

Sufentanil Does Not Increase Cerebral Blood Flow in Healthy Human Volunteers

Nikolaus Mayer, M.D.,* Christian Weinstabl, M.D.,* Ivo Podreka, M.D.,† Christian K. Spiss, M.D.‡

The effect of sufentanil on human cerebral blood flow (CBF) was studied in seven unpremedicated, healthy volunteers 31 ± 3.5 yr of age (mean \pm SD) and either sex. CBF ($\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) was measured noninvasively with the ^{133}Xe clearance technique and a scintillation camera before and after sufentanil $0.5 \mu\text{g}/\text{kg}$ administered intravenously. This technique provides values for global blood flow and for gray and white matter blood flow, and from 13 preselected regions in one hemisphere. After the administration of sufentanil, the volunteers were stimulated verbally in order to prevent their loss of consciousness and hypercarbia. Heart rate (HR), arterial pressure, oxyhemoglobin saturation, and end-tidal CO_2 (ET_{CO_2}) were recorded during the measurements. Neither global CBF (46.1 ± 1.6 control and 43 ± 1.9 after sufentanil, mean \pm SEM) nor gray (76.5 ± 3.2 and 70.9 ± 6.1) or white (22.7 ± 1.5 and 24.2 ± 1.6) matter blood flow changed significantly after sufentanil administration. As well, no significant differences in HR (72 ± 4 control and 79 ± 4 beats per min after sufentanil) and ET_{CO_2} (39.8 ± 1.4 and 41.1 ± 1.1 mmHg) were observed. It is concluded that sufentanil has no significant effect on CBF in healthy human volunteers. (Key words: Anesthetics, intravenous: sufentanil. Brain: blood flow. Measurement techniques: blood flow; Fick principle; radioactive tracers.)

SUFENTANIL, a synthetic opioid, five to ten times more potent than fentanyl,¹ induces only minor alterations of heart rate (HR), cardiac output, arterial blood pressure, and peripheral vascular resistance.² Although sufentanil is frequently used in neurosurgical anesthesia, its cerebrovascular effect remains less well defined. It has been demonstrated that sufentanil decreases cerebral blood flow (CBF) and cerebral metabolic demand in rats,³ but two investigations recently challenged these findings by demonstrating increased CBF and cerebral vasodilation in dogs[§] and increased cerebrospinal fluid pressure in humans with decreased intracranial compliance[¶] after the

administration of sufentanil. However, the effect of sufentanil on CBF in humans with normal intracranial compliance and a normal responsiveness of the cerebral vasculature has not been studied. Using a noninvasive CBF measurement technique, the current study was designed to examine the effect of sufentanil on CBF in healthy human volunteers.

Materials and Methods

Seven healthy volunteers of either sex, 31 ± 3.5 yr of age (mean \pm SD), were studied after Institutional Committee on Human Research approval and after informed consent was obtained from each individual. None of the volunteers had a history of cerebral vascular disease or required drug therapy. The volunteers were advised to fast for at least 8 h prior to the beginning of the investigation and received no preanesthetic medication.

CBF was measured noninvasively by iv injection of ^{133}Xe and a scintillation camera (series 100, Ohio-Nuclear, Solon, OH) equipped with special hexagonal collimators. The technical details of this noninvasive method have been described in detail previously.^{4,5} Briefly, ^{133}Xe with a radioactivity of 25 mCi (925 Mbq) was dissolved in 20 ml of normal saline and injected intravenously by means of an infusion pump (Braun, Melsungen, Federal Republic of Germany) over a period of 60 s. The isotope concentration was recorded during 6-s sampling periods over one hemisphere for the following 11 min. Radioactivity was determined over the skull and in the end-tidal gases (Detektor Ratemeter, Nuclear-Chicago, Des Plaines, IL). The latter was assumed to be proportional to the arterial ^{133}Xe concentration. End-tidal gas sampling was conducted with a tight-fitting mouth piece and the nose plugged. Thirteen separate regions of interest, in the same pattern for each volunteer, were selected, and the ^{133}Xe clearance curves were derived for these regions (rCBF) and for the entire hemisphere. After correction for background activity, these curves were deconvoluted and analyzed by a two-compartment model, originally developed by Obrist *et al.*,⁶ based on the Fick principle as applied to an inert diffusible gas.⁷ The first compartment represents blood flow in the gray matter (CBFg) and the second compartment is associated with white matter blood flow (CBFw).

Arterial blood pressure was measured noninvasively by plethysmography and an inflatable cuff attached to the upper arm (Dinamap Critikon, Tampa, FL) every 2 min

* Anesthetist.

† Associate Professor of Neurology.

‡ Associate Professor of Anesthesiology.

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Address reprint requests to Dr. Mayer: Department of Anesthesia and General Intensive Care, University of Vienna, Spitalgasse 23, A-1090, Vienna, Austria.

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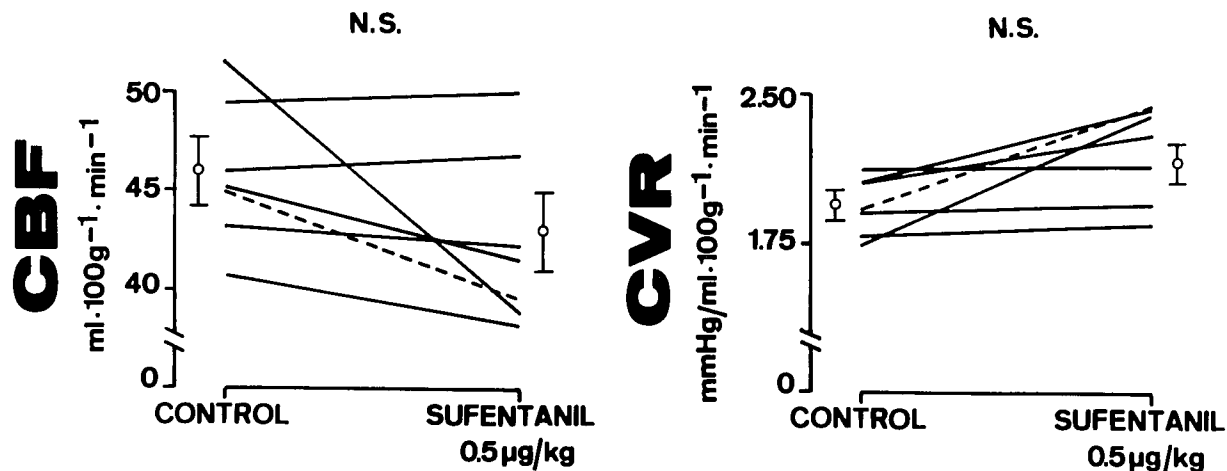


FIG. 1. Cerebral blood flow (CBF), (left panel) and vascular resistance (CVR), (right panel) responses to sufentanil. Neither CBF nor CVR changed significantly following 0.5 µg/kg sufentanil iv. The responses of the volunteer who received 1 µg/kg sufentanil are shown as dashed lines.

during the control period and then every minute after sufentanil. Cerebral vascular resistance (CVR) was calculated as mean arterial pressure (MAP) divided by CBF. HR (lead II ECG) and respiratory waves were monitored and recorded continuously throughout the protocol (model 78534 A, Hewlett Packard, Waltham, MA). Arterial oxyhemoglobin saturation (SpO₂) was registered continuously with a pulse oximeter (model N200, Nellcor, Hayward, CA), and ET_{CO₂} was recorded with a capnometer (Siemens, Erlangen, Federal Republic of Germany) attached to the mouthpiece.

Our initial intention was to study a dose of 1 µg/kg sufentanil. This dose, however, induced considerable hypotension together with extreme discomfort including nausea, sweating, and finally vomiting in the first volunteer studied. Therefore, it was decided to proceed with 0.5 µg/kg. No serious side effects were observed with this dose, and each volunteer felt normal 3 h after administration of sufentanil. Data analysis is confined to the six individuals who received 0.5 µg/kg sufentanil, and the CBF and CVR responses to 1 µg/kg from the first volunteer are presented as dashed lines in figure 1.

Recordings of CBF, arterial blood pressure, HR, SpO₂, and ET_{CO₂} were obtained from the reclining individuals during a control period, without any pharmacologic intervention and after 0.5 µg/kg sufentanil. Each volunteer served as his or her own control. In order to allow further decrease of any remaining radioactivity, at least 1.5 h elapsed between these two measurements. During this time, an infusion of 15 ml/kg Ringer's solution compensated for the 8 h preinvestigational fluid deprivation. One minute after injection of sufentanil, the radioactive tracer was injected and the individual was closely observed and verbally stimulated to prevent sleep or respiratory depression.

The data were analyzed with one-way analysis of variance, and Student's paired *t* test was performed where appropriate. *P* < 0.05 was accepted as significant.

Results

CBF and CVR were within the normal range for this laboratory during the control period. After administration of 0.5 µg/kg sufentanil, there were no significant changes in global CBF (46.1 ± 4 ml · 100 g⁻¹ · min⁻¹ [mean ± SEM] during the control and 43 ± 4.6 ml · 100 g⁻¹ · min⁻¹ after sufentanil) or CVR (1.95 ± 0.06 mmHg/ml · 100 g⁻¹ · min⁻¹ during the control and 2.18 ± 0.10 mmHg/ml · 100 g⁻¹ · min⁻¹ after sufentanil) (fig. 1). In addition, neither CBF_g nor CBF_w changed significantly after administration of sufentanil (table 1). In two areas in the frontotemporal region and in the parietooccipital region, rCBF decreased 13.3 ± 2.8% and 13.8 ± 4.6%, respectively (fig. 2). With the exception of the latter, none of the CBF changes reached statistical significance. The volunteer who received 1 µg/kg sufentanil had a CBF and CVR response similar to that of three individuals who received 0.5 µg/kg (fig. 1).

HR and arterial blood pressure remained stable throughout the entire protocol, and SpO₂ and ET_{CO₂} were always within the normal physiologic range. Since there were no significant differences in the measured variables over time during the control period and after sufentanil administration, the respective data were pooled (table 1).

Discussion

The principal finding of this study is that sufentanil does not alter global CBF in healthy volunteers with presumed normal intracranial compliance and normal cerebral vascular responsiveness prior to the administration

TABLE 1. Cerebral Blood Flow in Gray and White Matter, Heart Rate, Mean Arterial Pressure, Arterial Oxygen Saturation, and End-Tidal CO₂ During the Control Period and Following 0.5 μg/kg Sufentanil IV

	Control	Sufentanil 0.5 μg/kg
CBF _g (ml · 100 g ⁻¹ · min ⁻¹)	76.5 ± 3.2	70.9 ± 6.1
CBF _w (ml · 100 g ⁻¹ · min ⁻¹)	22.7 ± 1.5	24.2 ± 1.6
HR (beats per min)	72 ± 4	79 ± 4
MAP (mmHg)	89 ± 2	94 ± 2
SaO ₂ (%)	97 ± 1	97 ± 1
ETCO ₂ (mmHg)	39.8 ± 1.4	1.1 ± 1.1

All values are mean ± SEM, no significant differences between values during control and following sufentanil; n = 6.

CBF_g = cerebral blood flow in grey matter. CBF_w = cerebral blood flow in white matter. SaO₂ = arterial oxyhemoglobin saturation. ETCO₂ = end-tidal CO₂.

of sufentanil. It also has no effect on the distribution of CBF between gray and white matter, as it has been documented previously for a diazepam-fentanyl mixture.⁸ In two areas, however, rCBF decreased after sufentanil. The local effect in the fronto-temporal region might be ascribed to the feelings of drowsiness experienced by each volunteer, since this a common feature of opioids when given to normal, pain-free individuals.⁹ Although opioid

receptors have been identified in the amygdala,¹⁰ a structure, among others, representative for the parieto-occipital region, we have no explanation for the rCBF decrease in this area, nor do we assign a major clinical importance to it.

Though the result of this study is clear in purely pharmacologic terms, it provides no information regarding the cerebrovascular effects of sufentanil used under truly anesthetic conditions and particularly when other drugs are added. In addition, we cannot exclude that sufentanil might well affect cerebral circulation in patients with decreased intracranial compliance or when used in more clinically relevant doses. Another limitation is that, in order to prevent respiratory depression and sleep, the volunteers were verbally stimulated after administration of sufentanil. It is tempting to speculate that this stimulation acts to increase CBF, thereby raising the chances of seeing a further increase with sufentanil. Since CBF did not change after sufentanil, the variable introduced by repeated verbal stimulation substantiates the finding that sufentanil has no significant effect on human CBF.

The current result is in contrast with the report of Milde and Milde,¹¹ which actually stimulated this investigation. These authors reported increases of CBF up to a

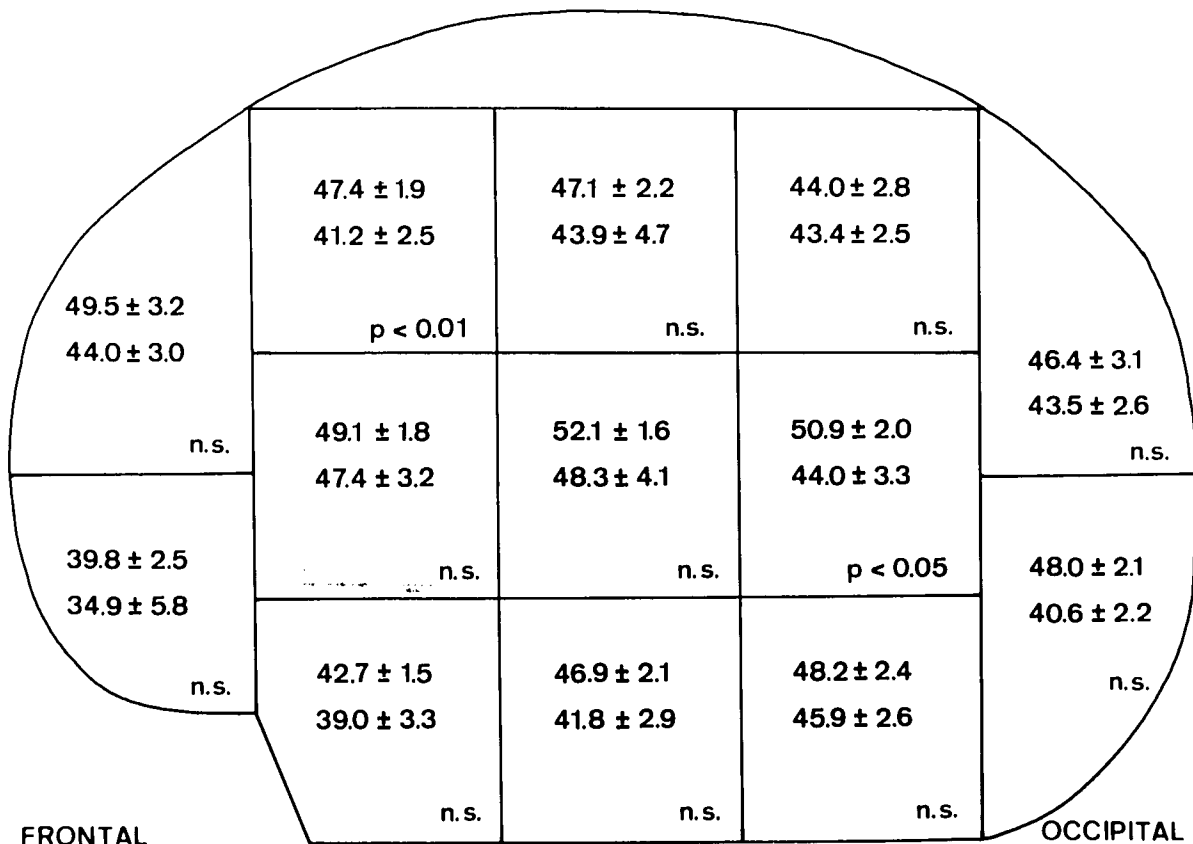


FIG. 2. Regional cerebral blood flow (rCBF) in 13 areas during the control period (upper lines) and following 0.5 μg/kg sufentanil (lower lines). While in a frontotemporal region and a parieto-occipital region, blood flow decreased; all other areas responded with no significant, although unidirectional, blood flow alterations.

maximum of 31% in acutely instrumented dogs after an iv bolus dose injection of sufentanil ranging from 2 to 200 $\mu\text{g}/\text{kg}$. While species differences, especially in studies addressing canine responses to opioids,¹¹ may account for some of the conflicting findings, the dogs also were anesthetized and their lungs mechanically ventilated throughout the entire experiment, whereas the volunteers were kept awake and breathed spontaneously. These different ventilation regimens might have led to the lower PaCO₂ levels in Milde and Milde's dogs, thus offering a greater reserve to cerebral vessel dilation after sufentanil.

Irrespective of the species and of the CBF measurement method used as well as of the variety of drugs added, previous studies revealed a more homogeneous picture of the cerebrovascular effects of sufentanil. Keykhah *et al.*³ studied a broad range of sufentanil doses in rats and reported decreases of CBF in comparison to a control group anesthetized with N₂O. The latter has been shown to increase CBF in dogs,¹² thereby increasing the chance of a CBF decrease after sufentanil administration. However, similar CBF responses to sufentanil, without additional drugs, were documented in nonhuman primates with both normal and decreased intracranial compliance.** Also in patients undergoing elective coronary artery surgery, CBF decreased after the administration of 10 $\mu\text{g}/\text{kg}$ sufentanil while arterial blood pressure remained stable.†† A recent investigation by Young *et al.*¹³ indicated no difference between the cerebrovascular effects of sufentanil and isoflurane, administered with an inspired concentration that has no effect on CBF.^{14,15} These findings have led to the recommendation that sufentanil can be used safely for patients undergoing neurosurgical^{16,17} and neurovascular procedures.¹³

In conclusion, the lack of effect of sufentanil on CBF in healthy volunteers agrees with numerous other studies documenting negligible effects of opioids on cerebrovascular dynamics.^{18,19} These favorable effects, however, require confirmation by studies in humans during anesthesia and in those in whom intracranial compliance is decreased.

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