

Cerebral Hyperemia During Recovery from General Anesthesia in Neurosurgical Patients

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Changes in the cerebral circulation during recovery from neurosurgical anesthesia are poorly understood. We used transcranial Doppler to compare cerebral blood flow velocity changes (Vmca) during recovery after anesthesia. In the first part of the study, 30 patients were randomized to propofol- or isoflurane-based anesthesia. Vmca, mean arterial pressure (MAP), and CO₂ partial pressure (Paco₂) were measured before anesthesia, at tracheal extubation, at 5 to 60 min after extubation, and at 24 h after anesthesia. There was a 60% increase in Vmca above the awake value at extubation. The increase in Vmca was significant at least for 30 min after extubation. There was no difference between the

Propofol and Isoflurane anesthesia groups. There was no correlation between Vmca and MAP or Paco₂ at any time. In the second part of the study, Vmca, MAP, and jugular venous bulb saturation in oxygen (Sjvo₂) were measured after isoflurane anesthesia. Sjvo₂ increased significantly at extubation, consistent with cerebral hyperemia. In conclusion, cerebral hyperemia occurs during recovery from general anesthesia independently of the anesthetic technique or hemodynamic or ventilatory changes. It is speculated that cerebral hyperemia is a nonspecific response to stress during emergence from anesthesia.

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Recovery from general anesthesia and extubation is a period of intense physiological stress for patients. Stress is difficult to define and may have different meanings. A general definition of stress may be a nonspecific response of an organism to a stimulus (stressor) (1). Here stress will be defined as the metabolic and hemodynamic reactions to recovery and extubation after anesthesia. After intracranial surgery, there is an increase in oxygen consumption, catecholamine blood concentrations, blood pressure, and heart rate (2). These systemic metabolic changes may not be relevant to most neurosurgical patients, who are usually free of cardiac or respiratory disease. But stress may induce changes in cerebral perfusion or cerebral metabolic rate of oxygen consumption (CMRO₂), which may be detrimental after neurosurgery. Systemic hypertension is a common consequence of stress during neurosurgical recovery (3), which has been associated with an increased risk of postoperative intracranial hemorrhage (4). But a causal relation between postoperative hypertension and cerebral hemodynamic changes or the risk of cerebral hemorrhage could not be made. It is unknown

to what extent early postoperative neurosurgical complications, such as cerebral hemorrhage or edema, may be related to physiologic changes of anesthesia recovery. The magnitude and the duration of stress-related changes in cerebral metabolism and circulation have not been studied during recovery from neurosurgical anesthesia and tracheal extubation. A better understanding of these changes may help to identify causes of cerebral complications. The aim of this study was to assess the changes in the cerebral circulation during neurosurgical recovery by using transcranial Doppler (TCD) ultrasonography. To search for an effect of the anesthetic technique, we compared recovery after IV or inhaled anesthesia.

Methods

After IRB approval and written informed consent, 38 patients were included in this study. In the first part of the study, 30 patients with ASA physical status I or II undergoing supratentorial tumor surgery were included in a double-blinded, randomized, prospective study. Patients requiring emergency surgery, who had clinical symptoms of intracranial hypertension, or who were treated for systemic hypertension were not included in the study. In 15 patients, anesthesia was maintained with isoflurane (0.4% to 1.2% expired), nitrous oxide in oxygen (fraction of inspired oxygen

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[FiO_2] = 0.5), fentanyl (5 to 10 $\mu\text{g}/\text{kg}$ IV), and atracurium IV (Group I). Nine patients had a meningioma, four had a glioma, and two had metastatic tumors. In the other 15 patients, anesthesia was maintained with propofol (3 to 9 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), air in oxygen ($\text{FiO}_2 = 0.5$), fentanyl (5 to 10 $\mu\text{g}/\text{kg}$ IV), and atracurium IV (Group P). In this group, nine patients had a meningioma, five had a glioma, and one had a metastatic tumor. In both groups, end-tidal CO_2 was maintained between 30 and 35 mm Hg during anesthesia. A 2-mHz ultrasound probe (EME TC 2-64; EME, Uberlingen, Germany) was used to measure middle cerebral artery (MCA) red blood cell flow velocity (Vmca) at a depth of 50 or 55 mm on the opposite side of surgery. The anesthesiologist performing the TCD measurement did not know which anesthetic technique was in use. Extubation was performed when the patient had resumed spontaneous ventilation and was able to follow commands. Unnecessary stimulation and delayed tracheal extubation were avoided as much as possible. The measures were recorded in the operating room immediately before anesthesia, in the recovery room at extubation, 5, 10, 15, 30, and 60 min after extubation, and on the neurosurgical ward 24 h after surgery. Arterial blood samples were drawn for the measurement of CO_2 partial pressure (Paco_2) during each Vmca measurement and under anesthesia in the operating room after completion of surgery. The hematocrit was measured on the same blood samples, and the values before anesthesia and at extubation were used for analysis. Mean arterial pressure (MAP) measured via a radial artery catheter was recorded at the same times. The data were summarized as mean \pm SD and were analyzed by using a two-way analysis of variance for repeated measures. Regression analysis was used to identify correlations between MAP or Paco_2 and Vmca at each time point. $P < 0.05$ was considered significant.

In the second part of the study, eight patients undergoing intracranial aneurysm surgery with perioperative monitoring of the jugular venous bulb saturation in oxygen (Sjvo_2) were studied. None of these patients had experienced a subarachnoid hemorrhage. Anesthesia was maintained with isoflurane, nitrous oxide in oxygen ($\text{FiO}_2 = 0.5$), fentanyl (5 to 10 $\mu\text{g}/\text{kg}$ IV), and atracurium IV. After the induction of anesthesia, the jugular venous catheter was placed on the right side, which was the side of the dominant jugular vein on the preoperative angiogram in all patients. Its proper placement in the jugular bulb was verified on a postoperative lateral skull radiograph film. Blood samples were drawn slowly (over approximately 1 min), to measure the Sjvo_2 value. Vmca, MAP, Sjvo_2 , and pulse saturation in oxygen were measured at the same times as in Group I and Group P and during anesthesia just after surgical closure of the skin under isoflurane (0.4% to 0.6% expired and nitrous oxide in

oxygen). The data were noted as mean (range). The data were compared with the baseline measure by using Wilcoxon's signed rank test, and the Bonferroni correction was applied for multiple comparisons.

Results

The mean age and duration of anesthesia were comparable between Group P and Group I (age: Group P, 46 ± 12 yr; Group I, 47 ± 12 yr; duration of anesthesia: Group P, 279 ± 82 min; Group I, 282 ± 64 min). The Paco_2 value under anesthesia after surgery was 34 ± 3 mm Hg in Group I and 33 ± 3 mm Hg in Group P. Boluses of nicardipine (1 or 2 mg) were given IV in three patients in Group I to treat systemic hypertension before extubation (MAP >125 mm Hg). No patient in Group P received any antihypertensive drug. Vmca values are shown in Figure 1. Paco_2 and MAP are given in Table 1. There was no significant difference between the two groups. The changes in Vmca were significant with time ($P < 0.0001$) until 30 min after extubation in Group I and 60 min after extubation in Group P compared with the preoperative value. Paco_2 and MAP were not significantly different between the two groups. Paco_2 did not change significantly with time. MAP changes with time were significant at extubation in Group P and 24 h after extubation in Group I. There was no correlation between Vmca and MAP or Paco_2 at any time during the study. The hematocrit value decreased from $39\% \pm 3\%$ to $34\% \pm 4\%$ in the 30 patients (from $39\% \pm 2\%$ to $32\% \pm 3\%$ in Group P and from $39\% \pm 4\%$ to $35\% \pm 4\%$ in Group I).

The changes in Vmca, Sjvo_2 , and MAP (eight patients) for the second part of the study are presented in Table 2. No patient was treated for hypertension in this group. Vmca increased significantly above the preoperative value after extubation. Sjvo_2 increased significantly above the value measured during anesthesia at extubation and 5 min after extubation.

Discussion

This study shows that there is a 60% increase in Vmca above the awake value at extubation. This increase in Vmca did not depend on the anesthetic technique (IV or inhaled) and lasted 30 to 60 minutes after extubation. Vmca changes reflect changes in cerebral blood flow (CBF) if the angle of insonation between the probe and the vessel, and the vessel diameter, remain constant. Although the probe was hand-held, the two operators performing TCD measurements had more than five years' experience with TCD and tried to limit as much as possible the variations in the angle of insonation. For a change in the angle of insonation from 0 to 10 degrees, the error in Vmca is 2%. For the MCA, the intraobserver variability for repeat measurements is $<10\%$ (5). This is far less than the magnitude of the changes measured in

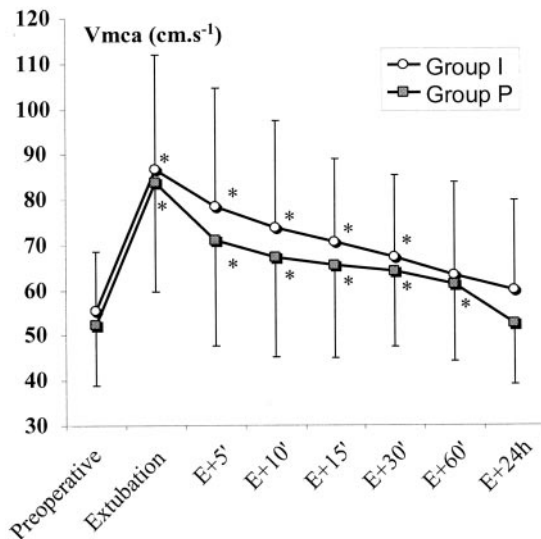


Figure 1. Mean middle cerebral artery blood flow velocity (Vmca) before anesthesia (preoperative), at extubation (extubation) and 5 min to 24 h after extubation (E + 5' to E + 24 h) in Group I and Group P (mean \pm SD). * $P < 0.05$ compared with baseline value.

this study, and small changes in the angle of insonation would not significantly alter the results. The diameter of the MCA is not significantly affected by changes in blood pressure (6,7), $Paco_2$ (7,8), or moderate hemodilution (9–11). The validity of TCD as an index of changes in CBF is supported by a good correlation between Vmca and ^{133}Xe -clearance CBF measurements of CO_2 reactivity (12). However, the effect of sympathetic stimulation on human MCA diameter is still controversial. By using indirect measurements of MCA diameter, Pott et al. (13) found that sympathetic activation had no effect, whereas Giller et al. (14) estimated a 10% decrease in diameter. A simulated orthostatic stress induced by lower-body negative pressure did not change MCA diameter measured by magnetic resonance imaging (8). Thus, vasoconstriction of the MCA cannot be excluded in this study, but available data do not support this hypothesis as a main mechanism to explain our results.

The cerebral arteriovenous difference in oxygen content ($AJDO_2$) and $Sjvo_2$ reflect the balance between cerebral oxygen supply and demand. A decrease in $Sjvo_2$ or an increase in $AJDO_2$ indicates increased oxygen extraction and relative cerebral hypoperfusion when there is no change in arterial oxygen content. An increase in $Sjvo_2$ or a decrease in $AJDO_2$ indicates relative cerebral hyperemia. Several studies have reported a decrease in $AJDO_2$ or an increase in $Sjvo_2$ during recovery from general anesthesia (15–18). These studies have several limitations. There was not any evaluation of CBF after extubation, and this made it difficult to understand the relative contributions of $CMRO_2$ and CBF in $AJDO_2$ changes. The $AJDO_2$ values were unstable during anesthesia; this did not allow a

stable reference value to be obtained. Finally, anesthesia was maintained with halothane, which increases CBF even at small inhaled concentrations (15–18).

Our $Sjvo_2$ measurements combined with TCD recordings confirm cerebral hyperemia. The baseline $Sjvo_2$ value was measured during anesthesia (isoflurane 0.4% to 0.6%), and this may limit interpretation of postoperative changes. However, isoflurane is known to maintain the coupling between CBF and $CMRO_2$. For concentrations <0.5 minimum alveolar anesthetic concentration (MAC), there is a parallel decrease in CBF and cerebral metabolism in experimental conditions (19). Sevoflurane, an anesthetic that has cerebrovascular effects similar to those of isoflurane, did not change Vmca or $AJDO_2$ compared with the awake state when administered at 0.5 MAC during propofol anesthesia (20). Thus, our baseline value should reflect the balance between oxygen supply and demand in awake patients. This assumption is validated by the finding that similar values were recorded under anesthesia and 30 to 60 minutes after extubation. Furthermore, the $Sjvo_2$ at extubation is largely above the upper normal value of 75% in healthy subjects. As in other studies, the duration of the increase in $Sjvo_2$ was short, usually <15 minutes (15,16). The peak value was observed at extubation and did not depend on the anesthetic technique. This suggests that cerebral hyperemia was related to the physiologic changes of recovery from anesthesia and not to intraoperative anesthetic or surgical factors. This study was not designed to test any mechanism of postoperative cerebral hyperemia. However, several hypotheses could explain our results.

Hemodilution increases Vmca. There was a 5% decrease in the hematocrit value during the operation in the 30 patients. There was a 2% change in Vmca for each 1% decrease in the hematocrit value (21). Thus, hemodilution was responsible for a 10% increase in Vmca. With hemodilution, CBF increases to maintain a constant oxygen delivery to the brain when the arterial oxygen content decreases. The balance between oxygen supply and demand is unchanged, and moderate hemodilution cannot explain changes in $Sjvo_2$.

Impaired cerebral autoregulation caused by a residual effect of anesthetics is also unlikely to explain the results. There was no difference between patients anesthetized with isoflurane or propofol. With propofol doses used for clinical care, cerebral pressure autoregulation and CO_2 reactivity remain intact (22). Furthermore, there was not any correlation between MAP and Vmca during recovery at any time. But CBF autoregulation is not an instantaneous process during blood pressure changes. It is possible that transient increases in MAP could induce transient increase in CBF and Vmca. Rapid increases in blood pressure may

Table 1. MAP and Paco₂ Before Anesthesia (Preop), at Extubation (Extub), and 5 min to 24 h (E + 5' to E + 24 h) After Extubation in Patients Anesthetized with Isoflurane (Group I) or Propofol (Group P)

Variable (mm Hg)	Preop	Extub	E + 5'	E + 10'	E + 15'	E + 30'	E + 60'	E + 24 h
MAP (Group I)	100 ± 14	108 ± 13	105 ± 13	101 ± 15	100 ± 12	102 ± 13	103 ± 10	90 ± 11*
MAP (Group P)	99 ± 13	113 ± 15*	105 ± 10	103 ± 11	102 ± 12	98 ± 10	95 ± 9	93 ± 9
Paco ₂ (Group I)	38 ± 3	37 ± 7	40 ± 6	39 ± 5	38 ± 5	40 ± 5	40 ± 6	
Paco ₂ (Group P)	36 ± 3	39 ± 5	40 ± 5	39 ± 5	41 ± 4	39 ± 4	38 ± 3	

Values are presented as mean ± SD.
MAP = mean arterial pressure.
* P < 0.05 compared with baseline value.

Table 2. Changes in Sjvo₂, Spo₂, Vmca, and MAP in Eight Patients During Recovery After Anesthesia for Intracranial Aneurysm Surgery

Variable	Preop	Anesth	Extub	E + 5'	E + 10'	E + 15'	E + 30'	E + 60'
Sjvo ₂ (%)		66 (55-72)	81* (70-95)	74* (67-85)	70 (55-79)	71 (87-81)	66 (50-81)	66 (52-78)
Spo ₂ (%)		100.0 (100)	99.4 (99-100)	99.5 (99-100)	99.5 (99-100)	99.6 (99-100)	99.5 (99-100)	99.4 (99-100)
Vmca (cm/s)	53 (30-86)	57 (36-86)	96* (56-138)	77* (56-122)	76* (52-126)	73* (50-116)	71* (44-120)	77* (44-126)
MAP (mm Hg)	96 (86-112)	89 (66-108)	101 (84-133)	97 (81-128)	95 (67-129)	94 (70-124)	93 (73-116)	93 (68-120)

Values are presented as mean (range).
Preop = before anesthesia; Extub = at extubation; E + 5' to E + 60' = 5 min to 24 h after extubation; Sjvo₂ = jugular venous bulb saturation in oxygen; Spo₂ = arterial saturation in oxygen; Vmca = mean cerebral blood flow velocity in the middle cerebral artery; MAP = mean arterial pressure.
* P < 0.01 compared with baseline value.

occur before extubation but are less likely to occur in neurosurgical patients after extubation, when the painful stimulus caused by the presence of the tracheal tube has been removed.

Hypercapnia or return to normocapnia after prolonged hyperventilation during anesthesia may increase Vmca. Compared with the preoperative value, the postoperative increase in Paco₂ was not statistically significant. Furthermore, there was no correlation between Paco₂ and Vmca at any time. Although Paco₂ changes were not significant, the patients were mildly hyperventilated during anesthesia. Over a few hours, CBF adapts to the imposition of hyperventilation and returns to normal. With termination of hyperventilation, CBF increases above the control level measured before hyperventilation (23). In this study, Paco₂ increased from 33 ± 3 mm Hg to 40 ± 5 mm Hg five minutes after extubation. Several investigators have reported Vmca changes from 2.5% to 4% per mm Hg change of Paco₂ (24). Assuming a 3% change in Vmca per mm Hg Paco₂ in our patients, there would be a mean 21% increase in Vmca caused by relative hypercapnia. This value would be less in case of incomplete adaptation of CBF to hypocapnia during anesthesia.

Stress-related changes in CMRO₂ and CBF have been demonstrated in animals and in humans (1). The response may depend on the stressful event, the level of stress, and the individual. This response usually

affects the entire brain, but CBF may increase independently of CMRO₂. A common adrenergic mechanism seems to be involved because pharmacological β-adrenergic blockade attenuates the cerebral stress response (25), and pharmacological stimulation of β receptors increases CBF and CMRO₂ (26,27). During neurosurgical recovery, an increase in blood catecholamine concentrations has been demonstrated (2). However, plasma catecholamines alone do not affect the cerebral circulation if the blood-brain barrier is intact and if CBF autoregulation is maintained (28,29). Experimentally, epinephrine and norepinephrine endogenous to the central nervous system may increase during recovery. On emergence from anesthesia, there is catecholamine activation in the vasomotor center in rats (30), and halothane withdrawal increases the neuronal activity in the locus ceruleus (31). A cerebral noradrenergic stimulation could explain a general increase in cerebral metabolism and blood flow.

Clinically, postoperative cerebral hyperemia may lead to adverse cerebral outcome. It may promote vasogenic edema, which may cause intracranial hypertension. In a retrospective study in 514 neurosurgical patients whose intracranial pressure was monitored after elective intracranial surgery, 89 had a sustained postoperative increase in intracranial pressure (32). Cerebral hyperperfusion may also lead to cerebral hemorrhage (33,34). There is an association

between intraoperative or early postoperative systemic hypertension and the risk of intracranial hemorrhage (4). Although a causal relation could not be established, systemic hypertension was a plausible cause of intracranial hemorrhage. In our study, cerebral hyperperfusion was observed without a significant change in MAP. The incidence of systemic hypertension after neurosurgery is >50% (3,4). It is likely that severe hypertension occurring during extubation would aggravate this hyperperfusion state.

In conclusion, we found that Vmca increased 60% above the preoperative value at extubation. SjvO₂ measurements indicated cerebral hyperemia. Vmca then gradually returned toward the baseline value but remained significantly increased until 30 to 60 minutes after extubation. These changes in the cerebral circulation were not related to the anesthetic technique or to changes in MAP or Paco₂. Cerebral hyperemia could be the result of CBF adaptation to hypocapnia during anesthesia, incomplete cerebral autoregulatory adaptation to transient changes in MAP, or stress-related changes in CBF. Further studies are needed to test these hypotheses.

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