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HAEMODYNAMIC RESPONSES TO STIMULATION OF THE SPLANCHNIC AND CARDIAC SYMPATHETIC NERVES IN THE ANAESTHETIZED CAT

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SUMMARY

1. The changes in cardiac output and mean right atrial pressure (R.A.P.) evoked at different circulating blood volumes by stimulation of the splanchnic sympathetic nerves were investigated in adrenalectomized cats under chloralose anaesthesia, with unopened chests and spontaneous respiration and with active vascular reflexes. The cardiac autonomic nerves were cut or blocked pharmacologically.

2. Stimulation of the distal ends of the splanchnic nerves at 4 Hz caused aortic pressure and R.A.P. to rise to maximum values at 2 min before declining slowly. Cardiac output rose more slowly to a steady state at 3 min; at higher circulating volumes it fell initially. Although the output increments were slower in development they were better sustained than those in total peripheral resistance. The proportionate output increments were largest and the R.A.P. increments least at low circulating volumes whereas at high volumes the R.A.P. increments were large but the output changes were small or negative; the pattern of changes resembled that resulting from infusion of blood.

3. Stimulation of the cardiac sympathetic nerves evoked a rise in output and a fall in R.A.P. related in magnitude to the initial value of R.A.P. On simultaneous stimulation of the splanchnic and cardiac sympathetic nerves the changes in output combined whereas the R.A.P. changes cancelled, to give output increments of 25–50 % with little change in R.A.P. at all circulating volumes.

4. At high circulating volumes infusion of blood did not usually alter output or aortic pressure, but splanchnic nerve stimulation increased peripheral resistance and aortic pressure and commonly evoked a rise in left ventricular stroke work which could not be accounted for by known adrenergic mechanisms or by elevation of left ventricular end-diastolic pressure.

5. Portal venous pressure was consistently elevated by splanchnic nerve stimulation; it rose more slowly than did aortic pressure or R.A.P. and was independent of a changing central venous pressure provided this did not exceed +5 mmHg. The cardiac output increments were not related to changes in the ratio between the input

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and output resistances of the portal vein and it is concluded that displacement of blood from the peripheral to the central vasculature was induced by contraction of capacitance vessels.

INTRODUCTION

Barnes, Bower & Rink (1980) reported that the magnitudes of the rise in cardiac output and fall in mean right atrial pressure (R.A.P.) evoked by stimulation of the cardiac sympathetic nerves were closely related to the initial value of R.A.P. It was argued that the fall in R.A.P. was largely responsible for the augmentation of venous return necessary to maintain filling of the heart, and that consequently at low values of R.A.P. the ability of cardiac stimulation to increase output was limited in the absence of changes in the peripheral circulation to maintain or elevate R.A.P. by displacement of blood towards the heart.

In the previous experiments venous return and R.A.P. were increased by expansion of the circulating blood volume. An alternative physiological mechanism may be an increase of activity in the splanchnic vasoconstrictor nerves, which would displace blood from the large portal, hepatic and splenic capacitances by active contraction of their walls (Mellander, 1960; Karim & Hainsworth, 1976; Rothe, 1983) and by passive drainage consequent upon a reduced arterial inflow (Krogh, 1912; Barcroft & Samaan, 1935; Coleman, Manning, Norman & Guyton, 1973; Caldini, Permutt, Waddell & Riley, 1974). Tigerstedt (1909) first observed that stimulation of the peripheral end of the splanchnic nerve in the rabbit could increase pressure and blood flow in the aorta despite a fall in heart rate. Greenway & Innes (1980) reported that in the cat splanchnic nerve stimulation could increase cardiac output, but only if the adrenal glands were not removed.

The experiments reported here investigate the interaction between the cardiac and splanchnic sympathetic nerves on the cardiac output and R.A.P. at different circulating blood volumes in cats with unopened chests, spontaneous respiration and active vascular reflexes, after removal of the adrenal glands to prevent release of circulating catecholamines. A preliminary account has been published (Barnes, Bower & Rink, 1978).

METHODS

Surgical procedures. The experiments were carried out on thirty-nine cats of both sexes which weighed between 2·4 and 5·4 kg (mean 3·77 kg). Anaesthesia was induced with chloroform and maintained with chloralose (Koch-Light Laboratories Ltd., 70 mg kg^{-1} I.A.). The adrenal glands were exposed on each side by a retroperitoneal approach through a flank incision and were removed with the aid of hot-wire cautery. The right and left greater and lesser splanchnic nerves were identified and cut and the distal ends were placed on shielded stimulating electrodes similar to those used on the cardiac nerves. The procedures and equipment used for recording heart rate, aortic and right atrial pressures and for exposure and stimulation of the cardiac sympathetic nerves without penetration of the pleura have been described elsewhere (Barnes *et al.* 1980).

Portal venous pressure was measured in some experiments through a soft vinyl catheter (SV45; Dural Plastics and Engineering) inserted through a vein from the spleen or terminal ileum; in two cats a second catheter (Insulon Medical V4; Bolab Inc.) enabled blood to be pumped from portal vein to aorta. In two experiments a 4F balloon catheter (Pulmoball 1153·04; Vygon) was passed down a jugular vein into the inferior vena cava at the level of the diaphragm; a stable partial

obstruction of flow was achieved by distension of the balloon with saline and the elevated venous pressure was measured through the tip orifice.

After completion of the dissection the cat was laid on its left side on a heated table. All manometers (EM750; Elcomatic Ltd.) were zeroed by reference to a Marriotte's bottle filled with saline to the level of the cat's mid-thoracic spine. The required parameters were recorded continuously on a six-channel pen recorder (Physiograph Six: E & M Instrument Co. Inc.). In later experiments fluoroscopy (Cardiovision; G.E.C. Ltd.) was used to guide insertion of catheters and a computer (JP1 with ADC12 interface; Jarogate Ltd.) stored 8 s mean values of all parameters on demand.

Measurement of cardiac output by thermal dilution. An extrapolating analog computer (Bower & Ead, 1976) derived cardiac output from measurement of the depression of blood temperature in the upper aorta induced by an injection of 1 ml 5% dextrose solution at room temperature into the right atrium. Further details and assessment of the technique are described by Barnes *et al.* (1980).

It is known that if the thermal indicator traverses the pulmonary vasculature between the sites of injection and temperature measurement, pulmonary oedema can cause erroneous cardiac output readings due to loss of indicator (Hosie, 1962). As the high intravascular pressures observed in the present experiments could lead to pulmonary oedema the possibility of artifact from this cause was investigated in two cats. An additional thermistor catheter was passed down a jugular vein, through the right heart and into the pulmonary artery under fluoroscopic guidance in order to obtain simultaneous thermal dilution curves from the pulmonary artery and aorta. Cardiac output readings obtained from the pulmonary artery were more scattered than those from the aorta; in the first cat aortic readings were 6% higher and in the second cat 21% lower than those from the pulmonary artery. In the latter the average discrepancy could be reduced to 12% by injecting the indicator more slowly; the values from the pulmonary artery were lower whereas the aortic values were unchanged. It is therefore considered that the discrepancies observed were attributable to incomplete mixing of blood and indicator in the pulmonary artery. In other respects the readings varied in parallel and there was no evidence of systematic error at high intravascular pressures.

Cardiac fluoroscopy. In order to ascertain whether errors of cardiac output measurement might arise from reflux of blood through the atrio-ventricular valves of the distended ventricles videotape records of the fluoroscopic image of the heart were obtained from two cats during intraventricular injection of 1–2 ml contrast medium. During some tests the heart was slowed by stimulation of the distal end of a vagus nerve. Infusion of dextran–saline solution gave R.A.P. values of up to +7 mmHg, rising to +12 mmHg during vagal stimulation. Contrast medium was injected into the left ventricle through a catheter introduced via the carotid artery; there was no evidence of reflux into the atrium in any test. Injection of medium into the right ventricle through a jugular venous catheter gave no evidence of reflux provided the catheter was inserted to the apex of the ventricle; if it was withdrawn by 0·5–1 cm traces of contrast medium entered the atrium during ventricular systole. When a valve cusp was hooked back by a bent wire inserted via a jugular vein the resulting reflux could be seen clearly. The R.A.P. wave form was monitored in most experiments and no v-wave abnormalities indicative of ventricular reflux were observed.

Measurement of left ventricular end-diastolic pressure. To measure pressure in the left ventricle a PP60 polythene catheter with a bevelled tip and a second orifice cut in the back to reduce risk of occlusion was passed down the left carotid artery to the ascending aorta and into the ventricle. The catheter was connected to a manometer (EM 750; Elcomatic Ltd.) through 5 cm of PP10 polythene tube and a size 20 needle for critical damping. The frequency response was estimated to be 40 Hz from the transient oscillations on sudden release of pressure. The pressure wave form was displayed on an oscilloscope; a sample-and-hold circuit and an oscilloscope bright-up pulse were triggered by the electrocardiogram through a variable delay so that a bright spot on the oscilloscope trace indicated the moment of sampling. The delay was set to place this just before ventricular systole and the pressure samples so obtained were displayed on the pen writer as a continuous record of end-diastolic pressure. A major problem which limited use of the technique was the development of cardiac dysrhythmias attributable to irritation of the endocardium by the stiff catheter tip.

Input/output resistance ratio of the portal vein. A value for the ratio between the resistance of all vessels supplying blood to the portal vein and of all those draining it can be derived from the ratio of the pressure gradients: (aortic–portal pressure)/(portal–hepatic venous pressure). Inflow must equal outflow but a knowledge of absolute values for flow or resistance is not required. Provided

the pressure in the portal vein suffices to keep it distended (Öberg, 1967) and in free communication with the splanchnic venous capacitances, its value may be used as an index of the balance between blood volume and wall tension in these capacitances. In the absence of a rise in wall tension any decrease in volume must be accompanied by a fall in pressure and hence a rise in the input/output resistance ratio, whether due to arterial constriction, venous dilatation or both. Active capacitance contraction may cause a net rise in portal venous pressure but, after completion of redistribution of circulating blood volume, an elevated resistance ratio will still indicate an element of passive drainage in the sense that portal venous pressure and volume are less than they would have been had the ratio not risen.

Occlusion of the hepatic artery caused a fall in portal venous pressure of about 0·75 mmHg, indicating that it has the characteristics of an input vessel. R.A.P. was observed to be sufficiently close in value to the pressure at the caval orifices of the hepatic veins to be a satisfactory alternative parameter. The undamped, matched signals from the aortic, portal and right atrial manometers were supplied to two differencing amplifiers to give the numerator and denominator signals which were passed to an analog divider to derive a voltage proportional to the ratio for display by the pen writer. In two experiments portal venous pressure was varied by means of a peristaltic pump (501; Watson-Marlow Ltd.) connected between a second portal venous catheter and a catheter passed up a femoral artery into the aorta.

Drugs and chemicals. The following drugs were used in the experiments: atenolol (I.C.I. Ltd.), atropine sulphate (B.D.H. Ltd.), heparin (Boots Ltd.). The drugs were dissolved in 0·9 % NaCl solution; doses in the text refer to the active principles. Contrast medium used for cardiography and to fill catheters during insertion was 54 % Na iothalamate injection B.P. (Conray 325; May and Baker Ltd.). Circulating blood volume was expanded with 6 % dextran 70 in 0·9 % NaCl solution (Macrodex; Pharmacia Ltd.). Other chemical solutions were made up with analytical grade reagents.

Experimental procedure. Atropine (1 mg kg^{-1} I.V.) was administered routinely to prevent vagal slowing of the heart. In all experiments either atenolol (2 mg kg^{-1} I.V.) was administered to block the cardiac sympathetic nerves or the nerves were exposed and cut on both sides; only the right nerve was prepared for stimulation as the left nerve had been found previously to add little to the responses. In all except one cat (Fig. 9) the adrenal glands were removed and the splanchnic nerves were cut and prepared for stimulation. The circulating blood volume was expanded with dextran–saline solution (10–20 ml kg^{-1} I.A.) until R.A.P. was raised to about 7 mmHg. Thereafter volume was changed between tests by removal or reinfusion of blood–dextran mixture. Two to four control measurements of cardiac output were obtained at intervals of 1 min before commencement of each test of nerve stimulation, and measurements during the test were started as soon as aortic temperature was stable at about 1·5 min and continued until either a steady state was reached or the output readings and pressure changes started to decline. At least 15 min recovery was allowed between tests; the heart takes some 10 min to recover (Barnes *et al.* 1980) and the cat's spleen takes about 20 min to refill after sympathetic stimulation (Greenway, Lawson & Stark, 1968).

Total peripheral resistance was calculated as (aortic pressure − R.A.P.)/(cardiac output) mmHg ml^{-1} min and left ventricular stroke work as (aortic pressure × cardiac output)/(heart rate × 7·5) millijoules.

Standard errors of means were derived by analysis of variance and linear combinations of means were compared by Student's *t* test (Snedecor & Cochran, 1967). Mean values are quoted plus and minus the standard error of the mean.

RESULTS

Responses to stimulation of the splanchnic nerves

After expansion of the circulating blood volume with dextran–saline solution, the responses to stimulation of the splanchnic nerves were tested at different volumes and initial values of R.A.P. An example of a test in one cat at an intermediate volume is shown in Fig. 1 with further details of this and of tests at higher and lower volumes in Figs. 2 and 3. Right and left cardiac and splanchnic sympathetic nerves had been cut and the right greater splanchnic nerves were stimulated at 4 Hz. After stimulation

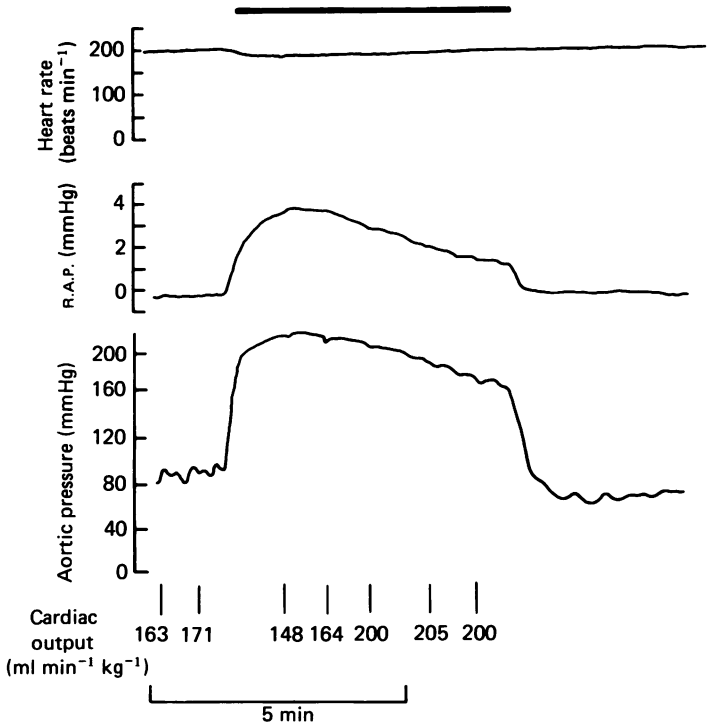

Fig. 1. Changes in heart rate, R.A.P., aortic pressure and cardiac output evoked by stimulation of the distal end of the right greater splanchnic nerve at 4 Hz during the signal bar. Bilateral adrenalectomy and cardiac sympathectomy; atropine (1 mg kg^{-1}) administered. Medium circulating blood volume; further details in Fig. 2.

was started the aortic and right atrial pressures rose to their maximum values at 1·5–2 min, aortic pressure rising faster than R.A.P. Thereafter the pressures declined slowly until stimulation was stopped at 4·5–5·5 min. At low volume, cardiac output rose slowly to a steady state 35 % above control at 3 min. At medium volume, cardiac output fell initially before rising to 18 % above control. At the highest volume and an initial R.A.P. of +3·5 mmHg, output fell by 23 % before returning slowly to control level. The combined pressure and output changes implied a large but transient increase in total peripheral resistance which accords with other reports of the pattern of resistance changes in the cat intestinal vascular bed during sympathetic stimulation (Folkow, Lewis, Lundgren, Mellander & Wallentin, 1964; Richardson & Johnson, 1969; Greenway, Scott & Zink, 1976). R.A.P. invariably rose during splanchnic nerve stimulation; the rise was small at low circulating volume and initial R.A.P. but became progressively larger as volume and initial R.A.P. were increased. The changes in cardiac output at the steady state are plotted against R.A.P. in Fig. 3.

The cardiac output and R.A.P. responses to stimulation of greater and lesser splanchnic nerves on both sides at 4 Hz in four other cats with cut cardiac nerves are shown in Table 1, with mean values in Figs. 5 and 6. Although the changes qualitatively resembled those described above, their magnitudes varied widely. The R.A.P. changes were smallest and the mean proportionate output changes largest at

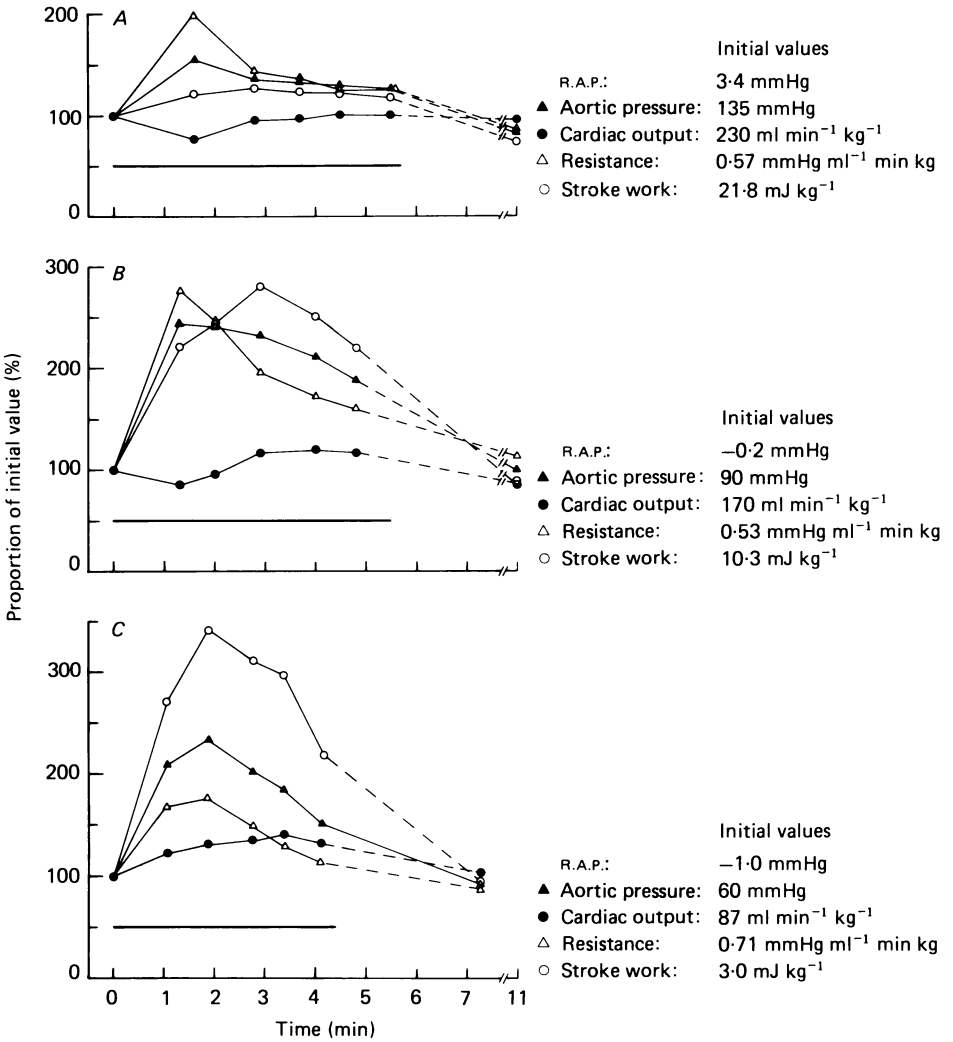

Fig. 2. Proportionate changes in aortic pressure, cardiac output, total peripheral resistance and stroke work evoked by stimulation of the right greater splanchnic nerve at 4 Hz during the signal bars in each graph. Circulating blood volumes: *A*, high; *B*, medium; *C*, low. Initially dextran–saline (20 ml kg^{-1}) was infused and blood–dextran (50 ml kg^{-1}) withdrawn; blood–dextran was reinfused at 10 ml kg^{-1} between *C* and *B* and at 35 ml kg^{-1} between *B* and *A*. Bilateral adrenalectomy and cardiac sympathectomy; atropine (1 mg kg^{-1}) administered.

the lowest circulating volume; as volume and initial R.A.P. were increased the R.A.P. increment also increased but the proportionate output increment fell and was not significant at the highest volume and initial R.A.P. of +2·9 mmHg (Fig. 5). The absolute output increments were greatest at medium volume in two of the cats, but at high volume they were small or negative, with only one cat giving a significant increase in output (Table 1). The mean absolute changes in output and in R.A.P. at each mean control R.A.P. value are plotted in Fig. 6 *A*; as in Fig. 3 they lie

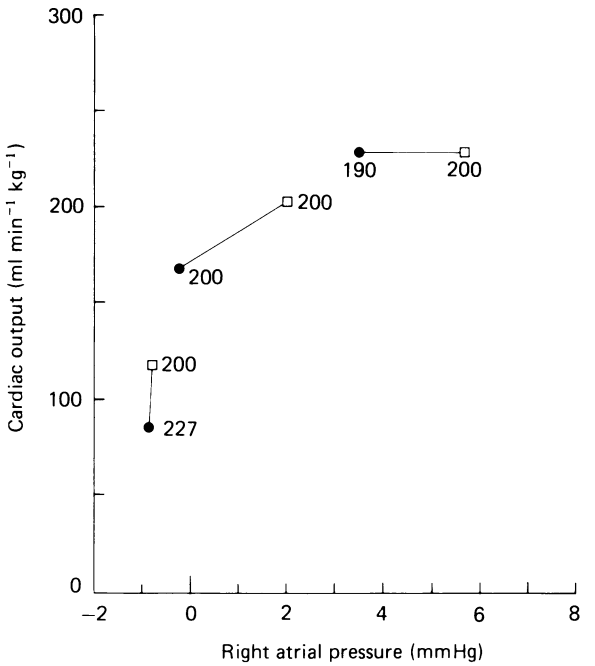

Fig. 3. Changes in cardiac output and R.A.P. evoked by stimulation of the distal end of the right greater splanchnic nerve at three circulating volumes. The lines which join the control points (●) and the test points (□) show the responses to stimulation at 4 Hz; the heart rate (beats min^{-1}) is shown next to each point. For further details see Fig. 2.

approximately along the curve formed by the control points and the pattern as a whole resembles that formed by change of circulating volume.

The splanchnic nerves were stimulated on both sides in two groups of cats with cardiac nerves intact but blocked by atenolol (2 mg kg^{-1} I.V.) and atropine (1 mg kg^{-1} I.V.). Stimulation at 2 Hz in the first group of five cats evoked an output increase of $20{\cdot}6 \pm 3{\cdot}7$ % at initial R.A.P. $-1{\cdot}9 \pm 0{\cdot}2$ mmHg and a decrease of $22{\cdot}6 \pm 3{\cdot}1$ % at initial R.A.P. $+3{\cdot}2 \pm 0{\cdot}4$ mmHg. Stimulation at 4 Hz in the second group of four cats evoked an output increase of $23{\cdot}2 \pm 3{\cdot}0$ % at initial R.A.P. $-0{\cdot}9 \pm 0{\cdot}3$ mmHg and a decrease of $17{\cdot}0 \pm 2{\cdot}6$ % at initial R.A.P. $+3{\cdot}9 \pm 0{\cdot}2$ mmHg.

Stimulation of the cardiac and splanchnic sympathetic nerves

The changes in cardiac output and R.A.P. evoked by stimulation of the right cardiac and right greater splanchnic nerves at 5 Hz separately and together at five different circulating volumes in one experiment are shown in Fig. 4. The results of stimulation of the cardiac nerves alone were consistent with those reported previously (Barnes *et al.* 1980). At low circulating volume and initial R.A.P. cardiac output did not change significantly and R.A.P. fell by 0·4 mmHg. As volume and initial R.A.P. were increased the rise in output and the fall in R.A.P. increased to maximum values of +20 % and −1·7 mmHg respectively. Splanchnic nerve stimulation augmented output and R.A.P. by 20 % and +0·2 mmHg respectively at low volume, changing to −4 % and +2·9 mmHg at the highest volume. On simultaneous stimulation of the cardiac and

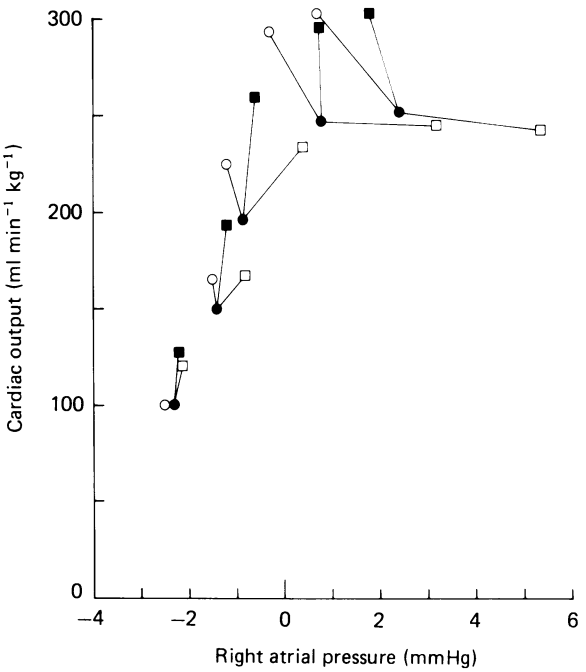

Fig. 4. Changes in cardiac output and R.A.P. evoked by separate and simultaneous stimulation of the right cardiac sympathetic and right greater splanchnic nerves at five different circulating volumes. Lines which join the control points (●) and the test points show the responses to cardiac nerve (○), splanchnic nerve (□) and simultaneous (■) stimulation at 5 Hz. Mean heart rates (beats min^{-1}): control, 167 ± 3·6; cardiac nerve, 229 ± 2·9; splanchnic nerve, 168 ± 3·2; simultaneous, 222 ± 3·0. Initially dextran–saline (20·8 ml kg^{-1}) was infused and blood–dextran (41·7 ml kg^{-1}) withdrawn. The volumes reinfused of blood–dextran at successive steps were: 8·3, 12·5, 12·5 and 8·3 ml kg^{-1}. Bilateral adrenalectomy and cardiac sympathectomy; atropine (1 mg kg^{-1}) administered.

splanchnic sympathetic nerves the output increments combined whereas the R.A.P. changes cancelled, to give cardiac output increments of 20–33 % at all circulating blood volumes with small, variable changes in R.A.P.

Table 1 and Figs. 5 and 6 summarize results from four consecutive experiments performed when the dissection and procedure had been standardized. The right cardiac and the right and left splanchnic nerves were stimulated at 4 Hz at three different circulating volumes set by reference to the initial R.A.P. and output values to be as comparable as possible in the four animals. As before, during cardiac nerve stimulation the R.A.P. changes and cardiac output increments were smallest at the lowest circulating volume; as volume and initial R.A.P. were augmented so were the falls in R.A.P. and the increments in output, both absolute and proportionate. During simultaneous stimulation the cardiac output changes attributable to splanchnic and cardiac nerves combined to give output increments ranging from 50·2 % at low volume to 26·5 % at high volume; changes in R.A.P. were small and variable. At the highest volumes the output increments during simultaneous stimulation were in all cases less than those evoked by cardiac nerve stimulation alone; however, the calculated left ventricular stroke work increments were greater in all except one cat due to the vasoconstrictor action of the splanchnic nerves.

TABLE 1. Changes in R.A.P. (ΔR.A.P.), cardiac output (Δc.o.), stroke work (Δs.w.), and heart rate (ΔH.R.) evoked by stimulation of all splanchnic nerves and of the right cardiac sympathetic nerves separately and together at 4 Hz at high (H.), medium (M.) and low (L.) circulating volumes in each of four cats. Significant changes in output and in stroke work are indicated as: $*P < 0.05$; $**P < 0.01$. Bilateral adrenalectomy and cardiac sympathectomy; atropine (1 mg kg^{-1}) administered

	Control values				Splanchnic nerves			
Cat	R.A.P. (mmHg)	C.o (ml min^{-1} kg^{-1})	S.w. (mJ kg^{-1})	H.R. (beats min^{-1})	ΔR.A.P. (mmHg)	ΔC.o. (ml min^{-1} kg^{-1})	ΔS.w. (mJ kg^{-1})	ΔH.R. (beats min^{-1})
57 H.	+2·4	183	14·9	174	+2·6	+5·2	+7·9**	+14
M.	−1·1	133	8·9	163	+2·9	+15·0	+4·4**	0
L.	−1·9	107	4·2	191	+0·4	+37·0**	+3·5**	+2
58 H.	+3·2	295	20·2	230	+2·7	−0·3	+10·4**	+11
M.	−0·8	229	16·4	216	+0·6	+47**	+7·1**	+1
L.	−1·9	157	8·9	218	+0·3	+18·5**	+1·9**	+4
59 H.	+2·8	246	18·3	211	+3·7	−20·7*	+10·5**	−10
M.	−1·6	142	8·2	203	+0·6	+25·8**	+8·8**	−23
L.	−2·1	82	3·3	197	+0·3	+33·7**	+3·7**	−21
60 H.	+3·2	283	17·2	204	+5·0	+33·1**	+21·4**	0
M.	−1·0	190	10·3	205	+1·9	+108**	+22·6**	−3
L.	−1·6	113	4·5	190	+0·5	+72·6**	+9·8**	+5

	Cardiac nerves				Splanchnic + cardiac nerves			
Cat	ΔR.A.P. (mmHg)	ΔC.o. (ml min^{-1} kg^{-1})	ΔS.w. (mJ kg^{-1})	ΔH.R. (beats min^{-1})	ΔR.A.P. (mmHg)	ΔC.o. (ml min^{-1} kg^{-1})	ΔS.w. (mJ kg^{-1})	ΔH.R. (beats min^{-1})
57 H.	−2·1	+71·5**	+8·2**	+63	−0·5	+66**	+9·2**	+60
M.	−0·9	+32**	+0·1	+68	+0·9	+67**	+7·3**	+55
L.	−0·2	+9·9	−0·4	+47	+0·1	+43·5**	+2·7**	+44
58 H.	−2·6	+96**	+13·4**	+41	0	+48**	+10·0**	+43
M.	−0·6	+32**	+0·7	+57	+0·3	+92**	+8·9**	+43
L.	+0·03	+18·5**	−0·2	+70	+0·3	+40·5**	+1·6**	+69
59 H.	−2·6	+65·2**	+5·9**	+66	+0·4	+55·5**	+12·5**	+40
M.	+0·1	+29·6**	+2·7**	+54	+0·7	+58·7**	+10·1**	+40
L.	−0·1	+19·7**	+1·1**	+31	+0·1	+47·5**	+5·2**	+23
60 H.	−2·9	+109**	+15·7**	+47	+3·3	+88·4**	+21·4**	+60
M.	−0·7	+25·9**	+2·7**	+55	+0·9	+102**	+18·6**	+56
L.	−0·2	+10·6**	−0·7	+65	−0·1	+86·4**	+9·3**	+56

Cardiac stroke work during splanchnic nerve stimulation

Although the changes in cardiac output resembled those induced by volume expansion, the increase in total peripheral resistance implied a greater load on the heart during nerve stimulation. An increase in calculated left ventricular stroke work was generally observed not only at low circulating volume and R.A.P. but also at high levels (Table 1 and Fig. 6*B*) at which it would be expected that the heart would be filled to its maximum diastolic volume and insensitive to further elevation of R.A.P. (Barnes *et al.* 1980). The increments were not related to the small and erratic changes

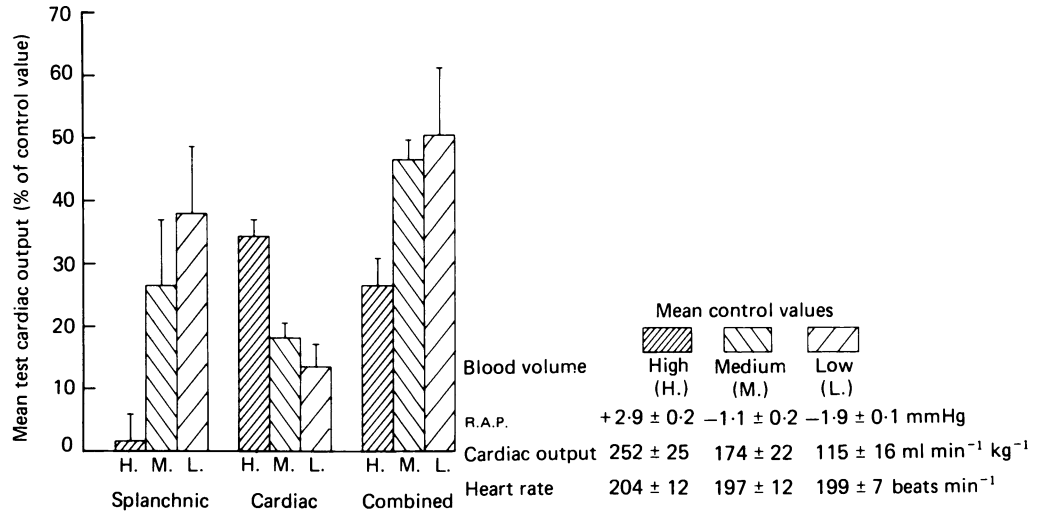

Fig. 5. Means and standard errors of means of the proportionate changes in cardiac output evoked by separate and simultaneous stimulation of the right cardiac sympathetic and of all splanchnic nerves at 4 Hz and at three circulating volumes (see key on Figure) in four cats. Bilateral adrenalectomy and cardiac sympathectomy; atropine (1 mg kg^{-1}) administered.

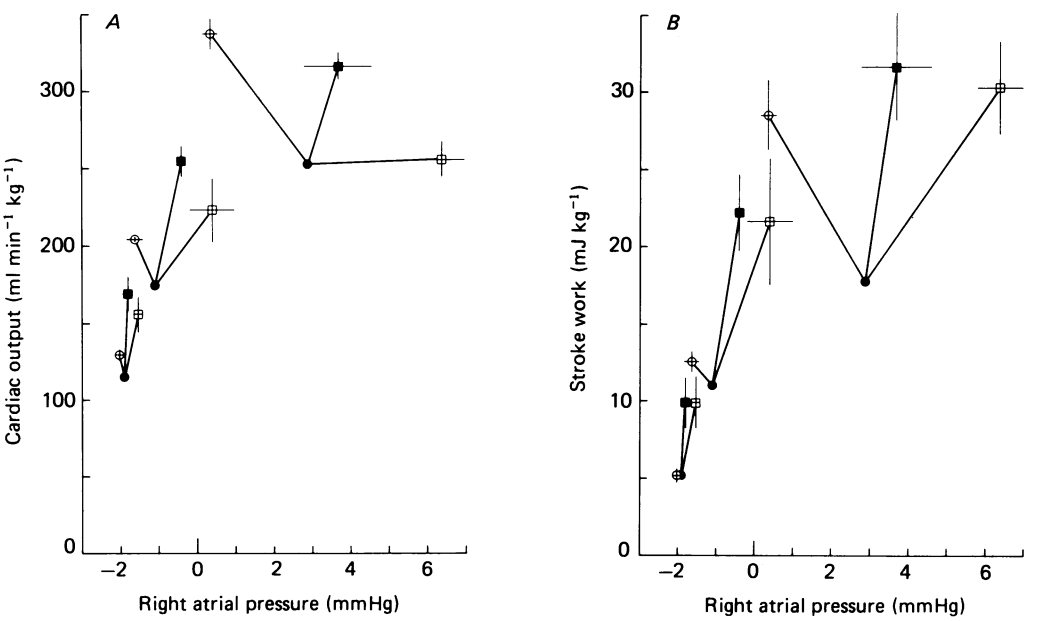

Fig. 6. Means and standard errors of means of changes in cardiac output, stroke work and r.a.p. evoked by separate and simultaneous stimulation of the right cardiac sympathetic and of all splanchnic nerves at three different circulating volumes in four cats. Lines which join the mean control values (●) and the test points show the means of the responses to cardiac nerve (○), splanchnic nerve (□) and simultaneous stimulation (■) at 4 Hz in the cats listed in Table 1. Bilateral adrenalectomy and cardiac sympathectomy; atropine (1 mg kg^{-1}) administered. *A*, mean changes in cardiac output and r.a.p. from mean control values. *B*, mean changes in stroke work and r.a.p. from mean control values.

TABLE 2. Effects on R.A.P., cardiac output (C.O.), stroke work (S.W.) and heart rate (H.R.) of blood withdrawal and of stimulation of all splanchnic nerves at 2 Hz in five cats at high circulating blood volume. Volume was expanded initially by infusion of dextran–saline (15 ml kg^{-1}); blood–dextran (5 ml kg^{-1}) was withdrawn before the first control values were obtained. Significant proportionate changes in cardiac output (ΔC.O. %) and in stroke work (ΔS.W. %) are indicated as: ** $P < 0.01$; *** $P < 0.001$. Bilateral adrenalectomy; atenolol (2 mg kg^{-1}) and atropine (1 mg kg^{-1}) administered

	Expanded circulating volume				Control values before and after splanchnic nerve stimulation				Splanchnic nerve stimulation					
Cat	R.A.P. (mmHg)	C.O. (ml min^{-1} kg^{-1})	S.W. (mJ kg^{-1})	H.R. (beats min^{-1})	R.A.P. (mmHg)	C.O. (ml min^{-1} kg^{-1})	S.W. (mJ kg^{-1})	H.R. (beats min^{-1})	R.A.P. (mmHg)	C.O. (ml min^{-1} kg^{-1})	S.W. (mJ kg^{-1})	H.R. (beats min^{-1})	ΔC.O. (%)	ΔS.W. (%)
46	6·2	149	15·7	143	4·2	159	16·7	146	8·5	136	18·8	145	−13·7***	+27·0***
					4·2	156	12·9	145						
47	5·0	182	20·1	157	3·0	183	19·8	154	10·0	123	20·2	164	−31·1***	+3·1
					4·2	174	19·4	170						
48	5·8	169	12·6	152	3·6	173	13·0	152	9·0	138	19·7	148	−18·6***	+39·7***
					3·8	166	15·2	153						
49	4·7	199	22·0	153	2·8	206	22·5	153	9·0	147	23·6	151	−26·9***	+9·5**
					3·0	196	20·6	156						
50	5·5	136	10·7	169	1·6	142	9·5	166	9·9	117	14·1	168	−22·5***	+28·2***
					1·8	160	12·5	171						

in heart rate observed after the cardiac sympathetic nerves were cut. If the nerves were left intact heart rate invariably fell during splanchnic nerve stimulation. In order to test whether the increment was attributable to release of catecholamines from extramedullary chromaffin tissue supplied by the splanchnic nerves, the effects of stimulation at 2 Hz were observed in five adrenalectomized cats treated with atenolol (2 mg kg^{-1} I.V.) and atropine (1 mg kg^{-1} I.V.); the results are shown in Table 2. After expansion of the circulating volume, blood dextran (5 ml kg^{-1}) was withdrawn to establish that volume and R.A.P. changes did not affect cardiac output or stroke work at this level. In each experiment splanchnic nerve stimulation caused output to fall significantly (mean change $-22{\cdot}6 \pm 3{\cdot}1$ %); nevertheless, stroke work increased (mean change $+21{\cdot}5 \pm 6{\cdot}6$ %) and in four cats the increment was significant ($P < 0{\cdot}001$). Heart rate changes were negligible. Significant stroke work increments ($P < 0{\cdot}02$) of 3·6–17·4 % were also elicited in each of a second group of four cats with initial R.A.P. values between +3·4 and +4·5 mmHg; the mean increment was $12{\cdot}4 \pm 3{\cdot}1$ % and cardiac output fell by $17{\cdot}0 \pm 2{\cdot}6$ %.

Left ventricular end-diastolic pressure. The calculated stroke work commonly developed more slowly than the pressure changes and did not reach its maximum until 2–3 min after the start of stimulation (Fig. 2). In order to examine the possibility that the time course of R.A.P. changes may not accurately reflect that of the forces filling the left heart the left ventricular end-diastolic pressure (L.V.E.D.P.) was measured. Variation of R.A.P. over the range +6·7 to −2·4 mmHg in one cat by withdrawal of blood–dextran yielded the relationship: L.V.E.D.P. = (1·9 + 2·1 × R.A.P.) mmHg; the coefficient of correlation r was 0·99 ($n = 37$).

The time course of the responses to change of circulating volume and to stimulation of the splanchnic nerves at 4 Hz in one cat is shown in Fig. 7. Withdrawal of 20 ml blood–dextran caused no significant changes in stroke work or cardiac output but evoked falls in R.A.P. from 5 to 3·3 mmHg and in L.V.E.D.P. from 17 to 12 mmHg. Stimulation of the splanchnic nerves caused L.V.E.D.P. to rise to a peak value of 26 mmHg within 0·5 min; R.A.P. rose more slowly to a maximum of 10 mmHg in 2·5 min. Both pressures fell steadily from their peak values throughout the rest of the stimulation period. Stroke work rose by 11 % within 2 min and then increased further to a level 25 % above control at 6 min despite the fall in L.V.E.D.P. Although atropine and atenolol had been administered heart rate fell by 10 % during the test. After cessation of stimulation the R.A.P., L.V.E.D.P., stroke work and heart rate returned to control values within 2 min.

Recordings from two more cats showed similar time courses of R.A.P. and L.V.E.D.P. changes during splanchnic nerve stimulation. In the first, R.A.P. rose from 3 to 8 mmHg, then fell to 7 mmHg and L.V.E.D.P. rose from 12 to 17 mmHg, falling to 12 mmHg; the stroke work increment was $28 \pm 3{\cdot}8$ % ($P < 0{\cdot}001$). In the second, R.A.P. rose from 4 to 10 mmHg and fell to 6·4 mmHg, while L.V.E.D.P. rose from 10 to 30 mmHg, falling to 7 mmHg; the stroke work increment was $12{\cdot}4 \pm 4{\cdot}1$ % ($P < 0{\cdot}02$). In both experiments the increased level of stroke work was maintained throughout the test period despite the fall in L.V.E.D.P. Simultaneous output measurements from a pulmonary arterial thermistor in the second experiment were higher and more scattered than those from the aorta but both sets of measurements showed a significant rise in stroke work.

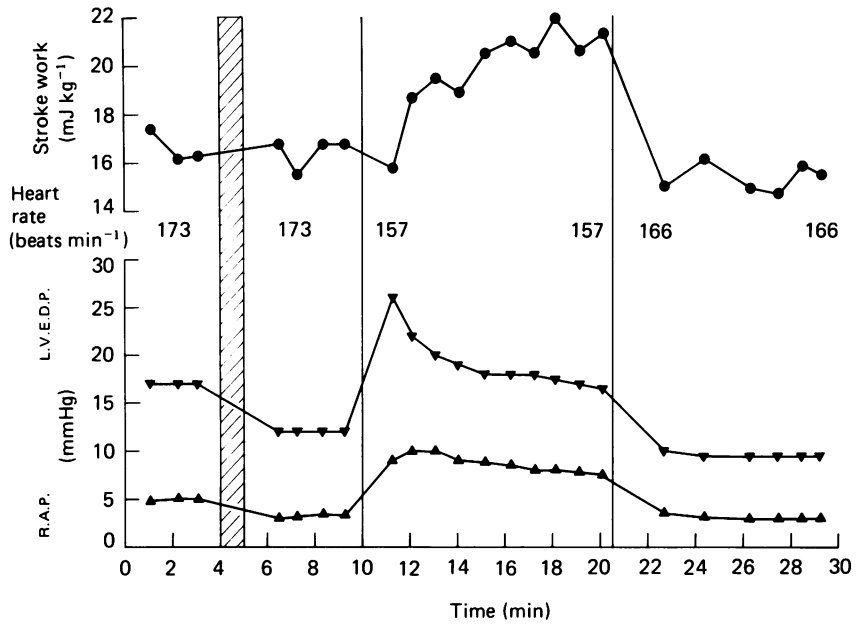

Fig. 7. Changes in stroke work, heart rate, L.V.E.D.P. and R.A.P. evoked by withdrawal of blood and by stimulation of all splanchnic nerves at high circulating volume. Graphs of stroke work (●), L.V.E.D.P. (▼) and R.A.P. (▲) share a common zero at the abscissa. Initially dextran–saline (13 ml kg^{-1}) was infused. At 4 min blood–dextran (4·4 ml kg^{-1}) was withdrawn, indicated by the hatched bar; between 10 min and 20·5 min the distal ends of all splanchnic nerves were stimulated at 4 Hz, indicated by the vertical lines. Bilateral adrenalectomy; atenolol (2 mg kg^{-1}) and atropine (1 mg kg^{-1}) administered.

Portal venous pressure during splanchnic nerve stimulation

Fig. 8 shows a record from an experiment in which the portal venous pressure was measured and the input/output resistance ratio derived and recorded. After the start of stimulation the portal pressure consistently fell before rising slowly to a peak value at 4–5 min, appreciably later than the aortic pressure and R.A.P. maxima. The delayed rise in portal pressure was reflected in a sharp initial increase of the resistance ratio, followed by a decline more rapid than that of total peripheral resistance. At the first cardiac output measurement during stimulation the ratio had increased by 144 % and the total peripheral resistance by 53 %, but during the final four measurements the ratio increment was only +11 % whereas total peripheral resistance was still 17 % above control.

The changes in portal venous pressure and resistance ratio were further examined during splanchnic nerve stimulation at 4 Hz in a group of six adrenalectomized cats with reduced circulating blood volumes and negative R.A.P. values; the cardiac nerves had been blocked with atropine and atenolol. The means of the control values and of the changes from control are shown in Table 3. In each cat cardiac output and the pressures in the aorta, portal vein and right atrium increased significantly; in one experiment portal venous pressure consistently fell before rising. The rise in total peripheral resistance was significant ($P < 0·05$) for the group as a whole but was less

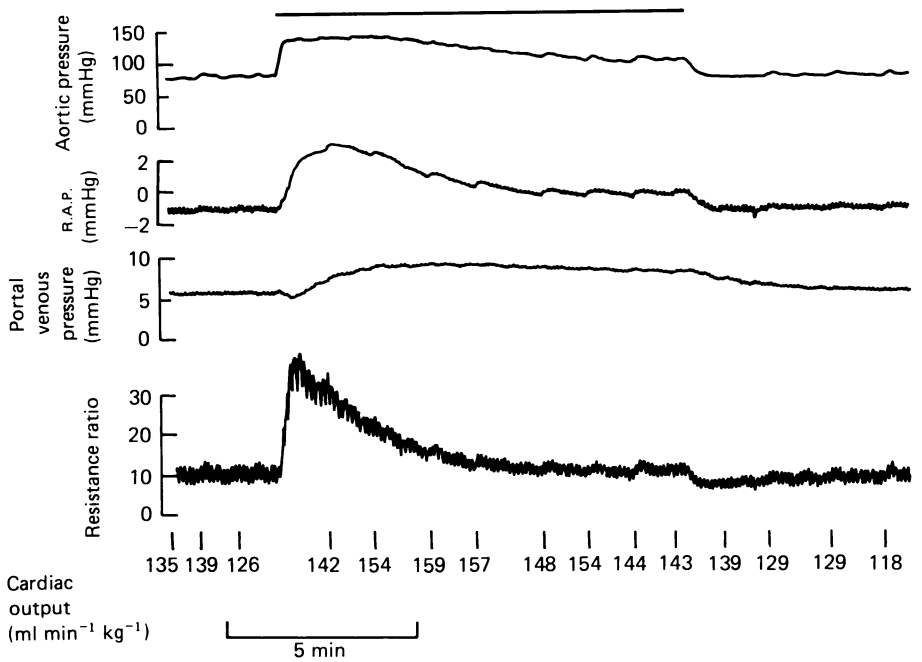

Fig. 8. Changes in aortic pressure, R.A.P., portal venous pressure, portal input/output resistance ratio and cardiac output evoked by stimulation of the distal ends of the right greater splanchnic nerve at 4 Hz during the signal bar. Bilateral adrenalectomy; atenolol (2·6 mg kg^{-1}) and atropine (1·3 mg kg^{-1}) were administered.

TABLE 3. Means and standard errors of means of changes in cardiovascular parameters evoked by stimulation of the distal ends of all splanchnic nerves at 4 Hz in six cats. Bilateral adrenalectomy; atenolol (2 mg kg^{-1}) and atropine (1 mg kg^{-1}) administered. Blood was withdrawn if necessary to obtain a negative R.A.P. For further explanation see text

	Control	Change	P
Aortic pressure:	77·3 ± 9·4 mmHg	+22·8 ± 3·1 mmHg	< 0·001
Portal pressure:	6·71 ± 0·23 mmHg	+2·77 ± 0·6 mmHg	< 0·01
R.A.P.:	−0·84 ± 0·21 mmHg	+0·86 ± 0·18 mmHg	< 0·01
Cardiac output:	106·7 ± 15·2 ml min^{-1} kg^{-1}	+20·5 ± 2·62 %	< 0·001
Peripheral resistance:	0·76 ± 0·075 mmHg ml^{-1} min kg	+7·65 ± 1·8 %	< 0·01
Resistance ratio:	9·33 ± 1·03	+6·1 ± 7·8 %	N.s.
Correlation coefficient r (Δratio/Δoutput): 0·818			< 0·05
Resistance ratio (R.A.P. = control):		−3·9 ± 6·0 %	N.s.
Correlation coefficient r (Δratio/Δoutput): 0·690			N.s.

than significant in three of the cats. After an initial transient rise the resistance ratio remained significantly elevated in only three experiments; the steady-state changes ranged from −18·8 % to +35·6 % and were not related to the changes in total peripheral resistance. Although the mean rise in resistance ratio was not significant there was a significant correlation between the changes in resistance ratio and in cardiac output.

A proportion of the observed increments in resistance ratio may have been due not to arterial constriction but to passive distension of partially collapsed hepatic veins by the rise in central venous pressures (Mitzner, 1974). The extent to which this prevents elevation of portal venous pressure was tested in two cats, one of which had its adrenal glands removed and splanchnic nerves cut, by progressive distension of

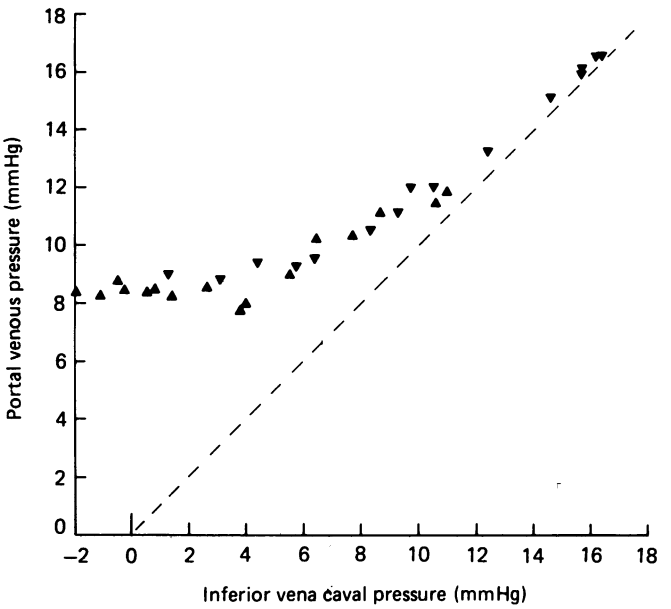

Fig. 9. Pressures recorded in the portal vein and inferior vena cava in two cats during progressive obstruction of the inferior vena cava by distension of a balloon-tipped catheter at the level of the diaphragm. The dashed line is the line of equality. In one cat (▲) both adrenal glands had been removed and all splanchnic nerves cut; the other cat (▼) was left intact. Atenolol (2 mg kg^{-1}) and atropine (1 mg kg^{-1}) were administered.

a balloon catheter in the inferior vena cava cranial to the diaphragm; the results are shown in Fig. 9. Elevation of R.A.P. did not affect portal venous pressure in either experiment until it exceeded +5 mmHg; thereafter portal pressure rose somewhat less than in proportion to R.A.P. As R.A.P. did not approach +5 mmHg in the experiments in Table 3 the contribution of passive distension of the hepatic veins to elevation of the resistance ratio could be discounted by recalculation of the ratios with R.A.P. held constant at its control value. The revised values for ratio changes ranged from −23·2% to +12%; only two cats showed a significant increase in resistance ratio and neither the mean change of $-3{\cdot}9 \pm 6{\cdot}0\%$ nor the correlation between the changes in ratio and in cardiac output were significant.

A change in resistance ratio was induced in two experiments by pumping blood from the portal vein to the aorta at the rate of 35 ml min^{-1}. This procedure, which in effect increased the input resistance to the portal vein, reduced portal venous pressure by 1·3 and 0·6 mmHg, increased the resistance ratio by 22·7% and 11·7%

and total peripheral resistance by 22·9% and 8·6% in each cat. However, cardiac output fell by 18% and 3·9%; as R.A.P. fell by 0·19 and 0·12 mmHg and stroke work also fell, the decline in output must be attributed to a decrease in the forces returning blood from the periphery rather than to back-loading of the heart.

DISCUSSION

In the experiments described here, stimulation of the splanchnic nerves evoked changes in cardiac output and R.A.P. which resembled those induced by infusion of blood–dextran solution; if a curve is drawn through the splanchnic nerve stimulation test points in Fig. 6*A* it falls close to one drawn through the control points. The simultaneous elevation of pressures in the aorta and right atrium shows clearly that splanchnic nerve stimulation could induce the sustained transfer of a volume of blood from the peripheral to the central vessels in the whole animal. If the heart still had scope to distend and thus to increase its force of contraction by the Starling effect, part of this volume was transferred to the aorta to increase arterial pressure and flow. This is consistent with the report by Greenway & Innes (1980) that the output increment evoked by splanchnic nerve stimulation was abolished by adrenalectomy but could be restored by procedures which prevented back-loading of the heart.

Stimulation of the cardiac sympathetic nerves evoked a rise in output and fall in R.A.P. related in magnitude to the initial value of R.A.P., as reported previously (Barnes *et al.* 1980). Due to the combined chronotropic and inotropic effects a curve drawn through the cardiac nerve stimulation test points in Fig. 6*A* is displaced upwards relative to one drawn through the control points.

Cardiac output was augmented most by simultaneous stimulation of the cardiac and splanchnic sympathetic nerves, which gave increments of the order of 50% at low volumes and 25% at high volumes with small, variable changes in R.A.P. The increments at high volume were generally slightly less than those evoked by stimulation of cardiac nerves alone, possibly due to elevation of peripheral resistance by the splanchnic nerves. The cardiac sympathetic activity enabled the heart to accept the volume of blood expelled from the splanchnic vasculature with little change in R.A.P. and to transfer it to the aorta to give a sustained increase in arterial flow. The sympathetic nervous system is thus equipped with two complementary mechanisms for augmenting the cardiac output with little change in R.A.P. at any circulating volume. Simultaneous activation would normally be expected to occur in most physiological responses, but the relative importance of the two mechanisms will depend on the initial R.A.P. and diastolic volume of the heart.

Left ventricular stroke work

Although the output responses to infusion and to splanchnic nerve stimulation are similar, the arteriolar constrictor action of the nerves imposes an additional load on the heart. Consequently the output responses in Fig. 6*A* differ from the stroke work changes in Fig. 6*B* in which a curve drawn through the splanchnic nerve stimulation test points is displaced upwards relative to one drawn through the control points; there appears to have been a cardiac inotropic influence comparable to that exerted

by the cardiac sympathetic nerves. Similarly, Herndon & Sagawa (1969) reported that in the dog cardiac function curves which related output to R.A.P. differed little at aortic pressures of 50, 100 and 150 mmHg.

This anomalous stroke work increment varied greatly between animals and was absent from some. No satisfactory explanation can yet be offered but the following mechanisms may have contributed.

The Starling effect due to increased diastolic volume of the left ventricle could still resist back-loading of the heart at high R.A.P. if the limitation to further increase of output on infusion is imposed by maximal filling of the right ventricle. L.V.E.D.P. was however observed to increase with R.A.P. at all levels tested and the augmented stroke work was maintained or even further increased while R.A.P. and L.V.E.D.P. were falling (Fig. 7); this argues against diastolic volume expansion as the inotropic mechanism.

Homeometric autoregulation, described as a slowly developing increase in contractility observed on back-loading the heart at constant total coronary blood flow (Sarnoff, Mitchell, Gilmore & Remensnyder, 1960), could underlie the increment and account for its slow development and variability. The aetiology is still obscure and may include redistribution of coronary blood flow (Monroe, Gamble, Lafarge, & Vatner, 1974) and slow changes in intracellular calcium metabolism (Allen & Kurihara, 1982); its magnitude varies greatly and some experimenters have been unable to demonstrate it (Elzinga, Noble & Stubbs, 1977).

Release of inotropic factors. Extramedullary chromaffin tissue and nerve endings may have released catecholamines but there was no consistent cardiac acceleration and stroke work was still increased in animals with β_1 receptors blocked by atenolol (Table 2). It is not certain from the available information whether atenolol reduced the magnitude of the increment. Other chemical factors such as glucagon (Farah, 1983) may also be released in quantities sufficient to exert an inotropic action. Such a mechanism may be expected to be slow in onset and variable in magnitude, but it might also be expected to outlast the period of stimulation rather more than was observed.

Displacement of blood from the splanchnic vasculature

The vessels of the liver, spleen and intestines contain a reserve of blood which can be displaced by sympathetic activation (Mellander, 1960; Greenway *et al.* 1968; Greenway, Stark & Lautt, 1969; Brooksby & Donald, 1971, 1972); they are thought to supply two-thirds of the volume of blood removed in non-hypotensive haemorrhage in the cat (Greenway & Lister, 1974). Although active contraction of capacitance vessels occurs (Karim & Hainsworth, 1976), a sustained displacement of blood from peripheral to central vessels may also be induced by splanchnic arterial constriction. Experimentally, cardiac output can be increased by mechanical obstruction of the descending aorta (Barcroft & Samaan, 1935) or of the superior mesenteric artery (Groszmann, Blei, Kniaz, Storer & Conn, 1978). Theoretical models (Coleman *et al.* 1973; Caldini *et al.* 1974) show the basis of the blood displacement to be diversion of flow by differential arterial constriction from a vascular bed with a long time constant for venous drainage to a parallel bed with a short time constant.

The models treat arterial and venous resistances as independent, but the hepatic

veins behave as collapsible vessels in which resistance varies inversely with flow, thereby stabilizing intravascular pressure at the site of collapse, with important haemodynamic consequences (Mitzner, 1974). First, on reduction of blood flow by arterial constriction the hepatic veins partially collapse, preventing passive drainage of blood from the portal vein and directly increasing resistance to venous return; the total effect is that of closure of an arterio–venous shunt (Guyton & Sagawa, 1961). Secondly, a rise in portal venous pressure induced by capacitance contraction expands the hepatic veins, facilitating active expulsion of blood. Thirdly, if blood displacement by either mechanism raises central venous pressure then passive expansion of the hepatic veins prevents elevation of portal venous pressure and consequent pooling of blood, provided the collapse pressure of about 5 mmHg is not exceeded (Fig. 9). In the present experiments on the effects of pumping blood from the portal vein to the aorta, the small increase in resistance ratio and reduction in output observed implies that venous resistance increased less than in proportion to arterial resistance and that the resulting volume displacement nearly, but not quite, compensated for the elevation of resistance to venous return by collapse of the hepatic veins.

The simultaneous elevation of aortic pressure, portal venous pressure, R.A.P. and L.V.E.D.P. during splanchnic nerve stimulation pointed clearly to a sustained rise in mean circulatory filling pressure attributable to capacitance contraction. There was also an initial rapid increase in the resistance ratio which could be attributed to intense arteriolar constriction in the first instance and also to expansion of the hepatic veins by the rising central venous pressure later. Nevertheless, when the autoregulation characteristic of the cat's intestinal arterioles developed the ratio soon fell, in some cases to less than the control value, and the fall was emphasized if the contribution of the rising R.A.P. was discounted. As total peripheral resistance was elevated even when the resistance ratio fell below control level there was probably active constriction of the hepatic veins.

In most experiments the cardiac output increment followed the time course of the portal venous pressure changes rather than the resistance ratio and, furthermore, output rose even when the ratio fell far below its control value. It therefore appears that although arteriolar constriction may contribute to the early phase of blood transfer, in the cat capacitance contraction is the principal mechanism by which splanchnic nerve stimulation augments venous return.

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