

Remifentanil and nitrous oxide reduce changes in cerebral blood flow velocity in the middle cerebral artery caused by pain

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Background. Cerebral blood flow is affected by painful stimuli, and analgesic agents may alter the response of cerebral blood flow to pain. We set out to quantify the effects of remifentanil and nitrous oxide on blood flow changes caused by experimental pain.

Methods. We simulated surgical pain in 10 conscious volunteers using increasing mechanical pressure to the tibia. We measured changes in cerebral blood flow velocity in the middle cerebral artery (CBFV_{MCA}) caused by the pain, using transcranial Doppler sonography. We gave increasing doses of remifentanil (0.025, 0.05 and 0.1 $\mu\text{g kg}^{-1} \text{min}^{-1}$) or nitrous oxide [20%, 35% and 50% end-tidal concentration ($F_{E'}\text{N}_2\text{O}$)] and compared these effects on blood flow changes.

Results. Nitrous oxide increased CBFV_{MCA} only when given at 50% $F_{E'}\text{N}_2\text{O}$. Remifentanil did not affect CBFV_{MCA}. Pain increased CBFV_{MCA}. Both agents attenuated this pain-induced change in CBFV_{MCA} with the exception of nitrous oxide at 20% $F_{E'}\text{N}_2\text{O}$.

Conclusions. Inhalation of nitrous oxide or administration of remifentanil attenuated pain-induced changes in CBFV_{MCA}.

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The degree and extent of changes in cerebral blood flow (CBF) caused by pain depends on the characteristics of the stimulus^{1–3} and its site of application.³ To investigate the effects of surgical pain on cerebral haemodynamics we used mechanical pressure, which closely mimics surgical pain, in volunteers. We used transcranial Doppler sonography (TCD) to assess pain-induced changes in cerebral haemodynamics.

Analgesics such as remifentanil and nitrous oxide reduce the sensation of pain, so effects on CBF are likely. We measured CBF velocity in the middle cerebral artery (CBFV_{MCA}) when remifentanil or nitrous oxide were given to volunteers experiencing pain caused by increasing mechanical pressure.

Methods

After approval by the local university ethics committee and with written informed consent, 10 right-handed, non-

smoking male volunteers (ASA physical status I) with no history of any drug or alcohol abuse took part in this study. The volunteers were randomly assigned by computer (SPSS random function, Version 11.0, SPSS inc., Chicago, IL, USA) to receive remifentanil or nitrous oxide on one day, with the other drug being investigated the next day. Investigation of the effect of the analgesic was preceded by control measurements of CBFV_{MCA}, with and without pain caused by mechanical pressure.

A continuous infusion of remifentanil was given at three doses: 0.025, 0.05 and 0.1 $\mu\text{g kg}^{-1} \text{min}^{-1}$, in ascending order. Each continuous infusion was preceded by a loading dose (e.g. 25% increased infusion rate for 5 min). After an additional 15 min of steady-state infusion of remifentanil, CBFV_{MCA} was measured with and without pain. Further control measurements were made 20 min after stopping the remifentanil infusion.

The volunteers inhaled three different mixtures of nitrous oxide in oxygen [20%, 35%, 50% end-tidal concentration

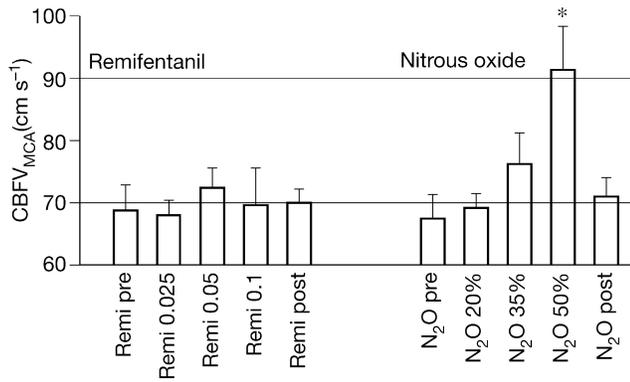


Fig 1 Cerebral blood flow velocity (CBFV_{MCA}) at control (Remi pre; Remi post; N₂O pre; N₂O post) and during administration of remifentanil (0.025, 0.05, 0.1 $\mu\text{g kg}^{-1} \text{min}^{-1}$) or nitrous oxide (20%, 35%, 50% FE'_{N₂O}). Data are mean (SD); n=10. *P<0.05 compared with control.

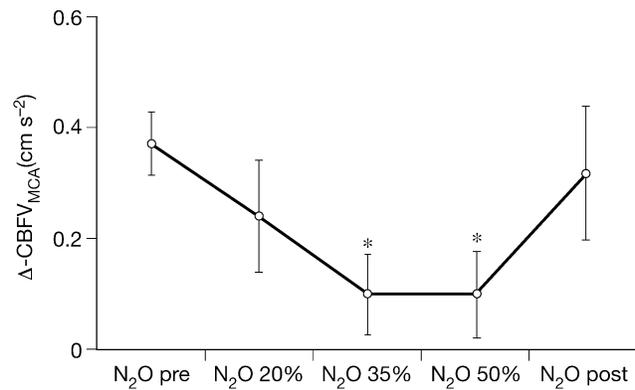


Fig 2 Changes in $\Delta\text{-CBFV}_{\text{MCA}} \text{ s}^{-1}$ at control (N₂O pre, N₂O post) and during administration of nitrous oxide (20%, 35%, 50% FE'_{N₂O}). Data are mean (SD); n=10. *P<0.05 compared with control.

(FE'_{N₂O}) in ascending order. A minimum of 20 min was allowed for stabilization of the end-tidal concentration before measuring CBFV_{MCA} with and without pain. Further control measurements were made 20 min after stopping nitrous oxide inhalation.

Pain was caused with a locally constructed pneumatic piston (contact area 1.2 cm²), which was fixed to the anterior margin of the left tibia, 5 cm above the ankle. The pressure in the piston was increased by 20 kPa (or 2.4 N) every 5 s. The volunteers were instructed to switch off the device when pain became intolerable. To avoid tissue damage, the pressure was stopped after 90 s. The supply pressure was computer controlled using locally developed software.

CBFV_{MCA} was measured by TCD using a fixed 2-MHz-pulsed TCD device (Multi-Dop-L, DWL, Sipplingen, Germany). The Doppler probe was placed on the right side of the head above the zygomatic arch between the lateral margin of the orbit and the ear, and directed toward the M1 segment of the middle cerebral artery at a depth of 50–55 mm, depending on the quality and stability of the signal.

Only one side was measured to avoid any variation related to changes in the site of recording. All TCD measurements were made by the same investigator.

During the experiment, the volunteer wore a closely fitting facemask and breathed at a constant FE'_{CO₂} (e.g. 40 mm Hg). This value was sustained by additional verbal command when necessary. To minimize the risk of acid aspiration, volunteers fasted for 6 h before the experiment. To assess sedative side-effects of the two drugs, the bispectral index (BIS) (BISTM Model A-2000TM (v 3.4); Aspect Medical Systems International BV, Leiden, The Netherlands) was measured.

The fraction of inspired and expired oxygen, end-tidal carbon dioxide concentration (FE'_{CO₂}), respiratory frequency, non-invasive mean arterial pressure and pulse oximeter haemoglobin saturation (SpO₂) were monitored

(Compact, Datex, Finland). QUICK CALTM calibration gas (REF: 755582; Datex, Finland) was used to calibrate the monitor.

Statistical analysis

Data are presented as mean (SE). Data were tested for normal distribution using the Kolmogorov–Smirnov test. Pairwise comparison of CBFV_{MCA} values at baseline and with the various doses of both agents with and without pain was performed using ANOVA for repeated measurements. Pain-induced changes in CBFV_{MCA} s⁻¹ ($\Delta\text{-CBFV}_{\text{MCA}}$ /duration of pain application in s) were calculated as follows:

$$\Delta\text{-CBFV}_{\text{MCA}} \text{ s}^{-1} =$$

$$\frac{\text{CBFV}_{\text{MCA}} (\text{drug and pain}) [\text{cm s}^{-1}] - \text{CBFV}_{\text{MCA}} (\text{drug only}) [\text{cm s}^{-1}]}{\text{duration of pain application [s]}}$$

P<0.05 was considered statistically significant.

Results

We studied 10 volunteers, mean age 27 (range 18–35) yr; mean weight, 79 (SD 11) kg; mean height: 182 (6) cm without complications. Haemodynamic values (heart rate, mean arterial pressure), respiratory parameters (SpO₂, FE'_{CO₂}, frequency) and BIS values were not affected by either nitrous oxide or remifentanil.

Control measurements of CBFV_{MCA} before and after administration of nitrous oxide or remifentanil were comparable (Fig. 1). Nitrous oxide increased CBFV_{MCA} with 50% FE'_{N₂O}, whereas remifentanil did not influence CBFV_{MCA} (Fig. 1).

Pain increased $\Delta\text{-CBFV}_{\text{MCA}} \text{ s}^{-1}$ at control (Figs 2 and 3). The increase in $\Delta\text{-CBFV}_{\text{MCA}} \text{ s}^{-1}$ was attenuated during administration of nitrous oxide (35% and 50% FE'_{N₂O}; Fig. 2) and all concentrations of remifentanil (Fig. 3).

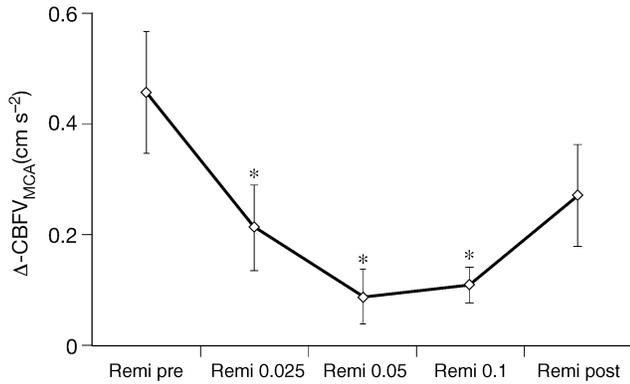


Fig 3 Changes in $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹ at control (Remi pre, Remi post) and during administration of remifentanyl (0.025, 0.05, 0.1 $\mu\text{g kg}^{-1} \text{min}^{-1}$). Data are mean (SD); $n=10$. * $P < 0.05$ compared with control.

Discussion

In our volunteers the increases in CBF caused by pain were reduced by both remifentanyl and nitrous oxide.

With TCD, blood flow velocities can be measured non-invasively and continuously through the intact skull.⁴ Assuming that the diameter of the large cerebral arteries in the circle of Willis (measuring points) does not change greatly, velocity changes will be related to changes in CBF.⁵ Hence changes in the calibre of the small resistance vessels caused by metabolic changes (e.g. during periods of pain) should cause corresponding velocity changes indicative of changes in CBF.

In a previous TCD study,⁶ thermal pain (e.g. cold pressor test) decreased CBFV_{MCA} . In a study using positron emission tomography (PET), chemical pain caused by capsaicin decreased global CBF.⁷ With regard to regional CBF, however, various PET studies found that pain could increase or decrease regional CBF. In fact, variations in both the intensity and the distribution of regional CBF changes have been observed depending on the physical characteristics of the stimulus (e.g. heat *vs* cold;¹² chemical *vs* electrical or laser³) or its site of application (skin *vs* subcutaneous or muscles). In the present study, pain caused by pressure combined the features of cutaneous, subcutaneous and muscular pain. Surgical pain possesses a combination of these qualities. The intensity of surgical pain depends on the site and stage of the operation. To mimic an episode of increasing pain intensity, we gradually increased pain intensity to the point of intolerance. To account for changes in pain threshold at baseline and during remifentanyl or nitrous oxide administration, the duration of pain application was taken into account when we calculated $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹.

When attention is directed towards or away from a painful stimulus, this can affect electrocortically evoked potentials^{8,9} as well as pain-induced changes in regional CBF.¹⁰ In the present study, attention was directed towards

the increasing pain, and the volunteers had to actively discontinue this stimulus when the pain became intolerable. We can assume that mechanical pain increased $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹ not only by its specific physical characteristics but also because of the high level of attention present. The importance of such attention is clear in the effects of non-painful cognitive tasks, which increase CBFV_{MCA} in volunteers.¹¹

In this study, both nitrous oxide and remifentanyl reduced the pain-induced increase in $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹. One possible explanation for this is that the state of attention of the subjects could have been altered by the agents. BIS monitoring and clinical impression, however, gave no indication of changes in vigilance and or attention in any volunteers at any time during the experiment. Thus, decreased pain perception with no obvious change in attention probably explains the decrease in $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹ during administration of nitrous oxide or remifentanyl. Alternatively, the observed changes in $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹ could merely reflect pain-induced changes in systemic haemodynamics. In the present study, nitrous oxide and remifentanyl did not cause any changes in arterial pressure or heart rate. Reliable non-invasive measurements during the relatively short periods of increasing pain (<90 s) were not possible. Cerebral autoregulation is maintained with these doses of remifentanyl.¹² Therefore, changes in arterial pressure (e.g. during increasing pain) are unlikely to have caused the observed changes in CBFV. However, nitrous oxide at 50% $\text{FE}'_{\text{N}_2\text{O}}$ does affect autoregulation,¹³ so the observed changes in $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹ could have been caused by circulatory effects.

The effect of the agents on CBFV_{MCA} in the absence of pain is of interest. In the absence of pain, remifentanyl had no effect on CBFV_{MCA} . Similarly, in a previous study, Paris and colleagues¹⁴ showed that an even higher dose (e.g. 2 $\mu\text{g kg}^{-1}$) of remifentanyl did not affect CBFV_{MCA} in anaesthetized patients. In spontaneously breathing volunteers, however, remifentanyl (0.1 $\mu\text{g kg}^{-1} \text{min}^{-1}$) increased regional CBF, especially at brain sites rich in opioid receptors, at a dose comparable to that used in the present study.¹⁵

In the absence of pain, nitrous oxide increased CBFV_{MCA} only at the highest dose used (50% $\text{FE}'_{\text{N}_2\text{O}}$). Nitrous oxide increases CBFV_{MCA} when given to normocapnic volunteers.¹⁶ Hyperventilation counteracted this nitrous oxide-induced increase in CBFV_{MCA} .^{16,17} Thus, pain-induced hyperventilation could have reduced CBFV_{MCA} when nitrous oxide was given during increasing pain. In the present study, however, normocapnia was meticulously maintained using FE'_{CO_2} , which correlates well with PaCO_2 .¹⁸⁻²⁰ In some cases, the changes in ventilation caused by pain were too short (e.g. duration of <60 s) to significantly alter PaCO_2 . Therefore, it is unlikely that changes in PaCO_2 were responsible for the changes observed in $\Delta\text{-CBFV}_{\text{MCA}}$ s⁻¹, whether during administration of nitrous oxide or remifentanyl alone or during the painful

stimulus and administration of analgesic. This is all the more important because cerebrovascular reactivity to carbon dioxide remains intact during administration of remifentanil²¹ and nitrous oxide.²²

In conclusion, we found that mechanical pain increases CBFV_{MCA} in human volunteers. These pain-induced changes in Δ -CBFV_{MCA} s⁻¹ were attenuated during inhalation of nitrous oxide or administration of remifentanil.

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