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PULMONARY VASCULAR CHANGES IN RESPONSE TO VARIATIONS IN LEFT AURICULAR PRESSURE

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It has been asserted (Dexter, Dow, Haynes, Whittenberger, Ferris, Goodale & Hellems, 1950; Gorlin, Lewis, Haynes, Spiegl & Dexter, 1951; Lewis, Gorlin, Houssay, Haynes & Dexter, 1952; Davies, Goodwin & van Leuven, 1954) that elevation of the left auricular pressure causes a greater increase in pulmonary arterial pressure under conditions in which the pulmonary capillary pressure might be expected to approach the colloid osmotic pressure of the blood. The elevation in pulmonary arterial pressure might be due to pulmonary arteriolar constriction. It was thought interesting to study this response in isolated lungs, and in cats under chloralose anaesthesia in which the left lung or the lower lobe of the left lung was separately perfused at constant volume inflow. Preliminary experiments have already been reported (Carlill & Duke, 1954, 1956).

METHODS

Experiments in isolated lungs. Isolated cats' lungs were perfused with the animal's own heparinized blood (1000 i.u. 'Liquemin' Roche/100 ml.) which was collected under chloralose anaesthesia (0·1 g/kg intraperitoneally). Perfusion was carried out at constant volume inflow using a Dale-Schuster pump (Duke, 1951). The arterial inflow reached the lungs via a cannula inserted through the wall of the right ventricle and tied into the pulmonary artery beyond the pulmonary valves. The venous outflow was collected into a venous reservoir from a cannula inserted into the left auricle. Both ventricles were compressed by a tape. The temperature of the perfusate was kept at 36–38° C during the experiments. In some experiments 20–30 ml. dextran ('Intradex', Glaxo) was added to the blood obtained from the animal. In all experiments the output per minute of the pump was measured after the end of the experiment using the same perfusate as had been used in the experiment. Calibration of the pump showed that the output decreased by about 5% for an inflow pressure change of 0–35 cm 0·9% NaCl solution.

Pulmonary arterial pressure changes were recorded with a tambour and could also be read on a manometer filled with 0·9% NaCl solution (Duke, 1954). Pulmonary vascular pressures during negative pressure ventilation were referred to atmospheric pressure. Changes in left auricular pressure were made by adjustments of a screw clip on the tubing leading to the venous reservoir. A T-piece on this tubing was connected to a manometer filled with 0·9% NaCl solution on which the left auricular pressure could be read and recorded by means of a small volume recorder

attached to the open end of the manometer. To change the left auricular pressure the screw clip was adjusted and pressures read over the succeeding 1–2 min, by the end of which time they were stabilized. The mean pulmonary arterial and left auricular pressures were taken as the arithmetic mean of the highest systolic and lowest diastolic values read over a period of approx. ½ min after the pressures were stable. The manometer zeros were adjusted so that they lay approx. 1·0 cm posterior to the mitral valve. Rapid deterioration in perfused lung preparations is caused by obstruction to the venous outflow, and for this reason high left auricular pressures were not maintained for longer than was necessary to obtain the readings.

The trachea was cannulated and the lungs were ventilated either by negative or by positive pressure. When ventilation was by positive pressure the lungs were *in situ* within the widely opened thorax and a Starling 'Ideal' pump was used (15 strokes/min). The maximum intratracheal pressure was sometimes kept constant at +8·5 or +9·5 cm H_2O during the experiments. The volume of air not entering the lungs at each pump stroke was measured by the method of Konzett & Rössler (1940). When the lungs were ventilated by negative pressure they were removed from the chest and supported within a glass jar (capacity 10 l.) placed horizontally on a warmed operating table. Air was sucked out of the jar using a Starling pump (15 strokes/min) and an adjustable leak in the lid of the jar enabled the negative pressure within to be varied. The pressure in the jar could be read on a water manometer. Drying of the lungs was prevented by placing 100–200 ml. 0·9% NaCl solution in the jar before the experiment. Before removal of the lungs the oesophagus was ligated in the neck and above the diaphragm, and all vessels entering or leaving the thorax were ligated and the vena azygos tied. The pulmonary artery and left auricle were cannulated, the ventricles tied and the heart, lungs and thoracic part of the oesophagus stripped from the chest and transferred to the glass jar. Positive pressure ventilation of the lungs was continued throughout the dissection of the preparation. The lungs were ventilated with O_2 from a Douglas bag via inspiratory and expiratory water valves in order to prevent anoxia when the tidal air was reduced by changing the extra-pulmonary negative pressure. Changes in lung blood volume were recorded by measuring changes in the volume of blood in the venous reservoir. With perfusion at constant volume inflow this record indicated changes in lung blood volume (Daly, 1938). The pulmonary arterial pressure recording system was calibrated after the experiment and the amount of blood entering or leaving the reservoir but passing into or out of the tambour and manometer and not the lungs was accounted for and subtracted from the venous reservoir record.

Experiments in the chloralosed animal. Left lung perfusion experiments were performed in the cat (wt. 2·0–4·0 kg) under chloralose anaesthesia (0·1 g/kg) with the method previously described (Duke, 1954). The left pulmonary artery was cannulated and perfused at constant volume inflow with a Dale-Schuster pump which obtained its blood directly from the right auricle. The right lung received its blood in the normal way. The chest was widely opened and ventilation was by positive pressure. Variations in left auricular pressure were made by altering the volume of 0·9% NaCl solution within a small rubber balloon inserted into the left auricle. The left auricle was cannulated with a glass T-piece. One arm of the T was tied into the auricle and one arm was connected to a saline manometer on which the pressure in the auricle could be read and recorded as in the experiments on isolated lungs. The remaining arm of the T was closed by a rubber cap. Before the experiment began a serum needle with a short length of rubber tubing attached was thrust through the cap and a small rubber balloon was tied on to the end of the needle. The balloon tubing and needle were filled with saline and freed of air bubbles, the open end of the tubing closed and the balloon withdrawn into the glass T piece. After the cannula was inserted the balloon was placed within the chamber of the auricle. Left pulmonary arterial pressure records were made as described for isolated lungs. The heart rate was frequently counted over 15 sec periods and the minute rate calculated.

Perfusion of the lower lobe of the left lung was also performed in the chloralosed animal. In this preparation the pulmonary artery and vein of the left lower lobe were cannulated, care being taken that so far as possible the nerves were not damaged. The artery was perfused with blood from

the right auricle and the venous outflow was led into a reservoir from which it drained into the left femoral vein. The left auricular pressure was varied as described above. The systemic B.P. was recorded from the right femoral artery. A square-wave electronic stimulator was used for stimulation of nerves.

RESULTS

Isolated lungs

Experiments using positive pressure ventilation. Twelve successful experiments were performed in which the lungs were perfused at rates varying from 22 to 86 ml. blood/min/kg. In five of these experiments the maximum intratracheal pressure was kept constant without materially affecting the results. In one experiment similar curves relating left auricular and pulmonary arterial pressures were obtained during positive pressure ventilation and without ventilation of the lungs.

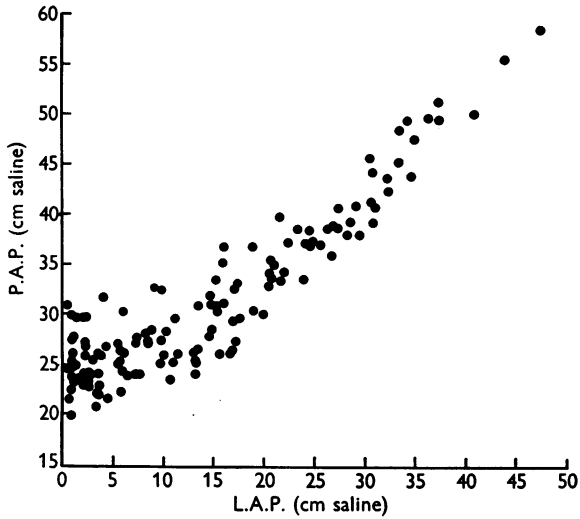

Fig. 1. The relationship of the pulmonary arterial to left auricular pressure in isolated perfused lungs. Six separate experiments. Positive pressure ventilation. Blood flow 40–80 ml./kg/min. P.A.P., pulmonary arterial pressure; L.A.P., left auricular pressure.

The relationship of the pulmonary arterial to left auricular pressures is shown in Figs. 1 and 2: Fig. 1 being derived from observations made in six different experiments, Fig. 2 from observations made on a single pair of lungs perfused at three different rates of blood flow. It can be seen that increasing the left auricular pressure from 0 to 10 or 15 cm 0·9% NaCl solution caused only a slight increase of pulmonary arterial pressure, but that the effect was much more pronounced when the left auricular pressure exceeded 15 cm. The greater the rate of blood flow through the pulmonary artery the higher the pulmonary arterial pressure for any given left auricular pressure (see Fig. 2),

although there is some evidence that the curves in Fig. 2 approximate to one another at levels above the physiological range. No significant differences were observed for readings taken with rising or falling pressures.

At constant volume inflow perfusion the pressure difference between pulmonary artery and left auricle gives a measure of the resistance of the vascular bed between these points. The resistance decreased as the left auricular pressure rose until the left auricular pressure was 10–15 cm 0·9% NaCl solution, thereafter very little change occurred (see Fig. 3).

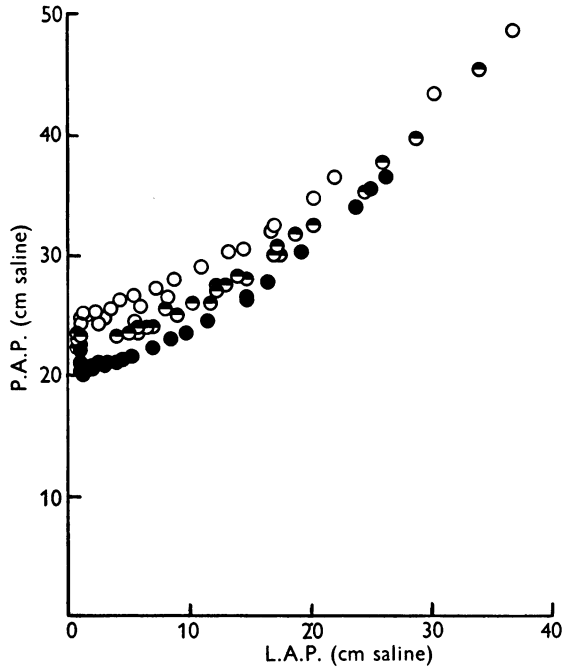

Fig. 2. The relationship of the pulmonary arterial to left auricular pressure. One isolated lung experiment perfused at three different rates of blood flow. Positive pressure ventilation. Ordinate and abscissa as in Fig. 1. Blood flow (ml./kg/min): ●, 46; ◓, 55; ○, 63.

Oedema occurred in two preparations after 1–2 hr of perfusion, and the pressure relationships were repeated after the onset of oedema. Oedema increased the pulmonary arterial pressure for any given left auricular pressure and the points became rather more scattered.

The lung blood volume was also related to the left auricular pressure. Fig. 4 shows the lung blood volume increase from an arbitrary initial zero plotted against the left auricular pressure and the resistance (calculated as arterial minus auricular pressure). Increasing the left auricular pressure from 0 to 20 cm 0·9% NaCl solution produced a sharp decrease in resistance, but further rises of left auricular pressure had no effect on the resistance. The

volume of blood in the vascular bed between the left auricle and pulmonary artery increased linearly with the left auricular pressure.

Experiments using negative pressure ventilation. When testing the effects of variations in the extrapulmonary negative pressure on the pulmonary arterial and left auricular pressure relationship, difficulty was experienced in obtaining consistent results. This was because the condition of the preparation altered during the perfusion period. Consistent results could, however, be obtained

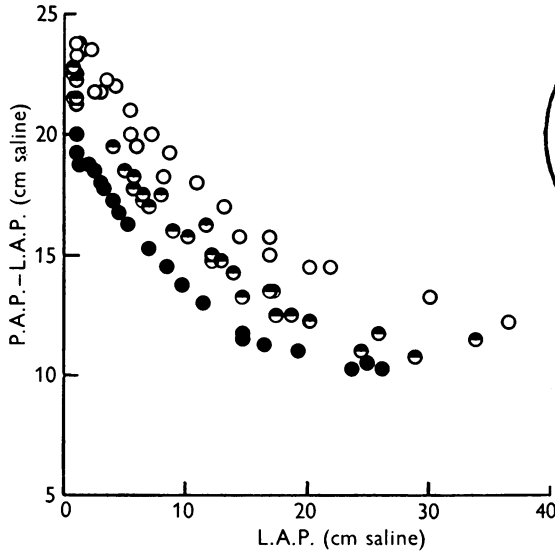

Fig. 3. The relationship of the left auricular pressure to the pulmonary vascular resistance. One pair of isolated lungs perfused at three different rates of blood flow. Positive pressure ventilation. Ordinate, P.A.P. – L.A.P. Abscissa, left auricular pressure. Blood flow (ml./kg/min): ●, 46; ◓, 55; ○, 63.

if the left auricular pressure was successively fixed at four or five points and the pulmonary arterial pressure read at two or three different extrapulmonary negative pressure values for each left auricular pressure. In this manner the test could be completed within half an hour, during which time the condition of the preparation did not materially alter.

In six preparations perfused at 27–46 ml. blood/kg/min it was found that, when the left auricular pressure was below approx. 15 cm 0·9% NaCl solution the pulmonary arterial pressure fell in response to lowering the extrapulmonary negative pressure. When the left auricular pressure was greater than approx. 15 cm 0·9% saline solution, the extrapulmonary negative pressure had no effect on the arterio-auricular pressure relationship (see Fig. 5).

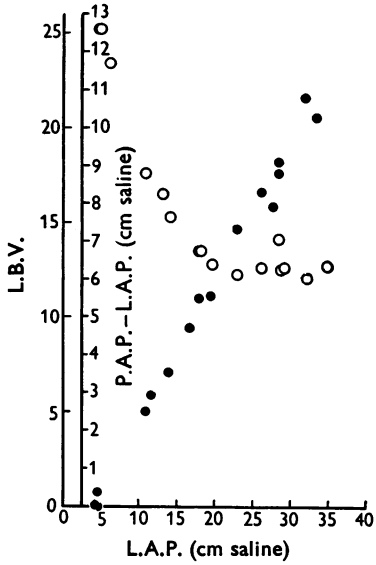

Fig. 4

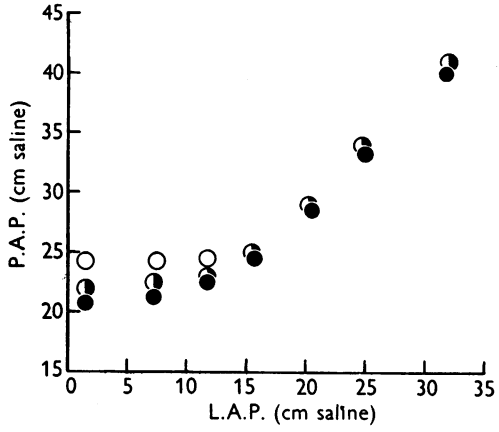

Fig. 5

Fig. 4. Isolated lungs. Ordinates, P.A.P. – L.A.P.; L.B.V., lung blood volume increase from arbitrary initial zero. Abscissa, left auricular pressure. ○, L.A.P. *vs.* P.A.P. – L.A.P.; ●, L.A.P. *vs.* L.B.V.

Fig. 5. Isolated lungs. Negative pressure ventilation using three different extrapulmonary negative pressures. ○, extrapulmonary negative pressure, 0 to minus 8 cm H_2O; ◑, extrapulmonary negative pressure, 0 to minus 14 cm H_2O; ●, extrapulmonary negative pressure, 0 to minus 20 cm H_2O.

Experiments in the chloralosed animal

Left lung perfusion. Twelve successful experiments were performed. Increasing the left auricular pressure caused changes in left pulmonary arterial pressure comparable to those obtained in isolated perfused lungs under positive pressure ventilation (see Fig. 6). Fig. 6 also shows that increasing the left pulmonary arterial inflow increased the left pulmonary arterial pressure for any given left auricular pressure. In four experiments, one of which is shown in Fig. 7, atropine (dose 1 mg) was injected intravenously and both stellate ganglia were removed and both cervical vago-sympathetic nerves were divided. It can be seen that there is no difference in the curves before and after atropine or after stellectomy and section of both cervical vago-sympathetic nerves.

The systemic blood pressure in these experiments was low (52–108 mm Hg), owing to the extensive operative procedures. The blood pressure was usually further reduced by increasing the left auricular pressure. Tests were performed

in order to ascertain whether or not the vasomotor centre and efferent pulmonary vasomotor nerves were capable of reacting under the conditions of the experiments. Increase of left auricular pressure caused a rise in heart rate (eight tests; see Fig. 8), or a fall (six tests). In four experiments, in which the caudal ends of the cut cervical vagi or the stellate ganglia were stimulated

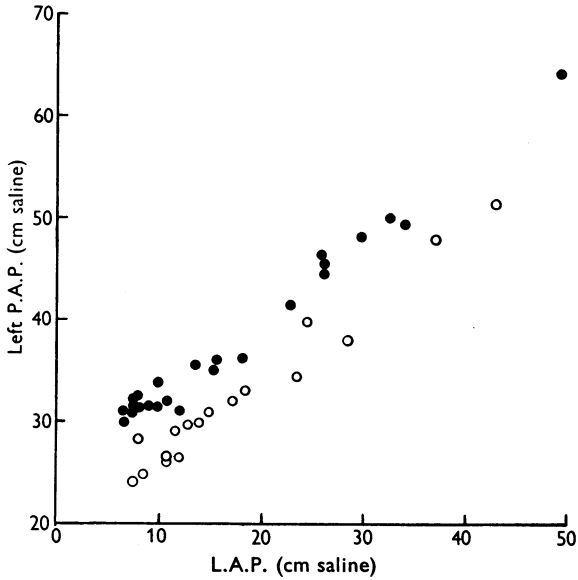

Fig. 6. Left lung perfusion. Chloralose anaesthesia. Two different rates of blood flow. ○, Blood flow, 20 ml./kg/min; ●, blood flow, 27 ml./kg/min.

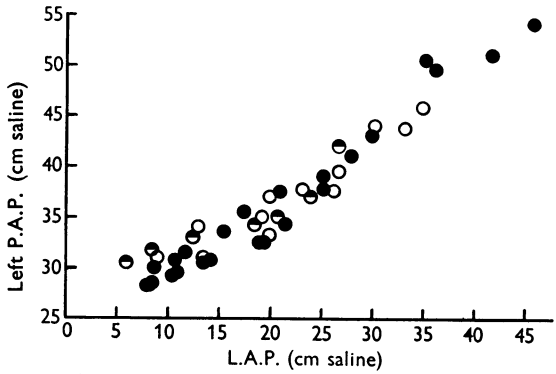

Fig. 7. Left lung perfusion. Chloralose anaesthesia. Relationship of left pulmonary arterial to left auricular pressure before and after injection of atropine (dose 1 mg) intravenously and after removal of stellate ganglia and section of cervical vagosympathetic nerves. ●, Before atropine; ○, after atropine; ◓, after atropine and vagotomy and stellectomy.

electrically, changes in left pulmonary arterial pressure were observed. The reactivity of the vasomotor centre was tested by observing the presence or absence of a reflex increase in blood pressure following occlusion of the carotid arteries in the neck. In seven consecutive experiments this reflex was present up to 2 hr of perfusion (see Fig. 9). In two experiments in which the cephalic end of the cut left lateral popliteal nerve was electrically stimulated, a reflex rise in blood pressure resulted (see Fig. 9).

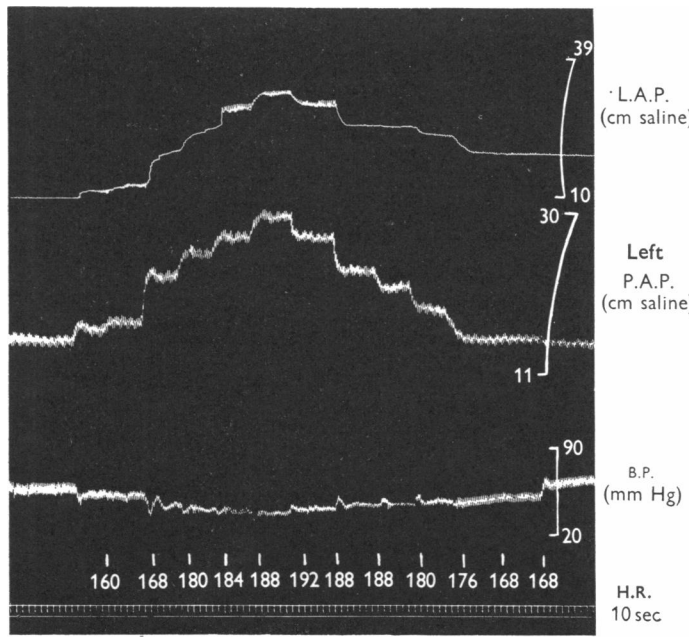

Fig. 8. Left lung perfusion. Chloralose anaesthesia. Positive pressure ventilation. B.P. = systemic blood pressure. H.R. = Heart beats/min. Time marker 10 sec.

(*b*) *Left lower lobe perfusion.* Six experiments were performed. Changes in left auricular pressure produced no effect on the pressure in the artery supplying the lower lobe of the left lung. With the methods used in this paper therefore no reflex effect on the pulmonary arterial pressure was demonstrable on changing the left auricular pressure. Direct effects on the pulmonary arterial pressure were, however, obtained in three of these preparations on stimulation of the cervical vago-sympathetic nerves and stellate ganglia. Changes in heart rate were also observed to follow changes in left auricular pressure.

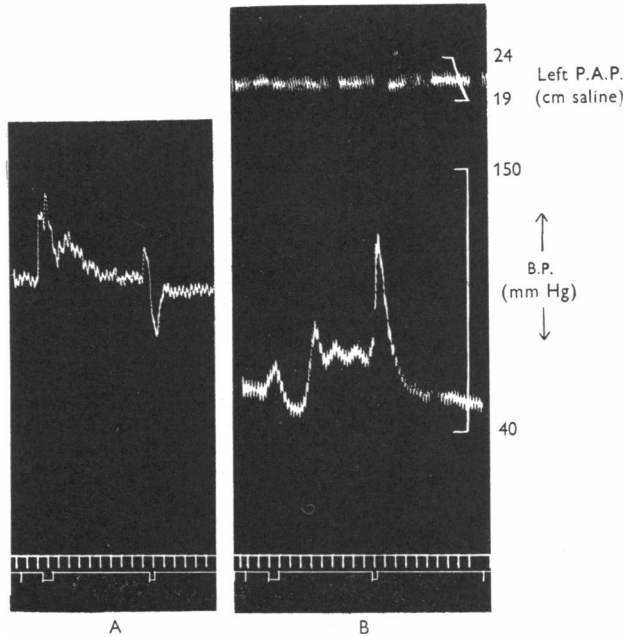

Fig. 9. Cat 2·3 kg. Chloralose anaesthesia. Open chest. Positive pressure ventilation. A, 12.08 p.m. Cephalic end left lateral popliteal nerve stimulated during first signal, 30 V, 1 msec, 100 c/s. Both common carotid arteries occluded during second signal. Perfusion of left lung begun at 12.20 p.m. B, 2.08 p.m. Stimulation of cephalic end left lateral popliteal nerve as in A, followed by carotid occlusion. Time marker 10 sec.

DISCUSSION

Evidence has been produced in these experiments that the vascular bed between the pulmonary artery and left auricle reacts to changes in left auricular pressure. Increasing the left auricular pressure from 0 to approx. 15 cm 0·9% NaCl solution produces a slight increase in pulmonary arterial pressure and a marked decrease in the resistance of the blood vessels between the pulmonary artery and left auricle. Further rises of left auricular pressure produce marked increases of pulmonary arterial pressure and negligible changes in resistance. The volume of blood in the lungs, however, increases linearly with changes in left auricular pressure for pressures between 0 and 35 cm 0·9% NaCl solution.

Lung blood volume and resistance changes can be produced by passive dilatation of the existing vascular channels in response to back pressure with or without concomitant opening up of new channels. Wearn, Ernstene, Bromer, Barr, German & Zschiesche (1934) showed that in the anaesthetized cat not all the subpleural capillary bed was open at any one time so that new channels

would probably be available. It is also possible that arterio-venous anastomoses are present which might open up (Gordon, Flasher & Drury, 1953; Prinzmetal, Ornitz, Simkin & Bergman, 1948; Pritchard, Daniel & Ardian, 1954).

Since the resistance remains constant with left auricular pressures greater than approx. 15 cm 0·9% NaCl solution the changes in lung blood volume appear to be due to changes in vessels which do not contribute to the resistance. At left auricular pressures below approx. 15 cm 0·9% NaCl solution dilatation of the vessels contributing to the resistance could be wholly or partly responsible for the increase in lung blood volume. Static pressure-volume relationships of the left auricle and extra-pulmonary parts of the pulmonary veins and also of the extra-pulmonary parts of the pulmonary arteries (Carlill & Duke, unpublished) showed that the increase in the volume of blood in these vessels only accounted for approx. 20% of the change in lung blood volume.

The experiments in which the left lung was perfused were performed in order to see if the responses obtained in isolated lungs were modified under more normal conditions by reflex or other effects. No evidence was obtained that this was the case. In these experiments the condition of the animal and the perfusion precluded any certainty that pulmonary and vascular reflex pathways were intact and operative. Stimulation of the cephalic end of the lateral popliteal nerve and occlusion of both carotid arteries produced changes in systemic blood pressure, so that the vasomotor centre was at least capable of responding to these stimuli. The efferent nerves to the pulmonary blood vessels of the left lung were also found to be responsive to electrical stimuli; but the afferent pathway of any reflex from the left auricle or pulmonary blood vessels could not be tested. The changes in heart rate which occurred in response to increase of left auricular pressure suggest that some auricular afferents were functioning, but this cannot be taken as incontrovertible evidence because it is conceivable that the changes in blood pressure which usually accompanied the change in left auricular pressure may have produced alterations in the rate of humoral secretions. Aviado, Li, Kalow, Schmidt, Turnbull, Peskin, Hess & Weiss (1951) have produced evidence that the pulmonary arterial conus is an important reflexogenic zone. The pressure in this region was not measured in the experiments now reported, but it is unlikely that it would have been lower than the left auricular pressure.

Dexter *et al.* (1950) and Gorlin *et al.* (1951) have postulated a reflex increase in pulmonary arteriolar resistance to increased left auricular pressure when the pulmonary capillary pressure approached the osmotic pressure of the plasma proteins. This reflex by reducing the pulmonary capillary pressure would help to prevent lung oedema. These findings were based on studies of pulmonary 'capillary' pressure in patients with cardiovascular diseases using the wedged catheter technique. The curves were compounded from a number

of individuals from each of whom one point was obtained. Pulmonary arteriolar resistance was calculated from pulmonary 'capillary' pressure, pulmonary arterial pressure and cardiac output. The difference between their results and those reported here could be accounted for by the difference in technique. For instance, many of their subjects were suffering from mitral stenosis, a condition in which a raised pulmonary resistance could be caused by organic changes in the pulmonary vessels (Goodwin, Steiner & Lowe, 1952; Bülow, Biörck, Axen, Krook, Wulff & Winblad, 1955) and a diminished cardiac output (Araujo & Lukas, 1952). It is also possible (Donald, 1956) that the hypertrophied pulmonary blood vessels in mitral stenosis can contract to increase the resistance to an extent which is not possible in the normal lung. This hypothesis has not been tested in the experiments reported in this paper.

SUMMARY

1. In isolated cats' lungs, perfused at constant volume inflow with the animals' own heparinized blood and under positive or negative pressure ventilation, an increase of left auricular pressure causes a rise in pulmonary arterial pressure, an increase in lung blood volume and a reduction in pulmonary vascular resistance.

2. When the left auricular pressure is less than approx. 15 cm 0·9% NaCl solution pulmonary arterial pressure changes are slight and resistance changes marked. For left auricular pressures in the range 15–35 cm 0·9% NaCl solution arterial pressure changes are marked and resistance changes slight. The lung blood volume increases linearly with increase in left auricular pressure.

3. The effects of changing the left auricular pressure on the left pulmonary arterial pressure in the cat under chloralose anaesthesia and with left lung perfusion are similar to those in isolated lungs. The response is not affected by atropinization, vagotomy and removal of the stellate ganglia.

4. In the cat under chloralose anaesthesia, changing the left auricular pressure produces no effects on the pulmonary arterial pressure of the perfused lower left lobe.

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