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THE DIRECT EFFECT ON PULMONARY STRETCH RECEPTOR DISCHARGE PRODUCED BY CHANGING LUNG CARBON DIOXIDE CONCENTRATION IN DOGS ON CARDIOPULMONARY BYPASS AND ITS ACTION ON BREATHING

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SUMMARY

1. Single fibre pulmonary stretch receptor discharge was recorded in dogs on cardiopulmonary bypass.

2. Inhalation of CO_2 depressed pulmonary stretch receptor discharge despite the absence of changes in arterial P_{CO_2}. This effect was particularly marked with airway CO_2 levels below 5%.

3. Changing arterial P_{CO_2}, without changing airway CO_2, had only small and insignificant effects on pulmonary stretch receptor discharge.

4. The effect of changes in airway CO_2 on pulmonary stretch receptor discharge was rapid and correlated well in time with the reflex tachypnoea produced when CO_2 was inhaled in conditions of cardiopulmonary bypass.

5. Stimulation of the central end of the cut vagus nerve was triggered from simultaneously recorded action potentials from a single pulmonary stretch receptor.

6. In these conditions, the reflex response to CO_2 could be simulated provided that the pulmonary stretch receptor had an end-expiratory discharge.

7. It is suggested that the vagally mediated tachypnoeic response to changes in airway CO_2 seen in conditions of cardiopulmonary bypass is due to the effect of CO_2 on the end-expiratory discharge of pulmonary stretch receptors.

INTRODUCTION

The influence of lung CO_2 concentration on the frequency of breathing has been demonstrated in dogs on closed-chest cardiopulmonary bypass, when lung CO_2 concentration alone can be altered while keeping arterial P_{CO_2} (P_{a,CO_2}) constant (Bartoli, Cross, Guz, Jain, Noble & Trenchard, 1974).

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It was shown that this is a vagal reflex, whereby inhaling CO_2 increases the frequency of breathing predominantly due to a decrease in expiratory duration. Since there is no significant change in P_{a,CO_2} in these circumstances, due to the absence of a functioning pulmonary circulation, this vagally mediated reflex must be due to an effect of CO_2 on receptors in the lung parenchyma or tracheo-bronchial tree. Inhaled CO_2 depresses the activity from pulmonary stretch receptors in dogs, cats and rabbits with normal circulations, where both P_{A,CO_2} and P_{a,CO_2} are increased (Mustafa & Purves, 1972; Schoener & Frankel, 1972; Sant'Ambrogio, Miserocchi & Mortola, 1974). The present studies were designed: (1) to demonstrate whether similar changes in activity from pulmonary stretch receptors occurred when either lung CO_2 or P_{a,CO_2} was changed in dogs on cardiopulmonary bypass; (2) to test the hypothesis that a change in the pattern of pulmonary stretch receptor activity in response to changing lung CO_2 concentration could be responsible for the change in the frequency of breathing. The technique used for these latter studies, first described by Bystrzycka & Huszczuk (1973), involved recording the activity in a single fibre from a pulmonary stretch receptor and linking this to electrical stimulation of the cut central end of a whole vagus nerve. Any effect of CO_2 on the pattern of pulmonary stretch receptor discharge would thus be reflected in a change in the pattern of stimulation of the vagus nerve.

METHODS

Twenty-one mongrel dogs (14–32 kg) were used in these studies. Anaesthesia was induced with thiopentone and surgery was performed with halothane (1–2%) in 50% O_2, 50% N_2O anaesthesia; this was replaced by chloralose (30–50 mg/kg) at least 30 min before any recordings were made. Closed-chest cardiopulmonary bypass was established in all the dogs as previously described (Bartoli *et al.* 1973, 1974) In this preparation, the concentration of CO_2 in the lungs can be changed without affecting P_{a,CO_2} and vice versa (Bartoli *et al.* 1974).

Arterial pressure and samples for blood gas analysis of P_{CO_2}, P_{O_2} and pH (Corning EEL electrode assembly) were obtained from a catheter inserted into the left carotid artery. Arterial pressure was measured with a Bell and Howell strain gauge. Air flow was monitored with a Fleish pneumotachograph (size no. 1) attached to an endotracheal tube; the differential pressure across the pneumotachograph was measured with a strain gauge (Statham PM 15) and the signal integrated to give a continuous record of tidal volume. Airway pressure was measured close to the pneumotachograph with a strain gauge (Statham PM 5). In eight dogs, the chest was opened so that this pressure represented transpulmonary pressure. Airway CO_2 concentration was continuously measured with an infra-red analyser (Beckman LB 2). All these variables were registered on an 8 channel direct writing ink pen recorder (Brush 480). The dogs were hyperoxic throughout the study since the gas equilibrating the blood at the oxygenator never contained less than 90% O_2. In addition O_2 was added to the inspired air and any increase in CO_2 concentration in the inspired air was always given in O_2.

Both cervical vagus nerves were dissected out and the right vagus nerve was

sectioned immediately, while the left nerve was prepared for sectioning later in the experiment. Single fibre activity from pulmonary stretch receptors was recorded from teased out slips of the cut peripheral end of the right vagus nerve in sixteen dogs. After pre-amplification (Hewlett Packard bioelectric amplifier 8811A) the signals were displayed on a cathode ray oscilloscope (Devices) and recorded on magnetic tape (Tandberg), together with air flow, CO_2 concentration and airway pressure, for subsequent analysis. Further analysis of single fibre activity was performed with a fibre optic oscillograph (Medelec) and a frequency impulse meter.

In some experiments, this activity from single fibres was processed to provide a trigger for a Digitimer (Devices) and isolated stimulator (Devices 2533). The output of this stimulator therefore gave pulses synchronous with each action potential recorded from the single fibre. This was used to stimulate the cut central end of the left vagus nerve. Compound action potentials were recorded more centrally along this vagus nerve, and the stimulation parameters were adjusted until only the A wave of the compound action potential was obtained. This method has previously been described in detail and the conduction velocity of the fibres concerned shown to be in the range 30–58 m/sec (Trenchard, 1970). This indicated that only the larger myelinated fibres were being stimulated, of which the fibres from pulmonary stretch receptors form the major contribution (Paintal, 1953; Guz & Trenchard, 1971). Non-myelinated and small myelinated (A_δ) fibres were not stimulated. Recordings were made from different pulmonary stretch receptors in the same dog, but the A wave was kept constant and therefore the same fibres would transmit information centrally. Only the pattern of stimulation would change.

Experimental procedure

Recordings were made from a small slip of the vagus nerve containing a single active pulmonary stretch afferent fibre both before and after a stable bypass had been established. The effect of adding CO_2 to the inspired gas in spontaneously breathing dogs on bypass was then studied; this enabled a comparison to be made between the effect of CO_2 on the pulmonary stretch receptor and the reflex effect on breathing mediated by the remaining intact vagus nerve. While recording from the same fibre, the dogs were paralysed and artificially ventilated and the effect of adding CO_2 to the inspired gas on the receptor discharge was obtained while the dog was ventilated at constant tidal volume and frequency. In eight dogs the chest was then opened bilaterally and a small expiratory resistance added so that the lungs returned to an end-expiratory level comparable with previous closed-chest values. The effect on the single fibres of increasing lung CO_2 was again tested. In the artificially ventilated dogs the left vagus was usually sectioned as low in the neck as possible in order to prevent any reflex efferent changes (such as changes in bronchial smooth muscle tone and bronchial mucous secretion rate) from influencing the results. Several additional single fibres in the same dog were examined for any response to increasing CO_2.

The response of some of the pulmonary stretch receptors to static lung inflation was also assessed at different levels of lung CO_2. This was performed in paralysed dogs with the ventilator switched off. Static lung inflations were made by applying various resistances to a stream of gas flowing across the end of the endotracheal tube. The inflations were therefore made at constant pressure and could be maintained until steady-state conditions were reached. Between each measurement the lungs were artificially ventilated so that the initial lung CO_2 concentration was constant before each measurement. The constant pressure inflations were then repeated at different lung CO_2 concentrations.

In some dogs, the response of pulmonary stretch receptor discharge to increasing

and decreasing P_{a,CO_2} was measured. The gas equilibrating the blood in the oxygenator was changed from its control concentration of 5% CO_2 in O_2 either up to 7 or 10% CO_2 in O_2 or down to 3 or 0% CO_2 in O_2. At least 5 min elapsed after charging the gas concentration for equilibration to be reached before any recordings were made. In a few dogs the effect of adding CO_2 to the inspired gas at different levels of P_{a,CO_2} was investigated.

The electrical stimulation studies were performed in six spontaneously breathing dogs. The effect of adding CO_2 to the inspired gas on the pattern of breathing was recorded first with one vagus nerve intact and then after bilateral vagotomy. The study was repeated with the central end of the vagus being stimulated, as previously described, with a pattern of activity obtained from a pulmonary stretch receptor. Several different receptors were used in each animal.

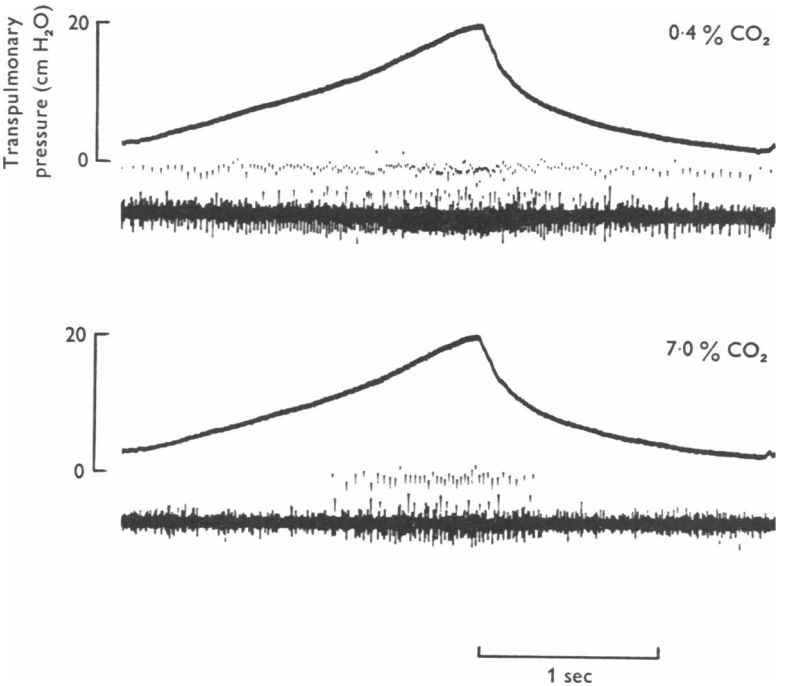

Fig. 1. Response of a single pulmonary stretch receptor to a change in end tidal CO_2 from a paralysed and ventilated dog on cardiopulmonary bypass. In both pairs of recordings the top trace is of transpulmonary pressure and the lower trace shows action potentials from a single pulmonary stretch receptor. One complete ventilator cycle is shown at two different levels of end tidal CO_2 (0·4 and 7%) for the same pulmonary stretch receptor.

RESULTS

Effect of changing inspired CO_2 concentration on pulmonary stretch receptor discharge

The addition of CO_2 to the inspired air produced a marked depression

of activity from pulmonary stretch receptors throughout the whole respiratory cycle. A typical effect in one fibre is shown in Fig. 1. Similar effects were obtained whether the dogs were artificially ventilated or breathing spontaneously. Fig. 2 shows the effect of increasing inspired CO_2 concentration in all the fibres studied, expressed as peak inspiratory and end-expiratory discharge, in ten paralysed animals ventilated at

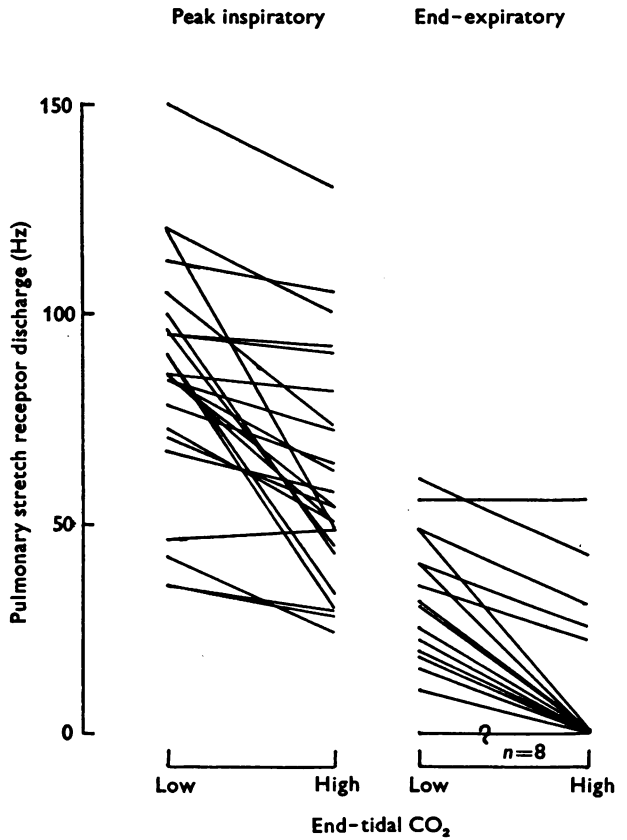

Fig. 2. The effect of changing airway CO_2 concentrations on pulmonary stretch receptor discharge. Peak inspiratory and end-expiratory discharge frequency in twenty-four pulmonary stretch receptors at low and high end-tidal CO_2 concentrations are shown.

constant volume. In seven animals the left vagus was cut to prevent reflex changes in the bronchial tone and in eight animals the chest was opened. The mean peak inspiratory discharge frequency in twenty-four fibres was 87 Hz $\pm$ 6 (S.E. of mean) with low airway CO_2 (0·3–0·8 % end-tidal) and 64 Hz $\pm$ 5 with high CO_2 (7·0–8·0 %). The probability of these changes occurring by chance was $< 0{\cdot}01$ (Wilcoxon signed rank test).

When an end-expiratory discharge was present at the lower CO_2 concentration it usually disappeared with the higher CO_2 concentration. The mean end-expiratory discharge was 21 Hz ± 4 (low CO_2) and 7 Hz ± 3 (high CO_2) ($P < 0{\cdot}01$). If no activity was present during expiration at the lower concentration it always remained absent as CO_2 was increased. Where the response of the same fibre has been investigated at several different levels of inspired CO_2 concentration, the maximal changes in receptor discharge were obtained over the lower range of airway CO_2 (Fig. 3).

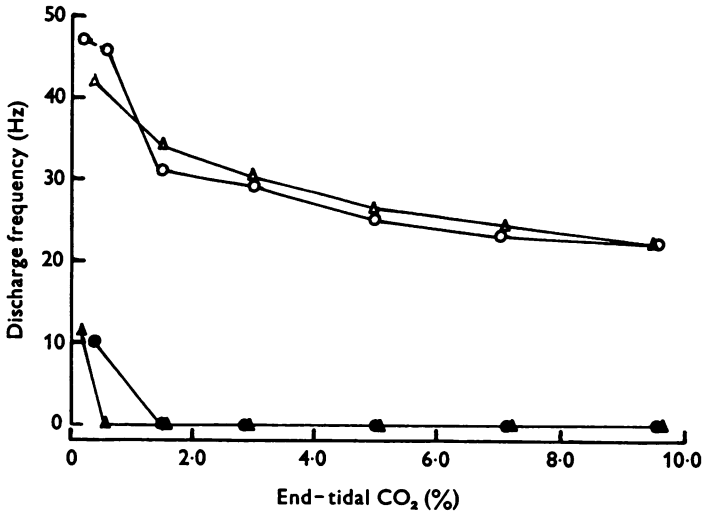

Fig. 3. Peak inspiratory discharge frequency (open symbols) and end-expiratory discharge frequency (filled symbols) of a single pulmonary stretch receptor at various steady-state levels of end-tidal CO_2. Measurements were made at two different levels of arterial P_{CO_2}; 41·7 mmHg (triangles) and 62·5 mmHg (circles).

In four cases pulmonary stretch receptor discharge was recorded under steady-state static conditions (without tidal ventilation) as described in Methods. The relation between discharge frequency and transpulmonary pressure showed an obvious shift when the inspired CO_2 was changed so that at any given level of transpulmonary pressure the discharge frequency was less at the higher airway CO_2. This can be seen for one fibre in Fig. 4.

Effect of changing P_{a,CO_2} *on pulmonary stretch receptor discharge*

Changing P_{a,CO_2} by altering the concentration of CO_2 in the gas equilibrating the blood in the oxygenator, produced only minor and inconsistent changes in pulmonary stretch receptor discharge (Fig. 5).

This occurred whether the CO_2 concentration in the equilibrating gas was decreased from 5% (usual concentration) to 3 or 0%, or increased to 7 or 10%. In seven fibres in five animals, changing the gas equilibrating the blood in the bypass from 5 to 10% CO_2 in O_2 changed the mean peak inspiratory discharge frequency from 78 ($\pm$11) to 77 ($\pm$12) Hz, and the end-expiratory frequency from 16 ($\pm$6) to 8 ($\pm$4). The probability of these changes occurring by chance was > 0·05 (Wilcoxon signed rank test). Blood gases were measured with 5% and 10% CO_2 in the bypass for only five of the seven fibres tested, and the mean P_{a,CO_2} had changed from 46 to 67 mmHg. The effect of increasing airway CO_2 concentrations was not changed by altering the P_{a,CO_2}.

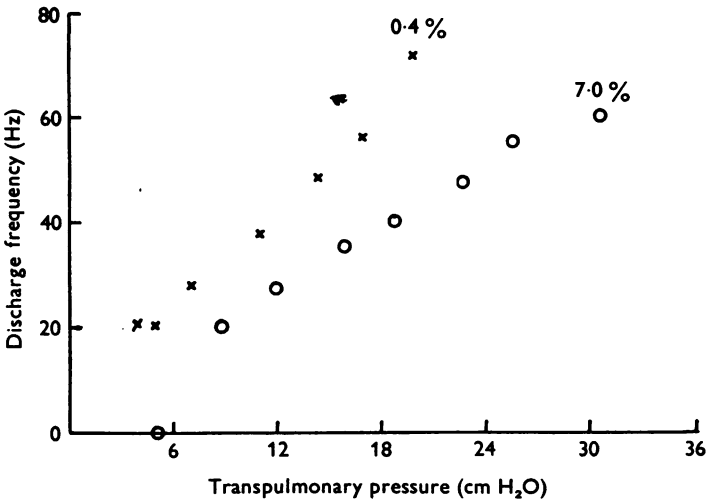

Fig. 4. The effect of changing the airway CO_2 on the relationship between discharge frequency of a single pulmonary stretch receptor and the transpulmonary pressure at different steady-state levels. The response at two different levels of end-tidal CO_2 are shown, 0·4% (crosses) and 7·0% (circles).

Comparison of the time relation between receptor response and reflex change in breathing when airway CO_2 is altered

The onset of the depression of discharge by CO_2 was very rapid, sometimes appearing during the first inspiration after the CO_2 was increased, but always taking effect by the first expiration (Fig. 6). The maximal effect did not usually appear until several breaths of the higher CO_2 concentration had been inspired but it took several breaths before the end-tidal CO_2 concentration reached a constant peak level.

In eight animals the reflex response to CO_2 with one vagus nerve

intact was measured while a pulmonary stretch afferent from the other vagus was recorded. The depression of discharge and the reflex tachypnoea occurred at the same time, and usually on the first breath (Fig. 7). Tidal volume was not greatly changed during the reflex response, and could not have been a cause of the fall in pulmonary stretch receptor discharge in these circumstances.

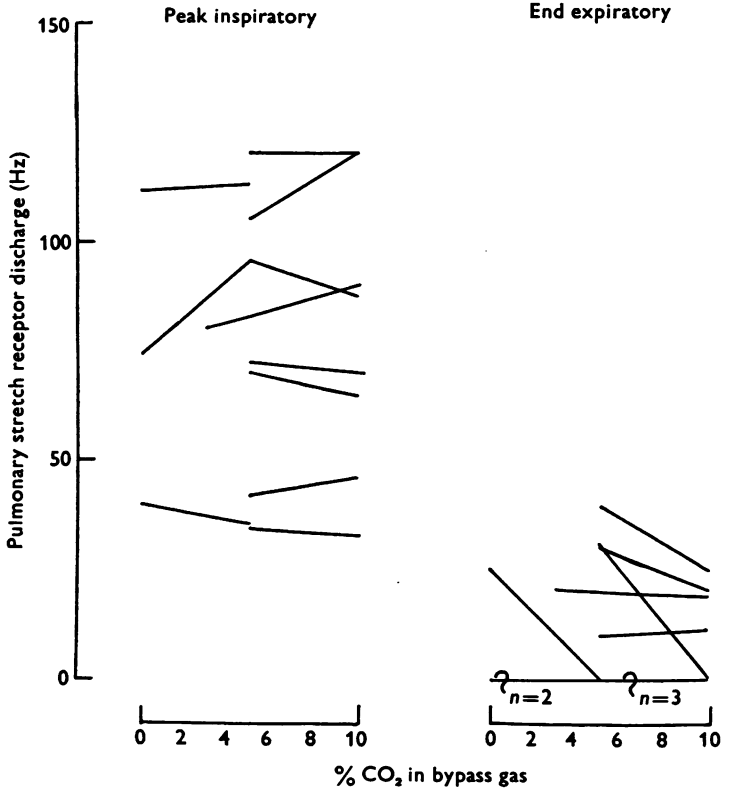

Fig. 5. Effect of changing arterial P_{CO_2} on pulmonary stretch receptor discharge. Peak inspiratory and end-expiratory discharge frequency of eight pulmonary stretch receptors with gases of different CO_2 content used in the bypass gas.

Simulation of reflex response by coupling stimulation of the central end of the vagus nerve to pulmonary stretch receptor discharge

The results from these experiments can be divided into two groups, depending upon whether the pulmonary stretch receptor discharge was present or absent during expiration. When an end-expiratory discharge was present, stimulation of the central end of the vagus, by triggering the stimulator from the recorded action potentials, produced a smaller tidal

volume and inspiratory duration, as well as a prolonged expiration compared with the breathing observed in the vagotomized state. On inhaling 7% CO_2 the end-expiratory discharge decreased or cut out completely: consequently, stimulation of the vagus nerve was reduced or abolished during expiration and the expiratory duration was shortened. The increase in frequency so produced simulated very closely the reflex response to CO_2 which is seen in dogs on bypass, when both or one vagus nerve is intact. This is shown in Fig. 8, which demonstrates the increase in the

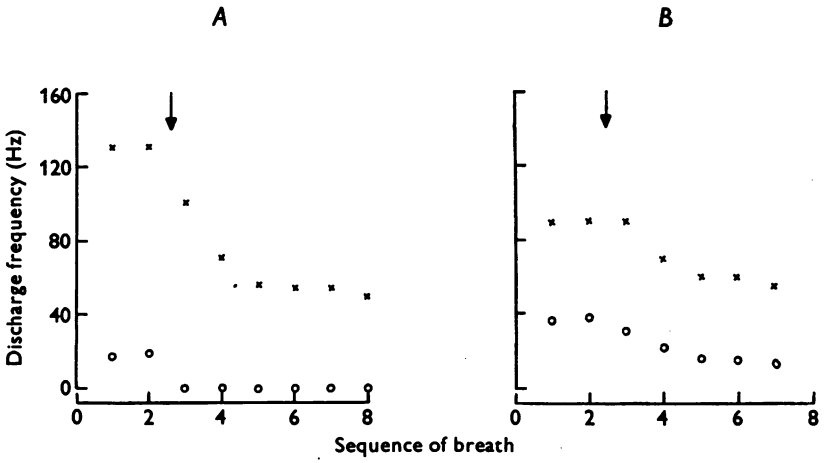

Fig. 6. Time relationship between inspiration of 7% CO_2 and the effect on pulmonary stretch receptor discharge. A sequence of breaths from two paralysed dogs ventilated at a constant tidal volume. 7% CO_2 was added to the inspired air at the arrows. Each graph shows the breath by breath peak inspiratory discharge frequency (crosses) and the end-expiratory discharge frequency (circles) for a single pulmonary stretch receptor.

frequency of breathing produced by 7% CO_2 with one vagus nerve intact; vagotomy abolished the response. When the central end of one of the cut vagus nerves was stimulated by coupling it to a pulmonary stretch receptor with an end-expiratory discharge (+E) there was an increase in breathing frequency when CO_2 was inhaled. However, this did not occur when the receptor had no end-expiratory discharge (−E).

Effect of changing the inspired CO_2 concentration on lung mechanics

Transpulmonary pressure can alter, even in a paralysed animal ventilated at a constant tidal volume, if airway resistance or lung compliance is changed by an increase in the inspired CO_2 concentration. This could alter the pulmonary stretch receptor discharge, since these receptors respond to the transpulmonary pressure difference rather than tidal volume directly

(Davis, Fowler & Lambert, 1956). A small fall in transpulmonary pressure was usual when the inspired CO_2 was increased; an example of this is shown in Fig. 9. In fourteen tests in five animals, with the vagus nerves intact, there was a mean percentage fall of peak inspiratory pressure of $6{\cdot}1 \pm 0{\cdot}7$ (S.E. of mean). Following vagotomy, the mean percentage fall was $5{\cdot}0 \pm 0{\cdot}7$ (S.E.of mean) in fifteen tests in seven animals (only two of these having the response tested before vagotomy).

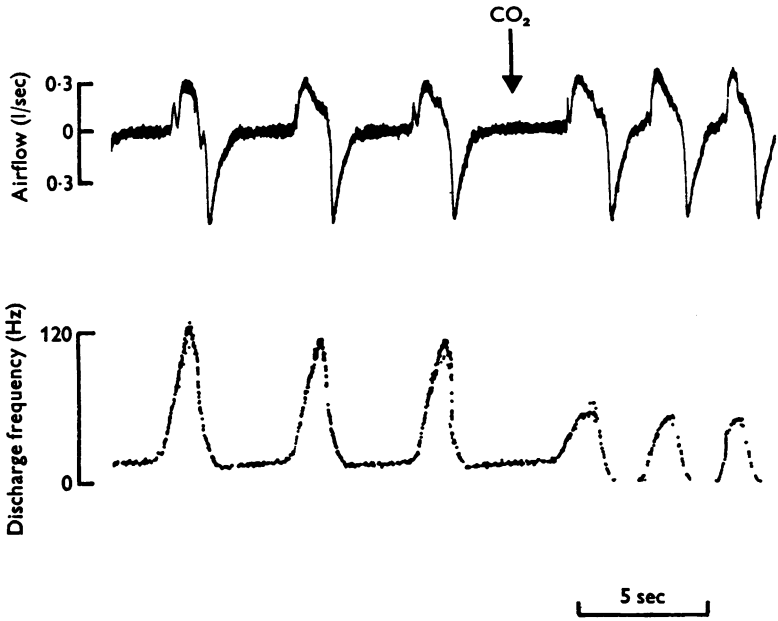

Fig. 7. Correlation between the reflex response to CO_2 and the effect on pulmonary stretch receptor discharge. A sequence of six breaths from an unparalysed dog with the left vagus nerve intact. The upper trace shows the airflow signal (inspiration upwards) and the lower trace shows the instantaneous frequency of discharge of a single pulmonary stretch receptor recorded from the cut right vagus nerve. CO_2 was added to the inspired air at the arrow.

DISCUSSION

These experiments demonstrate that the vagally mediated lung CO_2 reflex can be mediated by changes in expiratory pulmonary stretch receptor discharge frequency. Inhibition by CO_2 of pulmonary stretch receptor activity has been described for animals with normal circulation (Mustafa & Purves, 1972; Schoener & Frankel, 1972; Sant'Ambrogio *et al.* 1974). The present study has shown that increasing airway CO_2 concentration has a much more marked effect than changing arterial CO_2. Recently, Bartlett & Sant'Ambrogio (1976) have obtained similar results

when recording from slowly adapting stretch receptors located in a functionally isolated segment of trachea and bronchi. They found that whilst receptors in the bronchi were sensitive to changes in airway CO_2 those in the trachea were not. In the present study the receptor sites were not localized but nearly all the receptors studied showed a depression of discharge when airway CO_2 was increased (Fig. 2).

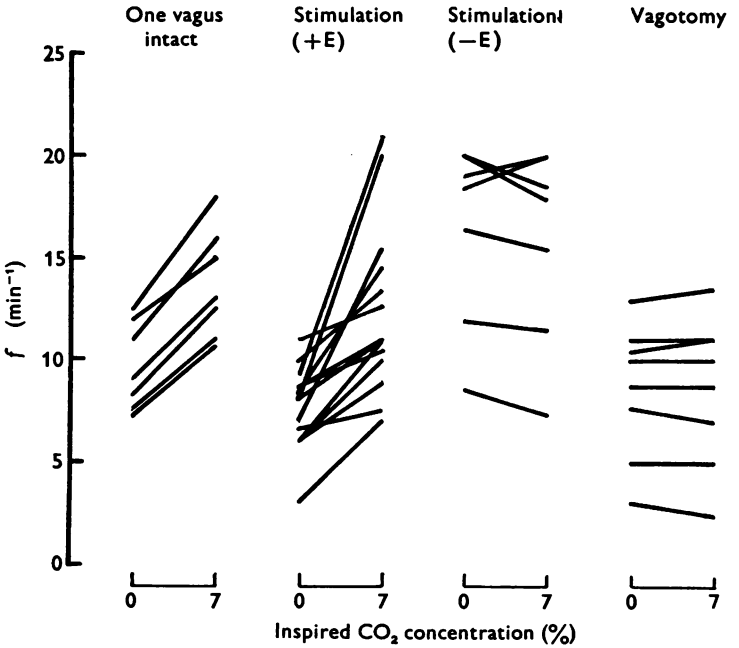

Fig. 8. Changes in the frequency of breathing produced by inhalation of 7% CO_2 in four different circumstances: with one vagus nerve intact; with stimulation of the central end of the vagus coupled to a pulmonary stretch receptor with an end expiratory activity (+E); with stimulation coupled to a pulmonary stretch receptor with no end-expiratory activity (−E); after bilateral vagotomy.

It has been suggested that pulmonary stretch receptor discharge during expiration prolongs the duration of expiration (Hering, 1868; Knox, 1973). It is therefore possible that the inhibition of this discharge during expiration by CO_2 could be responsible for the increased frequency of breathing, predominantly due to a shortening of expiratory duration, obtained when CO_2 is inhaled by dogs on cardiopulmonary bypass (Bartoli *et al.* 1974). To determine whether the end-expiratory discharge of pulmonary stretch receptors could be the mediator, the series of experiments involving triggered stimulation were performed. It was

only when the central end of the vagus nerve was stimulated with a pattern of activity from a pulmonary stretch receptor which included discharge during expiration that any increase in breathing frequency was observed as lung CO_2 concentration was raised. Depression of discharge during inspiration appeared not to influence the breathing frequency, probably because of the high initial pulmonary stretch receptor discharge

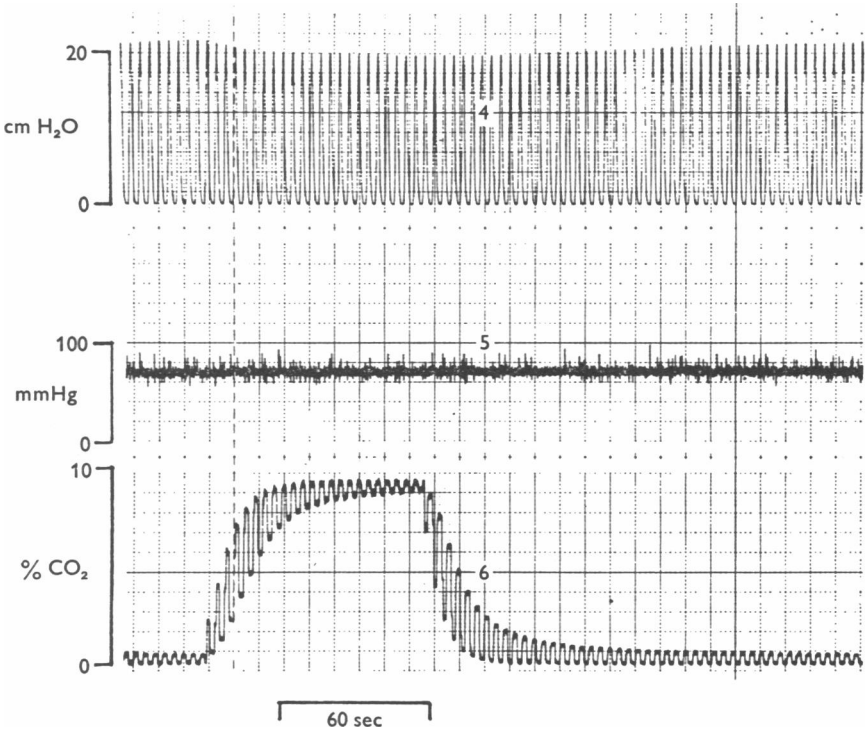

Fig. 9. The effect of end-tidal CO_2 on transpulmonary pressure in a paralysed dog ventilated at a constant tidal volume. The top trace shows transpulmonary pressure, the middle trace shows arterial pressure and the lower trace shows the end-tidal CO_2 concentration.

which is found at the low airway CO_2 prevailing in condition of cardiopulmonary bypass. Any change from this high frequency of discharge will thus be over the part of the hyperbolic curve relating the amount of inhibitory information required for termination of inspiration to inspiratory time where changes in inhibitory information have relatively little effect on inspiratory duration.

Although care was taken with the stimulation parameters to ensure that the majority of fibres being stimulated were from the pulmonary stretch receptors, it is obviously impossible in a nerve as complex as

the cervical vagus to exclude stimulation of other fibres. The non-myelinated fibres would certainly be excluded because of the high threshold voltage necessary to stimulate them but some fibres from lung irritant receptors might be stimulated. We tried to reduce the likelihood of this by reducing the stimulation voltage so that the compound action potential did not have an A_δ component. There is no evidence that irritant receptors are stimulated or inhibited by CO_2 (Sampson & Vidruk, 1975). However, the possibility that receptors other than pulmonary stretch receptors might be partly involved in the total CO_2 lung reflex is not completely excluded in the present study.

In contrast to the effect of changing airway CO_2, the present study has shown that changes in arterial P_{CO_2} produce small and inconsistent effects on pulmonary stretch receptor discharge. An important point to be taken into consideration, however, is that even in conditions of cardiopulmonary bypass it is not possible to obtain very low values of P_{a,CO_2}. The lowest P_{a,CO_2} obtained in this series was 18 mmHg, but the majority of dogs had P_{a,CO_2} values of above 25 mmHg, even when 100% O_2 was used as the exchange gas mixture in the bypass. Increases in alveolar P_{CO_2} from 25 mmHg upwards have relatively small effects on pulmonary stretch receptor discharge. The small depression of end expiratory discharge seen when the bypass gas was changed from 5–10% CO_2 did notr each statistical significance but it is of interest that Bartoli *et al.* (1974) found a small increase in the frequency of breathing when arterial P_{CO_2} was changed.

The means by which increases in airway CO_2 concentration depresses pulmonary stretch receptor discharge is unknown, but possible mechanisms are discussed by Sant'Ambrogio *et al.* (1974). Changes in airflow resistance produced by a direct or indirect effect of CO_2 cannot be the sole cause of the effect, since there was a clear difference in response to maintained lung inflation at different lung CO_2 concentrations. The slight fall in trans-pulmonary pressure (5·0%) produced by inhalation of CO_2 might have contributed to the decrease in peak frequency of discharge with constant volume inflation but is unlikely to explain the decrease in mean frequency from 87 to 64 Hz.

The present results raise the question of why vagotomy should prolong expiratory duration when depression of pulmonary stretch receptor discharge shortens expiratory duration. This may well be because expiratory duration depends not only on pulmonary stretch receptor activity during expiration but also on the length of the preceding inspiration (Boyd & Maaske, 1939; Clark & Euler, 1972). Lengthening of expiratory duration with vagotomy is thus achieved indirectly by lengthening of inspiratory duration despite the removal of pulmonary stretch receptor

activity during expiration. No such change in inspiratory duration has been shown when the airway CO_2 is increased in conditions of cardiopulmonary bypass.

The role of the lung CO_2 reflex in response to inhaled CO_2 in the intact dog would be smaller than is suggested by a response such as that shown in Fig. 7. Such large responses are obtained at airway CO_2 concentrations below the physiological range. Over the physiological range the effect is less marked (Fig. 3). Nevertheless, the increase in respiratory frequency during CO_2 breathing is attenuated or abolished by vagotomy (Scott, 1908; Bradley *et al.* 1974). This could be due to the removal of the vagal component of the inspiratory 'off switch' mechanism (Clark & Euler, 1972) but might partly be due to the mechanism described here.

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