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VENTILATION IN INTACT AND GLOSSOPHARYNGEAL NERVE SECTIONED ANAESTHETIZED RATS EXPOSED TO OXYGEN AT HIGH PRESSURE

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SUMMARY

1. The cause of the initial hyperventilation, which occurs on exposure to O_2 at high pressure (o.h.p.), has been investigated by measuring tidal volume (V_T), frequency of breathing (f) and hence ventilation ($\dot{V}_E$) in thirty-six barbiturate-anaesthetized rats, with or without their glossopharyngeal (IX) nerves sectioned, during 30–60 min of exposure to o.h.p. at 4, 6 or 8 atm absolute.

2. In intact rats the rates of rise of V_T, f and $\dot{V}_E$ with time during exposure to o.h.p. were smallest at 4 and greatest at 8 atm absolute. In IX-sectioned rats the rates of rise of V_T at 4, 6 and 8 atm absolute and of f at 4 atm absolute were similar to those of intact rats. At 6 atm absolute and even more so at 8 atm absolute, however, f decreased. Hence the slope of $\dot{V}_E$ in IX-sectioned compared with intact rats was similar at 4 atm absolute but smaller at 6 and 8 atm absolute. In fact at 8 atm absolute $\dot{V}_E$ remained constant in IX-sectioned rats.

3. Since the slope of $\dot{V}_E$ *versus* time in intact rats was steeper the greater the pressure and since the removal of carotid bodies in IX-sectioned rats reduced the $\dot{V}_E$ slope at 6 and 8 atm absolute, the stimulus to the hyperventilation induced by o.h.p. cannot be an accumulation of CO_2 in the brain resulting from the lack of O_2 desaturation of haemoglobin. This theory would predict that $\dot{V}_E$ should be identical at all pressures above 3·5 atm absolute.

4. The findings in the IX-sectioned rats indicate a major contribution of the carotid bodies to the f increase in o.h.p. They may be stimulated by a histotoxic hypoxia induced by early O_2 poisoning. Since the V_T increase on exposure to o.h.p. was both large and fairly similar in intact and IX-sectioned rats, it is suggested that a large part of the V_T increase was caused by stimulation of the central chemoreceptors by lactic acidosis induced by an o.h.p.-induced histotoxic hypoxia of the brain.

INTRODUCTION

On exposure to pure O_2 at high pressure (o.h.p.) above 3·5 atm absolute mammals exhibit an initial, slowly increasing hyperventilation which is followed by an irregular and then a slow deep dyspneic pattern of breathing until the onset of respiratory failure (Bean, 1945; Taylor, 1958, 1960; Clark & Lambertsen, 1971). The initial

increase in ventilation ($\dot{V}_E$) is largely due to an increase in tidal volume (V_T); frequency of breathing (f) either increases slightly, stays the same or decreases. The irregular breathing coincides with the appearance of convulsions, which are a manifestation of acute O_2 poisoning of the central nervous system (C.N.S.), and the higher the O_2 pressure the earlier these convulsions occur. Gross pulmonary damage from O_2 poisoning is not usually detected until after the convulsions have begun but microscopic evidence indicates that pulmonary damage develops slowly throughout the period of o.h.p. exposure. Both C.N.S. and pulmonary poisoning contribute to the eventual death. Anaesthetics, in particular barbiturates, prevent the convulsions, retard the development of pulmonary damage and prolong the survival time without modifying the progressive changes in breathing (Taylor, 1958, 1960; Clark & Larbertsen, 1971).

Our research is concerned only with the causes of the initial hyperventilation in o.h.p. At O_2 pressures above 3·5 atm absolute the resting O_2 requirements of the animal can be met from O_2 in physical solution in the arterial blood. Thus there is no desaturation of haemoglobin and the CO_2 buffering capacity of the venous blood decreases resulting in an increase in the P_{CO_2} in the tissues (Gesell, 1923; Bean, 1931). Such an accumulation of CO_2 in the brain could stimulate the central chemoreceptors and cause the observed hyperventilation on exposure to o.h.p. (Lambertsen, Stroud, Gould, Kough, Ewing & Schmidt, 1953*c*; Lambertsen, Kough, Cooper, Emmel, Loeschcke & Schmidt, 1953*a*). Indeed, increases in arterial and venous P_{CO_2} in dogs at 5 atm absolute of o.h.p. (Bean, 1931) and an increase in jugular venous P_{CO_2} in man at 3·5 atm absolute of o.h.p. (Lambertsen, Kough, Cooper, Emmel, Loeschcke & Schmidt, 1953*b*; Lambertsen, Ewing, Kough, Gould & Stroud, 1955) have been demonstrated. However, arterial and mixed venous P_{CO_2} actually decreased in anaesthetized rats and cats exposed to o.h.p. at 6 atm absolute; the P_{CO_2} increased only when severe respiratory failure followed the initial hyperventilation (Taylor, 1958, 1960; Drysdale & Taylor, 1964, 1965). Furthermore, doses of Tris buffer sufficient to cause a considerable metabolic alkalosis in anaesthetized cats did not reduce hyperventilation at 6 atm absolute of o.h.p. (Drysdale & Taylor, 1964, 1965). In a preliminary study in anaesthetized cats the greater the o.h.p. (3·5, 6 and 8 atm absolute) the greater was the rate of increase in $\dot{V}_E$ before respiratory failure and it was suggested that o.h.p. may have a direct stimulating effect on the respiratory centres before it poisons them (Kerr, Bateman, Drysdale & Taylor, 1968).

The effects of increasing pressures of o.h.p. on the initial hyperventilation have been re-examined by measuring the V_T and f of anaesthetized rats exposed to 4, 6 and 8 atm absolute pure O_2. These measurements are more accurate than those of earlier workers and the magnitude and time course of changes in V_T and f are analysed in more detail. If CO_2 accumulation in the brain is the stimulus, the slope of $\dot{V}_E$ *versus* time should be independent of pressure above 3·5 atm absolute whereas, if the drive is a direct effect of increased P_{CO_2} on the respiratory centres, the slope of $\dot{V}_E$ should increase with increasing o.h.p.

O.h.p. may, however, stimulate $\dot{V}_E$ via one or more respiratory receptors rather than by directly stimulating the respiratory centres. One of the suggested mechanisms of O_2 poisoning is by an increased production of O_2 free radicals which oxidize essential enzymes leading to a decreased O_2 consumption (Haugaard, 1968; Kovachich & Haugaard, 1981), that is a hyperoxic histotoxic hypoxia. Tissues with a high blood

flow and high metabolic rate, such as brain, have been shown to be the most susceptible to O_2 poisoning (Bohr & Bean, 1942; Dickens, 1946). The carotid bodies, which detect hypoxia and have their afferents in the glossopharyngeal nerves, should be particularly susceptible to O_2 poisoning because they have a high blood flow and a high metabolic rate (Daley, Lambertsen & Schweitzer, 1954; Purves, 1970). Hence the V_T and f of anaesthetized rats with their glossopharyngeal nerves sectioned were also examined during exposure to o.h.p. at 4, 6 and 8 atm absolute to determine the contribution of the carotid bodies to the initial hyperventilation.

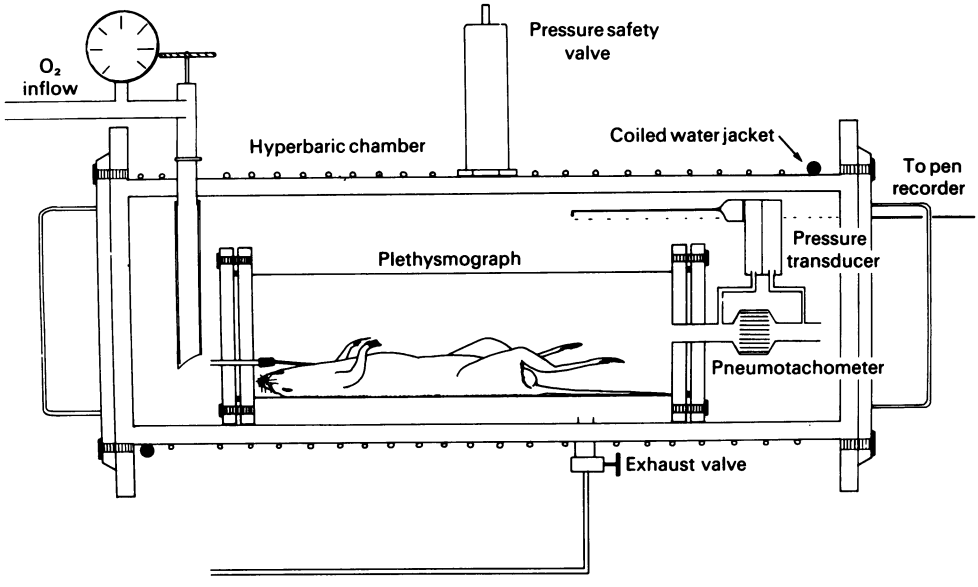

Fig. 1. Diagram of the experimental apparatus.

METHODS

Thirty-six male New Zealand Wistar rats (body wt. 275–325 g) were anaesthetized with pentobarbitone (50 mg/kg body wt. I.P.), followed 40 min later by sodium barbitone (200 mg/kg body wt. I.P.). These doses of anaesthetic resulted in a deep and long-lasting level of anaesthesia in which the limb-withdrawal reflex was barely present. This level would presumably lighten during the course of the experiment although it was not possible to test for this during the exposure to o.h.p. After tracheal cannulation, in half the rats the glossopharyngeal nerves were sectioned bilaterally where the nerves emerge from the skull (IX-sectioned); in the other half these nerves were exposed only (intact). Loss of the ventilatory response to a hypoxic inspirate (10% O_2) was taken as proof of complete glossopharyngeal nerve section. Twelve rats (six IX-sectioned and six intact) were exposed to 4 atm absolute (400 kPa), twelve rats to 6 atm absolute (600 kPa) and twelve rats to 8 atm absolute (800 kPa). The average exposure times to o.h.p. were (mean ± S.E. of the mean): intact, 4 atm absolute 59 ± 5, 6 atm absolute 44 ± 7, 8 atm absolute 27 ± 4 min; IX-sectioned 4 atm absolute 66 ± 9, 6 atm absolute 34 ± 9, 8 atm absolute 25 ± 4 min. Thus intact and IX-sectioned rats had statistically similar exposure times which were significantly shorter for each increment in pressure ($P < 0.001$, analysis of variance).

The anaesthetized rat was placed supine in a 1·3 l Perspex plethysmograph with its tracheal cannula open to a steel pressure chamber (Fig. 1). The rat in its plethysmograph was exposed to o.h.p. in this 8 l pressure chamber which was surrounded by a coiled water jacket through which water was circulated to maintain the temperature within the chamber at 32 °C. This minimized

adiabatic fluctuations and maintained the body temperature of the rat at 37 °C. The pressure chamber was flushed with pure O_2 until the O_2 concentration in the exhaust gas was > 98% (measured by a Beckman OMII O_2 analyser). Pressure was applied with Medical Compressed Oxygen B.P. from a 6800 l cylinder via a two-stage reduction valve at the rate of about 1 atm absolute/min and then held constant (±0·05 atm absolute) at the required level. The accumulation of CO_2 within the chamber was prevented by continuously flowing pure O_2 through a wide-bore tube, from the inlet of the pressure chamber to the immediate vicinity of the open end of the tracheal cannula, with a steady leak of O_2 flow through an exhaust valve (Fig. 1). There was no detectable CO_2 (measured by a Beckman LB2 CO_2 analyser) in the exhaust gas.

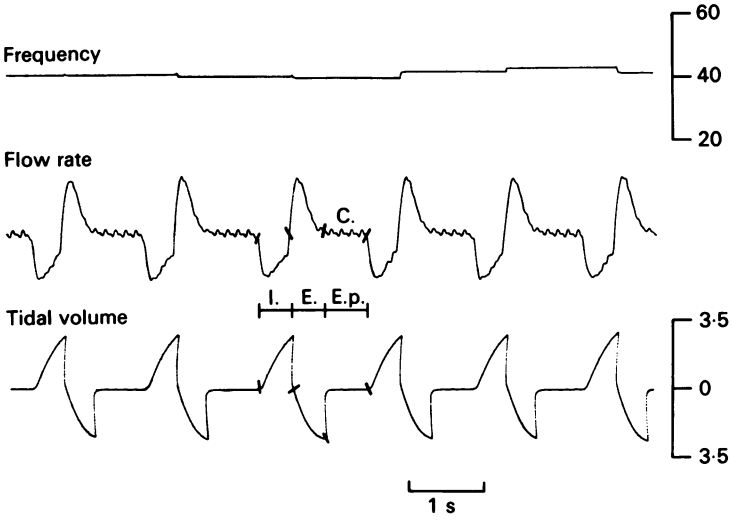

Fig. 2. Segment of experimental trace showing respiratory frequency (/min) and uncalibrated flow rate which when integrated gave tidal volume (ml) from a rat breathing pure O_2 at 6 atm absolute. I. = inspiration, E. = expiration, E.p. = expiratory pause, C. = cardiogenic oscillations.

V_T and f during exposure to o.h.p. were measured by flow plethysmography. The flow of gas through the Fleisch 000 pneumotachometer (Fig. 1) induced by respiratory movements was detected by a Grass volumetric differential pressure transducer, amplified and displayed by a Grass pen recorder as a flow trace. The flow signal triggered a Grass tachometer to display f and was integrated by a Grass integrator to measure V_T (Fig. 2). V_T and f were recorded continuously from the time of reaching the required pressure until V_T or f started to fall dramatically or breathing became irregular or dyspneic (slow and deep). The rats were then decompressed at a rate of about 0·5 atm absolute/min (Bean, 1945). After decompression, particularly from higher pressures, the rats' breathing remained depressed and irregular and the limb-withdrawal reflex was absent. The rats were then killed by cervical dislocation.

At intervals of 0·5 min during exposure to o.h.p., V_T (ml/100 g body wt.) was calculated using a volume calibration factor (see below) and the base line to mean peak or trough amplitude of 10 breaths from the volume trace. Frequency (breaths/min) was calculated from the average breath duration and $\dot{V}_E$ (ml/100 g.min) finally calculated as $V_T \times f$. Linear regression analyses (Sokal & Rohlf, 1969) of V_T, f and $\dot{V}_E$ during the exposure to o.h.p. were performed on the pooled data from the six intact and IX-sectioned animals for each pressure. Student's t test was used to determine whether slopes were significantly different from zero and the F test to determine any significant differences amongst the various slopes for each respiratory variable (Snedecor & Cochran, 1967).

The pneumotachometer was calibrated with room air at ambient pressure using a motor-driven syringe (Harvard 680 Rodent Respirator) delivering a range of volumes and frequencies similar to those observed during the course of the exposure to o.h.p. The pneumotachometer gave a linear

response, independent of the frequency, to all the volumes encountered in the experiments (Fig. 3). The volume calibration factor from the motor-driven syringe was corrected for the difference between the dynamic viscosities of room air at 20 °C ($1{\cdot}83 \times 10^{-5}$ N s/m²) and of 100 % O_2 at 32 °C ($2{\cdot}06 \times 10^{-5}$ N s/m²) by dividing by 1·13 (Blumenfeld, Turney & Crowley, 1973). It was not possible to calibrate the pneumoctachometer at increased pressure because the motor-driven syringe would not fit into the hyperbaric chamber. Theoretical calculations did, however, indicate that flow would be laminar and within the linear range of the pneumotachometer even at the highest encountered peak flow values of 8 atm absolute.

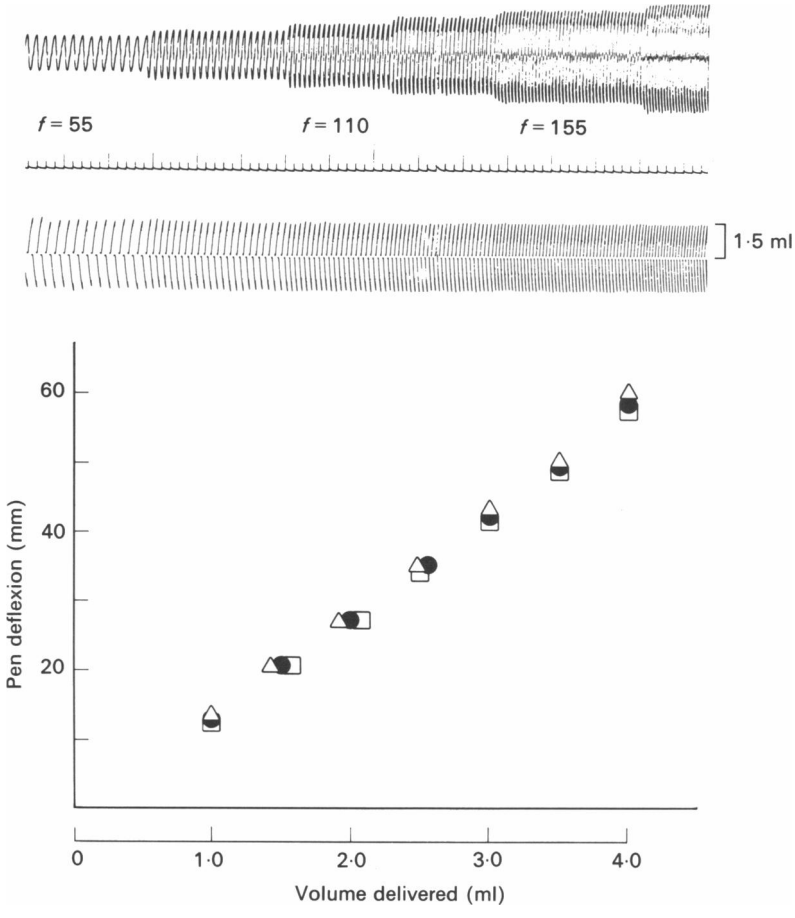

Fig. 3. Calibration of pneumotachometer with room air at ambient pressure. Pen record: upper trace is flow rate and lower trace is integrated flow rate (volume) for the same volume at different frequencies. Graph: various volumes delivered by the motor-driven syringe at frequencies of 55 (△), 110 (●) and 155/min (□) gave a linear response.

RESULTS

There was no increase in V_T or f on exposure to 10 % O_2 in N_2 at ambient pressure for 30 s in any of the IX-sectioned rats, confirming that the aortic bodies do not seem to be functionally significant in the $\dot{V}_E$ response to hypoxia in rats (Sapru & Krieger, 1977).

For both intact and IX-sectioned rats the mean initial f, measured in the first

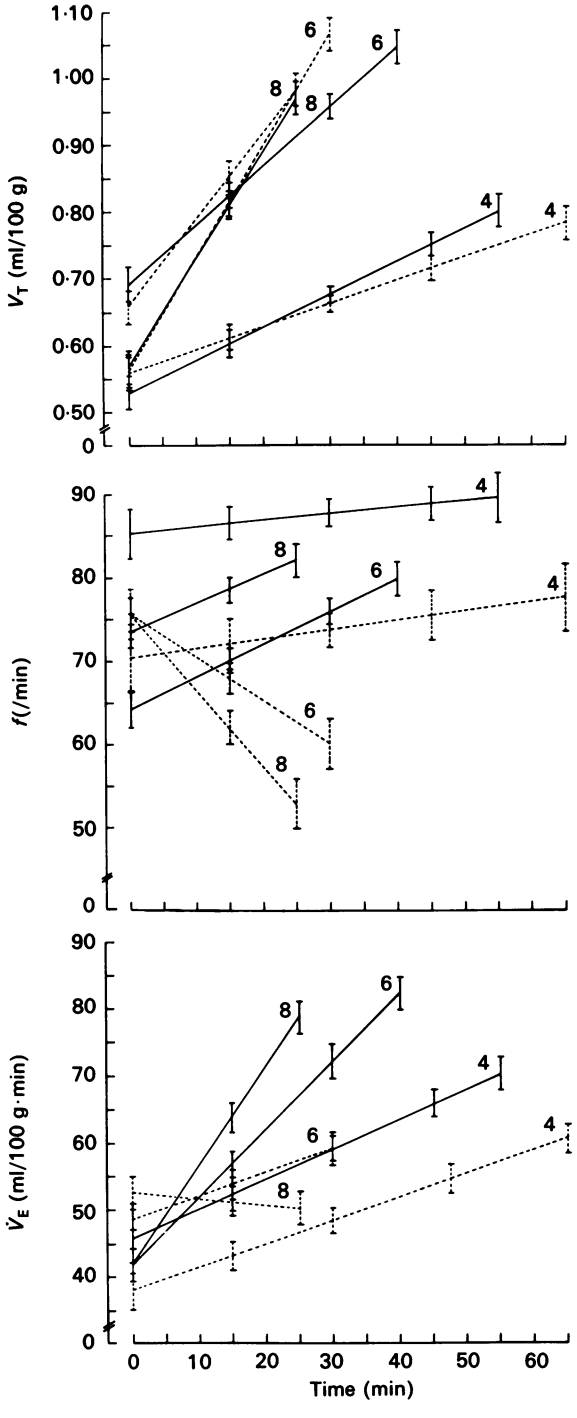

Fig. 4. Linear regression lines for tidal volume (V_T), frequency (f) and ventilation ($\dot{V}_E$) against time of exposure to O_2 at 4, 6 and 8 atm absolute in intact (——) and IX-sectioned (- - - -) rats. Bars indicate 95% confidence limits.

minute after the required pressure was obtained, was the same as that before compression. However, the mean initial V_T and hence $\dot{V}_E$ increased by 5–10%; this increase was similar in the two groups of rats and unaffected by the pressure (initial $\dot{V}_E$ intact: 4 atm absolute 44±3, 6 atm absolute 47±3, 8 atm absolute 41±3 ml/100 g.min; initial $\dot{V}_E$ IX-sectioned: 4 atm absolute 39±5, 6 atm absolute 46±4, 8 atm absolute 44±2 ml/100 g.min). Cardiogenic oscillations were very prominent at pressure (Fig. 2) but their amplitude was the same at 4, 6 and 8 atm absolute.

TABLE 1. Linear regression slopes of V_T, f and $\dot{V}_E$ *versus* time ± S.E. of the mean and the intercepts at zero time ± S.E. of the mean ($n > 300$) during o.h.p. at 4, 6 and 8 atm absolute in intact and IX-sectioned rats

	Intact		IX-sectioned	
O.h.p.	Slope	Intercept	Slope	Intercept
	Tidal volume (V_T, ml/100 g)			
4 atm absolute	0·005±0·0003	0·53±0·01	0·0035±0·0002	0·56±0·01
6 atm absolute	0·009±0·001	0·69±0·01	0·017 ±0·001	0·56±0·02
8 atm absolute	0·016±0·001	0·57±0·01	0·013 ±0·001	0·66±0·01
	Intact		IX-sectioned	
O.h.p.	Slope	Intercept	Slope	Intercept
	Frequency (f, breaths/min)			
4 atm absolute	0·07±0·03	85±1	0·11±0·03	70±1
6 atm absolute	0·39±0·03	64±1	−0·53±0·08	76±2
8 atm absolute	0·34±0·09	73±2	−0·91±0·05	76±1
	Intact		IX-sectioned	
O.h.p.	Slope	Intercept	Slope	Intercept
	Ventilation ($\dot{V}_E$, ml/100 g.min)			
4 atm absolute	0·44±0·02	46±1	0·35±0·02	38±1
6 atm absolute	1·01±0·03	42±1	0·35±0·06	48±1
8 atm absolute	1·50±0·10	42±2	−0·09±0·06	53±1

Individual and pooled data for intact rats of V_T, f and $\dot{V}_E$ were plotted against time at 0·5 min intervals of exposure to each particular atm absolute of o.h.p. Both V_T and $\dot{V}_E$ increased linearly with time, while the increase in f was slightly curvilinear with a progressively smaller rate of change with time during the exposure to o.h.p. Since the increases in f were small, however, application of linear regression analysis did not distort the f value ascribed to initial and final moments of o.h.p. exposure.

In the intact rat the slope of the increase in V_T *versus* time during exposure to o.h.p. (Fig. 4 and Table 1) was steeper the greater the pressure (8 atm absolute > 6 atm absolute > 4 atm absolute; $P < 0·001$). The increase in f was small at 4 atm absolute ($P < 0·05$) but greater at 6 atm absolute ($P < 0·001$) and at 8 atm absolute equal to that at 6 atm absolute. It is apparent from Fig. 4 that the 4 atm absolute group of intact rats were initially relatively rapid, shallow breathers and the 6 atm absolute group were relatively slow, deep breathers. The changes in V_T and f during exposure to o.h.p. resulted in the slope of $\dot{V}_E$ *versus* time being steeper the greater the pressure ($P < 0·001$).

V_T, f and $\dot{V}_E$ changed also in the IX-sectioned rats approximately linearly with time of exposure to o.h.p. and hence data were subjected to linear regression analyses. The slope of the increase in V_T with time in IX-sectioned rats (Fig. 4 and Table 1) was steeper the greater the pressure (6 atm absolute > 4 atm absolute; $P < 0.001$) although the slopes for 6 and 8 atm absolute were fairly similar. The slopes of V_T *versus* time at any given pressure were significantly flatter at 4 atm absolute ($P < 0.05$) and at 8 atm absolute ($P < 0.001$) and steeper at 6 atm absolute ($P < 0.001$) in IX-sectioned than in intact rats. In IX-sectioned rats the increase in f *versus* time at 4 atm absolute was the same as in intact rats but at 6 and 8 atm absolute f actually decreased and the fall was steeper the greater the pressure ($P < 0.001$). The rate of change of $\dot{V}_E$ in the IX-sectioned rats at 4 atm absolute was the same as in the controls, at 6 atm absolute it was considerably less ($P < 0.001$), while at 8 atm absolute it remained unchanged for the period of exposure.

DISCUSSION

Initially when exposed to pressure f was the same as before compression, but V_T and hence $\dot{V}_E$ were 5–10 % higher. Since this V_T increase was independent of the initial pressure of O_2, it is unlikely to be due to stimulation by o.h.p. during the period of compression. Nor is it likely to be due to lightening of anaesthesia, which has been shown to occur immediately on exposure to o.h.p. (Bean, 1931, 1945), since the depth of barbiturate anaesthesia in rats affects f as well as V_T (P. A. Cragg & D. B. Drysdale, unpublished observation). The initial increase in V_T may be the result of the flow integrator summing the increased, but pressure-independent, amplitude of the cardiogenic oscillations. Gelfand, Lambertsen, Petersen & Slater (1976) have thus shown that tiny oscillatory waves at ambient pressure are magnified considerably at high pressure and augment the integrator output.

During the 30–60 min period of exposure to o.h.p. the increase in $\dot{V}_E$ was due to an increase mainly in V_T in agreement with earlier work (Bean, 1945). In a carotid-body-intact animal f in o.h.p. has been reported to increase slightly, remain unchanged or decrease (Bean, 1945). In our intact rats f always increased while Taylor (1958) found f to remain unchanged in rats exposed to o.h.p. at 6 atm absolute. The effect of carotid body denervation on breathing during o.h.p. has only been examined in two other studies (Bean & Rottschafer, 1938; Taylor 1960). We found in IX-sectioned compared with intact rats that the slope of the $\dot{V}_E$ increase *versus* time was slightly less at 4 atm absolute, considerably less at 6 atm absolute and insignificantly different from zero at 8 atm absolute. For dogs exposed to o.h.p. at 5 atm absolute Bean & Rottschafer (1938) concluded that removal of the carotid bodies failed to prevent hyperventilation. We found in IX-sectioned rats that f decreased rather than increased during o.h.p. at 6 and 8 atm absolute whereas Taylor (1960) reported no obvious difference between the f response of carotid sinus nerve-sectioned and intact cats at 6 atm absolute. The differences between our data and those of earlier workers may be species dependent or may reflect the more accurate estimation of respiratory variables which is possible today.

The carotid bodies appear to contribute considerably to the increase in f at 6 and 8 atm absolute but only slightly to the increase in V_T during o.h.p. (Fig. 4). O_2 at

high pressure may induce a histotoxic hypoxia (Haugaard, 1968) within the carotid bodies. Certainly, intact rats exposed to hypoxia at ambient pressure respond with large increases in f and only small increases in V_T (Cragg & Drysdale, 1983).

The causes of the large decrease in f during 6 and 8 atm absolute of o.h.p. after carotid body denervation and the large increase in V_T during o.h.p. in both intact and IX-sectioned rats remain to be established. A possible balance of four factors that could be operating during 6 and 8 atm absolute of o.h.p. is proposed:

(i) Stimulation of the carotid bodies by a progressive histotoxic hypoxia during o.h.p. at 6 and 8 atm absolute, as stated above, is likely to increase f considerably more than V_T.

(ii) Over the 25–40 min period of each experiment the level of anaesthesia must undoubtedly have lightened causing small increases in f and V_T. However, the extent of this is uncertain since O_2 itself, because of its lipid solubility, exhibits an anaesthetic action at pressure (Paton, 1967) and because the limb-withdrawal reflex was absent after decompression.

(iii) Progressive damage to the respiratory centres caused by gradual O_2 poisoning is likely to depress considerably f and augment V_T as this is the breathing pattern commonly found in deteriorating anaesthetized rats which have been repeatedly exposed to severe hypoxia (P. A. Cragg & D. B. Drysdale, unpublished observation).

(iv) On the basis that damage to the respiratory centres is unlikely to have caused the large increase in V_T encountered in o.h.p., it is suggested that other respiratory receptors stimulated by o.h.p. may be responsible for much of the progressive increase in V_T and only some of the increase in f. The most likely receptor is the central chemoreceptor because when stimulated directly by acidity in the cat it causes increases in V_T with a negligible effect on f (Schlaefke, See & Loeschcke, 1970) or when stimulated indirectly by hypercapnia in IX-sectioned rats it causes a proportionately greater increase in V_T than in f (Cragg, Drysdale & Singh, 1981).

Accumulation of CO_2 in the brain as a consequence of the lack of O_2 desaturation of haemoglobin (Clark & Lambertsen, 1971) does not appear to be the major stimulus to hyperventilation during o.h.p. for two reasons. First, in intact rats the slope of $\dot{V}_E$ *versus* time during exposure to o.h.p. was steeper the greater the pressure which confirms preliminary results in anaesthetized cats (Kerr *et al.* 1968). If the hyperventilation had been due to CO_2 accumulation in the brain, both $\dot{V}_E$ and brain CO_2 would have reached a maximum at 3·5 atm absolute and $\dot{V}_E$ should have been identical in 4, 6 and 8 atm absolute of o.h.p. Secondly, there should not have been such a large and pressure-dependent difference in the responses of $\dot{V}_E$ and f to o.h.p. between intact and IX-sectioned rats because the central chemoreceptors in the medulla oblongata, which are the major CO_2 receptors of the body (Schlaefke, 1981), were present in both cases. Furthermore, IX-sectioned rats exposed to hypercapnia at ambient pressure respond by increasing both f and V_T (Cragg *et al.* 1981).

The central chemoreceptors may, however, be stimulated by two other mechanisms. First, since cerebral blood flow in anaesthetized dogs has been found to decrease progressively as o.h.p. increased from 0 to 2 atm absolute (McDowall, 1966), brain P_{CO_2} might increase and thus stimulate the central chemoreceptors. However, in conscious rats exposed to O_2 at 5 atm absolute it has been reported that cerebral blood flow after an initial fall returned to normal within 20 min of exposure, and that at

7 atm absolute no changes occurred throughout the period of exposure (Torbati, Parolla & Lavy, 1978). The second and in our view most likely possible mechanism involves central chemoreceptor stimulation by an increased concentration of lactic acid in the brain. An increased lactic acid concentration in the cerebrospinal fluid of anaesthetized cats exposed to O_2 at 6 atm absolute has been reported by Kerr *et al.* (1968). The lactic acid production may be caused by the histotoxic hypoxia (Bledsoe & Hornbein, 1981) induced by o.h.p. in the brain (Haugaard, 1968).

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