OBSERVATIONS ON HYPOXIC PULMONARY HYPERTENSION

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The increase in pulmonary arterial pressure that occurs when low concentrations of oxygen are inspired (von Euler and Liljestrand, 1946) is associated with a fall in pulmonary artery oxygen saturation, and results from an increase in pulmonary arteriolar resistance (Motley *et al.*, 1947; Lewis and Gorlin, 1952).

Experiments on isolated perfused lungs in cat and dog (Hall, 1953; Duke, 1954, 1957) suggest that it is the alveolar capillary region, rather than the arterioles, that are sensitive to anoxia, but whether it is the alveoli or the capillaries that are sensitive to oxygen lack is not known.

This has been investigated in the intact dog by maintaining the pulmonary artery saturation at near normal levels while the concentration of oxygen in the inspired air was reduced. It was found that the pulmonary vasopressor response was related to the oxygen content of blood in the pulmonary artery.

MATERIALS AND METHODS

The apparatus used is illustrated in Fig. 1, and consists essentially of a dog perfused from an extracorporeal circulation.

Preparation. Mongrel dogs of either sex, weighing between 5 and 12 kg., were anaesthetized with intraperitoneal nembutal and placed supine. A double-lumen number eight cardiac catheter or two single-lumen number six catheters were passed under fluoroscopic control via the right internal jugular vein into the right pulmonary artery. Pulmonary arterial pressure was continuously recorded on a Sanborn "polyviso" direct writer by a Sanborn electromanometer connected to one catheter. Samples of pulmonary blood for the analysis of gas, electrolytes, and metabolites were taken from the other catheter.

Systemic arterial pressure was also recorded on the Sanborn polyviso cardiograph by a Hansen capacitance manometer connected to a polythene cannula in the right femoral artery. Samples of femoral artery blood were taken for analysis by a direct puncture of this cannula.

A continuous electrocardiograph of one standard limb lead was also recorded on the polyviso.

An endotracheal tube was passed, the cuff was inflated in the trachea, and the dog allowed to breathe room air. The endotracheal tube could be connected to a spirometer, including a carbon dioxide absorber, which could be filled with gas of any desired composition.

The dog was given heparin 20 mg./kilo of body weight, and connected with the extra-corporeal circuit.

Extra-corporeal Circulation. Blood was conveyed from the left femoral artery of the dog through a polythene cannula to a pump, and then to an oxygenator mounted vertically on a stand. The oxygenator was modified from that described by Gott *et al.* (1957) and was made from two thin flexible rectangular polythene sheets, each 90 cm. $\times$ 55 cm., fused together to outline a continuous hollow channel. This consisted of a vertical limb 75 cm. $\times$ 5 cm. opening at the top into a reservoir 50 cm. $\times$ 15 cm. leading in turn into a zig-zag of 4 arms, each of which was 40 cm. $\times$ 5 cm. The oxygenator, which had a capacity of 700 ml., and the connecting tubing were primed with heparinized (15 mg./500 ml.) oxygenated compatible blood from a donor dog.

Blood entered at one corner of the base of the oxygenator, was carried upwards in the form of bubbles by a stream of gas entering at the same site, and flowed over into the reservoir at the top of the zig-zag, down which it ran to the exit at the base. During the downward course of the blood any persistent bubbles

FIG. 1.—Experimental arrangement. Catheters in pulmonary artery, cannulae in right atrium and both femoral arteries.

rose to the top, where a vent for priming allowed excess gas to escape. It was soon found that the femoral artery pressure alone maintained a good flow of blood into the base of the oxygenator, while the stream of oxygen carried it to the top. The pump therefore became unnecessary. The blood was not warmed in the extracorporeal circuit.

During perfusion the level of the blood in the reservoir was kept constant by means of an adjustable clamp on the oxygenator outlet tube. Blood flowed through this tube, via a flow-meter and a filter, to a cannula inserted into the left internal jugular vein and terminating in the right atrium (Fig. 2). There was no pump in this side of the circuit, gravity being sufficient to maintain a right atrial perfusion pressure of approximately 75 cm. of water.

At oxygen flows of 5 or 10 litres per minute, and blood flows of 200 or 400 ml. per minute respectively, the blood emerging from the oxygenator was at least 95 per cent saturated, whatever the saturation of the blood entering it.

The right atrium and hence the pulmonary artery could therefore be perfused with highly oxygenated blood at constant pressure and known flow rate, whatever the composition of the inspired air.

Cardiovascular Measurements. All pressures were calculated with reference to the right atrium as zero. Cardiac output was generally calculated from femoral and pulmonary artery oxygen saturation and oxygen uptake, using the Fick principle; in some experiments cardiac output was also estimated by the injection of I^{131} -labelled albumin and this method was used when the extracorporeal circulation was in action.

Chemical Determinations. Plasma sodium, potassium, and chloride were estimated by standard methods, lactic acid by the method of Barker and Summerson (1941) and pyruvic acid by the method of Friedemann

FIG. 2.—Details of cardiopulmonary preparation. Cardiac catheter terminating in right pulmonary artery, polythene cannula terminating in right atrium.

and Haugen (1943). Blood oxygen saturation was calculated from the oxygen content and capacity of blood samples using a Haldane gas analysis apparatus, pO_2 by the method of Roughton and Scholander and pH with a Cambridge electrometer.

RESULTS

The Reaction to Hypoxia in the Non-Perfused Dog. Studies were made on six dogs. Control observations were made initially with the dog breathing room air or 100 per cent oxygen, but not perfused with blood from the extracorporeal circuit. A mixture of 8 per cent oxygen and 92 per cent nitrogen was then given; the pulmonary arterial pressure rose within one minute (Fig. 3) and remained raised at 25–100 per cent above the resting level of 10–20 mm. Hg. The pulmonary capillary pressure, the femoral artery pressure, and the cardiac output remained unaltered (Fig. 4). Dogs were rendered hypoxic for about five minutes at a time and during this period the pulmonary arterial oxygen saturation fell progressively from the resting value of 50–70 per cent to about 10 per cent, the decrease being approximately proportional to the increase in pulmonary arterial pressure. Within one minute of again respiring the dog with room air or 100 per cent oxygen, the pulmonary arterial pressure fell to near original levels.

In two dogs pH and carbon dioxide content of the pulmonary artery blood were measured before and during respiration of 8 per cent oxygen. The pH fell and the pCO_2 increased, although in one

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FIG. 3.—Mean pulmonary arterial pressure changes during respiration of 8 per cent oxygen and 92 per cent nitrogen.

other dog no increase in bicarbonate in the pulmonary artery was found during hypoxia. In this latter dog pulmonary artery electrolytes (sodium, potassium, and chloride) and metabolites (pyruvic and lactic acid) were measured before and during hypoxia. There was no change in the electrolyte concentrations, but a slight increase was observed in the concentration of lactic and pyruvic acids (Table I). In another experiment the pulmonary artery of a dog respiring air was perfused with

TABLE I
EFFECT OF BREATHING 8 PER CENT OXYGEN AND 92 PER CENT NITROGEN FOR THREE MINUTES ON VARIOUS BLOOD COMPONENTS

	Dog respiring room air	After dog respired 8% O ₂ +92% N ₂ for 3 minutes
Plasma sodium	144.0 mEq./l.	145.0 mEq./l.
Plasma potassium	3.6 mEq./l.	3.7 mEq./l.
Plasma chloride	106.0 mEq./l.	107.0 mEq./l.
Blood pyruvic acid	0.96 mg. %	1.0 mg. %
Blood lactic acid	4.8 mg. %	5.9 mg. %
O ₂ saturation %	72	40
pO ₂	35	20
pCO ₂	42	52
Plasma bicarbonate	23 mEq./l.	24 mEq./l.
pH	7.50	7.48

FIG. 4.—Effect of breathing 8 per cent oxygen and 92 per cent nitrogen on mean pulmonary artery pressure, pulmonary artery oxygen saturation, mean pulmonary capillary pressure, femoral artery pressure, and cardiac output.

20 mg. of lactic acid in 10 ml. saline, and subsequently 10 mg. of lactic acid in 10 ml. saline. The pulmonary arterial pressure remained unaltered during either perfusion.

The Effect on the Reaction to Hypoxia on Perfusing the Pulmonary Artery with Well Oxygenated Blood. Since the rise in pulmonary arterial pressure during hypoxia was accompanied by a progressive fall in pulmonary arterial oxygen saturation, it was decided to observe the effect of perfusing the right atrium, and hence the pulmonary artery, with well oxygenated blood while the dog was breathing 8 per cent oxygen.

Each of a series of experiments with six dogs commenced with the animal breathing air for five minutes while control observations were made. The right atrium was then perfused with oxygenated blood (95 per cent saturated) at 250–350 ml. per minute. This procedure alone was followed by an increase of about 8–10 mm. Hg in the mean pulmonary arterial pressure which was maintained thereafter (Fig. 5). During this period the pulmonary artery oxygen saturation increased by about

FIG. 5.—Effect of perfusing right atrium with oxygenated blood on pulmonary arterial pressure of dog breathing air. Resting cardiac output (I_{131})=640 ml./min. Perfusion rate=250 ml./min.

FIG. 6.—The effect of breathing 8 per cent oxygen and 92 per cent nitrogen in a dog undergoing right atrial perfusion with well oxygenated blood. Cardiac output=820 ml./min. Perfusion rate=250 ml./min.

5 per cent. After a steady state had been attained, hypoxia was induced by respiring the dog with 8 per cent oxygen and 92 per cent nitrogen. This produced a further rise in the pulmonary arterial pressure, although much less than in the non-perfused dog breathing 8 per cent oxygen (Fig. 6). The systemic pressure remained unaltered. At the end of a five-minute perfusion period the pulmonary artery oxygen saturation had fallen to about 50 per cent. When perfusion ceased but hypoxia was maintained, the pulmonary arterial pressure rose as the pulmonary artery oxygen saturation fell below 50 per cent (Fig. 7).

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region from which pressor impulses arise. It is known that during hypoxia bronchomotor changes occur (Duke, 1954) and it is likely that the alveoli themselves are also sensitive to oxygen lack. When an isolated lobe of a dog's lung, which was being perfused with well-oxygenated arterial blood at constant pressure and flow rate, was ventilated with 100 per cent nitrogen there was a small but immediate rise in pulmonary vascular resistance (Hall, 1953). Since the alveolar capillaries were being bathed in arterial blood, the vasoconstrictor mechanisms were apparently initiated from regions in the alveoli sensitive to oxygen lack. Such an additional mechanism operating in the intact animal may explain the inability to restore completely the pulmonary arterial pressure to normal by perfusing the lungs of an hypoxic dog with well oxygenated blood, but this may also be due to the impossibility of restoring the pulmonary artery oxygen saturation to normal levels. The perfusion rate was always much less than the cardiac output, and hence the highly oxygenated blood was always diluted with two to three times its volume of poorly oxygenated blood.

These experiments suggest, therefore, that the pulmonary vessels are sensitive to anoxia, in addition to the alveoli. However, they do not localize the site sensitive to oxygen lack, which Duke (1951, 1954) and Hall (1953) have shown to be in the region of the alveolar capillaries.

Neither have these experiments elucidated the nature of the sensitizing stimulus, but they strongly suggest that it is the diminished oxygen saturation. Duke (1954), however, considers that the pO_2 may be more important than the saturation. On the other hand the sensitizing stimulus may be some change in the concentration of the circulating metabolites associated with diminished oxygen saturation.

Although during hypoxia there is a slight increase in the concentration of lactic and pyruvic acids, perfusion with these substances was not followed by a rise in pulmonary arterial pressure. Similarly carbon dioxide accumulates in the blood during hypoxia, but respiration of 5 per cent carbon dioxide in air did not produce a rise in pressure. Therefore, it is unlikely that the stimulus is lactic or pyruvic acids or carbon dioxide, but it could be some other undetermined metabolite.

It is known that 5 hydroxytryptamine when injected into the pulmonary artery produces an increase in pulmonary pressure, but Duke (1957) has shown that the rise during hypoxia is not related to this substance. Therefore it appears that while there are a variety of substances that may stimulate receptors during hypoxia, it is most likely that they are directly sensitive to oxygen lack.

One possible clinical application of these observations is the relief of acute right heart failure in *cor pulmonale*, especially that due to chronic bronchitis, utilizing a heart-lung machine in a manner, and for a period of time, not yet determined. By raising the pulmonary arterial oxygen saturation it may be possible to lower the raised pulmonary arterial pressure in this condition and so diminish right ventricular work. Experiments on these lines are projected.

SUMMARY

Vascular responses were studied in anaesthetized dogs during the inhalation of 8 per cent oxygen and 92 per cent nitrogen for short periods.

The increase in pulmonary vascular resistance was associated with a fall in the pulmonary artery oxygen saturation and could be reduced by maintaining the pulmonary artery oxygen saturation in the region of 50 per cent by perfusing the right atrium with well oxygenated blood from an extracorporeal system.

It is concluded that the mechanism producing pulmonary hypertension in the hypoxic dog is not only initiated by impulses from receptors located in the air passages but is also elicited from receptors in the pulmonary capillaries themselves.

The possible clinical applications of this observation are discussed.

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