

Histamine release, pulmonary blood shunts, and rapid, shallow breathing in the dog

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Trimetaphan (Arfonad), which acts as a histamine-releasing agent in dogs, was observed to increase the shunt of blood through the lungs. Although external examination of the lungs showed no appreciable collapse, more detailed examination of lungs fixed by perfusion showed that the shunt could be explained on the basis of alveolar collapse and there was no need to postulate the opening of anatomical shunts. Histamine-releasing agents or histamine produced rapid, shallow breathing, which persisted after inflation of the lungs sufficient to restore the elastic and non-elastic resistance of the lungs to normal. It seems possible that the rapid, shallow breathing is due to sensitization of vagal nerve endings by the histamine or by some other substance released from the mast cells.

Functional shunts of blood in the lungs, by-passing the ventilated alveoli, have been shown to occur during and after anaesthesia (Bendixen, Hedley-Whyte, and Laver, 1963; Bendixen, Bullwinkel, Hedley-Whyte, and Laver, 1964; Hedley-Whyte, Laver, and Bendixen 1964; Sykes, Young, and Robinson, 1965) and after myocardial infarction (Pain, Stannard, and Sloman, 1967) and pulmonary embolism (Stein, Alkalay, and Bruderman, 1962). Channels by which blood may bypass alveolar capillaries have been demonstrated in the proximal part of the acini of the lung of man (Tobin, 1966), but it is usually assumed that the shunt of blood that occurs during anaesthesia is due to the passage of blood through collapsed areas of the lung (Bendixen *et al.*, 1964; Bendixen and Laver, 1965). Several workers (Coryllos and Birnbaum, 1929; Björk, 1953; Björk and Salén, 1950; Moore, 1931; Peters and Roos, 1952) have shown that when the lung of man or dog is made airless blood flow continues through the collapsed lung for several hours.

During experiments on the action of *Ancistrodon rhodostoma* venom (a snake venom with a thrombin-like activity. The purified coagulant fraction is now produced under the trade name Arvin.) on dogs, hypotension was produced with the histamine-releasing agents, trimetaphan (Arfonad) or Compound 48/80, and an increased pulmonary venous shunt was noted to occur. The experiments reported in this paper were carried out to investigate further the reason for the shunt,

and to determine whether the amount of shunt could be explained on the basis of atelectasis alone or whether it is necessary to postulate anatomical shunts which open in ventilated regions of the lung. Observations were also made on the rapid, shallow breathing which occurred in many of the animals.

METHODS

The main series of experiments was carried out on 25 mongrel dogs weighing from 6.0 to 14.3 kg. Throughout the experiments the dogs were in the supine position. The procedure in most of the experiments was as follows:

As soon as possible after anaesthesia a cuffed endotracheal tube was inserted and the functional residual capacity (F.R.C.) was measured by a helium dilution method. An intra-oesophageal balloon was inserted and pressure-volume loops were recorded as described below. Cannulae were inserted into the inferior vena cava via the femoral vein and into the aorta via the femoral artery. A no. 7 cardiac catheter was passed into the pulmonary artery. The measurement of F.R.C. was then repeated, the interval between the first and second measurement being usually about 40 minutes. The dog was connected to a closed-circuit spirometer system and the dog's lungs and the circuit were washed out with oxygen. The tidal volume was recorded on a kymograph, and a low-torque potentiometer, rotated by the spirometer cord, was used to record volume on the Y axis of a cathode-ray oscilloscope. The intra-oesophageal pressure was recorded on the X axis using a differential capacitance manometer backed off to the intra-

tracheal tube, and time intervals on the resulting pressure-volume loop were indicated by interruption of the beam every 1/10th second. The static compliance of the lung was recorded at the end of an inspiration by clamping off the tracheal tube distal to the point of connexion of the backing-off tube.

When a steady rate of oxygen uptake was recorded, an arterial blood sample was taken for measurement of oxygen and carbon dioxide tensions using Clark and Severinghaus electrodes respectively. A sample of gas was taken from the spirometer circuit for measurement of the oxygen tension of the inspired gas. The pulmonary and systemic arterial pressures were measured using strain gauge manometers, and simultaneous samples of pulmonary artery and aortic blood were taken for measurement of oxygen content by the Roughton-Scholander syringe method (Roughton and Scholander, 1943). The cardiac output was calculated by the Fick principle for oxygen. The mean systemic pressure has been calculated as the diastolic pressure plus one-third of the pulse pressure and the systemic resistance recorded as mm. Hg/(l./min.). It was thought to be undesirable in this experiment to wedge the catheter repeatedly, and so the pulmonary vascular resistance was not measured. Both strain gauge manometers were placed level with the highest part of the sternum with the dog supine.

After measurement of the first cardiac output the dogs were allowed to breathe pure oxygen in the spirometer circuit for a further 30 min. and the measurement of cardiac output, arterial gas tensions, and of lung mechanics was repeated. The dog was then disconnected from the circuit and allowed to breathe air for a few minutes to wash excess oxygen out of the lungs, and the measurement of F.R.C. was repeated. After reconnecting the dog to the spirometer circuit and washing out the lungs with oxygen continuous recordings of pulmonary and systemic arterial pressures were made and the dog was given 3-5 mg. trimetaphan intravenously. Trimetaphan was given to all the dogs in this study except dog 13, to which Compound 48/80 (1 mg./kg) was given, but previous studies had shown that the respiratory and haemodynamic effects of trimetaphan and Compound 48/80 were similar. The arterial oxygen tension was measured about 10-15 min. later and, if the tension had fallen considerably, the tension measurement was repeated together with a measurement of cardiac output. The dog was then allowed to breathe air for a few minutes before the measurement of F.R.C. was repeated. After this the dog was reconnected to the oxygen circuit, the lungs were washed out with oxygen, and the arterial oxygen tension was measured again to make sure that a pulmonary shunt was still present. The dog then breathed air for a few minutes and was killed by an intravenous injection of pentobarbitone.

In order to investigate the role played by alveolar nitrogen in lung collapse, three of the dogs breathed air only slightly enriched with oxygen during and after administration of the histamine-releasing agent. The results on these dogs are recorded separately in the Tables. To three dogs large doses of histamine

(5-12 mg.) were given intravenously instead of the histamine-releasing agents.

After development of the shunt in some of the dogs the lungs were inflated 10 times with air or oxygen to an intratracheal pressure of 30 or 40 cm. water. The measurements of lung mechanics and of the shunt were then repeated.

Vagal block was produced in some of the dogs by cooling the vagal nerves to 2-4° C. on brass thermodes.

Three dogs were studied as controls. In these the same procedures were carried out at the same time intervals but trimetaphan was not given.

FURTHER TREATMENT OF THE LUNGS In the dogs in which the lungs were forcibly inflated at the end of the experiment, detailed examination of the lungs was not made after death. These lungs were fixed by intratracheal distension with formol saline and a few blocks were taken from them. In three experiments the thorax was opened and, with the lungs still *in situ*, one pulmonary artery was infused with a gelatine-Micropaque mixture. When the gelatine had set the lungs were carefully removed from the body and fixed by intratracheal infusion with formol saline. In one dog this gelatine-Micropaque mixture was injected through a wedged catheter before the chest was opened. After fixation the lungs were sliced and radiographs were taken of the slices at 40 kV. using a beryllium window tube. Blocks of the lungs were then taken for histology.

In later experiments the main object was to fix the lungs without altering their state of collapse. Formol saline was perfused into the inferior vena cava before the chest was opened. About 8 l. was perfused over 2-3 hours, the vascular system being drained through the arterial cannula. The dog was left intact overnight, and the lungs were removed on the following day and floated on a bath of formol saline. After further fixation the volume of the lungs was measured by displacement of water and the lung was cut into 6 mm. slices.

QUANTITATIVE HISTOLOGY OF THE LUNGS A count of the proportions of non-parenchyma, collapsed lung, and aerated lung was made on the lung slices using a microscope at $\times 8$ magnification and a Zeiss I integrating eyepiece (Dunnill, 1962). Blocks of tissue of standard size were then cut, in a random manner, from the slices, and 5 μ sections were stained with haematoxylin and eosin. A further proportional count of non-parenchyma and collapsed and aerated lung was made on the sections using the Zeiss I integrating eyepiece and the microscope at $\times 16$ magnification.

In order to obtain some measure of the relative patency of the vessels in the collapsed and aerated parts of the lung a proportional count of (1) the lumen of the blood vessels, (2) lung tissue, and (3) air space was made on collapsed areas of the lung and repeated on aerated areas. A $\times 500$ magnification was used. The relative proportion of vessel lumen to lung tissue, as measured by this method, is approxi-

mate only, since the thickness of the section (5μ) is large in relation to the size of the lumen being measured, but the errors are reduced when comparing the proportions in aerated and in collapsed lung.

RESULTS

Trimetaphan and Compound 48/80 both release histamine from mast cells in the dog, and trimetaphan has, in addition, a ganglion-blocking action. The response of mast cells to these compounds is rapid (Uvnäs, 1963), and the arterial blood level of histamine reaches a maximum in about one minute (Fig. 1). The circulating histamine is rapidly removed, probably mainly by the lung (unpublished observations).

HAEMODYNAMIC EFFECTS An intravenous injection of trimetaphan or of Compound 48/80 produces a fall in systemic blood pressure, starting about 20 sec. after the injection, and the blood pressure reaches its minimum about one minute after the injection. In about half of the experiments the pulmonary artery pressure rose and reached a maximum about one minute after the injection, and then gradually fell below the initial level (Table I, unpublished).¹ In the other experiments, there was only a gradual fall in the pulmonary arterial pressure. The pulmonary artery pressure rose in all three dogs given histamine intravenously.

RESPIRATORY EFFECTS The effect on respiration was variable. Figure 2 shows a respiratory record of the type usually produced. Respiration often stopped abruptly, and was followed by apnoea for several minutes. During this time there was an occasional small shift (about 20 ml.) in the respiratory level in an expiratory direction, such as might occur if the alveolar ducts were closing

¹Tables I, III, and IV are deposited with the B.M.A. Library, from whom copies may be obtained on request

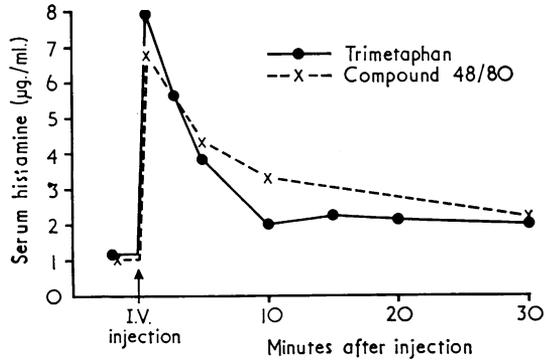


FIG. 1. Serum histamine measurements (expressed as acid phosphate) in the arterial blood after the intravenous injection of trimetaphan (mean of four dogs) or of Compound 48/80 (mean of two dogs).

and expelling their contents up the airways. In some dogs inflation of the lungs was attempted during this apnoea, and the compliance was very low, suggesting that most of the airways had closed off.

For the first part of the apnoeic period there were usually no inspiratory efforts, but these gradually became apparent on the pulmonary artery pressure and intra-oesophageal pressure tracings, and the tidal volume increased but remained smaller than before the administration of trimetaphan. The respiratory rate was slow at first but increased over 10–15 min. after trimetaphan to reach its maximum rate. Figure 3 shows the progressive changes in blood-gas tensions after the administration of trimetaphan.

The changes in F.R.C. and venous shunt through the lungs during the course of the experiment are shown as mean values in Table II. A reduction in F.R.C. often occurred during the period of air breathing whilst the cannulation procedures were being done, and in the dogs in which it was measured there was a further fall during the half-hour period of oxygen breathing, but in spite

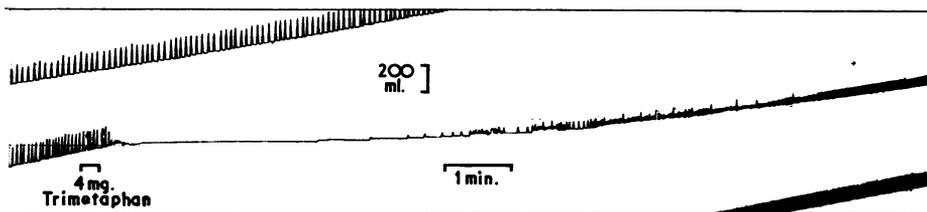


FIG. 2. The effect of an intravenous injection of trimetaphan on respiration. The portion of the record in the bottom right-hand corner is part of the respiratory tracing 50 min. later.

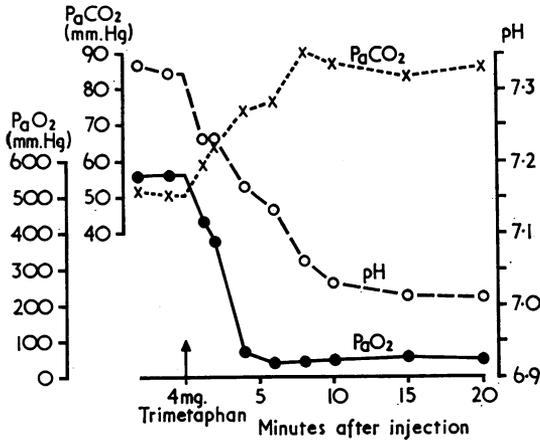


FIG. 3. The effect of an injection of trimetaphan on arterial blood gas tensions and pH. Dog 22 breathing 100% oxygen.

TABLE II

EFFECT OF HISTAMINE RELEASE ON LUNG VOLUMES AND VENOUS SHUNT (MEAN VALUES)

	Initial F.R.C. (ml.)	After Cannulation		After 30 min. on O ₂		After Histamine Release	
		F.R.C. (ml.)	Shunt %	F.R.C. (ml.)	Shunt %	F.R.C. (ml.)	Shunt %
<i>Breathing oxygen during histamine release</i>							
Mean of 9 dogs	461	—	5.6	389	4.4	373	30.0
<i>Control dogs breathing oxygen</i>						Equivalent time interval	
Mean of 3 dogs	372	361	5.1	—	—	319	2.7

of this the venous shunt did not increase. After trimetaphan administration there was a considerable increase in shunt with no significant change in F.R.C.

The changes in the mechanical properties of the lungs are shown in Table III (unpublished). After injection of trimetaphan the measurements could not be made until respiration had been re-established. The elastic resistance of the lungs when breathing first started was often very high, but fell rapidly to a level considerably above the initial value. Figures 4 and 5 show changes in lung mechanics in two of the dogs. The mean respiratory frequency increased from 12/min. before trimetaphan to 30/min. afterwards with maximum rates of 55/min. in some dogs. Analyses of these results show a significant correlation between the increase in elastic resistance and the increase in non-elastic resistance ($r = +0.581$, S.E.

0.258) but no significant correlation between the increase in elastic resistance and the shunt ($r = +0.184$), increase in respiratory frequency and increase in shunt ($r = -0.016$), or increase in frequency and increase in elastic resistance ($r = -0.133$).

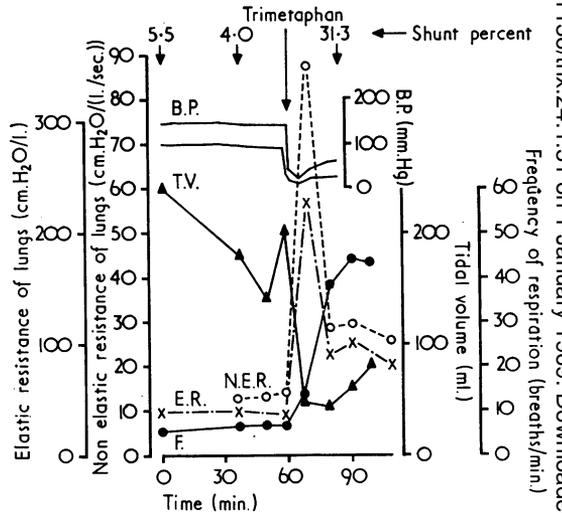


FIG. 4. Dog 5. The effect of trimetaphan on systemic blood pressure, respiration, the mechanical properties of the lungs and the shunt of blood through the lungs. T.V.=tidal volume; F=frequency of respiration; E.R.=elastic resistance; N.E.R.=non-elastic resistance.

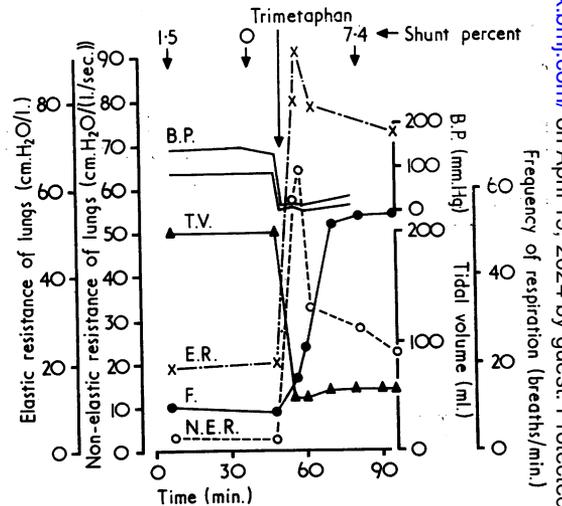


FIG. 5. Dog 15. Legend as for Figure 4.

EFFECT OF LUNG INFLATION After measurement of the shunt following trimetaphan injection the lungs of six dogs were inflated, usually to 40 cm. water. The inflation was held for a few seconds and repeated 10 times. The results are shown in Table IV (unpublished), and a representative chart is shown in Figure 6. Immediately after inflation the respiratory rate was usually even faster, but this appeared to be because the lungs were inflated with air rather than oxygen, which the dogs had been breathing up to the time of inflation. When the lungs were inflated with oxygen the respiratory rate did not change. Inflation usually

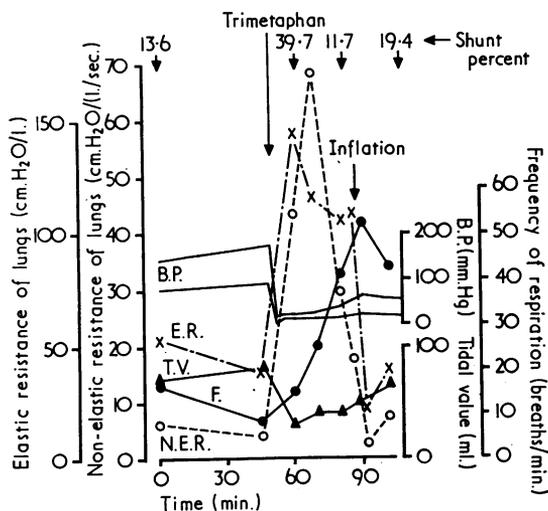


FIG. 6. Dog 10. Results to show the effect of repeated inflation of the lungs to 40 cm. water pressure. Legend as for Figure 4.

produced a considerable decrease in elastic resistance, in non-elastic resistance, and in the venous shunt, particularly when this was high before inflation. The decrease in elastic and non-elastic resistance was usually out of proportion to the increase in F.R.C., which also usually occurred after inflation.

EFFECT OF LARGE DOSES OF HISTAMINE To three dogs large doses of histamine acid phosphate, 5, 10, and 12 mg. respectively, were given to see if these could reproduce the effect of the trimetaphan. The histamine content of the arterial plasma half a minute after the injection was 7-10 $\mu\text{g.}/\text{ml.}$, expressed as acid phosphate, a level comparable to that attained after the administration of trimetaphan. These doses of histamine produced

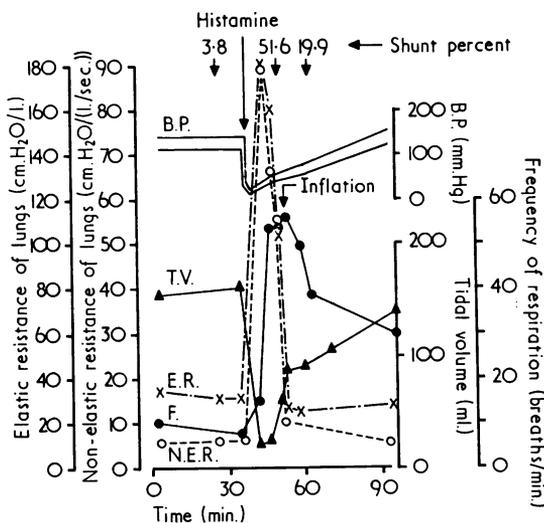


FIG. 7. Dog 25. The effects of a large intravenous dose of histamine on blood pressure, respiration, and the mechanical properties of the lungs. Legend as for Figure 4.

a fall of systemic blood pressure similar to that after trimetaphan (Table I (unpublished) and Fig. 7), but the pulmonary artery pressure rose considerably in contrast to the fall or moderate rise after trimetaphan. After the injection there was a period of apnoea followed in two dogs by rapid, shallow breathing identical in character to that after histamine release. Inflation of the lungs to 40 cm. water pressure reduced the elastic resistance of the lungs to below the initial level. In one dog the breathing was slow after inflation, but the rapid, shallow breathing continued unchanged in the other.

VAGAL BLOCK Cooling the vagi to 2-4° C. slowed the rate and increased the depth of breathing, but the rate remained faster than is usually seen after vagal block. The reason for the faster rate was probably the high arterial Pco_2 , which developed during rapid, shallow breathing, and the results of vagal block were not helpful in elucidating the cause of the rapid, shallow breathing.

MACROSCOPIC APPEARANCE OF THE LUNGS In nine dogs the chest was opened soon after death. The dependent edges of the lung were usually congested for about 1 cm. from their lowermost point, but in seven of the nine dogs no obvious collapse was seen on the surface of the lungs. In one dog, several small areas of collapse were seen on the anterior surface of the lungs, and in an-

other there was an area of collapse of about 1 sq. cm. on the surface of the left lung.

In the slices of the lungs fixed in the thorax the collapsed parts were seen to have an irregular distribution. In some cases the collapse was sub-pleural and parallel to the pleural surface, some areas were adjacent to the segmental bronchi and others were scattered irregularly throughout the lung. Occasionally, a segment of the lung was collapsed. One pair of lungs was first embedded in gelatine and sliced in planes at right angles to the axis of the trachea in an attempt to follow the course of the bronchi and to see if the collapse had any segmental relationship. Very occasional bronchi appeared to be contracted and occluded, but for the most part the bronchi adjacent to and passing through the collapsed areas were patent.

INJECTION STUDIES The Micropaque-gelatine injection mass was not found in the pulmonary veins of any of the four lungs injected. Microscopic examination showed that with the pressures used the injection mass had entered vessels down

to a diameter of about 15 μ . The radiographs of slices of the injected lungs were examined under a low-power microscope, but no evidence of arteriovenous anastomoses was seen.

QUANTITATIVE HISTOLOGY The results of point counting of the lung slices and sections are shown in Table V. Small areas of collapse could not be identified on the slices and so the proportion of collapsed lung recorded was less than on the sections. No definite collapsed areas could be seen on the slices from the control lung, and point counting was not practicable. The areas of collapsed lung must represent a much larger area when in the aerated state. The results in Table VI show that the tissue in aerated lung comprises 30–40% of the total volume, so that collapsed lung would have occupied a volume 2½–3 times greater when it contained air. From this it would follow that the figure of 20% of the area of the lung collapsed and 66% aerated, as in dog 14 (Table V), would correspond to collapse of approximately 50% of the lung parenchyma.

The figures in Table V show a good correspon-

TABLE V
QUANTITATIVE HISTOLOGY OF THE LUNGS. RESULTS OF POINT COUNTING

Dog	Shunt %	Lung Slices Magnification $\times 8$ Percentage of Total Volume			Lung Sections Magnification $\times 16$ Percentage of Total Volume		
		Non-parenchyma	Collapsed Lung	Aerated Lung	Non-parenchyma	Collapsed Lung	Aerated Lung
<i>Control</i>							
18	3.0	— ¹	—	—	11.8	1.5	86.7
19	3.0	— ¹	—	—	9.5	1.2	89.3
20	2.1	— ¹	—	—	11.5	2.2	86.3
<i>After Trimetaphan</i>							
14	18.5	16.3	18.2	65.5	13.4	20.3	66.3
15	7.4	— ²	—	—	11.8	5.0	83.2
16	29.0	16.5	13.1	70.4	15.7	23.6	60.7
17	14.4	11.8	8.8	79.4	15.6	8.6	75.8

¹No collapsed areas seen on lung slices
²Only a few isolated collapsed areas seen

TABLE VI
ESTIMATE OF RELATIVE PATENCY OF VESSELS IN COLLAPSED AND AERATED PARTS OF LUNGS
(POINT COUNT AT MAGNIFICATION $\times 500$)

Dog	Collapsed Areas				Aerated Areas			
	Air Space	Vessel Lumen	Lung Tissue	Ratio Vessel Lumen: Lung Tissue	Air Space	Vessel Lumen	Lung Tissue	Ratio Vessel Lumen: Lung Tissue
<i>Control</i>								
18	— ¹	—	—	—	63.1	18.2	18.7	0.973
19	— ¹	—	—	—	67.6	18.9	13.5	1.400
20	— ¹	—	—	—	70.2	18.2	11.6	1.568
<i>After Trimetaphan</i>								
14	16.6	40.5	42.9	0.944	61.9	18.8	19.3	0.974
16	2.8	55.1	42.1	1.310	70.1	14.3	15.6	0.917
17	2.8	57.1	40.1	1.424	71.5	17.1	11.4	1.500

¹Insufficient collapsed areas for a count to be made

dence between the amount of collapsed lung and the size of the shunt. Since the collapsed lung represents an even larger volume of aerated lung the results suggest that the blood flow through the collapsed lung is reduced. The measurements in Table VI show that the lumen of the small blood vessels is not reduced in the collapsed as compared with aerated lung, but during life there may be other factors, such as active vasoconstriction, which are responsible for a reduced blood flow.

DISCUSSION

The initial experiments with trimetaphan were of interest because large right-to-left shunts of blood through the lungs could be produced without any apparent cause. The venous to arterial shunt of blood which occurs during anaesthesia in man is presumed to occur through collapsed areas of the lungs, because it occurs in conditions of reduced ventilation conducive to lung collapse and can be reversed by hyperventilation of the lungs. Chest radiographs of the dogs in this series showed no evidence of gross collapse of the lungs, and at necropsy inspection of the lungs showed only small areas of collapse. It seemed possible that arteriovenous shunts could be opening up in the lung parenchyma (Tobin, 1966). Quantitative measurements on the slices and sections of the lung fixed by perfusion, however, showed that the amount of collapse was sufficient to account for all the venous shunt measured, and in these dogs it was not necessary to postulate opening of anatomical shunts.

Although no evidence of lung collapse was seen in postero-anterior radiographs of the chest taken in the supine position, considerable lung collapse could remain undetected. Prys-Roberts, Nunn, Dobson, Robinson, Greenbaum, and Harris (1967) have found that in supine man lung collapse, as judged by the development of a right-to-left shunt, is difficult to detect by radiography. Radiographs of the dog, taken at the F.R.C. in the supine position, show relatively small lung fields and are less easy to interpret than in man.

The control dogs showed shunts within the normal limits for the oxygen breathing method and there was no significant increase during the duration of the experiment. Moreover, at necropsy only a small degree of lung collapse was seen. Griffo and Roos (1962) have shown that the change of lung compliance with time is no greater in dogs breathing oxygen than it is in those breathing air. The changes which they observed were greatest during the first 10 minutes after the

start of the observations, but the measurements were preceded by several deep inflations of the lungs and the change observed was probably mainly a recovery (of surface tension forces, etc.) from the hyperinflation rather than due to progressive atelectasis in the lungs. The first measurements of lung compliance in the dogs in this series were made about 15 minutes after the start of anaesthesia, and so if any change in compliance occurred with induction of anaesthesia it would not have been observed in these dogs.

The dogs given trimetaphan showed no significant difference in the compliance of the lungs between the initial measurements and those just before the trimetaphan was given, but the control animals, observed over a longer period of about two and a half hours, showed an increase in the elastic resistance. The venous shunt did not increase and there was no appreciable collapse in the control lungs at necropsy, suggesting that compliance changes were not due to lung collapse. This conclusion is at variance with the results of Anthonisen (1964), who found that in apnoeic cats there was a significant positive correlation between the fall in compliance and the increase in shunt flow.

Inflation of the lungs at the end of the experiment often reduced both the elastic resistance and the non-elastic resistance to levels below those of the initial measurements, even though the F.R.C. was only restored to the initial level and was sometimes smaller than initially. It is probable that hyperinflation produces some change in the physical characteristics of the expanding lung by temporary reduction of surface tension forces or overstretch of the 'elastic' elements of the lung tissue.

Trimetaphan in man has the dual action of histamine release and ganglion blockade (Payne, 1956). The effect of trimetaphan in the dog closely resembles that of the histamine-liberating Compound 48/80. A dose of 0.3–0.5 mg./kg. of trimetaphan causes a profound prolonged fall of blood pressure in the dog, whereas in man 2 mg./kg. produces only a moderate fall in blood pressure. On the other hand, ganglion-blocking agents such as hexamethonium are less effective in the dog than in man and it is probable that the fall in blood pressure and the other effects observed in the dog are due almost entirely to histamine release.

Certain factors suggest that the main response to the administration of trimetaphan is closure of all or most of the medium-sized or smaller bronchi, rather than a general contraction of the

alveolar ducts as noted by Nadel, Colebatch, and Olsen (1964) after barium sulphate embolization. These factors are:

(a) There was no appreciable expulsion of air from the lungs. In man the respiratory bronchioles and alveolar ducts contain about one-third of the total lung volume and a similar relationship probably exists in the dog, *i.e.*, about 100–150 ml. would be contained in the respiratory bronchioles and alveolar ducts of a 10 kg. dog. Contraction of this volume of lung, sufficient to produce the observed changes in elastic and non-elastic resistance, would have resulted in expulsion of most of the contained air.

(b) During the first minute or two after trimetaphan, 30 or 40 cm. water intratracheal pressure produced almost no expansion of the lung.

(c) The fall in arterial PO_2 and thus the development of a shunt (collapse of alveoli) is gradual and takes about 5 minutes to develop fully. This change is similar to, and only slightly faster than, that produced when one bronchus is blocked by a balloon (unpublished observations).

It is probable that the sequence of events after the administration of trimetaphan is, first, closure of the conducting bronchi with trapping of oxygen in the alveoli and alveolar ducts. These alveoli then gradually collapse as the oxygen is absorbed, but as the histamine effect wears off the bronchi relax and there is a rapid fall of both elastic and non-elastic resistance. In the absence of deep breaths the collapsed alveoli remain collapsed.

In these experiments the absence of lung collapse in dogs breathing air is easily understood if one considers the relative volume changes in an occluded segment of the lung containing air or pure oxygen. A dog under the conditions of these experiments has an oxygen consumption per minute equivalent to about one-fifth of the functional residual capacity (the equivalent figure for man would be about one-tenth of the F.R.C.). Thus one minute after occlusion of the conducting airways in a dog breathing oxygen, the volume of the occluded section will have fallen by about 20%, since oxygen is taken from the lungs at the normal rate but almost no carbon dioxide is given off into the alveolar gas. At the end of one minute some alveolar collapse is already evident, as shown by the fall in arterial oxygen tension. Since the circulation continues through the collapsed lung (Björk and Salén, 1950) the rate of removal of gas will continue almost unchanged, so that after about 5 minutes the whole of the contained gas will have been absorbed and the lung will be completely collapsed. On the other hand, when

the occluded segment of the lung contains air the initial tension of oxygen will be about 100 mm. Hg, which corresponds to about one-seventh of the total gas volume. Oxygen will be absorbed only until the oxygen tension of the alveolar gas falls to that of the mixed venous oxygen tension (usually about 40 mm. Hg). Thus within a few minutes after bronchial occlusion only about 8% of the initial gas volume will have been absorbed. Further reduction of volume involves transfer of nitrogen into the circulating blood, and this is a slow process, so that the bronchi have usually reopened before the further reduction in gas volume takes place. However, whilst the bronchi are still closed, even though the segment of lung still contains gas, it will act as a physiological shunt, since the blood passing through the segment will not be oxygenated.

The action of histamine, which appears to be on the conducting bronchi rather than on the respiratory bronchi and alveolar ducts, is similar to that observed when histamine is injected into the bronchial arteries (DeKock, Nadel, Zwi, Colebatch, and Olsen, 1966). Large doses of histamine given intravenously have effects similar to those of intrabronchial injection, and the amount of histamine liberated in these dogs was such that high concentrations were present in the systemic arterial blood. The type of response could be governed by the site of maximum histamine release in the lungs, but the major part of the released histamine comes from the liver, gut, and other organs. The lungs and liver of the dog contain similar quantities of histamine per gram of tissue, *i.e.*, about 10–40 $\mu\text{g./g.}$ (Feldberg, 1956), and since the liver of the dog weighs about three times as much as the lungs, a major portion of the histamine will enter the lungs through the pulmonary artery.

The reason for the rapid, shallow breathing after histamine-releasing agents is not clear. Similar rapid, shallow breathing was described by Dunn (1920) after starch emboli in goats, and it has also been described in cats after barium sulphate emboli (Nadel *et al.*, 1964) which appeared to release histamine. Emboli of small blood clots in dogs do not cause persistent, rapid, shallow breathing (Marshall and Allison, 1962). In this series of experiments the rapid breathing did not start immediately after the period of apnoea, but the rate usually increased gradually to a maximum 10–15 minutes after the trimetaphan administration. Once established, it usually continued until the end of the experiment, *i.e.*, for one hour or more.

The rapid, shallow breathing is not due to hyperthermia because the dogs had a normal temperature and the respiratory frequency was lower than that in heat panting (Crawford, 1962). It is unlikely to be due to a deflation reflex because hyperinflation of the lung increased the lung volume but had no effect on the type of respiration. The collapse of one lung, which occurs after occlusion of a main bronchus, does not produce the same type of respiration. Since rapid respiration persisted after hyperinflation had reduced the elastic resistance of the lungs below the control level, and since the elastic resistance of the combined lung-thorax system was also not appreciably increased (as determined by the volume change in the chest produced by an increase in intratracheal pressure), the rapid, shallow breathing cannot be attributed to an attempt to adopt a more efficient pattern of breathing (Otis, Fenn, and Rahn, 1950). Neither was the rapid respiration due to anoxia, since it developed whilst the dogs were breathing pure oxygen and had a normal or high arterial oxygen saturation. In contrast to the hyperventilation which occurs in goats (Dunn, 1920) or sheep (Halmagyi and Colebatch, 1961) after pulmonary microembolism, the dogs were hypoventilating and the arterial carbon dioxide tension, which was usually high initially, rose progressively with the onset of the rapid respiration to attain plateau after 5–10 minutes (Fig. 3). The serum bicarbonate remained constant for about 8 minutes and then fell, presumably due to a metabolic acidosis caused by the low cardiac output. This type of breathing is not caused by the respiratory acidosis because acute respiratory acidosis, produced by rebreathing, increases both the rate and the depth of respiration. Although there is a positive correlation between the size of the venous shunt and the arterial P_{CO_2} ($r = +0.52$; S.E. 0.146) this does not necessarily imply any causative relationship between these two factors. The respiratory frequency did not show a positive correlation with P_{CO_2} ($r = +0.093$; S.E. 0.146).

The systemic blood pressure was low after trimetaphan, but was usually rising at the time the rapid breathing started. In other experiments a systolic blood pressure of 30–40 mm. Hg has been produced in dogs by bleeding, and these dogs developed rapid, deep breathing with alveolar hyperventilation and a fall in P_{aCO_2} .

The type of respiration after histamine release is very similar to, but more marked than, that produced by veratrine (Widdicombe, 1954) or histamine administration in cats and rabbits

(Widdicombe, 1961), or by barium sulphate embolization (Nadel *et al.*, 1964). Under these conditions rapid, shallow breathing has been attributed to bronchial constriction or closure produced by the drug or to histamine release. Both trimetaphan and histamine are capable of producing rapid, shallow breathing lasting many minutes. In each case the rapid, shallow breathing may continue after inflation of the lungs even though the elastic resistance and non-elastic resistance have been restored to normal or subnormal levels. In one dog the rapid, shallow breathing produced by histamine injection, although it had continued unchanged for 10 minutes, was slowed and deepened by inflation.

The prolonged rapid, shallow breathing, unaffected by inflation, may be associated with the higher levels of histamine in the region of the bronchi. The arterial blood levels after administration of 10–12 mg. histamine were comparable with those after administration of trimetaphan. The rapid, shallow breathing lasted longer than, and appeared to be independent of, the bronchoconstrictor effect of the histamine. It seems probable that large concentrations of histamine sensitize the stretch receptors of the lungs and decrease the depth of inspiration in much the same way that trichloroethylene produces rapid, shallow breathing during anaesthesia (Whitteridge and Bülbring, 1944). Trimetaphan acts by disrupting the mast cells and liberating histamine, but histamine itself may degranulate mast cells (Asboe-Hansen and Wegelius, 1956), and trimetaphan, administered to dogs after recovery from a large dose of histamine, has a diminished effect both as regards the amount of histamine liberated and the effect on the mechanical properties of the lungs. It is possible that it is not histamine but some other substance liberated from the mast cells which sensitizes the stretch receptors.

The changes in F.R.C. are not necessarily a good measure of the degree of lung collapse. The lung collapse is presumed to occur as a result of the injection of trimetaphan, since the control lungs under the same conditions showed almost no collapse, and yet the mean F.R.C. after trimetaphan was only 4% lower than the F.R.C. before the injection (Table II). In dogs 14, 15, 16, and 17, in which the amount of collapse was measured, the F.R.C. fell only in dog 17 as a result of the injection; in the other dogs 20.3, 5.0, and 23.6% respectively of the lung was collapsed. It is apparent that when some of the lung collapses the aerated part of the lung is extended beyond its normal size, but measurement of alveolar diameter

by the method of mean linear intercepts (Dunnill, 1962) did not show any difference in alveolar size between the control lungs (dogs 18, 19, and 20) and the lungs with most collapse (dogs 14 and 16). Measurements of F.R.C. in a dog in which the left lung was completely collapsed gave 339 ml. for both lungs before collapse, and 300 ml. after collapse of the left lung, a reduction of only 12% when approximately 40% of the lung parenchyma was collapsed.

It is interesting to speculate on the relationship between the rapid, shallow breathing in these experiments and the dyspnoea of pulmonary embolism in man. In these experiments a very strong histamine-liberating stimulus had been given and the respiration was extremely rapid but shallow, so that the alveolar ventilation was reduced and the arterial PCO_2 rose. After pulmonary embolism in man the subject feels short of breath and the alveolar ventilation is increased, so that the arterial PCO_2 falls. In contrast to the effect of barium sulphate microembolism, emboli of blood clots do not cause persistent rapid, shallow breathing in the dog and there is no definite evidence of histamine release (Marshall and Allison, 1962). Nevertheless, it is possible that emboli may have some effect on the nerve endings in the lung. The stretch reflexes from the lungs of man and dog are so dissimilar in their effects that it is conceivable that stimulation of vagal nerve endings in the lungs of conscious man might give rise to a sensation of dyspnoea, whereas in the anaesthetized dog they cause rapid, shallow breathing.

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