Effects of Unilateral Hypoxia and Hypercapnia on Pulmonary Blood Flow Distribution in the Dog

HANS G. BORST, JAMES L. WHITTENBERGER, ERIK BERGLUND AND MAURICE McGROR

WITH THE TECHNICAL ASSISTANCE OF Eleanor Gotz and Philip E. Waithe

From the Department of Physiology, Harvard School of Public Health, Boston, Massachusetts

ABSTRACT

BORST, HANS G., JAMES L. WHITTENBERGER, ERIK BERGLUND, AND MAURICE McGROR. Effects of unilateral hypoxia and hypercapnia on pulmonary blood flow distribution in the dog. Am. J. Physiol. 191(3): 446-452. 1957.—Effects of hypoxia and of hypercapnia on pulmonary blood flow distribution were examined in 19 dogs. The blood flow through each lung was continuously recorded; the test gas was administered to one lung, and the other lung was used as the control. Low oxygen gas mixtures were administered to one lung for periods of 2-47 minutes. When constriction occurred, it began within one-half minute after the gas administration was started and reached a plateau within 8-20 minutes. Vasodilation was never observed. In most animals no vasomotor effect of hypoxia was found early in the experiment (less than 6 hr. after induction of anesthesia), but seven of the early nonreactors became positive later in the experiment. After 6-8 hours from induction of anesthesia, all animals tested showed a vasoconstrictor response to hypoxia. The administration to one lung of 5 or 10% carbon dioxide for 2-10 minutes was always accompanied by vasoconstriction in that lung. In dogs that showed unilateral pulmonary vasoconstriction during hypoxia, further vasoconstriction was produced by adding 5% carbon dioxide. Some of the contradictory results of other investigators may be explained by the refractory period observed in these experiments.

In 1946 von Euler and Liljestrand reported that respiratory hypoxia and hypercapnia produced an elevation of the pulmonary artery pressure in the cat (1). They suggested, as Beyne had (2), that this was due to a local vasoconstrictor response in the lung. Subsequent investigations on this subject have given conflicting results (see 3, 4).

Both hypercapnia and hypoxia may produce reactions of the organism as a whole which could influence pulmonary vascular pressures and resistance, e.g., changes in cardiac output and left atrial pressure. In testing for the presence of a local vasoconstrictor mechanism, it is therefore desirable to supply the stimulus to one lung only and use the other lung as a control. The necessity of using the Fick method, with either estimates of pulmonary venous oxygen content or attempts at blood sampling from the pulmonary veins, can be avoided by direct and continuous measurement of the blood flow to each lung.

In the present study the problem has been reinvestigated, using the methods mentioned above. The results to be described indicate that another hitherto neglected factor has to be considered, namely the time interval between the onset of the experiment and the exposure to the test gas.
METHODS

Nineteen dogs weighing between 14 and 29 kg were anesthetized with either morphine-chloralose-urethane (1.7, 56, and 560 mg/kg), chloralose and urethane (82 and 820 mg/kg) or Nembutal (31 mg/kg) as initial doses. The experimental preparation has been described previously (5). The animals were tracheotomized and a G. Wright double lumen cannula (6) was inserted in the airway, effectively separating the ventilation of the two lungs (fig. 1). The thorax was opened by sagittal sternotomy. The lungs were ventilated with a pair of Starling pumps and the end-expiratory pressures were held equal in both lungs at 5–7 cm H$_2$O in order to prevent lung collapse. The tidal volumes were adjusted to make peak inspiratory pressures equal. Absence of leakage between the two lungs was ascertained repeatedly.

The right ventricle was replaced by a pump circuit fed from a reservoir into which the systemic venous blood was diverted. The blood was pumped into the lungs via two cannulae tied into the main pulmonary artery and the left pulmonary artery respectively (fig. 1). The procedure was performed rapidly without interruption of the circulation and without significant blood loss. Donor blood and dextran were used to fill the extracorporeal system. Pump output was adjusted to maintain a normal systemic arterial blood pressure. Blood flow to each lung was measured with Shipley-Wilson rotameters. Both pulmonary artery pressures distal to the cannulae, left atrial pressure and femoral artery pressure were measured with electromanometers. When desired, the airway pressure in either lung was determined with an inductance manometer. In some experiments the end-expiratory carbon dioxide level in either lung was measured with a Liston-Becker rapid infrared analyzer as described by Collier et al. (7). All these values were recorded on direct-writing oscillographs. Arterial oxygen saturations were determined with the manometric technique of Van Slyke and Neill.

The lungs were inflated with room air, except when hypoxia tests were done. All test gases were administered unilaterally. Before and during hypoxia runs, the control lung received 30% oxygen in nitrogen (in a few runs, 40, 50 or 100% oxygen) in order to limit arterial unsaturation. When the effect of unilateral carbon dioxide breathing was examined, the control lung was ventilated with room air.

Since total pulmonary blood flow was held constant during each test, redistribution of flow to the two lungs in response to unilateral alterations in inspiratory gas tension denoted a change of vasomotor tone (see fig. 2, 4). When flow redistribution was marked, there was a noticeable deviation from each other of the two pulmonary artery pressures which was caused by the resistance of the apparatus interposed between the pump and the pulmonary arteries. A consequence of this artificial deviation is that flow redistribution was somewhat less than would have occurred if the pressures had remained equal.

RESULTS

Hypoxia Experiments. Nitrogen alone and gas mixtures containing 5 or 10% oxygen in
nitrogen were administered to one lung 90 times in 18 experimental animals. The test gas was given for periods of 2–47 minutes (usually more than 6 min.).

Ten animals showed unilateral pulmonary vasoconstriction at some time during the experiment. When present, the reaction to hypoxia always started within 30 seconds and rapidly progressed for the first few minutes; a plateau was reached between 8 and 20 minutes. Flow reduction of all degrees, up to 46% of its original value, were observed in the hypoxic lung. When nitrogen was given, the test lung became distinctly blue. On discontinuation of the hypoxic stimulus, flow distribution of the two lungs returned to the control level within a few minutes. A typical experiment of this sort is shown in figure 2.

Figure 3 illustrates the time sequence of hypoxia runs. Most animals failed to react to hypoxia early in the experiment; seven of these showed repeated and consistent unilateral vasoconstriction later on. Of eight animals tested 8 or more hours after induction of anesthesia, hypoxia caused vasoconstriction in each. Seven animals had no vasomotor response to hypoxia. However, a possible ‘late’ vasoconstriction may have been overlooked, since none of these animals was tested 8 or more hours after induction of anesthesia.

In the animals not reacting with a flow redistribution, the pulmonary arterial pressure followed directionally the changes in left atrial pressure. There was no definite evidence of bilateral increase of pulmonary vascular tone.

When one lung was ventilated with high oxygen mixtures (30–100%) and the other lung with room air, no change of vasomotor tone was observed. The airway pressures did not change, whether or not pulmonary vasoconstriction was produced by hypoxia.

The response of femoral artery pressure to the systemic hypoxia was variable (table 1). The left atrial pressure usually, but not always, changed in the same direction as the femoral artery pressure, the maximal change was 3.7 cm H$_2$O.

In searching for factors which may influence hypoxic pulmonary vasoconstriction, attention was paid to six items.

**Anesthesia.** Both Nembutal and chloraloseurethane anesthesia were associated with vasoconstrictor responses. Both were also associated with failure to react (fig. 3). In two reacting animals 500 and 600 mg Nembutal, respectively, were added in successive doses to produce profound depths of anesthesia and eventually myocardial failure. No change in the hypoxic pulmonary vasoconstrictor reaction was found.

**Ventilation.** The animals were hyperventilated to a variable degree. In those animals in which end-expiratory carbon dioxide was measured, it varied between 1.2 and 4.4%. Hypoxic vasoconstriction was observed with alveolar carbon dioxide levels varying between 4.4 and 2.1%. Failures to react were also found with the same range of carbon dioxide. In one reacting dog alveolar carbon dioxide was reduced deliberately from 4.1 to 2.1% without modification of the hypoxic vasoconstrictor response.

**Systemic arterial unsaturation.** In table 1 is seen that substantial pulmonary vasoconstriction occurred in five experiments in which arterial saturation was above 80% when vasoconstriction had become maximal. Oximeter measurements indicated that the reacting and nonreacting animals received a comparable
HYPOXIA AND HYPERCAPNIA ON PULMONARY BLOOD FLOW

Fig. 3. Chart of pulmonary vascular responses to exposures to 10% oxygen (△△), 5% oxygen (□□), and nitrogen (XXX) in 17 dogs. MCU = morphine, chloralose and urethane. CU = chloralose and urethane. NEMB = Nembutal. Time scale starts at the induction of anesthesia. Horizontal lines start at time of pulmonary artery cannulation. Downward deflection denotes no pulmonary vasomotor response to the gases; upward deflection denotes pulmonary vasomotor response (constriction).

degree of hypoxic stimulation in terms of arterial unsaturation.

Epinephrine. On the assumption that circulating epinephrine was insufficient in these animals, epinephrine was infused intravenously into two dogs which reacted and two which did not react to hypoxia. In neither group was there any alteration of response to hypoxia, although femoral artery pressure had been increased by the infusion.

Unilateral injection of epinephrine produced local vasoconstriction at any time during the experiment whether or not there was a reaction to hypoxia (8).

Ganglionic blockade. Tetra-ethyl-ammonium and hexamethonium in doses high enough to markedly reduce systemic blood pressure were given to two animals without modification of the hypoxic vasoconstrictor response.

Vagotomy. In one animal both vagus nerves were severed when unilateral hypoxic vasconstriction had reached a plateau. No change in flow distribution resulted.

Carbon Dioxide Experiments. Eight animals received unilateral ventilation with 5% carbon dioxide in 19 runs and with 10% carbon dioxide in 2 runs. The gas mixtures were administered for periods of 3-10 minutes. All animals reacted to carbon dioxide administration with unilateral vasoconstriction (fig. 4). The reaction was rapid in onset (10-15 sec.) and reached a maximum value at 2-3 minutes. Unilateral decrease in flow amounted to 3-24% (average: 7%), but in all but one the decrease was less than 15%. In 5 of 13 runs in which carbon dioxide was given for longer than 3 minutes, reversal of the flow distribution towards control values occurred.

Five per cent carbon dioxide was administered to one animal in which a reaction to hypoxia had already been obtained. The lung vessels constricted further when carbon dioxide
TABLE I. DATA ON LUNG BLOOD FLOW, PRESSURES AND ARTERIAL SATURATIONS FROM 8 EXPERIMENTS

<table>
<thead>
<tr>
<th>Run No.</th>
<th>Insp. % O₂</th>
<th>Flow in Test Lung</th>
<th>PA</th>
<th>LA</th>
<th>FA</th>
<th>Art. % Sat.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
<td>R</td>
<td>Direct.</td>
<td>C</td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>min. cc min.</td>
<td>cm H₂O</td>
<td>cm H₂O</td>
<td>mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experiment 33</td>
<td>5</td>
<td>10</td>
<td>Air</td>
<td>9</td>
<td>500</td>
<td>952</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Air</td>
<td>10</td>
<td>1.5</td>
<td>280</td>
<td>542</td>
</tr>
<tr>
<td>Experiment 35</td>
<td>7</td>
<td>30</td>
<td>0</td>
<td>6</td>
<td>845</td>
<td>745</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>30</td>
<td>12</td>
<td>1200</td>
<td>500</td>
<td>31.4</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>30</td>
<td>11</td>
<td>1060</td>
<td>1000</td>
<td>31.3</td>
</tr>
<tr>
<td>Experiment 37</td>
<td>5</td>
<td>30</td>
<td>15</td>
<td>685</td>
<td>645</td>
<td>11.0</td>
</tr>
<tr>
<td>Experiment 38</td>
<td>7</td>
<td>30</td>
<td>13</td>
<td>700</td>
<td>600</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>30</td>
<td>10</td>
<td>1600</td>
<td>700</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>30</td>
<td>10</td>
<td>1135</td>
<td>500</td>
<td>28.0</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>30</td>
<td>9</td>
<td>1305</td>
<td>1300</td>
<td>30.3</td>
</tr>
<tr>
<td>Experiment 43</td>
<td>9</td>
<td>30</td>
<td>25</td>
<td>500</td>
<td>470</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>30</td>
<td>12</td>
<td>770</td>
<td>570</td>
<td>33.0</td>
</tr>
<tr>
<td>Experiment 45</td>
<td>2</td>
<td>30</td>
<td>0</td>
<td>25</td>
<td>680</td>
<td>595</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>30</td>
<td>0</td>
<td>10</td>
<td>575</td>
<td>395</td>
</tr>
<tr>
<td>Experiment 64</td>
<td>2</td>
<td>0</td>
<td>40</td>
<td>25</td>
<td>840</td>
<td>840</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>40</td>
<td>19</td>
<td>1200</td>
<td>1200</td>
<td>21.0</td>
</tr>
</tbody>
</table>

* In 7 of these hypoxia caused pulmonary vasoconstriction. Flow and pressures denote (mean) values at the end of control period (C) and at the time of maximal flow response (H). Total pulmonary flow was kept constant through each run.

was administered in addition to nitrogen on the same side.

The effect of these short-term administrations of carbon dioxide on the general circulation was not consistent. Femoral artery pressure either was maintained or decreased slightly, and left atrial pressure increased by a small amount in the majority of animals. Pulmonary arterial pressure increased by a small amount.

**DISCUSSION**

Direct recording of the blood flow to each lung in the relatively intact animal, as in the preparation used in this study, offers several advantages over other methods. It eliminates possible errors in estimation of blood flow by the Fick method in the unsteady state (9) and the necessity for measuring or assuming values for pulmonary venous content (differential pulmonary flow by the Fick method). The instantaneous flow recording also makes possible the study of changes with time.

The ventilation of the two lungs was completely and reliably separated. Gas mixtures were administered unilaterally while total pulmonary flow was kept constant. Therefore, one lung was used as the control while the other was tested. Local pulmonary effects could thus be differentiated from general circulatory effects.

Although the lungs were perfused by an extracorporeal pump, blood flow was maintained in the 'physiologic' range for many hours without the development of pulmonary hypertension or edema. Innervation of at least the right lung was undisturbed.

**Hypoxia.** The results obtained by these direct methods confirm the possibility that alveolar hypoxia may cause local vasoconstriction. However, no local effect of hypoxia was demonstrated within the first few hours after the induction of anesthesia and the operative procedure. After this period, all animals tested showed a consistent and rapid vasoconstrictor response. In no animal did a constrictor response ever disappear once it was demonstrated. This raises new questions about the nature of the phenomenon.

The late development of the vasoconstrictor response in these experiments might conceivably be related to the general condition of the animals, the depth of anesthesia, progressive deterioration of the lungs, or other factors. The animal had undergone extensive surgery before the first hypoxia test, but there had been no significant interruption of the circulation and no anoxic episodes, nor was there any evidence that the animal was in poor condition at the time of the early hypoxia tests.

In some animals the left atrial pressure rose in the late hours of the experiment, indicating that myocardial contractility was diminished. This deterioration was not marked, however, and the responsiveness of the heart to epinephrine and other drugs was good throughout
the experiment. Also, pulmonary vasomotor responses to administration of epinephrine, and other drugs (8) occurred with comparable vigor both early and late in these experiments.

Gross loss of lung function was avoided by periodic inflation to a transmural pressure of approximately 20 cm H2O; this prevented the development of atelectasis and hypostatic congestion. The constancy of repeated volume-pressure curves of the lungs and absence of changes in vascular resistance with time (compared at equal pulmonary artery and left atrial pressures) indicates that the lungs remained essentially intact throughout the hypoxia experiments.

It has been stated that the responsiveness of the pulmonary vascular bed is greatest when anesthesia is light or absent (10). In our experiments the response, when present, was uninfluenced by the depth of anesthesia. In one animal Nembutal was added in increasing doses in a deliberate attempt to modify the constrictor response until cardiac arrest was produced; the local hypoxic response remained vigorous even while the circulation was maintained by manual massage of the heart.

The possible role of nervous regulation of the local response to hypoxia was not emphasized in this study. However, the nerve supply to the right lung was probably not interrupted, while that to the left lung was almost certainly damaged. This apparently made no difference, for when the reaction was present, it was of the same order of magnitude on both sides. Further, ganglionic blockade and cervical vagotomy did not influence the reaction. It is concluded that the reaction was not under central nervous control. The possibility of axon reflexes was not ruled out.

The period of refractoriness, during which there was no constrictor response, demonstrates that a local response to alveolar hypoxia may exist in the same animal during some conditions but not during others. A refractory period was found in isolated cat lungs by Duke (11). Stroud and Rahn (10) found that some of their dogs did not show a constrictor response to unilateral hypoxia shortly after the animals were anesthetized, but did react later as the anesthesia became lighter. They attributed this to Nembutal, but it could have been a refractory period similar to that observed in our experiments. Failure to elicit vasoconstrictor responses in animals or in man therefore does not prove that the local hypoxic vasoconstrictor mechanism does not exist in these species.

In some studies only a portion of the dogs examined showed a vasoconstrictor response to unilateral hypoxia (12, 13). It is possible that a refractory period was overlooked in these studies. In rabbits a slow vasoconstrictor response to unilateral hypoxia was found (14). It is uncertain whether this is due to a slowly disappearing refractory period or is a different phenomenon in the rabbit.

Only a few attempts have been made to determine responses to unilateral hypoxia in man, and the results are conflicting (15-17; and personal communication from Dr. A. Cournand). Positive results (vasoconstriction in the hypoxic lung) obtained by Blakemore et al. (16) are subject to criticism on the basis of lack of steady state conditions. Fishman et al. (17) observed no diversion of blood flow when 10% oxygen was breathed for periods of 15-25 minutes; however, Cournand and co-workers have recently extended these observations to 4 and 6% oxygen, and at these levels a reduction in flow through the hypoxic lung occurred in three cases out of five tested.

**Hypercapnia.** A local pulmonary vasoconstrictor response to inspired carbon dioxide was found whenever the test was made, re-
regardless of the duration of anesthesia. The return of flow distribution toward control values after 2–3 minutes of unilateral ventilation with carbon dioxide was thought to be due to the onset of vasoconstriction in the control lung as the pulmonary arterial and alveolar carbon dioxide concentrations increased on the control side. No quantitative study was made of this phenomenon.

Several investigators (11, 18–20) have demonstrated carbon dioxide-induced pulmonary vasoconstriction in excised mammalian lungs, including the dog (20). Others, using either excised lungs (19) or the whole animal (10) did not observe pulmonary vasomotion in the dog due to carbon dioxide breathing. It should be emphasized that a transient vasoconstrictor effect of carbon dioxide may be overlooked if a continuous blood flow recording is not used. This is also true when only one lung is tested.

Lowered Alveolar Carbon Dioxide Tension During Hypoxia. Since, in these experiments, pulmonary vasoconstriction could be produced by an increase of alveolar carbon dioxide as well as by a low alveolar oxygen, the effect or reciprocal changes in the two gas concentrations in one lung should be considered. As ‘pure’ nitrogen is administered to one lung, the alveolar oxygen rapidly falls and oxygen diffuses into the lung from the blood. A steady state is reached at an alveolar oxygen tension somewhat lower than the pulmonary arterial oxygen tension. Meanwhile, the level of alveolar carbon dioxide is also reduced because of the Haldane effect on the carbon dioxide dissociation curve (21), even if there is no reduction of flow through that lung. The lowering of the alveolar carbon dioxide presumably has a vasodilator effect which conceivably could counteract the vasoconstrictor effect of low oxygen. Preliminary attempts to maintain the carbon dioxide constant, by adding in-spired carbon dioxide, were not successful. However, it seems unlikely that the negative results early in our experiments were due to the exact counterbalancing of low oxygen and low carbon dioxide effects.

REFERENCES