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VARIATIONS IN THE COMPONENTS OF THE VENTILATION HINDRANCE OF CAT LUNGS

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The non-linear relation between work/cycle and ventilation frequency for the lungs of the open-chest rat preparation has been interpreted in terms of two types of flow-resistance in the lung, one dependent on the nature of the ventilating gas and the other gas-independent (Mount, 1955), corresponding to the 'air viscance' and 'structure viscance' of Bayliss & Robertson (1939). Similar observations have now been made on cat lungs under comparable conditions, and in addition the effects of nerve stimulations and the actions of some drugs have been recorded.

The total pressure variation across the lungs when lung volume is varied cyclically may be termed the hindrance pressure, which is the vector sum of the pressures developed across the lungs in relation to flow-resistance and compliance, these two pressures depending on the rate of lung volume change and lung volume respectively. In order to observe short-term effects of drug action and nerve stimulation on these two components of the hindrance pressure continuous recording is desirable, and a method has been developed for this purpose. Factors involved in this type of recording, derived from the pressure-volume diagram, have been discussed previously (Mount, 1955).

METHODS

Cats (wt. 2·3–4·0 kg) were anaesthetized with 0·05 g chloralose and 0·5 g urethane/kg intraperitoneally. The trachea was cannulated and the chest opened by a mid-line incision; the internal mammary vessels were tied and divided, and the phrenic nerves cut. With the diaphragm thus paralysed, the chest was opened widely to interfere as little as possible with lung movement. The left and right cervical vagosympathetic nerves were exposed, separated into their predominantly vagal and predominantly sympathetic bundles, and cut between ligatures. Nerve stimulations were carried out by a square-wave electronic stimulator. Drugs were injected in the cannulated right femoral vein.

A Starling Ideal pump was used for positive pressure ventilation of the lungs both during the preparation procedure and later in the experiment in intervals when the lungs were switched from the recording pump, as described below. Water valves controlled inspiratory and expiratory

pressures with the Starling pump; pressure at the end of expiration was generally kept at 2 cm water with both pumps.

The ventilation hindrance and its components were assessed from tracheal pressure measurements during ventilation by the recording pump at constant stroke volume. The stroke volumes used were in the region of 40 ml., with frequencies of 9, 24·5 and 51 c/min. The pump was made on the crankshaft principle, with a long connecting rod and adjustable stroke volume, and was nearly sinusoidal in its volume delivery against time. When the recording pump was in operation, CO_2 was absorbed in a soda-lime tube, and the pump–soda-lime–lungs system was closed throughout each cycle except at the end of each expiration (i.e. at bottom dead centre of the pump stroke) when the system was opened by a trigger mechanism for a brief interval to a reservoir of oxygen at a pressure of 2 cm water; this ensured that each pump cycle began at this base-line pressure, and simultaneously it restored the volume decrease of the system due to oxygen consumption by the cat and absorption of expired CO_2 by the soda-lime. The lungs could be ventilated either by air or by gas delivered from a spirometer.

The principal type of recording used operated as follows. Tracheal pressure was transmitted directly to three membrane manometers in parallel, with their writing points arranged one above the other on the kymograph. The bottom manometer recorded the pressure variation throughout the cycle as a continuous trace; this overall pressure swing was the ventilation hindrance pressure, P_z. The middle manometer moved in phase with the bottom one, but the writing point moved parallel to the drum surface and 2–3 mm from it, only making contact with the paper at instants of top and bottom dead centres of the pump (instants of no gas-flow in the trachea), when the point was very briefly pulled laterally on to the drum by an electromagnet situated near the fulcrum of the manometer lever, and activated by contacts on the pump piston rod. The vertical distance between the two lines of dots so recorded gave P_c, the compliance pressure; P_c is inversely proportional to the compliance and is a direct measure of the elastance. The top manometer also moved in phase with the other two, but only wrote on the drum when the pump piston was at mid-stroke, and therefore travelling at its maximum velocity, again using an electromagnet and contact arrangement. The vertical distance between these lines of dots gave P_r, the maximum flow-resistance pressure, the sum of the dynamic components of pressure associated with maximum flow-rate in each direction.

Fig. 1 shows recordings of the three pressures from a model; the shape of the pressure–volume diagram in any given case could be obtained by switching the contacts so that both P_r and P_c were recorded by the same manometer, and could be plotted with values relative to each other against lung volume as determined by pump piston position.

In addition, in two experiments with the same recording pump system, pressure was measured with a condenser manometer and P_r and P_c displayed on the oscilloscope by a modification of the method described previously (Mount, 1955). This type of recording gave results similar to those obtained on the kymograph, but in view of the necessity for photographic procedures was much less convenient than direct display on the kymograph, with the great facility which the latter provided for immediate comparison of values at different times in the course of an experiment. However, the manometers used with kymograph recording had natural frequencies between 10 and 11 c/sec, and this limited the frequency range for faithful recording to approximately 60 c/min.

A correction, unnecessary in the case of oscilloscope recording, was applied to results from the direct kymograph method if it was desired to refer these to zero values. When an electromagnet was energized from the pump contacts whilst its corresponding manometer lever was moving in the vertical plane, the lever continued to move vertically during the small but finite period in which the pointer was accelerated horizontally on to the drum, with the consequence that the pressure level at the instant of drum recording was slightly different from that at the instant of the pump contact being made. The correction to be subtracted depended on the vertical velocity of the manometer lever at contact time, and this velocity was proportional to pump frequency and P_z amplitude (to which all three manometers were subject), and was determined by the point in

the P_z cycle at which contact was made. In practice, P_r was the only value requiring correction; unless the flow-resistance was very large, the P_c manometer lever was nearly stationary (i.e. at point of reversal) at the time its electromagnet was energized.

The correction required was measured on models with compliance and flow-resistances (rubber bag and glass tubes) of the same order as those found in cat lungs. Tests on a compliance alone, using hydrogen as well as air as the working gas, showed that the apparatus connexions (soda-lime tube and connecting tubes) had no measurable flow-resistance at the stroke-volumes and frequencies used in the cat experiments. With compliance alone the plots for P_r on air were indistinguishable from those on hydrogen, and gave the correction necessary for mechanical lag of the recording lever under the given conditions of frequency, P_z and zero flow-resistance. With the introduction of flow-resistance, P_r on air showed higher values than P_r on hydrogen for the same frequency and stroke-volume, as expected from the lower viscosity and density of hydrogen.

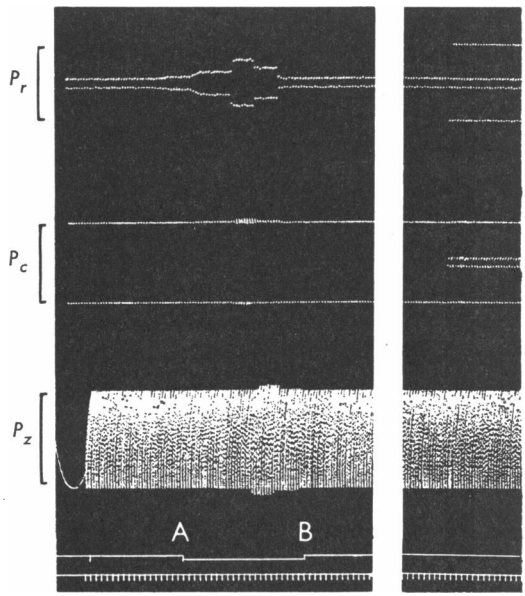

Fig. 1. P_r, P_c and P_z for a resistance-compliance model. Between A and B stepwise changes were made in flow-resistance, without change in compliance. On the right of the figure the two upper manometers were each recording both P_r and P_c, thereby giving the shape of the pressure-volume diagram. Ordinate calibrations: 10 cm H_2O. Time marks: 5 sec. Pump frequency: 24·5 per min.

RESULTS

Measurements of P_r, P_c and P_z were made in eight cats. In each animal the circulation was intact at the time the observations were made, with heart-rates ranging from 160 to 230/min. Respiratory efforts were just suppressed by the ventilation supplied by the recording pump; the cessation of artificial respiration caused the rapid onset of marked respiratory movements. All the observations reported were made after section of both cervical vagus and sympathetic nerves.

Variation of frequency. In Table 1 values for P_r at pump frequencies of 9 and 51 c/min are related to the value at 24·5 c/min taken as unity, for Expts. 2–5 and 8 in the absence of drug action or nerve stimulation. The results from a simple resistance-compliance model and the theoretical viscous flow ratio values, included for comparison, refer only to a rigid tube system such as that in the model employed. No attempt was made to compare the lungs with models containing elastic tubes of which the calibre, and therefore the flow-resistance, would vary during the ventilation cycle. In Expt. 2 oscilloscope recording was used, and consequently P_r did not require the correction for mechanical lag of the manometer lever applied to the three-manometer kymograph measurements in the other four experiments. Lowering the frequency from 24·5 to 9 c/min produced a much smaller decrease in P_r in the lungs than that found in the model or from the theoretical prediction of P_r assuming streamline flow. In addition, P_c showed a small rise with rise in frequency.

TABLE 1. Values for P_r at frequencies of 9 and 51 c/min referred to P_r at 24·5 c/min as unity. The figures in brackets in the third column are actual values for P_r (cm H_2O) at 24·5 c/min.

Frequency (c/min)...	9	24·5	51
Expt. 2	0·86	1·0 (1·18)	2·80
Expt. 3	0·76	1·0 (0·54)	1·51
Expt. 4	0·62	1·0 (1·46)	2·06
Expt. 5	0·81	1·0 (0·48)	2·10
Expt. 8	0·87	1·0 (0·75)	1·69
Means of expts.	0·78	1·0	2·03
Model	0·29	1·0 (0·51)	3·45
Theoretical viscous flow ratio	0·37	1·0	2·08

Pilocarpine hydrochloride. The action was examined in six cats, the total dose in each experiment being 2 mg intravenously given as 1 mg injections separated by a variable time interval. In every cat the proportionate effect on P_r was greater than that on P_c; the action is typified in Fig. 2. If the initial values of both P_r (corrected) and P_c were taken as unity, at the peak effect P_r was 8·8 (range 2·4–17·0), and P_c was 1·9 (range 1·0–2·6).

Cervical vagus stimulation. A total of fifty-four square-wave stimulations of the cut caudal end of the left or right cervical vagus were made in six cats, including stimulations after the administration of pilocarpine. The usual stimulus was at 5 V, with a pulse-width of 1 msec and a frequency of 50 c/sec, but pulse-widths of 0·1 and 10 msec were also used without measurable variation in effect. Stimulation produced increases in both P_r and P_c, with a greater effect on P_r in every case (Fig. 3). As an approximate average for the whole series, including those after pilocarpine, and taking initial values of both P_r (corrected) and P_c as unity, P_r was increased at the peak effect to 4·0 and P_c to 1·4. Vagal stimulations during the action of pilocarpine in three experiments produced smaller proportionate effects on both P_r and P_c than in the

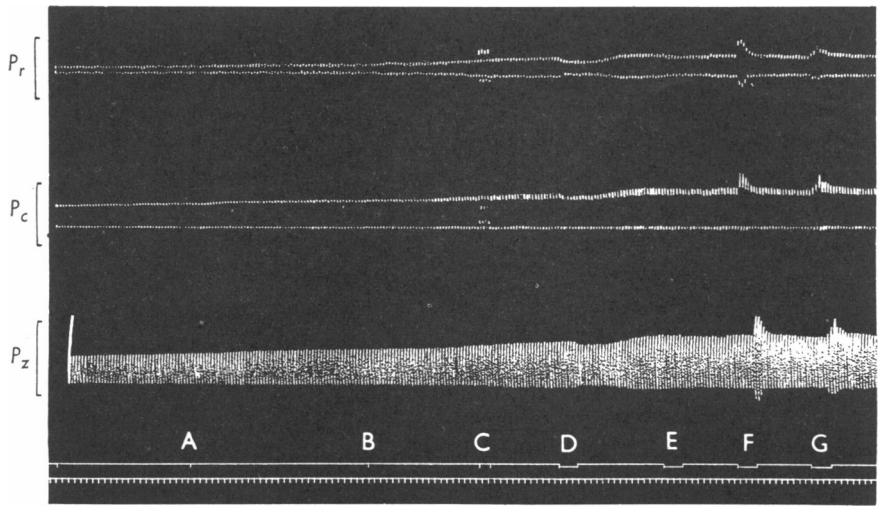

Fig. 2. P_r, P_c and P_z from Expt. 4 (cat, ♂, 3·4 kg). At A and B 1 mg pilocarpine hydrochloride was injected intravenously, followed by an increase in P_r and a smaller increase in P_c. At C, P_r and P_c were recorded jointly by both upper manometers. Stimulations of caudal ends of cut nerves: D, right cervical sympathetic; E, left cervical sympathetic; F, right cervical vagus; G, left cervical vagus. All stimulations were at 5 V, 1 msec pulse duration and 50 c/sec. Ordinate calibrations: 10 cm H_2O. Time marks: 5 sec. Pump frequency: 24·5 per min. Pump stroke volume: 37 ml.

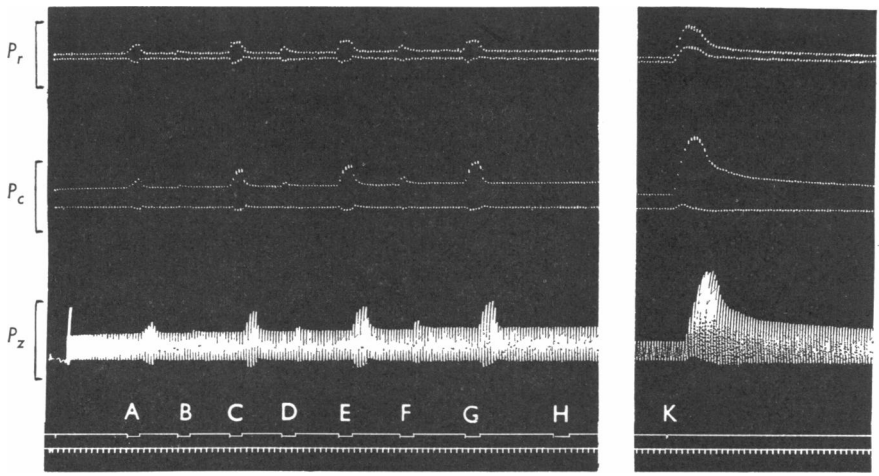

Fig. 3. P_r, P_c and P_z from Expt. 5 (cat, ♂, 3·5 kg). Stimulations of caudal ends of cut nerves: A, C, E and G, left cervical vagus; B, D and F, left cervical vagus and left cervical sympathetic together; H, left cervical sympathetic alone. All stimulations were at 5 V, 1 msec pulse duration and 50 c/sec. At K 200 μg histamine acid phosphate was injected intravenously 1½ hr after H. The relative positions of manometer writing-points were the same in the second part of the tracing as in the first. Ordinate calibrations: 10 cm H_2O. Time marks: 5 sec. Pump frequency: 24·5 per min. Pump stroke volume: 37 ml.

absence of the drug, but the increments due to stimulation were similar in each case (Fig. 2).

Cervical sympathetic stimulation. A total of fifty-one square-wave stimulations of the caudal end of the cut right or left cervical sympathetic nerve were made in six cats. There was no marked effect due to pulse-width variation through 0·1, 1, and 10 msec in any given case. Eighteen stimulations in six cats with no 'background' activity in the lungs (that is, no previous factors tending to increase P_r and P_c) produced no measurable effect on any occasion. Eighteen stimulations in five cats under the influence of pilocarpine failed to produce any effect in seven instances (all in Expt. 3); the remaining eleven reduced both P_r and P_c, the effect on P_r being proportionately greater than that on P_c (Fig. 2). A reduction of both values also occurred with stimulation on the background provided by 20 μg carbachol given intravenously. Sympathetic stimulation during vagal stimulation reduced the characteristic effects due to vagal activity. Fig. 3 shows alternate stimulations of the left cervical vagus alone, and left cervical vagus and sympathetic together, in Expt. 5.

Histamine. With doses ranging from 50 to 500 μg in four cats, P_r and P_c both tended to increase (Fig. 3), but here the proportionate effect on P_c was comparable with that on P_r. Clamping off the right lung in two experiments produced an effect similar to that brought about by the injection of (very approximately) 200 μg histamine.

Pulmonary blood volume. This was varied briefly within wide limits in three cats. Loose ligatures were passed round the aorta and pulmonary artery separately, and tightened for short periods to produce accumulation of blood in the lungs and emptying of blood from the lungs respectively. Tightening the aortic ligature, thereby tending to increase pulmonary blood volume, produced a small rise in P_c without effective change in P_r. Tightening the pulmonary artery ligature, tending to empty the lungs of blood, produced a fall in P_c, again without definite change in P_r. Clamping across the base of the heart produced no change in either P_r or P_c, but exsanguination of the lungs by excision of the heart was quickly followed by a rise in both values.

Ventilation with hydrogen and 20% *oxygen.* This was carried out in two experiments in an attempt to determine the fraction of P_r due to gas-flow-resistance, by varying the viscosity and density of the working gas and assuming the tissue fraction of P_r to remain constant. Over the frequency range used there was no measurable change in P_r on changing the ventilating gas except at 51 c/min, the highest frequency used, when P_r decreased by 10–20%, much less than would be expected from the physical characteristics of the gas. Similarly, no consistent effect was produced on the results of drug action and nerve stimulation.

DISCUSSION

Under the conditions of these experiments on the open-chest cat with the pulmonary circulation intact, P_r, at constant stroke volume, tended to remain high as frequency fell, in contrast with a simple resistance-compliance model with rigid tubes where P_r decreased smoothly towards zero. This is in accordance with observations made previously on the open-chest rat (Mount, 1955) over the lower range of the frequencies used in the rat experiments. P_r values were not decreased by substituting hydrogen and 20% oxygen for air except at the highest frequency used, 51 c/min, and then the effect was markedly less than that expected from the viscosity and density of the gas mixture relative to air. This was also the case over the corresponding frequency range with hydrogen in exsanguinated rat lungs; with higher frequencies in the rat, P_r (derived from work/cycle) became increasingly dependent on the physical characteristics of the working gas (Mount, 1955). These findings for cat lungs confirm those of Bayliss & Robertson (1939), and lead to the conclusion that under the positive pressure ventilation conditions of these experiments there is a resistance factor, distinct from gas-flow-resistance, which produces much larger effects on P_r at the frequencies used. This factor may be a true tissue deformation resistance, or it could result from surface tension effects in the lung airways. The former possibility has been discussed previously in relation to the rat, and a model described which satisfies the observations made in terms of a gas-flow-resistance and a tissue deformation resistance.

As regards a possible explanation in terms of surface tension, McIlroy, Mead, Selverstone & Radford (1955) have suggested that in experiments under conditions comparable with those used here the resistive component recorded is due largely to hysteresis resulting from surface tension effects in the lungs. That this suggestion may not apply in the present series in the absence of drug or nervous action on the lungs has been indicated by observations of work/cycle on the open-chest rat at base-line expiration pressures of 0, 2 and 4 cm H_2O, and of P_r on the open-chest cat at expiration pressures of 0, 2, 4, 6 and 8 cm H_2O. Pressure variations produced little effect in either preparation provided that the pressure was 2 cm H_2O or higher, although hysteresis was demonstrated by the systematically smaller values of P_r at any given base-line expiration pressure when the base-line pressure was being decreased from a high level to a low level, as compared with P_r values at corresponding pressures when the latter were being increased. However, if the pressure at the end of the cycle was 0 cm H_2O (that is, atmospheric) work/cycle and P_r were increased. An expiration pressure of 2 cm H_2O has been used throughout this work, with the exceptions noted above, and it is concluded that this pressure is sufficient to prevent collapse of the unstimulated lung.

Although there may not be marked interference from the effects of apposi-

tion of the internal surfaces of the lung airways in the unstimulated lung, it is probable that drug and nervous activity which causes smooth muscle contraction and increased glandular secretion renders partial or complete closure of airways more likely, and the force necessary to reopen the channels would overshadow the forces required to overcome tissue deformation resistance and gas-flow-resistance. Thus, with a powerful smooth muscle stimulant such as histamine, the tendency to closure of airway units due to bronchial muscle contraction would reduce the effective compliance with a population of bronchioles of varying sensitivity to closing effects, and in the extreme case the pressure-volume characteristics recorded would be those of the tracheobronchial tree alone. In addition, as suggested by Radford & Lefcoe (1955), the surface tension of the bronchial lining layer would tend to exaggerate the effect of bronchoconstriction since, once constricted with apposition of walls, relatively much greater forces would be required to reopen the airways. The base-line end-expiratory pressure of 2 cm H_2O would not influence this effect to any degree since the increase in wall tension due to bronchial muscle activity would be expected to correspond with higher intraluminal pressures than those encountered in these experiments. Any surface tension effects depend on the surface tension coefficient of the internal lining layer of the airway wall. The observations reported by Pattle (1955) suggest that this coefficient may be of very small order in the alveolar region of the lung, although they do not preclude the possibility of considerable surface tension in the bronchial tree.

The vagal effects on cat lungs, the increase in P_r being more marked than that in P_c, were unchanged by the previous injection of pilocarpine; the effects of pilocarpine and stimulation of the vagus were additive. No conclusions can be drawn regarding effects on the gas-flow-resistance since this was such a small part of the total resistance, as shown by ventilation with a hydrogen-oxygen mixture. In two experiments P_r and P_c were reduced on first cutting both vagi, an effect similar to the bronchodilatation observed by Daly & Mount (1951) under comparable conditions.

When the cervical sympathetic nerves were sectioned whilst recording was in progress no change was observed in any experiment in either P_r or P_c. In order to demonstrate the effects of stimulation of the sympathetic nerves it was necessary first to increase P_r and P_c by injection of pilocarpine or carbachol or by stimulation of the vagus. Sympathetic stimulation on these backgrounds tended to reverse the initial increases in P_r and P_c, the reversal being proportionately greater for P_r than for P_c.

Temporary separate occlusion of the pulmonary artery and aorta produced small changes in compliance, but no definite effects on flow-resistance. From the relative magnitudes of the effects of vessel occlusions and of drugs and nerve stimulation on P_r and P_c it is unlikely that the changes produced by

drug and nervous action in these ventilation factors are due to effects on the pulmonary circulation.

The continuous direct display of P_r and P_c used in the present work has demonstrated the uniformity of response to given tests in different experiments. The gas-independent flow-resistance determined the magnitude of P_r in these experiments, and was so large relative to gas-flow-resistance that variations in the latter with different stimuli could not be satisfactorily measured. The relative contributions of surface-tension effects and tissue deformation resistance to P_r remain undetermined; whilst these surface tension forces may be dominant when bronchoconstrictor agents are affecting the lungs, it is questionable whether they exert a deciding influence on the magnitudes of P_r and P_c in the open-chest animal in the absence of such agents if the base-line end-expiration pressure across the lungs is 2 cm H_2O or more.

SUMMARY

1. Ventilation flow-resistance pressure, P_r, and compliance pressure, P_c (the two components of the hindrance pressure, P_z) were recorded for the lungs of the open-chest cat using a method which allowed continuous observation of the three pressures on the kymograph.

2. With ventilation frequencies of 9, 24·5 and 51 c/min P_r tended to remain high as frequency fell.

3. Factors influencing flow-resistance, and the actions of some drugs and nerve stimulations, are discussed.

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