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THE REFLEX EFFECTS OF ALTERATIONS IN LUNG VOLUME ON SYSTEMIC VASCULAR RESISTANCE IN THE DOG

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SUMMARY

1. The reflex effects of alterations in lung volume on systemic vascular resistance have been studied in anaesthetized dogs under conditions in which the systemic circulation was perfused at constant blood flow. The pressures in the isolated perfused carotid sinuses and aortic arch, and the arterial blood P_{O_2} and P_{CO_2} were maintained constant.

2. A maintained inflation of the lungs produced by injection of air into the trachea caused a fall in systemic arterial perfusion pressure, indicating vasodilatation. The size of the systemic vasodilator response varied directly with the pressure and volume of gas used to inflate the lungs. A similar effect was observed when the tidal volume of lungs ventilated by an intermittent positive pressure was increased.

3. Collapse of the lungs by creating a pneumothorax in closed-chest spontaneously breathing animals evoked a systemic vasoconstrictor response which was reversed when the lungs were re-expanded.

4. These vasodilator responses were abolished by dividing the pulmonary branches of the thoracic vagosympathetic nerves. Evidence is presented that the afferent fibres run in the cervical vagosympathetic nerves and through the stellate ganglia.

5. The responses were unaffected by atropine, but were abolished by hexamethonium, guanethidine and by bretylium tosylate, indicating that they are mediated via the sympathetic nervous system.

6. Evidence is presented that the lungs are a constant course of afferent impulses inhibiting the 'vasomotor centre', and that the lung inflation–systemic vasodilator reflex is a potential mechanism operating in eupnoeic breathing.

INTRODUCTION

When the lungs of the cat or dog are artificially inflated, either by a positive pressure applied to the trachea or by a negative pressure applied to the surface of the lungs, an increase in heart rate occurs (Hering, 1871; Anrep, Pascual & Rössler, 1936*a*, *b*; Daly & Scott, 1958; Ledsome & Linden, 1964*a*; Scott, 1966). This response is reflex in nature and dependent on the integrity of the innervation to the lungs; the afferent pathway lies mainly, if not entirely, in the cervical vagosympathetic nerves.

A reflex from the lungs affecting the systemic blood vessels was first described by Brodie & Russell (1900). They showed in the atropinized and non-atropinized cat that suddenly changing the pressure of the respired air from atmospheric to a positive or negative pressure caused a fall in blood pressure which was approximately proportional to the change in air pressure. They concluded on the basis of plethysmographic studies that this response was due to vasodilatation. Salisbury, Galletti, Lewin & Rieben (1959), using a preparation in which the systemic circulation was perfused at constant blood flow, found that inflation of the lungs caused a reduction in systemic arterial perfusion pressure. They did not find any correlation between the size of the response and the inflation pressure and reported no values for the inflation volumes used in their experiments. The responses were shown to be reflex in nature, being abolished by division of the pulmonary branches of the vagus nerves (Brodie & Russell, 1900) or of the cervical vagosympathetic nerves (Salisbury *et al.* 1959).

The view has been expressed that the reflex circulatory effects of normal lung inflation and deflation are insignificant (Aviado & Schmidt, 1955, p. 276). However, it has been shown that a pulmonary reflex dependent on changes in lung volume plays an important role in determining the vascular changes brought about by stimulation of the carotid body chemoreceptors (Daly & Scott, 1958, 1962, 1963; Daly & Ungar, 1966; Scott, 1966).

The systemic vascular responses elicited by inflation and deflation of the lungs have been re-examined in the dog using preparations with controlled perfusion of the systemic circulation. Our results, some of which have been reported briefly elsewhere (Daly, Hazzledine & Ungar, 1966) indicate that changes in lung volume within the physiological range have appreciable effects on systemic vascular resistance.

METHODS

Full details of the two types of preparation used in this study have been described elsewhere (Daly, Hazzledine & Howe, 1965; Daly & Ungar, 1966), and therefore only the essential points of the techniques will be given here.

Two dogs were used for each experiment. The recipient (test) dogs varied in weight from 10·1 to 14·8 kg and after premedication with morphine hydrochloride (2 mg/kg subcutaneously) were anaesthetized with a mixture of *a*-chloralose (0·055 g/kg) and urethane (0·55 g/kg) intravenously. The systemic circulation was perfused at constant volume flow by means of a Dale–Schuster pump through cannulae inserted into the femoral and vertebral arteries (Daly *et al.* 1965). The systemic blood returning to the right atrium was oxygenated in the isolated perfused lungs of a second dog, before being returned to the systemic circulation of the recipient animal. There was therefore no blood flowing through the pulmonary circulation of the recipient dog except for a small quantity entering through anastomotic channels between the bronchial and pulmonary vascular systems. In a few experiments, however, the lungs of the recipient animal were perfused at constant head of pressure (14–20 mm Hg) with venous blood via a cannula inserted through the wall of the base of the right ventricle into the main pulmonary artery. The cannula was held in place by a thread tied round the artery to ensure that no blood leaked back into the right ventricle and right atrium.

The two types of preparation referred to differed only in the extent to which the pressures in the arterial baroreceptor areas were controlled to prevent reflex compensatory changes in systemic vascular resistance when alterations in systemic arterial blood pressure were evoked. In type I preparation (Daly *et al.* 1965) the aortic arch only was isolated from the circulation and perfused by means of a pump, whereas in type II preparation (Daly & Ungar, 1966) both the carotid sinuses and the aortic arch were isolated and perfused by separate pumps. The perfusion pressures were maintained constant by Starling-type resistances.

In a few experiments, lung inflation reflexes were elicited on a background of increased systemic vascular resistance brought about by stimulation of the carotid or aortic body chemoreceptors. The chemoreceptors were excited by changing the composition of the carotid or aortic arch perfusate from oxygenated to hypoxic hypercapnic blood (Daly & Ungar, 1966).

Systemic vascular resistance. Since the systemic blood flow was maintained constant, a change in vascular resistance can be taken as being proportional to the change in the pressure difference across the perfused vascular bed, i.e. mean arterial perfusion pressure minus mean right atrial pressure. The right atrial pressure was maintained at approximately zero pressure and the change in vascular resistance could therefore be expressed as a percentage change in the arterial perfusion pressure.

Ventilation of the recipient lungs. With a widely open chest, the lungs were ventilated with room air by means of a Starling 'Ideal' pump, respiratory frequency 20 c/min. In some experiments no ventilation was carried out; the trachea was open to the atmosphere and the lungs were therefore collapsed. In others the lungs collapsed against a resistance of up to 10 cm H_2O. The lungs were inflated by injecting through the tracheal cannula known quantities of air from a syringe. The volume was measured at atmospheric pressure and was corrected for the pressure at which the lungs were inflated, taking into account the initial volume of air in the syringe and the volume of the connecting tube between the syringe and tracheal cannula.

The effects of deflation of the lungs were studied in some preparations. For this purpose the chest was closed, and after inserting a wide-bore tube (14 mm) through the fourth right intercostal space near the mid-sternal line the air was withdrawn from the thorax and spontaneous ventilation re-established. Collapse of the lungs was effected by opening the tube.

Block of nerve conduction. Conduction in the cervical vagosympathetic nerves was blocked by placing each nerve on a cooling device, 1·5 cm long, through which was pumped a mixture of glycol and water at different temperatures. The temperature was measured with a copper–constantan thermocouple situated in the thermode, using a galvanometer (Cambridge Instrument Co., Ltd.) which was calibrated before and after each experiment.

Blood gas analyses. Samples of systemic arterial blood were taken and analysed for oxygen

and carbon dioxide contents, haemoglobin, P_{O_2}, P_{CO_2} and pH. The methods used have been described previously (Daly & Hazzledine, 1963; Daly & Ungar, 1966).

Drugs. The following drugs were used in this investigation: decamethonium iodide (Light and Co., Ltd.), atropine sulphate (British Drug Houses, Ltd.), hexamethonium bromide (May and Baker, Ltd.), bretylium tosylate (Burroughs Wellcome, Ltd.) and guanethidine ('Ismelin', Ciba Laboratories, Ltd.). In all experiments coagulation of the blood was prevented by heparin ('Pularin', Evans Medical, Ltd., 25 mg/kg).

RESULTS

The initial control values for systemic arterial perfusion pressure, the pressures in the carotid sinuses and aortic arch, and arterial blood P_{O_2}, P_{CO_2} and pH in the two types of preparation are shown in Table 1.

TABLE 1. Initial control values for systemic arterial perfusion pressure, carotid sinus and aortic arch perfusion pressures, and for the composition of the blood perfusing the systemic circulation and the carotid sinuses and aortic arch

	Type I preparation	Type II preparation
No. of experiments	10	12
Dog wt. (kg)	12·8 ± 0·54 (9·3–15·5)	12·7 ± 0·22 (11·7–14·0)
Systemic arterial perfusion pressure (mm Hg)	121·6 ± 4·2 (102–142)	126 ± 3·0 (105–150)
Carotid sinus perfusion pressure (mm Hg)	121·6 ± 4·2 (102–142)*	121 ± 2·3 (110–140)
Aortic arch perfusion pressure (mm Hg)	111·5 ± 2·3 (102–122)	121·0 ± 2·7 (104–140)
Systemic, carotid sinus and aortic arch perfusate		
P_{O_2} (mm Hg)	> 100 (56–> 100)	157 ± 23 (83–271)
P_{CO_2} (mm Hg)	43·8 ± 0·8 (35–53)	41·6 ± 2·3 (28–52)
pH	7·35 ± 0·013 (7·24–7·46)	7·39 ± 0·029 (7·31–7·49)

The open values are the means ± S.E.M.; those in parentheses the range.

* As the carotid sinuses were not separately perfused in type I preparations, the carotid sinus and systemic arterial pressures are the same.

Effects of altering the volume of the lungs

Maintained increase in lung volume. In animals with open chest, the lungs were inflated with up to 800 ml. gas from a syringe and the inflation maintained for periods up to 1 min. In twenty-four out of a total of twenty-seven experiments including type I and type II preparations a fall in systemic arterial perfusion pressure occurred within 2–4 sec, indicating a reduction in systemic vascular resistance. Lung inflation also reduced or abolished spontaneous rhythmic movements of the diaphragm and ribs through the Hering–Breuer reflex. No change in perfusion pressure was observed in the remaining three experiments.

In twenty-two of the twenty-four experiments the effects of inflation of the collapsed lungs with a standard volume of 375 ml. room air were observed. In ten of these experiments in which only the aortic arch per-

fusion pressure was maintained constant, the carotid sinus pressure being the same as the systemic arterial perfusion pressure (type I preparation), inflation of the lungs resulted in a fall in systemic perfusion pressure in twenty-two tests (two experiments), there being no change in pressure in the remaining ten tests (two experiments). The average fall in perfusion pressure in all thirty-two tests was $8{\cdot}3 \pm 1{\cdot}6$ mm Hg (range 0–37), representing a reduction in systemic vascular resistance of $6{\cdot}9 \pm 1{\cdot}3\,\%$ (range 0–29).

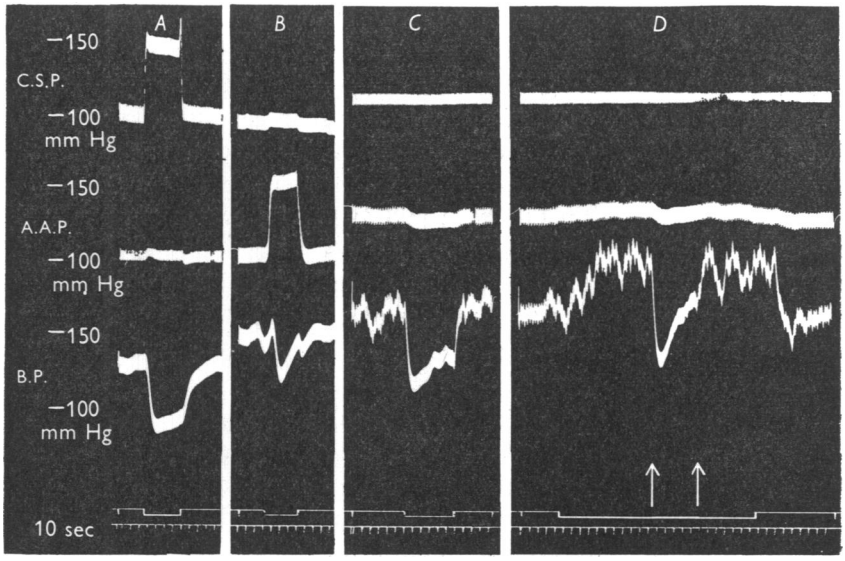

Fig. 1. Dog, female, 13·8 kg. Morphine-chloralose-urethane. Separate perfusion of the isolated carotid sinuses, isolated aortic arch and of the systemic circulation. Systemic blood oxygenated in isolated perfused lungs of a donor dog. Open chest. Recipient lungs collapsed; no ventilation. *A*, stimulation of the carotid sinus baroreceptors by raising the carotid sinus perfusion pressure; *B*, stimulation of the aortic arch baroreceptors by raising the aortic arch perfusion pressure; *C*, lungs inflated with 300 ml. air; *D*, stimulation of the aortic bodies by hypoxia hypercapnic blood during continuous signal. Between arrows ↑↑, lungs inflated with 300 ml. air. Time marker, 10 sec. C.S.P., carotid sinus pressure; A.A.P., aortic arch pressure; B.P., systemic arterial perfusion blood pressure.

In the remaining twelve experiments in which both the carotid sinus and aortic arch pressures were maintained constant (type II preparation), a fall in systemic perfusion pressure occurred in all thirty-four tests, the average reduction being $24{\cdot}2 \pm 2{\cdot}8$ mm Hg (range 6–60), representing a diminution in vascular resistance of $16{\cdot}9 \pm 1{\cdot}8\,\%$ (range 5–41). These responses are significantly larger than those obtained in the experiments in which only the aortic arch pressure was maintained constant ($P < 0{\cdot}001$). The typical response is illustrated by Fig. 1*C* taken from an experiment

in which the lungs were inflated with 375 ml. air for 1 min. The systemic perfusion pressure fell by 48 mm Hg from 170 to 122 mm Hg, and gradually recovered to 130 mm Hg. This response may be compared with those elicited by stimulation of the carotid sinus and aortic arch baroreceptors by raising the perfusion pressures in the carotid sinus and aortic arch respectively (Fig. 1*A*, *B*).

The larger reductions in systemic vascular resistance occurring on inflation of the lungs in the series of experiments in which both the carotid sinus and aortic arch pressures were maintained constant suggests that under normal conditions the response may be wholly or partly compensated by reflexes from the arterial baroreceptors. Further evidence in support of this contention was obtained by comparing the responses to inflation of the lungs while the carotid sinus and aortic arch pressures were maintained constant, to exclude the participation of arterial baroreceptor reflexes (Page, McCubbin & Green, 1956; Daly & Luck, 1959; Daly & Scott, 1965), and under conditions in which there was normal activity of the carotid and aortic baroreceptors, achieved by maintaining the isolated carotid sinus and aortic arch pressures at the same level as the systemic arterial perfusion pressure. It was found that in two of five experiments, the reduction in systemic vascular resistance occurring on inflation of the lungs while the participation of the arterial baroreceptors was excluded was abolished when the test was repeated after the normal activity of the baroreceptors had been re-established. In the remaining three experiments, the response was reduced in size. Thus, provided the participation of the arterial baroreceptor reflexes was excluded, prolonged inflation of the lungs caused a persistent reduction in systemic perfusion pressure, although in almost all tests there was some initial recovery of the pressure (Fig. 1*C*).

The systemic vascular responses to inflation of the lungs were found to be independent of the composition of the gas used. In two experiments inflations with 375 ml. of room air, 100 % N_2 or a mixture of 10 % CO_2, 21 % O_2 and 69 % N_2 evoked similar systemic vasodepressor responses. Likewise, the size of the responses was unaffected by the gas temperature over the range 15–37° C, measured in the trachea.

These vascular responses were also unaffected by the concomitant changes in the spontaneous rhythmic movements of the diaphragm and ribs. For example, they were not appreciably altered by the previous abolition of respiratory movements either by injection of a neuromuscular blocking agent, decamethonium (0·25 mg/kg), or by lowering the arterial blood P_{CO_2} through hyperventilating the isolated perfused lungs of the donor dog.

In most experiments tests of lung inflation were carried out while no blood was flowing through the pulmonary circulation. It was therefore

necessary to find out whether similar responses occurred when the lungs were perfused with blood. Three preparations were modified so that oxygenation of the blood could be carried out either in the isolated perfused lungs of the donor dog or in the recipient animal's lungs perfused through the pulmonary artery (Daly *et al.* 1965). It was found that the size of the responses to inflation of the recipient dog's lungs with a given volume of gas was the same whether or not there was blood flowing through the pulmonary circulation. These inflations were of less than 10 sec duration to obviate changes in arterial blood gas composition.

Factors determining size of the vascular response. The size of the systemic vascular responses to inflation of the lungs depended amongst other factors on the degree of pre-existing vasomotor tone. This was demonstrated in five experiments by observing the response to lung inflation at different levels of 'background' vasomotor tone which was determined reflexly through changes in activity of the arterial baroreceptors brought about by altering the carotid sinus and aortic arch pressures. The response to inflation of the lungs with a given volume of room air was enhanced when the vasomotor tone was increased (five experiments), and diminished (four experiments) or abolished (one experiment) when it was decreased. Re-establishing the original level of tone restored the lung-inflation response to its original size. The responses observed in one experiment are shown in Fig. 2.

Studies of the effects of lung inflation were also made under conditions in which vasomotor tone was increased by stimulation of the carotid or aortic bodies by hypoxic hypercapnic blood (see Daly & Ungar, 1966). The results which are depicted in Fig. 3 show that with one exception (Expt. 2) the fall in systemic arterial perfusion pressure in response to inflation of the lungs was always greater when the test was carried out during chemoreceptor stimulation.

In the left-hand section, inflation of the lungs while there was no stimulation of the carotid body chemoreceptors evoked a fall in systemic arterial perfusion pressure in four of the five experiments (●–○). In the fifth experiment (no. 13) there was no response in three tests. The carotid bodies were then stimulated and this resulted in a rise in perfusion pressure in all tests (●–■). In Expts. 11, 12 and 14 inflation of the lungs during carotid body stimulation now had an enhanced effect; in one experiment (no. 13) in which no response occurred in the control tests, a striking fall now appeared, and in the remaining one (no. 2), the response was unaffected. The lung inflation vasodepressor responses were similarly affected by stimulation of the aortic bodies (Fig. 3, right-hand section).

Another factor determining the size of the systemic arterial perfusion depressor response was the volume of air used to inflate the lungs. In

Fig. 4, which shows the results obtained in seven experiments, each point was obtained by inflating the lungs with a known volume of air, after which the lungs were allowed to collapse. It will be noted that although in each experiment there is a considerable difference in the size of the response

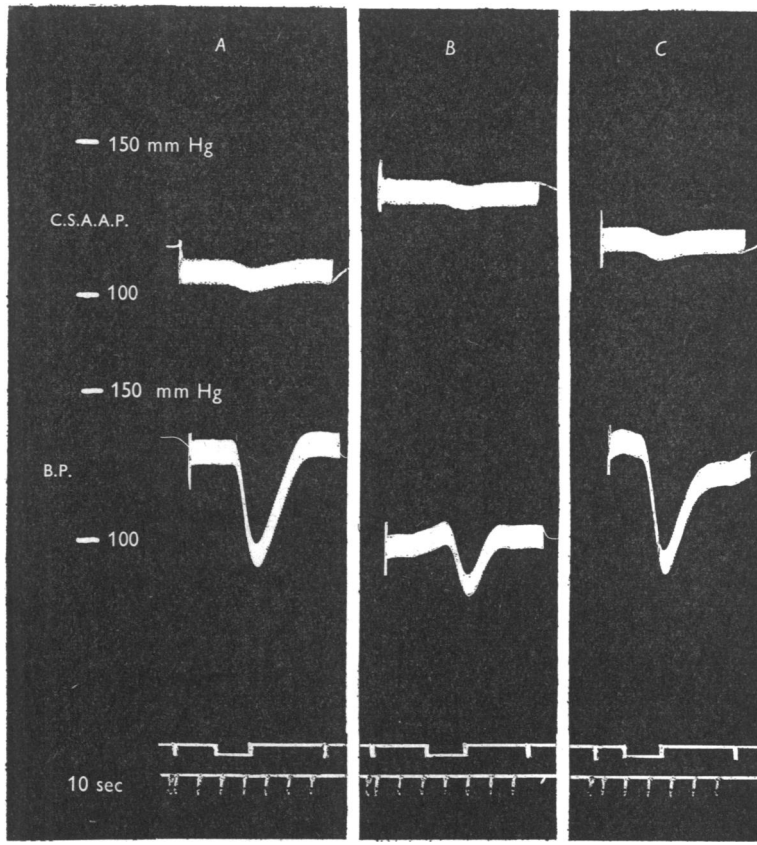

Fig. 2. Dog, male, 13·0 kg. Morphine-chloralose-urethane. Separate perfusions of the systemic circulation and the isolated carotid sinuses and isolated aortic arch. Systemic venous blood oxygenated in the isolated perfused lungs of a second dog. *A*, *B* and *C* show the effects of inflating the recipient dog's lungs with 370 ml. room air. *A* and *C* are the control tests; in *B*, the lungs were inflated while the pressures in the carotid sinuses and aortic arch were increased. Note the diminished systemic depressor response compared with the two controls. Time marker, 10 sec. C.S.A.A.P., carotid sinus and aortic arch pressures.

evoked by a given inflation volume, there is nevertheless in all experiments a progressive reduction in systemic vascular resistance as the volume of the lungs is increased. The threshold volume varied in different experiments from 50 to 200 ml. In contrast to the findings of Salisbury *et al.* (1959) it

was found that the reduction in systemic vascular resistance was also closely related to the inflation pressure (Fig. 5), the threshold being 5·5–10·5 cm H_2O.

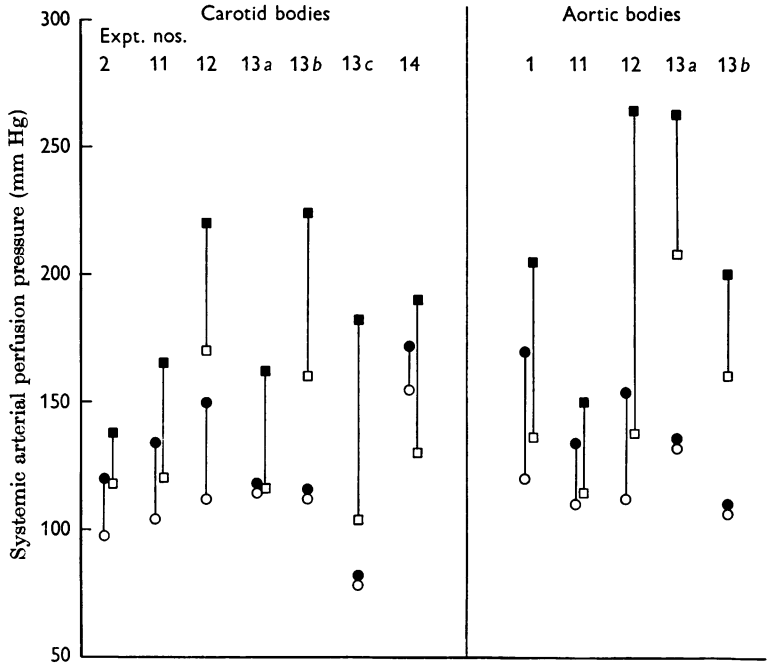

Fig. 3. The effects of inflation of the lungs with 375 ml. air on the systemic arterial perfusion pressure with no stimulation of the arterial chemoreceptors (●—○) and during evoked stimulation of the carotid or aortic bodies by venous blood (■—□). ●, ■, control values for perfusion pressure during deflation of the lungs; ○, □, values during inflation of the lungs.

A similar relation between systemic vascular resistance and the lung inflation pressure and volume was obtained in three preparations in which the lungs were prevented from collapsing completely by applying an expiratory resistance so that the expiratory pressure was 4, 6, and 10 cm H_2O respectively. These results, together with those obtained in the same experiments without an expiratory resistance, are shown in Fig. 5.

Changes in pulmonary ventilation. The lungs were ventilated rhythmically at a constant rate by means of a Starling 'Ideal' pump. In six of seven experiments, increasing the tidal volume from 100 to 350 ml. resulted in a fall in systemic arterial perfusion pressure of 5–40 mm Hg, representing a reduction in vascular resistance of 5–26 %. In the seventh experiment, no change in pressure occurred. The average fall in pressure for the seven experiments was 14·7 mm Hg, representing an average reduction in vascular resistance of 11·2 %.

Collapse of the lungs. In two spontaneously breathing animals, the effects of collapsing the lungs by creating a bilateral pneumothorax were studied. The results obtained in one of these experiments is shown in Fig. 6*A*. At the first arrow, a bilateral pneumothorax was created causing collapse of the lungs and this resulted in a striking rise in systemic arterial perfusion pressure from 120 to 210 mm Hg, representing an increase in vascular resistance of 75 %. The lungs were then re-expanded by a negative pressure applied to the thorax (second arrow), whereupon the perfusion pressure fell to its original level. It should be re-emphasized that during the

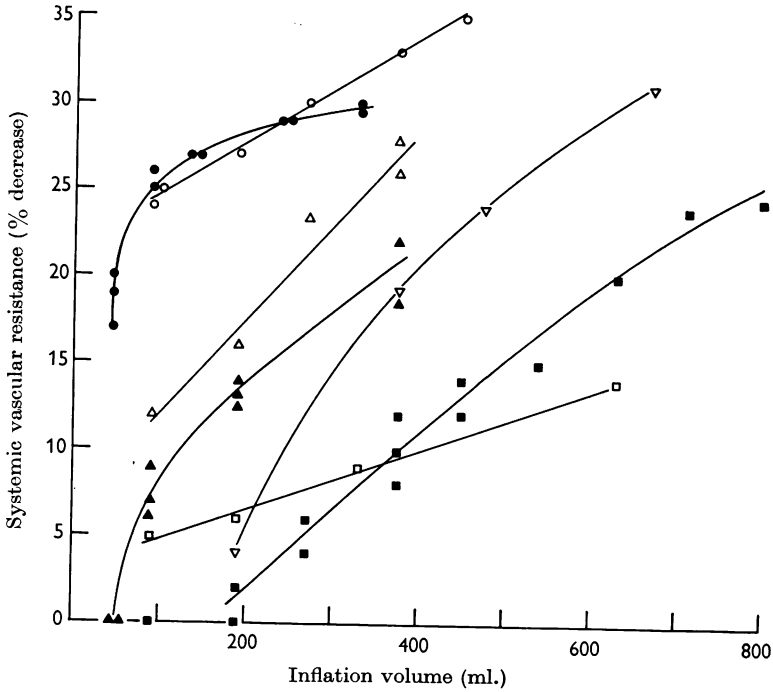

Fig. 4. The effects of maintained inflation of the lungs with different gas volumes on systemic vascular resistance in seven open-chest animals. During deflation the intra-tracheal pressure was zero.

period of collapse of the lungs, no change in the arterial blood P_{O_2} or P_{CO_2} occurred because ventilation of the isolated perfused donor lungs was maintained constant. It was observed that collapse of the lungs caused slowing and deepening of the recipient dog's respiratory movements of the chest due to loss of the Hering–Breuer reflex, but the accompanying rise in perfusion pressure was not related to these changes because a similar response occurred after they had been abolished by decamethonium (Fig. 6*B*). Finally, a single maintained inflation of the lungs with 300 ml. air resulted in a fall in systemic perfusion pressure (Fig. 6*C*).

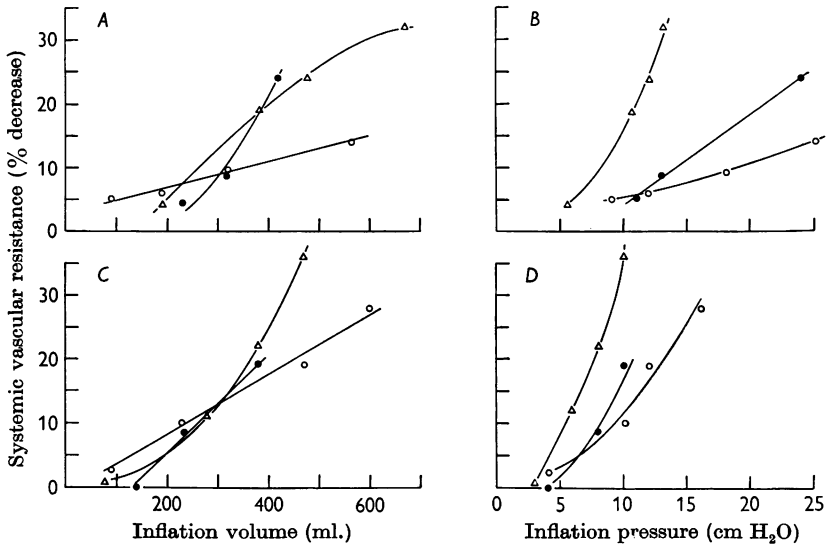

Fig. 5. The effects of maintained inflation of the lungs with different pressures and volumes on systemic vascular resistance in three experiments. In *A* and *B* respectively the inflation volume and inflation pressure are plotted against vascular resistance. Between inflations, the lungs were allowed to collapse. In *C* and *D* the same relations are shown, but the lungs were inflated from an expiratory pressure of 4 (▲), 6 (●) and 10 (○) cm H_2O respectively in the three experiments. In *D* the inflation pressure is the difference between those at the beginning and completion of inflation.

Reflex nature of the vascular responses

Cutting or cooling the vagosympathetic nerves. In four experiments the reductions in systemic vascular resistance occurring in response to a maintained inflation of the lungs and to an increase in the tidal volume of rhythmically ventilated lungs were unaffected by division of the thoracic vagosympathetic nerve trunks caudal to the hilum of the lungs. They were abolished, however, by denervation of the lungs, carried out by cutting the thoracic vagosympathetic nerve on the left side between the aorta and the left pulmonary artery, and on the right at the level of the vena azygos. These results therefore confirm those of Brodie & Russell (1900). The responses to lung inflation could also be abolished by crushing with a clamp the hila of all the lobes of the lungs extrapericardially.

In three experiments division of either cervical vagosympathetic nerve reduced the responses, which were then abolished by cutting the remaining nerve. In two further experiments division of both cervical vagosympathetic nerves considerably diminished, but did not abolish the response. In one of these, the remaining pathway was examined and it was

found that blocking transmission through the stellate ganglia with procaine hydrochloride (1 %, w/v) abolished the residual systemic arterial depressor response (Fig. 7).

In five experiments, tests were carried out to determine the temperature of the cervical vagosympathetic nerves at which the vascular response was abolished and the results are summarized in Fig. 8. The reduction in systemic arterial perfusion pressure evoked by a maintained inflation of the lungs was abolished by cooling the nerves to between 2° and 7° C.

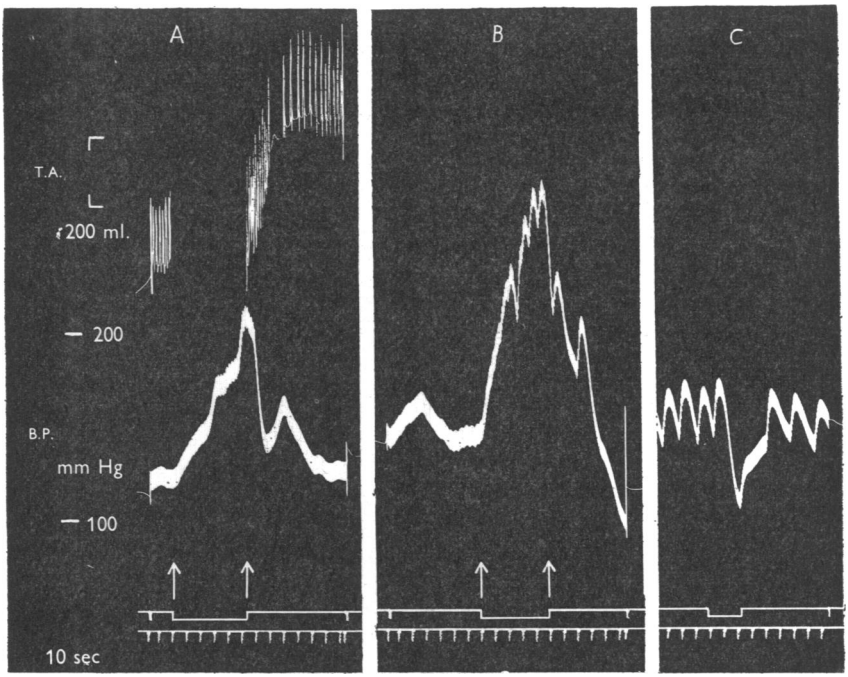

Fig. 6. Dog, male, 12·8 kg. Morphine-chloralose-urethane. Separate perfusion of the isolated carotid sinuses, isolated aortic arch and of the systemic circulation. Systemic blood oxygenated in isolated perfused lungs of a donor dog. Carotid sinus and aortic arch pressures maintained constant. Closed chest. Spontaneous breathing. In *A*, lungs collapsed at first arrow, ↑, by creating bilateral pneumothorax, and re-expanded at second arrow ↑. Between *A* and *B*, spontaneous respiratory movements paralysed by decamethonium (0·25 mg/kg). In *B*, test repeated. In *C*, open pneumothorax with lungs in collapsed position. During signal, inflation of lungs with 300 ml. air into the trachea. T.A., tidal air volume. Time marker, 10 sec.

Spontaneous respiratory movements were present in three of the five experiments and in these the Hering–Breuer inhibitory reflex disappeared between 5° and 9·5° C. Both the vascular and respiratory responses reappeared on warming the nerves. In two further experiments not in-

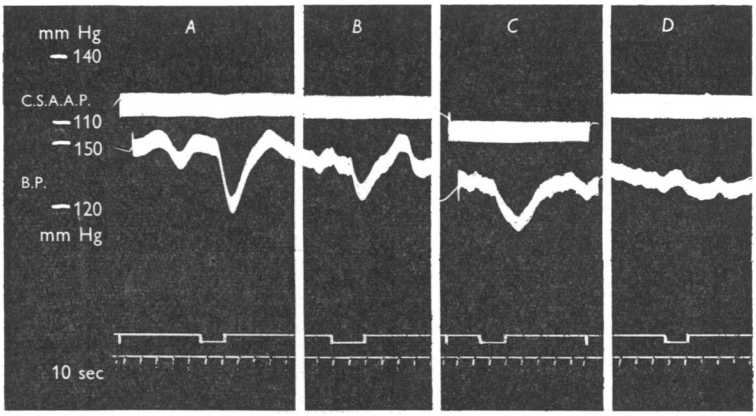

Fig. 7. Dog, male, 13·0 kg. Morphine-chloralose-urethane. Separate perfusions of the systemic circulation and the isolated carotid sinuses and isolated aortic arch. Systemic venous blood oxygenated in the isolated perfused lungs of a second dog. *A–D* show the effects of inflation of the lungs with 375 ml. room air. In *B* the cervical vago-sympathetic nerves were cooled to −1° C. Between *B* and *C* the cervical vago-sympathetic nerves were cut. Between *C* and *D* procaine hydrochloride was applied to both stellate ganglia. Time marker, 10 sec.

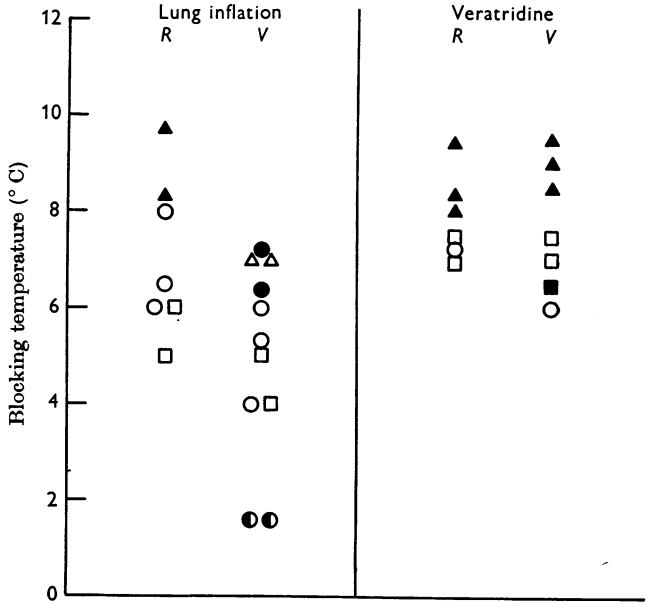

Fig. 8. The effects of cold blocking the cervical vagosympathetic nerves on the respiratory (*R*) and vascular (*V*) responses evoked by maintained inflation of the lungs and by veratridine injected into the pulmonary circulation. Each symbol represents an experiment.

cluded in Fig. 8, cooling the cervical vagosympathetic nerves to $-1°$ C reduced but did not abolish the vascular responses to inflation of the lungs. In these experiments, which are referred to above, division of the nerves also failed to abolish them.

These results indicate that the cervical vagosympathetic nerves are the main afferent pathway for the lung inflation–systemic vasodepressor reflex, and that in some animals at least there may be an additional pathway by way of the stellate ganglia.

Action of drugs. In two experiments, atropine in doses of 5 mg added to the main reservoir had no effect on the vascular responses to inflation of the lungs. On the other hand, it was found in non-atropinized preparations that the responses were abolished by hexamethonium, 100–200 mg (three experiments), and guanethidine, 200–300 mg (three experiments). Subsequent injections of acetylcholine, 10–20 μg, into the arterial inflow tubing invariably caused a fall in systemic arterial perfusion pressure showing that in these experiments failure of lung inflation to evoke a response after administration of the drugs was not due to the blood vessels being fully dilated and therefore incapable of further dilatation.

These results indicate that the efferent pathway for the lung inflation reflex is mediated by the sympathetic nervous system.

Comparison of the values for systemic arterial perfusion pressure before and after denervating the lungs by cutting the pulmonary branches of the thoracic vagosympathetic nerves provided further information concerning the nature of the pulmonary receptors responsible for initiating the systemic vascular reflex. One way these responses may be brought about during distension of the lungs is by stimulation of 'inflation' receptors. Thus during collapse of the lungs their discharge would be expected to be minimal. On the other hand, an alternative mechanism by which the observed vascular responses could be initiated is by modification of the discharge from 'deflation' receptors (Paintal, 1957). The discharge from these receptors, in contrast to the 'inflation' receptors, would be maximum during collapse of the lungs and decrease as the lung volume increased. In five experiments, denervation of the lungs in a deflated position caused changes in systemic arterial perfusion pressure varying from -5 to $+5$ mm Hg. Since these changes were small, and occasionally in the opposite direction to those evoked by inflation of the lungs, it suggests that the frequency of discharge from the pulmonary receptors is lower when the lungs are collapsed than when inflated. When the lungs are inflated, the values for systemic arterial pressure after denervation are higher than those obtained before denervation. All these findings are compatible with the view that the pulmonary receptors concerned in this reflex are of the 'inflation' type.

Effect of veratridine. It has been shown previously that veratridine injected into the animal with a natural circulation causes a reflex fall in systemic blood pressure through an action on pulmonary receptors (Dawes, 1947; Aviado, Pontius & Schmidt, 1949; Aviado, Li, Kalow, Schmidt, Turnbull, Peskin, Hess & Weiss, 1951). In six of the present experiments injections of veratridine in doses of 10–25 μg were made into the pulmonary arterial inflow tubing to the recipient dog's lungs. A fall in systemic arterial perfusion pressure occurred varying from 13 to 62 mm Hg (average 26·9), representing a decrease in vascular resistance of 19·7 % (range 9–38) (Fig. 9*C*). This response was accompanied by a temporary diminution or cessation of rhythmic respiratory movements in three

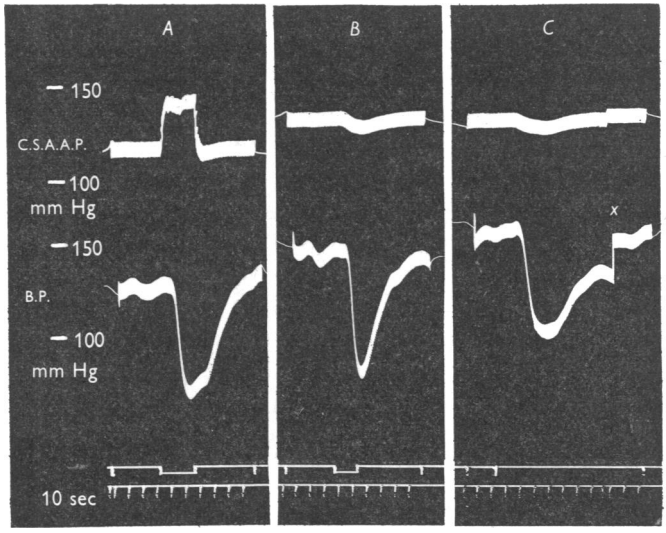

Fig. 9. Dog, male, 13·0 kg. Morphine-chloralose-urethane. Separate perfusions of the systemic circulation, isolated carotid sinuses and isolated aortic arch, and the pulmonary circulation of the collapsed lungs. Systemic venous blood oxygenated in the isolated perfused lungs of a donor dog. *A*, the pressures in the isolated carotid sinuses and aortic arch were temporarily increased. *B*, recipient lungs inflated with 375 ml. room air. *C*, injection of veratridine, 10 μg, into the pulmonary arterial inflow tubing of the recipient lungs. The paper was stopped for 2 min at *X*. Time marker, 10 sec.

experiments in which spontaneous movements were present in the control state. In three experiments changes in the rate of the beating atria were observed. Depending on the dose, either the rate decreased or the atria temporarily stopped beating.

Division of the cervical vagosympathetic nerves abolished the atrial, vascular and respiratory responses to veratridine. The results of cold blocking the nerves are summarized in Fig. 8, from which it will be noted

that the systemic vasodepressor responses were blocked between 6° and 9·5° C in four experiments, and that the inhibitory effect on respiration disappeared at 7–9·5° C (three experiments). The responses were restored to normal on rewarming the nerves.

DISCUSSION

The reduction in systemic vascular resistance occurring in response to inflation of the lungs must be due to predominance of vasodilatation since the systemic blood flow was maintained constant, but no studies have been carried out on the vascular territories participating in the response. The possibility that an increase in vascular resistance occurs in some areas cannot be ruled out.

Nearly all the inflation gas volumes used in the present experiments have been well within physiological limits and a striking feature is that a change in volume of 50 ml. or a change in intratracheal pressure of 3 cm H_2O may cause a detectable fall in systemic arterial perfusion pressure and vascular resistance. This reflex, therefore, is a potential mechanism modifying systemic vascular resistance in eupnoeic breathing. It should be emphasized, however, that these responses were obtained under conditions in which the pressures in the isolated perfused carotid sinuses and aortic arch were maintained constant to exclude compensatory reflexes from the arterial baroreceptors. In the animal with a natural circulation, the baroreceptor reflex may wholly or partly counteract that elicited by changes in volume of the lungs, and this view is supported by the evidence presented in this paper.

The size of the vasodilator responses depended on the degree of preexisting tone of the 'resistance' vessels engendered by the activity of the sympathetic nervous system so that increasing the level of this 'background tone' reflexly, either by reducing the pressure in the isolated carotid sinuses and aortic arch or by stimulating the carotid or aortic bodies, enhanced the response to inflation of the lungs. Provided this background tone was maintained constant, however, the size of the vasodilator responses was closely related to the volume and pressure of inflation.

The afferent pathway for the reflex lies mainly in the cervical vagosympathetic nerves, although in two experiments an extra-vagal pathway was demonstrated, and in one of these the response remaining after dividing the cervical vagosympathetic nerves was found to be abolished by blocking transmission through the stellate ganglia. A sympathetic pathway for afferent fibres from the lungs has been described previously (Barry, 1913; Fegler, 1933; Banister, Fegler & Hebb, 1949; Holmes & Torrance, 1959). It is assumed that the vagal afferent fibres make connexion with

the 'vasomotor centre' in the medulla. Those passing through the stellate ganglia may have a similar destination, though the possibility that some of them form a pathway for a spinal reflex, such as has been described in man (Gilliatt, Guttmann & Whitteridge, 1948), cannot be ruled out.

Evidence is presented which suggests that the pulmonary receptors concerned in the reflex changes reported here are stimulated during inflation of the lungs and that when the lungs are collapsed the discharge from the receptors is minimal. It is concluded therefore that in their normal partially inflated position in the chest the lungs are a constant source of afferent impulses reaching the vasomotor centre.

The vascular responses occurring on changing the volume of the lungs are unaffected by atropine, but are abolished by guanethidine and bretylium tosylate, suggesting they are mediated by adrenergic sympathetic vasoconstrictor fibres. The vasodilatation occurring when the lungs are inflated is due therefore to a reduction in discharge in these fibres. Thus the lungs in their normal position are a source of afferent impulses inducing an inhibitory effect on the vasomotor centre. This view is supported by the fact that deflation of the lungs by creating a pneumothorax results in systemic vasoconstriction.

Variations of impulse activity in sympathetic nerves in phase with respiration have been demonstrated by a number of workers. Bronk, Ferguson, Margaria & Solandt (1936) and Downing & Siegel (1963) found in the cat that with each inflation of the lungs by a pump there was a reduction in the impulse frequency in the inferior cardiac nerve. Bronk *et al.* (1936) attributed this to periodic inhibition of the centres by pulmonary stretch receptors because the rhythm disappeared after dividing the vagus nerves. A respiratory rhythm has also been observed in the cervical and abdominal sympathetic nerves, but was found to persist after cutting the vagus nerves (Adrian, Bronk & Phillips, 1932; Tang, Maire & Amassian, 1957). It was ascribed to an irradiation of impulses from the respiratory centre to the vasomotor centre by Adrian *et al.* (1932) and to the reflex effects of the changes in arterial baroreceptor activity engendered by respiratory variations in blood pressure by others (Tang *et al.* 1957; Iggo & Vogt, 1960). There is clearly a need here for further studies of this problem under controlled conditions.

The effects of altering the lung volume on the peripheral circulation have been studied in man. When a voluntary deep breath is taken, vasoconstriction occurs in the finger (Goetz, 1935; Bolton, Carmichael & Stürup, 1936; Gilliatt, 1948) and forearm and hand (Mulinos & Shulman, 1939). It has been suggested (Bolton *et al.* 1936) that the response is reflex in origin, but the site of the receptors has not been located. The conditions under which these experiments on man were carried out are different from

those described here. In man the lungs and chest were, in effect, expanded as a result of impulses arising from the respiratory centre and so in addition to afferent impulses from the expanding lungs, the vasomotor centre will also be affected by impulses from the respiratory centre (Fredericq, 1882; I. de B. Daly, 1930; Adrian *et al.* 1932; Tang *et al.* 1957). In the present experiments the lungs were expanded passively and the reflex systemic vasodilator responses occurred whether or not there was any activity of the respiratory centre as indicated by movements of the diaphragm and thorax. So far as we are aware, there is as yet no information on the interaction between the central respiratory and reflex pulmonary control of the vasomotor centre.

Nature of the pulmonary receptors

Whereas no special attempt was made in the present study to identify or locate the receptors in the lungs responsible for eliciting the systemic vasomotor reflex, some of our results are pertinent to this problem.

One interpretation of our results is that they are due to stretch or deformation of receptors residing in the pulmonary blood vessels. Stimulation of these receptors by raising the pressure in various parts of the pulmonary vascular bed causes bradycardia, systemic hypotension and systemic vasodilatation (Schwiegk, 1935; I. de B. Daly, Ludàny, Todd & Verney, 1937; Aviado *et al.* 1951; Coleridge & Kidd, 1963). Although this possibility cannot be excluded, two observations make it rather unlikely. First, it was found that the size of the reduction in systemic vascular resistance occurring in response to inflation of the lungs was the same whether or not blood was flowing through the pulmonary circulation, and second, veratridine, which caused reflex systemic vasodilatation when injected into the pulmonary artery, has no effect on the pulmonary arterial baroreceptors, at least in the cat (Bevan & Kinnison, 1965). It is also unlikely that the lung inflation–systemic vascular responses are due to excitation of receptors situated at the junctions of the pulmonary veins with the left atrium (Nonidez, 1937; Ledsome & Linden, 1964*b*), because they are abolished by crushing the hilum of the lungs extrapericardially, a procedure which leaves the cardiac responses to distension of the pulmonary vein–atrial junctions unaffected (Ledsome & Linden, 1964*b*).

An alternative explanation, and one we consider the more likely, is that the lung inflation–systemic vasodilator reflex is due to excitation of pulmonary stretch receptors. The following evidence is compatible with this view. (1) The majority of the nerve endings responsible for the reflex systemic vasomotor responses are intrapulmonary because after crushing the hila of the lung lobes inflation of the lungs has no effect on the systemic arterial perfusion pressure provided the inflation pressures are less than

about 15 cm H_2O. These intrapulmonary receptors are excited by deformation through an alteration in transpulmonary pressure, as indicated by the fact that the reflex can be elicited equally well by distension of the lungs by a positive intrapulmonary pressure as by a negative extrapulmonary pressure. (2) The receptors are unaffected by changing the composition of the gas used to inflate the lungs or its temperature. (3) They are 'inflation' receptors, with a low threshold to stretch, and are discharging in lungs in the expiratory position in the closed chest. This is characteristic of low-threshold pulmonary stretch receptors (e.g. Adrian, 1933; Paintal, 1966). (4) There is a close relation between the volume and pressure used to inflate the lungs and the degree of vasodilatation, suggesting that the pulmonary receptors concerned are probably of the slowly adapting type; and (5) veratridine, an alkaloid known to stimulate pulmonary stretch receptors (Meier, Bein & Helmich, 1949; Dawes, Mott & Widdicombe, 1951), caused a reflex reduction in systemic vascular resistance, a diminution in respiratory movements and slowing of the beating atria when injected into the pulmonary circulation. A second type of receptor in the lungs has recently been shown by Coleridge, Coleridge & Luck (1965) to be stimulated by veratridine. Since these receptors show no activity during eupnoeic breathing but are excited by hyperinflation of the lungs, they are unlikely to be responsible for the reflex vasomotor responses observed by us, at least those occurring with inflation volumes which result in the lungs not exceeding their normal function residual capacity.

Finally, the results of experiments on progressive cooling of the cervical vagosympathetic nerves must be considered. It has been shown previously that the Hering–Breuer inflation reflex is abolished at about 8° C (see Dawes & Comroe, 1954), and with this our finding of 7–9° C is in agreement. Although the reflex systemic vasodilatation in response to injection of veratridine was abolished by cooling the cervical vagosympathetic nerves to 7–9° C, that to inflation of the lungs was blocked at a somewhat lower temperature (2–7° C). Too much weight should not perhaps be put on this finding, for apart from the difficulty of ensuring a uniform temperature throughout a relatively large nerve like the dog's vagus, the interpretation of results obtained by this method presents problems which have recently been emphasized by Paintal (1965*a*, *b*, 1966). But clearly further evidence is required to substantiate the view that it is the pulmonary stretch receptors which are responsible for eliciting the responses described in this paper.

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