The Effects of Ketamine on Cerebral Circulation and Metabolism in Man

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The effects of ketamine on cerebral circulation and metabolism were studied in ten healthy patients before elective surgical operations. With intravenous administration of ketamine in two increments (3 mg/kg total), cerebral blood flow increased from a control value of 47 to 76 ml/100 g/min and cerebral vascular resistance decreased from 1.91 to 1.35 mm Hg/ml/100 g/min. Cerebral perfusion pressure and PaO₂ increased from 88 to 102 mm Hg and from 36.0 to 39.7 mm Hg, respectively, after ketamine. These data indicate that the increase in cerebral blood flow was mainly the result of cerebral vasoconstriction caused by ketamine. CMRO₂, CMRcerebro, and CMRcereb as indices of cerebral metabolism did not change significantly after ketamine. (Key words: Ketamine; Cerebral circulation; Cerebral blood flow; Cerebral metabolism.)

Knowledge of the cerebral circulation in anesthetized man has accumulated rapidly in the past five years. It has been reported that cerebral blood flow (CBF) increases with depth of anesthesia with halothane,2,3 or ether.4 CBF decreases during light cyclopropane anesthesia and increases during deep anesthesia.5 It is well known that thiopental decreases CBF.6,7 Although it has been believed that general anesthetics decrease cerebral oxygen consumption (CMRO₂), recent studies reveal no consistent changes in CMRO₂ with changing depths of anesthesia.8 The effects of ketamine on the cerebral circulation and metabolism of man have not been reported.

In this study some effects of ketamine on the cerebral circulation and carbohydrate metabolism of man were investigated. The results indicate that ketamine increases CBF but does not significantly alter cerebral metabolism.

Methods

Ten patients scheduled for elective operations and without cardiopulmonary or neurologic disorders were studied before operation. Mean age was 43 ± 3 (SE) years. Cerebral blood flow and metabolism were examined before and during ketamine anesthesia. The subjects were unstimulated throughout the study. Thirty minutes after intramuscular administration of 0.5 mg atropine, ketamine, 2 mg/kg, was given intravenously during one minute. An additional 1 mg/kg of ketamine was given intravenously 5 minutes later. Gas from the pharyngeal cavity was sampled continuously and passed through an infrared gas analyzer (Toshiba-Beckman) for monitoring of end-tidal CO₂. When respiratory depression occurred, respiration was assisted to maintain normocarbia. Fron-to-occipital EEG recordings were made at frequent intervals throughout the study, using a Nihon Koden electroencephalograph. With this dose of ketamine, electroencephalograms showed consistent, predominant 5-6-cps (15-25 μv) activity. Representative electroencephalograms are shown in Figure 1.

Rectal temperature was measured with a calibrated thermometer probe. Indwelling teflon catheters were placed in the brachial artery and the internal jugular bulb for blood sampling and pressure measurement.

While awake, patients breathed 100 per cent oxygen for 15 minutes, then inhaled a mixture of 10 per cent N₂O and 90 per cent oxygen for CBF measurement. In every study CBF was determined over a 14-minute period. Simultaneous arterial and internal jugular venous blood samples were obtained approximately 1, 3, 5, 7, 10, and 14 min after

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Before Ketamine

After Ketamine (During CBF Measurement)

![Graph showing before and after ketamine effects on EEG waves.]

Fig. 1. Representative electroencephalogram during ketamine anesthesia. Bipolar fronto-occipital recording (right). Before ketamine, β waves interposed by α waves were seen. After ketamine α waves disappeared and characteristic 5-6-cps waves (15-25 μV), occasionally with superimposed 18-20-cps waves, were recorded. 1, 3 min after ketamine, 2 mg/kg (start of CBF measurement). EEG was contaminated with electromyograms. 2, 3 min after additional ketamine, 1 mg/kg (at 4 min from start of CBF measurement). 3, 10 min from start of CBF measurement. 4, 14 min from start of CBF measurement.

The onset of inspiration of the N₂O gas mixture. The concentration of N₂O in the blood was determined by a gas chromatograph (Shimazu CC-4A-TF). A sample-vaporizing apparatus (Shimazu BGS-1), Molecular Sieve 13X, and thermal conductivity detector were used. The coefficient of variation of the reproducibility was less than 3 per cent. CBF was calculated by the Kety-Schmidt method. In this study the amount of blood necessary by each route for one CBF measurement was 5 to 6 ml. Following minutes after control measurements, ketamine, 2 mg/kg, was given; CBF measurement was started 2 to 3 minutes later.

During each CBF measurement arterial and internal jugular venous pressures were measured 4 minutes after the start and immediately before the cessation of inspiration of 10 per cent N₂O in oxygen for 14 minutes. Cerebral perfusion pressure was defined as the difference between mean arterial pressure and internal jugular venous pressure measured by water manometer with the zero point at the mastoid process. Cerebral vascular resistance (CVR) was calculated from perfusion pressure.
and CBF. Arterial and internal jugular venous blood were sampled simultaneously at each pressure measurement. $P_{O_2}$, $P_{CO_2}$, pH, and jugular venous $P_O$, $P_{CO_2}$, and pH were measured with an IL Meter (Model 113, Instrumentation Laboratory Inc., Boston, Massachusetts). Oxygen saturation (SO$_2$) and hemoglobin concentration (Hb) were measured with an oxygen saturation meter (OSM-I) and spectrophotometer (Hitachi 124 type), respectively. Oxygen content was calculated from hemoglobin oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from $P_{O_2}$ and oxygen solubility. Glucose, lactate, and pyruvate concentrations were determined enzymatically.10,11 Cerebral metabolic rates for oxygen (CMRO$_2$), glucose (CMR$_{glucose}$), lactate (CMR$_{lactate}$), and pyruvate (CMR$_{pyruvate}$) were computed as the product of CBF and the appropriate arteriovenous content difference. The oxygen–glucose index and the lactate–glucose index were calculated from the equation proposal by Cohen and co-workers.12

All determinations except CBF were done in duplicate, and the averages were used for statistical analysis. In this study, when $P_{O_2}$ and mean arterial pressure 4 minutes after the start of inhalation of 10 per cent N$_2$O in oxygen were more than 2 mm Hg and 5 mm Hg, respectively, different from the values immediately before the cessation of 10 per cent N$_2$O, the data were discarded retrospectively. Differences were analyzed by two-tailed t tests for matched pairs.

**Results**

There was no significant difference between body temperatures awake (36.2 ± 0.39°C) and CBF. Arterial and internal jugular venous blood were sampled simultaneously at each pressure measurement. $P_{O_2}$, $P_{CO_2}$, pH, and jugular venous $P_O$, $P_{CO_2}$, and pH were measured with an IL Meter (Model 113, Instrumentation Laboratory Inc., Boston, Massachusetts). Oxygen saturation (SO$_2$) and hemoglobin concentration (Hb) were measured with an oxygen saturation meter (OSM-I) and spectrophotometer (Hitachi 124 type), respectively. Oxygen content was calculated from hemoglobin oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from $P_{O_2}$ and oxygen solubility. Glucose, lactate, and pyruvate concentrations were determined enzymatically.10,11 Cerebral metabolic rates for oxygen (CMRO$_2$), glucose (CMR$_{glucose}$), lactate (CMR$_{lactate}$), and pyruvate (CMR$_{pyruvate}$) were computed as the product of CBF and the appropriate arteriovenous content difference. The oxygen–glucose index and the lactate–glucose index were calculated from the equation proposal by Cohen and co-workers.12

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**Results**

There was no significant difference between body temperatures awake (36.2 ± 0.39 °C)
and anesthetized (36.5 ± 0.2°C). Ketamine increased mean arterial blood pressure and internal jugular venous pressure. Cerebral perfusion pressure increased from 88 to 102 mm Hg during ketamine anesthesia. CBF increased from 47 to 76 ml/100 g/min, and CVR decreased from 1.91 to 1.36 mm Hg/ml/100 g/min (table 1). Arterial and jugular venous blood values are summarized in table 2. During anesthesia, there was no significant change in Pao2, but there was a significant increase in jugular venous Pao2 from 42.4 to 59.5 mm Hg. Paco2 increased significantly, from 36.0 to 39.7 mm Hg, during anesthesia. There was no significant change in arterial oxygen content, but internal jugular venous oxygen content increased significantly.

There was a linear relationship between CBF and jugular venous Pao2 as shown in figure 2 (r = 0.894, P < 0.01).

Table 3 shows the effects of ketamine on cerebral metabolism. The cerebral circulatory index, which is the reciprocal arteriovenous oxygen content, was 16.6 ml blood/ml oxygen in awake subjects; it was 31.2 ml blood/ml oxygen in anesthetized subjects. CMR O2 decreased from a control value of 2.82 to 2.48 ml/100 g/min with ketamine, but the change was not significant. Analysis of individual data disclosed that CMR O2 decreased in seven subjects and increased in three subjects. CMR glucose decreased in five of seven subjects examined, but the change in mean values was not significant. There was no significant change in CMR lactate or CMR pyruvate. Although there was a tendency for the oxygen-glucose index to increase and the lactate-glucose index to decrease during anesthesia, the changes in these indices were not significant.

**Discussion**

When intravenous anesthetics are being used, it is difficult to maintain a steady state for testing. EEG, end-tidal PCO2, and mean arterial pressure were monitored to evaluate anesthetic depth and to control variables which might affect cerebral circulation and metabolism during measurements. In this study, the final N2O concentration in the jugular bulb was used as an estimate of brain N2O concentration, and arteriovenous N2O difference was integrated for 14 minutes. Therefore, lower flows were overestimated and resting cerebral metabolic rates would be slightly higher than they should be. The error is considered minimal at the control CBF of 47 ml/100 g/min, however. As body temperature did not change, its well-known effects on cerebral circulation and metabolism can be ruled out.

It has been shown that inhalation of a high concentration of oxygen does not affect cerebral blood flow or vascular resistance. Furthermore, the data obtained were comparable, because PaO2 values awake and anesthetized did not differ significantly. The decrease
in \( P_{aCO_2} \) to 36 ± 2 (SE) mm Hg in the awake state apparently resulted from the hyperventilation which may be produced by inhalation of a gas mixture with a high oxygen concentration and by the patient’s faulty placement of the mask.

In contrast to thiopental, which in a concentration of 25 mg/l blood decreases CBF to 27.6 ml/100 g/min, ketamine increased CBF comparably to deep cyclopropane anesthesia. The striking increase in CBF in the present study is discussed in relation to \( P_{aCO_2} \), perfusion pressure, and drug effects. Their relationships are largely coincidental, making quantitative analysis difficult, but estimates can be made from known values for awake and anesthetized man.

It is generally accepted that the relationship of CBF to \( P_{aCO_2} \) (20 to 55 mm Hg) is reasonably linear, and that for each 1-mm Hg increase in \( P_{aCO_2} \), CBF rises about 1 ml/100 g/min. The response of the cerebral circulation to changes in \( P_{aCO_2} \) is maintained during general anesthesia with either intravenous or inhalation agents, but sensitivity of the cerebral vessels to alterations in \( P_{aCO_2} \) differed from that of normal awake man; halothane (1.2 per cent) and cyclopropane (21 per cent), which increase CBF, increased sensitivity, while thiopental decreased it. In the present study, if normal sensitivity to \( P_{aCO_2} \) were retained during ketamine anesthesia, the 3.7-mm Hg increase in \( P_{aCO_2} \) should have increased CBF approximately 4 ml/100 g/min. Even if sensitivity increased about 60 per cent, this alteration in \( P_{aCO_2} \) would increase CBF less than 7 ml/100 g/min.

Increases in CBF must also be evaluated from the relationship between perfusion pressure and cerebral vascular resistance. CBF in normal awake man tends to remain constant over a range of mean arterial pressures from 50 to 150 mm Hg because of autoregulation of the cerebral vessels. With ketamine, mean cerebral perfusion pressure increased 14 mm Hg compared with the control value but remained in the range from 93 to 139 mm Hg. Thus, in the present investigation, cerebral vasoconstriction may also have occurred as a compensatory mechanism in response to the increased perfusion pressure. If such cerebral autoregulation is complete during ketamine anesthesia, CVR must increase, keeping CBF constant, but this drug produces a striking increase in CBF and decreases CVR by its direct vasodilating action. The increase in CVR produced by autoregulation may be masked in the decreased CVR. Smith and associates reported that autoregulation is complete during nitrous oxide anesthesia and during cyclopropane anesthesia with hypertension. However, during cyclopropane anesthesia with hypotension the cerebral vessels could not dilate enough to maintain the supranormal CBF typical with this agent. CVR, CBF, and cerebral perfusion pressure during

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<th>Table 3. Cerebral Blood Flow and Carbohydrate Metabolism during Ketamine Anesthesia: Indices of Cerebral Circulation and Metabolism</th>
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<td><strong>Control</strong></td>
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<td><strong>Mean</strong></td>
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<td><strong>Cerebral circulatory index</strong>&lt;br&gt;(ml blood/ml oxygen)</td>
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<td><strong>CMHbO2</strong>&lt;br&gt;(ml/100 g/min)</td>
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<td><strong>Oxygen-glucose index</strong></td>
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<td><strong>Lactate-glucose index</strong></td>
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* Seven subjects.
† Six subjects.
ketamine anesthesia are similar to those during cyclopropane anesthesia. This suggests that autoregulation during ketamine anesthesia is complete unless the physiologic limit of CVR is exceeded because of hypotension and the intrinsic responsiveness of the cerebral vessels is impaired. In this study the effects of changes in perfusion pressure on CBF were not investigated, making it difficult to clarify the direct effect of ketamine on cerebral autoregulation.

It is well known that thiopental causes significant and nearly proportional reductions in CMRO₂ and CBF. Cohen and associates observed a 15 per cent depression of CMRO₂ with halothane in man. Theye and Michenfelder showed a 23 per cent decrease of CMRO₂ in the dog, suggesting that halothane is a direct cerebral metabolic depressant. Cyclopropane depressed CMRO₂, but there was no correlation with depth of anesthesia. Alexander and associates reported that 70 per cent N₂O caused a 15 per cent decrease of CMRO₂ in man. On the other hand, Theye and Michenfelder showed that 70 per cent N₂O stimulated CMRO₂ in the dog. Wollman and co-workers showed that CMRO₂ during general anesthesia in man was below normal at all depths of anesthesia, but appeared to be least depressed at moderate depths. Thus, there were no consistent changes in CMRO₂ with increasing depths of anesthesia even when body temperature was unchanged. With ketamine, mean CMRO₂ and CMRglucose were reduced 12 and 29 per cent, respectively. These decreases are similar to those observed in man anesthetized with other agents. However, the variability of the data and the small number of subjects combine to make it impossible to demonstrate statistical significance for the decreased metabolic rates in this study.

The cerebral circulatory index in anestheitized normocarbic man is normal up to 1 minimal alveolar concentration (MAC), but increases approximately linearly with depth of anesthesia, reaching 34 ml blood/ml oxygen at 3 MAC. The cerebral circulatory index during ketamine anesthesia was 31.2 ml blood/ml oxygen, comparable to that of cyclopropane at 2.5 MAC. The reason for the increased cerebral circulatory index, as well as the relationship between cerebral metabo-

References


15. Turner J, Lambertson CJ, Owen SC, et al.: Effects of 0.08 and 0.8 atmospheres of inspired $P_{O_2}$ upon cerebral hemodynamics at a "constant" alveolar $P_{O_2}$ of 43 mm Hg. Fed Proc 16:130, 1957


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**Respiration**

**WATER HANDLING AND CHRONIC OBSTRUCTIVE LUNG DISEASE** Because of the association of edema with chronic pulmonary disease, the authors tested the responses of 20 patients with chronic obstructive airway disease to a water load of 20 ml/kg and compared these responses with those of 13 healthy subjects. It was found that the percentage of water load excreted by the patients in 4 hours was significantly lower (mean 51 per cent) than that in the control group (mean 106 per cent). Maximum urine flow, osmolar clearance, free water clearance, and creatinine clearance were also significantly lower in the patients. A significant inverse relationship between the percentage of water load passed and arterial $P_{O_2}$ was found. Although glomerular filtration was reduced in the patients, the authors did not feel this to be an important factor in the impaired water-load response. The precise mechanism for the impairment remains unclear, and further studies are in progress to examine proximal tubular function and vasopressin activity under these circumstances. (White, R. J., and Woodings, D. F.: Impaired Water Handling in Chronic Obstructive Airway Disease, Brit. Med. J. 2: 561 (June) 1971.)