ed) Neurological and neurosurgical intensive care, 3rd edn. Raven, New York, pp 11–27
7. Siesjo BK, Folbergrova J, MacMillan V (1992) The effect of hypercapnia upon intracellular pH in the brain, evaluated by the bicarbonate-carbonic acid method and from the creatine phosphokinase equilibrium. J Neurochem 9:2483–2495
8. Lachmann B (1992) Open up the lung and keep the lung open. Intensive Care Med 18:319–321
9. Ventakatesh B, Clutton Brock TH, Hendry SP (1994) A multiparameter sensor for continuous intra arterial blood gas monitoring: a prospective evaluation. Crit Care Med 22:588–594
10. Zauner A, Doppenberg E, Soukup J, Menzel M, Young HF, Bullock R (1998) Extended neuromonitoring: new therapeutic opportunities. Neurol Res 20 [Suppl 1]:S85–S90
11. McKinley BA, Morris WP, Parmley L, Butler BD (1996) Brain parenchyma PO_2, PCO_2, and pH during and after hypoxic, ischemic brain insult in dogs. Crit Care Med 24:1858–1868

12. Menzel M, Rieger A, Roth S, Soukop J, Furka I, Miko I, Molnar P, Peuse C, Hennig C, Radke J (1998) Comparison between continuous brain tissue PO_2, PCO_2, pH and temperature and simultaneous cerebrovenous measurement using a multisensor probe in a porcine intracranial pressure model. J Neurotrauma 15:4:265–276
13. Zauner A, Bullock R, Di X, Young HF (1995) Brain oxygen, CO_2, pH and temperature monitoring: evaluation in the feline brain. Neurosurgery 37:1168–1177
14. Lachmann B, Danzmann E, Haendly B, Jonson B (1982) Ventilator settings and gas exchange in respiratory distress syndrome. In: Prakash O (ed) Applied physiology in clinical respiratory care. Nijhoff, The Hague, pp 141–176
15. Maas AIR, Fleckenstein W, de Jong DA (1993) Monitoring cerebral oxygenation: experimental studies and preliminary clinical results of continuous monitoring of cerebrospinal fluid and brain tissue oxygen tension. Acta Neurochir (Wien) 59 [Suppl]:50–57
16. Menzel M, Doppenberg EMR, Zauner A, Soukop J, Reinert MM, Bullock R (1999) Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. J Neurosurg 91:1–10
17. Lenninger-Follert E, Lubbers DW, Wrabetz W (1975) Regulation of local tissue PO_2 of brain cortex at differential arterial O_2 pressures. Pflugers Arch 359:81–95
18. Lubbers DW, Baumgartl H, Zimelka W (1994) Heterogeneity and stability of local PO_2 distribution within the brain tissue. Adv Exp Med Biol 345:567–574
19. Siesjo BK (1980) Cerebral metabolic rate in hypercarbia – a controversy. Anesthesiology 52:461–465
20. Laffey JG, Kavanagh BP (1999) Carbon dioxide and the critically ill – too little of a good thing? Lancet 354:1283–1286
21. Brian JE (1998) Carbon dioxide and the cerebral circulation. Anesthesiology 88:1365–1386
22. Lanier WL, Weglinski MR (1991) Intracranial pressure. In: Cucchiara RF, Michenfelder JD (eds) Clinical neuroanesthesia. Churchill Livingstone, New York, pp 77–110
23. Raichle ME, Stone HL (1972) Cerebral blood flow autoregulation and graded hypercapnia. Eur Neurol 6:1–5
24. Nunn JF (1993) Carbon dioxide. In: Nunn JF (ed) Applied respiratory physiology. Butterworth, London, pp 219–228
25. Hoffmann W, Charbel F, Edelmann G (1995) Brain tissue PO_2, PCO_2 and pH during increases in blood O_2 and CO_2. Anesthesiology 83:A521