EFFECT OF ARTERIAL CO₂ PRESSURE ON THE RESPONSE OF CEREBRAL AND HIND-LIMB BLOOD FLOW AND METABOLISM TO ISOPRENALENE INFUSION IN THE DOG

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SUMMARY

1. Cerebral blood flow, oxygen and glucose consumption, hind-limb blood flow and oxygen consumption, blood pressure and heart rate were measured in seven ventilated dogs.
2. Inhalation of 5% CO₂ caused a significant increase in cerebral blood flow and a significant decrease in cerebral glucose utilization.
3. Isoprenaline infusion (0.4 μg kg⁻¹ min⁻¹) caused a rise in cerebral blood flow, oxygen and glucose consumption. There was also an increase in peripheral blood flow and in most instances an increase in peripheral oxygen utilization.
4. The inhalation of 5% CO₂ during isoprenaline infusion abolished the increase in cerebral blood flow, in cerebral glucose consumption and heart rate. Cerebral oxygen consumption was significantly decreased to below control values. Once the administration of 5% CO₂ was discontinued an increase in peripheral oxygen consumption became apparent.
5. The possible therapeutic implications of these findings are outlined.

An increase in arterial CO₂ pressure causes an increase in cerebral blood flow. This fact has repeatedly been demonstrated in animals and in man (Lassen, 1959). Laubie & Drouillat (1967) showed that the catecholamine isoprenaline caused an increase in both cerebral blood flow and cerebral oxygen consumption. It might therefore be supposed that if CO₂ were administered during an isoprenaline infusion a very large increase in cerebral blood flow would occur. If the response were synergistic or additive there would possibly be important therapeutic implications for patients with cerebrovascular insufficiency.

Respiratory acidosis, however, modifies the cardiovascular effects of several catecholamines. Hypercapnia decreases the chronotropic, pressor and inotropic responses to adrenaline, noradrenaline and isoprenaline (Burget & Visscher, 1927; Bygdem & Von Euler, 1962; Manley, Nash & Woodbury, 1964; Wood, Manley & Woodbury, 1963;...
Schroeder, Robison, Miller & Harrison, 1970). Schroeder et al. (1970) also demonstrated marked attenuation of isoprenaline-induced peripheral vasodilatation during respiratory acidosis in dogs.

Alterations in the metabolic response to catecholamine infusion, secondary to changes in acid–base balance have also been demonstrated. Nahas, Ligou & Mehlman (1960) showed that when noradrenaline, adrenaline and isoprenaline were administered to apnoeic dogs, total-body oxygen uptake increased only if arterial pH was maintained at physiological values. If the arterial pH was allowed to fall in response to the rising CO₂ pressure, then the catecholamines failed to cause a significant change in oxygen consumption.

The main purpose of this investigation was to determine the effect of changes in CO₂ pressure on the response of cerebral blood flow and cerebral metabolism to an isoprenaline infusion. To obtain as full a picture as possible, changes in hind-limb blood flow and oxygen consumption, arterial blood pressure and heart rate were also monitored. Changes in hind-limb glucose utilization were not followed as it was impossible to tell whether glucose was being derived from local glycogen breakdown or not.

METHODS

Seven mongrel dogs of mean weight 13.5 kg (SD ± 4) were anaesthetized with sodium pentobarbitone in a dosage of 25 mg/kg body weight. Tracheostomy was carried out and the dogs were ventilated at constant rate and depth throughout the experiment. Variations in end-tidal CO₂ concentration were monitored continuously by means of a Beckmann i.r. gas analyser.

Cerebral blood flow

Cerebral blood flow was measured by the method of Ingvar & Lassen (1962) by using intracarotid injection of ⁸⁵Kr. The left superior thyroid artery was identified and the left common carotid artery catheterized via this vessel. Craniotomy and removal of the dura was carried out in the conventional manner. Radioactivity was measured with a small Geiger counter placed over the left parietal region. The radioactive gas dissolved in saline was injected slowly over approx. 1 min so that a constant amount of radioactivity monitored over the parietal region was obtained for 45 s. Cortical blood flow was then obtained from the analysis of the first 100 s of the ensuing decay curve as suggested by Lassen (1959).

An electromagnetic flow meter was placed around the right femoral artery so that percentage changes in hind-limb blood flow could be followed.

A catheter was placed in the aorta via the left femoral artery so that arterial blood pressure could be recorded continuously and arterial blood samples obtained. The arterial blood pressure was monitored with a Statham P23 AC transducer and the mean obtained electronically. A tributary of the right femoral vein was cannulated so that samples of venous blood from the limb could be obtained. A small catheter was placed in the superior sagittal sinus in such a way that flow was not impeded but samples of cortical venous blood could be obtained.

In the calculation of cerebral metabolism it was assumed that the superior sagittal sinus drains blood only from the cortex. There is good evidence in the dog to justify this assumption (Hegadus & Shackleford, 1965). In the calculation of hind-limb metabolism it was
assumed that changes in femoral artery flow were indicative of changes in total limb flow and that the samples of right femoral vein blood were representative of venous blood from all the hind limb.

Oxygen content was measured by the method of Linden, Ledsome & Norman (1965) and glucose by a glucose oxidase method (Hill, 1965). pH, $P_aO_2$ and $P_aCO_2$ were measured with appropriate radiometer electrodes. The values were corrected for changes in ambient temperature according to the nomogram of Severinghaus, Stapfel & Bradley (1965). Flow determinations and blood sampling were performed during the last 5 min of each 15 min period. The increase in arterial CO$_2$ pressure was effected by the administration of 5% CO$_2$ in air.

**RESULTS**

Since the electromagnetic flow meter gave only percentage changes in hind-limb flow, changes in oxygen and glucose consumption of the hind limb had also to be expressed as percentage change.

To facilitate comparison between the effects on cerebral and peripheral metabolism all changes have been expressed as a percentage of the first control values. The absolute control values (mean±SEM) were as follows: cortical blood flow = $110±9.0$ ml min$^{-1}$ 100 g$^{-1}$; cortical oxygen consumption = $10.0±1.2$ ml min$^{-1}$ 100 g$^{-1}$; cortical glucose consumption = $18.2±6.0$ mg min$^{-1}$ 100 g$^{-1}$.

*Administration of 5% CO$_2$*

The administration of 5% CO$_2$ caused a rise in mean CO$_2$ pressure from 40 to 62 mmHg. There was no significant change in blood pressure or peripheral blood flow, indicating no change in peripheral vascular resistance. An increase in cerebral blood flow, unaccompanied by a significant change in cerebral oxygen utilization was observed. There was, however, a significant fall in cerebral glucose consumption, as well as a slight insignificant fall in heart rate (Table 1).

*Isoprenaline infusion*

The administration of isoprenaline at a rate of $0.4$ μg min$^{-1}$ kg$^{-1}$ caused an increase in cerebral and in peripheral blood flow, accompanied by a moderate increase in cerebral oxygen consumption and a large increase in cerebral glucose uptake. In a number of dogs there was an increase in peripheral oxygen utilization but this was not enough to attain statistical significance at the 5% level. In addition there was a slight decrease in mean arterial blood pressure and in increase in heart rate (Table 1).

*Administration of 5% CO$_2$ during isoprenaline infusion*

After 15 min of infusion CO$_2$ was once more administered. Cerebral blood flow and cerebral glucose consumption fell towards control values but the fall in oxygen consumption by the brain was even more marked. These values were found to be significantly lower than those obtained during isoprenaline alone. Oxygen consumption by the hind limb was decreased from the previous slightly elevated value but this was not significant. The increase that had been observed in peripheral blood flow was not markedly attenuated (Table 1).
After the 5% CO₂ inhalation had been discontinued for approx. 15 min, cerebral blood flow, oxygen consumption and glucose consumption were again found to be at their previous high values and a significant increase in peripheral oxygen consumption became apparent.

**Table 1.** Effect of 5% CO₂ on the response of cerebral and peripheral blood flow, cerebral oxygen consumption, cerebral glucose consumption, blood pressure and heart rate to an isoprenaline infusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Control</th>
<th>5% CO₂</th>
<th>Control</th>
<th>Isoprenaline</th>
<th>5% CO₂</th>
<th>Isoprenaline</th>
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<tbody>
<tr>
<td>Peripheral blood flow (%)</td>
<td>100</td>
<td>100±1</td>
<td>97±3</td>
<td>97±3</td>
<td>124±8*</td>
<td>115±9*</td>
<td>136±13*</td>
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<tr>
<td>Peripheral O₂ consumption (%)</td>
<td>100</td>
<td>98±2.5</td>
<td>97±14</td>
<td>105±7</td>
<td>113±15</td>
<td>91±20</td>
<td>135±13*</td>
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<tr>
<td>MAP (mmHg)</td>
<td>129±9</td>
<td>124±8</td>
<td>138±5</td>
<td>129±6</td>
<td>102±9*</td>
<td>106±8*</td>
<td>94±10*</td>
</tr>
<tr>
<td>Pa,CO₂ (mmHg)</td>
<td>40±2</td>
<td>40±2</td>
<td>62±3*</td>
<td>38±3</td>
<td>38±3</td>
<td>67±4*</td>
<td>36±4</td>
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<tr>
<td>Heart rate (%)</td>
<td>100</td>
<td>100±0.4</td>
<td>93±3</td>
<td>96±2</td>
<td>127±8*</td>
<td>102±5†</td>
<td>125±8*</td>
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<tr>
<td>CBF (%)</td>
<td>100</td>
<td>100±1</td>
<td>126±6*</td>
<td>104±2</td>
<td>132±9*</td>
<td>101±10†</td>
<td>129±5*</td>
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<tr>
<td>CMRO₂ (%)</td>
<td>100</td>
<td>100±1</td>
<td>95±4</td>
<td>99±6</td>
<td>137±5*</td>
<td>75±13†</td>
<td>129±2*</td>
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<tr>
<td>CMRG (%)</td>
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<td>100±4</td>
<td>70±10*</td>
<td>104±5</td>
<td>178±22*</td>
<td>104±30†</td>
<td>156±6*</td>
</tr>
</tbody>
</table>

Means ± SEM are shown; * significantly different from control values at 5% levels; † significantly different from values obtained during initial isoprenaline infusion at 5% levels.

MAP = mean arterial blood pressure; CBF = cerebral blood flow; CMRO₂ = cerebral oxygen consumption; CMRG = cerebral glucose consumption.

The chronotropic response to isoprenaline was abolished during the 5% CO₂ inhalation period.

All variables returned to approximate control values after the infusion of isoprenaline was discontinued. The rate of return, however, varied somewhat from animal to animal.

**DISCUSSION**

Lassen (1959) pointed out in his review on cerebral blood flow and oxygen uptake that changes in flow after CO₂ administration are unaccompanied by changes in cerebral oxygen utilization. The inhalation of 5% CO₂ in the present experiments caused the expected increase in cerebral blood flow whereas oxygen consumption was unchanged. There was, however, a fall in cerebral glucose consumption. These findings are compatible with those of Craighead Alexander, Smith, Strobel, Stephen & Wollman (1968) who showed that cerebral glucose utilization in man is dependent on Pa,CO₂ values. Thus they showed that a fall in arterial CO₂ pressure was associated with an increase in glucose utilization. Glucose uptake and lactate production of brain slices is also increased when pH is shifted in an alkaline direction (Domonkos & Huszak, 1959).

The administration of isoprenaline caused the expected increase in both peripheral and cerebral blood flow and oxygen utilization. A very large increase in glucose consumption by the brain was also noted. Since glucose consumption showed a greater increase than oxygen consumption as a result of the infusion it is possible that some glucose was metabolized anaerobically to lactate.
The administration of 5% CO$_2$ during isoprenaline infusion altered both the vascular and metabolic responses. Peripheral and cerebral blood flow fell. Hind-limb oxygen consumption fell but the fall in cerebral oxygen utilization was more pronounced. Cerebral oxygen consumption under these circumstances was 25% below control values. Visible swelling of the brain was noted at this time in several dogs.

These findings are in agreement with those of Schroeder et al. (1970) who demonstrated marked attenuation of isoprenaline-induced vasodilatation during respiratory acidosis in dogs, and the findings also agree with those of Nahas et al. (1960) who demonstrated that the metabolic changes occasioned by catecholamines were dependent on arterial pH.

The chronotropic response to isoprenaline was completely abolished by inhalation of 5% CO$_2$.

The results demonstrate that the effect of isoprenaline on cerebral oxygen consumption is not only attenuated by CO$_2$, but is actually reversed. Cerebral oxygen consumption was significantly lower at this time than during control periods. Since isoprenaline may cause lactic acidosis by increased glucose breakdown and since CO$_2$ administration also causes a fall in pH, changes in intracellular pH may in some way be implicated in the fall of cerebral oxygen consumption and the subsequent swelling of the brain.

Both CO$_2$ (Lassen, 1959) and isoprenaline (Laubie & Drouillat, 1967) are potent cerebral vasodilators. However, from the above findings their concurrent use for the treatment of cerebral insufficiency would appear to be inadvisable. Also, if there were a local accumulation of CO$_2$ in a poorly perfused area of brain, then isoprenaline infusion could conceivably decrease flow into such an area while increasing flow to normal areas. Similarly in the periphery, if poor tissue perfusion and tissue acidosis were present, isoprenaline might cause vasoconstriction with vasodilatation in areas where tissue perfusion was already good.

Although it is dangerous to draw too many conclusions from animal work, it would seem reasonable, until evidence in man is obtained to the contrary, for isoprenaline to be used with caution in patients with peripheral or cerebrovascular disease.

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REFERENCES


