Effects of Inhalation of Oxygen on Blood Flow and Microvasculature of Ischemic and Nonischemic Cerebral Cortex

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Abstract: Effects of Inhalation of Oxygen on Blood Flow and Microvasculature of Ischemic and Nonischemic Cerebral Cortex

The right middle cerebral artery was occluded in cats, and \( P_{\text{aO}_2} \) was increased by increasing the amount of oxygen inhaled by the animals at atmospheric pressure. Cortical blood flow (CBF) was measured with Krypton-85, and observations and photographs of the superficial cortical microvasculature were made bilaterally. In two of five animals, increasing the \( P_{\text{aO}_2} \) caused constriction of surface arterioles of the nonischemic hemispheres, with an associated decrease of CBF; in the three other animals, there were no circulatory responses to the increased \( P_{\text{aO}_2} \). In seven animals, increasing the \( P_{\text{aO}_2} \) had no apparent effect on CBF or arteriolar caliber of the ischemic cerebral hemispheres. In four animals, at \( P_{\text{aO}_2} \) greater than 400 torr, reactivity to increases of \( P_{\text{aCO}_2} \) was preserved in nonischemic cortex but impaired in ischemic cortex. Reddening of venous blood of the microvasculature of ischemic cerebral cortex occurred when \( P_{\text{aO}_2} \) was increased, indicating that more oxygen was made available to the ischemic cerebral tissue. However, no beneficial effects could be demonstrated on the changes in the microvasculature produced by ischemia.

ADDITIONAL KEY WORDS cerebral infarction microcirculation of brain oxygen therapy krypton hyperoxia

Constriction of superficial cortical arterioles and decreases of cerebral blood flow may accompany increases of arterial oxygen tension (\( P_{\text{aO}_2} \)) in humans and animals, particularly if oxygen is inhaled at pressures greater than 1 atmosphere. The effects of oxygen on the cerebral circulation are inconsistent, however, and a change of \( P_{\text{aO}_2} \) is a much less potent stimulus to the regulatory mechanisms of the cerebral circulation than is a change of perfusion pressure or arterial carbon dioxide tension (\( P_{\text{aCO}_2} \)).

Despite the known effects of oxygen on the cerebral circulation, inhalation of oxygen is used frequently for the treatment of cerebral infarcts in humans. Hyperbaric oxygenation of humans or animals has been used experimentally in studies of cerebral ischemia and for the treatment of cerebral infarcts and other conditions. Hyperbaric oxygenation can cause an increase of the amount of oxygen available to the brain, which may more than compensate for arteriolar constriction and decreased blood flow; if the toxic effects of hyperbaric oxygenation can be avoided, some patients with cerebral infarcts may benefit from it. The use of a hyperbaric

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The present study was designed to assess the effects of increases of PaO₂ produced by inhalation of oxygen at atmospheric pressure on the circulation in ischemic cerebral tissue. Cortical blood flow (CBF) and the caliber of superficial cortical arterioles were measured in ischemic and nonischemic cerebral hemispheres at normal and at high PaO₂, and the reactivity of the cortical circulation to changes of PaCO₂ was determined at high PaO₂.

Methods

Seven adult cats, ranging in weight from 2.5 to 4 kg, were anesthetized with halothane, and in each a tracheal stoma was made. Catheters were placed in the abdominal aorta through a femoral artery, in the inferior vena cava through a femoral vein, and in the brachiocephalic artery through the right subclavian artery. The right middle cerebral artery (MCA) was occluded by an extradural approach. Wide bilateral cranietomies were made, and the surface of the brain was protected with a thin sheet of plastic (Saran). Bilateral electrocorticograms were recorded on a polygraph from screw electrodes abutting the dura. Mean systemic arterial blood pressure (MABP) was recorded with a strain gauge attached to the catheter in the abdominal aorta. Rectal temperature was monitored with a thermometer.

After completion of the surgical procedures, the concentration of halothane was reduced to 0.3% to 0.5%. d-Tubocurarine was injected intravenously in an amount just sufficient to abolish respiratory movements, and the animals were ventilated mechanically with a respirator. Arterial P_{CO₂}, pH, P_{O₂}, and hematocrit value were measured from blood obtained from the abdominal aorta. P_{CO₂} was kept near normal (30 torr for cats) by adjusting the amount of CO₂ in the gas mixture used for ventilating the animal, except when P_{CO₂} was deliberately increased to test cerebral vascular reactivity at high P_{O₂}, P_{CO₂} was varied by changing the amount of oxygen in the gas mixture, from as little as 20% to as much as nearly 100%.

At varying levels of P_{O₂}, CBF was measured from both hemispheres simultaneously by external detection of the beta activity of Krypton-85 injected into the brachiocephalic artery. The data were obtained in digital form and a kinetic analysis was used. The superficial cortical microvasculature was observed through an operation microscope, and macrophotographs were...
made bilaterally for measurements of the calibers of arterioles 50 to 250 microns in diameter. Measurements of PaCO₂, PaO₂, arterial pH, and hematocrit value were made at the time of each determination of CBF.

Data from the nonischemic hemispheres of two animals were discarded because of excessive bleeding from bridging cortical-dural veins. In one experiment, technical difficulties prevented the measurement of CBF, but studies of the microvasculature were possible.

**Results**

**Nonischemic Cortex**

Nineteen measurements of CBF from the nonischemic hemispheres of four cats, made at PaO₂ ranging from 110 to 505 torr, were available for analysis. Eight measurements of CBF were made at PaO₂ less than 150 torr; values ranged from 1.02 to 1.41 ml/gm/min, with a mean of 1.22 ± 0.16 (SD). At PaO₂ greater than 400 torr, five values for CBF ranged from 0.95 to 1.62 ml/gm/min, with a mean of 1.22 ± 0.31. The difference between the mean CBF values at normal and at high PaO₂ was not statistically significant. Individual CBF values obtained at the lowest and the highest PaO₂ for each animal are shown in table 1.

CBF decreased at high PaO₂ in the nonischemic hemisphere of only one animal (no. 7). The caliber of the arterioles of the superficial microvasculature also decreased in the nonischemic hemisphere of this animal (fig. 1). Arteriolar constriction occurred at high PaO₂ in one other animal (no. 5), but in this animal MABP increased as PaO₂ was increased, and the constriction may have been due to autoregulatory responses of the arterioles to the change of perfusion pressure. In two animals there was no change of CBF or arteriolar caliber when PaO₂ was increased; in one animal, CBF increased for unknown reasons.

In four animals PaCO₂ was increased while PaO₂ was maintained at greater than 400 torr. In all four there was appropriate

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**FIGURE 1**

Superficial cortical microvasculature of animal 7. A: Nonischemic hemisphere, normal PaO₂ (134 torr). CBF = 1.18 ml/gm/min; MABP = 91 mm Hg; PaCO₂ = 42 torr. B: Nonischemic hemisphere after PaO₂ was increased to 505 torr. Note constriction of arterioles (arrows). CBF decreased to 0.99 ml/gm/min; MABP and PaCO₂ remained constant. C: Ischemic hemisphere, same time as in A. CBF = 0.35 ml/gm/min. D: Ischemic hemisphere after PaO₂ was increased, same time as in B. Note failure of arterioles to constrict (arrows). CBF = 0.22 ml/gm/min.
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dilatation of the surface arterioles of the nonischemic hemispheres and, in the two animals for which CBF measurements were available, there were appropriate increases of CBF. Thus, the usual responses of the cerebral circulation to changes of PaO₂ were not influenced by high PaO₂.

ISCHEMIC CORTEX
Thirty-one measurements of CBF from the ischemic hemispheres of six animals, made at values of PaO₂ ranging from 110 to 525 torr, were available for analysis. At PaO₂ less than 150 torr, 12 values of CBF ranged from 0.35 to 0.92 ml/gm/min, with a mean of 0.77 ± 0.11. This mean CBF value for ischemic cortex was significantly lower than the mean CBF value for nonischemic cortex at PaO₂ less than 150 torr (P < 0.01). Eight values of CBF obtained from the ischemic hemispheres at PaO₂ greater than 400 torr ranged from 0.22 to 1.09, with a mean of 0.84 ± 0.17. This CBF value was lower than that for nonischemic cortex at high PaO₂, but statistical significance was not reached. The difference between the mean CBF values for ischemic cortex at normal and at high PaO₂ was not statistically significant.

There were no changes of the calibers of the surface arterioles of the ischemic hemispheres when PaO₂ was raised (fig. 1), except for one animal (no. 2) in which arteriolar constriction occurred. However, in this animal, ischemic changes in the microvasculature increased in severity, and the arteriolar constriction probably was related to ischemia rather than to the change of PaO₂. In this animal and one other (no. 7), decreases of CBF occurred as ischemic changes in the microvasculature progressed.

Increases of CBF occurred in two animals when PaO₂ was increased. In one of these (no. 1) there was an associated increase of MABP; thus, the change of CBF probably was due to an impairment of autoregulation rather than to the change of PaO₂. In the other animal, CBF of the nonischemic cerebral hemisphere also increased when PaO₂ was increased. The cause of the bilateral increases of CBF in this animal was not evident.

There were no changes of the calibers of the surface arterioles of the ischemic cerebral hemispheres of the four animals in which PaCO₂ was increased while PaO₂ was maintained greater than 400 torr. CBF measurements, available for three of these animals, likewise did not change. Thus, the impaired reactivity of the cerebral circulation to changes of PaCO₂ produced by ischemia was not modified by high PaO₂, although no paradoxical response (a decrease of CBF or constriction of arterioles with an increase of PaCO₂) was seen in any of the four animals.

MISCELLANEOUS RESULTS
The electrocorticograms recorded from the ischemic cerebral hemispheres were different (lower amplitude and slower frequency) from those recorded from the nonischemic hemispheres. No consistent changes of the electrocorticograms of either the ischemic or the nonischemic hemispheres occurred with changes of PaO₂.

When PaO₂ was increased, the blood in the superficial venous vessels of both the nonischemic and the ischemic cerebral hemispheres became more red.

In individual animals, no changes of PaCO₂ occurred as a result of the changes of PaO₂.

Discussion
Various theories have been advanced to explain the influences of arterial oxygen content on the cerebral circulation. Included among the postulated mechanisms are: (1) a direct effect of oxygen on the state of contraction of the smooth muscle of the walls of arteriolar vessels, (2) a reflex arc involving chemoreceptors and the autonomic nervous system, and (3) a decrease in the rate of formation of vasoactive metabolites because of the presence of oxygen in excess. Any of these mechanisms could be affected by ischemia, so that cerebrovascular reactivity to increases of PaO₂ would be impaired or lost. A similar impairment of reactivity to changes of PaCO₂, produced by ischemia, has been demonstrated previously and again in the present study.

If oxygen inhalation were effective in producing arteriolar constriction and decreased CBF in nonischemic brain tissue, with a resultant increase of local cerebral vascular resistance (CVR), then an impairment of vascular reactivity in ischemic cerebral tissue might prevent a change of CVR and cause a redirection of the flow of blood with an increase of CBF in the ischemic tissue. Such an
effect would be similar, but in the opposite direction, to the paradoxical effect of changes of PaO\textsubscript{2} on CBF of ischemic cerebral tissue.\textsuperscript{38} However, increased CBF of ischemic cortex due to an increase in PaO\textsubscript{2} was not demonstrated in the present study.

The rationale for the use of oxygen for the treatment of cerebral infarcts in humans is, of course, not based on possible effects on blood flow. Rather, it is postulated that increased oxygen saturation of the blood will provide increased delivery of oxygen to ischemic cerebral tissue to preserve or restore function to tissue that is somewhat hypoxic or to prevent the extension of an infarct. Although well-controlled studies of the effects of oxygen inhalation on human cerebral infarcts are scarce, the administration of oxygen at high pressures may be beneficial in certain circumstances.\textsuperscript{29-26}

In the present study, the venous blood of the superficial cortical microvasculature of the ischemic cerebral hemispheres became more red when PaO\textsubscript{2} was increased. From this it may be inferred that venous oxygen saturation was increased and that an increased amount of oxygen was made available to the ischemic cerebral tissue unless "shunting" occurred. However, no beneficial effects could be demonstrated; instead, ischemic changes became progressively more severe in the microvasculature of two animals despite reddening of the venous blood. The ischemic cerebral tissue may not have been able to utilize the increased amount of oxygen made available to it, because of impairment of metabolic processes by ischemia\textsuperscript{68} or because of a lack of glucose. It is unlikely that the increased PaO\textsubscript{2} caused reactive hyperemia with resultant reddening of venous blood.\textsuperscript{26, 87}

The results of the present study indicate that inhalation of oxygen can produce vasoconstriction and decreased CBF in normal cerebral cortex, but these circulatory responses are inconstant, of minor degree, and less than those produced by changes of PaCO\textsubscript{2}. Moreover, the inhalation of oxygen at atmospheric pressure probably has no beneficial effect on the process of cerebral infarction, although additional studies are needed in humans and in animals allowed to survive for various periods after MCA occlusion.

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