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MODIFICATION BY LUNG INFLATION OF THE VASCULAR RESPONSES FROM THE CAROTID BODY CHEMORECEPTORS AND OTHER RECEPTORS IN DOGS

BY M. DE BURGH DALY*, JANE WARD† AND L. M. WOOD*

From the Department of Physiology, St. Bartholomew's Hospital Medical College, Charterhouse Square, London EC1M 6BQ

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SUMMARY

1. The reflex effects of increasing pulmonary ventilation on the responses of the hind-limb and systemic vascular resistances to stimulation of the carotid body chemoreceptors and carotid sinus baroreceptors and to distension of the urinary bladder have been studied in the anaesthetized dog. A preparation was used incorporating total cardiopulmonary bypass to maintain the arterial blood gas composition constant when alterations in pulmonary ventilation were made. The regions of both carotid bifurcations, the arch of the aorta and the cerebral circulation were independently perfused at constant pressure so as to exclude secondary reflexes from arterial baroreceptors.

2. Four levels of pulmonary ventilation were used: 0·095, 0·285, 0·475 and 0·665 l min^{-1} kg^{-1} body weight, at a constant frequency of 19 cycles min^{-1}. Increasing the pulmonary ventilation *per se* in steps from 0·095 to 0·665 l min^{-1} kg^{-1} resulted in a significant progressive reduction in hind-limb and systemic vascular resistances which were shown to be due to a reflex from the lungs.

3. Stimulation of the carotid body chemoreceptors by hypoxic hypercapnic blood resulted in an increase in hind-limb and systemic vascular resistances when carried out at each of the four levels of pulmonary ventilation. The size of the increases in vascular resistances, however, was progressively and significantly reduced as the pulmonary ventilation was increased. This partial inhibition of the carotid body reflex vasoconstrictor response was dependent on the innervation of the lungs.

4. Stimulation or unloading of the carotid sinus baroreceptors by altering the perfusion pressure in the vascularly isolated carotid bifurcation regions caused a significant decrease and increase respectively in hind-limb and systemic vascular resistances at all four levels of pulmonary ventilation. Unlike the responses to chemoreceptor stimulation, the size of these responses was unaffected by the level of pulmonary ventilation.

5. Distension of the urinary bladder resulted in a significant increase in hind-limb

* Present address: Department of Physiology, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF.

† Present address: Department of Physiology, United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, St. Thomas Street, London SE1 9RT.

and systemic vascular resistances. The size of these responses was also unaltered by changing the level of pulmonary ventilation.

6. These results indicate that there is an interaction between the inputs from the lungs and the carotid body chemoreceptors in the control of hind-limb and systemic vascular resistances. In contrast the inputs from the carotid sinus baroreceptors and the urinary bladder were unaffected by the input from the lungs.

INTRODUCTION

The direction and size of the peripheral vascular response to stimulation of the carotid body chemoreceptors depend to a large extent on the magnitude of the accompanying changes in pulmonary ventilation. In both anaesthetized and conscious dogs that are artificially ventilated, stimulation of the carotid bodies causes an increase in hind-limb and peripheral vascular resistances (Bernthal, 1938; Daly & Scott, 1962, 1963; Daly & Ungar, 1966; Angell-James & Daly, 1969; Rutherford & Vatner, 1978; Daly, Korner, Angell-James & Oliver, 1978; Hainsworth, Karim, McGregor & Wood, 1983). When, however, ventilation is allowed to increase spontaneously, the vasoconstrictor responses are smaller or may be reversed to vasodilatation (Daly & Scott, 1962, 1963; Daly & Ungar, 1966; Angell-James & Daly, 1969).

The mechanism by which an alteration in pulmonary ventilation modifies the vascular responses to carotid body stimulation is a vagal reflex from the lungs, initiated by an increase in tidal volume and probably also in the rate of change in volume (Daly & Scott, 1962, 1963; Daly & Ungar, 1966; Angell-James & Daly, 1969). This pulmonary reflex results in vasodilatation due to an inhibition of sympathetic vasconstrictor tone (Daly, Hazzledine & Ungar, 1967; Daly & Robinson, 1968; Angell-James & Daly, 1969; Daly, Litherland & Wood, 1983). What is not clear, however, is whether the inputs from the carotid bodies and lungs are integrated in a purely additive way and/or whether there is a central inhibition of the carotid chemoreceptor vasoconstrictor response by excitation of pulmonary receptors. This is the subject of the present paper.

Besides looking into the way different levels of pulmonary ventilation affect carotid chemoreceptor reflexes, we have, for comparison, also made a study of the way pulmonary ventilation affects the vascular responses to two other inputs to the nervous system: distension of the urinary bladder, and unloading and stimulation of the carotid sinus baroreceptors. Reflex vasoconstrictor responses result from bladder distension (Guttman & Whitteridge, 1947; Mukherjee, 1957; Taylor, 1968; Daly & Wood, 1982) and unloading the baroreceptors, whereas vasodilatation occurs on stimulation of the baroreceptors (for review see Kirchheim, 1976). Studies of the effects of the pulmonary vagal input on reflexes from carotid chemoreceptors, carotid baroreceptors and visceral receptors were made in each and the same experiment so that a comparison of the effects could be made.

Using a modified preparation involving cardiopulmonary bypass (Daly & Ungar, 1966), it was possible to study the responses to stimulation of the carotid bodies and to changes in pulmonary ventilation, both separately and together, in the absence of alterations in arterial blood gases, in input from arterial baroreceptors,

and in cerebral perfusion pressure. Some of these results have already been reported briefly (Daly, Ward & Wood, 1984).

METHODS

The preparation used was a modification of that described previously (Daly & Ungar, 1966). Only an outline and the modifications to the preparation will be given here.

The experiments were performed on mongrel dogs of either sex, mean weight 13·8 ± 1·9 kg, range 10·2–15·8 kg. After pre-medication with morphine hydrochloride, 1 mg kg^{-1} subcutaneously, the animals were anaesthetized with a mixture of α-chloralose (Establissements Kuhlmann, Paris; 0·056 g kg^{-1}) and urethane (British Drug Houses Ltd.; 0·56 g kg^{-1}) given intravenously.

The trachea was cannulated just below the larynx and the animal spontaneously breathed air enriched with oxygen, 0·2 l min^{-1}, until the initial surgical procedures were completed. Positive pressure ventilation was then applied by means of a Starling 'Ideal' pump at a rate of 19 cycles min^{-1} and a tidal volume of about 17 ml kg^{-1} with 40 % O_2 in N_2. An end-expiratory pressure of 3 cmH_2O prevented complete collapse of the lungs. After cardiopulmonary bypass had been established, the lungs of the experimental animal were ventilated with room air. Rectal temperature was monitored throughout the experiment and maintained between 36·7 and 38·7 °C. All the perfusion apparatus and the perfusion tubing between the animal and blood reservoirs were immersed in a special water bath maintained at 38 °C.

Cardiopulmonary bypass and perfusion of the systemic circulation

For each experiment a second animal, a greyhound, was pre-medicated with morphine hydrochloride, 1 mg kg^{-1} subcutaneously, and anaesthetized with a mixture of α-chloralose, 0·0616 g kg^{-1}, and urethane, 0·616 g kg^{-1}, intravenously. The animal was then bled to death and the blood used to prime the perfusion circuit. The lungs were then prepared for isolation, perfusion and ventilation as described by Daly *et al.* (1967), and used as an extracorporeal oxygenator for the experimental animal.

The chest of the experimental animal was opened in the mid-sternal line. The right atrium was cannulated and venous blood drained into the small venous reservoir (r.a.res.) from which it overflowed into the main reservoir (Fig. 1). This venous blood was oxygenated by the extracorporeal isolated lungs perfused via the pulmonary artery by pump P1. Ventilation of these lungs was achieved by means of a second Starling 'Ideal' pump, with 40 % O_2 in N_2 at a rate of 19 cycles min^{-1}. The tidal volume was set at 500 ml and CO_2 was added to the inspired gas via a rotameter at a rate which maintained the arterial P_{CO_2} (P_{a,CO_2}) of the recipient animal within normal limits.

The oxygenated blood from the cannulated left atrium of the extracorporeal isolated perfused lungs drained into the small arterial reservoir (l.a.res.). The output of the pump P1 was adjusted so that at all times it was just greater than the combined outputs of pumps P2, P3, P4 and P5. Thus the arterial reservoir was always kept full with a small amount of arterial blood overflowing into the main reservoir.

Arterial blood was then pumped by pump P2 through cannulae in the proximal ends of both femoral arteries to perfuse the thorax and abdomen, and in the distal end of the right femoral artery to perfuse the right hind limb. Systemic perfusion pressure was measured from a catheter placed in the abdominal aorta just below the level of the diaphragm via the proximal end of the left femoral artery.

Venous pressure was measured by a catheter placed in the abdominal inferior vena cava via the right femoral vein. It was held constant because the blood returning to the right atrium drained into the small venous reservoir maintained at a constant level. Thus, with venous pressure held constant and with systemic perfusion at constant flow, changes in the systemic perfusion pressure were used as an index of changes in the vascular resistance of the thorax, abdomen and right hind limb. This will be referred to as the systemic vascular resistance. At the start of the experimental procedures the output of pump P2 was adjusted to give a mean systemic perfusion pressure of 100–110 mmHg.

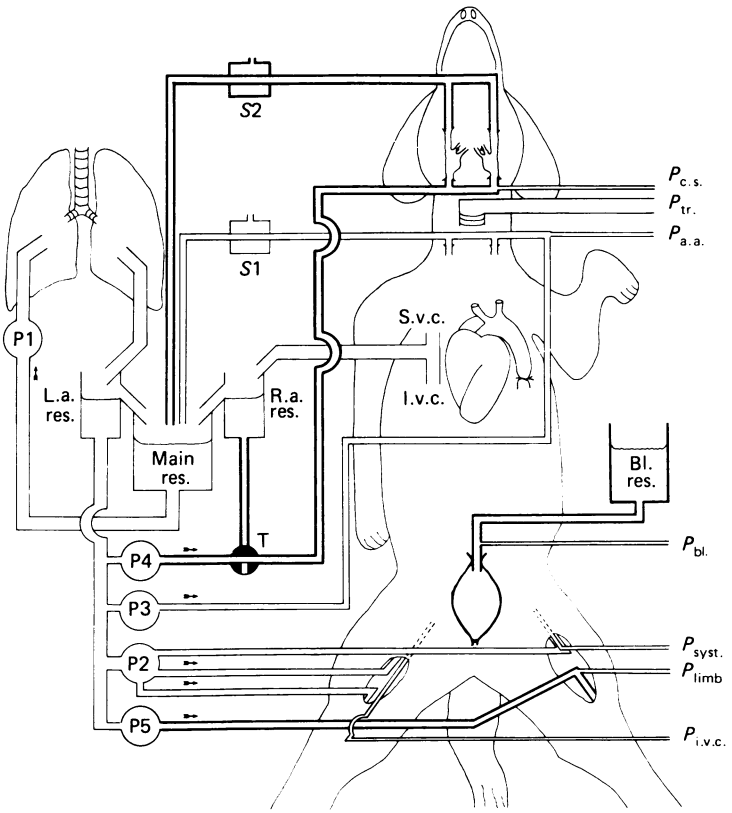

Fig. 1. Diagrammatic representation of the preparation used. Total cardiopulmonary bypass, the mixed venous blood being oxygenated in an extracorporeal isolated perfused and ventilated lung preparation of a donor animal. Blood drained from the right atrium of the experimental animal into a small venous reservoir (r.a.res.) from which it overflowed into the main reservoir. Blood from the main reservoir was pumped, by pump P1, into the pulmonary artery of the extracorporeal lungs from whence it drained via the left atrium into the small left atrial reservoir (l.a. res.). A small excess of this pulmonary flow compared with the total systemic blood flow overflowed into the main reservoir (main res.). Various parts of the systemic circulation were perfused with blood from the small left atrial reservoir as follows: pump P2 perfused at constant flow the thorax, abdomen and right hind limb; pump P3 perfused at constant pressure, via the proximal ends of both common carotid arteries, the arch of the aorta and the cerebral and coronary circulations; the pressure was controlled by a Starling resistance, *S*1, which controlled the overflow from the pump into the main reservoir. The aorta was tied just distal to the origin of the left subclavian artery. Pump P4 perfused at constant pulsatile and mean pressures, the vascularly isolated regions of both carotid bifurcations. The perfusion pressure was controlled by the Starling resistance *S*2 which controlled the outflow from the regions into the main reservoir. Stimulation of the carotid bodies was achieved by turning the tap T so that hypoxic hypercapnic blood from the small venous reservoir now perfused the carotid bifurcation regions. Pump P5 perfused at constant flow the vascularly isolated left hind limb. Blood returning via the superior and inferior venae cavae (s.v.c., i.v.c.) drained into the right atrial reservoir (r.a. res.), and thence into the main reservoir. The bladder was cannulated suprapubically and distended with isotonic saline at 37 °C by raising the reservoir (bl. res.) to the appropriate height above the animal. Catheters were appropriately sited for measurement of systemic perfusion pressure ($P_{syst.}$), carotid sinus perfusion pressure ($P_{c.s.}$), aortic arch perfusion pressure ($P_{a.a.}$), left hind-limb perfusion pressure (P_{limb}), inferior vena caval pressure ($P_{i.v.c.}$), urinary bladder pressure ($P_{bl.}$), and tracheal pressure ($P_{tr.}$). For clarity, different line thicknesses are used to delineate the perfusion circuits, and the lungs of the test animal, supplied by the bronchial circulation, are not shown.

Perfusion of the aortic arch and the cerebral circulation

Blood from the arterial reservoir was pumped at a constant flow by pump P3 through cannulae in the proximal ends of both common carotid arteries (Fig. 1). The aorta was ligated just distal to the origin of the left subclavian artery. Thus the blood perfused the region of the aortic arch, coronary circulation, and, via the vertebral arteries, the cerebral circulation. The perfusion pressure was set to approximately 100 mmHg and and was maintained constant by means of a Starling resistance which controlled the overflow from the pump into the main reservoir. The amount of overflow was sufficient to ensure that the pressure remained constant throughout the experimental tests which resulted in changes in vascular resistance. The perfusion pressure was measured via a side arm of the perfusion cannulae in the proximal ends of both common carotid arteries.

Perfusion of the carotid sinuses and stimulation of the carotid bodies

Both carotid bifurcation regions was vascularly isolated and perfused with blood from the arterial reservoir at constant flow with pulsatile pressure by means of a special pump P4 (Bacon, Daly, Daly & Scott, 1976). The internal carotid, occipital, ascending pharyngeal and pharyngeal arteries were tied, together with any other small vessels that could be found. Blood drained from the regions via both external carotid arteries and through a Starling resistance which controlled the perfusion pressure, initially set to 110 mmHg, and then into the main reservoir. The perfusion pressure was measured via a side arm of the perfusion cannulae in the distal ends of both common carotid arteries. In some animals the sympathetic supply from the superior cervical ganglion to the carotid bifurcation regions was cut. Stimulation of the carotid body chemoreceptors by hypoxic hypercapnic blood was achieved, with no change in the perfusion pressure, by turning the three-way tap, T, so that hypoxic hypercapnic blood from the small venous reservoir perfused the region (Fig. 1).

Perfusion of the left hind limb

The left hind limb was vascularly isolated by ligating (1) the left external iliac artery around the systemic perfusion cannula and (2) the aorta between the origin of the external iliac arteries and its trifurcation into the internal iliac and median sacral arteries. It was perfused at constant flow by pump, P5, with blood from the arterial reservoir through the distal end of the left femoral artery. Vascular isolation of the limb was shown to be adequate because on stopping the pump, P5, the perfusion pressure fell below 20 mmHg, when the mean systemic perfusion pressure was above 100 mmHg. A venous bypass in the form of a rigid wide-bore polyethylene cannula was inserted, via the left femoral vein, into the abdominal vena cava. It was positioned in such a way that it conducted blood from the femoral vein to a position in the abdominal vena cava above the level of the bladder, adjacent to the venous pressure catheter. Limb perfusion pressure was measured from a side arm of the perfusion cannula in the distal end of the femoral artery. Thus in the absence of changes in venous pressure and with constant flow perfusion, changes in limb perfusion pressure were used as an index of changes in vascular resistance.

Distension of the urinary bladder

A wide-bore cannula with a side arm for pressure measurement, was tied into the wall of the bladder at its apex through a small mid line abdominal incision, and connected to a reservoir containing sodium chloride solution (154 mM) at a temperature of 37 °C. To prevent escape of urine through the urethra in male dogs, the urethra was occluded by tying in a blocked cannula; in females, a solid vaginal speculum of appropriate size was inserted. Tests of distension of the bladder were carried out by raising the height of the reservoir equivalent to about 50 mmHg.

Surgical denervation of the lungs

This was carried out in three dogs using the method of Daly & Scott (1958).

Blood gas analysis

At regular intervals during each experiment samples of arterial blood were withdrawn anaerobically and were analysed immediately for P_{O_2}, P_{CO_2} and pH using blood gas electrodes and analyser (Model 43, Instrumentation Laboratory (U.K.) Ltd.). The arterial P_{O_2} (P_{a,O_2}) never fell below

TABLE 1. Initial control values for measured variables in the test animal at the start of the experimental period. Values are means ±S.E. of mean

Number of animals	9
Body weight (kg)	13·8±1·9
Mean systemic perfusion pressure (mmHg)	109±16
Mean hind-limb perfusion pressure (mmHg)	128±13
Hind-limb blood flow (ml min^{-1})	58±19
Inferior vena caval pressure (mmHg)	4±2
Heart rate (beats min^{-1})	146±21
Carotid sinus perfusion pressure (mmHg)	
Systolic	159±10
Diastolic	75±12
Mean	112±8
Aortic arch and cerebral perfusion pressure (mmHg)	
Systolic	156±16
Diastolic	75±10
Intrinsic respiratory frequency (min^{-})	14·9±9·2
Respiratory pump stroke (ml)	225±18
Tracheal peak pressure (mmHg)	9±4
Arterial blood	
P_{O_2} (mmHg)	108±22
P_{CO_2} (mmHg)	38±3
pH	7·419±0·036
Haematocrit (%)	41±8
Rectal temperature (°C)	37·7±0·6

100 mmHg. Metabolic acidosis was corrected with an intravenous infusion and/or bolus injections of molar sodium bicarbonate solution.

After completion of the operative procedures and before connecting the perfusion circuit, clotting of the blood was prevented by giving heparin (Pularin, Evans Medical Ltd., Poole, Dorset) 1500 i.u. kg^{-1} intravenously.

Measurement of variables

All of the variables were recorded on direct writing ultra-violet light recorder (S.E. Laboratories Ltd., Feltham, Middlesex). The pressures were measured using strain gauges (Model P23Gb, Statham Ltd., Puerto Rico). Mean pressures were obtained by passing the carrier amplifier output through resistance–capacity (RC) networks with a time constant of 1 s. Zero reference pressures were obtained post mortem with the catheter tips exposed to air *in situ*.

As an index of the changes in respiration rib movements were recorded by means of a linear displacement transducer, which was calibrated at the end of each experiment in millimetres.

Experimental procedure

Tests of stimulation of the carotid bodies, of stimulating and unloading the carotid sinus baroreceptors and of distension of the urinary bladder were performed at four different levels of pulmonary ventilation of the experimental animal chosen at random. The levels of tidal volume were 5, 15, 25 and 35 ml kg^{-1} body weight which, at a ventilation frequency of 19 cycles min^{-1}, corresponded to a respiratory minute volume of 0·095, 0·285, 0·475 and 0·665 l min^{-1} kg^{-1} respectively, that is, all within the normal physiological range. The corresponding peak lung inflation pressures were 3·9±0·3, 8·7±1·0, 11·4±0·9 and 13·3±1·2 mmHg respectively.

All measurements of physiological variables were taken during peak limb perfusion pressure response, usually 30 s after applying a stimulus.

Analysis of results

All values are expressed as the mean ±S.E. of mean. The data resulting from altering the inputs from the carotid chemoreceptors and baroreceptors, and from the urinary bladder receptors were plotted against the level of pulmonary ventilation. Student's *t* test was used to evaluate the significance of the differences between sets of paired observations.

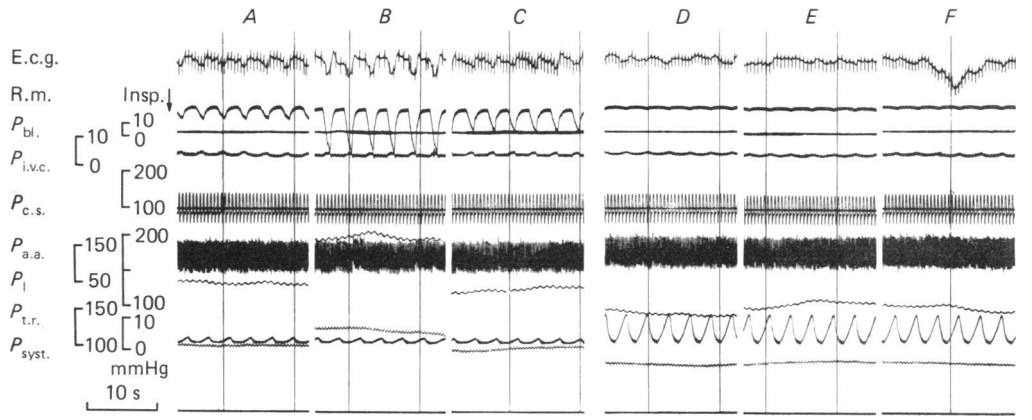

Fig. 2. The effects of stimulation of the carotid body chemoreceptors at two levels of pulmonary ventilation. Dog on cardiopulmonary bypass. Artificial respiration, frequency 19 cycles min^{-1}. The following variables were held constant: arterial blood gases, urinary bladder pressure, carotid sinus perfusion pressure, aortic arch and cerebral perfusion pressures, and inferior vena caval pressure. Systemic circulation and left hind limb each perfused at constant blood flow. *A–C*, pulmonary ventilation of test lung 0·095 l min^{-1} kg^{-1}. *D–F*, pulmonary ventilation 0·665 l min^{-1} kg^{-1}. In *B* and *E*, stimulation of carotid bodies by substituting mixed venous blood for arterial blood perfusion of the vascularly isolated carotid bifurcation regions. Arterial blood/mixed venous blood composition: P_{O_2} 107·8±21·7/41·3±0·2 mmHg; P_{CO_2} 37·9±3·7/45·9±0·7 mmHg; pH 7·419±0·036/7·372±0·004. Note the smaller rises in systemic and hind-limb perfusion pressures in response to carotid body stimulation in *D–F* compared with *A–C*. Records from above downwards: e.c.g., electrocardiogram; r.m., rib measurements (inspiration downwards); $P_{bl.}$, urinary bladder pressure; $P_{i.v.c.}$, inferior vena caval pressure; $P_{c.s.}$ phasic and mean carotid sinus pressures; $P_{a.a.}$ phasic pressure in aortic arch and cerebral circulation; P_{limb}, hind-limb mean perfusion pressure; $P_{tr.}$, tracheal pressure; $P_{syst.}$, systemic mean perfusion pressure. Time marker and calibration, 10 s.

RESULTS

Vascular responses to changes in pulmonary ventilation

When the lungs of the test animal were rhythmically ventilated at four different levels of tidal volume, with the respiration frequency, arterial blood gases and the carotid sinus and aortic arch perfusion pressures held constant (Table 1), increasing the tidal volume from 5 to 35 ml kg^{-1}, or respiratory minute volume from 0·095 to 0·665 l min^{-1} kg^{-1}, caused a progressive stepwise reduction in hind-limb and systemic perfusion pressures in twenty-one tests in nine dogs. Over the full range of ventilation the hind-limb perfusion pressure decreased by 26·0±5·2 mmHg from a control value of 130·0±5·8 mmHg, or by 20% ($P < 0·01$). The systemic perfusion pressure fell by 11·4±3·6 mmHg from a control value of 127·2±6·7 mmHg or by 8·5% ($P < 0·01$). Since the hind-limb and systemic blood flows were held constant, these reductions in perfusion pressure indicate vasodilatation. The responses were abolished by surgical denervation of the lungs and were therefore reflex in nature.

Increasing the pulmonary ventilation also resulted in a progressive reduction in the amplitude of the movements of the ribs, indicating a decrease in central respiratory drive (Fig. 2; Tables 2–4). This response too was abolished by denervation of the lungs showing that it was due to the Hering–Breuer respiratory reflex.

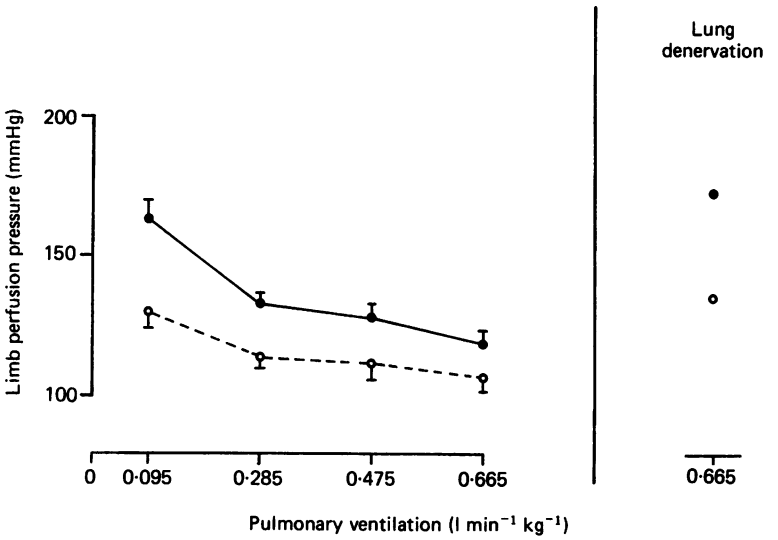

Fig. 3. The effects of stimulation of the carotid bodies on hind-limb perfusion pressure (constant blood flow) at four levels of pulmonary ventilation, 0·095, 0·285, 0·475 and 0·665 l min^{-1} kg^{-1}, respiratory frequency 19 cycles min^{-1}. Dogs on total cardio-pulmonary bypass. Arterial blood P_{O_2}, P_{CO_2} and pH, and the carotid sinus, aortic arch and cerebral perfusion pressures held constant. Left-hand panel: lower curve shows the effects of increasing pulmonary ventilation *per se* with arterial blood perfusion of the carotid bodies; upper curve: stimulation of the carotid bodies at different levels of pulmonary ventilation. Mean values ± S.E. of mean; twenty-one tests in nine dogs. Right-hand panel: effects after surgical denervation of the lungs (method of Daly & Scott, 1958); mean values for three tests in three dogs.

Responses to single inflation of the lungs

In eight tests in eight dogs two levels of lung inflation with room air from a syringe were used. The smaller of the two was 15 ml kg^{-1} corresponding to a mean volume of 210·4 ± 9·6 ml and a mean inflation pressure of 6·6 ± 0·7 mmHg. The larger was 25 ml kg^{-1} corresponding to a mean volume of 353·1 ± 16·0 ml and a mean inflation pressure of 8·3 ± 0·7 mmHg. All inflations were carried out from an end-expiratory pressure of 3 cmH_2O (2·2 mmHg).

Single inflations of the lungs with 15 ml kg^{-1} resulted in a significant reduction in hind-limb perfusion pressure of 18·8 ± 2·2 mmHg from a control value of 143·9 ± 7·4 mmHg, or by 13·1 % ($P < 0·01$) and a significant reduction in systemic perfusion pressure of 10·6 ± 2·8 mmHg from 110·8 ± 5·3 mmHg, or by 9·6 % ($P < 0·01$). Rib movements were significantly reduced by a mean of 5·4 ± 2·6 mm from 6·1 ± 2·5 mm, or by 88·6 % ($P < 0·05$), showing the presence of the Hering–Breuer respiratory reflex.

Single inflations of both lungs to 25 ml kg^{-1} resulted again in a significant and larger reduction in limb perfusion pressure of 26·6 ± 8·0 mmHg from 144·4 ± 7·7 mmHg, and a significant and again larger reduction in systemic perfusion pressure of 12·1 ± 4·0 from 112·4 ± 5·0 mmHg. Rib movements were abolished completely from a control value of 7·8 ± 2·8 mm, again showing the presence of the Hering–Breuer reflex. Denervation of the lungs abolished these responses.

TABLE 2. Respiratory and vascular responses to stimulation of the carotid body chemoreceptors. Values from nine dogs are means ±S.E. of mean

Respiratory minute volume ($l\ min^{-1}\ kg^{-1}$)	Innervated test lung ($n = 21$)				Denervated test lung ($n = 3$)
	0·095	0·285	0·475	0·665	0·665
Tracheal pressure (mmHg)	4±0	9±1	11±1	13±1	13
	Limb perfusion pressure (mmHg)				
Control	130±6	114±4	112±6	107±5	136
Test	163±6	133±4	127±5	119±5	173
Response	+33±5	+19±3	+15±4	+12±2	+37
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Systemic perfusion pressure (mmHg)				
Control	123±6	102±6	99±7	102±2	105
Test	139±7	111±6	105±7	108±6	156
Response	+16±5	+9±1	+6±2	+6±2	+51
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Rib movements (mm)				
Control	4·9±1·3	3·9±1·7	1·7±0·8	0·4±0·3	11·4
Test	9·2±1·6	7·3±1·9	5·4±2·0	1·7±0·6	17·7
Response	+4·3±0·9	+3·4±1·4	+3·6±1·5	+1·3±0·5	+6·2
P	< 0·01	< 0·05	< 0·05	< 0·05	

Stimulation of the carotid body chemoreceptors

In twenty-one tests in nine dogs, stimulation of the carotid bodies by changing the composition of the blood perfusing the carotid bifurcation regions from arterial blood (P_{O_2} 107·8±21·6 mmHg, P_{CO_2} 37·9±3·7 mmHg, pH 7·419±0·036) to hypoxic hypercapnic blood from the right atrial reservoir (P_{O_2} 41·3±0·2 mmHg, P_{CO_2} 45·9±0·7 mmHg, pH 7·372±0·004) invariably caused an increase in movements of the ribs (Fig. 2). It also resulted in a significant ($P < 0·01$) increase in hind-limb and systemic perfusion pressures, indicating a vasoconstriction, at all four levels of pulmonary ventilation (Fig. 3). Examination of the responses in Figs. 2 and 3 indicate, however, that the size of the vascular responses was not the same at all levels of pulmonary ventilation; it decreased as ventilation increased. The response at the smallest level of ventilation of 0·095 $l\ min^{-1}\ kg^{-1}$ was significantly greater than the responses at all other levels of ventilation ($P < 0·05$). It will also be noted in Fig. 2 that the smaller vascular responses to stimulation of the carotid bodies occurring at a pulmonary ventilation of 0·665 $ml\ min^{-1}\ kg^{-1}$ compared with those at 0·095 $l\ min^{-1}\ kg^{-1}$ took place under conditions in which the following variables were maintained constant: the carotid sinus perfusion pressure, the aortic and cerebral perfusion pressure, and the inferior vena caval pressure. The gaseous composition of the arterial blood was also held constant. The responses were similar in experiments in which the sympathetic supply to the carotid bodies had been cut.

After denervation of the lungs, the reduction in hind-limb and systemic perfusion

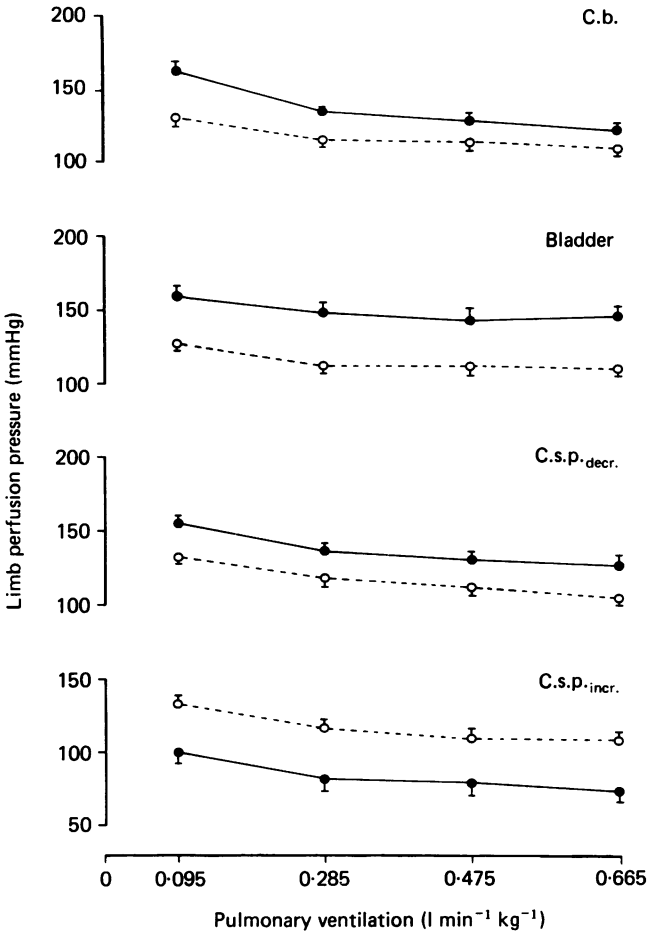

Fig. 4. The effects of stimulation of the carotid bodies (c.b), stimulation (c.s.p.$_{incr.}$) and unloading (c.s.p.$_{decr.}$) of the carotid sinus baroreceptors, and of distension of the urinary bladder on hind-limb perfusion pressure at four levels of pulmonary ventilation. For comparison the data for stimulation of the carotid bodies is re-plotted from Fig. 3. Dogs on cardiopulmonary bypass. Arterial P_{O_2}, P_{CO_2} and pH and the carotid sinus (except when under test), aortic arch and cerebral perfusion pressures held constant. In each of the four panels, (open circles), the effects of increasing pulmonary ventilation *per se* under control conditions; filled circles, effects of stimulation of the carotid bodies (twenty-one tests, nine dogs), stimulation of the carotid baroreceptors (seventeen, eight), unloading the carotid baroreceptors (seventeen, eight) and distension of the urinary bladder (twenty-one, nine), respectively, at four different levels of pulmonary ventilation. Mean values ± S.E. of mean.

pressures due to increasing pulmonary ventilation *per se* did not occur, while the increases in the pressures occurring on stimulation of the carotid bodies became the same at all levels of pulmonary ventilation (Table 2). It is concluded that the inhibition of the vascular responses to carotid body stimulation by increasing the pulmonary ventilation is due to an input from the lungs.

TABLE 3. Respiratory and vascular responses to stimulation (A) and unloading (B) the carotid baroreceptors by raising and lowering respectively the carotid sinus perfusion pressure. Values from eight dogs are means ±S.E. of mean. N.s., not significant

Respiratory minute volume ($l\ min^{-1}\ kg^{-1}$)	Innervated test lung ($n = 17$) 0·095	0·285	0·475	0·665	Denervated test lung ($n = 3$) 0·665
Tracheal pressure (mmHg)	4±0	8±1	11±1	13±1	13
A. Stimulation of baroreceptors (perfusion pressure raised by 17±1 mmHg)					
	Limb perfusion pressure (mmHg)				
Control	133±6	116±6	109±7	108±5	122
Test	100±8	81±9	79±9	74±7	101
Response	−33±5	−35±6	−30±5	−35±4	−21
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Systemic perfusion pressure (mmHg)				
Control	114±6	100±7	98±7	96±6	106
Test	90±6	77±6	81±6	76±4	93
Response	−24±4	−23±5	−17±4	−20±4	−13
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Rib movements (mm)				
Control	5·1±1·5	4·8±2·3	1·4±0·7	0·4±0·2	6·0
Test	5·1±1·5	4·8±2·3	1·4±0·7	0·4±0·2	6·0
Response	0·0	0·0	0·0	0·0	
P	N.s.	N.s.	N.s.	N.s	
B. Unloading of baroreceptors (perfusion pressure lowered by 18±1 mmHg)					
	Limb perfusion pressure (mmHg)				
Control	132±6	117±6	111±7	103±6	94
Test	154±6	135±5	129±5	125±7	107
Response	+22±3	+18±4	+18±4	+22±4	+13
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Systemic perfusion pressure (mmHg)				
Control	111±6	100±7	99±7	95±6	103
Test	122±7	110±8	110±8	108±7	112
Response	+11±3	+10±4	+11±3	+13±3	+9
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Rib movements (mm)				
Control	4·8±1·5	4·9±2·4	1·4±0·8	0·4±0·2	5·4
Test	4·8±1·5	4·9±2·4	1·4±0·8	0·4±0·2	5·4
Response	0·0	0·0	0·0	0·0	0·0
P	N.s.	N.s.	N.s.	N.s.	

Carotid sinus baroreceptor reflex

Stimulation of baroreceptors. In seventeen tests in eight dogs, raising the carotid sinus perfusion pressure by a mean of 17·4 ± 0·9 mmHg from 118·5 ± 0·5 mmHg resulted in a significant reduction in the hind-limb and systemic perfusion pressure at all levels of pulmonary ventilation (Fig. 4, Table 3A) ($P < 0·01$). Unlike the responses to carotid body stimulation, the size of both vascular responses was unaffected by the level of pulmonary ventilation (for the six comparisons of the responses at each of the four levels of pulmonary ventilation, the range of P values were, for systemic perfusion pressure, $> 0·4 -> 0·1$, and for limb perfusion pressure, $> 0·6 -> 0·1$).

Unloading the baroreceptors. In seventeen tests in eight dogs reducing the carotid sinus perfusion pressure by a mean of 18·3 ± 0·5 mmHg from 118·2 ± 0·5 mmHg resulted in a significant increase in the hind-limb and systemic perfusion pressures at all four levels of pulmonary ventilation (Fig. 4, Table 3B) ($P < 0·01$). As above, the size of both responses was unaffected by the level of pulmonary ventilation (range of P values: for systemic perfusion pressure, $> 0·9 -> 0·1$; for limb perfusion pressure, $> 0·4 -> 0·1$).

TABLE 4. Respiratory and vascular responses to urinary bladder distension to 50 ± 4·7 mmHg. Values from nine dogs are means ± S.E. of mean

Respiratory minute volume ($l\ min^{-1}\ kg^{-1}$)	Innervated test lung ($n = 21$)				Denervated test lung ($n = 3$)
	0·095	0·285	0·475	0·665	0·665
Tracheal pressure (mmHg)	4 ± 0	9 ± 1	11 ± 1	13 ± 1	13
	Limb perfusion pressure (mmHg)				
Control	127 ± 5	111 ± 5	111 ± 7	108 ± 5	118
Test	159 ± 7	147 ± 7	141 ± 9	144 ± 6	136
Response	+32 ± 4	+36 ± 5	+30 ± 6	+36 ± 5	+18
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Systemic perfusion pressure (mmHg)				
Control	112 ± 6	103 ± 6	103 ± 8	105 ± 7	105
Test	126 ± 8	123 ± 9	117 ± 9	123 ± 8	109
Response	+14 ± 2	+20 ± 3	+14 ± 3	+18 ± 3	+4
P	< 0·01	< 0·01	< 0·01	< 0·01	
	Rib movements (mm)				
Control	5·2 ± 1·1	4·3 ± 1·5	1·9 ± 0·9	0·4 ± 0·2	7·2
Test	5·6 ± 1·2	5·2 ± 1·6	3·3 ± 1·8	0·7 ± 0·3	8·0
Response	+0·3 ± 0·4	+0·9 ± 0·4	+1·3 ± 1·1	+0·3 ± 0·4	+0·8
P	N.S.	< 0·05	N.S.	N.S.	

Distension of the urinary bladder

In twenty-one tests in nine dogs distension of the urinary bladder to 50·2 ± 4·7 mmHg resulted in a significant increase in the hind-limb and systemic perfusion pressures

at all four levels of pulmonary ventilation (Fig. 4, Table 4) ($P < 0{\cdot}01$). Again, unlike the responses to carotid body stimulation, but similar to the responses to activation of the carotid sinus baroreceptor reflex there was no significant difference between the responses of hind-limb and systemic perfusion pressures at any level of pulmonary ventilation (range of P values: for systemic perfusion pressure, $> 0{\cdot}4 - > 0{\cdot}1$; for limb perfusion pressure, $> 0{\cdot}8 - > 0{\cdot}2$). The size of the responses to bladder distension at the four levels of pulmonary ventilation was again unaffected by denervation of the lungs (Fig. 3, Table 4).

DISCUSSION

The present investigation has shown that there is an interaction of a lung inflation reflex with the constrictor response of the systemic and hind-limb vascular beds which is specific to stimulation of the carotid body chemoreceptors, such that as the pulmonary ventilation is increased the vasoconstrictor response is reduced. In contrast the vasoconstriction of both vascular beds in response to lowering the carotid sinus perfusion pressure and to distension of the urinary bladder was unaffected by the level of pulmonary ventilation. The vasodilatation in both vascular beds in response to increasing the carotid sinus perfusion pressure was also unaffected. These aspects of our results will be discussed separately.

The effects of lung inflation

It has been shown previously that an increase in tidal volume whether produced by single inflations of the lungs or rhythmically in ventilated lungs causes a reflex reduction in systemic and hind-limb vascular resistances (Daly *et al.* 1967; Daly & Robinson, 1968; Angell-James & Daly, 1969; Daly *et al.* 1983) and a decrease in discharge activity in pre- and post-ganglionic cervical and splanchnic sympathetic nerves (Adrian, Bronk & Phillips, 1932; Bronk, Ferguson, Margaria & Solandt, 1936; Gootman, Feldman & Cohen, 1980; Polosa, Gerber & Schondorf, 1980). The present experiments confirm and extend these results. Our observed vasodilator responses occurred in the absence of changes in both the arterial blood gases and the arterial baroreceptor activity, but were abolished by denervation of the lungs. They are therefore reflex in origin and initiated by changes in the activity of pulmonary receptors. Under these experimental conditions no vasoconstrictor responses were observed (cf. Hainsworth, 1974; Wood, Hainsworth & McGregor, 1985). Our results showed further that increasing the respiratory minute volume at constant frequency caused a progressive reduction in systemic and hind-limb vascular resistances. In the resting conscious dog, the tidal volume is 13·5 ml kg^{-1} and respiratory minute volume 0·22 ml min^{-1} kg^{-1} (Hemingway & Nahas, 1953). Thus the highest values used in the present experiments of 35 ml kg^{-1} and 0·665 l min^{-1} kg^{-1} respectively represent increases of about 260% and 300% over resting levels, which are well within the normal physiological range. Higher levels of pulmonary ventilation were deliberately not used so that peak inflation pressure did not exceed 15 mmHg, a value above which there is a danger of damaging the lungs (Hering, 1871; Anrep, Pascual & Rössler, 1936; Hainsworth, 1974).

The range of respiratory minute volume used in this study was 0·095–0·665 l min^{-1} kg^{-1}. It follows therefore that a reduction in pulmonary ventilation

from the eupnoeic level (0·22 l min^{-1} kg^{-1}) would have resulted in a reflex vasoconstriction (Fig. 3). A similar result was obtained by Daly *et al.* (1967) on the basis of experiments in which single inflations and deflations of the lungs were carried out. Their conclusion, to which our present findings lend support, was that the lungs in their inflated position in the chest are a constant source of afferent impulses which maintain a state of partial inhibition of sympathetic vasomotor tone.

In our animals showing spontaneous respiratory movements, increasing the pulmonary ventilation caused a progressive reduction in the amplitude of the movements of the ribs. This was probably due to excitation of pulmonary stretch receptors, because the response was dependent on the integrity of the innervation of the lungs.

Modulation of carotid chemoreceptor responses

As demonstrated previously, stimulation of the carotid bodies in artificially ventilated animals invariably causes an increase in systemic and hind-limb vascular resistances (for references, see Introduction). In spontaneously breathing animals however, vasodilatation often occurs in association with the reflex increase in pulmonary ventilation (Daly & Scott, 1962, 1963; Daly & Ungar, 1966; Daly *et al.* 1978) due to a reflex from the lungs and in part to a reduction in arterial P_{CO_2} (Daly & Ungar, 1966). The role of the pulmonary reflex in the vascular responses to asphyxia was demonstrated by Angell-James & Daly (1969). They showed that stimulation of the peripheral arterial chemoreceptors caused an increase in pulmonary ventilation but no systemic vasoconstrictor response until the lungs were denervated. The systemic vasodilator response to systemic hypoxia is also considerably attenuated by denervation of the lungs (Kontos, Goldin, Richardson & Patterson, 1967).

The present experiments clearly demonstrate that increasing the pulmonary ventilation in steps caused a significant progressive stepwise diminution in the size of the vasoconstrictor response to stimulation of the carotid bodies. Under these conditions, selective denervation of the lungs abolished this modulation, indicating that it must have been due to a change in activity of pulmonary receptors.

In these experiments it was essential to control a number of variables which might otherwise affect the interpretation of our results. Thus the arterial blood gases were held constant throughout each experiment by total cardiopulmonary bypass using extracorporeal isolated perfused and artificially ventilated lungs. Changes in the activity of arterial baroreceptors were excluded by perfusing the carotid sinuses and the arch of the aorta at constant pulsatile pressure. The gaseous composition of both the arterial and the mixed venous blood (used to stimulate the carotid bodies) was repeatedly checked to ensure that the stimulus to the carotid bodies remained constant throughout the experiment. There is, however, a possibility that the resulting chemoreceptor discharge actually did decrease as the pulmonary ventilation increased through a change in carotid body blood flow brought about by an alteration in sympathetic nerve activity to the carotid body vasculature which resulted from the pulmonary inflation reflex itself (Daly, Lambertsen & Schweitzer, 1954; Acker & O'Regan, 1981). Such a mechanism is unlikely to account for all of the observed changes in the response since similar results were obtained in experiments in which

the sympathetic fibres from the superior cervical ganglion to the carotid body were cut.

The interaction between inputs from the carotid bodies and receptors in the lungs goes some way to explain how it is that in the spontaneously breathing dog selective stimulation of the carotid bodies may cause vasodilatation (Daly & Scott, 1962,

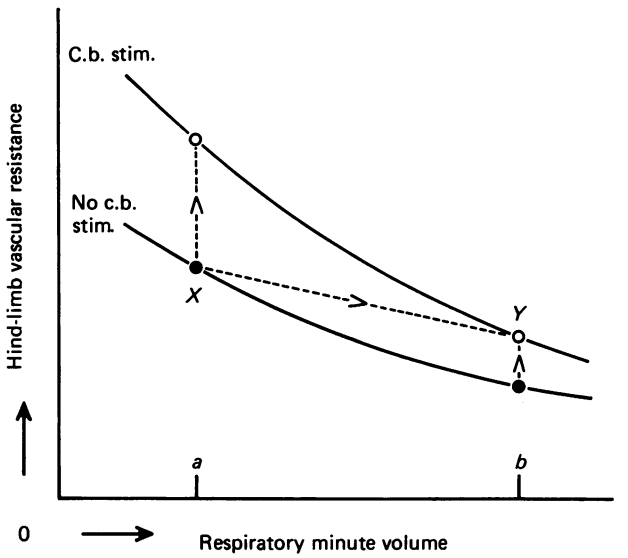

Fig. 5. Diagrammatic representation of the effects of stimulation of the carotid bodies (c.b.) on hind-limb vascular resistance at constant artificial ventilation and during spontaneous hyperventilation with the P_{a,CO_2} held constant. The lower curve shows the effects of increasing pulmonary ventilation *per se* causing reflex vasodilatation; the upper curve during chemoreceptor stimulation. Stimulation of the carotid bodies at a constant level of ventilation (*a*) causes hind-limb vasoconstriction (left vertical interrupted line), and a smaller response at increased level of ventilation (*b*) (right vertical interrupted line). In the spontaneously breathing animal, the eupnoeic level of ventilation and vascular resistance is represented by point *X* on lower curve. During stimulation of the carotid bodies, ventilation increases to (*b*) and the corresponding level of vascular resistance is point *Y* on the upper curve. Thus carotid body stimulation associated with a spontaneous increase in pulmonary ventilation causes vasodilatation (interrupted line *X*–*Y*). For further details, see text.

1963; Daly & Ungar, 1966). This is illustrated in Fig. 5 which is a diagrammatic representation of the results contained in Fig. 3. The change in hind-limb vascular resistance is plotted against respiratory minute volume. The lower curve represents the vascular response to increasing respiratory minute volume *per se*, the upper curve the effects of stimulation of the carotid bodies at different levels of respiratory minute volume, e.g. at the eupnoeic level of ventilation (*a*) and at an increased level (*b*). The respective sizes of the vasoconstrictor responses to stimulation of the carotid bodies at the two levels of ventilation is shown by the vertical interrupted lines. Considering now the effects of stimulating the carotid bodies in the spontaneous breathing animal: the point corresponding to the eupnoeic level of pulmonary ventilation and vascular resistance, without chemoreceptor stimulation, will lie on

the lower curve at X. During stimulation of the chemoreceptors in which there is a potential reflex vasoconstrictor response associated with an increase in respiratory minute volume, the corresponding levels of pulmonary ventilation and vascular resistance will now lie on the upper curve at point Y. Thus under these conditions stimulation of the carotid bodies results in hyperventilation and vasodilatation (X–Y). Putting aside for the moment other mechanisms which determine the direction and size of the vascular response to stimulation of the carotid bodies (Daly, 1983), it is evident that a pulmonary reflex plays an important role in this respect. The vascular response to stimulation of the carotid bodies under steady state conditions will depend on a number of factors: the magnitude of the inputs from the carotid bodies and pulmonary receptors, the gain of the respective reflex responses of ventilation and vascular resistance, and the degree of interaction between them.

Inputs from the baroreceptors and urinary bladder

Stimulation and unloading of the baroreceptors by increasing and decreasing the carotid sinus perfusion pressure resulted in a fall and rise of systemic and hind-limb vascular resistances (Kirchheim, 1976). We have also confirmed that distension of the urinary bladder caused a reflex increase in peripheral vascular resistance, as described previously (Guttman & Whitteridge, 1948; Mukherjee, 1957; Taylor, 1968; Daly & Wood, 1982). Responses to stimulation of the baroreceptors and to urinary bladder distension were in contrast to those to chemoreceptor stimulation, in that they were unaffected by the level of pulmonary ventilation either before or after pulmonary denervation. We are confident that these differences in the responses are real and cannot be ascribed to differences in the experimental conditions or techniques. First, the effects of changing pulmonary ventilation were tested on the reflex responses from all three groups of receptors in each of eight of nine experiments carried out. Secondly the experimental techniques and conditions under which the reflexes were studied were identical in all the experiments. Finally, the magnitude of the stimulus to the three groups of receptors, and, in the case of the baroreceptors, the degree of unloading, was chosen so that the reflex responses were approximately the same size and were well within the normal range of physiological control. This means that the reflex vascular responses from all three receptors were directly comparable.

The nature of the central integration which could explain our findings is, on present evidence, unclear. There is abundant evidence that the discharge of sympathetic nerves is modulated by respiration in animals (Adrian *et al.* 1932; Tang, Maire & Amassian, 1957) and man (Wallin, 1981).

The respiratory modulation of firing rate is also synchronous with oscillations in hind-limb blood flow (Koepchen, Seller, Polster & Langhorst, 1968). The pattern of firing is thought at present to be the result of an excitatory synaptic input from brain stem inspiratory neurones (Preiss, Kirchner & Polosa, 1975; Gerber & Polosa, 1978); it can be suppressed by activation of pulmonary stretch receptors which inhibit inspiratory neurones (Gerber & Polosa, 1978; Gootman *et al.* 1980). In the present experiments the reflex vasodilatation resulting from lung inflation could be due to a decrease of sympathetic activity through selective suppression of the inspiratory synchronous component. This cannot be the whole explanation, however, because when the inspiratory synchronous activity in sympathetic nerves is suppressed by lowering the arterial P_{CO_2}, which also abolishes spontaneous respiratory movements,

lung inflation still causes reflex vasodilatation (Daly *et al.* 1967), indicating that there is another mechanism for the reduction of sympathetic activity. Although the arterial baroreceptor reflex occurs whether or not inspiratory synchronicity of the sympathetic discharge is present (Gerber & Polosa, 1978), there is no comparable information about the carotid chemoreceptor and urinary bladder receptor reflexes and still less about the site of integration of sympathetic effects between the pulmonary input and the inputs from the other three receptors under discussion. Nevertheless the fact that only the vasoconstriction in response to carotid chemoreceptor stimulation was affected by a pulmonary inflation reflex lends further support to the concept that the sympathetic nervous system is organized in a way which allows selective control of the post-ganglionic innervation.

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