

# High-dose Remifentanyl Does Not Impair Cerebrovascular Carbon Dioxide Reactivity in Healthy Male Volunteers

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**Background:** Cerebrovascular carbon dioxide reactivity during high-dose remifentanyl infusion was investigated in volunteers by measurement of regional cerebral blood flow (rCBF) and mean CBF velocity (CBFv).

**Methods:** Ten healthy male volunteers with a laryngeal mask for artificial ventilation received remifentanyl at an infusion rate of 2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  under normocapnia, hypocapnia, and hypercapnia. Stable xenon-enhanced computed tomography and transcranial Doppler ultrasonography of the left middle cerebral artery were used to assess rCBF and mean CBFv, respectively. If required, blood pressure was maintained within baseline values with intravenous phenylephrine to avoid confounding effects of altered hemodynamics.

**Results:** Hemodynamic parameters were maintained constant over time. Remifentanyl infusion at 2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  significantly decreased rCBF and mean CBFv. Both rCBF and mean CBFv increased as the arterial carbon dioxide tension increased from hypocapnia to hypercapnia, indicating that cerebrovascular reactivity remained intact. The average slopes of rCBF reactivity were  $0.56 \pm 0.27$  and  $0.49 \pm 0.28 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$  for 2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanyl, respectively (relative change in percent/mmHg:  $1.9 \pm 0.8$  and  $1.6 \pm 0.5$ , respectively). The average slopes for mean CBFv reactivity were  $1.61 \pm 0.95$  and  $1.54 \pm 0.83 \text{ cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$  for 2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanyl, respectively (relative change in percent/mmHg:  $1.86 \pm 0.59$  and  $1.79 \pm 0.59$ , respectively). Preanesthesia and postanesthesia values of rCBF and mean CBFv did not differ.

**Conclusion:** High-dose remifentanyl decreases rCBF and mean CBFv without impairing cerebrovascular carbon dioxide reactivity. This, together with its known short duration of action, makes remifentanyl a useful agent in the intensive care unit when sedation that can be titrated rapidly is required.

REMIFENTANIL hydrochloride is a synthetic opioid with potent and selective  $\mu$ -opioid receptor agonist activity. It is rapidly metabolized by blood and tissue esterases, with an elimination half-life of approximately 9 min. Its ultra-short and predictable duration of action would seem to

make it a useful agent for neurosurgical anesthesia and critical care, where rapid emergence and assessment of the patient is of major importance.

Assuming an increasing demand of remifentanyl during a prolonged stay in the intensive care unit, we investigated cerebral hemodynamics and cerebral blood flow (CBF) reactivity, *i.e.*, the regulatory response of cerebral blood vessels to changes in arterial carbon dioxide tension ( $\text{Paco}_2$ ). Both increases and decreases in CBF have been described, depending on the study conditions, species and model used, opioid regimens, and presence of confounding variables.<sup>1-10</sup>

Baker *et al.*<sup>11</sup> demonstrated that remifentanyl-nitrous oxide ( $\text{N}_2\text{O}$ ) anesthesia preserved cerebrovascular reactivity to changes in  $\text{Paco}_2$ . However, they used relatively low infusion doses (load, 1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; maintenance, 0.35  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) compared with those that might be necessary during a prolonged stay in the intensive care unit. Lorenz *et al.*<sup>12</sup> observed an increased regional cerebral blood flow (rCBF) with a smaller dose of remifentanyl (0.1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) but an equal or an even more pronounced increase in rCBF when using  $\text{N}_2\text{O}$  in healthy volunteers. Paris *et al.*<sup>13</sup> studied normocapnic patients undergoing cardiac surgery without background anesthetics or  $\text{N}_2\text{O}$  and at higher doses of remifentanyl (1 and 3  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). They demonstrated that remifentanyl decreased mean cerebral blood flow velocity (CBFv). However, absolute CBF cannot be inferred from measurements of mean CBFv alone, and the authors did not investigate vascular reactivity under conditions of hypocapnia and hypercapnia.

Therefore, we designed a study to define the dose response of high-dose remifentanyl infusion on CBF and CBF reactivity in healthy volunteers without background  $\text{N}_2\text{O}$  anesthesia, measuring rCBF by xenon-enhanced computed tomography (Xe-CT) and mean middle cerebral artery CBFv by transcranial Doppler ultrasonography (TCD).

## Materials and Methods

After obtaining institutional review board approval (University of Vienna, Vienna, Austria) and written, informed consent, we studied 10 healthy male volunteers. We excluded subjects with a history of drug or alcohol abuse, a surgical procedure in the preceding 6 months, or any detectable abnormalities on physical examination.

To initiate the study, unpremedicated, fasting subjects

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underwent intravenous fluid loading with 10 ml/kg lactated Ringer's solution. A tightly fitting facemask was applied, and the subjects breathed a mixture of oxygen and air with a fraction of inspired oxygen of 0.5. The subjects maintained normal minute ventilation, guided by end-tidal carbon dioxide ( $ET_{CO_2}$ ) values close to 40 mmHg, with blood gas controls of  $P_{aCO_2}$ . Mean CBFv by TCD of the left middle cerebral artery before baseline assessment of rCBF by Xe-CT was then performed (NORMO-PRE).

A loading dose of remifentanil at a rate of  $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  was commenced *via* an infusion pump (Perfusor Secura FT; B. Braun, Melsungen, Germany) until loss of consciousness occurred and was then decreased to 2 or  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  according to the randomization. Chest wall rigidity, if present, was noted. A propofol bolus of 0.5–1 mg/kg was administered to facilitate insertion of a laryngeal mask. Mechanical ventilation was adjusted sequentially to achieve arterial  $P_{aCO_2}$  values of 35–45 mmHg (NORMO-2), 25–32 mmHg (HYPO-2), and 50–55 mmHg (HYPER-2). Cisatracurium bromide was administered in aliquots of 10 mg intravenously if chest wall rigidity prevented achievement of target  $P_{aCO_2}$  values. At each level of  $P_{aCO_2}$ , TCD measurements before Xe-CT were performed to avoid confounding effects of xenon and to obtain data under conditions of normocapnia, hypocapnia, and hypercapnia.

The remifentanil infusion dose was then increased to  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and additional TCD and Xe-CT measurements were performed during hypercapnia (HYPER-4) and hypocapnia (HYPO-4). Thereafter, the remifentanil infusion was discontinued, and the final TCD measurements and Xe-CT were made during spontaneous ventilation with  $ET_{CO_2}$  and  $P_{aCO_2}$  in the normal range (NORMO-POST).

To avoid the possible influence of the sequence of remifentanil dosing, we actually randomized subjects to start with either the low-dose ( $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) or high-dose ( $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) infusion. Thus, in the subjects who were randomized to start with the high-dose infusion, the sequence of measurements was (1) NORMO-PRE, (2) NORMO-4, HYPO-4, HYPER-4, (3) HYPER-2, HYPO-2, and (4) NORMO-POST. We wished to focus our attention on carbon dioxide reactivity rather than absolute changes in CBF during remifentanil infusion. Therefore, we decided to decrease radiation exposure to our subjects by omitting a second normocapnic CBF assessment for each dose. We accepted that this would diminish the statistical power of the normocapnic data by decreasing the number of subjects in this group to five.

At each remifentanil infusion dose adjustment or minute ventilation change, sufficient time for equilibration (minimum 15 min) was allowed. After discontinuation of remifentanil, we recorded the time until recovery of spontaneous ventilation and return of full conscious-

ness with removal of the laryngeal mask. The presence of emergence delirium, nausea, vomiting, or respiratory depression was noted.

To avoid the confounding effects of altered hemodynamics, hypotension was treated with intravenous phenylephrine ( $0.5\text{--}2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and bradycardia with intravenous glycopyrrolate to maintain mean arterial pressure or heart rate within 10% of baseline values. Standard monitoring (Hewlett Packard, Palo Alto, CA) was used, including a radial artery cannula for continuous monitoring of blood pressure and blood gas sampling (AVL Opti, Critical Care Analyzer; AVL, Graz, Austria) to adjust ventilator settings.

Xenon-enhanced computed tomography was performed on a Somatom PLUS scanner (Siemens, Erlangen, Germany) using an optimized 3-min washin/3-min washout protocol.<sup>14</sup> End-expiratory xenon and carbon dioxide concentrations were measured throughout the examination. In the washin phase, a mixture of 30% xenon gas and 70% oxygen was inhaled. One axial slice was evaluated at the level of the deep white matter of the left and right hemisphere. Time-dependent xenon concentration within various tissue segments in the brain was used to derive CBF in each tissue volume (voxel) of the computed tomographic image. The slice thickness was 8 mm, and the matrix of the calculated functional maps was  $256 \times 256$  voxels. Maps of rCBF and xenon-enhancement/voxel were calculated after the measurement based on the formulations of Kety and Schmidt.<sup>15,16</sup> For the calculation of rCBF, the recorded xenon end-tidal values are converted into an estimated time-dependent computed tomographic enhancement of arterial blood.<sup>17</sup> Because of the small pixel size, a single compartment model for further analysis was assumed.<sup>14–17</sup>

For further evaluation of vascular reactivity, rCBF (in  $\text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$ ) was traced over the normocapnic, hypocapnic, and hypercapnic measurements and plotted for six regions of interest for the investigated slice. These included left frontal, left parietal, left occipital, right occipital, right parietal, and right frontal regions.

The rCBF reactivity was defined as the rCBF change per mmHg change in  $P_{aCO_2}$  ( $\text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ ). Relative rCBF reactivity (percent change/mmHg) was determined by the formula:

$$\frac{[(\text{rCBF}_{\text{hyper}} - \text{rCBF}_{\text{hypo}})/\text{rCBF}_{\text{hyper}}]}{(P_{aCO_2 \text{ hyper}} - P_{aCO_2 \text{ hypo}})} \cdot 100,$$

where hypo = during hypocapnia, and hyper = during hypercapnia.

As a second method to assess cerebral vascular reactivity,<sup>18</sup> TCD of the left middle cerebral artery was performed before every Xe-CT using a 2-MHz pulsed Doppler monitoring probe placed at the left transtemporal window (Multidop 10; DWL, Sipplingen, Germany). Insonation of the middle cerebral artery was initiated at a

**Table 1. Regional Cerebral Blood Flow, Hemodynamic Parameters, and Cerebral Blood Flow Velocity during Remifentanyl Anesthesia and Different Carbon Dioxide Levels**

rCBF of Brain Area	Normocapnia				Hypocapnia		Hypercapnia	
	Before Anesthesia	After Anesthesia	2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	4 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	4 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	4 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$
	n = 10		n = 5		n = 10			
ROI, $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$								
1	53 ± 21	41 ± 2	19 ± 7*	16 ± 5*	13 ± 4*	13 ± 4*	25 ± 7*	23 ± 8*
2	62 ± 18	49 ± 8	24 ± 8*	17 ± 4*	16 ± 5*	15 ± 5*	30 ± 9*	29 ± 10*
3	45 ± 12	37 ± 6	19 ± 7*	16 ± 4*	14 ± 6*	15 ± 5*	25 ± 7*	24 ± 9*
4	47 ± 15	39 ± 7	21 ± 7*	16 ± 4*	14 ± 5*	14 ± 4*	27 ± 8*	27 ± 11*
5	65 ± 23	47 ± 8	24 ± 8*	17 ± 4*	15 ± 5*	15 ± 4*	29 ± 8*	28 ± 8*
6	54 ± 30	45 ± 11	19 ± 8*	15 ± 3*	13 ± 4*	12 ± 4*	25 ± 8*	23 ± 8*
1-6	54 ± 21	43 ± 8	21 ± 7*	16 ± 4*	14 ± 5*	14 ± 4*	27 ± 8*	26 ± 9*
MAP, mmHg	91 ± 11	93 ± 12	94 ± 5	90 ± 7	91 ± 8	96 ± 16	92 ± 14	95 ± 9
HR, beats/min	65 ± 11	73 ± 15	60 ± 11	54 ± 7	61 ± 9	65 ± 11	60 ± 9	62 ± 10
CBFv, cm/s	72 ± 17	84 ± 22	54 ± 11*	61 ± 14*	41 ± 13*	38 ± 9*	85 ± 37	83 ± 28
PI	0.85 ± 0.15	0.72 ± 0.21	0.83 ± 0.19	0.85 ± 0.21	0.94 ± 0.18	1.04 ± 0.28	0.74 ± 0.10	0.77 ± 0.17
Paco <sub>2</sub> , mmHg	42 ± 3	39 ± 7	41 ± 5	44 ± 3	29 ± 3	27 ± 3	54 ± 6	55 ± 7

Values are shown as mean ± SD.

\*  $P < 0.01$ .

CBFv = cerebral blood flow velocity; PI = pulsatility index; rCBF = regional cerebral blood flow; ROI = region of interest; ROI 1-6 = mean of all pooled brain areas.

depth of 45 mm. The correct position was determined manually before each measurement by first locating the bidirectional flow pattern typical of the bifurcation of the internal carotid artery into middle cerebral and anterior communicating arteries. Then, the insonation depth was increased to the point of the maximal signal intensity, and a series of readings of middle cerebral artery blood flow velocity was obtained, including mean (Vm), peak systolic (Vs), and peak diastolic (Vd) velocity. A pulsatility index (PI) was calculated by dividing the difference between Vs and Vd by Vm:

$$\text{PI} = (\text{Vs} - \text{Vd})/\text{Vm}.$$

Vascular reactivity was defined in terms of mean CBFv as the mean CBFv change per mmHg change in  $\text{PaCO}_2$  ( $\text{cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$ ). Relative mean CBFv reactivity was determined by the formula:

$$\frac{[(\text{CBFv}_{\text{hyper}} - \text{CBFv}_{\text{hypo}})/\text{CBFv}_{\text{hyper}}]}{(\text{PaCO}_{2 \text{ hyper}} - \text{PaCO}_{2 \text{ hypo}})} \cdot 100,$$

where CBFv = mean CBFv, hypo = during hypocapnia and hyper = during hypercapnia.

All values are given as mean ± SD. Data were analyzed by analysis of variance for repeated measurements followed by a Fisher *post hoc* test. To assess rCBF and mean CBFv changes produced by different drug doses in a given group, a paired Student *t* test was used. A *P* value less than 0.05 indicated a significant difference. An *a priori* power analysis was performed. This analysis demonstrated that a sample size of 10 patients would provide approximately 80% power at  $\alpha = 0.05$  to detect a CBF change of  $30 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  from baseline. This information was based on an expected 30% CBF change

from baseline for remifentanyl<sup>19</sup> and a CBF change of 2% per mmHg carbon dioxide.<sup>11</sup>

## Results

All volunteers ( $n = 10$ ; age,  $27 \pm 6$  yr; weight,  $71 \pm 9$  kg; height,  $179 \pm 4$  cm) completed the study without complication. Data for rCBF, hemodynamics, and mean CBFv are summarized in table 1. Hemodynamics (mean arterial pressure and heart rate) remained unchanged through the study. Requirement for phenylephrine or glycopyrrolate was similar at both remifentanyl doses as well as the use of cisatracurium to facilitate ventilation during the study (table 2). Two volunteers required a cisatracurium bolus after induction of anesthesia because of chest wall rigidity. The rCBF and mean CBFv values were not significantly different before and after remifentanyl infusion but were significantly decreased during the infusion of remifentanyl. However, cerebrovascular reactivity to carbon dioxide was preserved.

During remifentanyl infusion at 2 and  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , rCBF and mean CBFv increased as the  $\text{PaCO}_2$  increased. The average slope of the rCBF reactivity was  $0.56 \pm 0.27$  and  $0.49 \pm 0.28 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  per mmHg  $\text{PaCO}_2$  change, at 2 and  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanyl, respectively. This corresponded to a relative CBF reactivity of  $1.9 \pm 0.8$  and  $1.6 \pm 0.5\%$  change per mmHg, respectively (not significant).

The average slopes of the mean CBFv reactivity were  $1.61 \pm 0.95$  and  $1.54 \pm 0.83 \text{ cm/s}$  per mmHg  $\text{PaCO}_2$  change at 2 and  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanyl, respectively. This corresponded to relative CBF reactivities of



**Table 2. Total Amount of Cisatracurium, Cardiovascular Support with Glycopyrrolate, and Phenylephrine (for Phenylephrine, Including Time during Which the Drug Was Infused)**

Volunteer	Cisatracurium, mg	Glycopyrrolate, mg	$2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$		$4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	
			Phenylephrine, mg	Infusion Time, min	Phenylephrine, mg	Infusion Time, min
1	10	0.4	1.82	70	0.32	19
2	20	0	1.8	96	0.37	29
3	10	0	0.14	42	0	0
4	10	0.4	3.05	111	1.81	64
5	30	0.2	0	0	0	0
6	20	0.4	1.32	66	2.34	118
7	20	0.3	0.33	49	0.82	97
8	10	0.4	0.92	55	2.26	125
9	30	0.4	0.66	72	1.73	105
10	10	0.2	0	0	0	0
Mean $\pm$ SD	17 $\pm$ 8.23	0.27 $\pm$ 0.16	1 $\pm$ 0.99	56 $\pm$ 36	1 $\pm$ 0.97	56 $\pm$ 52

1.86  $\pm$  0.59 and 1.79  $\pm$  0.59% change per mmHg  $\text{Paco}_2$ , respectively (not significant).

Bivariate calculations (Pearson) between Xe-CT and TCD on raw data and relative carbon dioxide reactivities to identify a correlation slightly missed significance because of variance and a very small sample size ( $n = 10$ ). Nonetheless, rCBF measured with Xe-CT and mean CBFv measured with TCD showed a consistent and significant response to alterations in  $\text{Paco}_2$ , which is demonstrated in figure 1, where individual CBF data of the left parietal region of interest, the brain region corresponding to the left middle cerebral artery, and mean CBFv are shown. The results were similar in all other regions of interest (data not shown).

The mean duration of anesthesia was 102  $\pm$  12 min, and the total study duration was 4.3  $\pm$  0.3 h. Emergence from anesthesia was rapid. Patients breathed spontaneously an average of 2.3  $\pm$  1.7 min after discontinuation of remifentanil. The laryngeal mask was removed after a mean of 7.4  $\pm$  2.9 min, with no incidence of respiratory depression.

## Discussion

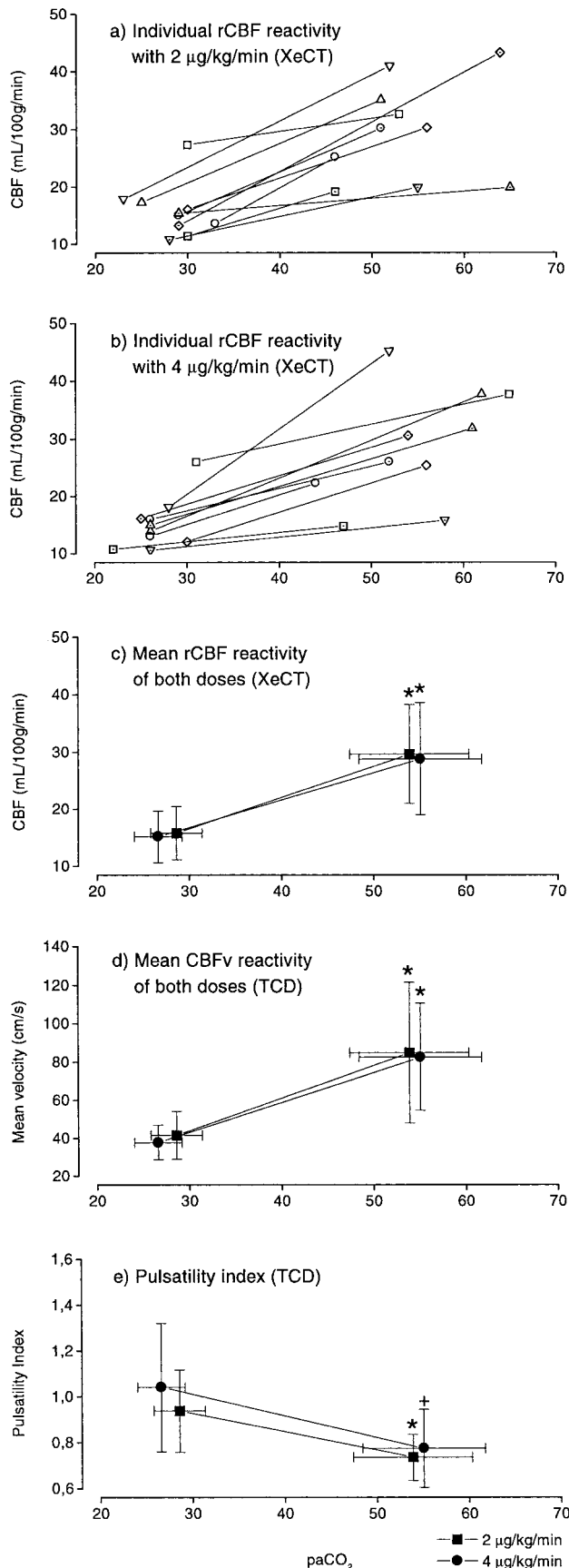
This study demonstrates that human CBF reactivity to arterial carbon dioxide tension remains intact under remifentanil-air anesthesia. Unlike previous studies, our findings are based on the simultaneous direct (Xe-CT) and indirect (TCD) assessment of CBF, which both confirmed that carbon dioxide reactivity is preserved independently of the dose (2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) of remifentanil.

Similar observations were made by Baker *et al.*<sup>11</sup> with 0.35  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanil and background  $\text{N}_2\text{O}$  anesthesia, but they noted greater CBF reactivity: 3.6  $\pm$  1.2% per mmHg carbon dioxide compared with our findings of 1.9  $\pm$  0.8 and 1.6  $\pm$  0.5% per mmHg carbon dioxide (at 2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanil infusion, respectively). In another study from the same group,<sup>20</sup> carbon dioxide reactivity for remifentanil- $\text{N}_2\text{O}$

anesthesia was 2.6  $\pm$  3.6% per mmHg carbon dioxide and was similar to an equipotent fentanyl- $\text{N}_2\text{O}$  anesthesia (4.5  $\pm$  2.2% per mmHg carbon dioxide). The quantitative difference in CBF reactivity between the study of Baker *et al.* and our study might be because we used 5- to 10-fold greater doses of remifentanil and made measurements over a different  $\text{Paco}_2$  range. Also, CBF reactivity to carbon dioxide has traditionally been described by a linear model, whereas the true response curve is sigmoidal. This brings up an intriguing question of whether or not remifentanil dosing causes a shift in CBF reactivity. CBF increases from hypocapnia to normocapnia during low-dose remifentanil but not during high-dose remifentanil (table 1). However, there is no difference in CBF reactivity from hypocapnia to hypercapnia between the two doses of remifentanil (fig. 1). This suggests that the cerebrovasoconstrictor effect of high-dose remifentanil overrides normocapnia but not hypercapnia. Unfortunately, because of the small sample size of normocapnic patients, these data did not reach statistical significance, and the difference in response slopes could be an artifact of where on the sigmoidal carbon dioxide response curve CBF reactivity was plotted. Furthermore, we have not compared CBF reactivity to the awake state, which is necessary to identify a quantitative shift under remifentanil anesthesia.

Although it varied in magnitude, rCBF significantly decreased in every region of interest during both doses of remifentanil infusion (2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; fig. 1).

After discontinuation of remifentanil, rCBF was not significantly different from baseline values before anesthesia, presumably reflecting remifentanil's rapid elimination in plasma. In other descriptions of cerebral hemodynamics during remifentanil- $\text{N}_2\text{O}$ <sup>11,20</sup> or fentanyl- $\text{N}_2\text{O}$  anesthesia<sup>10</sup> with doses lower than in our study, under comparable  $\text{Paco}_2$  conditions, CBF was reported as 31  $\pm$  7, 36  $\pm$  11, and 31  $\pm$  4 ml  $\cdot$  100 g<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, respectively. In contrast, the values for cumulative CBF that we measured in five normocapnic volunteers in our



study were  $21 \pm 2$  and  $16 \pm 1 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  for remifentanyl at 2 and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively.

These differences could be accounted for by various reasons. Higher CBF values in studies using N<sub>2</sub>O might be attributed to its potent cerebral vasodilating effects, which caused a significantly more pronounced increase of CBF in all gray matter regions compared with remifentanyl in conscious humans.<sup>12</sup>

Lower CBF values in our study likely result from a direct constrictive effect of high-dose opioids on cerebral blood vessels. We attempted in our study to minimize the influence of autoregulation on CBF by maintaining constant blood pressure with a phenylephrine infusion, which itself has no direct effect on cerebral vasculature.<sup>21,22</sup> Therefore, decreased rCBF points toward opioid-induced vasoconstriction. Furthermore, opioid administration is generally believed to suppress brain activity. For example, in animal<sup>23</sup> and human<sup>24</sup> studies, infusion of sufentanil induces a significant decrease in cerebral metabolic rate for oxygen coupled with changes in cerebral hemodynamics. Although we did not measure cerebral metabolic rate, with intact metabolic coupling, reduced CBF might reflect diminished metabolic demands under the high-dose remifentanyl administration in our study.

However, some investigations on human brain revealed significant rCBF increases and failed to demonstrate a global suppression of neuronal activity after the administration of fentanyl<sup>3</sup> or remifentanyl<sup>12,25</sup> at a low dose. In these studies, both drugs induced changes in relative rCBF in areas involved in pain processing as assessed with positron emission tomography<sup>3,25</sup> or contrast-enhanced magnetic resonance imaging.<sup>12</sup> Although one could argue that agonist actions of remifentanyl on neuron-located opioid receptors can result in an increased synaptic energy demand,<sup>26</sup> the more than 20-fold higher remifentanyl dose in our study makes it unlikely that we would have observed effects other than related to vasoconstriction or brain activity suppression of opioids.

Our findings are in keeping with others that have indicated that remifentanyl exerts a dose-related suppression of mean CBFv while maintaining vascular carbon dioxide reactivity and flow-metabolism coupling. In a study in cardiac patients ventilated with oxygen without background anesthesia,<sup>13</sup> CBFv was decreased 9% (not significant) by 1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanyl and by

**Fig. 1.** Cerebral blood flow reactivity after remifentanyl infusion. For individual and cumulative regional cerebral blood flow (rCBF) changes assessed by xenon-enhanced computed tomography (XeCT) data from the left parietal region of interest (a-c) have been selected to underline corresponding mean cerebral blood flow velocity (CBFv) changes in the left middle cerebral artery as assessed by transcranial Doppler sonography (TCD). \* $P < 0.01$ , + $P < 0.05$  versus hypocapnia. PaCO<sub>2</sub> = arterial carbon dioxide tension.

31% ( $P < 0.05$ ) by  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanil. The authors interpreted these data to suggest that  $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  may be the threshold above which remifentanil progressively depresses mean CBFv. A similar dose-response effect has been reported for sufentanil,<sup>4</sup> with a 27–30% decrease in mean CBFv noted at  $6 \mu\text{g}/\text{kg}$  but not at  $3 \mu\text{g}/\text{kg}$ . In our study, the missing dose-response relation of remifentanil 2 and  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  with mean CBFv suggests a near maximum response of the drug. The decreased pulsatility index we saw with hypercapnia represents decreased vascular resistance and also suggests that the bulk of change in CBF is in response to increases in  $\text{Paco}_2$ .

The hemodynamic responses to remifentanil we encountered are well known. Opioid-induced decreases in heart rate and blood pressure required the administration of glycopyrrolate and phenylephrine to prevent bradycardia and hypotension. In fact, the cardiovascular support required in this study was modest, with some volunteers requiring no support at all. It was not significantly different at the two dosing regimens, suggesting that a maximal hemodynamic effect had been achieved. Other side effects were a moderate chest wall rigidity due to the high induction dose of remifentanil, but only two patients needed a 10-mg bolus of cisatracurium after induction to facilitate ventilation. All other volunteers received cisatracurium, a drug with no influence on cerebral hemodynamics,<sup>27,28</sup> during the study if chest wall rigidity prevented achievement of target  $\text{Paco}_2$  values.

This study has certain methodologic limitations. Inhaled xenon, an inert gas used for measurements of CBF, is known to influence CBF itself in a dose-dependant fashion. Autoradiographic studies in rats revealed a doubling of rCBF in some neocortical structures after 80% xenon inhalation for 1- and 2-min periods but no effect on rCBF after 40% xenon inhalation for 1 min.<sup>29</sup> Microsphere studies in baboons revealed a 17% increase in CBF when a 35–42% xenon-oxygen mixture was inhaled for more than 2 min,<sup>30</sup> and in humans, 30–35% xenon inhaled for 4.5 min was associated with CBF increases as much as 35% above baseline.<sup>31</sup>

Obrist *et al.*<sup>32</sup> attempted to quantify xenon-induced cerebral blood flow activation during xenon computed tomography. They developed a computer simulation model based on repeated TCD measurements of blood velocity during 4.5 min of stable xenon inhalation. In contrast to the peak 35% increase in blood flow velocity encountered during xenon inhalation, a computer-assisted analysis revealed only minor (3–5%) increases in calculated CBF.<sup>32</sup> In our study, we attempted to minimize activation bias by keeping xenon inhalations brief (3 min) and the inspired xenon concentration low (30%). It is reasonable to expect that at these levels, exposure to xenon would have exerted little influence on the validity of our CBF measurements. Under condi-

tions of reduced global CBF, the situation is different. The concentration of diffusible tracer in tissue, which is necessary for measurement of enhancement over time, especially in low-flow compartments, may be comparably low. Therefore, a greater error with underestimation of real rCBF than in normal flow conditions mainly in the white matter is possible. This might explain why almost ischemic-looking rCBF values during remifentanil exposure in hypocapnia unlikely were ischemic. First, the expected ischemic range of  $15\text{--}20 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  refers to gray matter.<sup>33</sup> Because our regions of interest represent an average of both gray and white matter, lower values will be tolerable. Second, in a study about rCBF measurements in patients with acute ischemia rCBF, values in the range  $11\text{--}20 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  were found in at least 20% of the area of the nonischemic hemisphere.<sup>34</sup> In the same study, in follow-up examinations, no infarct could be found in those areas. Third, both studies were performed in awake patients while under high-dose opioid anesthesia; because of additional suppression of brain activity, decreased rCBF values may also reflect decreased metabolic demand. Finally, all volunteers required ultrashort and predictable time to regain consciousness after anesthesia or to remove the laryngeal mask. None of the volunteers showed any neurologic sign indicative of a preceding ischemic period.

In conclusion, we have demonstrated that infusion of high-dose remifentanil ( $2$  and  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) in healthy male volunteers decreases CBF but leaves cerebrovascular reactivity to acute changes in  $\text{Paco}_2$ . Our results are based on both direct (Xe-CT) and indirect (TCD velocity) measurements of CBF, which both significantly increased with an increase in  $\text{Paco}_2$ .

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