EFFECT OF NITROUS OXIDE ON CEREBRAL BLOOD FLOW IN NORMAL HUMANS


SUMMARY

We have studied the effect of nitrous oxide on cerebral blood flow (CBF) in 24 healthy male volunteers. Hemispherical cerebral blood flow (CBF) was measured using the xenon-133 inhalation technique, blood flow velocities in the right middle cerebral artery were calculated using transcranial Doppler ultrasound and the pulsatility index (PI)—the inverse of which is theoretically proportional to flow in the vessel under investigation—was derived from data of the spectrally analysed pulse wave form taken from the middle cerebral artery. Each variable was measured with the subject inhaling 100% oxygen (1st baseline), 30% nitrous oxide in oxygen, 100% oxygen (2nd baseline) and 60% nitrous oxide in oxygen. CBF was significantly greater with 30% (0.01 > P > 0.001) and 60% nitrous oxide (P < 0.001) compared with baseline, although the difference between 30% and 60% nitrous oxide was not significant. Changes in 1/PI correlated closely with those in hemispherical CBF. Blood flow velocities increased significantly with 30% (P < 0.001) and 60% nitrous oxide (0.005 > P > 0.001), the difference between 30% and 60% nitrous oxide also being significant (0.005 > P > 0.001). We observed a plateau in the change in CBF caused by nitrous oxide and suggest that this may be explained by activation of intact autoregulatory mechanisms in healthy human brain. (Br. J. Anaesth. 1993; 70: 154–159)

KEY WORDS


After conflicting reports on the influence of nitrous oxide on cerebral haemodynamics in the 1960s and 70s [1–3], there has been much debate as to the advantages and disadvantages of this agent in neurosurgical anaesthesia [4]. In particular, there is accumulating evidence to show that nitrous oxide increases cerebral blood volume [5], intracranial pressure (ICP) [6–8] and cerebral blood flow (CBF) [7–13]. This is undesirable in neurosurgical practice and may adversely affect outcome. The evidence to date has been gathered from animal experiments [2, 3, 5, 8–10, 12, 13] and studies in patients with neurological disease [6, 7] and in normal anaesthetized humans [1, 11]. Species differences, intracerebral pathology and drug interactions may have had an important bearing on the results obtained.

The aims of our study were threefold: first, to identify the influence of nitrous oxide, second, to examine the effect of altering nitrous oxide concentrations and third, to compare the effects of large (60%) and small (30%) concentrations of nitrous oxide on CBF and transcranial Doppler ultrasound measurements (blood flow velocities in the right middle cerebral artery and the Pulsatility Index) in normal individuals.

SUBJECTS AND METHODS

After approval by the hospital's Ethics Committee, we studied 24 healthy male volunteers (mean age 28.5 yr, range 19–38 yr) with their informed consent. Each submitted to a routine clinical history, 12-lead ECG and haematological screen. In light of the known effects of nitrous oxide on haemopoiesis [14], the presence of an abnormal full blood count would have led to exclusion from the study. They were starved for 6 h before the study and requested not to smoke or consume caffeine-containing drinks for 12 h preceding the measurements, as both have been shown to affect CBF [15, 16].

Procedure

Three variables were examined in each volunteer: CBF was measured using the xenon-133 inhalation technique [17]; blood flow velocities, calculated from the time-averaged mean velocity (Vtam) taken over the cardiac cycle in the right middle cerebral artery (MCA), were monitored using transcranial Doppler ultrasound [18]; and the Pulsatility Index (PI)—defined as systolic velocity minus diastolic velocity divided by mean velocity—was calculated (Doptek Spectrascan with microcomputer) from the spectrally analysed pulse wave velocities obtained from the MCA. The inverse of this variable (1/PI) is theoretically proportional to flow [19]. Vtam and PI were averaged over at least nine cardiac cycles to allow for normal variations, particularly respiratory variations. These variables were assessed with the following gas mixtures:

- 100% oxygen (1st baseline)
- 30% nitrous oxide
- 60% nitrous oxide

...
baseline 100% oxygen; 30% nitrous oxide in oxygen; 100% oxygen to confirm a return to baseline values; and 60% nitrous oxide. Each volunteer was allowed to breathe 100% oxygen in order to aid recovery from the effects of 60% nitrous oxide.

Flow velocities in the MCA were monitored continuously using a Doppler ultrasound technique. The Doppler ultrasound transducer was placed on the skin surface just above the right zygomatic arch where the temporal bone is relatively thin, and the MCA insonated.

Other variables monitored continuously were: peripheral oxygen saturation ($Sp_{O_2}$), heart rate (HR), inspired oxygen concentration, end-tidal carbon dioxide $Pe_{CO_2}$, (Ohmeda OxiCap 4700) and non-invasive mean arterial pressure (MAP) (Nippon Pe Co). Comments made by the volunteers on the effects of nitrous oxide and observed effects of 30% and 60% nitrous oxide were recorded. All the results are expressed as the difference and the mean difference of the measurements obtained in order to compensate for age related variations in cerebral haemodynamics bearing in mind the 20-yr age range in our volunteers.

Statistical analysis

Data were analysed by Student’s t test. The mean differences are reported with one SEM and $P < 0.05$ was taken as statistically significant. The 95% confidence limits on those means are also given. All calculations were made using Unistat III (Unisoft Ltd) on a Caf computer.

RESULTS

Of the 24 volunteers, 20 completed the study and four withdrew at various stages, for the following reasons: breathholding during the 60% nitrous oxide measurement, hysterical and uncontrollable laughter during the 60% nitrous oxide measurement, withdrawal of consent after distressing experiences caused by 30% nitrous oxide and severe abreaction during the 30% nitrous oxide measurement.

Comparison of 100% oxygen and 30% nitrous oxide, 100% oxygen and 60% nitrous oxide, and 30% and 60% nitrous oxide has given us differences and mean differences in CBF, $V_{tam}$, $1/PI$, HR, MAP and $Pe_{CO_2}$ (tables I-IV). $Sp_{O_2}$ remained within
the range 97–100 % in all subjects. Analysis of data obtained for the 100 % oxygen measurements used values recorded during the first baseline run. Comparison between the two 100 % oxygen measurements showed no statistically significant difference in the variables examined (table V) confirming a return to normal baseline values after the 30 % nitrous oxide measurement. 

There was no significant change in MAP and $P\text{E}_{\text{CO}_2}$ during the study (table IV). Heart rate increased significantly with 60 % nitrous oxide compared with 100 % oxygen and 30 % nitrous oxide, but not with 30 % nitrous oxide compared with 100 % oxygen (table IV). There were significant increases in CBF and 1/PI with 30 % nitrous oxide compared with baseline. The increases with 60 % nitrous oxide were not greater than those observed with 30 % nitrous oxide (tables I, III). $V_{\text{tam}}$ increased significantly with 30 % nitrous oxide compared with baseline followed by a further significant increases in this variable with 60 % nitrous oxide (table II).

Of increasingly apparent interest during the course of the trial were the potent behavioural and psychological effects of nitrous oxide. Most enjoyed the experience, although some found it distressing. All volunteers were anxious, in spite of attempts to reduce the inevitable apprehension that participation in such a study would generate. All experienced amplification of sound. Thirteen of the remaining 20 volunteers dreamed with 60 % nitrous oxide and one dreamed with both 30 % and 60 % nitrous oxide.

We have compared data from dreamers and non-dreamers, but care must be taken in interpreting this analysis, as poor recall of events was frequent and, of those who claimed not to have dreamed, several may simply not have remembered. Comparison was limited to the 60 % nitrous oxide measurement as there was only one incidence of dreaming with 30 %.

In contrast with non-dreamers, CBF, $V_{\text{tam}}$ and 1/PI increased in all subjects who experienced dreams. Only the increase in 1/PI was statistically significant (table VI), although the 95 % confidence limits suggest that, with greater numbers, the increase in CBF and $V_{\text{tam}}$ would also be significant.

**DISCUSSION**

We have shown that nitrous oxide administered in oxygen increased CBF in normal humans. A constant $P\text{E}_{\text{CO}_2}$, and, by implication, a constant arterial carbon dioxide tension, were maintained in the presence of nitrous oxide, but not with 30 % nitrous oxide compared with 100 % oxygen (table IV). There were significant increases in CBF and 1/PI with 30 % nitrous oxide compared with baseline. The increases with 60 % nitrous oxide were not greater than those observed with 30 % nitrous oxide (tables I, III). $V_{\text{tam}}$ increased significantly with 30 % nitrous oxide compared with baseline followed by a further significant increases in this variable with 60 % nitrous oxide (table II).

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**Table II. Differences in $V_{\text{tam}}$ between 100 % oxygen and 30 % nitrous oxide (100–30), 100 % oxygen and 60 % nitrous oxide (100–60) and 30 % nitrous oxide and 60 % nitrous oxide (30–60).**

* Difference significant ($P < 0.05$). CL = Confidence limits

**Table III. Differences in 1/PI between 100 % oxygen and 30 % nitrous oxide (100–30), 100 % oxygen and 60 % nitrous oxide (100–60) and 30 % nitrous oxide and 60 % nitrous oxide (30–60).**

* Difference significant ($P < 0.05$). CL = Confidence limits

**Table IV. Mean differences in MAP, heart rate and $P\text{E}_{\text{CO}_2}$ between 100 % oxygen and 30 % nitrous oxide (100–30), 100 % oxygen and 60 % nitrous oxide (100–60) and 30 % nitrous oxide and 60 % nitrous oxide (30–60). n = 20.**

* Difference significant ($P = 0.05$).
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TABLE V. Mean (SEM) differences [95% confidence limits] in CBF, Vtam, 1/PI, Pr'co2, HR and MAP between both measurements of 100% oxygen. n = 20

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100% O2 (mean (SEM))</th>
<th>60% N2O (mean (SEM))</th>
<th>95% CL</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 g min⁻¹)</td>
<td>+3.85 (2.49)</td>
<td>[−1.03, +8.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vtam (cm s⁻¹)</td>
<td>−3.05 (2.22)</td>
<td>[−7.40, +1.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/PI</td>
<td>−0.25 (0.492)</td>
<td>[−0.12, +0.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr'co2 (kPa)</td>
<td>+0.02 (0.10)</td>
<td>[−0.17, +0.21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>+0.4 (1.54)</td>
<td>[−2.12, +3.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>+0.13 (1.22)</td>
<td>[−2.26, +2.52]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

degree. This was countered by using each subject as his own control. We do not believe that apprehension increased with inhalation of 30% nitrous oxide. The introduction of 60% nitrous oxide, however, coincided with a statistically significant increase in heart rate; this is explained most easily by increasing levels of anxiety. We cannot exclude this as having an influence on the results obtained. Dreaming is accompanied by a marked increase in mental activity and comparison between dreamers and non-dreamers suggests this may also have contributed, albeit insignificantly, to the observed increase in CBF caused by 60% nitrous oxide. When considering the influence of increasing anxiety and dreaming on cerebral haemodynamics, it is important to remember that the greatest changes occurred with 30% nitrous oxide when these factors were absent. Thus any contribution to the further significant increase observed with 60% nitrous oxide is unlikely to be important. Our results, interpreted with analysis of the spectrally analysed pulse wave velocities (fig. 2) suggest that vasodilatation was the immediate cause of increased CBF; this supports much of the available evidence [6, 21, 22]. However, we can only speculate on the mechanism by which nitrous oxide causes vasodilatation. A review of the literature leads us to support the theory that nitrous oxide acts predominantly by direct action on vascular smooth muscle or endothelium [22, 23]. The results of recent research into the properties of nitric oxide may shed some light on the mode of action of nitrous oxide. Nitric oxide is believed to be endothelium-derived relaxing factor (EDRF) [24], which is released from endothelial cells in response to stimulation by vasoactive substances. Synthesis of nitric oxide certainly appears to have an important influence on both basal tone and response of large cerebral arteries to acetylcholine in vivo [25]. Nitric oxide, in addition to other vasodilators such as nitroprusside and glyceryl trinitrate, facilitates conversion of glyceryl triphosphate to cyclic glycerol monophosphate which leads to vascular smooth muscle relaxation [26]. There is no evidence to support the theory that nitric oxide and nitrous oxide have similar modes of action, but the possibility makes interesting speculation. Alternatively, nitrous oxide may cause vasodilatation indirectly by increasing the cerebral metabolic rate for oxygen (CMRO2), although the evidence for this is conflicting [23]. Nitrous oxide has been shown to increase CMRO2 markedly [10], moderately [9, 11] or not at all [3, 8], whilst consistently increasing CBF to a similar degree. Furthermore, in the isolated perfused brain preparation [22], cerebrovascular

TABLE VI. Mean differences in CBF, Vtam, 1/PI, Pr'co2, HR and MAP between dreamers and non-dreamers for 100% oxygen and 60% nitrous oxide. n = 20. *Difference significant (P < 0.05)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100% O2 (mean (SEM))</th>
<th>60% N2O (mean (SEM))</th>
<th>95% CL</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 g min⁻¹)</td>
<td>+0.43 (1.82)</td>
<td>[−4.60, +2.02]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vtam (cm s⁻¹)</td>
<td>−3.13, +3.99</td>
<td>[−8.55, −0.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/PI</td>
<td>+3.54 (2.15)</td>
<td>[−16.59, +5.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr'co2 (kPa)</td>
<td>−0.76, +7.66</td>
<td>[−5.95, +27.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>+0.1 (0.06)</td>
<td>[−0.27, +0.09]*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>−0.20, +9.22</td>
<td>[−0.46, +0.07]</td>
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</tbody>
</table>

Fig. 2. MCA transcranial Doppler ultrasound waveforms showing changes in pulse wave velocities (Y axis) with time (X axis).

tone decreased significantly with CMRO₂ remaining unchanged. This suggests that, in the presence of nitrous oxide, changes in CBF are independent of changes in CMRO₂.

The most interesting aspect of our results is the existence of a plateau to the increase in CBF caused by nitrous oxide at or before a concentration of 30%, confirmed with 1/PI. The only previous suggestion that nitrous oxide may have a biphasic effect came from Cole and Shapiro, who investigated the influence of increasing concentrations of nitrous oxide on cerebral and spinal cord glucose metabolism in the rat [27]. They found that, whereas 30% nitrous oxide increased metabolism, 60% nitrous oxide had the opposite effect. In this study, enflurane was administered concurrently with nitrous oxide in varying concentrations to maintain a constant MAC value and this may have affected the results. Whether we accept Cole and Shapiro’s findings as having relevance to our study depends on whether we recognize a strong link between CBF and cerebral metabolism in the presence of nitrous oxide. We believe autoregulation of the small calibre vessels of the brain is the most likely explanation for the plateau described. This is supported by the fact that nitrous oxide does not affect autoregulatory mechanisms [28]. However, the same assumption cannot be made of the large-calibre vessels. Unlike CBF, Vtam increased steadily and significantly for both concentrations of nitrous oxide (the MCA monitored in our healthy volunteers is representative of a large calibre vessel). We believe the differences in CBF and Vtam measurements lend further support to suggested differences in behaviour between the small and large calibre vessels of the brain. However, with indirect measurements, we are unable to support this theory.

Autoregulation has to be intact for the effects of nitrous oxide on CBF to be self-limiting. In those patients with intracerebral pathology in whom it is partially or totally abolished, there is evidence to suggest that nitrous oxide has a marked deleterious effect on cerebral haemodynamics [6]. Until recently, there have been no studies relating the use of nitrous oxide to neurological outcome. Baughman and colleagues examined this, together with neurohistopathological outcome, in rats subjected to incomplete cerebral ischaemia and given nitrous oxide alone, isoflurane alone or both agents in combination [29]. They found that nitrous oxide attenuated the cerebral protective effect of isoflurane and, when given alone, was associated with the worst prognosis. There is increasing interest in the pulsatility index as a reliable indicator of cerebral perfusion, and its potential as a continuous non-invasive monitor is considerable. Our results confirm the relationship of 1/PI to CBF: both demonstrated the plateau we have described. Although 1/PI was not shown to increase significantly with 30% nitrous oxide (this we believe was probably a reflection of the small number of subjects in our study), the overall trend was the same.

In conclusion, we believe two important facts have emerged from our study: first, nitrous oxide increases CBF. Second, the effect of nitrous oxide reaches a plateau at approximately 30%. We suggest that intact autoregulation is the most likely explanation for this latter observation. In light of this, the use of nitrous oxide must be considered very carefully in patients with cerebral pathology in whom autoregulation is impaired.

REFERENCES
Nitrous Oxide and CBF


