Effects of Anoxia on Postarteriolar Pulmonary Vascular Resistance

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Studies on an isolated pulmonary lobe, perfused in situ from a carotid artery under regulated arterial pressure, showed that changes in its ventilation from room air to nitrogen promptly causes a slight but definite increase in pulmonary vascular resistance which, from the nature of the experimental arrangements, must lie beyond the pulmonary arterioles.

In the foregoing communication Hirrimann and Wiggers reported that the blood flow of a lung lobe perfused under constant pressure was reduced during progressively developing anoxia. It could not be determined from these experiments whether the increased pulmonary vascular resistance resulted from direct action of anoxia or involved indirect reactions; nor could the site of action be assessed. The present studies on perfused denervated lungs were instituted with the hope that additional information on these questions might be yielded.

The effects of nitrogen respiration on perfused lungs have of course been studied previously, with the general conclusion that anoxia thus created causes increased resistance to pulmonary blood flow. However, all these experiments were conducted on lungs of cats and rabbits, using blood previously removed from the body, often diluted with saline or dextran. Since species differences are possible, studies need to be extended to the dog.

It is generally recognized that blood pumped from a reservoir differs markedly from blood within its natural blood vessels. Owing to unequal sedimentation at different times, defibrinated or heparinized blood tends to vary as to corpuscular content and viscosity during perfusion and, when diluted with saline, induces pre-edematous or edematous states more quickly than is generally appreciated. The composition of the plasma of withdrawn blood quickly changes, and when agitated by pumps the blood undergoes hemolysis. When reperfused it gathers substances which, being uneliminated or destroyed by passage through the kidney or liver, may affect the reactivity of pulmonary vessels or bronchioles. All of these disadvantages can be avoided by perfusing an isolated lobe with blood derived directly from the arterial system of the animal.

Vascular resistance can be calculated theoretically when either pressure or flow are kept constant, but in the study of pulmonary vascular resistance most investigators have chosen to maintain a constant flow and to register the changes in pulmonary arterial pressure developed by the pump. However, the magnitude of the peripheral vascular changes are apt to be overestimated, because considerable change in pulmonary arterial pressure can be effected by relatively small changes in arterial resistance. This was one reason for adopting the alternate procedure of maintaining a constant arterial pressure and, after allowing time for equilibration of capacity changes, measuring the venous outflow volume. Further, setting the pulmonary arterial pressure at different levels, pressure/flow calculations can be made at these stabilized pressures, thus enabling one to differentiate changes in calculated peripheral resistance which are produced passively by pressure changes from those that take place independently.

Method

Dogs weighing 14 to 20 kilograms were anesthetized with morphine and sodium barbital or pentobarbital. The chest was opened under artificial respiration. The branch of the pulmonary...
artery to the lower left lobe was perfused by blood led directly from the carotid artery. Pulmonary arterial pressure was maintained constant within 1 cm. of saline pressure for any given series of flow determinations by adjusting a screw clamp on the tubing from the carotid artery. The blood from the pulmonary vein flowed into a funnel from a tube kept at a fixed level, usually 6 to 8 cm. above the level of the pulmonary vein. From the funnel it was returned to the jugular vein of the animal. Venous outflow was measured by allowing blood to flow into a special graduated cylinder (accurate to 0.1 cc.) instead of the funnel.

The dog was maintained on room air throughout the experiments by means of a respirator which ventilated the right lung and upper two-thirds of the left. A separate "constant volume" respirator ventilated the lower left lobe. It could be made to pump either room air or nitrogen by simply switching a clamp on the respirator intake.

The experimental procedure was briefly as follows. The pulmonary arterial pressure was set at a low or high level. As soon as outflow rates were constant, four separate but consecutive aliquot flows were measured for 5 or 10 seconds each, with the lobe being respirated with room air. The lobe was then ventilated with nitrogen. After 15 seconds to allow for gas equilibration throughout the dead space, four more aliquot flows were taken within one minute. Following this, the lobe was returned to ventilation with room air and after 15 seconds four consecutive determinations of flow were again made. This three-stage procedure (control, nitrogen, and recovery) which was carried out in three minutes was then repeated at progressively increasing or decreasing pulmonary arterial pressures until five or more sets of data had been realized.

Resistance changes due solely to respiration have been reported by Edwards. To avoid any systematic change of the ratio of inspiration to expiration between the different stages it was necessary to take the flows in a consecutive but separate manner. As the respirator rate was 20 per minute, averaging these four flows for the flow per unit time avoided this difficulty.

In four experiments femoral arterial blood samples were drawn for oxygen determinations. Two blood samples were drawn while the lobe was ventilated with air, one before exposure to nitrogen and the second following a prolonged period of nitrogen breathing. Two samples were also drawn during the nitrogen ventilation period.

**Results**

Ten series of complete flow determinations at different pulmonary arterial pressures were made on eight dogs. Within 15 seconds after switching to nitrogen the venous outflow dropped to a lower level. It remained at this level for 15 minutes, the longest period of observation. The magnitude of the decrease at different perfusion pressures, as indicated in table 1, was of the order of approximately 10 per cent. In all instances the venous outflow rate after recovery approximated or exceeded the control rate.

The results of a typical experiment are plotted in figure 1. All the data in curve A represent changes within the first minute. In each experiment and at each pressure used, flow studies were continued for 15 minutes, but since no significant additional changes
took place after the first 15 seconds, these data do not require consideration. In curve A the open circles and crosses depicting flows at different perfusion pressures before and after recovery from nitrogen breathing practically coincide. The solid circles in curve B indicate the reduction of flows at different perfusion pressures during nitrogen ventilation. The curve obviously shifts to the right, indicating a slight increase in resistance. The separation of the curves at the top shows that calculated resistance changes following nitrogen breathing would be greater at higher than at lower pressures.

Oxygen determinations in four experiments revealed a reduction in oxygen content of the pulmonary venous blood, but the oxygen content of the animals' arterial blood varied only slightly over experimental ranges. In other words, no generalized anoxia existed.

The existence of a slight increase in pulmonary resistance during anoxia also becomes apparent in the data from all experiments plotted in figure 2. The plot compares results from 59 tests at equivalent perfusion pressures ranging from 11 to 34 mm. Hg. The ordinates indicate blood flow during room air ventilation; the abscissas indicate the flow during nitrogen ventilation. In this method of plotting, the diagonal line drawn at a 45 degree angle to the abscissas and ordinates represents the regression line around which points would scatter if the resistance to flow had not altered. Obviously, all points fall above this line, indicating a greater flow during ventilation with room air, and a greater trend in divergence the greater the rate of flow (and pressure).

**Discussion**

By determining pressure/flow relations at pulmonary arterial pressure ranges from 11 to 34 mm. Hg and ventilating a lung lobe in situ alternately with air and nitrogen, it was shown that anoxia promptly causes a slight but unquestionable increase of resistance in the pulmonary circuit. Since no generalized anoxia developed and since nerve fibers accompanying the bronchi were tied, reflex, central nervous, or hormonal effects of anoxia were excluded. Since the bronchial arteries were also ligated, changes in flow through this system could not have been involved. In short, the increased resistance must have been localized in the pulmonary circuit. Since the lobe was perfused with oxygenated blood, anoxia must have acted on capillaries or vessels beyond. The findings are at variance with conclusions of Aviado and associates who found that reduction of oxygen concentration in insufflated air results in slight reduction in pulmonary vascular resistance under a similar type of perfusion. The results agree, however, with observations of Nisell. Since much greater shifts in curves expressing pressure/flow relations occur as a mechanical result of lung inflation, it would be premature to assign the changes definitely to venomotor actions as Nisell has done. Also, these experiments do not exclude the possibility that, in the body, anoxia may affect pulmonary arteriolar resistance.

**Summary**

1. The direct effect of anoxia on pulmonary vascular resistance was studied in an isolated pulmonary lobe by perfusing it in situ with arterial blood from a carotid artery under regulated pressure and inflating it alternately
with room air and nitrogen. The volume of ventilation was kept constant.

2. Venous outflow was measured after each alternation of ventilation at various constant levels of pulmonary arterial pressure.

3. The pressure/flow relationship in individual and all experiments was plotted in different ways. These indicated clearly that reduction of alveolar oxygen promptly induces a slight but definite increase in pulmonary vascular resistance, which, from the circumstances of perfusion, must have taken place beyond pulmonary arterioles.

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