

## Cerebral Blood Flow and Metabolism during Morphine-Nitrous Oxide Anesthesia in Man

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The effects of two levels of morphine-nitrous oxide anesthesia on cerebral blood flow (CBF) and cerebral metabolism ( $CMR_{O_2}$ ) were measured in healthy male volunteers. CBF and metabolic measurements were made in the awake control state, after morphine, 1 mg/kg, with 70 per cent nitrous oxide and 30 per cent oxygen, and at a total dose of 3 mg/kg morphine with the same concentrations of nitrous oxide and oxygen. Ventilation was controlled and carbon dioxide added to inspired gas to maintain  $P_{aCO_2}$  constant at 40 torr. CBF was  $48.2 \pm 4.4$  (SEM) ml/100 g/min during the control phase;  $45.7 \pm 6.4$  ml/100 g/min after 1 mg/kg morphine, and  $44.3 \pm 4.9$  ml/100 g/min after 3 mg/kg morphine. The latter values are not significantly different from control. Cerebral metabolic rates for oxygen, glucose, and lactate were normal in the control phase and did not change significantly when morphine was present at either level. It is concluded that morphine-nitrous oxide anesthesia produces no alteration of cerebral blood flow or metabolism in normal man at the two dose levels studies. (Key words: Anesthetics, intravenous, morphine; Brain, blood flow; Brain, metabolism, lactate.)

THE USE OF MORPHINE SULFATE in large doses has become a popular anesthetic technique for patients undergoing cardiac surgery. We previously reported that the anesthesia produced by a single dose of morphine, 2 mg/kg, in the presence of nitrous oxide did not alter the ability of the brain to autoregulate in response to changing arterial pressure.<sup>1</sup> The present paper amplifies on our earlier work by reporting results of measurements of cerebral blood flow (CBF) and metabolism ( $CMR_{O_2}$ ) in volunteers, awake and following morphine sulfate in doses of 1 and 3 mg/kg.

### Methods

Six fully informed, healthy male volunteers were accepted for the study after histories were obtained and physical and laboratory examinations were

performed. Laboratory examinations included complete blood count, electrocardiogram, chest roentgenogram, routine urinalysis and examination of urine for narcotic drugs.

On the day of study all sampling and monitoring lines were placed with the volunteer awake and unpremedicated. These included peripheral venous, radial arterial, and central venous catheters, percutaneous internal jugular-bulb needle, electrocardiogram leads, and rectal thermistor probe. All pressures were continuously recorded on a Grass polygraph via Statham transducers.

Each volunteer was studied awake as his own control. Four subjects breathed nitrogen, 70 per cent, and oxygen 30 per cent, while two subjects inadvertently breathed 100 per cent oxygen during the control measurements. Following medication with atropine sulfate, 0.4 mg, intravenously, anesthesia was induced by the simultaneous administration of nitrous oxide, 70 per cent, and oxygen, 30 per cent, by mask and morphine sulfate intravenously at a rate of 10 mg/min to a dose of 1 mg/kg. *d*-Tubocurarine, 0.7 mg/kg, was given intravenously, after which intubation of the trachea was performed. Additional *d*-tubocurarine, average total dose 0.82 mg/kg, was given between measurements to prevent body movement. Approximately an hour was allowed between administration of morphine and measurement of CBF and  $CMR_{O_2}$  in order to obtain precise control of the arterial carbon dioxide tension ( $P_{aCO_2}$ ). Upon completion of those measurements, a second dose of morphine, 2 mg/kg, was given at a rate of 10 mg/min for a total of 3 mg/kg.

Ventilation was controlled with a Bird ventilator set to deliver 125 ml/kg/min through a nonbreathing circuit. Expired ventilation was measured by a dry gas meter. Carbon dioxide was added to maintain  $P_{aCO_2}$  at 40 torr. End-tidal carbon dioxide tension ( $P_{ETCO_2}$ ) was measured by a Godart capnograph and continuously recorded on a Grass polygraph. Blood-gas tensions and pH were measured with Clark and Severinghaus electrodes in an Instrumentation Laboratories 113 Ultramicro device. Oxygen was determined manometrically.<sup>2</sup> A fluorometric technique was used to assay for plasma morphine.<sup>3</sup>

Temperature was maintained at 37 C using infrared lamps. Cerebral blood flow was measured with a <sup>85</sup>Kr-uptake technique utilizing a liquid scintillation counting method.<sup>4,5</sup>  $CMR_{O_2}$  was calculated from CBF and the arteriovenous oxygen content difference. Lactate, pyruvate, and glucose were

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determined by enzymatic analysis.<sup>6</sup> Blood lost through sampling was immediately replaced with an equal volume of plasma protein fraction. Data were analyzed by two-dimensional analysis of variance and by critical difference testing at  $P < .05$ , except for values for plasma morphine, which were analyzed by paired t test.

The experimental conditions during the study are shown in table 1. Mean airway pressure and jugular-bulb venous pressure, accounted for a statistically significant decrease in cerebral perfusion pressure. However, cerebral perfusion pressure remained within the limits of cerebral autoregulation, which have been shown to be unaffected by nitrous oxide-morphine anesthesia.<sup>1</sup> Cerebral perfusion pressures were similar at the two levels of anesthesia in this study. There was no change in arterial oxygen tension when we consider only the mean oxygen tension of the subjects who breathed the nitrogen-oxygen mixture during the control phase. When the two subjects who breathed oxygen during the control phase are included, the mean control oxygen tension increases, but by a statistically insignificant amount, and the deviation remains within limits

TABLE 1. Experimental Conditions During Measurement of Cerebral Blood Flow and Metabolism

	Awake Control	Morphine 1 mg/kg	Morphine 3 mg/kg
Mean arterial pressure (torr)			
Mean	96.1	81.2*	78.4*
SE	2.4	5.2	3.4
Jugular-bulb venous pressure (torr)			
Mean	9.2	12.6*	12.9*
SE	0.6	0.7	0.6
Cerebral perfusion pressure (torr)			
Mean	85.9	68.6*	65.4*
SE	2.0	5.8	3.8
Mean airway pressure (torr)			
Mean	1.8	8.3*	8.0*
SE	0.4	1.2	1.0
Rectal temperature (C)			
Mean	37.2	36.8	36.8
SE	0.1	0.2	0.3
P <sub>aO<sub>2</sub></sub>			
Mean	137.2†	168.2	171.4
SE	9.18	6.3	5.0
P <sub>aCO<sub>2</sub></sub>			
Mean	41.2	42.2	42.2
SE	1.2	0.8	0.8
pH <sub>a</sub>			
Mean	7.394	7.359	7.363
SE	.010	.004	.005
Plasma morphine (μg/ml)			
Mean	—	.033	0.190†
SE	—	.017	0.021

\* Significantly different from control,  $P < 0.05$ .

† Significantly different from 1 mg/kg,  $P < 0.05$ .

‡ Mean for four subjects with F<sub>I<sub>O<sub>2</sub></sub> 30 per cent. When values for all subjects are included the mean P<sub>aO<sub>2</sub></sub> is 275.9 torr with a standard error of 87.9.</sub>

TABLE 2. Cerebral Circulatory and Metabolic Values Awake and at Two Dose Levels of Morphine

	Awake Control	Morphine 1 mg/kg	Morphine 3 mg/kg
CBF (ml/100 g/min)			
Mean	48.2	45.7	44.3
SE	4.4	6.4	4.0
CVR (torr/ml/100 g/min)			
Mean	1.89	1.66	1.51
SE	0.18	0.27	0.23
CMR <sub>O<sub>2</sub></sub> (ml/100 g/min)			
Mean	3.23	2.91	3.25
SE	0.38	0.29	0.41
CMR glucose (mg/100 g/min)			
Mean	4.15	3.29	3.49
SE	0.67	0.42	0.78
CMR lactate (μm/100 g/min)			
Mean	5.78	3.16	2.75
SE	1.20	1.30	0.82

that should not significantly affect CBF.<sup>7</sup> Rectal temperature, P<sub>aCO<sub>2</sub></sub>, and pH were unchanged from control levels. Elapsed time from the 1 mg/kg dose to CBF measurement was 60 ± 5 minutes, and that from the 2 mg/kg dose was 53 ± 4 minutes. These elapsed times are not significantly different. Measurement of plasma morphine levels demonstrated the expected increase following administration of morphine.

## Results

The hemodynamic variables of CBF and cerebrovascular resistance (CVR) during the awake state were within the range of normal for this laboratory (table 2). In view of the decrease in cerebral perfusion pressure, a concomitant decrease in cerebrovascular resistance is expected to maintain CBF constant. The resistance decreased, but the change was not significant.

Cerebral metabolic rates for oxygen and glucose uptake were within the range of normal during the awake state (table 2). Neither changed significantly during morphine anesthesia. Cerebral metabolic rate for lactate production likewise showed no significant difference from the normal awake value.

## Discussion

Our data demonstrate no change in CBF at the two levels of morphine-nitrous oxide anesthesia studied. Cerebral autoregulation appeared to be unimpaired by morphine-nitrous oxide in that CVR decreased somewhat when perfusion pressure decreased. Had a larger number of subjects been studied, a significant decrease in cerebrovascular resistance might have been found. This is consistent with results of other work from this laboratory which specifically measured autoregulation.<sup>1</sup>

Cerebral metabolic rates for oxygen, glucose, and lactate were unchanged from control at both levels

of morphine anesthesia. Our data confirm those of McCall *et al.*, who showed no change in CBF or  $CMR_{O_2}$  following morphine, 30 mg.<sup>8</sup> They are different from those of Moyer *et al.*, who reported a significant decrease in  $CMR_{O_2}$  following intravenous administration of morphine, 60 mg.<sup>9</sup> We can offer no satisfactory explanation for this discrepancy. There were, however, a number of differences among the studies which might help to account for the differences in results. First, there was a difference in morphine dosage. Moyer *et al.* gave 60 mg morphine to each volunteer, while we studied the effects of 1 and 3 mg/kg. Second, Moyer *et al.* did not control  $Pa_{CO_2}$  and did not find as much increase in CBF as might be expected from the extent of hypercarbia reported to be present in their volunteers. However, they had to calculate  $Pa_{CO_2}$  from carbon dioxide content since the carbon dioxide electrode was not yet available when they did their study. Third, there was a difference in the techniques for measurement of CBF. Moyer *et al.* used the nitrous oxide technique of Kety and Schmidt, while we used the radioactive krypton technique. While McCall *et al.* also gave a different dose of morphine, used the nitrous oxide technique for measurement of CBF, and did not attempt to control  $Pa_{CO_2}$ , they found no increase in  $Pa_{CO_2}$  and no change in CBF or  $CMR_{O_2}$ .

In another investigation, we studied cerebral autoregulation in the presence of nitrous oxide and morphine, 2 mg/kg.<sup>1</sup> In that study  $CMR_{O_2}$  was normal in the presence of morphine and unchanged by both high and low arterial pressures. This is in contrast to our findings with halothane, enflurane, and isoflurane, which, at a given blood pressure, increase CBF in a dose-related fashion.

We therefore conclude that morphine-nitrous oxide anesthesia produces no alteration of cerebral blood flow or metabolism of clinical importance in normal man over the dose range of 1 to 3 mg/kg. In clinical circumstances where ventilation is controlled, large doses of morphine used for anesthesia should not affect normal cerebral blood flow and metabolism.

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