Experimental Physiology

Responses to stimulation of coronary and carotid baroreceptors and the coronary chemoreflex at different ventricular distending pressures in anaesthetised dogs

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Stimulation of left ventricular mechanoreceptors was believed not only to exert important effects on the circulation, but also to influence the responses to baroreceptor reflexes. However, most previous work is flawed due to inadequate localisation of stimuli to specific reflexogenic areas. In this study, we applied a discrete stimulus to left ventricular mechanoreceptors to examine other reflexes known to effect the circulation. Dogs were anaesthetised, artificially ventilated and a cardiopulmonary bypass established. The pressure distending the left ventricle was controlled through an apical cannula with the aortic valve obstructed by a balloon. Changes in ventricular systolic and end-diastolic pressure had only a small effect on vascular resistance, assessed as perfusion pressure in the systemic circulation (flow constant). Responses to changes in carotid or coronary pressure or to stimulation of chemosensitive afferents by injecting veratridine into the coronary circulation were always much larger. Responses to stimulation of these reflexes were little affected by the level of stimulus to the ventricular receptors. These experiments confirm that responses to stimulation of ventricular mechanoreceptors are very small and show that they remain small at different levels of input to other baroreceptive regions. There was no evidence of interaction between ventricular mechanoreceptor reflexes and carotid or coronary baroreceptors or ventricular chemosensitive reflexes. *Experimental Physiology* (2001) **86.3**, 381–390.

The left ventricle is richly innervated with non-myelinated vagal afferents, stimulation of which leads to profound depressor responses (see Hainsworth, 1991). Discharge from these nerve endings may be sparse and irregular (Coleridge *et al.* 1964) or show cardiac rhythm relating to both ventricular systolic and diastolic pressures (Thorén, 1977). The physiological or pathophysiological role of reflexes originating in the left ventricle, however, is still not established. We recently reported that discrete stimulation of mechanosensitive ventricular afferents, which required end-diastolic distension, resulted in relatively small reflex responses whereas much larger responses occurred following moderate pressure changes in the coronary arteries (Wright *et al.* 2000; Drinkhill *et al.* 2001). We therefore suggested that the large responses from mechanical stimulation of the ventricle seen in earlier studies were likely to have been due to stimulation of coronary baroreceptors. The question then remains as to what exactly is the role of left ventricular mechanoreceptors.

One widely held view is that left ventricular receptors are likely to be involved in conditions associated with abnormal distension (Mark, 1983; Abboud, 1989; Persson, 1991; Thames & Dibner-Dunlap, 1991; Thames *et al.* 1993). It is suggested, in particular, that during myocardial ischaemia or in heart failure, when the left ventricle is likely to be abnormally distended, one of the effects of this may be to cause depression of the baroreceptor reflex. Evidence for such reflex interactions has been sought in a variety of ways. These include examining the effects on responses to carotid baroreceptor stimulation of interruption of cardiac vagal afferents by vagal cooling (Öberg & White, 1970; Mancia *et al.* 1973, 1975, 1976) or vagotomy (Guazzi *et al.* 1962; Mancia *et al.* 1973). Clearly, such procedures do not provide stimuli that are localised to ventricular receptors. Others have stimulated ventricular chemosensitive afferents with chemical agents and reported a depression of baroreflex responses (Chen, 1979; Holmberg *et al.* 1983). These results, however, are not related to mechanical events and interpretation is also complicated by tachyphylaxis, which is known to occur in response to the repeated application of chemical stimulants.

There have been no adequate studies that have applied a discrete stimulus to ventricular mechanoreceptors and examined the effects on other reflex responses. It was the purpose of the present study to do this, and in particular to examine effects of ventricular distension on responses to stimulation of carotid and coronary baroreceptors and left ventricular chemosensitive endings. In carrying out this study,

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we paid particular attention to the definition of reflex interaction by Tutt *et al.* (1988), which required a change to be demonstrated in the stimulus–response relationship of a reflex that was not due solely to non-linearities or saturation of the efferent limb.

METHODS

Animals and preparation

Sixteen beagle dogs of both sexes weighing between 15 and 20 kg (mean, 17.2 ± 0.3 kg) were anaesthetised with α-chloralose (100 mg kg^{-1} I.V. in saline; Vickers Laboratories Ltd, Pudsey, Yorks, UK) infused through a catheter inserted under local anaesthesia (2% lignocaine hydrochloride) through the right saphenous vein, so that its tip lay in the inferior vena cava. Surgical anaesthesia was maintained throughout the duration of the experiments by further infusions of α-chloralose (0.5–1.0 mg kg^{-1} min^{-1}). Prior to major surgical procedures, alfentanil (Janssen-Cilag Ltd, High Wycombe, Bucks, UK) was given intravenously (30 μg kg^{-1} over a 10 min period), and then it was infused at 2.5 μg min^{-1} until 60 min prior to the start of the experimental protocol. At intervals throughout the experiment, the depth of anaesthesia was assessed from the stability of blood pressure and observing only small muscular contractions in response to toe pinch or to a sharp tap on the surgical table.

A longitudinal midline incision was made in the neck, the trachea intubated and the lungs artificially ventilated with 40% oxygen-enriched air using a Starling 'Ideal' pump set at 17 ml kg^{-1} and 18 strokes min^{-1}. Arterial P_{O_2}, P_{CO_2} and pH were determined at intervals during the experiments using a pH/blood gas analyser (Instrumentation Laboratory, model IL 1610) and were maintained within normal limits (see below) by altering the stroke volume of the respiratory pump, the rate of oxygen inflow and infusions of molar sodium bicarbonate solution, when required.

Both carotid sinus regions were prepared by ligating all branches arising from the carotid bifurcations, except the external carotid and lingual arteries, which were used for subsequent perfusion. The left side of the chest was exposed by a mid-sternal split and by dividing the fifth intercostal space. Once the pleural cavity was opened, the expiratory output from the pump was immersed in 3 cm of water (2.3 mmHg, expiratory resistance) to prevent lung collapse. The upper six pairs of intercostal arteries were tied and then divided to mobilise a length (approximately 5 cm) of the descending aorta. The left subclavian artery was dissected free. Two snares were threaded around the brachiocephalic artery, carefully avoiding the ansae subclaviae. The pericardium was opened to allow access to the atria and left ventricles. Finally, a nylon cord was passed around the root of the ascending aorta (0.5–1.0 cm from its origin), just distal to the coronary ostia.

The animal received an intravenous injection of heparin (500 i.u. kg^{-1} I.V.; Leo Laboratories Ltd, Princes Risborough, UK) prior to cannulation and connection of the perfusion circuit (see Fig. 1). The perfusion circuit was part-filled with 2 l of a mixture 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), and Dextran in dextrose solution (50 : 50 mixture, 50 g l^{-1} dextran, molecular weight 181 000). Blood cells from a previous experiment, which had been centrifuged and washed, were added to the perfusate. The perfusion circuit was then connected in the following sequence. A curved stainless-steel cannula was inserted into the root of the aorta to convey blood to the main arterial reservoir (see A in Fig. 1). The descending aorta was cannulated and a pump perfused the sub-diaphragmatic circulation at a constant flow, which was initially set to give a systemic perfusion pressure of 150 mmHg. The central and peripheral ends of the left subclavian artery were cannulated and the aortic arch and cephalic regions were perfused from a reservoir maintained at a constant pressure (see C in Fig. 1). A full heart–lung bypass was achieved by inserting cannulae into the left and right atria and the inferior vena cava (7 and 10 mm I.D.), to drain blood to an open reservoir (see D in Fig. 1). The blood from reservoir D was pumped through a membrane gas exchange unit (Sorin Monolyth Integrated Membrane Lung, Sorin Biomedica Cardio, Saluggia, Italy) and into reservoir A from which it was distributed to the remainder of the perfusion circuit. A stab incision was made in the apex of the left ventricle, and a cannula (8 mm i.d.) was inserted and secured into position by a purse-string suture. From reservoir A, blood was pumped at constant flow through a damping chamber and into the left ventricle. The outflow from the ventricle passed through the same cannula with the pressure controlled by a Starling resistor (Knowlton & Starling, 1912), to drain into reservoir D.

Left and right common carotid arteries were cannulated and perfused at a constant pressure (see B in Fig. 1) and drained by cannulae inserted into the central ends of both lingual arteries. The snare placed around the root of the ascending aorta was tied onto the aortic root cannula to create a pouch of the aorta (see Fig. 2). The pressure perfusing the aortic pouch, which also controlled cephalic pressure in most experiments, was controlled by an independent reservoir (C in Fig. 1), which was connected to cannulae in the central and peripheral ends of the left subclavian artery. The pressure applied to the main arterial reservoir (A in Fig. 1) controlled pressure at the aortic root (coronary pressure).

The method by which the left ventricle was isolated from the coronary circulation has already been described (see Wright *et al.* 2000). Isolation of pressure stimuli to the left ventricle and coronary arteries was achieved by passing a balloon catheter (atrioseptostomy catheter, Baxter International Inc., McGaw Park, IL, USA) through the aortic root cannula and into the left ventricle. This balloon catheter was inflated with 2–3 ml of saline and then withdrawn sufficiently to occlude the aortic valve (see Fig. 2). Adequate obstruction was inferred from the independence of coronary and left ventricular pressures. The position of this balloon catheter was always inspected and its position confirmed *post mortem*. Finally a catheter (see Fig. 2) was advanced through the lumen of the aortic root cannula and was positioned adjacent to the coronary ostia to permit the coronary injections of veratridine.

Nylon catheters attached to strain gauges (Gould-Statham P23 ID, Oxnard, CA, USA) were used to record pressures in: the right carotid cannula (carotid sinus pressure); the left subclavian artery cannula (aortic and cephalic perfusion pressures); the aortic root cannula (coronary arterial pressure); the apical left ventricular cannula (left ventricular pressures); the right femoral artery cannula (systemic arterial perfusion pressure); and, in some, the atrial cannula (left atrial pressure). All pressures were recorded on a direct-writing electrostatic recorder (Model ES 1000, Gould Electronics, Ballainvilliers, France) and a magnetic tape (Racal V-store, Racal Recorders Ltd, Southampton, UK). Data were analysed on-line using a real-time data acquisition unit (Fastdaq, Lectromed, Letchworth, UK). The temperature of the animal was recorded by placing a thermistor probe in the oesophagus and temperature was maintained between 37 and

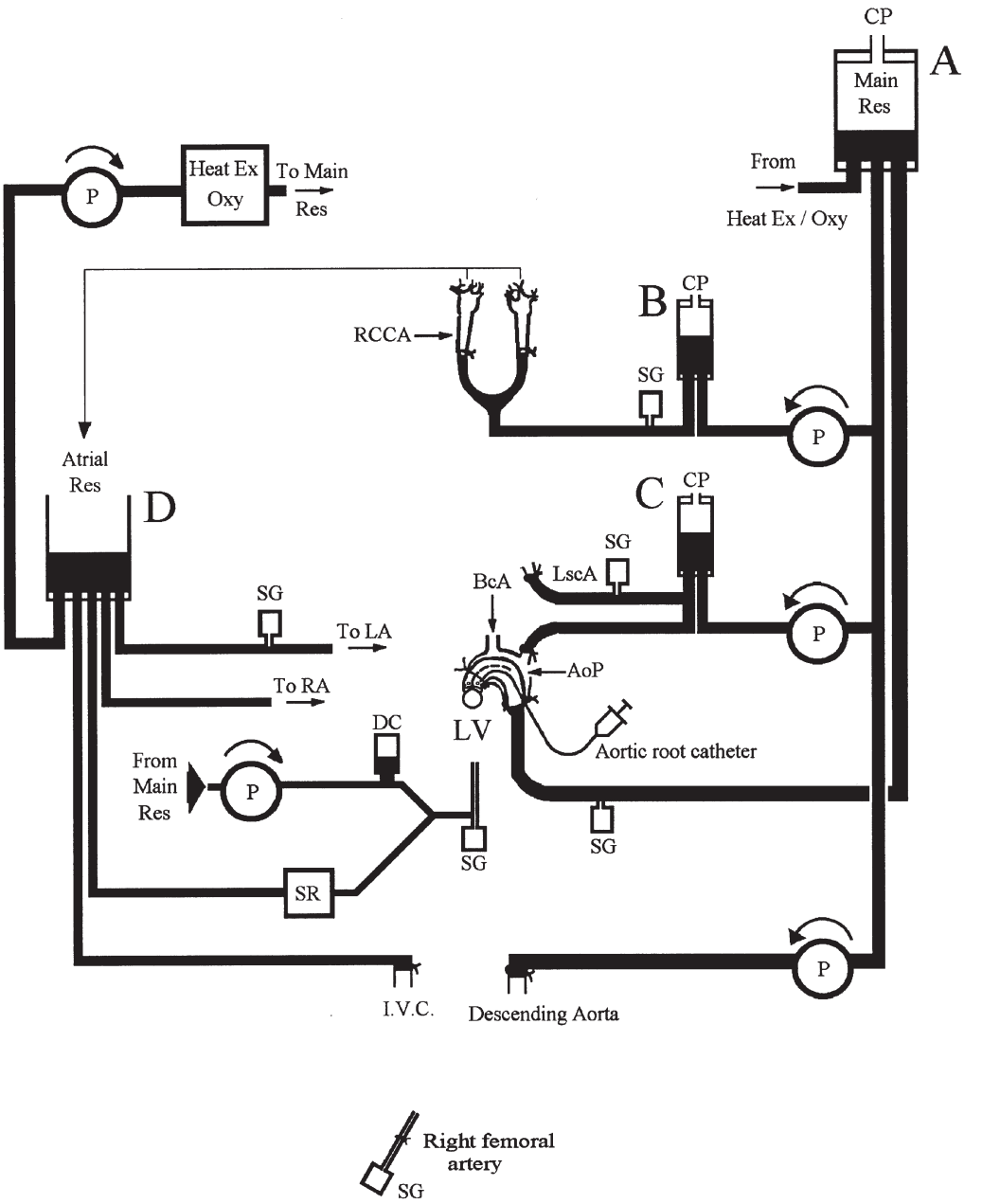

Figure 1

Diagram of experimental preparation. A large curved stainless-steel cannula tied into the aorta, distal to both the coronary ostia and the left subclavian artery (LscA), created a pouch of the aorta outside this cannula and conveyed blood to a pressurised main arterial reservoir. A total cardiopulmonary bypass was achieved by draining blood through cannulae tied in the inferior vena cava and both atrial cannulae and into reservoir D, from which it was pumped through an integrated heat exchanger/oxygenator and then to reservoir A. From this reservoir, blood was pumped to: (i) reservoir B and at a constant pressure into cannulae tied into both common carotid arteries; (ii) reservoir C and at constant pressure into cannulae tied into the central and peripheral ends of the left subclavian artery; (iii) the descending aorta at constant flow; and (iv) the left ventricle (LV) through a damping chamber at constant flow and out through a Starling resistor to closed reservoir D. Cannulae inserted in both lingual arteries drained blood from the carotid bifurcation region to reservoir D. The LV was isolated from the coronary circulation by a balloon catheter inserted into the LV, which was positioned to occlude the aortic valve. The insertion of an aortic root catheter, positioned to lie adjacent to the coronary arteries, provided a site for the intra-coronary injection of veratridine. Abbreviations: AoP, aortic pouch; BcA, brachial cephalic artery; CP, constant pressure; DC, damping chamber; LscA, left subclavian artery; IVC., inferior vena cava; SG, strain gauge transducer; P, pump; Res, reservoir; SR, Starling resistor.

39 °C by use of a heat exchanger incorporated into the perfusion circuit and by heating the animal table.

All experiments were conducted in accordance with the current UK legislation, the Animals (Scientific Procedures) Act, 1986, and all experiments were terminated by exsanguination of the animal while under deep anaesthesia.

Experimental protocol

Following the connection of the perfusion circuit, 30 min was allowed for the animal to reach a stable state. During this time, arterial blood gases were analysed and corrected so that the respective values of pH, P_{O_2} and P_{CO_2} were 7.4 ± 0.1, 219.7 ± 51.5 and 38.7 ± 2.5 mmHg (means ± S.D.). The haematocrit of arterial blood was 19 ± 3% (mean ± S.D.; range 12–24).

The following procedures were performed.

Carotid and coronary pressure tests. Single large-pressure stimuli were applied at the start of and at intervals during the experiment to establish the viability of the preparation (see Data analysis, below). Coronary pressure was increased in a step from 60 to 180 mmHg and carotid pressure in a step from 60 to 240 mmHg. Pressures were held at each value for 1–2 min to allow steady-state responses to be obtained.

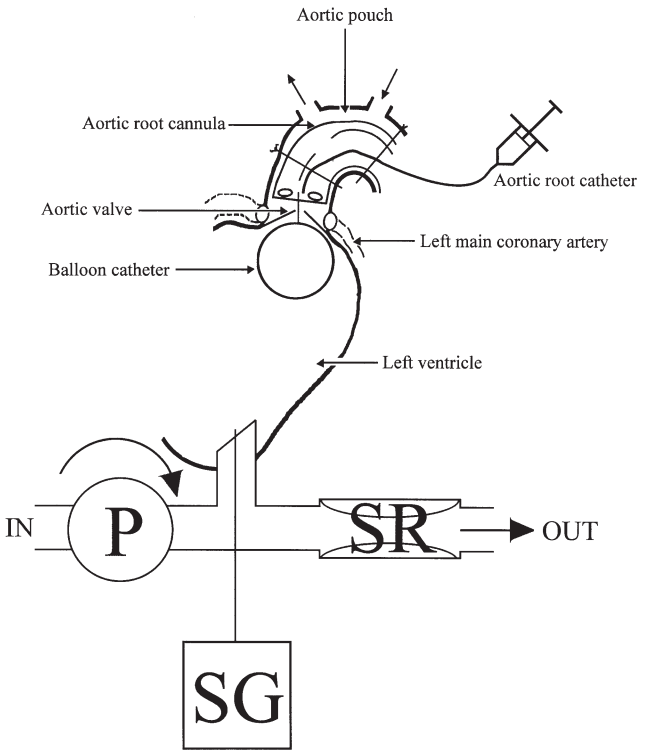

Figure 2

Diagram showing the position of the left ventricular balloon catheter. This balloon catheter was passed retrogradely across the aortic valve, inflated within the cavity of the left ventricle and then withdrawn and positioned to occlude the aortic valve, in order to isolate the left ventricle from the coronary circulation. The position of the aortic root catheter (site of intra-coronary injection) is also shown and this was positioned to lie adjacent to the coronary ostia.

Coronary pressure tests at different ventricular pressures. Coronary arterial pressure was increased in steps of 30 mmHg from 60 to 180 mmHg with left ventricular systolic and end-diastolic pressures held at approximately 70 and 12 mmHg, respectively. Pressures were held at each step for 60 s to allow steady states to be achieved. Coronary pressure was then decreased to 60 mmHg and the averages of the values at the two low coronary pressures were taken as baseline values. Vascular and heart rate responses to each step were calculated from these baseline values. Next, ventricular pressures were increased to approximately 147 and 41 mmHg and the sequence of coronary pressure steps was repeated. Finally, ventricular pressures were reduced to the low values and the coronary pressure test again repeated. In some experiments, we reversed the order of pressure changes, going from high to low to high ventricular pressures.

Carotid baroreceptor tests at different ventricular pressures. A similar procedure was carried out as described above. Carotid pressure was changed in 30 mmHg steps from 60 to 240 mmHg with ventricular systolic and end-diastolic pressures held first at the low, then high, and finally at the low value again. As before, the order of the ventricular pressures was varied between experiments.

Intra-coronary injection of veratridine at low and high ventricular pressures. Heart rate and perfusion pressure responses were assessed to the intra-coronary injections of veratridine (30–60 μg). This procedure was performed at different ventricular pressures. Steady-state values taken before and after the injection of veratridine were averaged to give control values. Responses to veratridine were taken as the peak change (from 5 s running averages) from the control level. In between tests, at least 15 min was allowed to lapse to avoid tachyphylaxis. The responses obtained at the higher ventricular pressures were compared with those recorded at the low levels, obtained before and after the increase in ventricular pressures. In some experiments, the order in which different ventricular pressures were applied was changed to high–low–high.

Data analysis

Vascular responses were accepted for analysis from those animals in which a step increase in coronary pressure from 60 to 180 mmHg decreased systemic perfusion pressure by at least 23 mmHg (approximately a 20% decrease in vascular resistance). In tests in which the effects of changing ventricular pressure were assessed, animals were divided into two groups. The first included the results from all the animals studied, and the second group included only those in which a step increase in ventricular pressure reduced systemic perfusion pressure by 6% or more.

Plots were drawn of systemic vascular resistance against mechanoreceptor distending pressures for both low and high ventricular pressures (control values for perfusion pressure at the low ventricular pressures expressed as 100%). Stimulus–response curves were further analysed using a commercial curve-fitting computer program (GraphPad v2.0; GraphPad Software Inc., San Diego, CA, USA) which derived a sigmoid curve to fit the points. From each curve, various measurements were derived. Saturation pressure was taken as the mechanoreceptor pressure corresponding to 95% of the total perfusion pressure response. Values of maximum slope were obtained from the peak differential of the fitted sigmoid function, and the inflexion pressures were those which corresponded to the peak of the differential.

Stimulus–response curves performed at the low and high ventricular pressures were compared, and levels of significance

were assessed using Student's paired t test and considered statistically significant when $P < 0.05$. Data presented are of means ± S.E.M.

RESULTS

During the testing of responses to stimulation of carotid, coronary and ventricular mechanoreceptor and ventricular chemosensitive nerves (see procedures below), pressures perfusing the regions not being investigated were held constant at the following values: carotid, 64.1 ± 0.8 mmHg; coronary, 82.2 ± 3.0 mmHg; aortic pouch (and cephalic circulation), 124.4 ± 5.1 mmHg; ventricular systolic and end-diastolic pressures, 57.8 ± 4.2 and 11.4 ± 1.3 mmHg. In five animals, the cephalic region was perfused separately from the aortic pouch at 133.4 ± 9.7 mmHg. Also, in 12 animals in which the left atrial pressure was recorded, the bypass maintained it at a mean value of 0.2 ± 0.2 mmHg.

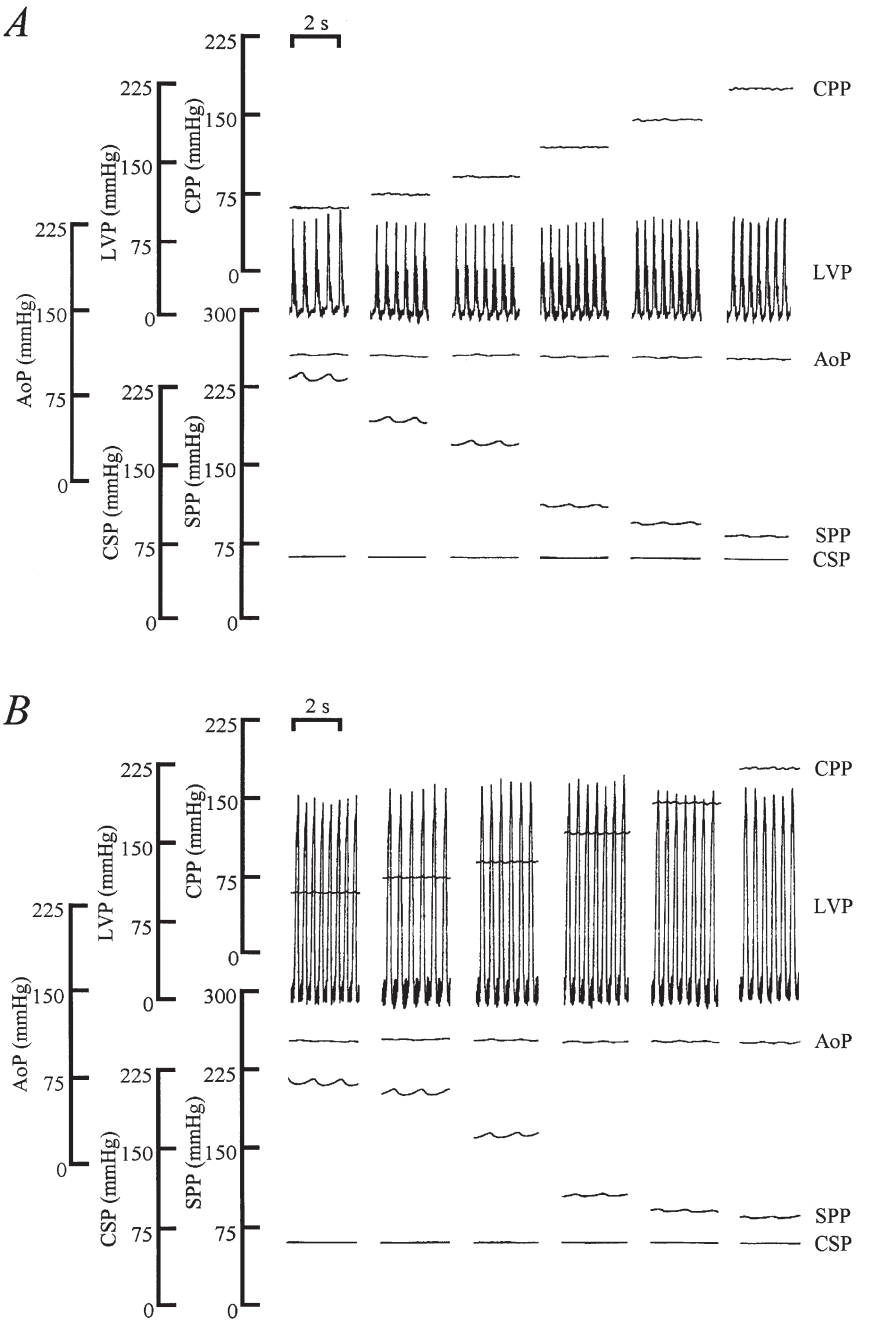

Figure 3

Response of systemic perfusion pressure to stepwise changes in coronary perfusion pressure between 60 and 180 mmHg at low (*A*) and high (*B*) ventricular pressures. Traces are shown of coronary perfusion pressure (CPP), left ventricular pressure (LVP), aortic pouch pressure (AoP), systemic perfusion pressure (SPP) and carotid sinus pressure (CSP). Note the reduction in systemic perfusion pressure at the higher ventricular pressures, at a coronary pressure of 60 mmHg.

Responses to single-step changes in aortic root (coronary arterial) or carotid sinus pressure

In 16 dogs, a step increase in coronary arterial pressure between 63.3 ± 1.0 and 180.5 ± 2.7 mmHg resulted in a decrease in systemic perfusion pressure from 170.7 ± 9.1 to 101.3 ± 6.5 mmHg (−39.2 ± 3.5%; $P < 0.0001$), but no significant change in heart rate (from 175 ± 8 to 176 ± 6 beats min^{-1}; $P > 0.05$, Student's paired t test). In these same animals, increasing carotid sinus pressure between 63.8 ± 0.4 and 194.5 ± 4.3 mmHg decreased systemic perfusion pressure from 139.2 ± 4.1 to 87.2 ± 4.4 mmHg (−36.7 ± 3.2%; $P < 0.0001$) and heart rate from 171 ± 6 to 146 ± 7 beats min^{-1} (−25 ± 6; $P < 0.001$, Student's paired t test).

Responses to changes in coronary pressure at different ventricular pressures

In seven animals coronary pressure was increased in steps of approximately 30 mmHg between 65.4 ± 0.8 and 183.4 ± 0.7 mmHg with ventricular pressures held at the low values of 69.7 ± 4.3 and 12.0 ± 2.2 mmHg (peak and end-diastolic) and the high values of 146.5 ± 12.9 and 40.7 ± 17.6 mmHg. This resulted in step decreases in perfusion pressure from 179.2 ± 15.3 to 100.2 ± 6.3 mmHg (−40.6 ± 7.4%; $P < 0.005$) and at the high pressures from 167.5 ± 15.2 to 99.5 ± 7.0 mmHg (−34.4 ± 7.5%; $P < 0.005$). An example of traces obtained from one of these dogs is shown in Fig. 3 and this emphasises the large responses to changes in coronary pressure and the smallness of the effect of the ventricular pressure. Mean vascular responses are compared in Fig. 4*A*. Overall, vascular responses were significantly ($P < 0.05$) smaller at the higher ventricular pressures, but values of maximum slope, and inflexion and saturation pressures were not different ($P > 0.05$; see Table 1).

Figure 4*B* shows the results from those three animals most responsive to changes in ventricular pressure. At the higher ventricular pressure, the decreases in vascular resistance were smaller (decreasing by 37.3% (range, 21.5–60.8%) compared with 46.7% (32.5–67.1%) at the low ventricular pressures). However, until the responses approached saturation values, the curves were approximately parallel. Values of maximum slope, and inflexion and saturation pressures were similar (see Table 1).

Responses to changes in carotid sinus pressure at low and high ventricular pressures

In eight animals, carotid sinus pressure was increased in 30 mmHg steps between 64.2 ± 0.4 and 243.2 ± 1.0 mmHg at the high and low ventricular pressures. Overall, at the lower ventricular pressures, perfusion pressure and heart rate decreased from 154.4 ± 10.9 to 109.2 ± 9.4 mmHg (−29.4 ± 2.9%; $P < 0.0001$) and from 187 ± 17 to 166 ± 19 beats min^{-1} (−21 ± 5 beats min^{-1}; $P < 0.005$) . At the higher ventricular pressures, perfusion pressure and heart rate decreased from 151.4 ± 10.8 to 105.6 ± 8.5 mmHg (−28.2 ± 3.7%; $P = 0.0001$) and from 182 ± 15 to 161 ± 15 beats min^{-1} (−22 ± 5 beats min^{-1}; $P < 0.005$, Student's paired t test). The responses were not significantly different from those obtained at the lower distension pressures

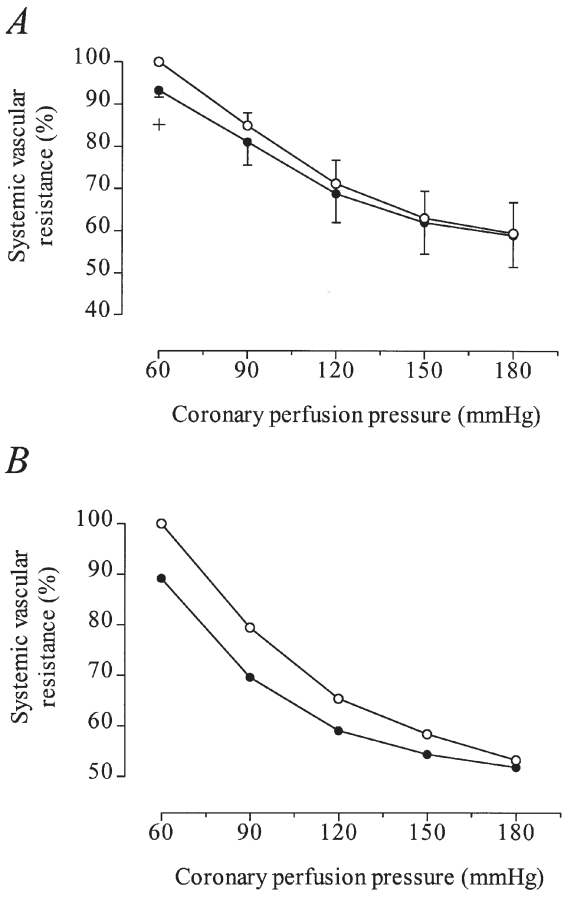

Figure 4

Reflex responses of systemic perfusion pressure to step increases in coronary pressure at low (○) and high (●) ventricular pressures. *A* shows the results from all seven of the animals studied, whereas *B* shows the results from those three animals most responsive to changes in ventricular pressure. Resting levels of perfusion pressure were: *A*, 179.2 ± 15.3 and 167.5 ± 15.2 mmHg; *B*, 174.6 mmHg (range, 141.2–217.8 mmHg) and 156.6 mmHg (122.9–201.8 mmHg) (low and high, respectively). '+' indicates $P < 0.05$, when corresponding values at the low and high ventricular pressures were compared (Student's paired t test). Overall, there was a reduction in the vascular response at the higher ventricular pressures, but there was no difference in maximal slopes (see Table 1). Perfusion pressures are related to the values recorded at the low ventricular pressures that were expressed as 100% and values are presented as means ± S.E.M. (*A*) or means (*B*).

Table 1. Values of maximum slopes, inflexion pressures and saturation pressures for coronary and carotid baroreflexes, at low and high ventricular pressures (LVP)

Baroreceptor	No. of dogs	Slope (mmHg mmHg^{-1})		Inflexion pressure (mmHg)		Saturation pressure (mmHg)	
		Low LVP	High LVP	Low LVP	High LVP	Low LVP	High LVP
Coronary	7	9.5 ± 2.2	10.0 ± 2.6	103.0 ± 4.5	102.8 ± 7.7	157.1 ± 5.5	157.2 ± 7.7
	3	10.0 (7.4–14.6)	9.4 (4.3–16.3)	98.7 (91.1–110.8)	90.1 (85.3–93.0)	157.5 (142.1–170.2)	158.7 (147.5–167.0)
Carotid	8	4.2 ± 0.7	5.4 ± 0.8	151.6 ± 10.0	146.9 ± 13.7	198.1 ± 8.1	201.3 ± 7.9
	3	3.5 (1.9–5.5)	5.4 (3.0–6.7)	174.2 (152.9–187.9)	164.6 (134.5–203.9)	214.6 (200.0–236.8)	208.5 (183.0–240.1)

No significant difference was found when corresponding values at low and high ventricular pressures were compared ($P > 0.05$, Student's paired t test). Numbers in parentheses are ranges and all other values are presented as means ± S.E.M.

($P > 0.05$, Student's paired t test). The responses of perfusion pressure at each step in carotid pressure and at both ventricular pressures are plotted in Fig. 5. Figure 5*A* shows data from all experiments, and clearly the stimulus–response curves overlapped. In Fig. 5*B*, obtained from the more responsive animals, the stimulus–response curves appeared parallel and, unlike the responses to changes in coronary pressure shown in Fig. 4, there was no evidence of convergence. No difference was found between maximal slopes, and inflexion and saturation pressures (see Table 1).

Responses to veratridine at low and high ventricular pressures

Figure 6*A* shows the maximal responses from six animals to the coronary injection of veratridine at the two ventricular pressures. At the low and high levels of ventricular pressure, perfusion pressure decreased from 138 ± 6.5 to 104 ± 6.5 mmHg (−24.2 ± 2.0%; $P < 0.0001$) and from 126 ± 5.2 to 99 ± 7.4 mmHg (−22 ± 3.4%; $P < 0.005$). These responses were not significantly different ($P > 0.05$, Student's paired t test). Heart rate decreased from 190 ± 16 to 158 ±

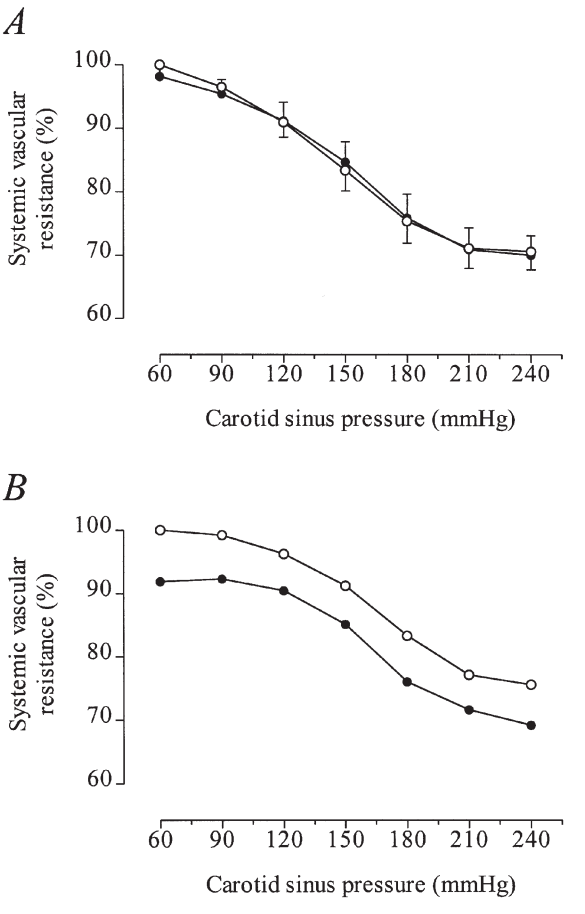

Figure 5

Responses of systemic perfusion pressure to stepwise changes in carotid sinus pressure at low (○) and high (●) left ventricular pressures. *A* shows the results from all eight animals studied and *B* shows the means from three animals most responsive to changes in ventricular pressures. Resting levels of perfusion pressure were: *A*, 154.4 ± 10.9 and 151.4 ± 10.8 mmHg; *B*, 151.0 mmHg (range, 133.2–161.8 mmHg) and 139.3 mmHg (121.7–148.7 mmHg) (low and high, respectively). The results in *B* indicate that at the high ventricular pressures there was a downwards and parallel shift in perfusion pressure, which was not evident in *A*.

12 beats min^{-1} (−32 ± 10 beats min^{-1}; $P < 0.05$) and from 184 ± 11 to 160 ± 17 beats min^{-1} (−24 ± 7 beats min^{-1}; $P < 0.05$) at low and high ventricular pressures, respectively. Although the response at the high ventricular pressure was smaller, it was not significant different ($P > 0.05$, Student's paired *t* test).

Figure 6*B* shows the maximal responses from the three animals most responsive to changes in ventricular pressure. Vascular responses were little different at the different levels of ventricular pressure, perfusion pressure decreased by 22.9% (range, 17.5 to 28.5%) and 18.4% (12.7 to 26.4%) at the low and high levels, respectively. The heart rate response was, however, smaller at the higher ventricular pressures, decreasing by 17 beats min^{-1} (range, 15–21 beats min^{-1}) compared with 43 beats min^{-1} (range, 16–71 beats min^{-1}) at the lower level.

DISCUSSION

Although there have been several previous investigations which attempted to examine interactions between ventricular receptors and baroreceptor reflexes, none has succeeded in applying localised mechanical stimuli to two or more specific regions. This study is the first in which the pressures distending ventricular mechanoreceptors and other reflexogenic areas have been controlled in a discrete manner. We previously showed that the responses even to gross distension of the left ventricle were small and the present study confirms that the ventricle is not of major importance on its own in cardiovascular regulation. Furthermore, the absence of large responses to changes in ventricular pressure could not have been due to the preparation being unresponsive because of near-maximal vasoconstriction or vasodilatation, since the baroreceptor stimulus–response curves virtually overlapped.

Previous work by others has suggested that the stimulation of ventricular receptors decreases the sensitivity of the carotid baroreceptor reflex. However, in those studies in which an interactive effect was claimed to have been shown, only those of ventricular receptors with chemosensitive endings were stimulated (Chen, 1979; Holmberg *et al.* 1983). In fact, even the apparent interactions seen when stimulating the chemosensitive endings may not actually be a true interaction because the reduction of responses may well have been due to limitation of the efferent limb of the reflexes as neurogenic

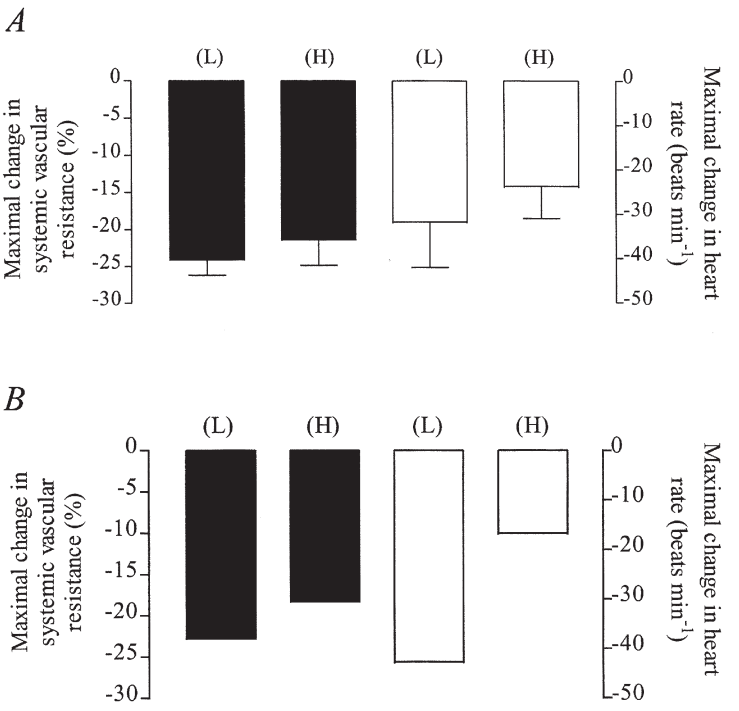

Figure 6

Changes in systemic perfusion pressure (■) and heart rate (□) to the coronary injection of veratridine (30–60 μg) at low (L) and high (H) ventricular pressures. *A* shows the results from all six animals studied and *B* shows the means from those three animals most responsive to changes in ventricular pressures. Resting levels of perfusion pressure and heart rate were: *A*, 138.0 ± 6.5 and 126.0 ± 5.2 mmHg and 190 ± 16 and 184 ± 11 beats min^{-1}; *B*, 147.4 mmHg (range, 135.1–159.2 mmHg) and 125.8 mmHg (range, 110.9–135.6 mmHg) and 220 beats min^{-1} (range, 190–248 beats min^{-1}) and 206 beats min^{-1} (range, 196–220 beats min^{-1}) (low and high, respectively). In all the six animals studied, no significant difference was observed between the maximal responses of vascular resistance or heart rate. In the three more responsive animals, the heart rate response was reduced at the higher ventricular pressures. Absolute changes in heart rate are shown. Responses of perfusion pressure are presented as a change from control conditions (taken as 0%), with values presented as either mean ± S.E.M. (*A*) or means (*B*).

vasomotor activity approaches zero (Tutt *et al.* 1988). The previous attempts to study interactions with ventricular mechanosensitive receptors have all been deficient due to inadequate localisation of the stimulus to the ventricle. These procedures, which involve widespread changes in pressure (Holmberg *et al.* 1983; Ludbrook & Graham, 1984; Holmberg & Zucker, 1986) or even our earlier work in which pressure changes were applied to the aortic root (Tutt *et al.* 1988; Vukasovic *et al.* 1989) must have influenced many other reflexogenic areas, particularly the coronary arterial baroreceptors.

In this study, we observed no evidence of interaction between the ventricular mechanoreceptor reflexes and the carotid baroreflex. Overall, there was almost no difference in the stimulus–response curves to step changes in carotid pressure at high and low ventricular pressures. When we examined responses from the most responsive preparations, it was seen that the stimulus–response relationships remained parallel, indicating that the reflexes summated in a simple arithmetic manner.

The possibility of interaction between ventricular and coronary mechanoreflexes has not been examined before and the results do seem at first sight to indicate that there may be a slight depression of the responses to coronary baroreceptor reflexes at the higher ventricular pressure. There was a significant difference between the perfusion pressures at the low coronary pressure and the different ventricular pressures. The overall response to the entire change in coronary pressure was smaller at the high ventricular pressures, showing that the curves converged. This was even better seen in the more responsive preparations. However, we would argue that this too represents simple arithmetic summation. Firstly, there was no difference in the maximum slopes of the coronary response curves at the different ventricular pressures. Also, the responses to the coronary reflex in this group were very large, considerably larger than those to the carotid reflex, and what is likely to explain the convergence of the curves is simply that the responses were near maximal: sympathetic activity to the resistance vessels was approaching zero and could not decrease further.

The possible interaction between the ventricular mechanoreceptor reflexes and chemosensitive receptor reflex was examined in a different way. It was not possible to apply graded stimuli to chemosensitive afferents because repeated stimuli are known to cause tachyphylaxis, leading to a large depression of the responses (Cramer, 1915; Dawes & Comroe, 1954; Hainsworth *et al.* 1989; Hainsworth, 1991). To avoid this problem we stimulated the chemosensitive afferents by bolus injections of veratridine into the aortic root, allowed a period of at least 10 min between successive injections, and bracketed tests at one ventricular pressure with paired tests at the other. The results obtained show that both vascular and cardiac responses were not significantly affected by ventricular pressure. The cardiac responses in the three preparations that were most sensitive to ventricular pressure changes were consistently smaller at the high ventricular pressure (mean change, 17 *versus* 43 beats min^{-1}). The dose of veratridine and the coronary perfusion pressure were the same so the applied stimuli are likely to have been similar. With only one dose, it is clearly impossible to construct a stimulus–response curve so we cannot be certain that the reduction in response was not due to non-linearity of the efferent limb of the reflex. However, heart rate did not approach minimal levels so it does seem possible that there could have been an interactive effect. It is clearly not possible to know at what part of the reflex arc interaction may have occurred. However, one possibility is that it may have occurred at the sensory receptor itself. Previous work has shown that, although some ventricular receptors are predominantly mechanosensitive and some are mainly chemosensitive, there are many which respond to both stimuli (Coleridge *et al.* 1964; Sleight & Widdicombe, 1965) and it is conceivable that if these were stimulated by a high distending pressure there may have been less scope for a further increase when chemical agents were applied.

The importance of this study is that it has reinforced the view that ventricular mechanoreceptors are unlikely to be of importance as physiological regulators. We previously showed that whatever stimuli were applied, changes in systolic pressure, end-diastolic or inotropic state, responses were always small (Drinkhill *et al.* 2001). Indeed, it was only when diastolic pressure increased abnormally that any significant responses were obtained at all. This study has not only confirmed those earlier findings but has shown that responses were unlikely to have been 'masked' by other reflexes. We believe that, although essentially a negative finding, the implications of this work are not inconsiderable. The previous widely held view was that ventricular receptors were important regulators, being important for mediating responses to intra-thoracic blood volume changes (Aviado & Schmidt, 1959; Salisbury *et al.* 1960; Ross *et al.* 1961; Mark *et al.* 1973; Chevalier *et al.* 1974; Zelis *et al.* 1977) and even responsible for initiating vaso-vagal responses (Öberg & Thorén, 1972; Abboud, 1989). Other mechanisms must now be sought to explain responses not due to sinoaortic baroreceptors. Stimulation of baroreceptors in the coronary arteries can go a long way to explaining responses previously thought to be due to ventricular receptors but changes in pressure in vessels in other regions of the circulation such as abdominal arteries or veins (Drinkhill *et al.* 1997) may prove to be of greater importance than has hitherto been recognised.

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