Journal of Physiology (1992), **447**, *pp.* 409–423
With 6 figures
Printed in Great Britain

HAEMODYNAMIC EFFECTS OF DISTENSION OF THE DESCENDING COLON IN ANAESTHETIZED DOGS

BY A. CEVESE*, D. A. S. G. MARY†, R. POLTRONIERI*, F. SCHENA* AND G. VACCA‡

*From the *Institute of Human Physiology, University of Verona, Verona, Italy, the †Department of Cardiovascular Studies, The University, Leeds and the ‡Department of Anatomy and Human Physiology, University of Torino, Torino, Italy*

(*Received 5 February 1991*)

SUMMARY

1. This study was undertaken to determine whether distension of the descending colon in anaesthetized dogs reflexly affects the heart rate, arterial blood pressure or the left ventricular inotropic state.

2. Experiments were performed on twenty-six dogs, which were anaesthetized with sodium pentobarbitone and artificially ventilated. A segment of the distal descending colon was isolated and was distended with warm Ringer solution at a steady intraluminal pressure.

3. In each animal, distension of the colon caused an increase in heart rate and aortic blood pressure. The response of an increase in heart rate was augmented by preventing changes in aortic blood pressure, and was graded in seven dogs by step increments in the distending pressure. In the same animals, distension of the colon always caused a small increase in left ventricular $(dP/dt)_{max}$ at constant heart rate and aortic blood pressure.

4. In four of the twenty-six dogs, cutting the pelvic nerves did not abolish the observed responses to the distension. In seven of the twenty-six dogs, which included the four animals with sectioned pelvic nerves, cutting the hypogastric nerves completely abolished all the observed responses.

5. In thirteen of the twenty-six dogs, propranolol or bretylium tosylate completely abolished the reflex increases in heart rate and left ventricular $(dP/dt)_{max}$, and phentolamine or bretylium tosylate abolished the reflex increase in aortic blood pressure.

6. These results showed that distension of the colon reflexly increased the heart rate, arterial blood pressure and left ventricular inotropic state. These reflex responses were mediated by sympathetic effects and their afferent limb involved the hypogastric nerves.

All reprint requests to be addressed to Professor A. Cevese, Istituto di Fisiologia Umana, Università di Verona, Strada Le Grazie 8, I-37134 Verona, Italy.

MS 9130

INTRODUCTION

It has been shown that the walls of the urinary bladder contain mechanoreceptors which discharge into the hypogastric and pelvic nerves (see Mary, 1989). Distension of the urinary bladder was found to cause reflex increases in heart rate and arterial blood pressure and a small or negligible increase in the left ventricular inotropic state (Mukerjee, 1957*a*,*b*; Daly & Wood, 1982, 1983; Daly, Ward & Wood, 1985; Hassan, Hicks, Walters & Mary, 1987*a*, *b*; Ramadan, Drinkhill & Mary, 1989; Cevese, Poltronieri, Schena, Vacca & Mary, 1990). The descending colon has also been shown to contain mechanoreceptors which discharge into the hypogastric and pelvic nerves (Janig & Morrison, 1986; Grundy & Scratcherd, 1989). However, reports on the results of distension of the colon have been contradictory; in two reports an increase or a decrease in arterial blood pressure has been observed (Watkins, 1938 and Ness & Gebhart, 1988, respectively).

The present investigation was planned to determine whether distension of the distal descending colon reflexly affects the heart rate, arterial blood pressure or left ventricular inotropic state. Preliminary reports of this work have been published (Cevese, Poltronieri, Schena, Mary & Vacca, 1990; Vacca, Cevese, Poltronieri, Schena & Mary, 1991).

METHODS

Dogs weighing between 14 and 40·5 kg were given morphine chloride (2 mg kg^{-1}; I.M., Molteni, Firenze, Italy) and anaesthetized by sodium pentobarbitone (30 mg kg^{-1}; I.V., Siegfried Zofingen, Switzerland). The animals were artificially ventilated with oxygen-enriched air (approximately 40%) using a Harvard respiratory pump (Harvard 607, Harvard Apparatus Co., Millis, MA, USA). Anaesthesia was maintained throughout the experiments by a continuous I.V. infusion of sodium pentobarbitone (3·5 mg kg^{-1} h^{-1}).

The chest was opened in the left fourth intercostal space. The pericardium was cut and an electromagnetic flowmeter (Model BL 610, Biotronix Laboratory Inc., Silver Spring, MD, USA) probe was positioned around the ascending aorta to measure blood flow. The flowmeter was calibrated against measurements of the cardiac output obtained by thermodilution (Model COM1, American Edwards Laboratories, CA, USA). For this purpose, a Swan-Ganz catheter was positioned in the pulmonary artery, and the cardiac output was repeatedly measured until a steady state was achieved (less than 10% variation in cardiac output and less than 2% heart rate change).

Through a mid-line abdominal incision, the colon was separated from the urinary bladder in the pelvic cavity. The bladder was cannulated to keep it empty throughout all the experiments. A segment of about 15 cm of the colon was isolated between two ligatures; one of these included a double-lumen cannula which was used to measure the luminal pressure with a Statham strain gauge (P23 ID, Gould, Statham Laboratories, USA) and to distend the colon with warm Ringer solution. This solution was kept in a reservoir maintained at 38 °C and was driven into the colon by compressed air. The pressure exerted was measured by a mercury manometer connected to the reservoir and controlled using a Starling resistance fitted to the compressed air supply. This method enabled distension of the colon at pre-set values of intraluminal pressure which could be maintained at constant level.

Pressures in the ascending aorta and in the left ventricle were recorded using two catheter-tip strain gauges (Millar Instrument Inc., Huston, TX, USA) inserted respectively into the right femoral artery and through the tip of the left atrial appendage. The pressure in the right atrium was recorded using a cannula connected to a pressure transducer (Statham P23 ID, Gould, Statham Laboratories, USA) introduced through the right atrial appendage. In some animals the pelvic nerves at the level of the rectum and the hypogastric nerves in the abdomen were exposed. In other animals the two vagosympathetic trunks were isolated in the neck. Arterial blood samples were obtained through a plastic cannula inserted into a branch of the abdominal aorta or into the left internal mammary artery; from these, the pH, P_{CO_2} and P_{O_2} were monitored using a gas analyser

(IL 213, IL Instrumentation Laboratory Lexington MA, USA) and maintained within normal limits as previously described (Linden & Mary, 1983). The temperature of the animals was monitored and kept constant during the experiments within the range of 37 to 38·5 °C.

Two methods were used to prevent changes in aortic blood pressure during the experiments. Initially, a large capacity syringe (100 ml, primed with 10 ml of saline at 38 °C) connected to the left femoral artery was used. The increase in aortic blood pressure which resulted from distension of the colon was prevented by withdrawal of blood. This blood was returned to the animal after the release of the distension. The volume of blood involved was 70 ml (mean; range 30–140), and there were no significant changes in the haematocrit ($P > 0·05$). However, there were decreases in cardiac output, left ventricular and right atrial pressures. In the same animals, a different method was used to prevent changes in aortic blood pressure. A balloon was tied to the end of a catheter, and was placed in the descending aorta through the left femoral artery. The aortic blood pressure was prevented from changing by inflation of the balloon to raise the arterial pressure above that caused by distension of the colon. In preliminary studies, there were no qualitative differences between responses to the distension using the blood withdrawal and those using the aortic balloon (Vacca *et al.* 1991). For the present investigations, data obtained from either method were used only when changes in cardiac output, right atrial and left ventricular end-diastolic pressure were less than 10%. To pace the heart, electrodes were sewn on the left atrial appendage and connected to a stimulator (WPI Digipulser series 1800, W-P Instruments Inc., New Haven, CO, USA) which delivered pulses of 3–5 V with 2 ms duration at the required frequency. Coagulation of the blood was prevented by I.V. injection of heparin (Liquemin, Roche; initial dose, 500 IU kg^{-1}; subsequent doses, 50 IU kg^{-1} every 30 min).

The aortic, left ventricular, right atrial pressure and the intraluminal pressure of the colon were monitored together with the cardiac output and the electrocardiogram using an oscilloscope (VR-12, Electronics for Medicine, Pleasant Ville, NY, USA). The cardiac output and all the pressures were also recorded together with the maximal rate of rise of systolic left ventricular pressure, labelled as $(dP/dt)_{max}$, and heart rate using an electrostatic strip chart recorder (Gould ES 1000, Gould Allco, Longjumeau, France). The heart rate was obtained from the electrocardiogram. In addition, a computerized data acquisition system was used to store experimental data on floppy disks after A/D conversion at 512 Hz, and for analysis of heart rate, left ventricular $(dP/dt)_{max}$ and end-diastolic pressure, right atrial pressure and phasic aortic blood pressure and flow (Cevese, 1986).

At the end of each experiment the animal was killed by I.V. injection of 20 ml of a 10 M solution of potassium chloride.

Experimental protocol

The experiments were performed after a steady state had been attained for at least 30 min with respect to heart rate, mean aortic blood pressure, cardiac output, right atrial and left ventricular pressure and $(dP/dt)_{max}$.

The colon was distended for a period of 75 s. After the release of the distension, observations were continued for a further 4 min. The test period was during the last 15 s of distension when a steady state had been attained. The response to each distension was calculated as the difference between means of variables during the test period and their average during the two 15 s steady-state control periods immediately before the distension and after its release when a steady state was attained. Any change in measured haemodynamic variables brought about by the distension was considered as a response only when it was reversed by the release of the distension.

In an initial study, experiments of distension of the colon were completed without preventing changes in heart rate or aortic blood pressure. The experiments of the distension were repeated whilst preventing changes in aortic blood pressure to examine the effect of distension on the heart rate. The effect of distension on left ventricular $(dP/dt)_{max}$ was examined by repeating the experiments whilst preventing changes in heart rate and aortic blood pressure. The heart rate was kept constant by atrial pacing to a cardiac frequency faster than that observed beforehand during the distension in each animal.

To examine the reflex nature of the responses to distension of the colon, the experiments of distension were performed before and after sectioning either the pelvic or hypogastric nerves.

The efferent mechanisms causing the reflex increase in heart rate, aortic blood pressure and left ventricular $(dP/dt)_{max}$ were explored using the distension experiments before and after giving blocking agents such as propranolol (0·5 mg kg^{-1}, I.V.; Sigma, St Louis, MO, USA), bretylium tosylate (10 mg kg^{-1}, I.V.; Serva, Heidelberg, Germany) or phentolamine (1·0 mg kg^{-1}, I.V.; Sigma,

St Louis, MO, USA), and by cutting both vagosympathetic trunks. The dose of propranolol has been shown to prevent changes in the left ventricular inotropic state (Harry, Kappagoda, Linden & Snow, 1973), and that of bretylium tosylate has been shown to abolish the cardiac responses to stimulation of efferent cardiac sympathetic nerves (Ledsome & Linden, 1964). The dose of phentolamine has been shown in preliminary experiments in the same animal preparations (Cevese & Vacca, unpublished observations) to prevent the maximal pressor effect of doses of phenylephrine (10 μg kg^{-1}, I.V.).

Student's paired t test was used to examine changes in measured variables. The relationship between the distension pressure and changes in heart rate was examined using least square procedures for linear correlation analysis. Group data are presented as means $\pm$ S.D. and range.

RESULTS

In twenty-six dogs, recordings commenced approximately 5 h after the induction of anaesthesia. The pH, P_{CO_2} and P_{O_2} of arterial blood respectively were 7·41 (mean; range 7·36–7·48), 36·5 mmHg (mean; range 30–43), 120·6 mmHg (mean; range 90–156), and the haematocrit was 41% (mean; range 33–48).

In these animals 161 experiments of distension were performed. The pressure used to distend the colon ranged between 30 and 60 mmHg. For each animal the same pressure was used.

Changes caused by distension of the colon

Initially, an experiment of distension was performed in each of the twenty-six dogs using increments of the intraluminal pressure in the colon of 49 mmHg (mean; range 30–60). An example of the changes caused by this distension in one experiment is shown in Fig. 1. There was an increase in heart rate, aortic blood pressure and left ventricular $(dP/dt)_{max}$. These increases reached a peak within 15 s, and declined to reach steady levels during the distension period when they were still greater than the control values before and after the distension. Group values of data in all the experiments during the test period of the distension are given in Table 1.

Within 15 s of the distension period in all the twenty-six experiments the heart rate increased by 8·8 beats min^{-1} $\pm$ 9·1 (range 2–32), mean aortic blood pressure increased by 12·3 mmHg $\pm$ 5·4 (range 5–29), cardiac output increased by 0·15 l min^{-1} $\pm$ 0·29 (range $-0·05$ to 1·47), and left ventricular $(dP/dt)_{max}$ increased by 290 mmHg s^{-1} $\pm$ 236 (range 37–918). These increases were significant (respectively, $P < 0·001$, $P < 0·001$, $P < 0·02$ and $P < 0·001$; paired t test). The changes in right atrial and left ventricular end-diastolic pressure were small and insignificant (respectively, $P > 0·05$ and $P > 0·05$; paired t test).

Group data and individual changes in aortic blood pressure obtained during the steady state of the distension (test period) are shown respectively in Table 1 and Fig. 2*A*. Despite the buffering action of baroreceptor reflexes, the increase in aortic blood pressure was present in all the dogs. These changes were accompanied by increases in heart rate and left ventricular $(dP/dt)_{max}$, and cardiac output. There were no significant changes in right atrial or left ventricular end-diastolic pressure (Table 1).

In eleven of the twenty-six animals, eleven experiments of distension were performed following the administration of bretylium tosylate (six dogs) or phentolamine (five dogs). Individual responses are shown in Fig. 2*B*. In these experiments, before giving the chemical agents, the aortic blood pressure significantly

increased by 9·3 mmHg ± 4·2 (range 5–17) from values during the control periods of 109 mmHg ± 17·1 (range 86–144). After giving the chemical agents, the changes in aortic blood pressure during the distension amounted to 1·6 mmHg ± 2·4 (range −1·7 to 5·5) relative to its value during the control periods of 93 mmHg ± 27·8 (range 62–146).

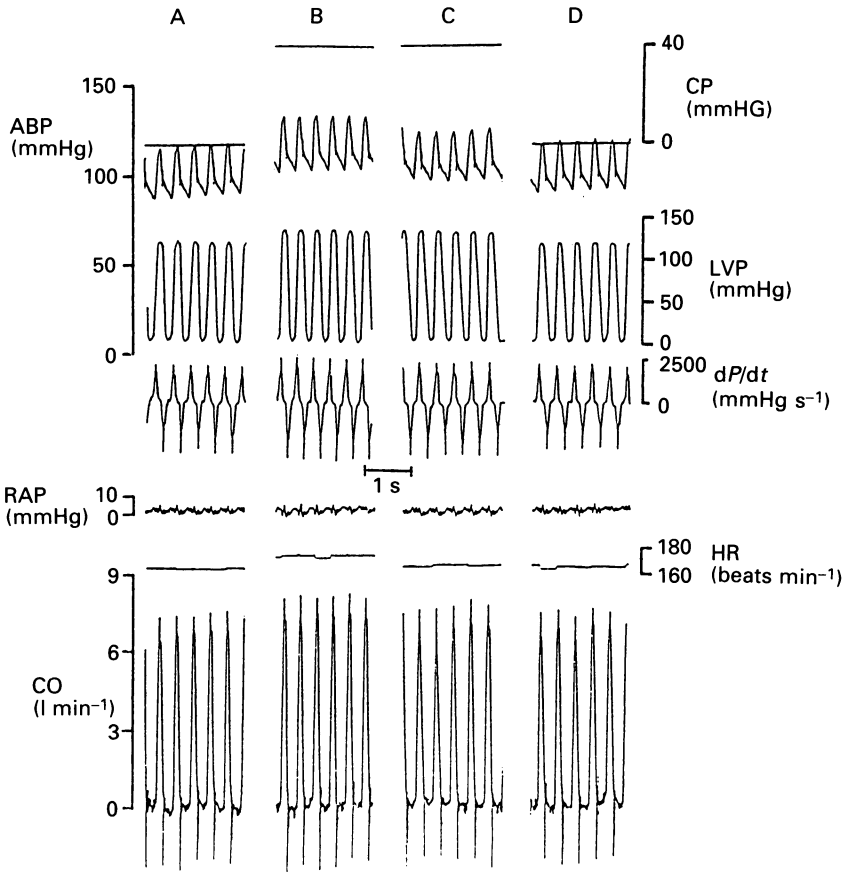

Fig. 1. Example of experimental recordings taken before (A), during (B and C) and after (D) distension of the colon. Recordings in B and C were taken respectively at the beginning and the end of distension. From the top down are shown pressure in the colon (CP), aortic blood pressure (ABP), left ventricular pressure (LVP), left ventricular $(dP/dt)_{max}$ (dP/dt), right atrial pressure (RAP), heart rate (HR) and cardiac output (CO).

Response of heart rate

To avoid interference by baroreceptor reflexes, in twenty-three of the twenty-six dogs, twenty-nine experiments of distension were performed whilst preventing changes in aortic blood pressure. In these experiments the intraluminal pressure of the colon was increased by 49·7 mmHg (mean; range 30–60).

In each case, distension increased the heart rate within 15 s and this increase remained till release of the distension. This response amounted to 10·2 % of heart rate values during the control periods (Table 1 and Fig. 3*A*), and was accompanied by a

TABLE 1. Changes in haemodynamic variables during distension of the colon in the twenty six dogs

Data	Average control	Distension (test period)	Change	P
		Distension of the colon (n = 26 dogs)		
HR	157 ± 13·0 (133–176)	160 ± 13·9 (132–200)	3·6 ± 6·2 (−4–26)	< 0·01
ABP	108 ± 15·5 (86–144)	115 ± 16·1 (93–151)	7·4 ± 4·6 (1·0–21)	< 0·001
dP/dt	1977 ± 486 (1376–3432)	2145 ± 500 (1485–3615)	168 ± 156 (−21–670)	< 0·001
LVEDP	6·9 ± 3·5 (1·8–13·8)	7·2 ± 3·7 (1·5–14·8)	0·23 ± 0·6 (−1·0–1·6)	> 0·05
RAP	3·3 ± 2·2 (−0·2–9·6)	3·4 ± 2·3 (−0·1–9·9)	0·08 ± 0·2 (−0·5–0·8)	> 0·05
CO	1·94 ± 0·6 (1·0–3·1)	2·05 ± 0·6 (1·0–3·2)	0·11 ± 0·2 (−0·07–0·8)	< 0·01
		Responses with constant ABP (n = 23 dogs)		
HR	155 ± 13·7 (120–176)	171 ± 18·2 (134–219)	15·8 ± 12·1 (5–43)	< 0·001
ABP	109 ± 16·8 (84–151)	109 ± 15·2 (85–152)	0·2 ± 1·3 (−2·1–4·3)	> 0·40
dP/dt	1967 ± 601 (1281–3887)	2156 ± 622 (1387–4074)	190 ± 154 (17–686)	< 0·001
LVEDP	6·7 ± 3·4 (1·3–13·8)	6·5 ± 3·3 (1·3–13·6)	−0·22 ± 0·4 (−1·3–0·2)	< 0·02
RAP	3·3 ± 2·1 (−0·1–8·9)	3·1 ± 2·1 (−0·1–9·2)	−0·07 ± 0·2 (−0·4–0·3)	> 0·05
CO	1·92 ± 0·7 (1·0–3·6)	1·93 ± 0·7 (1·0–3·3)	0·01 ± 0·1 (−0·3–0·2)	> 0·60
		Responses with constant ABP and HR (n = 23 dogs)		
HR	174 ± 16·4 (154–222)	174 ± 16·3 (154–222)	0·01 ± 0·2 (−0·4–1·0)	> 0·60
ABP	109 ± 18·1 (68–150)	109 ± 18·0 (68–150)	0·4 ± 1·3 (−1·5–3·0)	> 0·10
dP/dt	2074 ± 622 (1303–3609)	2205 ± 581 (1360–3916)	130 ± 75 (42–307)	< 0·001
LVEDP	6·6 ± 3·9 (0·9–15·2)	6·4 ± 3·9 (0·9–14·0)	−0·24 ± 0·5 (−1·2–0·6)	< 0·05
RAP	2·7 ± 2·0 (−0·9–6·1)	2·6 ± 1·9 (−0·9–6·0)	−0·1 ± 0·3 (−0·6–0·14)	> 0·10
CO	1·81 ± 0·7 (0·8–3·1)	1·76 ± 0·6 (0·9–2·9)	−0·05 ± 0·1 (−0·2–0·10)	< 0·05

Data are presented as mean ± S.D. (range). P (two tailed) values were obtained using paired t test.

HR, heart rate in beats min^{-1}; ABP, mean aortic blood pressure in mmHg; dP/dt, left ventricular $(dP/dt)_{max}$ in mmHg s^{-1}; LVEDP, left ventricular end-diastolic pressure in mmHg; RAP, mean right atrial pressure in mmHg; CO, cardiac output in l min^{-1}.

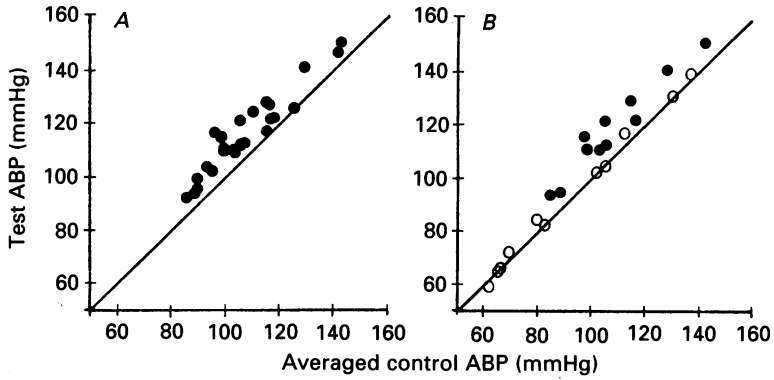

Fig. 2. The response of mean aortic blood pressure (ABP) to distension of the colon (*A*) and the effect of giving bretylium tosylate (10 mg kg^{-1}, I.V) or phentolamine (1·0 mg kg^{-1}, I.V.) on the response (*B*). The values obtained during distension (Test) are plotted on the ordinate against the average of control periods before and after the distension (Averaged control) on the abscissa. The continuous line is the line of no change. In *A*, twenty-six experiments of distension in twenty-six dogs always increased ABP ($P < 0·001$). In *B*, in eleven experiments in eleven of the twenty-six dogs, the chemical agents abolished the response. ●, before ($P < 0·001$) and, ○, after ($P > 0·05$) chemical agents.

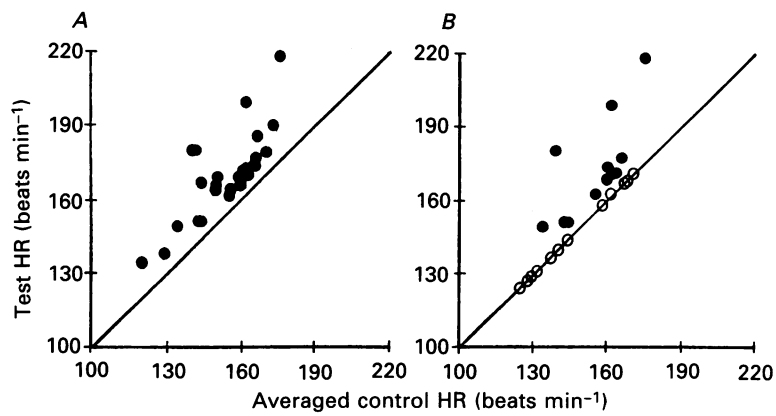

Fig. 3. The response of heart rate (HR) to distension of the colon at constant aortic blood pressure (*A*) and the effect of giving bretylium tosylate (10 mg kg^{-1}, I.V.) or propranolol (0·5 mg kg^{-1}, I.V.) on the response (*B*). The values obtained during distension (Test) are plotted on the ordinate against the average of control periods before and after the distension (Averaged control) on the abscissa. The continuous line is the line of no change. In *A*, twenty-nine experiments of distension in twenty-three dogs always increased HR ($P < 0·001$). In *B*, in twelve experiments in eleven of the twenty-three dogs, the chemical agents abolished the response. ●, before ($P < 0·005$) and, ○, after ($P > 0·05$) chemical agents.

significant increase in left ventricular $(dP/dt)_{max}$. The changes in cardiac output, right atrial and left ventricular end-diastolic pressure were small and variable (Table 1).

This response of an increase in heart rate was significantly greater ($P < 0·001$; paired *t* test) than that obtained in the same dogs before the control of aortic blood pressure.

In eleven of the twenty-three animals in which the aortic blood pressure was kept constant, twelve experiments of distension were performed following the administration of propranolol (seven dogs) or bretylium tosylate (four dogs). Individual responses are depicted in Fig. 3*B*. Before the administration of the chemical agents,

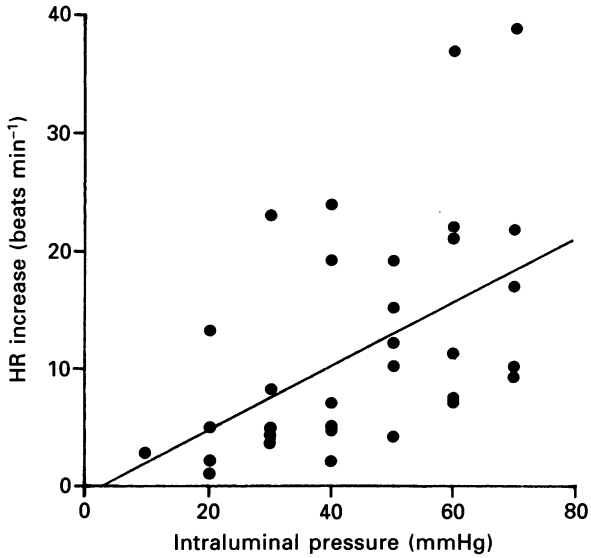

Fig. 4. A plot of the relation between the magnitude of response of an increase in heart rate (HR) and the intraluminal pressure used to distend the colon in seven dogs in which the aortic blood pressure was kept constant. The continuous line is the computed correlation line. $P < 0{\cdot}003$.

the distension significantly increased the heart rate by 18 beats $min^{-1} \pm 15$ (range 6–43) from values during the control periods of 155 beats $min^{-1} \pm 13{\cdot}2$ (range 135–176). Following the administration of the chemical agents the changes in heart rate were 0·3 beats $min^{-1} \pm 0{\cdot}5$ (range $-0{\cdot}5$ to 1·3) from values during the control periods of 145 beats $min^{-1} \pm 17{\cdot}1$ (range 125–171). Propranolol or bretylium tosylate thus completely abolished this response, indicating involvement of efferent sympathetic effects and lack of contribution of an efferent vagal component. In five of the eleven dogs, cutting of the vagosympathetic trunks caused an increase in heart rate of 13·5 beats $min^{-1} \pm 4{\cdot}8$ (range 9–21).

Response of heart rate to graded distension

In seven of the twenty-six dogs, the effect of graded distension of the colon on heart rate was examined whilst preventing changes in aortic blood pressure. The intraluminal pressure of the colon was increased in steps of 10–20 mmHg up to 70 mmHg, and a total of thirty-two steps were performed.

The lowest intraluminal pressure which caused an increase in heart rate was 24 mmHg $\pm$ 9·8 (range 10–40). With this and all higher levels of pressure there was always an increase in heart rate (at least $P < 0{\cdot}005$; paired t test).

In each animal, the magnitude of the increase in heart rate obtained during the

highest intraluminal pressure increment was always greater than that during the lowest pressure increment. The respective increases in the seven dogs were 20·4 beats min^{-1} (mean; range 9–39) and 3·1 beats min^{-1} (mean; range 1–5); the differences between the two increases were significant ($P < 0{\cdot}0025$; paired t test).

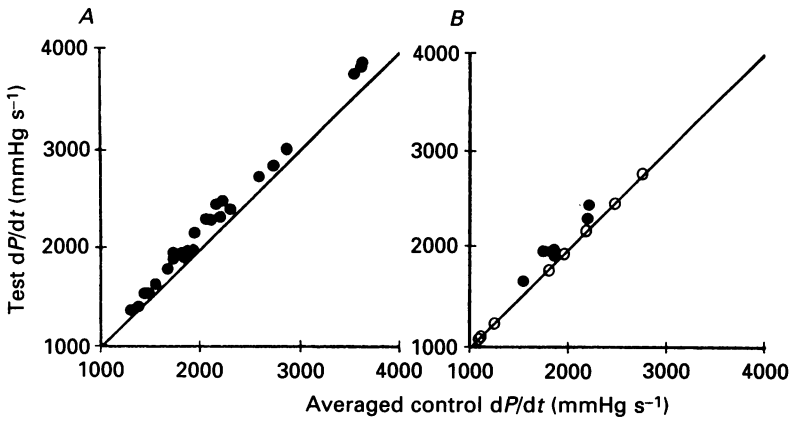

Fig. 5. The response of left ventricular $(dP/dt)_{max}$ to distension of the colon at constant heart rate and aortic blood pressure (A) and the effect of giving bretylium tosylate (10 mg kg^{-1}, I.V.) or propranolol (0·5 mg kg^{-1}, I.V.) on the response (B). The values obtained during distension (Test) are plotted on the ordinate against the average of control periods before and after the distension (Averaged control) on the abscissa. The continuous line is the line of no change. In A, twenty-seven experiments of distension in twenty-three dogs always increased dP/dt_{max} ($P < 0{\cdot}001$). In B, in eight experiments in six of the twenty-three dogs, the chemical agents abolished the response. ●, before ($P < 0{\cdot}005$) and, ○, after ($P > 0{\cdot}10$) chemical agents.

In each animal, the increase in heart rate was linearly related to the distending pressure (at least r (correlation coefficient) = 0·90; $P < 0{\cdot}05$). Similarly, when the data of the increases in heart rate on the distending pressure in all the animals were pooled, there was a significant ($r = 0{\cdot}51$; $P < 0{\cdot}003$) linear relation (Fig. 4).

Response of left ventricular inotropic state

To examine the direct effect of distension on left ventricular inotropic state in the twenty-three dogs, twenty-seven experiments were performed to measure left ventricular $(dP/dt)_{max}$ whilst preventing changes in heart rate and aortic blood pressure. The intraluminal pressure of the colon was increased by 49·3 mmHg (mean; range 30–60).

In each experiment a response of an increase in left ventricular $(dP/dt)_{max}$ was obtained. The increase in all the dogs (Table 1 and Fig. 5A) amounted to 6·3% of the values during the control periods. The changes in cardiac output, right atrial and left ventricular end-diastolic pressure were small and variable (Table 1).

In six of the twenty-three animals in which the heart rate and aortic blood pressure were kept constant, eight experiments of distension were repeated following the administration of propranolol (two dogs) or bretylium tosylate (four dogs). The effects of these chemical agents on individual responses are shown in Fig. 5B. Before

the administration of the chemical agents, the distension significantly increased left ventricular $(dP/dt)_{max}$ by 134 mmHg $s^{-1} \pm 64$ (range 47–266) from values during the control periods of 1931 mmHg $s^{-1} \pm 283$ (range 1543–2214). After giving the chemical agents, the changes amounted to 12 mmHg $s^{-1} \pm 17$ (range −12 to 37) relative to values during the control periods of 1912 mmHg $s^{-1} \pm 673$ (range 1040–2739).

Afferent limb of the responses

In four of the twenty-six dogs, the experiment of distension was repeated after cutting the pelvic nerves, and then after cutting the hypogastric nerves in addition. In a further three of the twenty-six dogs, the experiment of distension was repeated after cutting the hypogastric nerves only. A pressure of 60 mmHg was used to distend the colon and elicit the responses during sixteen experiments in the seven dogs, without controlling changes in heart rate and aortic blood pressure.

Cutting of the pelvic nerves had a small effect on the control data. There were small changes in aortic blood pressure of −10·3 mmHg ± 9 (range −19 to 0·4), heart rate of 5 beats $min^{-1} \pm 9{\cdot}5$ (range −5 to 17) and left ventricular $(dP/dt)_{max}$ of −129 mmHg $s^{-1} \pm 302$ (range −581 to 25); respectively, $P > 0{\cdot}10$, $P > 0{\cdot}30$ and $P > 0{\cdot}40$; paired t test). Cutting the pelvic nerves did not abolish the distension-evoked increases in heart rate or aortic blood pressure. After cutting the pelvic nerves, the increases in heart rate and aortic blood pressure obtained before interference by the buffering influence of the baroreflex respectively were 8·3 beats min^{-1} (mean; range 2–14) and 17·3 mmHg (mean; range 6–28). Despite the small number of animals, these changes were significant (respectively, $P < 0{\cdot}05$ and $P < 0{\cdot}05$; paired t test). In the same animals before cutting the pelvic nerves, the corresponding increases respectively were 5·5 beats min^{-1} (mean; range 3–9) and 12·8 mmHg (mean; range 5–17) (respectively, $P < 0{\cdot}05$ and $P < 0{\cdot}02$; paired t test).

Considering the group of seven dogs, the data after cutting the hypogastric nerves were compared with those beforehand (three dogs) and with those after cutting the pelvic nerves (four dogs). The effects of this procedure on the control data were: small decreases in aortic blood pressure of −4·5 mmHg ± 2·7 (range −8 to −1), small increases in heart rate of 2 beats $min^{-1} \pm 7{\cdot}7$ (range −8 to 15) and small decreases in left ventricular $(dP/dt)_{max}$ of −66 mmHg $s^{-1} \pm 80$ (range −165 to 75); respectively, $P < 0{\cdot}005$, $P > 0{\cdot}50$ and $P > 0{\cdot}05$; paired t test).

Cutting the hypogastric nerves drastically reduced or abolished the responses of an increase in heart rate, mean aortic blood pressure and left ventricular $(dP/dt)_{max}$. The respective changes amounted to −0·3 beats $min^{-1} \pm 1{\cdot}5$ (range −2·8 to 2·4), 1·2 mmHg ± 2·4 (range −2 to 5·4) and −13 mmHg $s^{-1} \pm 31$ (range −85 to 19). These changes were not significant (respectively, $P > 0{\cdot}50$, $P > 0{\cdot}10$ and $P > 0{\cdot}10$; paired t test). In the same animals before cutting the hypogastric nerves, the corresponding responses were 13·6 beats $min^{-1} \pm 6{\cdot}2$ (range 7–23), 9·6 mmHg ± 5·4 (range 5–21) and 111 mmHg $s^{-1} \pm 96$ (range 47–279); respectively, $P < 0{\cdot}005$, $P < 0{\cdot}005$ and $P < 0{\cdot}025$; paired t test. There were no significant changes in cardiac output, right atrial or left ventricular end-diastolic pressure (respectively, $P > 0{\cdot}10$, $P > 0{\cdot}50$ and $P > 0{\cdot}20$; paired t test). Figure 6 illustrates comparisons of the three responses after nerve section with those beforehand in the same animals.

DISCUSSION

In the colon and the rectum of the cat and dog, slowly adapting receptors which respond to distension have been shown to discharge into afferent pelvic and hypogastric nerves (Janig & Morrison, 1986; Grundy & Scratcherd, 1989). However,

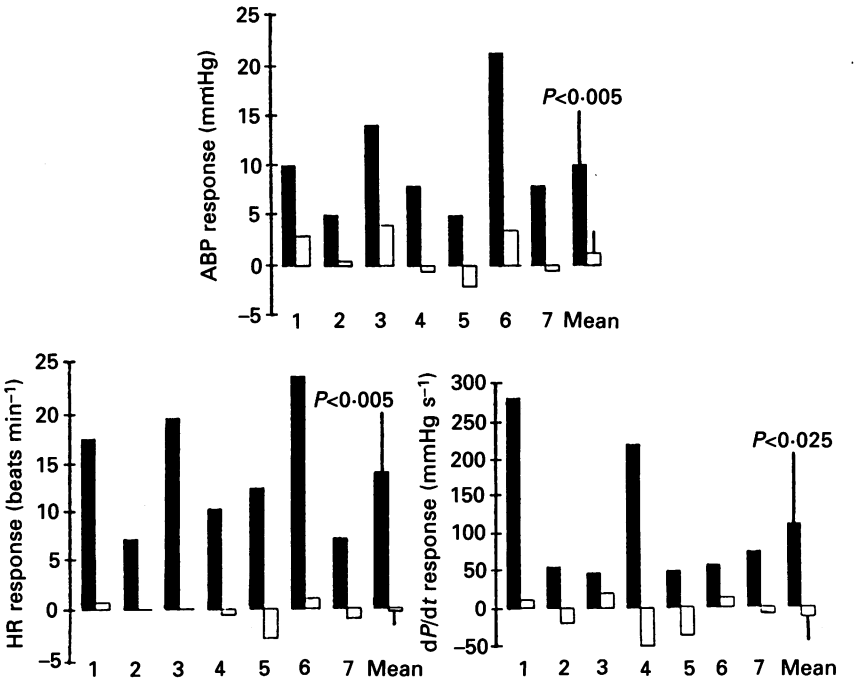

Fig. 6. The magnitude of increases in aortic blood pressure (ABP), heart rate (HR), and left ventricular $(dP/dt)_{max}$ in response to distension of the colon obtained before and after cutting the hypogastric nerves in seven dogs (numbered 1 to 7). The responses before cutting the nerves are shown in filled columns, and those after cutting the hypogastric nerves are shown as open columns. The height of the final columns indicate group changes and the extremity lines indicate S.D. Cutting the hypogastric nerves abolished the increase in aortic blood pressure, the increase in heart rate at constant ABP and the increase in left ventricular $(dP/dt)_{max}$ at constant HR and ABP.

the reported effects of the distension of the colon on haemodynamic variables have been scarce and inconsistent.

In one report involving anaesthetized cats, in some of which the abdomen was opened and the urinary bladder was displaced outside the abdomen, a rubber balloon mounted on the end of a glass cannula was inserted through the rectum and was distended by warm saline (Watkins, 1938). Distension lasted for about 10 s and resulted in a decrease of mean arterial blood pressure. However, the report did not examine changes in other haemodynamic variables or the reflex nature of this decrease in blood pressure.

In another report in rats, in which the abdomen was not opened, a latex balloon was inserted through the anus and the descending colon and the rectum were

distended by injecting air into the balloon (Ness & Gebhart, 1988). The distensions used increments in balloon pressure between 20 and 100 mmHg and lasted 20 s. Under the effect of ether, distension caused an increase in heart rate and arterial blood pressure the magnitudes of which were linearly related to values of balloon pressure. These increases were reduced or abolished by pharmacological blockade of vagal and sympathetic effects. In contrast, distension under deep sodium pentobarbitone or chloralose anaesthesia was found to cause a decrease in heart rate and arterial blood pressure; these were not investigated any further because of instability of responses (Ness & Gebhart, 1988). However, it is possible that distension of the colon and rectum in an intact abdomen may interfere with venous return, and may affect the urinary bladder which is known to be the source of similar reflex responses (see Mary, 1989).

In the present investigations in anaesthetized dogs, it was shown that distension of the descending colon always caused an increase in heart rate and arterial blood pressure. The abdomen was opened and the urinary bladder was separated from the colon and kept empty; this design avoided any interference by obstruction of venous return and reflexes related to the urinary bladder. The pressure used to distend the colon was much lower than that of over 100 mmHg which is reported to damage the walls of the colon and the rectum (Ness & Gebhart, 1988). The responses were examined in the steady state, and care was taken to prevent changes in arterial blood pressure which reflexly may affect the response of increase in heart rate. With such a control of changes in arterial blood pressure, the response of an increase in heart rate was augmented and it was possible to show that the magnitude of this response was linearly related to the pressure used to distend the colon. In addition, the same distension in the same animals always caused an increase in left ventricular $(dP/dt)_{max}$. This was obtained in the absence of changes in any of the other haemodynamic variables indicating that the distension caused a small increase in left ventricular inotropic state (Furnival, Linden & Snow, 1970). Finally, it was shown that the three responses occurred reflexly since they were abolished by cutting the hypogastric nerves. Cutting the pelvic nerves did not abolish these responses, making it possible that the afferent limb of the reflex was in the hypogastric nerves.

These findings were similar to those obtained during distension of the urinary bladder. The urinary bladder has also been shown to contain receptors which respond to distension and discharge into afferent pelvic and hypogastric nerves (see Mary, 1989). In dogs anaesthetized with chloralose or sodium pentobarbitone it has been shown that distension of the urinary bladder caused reflex increases in heart rate and arterial blood pressure, and a small or negligible increase in the left ventricular inotropic state. These reflex effects involved afferent pathways in the pelvic and hypogastric nerves and efferent pathways in vagal and sympathetic cardiac nerves (Mukerjee, 1957*a*,*b*; Daly & Wood, 1982, 1983; Daly *et al.* 1985; Hassan *et al.* 1987*a*, *b*; Ramadan *et al.* 1989; Drinkhill, Mary, Ramadan & Vacca, 1989; Cevese *et al.* 1990).

Despite the similarity of reflex responses to distension of the colon and the urinary bladder, there were differences in the reflex mechanisms involved. The afferent limb of the reflex was found in the hypogastric nerves in the case of the colon and in both the pelvic and hypogastric nerves in the case of the urinary bladder. It has previously

been shown in anaesthetized cats that application of chemical agents to the serosal surfaces of the gastrointestinal tract (stomach and jejunum) or distension of the stomach caused similar responses which were not affected by vagotomy but were abolished by removal of the coeliac or superior mesenteric ganglion (Longhurst, Spilker & Ordway, 1981; Longhurst, Stebbins & Ordway, 1984; Ordway, Boheler & Longhurst, 1988). The differences in the afferent limb between reflexes originating in the urinary bladder and the colon, which is part of the gastrointestinal tract, did not seem to be related to the location of receptors in the layers of the colon. Studies of receptors in the colon which respond to distension have indicated that muscular receptors in the cat discharge into the pelvic nerves and that serosal receptors in cats and dogs discharge into the hypogastric and pelvic nerves (see Grundy & Scratcherd, 1989).

There were other differences between reflex responses to distension of the colon and the urinary bladder. In the case of the colon the increase in heart rate was mediated by sympathetic effects, and in the case of the urinary bladder by both vagal and sympathetic effects. It has been shown that distension of the urinary bladder in anaesthetized dogs causes respectively a decrease and an increase in efferent vagal and sympathetic nerve activity (Hassan *et al.* 1987*a*, *b*). In the present investigation, the effect of distension of the colon on efferent vagal activity was not examined. However, the absence of an efferent vagal effect was not due to low levels of basal vagal tone since vagotomy still caused a significant increase in heart rate.

The range of pressure used to distend the colon in the present investigation was within that reported normally in man of up to 60 mmHg (Chaudhary & Truelove, 1961*a*, *b*, *c*), and in the dog of up to 40 mmHg (Garas, Besbeas, Vassilopoulos, Peteras & Ramandanis, 1976). In addition, we showed in the present investigation that the response of an increase in heart rate could be graded according to the values of the distension pressure applied to the colon, ranging between 10 and 70 mmHg. It is therefore possible that the reflexes of an increase in heart rate and in arterial blood pressure also operate in man.

In conclusion the present investigations have shown that distension of the descending colon caused reflex increases in heart rate, aortic blood pressure and left ventricular inotropic state. These reflex responses were mediated by sympathetic effects and their afferent limb involved the hypogastric nerves.

The authors wish to express their gratitude for the excellent technical help given by Miss G. Cerutti.

REFERENCES

CEVESE, A. (1986). Automatic elaboration of haemodynamic data. In *Neural Mechanisms and Cardiovascular Disease*, ed. LOWN, B., MALLIANI, A. & PROSDOCIMI, M., pp. 553–554. Liviana Press, Padova, Italy.

CEVESE, A., POLTRONIERI, R., SCHENA, F., MARY, D. A. S. G. & VACCA, G. (1990). Reflex tachycardia and pressor responses to distension of the descending colon in anaesthetized dogs. *Medical Science Research* **18**, 613–614.

CEVESE, A., POLTRONIERI, R., SCHENA, F., VACCA, G. & MARY, D. A. S. G. (1990). The effect of distension of the urinary bladder on left ventricular inotropic state in anaesthetized dogs. *Cardioscience* **1**, 247–253.

CHAUDHARY, N. A. & TRUELOVE, S. C. (1961*a*). Human colonic motility: a comparative study of normal subjects, patients with ulcerative colitis, and patients with the irritable colon syndrome. I. Resting patterns of motility. *Gastroenterology* **40**, 1–17.

CHAUDHARY, N. A. & TRUELOVE, S. C. (1961*b*). Human colonic motility: a comparative study of normal subjects, patients with ulcerative colitis, and patients with the irritable colon syndrome. II. The effect of prostigmin. *Gastroenterology* **40**, 18–26.

CHAUDHARY, N. A. & TRUELOVE, S. C. (1961*c*). Human colonic motility: a comparative study of normal subjects, patients with ulcerative colitis, and patients with the irritable colon syndrome. III. Effects of emotions. *Gastroenterology* **40**, 27–36.

DALY, M. DE B., WARD, J. & WOOD, L. M. (1985). The effect of distension of the urinary bladder on left ventricular dP/dt_{max} in the anaesthetized dog. *Journal of Physiology* **362**, 36*P*.

DALY, M. DE B. & WOOD, L. M. (1982). Effects of distension of the urinary bladder on the carotid sinus baroreceptor reflex in the dog. *Journal of Physiology* **325**, 16*P*.

DALY, M. DE B. & WOOD, L. M. (1983). Effects of distension of the urinary bladder on the respiratory and cardiovascular responses elicited by stimulation of carotid body chemoreceptors in the dog. *Journal of Physiology* **341**, 47*P*.

DRINKHILL, M. J., MARY, D. A. S. G., RAMADAN, M. R. M. & VACCA, G. (1989). The effect of distension of the urinary bladder on activity in efferent renal fibres in anaesthetized dogs. *Journal of Physiology* **409**, 357–369.

FURNIVAL, C. M., LINDEN, R. J. & SNOW, H. M. (1970). Inotropic changes in the left ventricle: the effect of changes in heart rate, aortic pressure and end-diastolic pressure. *Journal of Physiology* **211**, 359–387.

GARAS, J., BESBEAS, S., VASSILOPOULOS, B., PETERAS, H. & RAMANDANIS, G. (1976). Telemetric estimation of the descending colon pressure changes on dogs before and after total and selective vagotomy. *European Surgical Research* **8**, 411–418.

GRUNDY, D. & SCRATCHERD, T. (1989). Sensory afferents from the gastrointestinal tract. In *Handbook of Physiology*, section 6, *the Gastrointestinal System*, vol. I, *Motility and Circulation*, part 1, ed. SCHULTZ, S. G., WOOD, J. D. & BAUNER, B. B., pp. 593–620. American Physiological Society, Bethesda, MD, USA.

HARRY, J. D., KAPPAGODA, C. T., LINDEN, R. J. & SNOW, H. M. (1973). Action of propranolol on the dog heart. *Cardiovascular Research* **7**, 729–739.

HASSAN, A. A. M., HICKS, M. N., WALTERS, G. E. & MARY, D. A. S. G. (1987*a*). Effect of distension of the urinary bladder on efferent cardiac sympathetic nerve fibres which respond to stimulation of atrial receptors. *Quarterly Journal of Experimental Physiology* **72**, 1–11.

HASSAN, A. A. M., HICKS, M. N., WALTERS, G. E. & MARY, D. A. S. G. (1987*b*). Effect on efferent cardiac vagal nerve fibres of distension of the urinary bladder in the dog. *Quarterly Journal of Experimental Physiology* **72**, 473–481.

JANIG, W. & MORRISON, J. F. B. (1986). Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. In *Progress in Brain Research*, vol. 67, *Visceral Sensation*, ed. CERVERO, F. & MORRISON, J. F. B., pp. 87–114. Elsevier Science Publishers, Oxford.

LEDSOME, J. R. & LINDEN, R. J. (1964). The effect of bretylium tosylate on some cardiovascular reflexes. *Journal of Physiology* **170**, 442–455.

LINDEN, R. J. & MARY, D. A. S. G. (1983). The preparation and maintenance of anaesthetized animals for the study of cardiovascular function. In *Techniques in the Life Sciences, Cardiovascular Physiology*, ed. LINDEN, R. S., pp. 1–22. Elsevier Scientific Publishers, Ireland.

LONGHURST, J. C., SPILKER, H. L. & ORDWAY, G. A. (1981). Cardiovascular reflexes elicited by passive gastric distension in anaesthetized cats. *American Journal of Physiology* **240**, H539–545.

LONGHURST, J. C., STEBBINS, C. L. & ORDWAY, G. A. (1984). Chemically induced cardiovascular reflexes arising from the stomach of the cat. *American Journal of Physiology* **247**, H459–466.

MARY, D. A. S. G. (1989). The urinary bladder and cardiovascular reflexes. *International Journal of Cardiology* **23**, 11–17.

MUKERJEE, S. R. (1957*a*). Effect of bladder distension on arterial blood pressure and renal circulation in acute spinal cats. *Journal of Physiology* **138**, 300–306.

MUKERJEE, S. R. (1957*b*). Effect of bladder distension on arterial blood pressure and renal circulation: role of splanchnic and buffer nerves. *Journal of Physiology* **138**, 307–325.

NESS, T. J. & GEBHART, G. F. (1988). Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudoaffective reflexes in the rat. *Brain Research* **450**, 153–169.

ORDWAY, G. A., BOHELER, K. R. & LONGHURST, J. C. (1988). Stimulating intestinal afferents reflexly activates cardiovascular system in cats. *American Journal of Physiology* **254**, H354–360.

RAMADAN, M. R. M., DRINKHILL, M. J. & MARY, D. A. S. G. (1989). The effect of distension of the urinary bladder on activity in efferent vagal fibres in anaesthetized dogs. *Quarterly Journal of Experimental Physiology* **74**, 493–501.

VACCA, G., CEVESE, A., POLTRONIERI, R., SCHENA, F. & MARY, D. A. S. G. (1991). The effect of distension of the descending colon on left ventricular dP/dt_{max} in anaesthetised dogs. *Medical Science Research* **19**, 141–142.

WATKINS, A. L. (1938). Reflex responses of the nictitating membrane and the blood pressure to distension of the bladder and rectum. *American Journal of Physiology* **121**, 32–39.