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CARDIOVASCULAR CHANGES ASSOCIATED WITH AUGMENTED BREATHS IN NORMOXIA AND HYPOXIA IN THE RAT

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SUMMARY

1. In the present study, anaesthetized rats showed respiratory gasps (augmented breaths) at regular intervals during air breathing and at increased frequency during hypoxia (breathing 15, 12, 8 or 6% O_2 in N_2). Each augmented breath was accompanied by transient vasodilatation in hindlimb skeletal muscle and sometimes bradycardia. In hypoxia these changes were superimposed upon more gradual muscle vasodilatation and tachycardia.

2. Both the augmented breaths and the transient muscle vasodilatations disappeared immediately after bilateral vagotomy but both sometimes reappeared 1–2 h later, particularly in hypoxia.

3. The transient vasodilatation in skeletal muscle sometimes preceded the augmented breath, indicating that the vasodilatation was not a reflex initiated by pulmonary stretch receptors secondary to the augmented breath. Moreover, hyperinflation of the lungs to 5–10 mmHg evoked the Breuer–Hering respiratory reflex but had no effect upon the cardiovascular variables.

4. Addition of SO_2 (300–400 p.p.m.) to the inspirate, which others have shown preferentially blocks pulmonary stretch receptors, abolished the Breuer–Hering reflex, but had no significant effect on baseline levels of muscle vascular conductance or heart rate during normoxia, nor on the gradual increases in these variables during hypoxia (8% O_2). Moreover, augmented breaths still occurred during air breathing and during hypoxia, each being associated with transient muscle vasodilatation.

5. These results indicate that pulmonary stretch receptors have little reflex effect upon the cardiovascular system of the rat either in normoxia or hypoxia. Rather, we suggest that transient muscle vasodilatation and possibly bradycardia, as well as an augmented breath, are all part of a primary reflex, initiated by pulmonary irritant receptors, and facilitated by peripheral chemoreceptor stimulation, repetition of which is an integral part of the response to hypoxia.

INTRODUCTION

We recently began to investigate the cardiovascular response evoked by systemic hypoxia in the rat and soon became aware that not only did our experimental

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animals show respiratory gasps (augmented breaths) regularly in normoxia and at an increased frequency during hypoxia, as has been noted before (e.g. Bartlett, 1971; Glogowska, Richardson, Widdicombe & Winning, 1972), but that each augmented breath was generally accompanied by transient, but often pronounced vasodilatation in skeletal muscle and a fall in arterial pressure. There is substantial evidence that augmented breaths are due at least in part to stimulation of lung irritant receptors (Glogowska *et al.* 1972). However, there is no recognized cardiovascular reflex attributable to lung irritant receptors (Widdicombe, 1982). On the other hand, the greatly increased inspiration of an augmented breath would be expected to stimulate pulmonary stretch receptors. It is known that stimulation of these receptors in the dog can produce reflex dilatation, particularly in skeletal muscle (Daly & Scott, 1962) but, there have been no published reports of a cardiovascular reflex initiated by pulmonary stretch receptors in the rat. Since the augmented breaths and transient dilatations seemed to make a substantial contribution to the response to hypoxia in the rat, we thought it important to investigate the mechanisms that might underlie them.

In the rabbit, administration of sulphur dioxide (SO_2) via the inspirate successfully blocks pulmonary stretch receptor activity but not irritant receptor activity (Davies, Dixon, Callanan, Huszczuk, Widdicombe & Wise, 1978). Therefore, as part of the present study we attempted to use SO_2 in the rat to differentiate between the effects of the two types of receptors. Some of our findings have already been published in brief (Marshall & Metcalfe, 1986*a–c*).

METHODS

Experiments were performed on nine male Sprague–Dawley rats. Anaesthesia was induced with O_2–N_2O (60–40) containing halothane (ICI) and was subsequently maintained with a continuous infusion of Saffan (Glaxovet Ltd) via a cannula placed in the right jugular vein. Saffan was given at a rate of 13·6–9·5 mg total steroids kg^{-1} h^{-1} during surgery and at 7–5·4 mg kg^{-1} h^{-1} during the experimental period. The depth of anaesthesia during the experimental period was maintained at a level such that a sharp paw pinch induced a gentle withdrawal reflex and elevation of arterial pressure and heart rate, but there were no spontaneous movements.

The trachea was cannulated with a stainless-steel, T-shaped cannula to allow subsequent monitoring of tidal volume, respiratory frequency and minute volume via an F100L flow head and electrospirometer (Mercury CS6). Air or gas mixtures were blown across the end of the flow head by an air pump (Reciprocator, Stanhope Seta Ltd) at a rate of about 1·2 l min^{-1}. In each animal both vagi were separated from surrounding tissue and a fine cotton thread was looped around each one to facilitate sectioning of them later in the experiment. Arterial pressure was monitored via a pressure transducer (Bell & Howell) connected to a cannula placed in the right femoral artery, and heart rate was derived from the pressure record by an instantaneous rate meter (Lectromed, 4522). In each experiment, blood flows were recorded from the left femoral and left renal arteries using cuff-type electromagnetic transducers and meters (Carolina Medical Electronics Inc.); these were calibrated *in vitro* by constant flow perfusion. The femoral artery was approached from the medial aspect and the circulation to the paw excluded by a stout ligature, so that the flow recorded was predominantly that to skeletal muscle. The renal artery was approached from the flank and the abdominal cavity was resealed after placement of the transducer. A zero flow signal was obtained regularly from each artery during the experimental period by occluding the artery with a pair of small forceps, the tips of which were covered in soft polyvinyl chloride to avoid damage to the artery. Vascular conductance was computed on-line for each artery using a two-channel, custom-built electronic divider which made a beat-by-beat division of arterial blood flow by arterial pressure. All cardiovascular and respiratory variables were displayed on a pen recorder (Ormed MX8).

The brachial artery was cannulated to allow 140 μl samples of arterial blood to be taken for the measurement of blood oxygen (P_{a,O_2}), carbon dioxide (P_{a,CO_2}) and pH, using a blood micro system (Radiometer, BMS Mk2) and digital acid–base analyser (Radiometer, PHM72 Mk2).

Hypoxic gas mixtures (15, 12, 8 and 6% O_2) were made up freshly for each experiment in polyvinyl chloride Douglas bags using room air and nitrogen (BOC); the oxygen content was measured using a mass spectrometer (Medishield multi-gas monitor MS2) using air (21% O_2) as full scale calibration. Addition of SO_2 (BDH, 200–400 p.p.m.) to air and to hypoxic mixtures held in gas bags was calculated volumetrically and carried out from a 20 ml syringe.

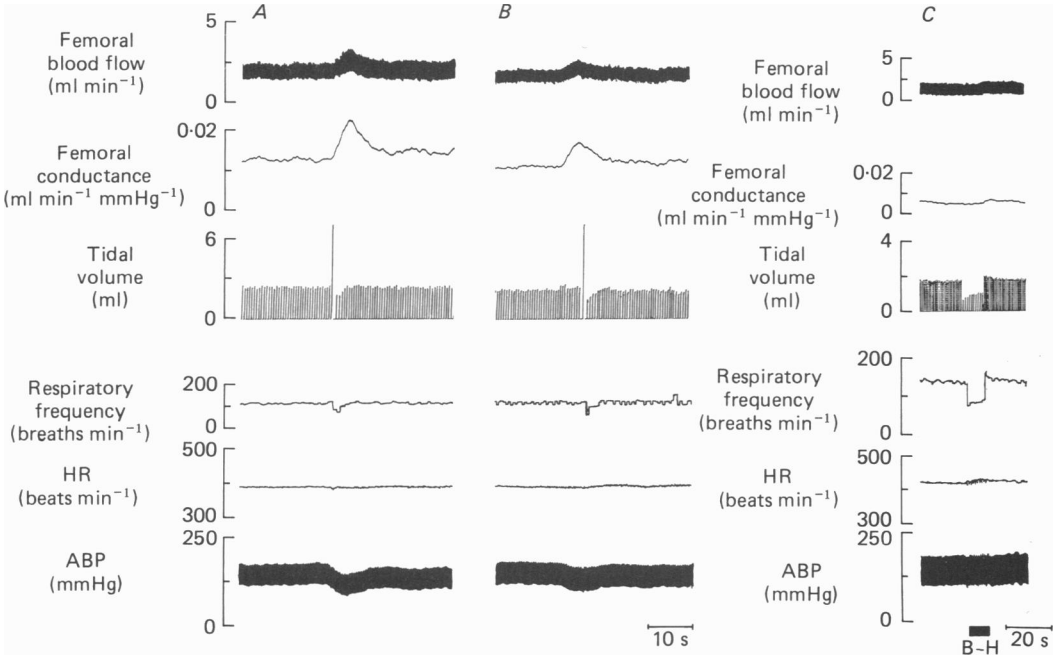

Fig. 1. Examples of spontaneous augmented breaths and associated hindlimb vasodilatation (*A* and *B*) and of Breuer–Hering reflex (B–H; *C*). Traces from above down; blood flow in femoral artery, femoral vascular conductance, respiratory tidal volume and frequency, heart rate (HR) and arterial blood pressure (ABP). As indicated by the time marker, chart speed was faster in *A* and *B* than in *C*. Note that in *B* the muscle vasodilatation preceded the augmented breath. In *C*, the stimulus marker indicates a 10 s period of lung hyperinflation to 10 mmHg. Note that although this induced a marked decrease in respiratory frequency, there was no effect upon cardiovascular variables.

Once the rat had been maintained at a stable level of anaesthesia (see above) for 1–2 h, continuous recordings were made of the respiratory and cardiovascular variables in normoxia and in response to 3 min periods of graded levels of hypoxia (15, 12, 8 and 6% O_2). The order of administration of the gas mixtures was randomized. Arterial blood samples for the measurement of blood gases were taken in normoxia and at the end of the second minute of hypoxia. The effect of stimulation of the pulmonary stretch receptors was assessed by hyperinflating the lungs. For this purpose a Y-tube was attached to the end of the flow head of which one arm was wide-bored and presented no significant extra resistance to air flow as far as could be determined from the recording of respiration. However, the other arm was of narrow diameter such that when the wide arm was closed pressure at the trachea, as determined *in vitro*, was raised by 10 mmHg. In each experiment the concentration of SO_2 in air administered from a Douglas bag was increased from 200 to 400 p.p.m. until the Breuer–Hering reflex effect on respiration was abolished; this same concentration was then added to the 8% O_2 mixture.

Results are expressed as mean +S.D. All statistical analyses were carried out using Student's paired *t* test.

RESULTS

Augmented breaths and associated cardiovascular changes

During air breathing, the respiratory pattern of each animal was interrupted at intervals of one every 3 min by a gasp or augmented breath. These comprised an additional inspiration at the peak of a normal inspiration and were followed by

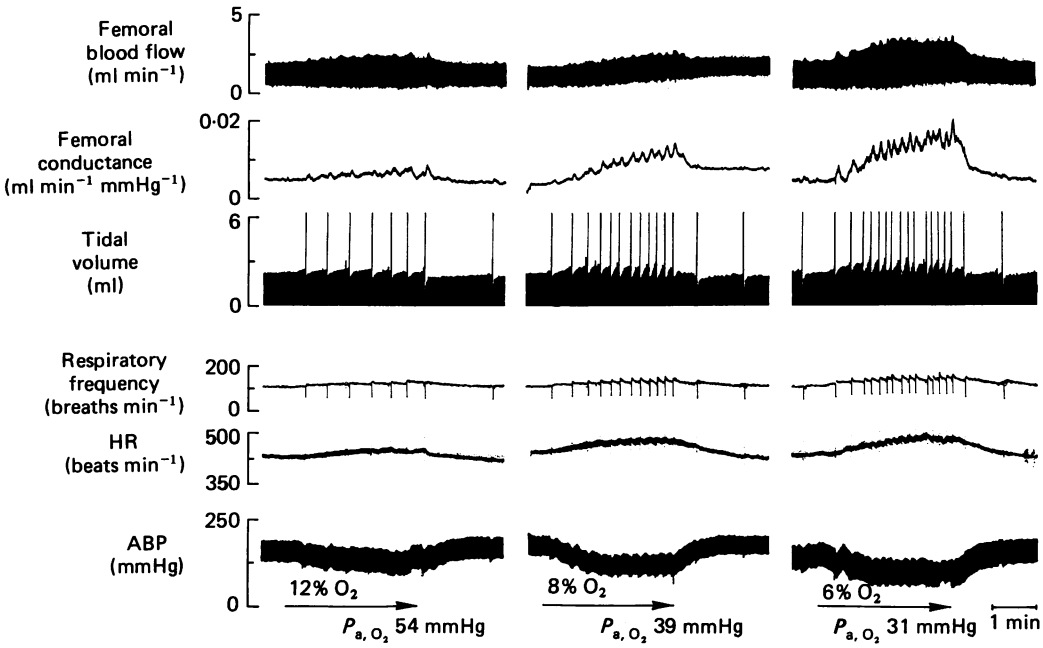

Fig. 2. Effects of graded levels of hypoxia upon respiratory and cardiovascular variables. Traces and abbreviations as in Fig. 1. Arrow beneath each panel indicates period of breathing hypoxic mixture (12, 8 and 6% O_2 in N_2). The P_{a,O_2} values are those measured at the end of the second minute of hypoxia. Note the respiratory and cardiovascular changes are graded with the level of hypoxia, including the frequency of augmented breaths, each being associated with further muscle vasodilatation.

several breaths of lower tidal volume at lower frequency than normal (see Fig. 1; cf. Glogowska *et al.* 1972). Generally, each augmented breath was accompanied by a fall in arterial pressure and transient dilatation in hindlimb skeletal muscle, such that femoral vascular conductance increased by up to 70% and femoral blood flow increased, the whole change lasting 10–15 s. There was also a transient increase in renal vascular conductance, but renal blood flow either remained constant or fell with the arterial pressure. In some animals there was also a transient bradycardia (cf. Marshall, 1987). These cardiovascular changes generally seemed to begin with the augmented breath, but analysis at a faster chart speed revealed that they sometimes began before the augmented breath (Fig. 1). Since there was the possibility that the renal vascular change was merely a myogenic response to the fall in arterial pressure and in view of the lability of the cardiac response, we have concentrated below upon the muscle vasodilatation.

Effect of hypoxia

Administration of hypoxic mixtures induced hyperventilation, tachycardia, a fall in arterial pressure and a gradual increase in femoral and renal conductance, all of which were graded with the level of hypoxia (Fig. 2). Concomitantly, the frequency of augmented breaths increased to an extent which was graded with the level of hypoxia, i.e. from one every 3 min during air breathing to $3{\cdot}4 \pm 0{\cdot}1$, $5{\cdot}8 \pm 0{\cdot}1$, $11{\cdot}7 \pm 0{\cdot}2$ and $14{\cdot}3 \pm 0{\cdot}2$ over the 3 min periods of breathing 15, 12, 8 and 6% O_2

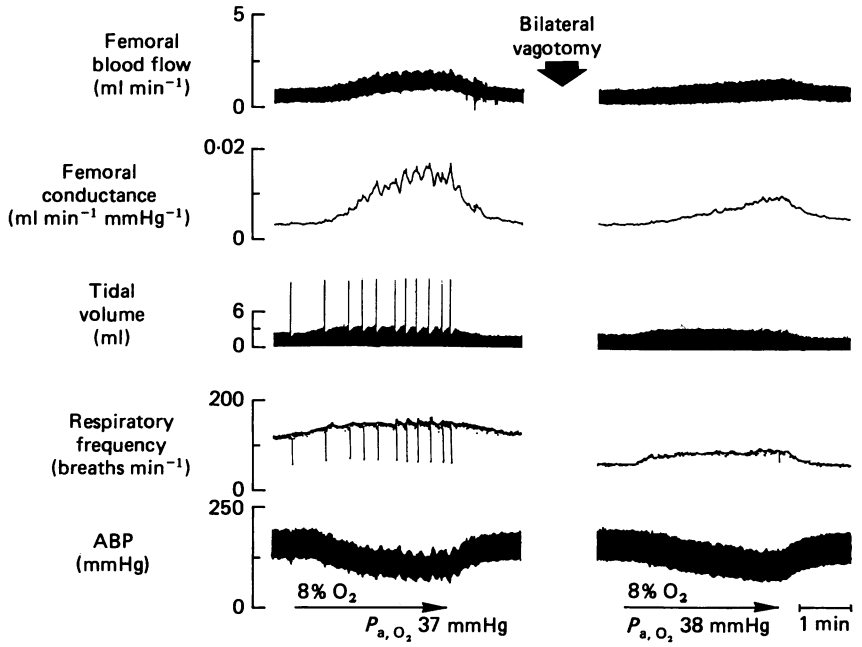

Fig. 3. The effect of acute bilateral vagotomy upon augmented breaths induced during hypoxia. Traces as in Fig. 1, except no heart rate recording. The right-hand panel was recorded 30 min after bilateral vagotomy. Note absence of augmented breaths and transient vasodilatations.

respectively. As in normoxia, each augmented breath was accompanied by a transient fall in arterial pressure and femoral vasodilatation. These were often larger than those seen during normoxia and were superimposed upon the more gradual changes induced by hypoxia (Fig. 2).

Effect of vagotomy

Bilateral vagotomy generally abolished augmented breaths and their accompanying cardiovascular changes both during normoxia and hypoxia, for the remainder of the experiment, leaving the more gradual hypoxia-induced changes (Fig. 3). However, in three animals augmented breaths were again observed 1–2 h after vagotomy, at irregular intervals during normoxia and more frequently during hypoxia; their frequency was never as great as with vagi intact and any transient femoral vasodilatations that accompanied them were smaller.

Effect of lung hyperinflation

Hyperinflation with pressures of 10 mmHg produced the expected Breuer–Hering reflex effect on respiration, i.e. a decrease in respiratory frequency, but there was no measurable effect upon the cardiovascular variables (Figs 1 and 4). Hyperinflation with pressures > 10 mmHg was avoided since this apparently impeded venous return and reduced stroke volume, judging from the observed fall in pulse pressure.

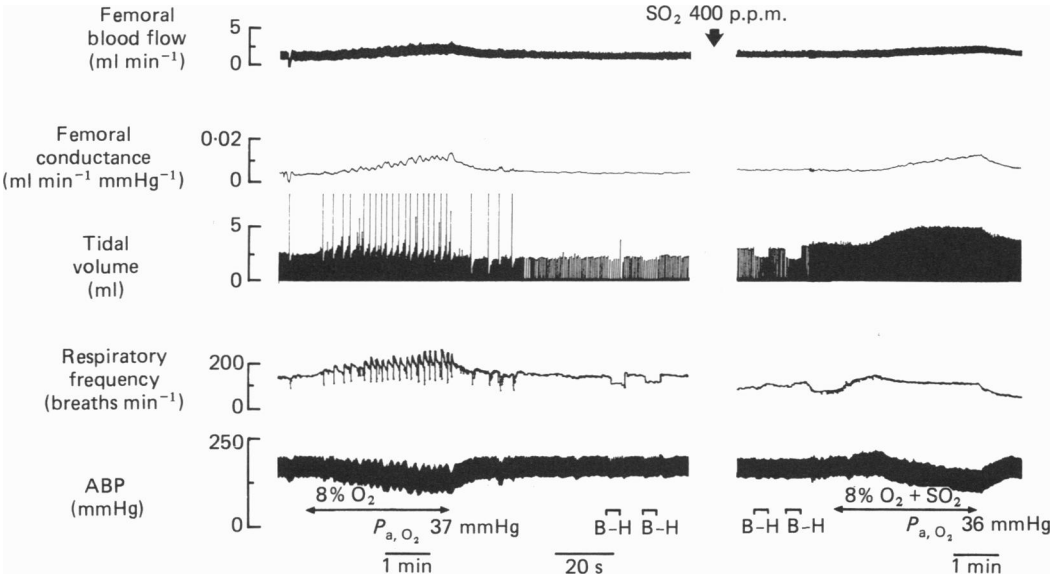

Fig. 4. Effect of SO_2 inhalation upon response to hypoxia and on Breuer–Hering reflex. Traces as in Figs 1 and 2, except no heart rate recording. Note SO_2 (400 p.p.m.) abolished the Breuer–Hering reflex evoked by lung hyperinflation to 10 mmHg, and in this animal it also abolished augmented breaths and transient vasodilatations. However, SO_2 had no effect upon baselines of cardiovascular variables, nor upon the gradual increase in femoral vascular conductance and decrease in arterial pressure induced by hypoxia.

Effects of sulphur dioxide

In the rabbit, addition of 200 p.p.m. SO_2 to inspired air for 10 min produced blockade of pulmonary stretch receptors which lasted 20–60 min (Davies *et al.* 1978). By contrast, our experiments indicated that in the rat, not only were higher SO_2 concentrations required to achieve pulmonary stretch receptor blockade but the effect was shorter lasting. Thus, in order to maintain blockade of the Breuer–Hering reflex for the duration of a 3 min test period of breathing 8% O_2, it was necessary to add 300–400 p.p.m. SO_2 to the hypoxic mixture; to achieve stable blockade during normoxia, air containing 300–400 p.p.m. SO_2 was administered from a gas bag (see Methods). Within 5 min of returning to air breathing a Breuer–Hering reflex of comparable magnitude to that seen in the control state could again be evoked.

The administration of SO_2 in air not only abolished the Breuer–Hering reflex but induced a decrease in the baseline respiratory frequency and an increase in the baseline level of tidal volume (Fig. 4), as would be expected if pulmonary stretch

TABLE 1. Effects of SO_2 on cardiovascular and respiratory variables in normoxia and on responses induced by hypoxia

	Air	8% O_2	Mean % change	Air + SO_2	8% O_2 + SO_2	Mean % change
Heart rate (beats min^{-1})	443·1 ± 34·0	445·7 ± 63·1	4·7 ± 18·3 (7)	444·3 ± 27·1	467·1 ± 54·7	5·1 ± 11·4 (7)
Arterial pressure (mmHg)	161·5 ± 22·4	127·4 ± 29·3*	−21·2 ± 14·4 (9)	164·0 ± 18·5	132·0 ± 19·3*	−18·6 ± 14 (9)
Respiratory frequency (breaths min^{-1})	100·1 ± 27·5	130·8 ± 21·5*	38·6 ± 36·8 (8)	78·0 ± 21·0†	111·0 ± 19·3*†	46·3 ± 29·4 (8)
Tidal volume (ml)	2·31 ± 0·44	2·56 ± 0·38*	12·0 ± 8·2 (9)	3·02 ± 0·58†	4·10 ± 1·14*†	34·8 ± 19·5† (9)
Minute volume (ml min^{-1})	217·0 ± 39·0	326·9 ± 54·1*	54·6 ± 37·4 (8)	234·0 ± 81·8	447·3 ± 148·0*	94·5 ± 33·0† (8)
Femoral flow (ml min^{-1})	1·199 ± 0·454	1·302 ± 0·331	16·6 ± 35·9 (9)	1·240 ± 0·391	1·418 ± 0·430*	20·8 ± 14·6 (9)
Femoral conductance (ml min^{-1} $mmHg^{-1}$)	0·0076 ± 0·0033	0·0107 ± 0·0035*	53·9 ± 62·2 (9)	0·0075 ± 0·0021	0·0110 ± 0·0037*	46·2 ± 36·3 (9)
Renal flow (ml min^{-1})	7·884 ± 1·848	7·444 ± 2·745	−7·2 ± 20·5 (9)	7·078 ± 2·287†	7·063 ± 2·496	0·1 ± 1·4 (9)
Renal conductance (ml min^{-1} $mmHg^{-1}$)	0·0554 ± 0·0120	0·0620 ± 0·0209	13·4 ± 35·4 (9)	0·0486 ± 0·0166†	0·05580 ± 0·0149	20·6 ± 28·1 (9)
P_{a,O_2} (mmHg)	83 ± 7·5	37 ± 10*	−55 ± 10 (9)	82 ± 11	34 ± 6*	−58 ± 4·9 (9)
P_{a,CO_2} (mmHg)	34 ± 4·9	25 ± 2·3*	−24 ± 6·2 (9)	28 ± 4·7†	19 ± 3·6*†	−31 ± 3·8 (9)
pH_a	7·424 ± 0·07	7·537 ± 0·08*	1·5 ± 0·71 (9)	7·500 ± 0·01†	7·610 ± 0·03*†	1·5 ± 0·5 (9)

* Indicates significant difference ($P < 0·05$) between air breathing and 8% O_2 values, with or without SO_2.
† Indicates significant difference ($P < 0·05$) between values attained with and without SO_2, using paired t test.
Number of pairs of values are given in parentheses. All values are mean ± S.D.

receptor activity was blocked (cf. Davies *et al.* 1978); respiratory minute volume was unchanged (Table 1). Augmented breaths still occurred with transient dilatations as in the control state but their frequency was reduced to one every 5 min. Although P_{a,CO_2} was lower during SO_2 administration, P_{a,O_2} was unchanged. There were no significant changes in the baseline levels of arterial pressure, heart rate or femoral vascular conductance, but renal vascular conductance was significantly decreased (Table 1).

During administration of 8% O_2 plus SO_2, the frequency of augmented breaths was substantially lower than with 8% O_2 alone (3·2 and 11·8 breaths min^{-1} respectively, over the 3 min test period) and exceptionally, as in Fig. 4, augmented breaths did not occur. However, each augmented breath that did occur was accompanied by transient changes in the cardiovascular variables that were not obviously different from those recorded in the absence of SO_2 and which were superimposed upon the more gradual changes induced by hypoxia.

In order to compare the gradual responses to 8% O_2 with and without SO_2, a smooth line was drawn by eye through the gradual change in the recording of each variable and measurements were made at the end of the second minute of the 3 min test period, i.e. the same time at which blood samples were withdrawn for gas analyses. Analysis of these data (Table 1) showed that 8% O_2 plus SO_2 produced a significantly greater incrase in tidal volume and in minute volume than did 8% O_2 alone. The fall in P_{a,CO_2} was slightly greater, but the fall in P_{a,O_2} was the same as that induced with 8% O_2 alone. The magnitudes of the tachycardia, the fall in arterial pressure and the gradual increases in femoral and renal vascular conductances were not consistently altered when SO_2 was added to the 8% O_2; in some cases they were slightly greater, in others slightly smaller. Not surprisingly there were no statistically significant differences between the changes recorded with 8% O_2 and with 8% O_2 plus SO_2 for any of the cardiovascular variables.

DISCUSSION

In the present study, rats anaesthetized with Saffan showed 'spontaneous' augmented breaths at regular intervals during air breathing. Recently, it was found that rats anaesthetized with pentobarbitone also showed regular augmented breaths during air breathing (Marshall, 1987). The frequency of the augmented breaths recorded in our studies was very similar to that reported previously for conscious, as well as for anaesthetized, rats (Bartlett, 1971). Regular augmented breaths during spontaneous breathing have also been recorded in a variety of other species including the cat, rabbit, horse and man (McCutcheon, 1953; Glogowska *et al.* 1972; Cherniack, von Euler, Glogowska & Homma, 1981; Marshall & Metcalfe, 1987*b*) and they are also a prominent feature of the breathing pattern in newborn mammals, including human infants (Cross, Klaus, Tooley & Weisser, 1960; Thach & Taeusch, 1976). The findings of the above studies, in particular the comparative study of McCutcheon (1953), indicate that small mammals show augmented breaths more frequently than large mammals. There is much support for the view that augmented breaths prevent or reverse atelectasis (Reynolds, 1962; Glogowska *et al.* 1972), so that small mammals with small alveoli, which might be expected to be particularly suspectible to alveolar

collapse, are apparently equipped with a repeating mechanism which counteracts this tendency (Bartlett, 1971).

In the present experiments we found that the frequency of augmented breaths was increased in hypoxia to an extent that was graded with the level of hypoxia. Previously, it was noted that an augmented breath could be initiated by brief, selective stimulation of carotid chemoreceptors (Marshall, 1987). In both studies augmented breaths were abolished in the short term by vagotomy, but in some animals of the present study they reappeared after 1–2 h and again were more common in hypoxia. These results are in full accord with those of others (Bartlett, 1971; Glogowska *et al.* 1972; Cherniack *et al.* 1981). They are also consistent with the strong evidence based on detailed analyses of the nature and underlying mechanisms of augmented breaths, that the most important input for their initiation is from rapidly adapting lung irritant receptors with vagal afferents, but that they can also be facilitated by stimulation of peripheral chemoreceptors (Glogowska *et al.* 1972; Widdicombe, 1982). The lung irritant receptors are apparently stimulated by a decrease in compliance as occurs with atelectasis; they are probably sensitive to the velocity of respiratory air flow (Reynolds, 1962; Glogowska *et al.* 1972; Widdicombe, 1982). Thus, augmented breaths can be initiated experimentally by rapid inflations or deflations but they can also be evoked by hyperpnoea, which has led to the proposal that stimuli which increase inspiratory flow cause an increase in the activity of irritant receptors which stimulates inspiration and initiates augmented breaths, so setting up a positive feed-back (Glogowska *et al.* 1972). Although each augmented breath is followed by a refractory period during which further augmented breaths cannot be elicited, this refractory period is shortened during hypoxia which allows their frequency to reach even higher levels than during other respiratory stimuli (Cherniak *et al.* 1981).

To our knowledge, ours is the first report that cardiovascular changes are closely associated with augmented breaths both in normoxia and hypoxia. The most obvious component, upon which we have concentrated, was transient vasodilatation in skeletal muscle, but we also observed a less consistent bradycardia and an increase in renal vascular conductance, which may have been an autoregulatory response to the concomitant fall in arterial pressure (see Results). Since the increase in muscle vascular conductance sometimes preceded the large inspiration of the augmented breath, it is very unlikely to have been a manifestation of the reflex vasodilatation initiated by pulmonary stretch receptors, such as can be demonstrated in the dog (Daly & Scott, 1962). This view is supported by the fact that experimentally induced hyperinflation of the lungs with pressures of up to 10 mmHg, which was sufficient to evoke a substantial Breuer–Hering reflex on respiration, failed to produce any measurable cardiovascular change. Indeed, these results suggest that the reflex effect exerted on the cardiovascular system by pulmonary stretch receptors is weak in the rat. Accordingly, the most obvious explanation for the transient vasodilatation, and possibly the bradycardia, is that they, like the augmented breath, are all part of a primary reflex which can be triggered by lung irritant receptors and facilitated by peripheral chemoreceptors. Interestingly, there have been previous reports based on experiments on dogs that rapid lung inflation with pressures > 15 mmHg could evoke bradycardia and hindlimb vasodilatation (Glick, Wechsler & Epstein, 1969;

Hainsworth, 1974). It is tempting to suggest that such manoeuvres were sufficient to stimulate rapidly adapting irritant receptors and thereby to evoke the cardiovascular changes we have described.

It was an aim of the present study to use SO_2 as a means of differentiating between the effects of the pulmonary stretch receptors and irritant receptors since in the rabbit administration of 200 p.p.m. SO_2 in air for 10 min was sufficient to abolish the Breuer–Hering reflex and block activity from stretch receptors, but not that from irritant receptors (Davies *et al.* 1978). In the rat, maintained administration of 300–400 p.p.m. SO_2 was necessary to block the Breuer–Hering reflex and once this had been achieved the frequency of augmented breaths during air breathing and the increased frequency during hypoxia were substantially lower than those recorded in the absence of SO_2. This could indicate that SO_2 was non-selective in our experiments and inhibited irritant receptor as well as stretch receptor activity. However, in the rabbit also, the frequency of spontaneous augmented breaths was reduced after SO_2 and such breaths were less readily elicited by inflation and deflation, yet the tonic activity of the irritant receptors was increased by SO_2 rather than decreased (Davies *et al.* 1978; Davies & Roumy, 1982). An alternative explanation for these findings is that since SO_2 induced an increase in tidal volume, as is consistent with pulmonary stretch receptor blockade (see also Davies *et al.* 1978), lung compliance was increased, so raising the threshold for initiation of augmented breaths (see above). Whether this is the correct explanation or not, it is to be noted that when the respiratory reflex from stretch receptors was blocked by SO_2 the augmented breaths that did occur, either in normoxia or hypoxia, were still associated with transient vasodilatations. This reinforces the view that they were not initiated by pulmonary stretch receptors.

The administration of SO_2 did reduce the baseline level of renal vascular conductance, which is compatible with previous reports that vagal afferents from cardio-pulmonary receptors exert a particularly strong, tonic inhibitory influence on sympathetic activity to the kidney (e.g. Mancia, Shepherd & Donald, 1976). However, SO_2 had no significant effect upon the baseline levels of the other cardiovascular variables. Further, the more gradual cardiovascular changes induced by hypoxia, i.e. the gradual vasodilatation and tachycardia upon which the transient responses were superimposed, were not significantly different when SO_2 was present, indicating strongly that reflex tachycardia and vasodilatation initiated by pulmonary stretch receptors played little part in their genesis either. Thus, taken together the present results suggest that in the rat the pulmonary stretch receptors have little or no reflex effect upon the cardiovascular system either during normoxia or hypoxia. This is consistent with the conclusion drawn from recent experiments on the reflex effects of selective stimulation of carotid chemoreceptors in the rat (Marshall, 1987). In this respect, therefore, the rat contrasts with the dog in which reflex tachycardia and vasodilatation elicited by pulmonary stretch receptors secondary to the concomitant hyperventilation play a large part in the cardiovascular response to brief chemoreceptor stimulation and to systemic hypoxia (Daly & Scott, 1962; Koehler, McDonald & Krasney, 1980). On the other hand, the maintained close link between the augmented breaths and transient vasodilatations in the presence of SO_2 is consistent with our suggestion that they have a common genesis, which is predominantly the irritant receptor input.

Given that the rat has no sympathetic cholinergic dilator supply to skeletal muscle, it seems reasonable to assume that the transient vasodilatations were mediated by inhibition of sympathetic vasoconstrictor tone; certainly such dilatations were abolished when sympathetic noradrenergic tone was attenuated with guanethidine (Marshall & Metcalfe, 1987*a*). This implies that irritant receptor activity can increase inspiratory drive and yet inhibit sympathetic preganglionic activity. This is of particular interest in view of the substantial evidence that the majority of sympathetic preganglionic neurones have a respiratory-related discharge, with an increase in activity in inspiration, and that their activity is increased by stimuli which increase central inspiratory drive (e.g. Bachoo & Polosa, 1987). On the basis of lesions and electrical stimulation at various sites in the medulla oblongata, it has been proposed that neurones within a discrete region of the lateral tegmentum comprise the central pattern generator for rhythmic augmented breaths which is separate from that concerned with the neurogenesis of eupnoea and whose pacemaker activity may be modified by a variety of excitatory and inhibitory inputs (St John, Bledsoe & Sokol, 1984; St John, Bledsoe & Tenney, 1985). It could be that when the activity of this pattern generator is increased, for example by input from lung irritant receptors, it provides an inhibitory input to sympathetic preganglionic neurones which overrides any excitatory influence exerted upon them via inspiratory neurones. Another, but not mutually exclusive, possibility is that irritant receptors have a more direct and overriding inhibitory input to sympathetic preganglionic neurones. Proper elucidation of the mechanisms involved must await neurophysiological evidence. Meanwhile, the recent report of Bachoo & Polosa (1987) is of interest, for they found that sympathetic fibres with an inspiratory-related discharge were inhibited during the phase of phrenic discharge associated with the augmented breath. Further, it is known that there is a population of sympathetic preganglionic neurones which, although they may be predominantly silent under experimental conditions, show an expiratory pattern of discharge when activated by glutamate, which is consistent with their receiving an inhibitory or disfacilitatory input coincident with inspiration (Gilbey, Numao & Spyer, 1986). Both of these observations are compatible with and would go some way towards explaining the transient vasodilatations associated with augmented breaths reported in the present study.

Thus, we have described a cardiovascular change that is associated with augmented breaths, its most obvious component being a short-lasting vasodilatation in skeletal muscle that is mediated by inhibition of sympathetic vasoconstrictor tone. We propose that this muscle vasodilatation, like the augmented breath, is part of a primary reflex initiated principally by lung irritant receptors and that during hypoxia when the frequency of augmented breaths is increased, the closely associated transient muscle vasodilatations become an integral part of the overall cardiovascular response. We have already described comparable transient muscle vasodilatations associated with augmented breaths in the cat (Marshall & Metcalfe, 1987*b*). Since augmented breaths are a normal feature of respiration in a wide variety of mammalian species (see above), it seems reasonable to propose that associated muscle vasodilatations are too. Given that the frequency of augmented breaths both in normoxia and hypoxia is relatively low in larger mammals, the transient dilatations may be of minor importance, except perhaps at high altitude or in severe

hypoxia of respiratory disease. However, in small, including newborn, mammals in whom augmented breaths are considered to be particularly important in preventing atelectasis and in the initial inflation of the lungs (Cross *et al.* 1960), the accompanying vasodilatation may be functionally important in ensuring that the additional O_2 loaded at the lungs is distributed to skeletal muscle.

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