THE REFLEX EFFECTS OF INTRALARYNGEAL CARBON DIOXIDE ON THE PATTERN OF BREATHING

By H. A. BOUSHEY* AND P. S. RICHARDSON

From the University Laboratory of Physiology, Parks Road, Oxford OX1 3PT

SUMMARY

1. The reflex effects on the pattern of breathing and total lung resistance of introducing 30, 10 and 5 % CO_2 in air into the larynx have been studied in anaesthetized and decerebrate cats breathing through a tracheostomy tube.

2. Flowing 30 % CO_2 into the larynx caused a two-phased response. First, respiratory frequency and tidal volume decreased, with a consequent fall in minute ventilation. After two to ten breaths, frequency remained slow, but tidal volume increased beyond the control level, so that minute ventilation was restored to control levels.

3. Flowing 5 or 10 % CO_2 into the larynx caused slowing of breathing with small and inconsistent changes in tidal volume. Minute ventilation was significantly diminished.

4. Off effects, on re-introducing air into the larynx, after 2 and 10 min of CO_2 exposure, suggested that the reflex response diminishes with increased duration of exposure to CO_2.

5. None of the concentrations of intralaryngeal CO_2 changed total lung resistance or compliance.

6. CO_2 mixtures in the larynx generally caused no change in blood pressure or pulse rate of the cats.

7. The reflex effects of intralaryngeal CO_2 were abolished by denervating the larynx.

8. Hypoxic mixtures introduced into the larynx did not change breathing.

INTRODUCTION

Kratchmer (1870) showed that passing CO_2 into the upper airway of cats and rabbits caused apnoea and bradycardia and that this response was abolished by cutting the trigeminal nerves. He also found that introducing

* Present address: Cardiovascular Research Institute and Department of Medicine, University of California Medical Center, San Francisco, California.

CO_2 into the larynx caused some changes in breathing, but he considered the reflexes from this part of the airway to be less important than those arising from the nose, and he did not report on them in detail. He did not specify the concentrations of CO_2 used.

Since Kratchmer's report several investigators have looked for airway chemoreflexes (Pi-Suñer & Puche, 1930; Peterson & Fedde, 1968; Kao, 1963) or for pulmonary receptors whose rate of firing is modified by the composition of gases in the lungs (Adrian, 1933; Schoener & Frankel, 1972; Fedde & Peterson, 1970), but these studies have concentrated on the lower respiratory tract. As recent work (Boushey, Richardson & Widdicombe, 1972) has confirmed that laryngeal stimulation with irritant gases can profoundly alter the pattern of breathing, we have studied the effects of flowing known concentrations of CO_2 and O_2 into the cat larynx on the pattern of breathing, total lung resistance, compliance, blood pressure and pulse rate.

METHODS

We used five decerebrate and six anaesthetized cats. In the latter anaesthesia was induced with I.P. sodium pentobarbitone (Nembutal, Abbot) 32 mg/kg, and anaesthesia was maintained with additional injections through a femoral venous catheter.

Cats were prepared for decerebration under halothane anaesthesia (Fluothane, I.C.I.). Both common carotid arteries were tied to reduce bleeding from the cut brain stem. The carotid ligatures were placed above the point of branching of the superior thyroid arteries, safeguarding the blood supply to the larynx. We then performed a mid-collicular decerebration and allowed the animals at least an hour to recover from the anaesthetic before undertaking experimental studies.

In each animal we inserted a polyethylene cannula pointing distally into the lower cervical trachea, taking care to identify and spare the recurrent laryngeal nerves. The animal breathed through this cannula. We placed threads around the superior and recurrent laryngeal nerves to identify them and to ease denervation of the larynx later in the experiment. In the first five experiments (one decerebrate and four anaesthetized cats) we opened the ventral wall of the larynx in the mid line and flowed gases directly on to the mucosa. In later experiments (four decerebrate and two anaesthetized cats), we wanted to ensure that no gases touched the cut edges of the larynx or of other organs supplied by the superior or recurrent laryngeal nerves. To allow this we passed gas mixtures into a second tracheal cannula tied into the upper part of the trachea and pointing rostrally. Gases passed upwards from this cannula through the unopened larynx and escaped through a slit cut in the pharyngeal wall (which is supplied by the glossopharyngeal nerve). Gases given to the larynx in either way were not breathed by the cats.

In all cats we measured these variables: blood pressure, which was recorded from the left femoral artery catheter by means of a capacitance manometer (Consolidated Electrodynamics Corporation), transpulmonary pressure, measured from an air-filled polyethylene catheter tied into a lower intercostal space in the right anterior axillary line and from a wide-bore needle inserted into the tracheal cannula, using a differential capacitance manometer (Hilger), range $\pm$ 25 cm H_2O, and tidal volume and flow, which were measured from a Fleisch pneumotachograph head in series with the lower tracheal tube and connected to an inductance differential pressure recorder and integrator (Godart). In seven experiments we measured end-tidal CO_2 with a

Beckman Spinco L.B.I. infra-red analyser, sampling from the lower tracheal cannula at 300–400 ml./min. We measured rectal temperature with a mercury thermometer. Total lung resistance and compliance were measured by the subtractor method of Mead & Whittenberger (1953), as modified by Nadel & Widdicombe (1962).

We recorded blood pressure, tidal volume, flow, transpulmonary pressure, signal, and a spoken commentary on magnetic tape on a seven channel tape recorder (Ampex SP-300). This allowed re-evaluation of total lung resistance and compliance and other variables after the experiment. During each experiment we also recorded blood pressure, tidal volume, and end-tidal (or pharyngeal, see below) CO_2 on ultra-violet sensitive paper with a Honeywell UV-31 recorder.

We used three concentrations of CO_2 to stimulate the larynx: 30, 10, and 5 %. 30 % CO_2 was mixed from commercial air and CO_2 cylinders by flowing the gases through rotameters into a polyethylene Douglas bag. Once mixed, the gas was stored no longer than 4 hr. We gave 30 % CO_2 into the larynx from a 50 ml. syringe without warming or moistening it, and injected the same volume of air as a control. 5 and 10 % CO_2 in air were obtained from ready mixed cylinders (British Oxygen, Special Gases Division). Concentrations were accurately determined with a Lloyd–Haldane apparatus. As we found that dry air at room temperature caused a very small slowing of breathing when insufflated into the laryngeal lumen, we warmed all gases (except 30 % CO_2) to 37 °C and moistened them by passage over wet pummice chippings before they entered the larynx. 5 and 10 % CO_2 in air, N_2, and air control mixtures were passed through a rotameter, and their flow was adjusted to 0·5 l./min. Because of the rotameter, the heating coil and moistening chamber, there was an appreciable time lag between changing the gases and the new gas arriving at the larynx. To record the moment of arrival in the larynx of the gas mixtures, we fixed a sampling line from the CO_2 meter to the slit made in the pharynx where the perfused gas escaped. At times of change we switched the CO_2 meter from the lower trachea to the pharynx and thus recorded when the CO_2 or air front arrived.

In all experiments it was necessary to keep the laryngeal mucosa free from mucus. This was troublesome in animals studied with the larynx closed, so after testing the effects of two levels of CO_2 in the larynx on total lung resistance and compliance, we gave atropine sulphate (0·5 mg/kg) I.V. This prevented reflex changes in total lung resistance so measurements of this variable after atropine are not reported here.

<div align="center">RESULTS</div>

Effect of 30 % CO_2 in the larynx on the pattern of breathing

We measured the effects of 30 ml. 30 % CO_2 injected into the larynx from a syringe on the pattern of breathing of five anaesthetized and three decerebrate cats. Table 1 summarizes the results. Decerebrate cats gave a clearly two-phased response (Fig. 1). First, during the passage of CO_2 through the larynx, the frequency of breathing slowed and tidal volume fell. The depressed tidal volume persisted for one to ten breaths. Later, at the end of the injection or shortly thereafter, tidal volume increased to levels greater than in the control period, whereas frequency remained slow. The mean reduction of minute volume in the initial period was 44 %. Late minute volume was in some cases depressed, and in others, when tidal volume increased substantially, it was increased. All these changes are

statistically significant except the late change in minute volume (see Table 1). Changes in end-tidal CO_2 reflected the changes in minute volume.

The effects of intralaryngeal injection of 30 % CO_2 in anaesthetized cats were similar, except that the changes in the variables measured were
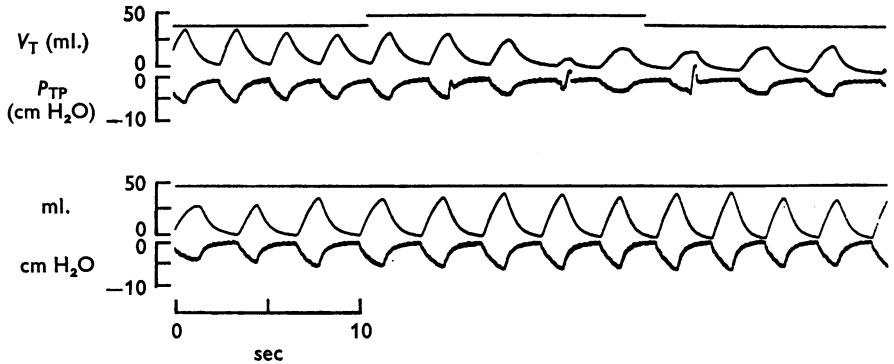

Fig. 1. From above downwards; signal, tidal volume (V_T), transpulmonary pressure (P_{TP}). The two records are continuous. 50 ml. 30 % CO_2 enters the larynx at the signal. Breathing first becomes shallow and slow; later, deep and slow. Note the irregularities on the transpulmonary pressure trace.

TABLE 1. Percentage changes (mean and S.E.) in tidal volume (V_T), frequency (f) and minute ventilation $(\dot{V})$ when 30 % CO_2 was flowed through the larynx of decerebrate and anaesthetized cats. 'Early' denotes the period during the CO_2 flow through the larynx when tidal volume was depressed. 'Late' denotes five breaths measured 15 sec after the end of the CO_2 injection. Comparisons are made with the five breaths before the CO_2 injection. n denotes the number of trials

	f	V_T	$\dot{V}$
Decerebrate cats	$-28{\cdot}07\%$	$-22{\cdot}03\%$	$-44{\cdot}03\%$
Early	$\pm 5{\cdot}81$	$\pm 6{\cdot}29$	$\pm 7{\cdot}43$
	$n = 6$	$n = 6$	$n = 6$
	$P < 0{\cdot}01$	$P < 0{\cdot}05$	$P < 0{\cdot}01$
Late	$-18{\cdot}00\%$	$\pm 21{\cdot}08\%$	$\pm 0{\cdot}58\%$
	$\pm 4{\cdot}36$	$\pm 4{\cdot}06$	$\pm 8{\cdot}00$
	$n = 6$	$n = 6$	$n = 6$
	$P < 0{\cdot}01$	$P < 0{\cdot}01$	n.s. .
Anaesthetized cats	$-16{\cdot}06\%$	$-8{\cdot}04\%$	$-23{\cdot}08\%$
Early	$\pm 3{\cdot}85$	$\pm 3{\cdot}02$	$\pm 3{\cdot}57$
	$n = 8$	$n = 8$	$n = 8$
	$P < 0{\cdot}01$	$P < 0{\cdot}05$	$P < 0{\cdot}001$
Late	$-16{\cdot}06\%$	$+9{\cdot}04\%$	$-9{\cdot}02\%$
	$\pm 3{\cdot}12$	$\pm 2{\cdot}44$	$\pm 2{\cdot}50$
	$n = 7$	$n = 7$	$n = 7$
	$P < 0{\cdot}01$	$P < 0{\cdot}01$	$P < 0{\cdot}05$

smaller and that minute ventilation remained depressed until the pattern of breathing returned to normal.

Decerebrate animals frequently made short expiratory or inspiratory-expiratory efforts in response to intralaryngeal CO_2 during the period when their respiratory rhythm was most slowed (Fig. 1). They occurred at all concentrations of CO_2 but we did not see them in anaesthetized cats.
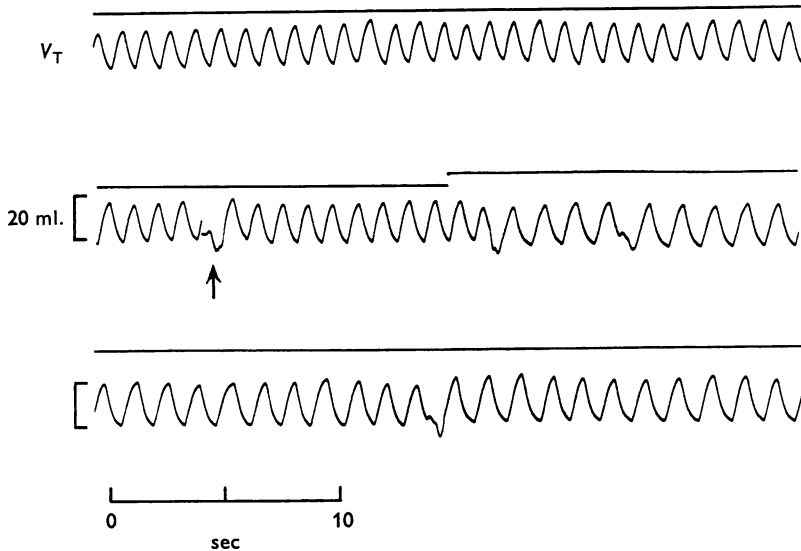

Fig. 2. The effect of 5 % CO_2 in the larynx on breathing in a decerebrate cat. Upper trace, signal; lower trace, tidal volume (V_T). The three records are continuous. The arrow in the middle record shows where the pneumotachograph volume trace zeros itself and is then adjusted to the centre of the film. Shortly after this, at the signal, CO_2 enters the larynx and breathing slows from 55·5 to 40·5/min.

Effects of 5 and 10 % CO_2 in the larynx

The effects of flowing 5 or 10 % CO_2 into the larynx were studied in all cats. Both mixtures caused slowing of breathing with small and inconsistent effects on tidal volume (Fig. 2). Table 2 summarizes the changes in frequency, tidal volume and minute volume 20 sec after CO_2 is introduced into the larynx. The decreases in frequency and in minute volume are significant for both concentrations of CO_2 in both anaesthetized and decerebrate cats. The changes were greater in decerebrate animals and in the trials with the higher concentration of CO_2. Unlike the response to 30 % CO_2, the decrease in frequency only developed over several breaths (Fig. 3).

TABLE 2. Percentage changes (mean and s.e.) in frequency (f), tidal (V_T) volume and minute ventilation $(\dot{V})$ on flowing 5 and 10 % CO_2 into the larynx of anaesthetized and decerebrate cats.

The percentage changes are for five breaths measured after 20 sec of CO_2 in the larynx compared with the five breaths before CO_2 entered

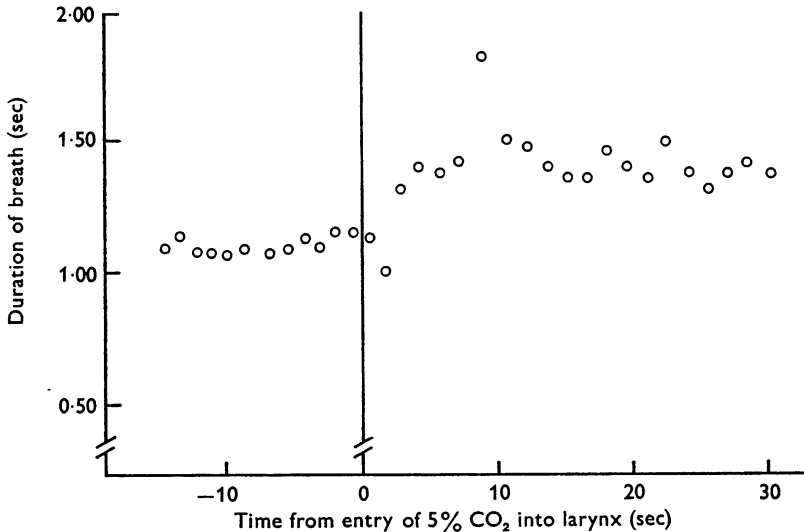|	f	V_T	$\dot{V}$
5 % CO_2			
Decerebrate	$-11\cdot3 \pm 1\cdot77$	$+0\cdot42 \pm 2\cdot09$	$-11\cdot1 \pm 2\cdot75$
	$n = 15$	$n = 15$	$n = 15$
	$P < 0\cdot001$	n.s.	$P < 0\cdot01$
Anaesthetized	$-4\cdot73 \pm 1\cdot134$	$-0\cdot69 \pm 0\cdot4$	$-4\cdot86 \pm 0\cdot68$
	$n = 22$	$n = 13$	$n = 13$
	$P < 0\cdot01$	n.s.	$P < 0\cdot001$
10 % CO_2			
Decerebrate	$-16\cdot6 \pm 1\cdot80$	$-2\cdot7 \pm 4\cdot3$	$-17\cdot0 \pm 3\cdot34$
	$n = 16$	$n = 16$	$n = 16$
	$P < 0\cdot01$	n.s.	$P < 0\cdot001$
Anaesthetized	$-4\cdot72 \pm 1\cdot4$	$-0\cdot55 \pm 1\cdot35$	$-6\cdot8 \pm 2\cdot64$
	$n = 13$	$n = 6$	$n = 6$
	$P < 0\cdot01$	n.s.	$P < 0\cdot05$

Fig. 3. The effect of 5 % CO_2 on the time taken for each breath in a decerebrate cat. At the zero time 5 % CO_2 enters the larynx. By the third breath breathing has slowed.

Adaptation of the reflex

We studied the adaptation of the reflex by measuring the size of the off response (the change in breathing on switching from carbon dioxide to air) at 2 and 10 min in decerebrate cats. For this study we pooled results from 5 and 10 % CO_2 trials.

Table 3 summarizes the results. The off-effects at 2 min were approximately equal and opposite to the on-effects. When CO_2 mixtures have been passing through the larynx for 10 min, switching to air still increased frequency and minute volume, but the increase in frequency was smaller, and the increase in minute volume is not significant.

TABLE 3. Percentage changes (mean and S.E.) in breathing on switching from CO_2 mixture to air flowing through the larynx. This Table pools results from 5 and 10 % CO_2 in decerebrate cats.

The percentage changes are calculated for five breaths measured 20 sec after the switch back to air compared with five breaths immediately before the change

	Frequency	Tidal volume	Minute ventilation
2 min off-effect	$+11\cdot3 \pm 2\cdot20$	$+3\cdot0 \pm 1\cdot79$	$+16\cdot3 \pm 3\cdot15$
	$n = 15$	$n = 15$	$n = 15$
	$P < 0\cdot001$	n.s.	$P < 0\cdot001$
10 min off-effect	$+3\cdot53 \pm 1\cdot23$	$+3\cdot29 \pm 2\cdot38$	$+8\cdot35 \pm 4\cdot41$
	$n = 11$	$n = 11$	$n = 11$
	$P < 0\cdot05$	n.s.	n.s.

TABLE 4. This Table compares the size of the effect of stopping the flow of CO_2 through the larynx (the 'off-effect') with the effect of starting the flow ('on-effect') on two variables, respiratory frequency (f) and minute ventilation ($\dot{V}$). The comparison is done for 2 and 10 min off-effects separately. The data are from decerebrate cats only. Results from 5 and 10 % CO_2 are pooled. A positive number means that the off-effect was greater than the on-effect and conversely, a minus number means the off-effect was less than the on-effect. Figures (means and S.E.) are based upon paired values (i.e. the on-response at the beginning of a run compared with the off-response at the end of the same run). Probability values are by Student's t test. n is the number of trials

	f (breaths/min)	$\dot{V}$ (ml./min)
2 min off-effect minus the on-effect	$-0\cdot69 \pm 1\cdot25$	$+17\cdot0 \pm 37\cdot8$
	$n = 14$	$n = 14$
	n.s.	n.s.
10 min off-effect minus the on-effect	$-4\cdot1 \pm 1\cdot9$	$-20\cdot3 \ (\pm 72\cdot2)$
	$n = 10$	$n = 10$
	$P < 0\cdot01$	n.s.

To confirm that this reflex adapted over 10 min, we have compared the magnitude of the off response after runs lasting 2 and 10 min with the size of the on response at the start of the same run. Table 4 shows the results of

this paired comparison analysis. Our data fail to show a significant drop in the strength of the reflex over a 2 min period, but do show that after 10 min there had been a significant escape from the initial depression of frequency.

Effects of CO_2 in the denervated larynx

In two anaesthetized and three decerebrate cats which had given clear responses to all strengths of CO_2 tested, we cut the superior and recurrent laryngeal nerves and repeated the tests. In none of the trials was there any change in frequency or tidal volume.

Effects of hypoxic mixtures in the larynx

In one decerebrate cat (that gave a clear and consistent response to all strengths of CO_2 mixture) we twice tested the effects on breathing of switching the flow of gas through the larynx from pure O_2 to pure N_2. In neither case was there any change in tidal volume or rate of breathing.

Effects of intralaryngeal CO_2 on total lung resistance and compliance

We measured total lung resistance and compliance in all cats. No changes were noted in these variables in response to any strength of CO_2 tested, although other irritant gases injected into the larynx have been previously noted to cause a striking increase in total lung resistance (Boushey *et al.* 1972).

Effects of intralaryngeal CO_2 on cardiovascular function

5 and 10 % CO_2 mixtures in the larynx had no effect on pulse or blood pressure. 30 % CO_2 had small and inconsistent effects on blood pressure, but we felt this was more likely a secondary effect of the change in the pattern of breathing than a direct reflex effect. In one decerebrate cat, 30 % CO_2 caused a slight slowing of a previously steady pulse rate in each of two trials (140/min to 125/min and 130/min to 125/min). This slowing of the pulse rate was not preceded by a rise in blood pressure, and lasted for two to three breaths.

DISCUSSION

We have demonstrated that introducing gas mixture rich in carbon dioxide into the larynx of the cat has clear reflex effects on the pattern of breathing and that this reflex depends upon intact laryngeal innervation. Although 30 % CO_2 is not a physiological, nor even pathological stimulus as Cordier & Heymans (1935) noted, a number of physiological studies have used inspired gas mixtures containing from 15 to 30 % CO_2 to investigate chemoreceptors. In the animal studies of this nature (Pi–Suner,

1947; Dutton, Chernick, Moses, Bromberger-Barnea, Permutt & Riley, 1964) the inspired gas was introduced through a tracheal cannula, and so by-passed the larynx. In the human studies, however, the gases were inhaled in the usual manner through the upper airway (Riley, Dutton, Fuleihan, Nath, Yoshimoto, Sipple, Permutt & Bromberger-Barnea, 1963; Cunningham, Elliott, Lloyd, Miller & Young, 1965; Leigh, 1972). Cunningham and his co-workers (1965) report that their subjects sensed the high CO_2 gas mixtures which, according to one 'caught the back of the throat like ether'. Investigators using these strengths of CO_2 should keep in mind that reflexes from the larynx, nose (Kratchmer, 1870), and possibly even the lower respiratory tract (Pi-Suner & Puche, 1930) might influence the response.

We have also shown that under the conditions of our experiments introducing 5 and 10 % CO_2 (approximately 36 and 71 mm Hg respectively) into the larynx caused a slowing of breathing and a reduction in minute volume. It does not seem likely that intralaryngeal CO_2 exerts a tonic influence on normal breathing because during these experiments the larynx was filled with CO_2 throughout the respiratory cycle instead of just during expiration as in normal conditions. Moreover, the off changes in frequency and minute volume noted when air replaces 5 or 10 % carbon dioxide in the larynx are smaller after CO_2 has been in the larynx for 10 min than they are after 2 min, and the off-effects at 10 min are considerably smaller than the on-effects. These findings imply that the reflex adapts to a continuous stimulus and may therefore play little or no part in the control of normal breathing. It could be important under exceptional circumstances, as in suffocation or in experimental physiology where step-wise changes are made in inspired CO_2 concentrations.

The average strength of the reflex was greater in decerebrate than anaesthetized cats. One possible reason for this is that anaesthetic may partly block the nervous pathway of this reflex in the brain: another is that in these experiments the anaesthetized animals produced more laryngeal mucus and this would have slowed CO_2 diffusion to and from the laryngeal epithelium.

We have considered whether this reflex might account for the 'tube breathing' effects described by Cunningham, Howson & Pearson (1971). These workers have described small but consistent changes in ventilation in response to changing the phase of the respiratory cycle in which a CO_2 front entered the airways. Reflexes from the larynx do not appear to be responsible for their observations for two reasons. First, tube breathing affected ventilation only under hypoxic conditions, and the laryngeal reflex we describe was not sensitive to an inspired P_{O_2} of nearly zero. Secondly, the 'tube breathing' effect requires a rapidly effective reflex

which could change breathing within one respiratory cycle. The laryngeal reflex response to CO_2 only developed its full strength over some two to four breaths in response to modest levels of CO_2.

The reflex we describe in response to 30 % CO_2, an initial decrease in frequency and in tidal volume followed by slow, deep breathing, resembles the response to dilute ammonia vapour (Boushey et al. 1972). But no dilution of ammonia vapour caused slowing of breathing without a change in tidal volume, as did 5 and 10 % CO_2. We surmise that a different population of receptors may be responsible for the reflex response to low concentrations of CO_2.

The airway chemoreflex which we report here is not unique in the animal kingdom. Recently, Peterson & Fedde (1968) and Fedde & Peterson (1970) have described airway reflexes which respond to changes of P_{CO_2} in the lungs of chickens. In the later paper, they recorded from vagal afferent fibres whose activity was inhibited by CO_2. They concluded that the nerve endings of these fibres were in the airways because of the short latency of the effect and because the response survived clamping the pulmonary arteries. King, McLelland, Molony & Mortimer (1969) have found similar fibres in chickens' vagus nerves. Schoener & Frankel (1972) have shown that rat pulmonary stretch receptors fire more vigorously for a given level of stretch during hypocapnia; however, the changes in activity took about 30 min to develop. Adrian (1933) reported a modest depression of pulmonary stretch receptor activity when cats breathed gases rich in CO_2.

We have made preliminary studies on afferent nervous impulse traffic from the cat larynx in response to CO_2. The results indicate that at least two types of afferent end organs have their impulse frequency changed by the same CO_2 concentrations as used in this study.

We do not know why cats should have developed a laryngeal reflex which inhibits breathing while other CO_2 sensitive reflexes excite it, but there are at least two possibilities. First, this reflex may have no special teleological significance but carbon dioxide, may act as a mildly irritant gas and so, to a small extent, excite laryngeal protective reflexes (Boushey et al. 1972). Secondly, it is possible that the temporary inhibiting effect of CO_2 on breathing may prevent hunting of minute volume when a cat's inspired CO_2 increases rapidly as in suffocation or recovery from hyperventilation. The time course of the adaptation of this reflex (it adapts substantially between 2 and 10 min, i.e. around the time taken to achieve steady-state ventilation) would make it suitable for this role.

REFERENCES

ADRIAN, E. D. (1933). Afferent impulses in the vagus and their effect on respiration. *J. Physiol.* **79**, 332–358.

BOUSHEY, H. A., RICHARDSON, P. S. & WIDDICOMBE, J. G. (1972). Reflex effects of laryngeal irritation on the pattern of breathing and total lung resistance. *J. Physiol.* **224**, 501–513.

CORDIER, D. & HEYMANS, C. (1935). La controle réflexe du centre respiratoire. *Annls Physiol. Physicochim. bio.* **11**, 620–683.

CUNNINGHAM, D. J. C., ELLIOT, D. H., LLOYD, B. B., MILLER, J. P. & YOUNG, J. M. (1965). A comparison of the effects of oscillating and steady state alveolar partial pressures of oxygen and carbon dioxide on pulmonary ventilation. *J. Physiol.* **179**, 498–508.

CUNNINGHAM, D. J. C., HOWSON, M. G. & PEARSON, S. B. (1971). The respiratory stimulating effect of 'tube breathing' simulated without a tube. *J. Physiol.* **218**, 71–72P.

DUTTON, R. E., CHERNICK, V., MOSES, H., BROMBERGER-BARNEA, B., PERMUTT, S. & RILEY, R. L. (1964). Ventilatory response to intermittent inspired carbon dioxide. *J. appl. Physiol.* **19**, 931–936.

FEDDE, M. R. & PETERSON, D. F. (1970). Intrapulmonary receptor response to changes in airway gas composition in *Gallus domesticus. J. Physiol.* **209**, 609–625.

KAO, F. F. (1963). An experimental study of the pathways involved in exercise hyperpnoea employing cross-circulation techniques. In *The Regulation of Human Respiration*, ed. CUNNINGHAM, D. J. C. & LLOYD, B. B., pp. 461–502. Oxford: Blackwell.

KING, A. S., MCLELLAND, J., MOLONY, V. & MORTIMER, M. F. (1969). Respiratory afferent activity in the avian vagus: apnoea, inflation and deflation. *J. Physiol.* **201**, 35–36 P.

KRATCHMER, F. (1870). Über Reflexe von der Nasenschleimhaut auf Athmung und Kreislauf. *Sber. Akad. Wiss. Wien* **62**, 147–170.

LEIGH, J. (1972). Dependence of peripheral chemoreflex response to CO₂ in man on P_{O_2}. *J. Physiol.* **225**, 63P.

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). Reflex effects of upper airway irritation on total lung resistance and blood pressure. *J. appl. Physiol.* **17**, 861–865.

PETERSON, D. F. & FEDDE, M. R. (1968). Receptors sensitive to carbon dioxide in the lungs of chicken. *Science, N.Y.* **162**, 1499–1501.

PI-SUNER, A. (1947). The regulation of respiratory movements by peripheral chemoreceptors. *Physiol. Rev.* **27**, 1–38.

PI-SUNER, A. & PUCHE, J. (1930). La sensibilité chimique pulmonaire étudiée par la technique de la tête isolée. *C. r. Séanc. Soc. Biol.* **103**, 735–736.

RILEY, R. L., DUTTON, R. E., FULEIHAN, F. J. D., NATH, S., HURT, H. H., YOSHIMOTO, C., SIPPLE, J. H., PERMUTT, S. & BROMBERGER-BARNEA, B. (1963). Regulation of respiration and blood gases. *Ann. N.Y. Acad. Sci.* **109**, 829–851.

SCHOENER, E. P. & FRANKEL, H. M. (1972). Effect of hyperthermia and Pa_{CO_2} on the slowly adapting pulmonary stretch receptor. *Am. J. Physiol.* **222**, 68–72.