Experimental Physiology

Absence of reflex vascular responses from the intrapulmonary circulation in anaesthetised dogs

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The aim of this investigation was to determine whether reflex cardiovascular responses were obtained to localised distension of the intrapulmonary arterial and venous circulations in a preparation in which the stimuli to other major reflexogenic areas were controlled and the lung was shown to possess reflex activity. Dogs were anaesthetised with α-chloralose, artificially ventilated, the chests widely opened and a cardiopulmonary bypass established. The intrapulmonary region of the left lung was isolated and perfused through the left pulmonary artery and drained through cannulae in the left pulmonary veins via a Starling resistance. Intrapulmonary arterial and venous pressures were controlled by the rate of inflow of blood and the pressure applied to the Starling resistance. Pressures to the carotid, aortic and coronary baroreceptors and heart chambers were controlled. Responses of vascular resistance were assessed from changes in perfusion pressures to a vascularly isolated hind limb and to the remainder of the subdiaphragmatic circulation (flows constant). The reactivity of the preparation was demonstrated by observing decreases in vascular resistance to large step changes in carotid sinus pressure (systemic vascular resistance decreased by $-40 \pm 5\%$), chemical stimulation of lung receptors by injection into the pulmonary circulation of veratridine or capsaicin (resistance decreased by $-32 \pm 4\%$) and, in the four dogs tested, increasing pulmonary stroke volume to 450 ml (resistance decreased by $-24 \pm 6\%$). However, despite this evidence that the lung was innervated, increases in intrapulmonary arterial pressure from 14 ± 1 to 43 ± 3 mmHg or in intrapulmonary venous pressure from 5 ± 2 to 34 ± 2 mmHg or both did not result in any consistent changes in systemic or limb vascular resistances. In two animals tested, however, there were marked decreases in efferent phrenic nerve activity. These results indicate that increases in pressure confined to the intrapulmonary arterial and venous circulations do not cause consistent reflex vascular responses, even though the preparation was shown to be reflexly active and the lung was shown to be innervated. *Experimental Physiology* (2000) **85.4**, 421–430.

The pulmonary circulation is widely believed to have a physiological role in cardiovascular homeostasis (Aviado & Schmidt, 1955; Shepherd, 1981) and to form part of a group of low pressure receptors often loosely referred to as 'cardiopulmonary receptors' (see Hainsworth, 1991). The function of these receptors is thought to induce reflex vasodilatation when pulmonary vascular volume and pressures increase (Donald & Shepherd, 1978). The main pulmonary artery has been shown to be capable of inducing reflex responses when distended, but their effect is to induce reflex vasoconstriction and an increase in respiratory drive (Ledsome *et al.* 1980; McMahon *et al.* 2000), although in contrast a vasodilatation over lower pulmonary pressures has also been reported (Coleridge & Kidd, 1963).

The role of the intrapulmonary parts of the pulmonary circulation in normal circulatory control has not yet been adequately demonstrated. This region is certainly well innervated since injections of chemical stimulants induce powerful reflex vasodilatation in the systemic circulation (Dawes & Comroe, 1954; Clifford *et al.* 1987). Large increases in pulmonary vascular pressures (> 50 mmHg) have been reported to cause decreases in vascular resistance (Churchill & Cope, 1929; Daly *et al.* 1937; Parin, 1947; Aviado *et al.* 1951; Lloyd, 1975; Schultz *et al.* 1982; Hatridge *et al.* 1989). However, these studies have not reported responses to distension of the pulmonary circulation with the more moderate pressures likely to be encountered in life. Furthermore, in many the stimuli were not adequately localised to the intrapulmonary circulation so that changes in pressure in the main pulmonary trunk (Daly *et al.* 1937; Schultz *et al.* 1982) and to other reflexogenic regions would be likely to have complicated the interpretation of any results.

The present study was undertaken with the objective of investigating the vascular responses during intrapulmonary arterial and or venous distension particularly over the physiological range. To examine this we used perfusion techniques which allowed independent control of pressures in the intrapulmonary circulation, whilst maintaining constant pressure to other reflexogenic regions with blood gases and respiration controlled. A preliminary account of this work has recently been published (McMahon *et al.* 1999).

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METHODS

Dogs of either sex, weighing 15–21 kg, were premedicated with pentobarbitone sodium (6 mg kg^{-1}; Rhône Mérieux Ltd, Dublin, Ireland) and anaesthetised with an intravenous 1% solution of α-chloralose (100 mg kg^{-1}; Vickers Laboratories Ltd, Leeds, UK) dissolved in saline. Anaesthesia was maintained by a continuous I.V. infusion of α-chloralose (0.5–1.0 mg kg^{-1} min^{-1}). Before and during major surgery, alfentanil hydrochloride (Janssen-Cilag Ltd, High Wycombe, Bucks, UK) was infused I.V. at 30 μg kg^{-1} min^{-1} over 20 min and then at 2.5 μg kg^{-1} min^{-1} to the end of surgery. The depth of anaesthesia was assessed from the stability of blood pressure and heart rate, the absence of a response to toe pinch and only very small reflex movements to a loud auditory stimulation.

The trachea was cannulated and the animal was artificially ventilated with O_2-enriched air by a Starling 'Ideal' pump, initially set at 17 ml kg^{-1} and 18 strokes min^{-1}. Molar sodium bicarbonate was infused as required to maintain normal pH values (see below).

The carotid sinuses were vascularly isolated by ligating all branches arising from the bifurcation of the common carotid artery, except the lingual artery, whilst leaving innervation intact. The sternum was split along the midline, and the left side of the chest was divided between the 4th and 5th ribs. When the pleural cavity was opened a positive end-expiratory pressure was maintained at 3 cmH_2O.

The descending aorta was mobilised by tying and dividing the first seven pairs of intercostal arteries. A snare was passed around the left pulmonary artery just proximal to the first lobar artery. All the left pulmonary veins were identified and prepared for later cannulation by carefully freeing them from the surrounding connective tissue before they enter the left atrium. The pericardium was opened to expose the right atrium for subsequent cannulation.

Prior to cannulation of the blood vessels and attachment of the perfusion circuit the animal was given heparin I.V. (500 i.u. kg^{-1}). The perfusion circuit (Fig. 1) was partly filled with a heparinised mixture of equal parts of mammalian Ringer solution (g l^{-1}: NaCl, 6.9; KCl, 0.35; $CaCl_2$, 0.28; $MgSO_4$, 0.14; $NaHCO_3$, 2.09; KH_2PO_4, 0.16; glucose, 1.0), dextran in dextrose solution (50 g l^{-1} dextran, molecular weight 181 000) and blood cells obtained from a previous experiment and washed. This extracorpeal circuit was attached to the animal in the following sequence. A cannula was inserted into the central end of the thoracic aorta, initially to convey blood into the pressurised main reservoir and, after establishing the cardio-pulmonary bypass, to control pressure to the aortic arch and the

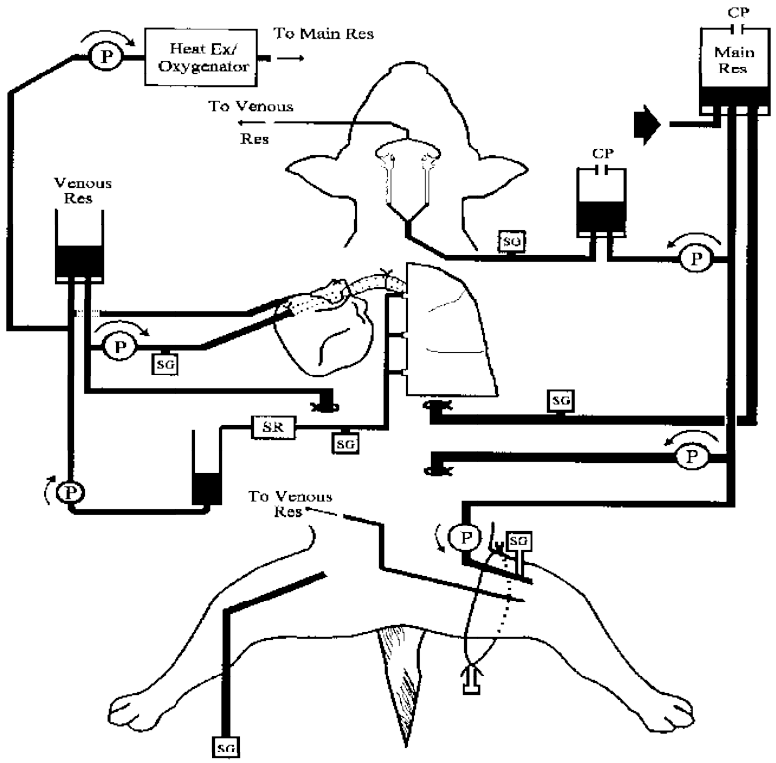

Figure 1

Diagram of experimental preparation. Pressure was applied to the main reservoir to maintain perfusion pressure to the coronary and aortic arch baroreceptors via a cannula in the ascending aorta. Carotid sinus regions were perfused at constant pressure from a blood-filled reservoir. Cannulae in the inferior vena cava (IVC) and right atrium drained blood into the venous reservoir. Venous blood was pumped into the left intra-pulmonary artery via a cannula passed into it via the wall of the right ventricle, and the left lung was drained through cannulae in the left pulmonary veins into the venous reservoir. Blood from this reservoir was pumped through a membrane oxygenator/heat exchanger to the main reservoir. The subdiaphragmatic and hind limb circulations were perfused at constant flows. CP, constant pressure; P, pump; SG, strain gauge transducer; SR, Starling resistor.

coronary and cephalic circulations. Another cannula was inserted into the distal end of the thoracic aorta at the level of the diaphragm through which blood was pumped to perfuse the subdiaphragmatic circulation at constant flow. In some animals a hind limb was vascularly isolated and perfused at constant flow as previously described by Challenger *et al*. (1987).

A cannula (7 mm i.d.) was inserted into the right atrium via the atrial appendage and another cannula (10 mm i.d.) drained the inferior vena cava. These cannulae drained blood into an open reservoir from which it was pumped through a Monolyth Membrane Oxygenator (Sorin Biomedica Cardio, Saluggia, Italy) to the main reservoir for distributing to the various parts of the circuit. Both common carotid arteries were cannulated and perfused with blood at constant pressure and this region was drained via cannulae inserted into the lingual arteries into the open reservoir.

A cannula (4 mm i.d.) was inserted through a stab wound in the wall of the right ventricle, sealed with a purse string suture, and passed through the pulmonary trunk and into the left pulmonary artery to the first lobar artery where it was securely tied. The baroreceptors situated at the bifurcation of the extrapulmonary artery (Coleridge *et al*. 1961) were therefore excluded from the test region. Cannulae (1.5 and 3 mm i.d., dependent on vein size) were inserted centrally into all left pulmonary veins and these drained blood from the left lung into the open reservoir via a Starling resistor. The left lung was perfused with venous blood taken from the inferior vena cava outflow.

In two animals efferent nerve discharge was recorded from the desheathed left phrenic nerve in the thorax. The nerve was cut proximal to the recording site and a portion of the nerve was placed in a small plastic tray filled with warm (37 °C) paraffin oil. A binocular microscope was used to expose the nerve trunk from which efferent activity was recorded using bipolar silver electrodes. The electrode output was amplified and filtered (Neurolog, Digitimer Ltd, Welwyn Garden City, Herts, UK). The action potentials were subsequently displayed on a digital storage oscilloscope (Model OS 1420, Gould Ltd, Hainault, Essex, UK). The signal also passed into a spike processor (Model D130, Digitimer Ltd).

Blood pressures were recorded using saline-filled nylon catheters attached to strain gauges (Gould-Statham P23 ID), connected to: the left pulmonary cannula (intrapulmonary artery pressure), the left pulmonary venous cannula (intrapulmonary venous pressure), the lumen of the aortic cannula (aortic perfusion pressure), the right carotid cannula (carotid sinus pressure), the limb perfusion cannula (limb perfusion pressure) and the right femoral artery (systemic perfusion pressure). ECG (lead II) was recorded. All signals were amplified (EMMA system, SE Laboratories, Feltham, UK) and recorded on VHS tape (Racal V-Store; Racal Recorders Ltd, Southampton, UK) and a direct-writing electrostatic recorder (Gould ES1000). The taped signals were digitised (100 Hz) for subsequent computer analysis (Fastdaq, Lectromed, Letchworth, UK). Before each experiment the pressure transducers were calibrated over a range of 0–225 mmHg against a mercury column, except the pulmonary artery and venous transducers where the range was 0–150 mmHg.

The temperature of the animal was recorded by a thermister probe in the oesophagus and was maintained at 37–39 °C by heat exchangers incorporated into the circuit and in the oxygenator and by heaters under the animal table.

These experiments were carried out in accordance with the current UK legislation, the Animals (Scientific Procedures) Act, 1986. Experiments were terminated by exsanguination of the animal.

Experimental protocol

After connecting the animal to the perfusion circuit, pressures were allowed to stabilise and blood gases were measured and corrected as necessary to achieve values (means ± S.E.M., $n = 10$) for P_{O_2} of 201 ± 20 mmHg, P_{CO_2} of 41 ± 2 mmHg and pH 7.4 ± 0.03. Haematocrit was 21 ± 1 %.

Before and after the tests of changes in pulmonary vascular pressures, the responsiveness of the preparation was confirmed by increasing carotid pressure in a single step from 64 ± 1 mmHg to 208 ± 6 mmHg for 1 min before lowering carotid pressure back to control. The pulmonary chemoreflex was elicited by injecting veratridine (40 μg) or capsaicin (100 μg) into the intrapulmonary inflow cannula.

The pressures in the intrapulmonary arterial or venous circulations or both were increased in single steps. Distension mainly of the intrapulmonary arteries was achieved by increasing the rate of the pump perfusing the left pulmonary artery, and predominantly venous distension was achieved by applying a resistance to the venous outflow at the Starling resistor, thus impeding blood flow from the venous compartment. Pressure was increased from the control level for 2 min and then it was lowered back to the control level for a further 2 min before the next increase in intrapulmonary pressure. Pressure perfusing the aortic arch and coronary baroreceptors (McMahon *et al*. 1996) was maintained constant throughout the tests at 98 mmHg and that to the carotid baroreceptors was maintained at near 60 mmHg.

Ventilatory rate and stroke volume were unchanged once the cardiopulmonary bypass was established. When recordings were made of phrenic nerve activity the ventilator was switched off and the lungs were allowed to deflate against a pressure of 3 cmH_2O. The response of vascular resistance was estimated from changes in systemic and hind limb perfusion pressures. In four animals a bronchial catheter was inserted down the trachea which allowed independent lung inflation. The left lung was distended by increasing the stroke volume delivered by the Starling 'Ideal' pump from 50 ml to 400–600 ml for 1–2 min then returning to 50 ml.

All values reported are means ± S.E.M. and statistical significance was assessed by Student's paired *t* test.

RESULTS

Results are presented from 10 animals. Perfusion pressures before increasing pulmonary pressures were 149 ± 8 mmHg to the systemic circulation and 142 ± 7 mmHg ($n = 8$) to the hind limb. The temperature of the blood perfusing the intrapulmonary region was 37–38 °C.

Response to carotid baroreceptor stimulation

An example of a carotid baroreceptor test is shown in Fig. 2. Carotid sinus pressure was increased from 63 to 217 mmHg for 1 min. In response, systemic perfusion pressure decreased from 205 to 90 mmHg, a 56 % reduction. Similar responses were obtained in all 10 animals (see Table 1), where an increase in carotid sinus pressure from 64 ± 1 to 208 ± 6 mmHg caused systemic perfusion pressure to decrease from 158 ± 10

Table 1. Individual systemic perfusion pressure responses (%) to carotid baroreceptor stimulation, chemical infusion into left pulmonary circulation, inflation of the left lung and increases in pulmonary vascular pressures

	Procedure				
Dog	Carotid baroreceptor stimulation	Chemical stimulation	Lung inflation	Increase in PAP	Increase in PVP
1	–48.5	–12.9	–16.2	+7.4	+1.7
2	–55.9	–26.8	–40.9	—	–2.0
3	–40.3	–36.3	–24.0	–1.9	–5.3
4	–14.5	–28.9	–14.7	–1.6	–0.6
5	–24.7	–57.9	—	–2.1	+ 6.1
6	–31.1	–32.0	—	–5.9	—
7	–48.8	–18.0	—	–2.2	0
8	–23.6	–31.8	—	+8.3	–2.5
9	–55.6	–44.0*	—	—	+ 5.2
10	–57.3	–31.6*	—	+9.8	+ 1.7

Responses were obtained to increases in carotid sinus pressure from 64.1 to 208 ± 6 mmHg, injection into the pulmonary circulation of veratridine (40 μg) or capsaicin (100 μg; *), increasing lung inflation from 50 to between 400 and 600 ml, increases in pulmonary arterial pressure (PAP) from 18 to 30–43 mmHg and increases in pulmonary venous pressure (PVP) from 3–5 to 19–34 mmHg.

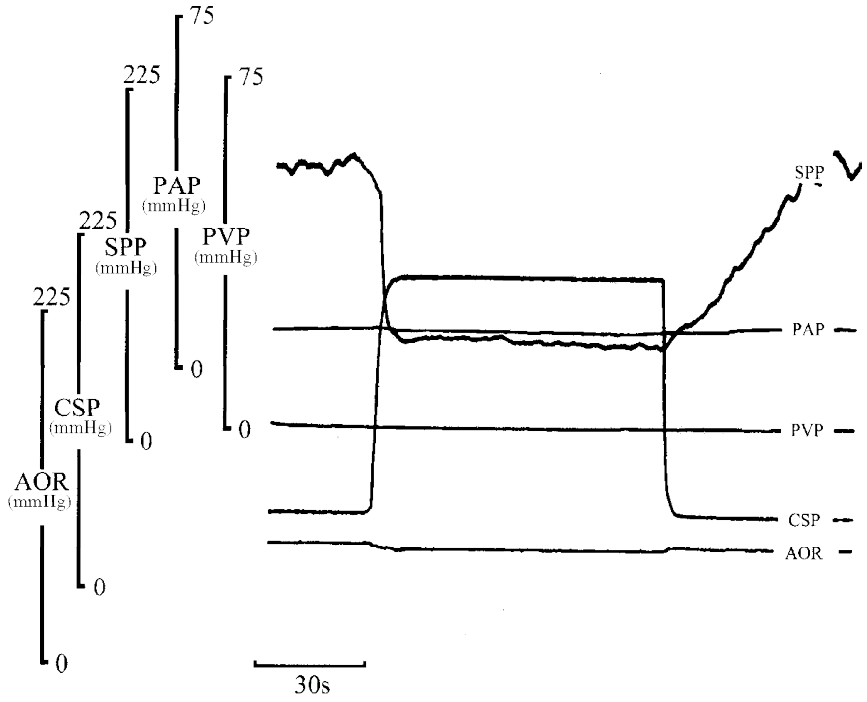

Figure 2

Responses to changes in carotid sinus pressure. The traces are of systemic perfusion pressure (SPP), intrapulmonary arterial pressure (PAP), intrapulmonary venous pressure (PVP), carotid sinus pressure (CSP) and aortic root pressure (AOR). Pressure perfusing the carotid sinuses was increased from 63 to 217 mmHg then returned to 63 mmHg. The increase in CSP induced a decrease in systemic perfusion pressure and an increase when carotid pressure was reduced.

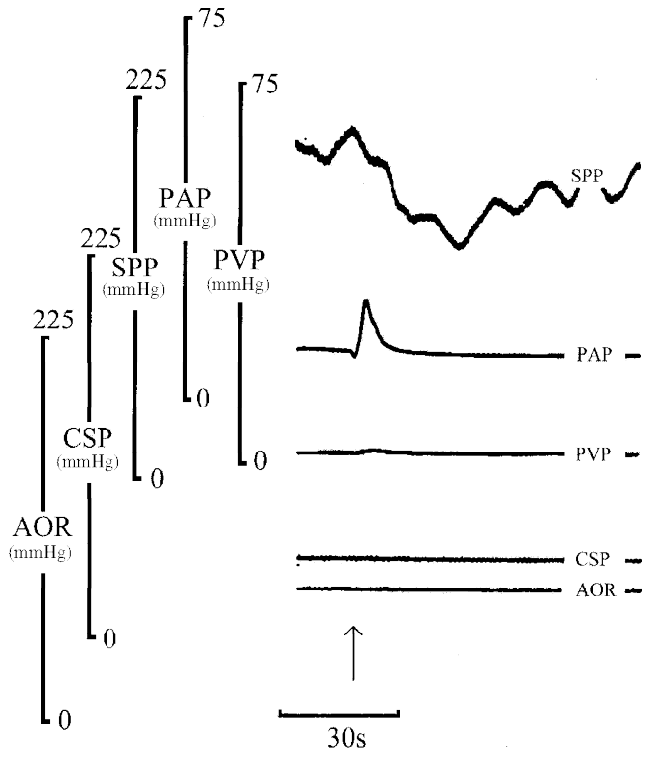

Figure 3

Responses to pulmonary chemoreflex. The traces are of systemic perfusion pressure (SPP), intrapulmonary arterial pressure (PAP), intrapulmonary venous pressure (PVP), carotid sinus pressure (CSP) and aortic root pressure (AOR). Veratridine (40 μg) was injected into the cannula perfusing the left pulmonary artery (at arrow) to provoke the pulmonary chemoreflex. A decrease in systemic perfusion pressure occurred in response to this stimulus.

to 93 ± 7 mmHg, a decrease of 65 ± 10 mmHg (-40 ± 5 %, $P < 0.0001$). In eight animals responses were also assessed in a limb. An increase in carotid pressure from 63 ± 1 to 207 ± 8 mmHg caused limb perfusion pressure to decrease from 157 ± 10 to 118 ± 9 mmHg, a decrease of 40 ± 8 mmHg (-25 ± 5 %, $P < 0.002$).

Responses to injections of chemical agents into the left intrapulmonary artery

Figure 3 shows an example of a response evoked by injecting veratridine (40 μg) into the intrapulmonary circulation. Systemic perfusion pressure decreased from 211 to 154 mmHg, a 27 % reduction. Similar responses were obtained in all animals when either veratridine (40 μg; $n = 8$) or capsaicin (100 μg; $n = 2$) was administered into the intrapulmonary circulation (see Table 1): systemic perfusion pressure decreased by 53 ± 9 mmHg from 161 ± 12 mmHg (-32 ± 4 %, $P < 0.0003$; $n = 10$) and hind limb perfusion pressure decreased by 34 ± 12 mmHg from 148 ± 13 mmHg (-21 ± 6 %, $P < 0.003$, $n = 8$).

Responses to left lung inflation

Figure 4 shows the responses from one dog to lung inflation. The left lung was inflated by increasing stroke volume from 50

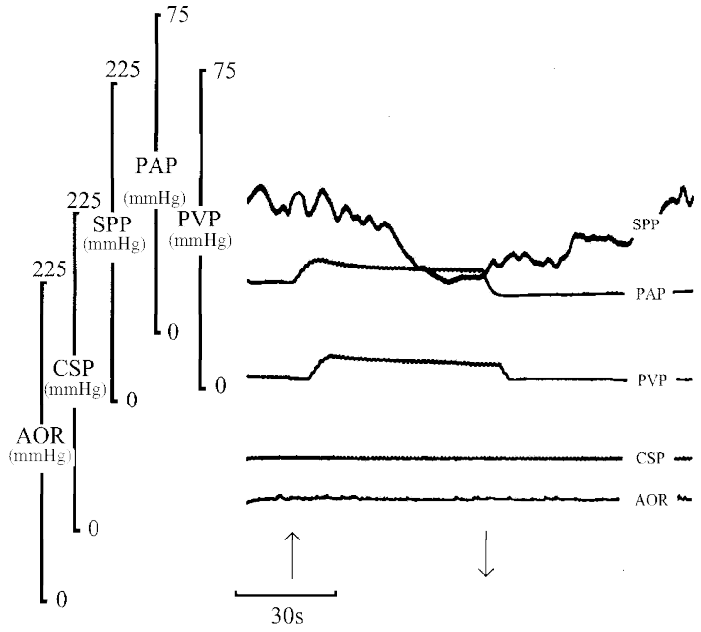

Figure 4

Responses to increasing inflation volume to the left lung. The traces are of systemic perfusion pressure (SPP), intrapulmonary arterial pressure (PAP), intrapulmonary venous pressure (PVP), carotid sinus pressure (CSP) and aortic root pressure (AOR). The stroke volume of air to the left lung was increased from 50 to 400 ml per stroke at first arrow (stroke rate 18 min^{-1}) and decreased to 50 ml at second arrow. A decrease in systemic perfusion pressure was observed in response to this stimulus.

to 400 ml for 1 min before returning the stroke volume back to 50 ml. In response, systemic perfusion pressure decreased from 162 to 96 mmHg, a 41 % reduction, and returned to the initial level upon lung deflation. The mean responses from the four animals (see Table 1) in which this response was investigated was that increasing the stroke volume to the left lung to 400–600 ml ($n = 4$) caused systemic perfusion pressure to decrease by 37 ± 11 mmHg from 149 ± 17 mmHg (-24 ± 6 %).

Distension predominantly of intrapulmonary arteries

Figure 5 shows original traces from one animal recording the response to an increase in intrapulmonary arterial pressure with carotid and aortic pressures held constant. Following the increase in pulmonary arterial pressure from 18 to 32 mmHg there was a transient decrease in systemic perfusion pressure and a change in the steady-state systemic perfusion pressure of +5 mmHg from control (159 mmHg). Intrapulmonary venous pressure changed from 2 to 5 mmHg during the test.

In eight animals studied, intrapulmonary arterial pressure was increased to 30 ± 1 mmHg. In five animals there was a transient decrease in systemic perfusion pressure of between 6 and 15 mmHg. The steady-state responses were decreases of between 1 and 7 mmHg in six dogs and increases of 5 mmHg in two dogs. Increasing arterial pressure to 43 ± 3 mmHg evoked transient decreases of systemic perfusion pressure of between 2 and 21 mmHg in six dogs. Steady-state responses were decreases of between 2 and 4 mmHg in three dogs and increases between 9 and 15 mmHg in a further three dogs. The group results for intrapulmonary arterial distension tests from 10 animals are shown in Fig. 6 and show no significant overall responses.

Venous distension

Venous distensions were performed in ten dogs. The group data from these tests are presented in Fig. 7. Increases in venous pressure from 3 ± 2 to 19 ± 2 mmHg in eight animals tested provoked transient decreases in systemic perfusion pressure of between 1 and 11 mmHg in four of these dogs, steady-state decreases of between 2 and 9 mmHg in four dogs and increases of between 1 and 4 mmHg in a further four dogs. Increasing venous pressure from 5 ± 2 to 34 ± 2 mmHg in seven dogs, evoked transient decreases in systemic perfusion pressure of between 2 and 10 mmHg in four dogs, steady-state decreases of between 1 and 5 mmHg in three dogs, increases of between 2 and 10 mmHg in three and no change in one dog. Overall, increases in intrapulmonary venous pressure did not induce consistent changes in systemic vascular resistance.

Combined intrapulmonary arterial and venous distension

Figure 8 is an example of traces from one animal in which intrapulmonary arterial and venous pressures were increased in a single large step from 15 mmHg (arterial) and 2 mmHg

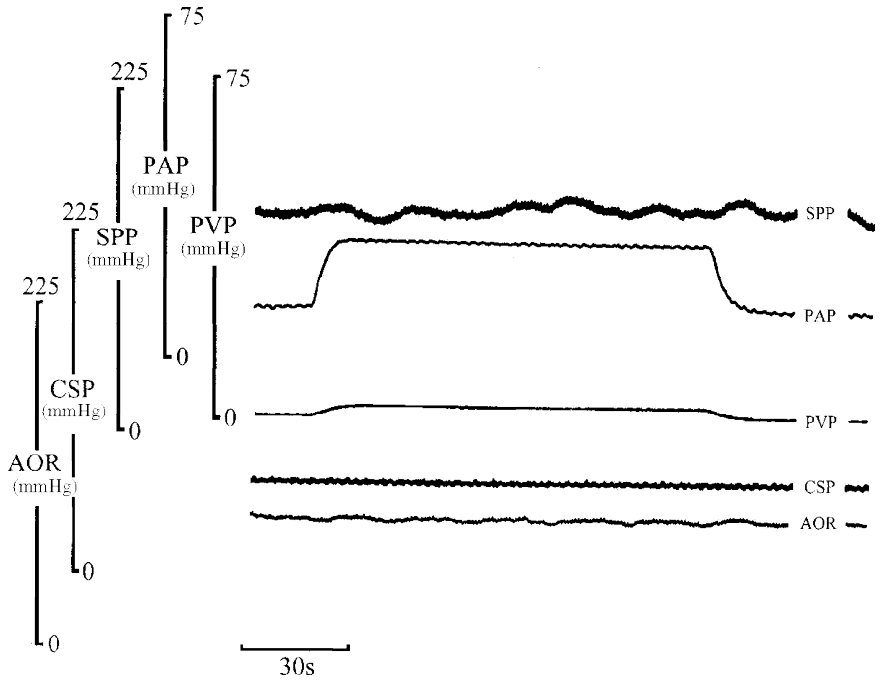

Figure 5

Systemic perfusion pressure response to intrapulmonary arterial distension. The traces are of systemic perfusion pressure (SPP), intrapulmonary arterial pressure (PAP), intrapulmonary venous pressure (PVP), carotid sinus pressure (CSP) and aortic root pressure (AOR). An increase in intrapulmonary arterial pressure from 18 to 32 mmHg was accompanied by a small change in pulmonary venous pressure but no effect on systemic perfusion pressure.

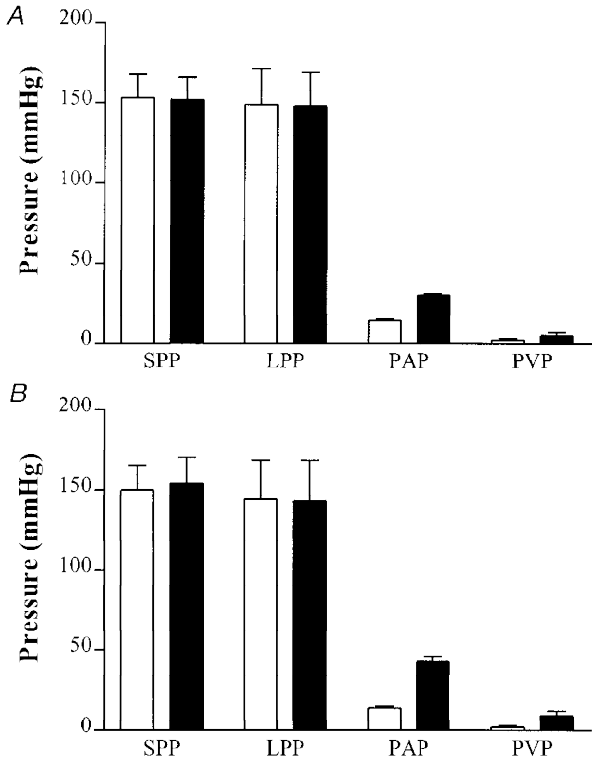

Figure 6

Vascular responses to changes in intrapulmonary arterial pressure (PAP) from low (□) to high values (■). *A*, intrapulmonary arterial pressure increased from 14 to 30 mmHg (systemic perfusion pressure (SPP), $n = 8$; hind limb perfusion pressure (LPP), $n = 5$). *B*, intrapulmonary arterial pressure increased from 14 to 43 mmHg (SPP, $n = 6$; LPP, $n = 4$). Note at both arterial pressures tested there was no change in SPP or LPP perfusion pressures. PVP, intrapulmonary venous pressure.

(venous) to 70 mmHg (arterial) and 64 mmHg (venous). This figure shows a transient decrease in systemic perfusion pressure, but no change in the steady state.

Similar tests were performed in five animals in which intrapulmonary arterial and venous pressures were increased from 19 ± 2 and 1 ± 1 mmHg to 53 ± 8 and 49 ± 8 mmHg, respectively. In two animals there were transient decreases in systemic perfusion pressure of 17 mmHg (−10 %) and 26 mmHg (−19 %) but in three others there were no transient responses. Overall in the five dogs there was no consistent changes in steady-state systemic perfusion pressure (change of 2 ± 2 mmHg ($+1 \pm 1$ %) from the control level of 147 ± 5 mmHg) and hind limb perfusion pressure (change of -6 ± 3 mmHg (-4 ± 2 %) from the control level of 129 ± 12 mmHg).

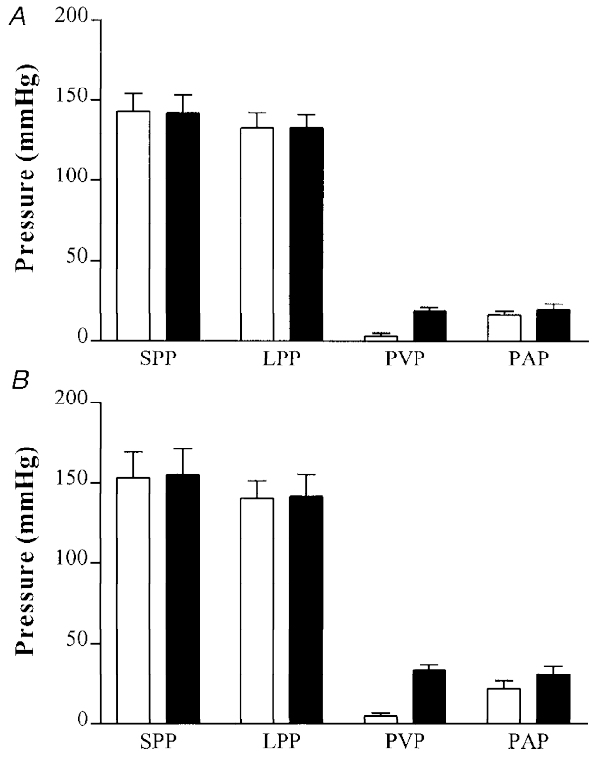

Figure 7

Vascular responses to changes in intrapulmonary venous pressure (PVP) from low (□) to high values (■) at near constant pulmonary arterial pressure. *A*, intrapulmonary venous pressure increased from 3 to 19 mmHg (systemic perfusion pressure (SPP), $n = 8$; hind limb perfusion pressure (LPP), $n = 7$). *B*, intrapulmonary venous pressure increased from 5 to 34 mmHg (SPP, $n = 7$; LPP, $n = 6$). Note at both venous pressures tested there was no change in SPP or LPP perfusion pressure. PAP, intrapulmonary arterial pressure.

Recordings of phrenic nerve activity were made in two of these animals. In one animal increases in intrapulmonary arterial and venous pressures to 59 and 50 mmHg, respectively, reduced phrenic discharge from 60 to 26 impulses s^{-1} and in the other, increases in intrapulmonary arterial and venous pressures to 69 and 68 mmHg, respectively, reduced phrenic nerve discharge from 14 to 6 impulses s^{-1}. There were no transient vascular responses and only a small decrease in the steady-state value of systemic perfusion pressure of −2 mmHg in one animal, no change in the other and limb perfusion pressure responses of −1 and −4 mmHg, respectively. The inhibition of phrenic nerve activity was reversed upon returning intrapulmonary pressures to control values.

DISCUSSION

We have demonstrated in this study that physiological increases in intrapulmonary vascular pressures, in a preparation in which the stimulus was localised and responses from other reflexogenic regions were largely prevented, did not evoke a consistent change in systemic or hind limb vascular resistance.

To our knowledge this is the first study to examine reflex responses from graded increases in blood pressure applied specifically to the intrapulmonary arterial and venous compartments, whilst preventing changes in inputs from other reflexogenic regions including the main pulmonary trunk and pulmonary vein–arterial junction. Pressures to baroreceptors in the carotid sinuses, aortic arch and coronary arteries (McMahon *et al.* 1996) were also held constant, and bypassing the heart would have controlled pressures to cardiac receptors (Hainsworth, 1991). Ventilation and blood gas composition were also carefully controlled.

Previous investigators have reported conflicting responses of systemic vascular resistance to changes in intrapulmonary pressures, with some reporting a vasodilatation in the systemic circulation (Churchill & Cope, 1929; Parin, 1947; Aviado *et al.* 1951; Lloyd, 1975; Hatridge *et al.* 1989) and others no change in systemic vascular resistance (Wead *et al.* 1987; Giesbrecht & Younes, 1993). However, in none of these studies were the experimental criteria set out in this investigation fully satisfied. None made an attempt to control secondary responses from arterial baroreceptors which, due to the buffering actions of the baroreflex, might have accounted in part for the weak vascular responses to pulmonary distension. In one study by Lloyd (1975), the pulmonary circulation was actually distended with gas (95 % O_2–5 % CO_2) which makes any results difficult to interpret. In several other studies the left atrium was also exposed to the stimulus and so it is quite likely that responses may be the result of stimulation of atrial receptors (Linden & Kappagoda, 1982). Various techniques have been used for draining the pulmonary circulation: usually it drained freely through the pulmonary veins (Aviado *et al.* 1951; Wead *et al.* 1987; Hatridge *et al.* 1989; Giesbrecht & Younes, 1993), but in some studies the pulmonary veins were tied, creating a closed sac (Churchill & Cope, 1929; Parin, 1947). The effect of this on the responses is not known.

In those reports which indicated that intrapulmonary vascular distension did induce reflex vascular responses, very high pressures (up to 110 mmHg) were applied (Churchill & Cope, 1929; Parin, 1947; Aviado *et al.* 1951; Lloyd, 1975; Hatridge *et al.* 1989). We have also shown that combined increases in intrapulmonary pressures to extreme levels (> 50 mmHg) did sometimes induce transient decreases in vascular resistance. The extreme pulmonary pressures necessary to induce responses throws into doubt the physiological relevance of these observations, as no responses were observed in this study over the normal range of pressures found in dog's intrapulmonary circulations (17 mmHg, mean pulmonary arterial

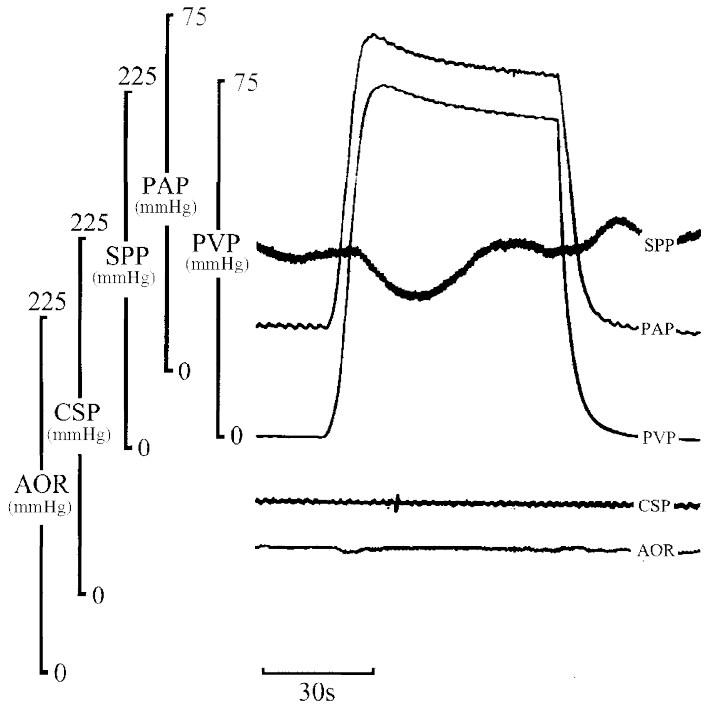

Figure 8

Systemic perfusion pressure response to large combined intrapulmonary arterial and venous distension. The traces are of systemic perfusion pressure (SPP), intrapulmonary arterial pressure (PAP), intrapulmonary venous pressure (PVP), carotid sinus pressure (CSP) and aortic root pressure (AOR). Note the transient decrease in systemic perfusion pressure following the increase in pulmonary vascular pressures, although this returned to control levels during the maintenance of the high pulmonary vascular pressure.

pressure: Katz & Steinitz, 1939) and (9 ± 3 mmHg, venous/pulmonary capillary wedge pressure: Howard *et al.* 1990). The use of very high pressures is likely to result in damage to the integrity of the pulmonary vasculature causing pulmonary oedema. In our investigation we were careful to prevent formation of oedema and not only limited the distending pressures in most experiments, but also allowed pressures to return to low levels for at least 2 min before subsequent changes in pressure.

Due to the absence of significant responses to distension of pulmonary vessels it is necessary to exclude the possibility that afferent nerve fibres from the pulmonary region might have been damaged during surgery. In all preparations we showed that the afferent nerve fibres from the left lung were intact by demonstrating a pulmonary chemoreflex to chemical injection. It is unlikely that the chemical stimuli activated receptors other than those in the pulmonary circulation as this region was vascularly isolated. Responses were similar to those reported in previous investigations (e.g. Hainsworth, 1974). Responses to left lung inflation which were similar to those previously reported were also demonstrated (Daly *et al.* 1986). We also showed that the systemic and hind limb vasculatures were responsive to carotid baroreceptor stimulation, again giving responses quantitatively similar to those previously reported (Challenger *et al.* 1987; McMahon *et al.* 1996). Furthermore, in two animals, increasing intrapulmonary vascular pressures reduced efferent phrenic nerve discharge by over 50 %. This is compatible with reports by Aviado *et al.* (1951) and Lloyd (1978) and shows that, even though there were no consistent vascular responses, distension of the pulmonary circulation must have stimulated afferent nerves which selectively inhibited respiration.

In the accompanying paper (McMahon *et al.* 2000) we reported the enhanced responses to stimulation of extra-pulmonary arterial baroreceptors by the addition of a negative intrathoracic pressure of −20 mmHg. In all experiments in the current study the chest was open so there was no possibility of examining the effects of intrathoracic pressure on transmural pulmonary vascular pressures. However, it is unlikely that the addition of a negative intrathoracic pressure in these experiments would have had a major effect on the vascular responses as only small and transient responses were ever observed and these were obtained only at pressures well in excess of those which would ever be encountered in life, even allowing for the additive effect of a negative intrathoracic pressure.

To conclude, we did not observe consistent changes in vascular resistance during distension of the intrapulmonary arterial and venous circulations over a wide range of pressures, in preparations in which the integrity of the afferent innervation from the left lung had been established. These results indicate that the intrapulmonary circulation does not make a physiologically significant contribution to reflex cardiovascular control.

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