

Effects of Nitrous Oxide on Human Regional Cerebral Blood Flow and Isolated Pial Arteries

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Background: Results from previous studies on the effect of nitrous oxide (N₂O) on the cerebral circulation are conflicting. Early reports claim N₂O to have no effect whereas recent findings demonstrate a cerebral cortical vasodilatation during N₂O inhalation, but the regional cerebral blood flow (CBF) in the subcortical structures is unknown.

Methods: Regional CBF was measured three-dimensionally with single photon emission computer-aided tomography after injection of xenon 133 in 8 spontaneously breathing men (mean age 29.6 yr) during normocapnia and hypocapnia with and without inhalation of 50% N₂O. 8 isolated human pial arterial segments were mounted in organ baths. The segments were contracted with prostaglandin F_{2α} and subjected to 30% oxygen and 5.6% carbon dioxide in nitrogen or N₂O.

Results: Normocapnic young men had a global CBF of 55 ± 4 ml · 100 g⁻¹ · min⁻¹. Decreasing end-tidal CO₂ tension by 1.3 kPa (9.3 mmHg) reduced CBF uniformly, with a decrease in global CBF to 45 ± 2 ml · 100 g⁻¹ · min⁻¹ ($P < 0.0001$). During normocapnia, inhalation of 50% N₂O increased mean CBF to 67 ± 7 ml · 100 g⁻¹ · min⁻¹ ($P < 0.0001$). Inhalation of 50% N₂O during hypocapnia increased mean CBF to 63 ± 5 ml · 100 g⁻¹ · min⁻¹ ($P < 0.0001$). During N₂O inhalation there was no significant difference in mean CBF between normo- and hypocapnia. However, during hypocapnia, but not during normocapnia, N₂O inhalation significantly changed the distribution of regional CBF ($P < 0.0001$). Compared with hypocapnia without N₂O, flow increased through the frontal (143%), parietal (140%) and temporal (133%) regions as well as through insula (151%), basal ganglia (145%) and thalamus (133%). In isolated human pial arteries, addition of N₂O changed neither

basal tension, nor the contraction elicited by prostaglandin F_{2α}.

Conclusions: Inhalation of 50% N₂O increased global CBF mainly by augmenting flow in frontal brain structures. In contrast, changes in carbon dioxide without N₂O affected CBF uniformly in the brain. The uneven change in distribution of the CBF when N₂O was added during hypocapnia, the reduced carbon dioxide response, and the lack of effect of N₂O on isolated human pial arteries suggest that N₂O may increase metabolism in selected brain areas. (Key words: Anesthetics, gases: nitrous oxide. Brain: cerebral blood flow; regional cerebral blood flow. Carbon dioxide: hypocapnia; normocapnia. Measurement techniques: single-photon-emission computer-aided tomography. Arteries: contractile response; pial; prostaglandin F_{2α}.)

NITROUS oxide (N₂O) has been used for anesthesia during neurosurgical procedures for half a century because it has been thought to have only little effect on the cerebral circulation.^{1,2} However, as early as the 1970s it was shown that N₂O can have potentially striking effects on intracranial pressure.^{3,4} The literature regarding the effects of N₂O on the brain is confusing, probably because of species differences but also because of interactions with other drugs or interventions.^{5,6} In humans, evidence supporting the conclusion that N₂O is a cerebral vasodilator in the absence of other interventions,⁵ has only been obtained from two-dimensional cerebral blood flow (CBF) studies on superficial cortical blood flow.^{7,8} The regional distribution of CBF in deep brain structures, investigated in swine during inhalation of 50% N₂O, shows a uniform increase in all regions except the corpus callosum.⁹ The reason for this vasodilation is still unknown but may be increased cerebral metabolism^{10,11} or a more-or-less direct influence of N₂O on the cerebral vessels.¹²

The aim of the current study was to evaluate the effect of 50% N₂O on CBF and its distribution by using a three-dimensional regional CBF (rCBF) technique in humans during normo- and hyperventilation. In addition, the direct cerebrovascular action of N₂O was investigated in isolated human pial arteries.

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Materials and Methods

Eight male volunteers aged 22–40 (mean 29.6) yr participated in the study. The protocol was approved by the ethics committee for human studies and the isotope committee at the University of Lund. Written informed consent was obtained from each participant.

Experimental Procedure

The participants breathed into a face mask held in place by rubber bands. After air leaks had been eliminated, the participants were positioned in a single-photon-emission computer-aided tomographic scanner (see next section). The participants were breathing spontaneously during all CBF measurements. Compressed air was administered during the first 10 min and a sham CBF measurement, to accustom the subjects to the measurement procedure, was performed. Next, they were coached either to maintain end-tidal carbon dioxide tension (PET_{CO₂}) at control level (5.1 kPa = normocapnia) or to hyperventilate (PET_{CO₂} decreased by 1.0 to 1.5 kPa [7.5 to 11.3 mmHg] = hypocapnia) during inhalation of oxygen (O₂)-enriched air (30% O₂). Subsequently, a mixture of 20% nitrogen (N₂), 30% O₂ and 50% N₂O was administered continuously during the last two CBF measurements at normo- and hypocapnia. Compressed air and O₂ were mixed with flowmeters (Unit 760, Siemens-Elma, Solna, Sweden), and 50% N₂O with 30% O₂ in N₂ was delivered as a pre-mixed precision gas (Alfax, Malmö, Sweden). The quantities of carbon dioxide (CO₂), O₂, and N₂O in the inspiratory and expiratory gas mixtures were continuously measured, as was the arterial hemoglobin O₂ saturation, with an Ohmeda 4700 OxiCap (BOC Health Care, Louisville, KY). The order of the normocapnic and hypocapnic conditions was systematically altered, but N₂O inhalation always followed the air-breathing studies. CBF was measured after a 15-min steady-state period in each situation.

Three-dimensional Measurement of Cerebral Blood Flow

Each measurement of rCBF was performed after the injection of 2 GBq (40 mCi) xenon 133 in a cubital vein, followed by a rapid injection of 20 ml isotonic saline. The arterial tracer input was estimated by a detector over the right lung. The uptake and clearance of the tracer, in the brain, was recorded three-dimensionally with single photon emission computer-aided tomography on a Tomomatic 564 camera (Medimatic

A/S, Denmark) and the CBF was calculated from the recorded values by the method of Celsis *et al.*¹³ Like a computed-tomography scanner, this technique provides slices through the brain that represent an image of the flow. The three-dimensional distribution of xenon 133 in the brain was recorded in five contiguous 2-cm-thick slices, parallel to the orbitomeatal line, with the center of the lowest slice located 1 cm below the orbitomeatal line. The head position was controlled with light beams on the external auditory meatus and the nasion.

The recording time for each CBF measurement was 4 min, which resulted in about 0.5×10^6 counts/slice at 1–2 min and an intraslice resolution of about 2 cm full-width half-maximum. Standard sets of regions of interest corresponding to the brain lobes, cerebellum, pons, thalamus, and basal ganglia and the insula region, constructed from anatomic plates in an atlas of computed-tomography brain images,¹⁴ were applied to the brain slices and scaled to the actual head size according to the external brain diameters. Three-dimensional cerebral regions of interest were calculated from adjoining regions of interest in different brain slices representing the same structure. With the aid of the regions of interest, the mean CBF in various brain regions and the global mean CBF were calculated.

Other Measurements

Non invasive blood pressure was recorded before and after each CBF measurement (Colin Press-Mate, Colin Electronics, Japan). At the end of the study a blood sample was withdrawn to measure the hemoglobin concentration. The response to N₂O inhalation were recorded on an arbitrary scale of 0–100% in terms of wakefulness, motivation, impulsivity, vision, hearing, and touch.

Isolated Human Pial Arteries

The methods for preparation and recording of mechanical activity have been described previously.¹⁵ Briefly, pial arteries were removed from macroscopically normal parts of brains in patients (mean age 46 ± 9 yr, range 21–78 yr) without any cardiovascular disease, undergoing lobectomy for underlying gliomas.

Ring segments, 500–1,000 μ m in external diameter and approximately 2–3 mm long, were suspended between metal prongs in 5-ml organ baths containing Krebs solution. One of the prongs was connected to a force transducer (FT 03C, Grass, Quincy, MA) for registration of isometric tension and the output was re-

corded on a polygraph (7A, Grass). The ring segments were given a tension of 1 mN/mm (length) and allowed to accommodate for 60–90 min. Endothelium is preserved with this setup,¹⁶ and intact endothelial function was verified by adding substance P¹⁷ (10^{-6} – 10^{-5} M). The Krebs solution was maintained at 37°C and the contents of the baths were aerated with a gas mixture (precision gas produced by Alfax, Malmö, Sweden) composed of 5.6% CO₂ and 30% O₂ in either of N₂ or N₂O. Datex Normocap 102-24-02 (Datex, Helsinki, Finland) was used to constantly monitor the gas mixture. The CO₂ and O₂ tensions as well as pH in the Krebs solutions were subsequently analyzed on a Radiometer ABL 500 (Radiometer, Copenhagen, Denmark).

The composition (millimolar) of the Krebs solution was NaCl 119, NaHCO₃ 20, KCl 4.6, CaCl 1.5, NaH₂PO₄ 1.2, MgCl₂ 1.3, and glucose 11.0. Prostaglandin F_{2 α} (PGF_{2 α}) was supplied as an aqueous solution (Amoglandin, Astra, Sweden) and dilutions were made up with saline immediately before use.

After an equilibration period with 95% O₂ and 5% CO₂, contractions were induced by 124 mM K⁺, and experiments were not continued unless two reproducible contractions ($\pm 10\%$) were obtained. The contents of the organ baths were exposed to gas mixtures (see above) containing either N₂ or N₂O. After an accommodation period of approximately 20 min, cumulative concentration–response curves¹⁸ were obtained by inducing contractions by stepwise increments of PGF_{2 α} (molar): 2×10^{-8} , 2×10^{-7} , 2×10^{-6} , 2×10^{-5} , and 1×10^{-4} . The order of experimental conditions was systematically varied.

Calculations and Statistical Analysis

Cerebral Blood Flow. Global effects of N₂O and hypocapnia on the rCBF were analyzed by two-factor analysis of variance (ANOVA) with correction for departure from sphericity for the interaction data.¹⁹ *Post hoc* testing with a paired Student's *t* test (two-tailed) was made when ANOVA indicated significant effects, to clarify which results mainly contributed to the significance. $P \leq 0.05$ was considered statistically significant.

Change in rCBF was calculated as the difference in rCBF with and without N₂O. Relative distribution of rCBF in %, was calculated from the equation $100 \times \text{rCBF}/\text{mean CBF}$, in each measurement.

The relative change in distributions were the difference between the relative rCBF values for measurements, with and without N₂O.

rCBF effects were analyzed by repeated-measures ANOVA, separately for normo- and hypocapnia because the two groups were not identical because all subjects could not participate in the measurements. In each ANOVA the effect of N₂O on rCBF (in percentage of mean) was tested. *Post hoc* testing with a paired Student's *t* test (two-tailed) was made when ANOVA indicated significant effects, to clarify which regional effects mainly contributed to the significance. $P \leq 0.05$ was considered statistically significant. All values are given as means \pm SE. The CO₂ response was calculated as the change in CBF divided by the corresponding change in arterial CO₂ tension. The conversion factor from kilopascals to millimeters mercury was 0.1333.

Isolated Human Pial Arteries. The maximum response (E_m) in each preparation, obtained with PGF_{2 α} at control condition (30% O₂, 5.6% CO₂ in N₂) was defined as 100%. The contractions in the presence of N₂O were subsequently related to this response. The control E_m values for PGF_{2 α} amounted to 8.14 ± 1.28 mN ($n = 8$, five patients). Estimation of the concentrations producing half-maximum contraction (EC_{50}) were based on the geometric means of the concentration–response curves. Curve-fitting was performed with Graph Pad (ISI Software, Philadelphia, PA), using the sigmoidal curve formula and assuming that the highest measured value corresponded to E_m . The results are expressed as mean \pm SE, n denoting the number of observations.

Results

Physiologic values for the four groups are presented in table 1. In addition to the intended difference in PET_{CO_2} between the normo- and hypocapnic groups there was a statistically significant difference in mean arterial blood pressure, which increased during hypocapnia. The mean hemoglobin value was 140 g/l (range 120–154 g/l). All volunteers experienced changes in cerebral function. They reported a reduction in wakefulness, vision, hearing and touch whereas there was an increase in impulsivity. Because of the anesthetic effect of N₂O inhalation (decreased communication with the subject, motor activity, poor mask fit, and in one case anxiety), rCBF measurements during both normo- and hypocapnia and N₂O inhalation could not be made in all subjects. Consequently, for seven subjects, measurements were made with and without N₂O only during normocapnia, and in for seven subjects were made with and without N₂O only during hypo-

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Table 1.

	Normo	Hypo	Normo + N ₂ O	Hypo + N ₂ O
n	8	8	7	7
PET _{CO₂} (kPa)	5.5 ± 0.1	4.2* ± 0.1	5.2 ± 0.1	4.3* ± 0.2
PET _{CO₂} (mmHg)	41 ± 0.5	32 ± 0.9	39 ± 0.8	33 ± 1.2
SaO ₂ (%)	99.6 ± 0.3	99.8 ± 0.1	99.5 ± 0.2	99.5 ± 0.2
MABP (mmHg)	86 ± 13	91† ± 11	88 ± 17	94* ± 15
Pulse rate	65 ± 11	71 ± 22	72 ± 15	67 ± 12

Physiologic parameters during the different experimental conditions. Results are presented as mean ± SE; n = numbers of experiments. Values significantly different from the control condition are indicated by * ($P < 0.05$) or † ($P < 0.01$).

Normo = normocapnia; Hypo = hypocapnia; PET_{CO₂} = end-tidal carbon dioxide content; SaO₂ = arterial oxygen saturation; MABP = mean arterial blood pressure.

capnia. All measurements were successfully performed in six subjects. Characterization of the N₂O effect on the rCBF was made only in subjects for whom measurements were made both with and without N₂O in each condition (normo- and hypocapnia).

Effects of Nitrous Oxide on Cerebral Blood Flow during Normocapnia

Normocapnic subjects had a global CBF of 55 ± 4 ml · 100 g⁻¹ · min⁻¹. There were statistically significant differences in flow between the various brain regions ($P < 0.0001$, ANOVA) (fig. 1). Inhalation of 50% N₂O increased the mean CBF to 67 ± 7 ml · 100 g⁻¹ · min⁻¹ ($P < 0.005$) but induced no significant change in the distribution of rCBF (fig. 2). Comparing the individual

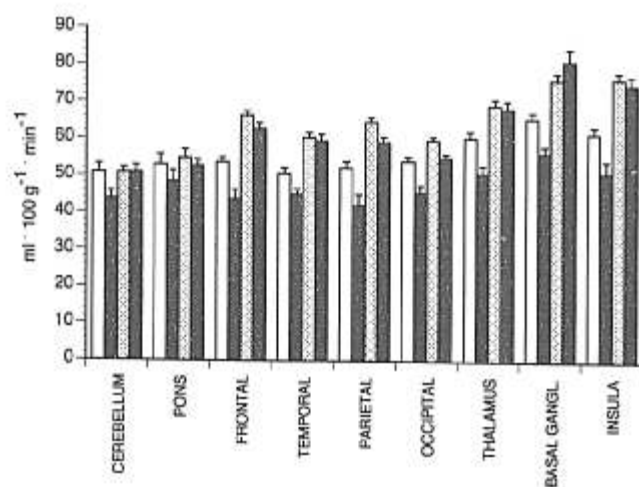


Fig. 1. Regional cerebral blood flow (CBF) (milliliters per 100 g per minute) during normocapnia (open squares), hypocapnia (filled squares), normocapnia with nitrous oxide (stippled squares), and hypocapnia with nitrous oxide (shaded squares). The results are means ± SE (n = 8).

regions of interest at normocapnia with normocapnia and N₂O, inhalation of 50% N₂O significantly increased flow in all regions except for cerebellum and pons as shown in figure 3.

Effects of Nitrous Oxide on Cerebral Blood Flow during Hypocapnia

During hypocapnia global CBF was 45 ± 2 ml · 100 g⁻¹ · min⁻¹. Inhalation of 50% N₂O increased global CBF significantly, to 63 ± 5 ml · 100 g⁻¹ · min⁻¹ ($P < 0.001$). There was a significant ($P < 0.0001$) change in the distribution of rCBF when N₂O was added during hypocapnia. There were relatively higher flow levels in the frontal (+28%, $P = 0.005$), regions and thalamus (+11%, $P < 0.05$) and relatively lower levels in the

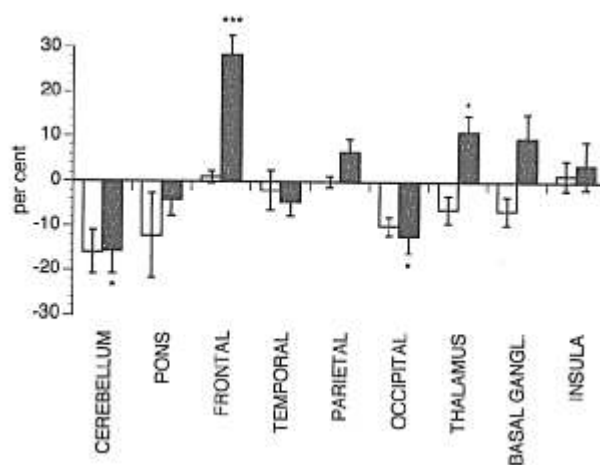


Fig. 2. Relative changes in percentage of mean cerebral blood flow (CBF) before nitrous oxide administration in the regional distribution of CBF at normocapnia (open squares) and hypocapnia (filled squares) caused by inhalation of nitrous oxide. Individual CBF changes (n = 7 in each group): * $P < 0.05$; *** $P < 0.005$.

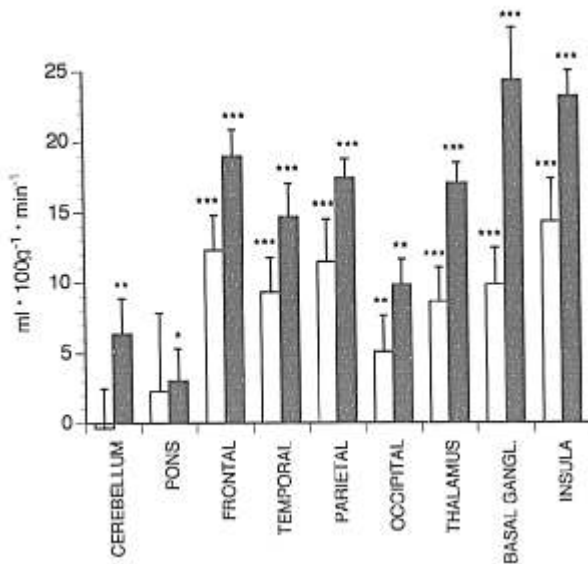


Fig. 3. Change in regional cerebral blood flow (CBF) (milliliters per 100 g per minute) caused by nitrous oxide during normocapnia (open squares) and hypocapnia (filled squares). Comparison with the respective control condition without nitrous oxide ($n = 7$ in each group): * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$.

cerebellum (-12% , $P < 0.05$) and occipital lobes (-12% , $P < 0.05$) (fig. 2).

In the different regions of interest, inhalation of 50% N_2O caused a significant increase in all regions as shown in figure 3.

Effects of Carbon Dioxide on Cerebral Blood Flow

Decreasing PET_{CO_2} by 1.3 kPa (9.3 mmHg) reduced CBF uniformly, with a significant decrease in global CBF from 55 ± 4 to 45 ± 2 $ml \cdot 100 g^{-1} \cdot min^{-1}$ ($P < 0.0001$).

When PET_{CO_2} was decreased by 0.9 kPa (6.5 mmHg) during inhalation of 50% N_2O the CBF was not significantly different. The calculated CO_2 response was 1.4 ± 0.1 without and 0.7 ± 0.2 $ml \cdot 100 g^{-1} \cdot min^{-1} \cdot mmHg^{-1}$ with N_2O .

Representative single-photon-emission computer-aided tomographic scans from one subject are presented in figure 4.

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N_2O failed to affect both the basal tone of the vessels and contractions elicited by $PGF_{2\alpha}$. The E_m value at control conditions (30% O_2 , 5.6% CO_2 in N_2) with $PGF_{2\alpha}$ was defined as 100% and the log EC_{50} value

was -5.70 ± 0.09 ($EC_{50} = 1.8 \times 10^{-6}$ M). Addition of 64% N_2O changed neither the E_m ($100 \pm 3\%$) nor the log EC_{50} (-5.65 ± 0.08 , $EC_{50} = 2.3 \times 10^{-6}$ M) values.

Discussion

In the current study, inhalation of 50% N_2O in normal young men increased global CBF from 55 to 67 $ml \cdot 100 g^{-1} \cdot min^{-1}$ during normocapnia and from 45 to 63 $ml \cdot 100 g^{-1} \cdot min^{-1}$ during hypocapnia. This increase in CBF during N_2O administration agrees with results from investigations on cortical blood flow in humans^{7,8} as well as CBF in dogs,¹² goats,¹⁰ pigs,^{9,20} and rats.²¹ The global CBF increment induced by N_2O was unevenly distributed, with the main increase in the frontal areas, a finding that agrees with that of Deutsch and Samra.⁷ However, their in-

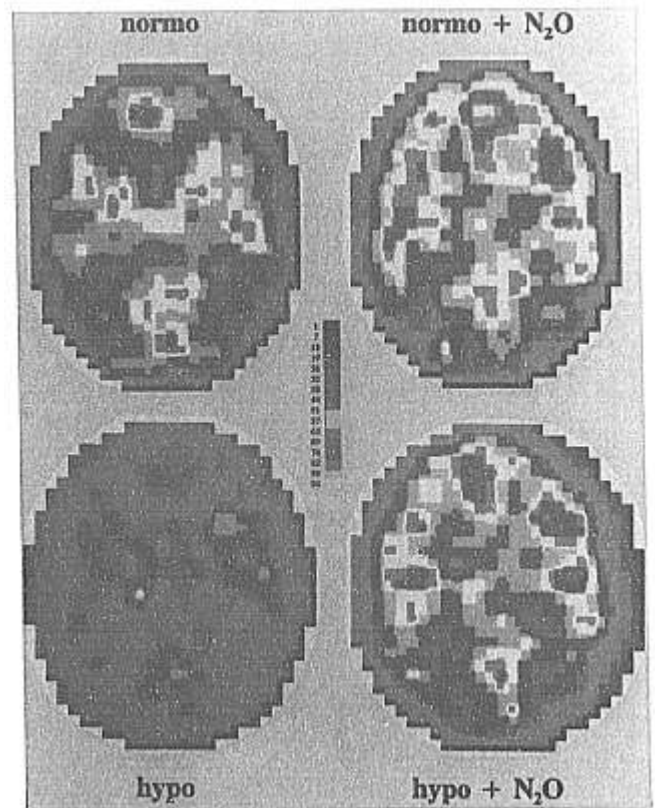


Fig. 4. Representative single-photon-emission computer-aided tomographic scans, from a single subject, illustrating regional cerebral blood flow (CBF) at normocapnia (norm) and hypocapnia (hypo), normocapnia with nitrous oxide (norm + N_2O), and hypocapnia with nitrous oxide (hypo + N_2O).

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vestigation was limited to the superficial cortical regions. In addition to the rCBF increase in the frontal, temporal, and parietal cortex, we found increased flow levels in basal ganglia, insula and especially in the thalamic region where the flow was higher than in all other regions with the exception of the frontal areas. The flow pattern gave the impression that N₂O inhalation increased flow through regions anatomically associated with the limbic system.²²

If N₂O stimulates certain areas in the brain, the effect might be alleviated by addition of other anesthetics.^{11,23} In support of this hypothesis, it has been reported that if N₂O is administered together with other anesthetics it has no effect on cortical blood flow in humans.^{1,24} However, some investigators have reported an increase in CBF during N₂O inhalation also when other anesthetics were given.^{25,26} In these studies the effect of N₂O was evaluated by substituting an equipotent dose of volatile anesthetic to keep an unchanged anesthetic level. With this setup the increase in CBF may be due either to the administration of N₂O or to the decrease in volatile anesthetic concentration.²⁶

In our study we found a global CBF of 55 ml · 100 g⁻¹ · min⁻¹ during normocapnia (PET_{CO₂} 5.5 kPa = 41 mmHg). Although if we did not measure arterial CO₂ tension, PET_{CO₂} can be used as a reliable substitute in young and healthy individuals.²⁷ At hypocapnia we found an expected reduction of CBF with a CO₂ reactivity of 1.4 ± 0.1 ml · 100 g⁻¹ · min⁻¹ · mmHg⁻¹ confirming the effect of CO₂ on the human circulation as reported already by Kety and Schmidt.^{28,29} They found a CO₂ reactivity for the whole brain of 1 ml · 100 g⁻¹ · min⁻¹ · mmHg⁻¹. In contrast, Messeter *et al.*,³⁰ using a method reflecting mainly cortical areas, reported a CO₂ reactivity of 2.2 ISI units · mmHg⁻¹, which, assuming a cortical λ value of 0.8, would correspond to a change in CO₂ of approximately 1.8 ml · 100 g⁻¹ · min⁻¹ · mmHg⁻¹. A greater CO₂ reactivity in cortical structures compared with the whole brain implies a redistribution of rCBF to subcortical brain structures when CO₂ is diminished. Previous investigations of regional cortical flow suggests an equal reduction in all cortical areas.³¹ Our study confirmed this observation and found that the uniform reduction of the rCBF extended to deep brain structures as well (figs. 1 and 4). The implied redistribution of the CBF to subcortical structures, in the interpretation of the various CBF techniques, must therefore be due to methodologic factors.

The CO₂ response during inhalation of 50% N₂O was reduced in our study, whereas the common opinion about the effect of N₂O on the CO₂ response is that it is intact in conjunction to general anesthesia.^{1,25,32} One theoretical explanation for this discrepancy is that the increased ventilation should increase the alveolar N₂O concentration. However, the resulting minor increase of the N₂O concentration could hardly account for the reduced CO₂ response, because an increase in N₂O from 30% to 60% augmented CBF by only 1.2 ml · 100 g⁻¹ · min⁻¹.⁸ The difference in CO₂ response between studies in which N₂O was administered with or without the addition of other anesthetics support the assumption that N₂O may selectively stimulate certain areas of the brain. The increased metabolic demand in awake persons will maintain the CBF even when arterial CO₂ tension is reduced. If administration of other anesthetics eliminates this increase in metabolism, the CO₂ response will return to normal.

The finding that N₂O had no influence on contractions in isolated human pial arteries eliminates several possible mechanisms of action, among others the possibility that N₂O stimulates the release of endothelium-derived relaxing factor from vascular sources or relaxes the arterial smooth muscle *via* a nitric oxide-resembling mechanism, as proposed by Field *et al.*⁸ Our *in vivo* results alone do not exclude the possibility that N₂O causes liberation of vasoactive substances *in vivo*, a suggestion previously proposed to be the case in rats³³ and in the isolated perfused canine brain.¹² However, that mechanism seems unlikely in light of the heterogenous increase in CBF found in our study. Instead, the N₂O-induced augmentation of the CBF may be a result of an increase in metabolism due to a selective activating effect on some brain structures. Such an effect of N₂O has been described in goat¹⁰ and rat,³⁴ even though the same coupling was not found in all rat studies.^{21,33}

In conclusion, decreasing PET_{CO₂} reduced CBF uniformly in the brain. Inhalation of 50% N₂O increased global CBF mainly by increasing flow in frontal brain structures. The CBF response to hypocapnia was decreased. Combined with the observation that N₂O had no effect on isolated human pial arteries, our *in vivo* data suggest that the N₂O-induced increase in CBF may be caused by increased metabolism in selected brain areas.

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