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Cerebral Blood Volume (CBV) in Humans during Normo- and Hypocapnia

Influence of Nitrous Oxide (N_2O)

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Background: **It is generally argued that variations in cerebral blood flow create concomitant changes in the cerebral blood volume (CBV). Because nitrous oxide (N_2O) inhalation both increases cerebral blood flow and may increase intracranial pressure, it is reasonable to assume that N_2O acts as a general vasodilatator in cerebral vessels both on the arterial and on the venous side. The aim of the current study was to evaluate the effect of N_2O on three-dimensional regional and global CBV in humans during normocapnia and hypocapnia.**

Methods: **Nine volunteers were studied under each of four conditions: normocapnia, hypocapnia, normocapnia + 40–50% N_2O, and hypocapnia + 40–50% N_2O. CBV was measured after ^{99m}Tc-labeling of blood with radioactive quantitative registration *via* single photon emission computer-aided tomography scanning.**

Results: **Global CBV during normocapnia and inhalation of 50% O_2 was 4.25 ± 0.57% of the brain volume (4.17 ± 0.56 ml/100 g, mean ± SD) with no change during inhalation of 40–50% N_2O in O_2. Decreasing carbon dioxide (CO_2) by 1.5 kPa (11 mmHg) without N_2O inhalation and by 1.4 kPa (11 mmHg) with N_2O inhalation reduced CBV significantly ($F = 57$, $P < 0.0001$), by 0.27 ± 0.10% of the brain volume per kilopascal (0.26 ± 0.10 ml · 100 g^{-1} · kPa^{-1}) without N_2O inhalation and by 0.35 ± 0.22% of the brain volume per kilopascal (0.34 ± 0.22 ml · 100 g^{-1} · kPa^{-1}) during N_2O inhalation (no significant difference). The amount of carbon dioxide significantly altered the regional distribution of CBV ($F = 47$, $P < 0.0001$), corresponding to a regional difference in ΔCBV when CO_2 is changed. N_2O inhalation did not significantly change the distribution of regional CBV ($F = 2.4$, $P = 0.051$) or $\Delta CBV/\Delta CO_2$ in these nine subjects.**

Conclusions: **Nitrous oxide inhalation had no effect either on CBV or on the normal CBV–CO_2 response in humans.**

NITROUS oxide (N_2O) has been safely used for anesthesia during neurosurgical procedures for half a century because it was thought to have little impact on cerebral circulation.[1,2] There are conflicting reports in the literature regarding the effects of N_2O on the brain, primarily because of species differences in both response and potency and also because of interactions with other drugs or interventions.[3,4]

However, in humans, N_2O increases cerebral blood flow (CBF)[5–7] and may increase intracranial pressure (ICP).[8,9] Evidence from both two- and three-dimensional CBF studies[5–7,10] support the conclusion that N_2O is a cerebral arterial vasodilator in the absence of other interventions.

It is generally believed that variations in CBF create concomitant changes in the cerebral blood volume (CBV). Because N_2O inhalation both increases CBF and may increase ICP, it is reasonable to assume that N_2O acts as a general vasodilatator in cerebral vessels both on the arterial and venous side.

The aim of the current study was to evaluate the effect of 40–50% N_2O on three-dimensional global CBV and in specified anatomical regions (rCBV) in humans during normocapnia and hypocapnia.

Methods

Ten healthy male volunteers participated in the study. One subject was excluded because of technical failure in labeling of the erythrocytes. The remaining subjects were 29–40 yr old (mean, 33 yr). The ethics committee for human studies and the isotope committee at the University of Lund (Lund, Sweden) approved the study. Written informed consent was obtained from each participant.

Experimental Procedure

Each subject was given a 200-mg oral dose of Iodine for thyroid protection. For radioactive labeling of the erythrocytes, 2 ml Stannous agent was administered through a dorsal hand vein, and, half an hour later, 600 MBq ^{99m}Tc-pertechnetate was administered through an antecubital vein, later used for blood sampling.

The subjects were equipped with a face mask held in place by rubber bands, and, after eliminating air leaks, they were positioned in the single photon emission computed tomography (SPECT) camera. All participants were breathing spontaneously during the measurement time.

Four SPECT measurements were performed after 15 min of steady state conditions: the first and second were during inhalation of atmospheric air with addition of extra oxygen to a total of approximately 50% O_2 either during normocapnia (end-tidal partial pressure of carbon

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dioxide approximately 5.5 kPa [41 mmHg]) or hypocapnia (end-tidal carbon dioxide [$ETCO_2$] decreased by more than 1 kPa [7.5 mmHg]); the third and fourth were during inhalation of a 40–50% N_2O mixture in 30% O_2, also during normocapnia and hypocapnia. Hypocapnia was achieved by guidance of the participants. The order between the normocapnic and the hypocapnic conditions was systematically varied.

The gases were mixed with flowmeters (unit 760; Siemens-Elema, Solna, Sweden). $ETCO_2$ and concentrations of N_2O and O_2 in the inspiratory and expiratory gas mixtures were recorded on a Datex Capnomac Ultima (Datex, Helsinki, Finland). Noninvasive blood pressure, heart rate, and arterial oxygen saturation were recorded for 5 min each using an HP Merlin (Hewlett Packard, Boeblingen, Germany).

SPECT Measurements

Measurement of the cerebral distribution of the ^{99m}Tc-labeled erythrocytes (and remaining ^{99m}Tc in plasma) was performed with use of a Ceraspect SPECT camera (DSI, Waltham, MA), giving a three-dimensional picture of the rCBV distribution. The distribution of ^{99m}Tc in the brain was recorded in 64 contiguous, 1.67-mm-thick slices, parallel to the orbitomeatal line, with the center of the lowest slice located approximately 1 cm below the orbitomeatal line. The interslice and intraslice resolution was approximately 10–15 mm. The head position was controlled with external radioactive markers on the external auditory meatus and the nasion. The SPECT recording (in a photo window of 126–154 KeV) was corrected for scattered radiation by subtraction of radioactivity simultaneously recorded in a lower energy window (112–126 KeV), and attenuation was then corrected with a factor of 0.15/cm.

For quantitation into anatomic regions (whole brain and lobes) of the three-dimensional distribution, the SPECT images were summed into 10 contiguous, 1-cm-thick slices and were analyzed with a region of interest (ROI) program based on an anatomic atlas.[11] The regions of interest were semi-automatically positioned within each slice, with adjustment to the subject's brain size, using anatomic markers as skull and position of major blood vessels (veins). The major veins were mainly (with the exception of the occipital region) located outside the ROIs of the brain lobes, but some were inevitably included in the ROI of the whole brain.

Blood Tests

To translate the measured brain radioactivity into blood volume, 5 ml venous blood was sampled every 20 min from an antecubital vein. The venous blood was collected in test tubes containing sodium heparin. The venous blood samples were centrifuged at 1,000*g* for 5 min. Total radioactivity concentrations in the whole blood, erythrocytes, and plasma were measured in an automatic well-type γ counter (1282 Compugamma; LKB Pharmacia, Åbo, Finland). The counting efficiency of the γ counter was determined using sources of ^{99}Tc^m-pertechnetate calibrated in a gas ionization chamber (CRC-35R; Capintec, Ramsey, NJ) with geometry similar to that of the blood samples. All radioactivity measurements were decay corrected to the time of ^{99}Tc^m-pertechnetate injection.

The measured radioactivity for erythrocytes and plasma were each fitted to a monoexponential decay curve and summed to a biexponential clearance curve. Values from the biexponential clearance curve at the time of the SPECT recording were used to calculate CBV.

Calculations and Statistical Methods

The regional radioactivity in the SPECT ^{99m}Tc measurements was translated into CBV level by division with the radioactivity per volume in the blood tests and was expressed as a percentage of the corresponding brain volume. When calculating the CBV per 100 g brain tissue, a density of 1.019 was used.[12] The values from the ROIs at normocapnia were equal to normal regional distribution of CBV. The carbon dioxide response was calculated as the change in CBV divided by the corresponding alteration in arterial carbon dioxide tension ($PaCO_2$). The factor used to convert kilopascals to millimeters of mercury was 0.1333.

All values are given as mean ± SD. Repeated-measures analysis of variance was used for statistical comparison of the groups. In the analysis of variance test of the CBV data, the different regions of interest were within-group

Table 1. Physiologic Parameters during the Different Experimental Conditions

	Normo	Hypo	Normo + 43% N_2O	Hypo + 42% N_2O
n	9	9	9	9
$ETCO_2$ (kPa) (mmHg)	5.4 ± 0.3	3.9 ± 0.4	5.2 ± 0.4	3.8 ± 0.5
	40.4 ± 2.6	28.9 ± 3.0	39.2 ± 2.7	28.5 ± 3.8
Sa_{O_2} (%)	99.3 ± 1.0	100 ± 0.5	100 ± 0.7	100 ± 0.5
BP_{mean} mmHg	86 ± 10	91 ± 21	93 ± 12	92 ± 9
Pulse rate (beats/min)	59 ± 10	62 ± 10	61 ± 10	60 ± 7

Values are presented as mean ± SD; n = number of participants. There were no values significantly different from the control condition (normo) other than the end-tidal carbon dioxide ($ETCO_2$) concentration.

Hypo = hypocapnia; BP_{mean} = mean arterial blood pressure; Sa_{O_2} = peripheral oxygen saturation; N_2O = nitrous oxide.

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Table 2. CBV Values in Percentage of the Brain Volume, Globally (Global CBV), and through Different Parts of the Brain

	Normo	Hypo	Normo + 43% N_2O	Hypo + 42% N_2O
Global CBV	4.2 ± 0.6	3.8 ± 0.5	4.3 ± 0.6	3.8 ± 0.5
Cerebellum	4.0 ± 0.7	3.8 ± 0.7	4.0 ± 0.8	3.6 ± 0.6
Frontal	2.6 ± 0.4	2.2 ± 0.4	2.9 ± 0.5	2.4 ± 0.3
Temporal	4.5 ± 0.7	4.1 ± 0.6	4.5 ± 0.7	4.1 ± 0.6
Parietal	3.2 ± 0.5	2.7 ± 0.5	3.4 ± 0.6	2.7 ± 0.4
Occipital	6.1 ± 1.2	5.5 ± 1.3	5.9 ± 1.5	5.3 ± 1.5
Subcortical	2.9 ± 0.5	2.4 ± 0.4	3.1 ± 0.6	2.6 ± 0.4

Values are presented as mean ± SD; number of participants was 9.

Normo = normocapnia; hypo = hypocapnia; CBV = cerebral blood volume; N_2O = nitrous oxide.

factors, and ET_{CO_2} and air–O_2/O_2–N_2O were between-groups factors. The *P* values for the analysis of variance interaction terms were corrected for departure from sphericity,[13] making the evaluation more conservative. $P \leq 0.05$ was considered statistically significant.

Results

Physiologic values of the four groups are presented in table 1. Except for the Pa_{CO_2} differences between the normocapnic and hypocapnic groups, there were no statistically significant differences.

Effects of CO_2 and N_2O on Global CBV

Without N_2O inhalation, global CBV during normocapnia (ET_{CO_2}, 5.4 kPa [41 mmHg]) was 4.25 ± 0.57% of the brain volume (4.17 ± 0.56 ml/100 g). Global CBV was unchanged (4.23 ± 0.58% of the brain volume (4.15 ± 0.57 ml/100 g)) during inhalation of 40–50% N_2O in O_2 (ET_{CO_2} , 5.2 kPa [39 mmHg]; table 2).

Decreasing CO_2 by 1.5 kPa (11 mmHg) without N_2O inhalation and by 1.4 kPa (11 mmHg) with N_2O inhalation reduced CBV significantly ($F = 57$, $P < 0.0001$), yielding a change of 0.27 ± 0.10% of the brain blood volume per kilopascal (0.26 ± 0.1 ml · 100 g^{-1} · kPa^{-1}) without N_2O inhalation and 0.35 ± 0.22% of the brain blood volume per kilopascal (0.34 ± 0.21 ml · 100 g^{-1} · kPa^{-1}) during N_2O inhalation (no significant effect of N_2O addition; fig. 1; whole brain).

Using the individual $\Delta CBV/\Delta CO_2$ of each subject to calculate CBV values at an ET_{CO_2} of 5.45 kPa (41 mmHg) yielded a global CBV during N_2O inhalation of 4.24 ± 0.63% of the brain volume (4.16 ± 0.62 ml/100 g) and a CBV difference between with and without N_2O inhalation of 0.00 ± 0.20% of the brain volume (0.00 ± 0.20 ml/100 g).

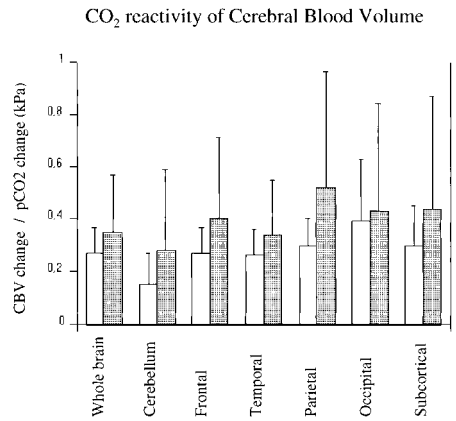
Effects of CO_2 and N_2O on Regional CBV

The amount of carbon dioxide significantly altered the regional distribution of CBV ($F = 47$, $P < 0.0001$; fig. 1), corresponding to a regional difference in $\Delta CBV/\Delta CO_2$. N_2O inhalation did not significantly change the distribution of rCBV ($F = 2.4$, $P = 0.051$) or $\Delta CBV/\Delta CO_2$ in these nine subjects (fig. 1). The absolute CBV for the different regions is given in table 2.

Discussion

Few human studies deal with the effect of anesthetics on the CBV, contrary to the large number of CBF studies dealing with this subject. In search of drugs or procedures reducing CBV, the effects of anesthesia on CBF and ICP have been used as indirect indicators of CBV effects. Indeed, a correlation has been found between CBF and CBV changes in some physiologic circumstances,[14] which, however, is not always the case,[15] especially in pathologic conditions[16–18] as well as during anesthesia.[19–22] Rapid changes in ICP are generally accepted to be due to a variation in CBV, but considering the magnitude of brain swelling sometimes occurring during neuroanesthesia, one may speculate whether mechanisms other than changes in CBV are involved.

In the current study, we found that in humans during normocapnia, 4.2% of the total brain volume consisted



The Cerebral Blood Volume (CBV) change (%) per change in CO_2 (kPa) during inhalation of 50% O_2 ( ), and of 40-50% N2O in O_2 ( ). Mean ± SD (n=9).

Fig. 1. The cerebral blood volume (CBV) change (%) per change in CO_2 (kPa) during inhalation of 50% O_2 (open bars) and of 40–50% N_2O in O_2 (filled bars). Mean + SD (n = 9). Pco_2 = partial pressure of carbon dioxide.

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of blood. This finding correlates well with previous studies[23–25] using techniques similar to ours. It is possible that the technique of labeling only the erythrocytes may slightly overestimate or underestimate the regional CBV because there may be local variations in hematocrit depending on the size of the vessels.[26] However, because of larger veins, the occipital region contains approximately twice the blood volume of the subcortical region, and since CO_2 reactivity is equal in both regions, such an effect seems unlikely.

Decreasing ET_{CO_2} by 1.5 kPa (11 mmHg) contracted the cerebral vessels, thereby reducing CBV to 3.8% of the brain volume or by 6.3% of the value at normocapnia per kilopascal (0.9%/mmHg), which represents a vasoreactivity similar to that found by Fortune *et al.*[27] However, we have previously observed[7] a decrease in CBF by 14%/kPa in a group similar to that used in the current study. This corroborates the conclusion by Fortune *et al.*[27] that relative changes in CBF are greater than relative changes in CBV in response to CO_2 variations.

CBV was not homogeneously distributed in the brain. We found relatively high rCBV values in the occipital, temporal, and cerebellar regions (table 2). The reason for this finding is unclear but may be the inclusion of large veins in the ROIs placed over these regions. Furthermore, CO_2 reactivity was lower in these areas compared with the rest of the brain. Because it is well-known that large conducting veins react poorly to vasoactive stimuli, this finding is in accordance with theory.

Inhalation of N_2O had no influence on global CBV. This is a surprising finding because N_2O increases ICP in patients with intracranial disorders[8,9] and increases CBV in dogs.[28] However, although Henriksen and Jorgensen[8] reported an ICP increase of 13–40 mmHg, Moss and McDowall[9] only observed a minor increase of 4 mmHg. This may be because of the fact that the patients in these two series all had different intracranial disorders and the fact that the latter investigation was performed during controlled ventilation. Therefore, it may be that the effect of N_2O on ICP is negligible in the absence of intracranial pathology. N_2O unquestionably increases CBF in humans during normocapnia,[5–7] presumably including dilatation of precapillary sphincters. The resultant increase in capillary hydrostatic pressure causes effusion of fluid into the extravascular space, particularly in the case of a disrupted blood–brain barrier. This would result in an increased ICP without any changes in CBV.

Nitrous oxide did not alter global CBV during hypocapnia in accordance with the findings of Archer *et al.*[28] in dogs. Contrary to the findings in dogs, we find an unchanged global CBV during normocapnia and therefore a preserved CO_2 response during N_2O inhalation.

In conclusion, we found that N_2O inhalation affected neither CBV nor the normal CBV–CO_2 response in humans.

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