Urinary bladder distension: its effects on carotid baroreceptor reflex left ventricular inotropic response in the dog

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1. The effects of distension of the urinary bladder on heart rate, maximum rate of change of left ventricular pressure (dP/dt max) and hindlimb vascular resistance together with their modulation at different carotid sinus pressures were studied in dogs anaesthetized with a mixture of chloralose and urethane and artificially ventilated.

2. When the carotid sinus mean perfusion pressure was raised in randomly selected steps from 60 to 210 mmHg, it caused a progressive bradycardia, and a reduction in left ventricular dP/dt max and in arterial blood pressure, together with vasodilatation in the perfused hindlimb. Distension of the bladder at each level of carotid sinus pressure resulted in tachycardia, a small but significant increase in left ventricular dP/dt max (160 ± 30 mmHg s^{-1}) and hindlimb vasoconstriction.

3. When heart rate and arterial blood pressure were held constant to exclude these secondary effects on left ventricular dP/dt max, raising the carotid sinus pressure caused a progressive reduction in left ventricular dP/dt max and hindlimb vasodilatation. Superimposition of tests of bladder distension at each level of sinus pressure resulted in variable responses, but overall there was a significant increase in left ventricular dP/dt max of 190 ± 54 mmHg s^{-1}. Hindlimb vasocontriction, however, was a consistent finding.

4. The gain of the relationship between the carotid sinus perfusion pressure and left ventricular dP/dt max was unaffected by distension of the bladder.

5. It is concluded that, when changes secondary to increases in heart rate and blood pressure are prevented, distension of the bladder causes a small but significant reflex increase in left ventricular dP/dt max. The responses, however, are variable and the possible reasons for this are discussed.

Distension of the urinary bladder causes a reflex acceleration of the heart, the efferent limb of this reflex involving vagal and sympathetic pathways (Taylor, 1968; Daly & Wood, 1982, 1983; Daly, Ward & Wood, 1985; Hassan, Hicks, Walters & Mary, 1987*a*, *b*; Ramadan, Drinkhill & Mary, 1989). The same pathways are involved in the accompanying reflex increase in coronary vascular resistance (Cevese, Drinkhill, Mary, Patel, Schena & Vacca, 1991).

The present investigation was carried out to determine the effect on the maximum rate of change of left ventricular pressure (dP/dt max) of distension of the urinary bladder, this measurement being a sensitive index of left ventricular contractility (Furnival, Linden & Snow, 1970).

In a previous study by us it was found that distension of the bladder modified the relationship between the pressure in the isolated perfused carotid sinus regions and the hindlimb vascular response (Daly *et al.* 1993). Since altering the carotid sinus pressure is known to cause reflex changes in left ventricular dP/dt max (Hainsworth & Karim, 1973; Hainsworth, McGregor, Rankin & Soladoye, 1984), we have also made a study of the effects of distension of the bladder on this relationship.

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Some of our results have been reported briefly elsewhere (Daly *et al.* 1985).

METHODS

The experiments were performed on mongrel dogs of either sex, the weights being recorded in Table 1. After premedication with morphine hydrochloride (1–2 mg kg^{-1} s.c.), the animals were anaesthetized with a mixture of 2% α-chloralose (56 mg kg^{-1}; Kuhlmann, Paris) and 20% urethane (560 mg kg^{-1}; Merck Ltd, Lutterworth, Leicestershire, UK) dissolved in 85 parts sodium chloride (154 mM) and 15 parts polyethylene glycol (molecular weight, 200; Carbowax; Union Carbide Ltd, Rickmansworth, Hertfordshire, UK).

Rectal temperature was monitored throughout each experiment and maintained between 36 and 39 °C. Penicillin (1 million i.u. I.V.; Crystapen; Glaxo Laboratories Ltd, Uxbridge, Middlesex, UK) was given at the beginning of each experiment.

The essential features of the experimental preparation are shown in Fig. 1 and were described in detail by Daly *et al.* (1993). Only the essential details are therefore briefly described here.

Respiration

Positive pressure ventilation was applied continuously by means of a Starling 'Ideal' pump (C. F. Palmer Ltd) at a rate of 20 cycles min^{-1}. The tidal volume was adjusted to maintain the arterial CO_2 pressure (P_{a,CO_2}) at 35–40 mmHg. An end-expiratory pressure of 3–5 cmH_2O prevented complete collapse of the lungs. In all experiments, oxygen enriched air was administered (inspired O_2 fraction (F_{I,O_2}), approximately 0·4).

Arterial blood pressure

In some experiments, the arterial pressure was maintained at a constant level by connecting a pressurized reservoir of blood to the systemic circulation of the animals via cannulae in two or more arteries pointing towards the heart. The two perfusion pumps (Fig. 1) drew blood from the reservoir, which ensured continuous mixing of blood between the reservoir and the animal.

The blood used to prime the extracorporeal system was taken from a donor animal up to 7 days previously and treated as described elsewhere (Daly *et al.* 1993).

Perfusion of the carotid sinuses

Both carotid sinus regions were vascularly isolated and perfused with blood from the blood pressure control system at constant flow with a pulsatile pressure, as described previously (Daly *et al.* 1993). The perfusion pressure, initially set at about 110 mmHg, was measured from the side-arm of the inflow cannula to the two common carotid arteries.

Perfusion of the left hindlimb

The left vascularly isolated hindlimb was perfused at constant flow through the femoral artery with arterial blood from the blood pressure control system by means of a roller pump (type MHRE 200; Watson-Marlow Ltd, Falmouth, Cornwall, UK). Details of the method, including the measurement of inferior vena caval pressure, have been described by Daly *et al.* (1993).

With constant-flow perfusion of the limb, changes in the hindlimb pressure gradient (the difference between femoral artery mean perfusion pressure and inferior vena caval pressure) were used as an index of changes in hindlimb vascular resistance.

Distension of the urinary bladder

A wide-bore cannula, with a side-arm for pressure measurement, was tied into the wall of the bladder at its apex through a mid-line abdominal incision, and connected to a reservoir containing sodium chloride solution (154 mM) at a temperature of 37 °C.

Measurement of left ventricular dP/dt max

The chest was opened in the fourth left intercostal space and in some animals the fifth rib was removed. Left ventricular pressure was measured in one of two ways: (1) after opening the pericardium, a stainless steel needle (bore, 2·5 mm; length, 12 cm) was introduced into the left ventricle via the apex of the heart. The pressure was measured by a strain gauge manometer (type P23Gb; Statham Instruments Inc., Hato Rey, Puerto Rico). (2) A catheter-tip manometer (implantable pressure transducer, type 12cr/4F; Gaeltec Ltd, Duntegan, Isle of Skye, UK) was inserted into the left ventricle via the left atrial appendage.

The output from the manometers was amplified and differentiated electrically. The pressure signal and its differential were recorded on a direct-writing ultraviolet light recorder (model SE2000 or SE2100; SE Laboratories Ltd, Feltam, Middlesex, UK). The manometers were calibrated statically against a mercury manometer, and when using the stainless steel needle–manometer system, zero reference pressure was obtained postmortem with the tip of the needle exposed to air *in situ*. The frequency response of the catheter–manometer system used in method (1) and of the catheter-tip manometer in method (2) was determined by applying a square-wave pressure transient as described by Fry (1960), and was found to be flat (± 5%) to 75 and 400 Hz, respectively.

A switched precision calibrator built into the amplifier and differentiator circuits enabled steady ramp functions to be applied to the differentiator to give calibration signals of 2000, 5000 and 10 000 mmHg s^{-1}.

The frequency response of the differentiator was assessed by applying a sine-wave input voltage from a signal generator. A Bode plot (log gain *versus* log frequency) was constructed and showed a critical frequency of 300 Hz. The differentiator gave a linear response (± 5%) up to a frequency of 130 Hz.

Cardiac pacing

When necessary, heart rate was maintained constant by electrical pacing through an electrode (a silver-plated fetal ECG electrode; Rolon; disposable fetal scalp electrode; Surgicraft Ltd, Redditch, Worcestershire, UK) fixed to the left or right atrial appendage. Typical pacing parameters were 15 V and 2 ms pulse duration, the frequency being set to slightly higher than that expected during the test period (Grass S88 Stimulator; Grass Medical Instruments).

After completion of the surgical procedures and before connecting the perfusion circuits, clotting of the blood was prevented by giving heparin (Pularin; 1500 i.u. kg^{-1} I.V.; Evans Medical Ltd, Horsham, West Sussex, UK).

Measurement of variables

All other variables were recorded on either a direct-writing ultraviolet light recorder (model 2100; S.E. Laboratories) or a hot-stylus recorder (M19 8-channel recorder; Devices Instruments Ltd, Welwyn Garden City, Hertfordshire, UK). Arterial, carotid sinus, hindlimb and inferior vena caval pressures were measured using strain gauges (Model P23Gb, Statham Instruments Inc., and Type 4-422-0001, Bell and Howell Ltd, Basingstoke, Hampshire, UK). The frequency response of the catheter–manometer systems for

the measurements of arterial pressure and carotid sinus pressure, determined as described by Fry (1960), were flat (± 5%) up to 22 and 12 Hz, respectively. Zero reference pressures were obtained postmortem with the catheter tips exposed to air *in situ*.

Blood gas analysis

At regular intervals during each experiment, arterial blood P_{O_2}, P_{CO_2}, pH and haematocrit were determined. Metabolic acidosis was corrected with an intravenous infusion and/or bolus injections of molar sodium bicarbonate solution.

Drugs

The following drugs were used: atenolol, a cardioselective β-blocker (ICI Pharmaceuticals, UK) and isoprenaline sulphate (Martindale Pharaceuticals, Romford, Essex, UK).

Experimental procedure

In the first series of experiments in which the carotid sinus pressure was not separately controlled, the pressure of the blood pressure control system was set to a level equal to the prevailing systemic blood pressure of the animal. The bladder was

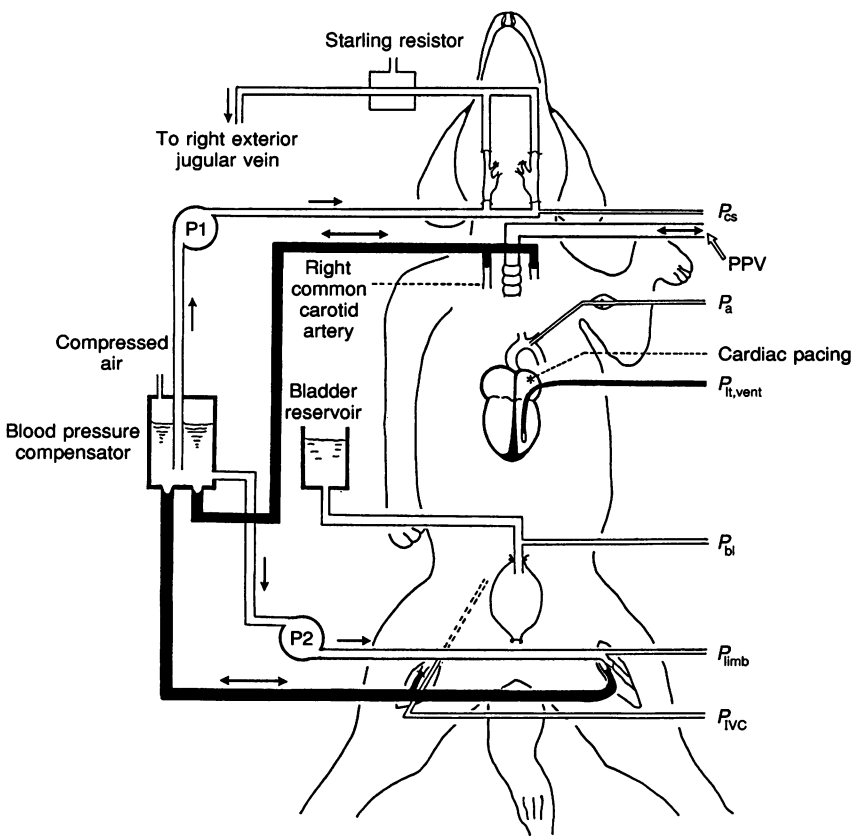

Figure 1. Diagrammatic representation of methods used for perfusion of the vascularly isolated carotid sinuses and of the vascularly isolated hindlimb, the measurement of left ventricular pressure and distension of the bladder

The chest was open and the dog ventilated artificially with positive pressure (PPV). Both carotid sinuses were perfused with blood supplied from the blood pressure compensator at a constant pulsatile flow by pump P1. Blood leaving the carotid sinus regions by the cannulated external carotid arteries was returned to the right external jugular vein via a Starling-type resistor, by which the carotid sinus mean pressure was controlled. The left hindlimb was vascularly isolated as described previously (Daly *et al.* 1993) and perfused through its femoral artery by pump P2, which was fed with blood from the blood pressure compensator, which was itself connected to both femoral and, in some experiments, also to both common carotid arteries. Blood pressure was controlled using the blood pressure compensator, which was filled with warm heparinized blood and maintained at the required pressure by a compressed air–air leak bypass system. The apex of the urinary bladder was cannulated and connected to a reservoir (bladder reservoir) containing sodium chloride solution (154 mM) maintained at a temperature of 37 °C. The following variables were measured: P_{CS}, carotid sinus pressure; P_a, arterial blood pressure from which the heart rate was obtained; $P_{lt,vent}$, left ventricular pressure from which left ventricular dP/dt max was derived; P_{bl}, urinary bladder pressure; P_{limb}, hindlimb perfusion pressure; and P_{IVC}, inferior vena caval pressure. For further details see text.

Table 1. Initial control values at the start of the experimental period, before blood pressure compensation or cardiac pacing, for blood gas, respiratory and cardiovascular variables

	CSP not controlled	CSP controlled, P_a controlled during bladder distension	CSP controlled, P_a controlled throughout
No. of animals	7	7	4
Body weight (kg)	14·8 ± 3·8	14·5 ± 3	16·8 ± 4·5
Mean P_a (mmHg)	122 ± 10	86 ± 18	104 ± 11
Heart rate (beats min^{-1})	105 ± 26	108 ± 25	161 ± 32
Arterial blood			
P_{O_2} (mmHg)	117 ± 30	114 ± 13	98 ± 4
P_{CO_2} (mmHg)	40 ± 4	41 ± 4	39 ± 2
pH	7·38 ± 0·06	7·39 ± 0·02	7·39 ± 0·04
Haematocrit (%)	46 ± 4	44 ± 3	46 ± 8
Rectal temperature (°C)	37·6 ± 1·0	37·2 ± 0·7	36·8 ± 0·6
LV end-diastolic pressure (mmHg)	6 ± 2	4 ± 2	8 ± 5
LV dP/dt max	3680 ± 600	3660 ± 1640	5290 ± 2380

Values are means ± S.D. CSP, carotid sinus pressure; P_a, arterial blood pressure; LV, left ventricular.

temporarily distended by raising the height of the bladder reservoir. Peak values were reached in 20–60 s, at which time all measurements were taken. The test was repeated at the same bladder distension pressure with the heart electrically paced at a rate higher than the maximum rate occurring during the previous bladder distension test. The tests were repeated both with and without cardiac pacing at several other bladder pressures up to 70 mmHg.

In the remaining two series of experiments, the carotid sinus regions were vascularly isolated and perfused at constant mean pressure with pulsatile flow. The carotid sinus mean pressure was initially set at the same level as the arterial pressure. When the cardiovascular variables had stabilized, the femoral arterial mean perfusion pressure was adjusted to the same pressure by altering the pump output, after which time the hindlimb blood flow was held constant.

The Starling resistor (Fig. 1) was then set to give carotid sinus mean pressures of 60, 90, 120, 150, 180 or 210 mmHg, which were selected in random order. In the second series of experiments, following each change in carotid sinus pressure the blood pressure was allowed to change with alterations in carotid sinus pressure but was then held constant at each carotid sinus pressure as the bladder was distended. When the cardiovascular variables had reached steady levels at a given carotid sinus pressure, usually after 0·5–1 min, the bladder was temporarily distended. Peak values were reached after 20–60 s, at which time all measurements were taken. In some experiments, pairs of tests were carried out both with and without cardiac pacing.

The third series of experiments were similar to the second except that blood pressure was held constant at about 100 mmHg at all carotid sinus pressures and heart rate was held constant by pacing. In this way, the observed changes in left ventricular dP/dt max were independent of alterations in heart rate and blood pressure.

Analysis of results

All values are expressed as means ± S.E.M. unless otherwise stated. Student's t test was used to evaluate the significance of the difference between sets of paired observations. Values were taken as being significantly different if $p < 0·05$.

In experiments in which responses were studied at different bladder distension pressures, regression lines from individual experiments were fitted by the method of least squares. The common slope of the slopes from individual experiments was calculated and its significance assessed by analysis of variance for the pooled data (Armitage & Berry, 1987).

RESULTS

The weights of the animals and the initial control values for the respiratory and cardiovascular variables and arterial blood gases in the three groups of experiments are shown in Table 1. In all experiments, arterial O_2 pressure (P_{a,O_2}) was greater than 90 mmHg.

Cardiovascular responses to bladder distension at different pressures

Blood pressure was controlled throughout at the initial blood pressure of the animal during tests of bladder distension, which were performed first without, and then with, the heart rate controlled by cardiac pacing.

In thirty-seven of forty-two tests of bladder distension in seven dogs, in which heart rate was unpaced, there was an increase in left ventricular dP/dt max; there was no change in two tests, and a decrease in the remaining three (Fig. 2*A*). The slopes of the individual regression lines of

left ventricular dP/dt max against bladder pressure were not significant ($p > 0{\cdot}05$) except for dog no. 20 in which left ventricular dP/dt max increased as the bladder pressure was increased ($p < 0{\cdot}01$). However, analysis of variance of the seven regression lines gave a common slope of 16·3 mmHg s^{-1} $mmHg^{-1}$, which was significantly different from zero ($p < 0{\cdot}02$). The slopes of the individual lines were not significantly different from each other ($p = 0{\cdot}07$).

In thirty-seven tests in six dogs with paced heart rate, bladder distension resulted in an increase in dP/dt max in twenty-seven tests; a decrease occurring in the remaining ten tests (Fig. 2*B*). In all but one dog, the relationship between left ventricular dP/dt max and bladder pressure was not significant. In dog no. 20, the slope of the regression line was significantly different from zero ($p < 0{\cdot}01$). Analysis of variance of the six regression lines gave a common slope (3 mmHg s^{-1} $mmHg^{-1}$), which was not significantly different from zero ($p = 0{\cdot}4$) with no significant difference in the slopes of the individual lines ($p = 0{\cdot}3$). There was a significant difference, however, in the position of the individual lines ($p < 0{\cdot}001$).

These variable left ventricular dP/dt max responses contrast with the consistent hindlimb vascular responses to bladder distension. In all tests (42 without and 37 with cardiac pacing) bladder distension gave rise to hindlimb vasoconstriction. Analysis of variance of the seven regression lines gave a common slope of 0·74 mmHg (hindlimb perfusion pressure) $mmHg^{-1}$ (bladder pressure) ($p < 0{\cdot}001$), with some indication of a difference between the individual slopes ($p < 0{\cdot}05$).

Figure 3 shows the records from a pair of representative experiments. In Fig. 3*A–C*, a test was carried out with blood pressure controlled but without cardiac pacing. Bladder distension to 40 mmHg caused an increase in heart rate, from 132 to 192 beats min^{-1}, and left hindlimb vasoconstriction as shown by an increase in perfusion pressure, from 118 to 143 mmHg, with no change in inferior vena caval pressure. Left ventricular dP/dt max increased from 3480 to 4500 mmHg s^{-1}. However, with the heart electrically paced at 216 beats min^{-1} and the blood pressure controlled throughout, bladder distension to 40 mmHg caused hindlimb vasoconstriction as before but only a very small increase in left ventricular dP/dt max (from 3980 to 4080 mmHg s^{-1}; Fig. 3*D–F*).

Response to bladder distension at different levels of carotid sinus pressure

Two series of experiments were carried out in which a standard rise in bladder pressure of 47·8 ± 6·0 mmHg (mean ± S.D.) was used to study the effects at different levels of pressure in the vascularly isolated carotid sinus regions.

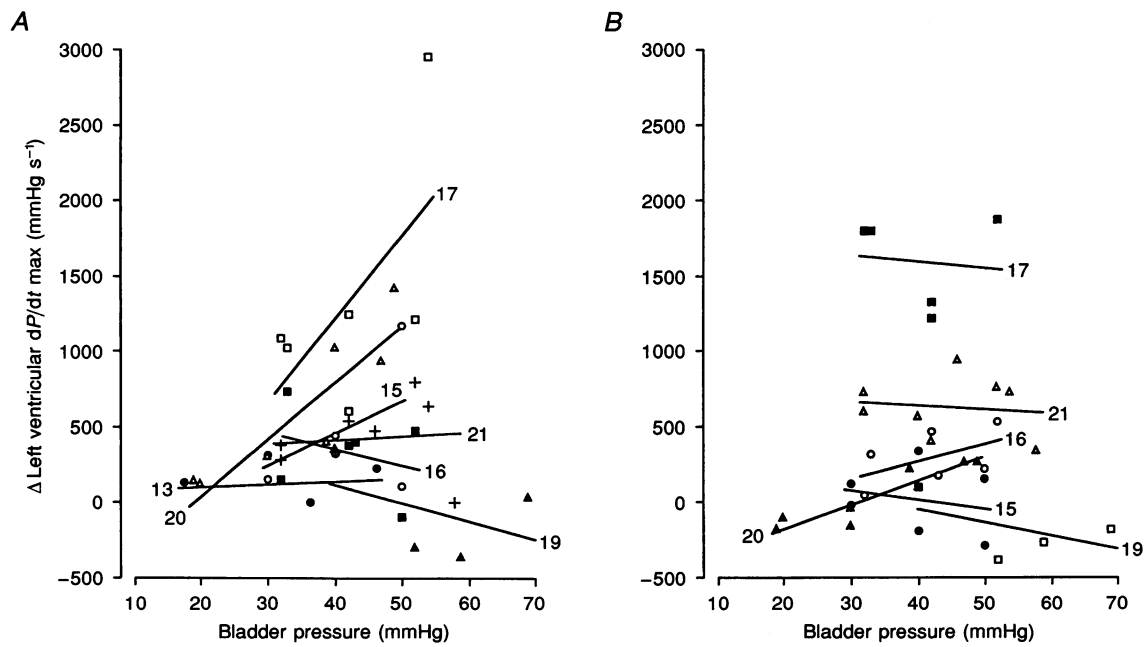

Figure 2. Effects of distension of the bladder to different pressures on left ventricular dP/dt max

The effects were studied with blood pressure controlled and heart rate free to change (*A*) and blood pressure controlled and heart rate maintained constant by electrical pacing (*B*). Each symbol represents results obtained from one dog. Regression lines, calculated by the method of least squares, are shown for each of the seven dogs. The identification number of each dog is shown.

Blood pressure controlled only during each bladder distension test

Blood pressure was maintained constant at the new prevailing blood pressure level following each change in carotid sinus pressure. Paired tests of bladder distension, first without and then with cardiac pacing, were carried out at each level of carotid sinus pressure. The results are summarized in Fig. 4.

With each 30 mmHg stthere was a fall in blood pressure in unpaced tests and in tests with cardiac pacing (Fig. 4). Superimposition of tests of distension of the bladder at each of the six levels of carotid sinus pressure resulted in a small but significant increase in blood pressure in unpaced tests (mean, 3·6 ± 0·5 mmHg; range, −8 to +18 mmHg; $n = 95$; $p < 0·001$) and in tests with cardiac pacing (mean, 2·1 ± 0·5 mmHg; range, −10 to +13 mmHg; $n = 90$; $p < 0·001$), even though the blood pressure control system was used.ep increase in carotid sinus pressure,

Raising the carotid sinus pressure caused only a small reduction in heart rate, as found previously (Daly *et al.* 1993) (Fig. 4). Distension of the bladder increased the heart rate by 14 ± 1 beats min^{-1} (range, −6 to +36 beats min^{-1}; $n = 95$ in 7 dogs; $p < 0·001$).

The right-hand panel of Fig. 4 shows the mean heart rates in the ninety tests of bladder distension in which the heart was electrically paced. As far as possible, the same pacing frequency was used in all tests in the same dog. Lower frequencies were sometimes necessary at a carotid sinus pressure of 210 mmHg to prevent pulsus alternans or other arrhythmias. However, the paced heart rate was always the same during bladder distension as during the control periods before and after distension.

Left ventricular dP/dt max. The pooled results from the tests carried out without cardiac pacing are shown in Fig. 4 (left-hand panel). As the carotid sinus pressure was raised from 60 to 210 mmHg, there was a progressive fall in left

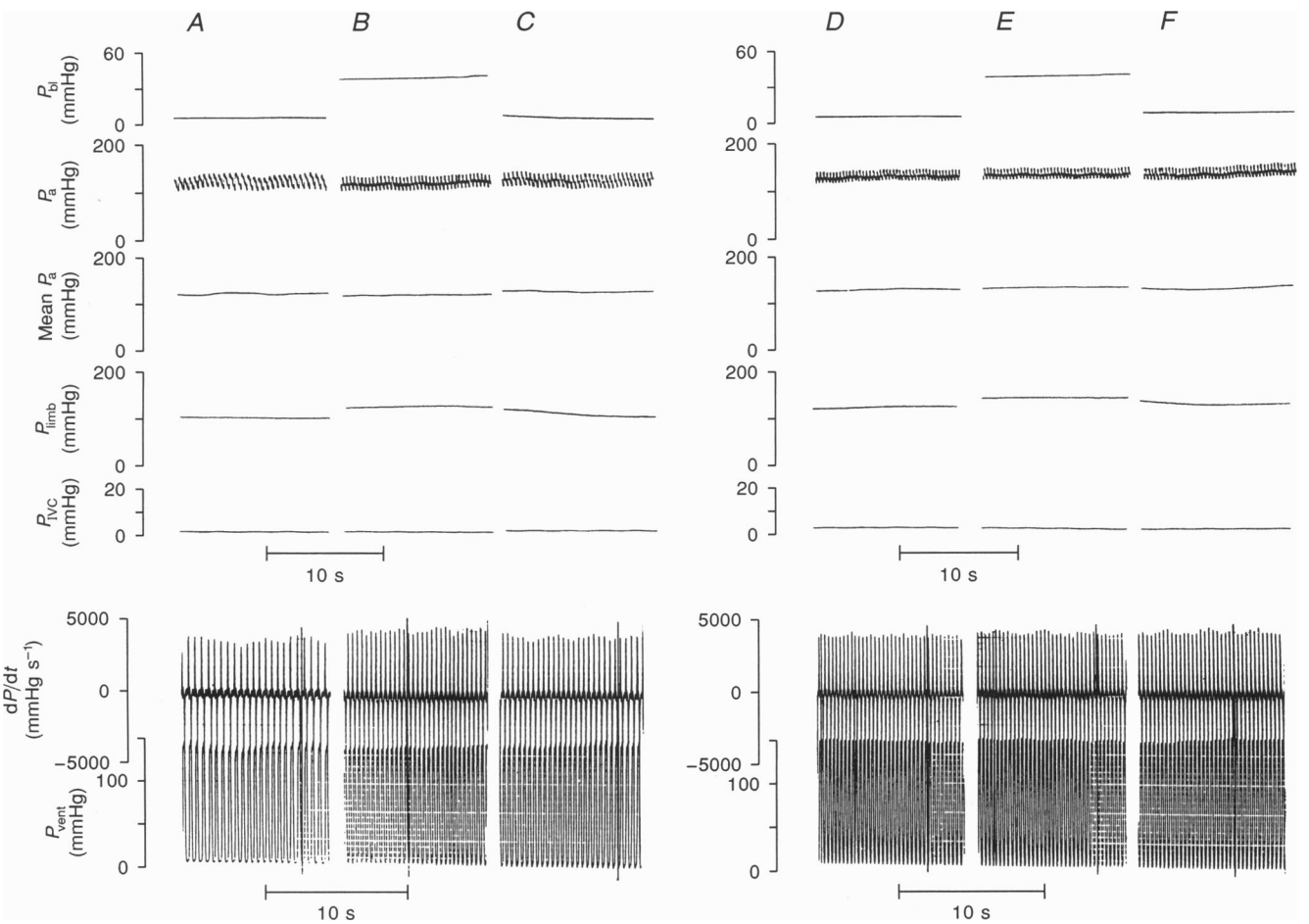

Figure 3. Effects of distension of the bladder

A–C, blood pressure controlled, heart rate free to change; *D–F*, blood pressure controlled and heart paced at 216 beats min^{-1}. Panels show control records before (*A* and *D*) and 25 s after (*C* and *F*) distension of the bladder to 40 mmHg (*B* and *E*; records taken 35 s into the tests). Records from above: P_{bl}, bladder pressure; P_a and mean P_a, phasic and mean arterial blood pressure, respectively; P_{limb}, left hindlimb perfusion pressure; P_{IVC}, inferior vena caval pressure (recorded on a Devices hot-stylus recorder); P_{vent}, left ventricular pressure and its differential dP/dt (recorded on an ultraviolet light recorder).

ventricular dP/dt max ($n = 15$; $p < 0{\cdot}001$). Distension of the bladder caused an increase in left ventricular dP/dt max in sixty-seven of the ninety-five tests, a decrease in twenty-two tests and no change in six tests. Overall in ninety-five tests at six different carotid sinus pressures, bladder distension caused a small increase in left ventricular dP/dt max of 160 ± 38 mmHg s^{-1} (range, -1220 to $+1260$ mmHg s^{-1}; $p < 0{\cdot}001$). At each different

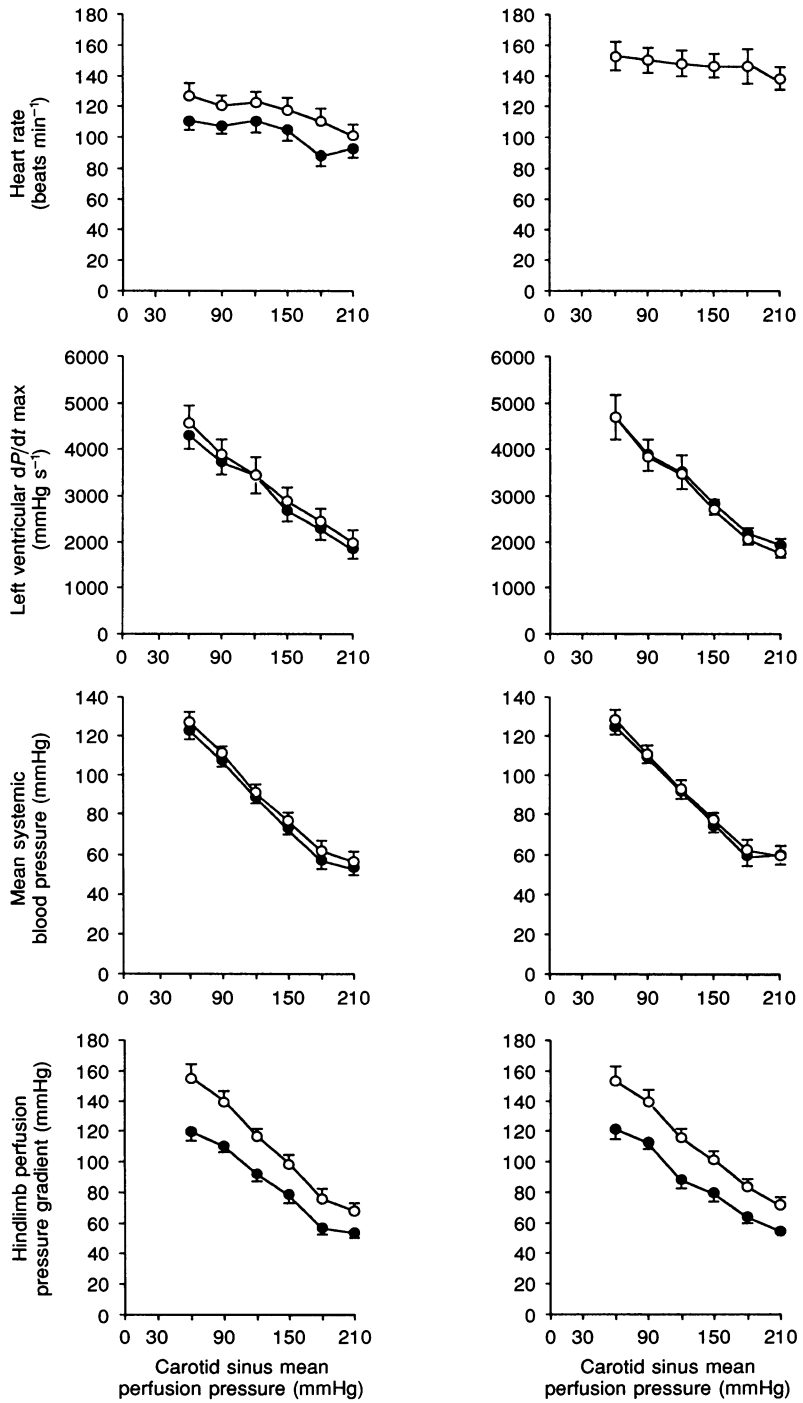

Figure 4. Effects of distension of the bladder on the relationship between carotid sinus mean pressure and heart rate, left ventricular dP/dt max, mean systemic blood pressure and hindlimb perfusion pressure gradient and the effects of distension of the bladder

Left-hand panels, blood pressure controlled only during bladder distension, with no cardiac pacing. Right-hand panels, blood pressure controlled only during bladder distension, with cardiac pacing. ●, control period before bladder distension; ○, bladder distension at the time of the peak hindlimb vascular response. Values are means ± S.E.M. ($n = 12$–17 observations in 7 dogs).

carotid sinus pressure, the mean left ventricular dP/dt max was higher during bladder distension than during the control period, but this was only significant at carotid sinus pressures of 150, 180 and 210 mmHg ($p < 0{\cdot}01$, $p < 0{\cdot}05$ and $p < 0{\cdot}05$, respectively; Fig. 4).

When the heart was paced during the period of bladder distension, raising the carotid sinus pressure evoked, as in the unpaced tests, a progressive fall in mean left ventricular dP/dt max. (Fig. 4; right-hand panel; $n = 14$; $p < 0{\cdot}001$). In thirty-one of the ninety tests of bladder distension at the six different levels of carotid sinus pressure, left ventricular dP/dt max increased; in fifty-two tests it decreased and in the remaining seven there was no change. The mean change in left ventricular dP/dt max at each carotid sinus pressure was a small increase (29 ± 69 mmHg s^{-1}) at a carotid sinus pressure of 60 mmHg and a small decrease at the other five carotid sinus pressures (-44 ± 47, -68 ± 51, -138 ± 104, -142 ± 56 and -144 ± 74 mmHg s^{-1} at carotid sinus pressures of 90, 120, 150, 180 and 210 mmHg, respectively). Overall, pooling the results from the ninety tests at six different carotid sinus pressures there was a small but significant fall in the left ventricular dP/dt max during bladder distension (-83 ± 29 mmHg s^{-1}; $p < 0{\cdot}01$; range, -1420 to $+740$ mmHg s^{-1}). In eighty-five of the ninety tests, the magnitude of the change was between -500 and $+500$ mmHg s^{-1}.

Left ventricular end-diastolic pressure. Distension of the bladder without cardiac pacing resulted in no significant change in left ventricular end-diastolic pressure ($0{\cdot}1 \pm 0{\cdot}1$ mmHg; range, -3 to $+4$ mmHg; $n = 95$; $p = 0{\cdot}32$); during pacing there was a fall of $0{\cdot}3 \pm 0{\cdot}1$ mmHg ($n = 90$; range, -2 to $+3$ mmHg), which was statistically significant ($p < 0{\cdot}02$).

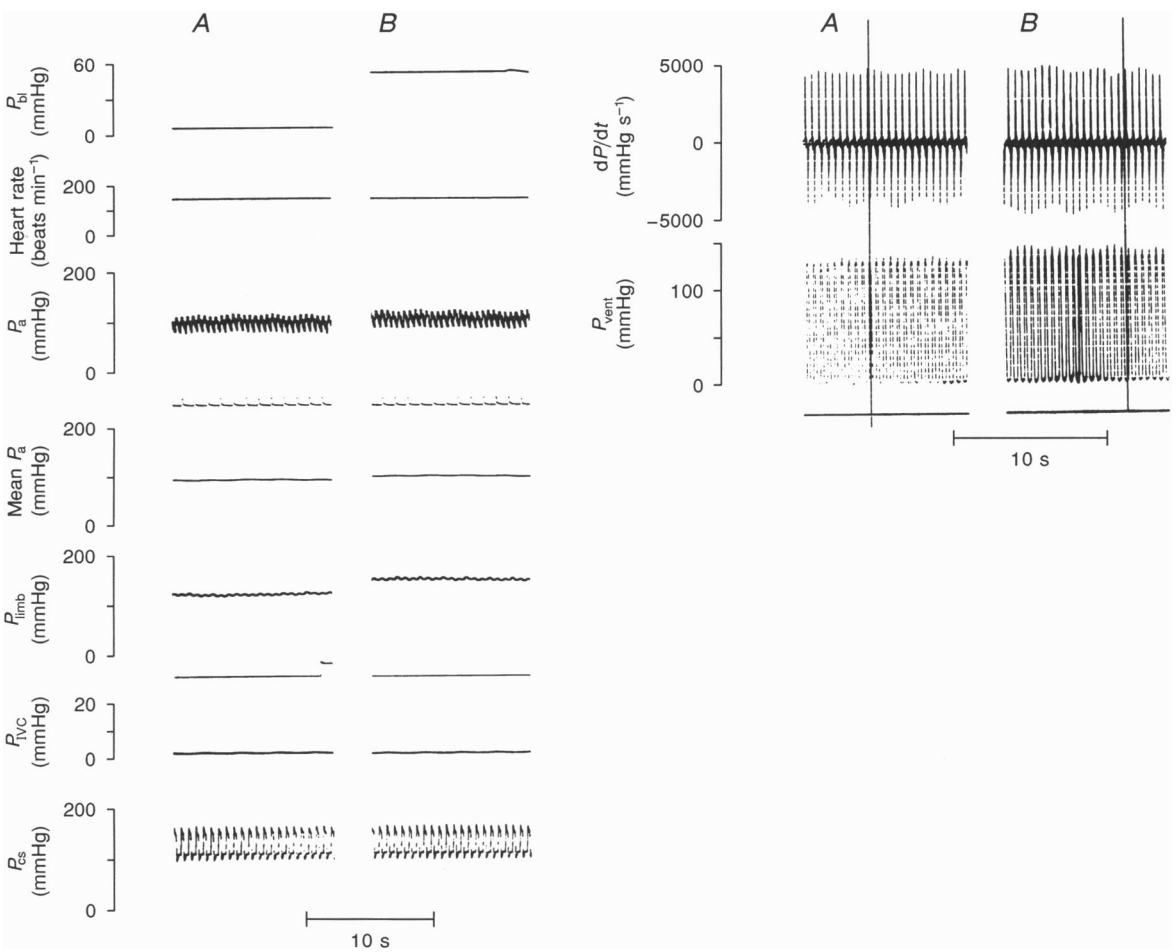

Figure 5. Effects of bladder distension in a test in which the blood pressure was held constant at about 100 mmHg and the heart paced at 138 beats min^{-1}

Records in *A* and *B* were taken simultaneously. *A*, control period immediately preceding bladder distension; *B*, approximately 30 s after the start of bladder distension to 49 mmHg. Traces on the left were recorded on a Devices hot-stylus recorder. Traces on the right were recorded on an ultraviolet light recorder. See legends to Figs 1 and 3 for symbols.

Figure 5 shows an example of a test of bladder distension of 49 mmHg in an experiment in which heart rate was controlled at 138 beats min^{-1} and the carotid sinus pressure (at 120 mmHg) and arterial blood pressure (at 100 mmHg) were held constant. There was no effect on the left ventricular dP/dt max or on left ventricular end-diastolic pressure, but vasoconstriction occurred as shown by a rise in hindlimb perfusion pressure from 120 to 150 mmHg with no change in inferior vena caval pressure.

Blood pressure controlled at all carotid sinus pressures and during tests of bladder distension

The mean control blood pressure was 102 ± 1 mmHg and this increased during bladder distension by 0·1 ± 0·3 mmHg (range, −5 to +7 mmHg), which was not significantly different from zero ($n = 59$ in 4 animals; $p = 0·67$; Fig. 6). At each carotid sinus pressure, the mean values for heart rate during the control period and during distension of the bladder were identical. However, it was sometimes necessary to use a lower pacing frequency at the two highest carotid sinus pressures (180 and 210 mmHg) to avoid pulsus alternans or other arrhythmias.

Left ventricular dP/dt max. Raising carotid sinus pressure in 30 mmHg steps resulted in a progressive reduction of left ventricular dP/dt max ($n = 10$; $p < 0·001$; Fig. 6). Superimposition of tests of distension of the bladder had variable effects on left ventricular dP/dt max. In the majority of tests (42 of 59) there was an increase in left ventricular dP/dt max; there was a decrease in sixteen, and no change in the remaining test. The responses ranged from an increase of 1240 mmHg s^{-1} to a decrease of 1200 mmHg s^{-1}, but in 90% of tests the changes ranged from +600 to −600 mmHg s^{-1}. The responses varied not only between animals but within the same animal at different stages of the experiment. From the pooled results, the mean changes in left ventricular dP/dt max were: 187 ± 166, 467 ± 105, 190 ± 101, 292 ± 143, −20 ± 87 and −83 ± 104 mmHg s^{-1} at carotid sinus pressures of 60, 90, 120, 150, 180 and 210 mmHg, respectively. Apart from the value of 467 ± 105 mmHg s^{-1} at 90 mmHg ($p < 0·01$), none of the other values were significantly different from zero (p values were 0·3, 0·09, 0·07, 0·18 and 0·5, respectively). Pooling the results of the

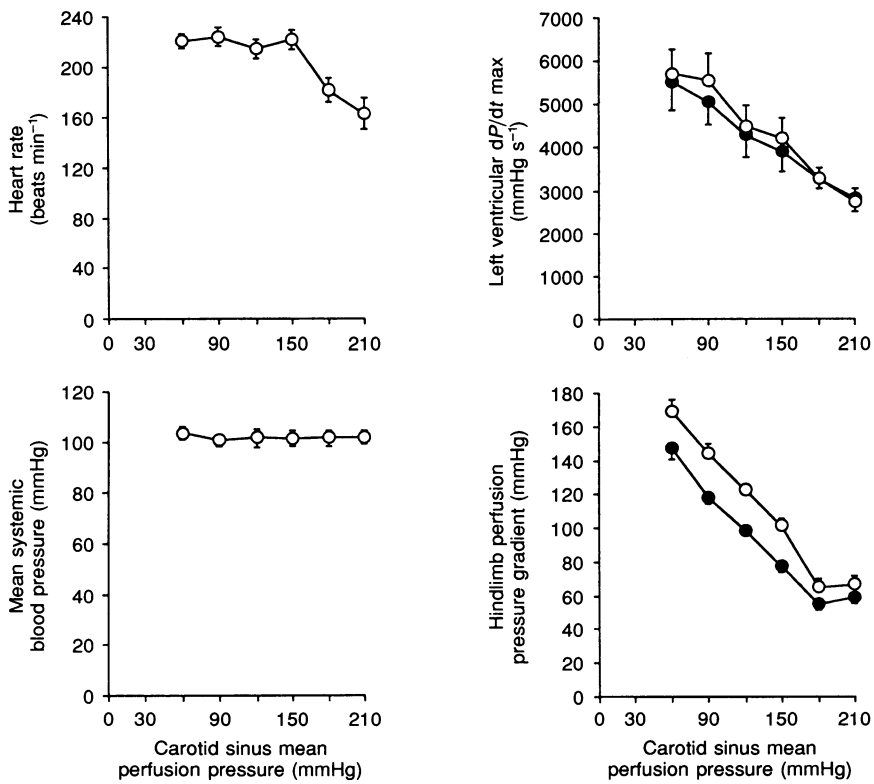

Figure 6. Effects of distension of the bladder on the relationship between carotid sinus pressure and left ventricular dP/dt max and hindlimb perfusion pressure gradient

Heart was paced and systemic blood pressure controlled at about 100 mmHg during alterations of carotid sinus pressure and bladder distension. ●, control period before bladder distension; ○, bladder distension at the time of the peak hindlimb vascular response. Lower pacing frequencies were necessary at the two highest values for carotid sinus pressure to avoid arrhythmias or pulsus alternans. Values are means ± S.E.M. ($n = 8$–11 observations in 4 dogs). For heart rate and mean systemic blood pressure, the values for control and bladder distension are superimposed.

fifty-nine tests from all six carotid sinus pressures, the mean response was an increase of 190 ± 54 mmHg s^{-1} ($p < 0.001$).

Bladder distension had no significant effect on left ventricular end-diastolic pressure (change, -0.1 ± 0.2 mmHg; $n = 59$; range, -4 to $+3$ mmHg; $p = 0.51$), the control value being 6.4 ± 0.5 mmHg.

Effects of atenolol

Atenolol (3 mg kg^{-1} I.V.) was given initially with additional doses if necessary until the heart rate and left ventricular dP/dt max responses to isoprenaline (5 μg I.V.) were abolished. Subsequently, observations were made while the arterial blood pressure and heart rate were controlled.

In the first of three experiments, bladder distension gave rise to a 15.8% reduction in left ventricular dP/dt max before atenolol and an 8.5% reduction after atenolol. In the second and third experiments, bladder distension initially resulted in 1.5 and 6% increases, respectively, in left ventricular dP/dt max and, after atenolol, the response was abolished in the second experiment and reversed to a fall of 3.2% in the third. However, it should be noted that β-blockade was associated with large changes in the baseline haemodynamic state. Left ventricular dP/dt max fell from 5850 to 1850 mmHg s^{-1} in the first experiment, from 6800 to 3050 mmHg s^{-1} in the second and from 7500 to 2420 mmHg s^{-1} in the third.

DISCUSSION

We have shown that stimulation of the carotid baroreceptors by step increases in carotid sinus perfusion pressure caused a reflex decrease in left ventricular dP/dt max, confirming the earlier results of Hainsworth & Karim (1973). In addition, distension of the bladder, although having variable effects on left ventricular dP/dt max, resulted in a reflex increase in this variable on pooling all the data.

The measurement of left ventricular dP/dt max has been found to be a sensitive index of left ventricular contractility (e.g. Furnival *et al.* 1970). However, both an increased heart rate and an increased blood pressure have a direct positive inotropic effect on the left ventricle (e.g. Bowditch, 1871; von Anrep, 1912; Sarnoff, Mitchell, Gilmore & Remensnyder, 1960; Furnival *et al.* 1970). In addition, an increase in blood pressure stimulates the arterial baroreceptors, which in turn causes reflex decreases in contractility and left ventricular dP/dt max (Hainsworth & Karim, 1972, 1973). Hence, in the final analysis, the reflex changes in left ventricular dP/dt max were determined under conditions of constant heart rate and arterial blood pressure.

There is some disagreement as to whether a change in preload alters left ventricular dP/dt max (e.g. Wallace, Skinner & Mitchell, 1963; Furnival *et al.* 1970). However, in the experiments reported here, the changes in left ventricular end-diastolic pressure were small and variable (range, ± 4 mmHg), indicating the absence of important changes in preload following bladder distension.

Carotid sinus baroreceptor reflexes

In the experiments in which blood pressure was allowed to fall as carotid sinus pressure was raised, some of the observed fall in left ventricular dP/dt max could have been secondary to the reduction in left ventricular after-load, although this effect might have been partly offset in turn by a reflex increase in left ventricular dP/dt max caused by unloading the aortic baroreceptors (Hainsworth & Karim, 1972). However, when blood pressure was controlled throughout and heart rate held constant, a stepwise reduction in left ventricular dP/dt max was still observed as carotid sinus pressure was raised from 60 to 150 mmHg, indicating a negative inotropic reflex effect of carotid baroreceptor stimulation. Further step reductions in left ventricular dP/dt max occurred as carotid sinus pressure was raised from 150 to 210 mmHg but, as a lower pacing frequency had to be used at carotid sinus pressures of 180 and 210 mmHg to prevent arrhythmias, part of the fall may have been due to the direct negative inotropic effect of the reduction in heart rate.

Responses to distension of the bladder

Compared with the reflex alterations in left ventricular dP/dt max evoked by changes in carotid sinus pressure, the responses to distension of the bladder were relatively small. For example, in the last series of experiments in which the largest responses to bladder distension were observed, the average rise in left ventricular dP/dt max in response to the standard test of distension of the bladder of about 50 mmHg was 190 mmHg s^{-1}. Under the same conditions of controlled blood pressure and heart rate, the slope of left ventricular dP/dt max to carotid sinus pressure was 18 mmHg s^{-1} $mmHg^{-1}$. Thus, the response to bladder distension was, in terms of the carotid baroreceptor reflex, equivalent to a fall in carotid sinus pressure of just 11 mmHg. The effects of bladder distension on left ventricular dP/dt max were variable, however, despite a protocol which successfully prevented changes in blood pressure and heart rate. They contrast with the consistent and brisk hindlimb vasoconstrictor responses, which were quantitatively similar to those described by Daly *et al.* (1993), thereby demonstrating the viability of the preparations used in the present study (Figs 4 and 6).

One possible explanation for the variable inotropic responses to bladder distension is that two or more factors are involved. It has been shown previously that, when heart rate is controlled by cardiac pacing, distension of the bladder causes a reflex decrease in coronary blood flow (Cevese *et al.* 1991). It is possible that this reflex coronary vasoconstriction could have a secondary negative inotropic effect which would oppose any direct positive inotropic effect

on the left ventricle in response to bladder distension. A negative inotropic effect of coronary vasoconstriction might be especially likely to occur when the heart is being paced at frequencies well above its natural rate. Pacing would be expected to increase myocardial oxygen consumption as well as reduce the diastolic time available for coronary perfusion of the left ventricle. The net effect on left ventricular dP/dt max in response to bladder distension could therefore depend on the relative size of a direct reflex positive inotropic effect and an indirect negative inotropic effect resulting from the reflex reduction in coronary perfusion.

In addition, the effect of the coronary vasoconstriction on coronary blood flow and contractility might depend on the prevailing blood pressure. In the series of experiments in which blood pressure was allowed to fall with each step increase in carotid sinus pressure, the blood pressure was lower in most tests than in the series in which the blood pressure was controlled at about 100 mmHg at all levels of carotid sinus pressure (Fig. 4; cf. Fig. 6). This may have contributed to the finding that decreases in left ventricular dP/dt max were more common in this series of experiments than in those in which blood pressure was controlled throughout at 100 mmHg.

Since few vagal efferent fibres innervate left ventricular muscle, any direct inotropic effect of bladder distension is likely to be mediated largely through the cardiac sympathetics. On the other hand, the reflex coronary vasoconstriction, and therefore any resulting negative inotropic effect, is mediated by both cardiac vagal and sympathetic efferent pathways (Cevese *et al.* 1991). Thus, the relative size of these opposing inotropic effects could depend on the degrees of background sympathetic and vagal activities at the start of each test.

In contrast to the variable responses described in the present paper, Cevese, Poltronieri, Schena, Vacca & Mary (1990) found an increase in left ventricular dP/dt max in response to bladder distension in all their tests. Some differences in haemodynamic state and relative activities in vagal and sympathetic efferent fibres between the work reported here and the experiments of Cevese *et al.* (1990) are also likely. Our dogs were anaesthetized with chloralose–urethane whereas Cevese *et al.* (1990) used pentobarbitone. Control values of left ventricular dP/dt max were lower (1781 ± 171 mmHg s^{-1}) and heart rates higher ($173{\cdot}4 \pm 4{\cdot}6$ beats min^{-1}) in their experiments (Cevese *et al.* 1990) than in the experiments reported here (e.g. in the first series, 4040 ± 224 mmHg s^{-1} and $120 \pm 4{\cdot}2$ beats min^{-1}). We took our measurements at the time of the peak responses about 30 s after the start of bladder distension, whereas Cevese *et al.* (1990) made their measurements 3 min after the start of bladder distension. If the time course of direct reflex stimulation of cardiac muscle and the indirect effects of coronary vasoconstriction differ, then the net effect of bladder distension on the paced heart may depend on the timing of measurements. The findings described here and those of Cevese *et al.* (1990) are in fact very similar in that any effect of bladder distension on left ventricular dP/dt max is small. The mean increase in left ventricular dP/dt max in response to bladder distension in their eight tests was 104 ± 52 mmHg s^{-1} from a control value of 1781 ± 171 mmHg s^{-1}, i.e. 5·8% (Cevese *et al.* 1990). The largest response, an increase of 461 mmHg s^{-1}, seems to have come from the experiment illustrated in their Fig. 1 (Cevese *et al.* 1990) in which the bladder was distended to 80 mmHg. This pressure is higher then that used in the experiments reported in this paper in which the maximum pressure used was 70 mmHg and most experiments were performed with pressures of about 50 mmHg. The average size of their remaining seven tests was an increase of only 46 mmHg s^{-1} or 2·7%. The main difference between their work (Cevese *et al.* 1990) and that reported here is that, in all eight tests of bladder distension carried out with heart rate and blood pressure controlled, left ventricular dP/dt max increased, albeit mostly by a small amount, whereas in the 186 tests made under similar conditions and reported here, both increases and decreases in left ventricular dP/dt max were observed. It is interesting to note that, in the experiments of Cevese *et al.* (1990) following β-blockade with propranolol, bladder distension caused an increase in left ventricular dP/dt max in two dogs, a decrease in four and no change in the remaining two (mean change, -47 ± 33; range, -233 to 43 mmHg s^{-1}). Propranolol would be expected to block the β-receptor-mediated inotropic effect but not the coronary vasoconstriction. Thus, the decrease in left ventricular dP/dt max observed by Cevese *et al.* (1990) in 50% of their tests following propranolol is compatible with the unmasking of a negative inotropic effect secondary to coronary vasoconstriction.

The effects of β-blockade (with atenolol) on the left ventricular dP/dt max response to bladder distension was also tested in three experiments reported here. However, the small variable effects that were seen are difficult to interpret as atenolol always caused changes in baseline haemodynamics including a large reduction in the control level of left ventricular dP/dt max.

In conclusion, bladder distension in uncontrolled preparations caused an increase in heart rate and in left ventricular dP/dt max. When the inotropic effects of increased heart rate and blood pressure were excluded, a small increase in left ventricular dP/dt max occurred but the responses tended to be variable in direction in contrast to those evoked by the carotid baroreceptors. A possible explanation is that the direct reflex increase in sympathetic discharge to the left ventricular muscle, tending to increase left ventricular dP/dt max on bladder distension, is offset by a reduction in the inotropic response resulting from the concomitant reflex fall in coronary blood flow (Cevese *et al.* 1991). In any individual experiment, therefore, the final

outcome would depend on the relative magnitude of these two effects, which in turn could depend on the baseline haemodynamic state and the prevailing sympathetic and vagal tone to the heart.

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