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THE PART PLAYED BY BRONCHIAL MUSCLES IN PULMONARY REFLEXES

BY

GWENDA R. BARER AND E. NUSSER

From the Nuffield Institute for Medical Research, University of Oxford

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A number of reflexes have been described whose receptors are in the lungs and which, on the efferent side, alter the rate and depth of breathing. It would be reasonable to suppose that some of these reflexes might also alter the tone of the bronchial muscles. Gilding and Nutt (1944) showed that stored plasma not only caused an alteration of respiratory movements which was abolished by cutting the vagi, but also caused large increases in intrapleural pressure, which they ascribed to bronchoconstriction. However, the point has not been thoroughly investigated, and it was therefore thought worth while studying the changes of tidal air in cats after injection of 2-α-naphthyl ethyl isothiourea, diphenhydramine, and veratrine, all of which substances excite pulmonary reflexes which alter breathing (Dawes, Mott, and Widdicombe, 1951; Jones, 1952).

The methods in common use for measuring tidal air do not permit direct measurement of changes in bronchial tone in the whole animal. They do not distinguish between bronchoconstriction and a displacement of air due to an increase of the volume of blood in the lungs. Experiments have therefore been performed to show the nature and magnitude of the effects on ventilation of changes in the pulmonary blood volume.

METHODS

Cats were anaesthetized with chloralose (50 or 60 mg./kg.), the chest was opened widely, and their lungs were ventilated with a pump delivering a constant stroke volume. The tidal air was measured by an "overflow" method (Konzett and Rossler, 1940), in which a fixed volume of air entering the trachea was allowed to rise to a predetermined pressure, and the excess of air escaping from the system was measured at atmospheric pressure. The volume measured varies inversely with the tidal air and for qualitative purposes is a sufficient indication of changes in tidal air, but it is not quantitatively accurate, since the air actually enters the lungs at positive pressure. Further errors are introduced by the fact that equilibrium is not reached in the bronchial system during the respiratory cycle. The system was calibrated directly by placing the excised lungs or a rubber bag in a chamber connected to a second float recorder (F_2, Fig. 1). It was found that, for a constant pump stroke and intratracheal pressure, the distribution of air between "lungs" (F_2) and overflow recorder (F_1) (which could be altered by varying the size of the inlet to the lungs or overflow

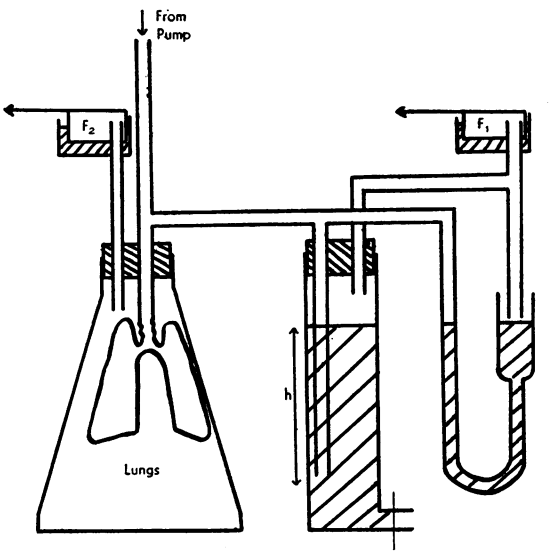

FIG. 1.—Overflow apparatus for measuring tidal air; h represents pressure at which lungs are ventilated.

with screw-clips) showed a linear relation. Hence the true change in lung volume (F_2) at each pump stroke, corresponding to the observed volume (F_1), could be calculated. The relation between F_1 and F_2 was always linear, but the slope varied with the elasticity of the bag, so that a bag had to be chosen which behaved similarly to the lungs *in vivo*; after excision the elasticity of the lungs was found to be greatly changed.

Pulmonary arterial pressure was measured with a condenser manometer using the method described by Dawes, Mott, and Widdicombe (1951). Left atrial

pressure was recorded either with a condenser manometer or with a saline manometer equipped with an overflow device to permit bleeding.

Drugs used were: 2-α-naphthyl ethyl isothiourea; diphenhydramine hydrochloride (Parke Davis); veratrine BPC (B.D.H.); and chlorbismol (May and Baker).

RESULTS

2-α-Naphthyl Ethyl Isothiourea.—The action of 2-α-naphthyl ethyl isothiourea was studied in 57 cats. In addition to the slowing of the heart, fall in blood pressure, and reflex changes in natural breathing already described (Dawes and Fastier, 1950; Dawes, Mott, and Widdicombe, 1951), this compound caused a decrease in tidal air of 3–20 ml. (5–16%) in all healthy animals (Fig. 2). This

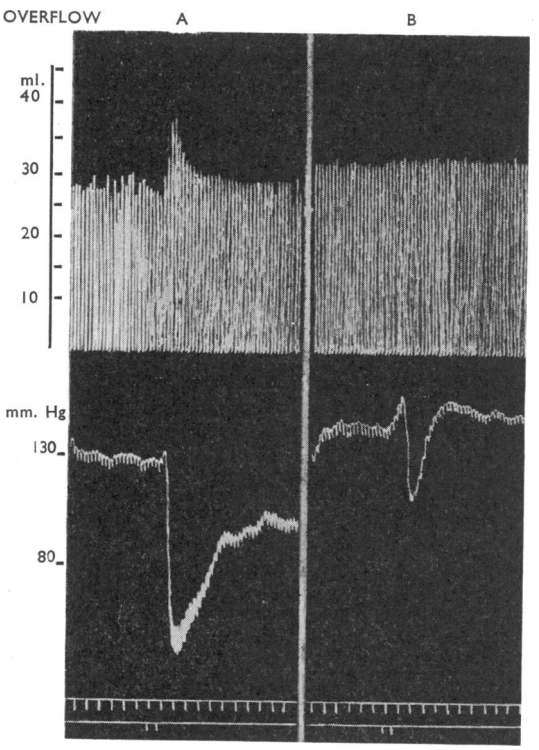

FIG. 2.—Cat, 3.8 kg.; chloralose. Records (above) of overflow from artificial respiration apparatus (inversely related to tidal air), and (below) of blood pressure. Time marks, 10 sec. intervals. A and B, intravenous injection of 50 μg. 2-α-naphthyl ethyl isothiourea. Between A and B cervical vago-sympathetic trunks cut. The tidal air is reduced by the injection when the vagi are intact.

effect was not obtained if there was the slightest respiratory infection (even though the depressor effect was present), and it was subject to rapid tachyphylaxis. The first response was often much larger than those which followed, and there was no correlation between the size of the respiratory response and the depth of the fall of blood pressure. After repeated doses it was usual to find that the reduction in tidal air ceased, while the depressor reflex persisted, although occasionally the opposite was observed. Unlike the effect on blood pressure the magnitude of the tidal air response seemed to bear no relation to the dose given (10–200 μg.). These points support the contention of Dawes and Mott (1950) and Dawes, Mott, and Widdicombe (1951) that the respiratory and depressor reflexes caused by the amidines are distinct. In nine cats in which both vagus and sympathetic were cut in the neck the effect of 2-α-naphthyl ethyl isothiourea on the tidal air was abolished (Fig. 2); in a tenth cat the effect was obtained after vagotomy, but this was abolished when all further nerve fibres running alongside the carotid arteries were cut. In six cats first the vagi and then the sympathetic were cut. In four of these the reduction of tidal air was abolished after vagal section only; in the other two the effect was still present until the sympathetics were also cut. It is therefore possible that there is some crossing of fibres between the main vagus and cervical sympathetic trunks.

In four cats in which 2-α-naphthyl ethyl isothiourea caused a large reduction of tidal air, this was diminished but not abolished by atropine, 2–5 mg. (Table I). In one cat a small response

TABLE I

Experiment No.	Dose of 2-α-Naphthyl Ethyl Isothiourea	Decrease in Tidal Air (ml. at Atmospheric Pressure)
1	50 μg.	12
	50 ,, +compensator	19·5
2	50 ,,	7
	50 ,, +compensator	12
3	50 ,,	7
	50 ,, after atropine	2·5
4	75 ,,	7
	75 ,, after atropine	3
5	25 ,, intravenously	10
	25 ,, to left atrium	1·3
	25 ,, intravenously	10·5
6	30 ml. saline intravenously	11·5

was not reduced, and in two other cats small responses were abolished.

In three cats repeated injections of 2-α-naphthyl ethyl isothiourea into the left atrium had no effect on the tidal air, while injections into the right atrium, intravenously, or into the pulmonary artery were effective (Table I). The receptors for the reflex effect on tidal air are therefore probably in the lungs.

In order to establish the independence of the reduction in tidal air and the fall of blood pressure, a blood pressure stabilizer was inserted into the

abdominal aorta in seven cats. In the presence of a functioning stabilizer there was an even greater reduction of tidal air after the administration of 2-α-naphthyl ethyl isothiourea than in controls (Table I). Two possible explanations suggested themselves. First, the normal decrease in tidal air could be a balance between a reflex decrease in tidal air due to 2-α-naphthyl ethyl isothiourea, and a reflex increase in tidal air consequent on the fall in blood pressure, such as Daly and Schweitzer (1952) have described in the dog. Secondly, when the stabilizer operates, a large volume of fluid (60–70 ml.) flows into the animal to keep the blood pressure constant; this might increase the pulmonary blood volume and displace air from the lungs. We have no evidence for or against the first hypothesis, but in favour of the second we were able to show that when the stabilizer operated there was a very large rise in left atrial pressure. Moreover, large volumes of saline injected intravenously or into the right atrium (20–40 ml.) produced considerable reductions in tidal air (Table I), even after section of the vagus and sympathetic chains in the neck. The question then arose as to whether the action of 2-α-naphthyl ethyl isothiourea on the tidal air was wholly or partly due to an increase in lung blood volume. Evidence for vascular changes in the lungs was therefore sought.

Measurements of left atrial pressure after administration of 2-α-naphthyl ethyl isothiourea were made in 12 cats with a saline, and in three with a condenser manometer. The mean rise in pressure was 3 cm. blood (limits 0–7 cm.). There was a rise in both systolic and diastolic pressures with gross changes in wave form (Fig. 3). In two cats in which a blood pressure stabilizer was operating the rise in pressure after the isothiourea was 9 and 12 cm. In three cats measurement of pulmonary arterial pressure confirmed the observations of Dawes, Mott, and Widdicombe (1951), and showed an increase in the pulse pressure, the systolic pressure rising and the diastolic pressure falling (Fig. 3). These measurements suggest the presence of pulmonary vascular changes, but not necessarily of changes in lung blood volume. If the decrease in tidal air were due solely to accumulation of blood in the lungs it might be possible to eliminate this effect by preventing the rise in left atrial pressure, although it was observed that there was no correlation between the size of the effect on tidal air and the rise of left atrial pressure. In nine cats an overflow device was inserted into the left auricular appendage; the overflow prevented a rise in pressure and the amount bled

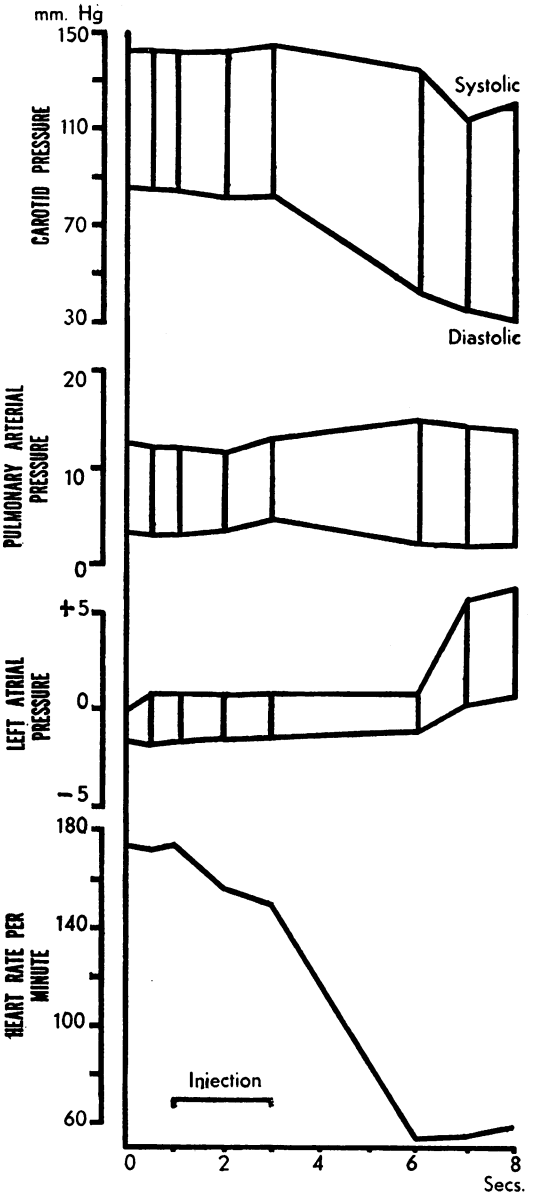

FIG. 3.—Cat, kg.; chloralose. Effect on circulation of injecting 100 μg. 2-α-naphthyl ethyl isothiourea (I.V.). Pressure measurements with condenser manometers.

varied from 4–20 ml. In every experiment a reduction of tidal air was still obtained, and was little if at all diminished, although quantitative comparisons are difficult because of tachyphylaxis. This procedure might not necessarily prevent a blood volume change in the lungs, but it should reduce it.

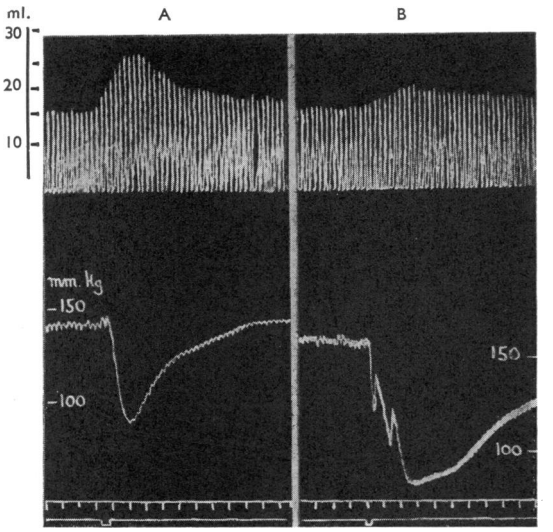

FIG. 4.—Cat, 1.8 kg.; chloralose. Records as in Fig. 2. Intravenous injection of 15 mg. diphenhydramine. Between A and B both cervical vago-sympathetic trunks were cut. The tidal air is somewhat reduced even after cutting the vagi.

Diphenhydramine.—Diphenhydramine (10–20 mg.) also caused a reduction in tidal air (20 cats, Fig. 4), but it was usually larger than that due to 2-α-naphthyl ethyl isothiourea, and could be obtained in unhealthy animals which were not sensitive to the latter compound. The effect was still obtained after section of the vagi and the cervical sympathetic in 11 cats, and there was still a fall of blood pressure. The reduction in tidal air was only obtained on intravenous injection and not after injection into the left atrium, and the left atrial pressure rose after injecting diphenhydramine. Large effects were still obtained after atropine. The latent period was often considerably greater than for the isothiourea. It is interesting that the effect of this compound on tidal air appears to be direct rather than reflex, for in other respects the pulmonary reflexes due to amidines and antihistamines were found to be similar in the cat (Jones, 1952). The effect may, however, be more complicated than at first appears, since after eserine diphenhydramine caused increases in tidal air in some cats, which were abolished by cutting the vagi.

Peptone.—It was decided to see if these reflexes could be excited by a substance known to produce anaphylactic symptoms. Bacteriological peptone in doses of 100–200 mg. produced a very large decrease in tidal air and a fall in blood pressure (five cats), but this was not abolished by section of the vagus and sympathetic (two cats), and no reflex inhibition of natural respiration (one cat) was obtained. The effect is probably a direct bronchoconstriction similar to that caused by histamine.

Embolism.—Emboli were produced by the intravenous injection of either air (5 ml.) or chlorbismol (0.5 ml.). Both produced a considerable decrease in tidal air which was not abolished by section of the vagus and sympathetic. One would suspect that pulmonary congestion due to obstruction by emboli was the cause of the displacement of air, but bronchoconstriction cannot be excluded. Air emboli but not chlorbismol produced a rapid fall in blood pressure.

Veratrine.—The action of veratrine (20–100 μg.) on tidal air was investigated in 17 cats and found to be variable. A considerable decrease in tidal air was found in four cats, a very small decrease in seven cats, and no change in four. In two cats (one had received eserine) the reverse effect, an increase in tidal air, was observed after 100 μg. veratrine (Fig. 5). The vagi and sympathetic were cut in eight cats, with results which depended on the initial response to veratrine. One cat which showed a large decrease in tidal air before vagotomy gave a large response afterwards; a second which had shown moderate decreases gave a very small decrease afterwards; two cats which had given very small decreases before section gave none afterwards (possibly because of tachyphylaxis), while two showed no responses either before or after nerve section. The two cats in which the reverse effect, an increase in tidal air, was obtained showed no response after cutting the vagus and

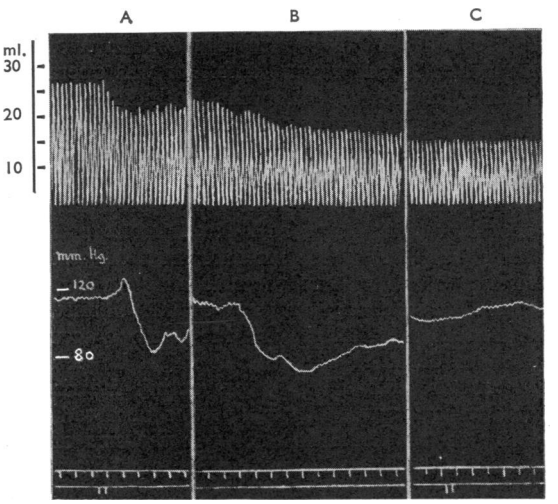

FIG. 5.—Cat, 3.7 kg.; chloralose. Records as in Fig. 2. A and C 100 μg. veratrine intravenously. At B the cervical vago-sympathetic trunks were cut.

sympathetic. Since the results are so variable it is not possible to say with certainty whether veratrine causes these changes in tidal air by reflex or direct action, but they suggest that the decrease in tidal air may be a direct action (confirming Mosey and Kaplan, 1952), while the increase is reflex. The changes in breathing and blood pressure are distinct, since they varied in size independently, and the latter was abolished by section of the vagus and sympathetic.

Discussion

All the pulmonary reflexes studied were shown to be accompanied by a decrease in tidal air, but only after 2-α-naphthyl ethyl isothiourea was the decrease of tidal air itself reflex in nature, and even there the pathway involved appeared complicated. After diphenhydramine and veratrine both decreases and increases in tidal air were recorded and only the latter were possibly reflex.

It has been emphasized that it is difficult to be certain whether the decreases in tidal air are due to bronchoconstriction or pulmonary congestion either with the method we used or with other methods. Theoretically the direct measurement of alveolar pressure is the only sound approach to the problem, but the practical solution of this method presents great difficulties. Vuilleumier (1944) tried to measure alveolar pressure indirectly by measuring pressure in the mouth during a sudden interruption of respiratory movement; the respiratory tract was assumed to reach an equilibrium pressure equal to that in the alveoli. However, the time intervals involved are extremely small, and no true equilibrium is attained, since the lungs continue to move.

For 2-α-naphthyl ethyl isothiourea, the balance of evidence was in favour of bronchoconstriction being responsible for the decrease of tidal air. The size of the response did not seem to be related to the degree of vascular disturbance in the lung, and an effect was still obtained when congestion was minimized by bleeding from the left atrium. In the presence of a blood pressure stabilizer the isothiourea caused a still larger decrease of tidal air on the other hand, and infusion of fluid into the lesser circulation produced definite decreases in tidal air. The effects of infusion were, however, never very large, and this procedure was not physiological, since large volumes of blood or saline (20–40 ml.) were rapidly injected intravenously or into the right side of the heart. It is hard to believe that such large blood volume changes could occur in the lung in the short interval before the tidal air decreases.

The reduction in tidal air after diphenhydramine must be due either to direct action on the bronchial muscles or to an increase in pulmonary blood volume. One point in favour of the latter was that repeated responses to diphenhydramine were obtained in an animal which failed to show a bronchoconstrictor response to histamine acid phosphate (200 μg.).

Attention has been drawn by many workers to the effect of pulmonary congestion on ventilation (Drinker, Peabody, and Blumgart, 1922; Christie and Hayward, 1943), and this has been suggested as the cause of the dyspnoea and decreased vital capacity of heart disease. Compression of the pulmonary veins caused a twofold increase of the lung blood volume in heart-lung preparations in cats (Drinker, Churchill, and Ferry, 1926), while the right pulmonary artery was able to accommodate a normal blood flow for the whole lung when the left was occluded.

It is clear, therefore, that the lungs can accommodate a large volume of blood. From the practical point of view the effect on the subject of bronchoconstriction or pulmonary congestion could be very similar. One observation was made during the present work which may be worth mentioning here. Adrenaline sometimes caused a decrease and sometimes an increase in tidal air. Both effects were present after cutting the vagi, and the decrease was sometimes abolished by preventing the blood pressure rise with a stabilizer. The decrease may therefore be due to accumulation of blood in the lungs, since when a stabilizer is in operation a considerable volume of blood flows out into it. This decrease in tidal air was often quite large, and it either completely masked the direct bronchodilator action of adrenaline or was followed by a brief dilatation.

Summary

1. The action of 2-α-naphthyl ethyl isothiourea, diphenhydramine, veratrine, peptone, and embolism on the tidal air was studied.

2. All these agents decreased the tidal air under certain circumstances. Only the decrease caused by 2-α-naphthyl ethyl isothiourea was abolished by cutting the vagi.

Diphenhydramine and veratrine occasionally caused increases in tidal air, an effect which was probably reflex.

3. Measures which increased the volume of blood entering the lungs decreased the tidal air, both before and after cutting the vagi. It was not always possible to decide whether a decrease in tidal air

was due to an alteration in bronchial tone or to an increase in pulmonary blood volume.

We wish to record our gratitude to Dr. G. S. Dawes for his help and advice in this work, and to Dr. W. F. Short for the 2-α-naphthyl ethyl isothiourea hydrochloride.

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