Regional cerebral blood flow (SPECT) during anaesthesia with isoflurane and nitrous oxide in humans

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Summary
Nitrous oxide and isoflurane have different effects on absolute cerebral blood flow (CBF) and regional distribution of CBF in humans. In this study we examined the effects of isoflurane in combination with nitrous oxide on CBF. We studied 10 patients (two groups of five patients, ASA I) anaesthetized with 50% nitrous oxide and either 0.5 or 1.0 MAC of isoflurane during normocapnia (\(P_{\text{a}}O_2\) 5–7 kPa) using two-dimensional CBF measurement (CBF\(_{\text{xenon}}\)) (i.v. \(^{133}\)Xenon washout technique) and a three-dimensional method for measurement of regional CBF (rCBF) distribution with SPECT (single photon emission computer-aided tomography with \(^{99m}\)Tc-HMPAO). The results were compared with 1.0 MAC of isoflurane from a previous study performed in exactly the same way as the present investigation. During normocapnia, anaesthesia with 50% nitrous oxide and 0.5 MAC of isoflurane resulted in a mean CBF\(_{\text{xenon}}\) of 45 (SEM 5) ISI units. Increasing the isoflurane concentration to 1.0 MAC had no significant effect on mean CBF\(_{\text{xenon}}\) (53 (5) ISI units). Both flow values were significantly \((P < 0.01)\) higher than the CBF\(_{\text{xenon}}\) value obtained when 1 MAC of isoflurane was administered alone (33 (3) ISI units). There were no significant differences in rCBF distribution regardless of whether or not isoflurane was given alone or together with nitrous oxide at 0.5 or 1 MAC. In all situations there were higher relative flows in subcortical regions (thalamus and basal ganglia, 10%) and in the pons (7–10% above average). rCBF in the cerebellum was approximately 10% greater than average. In summary, we have found that mean CBF was greater with combined nitrous oxide and isoflurane anaesthesia than previously found with isoflurane alone; however, relative flow distribution was similar. (Br. J. Anaesth. 1997; 78: 407–411).

Key words

Nitrous oxide has been used for anaesthesia during neurosurgical procedures for half a century as it was thought to have only little effect on the cerebral circulation.\(^1\)\(^2\) However, by the 1970s it was shown that nitrous oxide had marked effects on intracranial pressure (ICP)\(^\text{3,4}\) but the literature on the effects of nitrous oxide on the brain is confusing, probably because of species differences, but also because of interactions with other drugs or interventions.\(^5\)\(^6\) However, in humans, evidence supporting the conclusion that nitrous oxide is a cerebral vasodilator, in the absence of other interventions, has been obtained previously from cerebral blood flow (CBF) studies.\(^7\)\(^–\)\(^9\) Recent studies have shown that nitrous oxide increases blood flow velocity also when it is added to propofol or isoflurane anaesthesia.\(^10\)\(^–\)\(^11\) The reason for this vasodilatation is still unknown, but it may theoretically be caused by increased cerebral metabolism\(^10\)\(^–\)\(^13\) or by an indirect effect on the cerebral vessels\(^9\)\(^,\)\(^14\) as it is known that nitrous oxide is totally inert on isolated human pial arteries.\(^9\)

The aim of this study was to evaluate the effect of isoflurane in combination with 50% nitrous oxide on absolute CBF measured by i.v. \(^{133}\)Xenon\(^15\) combined with recording of the three-dimensional rCBF distribution with SPECT and \(^{99m}\)Tc-HMPAO in normocapnic patients.

Patients and methods
We studied 10 male patients, ASA I, undergoing inguinal herniorrhaphy. The study was approved by the Ethics Committee of the Medical Faculty and the Isotope Committee of the University of Lund. Written informed consent was obtained from each participant.

Experimental procedure
Ten patients were allocated randomly to one of two groups \((n = 5\) in each group\()\), to receive 50% nitrous oxide and 0.5 or 1 MAC of isoflurane during normocapnia. The group who received isoflurane alone also comprised five patients who have been reported...
previously. Subjects in the previous study were anaesthetized with 1 MAC of isoflurane alone, but otherwise treated in the same way as patients in the present investigation.

No premedication was given. Anaesthesia was induced with pethidine 0.75 mg kg\(^{-1}\) i.v. and propofol 2–2.5 mg kg\(^{-1}\). Suxamethonium 1 mg kg\(^{-1}\) was used to facilitate tracheal intubation. Mechanical ventilation was with a Servo ventilator (Siemens 900 C, Siemens Elema, Solna, Sweden). End-tidal carbon dioxide and concentrations of isoflurane were recorded on a Normocap 102-24-02 and a Normac gas monitor (Datex, Helsinki, Finland), respectively. Anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen. End-tidal concentrations of isoflurane and carbon dioxide (\(P_{\text{ET}}\text{CO}_2\)) were maintained as close as possible to the final experimental condition throughout anaesthesia.

At 10–20 min before the end of surgery, patients were kept anaesthetized with either 0.5 or 1 MAC of isoflurane and 50% nitrous oxide in oxygen for at least 30 min. When stable conditions were achieved and surgery had finished, mean CBF was measured using i.v. radioactive \(^{133}\)xenon clearance (CBF\(_{\text{xenon}}\). \(^{99m}\)Tc-HMPAO was given immediately after the CBF\(_{\text{xenon}}\) measurement and anaesthesia was maintained for 5 min more. No patient was studied sooner than 60 min after induction of anaesthesia (mean 69 min, range 60–85 min). After a post-anæsthetic recovery period of 1–2 h, patients were brought to the neurophysiological department for SPECT scanning.

During measurement of mean CBF\(_{\text{xenon}}\), haemoglobin concentration and arterial blood-gas samples were analysed using an ABL 500 (Radiometer, Copenhagen, Denmark). Temperature, heart rate and systemic arterial pressure were monitored throughout the procedure.

**MEASUREMENT OF MEAN CEREBRAL BLOOD FLOW**

Mean CBF\(_{\text{xenon}}\) was measured by injection of 0.5 Gbq (10 mCi) of \(^{133}\)xenon into a cubital vein, followed by rapid injection of 20 ml of isotonic saline. Uptake and clearance of the tracer substance were recorded with a scintillation detector with wide collimation (approximately 90° view), placed on the right side of the head and neck. Clearance through the lungs was recorded from expired air. A Novo Cerebrograph 10a (Simonsen Medical A/S, Randers, Denmark) was used for data collection with a sampling time of 11 min and subsequent flow calculation. CBF\(_{\text{xenon}}\) was expressed as the initial slope index (ISI)\(^{11}\) as it represents blood flow of all tissue recorded, but is highly dominated by gray matter blood flow and influenced little by extracerebral components.\(^{17}\)

**MEASUREMENT OF THREE-DIMENSIONAL CEREBRAL BLOOD FLOW DISTRIBUTION**

Regional distribution of CBF was measured by injection of a tracer substance, \(^{99m}\)Tc- HMPAO 0.5 Gbq (10 mCi) (Ceretec, Amersham, UK) into a cubital vein, followed by rapid injection of 20 ml of isotonic saline. This tracer substance is lipid soluble at the time of injection and is distributed in proportion to blood flow. In brain cells the carrier molecule HMPAO is converted within a few minutes to a water-soluble form which cannot cross the cell membrane. Hence, the amount of \(^{99m}\)Tc (half-life of 6 h) which remains trapped in the brain cells is proportional to rCBF distribution. Cerebral \(^{99m}\)Tc distribution was recorded three-dimensionally with a single photon emission computer-aided tomography (SPECT) scanner (Tomomatic 564, Medimatic A/S, Denmark) giving a picture of rCBF distribution at the time of \(^{99m}\)Tc-HMPAO injection.\(^{18,19}\) Three-dimensional distribution of \(^{99m}\)Tc-HMPAO in the brain was recorded in 10 contiguous, approximately 1-cm thick, slices parallel to the orbitomeatal (OM) line, with the centre of the lowest slice located 1 cm below the OM line. The head position was controlled with light beams on the external auditory meatus and the nasion. Slices were recorded in two interlacing sets of five slices each with a recording time of 10 min for each set, which gave approximately 10\(^6\) counts/slice and an intra-slice resolution of approximately 1 cm. The regions of interest were positioned automatically within each slice, with adjustment to the subject’s brain size.

**CALCULATIONS AND STATISTICAL METHODS**

The mean CBF\(_{\text{xenon}}\) value recorded from our detector corresponded to a weighted average of different brain regions, with the weight of each region in the average determined mainly by its \(^{133}\)xenon content and distance from the detector.\(^{20}\) Consequently, the CBF\(_{\text{xenon}}\) value from the parietal detector was an average between CBF in the closest cortical tissue (parietal cortex) and mean CBF, with dominance for the parietal cortex.

In the SPECT \(^{99m}\)Tc-HMPAO measurements, the average CBF level, calculated as the average number of counts through all regions, gray and white matters, was defined as 100% for presentation of relative flow values. Regions of interest were outlined in the brain slices by a program which was constructed from anatomical templates in a CT brain atlas.\(^{21}\) Three-dimensional cerebral regions of interest were calculated from adjoining regions of interest in different brain slices representing the same structure. The program gave the mean value in each region of interest and the size of the region of interest.

With the SPECT \(^{99m}\)Tc-HMPAO measurements, parietal and average CBF had virtually the same value (>> 100%) and therefore it was justifiable to approximate the recorded CBF\(_{\text{xenon}}\) value to parietal cortical CBF. Regional CBF values were calculated from CBF\(_{\text{xenon}}\) mean flow values and \(^{99m}\)Tc-HMPAO rCBF distribution, as described by Reinstrup and colleagues.\(^{16}\) Thus CBF\(_{\text{xenon}}\) values were equated with parietal values in the regional distribution obtained with SPECT.

The conversion factor from kPa to mm Hg was 0.1333. All values are given as mean (sem). Mean
CBF<sub>xenon</sub> values were tested by factorial design ANOVA, initially on global anaesthesia effects and post hoc on the addition of nitrous oxide to isoflurane anaesthesia. Regional CBF (99mTc-HMPAO distribution) was analysed by repeated measures ANOVA with anaesthetic type as between-group factor and regions of interest as within-group factors. 

**Results**

Physiological values of the three groups, at the time of mean CBF measurement, are presented in table 1.

**EFFECTS OF NITROUS OXIDE AND ISOFLURANE ON MEAN CBF<sub>xenon</sub> USING 133XENON**

There was a significant ($F=5.36$, $P=0.022$ ANOVA) effect on CBF<sub>xenon</sub> of anaesthesia type. Patients without any surgical stress anaesthetized with 50% nitrous oxide and 0.5 MAC of isoflurane (0.6%) had a mean CBF<sub>xenon</sub> of 45 (5) ISI units during normocapnia. CBF<sub>xenon</sub> during isoflurane anaesthesia at 1 MAC (1.2%) and during 50% nitrous oxide and 0.5 MAC of isoflurane did not differ significantly from the flow value with 0.5 MAC (53 (5) ISI units). Compared with 1 MAC of isoflurane alone (CBF<sub>xenon</sub> = 33 (3) ISI units) both CBF<sub>xenon</sub> values with nitrous oxide in addition to isoflurane were significantly increased ($F=8.16$, $P=0.014$).

**EFFECTS OF NITROUS OXIDE AND ISOFLURANE ON THREE-DIMENSIONAL CBF DISTRIBUTION**

Nitrous oxide and 0.5 or 1.0 MAC of isoflurane anaesthesia resulted in a pattern with an inhomogeneous CBF distribution ($F=61.6$, $P<0.0001$). During nitrous oxide and isoflurane anaesthesia, the regions with the highest relative CBF were the thalamus, basal ganglia and cerebellum (10% greater than average) followed by the pons (7–10% greater than average). This distribution did not differ from that found during anaesthesia with 1 MAC of isoflurane. Nitrous oxide did not differ significantly from the flow value with 0.5 MAC (53 (3) ISI units). Compared with 1 MAC of isoflurane alone (CBF<sub>rCBF</sub> = 33 (3) ISI units) both CBF<sub>rCBF</sub> values with nitrous oxide in addition to isoflurane were significantly increased ($F=8.16$, $P=0.014$).

**Discussion**

We have found that anaesthesia during normocapnia with 50% nitrous oxide and 0.5 or 1.0 MAC of isoflurane resulted in a global CBF of 44 and 53 ISI units, respectively. These values were significantly higher compared with a global CBF value of 33 ISI.
patterns of rCBF. This latter CBF value was lower than that in the awake state, which is in accordance with other recent reports and contradicts the previous common opinion that isoflurane increases CBF. In contrast, inhalation of 50% nitrous oxide in healthy young men increased global CBF from 55 to 67 ml 100 g−1 min−1, during normocapnia. This increase in CBF during nitrous oxide administration is in agreement with results from investigations on cortical blood flow in humans.

The CBF values found in this study were intermediate between values obtained when nitrous oxide and isoflurane are used alone. The finding that addition of nitrous oxide to a basic anaesthetic increases CBF has been established previously using two-dimensional methods. In these studies the effect of nitrous oxide was evaluated by substituting an equipotent dose of volatile anaesthetic in order to maintain an unchanged anaesthetic level. Recent studies have shown that nitrous oxide increases blood flow velocity also when it is added to an otherwise unchanged propofol or isoflurane anaesthesia.

We found that substituting 0.5 MAC of isoflurane with 50% nitrous oxide increased CBF and that a further, but non-significant, augmentation occurred when the concentration of isoflurane was increased to 1 MAC. Hence, the nitrous oxide-induced effect on blood flow is not attenuated by increasing anaesthetic depth with isoflurane up to 1 MAC. The finding that CBF tended to be higher when the isoflurane concentration was doubled may be explained by a direct vasodilator effect on vascular smooth muscle, caused by increased isoflurane concentrations.

We have reported previously that the global increase in CBF induced by nitrous oxide alone was distributed unevenly, with the main increase in the frontal, temporal and parietal cortex but also in the basal ganglia, insula and in the thalamic region. The flow pattern gave the impression that inhalation of nitrous oxide augmented flow through regions associated anatomically with the limbic system, probably because of selective activation of these areas. This pattern was entirely different from that seen with isoflurane. During 1 MAC of isoflurane anaesthesia, rCBF distribution showed higher CBF levels in the pons and subcortical structures (thalamus and basal ganglia) compared with the cortex. If nitrous oxide stimulates metabolism in some areas of the brain, the effect might be alleviated by addition of other anaesthetics which depress metabolism. This fits well with our present finding that nitrous oxide did not alter rCBF distribution induced by isoflurane anaesthesia. Isoflurane and halothane induced different patterns of rCBF. The reason for the selective difference in relative flow through different regions during isoflurane and halothane anaesthesia is unknown. The most likely explanation is based on the fact that the normal brain has a tight coupling between brain metabolism and flow and that the two volatile anaesthetics have different effects on metabolism in various parts of the brain. A flow metabolism relationship is evident during both isoflurane and halothane anaesthesia in the rat. Assuming that volatile anaesthetics have different effects on metabolism in various brain regions, together with the observations that addition of nitrous oxide to isoflurane increases CBF uniformly and that nitrous oxide has no effect on isolated cerebral arteries, we conclude that our study supports the hypothesis that nitrous oxide exerts an indirect vasodilator effect in the brain. Identification of the mediator(s) of this vasodilator effect merits further investigation.

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References


