

THE ACTIVITY OF VAGAL STRETCH ENDINGS DURING CONGESTION IN PERFUSED LUNGS

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In spite of considerable recent work, the factors responsible for cardiac dyspnoea are still far from clear. Christie (1938) has summarized the evidence showing that pulmonary congestion invariably accompanies cardiac dyspnoea, and that afferent vagal impulses from the lungs play a large part in the production of this dyspnoea. His hypothesis is that the vagal 'stretch' afferents record tension in the lung, and that the sensitivity of the endings is increased, as the lungs are more rigid in pulmonary congestion. The alternative view that another set of endings, capable of causing inspiration, is active in dyspnoea, is supported by the work of Partridge (1939) and Hammouda, Samaan & Wilson (1943), and recalls the suggestion of Adrian (1933) that 'deflation' endings may be of importance in pathological conditions.

As the point seemed to have considerable theoretical importance, we have tried to distinguish between these possibilities by recording the activity in vagal single fibre preparations from 'stretch' endings during experimental pulmonary congestion. Considerable difficulties were encountered in consistently producing pulmonary congestion in cats with natural circulation, and we therefore decided to work with perfused lungs in which all the vascular factors were under control.

METHOD

Two cats were used in each experiment, one as a blood donor and the other for the lung perfusion. The first cat was given 1 mg. atropine subcutaneously and was then anaesthetized with ethyl chloride and ether. A tracheal tube was inserted in order to give artificial respiration in the later stages of bleeding. Cannulae were put into the external jugular vein and into the abdominal aorta. 25 c.c. of blood were taken from the aorta and immediately replaced by 25 c.c. of warm Ringer's solution containing 10 μ g. adrenaline, which was slowly infused into the external jugular vein. This process was repeated three times (total volume of Ringer's solution infused was 75 c.c.), after which the cat was bled out. The total blood volume thus obtained was about 150 c.c. The blood was carefully defibrinated and filtered five times through muslin.

The second cat was also given 1 mg. atropine and anaesthetized with ethyl chloride and ether. One vagus nerve in the neck (usually the right one) was carefully exposed for a length of 3-4 cm.

A tracheal tube and cannulae in the jugular vein and abdominal aorta were inserted. The defibrinated and filtered blood from the first cat was put into a burette which was connected to the jugular vein. Again, 25 c.c. blood was removed from the aorta and then replaced by 25 c.c. defibrinated blood together with 10 μ g. adrenaline slowly infused into the jugular vein. This procedure was repeated until the whole of the defibrinated blood had passed through the cat, which was then bled out completely. Artificial respiration was started as soon as the cat stopped breathing and was continued with a small pump stroke throughout the subsequent manipulations. All the blood was once more carefully defibrinated and filtered five times.

The cat's chest was opened in the midline, the pericardium was split, a cannula was inserted into the pulmonary artery (Fig. 1, *PA*), a string was tied firmly around the bases of the ventricles and a second cannula was put into the left auricle (*LA*). The chest wall, which during the preparation

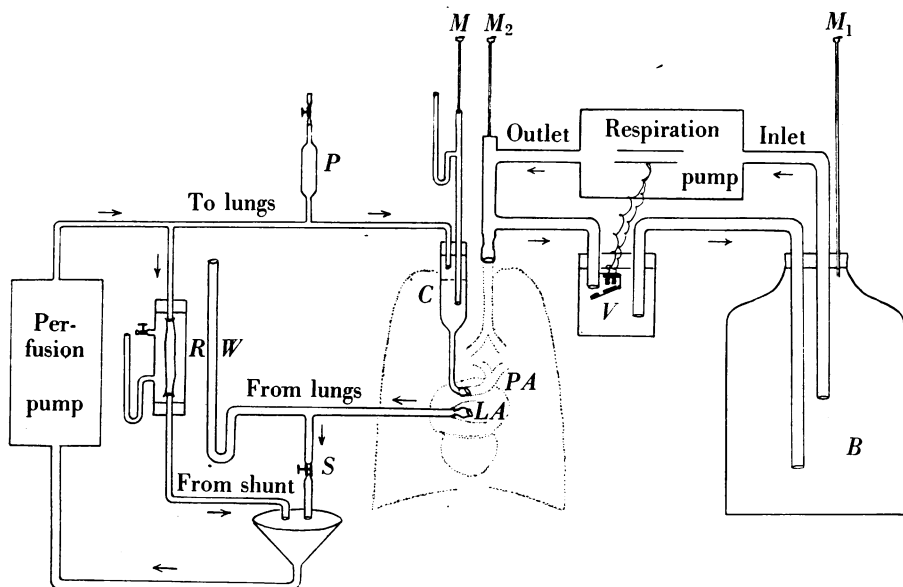


Fig. 1. Diagram of lung perfusion and respiratory circuit. For details see text.

had been pulled open, was now allowed to come back almost to its original position leaving a space for the two cannulae. At this point the frame of the moist chamber (described below) was put into position.

The lungs were perfused with a Dale-Schuster pump. The tube leading to the arterial cannula was connected by a side tube to a 20 c.c. pipette (*P*) the other end of which was closed and which was filled with air, thus acting as an air cushion. A second side tube led to a shunt through an artificial resistance set at 50 mm. Hg. Another air cushion was provided in the arterial cannula (*C*) itself: the glass tube inserted in the pulmonary artery was bent and widened into a tube of 2 cm. diameter held vertically. This cylinder was partly filled with blood, partly with air, and closed with a rubber stopper through which one glass tube let the blood in, while another was connected with a mercury manometer and also with a membrane manometer (*M*) for optical recording of the pulmonary arterial pressure. The venous pressure was measured by a water manometer (*W*) connected with the cannula in the left auricle. The pulmonary arterial pressure could be increased at will by raising the resistance in the shunt and/or by increasing the pump stroke. The venous pressure could also be raised at will by obstructing the outflow from the venous cannula with a screw clamp (*S*). At the beginning of each experiment the venous pressure was zero and the pulmonary arterial pressure 18–20 mm. Hg.

Cats' lungs, when perfused with defibrinated blood, easily become oedematous. Modrakowski (1914) first pointed out the necessity for washing out the blood vessels with defibrinated blood. In our own experiments, not only this precaution but also the reduction in pulse pressure by air cushions, the avoidance of excessive arterial pressure by including a shunt, and finally the inflation of the lungs with a small volume of air secured good results. In large and strong cats the perfusion could be maintained for 4-5 hr. without lung oedema developing. But even with the precautions described we still had occasional failures in which lung oedema began within half an hour of starting the perfusion. We are reporting here the results of six successful perfusions with a total of twelve reversible congestions.

The lungs were inflated with known volumes of air (40-80 c.c.) from a rigid pump similar in principle to the Starling Ideal Pump, running at 14 strokes per min. This allowed about 2 sec. for the completion of expiration. The rotary expiratory valve of the Starling Ideal Pump was replaced by an electromagnetic valve (*V*) worked by a commutator on the shaft of the pump. This valve was absolutely airtight. In order to detect any variation in the amount of air in the lungs at the end of expiration a 10 l. bottle (*B*) was connected to the expiratory outlet and to the pump inlet, thus producing a closed circuit. A sensitive membrane manometer recorded changes in pressure in this bottle and was calibrated by withdrawal of known amounts of air from the circuit. A second membrane manometer connected to the tracheal tube recorded the pressure during inflation and indicated gross changes in the resistance to inflation due to narrowing of bronchioles or changes in the lung parenchyma.

A moist chamber was required for the dissection of the single vagal fibres in the neck. The animal lay on a warm table. A wooden frame had pieces cut out to fit over the cat's head and belly. The right side of the frame had an opening with a rubber curtain through which the operator could pass his hands to dissect the vagus. Through a hole in the left side of the box a tube was passed and connected with the venous cannula. The glass top consisted of two glass plates which were slid on from both sides as soon as the perfusion had been started; they had a hole cut out to fit around the arterial cannula. Any spaces left were plugged with cotton wool. Warm moisture was produced by an immersion heater in a small dish of water covered with wet muslin.

Single fibre preparations were obtained by cutting down the vagus nerve with sharp needles. In spite of the absence of blood supply to the nerve and to the tissues of the neck it was usually possible to obtain responses from a number of pulmonary stretch afferents. Occasionally, when no response could be obtained, conduction was re-established by dissecting away fatty tissue surrounding the nerve in the anterior mediastinum and exposing the whole length of the nerve to air. In one dog, the lungs of which were successfully perfused, very few fibres were found to be alive in the neck and these rapidly failed after dissection. As pointed out by Daly & von Euler (1932), in connexion with the survival of vasomotor fibres to the lungs, a bronchial blood supply is essential in the dog. The fact that the nerve trunk and the tissues in the hilus of the lung are much thicker in the dog than in the cat probably accounts for the difference in survival of the vagal fibres. In these perfused lung preparations we have never found any activity in other than stretch fibres. Depressor fibres are known to have a smaller diameter and to belong to the δ group (O'Leary, Heinbecker & Bishop, 1934); such fibres are very sensitive to oxygen lack (Grundfest, 1939), and are unlikely to be active in these conditions. Nerve impulses were recorded by means of the usual amplifier, cathode ray tube and camera. Artefacts arising from the perfusion apparatus were avoided by earthing all parts which were electrically connected to the cat. The moist chamber was screened as far as possible and earthed.

RESULTS

The discharge from the stretch afferents from perfused lungs was in all respects similar to that seen in cats with normal circulation and in which the lungs were inflated with the same pump (Whitteridge & Bülbring, 1944). The relation between degree of inflation and frequency of vagal impulses was normal. In

successful perfusions the frequency of discharge with a constant pump stroke remained steady within $\pm 2\%$ over 20 min. At the end of some perfusions, when the lungs were not collapsing as well as in the beginning, there was a tendency for the frequency to rise progressively in spite of the constant pump stroke. When this occurred it was found that the pressure of air in the reservoir bottle began to fall, indicating that there was some retention of air in the lungs.

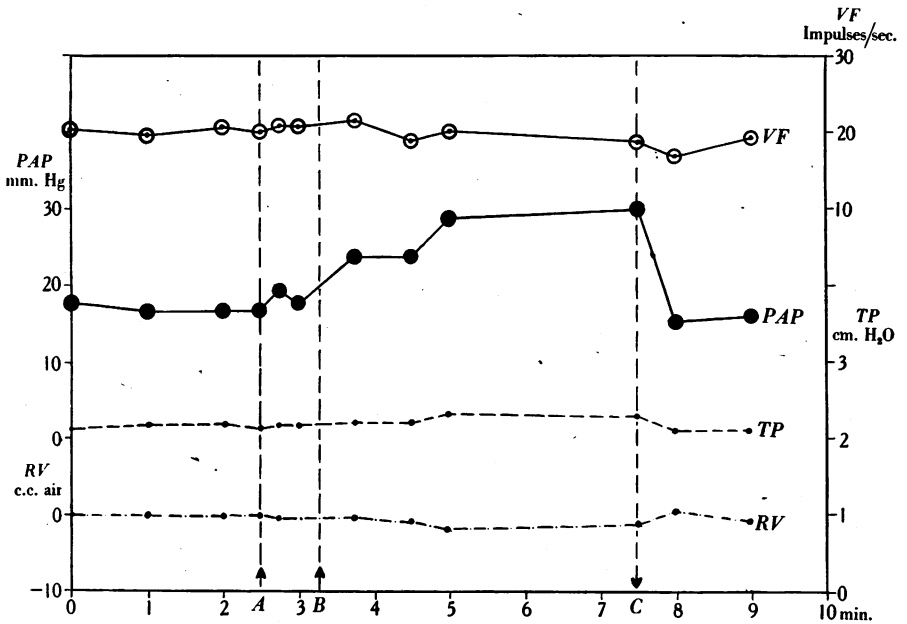


Fig. 2. Lung perfusion. Pulmonary congestion produced by raising the venous pressure to 10 cm. H₂O at A, and to 20 cm. H₂O at B. Venous obstruction removed at C. ○ (VF) = Peak frequency of discharge in a single vagal stretch afferent. ● (PAP) = Pulmonary arterial pressure. ----- (TP) = Tracheal pressure at full inflation. - - - - - (RV) = Pressure changes in the reservoir (these indicate changes in the opposite direction in volume of air in the lungs at expiration).

Congestion was produced in three ways: either by impeding the venous outflow up to complete occlusion, or by raising the arterial pressure (maximum 60 mm. Hg), or by impeding the venous outflow simultaneously with raising the perfusion pressure. During congestion the shunt was shut.

The effect of simple venous congestion, corresponding to 'back pressure' from the left atrium, is illustrated in Fig. 2. The change in pulmonary arterial pressure was at first slight owing to the known capacity of the lungs to accommodate large amounts of blood. It took about 3 min. before the pulmonary arterial pressure became steady at its new higher level. The frequency of discharge in the vagal stretch fibre, however, showed no significant change.

At the beginning of a period of congestion there was always an initial increase in the resistance of the lungs to inflation. This was recorded as an increase in the intratracheal pressure at the peak of inflation. In most experiments this increased resistance was maintained throughout the period of congestion and disappeared at the end.

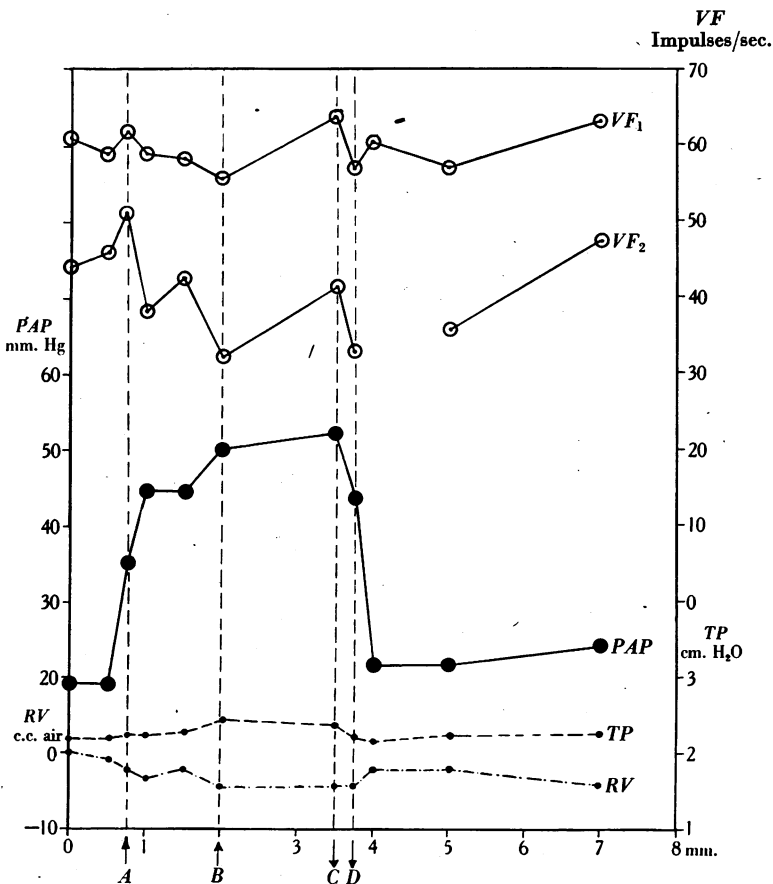


Fig. 3. Lung perfusion. Congestion was produced by raising the pump stroke at A and stopping the venous outflow at B. At C the venous clamp was removed and at D the pump stroke was lowered to the original level. Indications as Fig. 2.

During congestion there was also evidence of a retention of up to 4 c.c. air in the lungs, indicated by a decrease in pressure in the large reservoir bottle. At the end of the period of congestion the retained air was expelled.

In three experiments in which congestion was produced by impeding the venous outflow (nos. 1, 2, 8 in Table 1) there was once a small increase, once a small decrease and once no significant change in the frequency of stretch impulses. Three experiments were then carried out in which the perfusion pump

stroke was raised (nos. 3, 4, 5 in Table 1), thus increasing the pulmonary arterial pressure only, but not the venous pressure. At a pulmonary arterial pressure of 40 and 60 mm. Hg there occurred some increase in the resistance to inflation, a small retention of air in the lungs and a small increase in frequency of stretch impulses.

Much more severe congestion of the lungs was produced by raising the perfusion pressure and also impeding the venous outflow. Fig. 3 illustrates one such experiment in which the venous outflow was in fact completely occluded.

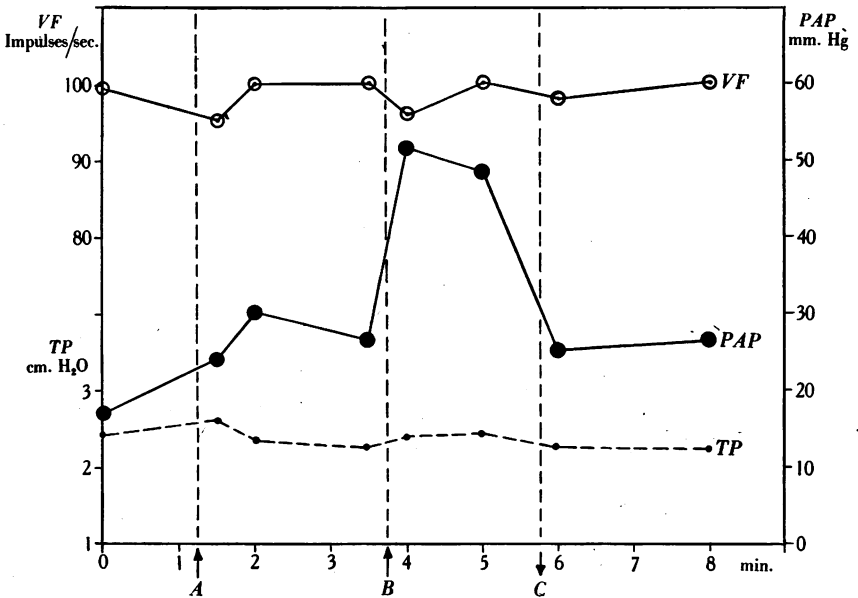


Fig. 4a. Comparison of the behaviour of vagal stretch endings (a) during congestion, (b) during exposure to 3% trichlorethylene. Fig. 4a at A venous pressure raised, at B pump stroke increased, at C return to normal conditions. Fig. 4b trichlorethylene administered from A to B.

There happened to be two fibres the frequency of which could be followed. In spite of an increase of 30 mm. Hg in the pulmonary arterial pressure the frequency of discharge in both fibres showed insignificant changes. Even this maximum congestion did not produce pulmonary oedema and the lungs withstood another period of congestion $1\frac{1}{2}$ hr. later.

Fig. 4a shows another experiment in which the venous pressure was raised and the pump stroke was then increased. Though the pulmonary arterial pressure rose from 17 to 51 mm. Hg the frequency of impulses dropped temporarily from 100 to 96 per sec. and never rose above the initial level throughout the period of congestion.

Contrasting sharply with the observations described is an experiment shown in Fig. 4*b* where 3% trichlorethylene was administered for 3½ min. The pulmonary arterial pressure fell slightly and the resistance to inflation also dropped slightly but the frequency of discharge in the vagal fibre rose from 106 to 166 per sec. The fact that the pulmonary arterial pressure fell, while

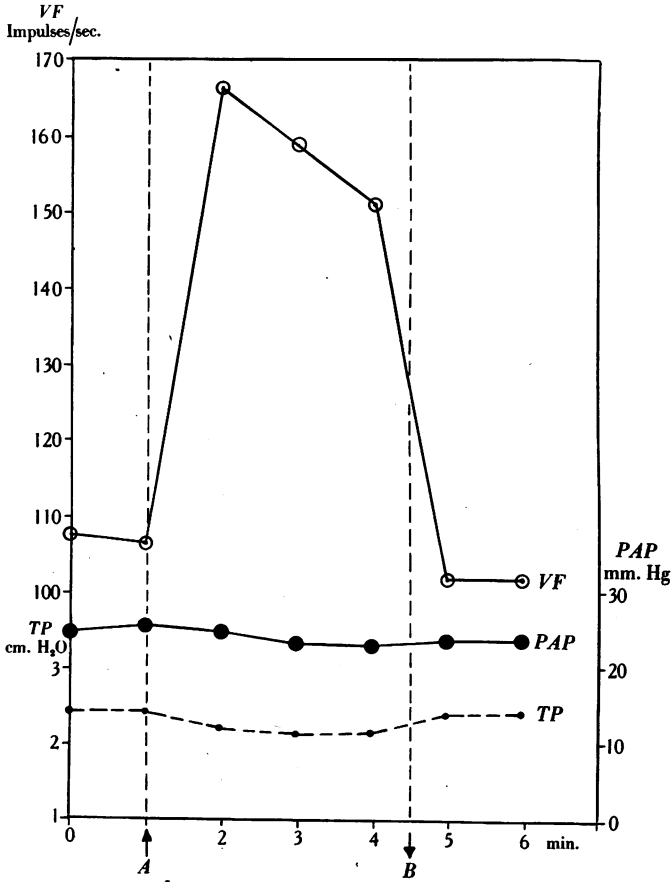


Fig. 4*b*. For explanation see Fig. 4*a*.

the output of the perfusion pump remained constant, indicates a vasodilator action of trichlorethylene. Fig. 5 shows three of the actual records from an experiment similar to that in Fig. 4*a*.

In Table 1 the mean of the peak frequencies of discharge from stretch receptors during congestion has been compared with the mean before and after congestion in each experiment. It will be seen that of the fourteen fibres studied there were significant increases in five, a significant decrease in one, while the remaining eight showed no significant change. All the differences

were very small and did not exceed 10 impulses/sec., whereas the increase caused by trichlorethylene amounted to 60 impulses/sec. and even larger

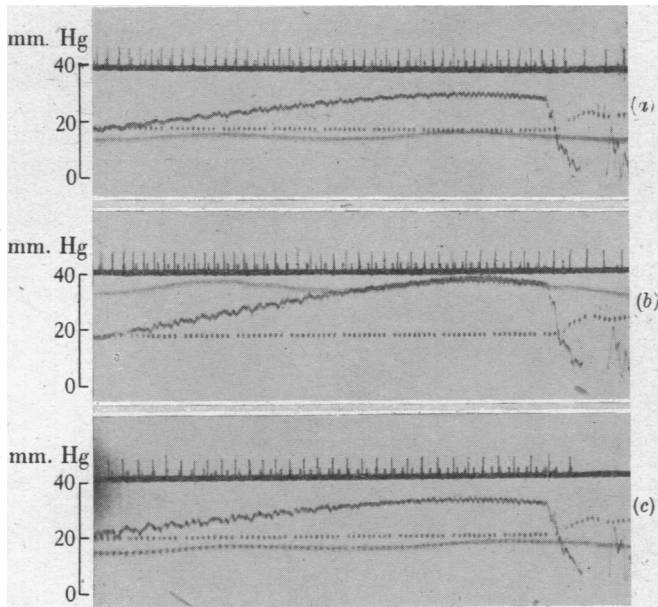


Fig. 5. Records during lung perfusion (a) before, (b) during, (c) after congestion of lung. The second half of inflation and the beginning of expiration is shown in each record. Records in (a) from above downwards: (1) impulses in two vagal stretch fibres (retouched); (2) tracheal pressure; (3) time marker $\frac{1}{10}$ and $\frac{1}{20}$ sec. superimposed on record of reservoir volume; (4) pulmonary arterial pressure.

TABLE 1. Peak frequency of impulses in vagal stretch fibres
Significant increase +, significant decrease -, no significant change 0

Exp.	Before and after congestion	During congestion	Difference	Result
1	102.8 ± 0.52 (2)	108.1 ± 0.87 (2)	+5.3	+
2	96.1 ± 0.2 (2)	92.7 ± 0.72 (3)	-3.4	-
3	93.2 ± 0.87 (4)	95.3 ± 1.07 (3)	+2.1	0
4	95.0 ± 0.40 (4)	100.1 ± 0.4 (2)	+5.1	+
5	91.7 ± 0.63 (4)	98.9 ± 0.45 (2)	+7.2	+
6	40.4 ± 1.98 (3)	31.2 ± 4.04 (4)	-9.2	0
7	91.7 ± 7.60 (5)	97.4 ± 0.56 (4)	+5.7	0
8	19.7 ± 0.52 (6)	20.2 ± 0.51 (6)	+0.5	0
9A	43.5 ± 1.64 (5)	49.7 ± 1.84 (5)	+6.2	+
9B	59.5 ± 0.70 (6)	62.6 ± 1.32 (5)	+3.1	0
10A	45.8 ± 1.01 (3)	39.7 ± 2.87 (6)	-6.1	0
10B	60.2 ± 1.00 (5)	59.3 ± 1.23 (6)	-0.9	0
11	99.2 ± 0.60 (3)	98.3 ± 1.07 (5)	-0.9	0
12	110.4 ± 0.55 (4)	119.1 ± 0.78 (5)	+8.7	+

Weighted mean difference +1.66 ± 0.871

increases have been seen when anaesthetics were administered to intact animals (Whitteridge & Bülbiring, 1944). In all cases, including the experiment

in which there was a significant fall in frequency of discharge, there was a retention of air in the lungs. By altering the stroke of the respiration pump it was found that an increase of 4 c.c. of air would be expected to produce an increase of about 2-7 impulses/sec. in different experiments. The mean differences for all fibres (weighted for the number of observations) was an increase of 1.66 impulses during congestion. From Fisher's Table of t (Fisher, 1941), P lies between 0.1 and 0.05, i.e. this difference is just below the level of significance and is certainly not more than would be produced by the retention of air. The increased scatter in the majority of cases during congestion suggests that the distribution of air to the different respiratory units has become less regular. It seems safe to assume that in Exp. 2 access of air to the relevant respiratory unit had been hindered, and it follows that other respiratory units must have received more air than before.

DISCUSSION

When this work was started we believed that, in conditions in which pulmonary congestion plays an important part, there probably is an increased sensitivity of vagal stretch endings. We were rather surprised to find that the frequency of impulses in vagal stretch fibres showed increases as small as 7% in our earlier experiments in which congestion was produced merely by impeding the venous outflow, and we imagined that we were not obtaining a sufficient degree of congestion. With normal capillary permeability one would expect pulmonary oedema to begin when the pressure inside the capillaries is just greater than that of the plasma proteins. In his perfusion experiments Modrakowski (1914) found that the lungs could tolerate pressures up to 80 mm. Hg on the arterial side and 35 mm. Hg on the venous side for short periods without the appearance of pulmonary oedema. In our experiments we approached these limits as closely as we dared and precipitated pulmonary oedema in two instances. Nevertheless we failed to observe more than a trifling change in the frequency of vagal stretch impulses.

The appearance of the paper by Trowell (1943) reminded us of the patchy interference with air inflow which may be produced by bronchial congestion. This he observed to follow very slight degrees of pulmonary congestion. In our experiments, in which the bronchiolar capillaries may have filled from the pulmonary veins, there was certainly some interference with the collapse of the lungs, as 2-4 c.c. of air was usually retained.

It is likely that this interference with airflow results in redistribution of air to the alveoli so that some may collapse and others show some degree of compensatory distension. It follows that a true picture of the effects of any agent causing congestion can only be obtained by observing as large a number of fibres as possible and by measuring the mean change in frequency of dis-

charge. From Table 1 it is clear that there is no evidence for an increased sensitivity of stretch endings during the greatest possible degree of congestion up to the point of lung oedema.

A more prolonged congestion was impracticable as it is impossible to rely on longer survival of a single fibre preparation.

The question may well be asked whether conditions in an open chest with inflation of the lungs with positive pressure are comparable with those in a closed chest. In fact, Drinker, Peabody & Blumgart (1922) found during congestion a considerable increase in the resistance of the lungs to inflation when the pleura remained intact, and a much smaller change with the pleura open. Christie (1938) ascribes the whole of the reflex effects of congestion to these observable changes in resistance to inflation. But in our experiments there was consistently an increase in resistance to inflation at the beginning of congestion, at which time the vagal frequency may rise or fall.

Since the mechanical conditions of our experiments were probably comparable with those in the perfusion of dog's lungs carried out by Daly, Ludany, Todd & Verney (1937), we think it highly unlikely that in their experiments any increase in sensitivity of stretch endings occurred. They found, however, that pulmonary congestion, produced by impeding the venous outflow, not only reflexly affected the systemic blood pressure but also stimulated the separately perfused respiratory centre. Both an increase in respiratory rate and an increased inspiratory tone were seen. We are therefore forced to the conclusion that there must be a second set of afferent fibres in the vagus which is capable of accelerating the respiration. This is the view put forward by Partridge (1939) and by Hammouda *et al.* (1943). So far, the only known method of increasing the sensitivity of stretch endings is by the administration of volatile anaesthetics (Whitteridge & Bülbiring, 1944). A re-investigation of the rapid breathing caused by multiple starch embolism (Walsh & Whitteridge, 1945) has shown that there is no consistent sensitization of stretch endings.

SUMMARY

1. A method is described for the perfusion of the cat's lungs and for simultaneously recording the activity in single vagal afferent fibres.

2. The lungs were congested for periods of from 2 to 5 min. by impeding the venous outflow up to complete occlusion or by raising the pulmonary arterial pressure up to 60 mm. Hg. Neither of these two methods, nor the combination of them, caused any significant change in the frequency of discharge from vagal stretch endings.

3. Reasons are given for believing that pulmonary congestion in the intact chest is not accompanied by increased sensitivity of vagal stretch endings, any more than in the perfused lungs.

4. These results cast doubt on a current hypothesis to explain cardiac dyspnoea. Reflexes arising from other than stretch afferents in the vagus may be involved.

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