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Is hyperventilation during general anesthesia potentially hazardous?

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INTRODUCTION

The normal range of the partial pressure of carbon dioxide ($PaCO_2$) is 36–45 mmHg (4.8 – 6.0 kPa). However, there are various situations, when anesthesiologists accept or clinically tolerate hypocapnia ($PaCO_2$ <36 mmHg) or hypercapnia ($PaCO_2$ >45 mmHg). This mini review aims to summarise the physiological effects, potential harms and consequences of hyperventilation/hypocapnia.

PHYSIOLOGIC BACKGROUND

Carbon dioxide (CO_2) is the end-product of aerobic metabolism. For a normal gas exchange with a balanced CO_2-production and output, an amount of 10-20 breaths per min at rest are needed. The term tachypnea is commonly described by an increased respiratory rate >20/min, which could be induced by exercise, pregnancy, pain, fever, and respiratory failure. In contrast, **hyperventilation is defined an exaggerated output of CO_2.** Increased alveolar ventilation by hyperventilation will lead to a small rise in alveolar partial pressure of oxygen. Due to the sigmoid shape of the oxygen binding curve levels of arterial oxygen content and mixed venous oxygen saturation are nearly unchanged. The slope of the CO_2-binding curve is steeper at hypocapnic conditions when compared to normocapnia, which results in a reduced venous-to-arterial carbon dioxide partial pressure difference. So, in basic conditions hyperventilation reduces the tissue pressure of CO_2 and will lead to respiratory alkalosis. Then the equilibrium of the CO_2/HCO_3^- buffer system ($CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$) is shifted to the left, the content of H^+ ions in the blood is reduced and pH is increased. Subsequent changes in Base Excess are effected by renal mechanisms, which take hours to develop.[1,2]

Peripheral tissue perfusion and oxygenation depend on various factors, including inspired oxygen concentration, arterial oxygen tension, hemoglobin concentration, cardiac output, vasomotor tone, and the autonomic stress response. Different concentrations of blood and tissue CO_2 together with changes in H^+ ion blood concentration are known to alter some of these parameters and may influence tissue perfusion and oxygenation.[3]

Systemic circulation

Under conditions of spontaneous circulation, hyperventilation will increase systemic vascular resistance and mean arterial pressure with a concomitant decrease in cardiac output.[4] Within $PaCO_2$ levels from 30 to 50 mmHg, these changes are small and in most cases clinically of minor relevance.[3]

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Pulmonary circulation

Ventilatory management may markedly affect pulmonary vascular resistance (PVR). Alveolar hypoxia is a potent pulmonary vasoconstrictor and use of high-inspired oxygen concentrations may result in additional pulmonary vasodilation in some patients. Hypercapnia is a potent pulmonary vasoconstrictor, and hypocapnia is a pulmonary vasodilator. The relationship between lung volume and PVR during mechanical ventilation is U-shaped with PVR. At low lung volumes, alveolar hypoxia and hypercapnia cause hypoxic pulmonary vasoconstriction whereas hyperinflation of the lungs per se leads to compression of the intra-alveolar vessels with marked increases in PVR.[5]

Cerebral circulation

Global cerebral blood flow (CBF) averages 50ml/min for each 100g of brain tissue. Due to autoregulation, CBF is kept constant within a wide range of hemodynamic conditions. Nevertheless, regional changes in blood distribution occur in response to changing patterns of neuronal activity. Examining the functional capacity of the cerebrovascular autoregulatory system by altering blood pressure is difficult and possibly hazardous to be performed as a routine clinical procedure. Therefore, Bloor and colleagues introduced CO_2-reactivity measurements to evaluate cerebrovascular reactivity.[1,6]

Changes in $PaCO_2$ (induced by hyper- or hypoventilation) are well known to change global CBF and the flow velocity of the middle cerebral artery (V_{MCA}), which can be explained by an increase or decrease of cerebral vascular resistance (CVR) and partly by cerebral perfusion pressure (CPP). Over a range of $PaCO_2$ values of 20-80 mmHg for each mmHg increase or decrease in $PaCO_2$ there is a 2-4% change in CBF or V_{MCA}.[6] Here, two mechanisms control CBF flow by changing blood vessel diameter and CVR: autoregulation maintains flow in the face of CPP changes, and brain metabolism adjusts flow to meet metabolic requirements.[7]

CPP usually is defined as the difference between MAP and intracranial pressure (ICP). Since the introduction of transcranial Doppler ultrasonography (TCD), a number of methods has been developed to assess the cerebral effective downstream pressure (EDP) by extrapolating instantaneous pressure-flow-velocity plots (ABP/V_{MCA}) to zero - the zero flow pressure (ZFP).[8] Thus, the effective CPP is defined by the difference between MAP and ZFP.

Comparisons between cerebrovascular CO_2-reactivity of CBF and V_{MCA} in humans under general anesthesia are very rare. Recent studies of our group could demonstrate that ZFP varies inversely with changes of $PaCO_2$. The effects of ventilatory changes on the cerebral circulation were substantial. Hyperventilation (30mmHg) exponentially reduced CBF, in total by 60%, and V_{MCA} by 41%, when compared with hypoventilation (50 mmHg). The hypocapnia-induced reduction in CBF under general anesthesia was

caused by both, an increase in CVR and a decrease in CPPe, as a consequence of an increase in ZFP (figure 1).[8,9]

The metabolic consequences of hyperventilation, when compared to hypoventilation, are substantial too. Hyperventilation reduces CBF, tissue CO_2 tension, jugular venous oxygen tension ($PjvO_2$), and thus cerebral oxygen delivery (cDO_2) (figure 2).[9] The CO_2-mediated alteration of brain cellular pH is the initial step leading to changes in vascular tone. The effect of pH on the cerebrovascular tone is mediated by nitric oxide, prostanoids, cyclic nucleotides, potassium channels, and intracellular calcium. Hyperventilation is associated with an increase in net cerebral efflux of lactate, which may be explained by different mechanisms:

- Dissociation of oxygen-bindings curve to the left as a result of the respiratory alkalosis, (Bohr-effect)
- Alkalosis induced change of redox-systems of lactate/pyruvate and NADH/NAD+, and
- Severe cerebral hypoperfusion with tissue hypoxia.

Recent investigations of lactate kinetics and oxygenation using lactate isotopes demonstrate simultaneous lactate uptake and release in the brain. These trials have shown that the glucose taken up by astrocytes is converted to lactate, and that the lactate released from astrocytes may be taken up by neurons and used as energy, especially in activated neurons, referred to as the astrocyte–neuron lactate shuttle hypothesis. Thus, partial metabolic compartmentalization appears to exist between astrocytes and neurons, with astrocytes feeding the neurons with lactate generated from glycolysis upon cerebral activation. A slight lactate efflux at hypocapnia may not necessarily indicate tissue hypoxia. However, the increase in net cerebral lactate efflux associated with hypocapnia and the concomitant decrease in CBF might be suspicious for anaerobic metabolism in relatively ischemic brain regions.[9]

HYPERVENTILATION IN CLINICAL PRACTICE AND OUTCOME

General Anesthesia

Intravenous anesthetics reduce CBF in a dose-dependent way that is coupled to the reduction in metabolism. However, large doses of propofol may cause vasodilation, which may overcome the response to CO_2. Ketamine appears to preserve CBF, but blunts the response to CO_2 Thiopental or midazolam appears to be the best choices of intravenous anesthesia if preservation of cerebrovascular reactivity to CO_2 is needed.

Inhalation anesthetics generally increase CBF in a dose-dependent manner that is uncoupled to the reduction in metabolism. Cerebrovascular autoregulation, including the response to CO_2, is maintained up to 1.0–1.5 MAC. Isoflurane best preserves the
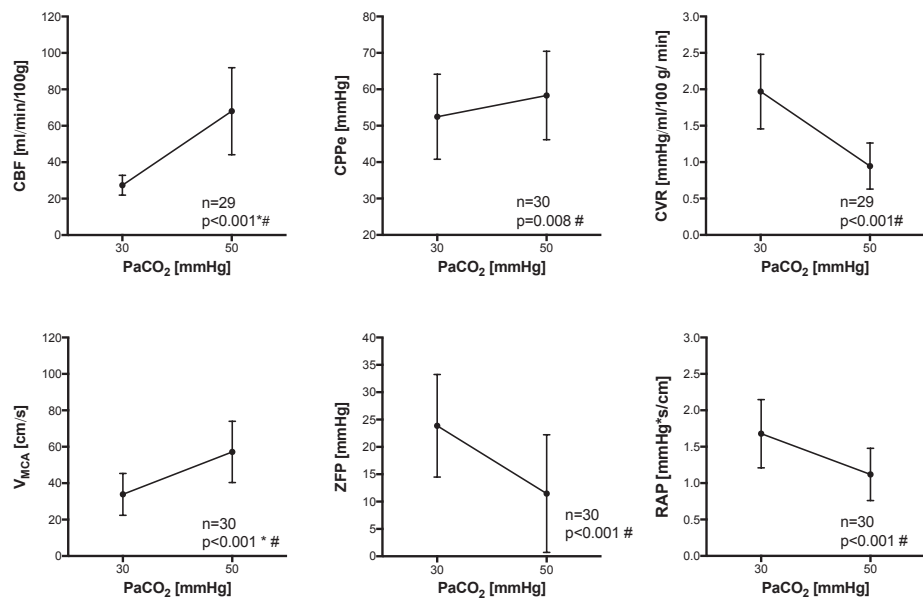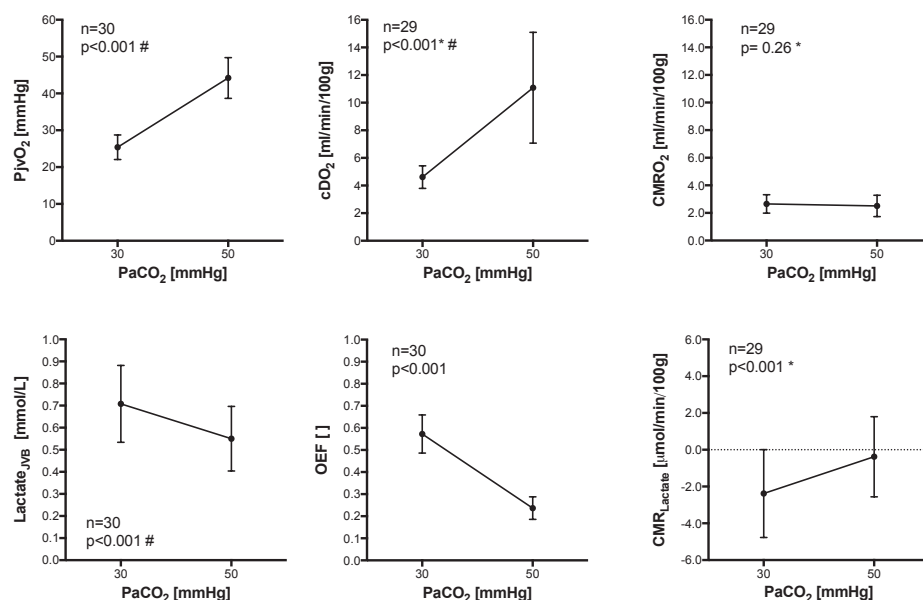
Figure 1

Figure 2

Modified from Grüne et al 2014[9] The P values, which refer to the difference between hyperventilation and hypoventilation, were calculated using two-sided t test for paired data (n=30).

* Statistical analyses of primary endpoints were adjusted by one-way ANOVA for repeated measurements with Bonferoni multiple comparison procedure (n=29).

\# Because the variances of some outcome variables substantially differed between hyperventilation *vs.* hypoventilation, these parameters were additionally examined by Welch test and nonparametric Wilcoxon signed-rank tests, which showed that the differences persist.

CBF = cerebral blood flow; cDO_2 = cerebral oxygen delivery; CMRL = cerebral metabolic rate of lactate; $CMRO_2$ = cerebral metabolic rate of oxygen; CPPe = effective cerebral perfusion pressure; CVR = cerebro-vascular resistance; OEF = oxygen extraction fraction; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2 = arterial partial pressure of oxygen; $PjvO_2$ = jugular venous partial pressure of oxygen; RAP = resistance area product; V_{MCA} mean = mean blood flow velocity of the middle cerebral artery; ZFP = zero-flow pressure.[9]

response to CO_2, when compared to other inhalational anesthetics. Sevoflurane appears to increase CBF slightly more than other inhalation anesthetics. Nitrous oxide increases both CBF and metabolism, but preserves the response to CO_2.[6]

The anesthetized brain might be less vulnerable to ischemia than the non-anesthetized brain as anesthesia reduces cerebral electric activity, metabolism, and flow. However, results of our study suggest that moderate hyperventilation, when compared to hypoventilation, in patients undergoing fentanyl-midazolam anesthesia partly impair cerebral aerobic metabolism at clinically relevant levels of hypocapnia.[9] Hyperventilation does not only reduce the total cerebral blood flow, but also changes the distribution of blood flow within the brain. Recent studies reveal that blood flow to the frontal, occipital, and parieto-occipital cortex, as well as the hippocampus is reduced relative to other areas of the brain within seconds to minutes of commencing hyperventilation. Alzheimer disease patients are predisposed to postoperative cognitive dysfunction. This group of patients has an increased vasoconstrictive response to hypocapnia and concomitantly a greater increase in oxygen extraction fraction (OEF) than control patients. So hyperventilation is associated with cognitive changes such as disturbed mentation, impaired concentration, and poor memory, which may be explained by reduced frontal cortical function.[1]

Despite routine end-tidal carbon dioxide monitoring, periods of inadvertent hyperventilation occur frequently during mechanical ventilation under general anesthesia. This is associated with unfavorable side effects such as cognitive dysfunction and increased length of hospital stay.[3,10]

Traumatic brain injury

Aggressive hyperventilation (arterial $PaCO_2$ < 25 mm Hg) formerly has been a cornerstone in the management of severe traumatic brain injury (TBI) for more than 20 years because it reduces cerebral blood volume and thus ICP. However, cerebral auto-

regulation is often abolished in the area surrounding damaged brain tissue or after an acute cerebral infarction. These blood vessels are often maximally dilated, presumably reflecting accumulation of acidic metabolic products. As a result, CBF to this area is already maximal (luxury perfusion), and changes in $PaCO_2$ have nearly no effect on its local blood distribution. Then, hypercapnia induced cerebral vasodilation of normal vessels could shunt blood away from the diseased area. Conversely, hyperventilation induced vasoconstriction theoretically could divert CBF to diseased areas (Robin Hood phenomenon). Based upon these competing concerns, recent guidelines on traumatic injury recommend to avoid hyperventilation, especially in the acute phase (the first 24 to 48 hours) following TBI. Mild to moderate hyperventilation can be considered at later stages, but $PaCO_2$ of less than 30 mmHg should always be avoided. If hyperventilation is used, jugular venous oxygen saturation ($SjvO_2$) or brain tissue oxygen tension ($PbrO_2$) measurements are recommended to monitor oxygen delivery.[11]

CONCLUSIONS

Up to now, there is no evidence to support the therapeutic or prophylactic use of induced hypocapnia in any therapeutic context. Overall, the benefits of preserving normocapnia for the maintenance of cardiac output and tissue oxygenation and perfusion, as well as for the maintenance of CPPe, CBF, CVRe, and cerebrovascular reactivity, are well defined. It is recommended to anesthesiologists to be familiar with the physiological effects of CO_2 and manage it according to their patient's situation.

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