Reflex Changes in Hindlimb and Renal Vascular Resistance in Response to Distention of the Isolated Pulmonary Arteries of the Dog

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SUMMARY We describe a preparation that uses a constant flow, right heart bypass for perfusion of an isolated pouch of the main pulmonary arteries at controlled pressures, and show that increments in pressure in the pulmonary arterial pouch are accompanied by increases in systemic vascular resistance and in hindlimb vascular resistance. These changes are demonstrated over the whole range of 5–120 cm H₂O pressure in the pulmonary arterial pouch. In contrast there are no significant changes in renal vascular resistance or heart rate. We find that changing the temperature of the perfusate in the pulmonary arterial pouch from 37°C to 30°C is associated with a decrease in systemic vascular resistance. Furthermore, the effects of raising the pulmonary arterial pouch pressure and of cooling are abolished by cervical vagotomy. These findings suggest that there is a tonic reflex vasoconstrictor tone generated by the activity of receptors lying in or close to the walls of the pulmonary arteries.

THE HISTOLOGICAL appearances of the different types of sensory nerve ending which exist in the walls of the pulmonary artery and its main branches have been reviewed in detail. That at least some of these sensory nerve endings may be regarded as pressoreceptors has been clearly demonstrated in both the dog and the cat. Electrophysiological techniques have shown that different fibers from sensory endings in the pulmonary arteries may be found in the vagus nerves as myelinated or unmyelinated fibers or may be found in the sympathetic system. Attempts to demonstrate the physiological response to stimulation of the pulmonary arterial baroreceptors have produced variable results and have left the physiological significance of the responses in doubt.

The present investigation was designed to study the reflex effect on systemic arterial pressure, hindlimb vascular resistance, renal vascular resistance, and heart rate, of distention of the main pulmonary artery and its branches with controlled increments in pressure. The aim was to determine whether reproducible reflex cardiovascular responses could be observed by using a more controlled stimulus and method of assessing responses than has been used previously.

Methods

The general plan of the preparation to be described was to create a right atrium to left pulmonary artery bypass through which the left lung was perfused at constant blood flow. This provided for adequate gas exchange and also ensured a constant output from the left ventricle in the steady state. Creation of the bypass then made it possible to establish a pulmonary arterial pouch consisting of the main pulmonary artery, most of the left pulmonary artery, and the right pulmonary artery and its major branches. This pulmonary arterial pouch was perfused with either venous blood or saline at different controlled pressures. Reflex responses were observed in heart rate, mean arterial pressure (systemic vascular resistance), and hindlimb vascular resistance by using an isolated, constant flow, perfused hindlimb preparation, or in renal vascular resistance by using an isolated, constant pressure or constant flow, perfused kidney preparation.

Mongrel dogs of 20–35 kg were injected with morphine sulfate (0.5 mg/kg, sc). One hour later under local anesthesia (mepivacaine hydrochloride, 1%) a polyethylene
catheter was inserted in a saphenous vein into the inferior vena cava and each dog was anesthetized by infusing chloralose (0.1 g/kg, iv) dissolved to make a solution of 1 g of chloralose per 100 ml of sodium chloride solution (0.9 g/100 ml). Subsequently, during the experimental procedures a steady state of light anesthesia and fluid input was maintained by the constant infusion of 0.5% chloralose solution (0.5 g of chloralose in 100 ml of 0.9% sodium chloride solution) into the external jugular vein; the solution was delivered by a motor-driven syringe pump (Harvard) at a rate of approximately 1.0 ml/min.

As soon as possible after the induction of anesthesia, artificial ventilation was started via a tracheal cannula with a mixture of 40% oxygen in air, supplied from a respirator pump (Harvard model 614) at a rate of 14 strokes/min and a stroke volume of approximately 13 ml/kg of body weight. When the chest was opened a resistance to expiration equivalent to 3 cm H2O was provided by an exhalation valve (Ohio Chemical).

Thoracotomy was performed by splitting the sternum in the midline, hemostasis being achieved by using electrocautery and bone wax. Before the pericardium was opened to expose the main pulmonary artery, propranolol (Ay-erst, Ay-64043), 0.3 mg/kg, was injected intravenously to reduce the tachycardia and arrhythmias which accompanied handling of the heart during the surgical procedures. A priming dose of heparin, 500 U/kg, iv (heparin sodium, 100 U/mg, Nutritional Biochemicals), was injected before establishment of the perfusion circuits. A maintenance dose of heparin, 50 U/kg, was administered every 30 minutes.

To create the right heart bypass blood was siphoned from the right atrium through a polyethylene tube (1-cm bore) inserted into the right atrial appendage and advanced into the right ventricle. The blood passed into a reservoir which was open to the atmosphere and was maintained at a constant temperature of 37°C by being immersed in a water bath. The reservoir and tubing was primed with 1 liter of a mixture of 50% dextran (6% dextran 75 in 0.9% NaCl) and 50% Ringer-lactate. From the reservoir the blood passed through an electromagnetic flow probe and was pumped into the cannulated left pulmonary artery and the left lung by a roller pump. For cannulation the left pulmonary artery was dissected free, close to its point of bifurcation at the root of the left lung and distal to the site of origin of the ductus arteriosus, care being taken to avoid the branches of the left vagus nerve in this area. The cannula was a double-lumen stainless steel cannula with an inner tube of 0.5-mm bore from which pressure was recorded and an outer tube of 5-mm bore for perfusion. The root of the main pulmonary artery was carefully separated from the aorta with minimal dissection and a ligature was tightened around the pulmonary artery close to the pulmonary valve, ensuring that the bypass was total. The pump flow rate was adjusted so that the systemic pressure was approximately the same as that which was present before the left lung perfusion was established; the average flow was 1,800 ml/min (range, 760–2,240 ml/min). Constant flow and thus constant cardiac output was maintained by feeding the signal from the electromagnetic flowmeter (Biotronex, BL 610) into a negative feedback circuit controlling the pump motor. The perfusion system is shown diagrammatically in Figure 1.

To create a pulmonary arterial pouch the root of the middle lobe of the right lung was tied tightly and retracted anteriorly. The branch of the right pulmonary artery supplying the lower lobes was dissected and cannulated with a single-lumen, stainless steel cannula with a 3-mm bore. This cannula provided the outflow from the pulmonary arterial pouch and was led to the reservoir. Stout ligatures were tied around the roots of the two lower lobes and the upper lobe of the right lung. The branch of the pulmonary artery supplying the right upper lobe was dissected and cannulated with a double-lumen stainless steel cannula, the inner tube of which had a bore of 0.5 mm for pressure recording, the larger outer tube having a 3-mm bore for perfusion. The cannula was L-shaped, with a lower limb 3.5 cm in length, and was inserted so that the angle was close to the superior vena cava. In this position the tip lay free in the right pulmonary artery close to the bifurcation of the main pulmonary trunk; this position ensured free pressure recording at all times. The pulmonary arterial pouch was perfused through the cannula in the upper pulmonary artery by means of a roller pump which drew venous blood from the reservoir or warm saline from a separate reservoir. Pressure in the pulmonary arterial pouch could be varied by controlling the speed of the roller pump and by a screw clamp placed on the outflow of the circuit. A diagram of the pulmonary arterial pouch perfusion is shown in Figure 1.

For hindlimb perfusion a flank incision was made on the left side, exposing a segment of the descending aorta between the renal arteries and the common iliac arteries. On tying the testicular, caudal mesenteric, and lumbar arteries in that section a stainless steel cannula with a 5-mm diameter was inserted, directed rostrally below the renal arteries. The arterial blood then passed through a constant flow roller pump and an electromagnetic flow probe and entered the dog through a double-lumen cannula (5-mm-bore outer tube, 0.5-mm-bore inner tube for pressure recording) inserted, directed caudally above the

![Figure 1 Diagram of method of right atrium to left pulmonary artery heart bypass and perfusion of an isolated pouch of the pulmonary arteries. The right heart bypass is shown as a solid line. The perfusion circuit for the pulmonary arterial pouch is shaded.](http://circres.ahajournals.org/lookup/doi/10.1161/01.CIR.65.2.295)
common iliac arteries. The pump speed was adjusted so that the perfusion pressure of the hindlimbs was approximately the same as the systemic pressure at the beginning of the experiment, and the blood flow was then kept constant throughout the experiment.

For kidney perfusion the descending aorta was dissected about 2.0 cm above and 5.0 cm below the renal arteries. Testicular or ovarian and lumbar arteries in that section were tied and cut. A stainless steel cannula with a 5-mm diameter was inserted into the left subclavian artery directing arterial blood through a roller pump and an electromagnetic flow probe to the descending aorta. The aorta was cannulated with a double-lumen cannula (5-mm-bore outer tube, 0.5-mm-bore inner tube) inserted, directed rostrally below the renal arteries. The aorta was then tied just above the renal arteries so that the kidneys were perfused solely by the pump. In some dogs the aorta was tied between the renal arteries and only one kidney was perfused. Renal perfusion pressure was measured through the 0.5-mm-bore inner cannula. Pump speed was adjusted so that the renal arterial pressure was approximately the same as systemic arterial pressure at the beginning of the experiment. Either constant flow (constant pump speed) or constant pressure (feedback control to the pump from the renal arterial pressure transducer) was possible, and both modes were used on separate occasions. All electromagnetic flow probes were calibrated at the end of the experiments with the dog's own blood.

Systemic arterial pressure was recorded through an 8-cm length of Teflon tubing (1-mm bore) from either the right femoral artery or the right brachial artery. To each cannula was attached a Statham strain gauge (model P23Gb); the pressures were recorded on an ultraviolet light recorder (Honeywell Visicorder 1508). Mean pressure was obtained by electrical integration. The pressure-recording systems were calibrated by using increments of pressure and either a saline or mercury manometer. Zero pressures were determined post mortem as the levels of the tips of the cannulas when free in air. The electrocardiogram was recorded from leads placed in the right leg and the tips of the cannulas when free in air. The electrocardiogram was recorded from leads placed in the right leg and left chest region. The signal was amplified by a preamplifier (Grass Instrument) and displayed on the ultraviolet recorder. All heart rates used in the results were counted from the electrocardiogram record over periods of at least 30 seconds. Mean arterial pressure and the pressure in the pulmonary arterial pouch was recorded on a four-channel recording systems were calibrated by using increments of pressure and either a saline or mercury manometer. Zero pressures were determined post mortem as the levels of the tips of the cannulas when free in air. The electrocardiogram was recorded from leads placed in the right leg and left chest region. The signal was amplified by a preamplifier (Grass Instrument) and displayed on the ultraviolet recorder. All heart rates used in the results were counted from the electrocardiogram record over periods of at least 30 seconds. Mean arterial pressure and the pressure in the pulmonary arterial pouch was recorded on a four-channel tape recorder (Hewlett-Packard no. 1105). Recordings were made at slow tape speed (15/16 inch/sec). To allow rapid scanning of the total record with a condensed time base the tapes were played back at fast tape speed (15 inches/sec) and slow recorder speed (2.5 mm/sec).

During the surgical procedures the dogs received a slow infusion of 100 ml of dextran (6% dextran 75 in 0.9% sodium chloride, Travenol) for each 13 kg of body weight (approximately 10% of their estimated blood volume). After completion of the surgical procedures, the dog was allowed to stabilize for about 15 minutes, and during this time samples of arterial blood were taken and pH, Pco2, and Po2 were measured using appropriate electrodes (Instrumentation Laboratory, model 113-51). Adjustments were made to the respiratory pump or small infusions (10-30 mEq of sodium bicarbonate solution, 1 ml) were given to maintain an arterial Pco2 between 35 mm Hg and 40 mm Hg and pH within the range of 7.3-7.4; no adjustments were made during the subsequent control or experimental periods. Po2 was always greater than 100 mm Hg. Succinyl choline (Scoline, Squibb), 0.5 mg/kg, was given to provide muscular relaxation when muscular jerks, which are a feature of chloralose anesthesia, were observed. In two instances after a loading dose had been given, the succinyl choline was given as a continuous infusion at a rate of 0.5 mg/min together with the chloralose infusion.

**EXPERIMENTAL PROTOCOL**

The isolated pouch of the main pulmonary artery and its branches were distented with varying pressures in 22 dogs. Recording began approximately 2 hours after thoracotomy had been performed. Before and after each period during which the pulmonary arterial pouch was perfused at a predetermined pressure, control periods were taken with the arterial pouch perfused at a low reference pressure. During these control periods a steady flow of fluid was maintained through the pulmonary arterial pouch.

In six dogs the pouch was perfused with blood at 37°C, taken from the reservoir, and the hindlimbs were perfused with a constant flow of arterial blood. Control pressure in the pulmonary arterial pouch was adjusted to about the same as that existing in the left pulmonary artery at the end of the experiment (average = 18 cm H2O). This pressure was maintained for 3 minutes and a record for measurement of variables was taken during the last minute of the period.

Perfusion pressure in the pouch was increased or decreased in steps of 10 cm of water in the range of 80 cm H2O. Then in steps of 20 cm of water until a maximum of 120 cm H2O was reached. The pressure was raised for 3 minutes, the same time as the control periods, and a record for measurement of variables was taken during the last 1 minute of each period. When mean systemic arterial pressure was constant through either the control or experimental periods, it was estimated by drawing a line by eye through the average pressure for the measurement period. When the mean arterial pressure varied considerably, the mean arterial pressure was estimated with a planimeter. The average pressures during the control periods before and after each experimental period were compared with those of the experimental period. Changes in systemic arterial pressure from control values were plotted against the mean pressure of pulmonary arterial pouch pressure. For statistical comparison between control values of systemic arterial pressure and values after increasing the pulmonary arterial pouch pressure by a set amount, the raw data were used. Heart rate changes were treated similarly.

In six other dogs the pulmonary arterial pouch and the kidneys were perfused; the kidneys were perfused either...
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with constant pressure or constant flow. Perfusion pressure in the pulmonary arterial pouch was varied in the same manner as in the limb perfusion experiments.

In an additional 10 dogs the pulmonary arterial pouch was perfused with saline, the temperature of which could be varied. During control periods the main pulmonary arterial pouch pressure was kept between 0 and 2 cm H₂O and the saline was kept just barely flowing (5 ml/min) to allow the temperature within the pouch to equilibrate to body temperature. Each control period was 4 minutes long and the variables were measured during the 4th minute. Perfusion pressure was raised by increasing the saline flow to the pouch (100 ml/min) and adjusting the screw clamp on the drainage tubing. In each case when the perfusion pressure was raised the flow of saline was relatively large compared to the control and thus the temperature in the pouch was expected to come close to that of the saline, usually 30°C. The pressure was raised for 3 minutes and variables were recorded during the 3rd minute. Approximately the same saline flow rate was used for each distention. In other tests pressure in the pouch was kept constant with a high steady perfusion flow and the temperature of the perfusing saline was altered rapidly by changing reservoirs. In eight of the last 10 dogs the vagus nerves were cut in the neck after completion of the above procedures and the experiment was repeated.

Before each experiment was started the ability of the preparation to respond in a reflex manner was checked by occluding both carotid arteries. In every case there was an increase in mean arterial pressure and an increase in heart rate. Renal and hindlimb vascular resistance also increased during carotid occlusion. In some experiments the integrity of the renal nerves was demonstrated by varying the cardiac output (left lung perfusion): increasing cardiac output decreased renal vascular resistance, and decreasing cardiac output increased renal vascular resistance. No quantification of these responses was attempted.

Results

PERFUSION WITH VENOUS BLOOD AT 37°C

The response of the systemic arterial pressure to changing pressure in the isolated pulmonary arterial pouch was the same in the six dogs in which the hindlimbs were perfused and the six dogs in which the kidneys were perfused; the results have therefore been pooled. The average results from these 12 dogs are shown in Figure 2. An increase in the pulmonary arterial pouch pressure caused a rise in the systemic pressure proportional to the rise in pulmonary arterial pouch pressure. The changes were small with increases in pouch pressure between 10 and 30 cm H₂O. However, although the changes were small they were consistent, and comparison of the systemic arterial pressure at control pulmonary arterial pouch pressure (18 cm H₂O) with systemic arterial pressure at a pulmonary arterial pouch pressure 20 cm H₂O higher (approximately 40 cm H₂O) indicated a highly significant difference (paired t-test, P < 0.005). When the pouch pressure reached 120 cm H₂O, an average increase of about 10% in the systemic pressure was observed. Because cardiac output was constant, changes represent changes in the total systemic vascular resistance. Mean systemic pressure during the control periods was 124 mm Hg and ranged from 104 to 149 mm Hg. The changes in heart rate observed during increases in pressure in the pulmonary arterial pouch were always small (Fig. 2) and usually within the range of error of counting over 30-second periods (±2 beats/min). However, on occasions when there were large increases in systemic arterial pressure in response to pulmonary arterial pouch distention there was an obvious slowing of the heart. Since this occurred only when systemic pressure increased significantly it was attributed to stimulation of the arterial baroreceptors which caused reflex bradycardia. Average heart rate during the control periods was 143 beats/min.

Hindlimb vascular resistance was measured in six dogs and was calculated by dividing the perfusion pressure to the limb by the blood flow. Since the hindlimb blood flow was constant and the reservoir was open to the atmosphere, changes in limb resistance were directly reflected by changes in the limb perfusion pressure. Limb resistance increased when the pulmonary arterial pouch pressure was raised above the control pressure (18 cm H₂O) and decreased slightly when the pouch pressure was lowered to 10 cm H₂O (Fig. 3). Compared to the increase in the systemic arterial pressure, the limb resistance almost always showed a greater percentage increase at any pulmonary arterial pouch pressure. The average control limb pressure was 99 mm Hg and ranged from 82 to 108 mm

![Figure 2](https://example.com/figure2.png) Changes in systemic pressure and heart rate caused by varying the pulmonary arterial pouch pressure between 5 cm H₂O and 120 cm H₂O. Values plotted are changes from control values observed with the pulmonary arterial pouch pressure maintained at 18 cm H₂O. Values shown are the averages in 12 experiments ± SEM.
Mean limb blood flow was 180 ml/min, ranging from 130 ml/min to 290 ml/min. Figure 4 is part of the record of an experiment recorded on tape and re-recorded with a condensed time base. Graded responses of the systemic arterial pressure and limb pressure are clearly seen in response to different pulmonary arterial pouch pressures in the range 50–80 cm H₂O (35–60 mm Hg). It also may be seen that peak responses were observed about 1 minute after the change in pulmonary arterial pouch pressure and that there was some reduction in response to a more steady state by the 3rd minute when measurements were made. In fact, the transient changes were more rapid and somewhat greater than appears from this record because the combination of the compressed time base and electronic damping of the systemic pressure and limb perfusion pressure traces increases the apparent time constant of the systems to 16 seconds. The pulmonary arterial pouch pressure trace was undamped and shows that the oscillations imposed on the system by the roller pump were usually less than 5 cm H₂O in amplitude.

Six dogs were prepared for kidney perfusion. In two of them two sets of pouch distentions were performed, thus a total of eight sets of results were available. Five tests were conducted with constant renal arterial perfusion pressure and in three there was constant renal blood flow. The change in renal resistance was measured as either the change in renal blood flow or the change in renal perfusion pressure. Because the results were similar in each case, they have been pooled. Figure 3 shows small and inconsistent changes in renal resistance in response to changes in pulmonary arterial pouch pressure. In contrast to the limb resistance, the renal vascular resistance was not significantly affected by changes of the pouch pressure. The average control renal arterial pressure was 105 mm Hg, with a minimum of 83 mm Hg and a maximum of 125 mm Hg. Because in some cases only one kidney was perfused and in others both kidneys were perfused, the average value of total renal blood flow was not calculated. In all experiments the renal blood flows were of the order of 1–3 ml/min per g of kidney perfused.
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FIGURE 6 Changes in mean systemic arterial pressure and heart rate associated with increasing pulmonary arterial pouch pressure from 0 to 2 cm H₂O and simultaneously cooling the pulmonary arterial pouch from 37°C to 30°C; average results (± SEM) from 10 dogs.

in every test when the temperature of the saline was changed from 37°C to 30°C or to 15°C. This effect was present at either low (15 cm H₂O) or high (80 cm H₂O) pulmonary arterial pouch pressure (Fig. 5). No quantifying analysis of these responses has been made at present because of limitations of equipment to give precise temperature control of the perfusion fluid.

In 10 dogs an experiment was performed to examine the interreaction of temperature and pulmonary arterial pouch pressure. The pulmonary arterial pouch was perfused with saline at 30°C. During the control periods flow was extremely slow and pressure was low (0–2 cm H₂O); during the experimental periods when the pressure was raised the flow was rapid, thus exerting a cooling effect on the pulmonary arterial wall. Figure 6 shows the changes in systemic pressure and heart rate observed during combined cooling and increasing pressure in the pulmonary arterial pouch. There was a reduction in systemic pressure when pouch pressures were low (10–60 cm H₂O). Distention of the pulmonary arterial pouch with higher pressures (60–120 cm H₂O) caused an increase in systemic pressure despite the cooling. The average control arterial pressure was 117 mm Hg and the heart rate was 152 beats/min. The changes in heart rate observed were always small.

EFFECT OF VAGAL SECTION

Perfusion of the pulmonary arterial pouch with saline at 30°C over the whole range of pressures was repeated after cutting both vagus nerves in the neck. After vagotomy the average control systemic arterial pressure was 107 mm Hg. There were no significant changes in systemic arterial pressure either in response to cooling or to changing pulmonary arterial pouch pressure (Fig. 7). The average control heart rate after vagotomy was 165 beats/min and there were no significant changes in heart rate.

Discussion

Many workers have described afferent nerve endings situated in the walls of the main pulmonary arteries. The endings are most frequently described as myelinated nerve fibers in the adventitia, terminating at the junction of the media and adventitia or penetrating the outer layers of the media and ending as an irregular collection of coiled fibers sometimes with swellings and enlargements on the terminal twigs. Many other nerve fibers, in addition to those terminating as specialized receptors, are also described.

Electrophysiological studies have clearly demonstrated that receptors with large myelinated afferent fibers in the vagus nerves actively discharge at pressures normally present in the pulmonary arteries of the dog. It has been
clearly shown\(^\text{12}\) that pulsatile pressure is a more effective stimulus to the receptors than is a steady pressure. Afferent impulses have also been studied in fine myelinated or unmyelinated nerve fibers arising from the pulmonary arteries.\(^\text{4}\) These endings did not respond to pressures within the physiological range but were stimulated by high pressures (60–110 mm Hg). The endings appear to be distributed over the main pulmonary artery and the right and left branches, whereas the endings of the large myelinated fibers are located almost exclusively in the right and left main pulmonary arteries. Coleridge et al.\(^\text{6}\) also noted some fibers whose endings were stimulated by both systemic hypoxia and a high pressure in their pulmonary sac (70–120 mm Hg). They suggested these were chemoreceptors located on or in the pulmonary artery wall, the blood supply of which, through the vasa vasorum, was occluded by extreme distention of the pulmonary artery. In addition Nishi et al.\(^\text{6}\) and Uchida\(^\text{6}\) have recently recorded action potentials from fibers in the cardiac sympathetic nerves of the cat which appeared to originate in the pulmonary artery. The endings showed only a transient burst of activity in response to an increase in pulmonary arterial pressure.

Despite the richness of the afferent innervation of the pulmonary arteries, the reflex effects of pulmonary arterial distention remain in doubt. Indeed, some reviewers\(^\text{7–8, 13}\) have attached little importance to reflexes arising from this area. Early experiments in cats,\(^\text{14–16}\) in which the pulmonary artery pressure in one lung was raised after ligation of the pulmonary veins, all showed bradycardia and hypotension independent of the integrity of the vagus nerves. However, several of these workers noted that they were able to show this effect in only a small proportion of their experiments. This technique, which distended the intrapulmonary vessels, does not affect the main pulmonary arteries where the majority of the receptors are now known to lie. Aviado et al.\(^\text{15}\) isolated the right side of the heart and raised the pressure in the right ventricle and main pulmonary arteries and observed a vagal reflex bradycardia but no hypotension. A complete bypass and oxygenator were used by Lewin et al.\(^\text{16}\), who then distended the main pulmonary arteries by means of a balloon or perfused the pulmonary arteries with blood (four dogs). They always observed an increase in systemic pressure but were unable to quantify the stimulus provided by the balloon and had to raise the perfused pulmonary artery pressure to 80–200 mm Hg to produce a reflex increase in systemic pressure. The phenomenon was abolished by vagotomy. A balloon “cuffed” cylinder was used by Oso-río and Russel\(^\text{16}\) to distend the main branches of the pulmonary arteries without interfering with blood flow. They reported an increase in pulmonary vascular resistance and variable changes, usually a decrease in systemic pressure; no heart rate changes were observed. Coleridge and Kidd\(^\text{20}\) inserted a metal sleeve into the left main pulmonary artery of dogs and perfused the right main pulmonary artery and that portion of the left pulmonary artery outside the sleeve with controlled pressures. When the pulmonary artery sac pressure was elevated to between 20 and 60 mm Hg there was either no effect (10 dogs) or a fall in systemic pressure (eight dogs), and in the majority of cases (58 of 72 cases) there was no change in heart rate. When the sac pressure was raised to over 80 mm Hg the systemic pressure increased in 28 of 30 tests. An increase in respiratory movements was also noted during high pressure distention of the sac.

It is apparent that with the exception of the experiments of Coleridge and Kidd\(^\text{20}\) and Lewin et al.\(^\text{16}\) previous studies of reflexes arising from pulmonary arterial distention have not localized the stimulus to the pulmonary artery and its right and left main branches where the receptors are known to lie. The present experiments were designed to allow distention of the pulmonary artery and its right and left branches at controlled pressure while cardiac output was maintained constant by means of a constant flow right heart bypass. This allowed changes in systemic vascular resistance to be directly related to changes in systemic arterial pressure. Also, since preliminary experiments had indicated that the system might be affected by small changes in temperature (later confirmed as described in Results), the temperature of the pulmonary arterial perfusate was maintained at that of the systemic blood. It is not possible, reviewing previous work, to determine whether temperature changes in pulmonary arterial perfusion may have been a factor contributing to the variability of some of the observed effects.

There is little doubt from the results described that increasing the pressure in the pulmonary arterial pouch causes an increase in systemic vascular resistance. Although the changes are relatively small over the physiological range of pulmonary arterial pouch pressure they do appear to form a continuum with the larger responses observed at higher pulmonary arterial pouch pressures. The use of a steady pulmonary arterial pouch pressure rather than a pulsatile one (which would have been more difficult to control adequately) is likely to underestimate the effects of small changes in pulmonary arterial pouch pressure. It should also be noted that the dogs had active arterial baroreceptor reflexes (as indicated by response to carotid occlusion) which would be likely to reduce the magnitude of the responses. The partially transient nature of the responses possibly can be accounted for in terms of modification of the response by arterial baroreceptor reflexes. Alternatively, this type of transient could be predicted because of rapid adaptation of the pulmonary arterial baroreceptors to increased stretch. Such partial rapid adaptation is likely from the known dynamic characteristics of the receptors.\(^\text{12}\) The results differ markedly from those of Coleridge and Kidd\(^\text{20}\) in that we have shown very significant increases in systemic pressure with 40 cm H\(_2\)O (30 mm Hg) pressure in the pulmonary arterial pouch, a pressure within the range in which they observed hypotension. Our hypothesis that an increase in afferent impulse discharge from the receptors in the walls of the pulmonary arteries causes an increase in systemic vascular resistance receives support from the observation that reducing the temperature of the perfusing fluid from 37°C to 30°C was associated with a significant fall in systemic arterial pressure. This relatively small temperature change is unlikely to block nerve fibers and must be the result of a reduction in activity in receptors in or close to the pulmonary arterial walls.
However, the demonstration of significant changes in systemic pressure in response to changes in temperature raises the possibility that all our observed effects were due to changes in temperature in the pulmonary arterial pouch. Since the pouch was in effect a blind sac, there may have been inadequate circulation of the warm blood with low distending pressures. This is unlikely because the inflow cannula was inserted with the tip close to the bifurcation of the pulmonary artery and directed to the left, and the constant motion of the overlying heart and aorta would promote mixing. In addition the rise in systemic pressure with increasing pulmonary arterial pouch pressure, seen when saline at 30°C was used, can be explained only in terms of the increase in pressure within the pouch opposing the effects of a decrease in temperature. This does not necessarily imply that the same receptors respond to temperature and to pulmonary arterial pouch pressure. Both baroreceptors and chemoreceptors have been shown to be affected by temperature.21,22 It seems unlikely that the endings described by Coleridge et al.4 as possible chemoreceptors and stimulated by high pressure in their pulmonary sac (70–120 mm Hg) could be involved in the responses observed over the lower range of pressures used (e.g., <40 cm H₂O).

The change in systemic vascular resistance observed in response to distention of a pulmonary arterial pouch has been demonstrated to be accompanied by a somewhat greater percentage increase in vascular resistance in the perfused hindlimbs but with no change in the vascular resistance in the kidneys. That the sensitivity of various vascular beds to arterial baroreceptor stimulation may differ has been clearly shown.23 Renal resistance vessel changes have been described as following courses identical to changes in muscle vessels but as showing less sensitivity.24 These differences have been correlated with varying vasoconstrictor fiber discharges in the cat.25 Under the other circumstances it has been shown that distention of the pulmonary vein-left atrial junction is associated with a decrease in renal vascular resistance26 and a decrease in efferent sympathetic nerve activity to the kidney,27 but with no change in hindlimb vascular resistance or efferent sciatic nerve activity. The pattern of response to pulmonary arterial distention differs from both of the above. However, since the pulmonary arteries and the left atrium both form a part of the low pressure vascular system,28 the pressures in these areas are altered in a similar fashion by changes in blood volume or the distribution of the blood volume. An increase in blood volume causing a rise in pulmonary arterial and left atrial pressure could cause a rise in systemic arterial pressure with no change or a fall in renal vascular resistance. Under these circumstances an increase in sodium excretion from the kidneys would be predicted.

It is apparent that neither increasing the pressure in the pulmonary arterial pouch nor cooling the pulmonary arterial pouch was associated with any significant changes in heart rate. The experiments may be criticized on the basis that propranolol, 0.3 mg/kg, was given during the preparation. However, it was approximately 3 hours after the propranolol had been given that the experimental records were taken, and by this time complete β-adrenergic block of the heart would not be expected. All dogs showed an increase in heart rate during carotid occlusion, indicating that at least a vagal efferent pathway was intact, and some dogs demonstrated sinus arrhythmia. Thus the failure to demonstrate changes in heart rate was not due to the inability of the heart to respond.

The effects of increasing the pressure in the pulmonary arteries and the effects of cooling the pulmonary arteries were wholly dependent on the integrity of the vagus nerves. It is likely, therefore, that the afferent pathway for the reflex responses is in the vagus nerves.

Recent work using indirect techniques of vagal section in animals with denervated arterial baroreceptors has suggested that impulses arising from cardiopulmonary receptors exert a tonic restraint on adrenergic discharge.29-32 The precise location of such cardiopulmonary receptors has not been identified. Our results demonstrate that receptors in or close to the walls of the pulmonary arteries generate a significant systemic vasoconstrictor tone which may be increased by pulmonary arterial distention. In less direct experiments it may be that this vasoconstrictor effect is overwhelmed by impulses from other cardiopulmonary receptors. However, the results of such indirect experiments must be interpreted with caution. It is likely that vagal section prevents a much more complex series of interactions than can reasonably be described as removal of either a net tonic inhibitory activity or an excitatory activity.

A physiological role for impulses arising from pulmonary arterial baroreceptors is not proved by the experiments described. However, the speculation that changes in blood volume or in the distribution of blood volume may affect the discharge from the pulmonary arterial baroreceptors and lead to modification of solute excretion by the kidney is an attractive one. Additional experiments will be needed to determine whether such a relationship exists.

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chronic labile hypertension produced by lesions of the nucleus tractus solitarii in the cat

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SUMMARY Bilateral electrolytic lesions of the nucleus tractus solitarii (NTS) were made at the level of the obex in seven cats. Within 1 hour the mean arterial pressure (MAP) rose to a maximum of 144 mm Hg (141% of control), and by 7 hours heart rate reached a peak of 236 beats/min (148% of control). The baroreceptor reflexes were abolished. After 24 hours the arterial pressure became extremely labile, with variations of 80–100 mm Hg observed. The lability occurred spontaneously and during behaviors that were self-initiated or elicited by environmental stimuli. The MAP in the lesion group was 144 mm Hg (180% of control) during the day, and 96 mm Hg (120% of control) at night. The lability, measured by the standard deviation, during the day in the lesion group was 4 times greater than in the control group and at night there were no differences. The heart rate of the lesion group was always higher than that of the control group but the lability of both groups was the same. We conclude that lesions of the NTS produced labile hypertension, probably by disinhibition of sympathetic activity through central interruption of the baroreceptor reflexes. The higher, more labile arterial pressures during the day may be caused by uninhibited increases in sympathetic activity elicited by environmental stimuli that are present during the day and absent at night. The daily variation of pressure may also be caused by somatomotor activity or by a daily rhythm of sympathetic activity which is unmasked by the lesions.

THE CENTRAL nervous system may play a critical role in the initiation of and/or maintenance of several models of experimental hypertension in animals and possibly of essential hypertension in man. Neurogenic hypertension may result from an imbalance between systems in the brain which excite or inhibit sympathetic discharge. The imbalance could favor increased sympathetic discharge which would enhance vasoconstriction and consequently elevate the arterial pressure.

Many attempts to produce animal models of experimental hypertension have aimed at increasing sympathetic discharge either by chronic electrical stimulation of the hypothalamus, by producing brain ischemia, by subjecting animals to stress, or by behavioral conditioning. Hypertension results from these procedures but it lasts, at most, for only a few weeks. Other studies have attempted to produce experimental hypertension by withdrawing inhibition of sympathetic
Reflex changes in hindlimb and renal vascular resistance in response to distention of the isolated pulmonary arteries of the dog.

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