The Effect of Ketamine on Regional Cerebral Blood Flow in Man

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Total (CBF) and regional (rCBF) hemispheric cerebral blood flows were measured by the intra-arterial $^{133}$Xe method in five neurologic patients before and 2 to 4 minutes after intravenous injection of ketamine. While the responses of CBF were variable, marked increases in rCBF were observed in the frontotemporal regions in four of four and in the parieto-occipital region in three of 5 patients. It is concluded that ketamine is probably not a direct cerebrovasodilator, but that it may affect rCBF secondary to drug-induced changes in regional neuronal activity. (Key words: Brain, regional blood flow, ketamine; Anesthetics, intravenous, ketamine.)

Recent studies have shown that ketamine increases total cerebral blood flow (CBF).1,2 Dawson et al.,1 using the venous outflow technique in dogs, found that ketamine increased CBF by 80 per cent and cerebral metabolic rate of oxygen (CMR$_{O_2}$) by 16 per cent. They concluded that ketamine is a cerebral metabolic stimulant and a cerebral vasodilator. Takeshita et al.,3 using the Kety-Schmidt technique in man, found a CBF increase of 62 per cent, but no elevation of CMR$_{O_2}$.

Several observations indicate that ketamine is a cerebral stimulant: the behavior of patients, the occurrence of hallucinations, and results of electrophysiologic studies.4,5 Cerebral activation caused by ketamine might take place only in some regions of the brain. If this were correct, one would expect to find regional differences in CBF after injection of ketamine. The possibility of regional differences in flow was not evaluated in previous studies because of the limitations of the techniques employed.1,2

The present study was undertaken to measure the effects of ketamine on cerebral blood flow in 35 small regions of one hemisphere in man.

Material and Methods

Five patients who were to undergo carotid angiography for diagnostic purposes were studied. Patients with acute severe stroke or clear-cut clinical evidence of cerebral tumor were excluded. Three of the five patients had cerebrovascular insufficiency, one later was found to have cerebral metastasis, and one later was found to have both an old cerebral infarct and cerebellar metastasis (table 1).

The study was explained to the patients as an experimental extension of the planned angiography ordinarily done with local anesthesia. The carotid puncture was performed with local anesthesia, as usual, but the injection of contrast material was made during ketamine anesthesia. All patients gave informed consent. No premedication was given except to patient 5, who received diazepam (Valium), 10 mg, im, 30 minutes prior to carotid puncture.

Regional cerebral blood flow (rCBF) was measured in 35 small areas of the hemisphere by the $^{133}$Xe intra-arterial injection method.6,7 Using the Seldinger technique, a small polyethylene catheter was placed in the internal carotid artery. $^{133}$Xe 1–3 mCi dissolved in 2–3 ml saline solution, was injected as a bolus, the washout of the isotope then being followed by 35 external detectors. The scintillation detectors consisted of thallium-activated sodium iodide crystals, 12 mm in diameter and 10 mm thick. They were collimated by cylindrical lead tubes 43 mm long and 12 mm in internal diameter. The detectors were closely packed together, the counting field of a detector being a truncated cone of the hemisphere. At a distance of 3 cm from the end of the col-

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TABLE 1. Summary of Five Cases

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years), Sex</th>
<th>History and Clinical Findings</th>
<th>Neuroangiologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>64, M</td>
<td>Nine years previously, a thoracic malignant melanoma had been removed. Periodic confusion, slight aphasia and disorientation for two weeks prior to the CBF measurement. No paresis. No papilledema. Died 10 weeks after CBF measurement. Autopsy showed multiple cerebral metastases from malignant melanoma, the two largest being in left frontal area and left corpus striatum.</td>
<td>Left carotid angiogram. No filling of the anterior cerebral artery. Brain scan: one lesion in left frontal basal area and one in right parieto-occipital area.</td>
</tr>
<tr>
<td>Patient 2</td>
<td>71, F</td>
<td>Ten days prior to the CBF measurement, sudden onset of left hemiplegia and dysarthria. At the time of the measurement, only slight residual deficit.</td>
<td>Right carotid angiogram: atherosclerosis. Occlusion of a branch of the middle cerebral artery with collateral supply.</td>
</tr>
<tr>
<td>Patient 4</td>
<td>48, M</td>
<td>Daily alcohol abuse for years. Slight diabetes treated with oral medication. Paresis of the left arm developed suddenly two months before CBF measurement. At the time of the measurement, slight supranuclear paresis of the left arm.</td>
<td>Right carotid angiogram: normal.</td>
</tr>
<tr>
<td>Patient 5</td>
<td>68, M</td>
<td>Developed right hemiplegia and aphasia 18 months before the CBF measurement. Partial remission. One month before the study, slight left-sided hemiplegia gradually developed. No remission. Died six weeks later. Autopsy showed an old cerebral infarct in the left temporal region, a 3-cm metastasis in the left cerebellar hemisphere, and a previously undiagnosed pulmonary carcinoma.</td>
<td>Right carotid angiogram: atherosclerosis. No filling of the anterior cerebral artery, delayed collateral supply.</td>
</tr>
</tbody>
</table>

limator, corresponding to the brain surface, the diameter of the cone was 2 cm. Sixty-five per cent of the counts came from this truncated cone of tissue; 35 per cent represented Compton scatter. Both Compton scatter and overlapping of the counting fields tended to smooth out regional differences in blood flow. From the logarithmically displayed clearance curves of the first 2 minutes, hemispheric cerebral blood flow was calculated as

\[ \text{CBF}_{\text{initial}} = 2 \times D_{\text{initial}} \text{ ml/100 g/min} \]

where 2 is the conversion factor from base 10 to natural logarithm multiplied by the tissue-to-blood partition coefficient of grey matter (0.87). D is the slope of the initial part of the curve in per cent of a decade per minute. Normally the logarithmically displayed clearance curve is linear for 1 to 2 minutes. The normal value for CBF_{initial} is 64 ml/100 g/min, with a standard deviation (SD) of 9 ml/100 g/min.²

Immediately after isotope injection, an arterial blood sample was taken via the catheter for determination of carbon dioxide tension (PaCO₂) using a Severinghaus electrode. Then intracarotid blood pressure was measured by an electromanometer. After a
FIG. 1. Patient 1. The numbers in the circles are the percentage changes of regional cerebral blood flow (rCBF) measured 2 to 4 minutes after intravenous injection of ketamine. The positions of the 35 circles correspond roughly to the areas of the brain seen by the detectors. The exact position is difficult to illustrate because both the brain surface and the surface of the block of the detectors have a spherical surface curvature. Empty circles indicate abnormal curves in the area of the frontal metastasis and peripheral detectors with low counting rates. The left hemisphere was studied, but the figure reversed to conform to figures 2–5.

TABLE 2. Cerebral Blood Flow (Average CBF_{max}), Arterial Carbon Dioxide Tension, and Mean Arterial Blood Pressure at Rest, during Angiotensin Infusion, and during Ketamine

<table>
<thead>
<tr>
<th>Patient</th>
<th>CBF (ml/100 gm/min)</th>
<th>( P_{\text{aCO}_2} ) (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>Best I</th>
<th>Angiotensin</th>
<th>Best II</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>53</td>
<td>43.6</td>
<td>83</td>
<td>48</td>
<td>44.6</td>
<td>97</td>
<td>42.3</td>
</tr>
<tr>
<td>Patient 2</td>
<td>59</td>
<td>43.7</td>
<td>110</td>
<td>55</td>
<td>46.1</td>
<td>122</td>
<td>43.3</td>
</tr>
<tr>
<td>Patient 3</td>
<td>43</td>
<td>43.1</td>
<td>94</td>
<td>42</td>
<td>37.3</td>
<td>112</td>
<td>77</td>
</tr>
<tr>
<td>Patient 4</td>
<td>54</td>
<td>43.3</td>
<td>139</td>
<td>56</td>
<td>41.2</td>
<td>132</td>
<td>53</td>
</tr>
<tr>
<td>Patient 5</td>
<td>36</td>
<td>38.4</td>
<td>94</td>
<td>36</td>
<td>37.2</td>
<td>114</td>
<td>39</td>
</tr>
</tbody>
</table>

*Calculation of CBF inaccurate due to distortion of Xenon-washout curves caused by head movements.

FIG. 2. Patient 2. Changes of rCBF (per cent) after injection of ketamine. Empty circles represent peripheral detectors with low counting rates.

flow study in the resting state, autoregulation of the cerebrovascular system was tested by repeating the study during moderate hypertension (mean arterial blood pressure increase of about 20 per cent) produced by intravenous infusion of angiotensin. An interval of at least 15 minutes elapsed between one flow measurement and the next. After measurements during hypertension a second resting flow value was usually performed. Fifteen minutes later, ketamine (2 mg/kg) was injected intravenously in 1 minute. Two minutes after termination of ketamine injection, CBF measurement was again initiated. Immediately after registration of the first 2 minutes of the washout curve, diazepam, 5–10 mg, was injected intravenously. Carotid angiography was then carried out via the intracarotid catheter. No complication was observed.

Results

Results are summarized in table 2 and figures 1–5. In three cases, CBF in the resting state was in the normal range (46–82 mg/100 g/min), but in two patients (3 and 5) CBF was somewhat reduced. Four patients (2, 3, 4 and 5) had normal, almost uniform distributions of flow. Patient 1 had abnormal Xenon-washout curves with a fast initial component (tissue peak) in the frontal area. This region corresponded to the location of a cerebral metastasis.
Induction of moderate hypertension by infusion of angiotensin had virtually no effect on average CBF and regional CBF (rCBF) in four patients. Normally, CBF remains unchanged within wide limits of mean arterial blood pressure (MABP)—so-called autoregulation. Thus, four patients had intact autoregulation. The fifth patient (patient 1) had intact autoregulation in much of the hemisphere. In the frontal area, however, evaluation of autoregulation was not possible because of abnormal washout curves (the tumor area).

After injection of ketamine, average CBF values increased 22, 83 and 166 per cent in patients 2, 3, and 4, respectively. Two patients (1 and 5) had essentially unchanged average CBF values. Marked changes in the rCBF were, however, observed in all patients (figs. 1–5). In four patients (2, 3, 4, and 5) rCBF increased in the frontal and the frontotemporal region. In the fifth patient (patient 1) curves from the frontal area could not be evaluated. Three patients (1, 2, and 4) had increases in rCBF in the parieto-occipital region. Patient 4 had a large increase in CBF throughout the entire hemisphere, especially pronounced in the frontal and parieto-occipital regions. MABP’s varied after ketamine administration. Three patients had increases of 16, 44, and 67 mm Hg, respectively, and two had decreases of 6 and 22 mm Hg, respectively (table 2). PuO2 increased in four patients from 2.9 to 5.7 mm Hg, but decreased 1.6 mm Hg in one patient (patient 1).

While the effect of ketamine lasted, four patients (1, 3, 4, and 5) had spontaneous movements of the eyes and of the extremities. Patient 4, an alcoholic man, became agitated. Of interest is that this patient also showed the most pronounced cerebral hyperemia. Only one patient (patient 2) remained immobile.

Discussion

Regional CBF increases were found after ketamine injection in all patients in the present series. It is difficult to imagine regional effects on blood vessels in the brains
of patients with intact autoregulation. Therefore, rCBF increases observed after ketamine injection cannot be explained by concomitant PaCO₂ or MABP elevations or any direct vasodilatory mechanism. In one patient (patient 4) ketamine caused an increase of MABP from 114 to 158 mm Hg, which is at the upper level of the normal autoregulatory range. Regional CBF increased 100 to 230 per cent. In this patient a breakthrough of autoregulation might have contributed to the increase of average CBF, but regional differences in flow were unlikely to be explained by the hypertension.

It seems more reasonable to explain the rCBF increases as related to regional cerebral activation. As mentioned in the introduction, several observations indicate that ketamine is a cerebral stimulant: the occurrence of hallucinations, electrophysiologic findings of seizure activity in cortical and subcortical structures in man and cats, and the observation of ketamine-induced convulsions in a patient with no history of epilepsy.

Movements of head, eyes, and extremities after ketamine administration also suggest cerebral activation.

Recent studies have shown rCBF increases during activation of brain regions. Olesen found that rCBF increased in the cortical motor area in man during contralateral arm work. Cooper et al. also found an increase in rCBF in the visual cortical area in man during stimulation with flickering light. Risberg and Ingvar described rCBF increases in the frontal and parieto-occipital areas in man during mental activity.

The question whether the increases in rCBF in the above-mentioned studies or after ketamine injection are related to increased metabolism cannot be answered definitely before studies of regional CMRO₂ are reported. The data of Dawson et al. suggest that ketamine might increase average CMRO₂, but that it might also induce a relative hyperemia or "uncoupling" of flow, i.e., increase flow more than metabolic demands. "Uncoupling" of flow has been found during anesthesia with volatile anesthetics, but only under conditions where CMRO₂ was reduced. That Takeshita et al. did not find an increase in average CMRO₂ does not necessarily exclude a global or regional increase of too short duration to be detected by the technique employed.

The effects of ketamine on cerebral hemodynamics, including an increase in intracranial pressure, have clinical implications. In patients with space-occupying lesions, any type of acute brain lesion, or histories of epilepsy, the use of ketamine would seem hazardous.

**ADDENDUM**

Recently Herschaft and Schmidt reported a 30 per cent reduction of CBF in man after intravenous injection of ketamine, 2 mg/kg. They found no evidence of regional changes in CBF measured by the intra-arterial Xe method. Prior to the administration of ketamine their patients were anesthetized with 60 per cent nitrous oxide and 0.4 per cent halothane. Anesthesia was induced with propanidid (Enpolol). This anesthesia produced a 10–20 per cent increase of control CBF above normal values for awake man. It is possible that the combined anesthesia modified the response of the brain to ketamine and thereby prevented regional CBF changes.

**References**

7. Olesen J, Paulson OB, Lassen NA: Regional
cerebral blood flow in man determined by the initial slope of the clearance of intravenously injected \(^{133}\)Xe. Stroke 2:519–540, 1971


