THE EFFECT OF CARBON DIOXIDE ON CEREBRAL BLOOD FLOW AND CEREBRAL METABOLISM IN DOGS

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SUMMARY

In 11 normally oxygenated, normotensive mongrel dogs, blood flow and oxidative metabolism of the brain was studied during normocapnia and during respiratory alkalosis and respiratory acidosis. During respiratory alkalosis (mean PaCO₂ 17.8 mm Hg) CBF decreased significantly from 61.0 to 33.9 ml/100 g/min (44%) while arteriovenous-substrate differences increased and the rates of oxygen and glucose metabolism remained constant. Cerebral venous-arterial difference of lactate was increased significantly as compared with the resting state. During hypercapnia CBF increased significantly from 61.0 (resting state) to 115.7 ml/100 g/min (89%) (mean PaCO₂ 64.7 mm Hg). The arteriovenous-substrate differences decreased while the cerebral metabolic rates remained constant. The data show that the relationship between PaCO₂ and CBF in the range 20–65 mm Hg PaCO₂ is expressed by a linear relationship: y = 2.88 + 1.69x; in this range, the oxidative metabolism of the brain is unchanged and the increased cerebral lactate production in respiratory alkalosis is not necessarily linked to tissue hypoxia.

It has been well established both qualitatively (Donders, 1850; Reigal and Jolly, 1871; Wolff and Lennox, 1930) and quantitatively (Kety and Schmidt, 1946, 1948; Patterson et al., 1955; Reivich, 1964; Alexander et al., 1964; Harper and Glass, 1965; Häggendal and Johansson, 1965; Shapiro, Wasserman and Patterson, 1965, 1966; Severynhaus and Lassen, 1967) that changes in arterial PCO₂ have a marked influence on cerebral circulation: arterial hypocapnia decreases and hypercapnia increases cerebral blood flow (CBF). However, the influence of altered carbon dioxide tension on the oxidative metabolism of the brain has been studied less extensively. One important problem is whether a decrease of CBF as a result of moderate hypocapnia will induce hypoxic changes in cerebral metabolism. It is well known that enzymatic activity is influenced by changes in tissue pH (Domonkos and Huszak, 1959; Leusen, Lacroix and Demeester, 1967; Folbergrova, Mac-Millan and Siesjo, 1972a, b). Thus it must be questioned whether changes in cerebral glucose metabolism may result from respiratory imbalance. These problems are very important in the treatment of neurological and neurosurgical patients with artificial hyperventilation and in patients with respiratory insufficiency. The aims of the present investigation were:

1) to gain better insight into the changes of CBF and oxidative metabolism of the brain under the condition of moderate hypocapnia;
2) to study the effect of respiratory acidosis on CBF and cerebral oxidative metabolism;
3) to show the CBF response to changes of PCO₂ in arterial blood in the normocapnic range and in moderate hypo- and hypercapnia.

MATERIAL AND METHODS

In 11 mongrel dogs weighing 22–35 kg (mean body weight 28 kg) we measured CBF by means of the Kety-Schmidt technique (Kety and Schmidt, 1945) as modified by Bernsmeyer and Siemons (1953). The animals were anaesthetized with nembutal, the trachea was intubated, muscle relaxation was obtained with pancuronium (Organon, München) and artificial ventilation, with halothane 0.5 vol% in oxygen, by means of an Engström respirator was commenced. Both femoral arteries and veins were exposed and cannulated with two catheters, one for pressure recording and one for blood sampling. In the other
artery a "Hemalock" cannula with a $\text{PCO}_2$-sensor (General Electric, Milwaukee: $\text{PCO}_2$ Amplifier A 3128A) was inserted for continuous monitoring of $\text{PACO}_2$. The intravenous catheters were used for measuring central venous pressure (CVP) and for the infusion of solutions. The superior sagittal sinus was exposed by a 2.5x1.0 frontal burr hole. A thin catheter was inserted into the sagittal sinus. The catheter tip was placed in the posterior part of the sinus where contamination with extracerebral venous blood is rare (Reinhard, Miller and Evans, 1962). Furthermore, the diploic veins joining the sinus were partly occluded with bone wax. The burr hole was also closed with bone wax and the wound was sutured in layers. Blood sampling was performed by means of motor-driven syringes which provided a continuous extraction of 1 ml blood/min. The cisterna magna was punctured with a double-barrelled needle to measure cerebrospinal fluid pressure (CSFP) continuously. Body temperature was kept in the normothermic range. Monitoring of mean arterial pressure (MAP), CSFP, sagittal sinus pressure (SSP) and central venous pressure (CVP) was performed using Statham transducers. These measurements, together with the electrocardiogram and heart rate, were recorded with a polygraph (12-channel multiscriptor, Hellige, FRG).

The first measurement took place in a normoxic, normotensive (in dogs a cerebral perfusion pressure, CPP, of about 100 mm Hg is normal) and normocapnic steady state of at least 30-min duration. Thereafter, hypercapnia was induced by adding 5-7% carbon dioxide to the inspired air. Thus $\text{PACO}_2$ was increased to about 65 mm Hg. The second measurement was performed after a hypercapnic, normotensive, normoxic steady state of at least 30 min. Then the animals were hyperventilated to produce hypocapnia of about 18.0 mm Hg $\text{PACO}_2$. The third measurement was made after a normoxic, normotensive and hypocapnic steady state of at least 30 min.

In arterial and sagittal sinus blood the volumes of oxygen and carbon dioxide were determined by gas chromatography (Weinhardt, Quadbeck and Hoyer, 1972). The concentrations of glucose and lactate and pH, $\text{PACO}_2$, $\text{PO}_2$, base excess and standard bicarbonate were measured in the Eschweiler apparatus. The metabolic rates of the substrates were calculated by the arteriovenous differences and cerebral blood flow.

Statistical analyses were performed using the Fridman test.

RESULTS

The mean values, standard deviations and statistical significance of CBF, $\text{PACO}_2$, cerebral perfusion pressure measurements and assessments of oxidative metabolism of the brain are listed in table I.

Cerebral blood flow (fig. 1)

In normocapnia (mean $\text{PACO}_2$ 36.5 mm Hg, CPP 103 mm Hg), the mean value of CBF was 61.0 ml/100 g/min. In hypercapnia (mean $\text{PACO}_2$ 64.7 mm Hg, CPP 101 mm Hg) CBF increased significantly, (115.7 ml/100 g/min, alpha=0.001): an increase of 89% compared with the resting value. In hypocapnia (mean $\text{PACO}_2$ 17.8 mm Hg, CPP 106 mm Hg) CBF decreased significantly by 44% to 33.9 ml/100 g/min (alpha=0.001).

Arterio-venous oxygen content difference ($\text{AVDO}_2$) and $\text{CMR oxygen}$ (fig. 2)

In normocapnia $\text{AVDO}_2$ (5.6 vol%) and $\text{CMR oxygen}$ (3.41 ml/100 g/min) did not differ from values obtained in other investigations in dogs. In hyper-

| Table I. Mean values, SD and statistical significance (Fridman test) of blood flow and oxidative metabolism of the brain during normo-, hyper-, and hypocapnia in 11 dogs. |
|---|---|---|
| $\text{PACO}_2$ (mm Hg) | 36.5±3.9 | 64.7±8.9 | 17.8±2.3 |
| CBF (ml/100 g/min) | 61.0±15.5 | 115.7±38.9* | 33.9±10.6* |
| $\text{AVDO}_2$ (vol %) | 5.60±0.75 | 3.13±1.83 | 9.40±1.80* |
| $\text{CMR oxygen}$ (ml/100 g/min) | 3.41±1.07 | 3.41±1.80 | 3.20±1.06 |
| $\text{CMR oxygen}$ (vol %) | 5.70±0.80 | 4.32±2.08 | 10.80±2.83* |
| $\text{VAD oxygen}$ (mg %) | 3.55±1.36 | 4.63±2.00 | 3.62±1.02 |
| $\text{AVD glucose}$ (mg% | 7.7±3.4 | 4.1±2.5 | 14.7±4.3* |
| $\text{CMR glucose}$ (mg% | 4.59±2.34 | 4.65±2.48 | 4.96±2.03 |
| $\text{VAD}$-lactate (mg%) | 1.00±0.27 | 0.40±0.41 | 3.00±1.80* |
| $\text{CMR}$-lactate (mg% | 0.61±0.32 | 0.50±0.45 | 1.09±0.80 |
| Lactate/glucose index | 0.13 | 0.11 | 0.22 |
| CPP (mm Hg) | 103.0±15.7 | 101.0±12.1 | 106.0±15.8 |

*alpha=0.001.
capnia and hypocapnia CMRO\textsubscript{2} remained constant while AVDO\textsubscript{2} decreased in hypercapnia (not statistically significant) and increased in hypocapnia (alpha=0.001), respectively.

**Venous-arterial carbon dioxide content difference (VADCO\textsubscript{2}) and CMR-carbon dioxide (fig. 3)**

In hypercapnia VADCO\textsubscript{2} decreased and CMRco\textsubscript{2} increased insignificantly, whereas in hypocapnia VADCO\textsubscript{2} increased significantly (alpha=0.001) and CMRco\textsubscript{2} remained constant.
FIG. 5. Cerebral VAD-lactate and CMR-lactate (mean values) during normocapnia (Paco₂ 36.5 mm Hg), hypercapnia (Paco₂ 64.7 mm Hg) and hypocapnia (Paco₂ 17.8 mm Hg) in 11 dogs.

Arterio-venous glucose difference and CMR-glucose (fig. 4)

In hypercapnia AVD-glucose decreased (but not significantly), while CMR-glucose remained constant. In hypocapnia AVD-glucose was nearly doubled (alpha=0.001) compared with the normocapnic values while glucose consumption remained constant.

VAD-lactate and CMR-lactate; lactate/glucose-index (fig. 5)

In normocapnia normal values of VAD-lactate, CMR-lactate and lactate/glucose-index (LGI=0.13) as compared with other experimental investigations were obtained. In hypercapnia both VAD-lactate and CMR-lactate decreased, but this decrease was not statistically significant: LGI remained constant (0.11). In hypocapnia a highly significant increase of VAD-lactate (alpha=0.001) was accompanied by an increase of CMR-lactate. The LGI was nearly doubled compared with the normocapnic value (0.22).

Po₂ and Pco₂ in sagittal sinus blood during normo-, hyper- and hypocapnia

The mean values, standard deviations and statistical significances of Po₂ and Pco₂ measurements in sagittal sinus blood are listed in table II. In normocapnia the cerebral venous Po₂ (cvPo₂) was 57.3 mm Hg and cvPco₂ was 43.5 mm Hg. In hypercapnia both cvPo₂ (77.9 mm Hg) and cvPco₂ (72.1 mm Hg) increased significantly. In hypocapnia cvPo₂ (37.8 mm Hg) and cvPco₂ (30.0 mm Hg) decreased significantly also.

The normocapnic values in this series do not differ from those obtained in other experimental investigations in our laboratory (Hamer et al., 1973; Hoyer et al., 1974).

According to Gottstein and colleagues (1971) the increase of AVD-glucose and AVD₂ occurs very quickly; they found that at 1-2 min after the start of hyperventilation the arteriovenous differences began to increase. After 5 min, a constant level was achieved. The significant increase of VAD-lactate in the cerebral venous blood in the present studies was also found in previous investigations (Wollman et al., 1965, 1968; Alexander et al., 1965, 1968). In our experiments LGI increased from a normal value of 0.13 in the resting state to 0.22 during hypocapnia, indicating increased glycolysis. That the source of increased cerebral venous lactate and increased LGI is increased glycolysis in the brain is also suggested by other experimental investigations (Granholm, Lukjanova and Siesjo, 1969; Granholm and Siesjo, 1969; Granholm and Siesjo, 1969).
Siesjö and Messeter, 1971; Siesjö and Plum, 1971). The last of these studies showed an increased lactate concentration in the brain during respiratory alkalosis. However, the present findings showed that the increased glycolysis is not related to a disturbance in cerebral oxygen consumption. It was also shown by Domonkos and Huszak (1959) that increased glycolysis in hypocapnia was accompanied by a normal oxygen consumption in the brain. Wayne, Demeester and Leusen (1970) explained the increased lactate production in the brain tissue during hypocapnia as a regulatory mechanism in the acid base balance and not as a sign indicating hypoxia. That cerebral lactacidosis in respiratory alkalosis does not necessarily originate from tissue hypoxia is further confirmed by the findings of Siesjö and Messeter (1971), Siesjö and Plum (1971) and Granholm and Siesjö (1971), who found unchanged concentrations of energy rich compounds in spite of an increased tissue concentration of lactate with PaCO₂ values as small as 16 mm Hg. This is consistent with the results of our study which showed an unchanged CMRO₂ and CMR-glucose at a mean PaCO₂ of 18 mm Hg compared with the normocapnic, normoxic resting state.

Moreover, the cerebral venous PO₂, which has been regarded as an index of the brain’s oxygen supply (Noell and Schneider, 1944; Opitz and Schneider, 1950; Thews, 1963), did not decrease during hypocapnia to critical values (cvPO₂ 38 mm Hg), of which the threshold was suggested as 19 mm Hg (Thews, 1963).

Under normoventilatory hypocapnia (mean PaCO₂ 64.7 mm Hg) we found an increase in the cerebral circulation by 89% (115.7 ml/100 g/min) of the resting value. This agrees with the results of Kety and Schmidt (1948), who reported an increase in CBF of about 75% in young humans who inhaled 5-7% carbon dioxide. Our data in hypercapnia demonstrated a decrease of the cerebral arteriovenous-substrate differences of oxygen, glucose and lactate. However, the cerebral metabolic rates of oxygen and glucose remained constant because of the CBF increase. This interference of CBF and arteriovenous-substrate differences was also shown by Kety and Schmidt (1948), Cohen and colleagues (1964) and Gottstein and colleagues (1971). Simultaneously with diminished VAD-lactate, LGI changed little (0.11) in our investigations. Assuming that a substrate concentration in the cerebral venous blood reflects the concentration in the brain tissue, our findings agree with those of Leusen, Lacroix and Demeester (1967), Wayne, Demeester and Leusen (1970) and Bain and Klein (1949), who found a decrease of lactate and pyruvate concentration in the cerebral tissue in hypercapnia. The normal CMR-oxygen and CMR-glucose which we found do not indicate a disturbed oxidative metabolism of the brain at a mean PaCO₂ of about 65 mm Hg. This is consistent with recent results of Siesjö, Folbergrová and MacMillan (1972) and Folbergrová, MacMillan and Siesjö (1972a, b), who described an unimpaired balance between substrate utilization and the energy state of cerebral tissue even at extreme hypercapnia of 150 mm Hg PaCO₂ corresponding to an intracellular pH of less than 6.7 units.

**Response of CBF to changes in PaCO₂ (fig. 1)**

Our CBF data obtained in 11 dogs during normo-, hyper- and hypocapnia within a PaCO₂ range from 15 to 83 mm Hg can be expressed by the equation: \(y = 2.88 + 1.69x\) where \(y = \text{CBF}\) and \(x = \text{PaCO}_2\). The regression coefficient for this equation is 0.85. This is consistent with other observations which showed the steepest increase in CBF in relation to PaCO₂ within this range (Reivich, 1964; Harper, 1965; Harper and Glass, 1965). We found an increase in flow of 89% over the mean PaCO₂ range 36.5–64.7 mm Hg and a 44% reduction over the range 36.5–17.8 mm Hg.

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**REFERENCES**


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EFFET DE L'ANHYDRIDE CARBONIQUE SUR LE DEBIT SANGUIN CEREBRAL ET LE METABOLISME CEREBRAL DES CHIENS

RESUME

On a étudié sur 11 chiens bâtards normotendus respirant normalement de l'oxygène, le débit sanguin et le métabolisme oxydatif du cerveau pendant une normocapnie, au cours d'une alcalose respiratoire et pendant une acidose respiratoire. Pendant l'alcalose respiratoire (Paco$_2$ moyen 17,8 mm Hg), le débit sanguin cérébral a baissé d'une manière appreciable de 61 à 33,9 ml/100 g/min (soit 44 %), alors que les différences du substratum artério-veineux ont augmenté et que les taux d’oxygène et le métabolisme du glucose sont restés constants. La différence veineuse-artérielle cérébrale du lactate a augmenté d’une manière importante par rapport à l’état de repos. Pendant l’hypercapnie, le débit sanguin cérébral a augmenté d’une manière appreciable de 61 (état de repos) à 115,7 ml/100 g/min (soit 89 %) (Paco$_2$ moyen 64,7 mm Hg). Les différences du substratum artério-veineux ont diminué alors que les taux du métabolisme cérébral sont restés constants. Les données indiquent que dans la relation entre le Paco$_2$ et le débit sanguin cérébral dans la plage des 20–65 mm Hg, le Paco$_2$ est exprimé par une relation linéaire: y=2,88+1,69x; dans cette plage le métabolisme oxydatif du cerveau demeure inchangé et l'augmentation de la production de lactate cérébral dans l'alcalose respiratoire n’est pas nécessairement reliée à une hypoxie des tissus.

DIE WIRKUNG VON KOHLENSTOFFDIOXYD AUF CEREBRALEN BLUTFLUSS UND CEREBRALEN METABOLISMUS BEI HUNDEN

ZUSAMMENFASSUNG

Bei 11 normal mit Sauertoffangereicherten, normotensiven, gemischtrassigen Hunden wurde der Oxydationsmetabolismus des Gehirns während Normokapnia und während Atmungskalkaloze und Atmungssäurestoffwechsel studiert. Während Atmungskalkaloze (Mittelwert von Paco$_2$ 17,8 mm Hg) sank der cerebrale Blutfuss (CBF) von 61,0 auf 33,9 ml/100 g/min (44 %), während die arteriell-venösen Subtratsunterschiede anstiegen und der Sauerdoff- und Glukosemetabolismus konstant blieben. Der cerebrale arteriell-venöse Unterschied in Laktat stieg wesentlich an, verglichen mit dem Ruhezustand. Während Hyperkalkaoze stieg CBF stark von 61,0 (Ruhezustand) auf 115,7 ml/100 g/min (89 %) an (Mittelwert der Paco$_2$ 64,7 mm Hg). Die arteriell-venösen Subtratsunterschiede verringerten sich, während der cerebrale Metabolismus konstant blieb. Die Angaben zeigen, daß das Verhältnis zwischen Paco$_2$ und CBF im Bereich von 20–65 mm Hg Paco$_2$, durch eine lineare Formel ausgedrückt wird: y=2,88+1,69x; in diesem Bereich ist der Oxydationsmetabolismus des Gehirns unverändert, und die erhöhte cerebrale Laktatproduktion bei Atmungskalkaloze steht mit Gewebe-Hypoxia nicht notwendigerweise in Zusammenhang.

EL EFECTO DEL BIOXIDO DE CARBONO EN EL FLUJO CEREBRAL DE LA SANGRE Y EN EL METABOLISMO CEREBRAL DE LOS PERROS

SUMARIO

Se estudió el flujo sanguíneo y el metabolismo oxidativo en el cerebro de 11 perros de raza desconocida normotensivo y con oxigenación normal, durante normocapnia y alcalosis y acidosis respiratorias. Durante la alcalosis respiratoria (media de Paco$_2$ 17,8 mm Hg) disminuyó el flujo cerebral de la sangre de manera importante de 61,0 a 33,9 ml/100 g/min (44 %), en tanto que aumentaban las diferencias del substrato arteriovenoso y permanecían constantes los regímenes del metabolismo de oxígeno y glucosa. La diferencia venoarterial del cerebro de un perro lactante aumentó de manera significativa en comparación con el periodo de descanso. Durante la hiperkapnia, aumentó bastante el flujo sanguíneo en el cerebro, de 61,0 (en el estado de descanso) a 115,7 ml/100 g/min (89 %) (promedio de Paco$_2$ 64,7 mm Hg). Las diferencias en el substrato arteriovenoso disminuían mientras permanecía constante el régimen metabólico cerebral. Los datos indican que la relación entre Paco$_2$ y el flujo sanguíneo cerebral entre los límites de 20 y 65 mm Hg Paco$_2$ se expresa por una relación lineal: y=2,88+1,69x. Entre estos límites, el metabolismo oxidativo del cerebro no varía y la producción de lactato cerebral en la alcalosis respiratoria no está por fuerza vinculado a la hipoxia de los tejidos.