J. Physiol. (1969), **201**, *pp.* 259–270
With 1 *text-figure*
Printed in Great Britain

THE EFFECT OF VAGOTOMY, VAGAL COOLING AND EFFERENT VAGAL STIMULATION ON BREATHING AND LUNG MECHANICS OF RABBITS

BY W. KARCZEWSKI* AND J. G. WIDDICOMBE
From the University Laboratory of Physiology, Oxford

(*Received* 11 *March* 1968)

SUMMARY

1. The effects of bilateral cervical vagotomy, of bilateral vagal cooling and of efferent vagal stimulation were studied on rabbits anaesthetized with pentobarbitone sodium. Total lung conductance, lung compliance, breathing frequency, tidal volume, end-tidal CO_2%, systemic arterial and right atrial blood pressures and heart rate were measured. Some of the rabbits were first paralysed and artificially ventilated.

2. The changes in lung conductance were consistent with the presence of a tonic efferent vagal discharge in bronchoconstrictor fibres, reflexly damped down by a tonic afferent vagal discharge dilator to the airways, probably the Hering–Breuer inflation reflex.

3. Neither vagotomy nor efferent vagal stimulation significantly influenced lung compliance, right atrial pressure or end-tidal CO_2%; vagal cooling lowered end-tidal CO_2% in spontaneously breathing rabbits, but did not affect the other variables.

4. Efferent vagal stimulation in the rabbit decreased lung conductance with no significant change in lung compliance.

5. In the rabbit, vagal efferent activity affects primarily the larger (resistance) air passages with little action on the distal (compliance-influencing) airways.

INTRODUCTION

Although the influence of the vagus nerves on the mechanical properties of the lungs has been studied previously, only in recent years have methods for measuring simultaneously resistance to air flow and dynamic lung compliance developed sufficiently to allow valid quantitative conclusions to be drawn. These recent results on the effects of vagotomy and of

* Present address: Polish Academy of Sciences, Institute of Experimental Pathology, Dworkowa 3, Warsaw, Poland.

efferent vagal stimulation show some similarities and some clear differences between cats (Olsen, Colebatch, Mebel, Nadel & Staub, 1965), dogs (Lim, Luft & Grodins, 1958; Nadel & Widdicombe, 1962; Olsen *et al.* 1965; Green & Widdicombe, 1966) and sheep (Colebatch & Halmagyi, 1963). In recent studies on the role of the vagus nerves in drug induced bronchoconstrictions and anaphylaxis in anaesthetized rabbits (Karczewski & Widdicombe, 1969*a*, *b*) we first determined (as control observations) the effect of vagotomy and efferent vagal stimulation on lung mechanics, breathing and some circulatory variables. These results are presented here.

METHODS

Thirteen rabbits, range of body weight 1·5–3·0 kg, were anaesthetized with pentobarbitone sodium (Nembutal, 30–40 mg/kg, intravenously). Tracheal cannulae were inserted and also femoral venous catheters for injections of drugs. The rabbits were supine. Blood pressure was recorded from the left femoral artery through a polyethylene catheter by a capacitance manometer (Southern Instruments). The undamped natural frequency of the manometer and catheter system was in the range 20–28 c/s, assessed by the method of Hansen (1949). Right atrial pressure was measured through a polyethylene catheter inserted through the right external jugular vein until pressure records typical of the right atrium were obtained. A capacitance manometer (Southern Instruments) was used; the undamped natural frequency of manometer and catheter system was in the range 15–27 c/s assessed by the method of Hansen (1949). Transpulmonary pressure was measured from an air filled soft-rubber catheter tied into the lower right anterior intrapleural space, and from a wide bore needle inserted through the rubber tube connexion to the tracheal cannula, using a differential capacitance manometer (Southern Instruments), range ± 50 cm H_2O. Tidal volume was measured by a Fleisch pneumotachograph 'head', linear range 0–110 ml./sec, connected to an inductance differential pressure recorder and integrator (Godart).

End-tidal CO_2% was measured with an infra-red absorption meter (Beckman-Spinco LB1), with a micro-sampling analysis cell connected distally to the pneumotachograph 'head' and sampling gas at 300 ml./min. End-tidal CO_2%'s were determined only when the record showed satisfactory 'plateaux' (Fig. 1); this applied except in occasional experiments when the rabbits breathed very rapidly and shallowly.

Records of systemic arterial blood pressure, right atrial blood pressure, tidal volume, transpulmonary pressure and tidal CO_2% were displayed on an oscilloscope (Tektronix 551) and photographed on 7 cm paper (with a modified Cossor camera). The photographic record was analysed after enlargement 3–4 times by a projector (designed and built by Dr E. H. J. Schuster).

'Mean systemic arterial blood pressure' was determined as diastolic pressure plus one-third of the pulse pressure. 'Mean right atrial pressure' was determined as the average of end-expiratory right atrial pressure minus simultaneous intrapleural pressure and peak inspiratory (zero air flow) right atrial pressure minus simultaneous intra-pleural pressure. At these two times of zero air flow it was assumed that transpulmonary pressure equalled intrapleural pressure in spontaneously breathing rabbits.

Lung compliance was assessed as the ratio of tidal volume to transpulmonary pressure difference at points of zero air flow, the end of expiration and the peak of inspiration. This is 'dynamic compliance' as usually measured and as defined by Mead (1961).

Lung conductance was measured by the 'subtractor' method of Mead & Whittenberger (1953), somewhat modified (Nadel & Widdicombe, 1962; Green & Widdicombe, 1966). This

involves displaying the component of transpulmonary pressure required to overcome resistance to flow and tracheal air flow on the two axes of an oscilloscope, to give 'loops', the slopes of which are proportional to total lung resistance, or its reciprocal, conductance.

The 'subtractor' method can be applied whenever there is a measurable and changing transpulmonary pressure from which pressures to overcome lung elasticity and total lung resistance to air flow can be computed. (In the experiments on paralysed rabbits the rapid expiratory air flow, due to passive collapse of the lung and chest wall, created the transpulmonary pressure as it passed through the resistance of the connecting tubes and expiratory valve of the pump.) The pressure required to overcome the elastic 'resistance' of the lungs is assumed to have a linear relation to lung volume, and a voltage proportional to lung volume is subtracted from the total transpulmonary pressure signal. If the correct proportion is chosen, the result of the subtraction is a voltage equivalent to the pressure producing flow, the relation of which to flow (the slope of the 'loops') gives total lung resistance and its reciprocal, conductance. It is concluded that the correct proportion of the electrical volume signal has been subtracted when the 'loops' approximate to straight lines, since subtraction of the wrong proportion opens out the loops, as may also alinearity of the lung volume/pressure (compliance) relation. The method was tested by measuring the added increment of resistance when a 'laminar' resistance of 1·2 cm H_2O/100 ml./sec was added to the tracheal airway; for fifteen measurements the mean and standard deviation were $1{\cdot}12 \pm 0{\cdot}41$ cm H_2O/100 ml./sec.

Transpulmonary pressure was displayed on the horizontal axis of an oscilloscope (Tektronix 502, dual beam) with time base switched off and one previously vertical amplifier connected to the horizontal deflexion plates, whilst air flow was displayed on the vertical axis. The volume signal was passed through a potentiometer to earth and the variable centre tap of the potentiometer was connected to the horizontal axis so as to be subtracted from the pressure signal. The effect of this was to subtract from the pressure signal a voltage proportional to lung volume. The potentiometer was adjusted until the 'loops' were as near straight lines as possible and the angles of the loops were measured from a protractor mounted on the front of the oscilloscope tube, and sometimes also photographed for subsequent analysis.

The vagi were cooled by placing them in grooves on brass thermodes, 5 mm long, through which saline from an ice–salt–water mixture flowed by gravity. The temperature of each thermode was measured by a thermocouple close to the nerve and recorded on a galvanometer, and the temperature was controlled by varying the rate of flow of the saline. No physiological variables were determined until both thermodes had been equal and constant in temperature (to 0·5° C) for at least 2 min. For each rabbit a temperature was chosen, in the range 8–10° C, at which the Hering–Breuer inflation reflex was just completely abolished; the reflex was assessed by observing the breathing response to gentle inflations of the rabbit's lungs (to 2–3 times the spontaneous tidal volume) and by occluding the tracheal cannula at the peak of inspiration. If breathing was inhibited or slowed this was taken as evidence that the afferent pathway for the inflation reflex was conducting a significant number of impulses. Abolition of the inflation reflex was not assumed to mean that other afferent pathways were unaffected. However, with these criteria, it is known that vagal afferent pathways other than that for the Hering–Breuer inflation reflex can still be effective (Dawes, Mott & Widdicombe, 1951; Troelstra, 1960; Widdicombe, 1967; Karczewski & Widdicombe, 1969*a*, *b*), and that vagal efferent bronchoconstrictor (Widdicombe & Nadel, 1963; De Kock, Nadel, Zwi, Colebatch & Olsen, 1966) and cardio-inhibitor (Dawes *et al.* 1951) fibres can still conduct impulses.

Vagotomy was performed in the mid-cervical region, and was always bilateral, as was the vagal cooling. The aortic nerves were not cut.

The efferent end of a cut cervical vagus was stimulated by placing it on a pair of platinum electrode wires, through which rectangular wave shocks of 0·5 msec duration at a frequency

of 20/sec were passed. The stimulus strength was adjusted to give just maximal responses of lung conductance, assessed immediately by the change in slope of the 'loops'. Higher stimulus frequencies caused larger changes in lung conductance, but also greater changes in blood pressure and heart rate than those shown in Table 2.

Anaesthetized rabbits were paralysed by intravenous injection of 5 mg succinylcholine or of 10 mg gallamine, the injections being repeated if the animals made respiratory movements. The pump frequency was 20–30 inflations/min, and the tidal volume was adjusted to maintain the end-tidal CO_2 % close to that during spontaneous breathing before paralysis (usually 3–4 %).

Results are expressed as mean values determined from ten to twenty measurements of each variable when the condition of the animal, assessed in particular by lung conductance and end-tidal CO_2 %, was stable. With vagal cooling, values were taken at least 2 min after the appropriate thermode temperatures were constant; after vagotomy 5–10 min were allowed to elapse; with vagal stimulation the interval was 1–2 min from the start of stimulation.

RESULTS

Tables 1 and 2 summarize the results, and Fig. 1 gives representative experimental records. In the tables results are given as percentage as well as absolute changes, since some variables (lung conductance, lung compliance and tidal volume) will depend on the size of the rabbit. However, the percentage values for right atrial pressure changes have little significance since the control values were near zero.

DISCUSSION

In spontaneously breathing rabbits vagotomy and vagal cooling cause changes in the pattern of breathing, and therefore in lung afferent activity and blood gas tensions, which will have secondary actions on the variables measured, by mechanical, nervous and chemical mechanisms. In paralysed rabbits these secondary effects are abolished or minimized.

Vagotomy and vagal cooling may change the variables being measured by interruption of afferent pathways other than those from the lung. These do not include the aortic nerve, which was left intact.

Lung conductance

Paralysed rabbits (Table 1). The small average increase in conductance (8 %) after vagotomy is probably due to the abolition of vagal bronchoconstrictor tone; with paralysed artificially ventilated dogs increases in conductance on bilateral vagotomy of 29 % (Nadel & Widdicombe, 1962) and 12 % (Green & Widdicombe, 1966) have been reported.

When the vagi were cooled to 8–10° C to block the Hering–Breuer inflation reflex but to leave at least some conduction in efferent vagal bronchoconstrictor fibres intact (Widdicombe & Nadel, 1963; De Kock *et al.* 1966), lung conductance showed a significant decrease (−28 %). A

TABLE 1. Effect of bilateral cervical vagotomy and vagal cooling on some respiratory and circulatory variables. Values are means (±S.E.) and are expressed as absolute values for controls and as absolute (abs) and % values for changes during cooling and after vagotomy. Statistical values apply to the significance of the mean change. ** $P < 0.01$, * $P < 0.05$

		Paralysed rabbits				Breathing rabbits			
				Change				Change	
Variable	Vagi	No.	Control (abs)	(abs)	(%)	No.	Control abs	(abs)	(%)
Lung conductance (ml./min/cm H_2O)	Cut	6	2·2±0·58	+0·2±0·06*	+8±2·5*	9	2·5±0·38	−0·7±0·20**	−26±6·1**
	Cooled	6	2·4±0·92	−0·6±0·20*	−28±5·1**	7	3·2±0·69	+0·3±0·20	+13±10·6
Lung compliance (ml./cm H_2O)	Cut	6	2·8±0·43	−0·1±0·12	−3±7·5	9	5·5±0·72	−0·4±0·29	−3±7·3
	Cooled	6	2·1±0·75	−0·1±0·07	−3±2·9	7	5·4±1·04	+0·3±0·61	+5±15·5
Resp. frequency (per min)	Cut	—	—	—	—	9	64±8·8	−34±5·4**	−52±8·2**
	Cooled	—	—	—	—	7	80±9·2	−23±4·6**	−34±7·2**
Tidal volume (ml.)	Cut	—	—	—	—	9	24±3·7	+19±2·3**	+81±7·4**
	Cooled	—	—	—	—	7	16±1·4	+5±1·3**	+30±7·7**
End-tidal CO_2 (%)	Cut	6	3·3±0·64	+0·3±0·27	+5±4·7	9	3·4±0·35	+0·2±0·14	+5±4·0
	Cooled	6	3·2±0·41	−0·2±0·12	−6±3·1	7	3·4±0·25	−0·2±0·06*	−6±2·2*
Arterial B.P. (mm Hg)	Cut	6	62±14·0	+24±9·5	+38±7·5**	8	75±7·1	+16±3·9**	+21±4·7**
	Cooled	6	77±6·8	+16±9·0	+22±10·6	7	91±5·7	+7±5·2	+9±4·1
Right atrial B.P. (mm Hg)	Cut	5	3·3±1·8	+0·4±1·0	+9±12·7	5	2·8±0·44	−0·3±1·75	−7±5·9
	Cooled	4	2·7±1·5	+0·6±1·0	+18±22·3	6	0·9±0·71	+1·5±1·72	+142±158
Heart rate (per min)	Cut	6	248±38·5	+4±12·2	+2±8·1	9	275±12·4	−4±2·3	−2±1·5
	Cooled	6	271±19·0	+7±8·5	+2±2·8	7	273±21·6	+3±3·7	+2±7·5

similar decrease in conductance on vagal cooling to 8–10° C has been seen in paralysed cats (Widdicombe & Nadel, 1963). It may be due to block of conduction in the afferent pulmonary stretch fibre pathway, which has a tonic dilator influence on the bronchial tree (Loofbourrow, Wood & Baird, 1957; Widdicombe & Nadel, 1963). That vagal efferent bronchoconstrictor tone is normally held in check by vagal afferent dilator discharge is supported by the fact that vagotomy greatly increases the activity in efferent vagal respiratory fibres in rabbits (Karczewski, 1965) cats and dogs (Widdicombe, 1966).

TABLE 2. Effect of stimulation of the distal cut end of a cervical vagus nerve on some respiratory and circulatory variables. Values are means (± S.E.) and are expressed as absolute values (abs) for controls and as absolute and % values for changes during vagal stimulation. Statistical values apply to the significance of the mean change: ** $P < 0.01$; * $P < 0.05$. All the rabbits were spontaneously breathing and bilaterally vagotomized

Variable	No.	Control (abs)	Change (abs)	Change (%)
Lung conductance (ml./min/cm H_2O)	7	2·5 ± 0·42	−0·9 ± 0·30*	−30 ± 5·8**
Lung compliance (ml./cm H_2O)	7	4·6 ± 0·48	−0·1 ± 0·15	−3 ± 3·4
Frequency of breathing (per min)	7	42 ± 5·7	+1·2 ± 0·85	+4 ± 4·1
Tidal volume (ml.)	7	45 ± 5·4	−1·5 ± 1·42	−3 ± 3·2
End-tidal CO_2 (%)	7	2·5 ± 0·27	−0·1 ± 0·07	−4 ± 2·8
Systemic arterial B.P. (mm Hg)	6	92 ± 6·8	−15 ± 6·3	−17 ± 6·5*
Right atrial B.P. (mm Hg)	6	2·2 ± 0·82	+0·5 ± 0·53	+22 ± 29·3
Heart rate (per min)	7	256 ± 12·2	−113 ± 11·5**	−52 ± 6·1**

Spontaneously breathing rabbits (Table 1). Lung conductance was decreased (−26%) by vagotomy in spontaneously breathing rabbits, presumably due to the change in the pattern of breathing since the decrease in conductance was not present in paralysed rabbits. Colebatch & Halmagyi (1963) found a decrease in average lung conductance in spontaneously breathing anaesthetized sheep on vagotomy and concluded that it was due to the more rapid air flows that occur with the deep expirations after vagotomy, with a passive collapse of the peripheral airways in expiration; they found that vagotomy decreased lung conductance in expiration by 34%, and increased that in inspiration by 28%, using the 'interruptor' method, with a mean decrease of 13% for both phases of respiration. In our experiments vagotomy often made the subtractor 'loops' rather alinear, with inspiratory and expiratory limbs at an angle. Since we took the average slope, and the expiratory limb was always longer since expiratory air flow was faster than inspiratory, our measurements in spontaneously breathing rabbits may be weighted in favour of

the expiratory decrease in conductance. With spontaneously breathing anaesthetized dogs, Lim *et al.* (1958) found no significant change in lung conductance on vagotomy, but their methods do not allow quantitative comparison with our results.

Vagal cooling to 8–10° C caused a variable change, on average an increase in lung conductance, in spontaneously breathing rabbits, but the changes in frequency of breathing and particularly tidal volume were

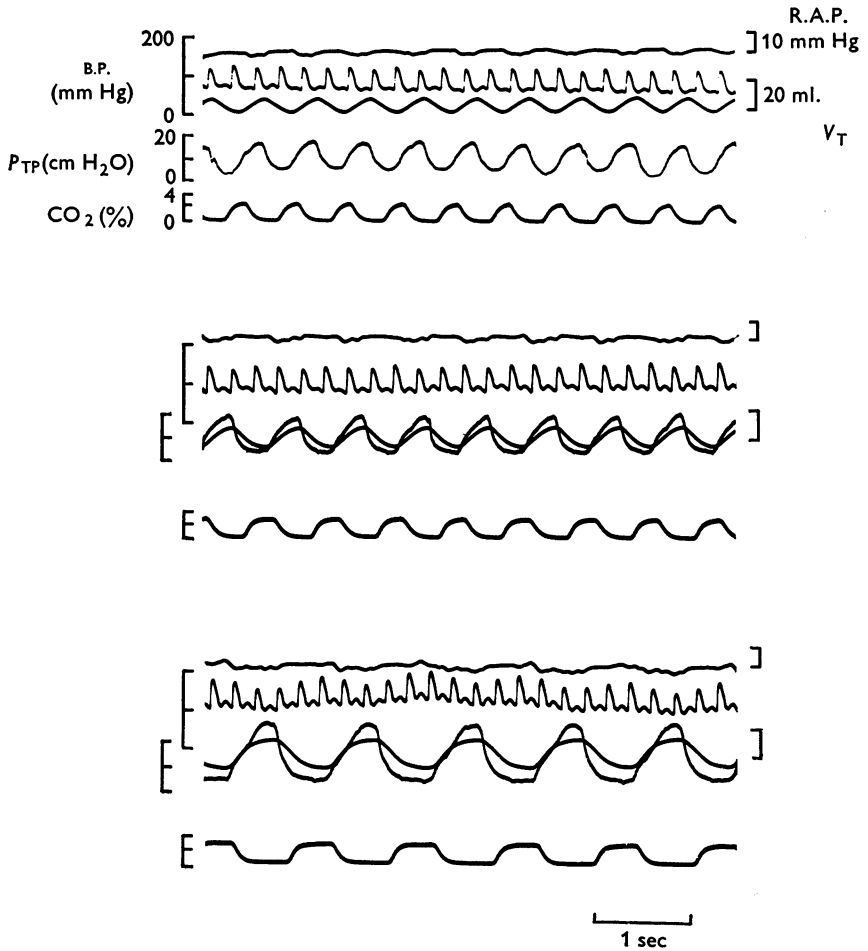

Fig. 1. Effect of bilateral vagotomy and bilateral vagal cooling to 8–10° C on, from above downwards, right atrial pressure (R.A.P.), systemic arterial pressure (B.P.), tidal volume (V_T), transpulmonary pressure (P_{TP}), and tidal CO_2% (alinear calibration scale). Uppermost record, control; middle record, vagi cooled to 8–10° C; lowest record, vagi cut. There was a shift in the level of the right atrial pressure and transpulmonary pressure records between the uppermost and middle records. Rabbit, 2·7 kg.

smaller than for vagotomy, so the passive mechanical decrease in expiratory conductance postulated above would be smaller. The new pattern of breathing would impose damages in the activity in vagal afferent pathways not blocked by cooling to 8–10° C which might exert a secondary reflex effect on lung conductance. Any hyperventilation (see below) would exert a nervously mediated dilator influence by blood gas changes (Loofborrow *et al.* 1957; Nadel & Widdicombe, 1962) acting via vagal efferent fibres not blocked at this temperature.

Stimulation of the cut (efferent) end of a cervical vagus nerve decreased lung conductance (−30 %; Table 2). Since the pattern of ventilation did not change significantly and both vagi were cut, so that vagal reflex changes in bronchomuscular tone were impossible, this effect must be due to a nervously induced bronchoconstriction. If both vagi had been stimulated, and the lungs are regarded as two initially equal resistances in parallel with unilateral efferent nerve supplies, the total decrease in conductance would have been about 60 %. Similar decreases in conductance on bilateral vagal efferent stimulation have been reported for sheep (44 %: Colebatch & Halmagyi, 1963), cats (89 %: Olsen *et al.* 1965) and dogs (83–89 %: Olsen *et al.* 1965; 36 %: Green & Widdicombe, 1966).

Lung compliance

Vagotomy, vagal cooling and efferent vagal stimulation had only small and insignificant effects on lung compliance in rabbits, whether they were spontaneously breathing or paralysed (Tables 1 and 2).

Bilateral vagotomy has no significant effect on lung compliance of cats (Olsen *et al.* 1965), sheep (Colebatch & Halmagyi, 1963) and dogs (Lim *et al.* 1958; Olsen *et al.* 1965; Green & Widdicombe, 1966), whether spontaneously breathing or paralysed.

With vagal stimulation, small or negative results have been obtained for dogs by Olsen *et al.* (1965); the rather large decrease in compliance (13 %) reported by Green & Widdicombe (1966) for the dog with both vagi stimulated may have been because the animals were open-chest and artificially ventilated with collapse of the lungs in deflation. There are discrepant results for the cat, since Olsen *et al.* (1965) found small changes in lung compliance on vagal stimulation whereas Schwieler (1966) reported a 30 % reduction in compliance on bilateral vagal stimulation. In the sheep, bilateral efferent vagal stimulation decreased compliance considerably (36 %) even although the lungs were forcibly inflated to prevent this (Colebatch & Halmagyi, 1963).

Our results with the rabbit therefore support the view of Olsen *et al.* (1965) that vagal constrictor fibres to the lungs act chiefly on the larger, conducting airways, and change lung conductance rather than compliance.

Pattern of breathing and end-tidal CO_2 %

Vagotomy caused the characteristic slower and deeper breathing (Table 1) associated with loss of the Hering–Breuer inflation reflex (see review by Widdicombe, 1964). However, cooling the vagus nerves to 8–10° C, at which temperature the inhibitory responses of breathing to lung inflation and to occlusion of the trachea at the peak of inspiration were completely abolished, did not cause such large changes in frequency or tidal volume (Table 1). Vagal cooling, compared with vagotomy, had a relatively larger effect on the frequency of breathing compared with tidal volume (Table 1); this is consistent with evidence that vagal afferent pathways blocked at 8–10° C exert a powerful effect on frequency of breathing, while those unimpeded at 8–10° C act more strongly on depth rather than the rate of breathing (Richardson, P. S. & Widdicombe, J. G., unpublished; Karczewski & Widdicombe, 1969*a*, *b*).

When breathing was assessed as minute volume, vagotomy caused a change from a mean of 1530 to 1280 ml./min (−16%), whereas vagal cooling changed minute volume from a mean of 1280 to 1180 ml./min (− 8%).

End-tidal CO_2 % did not change significantly after vagotomy (Table 1), which indicates that the conspicuous changes in the pattern of breathing are not accompanied by great or consistent changes in alveolar ventilation. A similar conclusion has been reached for vagotomy both in anaesthetized and unanaesthetized rabbits (Wiemer & Kiwull, 1965; Richardson & Widdicombe, 1965). However, vagal cooling to 8–10° C caused a small but significant decrease in end-tidal CO_2 % (Table 1): possibly the Hering–Breuer inflation reflex has a slight tonic depressant action on breathing in the anaesthetized rabbit, and its abolition by vagal cooling leads to alveolar hyperventilation and a decrease in end-tidal CO_2 %.

The effect of cold partial block of the vagus nerves may depend on the frequency of impulses (Paintal, 1966) so that high frequency vagal nervous discharges are more effectively blocked than low frequency discharges. However, at this thermode temperature (8–10° C) for the rabbit's vagus *all* conduction in slowly adapting low threshold pulmonary stretch fibres, mediating the Hering–Breuer inflation reflex, is blocked (Widdicombe, 1967). It is known that, with vagi at this temperature, vagal afferent pathways for reflexes other than the Hering–Breuer inflation reflex can still conduct impulses (Dawes *et al.* 1951; Troelstra, 1960; Karczewski & Widdicombe, 1969*a*, *b*). The results showing the effect of vagotomy and vagal cooling on breathing frequency and tidal volume (Table 1) indicate that some of these pathways may be augmenting breathing, a conclusion also reached for the rabbit by Troelstra (1960); these intact reflexes

include the Hering–Breuer deflation reflex (Troelstra, 1960), Head's paradoxical reflex (Widdicombe, 1967), and the pulmonary respiratory chemoreflex (Dawes & Comroe, 1954) which is activated by intravenous injections of phenyl diguanide into the rabbit (Dawes *et al.* 1951).

Stimulation of the efferent end of a cut vagus nerve did not significantly change the frequency or depth of breathing or end-tidal CO_2 % (Table 2), possibly because the cardiovascular changes were not excessive.

Cardiovascular variables

Vagotomy increased mean systemic arterial blood pressure, presumably mainly by interrupting afferent pathways (since heart rate did not change), and vagal cooling to 8–10° C had a smaller, statistically insignificant effect. As anticipated, blood pressure was decreased by efferent vagal stimulation, together with a considerable bradycardia. Vagotomy and vagal cooling had no significant effect on heart rate, suggesting an absence of vagal cardio-inhibitory tone in these anaesthetized rabbits. Right atrial pressure was not greatly or consistently changed by vagotomy, vagal cooling or efferent vagal stimulation, in spite of the cardio-inhibition by the latter. Colebatch & Halmagyi (1963) had a similar negative result for right atrial pressure on bilateral vagal stimulation in the sheep.

General conclusions

It is concluded that, in the anaesthetized rabbit, there is an afferent vagal tonic discharge which is blocked by cooling the vagi to 8–10° C. This discharge has a reflex dilator action on the airways, its abolition is responsible for the changes in breathing on vagal cooling and, since end-tidal CO_2 % decreased during vagal cooling, it exerts a weak inhibitory action on alveolar ventilation. The changes are consistent with the pulmonary stretch fibres for the Hering–Breuer reflex being chiefly responsible.

Vagotomy has effects further than those of vagal cooling. Minute volume is much more reduced and the fall in end-tidal CO_2 % is absent, results which are consistent with abolition of an afferent drive augmenting breathing and mediated by vagal fibres blocked only by cooling below 8–10° C. The small increase in lung conductance on vagotomy in paralysed rabbits could be due to the abolition of a vagal efferent bronchoconstrictor tonic discharge.

The changes in conductance in spontaneously breathing animals on vagotomy and vagal cooling are clearly due to the interaction of several effects. The change in pattern of breathing will not only exert passive mechanical effects on the airways, but may cause changes in blood gas tensions; hyperoxia and hypocapnia (Nadel & Widdicombe, 1962) cause nervously mediated bronchodilatations.

The lack of significant changes in lung compliance on vagotomy, vagal cooling and efferent vagal stimulation indicates that the distal airway smooth muscle is not under appreciable vagal nervous control. Similar negative findings with right atrial pressure are more difficult to interpret in terms of nervous control of the pulmonary vascular bed, in the absence of measurements of pulmonary blood flow.

The results also support the belief that findings obtained by methods which primarily measure lung compliance ('indirect methods') can only be equivocally interpreted in terms of airway conductance or calibre or in terms of bronchoconstriction (Widdicombe, 1963), since the latter variables can be influenced by vagal nervous discharge or by the pattern of breathing with little alteration of lung compliance (see also Karczewski & Widdicombe, 1969*a*, *b*). Such 'compliance' methods include that of Konzett & Rössler (1940) and measurements of dynamic compliance of the lungs, frequently used in pharmacological studies.

We are grateful to the Royal Society and the Medical Research Council for purchases of apparatus; to the Smith Kline & French Foundation and the Wanda Roehr Foundation for personal grants to W.K.; and to Mr C. Gant for technical assistance.

REFERENCES

COLEBATCH, H. J. & HALMAGYI, D. F. J. (1963). Effect of vagotomy and vagal stimulation on lung mechanics and circulation. *J. appl. Physiol.* **18**, 881–887.

DAWES, G. S. & COMROE, J. H. (1954). Chemoreflexes from the heart and lungs. *Physiol. Rev.* **34**, 167–201.

DAWES, G. S., MOTT, J. C. & WIDDICOMBE, J. G. (1951). Respiratory and cardiovascular reflexes from the heart and lungs. *J. Physiol.* **115**, 258–291.

DE KOCK, M. A., NADEL, J. A., ZWI, S., COLEBATCH, H. J. H. & OLSEN, C. R. (1966). New method for perfusing bronchial arteries: histamine bronchoconstriction and apnea. *J. appl. Physiol.* **21**, 185–194.

GREEN, M. & WIDDICOMBE, J. G. (1966). The effects of ventilation of dogs with different gas mixtures on airway calibre and lung mechanics. *J. Physiol.* **186**, 363–381.

HANSEN, A. T. (1949). Pressure measurement in the human organism. *Acta physiol. scand.* **19**, suppl. 68, 1–230.

KARCZEWSKI, W. (1965). Vagal control of breathing. (In Polish.) *Postępy Hig. Med. doświad.* **19**, 507–569.

KARCZEWSKI, W. & WIDDICOMBE, J. G. (1969*a*). The role of the vagus nerves in the respiratory and circulatory responses to intravenous histamine and phenyl diguanide in rabbits. *J. Physiol.* **201**, 271–291.

KARCZEWSKI, W. & WIDDICOMBE, J. G. (1969*b*). The role of the vagus nerves in the respiratory and circulatory reactions to anaphylaxis in rabbits. *J. Physiol.* **201**, 293–304.

KONZETT, H. & RÖSSLER, R. (1940). Versuchsanordnung zu Untersuchungen an der Bronchialmuskulatur. *Arch. exp. Path. Pharmak.* **195**, 71–74.

LIM, T. P. K., LUFT, U. C. & GRODINS, F. S. (1958). Effects of cervical vagotomy on pulmonary ventilation and mechanics. *J. appl. Physiol.* **13**, 317–324.

LOOFBOURROW, G. N., WOOD, W. B. & BAIRD, I. L. (1957). Tracheal constriction in the dog. *Am. J. Physiol.* **191**, 411–415.

MEAD, J. (1961). Mechanical properties of the lungs. *Physiol. Rev.* **41**, 281–330.

MEAD, J. & WHITTENBERGER, J. L. (1953). Physical properties of human lungs measured during spontaneous respiration. *J. appl. Physiol.* **5**, 779–796.

NADEL, J. A. & WIDDICOMBE, J. G. (1962). Effect of changes in blood gas tensions and carotid sinus pressure on tracheal volume and total lung resistance to airflow. *J. Physiol.* **163**, 13–33.

OLSEN, C. R., COLEBATCH, H. J. H., MEBEL, P. E., NADEL, J. A. & STAUB, N. C. (1965). Motor control of pulmonary airways studied by nerve stimulation. *J. appl. Physiol.* **20**, 202–208.

PAINTAL, A. S. (1966). Re-evaluation of respiratory reflexes. *Q. Jl exp. Physiol.* **51**, 151–163.

RICHARDSON, P. S. & WIDDICOMBE, J. G. (1965). Ventilatory responses to carbon dioxide in rabbits before and after cervical vagotomy. *J. Physiol.* **181**, 43–45*P*.

SCHWIELER, G. H. (1966). The effect of vagal stimulation on the bronchial tree in the cat. *Acta physiol. scand.* **66**, 495–500.

TROELSTRA, H. J. (1960). De invloed van afferente vagusimpulsen op ademniveau en-frequentie. Univ. of Groeningen Thesis. Groeningen: Hoitsema.

WIDDICOMBE, J. G. (1963). The regulation of tracheobronchial smooth muscle. *Physiol. Rev.* **43**, 1–33.

WIDDICOMBE, J. G. (1964). Respiratory reflexes. In *Handbook of Physiology*, section **3**, vol. I, pp. 583–630. Washington: American Physiological Society.

WIDDICOMBE, J. G. (1966). Action potentials in parasympathetic and sympathetic efferent fibres to the trachea and lungs of dogs and cats. *J. Physiol.* **186**, 56–88.

WIDDICOMBE, J. G. (1967). Head's paradoxical reflex. *Q. Jl exp. Physiol.* **52**, 44–50.

WIDDICOMBE, J. G. & NADEL, J. A. (1963). Reflex effects of lung inflation on tracheal volume. *J. appl. Physiol.* **18**, 681–686.

WIEMER, W. & KIWULL, P. (1965). Die Bedeutung der Nn. Vagi für die chemische Atmungs-steuerung des Kaninchens. *Pflügers Arch. ges. Physiol.* **283**, 8, *R*46.