Effects of Nitrous Oxide on Global and Regional Cortical Blood Flow

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We conducted regional cortical blood flow studies using the xenon-133 clearance technique on 12 volunteers during the administration of 25% and 50% N2O and during baseline conditions (breathing room air or 100% O2). Global cortical blood flow was very highly significantly increased above baseline measures in all subjects by 50% N2O (mean increase 37% above 100% O2 condition). A smaller but still significant increase was observed with 25% N2O. Analysis of regional cortical blood flow revealed heterogeneity in the pattern of changes; that is, the baseline pattern was altered by the inhalation of N2O, most often resulting in an accentuation of relative frontal blood flow. The anterior–posterior gradient in N2O-induced blood flow changes differs from that observed with simple vasodilatory agents, such as CO2, with which the increase is purely systemic and the baseline pattern is preserved. This indicates that N2O has differential effects on cerebral metabolism that may well reflect the typical alterations in experiential state reported by subjects. (Stroke 1990;21:1293–1298)

A considerable amount of both normative and clinical human data on regional cerebral blood flow (rCBF) has been gathered using the xenon-133 clearance technique. Although clinical populations have been studied in a wide variety of states, little information is available on the effects of reduced or altered level of consciousness on rCBF in normal subjects. Studies of clinical populations are typically compared with "baseline" values established in "resting-state" studies of normal volunteers. Such baselines may not be appropriate controls for patients who are not fully conscious, serving to confound the rCBF alterations associated with cerebral pathology with possible non–injury-specific changes associated with a reduced level of consciousness. In a recent investigation of comatose patients with head injury, we observed a profound decrease in relative frontal blood flow, resulting in a reversal of the anterior–posterior gradient observed in normal resting-state studies. The rCBF pattern returned to normal as the patients regained consciousness. These findings, coupled with previous studies of rCBF during coma and sleep, suggest that reduction of frontal blood flow may be a general effect of any state or condition involving reduced mental activity and thus should be interpreted with care when found in patients whose illness or treatment may alter their level of consciousness.

Could it be that similar changes occur during certain pharmacologic interventions, such as induction of general anesthesia? Nitrous oxide (N2O) has enjoyed a widespread acceptance in neuroanesthesia because studies using an animal model of head injury have shown that water content of the white matter and intracranial pressure were significantly lower in animals receiving pentobarbital or N2O-fentanyl/droperidol anesthesia than those given other halogenated inhalation anesthetics. Despite its widespread use in clinical practice and laboratory investigations, controversy regarding the effect of N2O on cerebral blood flow (CBF) and cerebral metabolism exists. Contradictory results have been obtained partly because of species differences and partly because of the concomitant use of other drugs in human studies.

Even though N2O was the tracer gas used for the measurement of CBF in humans, first described by Kety and Schmidt, the effect of N2O itself on CBF in humans has been the subject of only a few clinical investigations. Wollman et al6 studied the effect of 70% N2O on CBF in volunteers after inducing anesthesia with thiopental and paralysis with d-tubocurarine and observed that CBF was normal when Paco2 was normal but was halved when Paco2 decreased to 18.3 mm Hg. Another study from the same laboratory7 investigated the effect of 70% N2O after the administration of two doses of morphine sulfate and concluded that morphine-N2O anesthesia pro-
ducis no alteration of CBF in humans. Both these investigations suggested the lack of a vasodilatory effect of N$_2$O on cerebral blood vessels. In contrast, Henriksen and Jorgensen$^9$ found that when 66% N$_2$O was added to the inspired gas during induction of anesthesia in spontaneously breathing patients with intracranial disorders, intracranial pressure increased, providing indirect evidence that N$_2$O does have a cerebral vasodilatory effect. Similar findings have been reported by other investigators in both humans$^9$ and animals.$^{10}$ In a study using goats,$^{11}$ one of the few to examine the effects of N$_2$O in isolation from other anesthetics, the investigators reported 150% increases in both CBF and glucose consumption during 70% N$_2$O inhalation.

We studied the effect of N$_2$O on global CBF and rCBF in unpremedicated, awake, healthy human volunteers. We wanted to quantify the dose-response relation of N$_2$O for global CBF as measured by the xenon-133 clearance technique. Moreover, we were interested in examining any changes induced by the inhalation of N$_2$O in the normal pattern of rCBF. The extent to which changes in rCBF were inhomogeneous would indicate the extent to which they could be due not to purely systemic vasodilatory action, but rather to changes in cerebral metabolism. Finally, it was also of interest to consider how any changes in rCBF would correspond to the behavioral state induced by N$_2$O inhalation, especially in light of our hypothesis that there is a relation between frontal blood flow and level of consciousness.

Subjects and Methods

Institutional approval of the protocol was obtained. Twelve (six men and six women) healthy paid volunteers aged 22–40 (mean 32) years participated. Details of the study protocol were explained, and informed consent was obtained 1 day before rCBF was measured. The subjects reported to the laboratory after an overnight fast and sleep. On arrival, a slow (50–100 ml/hr) intravenous infusion of lactated Ringer’s solution was started and the subject was allowed to lie supine with his/her head resting in a plastic helmet. Electrocardiogram, heart rate, hemoglobin saturation (pulse oxymeter), and expired carbon dioxide tension ($P_{ETCO_2}$) were continuously monitored. Blood pressure was monitored every 5 minutes.

Because safety considerations demanded that an Fio$_2$ of >0.21 be used in volunteers breathing N$_2$O, each N$_2$O concentration used (25% and 50%) contained a balance of pure oxygen (O$_2$). For this reason, we felt that a control condition of 100% O$_2$ was most appropriate. In eight subjects rCBF was measured during the inhalation of 100% O$_2$, 25% N$_2$O, and 50% N$_2$O, in that order. Although O$_2$ concentrations of >20% have only minimal effects on rCBF$^{12,13}$ we compared the 100% O$_2$ condition (baseline) with a room air condition in the other four subjects, followed by the 50% N$_2$O condition. The O$_2$ and N$_2$O were administered through a tight-fitting face mask, and each gas mixture was inhaled for 15 minutes before initiation of the rCBF measurement and continued for the 11 minutes of the rCBF measurement. The interval between the end of one rCBF measurement and the start of the next was 25–30 minutes. Throughout the study period the noise level in the room was kept to a bare minimum (ambient equipment noise), and visual or auditory stimulation was avoided (other than softly asking the subject, approximately every 2–3 minutes, if he or she was all right).

We measured rCBF (more accurately, regional cortical blood flow) using the xenon-133 clearance technique described by Obrist et al$^{14}$ using a Novo 32C cerebrograph (Wilton, Conn.). Xenon-133 gas in a concentration of 5 mCi/l was inhaled by the subject for 1 minute. The arrival and clearance of xenon gas in cortical tissue was monitored for the next 11 minutes by 32 collimated and side-shielded scintillation detectors positioned in a radial array around the cerebrum in a plastic helmet system. The arrangement of these detectors with respect to the cerebral surface anatomy is diagramed in Figure 2.

Although we calculated all the standard indexes of rCBF, the measure used in the analysis is $f$$_r$ based on clearance of the most rapidly perfused tissue—almost entirely gray matter in normal subjects. This gray matter measure is most sensitive to changes in sensory and cognitive activity.$^{15}$

Changes in rCBF are usually expressed as a percentage deviation from the hemispheric mean blood flow. This generates a regional landscape independent of fluctuations in overall blood flow and facilitates the examination of changes purely in flow pattern. We analyzed changes in both these "normalized" values and in absolute values in the anterior and posterior cortical regions. Anterior and posterior regional values in each subject were calculated from the five detectors located over each region in each hemisphere. These regions are identical to those previously used in the study of comatose patients.$^1$

Data for global (mean) CBF during the 100% O$_2$, 25% N$_2$O, and 50% N$_2$O conditions in the 12 subjects were subjected to analysis of variance (ANOVA) for a randomized block design. Post hoc tests were made using $t$ intervals corrected for multiple comparisons by the Bonferroni method.

Results

Sedation produced by N$_2$O inhalation was dose-related and highly variable. No subject lost consciousness, and all found the 25% N$_2$O condition to be pleasant. Two subjects reported auditory and visual hallucinations during the 50% N$_2$O condition. Most subjects described their mental state as altered but active and focused on something—ranging from childhood memories to instrument hum in the laboratory to hallucinations. One subject dropped out of the study after 5 minutes of the 50% N$_2$O condition due to "unpleasant experience," and studies could not be completed on two other subjects during the
TABLE 1. Mean Cortical Blood Flow During Inhalation of Room Air, O\(_2\), and N\(_2\)O in Volunteers

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>(\text{P}_{\text{ET}}\text{CO}_2) (mm Hg)</th>
<th>Room air</th>
<th>100% O(_2)</th>
<th>25% N(_2)O</th>
<th>50% N(_2)O</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>37</td>
<td>40.3</td>
<td>...</td>
<td>65.50</td>
<td>60.70</td>
<td>83.30</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>23</td>
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<td>...</td>
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<td>123.70</td>
<td>140.40</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
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<td>58.10</td>
<td>75.60</td>
<td>74.15</td>
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<tr>
<td>4</td>
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<td>...</td>
<td>45.80</td>
<td>50.20</td>
<td>75.70</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>37</td>
<td>40.3</td>
<td>...</td>
<td>60.40</td>
<td>69.30</td>
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</tr>
<tr>
<td>6</td>
<td>F</td>
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<td>87.40</td>
<td>87.40</td>
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<td></td>
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<tr>
<td>7</td>
<td>M</td>
<td>40</td>
<td>40.3</td>
<td>61.45</td>
<td>60.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>37</td>
<td>42.5</td>
<td>67.60</td>
<td>74.10</td>
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<tr>
<td>9</td>
<td>M</td>
<td>37</td>
<td>36.7</td>
<td>61.50</td>
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<td>10</td>
<td>F</td>
<td>22</td>
<td>36.8</td>
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<td>72.90</td>
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<tr>
<td>11</td>
<td>F</td>
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<td>41.8</td>
<td>...</td>
<td>102.30</td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>32</td>
<td>40.3</td>
<td>...</td>
<td>74.50</td>
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</table>

\(\text{P}_{\text{ET}}\text{CO}_2\) recorded during subject's initial resting study. Values in subsequent studies were corrected for any changes in \(\text{P}_{\text{ET}}\text{CO}_2\), as described in text. M, male; F, female.

50% N\(_2\)O condition because they moved out of the rCBF apparatus.

Inhalation of N\(_2\)O resulted in slight (approximately 10%) increases in heart rate and blood pressure and a slight decrease in \(\text{P}_{\text{ET}}\text{CO}_2\) in most subjects. Maximum variation in \(\text{P}_{\text{ET}}\text{CO}_2\) was 3 mm Hg among the three rCBF measurements. Reported rCBF values have been corrected using a factor of 1 mm Hg change in \(\text{P}_{\text{ET}}\text{CO}_2\)=4% change in rCBF from baseline.\(^{16,17}\) Values for global CBF during the room air, 100% O\(_2\), and two N\(_2\)O conditions are shown in Table 1. In the four subjects in whom rCBF was measured during both the room air and the 100% O\(_2\) conditions, inhalation of 100% O\(_2\) did not significantly change rCBF (mean during room air and 100% O\(_2\) 69.49 and 70.97 ml/100 g/min, respectively; \(p>0.10\)). Thus, although we felt it was technically more correct to use the values obtained during the 100% O\(_2\) condition as a baseline to evaluate the effect of N\(_2\)O/O\(_2\) mixtures on rCBF, we feel confident that any experimental effects would generalize to a comparison with inhalation of room air. Figure 1 plots the data as percentage change from baseline values.

Analysis of global CBF showed a significant effect of condition (\(p=0.0001\)). Inhalation of 50% N\(_2\)O substantially increased CBF over baseline in every subject (Table 1, \(p=0.0001\)), by a mean of 37%. Inhalation of 25% N\(_2\)O increased CBF in seven of eight subjects (Table 1, \(p=0.015\)), by a mean of 14%. The difference between CBF values in the 25% and 50% N\(_2\)O conditions was also significant (\(p=0.0023\)).

Analysis of rCBF revealed heterogeneity in the changes. All except one subject showed a redistribution of the anterior-posterior gradient of rCBF recorded during the baseline condition. Figure 2 illustrates the mean regional values for the subjects studied in each condition.

Since nine subjects successfully completed both the 100% O\(_2\) and the 50% N\(_2\)O studies, a 2×2×2 (condition × region [anterior and posterior] × hemisphere) repeated-measures ANOVA was performed using \(f_i\) values. The ANOVA indicated a main effect for condition (\(F_{1,8}=27.5, p=0.0001\)), reflecting differences in mean \(f_i\) values between conditions, and a main effect for region (\(F_{1,8}=14.3, p=0.006\)), reflecting the overall difference between anterior and posterior \(f_i\) values in both conditions. The ANOVA also indicated a condition × region interaction (\(F_{1,8}=5.6, p=0.04\)). Figure 3 shows the main effects and the interaction. Note that the condition × region interaction is due to differential increases in anterior and posterior blood flow; that is, the anterior-posterior gradient is steeper in the 50% N\(_2\)O condition as a result of greater increases in anterior than in posterior blood flow. The increase in relative frontal blood flow was very pronounced in five subjects, whose mean anterior-to-posterior blood flow ratio (A/P) went from 1.10 at baseline to 1.23 during the 50% N\(_2\)O condition. Only one subject deviated substantially from this general pattern, showing a greater

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**Figure 1.** Effect of N\(_2\)O on global cerebral blood flow in humans. Data are plotted as percentage change in gray matter blood flow (index \(f_i\)) from baseline.
Figure 2. Top: Approximate locations of 16 detectors over one cerebral hemisphere. Detector placements were homologous for both hemispheres, giving total of 32 detectors. The five detectors over each hemisphere marked F1-F5 were used to calculate mean anterior (A) blood flow while the five detectors over each hemisphere marked P2, P3, P4, O1, and O2 were used to calculate mean posterior (P) blood flow. Bottom: Mean percentage of global gray matter blood flow (SD in parentheses) in anterior and posterior regions in the subjects studied in each condition.

Discussion

Our results show a significant dose-related effect of \( \text{N}_2\text{O} \) on both global CBF and on rCBF pattern. Our finding of increased global CBF with inhalation of \( \text{N}_2\text{O} \) contradicts some frequently cited clinical studies\(^6\)\(^7\) but is consistent with most animal studies and with some other human data. There are two possible explanations for these differences: 1) we used a maximum concentration of 50% \( \text{N}_2\text{O} \) (we were discouraged from using higher concentrations in normal volunteers by safety considerations) while some previous investigators used 70% \( \text{N}_2\text{O} \), or 2) the concomitant use of other drugs (barbiturates, muscle relaxants, and narcotics) in some previous studies masked the true effect of \( \text{N}_2\text{O} \) on CBF. Wollman et al\(^6\) induced anesthesia with 5 mg/kg thiopental in volunteers who had been premedicated with 1.5 mg/kg secobarbital; the volunteers were paralyzed with \( \text{d}-\text{tubocurarine} \), and anesthesia was maintained with 70% \( \text{N}_2\text{O} \) in 30% \( \text{O}_2 \). These authors observed that CBF remained unchanged from control values when a normal \( \text{Paco}_2 \) was maintained. They started measuring CBF approximately 60–90 minutes after the administration of thiopental and claimed that its blood level by that time was too low to affect CBF. They ignored the intramuscular administration of secobarbital, which is known to have a longer duration of action\(^18\) and might have "masked" the effect of \( \text{N}_2\text{O} \) on CBF. In the study by Jobes et al\(^7\), morphine sulfate and 70% \( \text{N}_2\text{O} \) were administered simultaneously. These authors found no significant change in CBF with \( \text{N}_2\text{O} \)-morphine anesthesia. Morphine sulfate alone decreases CBF in dogs\(^19\), and it is possible that the effect of \( \text{N}_2\text{O} \) on CBF was negated by the simultaneous administration of morphine sulfate. Our findings support the indirect evidence of increased CBF during \( \text{N}_2\text{O} \) inhalation in humans, previously reported as a rise in intracranial pressure.\(^8\)\(^9\) Our results also agree with reports\(^10\)\(^11\) of increased CBF with \( \text{N}_2\text{O} \) inhalation in different species, which included the use of 70% \( \text{N}_2\text{O} \).\(^11\)
conclude that the most reasonable explanation for the differences among reports is the concomitant use of other drugs.

The 10% increases in heart rate and blood pressure that we observed after the inhalation of N\textsubscript{2}O was most likely due to the well-known sympathetic stimulation reported with N\textsubscript{2}O\textsubscript{20} and is too small to have caused a significant change in CBF. Similarly, the decrease of up to 3 mmHg in \textit{PETCO\textsubscript{2}} that we observed is a known pharmacologic effect of N\textsubscript{2}O\textsuperscript{21} and would be expected to lower global CBF. As stated earlier, we have corrected for any variation in \textit{PETCO\textsubscript{2}} among conditions, but this correction made very little difference in the face of the very robust changes in CBF that we observed. Although the conditions were not counterbalanced in terms of order of presentation (due to practical and safety considerations), our main findings cannot be related to any known order of effects of repeated rCBF measurements; in fact, most investigators report slightly reduced global CBF in simple repeated scans\textsuperscript{15,22} and this has been our experience as well. Patterns of rCBF also do not usually vary across repeated rest-state measures and certainly not in the direction of increasing relative frontal blood flow.

In the seven subjects studied in both N\textsubscript{2}O conditions, the 25% N\textsubscript{2}O condition was always presented first. N\textsubscript{2}O is the least soluble of inhaled anesthetics and has been shown to reach tissue equilibrium in 5–10 minutes.\textsuperscript{23} We felt that the 25–30 minutes between rCBF measurements in our study was sufficient to preclude any synergistic effect of the two inhaled concentrations. In addition, going from a lower to a higher concentration minimizes the potential confounding of cumulative effects; that is, additive effects may prevent rigorous quantification of a dose–response effect but should not mask its existence. Moreover, the effect of 50% N\textsubscript{2}O inhalation on CBF in two subjects who did not receive 25% N\textsubscript{2}O was at least as great as that in the seven volunteers given both concentrations, which argues against an additive effect.

The heterogeneity of rCBF increases indicates that at least a component of N\textsubscript{2}O's action is not due simply to vasodilatory action on the intracranial vasculature since vasodilators such as CO\textsubscript{2} affect rCBF more homogeneously.\textsuperscript{24} Thus, the changes that we observed in the anterior–posterior gradient strongly suggest that N\textsubscript{2}O may alter cerebral metabolism.

The change in the rCBF pattern is very different from what we hypothesized would accompany pharmacologic alteration in the level of consciousness with anesthetics. However, N\textsubscript{2}O in the concentrations we used is not a complete anesthetic, and consequently there was a major difference between the level of consciousness in our subjects and that in sleeping or comatose subjects. Even the 50% N\textsubscript{2}O condition resulted in a state approximating stage II anesthesia (i.e., a state of delirium with uninhibited reactions\textsuperscript{25}). The greater accentuation of frontal blood flow may well reflect a disinhibition of frontal cortical activity, resulting in the general experiential state observed in most subjects—laughter, giggling, disinhibited behavior, and the "very focused" but "not self-controlled" mental activity reported by some individuals.
The most dramatic changes in the anterior–posterior gradient were observed during the 50% N₂O condition, but there were more inconsistencies across subjects in this condition than in the 25% N₂O condition. One truly outlying subject showed a large reduction in relative frontal blood flow during the 50% N₂O condition, while two subjects showed a slight decline in A/P during the 50% N₂O condition compared with the 25% N₂O condition (Figure 4). This phenomenon is in keeping with the marked clinical variations in dose responses of inhalation anesthetics. It is highly probable that a biphasic response governs CBF changes accompanying the induction of anesthesia, when initially there is an increase in hyperfrontality, representing a stage of disinhibition and release of frontal activity, which is followed by a reversal of the rCBF pattern as unconsciousness is attained. It is also possible that the disinhibited mental state induced by N₂O varies enough across subjects to account for several distinctly different rCBF patterns. Thus, the accentuation of hyperfrontality that we observed in most subjects could simply represent the most typical rather than the only experiential state induced by N₂O.

References

Key Words • cerebral blood flow • nitrous oxide • xenon • consciousness
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