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Effects of 1 MAC desflurane on cerebral metabolism, blood flow and carbon dioxide reactivity in humans

F. MIELCK, H. STEPHAN, W. BUHRE, A. WEYLAND AND H. SONNTAG

Summary

We investigated the cerebral haemodynamic effects of 1 MAC desflurane anaesthesia in nine male patients scheduled for elective coronary bypass grafting. For the measurement of cerebral blood flow (CBF) a modified Kety-Schmidt saturation technique with argon as inert tracer gas was used. Measurements of CBF were made before induction of anaesthesia and 30 min after induction under normocapnic, hypocapnic and hypercapnic conditions in sequence. Changes in mean arterial pressure after induction of anaesthesia and during the course of the study were minimized using norepinephrine infusion. In comparison with the awake state under normocapnic conditions, desflurane reduced mean cerebral metabolic rate of oxygen ($CMRO_2$) by 51% and mean cerebral metabolic rate of glucose (CMRglc) by 35%. Concomitantly, CBF was significantly reduced by 22%; jugular venous oxygen saturation (Sjv_{O_2}) increased from 58 to 74%. Hypo- and hypercapnia caused a 22% decrease and a 178% increase in CBF, respectively. These findings may be interpreted as the result of two opposing mechanisms: cerebral vasoconstriction induced by a reduction of cerebral metabolism and a direct vasodilator effect of desflurane. CBF alterations under variation of Pa_{CO_2} indicate that cerebrovascular carbon dioxide reactivity is not impaired by application of 1 MAC desflurane. (*Br. J. Anaesth.* 1998; **81**: 155–160)

Keywords: anaesthetics volatile, desflurane; brain, metabolism; brain, blood flow; brain, carbon dioxide reactivity

The pharmacokinetic properties of desflurane may be of major advantage for anaesthesia in neurosurgical procedures, as early neurological examination after the emergence period may be desirable. Thus, substantial information on the cerebral effects of this agent is required and may be of clinical importance.

The effects of desflurane on cerebral metabolism and haemodynamics have already been studied in animals. In these experimental settings, desflurane caused a dose-dependent decrease in cerebrovascular resistance, an accompanying increase in cerebral blood flow (CBF) and a significant decrease in the cerebral metabolic rate of oxygen ($CMRO_2$). Cerebral vasculature remained responsive to changes in Pa_{CO_2} at 0, 5–1, 5 MAC desflurane, even in the presence of moderate hypotension.[1–3]

However, few investigations have been performed in humans.[4–7] Results from these studies are inconsistent with respect to carbon dioxide reactivity of CBF. Data on cerebral metabolism are lacking and the cerebral consequences of desflurane in patients with unimpaired cerebral circulation are presently unknown.

Therefore, this study was designed to investigate the cerebral haemodynamic and metabolic effects of desflurane anaesthesia in patients without evidence of neurological or cerebrovascular disease.

Patients and methods

Nine male patients scheduled for elective coronary bypass grafting were included in the study. After approval by the local Ethical Committee, written informed consent was obtained from each patient. According to clinical examination and duplex-ultrasonic investigation of intra-extra cranial arteries none of the patients showed evidence of cerebrovascular disease. Patients with a history or laboratory evidence of hepatic, renal, central or peripheral nervous disease or long-term misuse of drugs were excluded from the study. None of the patients had received general anaesthesia within 30 days of surgery. Cardiac medication was continued until surgery and premedication consisted of flunitrazepam 2 mg by mouth on the evening before and the morning of the surgical procedure.

CATHETERIZATION PROCEDURE

Before induction of anaesthesia, routine haemodynamic monitoring was established and included electrocardiography (leads II and V_5) and arterial, central venous, and pulmonary arterial catheterization. The pressure line of the arterial catheter was replaced by a gas-tight catheter (6-French gauge, Goodale Lubin, USCI, CR Bard, Billerica, MA, USA). In addition, a jugular bulb catheter of the same size was inserted by retrograde cannulation of the right internal jugular vein and the correct position was controlled by fluoroscopy.

INDUCTION AND MAINTENANCE OF ANAESTHESIA

I.v. etomidate 0.3 mg kg^{-1} was given, followed by incremental concentrations of desflurane in oxygen

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using face-mask ventilation. Vecuronium 0.1 mg kg^{-1} was administered to facilitate tracheal intubation. After intubation, 1 MAC desflurane (6 vol%) was administered constantly without supplementary doses of hypnotics or analgesics throughout the study period. Additional doses of vecuronium were administered when necessary.

Patients' lungs were mechanically ventilated using a volume controlled ventilator (Cato, Dräger AG, Lübeck, Germany). A positive end-expiratory pressure of 5 mm Hg was applied in all patients. Desflurane was administered by a Devapor vaporizer (Dräger AG, Lübeck, Germany) mounted on the ventilator. Delivery of desflurane was achieved through a semi-open circuit with a gas flow rate of 6 litre min^{-1} at a $F_{I_{O_2}}$ 0.3. The inspiratory and expiratory concentration of desflurane and other respiratory gases were continuously monitored with an integrated infrared absorption spectrometer (PM 8050 cd, Dräger AG, Lübeck, Germany).

After induction of anaesthesia norepinephrine was administered continuously in order to keep mean arterial pressure constant when compared with control values. To prevent hypothermia, a forced-air warming device (Warm Touch, Mallinckrodt, USA) with a whole body blanket was applied before induction of anaesthesia and during the complete period of measurements.

STUDY PERIOD

Measurements were made in the awake, premedicated patient before induction of anaesthesia (I); these values were considered as baseline. The following measurements were made in sequence after intervals of at least 30 min after induction under normocapnic conditions with Pa_{CO_2} about 5.3 kPa (II), under hypocapnic conditions with Pa_{CO_2} about 4.0 kPa (III) and under hypercapnia with Pa_{CO_2} = 6.7 kPa (IV). The different levels of Pa_{CO_2} were achieved by adjusting the tidal volume of the ventilator inducing normo-, hyper- or hypoventilation, respectively.

At each measurement arterial, central venous, pulmonary capillary wedge and jugular bulb pressures were recorded on an eight-channel chart recorder; thermodilution measurements of cardiac output were taken at three random times during the respiratory cycle (Polymed CO computer, System 1281, Siemens, Munich, Germany).

TECHNIQUE OF CEREBRAL BLOOD FLOW MEASUREMENT

Cerebral blood flow was measured using a modified Kety-Schmidt inert gas saturation technique. Argon was used as the inert tracer gas.[8] A prepared gas mixture containing 70% argon and 30% oxygen was administered to the awake patient via a tight-fitting face mask and to the anaesthetized patient via the tracheal tube. During a 10 min wash-in period, blood samples from the arterial and the jugular bulb catheter were obtained simultaneously in duplicate at a constant rate by use of a high-precision aspiration pump (Braun Melsungen, Germany). The catheters had an identical deadspace and were known to exhibit only minimal loss of inert gas by diffusion. The determination of argon concentrations in arterial and cerebral venous blood samples were carried out by gas chromatography in triplicate.[9] A brain-blood partition coefficient of 1.10 was used for calculation of CBF.

Blood samples for measurements of electrolyte concentrations (Nova Electrolyte Analyser 1, Nova Biomedical, Waltham, MA, USA), blood glucose level (standard test combination, Boehringer Mannheim, Mannheim, Germany), oxygen saturation and haemoglobin content (CO-Oximeter Typ IL 282, Rotron Manufacturing, Woodstock, NY, USA) and oxygen and carbon dioxide .tension (ABL 3, Radiometer, Kopenhagen, Denmark) were obtained twice, at the beginning and the end of each argon wash-in period. Cerebral metabolic rate of oxygen ($CMRO_2$) and glucose (CMRglc) were calculated as the product of CBF and the respective arterial cerebrovenous content difference.

The relationship between pooled CBF and Pa_{CO_2} data was described by a monoexponential function ($y = ae^{bx}$) using a non-linear fitting procedure (SigmaPlot 1.02 Jandel Scientific).

STATISTICAL ANALYSIS

All results presented in tables and figures are expressed as mean values (SD). Statistical analysis was performed by one-way analysis of variance and subsequent paired Student's *t* tests, to compare the mean haemodynamic and metabolic variables between consecutive measurements. Because multiple tests were necessary to assess the time course of each variable, the level of significance ($\alpha = 0.05$) was adjusted by a sequentially rejective multiple test procedure according to Holm.[10]

Results

Measurements were made in all nine patients, but data from three patients under hypercapnic conditions (IV) had to be excluded because of technical difficulties. Mean age of the patients was 60 yr (range 47–68 yr), their mean body weight was 81.2 (10.8) kg and the mean height was 172 (3) cm. Metabolic and haemodynamic data are presented in table 1. Haemoglobin content was constant throughout the period of measurements and body temperature only minimally decreased after induction by 0.3 to 0.5°C. In accordance with the design of the study, arterial P_{CO_2} values did not differ between the control period (I) and normocapnia (II). Mean arterial P_{CO_2} during hypo- and hypercapnia was 3.9 (0.3) and 7.2 (0.5) kPa, respectively. Despite the administration of norepinephrine a 12% decrease in MAP occurred after induction of anaesthesia.

The application of 1 MAC desflurane induced a reduction of $CMRO_2$ compared with control values (I). Data obtained under normocapnic anaesthesia (II) showed a significant decline from 3.3 (0.7) to 1.6 (0.2) ml min^{-1} 100 g^{-1}. Hypocapnia (III) and hypercapnia (IV) produced a reduction to 2.1 (0.4) and 2.2 (0.6) ml min^{-1} 100 g^{-1}, respectively (fig. 1). Desflurane reduced the metabolic rate of glucose (CMRglc) significantly from 4.0 (0.7) to 2.6 (0.8) mg min^{-1} 100 g^{-1} under normocapnia (II) and also produced a decline to 2.4 (0.9) and 3.6 (2.6) mg min^{-1} 100 g^{-1} under hypocapnic (III) and hypercapnic (IV) conditions, respectively. CBF significantly decreased from 45 (10) ml min^{-1} 100 g^{-1}

Table 1 Mean (SD) metabolic and haemodynamic data of nine male patients. Study periods were: I = baseline = awake, before induction; II = normocapnia under 1 MAC desflurane 30 min after induction; III = hypocapnia under 1 MAC desflurane; IV = hypercapnia under 1 MAC desflurane; $CMRO_2$ = cerebral metabolic rate for oxygen; CMRglc = cerebral metabolic rate for glucose; CBF = cerebral blood flow; Sjv_{O_2} = oxygen saturation in jugular bulb; Sa_{O_2} = arterial oxygen saturation; ajvDO2 = arterio-jugular venous oxygen content difference; JBP = jugular bulb pressure; MAP = mean arterial pressure; CI = cardiac index; SVR = systemic vascular resistance; Pa_{CO_2} = arterial PCO_2; Pa_{O_2} = arterial PO_2; pHa = arterial pH; pHjv = jugular venous pH; Hb = haemoglobin concentration; Temp. = urine bladder temperature. Significant differences ⋆ = $P < 0.05$ compared with baseline measurement (I)

		I $n = 9$	II $n = 9$	III $n = 9$	IV $n = 6$
$CMRO_2$	(ml min^{-1} $100g^{-1}$)	3.3 (0.7)	1.6 (0.2)⋆	2.1 (0.4)⋆	2.2 (0.6)⋆
CMRglc	(mg min^{-1} $100g^{-1}$)	4.0 (0.7)	2.6 (0.8)⋆	2.4 (0.9)⋆	3.6 (2.6)
CBF	(ml min^{-1} $100g^{-1}$)	45 (10)	35 (6)⋆	24 (4)⋆	125 (55)⋆
Sjv_{O_2}	(%)	58.4 (5.8)	74.2 (5.8)⋆	53.0 (8.8)	88.3 (2.3)⋆
Sa_{O_2}	(%)	96.6 (0.8)	98.4 (0.4)⋆	98.7 (0.3)⋆	97.6 (1.1)
$ajvDO_2$	(ml 100 ml^{-1})	7.6 (1.0)	4.7 (1.0)⋆	8.8 (1.6)	1.9 (0.5)⋆
JBP	(mm Hg)	6 (1)	9 (3)⋆	9 (2)⋆	9 (6)
MAP	(mm Hg)	91 (11)	79 (10)⋆	86 (12)	92 (14)
CI	(litre min^{-1})	2.7 (0.4)	2.7 (0.6)	2.6 (0.5)	3.6 (0.7)⋆
SVR	(dyn s^{-1} cm^{-5})	1343 (248)	1133 (281)	1296 (329)	1045 (321)
Pa_{CO_2}	(kPa)	5.6 (0.5)	5.5 (0.3)	3.9 (0.3)⋆	7.2 (0.5)⋆
Pa_{O_2}	(kPa)	12.0 (1.2)	18.7 (4.6)⋆	18.5 (4.3)⋆	19.6 (5.5)⋆
pha		7.43 (0.03)	7.41 (0.02)	7.52 (0.02)⋆	7.33 (0.03)⋆
pHjv		7.37 (0.03)	7.37 (0.02)	7.44 (0.02)⋆	7.31 (0.03)⋆
Hb	(g dl^{-1})	14.3 (1.1)	14.0 (1.5)	14.0 (1.7)	14.2 (1.0)
Temp.	(°C)	35.9 (0.3)	35.4 (0.6)⋆	35.4 (0.7)⋆	35.6 (0.3)⋆

during the control period (I) to 35 (6) after the application of 1 MAC desflurane (II). Hypocapnia (III) induced a further decrease in CBF to 24 (4) ml min^{-1} 100 g^{-1} and hypercapnia (IV) a major increase to 125 (55) ml min^{-1} 100 g^{-1} (fig. 2). 1 MAC desflurane anaesthesia increased cerebral venous oxygen saturation (Sjv_{O_2}) from a mean value of 58% in the awake state (I) to a mean of 74% under normocapnic conditions (II) (fig. 3). Cerebrovascular carbon dioxide reactivity showed no impairment under the administration of 1 MAC desflurane. In the range of Pa_{CO_2}, the relationship between CBF and Pa_{CO_2} could best dc described by the monoexponential function $y = 4.29e^{0.442x}$ (fig. 4).

Discussion

Desflurane leads to a disproportionate decrease in CBF and metabolism resulting in a significant increase in jugular venous oxygen saturation. At the same time, however, 1 MAC desflurane preserves cerebrovascular carbon dioxide reactivity.

METHODOLOGICAL CONSIDERATIONS

For ethical reasons, patients in this clinical study received flunitrazepam for oral premedication, which we believe to be indispensable for patients suffering from coronary artery disease. Benzodiazepines, however are known to have mild cerebral vascular effects[11 12] and may thus have interfered with desflurane-induced changes in CBF and $CMRO_2$. As baseline measurements in our study were performed in premedicated patients, comparable conditions applied for all measurements and this additional pharmacological effect seems unlikely to have influenced the changes in cerebral haemodynamics. Similarly, induction of anaesthesia with etomidate preceded maintenance with desflurane. Etomidate is also known to reduce CBF and $CMRO_2$ in humans.[13 14]

The pharmacokinetic properties of etomidate, however, indicate that plasma concentrations after an induction dose decrease below the therapeutic range 5 min after application.[15 16] We therefore considered a 30-min period after induction of anaesthesia safe enough to exclude major interference of etomidate with the effects of desflurane on cerebral circulation.

Desflurane anaesthesia may reduce mean arterial pressure because of a decrease in systemic vascular resistance.[17] Norepinephrine was thus infused after induction of anaesthesia to prevent major changes in cerebral perfusion pressure and to minimize additional cerebral haemodynamic effects because of autoregulation of CBF. This additional pharmacological intervention is unlikely to have caused direct cerebral vascular or metabolic effects because application of $alpha_1$-agonists are known to have little or no direct effect on CBF in humans as long as the blood-brain barrier is intact.[18 19] Unfortunately, mean MAP slightly decreased after induction of anaesthesia despite norepinephrine administration. The resulting reduction in cerebral perfusion pressure thus has to be considered in the interpretation of changes associated with 1 MAC desflurane anaesthesia.

The Kety-Schmidt technique is widely accepted as a reference method for measurements of global CBF and cerebral metabolism.[20 21] In this study mean CBF during the baseline period in awake patients was 45 (10) ml min^{-1} 100 g^{-1} which is slightly lower than global CBF values found by Madsen and co-workers at corresponding Pa_{CO_2} levels.[22] This small difference, however, is probably caused by the effect of preanaesthetic benzodiazepine administration rather than by methodological differences. Our data are in close agreement with a clinical study by Weyland and co-workers, who investigated the time course of global CBF in cardiac surgical patients.[23] The baseline values of $CMRO_2$ we report here are similar to normal values found in previous investigations.[24 25]

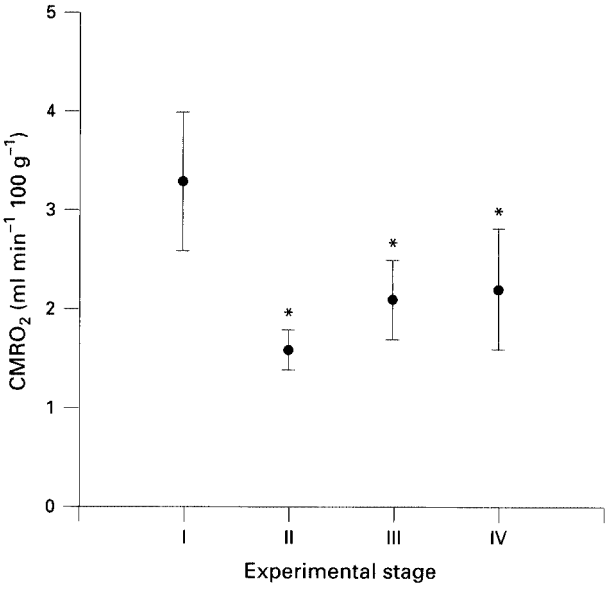

Figure 1 Mean (SD) changes of cerebral metabolic rate of oxygen ($CMRO_2$). I = awake; II = normocapnia under 1 MAC desflurane 30 min after induction; III = hypocapnia; IV = hypercapnia. *Significant difference from awake measurement (I). $P<0.05$.

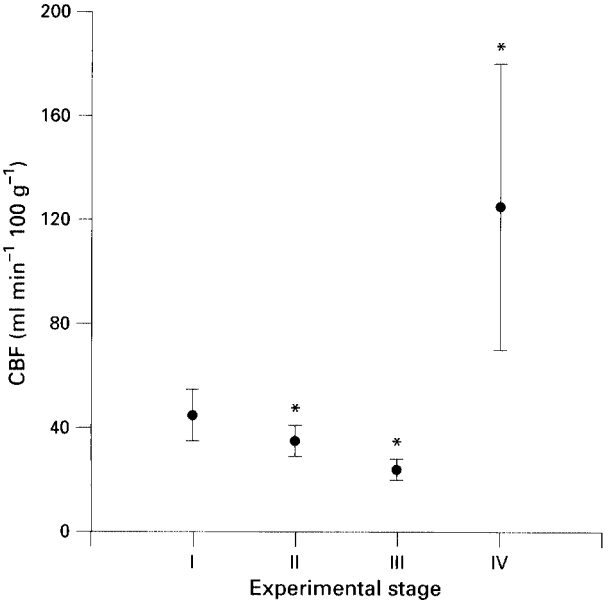

Figure 2 Mean (SD) changes of cerebral blood flow (CBF). I = awake; II = normocapnia under 1 MAC desflurane 30 min after induction; III = hypocapnia; IV = hypercapnia. *Significant difference from awake measurement (I). $P<0.05$.

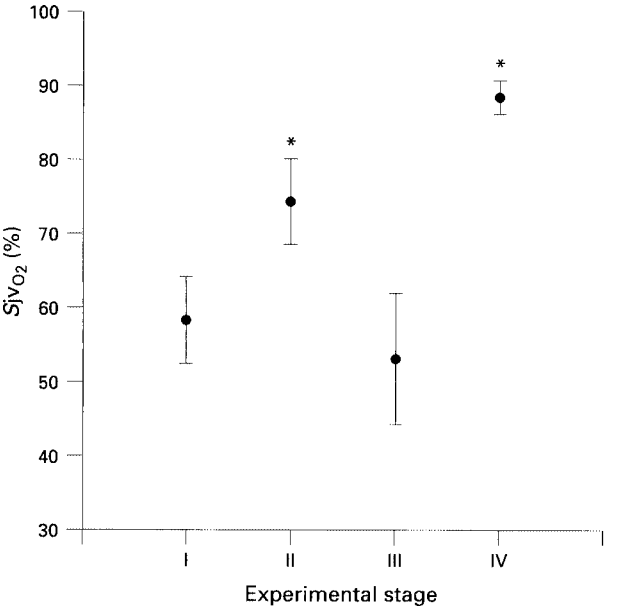

Figure 3 Mean (SD) changes of jugular venous oxygen saturation (Sjv_{O_2}) . I = awake; II = normocapnia under 1 MAC desflurane 30 min after induction; III = hypocapnia; IV = hypercapnia. *Significant difference from awake measurement (I). $P<0.05$.

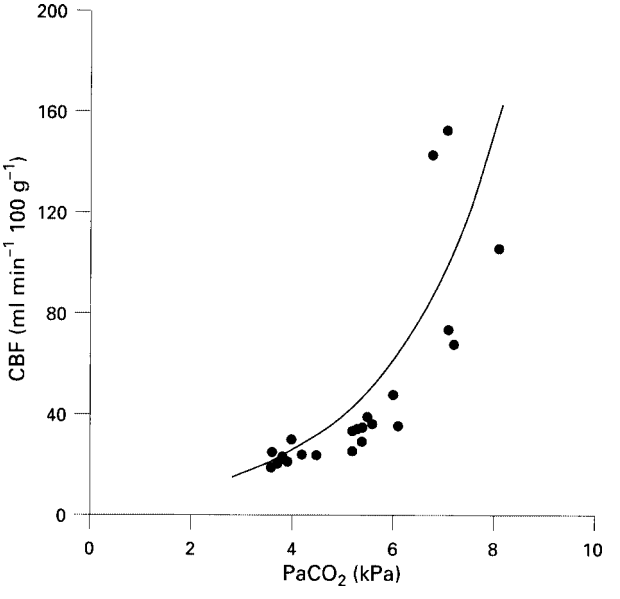

Figure 4 Relationship between cerebral blood flow (CBF) and arterial carbon dioxide pressure (Pa_{CO_2}) under 1 MAC desflurane anaesthesia. All measurements II - IV were included for evaluation. $y = 4.29e^{0.442x}$ with $n = 24$.

CEREBRAL METABOLISM

Administration of potent inhalation anaesthetics is known to reduce cerebral metabolism in a dose-dependent manner in animals as well as in humans. These data on the effect of 1 MAC desflurane are generally in agreement with findings on the effects of other inhalation anaesthetics. However, the reduction in $CMRO_2$ by 51% is greater than expected from previous clinical studies on the cerebral effects of other inhalation anaesthetics. The reduction in $CMRO_2$ is in line with comparable data from an experimental investigation in cats showing a 45% reduction in $CMRO_2$ after application of 1 MAC isoflurane when compared with a control group of animals under nitrous oxide anaesthesia.[26] As expected, the cerebral metabolic rate for glucose was also significantly reduced, but slightly less than was $CMRO_2$. In principle the resulting change in the oxygen-glucose index of the brain might suggest a change in metabolic substrates or pathways. The difference between the relative change in $CMRO_2$ and CMRglc, however, is well within the range found in other investigations on cerebral metabolism under different anaesthetics.

In analogy to the effects of most other anaesthetics it can be assumed that the reduction in cerebral metabolism was caused primarily by the reduction in cerebral activity associated with the anaesthetic effect

of desflurane; an intrinsic effect on cellular metabolism seems unlikely at a concentration of 1 MAC. Other inhalation anaesthetics, such as halothane, do not decrease cerebral metabolism when used as a supplement to deep i.v. anaesthesia.[27]

CEREBRAL BLOOD FLOW

Administration of 1 MAC desflurane caused a reduction of CBF by 22%, although Pa_{CO_2} remained unchanged. Until now, comparable data from humans are lacking. Results from a clinical investigation by Ornstein and co-workers[5] lack comparability, as measurements were obtained with the i.v.[133] xenon method and MAP was not stabilized. Furthermore, patients suffered from intracranial mass lesions and control measurements differed from this study, with CBF measured at three concentrations (1.0, 1.25 and 1.5 MAC) of desflurane under mild and moderate hypocarbia. The reduction of global cerebral metabolism and CBF after administration of desflurane suggests a preservation of coupling between metabolism and blood flow. In this study the 22% decrease in mean CBF, however, was disproportionate when compared with the reduction in $CMRO_2$ and CMRglc. This finding explains the observed increase in cerebral venous oxygen saturation and suggests a direct cerebral vasodilatory effect which partially counteracts the decrease in CBF associated with the reduction in cerebral metabolism. This hypothesis is supported by a recent investigation by Matta, Mayberg and Lam[28] who uncoupled the cerebral metabolic and vascular effects of desflurane by simultaneous propofol anaesthesia and demonstrated the direct cerebral vasodilatation during preexistent EEG silence under clinical conditions using a phenylephrine infusion to maintain MAP. Their results also support findings from an animal study,[1] which also showed a slight decrease in CBF during desflurane anaesthesia that most probably can be understood as the result of two opposing mechanisms: cerebral vasoconstriction caused by a reduction in cerebral metabolism and a direct vasodilator effect of desflurane.

In our patients, the understanding of the cerebral haemodynamic effects of desflurane is further complicated by a slight decrease in mean arterial pressure which occurred despite administration of norepinephrine and unchanged cardiac index. It therefore cannot be excluded that the mild reduction in global CBF also occurred as a consequence of the decrease in cerebral perfusion pressure and impaired autoregulation of blood flow. This, however, seems unlikely as the stable cerebral vascular resistance suggests that the vasodilatory effect of desflurane was completely counterbalanced by a metabolically-induced reduction in CBF and thus would not explain the significant increase in cerebral venous oxygen saturation. Although recent data obtained by transcranial Doppler sonography indicate that autoregulation of CBF might be impaired at higher desflurane concentrations,[6] previous studies in patients with intracranial mass lesions demonstrated preservation of cerebral vascular autoregulation.

Hypercapnia induces cerebral vasodilatation resulting in increased CBF. As it is well known that Pa_{CO_2} and CBF have an exponential relationship, hyper-perfusion in this setting must be regarded as drug-related effect. Overestimation of CBF for methodological reasons seems unlikely as $CMRO_2$ (as a product of CBF and $ajvDO_2$) during hypercapnia remained constant when compared with hypo- and normocapnia, respectively.

In this study Sjv_{O_2} values during baseline conditions and hypocapnia might be a matter of concern. Jugular venous oxygen saturation of the Sedated, non-ventilated patients (I) was significantly lower than under normocapnic anaesthesia. Under preexistent arterial normoxaemia benzodiazepine premedication probably causes a disproportionate minor reduction in CBF compared with cerebral metabolism and therefore contributes to the reduced oxygen saturation in the jugular bulb. An even lower jugular oxygen saturation was measured under hypocapnic anaesthesia (III). Under good arterial oxygen saturation, hypocapnia reveals a situation that has to be understood as an ischaemic threat, at least to the damaged brain and should be used with considerable care.

Futhermore, our results show that changes in CBF in response to variations of Pa_{CO_2} are comparable to respective changes in human volunteers,[29] indicating that cerebral vascular carbon dioxide reactivity is not impaired by administration of 1 MAC desflurane.

In summary, we conclude that in patients without evidence of cerebral vascular disease 1 MAC desflurane anaesthesia causes a decrease in global CBF as a consequence of a pronounced reduction in cerebral metabolism. These haemodynamic effects of changes in cerebral metabolism are partially counterbalanced by an intrinsic cerebral vasodilatory effect of desflurane which causes a reduction in cerebral oxygen extraction, but does not impair cerebral vascular carbon dioxide reactivity.

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