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ANALYSIS OF FACTORS THAT CONTRIBUTE TO CARDIOVASCULAR CHANGES INDUCED IN THE CAT BY GRADED LEVELS OF SYSTEMIC HYPOXIA

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SUMMARY

1. In cats anaesthetized with Saffan, which does not block afferent activation of the brain stem defence areas, we have analysed the cardiovascular changes induced by 3 min periods of graded systemic hypoxia (fraction of O_2 in inspirate, F_{i,O_2}, 0·15, 0·12, 0·08, 0·06).

2. At light levels of Saffan anaesthesia, hypoxia (particularly F_{i,O_2} 0·08 and 0·06) or selective stimulation of carotid chemoreceptors evoked the pattern of tachycardia, decrease in renal and mesenteric vascular conductance (RVC, MVC), but increase in femoral vascular conductance (FVC) which is characteristic of the alerting–defence response. This supports our view that activation of the defence areas is an integral part of the response to systemic hypoxia.

3. Hypoxia also induced an increase in frequency of augmented breaths which was graded with the level of hypoxia: 0·6 min^{-1} at F_{i,O_2} 0·21 to 1·1 min^{-1} at F_{i,O_2} 0·06; in some cats each of these was accompanied by a transient fall in arterial pressure (ABP) and increase in FVC. It is proposed that these responses were all part of a reflex elicited by lung irritant receptors and facilitated by peripheral chemoreceptors. However, their low rate of occurrence and the liability of the vasodilatation suggests they do not make major contributions to the overall response.

4. The above short-lasting responses were superimposed upon gradual changes whose magnitudes were graded with the level of hypoxia: hyperventilation, slight tachycardia, but bradycardia at F_{i,O_2} 0·6, small increases in ABP, FVC and MVC allowing femoral and mesenteric blood flow to increase, but decreases in RVC which maintained renal blood flow constant.

5. Vagotomy had no significant effect on these changes. Further, hyperinflation of the lungs with pressures of 10 mmHg evoked the Breuer–Hering reflex but had no noticeable cardiovascular effect. It is proposed that, in the cat, reflex tachycardia and vasodilatation elicited by lung stretch receptors play no significant part in the response to hypoxia.

6. By contrast, after pneumothorax, with ventilation and thereby arterial P_{CO_2}

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(P_{a,CO_2}) maintained constant, graded hypoxia produced graded bradycardia, decrease in MVC and RVC and no change in FVC. Taken together, these results suggest that in the spontaneously breathing cat, the response to hypoxia is dominated by the effects of hypocapnia secondary to hyperventilation, which by inhibiting peripheral and central chemoreceptor activity effectively counteracts the primary bradycardia and peripheral vasoconstriction elicited by hypoxic stimulation of peripheral chemoreceptors.

7. These proposals are compared with those drawn for other species.

INTRODUCTION

In recent experiments on rats anaesthetized with the steroid anaesthetic Saffan–Althesin (Glaxovet–Glaxo) which, unlike other commonly used anaesthetics, does not block transmission through the brain stem defence areas, we have provided the first evidence that by stimulating peripheral chemoreceptors, systemic hypoxia can evoke the cardiovascular and other autonomic components of the alerting stage of the defence response (visceral alerting response, Marshall, 1987; Marshall & Metcalfe, 1988*b*). This response, which includes tachycardia, a rise in arterial pressure, vasodilatation in skeletal muscle and vasoconstriction in renal and mesenteric circulation, was superimposed upon more gradual cardiovascular changes whose magnitude were graded with the level of hypoxia. These changes comprised tachycardia waning to bradycardia and a substantial fall in arterial pressure which was attributable to vasodilatation in all major vascular beds, including cerebral, mesenteric, renal and skeletal muscle, predominantly caused by the local vasodilator effects of hypoxia (Marshall & Metcalfe, 1988*b*, *c*). In addition, we not only confirmed previous evidence that graded hypoxia leads to a graded increase in the frequency of augmented breaths (Bartlett, 1971; Glogowska, Richardson, Widdicombe & Winning, 1972), but showed that each one of these was accompanied by a transient peripheral vasodilatation, fall in arterial pressure and sometimes by bradycardia. We deduced that these transient cardiovascular changes were part of a primary reflex initiated by rapidly adapting pulmonary irritant receptors and facilitated by peripheral chemoreceptors (Marshall & Metcalfe, 1988*a*).

Although it has been reported that systemic hypoxia induces behavioural alerting in other species, e.g. cat, dog, rabbit and man (Korner, Uther & White, 1969; Miller & Tenney, 1975; Koehler, McDonald & Krasney, 1980; Rose, Anderson & Carey, 1984; Rowell & Blackmon, 1986), there has been no investigation of whether this is accompanied by the characteristic cardiovascular components of the alerting response. However, it is clear from previous analyses of the gradual cardiovascular changes evoked by hypoxia in dog and rabbit (Uther, Hunyor, Shaw & Korner, 1970; Koehler *et al.* 1980) that there is considerable variation between species in the relative importance of the various reflexes, respiratory-dependent influences and local effects of hypoxia that contribute to the final response to hypoxia. Indeed, we have argued (Marshall & Metcalfe, 1988*b*) that the rat and other such small mammals are particularly susceptible to the local effects of hypoxia because they have a high rate of O_2 consumption per body weight which is readily compromised by hypoxia (Hill, 1959). Moreover, although augmented breaths are a common feature of

respiration in newborn and small adult mammals, they occur much less frequently in large adult species (McCutcheon, 1959). Thus, it was important to establish whether, and to what extent, the responses we have observed in the rat in systemic hypoxia occur in other larger species.

The species we chose for study was the cat, whose rate of O_2 consumption, in common with that of larger species like dog and man, is not reduced by hypoxia (see Hill, 1959). Saffan can be used successfully in the cat (Timms, 1981), whereas it commonly produces an anaphylactic reaction in the dog (Child, Currie, Davis, Dodds, Pearce & Twissell, 1970). Further we have already shown that in cats under Saffan anaesthesia, selective stimulation of carotid chemoreceptors can evoke the visceral alerting response (Hilton & Marshall, 1982). To our knowledge there has been no previous attempt to make a full analysis of the cardiovascular response evoked by systemic hypoxia in the cat. Weissman, Rubinstein & Sonnenschein (1976) made a brief report of changes in mesenteric, renal and hindlimb vascular resistance, but not heart rate, in cats that were paralysed, artificially ventilated and under Ketamine anaesthesia, which is known to block afferent activation of the defence areas (Timms, 1982). Some of the results have already been reported (Marshall & Metcalfe, 1987).

METHODS

Experiments were carried out on eighteen male or female cats (body weight: $3{\cdot}03 \pm 0{\cdot}1$ kg, mean $\pm$ S.E.M.). Anaesthesia was induced with O_2 and N_2 (80%:20%) and halothane and was maintained by a continuous infusion of Saffan given via a cannula placed in the right femoral vein, at 8–12 mg total steroids kg^{-1} h^{-1} during surgery and at 3–6 mg kg^{-1} h^{-1} during the experimental period (cf. Timms, 1981; Hilton & Marshall, 1982). The techniques used to record cardiovascular and respiratory variables were the same as those described previously (Hilton & Marshall, 1982), and the equipment was that described recently (Marshall & Metcalfe, 1988*a*). Briefly, arterial pressure (ABP) was recorded from the right femoral artery and heart rate (HR) was derived from the pulse pressure. In each experiment, blood flow was recorded using electromagnetic flowmeters and transducers, from the left femoral artery, with paw ligated so as to reflect mainly muscle blood flow, and from the cranial mesenteric and left renal arteries. A zero-flow signal was obtained at regular intervals by using an occluding snare placed distal to the transducer. Vascular conductance was computed on-line for each artery by an electronic divider as flow/arterial pressure. Ventilation was recorded from the tracheal cannula via a flow head and electrospirometer; air or one of the hypoxic mixtures (see below) was blown throughout across the end of the flow head by means of tubing connected to an air pump. All variables were displayed on an 8-channel pen recorder.

In each experiment a cannula was inserted retrogradely into the right lingual artery to allow selective stimulation of carotid body chemoreceptors by injection of isotonic NaH_2PO_4 as described previously (Hilton & Marshall, 1982). The effect of stimulation of pulmonary stretch receptors was tested during spontaneous respiration by hyperinflating the lungs. To this end, a Y-tube was attached to the flow head distal to the air pump (see above), of which one arm was wide-bored and had no effect on ventilation as far as could be judged from the recording. The other arm was of smaller diameter such that when the wide arm was closed this produced a static increase in pressure at the trachea of up to 10 mmHg, as determined *in vitro*. Although no measurements were made, this technique would be expected to have increased the animals' functional residual volume during the time that the wide arm was closed.

In eleven experiments, the vagal trunks were isolated and cotton ligatures were looped around them to facilitate sectioning later in the experiment. In the other seven experiments, after responses evoked by hypoxia had been tested during spontaneous respiration, a bilateral pneumothorax was created by making incisions through the chest wall between the 10th and 11th ribs on each side. In order to keep these incisions patent a polyethylene tube (1 cm diameter) was inserted into each one. During and after creation of pneumothorax, the animal was artificially

ventilated with an Ideal Pump, at a frequency and tidal volume comparable to that pertaining during spontaneous ventilation and adjusted if necessary to maintain constant baseline levels of arterial pressure and heart rate.

The test hypoxic mixtures (15, 12, 8 and 6% O_2 in N_2) were made up in PVC Douglas bags with the aid of a mass spectrometer. During spontaneous ventilation, air or one of the hypoxic mixtures was delivered across the end of the flow by means of an air pump at ~ 3 l min^{-1}. During artificial ventilation the gas bags were attached to the inflow of the ventilator; the time lag between switching to the hypoxic mixture at the inflow and the onset of hypoxia at the trachea was established with the aid of the mass spectrometer.

During a 1–2 h equilibration period following the end of surgery, the depth of anaesthesia was reduced to the experimental level (see above), such that a strong pinch of the paw evoked withdrawal of the paw and a rise in arterial pressure; there were no spontaneous movements. Then, recordings were made of respiratory and cardiovascular changes evoked by 3 min periods of exposure to each of the hypoxic mixtures (fraction of O_2 in inspirate, F_{i,O_2}, 0·15, 0·12, 0·08, 0·06). Two experimental runs were carried out, one in which femoral and renal blood flows were recorded and a second in which femoral and mesenteric flow were recorded. The order of these runs was randomized, as was the order of administration of the hypoxic mixtures within each run. Arterial blood samples (140 μl) were taken from a cannula placed in the right brachial artery during air-breathing and at the end of the 2nd minute of the hypoxic periods, to allow measurement of blood gases and pH using Radiometer equipment. The above protocol was repeated after bilateral vagotomy or after establishing bilateral pneumothorax.

Results are expressed as means ± S.E.M. All statistical analyses were carried out using Student's paired t test.

RESULTS

The baseline levels of the cardiovascular and respiratory variables are shown in Table 1.

TABLE 1. Mean values for respiratory and cardiovascular variables during air breathing (mean ± S.E.M., $n = 18$)

Respiratory frequency (breaths min^{-1})	28·4 ± 1·5
Tidal volume (ml)	32·3 ± 3·3
Mean arterial pressure (mmHg)	114 ± 3·8
Heart rate (beats min^{-1})	252·9 ± 6·3
Femoral blood flow (ml min^{-1})	4·8 ± 0·6
Femoral conductance (ml min^{-1} mmHg^{-1})	0·042 ± 0·005
Mesenteric blood flow (ml min^{-1})	56.42 ± 6·8
Mesenteric conductance (ml min^{-1} mmHg^{-1})	0·503 ± 0·248
Renal blood flow (ml min^{-1})	36·0 ± 5·6
Renal conductance (ml min^{-1} mmHg^{-1})	0·307 ± 0·03

Stimulation of carotid chemoreceptors

At regular intervals during these experiments tests were made of the effect of selective stimulation of carotid chemoreceptors. In all but three cats, carotid chemoreceptor stimulation evoked a rise in ABP and HR, renal and mesenteric vasoconstriction, but vasodilatation in hindlimb muscle (Fig. 1) accompanied by pupillary dilatation and retraction of the nictitating membrane. This is the pattern of response we have observed previously in cats lightly anaesthetized with Saffan and which we have deduced represents the visceral alerting response mediated via the

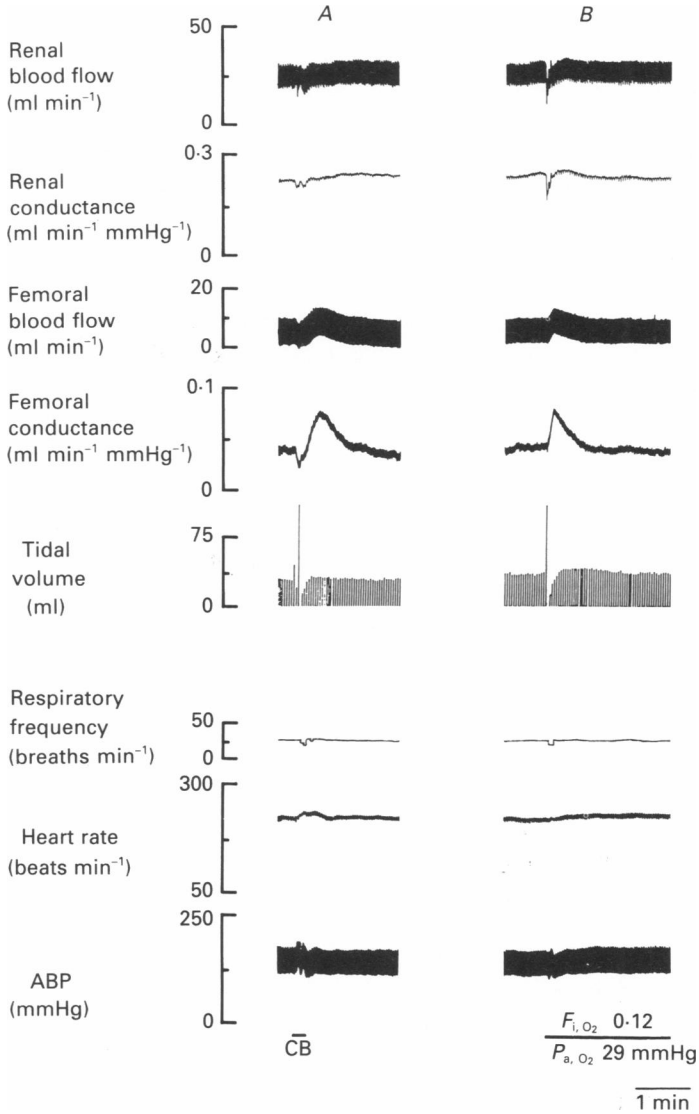

Fig. 1. The pattern of the visceral alerting response evoked by chemoreceptor stimulation (*A*) and at the onset of administration of 12% O_2 (*B*). Traces from above down: renal blood flow, renal vascular conductance, femoral blood flow, femoral vascular conductance, respiratory tidal volume and frequency, heart rate, arterial blood pressure (ABP). Bars beneath panels indicate period of injection of NaH_2PO_4 solution via the lingual artery (*A*) and period of breathing 12% O_2 (*B*). P_{a,O_2} and P_{a,CO_2} values are those measured at the end of the 2nd minute of hypoxia.

defence areas (Hilton & Marshall, 1982). In these animals, such a pattern of response was sometimes, but not always, elicited during the first 1–1·5 min of systemic hypoxia (Fig. 1); this was most common at F_{i,O_2} 0·08 and 0·06, but also occurred at F_{i,O_2} 0·12 and 0·15. In the remaining three animals, selective stimulation of carotid chemoreceptors evoked a rise in ABP, but vasoconstriction in hindlimb muscle as

well as in mesenteric and renal circulation, sometimes with bradycardia, rather than tachycardia. This is the response pattern which seems to correspond with the primary cardiovascular response evoked by carotid chemoreceptor stimulation in animals anaesthetized with chloralose or barbiturates (Daly, 1986) and which we have associated with deeper levels of Saffan anaesthesia (Hilton & Marshall, 1982; Marshall, 1986*a*); it was still evoked even when the rate of Saffan infusion was reduced to the lower end of the range used for the experimental period (see Methods). This situation has arisen regularly but equally infrequently in our previous series of experiments on cats and rats anaesthetized with Saffan (J. M. Marshall, unpublished observations). Our impression is that it occurs when, in the early stages of the experiment, Saffan is given at a rate that is somewhat higher than is necessary to maintain a surgical depth of anaesthesia, implying that Saffan can have some depressant action on the central nervous system which cannot be reversed during the period of an acute experiment.

Effects of systemic hypoxia

Even when systemic hypoxia evoked the visceral alerting response, this was superimposed upon gradual changes which were graded with the level of hypoxia and which occurred in all animals. Original traces are shown in Fig. 2 and the averaged changes reached at the end of the 2nd minute, when they usually reached a peak, are shown in Fig. 3. They comprised an increase in minute volume ($\dot{V}_e$) which was largely due to an increase in tidal volume (V_t). Concomitantly, arterial P_{O_2}, (P_{a,O_2}) fell as did arterial P_{CO_2} (P_{a,CO_2}); pH rose progressively as F_{i,O_2} was reduced, from 7·40 at F_{i,O_2} 0·21, to 7·54 at F_{i,O_2} 0·06. There was a small rise in ABP which reached significance at F_{i,O_2} 0·12 and 0·08. Although femoral vascular conductance (FVC) change little at F_{i,O_2} 0·15 and 0·12, mean FVC increased in more severe hypoxia, particularly at F_{i,O_2} 0·06, allowing a progressive increase in femoral flow over the full range of hypoxia. On average, mesenteric vascular conductance (MVC) increased progressively reaching a peak at F_{i,O_2} 0·08, allowing a progressive increase in mesenteric flow. By contrast, there was a small fall in renal vascular conductance (RVC) at each F_{i,O_2}, which allowed renal flow to remain more or less constant. At F_{i,O_2} 0·12 there was a small but significant increase in HR, but at more severe levels of hypoxia the changes in HR were more variable (note S.E.M. bars in Fig. 3) and the mean change for all eighteen cats was a bradycardia. It may be noted that the averaged data obtained during spontaneous ventilation for the subgroup of seven cats that were later studied under constant artificial ventilation showed a tachycardia both at F_{i,O_2} 0·08 and 0·06 (Fig. 6). This discrepancy may be attributed to the fact that this subgroup did not include the three cats in which carotid chemoreceptor stimulation failed to evoke the visceral alerting response, for in these three animals there was a greater tendency for the tachycardia evoked by severe hypoxia to wane during the final 1–1·5 min of the stimulus over the time at which our measurements were made. Since there was also a greater tendency in these three cats for the increase in respiratory frequency (F_r) to wane during the period of hypoxia, this helps to explain why the mean increase in F_r reached a peak at F_{i,O_2} 0·08 in the full group of eighteen cats, but increased progressively over the full range of hypoxia in the subgroup of seven cats (compare

Figs 3 and 6). As these animals and their responses seemed to be part of a continuum, there was no obvious reason to exclude them from the grouped data.

Augmented breaths

In addition to the changes so far described, augmented breaths (an additional inspiratory effort at the peak of a normal inspiration) occurred rather infrequently

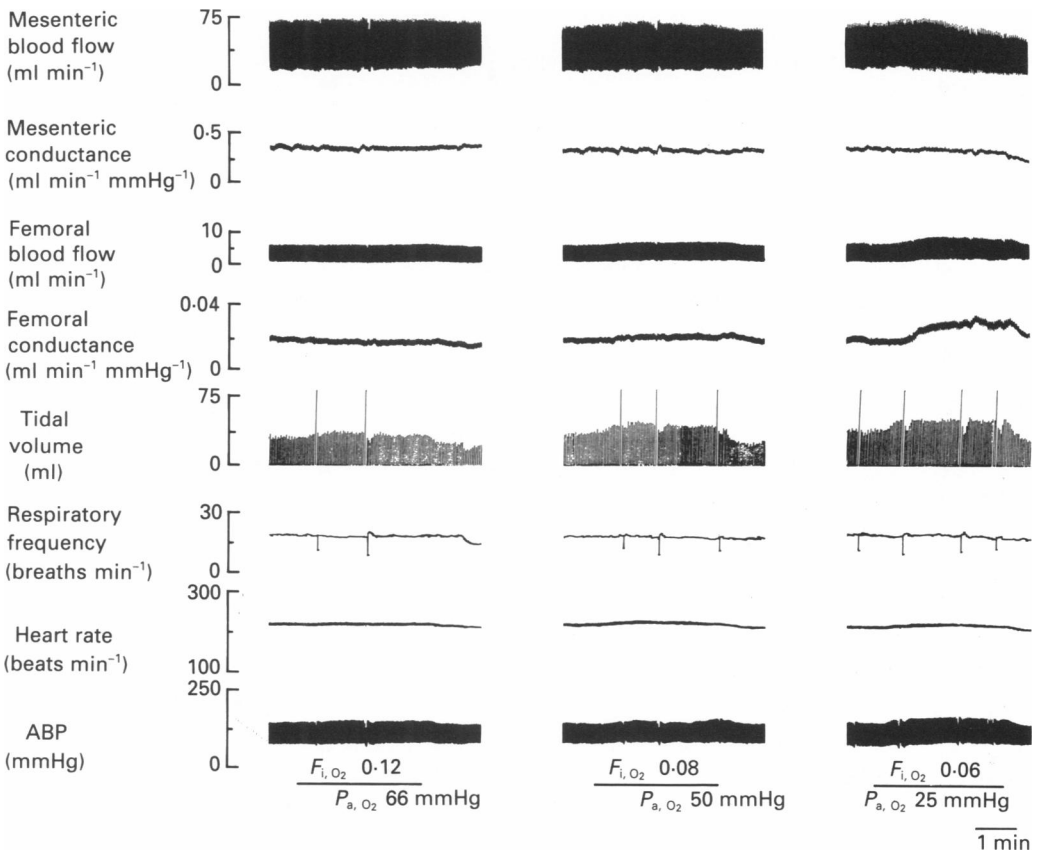

Fig. 2. Graded cardiovascular and respiratory responses evoked by graded levels of systemic hypoxia. Traces as in Fig. 1 with the exception that top two traces are mesenteric blood flow and mesenteric vascular conductance, respectively.

during normoxia, at approximately 1/6 min, but their frequency increased during hypoxia to an extent that showed some gradation with the level of hypoxia: $0{\cdot}9 \pm 0{\cdot}09$, $2{\cdot}5 \pm 0{\cdot}19$, $2{\cdot}6 \pm 1{\cdot}05$ and $3{\cdot}45 \pm 0{\cdot}23$ per 3 min period of hypoxia at F_{i,O_2} 0·15, 0·12, 0·08 and 0·06, respectively. In only eight out of eighteen cats, each augmented breath was accompanied by a small, transient rise in FVC (of 15–30% from control levels) and a transient fall in ABP (Fig. 4). There were no obvious changes in the other cardiovascular variables.

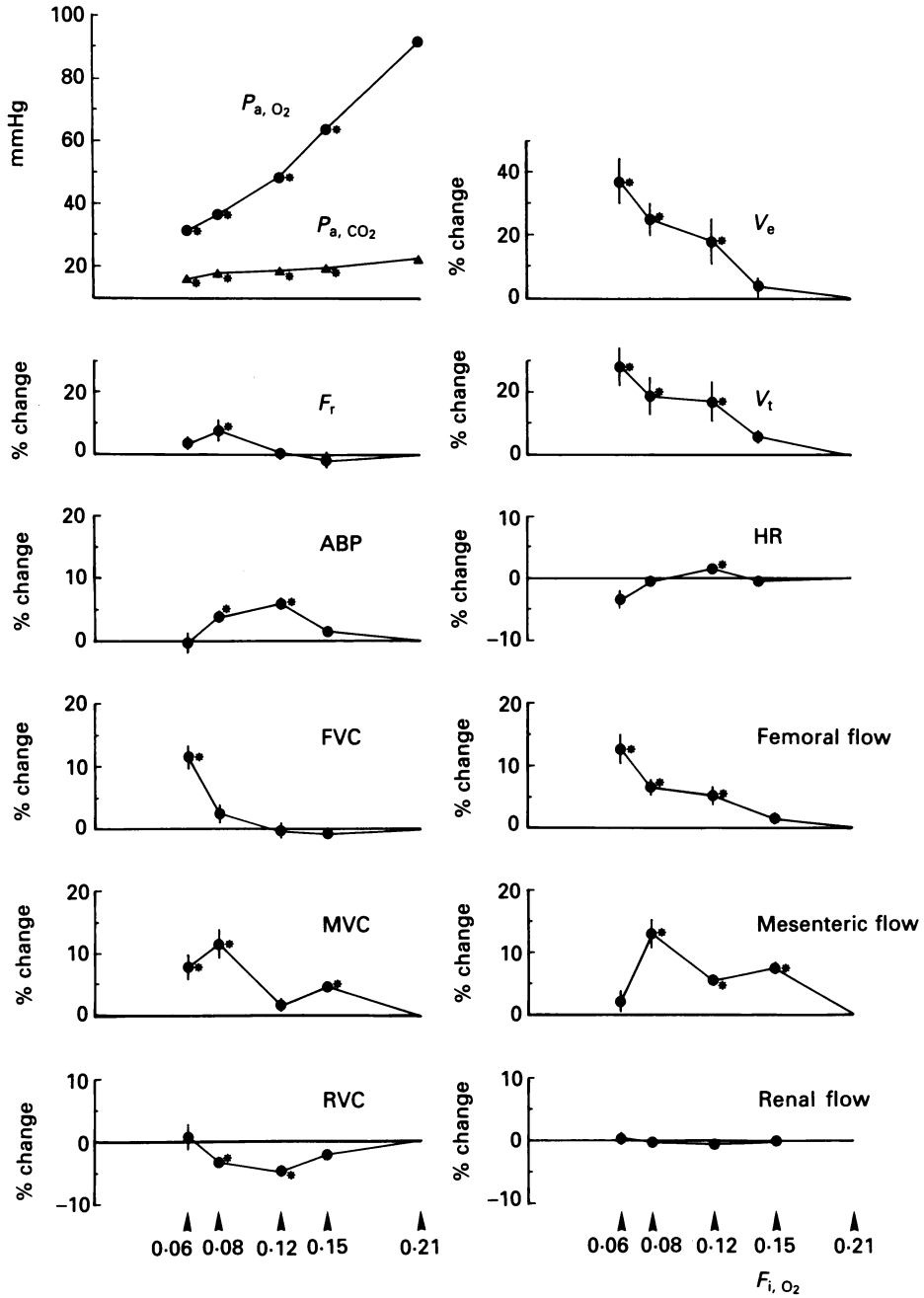

Fig. 3. Effects of graded levels of hypoxia upon respiration, arterial blood gases and cardiovascular variables. Graphs from above down show: P_{a,O_2} (●), P_{a,CO_2} (▲) and minute volume ($\dot{V}_e$); respiratory frequency (F_r) and tidal volume (V_t); arterial pressure (ABP) and heart rate (HR); femoral vascular conductance (FVC) and flow; mesenteric vascular conductance (MVC) and flow; renal vascular conductance (RVC) and flow. Each point represents mean of measurements made at end of 2nd minute of hypoxia; S.E.M. indicated by bar except when encompassed within symbol; $n = 18$ in each case. * Indicates significant difference between values recorded during air breathing and hypoxia ($P < 0{\cdot}05$).

Effects of hyperinflation of lungs

At intervals during these experiments the effect of hyperinflating the lungs was tested. Hyperinflation with pressures of up to 10 mmHg produced the expected Breuer–Hering reflex effect on respiration, i.e. a decrease in F_r, but there was no measurable effect on ABP, HR nor on the regional vascular conductance (Fig. 4).

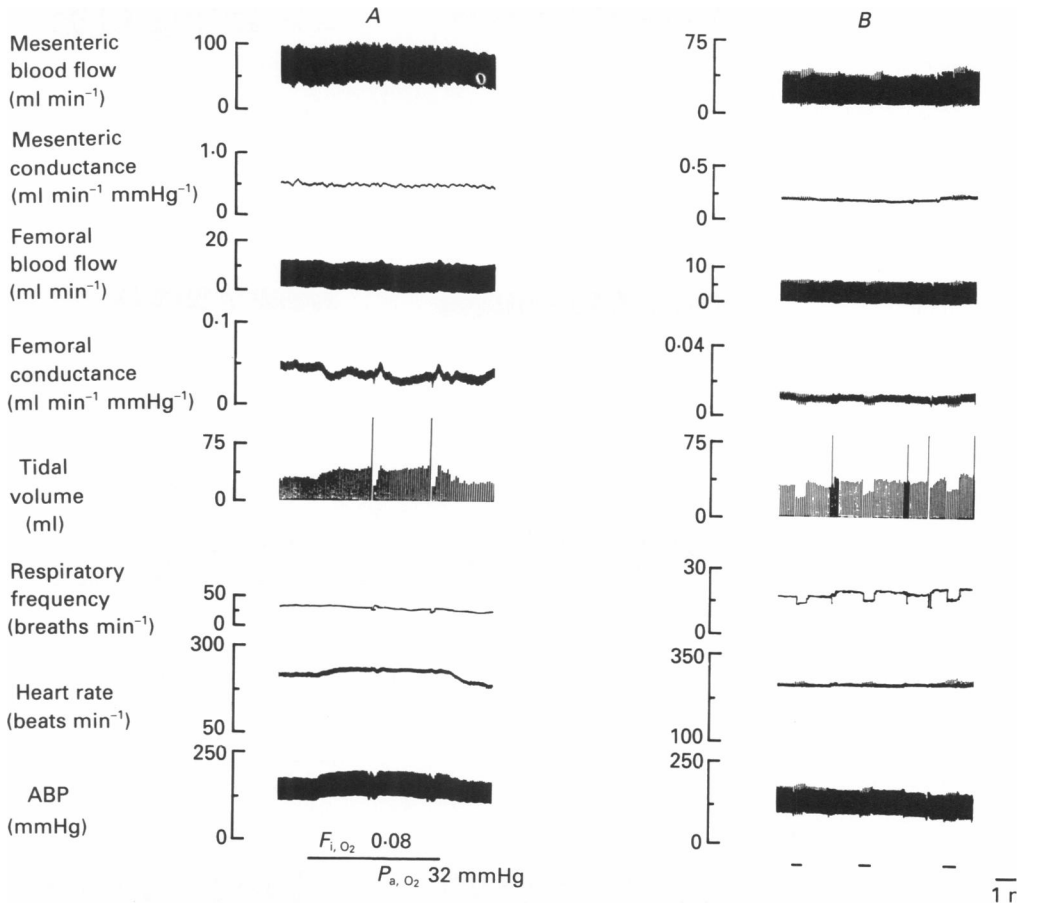

Fig. 4. Examples of augmented breaths during hypoxia (*A*), and Breuer–Hering reflex (*B*). Traces as in Figs 1 and 2. Note the two augmented breaths that occurred during hypoxia (F_{i,O_2} 0·08) in *A* were each accompanied by transient femoral vasodilatation and fall in arterial pressure. In *B*, the stimulus markers indicate periods of lung hyperventilation to 10 mmHg. Note that although there was a marked decrease in respiratory frequency, there was no effect on the cardiovascular variables.

Effects of vagotomy

Vagotomy produced the expected increase in baseline V_t and decrease in F_r, but there were no significant changes in baseline levels of P_{a,O_2}, P_{a,CO_2} or pH, nor in any of the cardiovascular variables, except RVC, which decreased by 12%.

After vagotomy, the full pattern of the visceral alerting response could still be elicited by selective stimulation of the carotid chemoreceptors and by systemic

hypoxia; notably there was no change in the magnitude of the increase in FVC, nor of the increase in HR.

As far as the gradual respiratory and cardiovascular changes were concerned: the levels of P_{a,O_2}, P_{a,CO_2} and pH recorded at each F_{i,O_2} were not significantly different

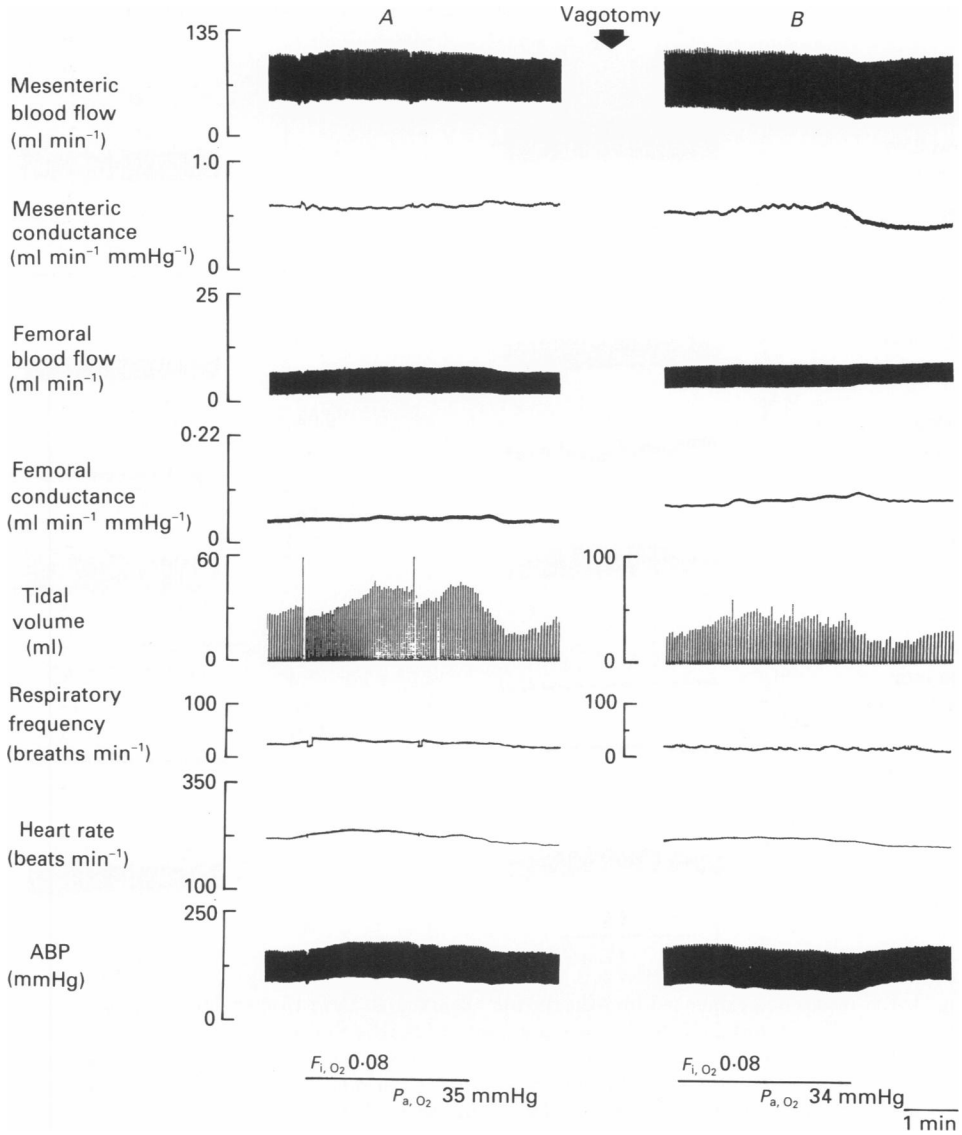

Fig. 5. Cardiovascular and respiratory responses evoked by 8% O_2 before (*A*) and after (*B*) vagotomy. Traces as in Fig. 2.

from those recorded before vagotomy. Correspondingly, the increases in $\dot{V}_e$ were not significantly altered, although an increase in V_t played a larger part after vagotomy than before (cf. Euler, Herrero & Wexler, 1970). Further, at each F_{i,O_2} there were no significant differences between the changes evoked before and after vagotomy for

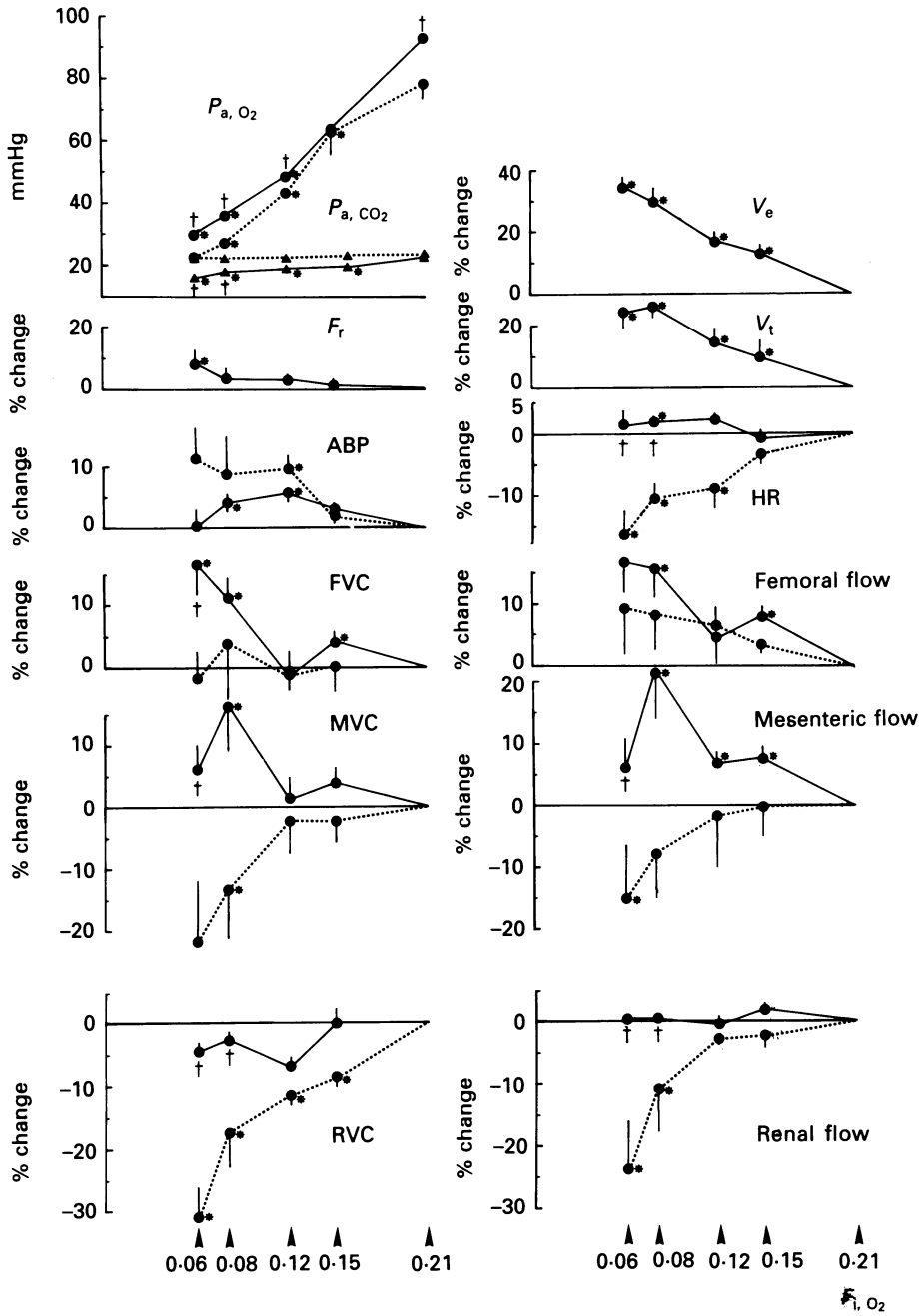

Fig. 6. Effects of graded levels of hypoxia upon respiration, arterial blood gases and cardiovascular variables during spontaneous ventilation (continuous lines) and constant artificial ventilation (dotted lines). Graphs as in Fig. 3. Each symbol represents mean of seven values. * Indicates significant differences between values recorded during ventilation in air and hypoxia; † Indicates significant difference between values recorded during spontaneous and constant ventilation ($P < 0{\cdot}05$).

any of the cardiovascular variables (Fig. 5). Concentrating on those variables which are of particular interest (see Discussion), and considering only the changes at F_{i,O_2} 0·08 and 0·06 when any difference might have been expected to become most evident, the mean changes in HR at F_{i,O_2} 0·08 and 0·06, before and after vagotomy, were $-1·6 \pm 2·29$ *vs.* $+2·0 \pm 0·06$ % from baseline and $-7·5 \pm 4·06$ *vs.* $+2·9 \pm 0·75$ %, respectively; this reflects a greater increase in HR after vagotomy in eight out of eleven cats in each case. For FVC, the mean increase was greater after vagotomy both at F_{i,O_2} 0·08 and 0·06: $10·3 \pm 4·17$ *vs.* $13·5 \pm 4·7$ % and $13·9 \pm 4·7$ *vs.* $22·8 \pm 16·6$ %, respectively, the increase being greater in eight and six out of the eleven cats, respectively. Further, the tendency for ABP to fall was greater after vagotomy at both F_{i,O_2} 0·08 and 0·06: $+0·22 \pm 4·14$ *vs.* $-6·9 \pm 1·9$ % and $-0·75 \pm 4·9$ *vs.* $-8·25 \pm 4·7$ %, respectively, reflecting a smaller increase in ABP, or a greater decrease in ABP in seven out of eleven at each F_{i,O_2}. The trends noted for each of the variables were apparently randomly distributed between the eleven cats.

After vagotomy, the Breuer–Hering reflex could not be evoked and in all but four cats, augmented breaths and any associated transient vascular changes no longer occurred; in the remaining four cats they re-appeared within 15–60 min (cf. Marshall & Metcalfe, 1988*a*).

Responses during constant artificial ventilation

During ventilation with air, the level of P_{a,O_2} was significantly lower than that recorded during spontaneous ventilation in air ($77·7 \pm 5·0$ *vs.* $92·0 \pm 1·2$ mmHg) but there were no significant differences between baseline levels of P_{a,CO_2} (Fig. 6) and pH, nor between the baseline levels of any of the cardiovascular variables. The visceral alerting response could still be elicited by selective stimulation of carotid chemoreceptors and by systemic hypoxia. However, the changes in blood gases and in the gradual cardiovascular changes evoked by hypoxia were markedly different from those recorded during spontaneous ventilation (Fig. 6). Thus at each F_{i,O_2}, P_{a,O_2} was generally lower than during spontaneous ventilation, while P_{a,CO_2} remained constant over the full range of hypoxia, rather than falling progressively as during spontaneous ventilation. The increases in ABP tended to be larger, though the difference between the spontaneous and constant ventilation values did not reach significance. In contrast to the changes in HR recorded during spontaneous ventilation, with ventilation held constant HR fell progressively as F_{i,O_2} was reduced, the differences being significant at F_{i,O_2} 0·08 and 0·06. Mean FVC showed no significant change from baseline over the full range of F_{i,O_2} values when ventilation was held constant, the effect being that the tendency for femoral flow to increase was reduced (Fig. 6). On other other hand, the increases in MVC seen during spontaneous ventilation were reversed to a progressive decrease as F_{i,O_2} was reduced, such that mesenteric flow fell progressively. RVC also decreased as F_{i,O_2} was reduced so that renal flow fell progressively, rather than remaining constant as during spontaneous ventilation.

DISCUSSION

The hypoxic mixtures used in the present study on the cat were the same as those used in our recent studies on the rat (Marshall & Metcalfe, 1988*a*, *b*; 1989) and the

levels of P_{a,O_2} attained at each F_{i,O_2} were virtually indentical in the two species; for example at F_{i,O_2} 0·12 they were 64·01 and 62·47 mmHg and at 0·06 they were 30·17 and 30·01 mmHg in cat and rat respectively (cf. Marshall & Metcalfe, 1988*b*). Moreover, although Koehler *et al.* (1980) used a rebreathing technique rather than fixed gas mixtures to produce graded hypoxia in conscious dogs, the range over which P_{a,O_2} fell spanned the range attained in our studies. Thus, it is possible to make meaningful comparisons between the results obtained in these three species. Some comparisons are also possible with results obtained in the rabbit which has been studied at two level of P_{a,O_2}: 50 and 30 mmHg (Uther *et al.* 1970; see Korner, 1980).

Activation of the defence areas

We have previously demonstrated that in cats that are highly anaesthetized with Saffan, selective stimulation of carotid chemoreceptors can evoke the visceral alerting response. This includes mesenteric and renal vasoconstriction and a tachycardia and muscle vasodilatation that are not initiated by pulmonary stretch receptors secondary to hyperventilation (cf. Daly, 1986) for they persist after vagotomy and when ventilation is maintained constant (Hilton & Marshall, 1982). In all but three of the present series of cats, this characteristic pattern of response could be evoked by carotid chemoreceptor stimulation and by systemic hypoxia, this being most common at F_{i,O_2} 0·08 and 0·06. This is in full accord with our observations on rats that were lightly anaesthetized with Saffan (Marshall & Metcalfe, 1988*b*). Since in the conscious animal, in all species studied, the visceral alerting response is accompanied by behavioural signs of alerting (Hilton, 1982), the present findings are fully compatible with reports that systemic hypoxia produces behavioural arousal in conscious cats, dogs, rabbits and man (see Introduction). Indeed, they lend further support to the view that activation of the defence areas, by peripheral chemoreceptors and initiation of the cardiovascular and autonomic components of the alerting response, is an integral part of the response to systemic hypoxia which is common to mammalian species.

An important question which then arises is to what level must P_{a,O_2} be lowered in order to cause significant activation of the defence areas. This is difficult to assess on the basis of experiments conducted under Saffan anaesthesia, for even though this agent does not block afferent activation of the defence areas to the same extent as other commonly used anaesthetics, it clearly does have some central blocking action, as evidenced by the observation that the visceral alerting response cannot be evoked by chemoreceptor stimulation when Saffan is infused at a high rate to maintain deep anaesthesia, and by the fact that this situation sometimes persists for several hours even when the infusion rate is considerably reduced (see Results and Hilton & Marshall, 1982; see Marshall, 1987, for further discussion). Thus, the variability, both between and within animals, in the level of hypoxia that was required to evoke the visceral alerting response may be explained by variability in the depressant actions of Saffan. Further, it may be that whether or not the visceral alerting response is evoked at a particular P_{a,O_2} is dependent upon the balance between the ability of chemoreceptors to activate the defence areas and the depressant action of hypoxia upon transmission through central neural pathways (see Bouverot, 1985) and it could be that this balance is more precarious when combined with the

depressant action of Saffan. With these provisos, our finding that in the cat as well as in the rat the visceral alerting response could be elicited at F_{i,O_2} 0·15, but was more common at F_{i,O_2} 0·08 and 0·06, suggests that the threshold level of P_{a,O_2} may be as high as 65 mmHg, but can be as low as 37–30 mmHg. In previous studies, behavioural arousal was noted in the rabbit (Korner *et al.* 1969) and in man (Rowell & Blackmon, 1986) when P_{a,O_2} was reduced to 30 mmHg and in the dog when P_{a,O_2} was reduced to 34 mmHg (Rose *et al.* 1984) or as it approached 25 mmHg (Koehler *et al.* 1980). These reports must have been dependent upon the observer's ability to detect and interpret changes in behaviour. Moreover, it would not be surprising if the strength of stimulus required to induce obvious signs of behavioural alerting were greater than that required to elicit the characteristic pattern of the visceral alerting response. It seems that resolution of this issue must await experiments on conscious animals in which behaviour and a full complement of cardiovascular variables are monitored continuously.

Augmented breaths

In the present experiments on cats, as in those on rats (Marshall & Metcalfe, 1988*a*), augmented breaths occurred at intervals during normoxia, their frequency increased in a graded fashion during graded hypoxia and they were accompanied by transient vasodilatations in muscle and falls in arterial pressure. It seems reasonable to propose, in accord with our previous conclusions, that the augmented breaths were initiated by rapidly adapting, lung irritant receptors and facilitated by peripheral chemoreceptor stimulation (cf. Glogowska *et al.* 1972) and that the muscle vasodilatation was part of the same primary reflex and mediated by a decrease in sympathetic vasoconstrictor tone (Marshall & Metcalfe, 1988*a*). However, in normoxia, the frequency of augmented breaths in the cat was only half that in the rat and at the most severe level of hypoxia, only about one-fifth of that in the rat, which accords with previous reports that the frequency of augmented breaths is graded with animal size (McCutcheon, 1953). Moreover, whereas in the rat transient muscle vasodilatation was an almost invariable accompaniment to each augmented breath (Marshall & Metcalfe, 1988*a*), they were associated in less than half of the cats used in the present study. Thus, while in the rat augmented breaths and their associated muscle vasodilatations may make a sustantial contribution to the increase in muscle blood flow that occurs in hypoxia (Marshall & Metcalfe, 1988*a*), the present findings suggest that in the cat they are only a minor component of the overall response; it is likely that they make even less contribution in larger species.

In normoxia, it is thought that irritant receptors and thereby augmented breaths are triggered by the decrease in lung compliance that results from atelectasis. Thus, larger animals may have a lower frequency of augmented breaths because their larger alveoli are less prone to collapse (Bartlett, 1971; Glogowska *et al.* 1972). In hypoxia, their increased frequency has been ascribed to the stimulation of irritant receptors caused by the increase in respiratory air flow that results from the hyperventilation elicited by the peripheral chemoreceptors (Glogoswska *et al.* 1972). Thus, the fact that their frequency increased far less in hypoxia in the cat than in the rat is compatible with the smaller increase in minute volume in the cat (cf. Marshall & Metcalfe, 1988*b*).

The gradual cardiovascular changes

There were striking qualitative and quantitative differences between the gradual changes evoked by hypoxia in the cat and those we recently reported for the rat (see Marshall & Metcalfe, 1988*b*). There are also differences between the response in the cat and those reported in the dog (see Koehler *et al.* 1980) and rabbit (Uther *et al.* 1970; Korner, 1980). In the discussion that follows, consideration is given to the mechanisms that may underlie the gradual cardiovascular changes induced by hypoxia in the cat and to their relative importance compared with those identified in other species.

The role of vagal afferents

Since stimulation of pulmonary stretch receptors can evoke reflex tachycardia and vasodilatation in the dog (see Daly, 1986), the question arises as to whether they played a role in determining the gradual cardiovascular changes seen in the cat. Interpretation of the effects of vagotomy is not straightforward, particularly for the heart rate changes, as this procedure would not only have severed afferents from pulmonary stretch receptors, from other cardio-pulmonary receptors, aortic baroreceptors and chemoreceptors, but also the vagal efferent supply to the heart. Thus, even though our observation that the heart rate changes evoked by hypoxia were not significantly affected by vagotomy might suggest that a reflex from the pulmonary stretch receptors made no significant contribution to the heart rate response, these experiments could not have shown whether, in the intact state, reflex tachycardia initiated by vagal afferents was tending to overcome a bradycardia mediated by vagal efferent fibres, initiated for example by carotid chemoreceptors (see Daly 1986). The tachycardia that persisted as the response to hypoxia after vagotomy may be explained by an increase in cardiac sympathetic activity arising from the effect of hypoxia upon the central nervous system (Downing, Mitchell & Wallace, 1963), or by a direct action of a fall in P_{a,CO_2} upon the cardiac pacemaker (Hanna, Lioy & Polosa, 1979; Marshall, 1986*b*).

By contrast, the observation that vagotomy had no significant effect upon the hindlimb vasodilatation induced by hypoxia is highly suggestive evidence against an important involvement of reflex vasodilatation mediated by pulmonary stretch receptors. The tendency for the muscle vasodilatation to be larger after vagotomy and for arterial pressure to fall rather than rise, may be explained by loss of reflex vasoconstriction elicited by aortic chemoreceptors (Daly, Hazzledine & Howe, 1965) and of regulation of arterial pressure by aortic baroreceptors.

We also found that experimentally induced hyperinflation of the lungs with pressures of up to 10 mmHg, which would have substantially stimulated pulmonary stretch receptors, had no measurable effect on the cardiovascular variables. Moreover, Daly, Litherland & Wood (1983) found that reflex tachycardia could not be elicited in the cat by hyperinflating the lungs, unless cardiac vagal tone was substantially increased by concomitant stimulation of the superior laryngeal nerve, nor could the reflex vasodilatation be elicited in skeletal muscle unless any counteracting reflex effects exerted by arterial baroreceptors were controlled. Putting this evidence together and given that baroreceptor activity probably

changed little in the present experiments, since arterial pressure changed by only a few mmHg over the full range of hypoxia, it seems very unlikely that the cardiac or the vascular components of the reflex intitiated by pulmonary stretch receptors made more than a minor contribution to the cardiovascular changes induced in the cat by systemic hypoxia. This is similar to the conclusion we recently drew for the rat (Marshall & Metcalfe, 1988*a*, *b*) and suggests that both species contrast strongly with the dog in which the reflex elicited by these receptors is considered to make a major contribution to the tachycardia induced by hypoxia, to be largely responsible for the vasodilatation in skeletal muscle and for keeping mesenteric and renal vascular resistance constant rather than allowing them to rise (Kontos, Mauck, Richardson & Patterson, 1965; Koehler *et al.* 1980). On the other hand, it was concluded that in the rabbit, the reflex from the pulmonary stretch receptors was responsible for the tachycardia and exerted a vasodilator influence on the peripheral vasculature at P_{a,O_2} 50 mmHg, but at P_{a,O_2} 30 mmHg it had no significant cardiac or vascular effect (see Korner, 1980, for references).

Other secondary effects of hyperventilation

In addition to stimulating pulmonary stretch receptors, hyperventilation gives rise to a fall in P_{a,CO_2} which may affect the cardiovascular system by unloading central chemoreceptors (e.g. Trzebski & Kubin, 1981), by attenuating the increase in peripheral chemoreceptor activity evoked by a given fall in P_{a,O_2} (Lahiri & Delaney, 1975) and by direct actions on the heart and vasculature (Daugherty, Scott, Dabney & Haddy, 1967; Hanna *et al.* 1979; Marshall, 1986*b*). In the experiments we carried out with constant artificial ventilation, P_{a,CO_2} measured at the end of the 2nd minute of hypoxia, when we made our measurements of the cardiovascular variables, was maintained constant over the full range of hypoxia. Thus, it is reasonable to assume that at this time, at each F_{i,O_2}, there would have been greater stimulation of central and peripheral chemoreceptors and a reduction in the local effects of CO_2 in comparison with the situation when ventilation was allowed to increase. However, because ventilation was not allowed to increase, the fall in P_{a,O_2} was greater at each F_{i,O_2} (see Fig. 6) and this would be expected to have further stimulated peripheral chemoreceptors, as well as to accentuate the local effects of hypoxia on the heart and vasculature (Daugherty *et al.* 1967; Rosen & Kjellmer, 1975). Moreover, the greater increase in central inspiratory drive expected from the enhanced stimulation of central and peripheral chemoreceptors could have exerted effects on the cardiovascular system by inhibiting cardiac vagal motoneurones and raising the excitability of sympathetic preganglionic neurones (Spyer, 1981).

In our experiments, with ventilation held constant, the tendency towards tachycardia disappeared and there was progressive bradycardia as F_{i,O_2} was reduced. This indicates that any tachycardia that might have been expected from the effect of greater stimulation of central chemoreceptors (Trzebski & Kubin, 1981), or of greater central inspiratory drive (Spyer, 1981), made no significant contribution to the response. In view of the evidence discussed above that stimulation of pulmonary stretch receptors does not readily evoke tachycardia in the cat, it is unlikely that the conversion of tachycardia to bradycardia could be explained by loss of this reflex. Rather, the greater stimulation of the peripheral chemoreceptors during constant

ventilation, produced by the lower levels of P_{a,O_2} and higher levels of P_{a,CO_2}, may have allowed predominance of the bradycardia mediated as a primary reflex by peripheral chemoreceptors (see Daly, 1986), and/or there could have been a greater direct inhibitiory influence of hypoxia on the cardiac pacemaker (Rosen & Kjellmer, 1975). Since the level of P_{a,O_2} at F_{i,O_2} 0·06 during spontaneous ventilation was not significantly different from that attained at F_{i,O_2} 0·08 during constant ventilation (30 *vs.* 27 mmHg, respectively, $P > 0·05$), it is possible to make comparisons at this P_{a,O_2} between the heart rate change evoked during spontaneous and during constant ventilation (Fig. 6). As the difference between them was almost as great as when compared at F_{i,O_2} 0·08 and 0·06, it may be deduced that the influence of the fall in P_{a,CO_2} predominated in determining the heart rate change. This leads to the proposal that in the spontaneously breathing cat, the hypocapnia induced by hyperventilation exerted a major role in attenuating the increase in peripheral chemoreceptor activity caused by hypoxia and unloading the central chemoreceptors, so allowing tachycardia mediated by the influence of hypoxia on the central nervous system and by a direct action of hypocapnia on the heart to overcome the bradycardia initiated by the peripheral chemoreceptors. Evidence that these effects could have been of sufficient magnitude to explain our findings is provided by previous experiments on cats (cf. Fig. 6), for perfusion of the brain with blood of P_{O_2} 30 mmHg produced a sympathetically mediated increase in heart rate of 15–20 beats min^{-1} or 6–8% from control levels (Downing *et al.* 1963), while a fall in P_{a,CO_2} of 6 mmHg produced an increase in heart rate of about 5–6 beats min^{-1} or 2–3% from control levels by a direct influence (Hanna *et al.* 1979). It seems therefore that hypocapnia exerts a similar effect in the cat as in the rat, for in the rat when P_{a,CO_2} was held constant this greatly attenuated the substantial tachycardia induced at F_{i,O_2} 0·15–0·08 and converted that induced at F_{i,O_2} 0·06 to bradycardia (Marshall & Metcalfe, 1989). By contrast, maintenance of P_{a,CO_2} in the dog only reduced the tachycardia at the more severe levels of hypoxia (Koehler *et al.* 1980).

Holding ventilation constant also substantially altered the changes in the regional vascular conductance, in that the increases in femoral and mesenteric conductance were converted to no change and a progressive decrease respectively and the decreases in renal vascular conductance, which had allowed renal flow to remain constant during spontaneous ventilation, were substantially accentuated, so that renal blood flow fell progressively as F_{i,O_2} was reduced. Qualitatively similar responses to hypoxia were reported by Weissman *et al.* (1976) in paralysed and artificially ventilated cats. Our results imply that in all three vascular beds prevention of the hyperventilatory response to hypoxia led to attentuation of vasodilator influences and/or acquisition of vasoconstrictor influences. In view of the evidence discussed above, it seems reasonable to propose that loss of reflex vasodilatation initiated by pulmonary stretch receptors would have had a minimal effect. However, accentuation of vasoconstrictor influences could be explained by a greater increase in sympathetic activity due to a greater central and peripheral chemoreceptor activity, a greater increase in central inspiratory drive and/or a larger influence of a fall in P_{a,CO_2} upon the central nervous system, all of which would be expected with ventilation held constant (see above). If the changes in the regional vascular conductances are compared at F_{i,O_2} 0·06 during spontaneous ventilation and

at F_{i,O_2} 0·08 during constant ventilation when the P_{a,O_2} values were similar (Fig. 6), it can be seen that the trends are the same as when the changes are compared at the same F_{i,O_2} values. This suggests that enhancement of sympathetic activity when ventilation was held constant can be mainly ascribed to the effect of maintaining P_{a,CO_2} constant. The fact that femoral vascular conductance did not fall during hypoxia when ventilation was constant suggests that there must still have been some counteracting vasodilator infuence on skeletal muscle. This could be accounted for by the local vasodilator influence of hypoxia (Daugherty *et al.* 1967), or by stimulation of β-adrenoceptors caused by circulating adrenaline, as has been proposed for the muscle vasodilation seen in the rabbit (Uther *et al.* 1970). The vasodilatation that occurred in the mesenteric circulation when ventilation was allowed to increase could be explained by the local influence of hypoxia (cf. Svanvik, Tyllstrom & Wallentu, 1968), while the lack of renal vasodilatation under these same conditions is in accord with the relative insensitivity of renal vasculature to the dilating influence of hypoxia (Daugherty *et al.* 1967). In other words, our findings suggest that in the spontaneously breathing cat, the influences of hypocapnia secondary to hyperventilation exerted a sufficiently strong inhibitory influence upon sympathetic vasoconstrictor activity to allow modest vasodilatation to predominate in muscle and mesenteric circulation and to limit vasoconstriction in kidney such that renal blood flow remained constant. In some contrast, we recently deduced that in the rat, the peripheral vascular response to hypoxia was dominated by the local dilator effect of tissue hypoxia and that hypocapnia had, at most, a small influence, tending to slightly augment the renal vasodilatation by an inhibitory influence on sympathetic activity, but to attenuate the vasodilatation in skeletal muscle by a local vasoconstrictor influence (Marshall & Metcalfe, 1989). Moreover, in the dog, the hypocapnia could only be held responsible for a small vasodilator influence in renal and mesenteric vasculature and apparently had no significant on skeletal muscle (Kontos *et al.* 1965; Koehler *et al.* 1980).

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