Effect of Unilateral Anoxia on Pulmonary Circulation

By FELIPE J. LANARI-ZUBIAUR, M.D. AND W. F. HAMILTON, PH.D.

Measurements were made of venous drainage from the right and left lower lobes of dogs' lungs. Blood supply was normal and breathing spontaneous. One lung was ventilated with air or oxygen and the other with nitrogen. Control and experimental flows were highly variable and though the anoxic lung received a smaller flow that was significantly different, the physiologic consequence of this fact is doubtful.

In 1946 Liljestrand and Von Euler showed that breathing low oxygen mixtures caused a rise in pulmonary arterial pressure. This response seems to be independent of nerve connections to the central nervous system and is not due to a backing up of left atrial pressure from failure of the left ventricle. It must therefore be due to a local action of anoxia upon the small pulmonary vessels. This conclusion is strengthened by the fact that atropine and certain adrenolytic agents do not decrease the response.

That this response occurs in man has been shown by Motley, Cournand, et al. and many others. It has further been shown that the increase in pressure can not be accounted for by an increase in cardiac output alone.

The fact that the pulmonary resistance is reduced in exercise when the mixed venous blood is anoxic, indicates that there must be a difference between the effects of blood-borne anoxia, which decreases pulmonary resistance, and air borne anoxia, which increases it.

On the other hand, it has been known for many years that the lung consolidated by pneumonia and the lung collapsed by pneumothorax, have a sufficiently high resistance to prevent flow in the abnormal lung. The increased resistance of these lungs has been attributed to increased tissue pressure, but since entrapped air would soon lose its oxygen, it may well be that active anoxic vasoconstriction as described by Liljestrand and Euler would participate in the shunting response. The shunting of blood away from the collapsed, consolidated, or anoxic lung will of course lessen the amount of venous admixture into the arterial stream and, since one lung can easily serve the requirements of resting respiration, such a response may have survival value. These considerations would apply only if the effect of air-borne anoxia were direct and local and were not the result of a generalized reflex.

A qualitative estimate of the change in the amount of venous admixture from the anoxic lung can be derived from the change in oxygenation of the mixed arterial blood. This estimate is sound if exchange can occur with the low-oxygen mixture in the anoxic lung. If, however, the anoxic lung is unventilated or collapsed, a change in saturation of the mixed arterial blood might be brought about by an increase in cardiac output. A lower A-V difference would lead to better oxygenation of the mixed venous blood passing unchanged through the unventilated lung and hence to a higher oxygen saturation of the mixed arterial blood.

Quantitative evaluation of a change in the pulmonary resistance depends upon simultaneous measurement of the flow and the pressure drop across the lungs. Thus a simple rise in pulmonary arterial pressure would not signify pulmonary vasoconstriction if it were due to increased flow or increased back pressure from a failing left ventricle. It follows that an evaluation not only of flow but also of pulmonary venous pressure is
needed in order to establish an increase in pulmonary resistance.

The obvious way of controlling these three variables is by perfusing the lungs. The surgery involved, the danger of altering the background of reflex control, and the fact that many agents which cause vasoconstriction in the perfused lung do not do so in the lung of the normal unanesthetized animal,\textsuperscript{11, 12} make this a procedure of limited usefulness.

In intact man or animals, measurement of flow presents the greatest hazard. The Fick procedure is misleading unless the subject has been on the anoxic regime long enough to be in a steady state,\textsuperscript{4} and the calculation of flow through the severely anoxic lung (with little or no oxygen uptake) is unsure.

The response to anoxic breathing by an increase in resistance of the pulmonary vasculature in man and in the cat seems to be well documented. Agreement is less consistent in the dog, and in either animal the recent work does not make clear whether the mechanism is local or reflex. (For reviews of the later literature see references 13 and 14.)

The contradictory conclusions in the literature, the difficulty of applying the Fick procedure in the anoxic state, and the hazards of perfusing isolated lungs, prompted us to use a method that would avoid these difficulties in so far as possible. In principle we measured the venous drainage from the lower lobes of the two lungs when the thorax was closed and breathing was spontaneous. Both lungs had a normal blood supply, delivered through intact pulmonary arteries and at exactly the same pressure. Venous flow was not impeded and the tubing was symmetrical. The spontaneous variation of flow was first evaluated when both lungs were breathing air, and the effects of alternating shifts of the gas supply to the two lungs from air to nitrogen, or from oxygen to nitrogen were then tested.

**METHODS**

Mongrel dogs ranging from 13 to 22 Kg. were premedicated with morphine (10 mg./Kg. subcutaneously). Half an hour later they were given 15 mg./Kg. of sodium pentobarbital intravenously. A special cannula, which allowed separate ventilation of each lung, was placed as low in the neck as possible. This cannula was essentially a tracheal cannula with two concentric channels, one opening directly into the trachea, the other connected to a plastic tube which went down the trachea and into the left main bronchus. Thoracotomy was performed at the fourth or fifth intercostal space on both sides. The tube in the left bronchus was tied securely and, after full heparinization of the animal, the veins from the lower lobes were cannulated with wide-bore plastic cannulas and the drainage of each was led into a Y-cannula pushed down into the thoracic cage through the right jugular vein. The chest was then closed, the animal placed in a prone position, and breathing became spontaneous usually at a rate of 15 to 30/min. In some dogs a mercury manometer for determination of the mean arterial pressure was placed in the right or left carotid artery. After 15 min. of spontaneous breathing of room air, the drainage from the lower lobes was simultaneously diverted through T-tubes into two graduated cylinders for a period of 10 sec. The blood was measured and returned through the left jugular and the measurements were repeated two or more times at intervals of 5 to 15 min. The 2 separate airways were then connected to Sanborn spirometers, one of which contained oxygen, the other nitrogen. Both provided for absorption of carbon dioxide.

Flow measurements were repeated as above, for various periods up to 90 min. The animal was then returned to air, the flows were remeasured and, when possible, the airways were reversed and the flows were measured again. Blood samples from the carotid artery and from the pulmonary drainage tubes were taken in some dogs for determination of oxygen and carbon dioxide content by the Van Slyke-Neill technic. Necropsy was performed after each experiment to check for the correct placement of the cannulas and to look for signs of edema or other forms of pulmonary pathology.

**RESULTS AND DISCUSSION**

**Experiments with Both Lungs Breathing Air.** These experiments were done as a control and included measurements on 5 animals. The first half-hour was arbitrarily used to establish a base line. The mean flow for this period was determined for each lung and taken as a mean control value (MCV). Figure 1 (upper curve) shows data from one of these dogs. Since flows in the two lobes
were different, per cent variations from the mean base line value for each lung were plotted. The steady fall of the absolute values is shown by the declining values of the curve. Variability was assessed by the usual statistical treatment of the differences between simultaneous points on the curves from the right and left lungs. The standard deviation of the control period was ±7.6 per cent; the later period was ±13.9 per cent. These large spontaneous variations make it hazardous to conclude that flow is different under one set of experimental conditions as compared with another unless an adequate number of observations is made to establish statistically the significance of the difference.

Experiments with One Lung Breathing Nitrogen. One hundred and thirty-three simultaneous comparisons were made between lungs breathing oxygen or air and lungs breathing nitrogen. Spontaneous variation was statistically assessed as above and was of the same order as with air breathing (standard deviation ±14.3 per cent. The flow through the air- or oxygen-breathing lobe was compared with that through the nitrogen-breathing lobe and tabulated as percentage change from the base line period for the same lung (table 1). In spite of the large spontaneous variations, the series as a whole indicates that flow through the anoxic lung is significantly lower than simultaneously measured flow through the lung breathing oxygen or air. There was no significant difference which depended upon whether air or oxygen was inhaled.

When individual animals are considered separately, the results are not predictable from measurement or even from animal to animal, even though the series as a whole...
Table 1.—Difference (X) Between Flow Through the Two Lobes of Dogs' Lungs Expressed as Per Cent of Control Flows. A Comparison of the Effects on Unilateral Flow when One Lung was Ventilated with Air or Oxygen and the Other with Nitrogen

<table>
<thead>
<tr>
<th>Groups for each lobe</th>
<th>Mean differences (%)</th>
<th>S.E.</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air — X_n</td>
<td>X' 24.6</td>
<td>±2.9</td>
<td>7.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>O2 — X_n</td>
<td>X' 18.1</td>
<td>±2.6</td>
<td>5.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Air — O2</td>
<td>X' — X'</td>
<td>±3.9</td>
<td>1.6</td>
<td>.31</td>
</tr>
</tbody>
</table>

indicated a greater resistance in the anoxic lung. Thus, in the 15 animals considered, 12 tests showed a significant (p < 5 per cent) decrease in flow in the anoxic lobe as compared with the oxygenated lobe. Six tests showed the same tendency but it was not significant. In 2 tests on each of 2 dogs, there was an opposite trend which again was not significant, while 1 dog showed a highly significant increase in flow on the anoxic side.

In these experiments it is assumed that the animals were in reasonably good physiologic condition. Breathing was deep, slow, and regular. Heart rate ranged between 160 and 80 min. (mean 130). Mean arterial pressure ranged from 120 to 60 mm. Hg (mean 90). The mixed arterial blood with both lungs breathing air was on the average 87 per cent saturated with oxygen, and with one lung breathing nitrogen it was 65 to 51 per cent saturated. Measurements were made in the prone position, which is said to be favorable for ventilation and perfusion of the lower lobes. The pulmonary artery branches and their accompanying nerves were uninjured. Flow through both lower lobes averaged 465 ml./min. with a range of 285 to 750 ml.

It would seem from these considerations that the lungs were being perfused under conditions as nearly normal as is compatible with sure measurement of flow, and that there is an over-all tendency for the anoxic lung to have a higher resistance than the oxygenated lung. That the weak, irregular response to anoxia has any meaning for survival is highly questionable. Generalized increase in pulmonary resistance from breathing depleted air would be a handicap to the circulation and a hazard to survival. It is doubtful that a vigorous pulmonary constrictive response to anoxic breathing could long survive in evolutionary development. However, a very weak response of a local (not general) nature might shunt blood away from an anoxic lung or lobe and thus reduce the stream of venous blood returning to the left heart, though this response is abrogated by a small increase of pulmonary vascular pressure resulting from mitral stenosis. It is difficult to see how, except as a result of bronchial obstruction, an isolated part of a lung can be exposed to depleted air. Bronchial obstruction leads to collapse, atelectasis, and thus to a mechanical increase in resistance which is probably greater than that produced by anoxia. Increased resistance to pulmonary flow due to anoxic vasoconstriction is therefore of temporary and questionable physiologic importance, having possible benefit only after bronchial obstruction and before atelectasis.

Summary

Venous drainage from the right and left lower pulmonary lobes was measured while one lung was breathing air or oxygen and the other lung was breathing nitrogen. The thorax was closed, the lungs expanded and spontaneous respiration was resumed. The lungs received blood at identical pressure from the heart via the two branches of the pulmonary artery which had not been disturbed and which had retained its accompanying nerves. One hundred thirty-three simultaneous direct measurements of flow indicated that the flow was 18 to 24 per cent less in the anoxic lung than in the oxygenated lung and that the difference was significant. Nevertheless, spontaneous variations (σ = ±14 per cent) were so great that prediction of flow differences of a single measurement could not be made and prediction of the response of an animal is hazardous. It is concluded that the physiologic
consequence of increased pulmonary resistance to flow due to anoxic breathing is of doubtful significance in the dog.

**Summary in Interlingua**

Le drainage venose ab le lobos pulmonar dextero- e sinistro-inferior esseva mesurate durante que le un del pulmones respirava aere o oxygene e le altre, nitrogeno. Le thorace esseva claudite, le pulmones se expandeva, e le respiration spontanea se reinitiava. Le pulmones recipieva sanguine de pression identic ab le corde via le duo branças del arteria pulmonar le qual hadeva remaniae intacte, retinente su nervos accompaniante. Cento trenta-tres simultanea mesuraciones directe del fluxo indicava que le fluxo in le pulmon anoxic esseva inferior per inter 18 e 24 pro cento in comparation con le pulmon oxygenate. Iste differentia esseva significative. Tamen, le variationes spontanea esseva si grande (σ = ±14 pro cento) que predictiones del differentia in le fluxo non poteva esser basate super un sol mesuration e que le prediction del responsa de un animal esseva riscona. Le conclusion es que le consequencias physiologic de un augmentate resistenzia al fluxo pulmonar, effectuate per respiration anoxic, es de significacion dubitose in le can.

**REFERENCES**


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