J. Physiol. (1973), **228**, *pp.* 139–155
With 7 text-figures
Printed in Great Britain

LEFT VENTRICULAR INOTROPIC AND PERIPHERAL VASOMOTOR RESPONSES FROM INDEPENDENT CHANGES IN PRESSURE IN THE CAROTID SINUSES AND CEREBRAL ARTERIES IN ANAESTHETIZED DOGS

By R. HAINSWORTH and F. KARIM

From the Cardiovascular Unit, Department of Physiology, University of Leeds, Leeds LS2 9JT

(*Received 29 June 1972*)

SUMMARY

1. The pressure perfusing the isolated carotid sinuses and the pressure perfusing the cerebral circulation were changed independently, and the resulting inotropic responses in the left ventricle and peripheral vasomotor responses were determined.

2. Inotropic responses were assessed by measuring changes in the maximum rate of change of left ventricular pressure (dP/dt max) with heart rate and mean aortic pressure held constant. Vascular resistance changes were usually assessed by perfusing the descending thoracic aorta at constant flow and measuring changes in perfusion pressure.

3. Decreases in carotid sinus pressure over the baroreceptor sensitivity range resulted in a 45% increase in dP/dt max and a 59% increase in vascular resistance.

4. Unless arterial oxygen tension was abnormally low, lowering cerebral perfusion pressure to 50 mm Hg resulted in little or no inotropic and vasomotor responses. In the presence of hypoxaemia ($P_{a,O_2} < 60$ mm Hg), lowering cerebral perfusion pressure to below about 80 mm Hg resulted in marked responses.

5. These experiments suggest that, unless arterial oxygen tension is abnormally low, the carotid sinus reflex and not cerebral hypotension is important in the control of the inotropic state of the heart and of vasomotor activity. With hypoxaemia, responses from cerebral hypotension may also be important.

INTRODUCTION

Although the effects of carotid sinus hypotension on heart rate and vascular resistance are well known (Heymans & Neil, 1958), there is still some uncertainty as to its effect on the inotropic state of the heart. There

are several reports describing a small positive inotropic response as carotid pressure was reduced, but this response was attributed by Downing & Gardner (1968) either to a concomitant fall in cerebral perfusion pressure or secondary to changes in systemic arterial blood pressure. Both inotropic and vasomotor responses are known to occur as a result of gross cerebral hypotension or hypoxaemia (Sagawa, Ross & Guyton, 1961; Downing, Mitchell & Wallace, 1963; De Geest, Levy & Zieske, 1965), but there is little information on the degree of cerebral hypotension or hypoxaemia required to induce responses. Therefore it is not known whether the carotid sinus reflex or cerebral ischaemia is of primary importance in the control of the inotropic state of the heart and of vasomotor tone.

In the experiments reported in this paper, we determined inotropic and vasomotor responses in carefully controlled preparations in which the pressure perfusing the isolated carotid sinuses was changed while the pressure in the rostral end of the animal, perfused through the brachiocephalic and left subclavian arteries, was held constant. We then determined the responses from changing brachiocephalic and left subclavian artery perfusion pressure with carotid sinus pressure held constant. In some experiments we also determined the effect of arterial hypoxaemia on the responses to cerebral hypotension. We were thus able to compare, in the same animals, the responses from carotid and cerebral hypotension and to determine the circumstances in which each mechanism was likely to be important.

METHODS

Dogs of weight 15–26 kg were anaesthetized by chloralose (0·1 g/kg; British Drug Houses) infused through a catheter which had been passed, under local anaesthesia, (decicain 2 %), through a saphenous vein so that its tip lay in the inferior vena cava. The chloralose was dissolved to make a solution, 1 g/100 ml. in sodium chloride solution (0·9 g/100 ml.). A state of light surgical anaesthesia was maintained during the experiment by further infusions of chloralose (about 10 mg/kg every 15 min). Following induction of anaesthesia the neck was opened in the mid line, the trachea cannulated and positive pressure ventilation started by means of a Starling 'Ideal' pump using 40 % oxygen in nitrogen humidified at room temperature. The rate of the pump was 18 strokes/min and the stroke volume was approximately 50 ml./3 kg body weight. When the pleura was opened a resistance to expiration was inserted equivalent to 3 cm water.

Both carotid sinuses were vascularly isolated, using a dissecting microscope to identify and tie the smaller branches. The internal carotid artery was tied about 1 cm distal to the sinus and the external carotid artery was tied just distal to the lingual artery. The occipital and ascending pharyngeal arteries were tied near their origins from the external carotid artery and any small branches arising from the carotid bifurcation were also tied. Polyethylene cannulae were tied in the lingual arteries to permit drainage of the blood from the isolated sinuses to a systemic vein. Both vagosympathetic trunks were cut in the neck.

The chest was opened widely by removing the fifth left rib. The upper lobe of the

left lung was tied at its root and removed to expose the descending thoracic aorta which was mobilized by dividing the upper three intercostal arteries on both sides between ligatures. The brachiocephalic and left subclavian arteries were dissected free of their attachments for about 1 cm near their origins. The pericardium was opened and two small silver electrodes were sewn on to the right atrial appendage. In two experiments the left ansa subclavia was exposed and a loose thread placed round it.

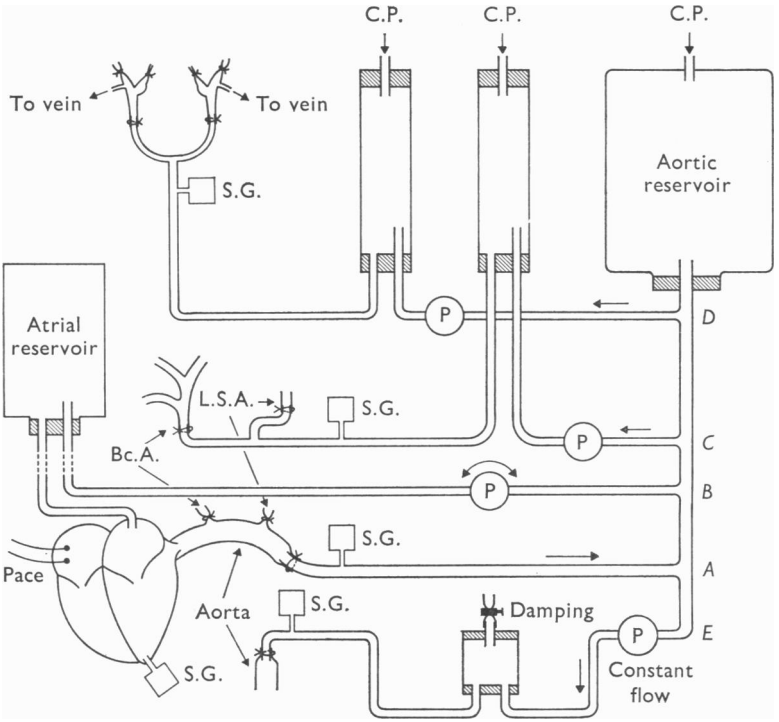

Fig. 1. Diagram of the experimental preparation. Bc.A., brachiocephalic artery; L.S.A., left subclavian artery; S.G., strain-gauge; C.P., constant pressure; P, roller pump. Blood received from a cannula in the descending aorta (*A*) passed to aortic reservoir and was pumped at controlled pressures into brachiocephalic and left subclavian arteries (*C*) and carotid sinuses (*D*). Blood was pumped at constant flow into the descending aorta (*E*). A reversible pump transferred blood between the aortic and atrial reservoirs (*B*), to minimize changes in left ventricular end-diastolic pressure.

The dog was given heparin (500 i.u./kg I.V., followed by 50 i.u./kg every half hour) and the perfusion circuit (Fig. 1), which had been primed with heparinized blood from a donor dog bled the same day, was connected to the dog. A 7 mm bore cannula connected to the atrial reservoir was inserted into the left atrium through the appendage. A stainless-steel cannula (1 cm i.d.), connected by means of tubing (1 cm i.d.) to the aortic reservoir (2 l. capacity) was tied in the central end of the descending aorta distal to the origin of the left subclavian artery (*A* in Fig. 1). The

pressure in the aortic reservoir was adjusted to maintain a constant pressure recorded in the aortic cannula. Blood from the aortic cannula and reservoir was distributed into different parts of the circulation (*B–E* in Fig. 1). Blood was pumped (*B*) into or out of the atrial reservoir to minimize the changes in left ventricular end-diastolic pressure which accompany a change in the inotropic state of the heart (*C*) at constant non-pulsatile pressure, into the cannulae tied in the distal ends of the brachiocephalic and left subclavian arteries to control cerebral perfusion pressure (*D*) at constant non-pulsatile pressure, into a Y-cannula tied in the distal ends of the common carotid arteries proximal to the carotid bifurcations to perfuse the carotid sinuses (*E*) in seventeen experiments, at a constant flow, into a wide cannula tied in the distal end of the descending aorta, and in four experiments, at constant pressure into cannulae tied in the distal end of the descending aorta and the distal end of the right femoral artery.

A stainless-steel cannula (length 5 cm, bore 1·5 mm) was inserted into the left ventricle through its apical dimple, tied by a purse string suture and clamped firmly in position.

Pressures were recorded using Statham strain gauges (Model P23 Gb) attached to the perfusion cannulae and the left ventricular cannula. After amplification by carrier amplifiers (S.E. Laboratories, Feltham, Middlesex) the pressure signals were recorded on photographic paper by a direct-writing ultra-violet light recorder (S.E. Laboratories). Mean pressures were obtained by passing the signals from the strain gauge amplifiers through R–C networks with time constants of 2 sec which were incorporated in the amplifiers. Zero pressures were recorded at the ends of the experiments as the pressures with the cannula tips free in air.

The output from the carrier amplifier for the left ventricular pressure transducer was distributed four ways: (1) through a variable series resistance to a galvanometer to record left ventricular pressure at normal arterial calibration (20 mm Hg = 10 mm paper), (2) directly to a galvanometer to record left ventricular end-diastolic pressure at greater sensitivity (10 cm H_2O = 10 mm paper), (3) to a digital cardiotachometer (Gilford Instruments Inc.), and (4) to an analogue differentiator to provide a signal of dP/dt which was amplified and recorded. The differentiator was calibrated using the method of Neal, Halpern & Reeves (1960).

Mean descending aortic or femoral artery blood flow was recorded using a cannulating transducer and a Statham Medicon M-4000 electromagnetic flowmeter. Zero flow was obtained by clamping the cannula at intervals during the experiment and the flowmeter with the transducer was calibrated at the end of the experiment using the animal's own blood.

Heart rate was held constant at a rate higher than the spontaneous rate at low carotid sinus pressure by electrically pacing the right atrial appendage using a Grass stimulator (Model S4). A thermistor probe (Yellow Springs Instruments Inc.) recorded oesophageal temperature which was maintained at 37–39° C by using heating lamps under the operating table. Arterial P_{O_2}, P_{CO_2} and pH were determined frequently during the experiment using standard electrode systems (Norman, Ledsome & Linden, 1965). P_{CO_2} and pH were adjusted to 34–40 mm Hg and 7·35–7·40 respectively by adjustments of the stroke of the respiratory pump and intravenous infusion of 1 M-$NaHCO_3$. Apart from experiments in which the effects of cerebral hypotension were determined at different oxygen tensions, P_{a,O_2} was always greater than 147 mm Hg.

Experimental procedure

Throughout all tests of changing the carotid or cerebral pressure, heart rate was held constant by electrical pacing. When carotid or cerebral pressure was changed

the pressures in other parts of the circulation were held almost constant. During all tests, mean aortic pressure changed by an average of +0·27 mm Hg (range −6 to +8 mm Hg). In tests of changing carotid pressure, cerebral pressure changed by an average of −0·5 mm Hg (range −8 to +9 mm Hg), and in tests of changing cerebral pressure carotid pressure changed by an average of 0·7 mm Hg (range −6 to +5 mm Hg).

In all tests measurements were made at a steady state obtained at least 1 min after changing carotid or cerebral pressure.

Carotid sinus pressure (non-pulsatile) was set to a level above that which was required to induce maximum depression of dP/dt max and maximum vasodilatation. It was then reduced to a level below which no further inotropic or vasomotor responses could be obtained and then again increased to its former high level. The values of dP/dt max and calculated vascular resistance at low carotid sinus pressure were compared with the means of the two values obtained at high carotid pressures. Vascular resistance changes were calculated as the percent change in the ratio pressure/flow, where the descending aorta was perfused at constant flow (seventeen dogs) or a femoral artery was perfused at constant pressure (four dogs).

Cerebral perfusion pressure was changed in a similar way with carotid sinus pressure remaining constant, and the resulting inotropic and vasomotor responses were determined.

In five dogs, carotid sinus pressure was decreased in steps of about 30 mm Hg over the baroreceptor sensitivity range (cerebral perfusion pressure constant). Cerebral pressure was then decreased in similar steps (carotid pressure constant).

In six dogs the responses to changing cerebral perfusion pressures were determined at different arterial oxygen tensions.

RESULTS

Effects of changes in carotid sinus pressure with constant cerebral perfusion pressure

Thirty-seven tests were done in twenty dogs. In these tests P_{a,O_2} was always > 147 mm Hg. An example of the responses obtained is shown in Fig. 2. A large step decrease in carotid sinus pressure resulted in an increase in dP/dt max and an increase in peripheral vascular resistance, seen as a decrease in femoral flow at constant perfusion pressure (e.g. Fig. 2) or an increase in descending aortic perfusion pressure at constant flow (e.g. Fig. 4).

Left ventricular end-diastolic pressure always decreased as dP/dt max increased despite an increase in left atrial filling effected by raising the height of the atrial reservoir. End-diastolic pressure decreased from 8·8 cm H_2O (mean, range 3–20) at high carotid pressure to 4·6 cm H_2O (mean, range 1–16) at low carotid pressure. Peak left ventricular pressure increased from 165 mm Hg (mean, range 136–256) to 185 mm Hg (mean, range 140–296).

The averages of the values from each dog (not the individual observations) are listed in Table 1.

In five dogs stepwise changes in carotid sinus pressure between 171 mm

Hg (mean, range 165–187) and 86 mm Hg (mean, range 68–120) resulted in stepwise changes in dP/dt max (Fig. 3C). Vasomotor responses occurred when carotid sinus pressure was changed in steps between 197 mm Hg (mean, range 156–220) and 93 mm Hg (mean, range 70–112) (Fig. 3D).

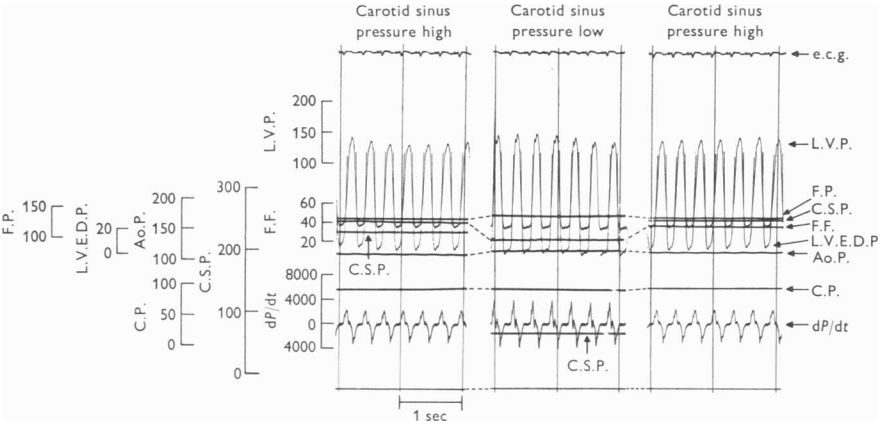

Fig. 2. Example of records showing effects of large step changes in carotid sinus pressure on dP/dt max and vascular resistance (dog no. 3). Heart paced at 200 beats/min. L.V.P., left ventricular pressure (mm Hg); L.V.E.D.P., left ventricular end-diastolic pressure (cm H_2O); F.P., femoral arterial perfusion pressure (mm Hg); C.S.P., carotid sinus pressure (mm Hg); F.F., femoral flow (ml./min); Ao.P., aortic pressure, measured in aortic cannula (mm Hg); C.P., cerebral perfusion pressure (mm Hg); dP/dt, first differential of left ventricular pressure (mm Hg/sec). Records show that as carotid pressure was decreased there was an increase in dP/dt max (heart rate, mean aortic pressure and cerebral pressure constant). Vascular resistance increased (decrease in flow to hind limb despite small increase in hind limb perfusion pressure).

Effects of interrupting left ansa subclavia on the responses to changing carotid sinus pressure

In two dogs a loose string was placed round both branches of the left ansa subclavia during the initial dissection. After pulling on the string to tear through the nerve, the inotropic responses from changing carotid sinus pressure were abolished. Before tearing the ansa, maximum changes in dP/dt max of +2350 and +1350 mm Hg/sec were observed, and after tearing the ansa the responses were +200 and −50 mm Hg/sec, respectively (e.g. Fig. 4). Vasomotor responses were unaffected and the heart responded to rapid intravenous injection of 10 μg noradrenaline by an increase in dP/dt max of 1585 mm Hg/sec.

Effects of changes in cerebral perfusion pressure with constant carotid sinus pressure ($P_{a.O_2}$ > 147 *mm Hg*)

Twenty-one tests were done in sixteen dogs. A large step decrease in cerebral pressure from 150 mm Hg (mean) to 55 mm Hg (mean) resulted in an average increase in dP/dt max of only 2·3% and in vascular resistance of only 3·8% (e.g. Fig. 5). These results, listed in Table 2, show that although these responses were statistically significant, they were very small compared with those obtained in the same dogs on lowering carotid sinus pressure to a similar level (Table 1).

TABLE 1. Inotropic responses of the left ventricle and vasomotor responses to changes in carotid sinus pressure with cerebral perfusion pressure, mean aortic pressure, and heart rate held constant. $P_{a.O_2}$ > 147 mm Hg. Values are means of responses from each dog

Dog no.	C.S.P. (mm Hg) A	C.S.P. (mm Hg) B	dP/dt max (mm Hg/sec) A	dP/dt max (mm Hg/sec) B	% increase in dP/dt max	V.R. % increase	C.P. (mm Hg)	Ao.P (mm Hg)	H.R. (beats/min)
1	266	76	4600	5500	19	59	154	148	210
2	162	90	2000	2700	35	67	126	104	180
3	242	88	2177	3315	52	37	126	119	195
4	287	56	3100	6140	98	61	91	117	240
5	174	73	4722	5605	19	11	110	116	210
6	245	49	2620	3950	50	18	153	137	170
7	242	78	3100	4540	46	23	78	145	240
8	229	61	3768	5110	37	56	140	107	230
9	236	57	3247	4133	27	57	135	126	240
10	192	40	3740	6100	63	38	138	120	200
11	247	68	2700	3800	41	21	142	131	205
12	216	72	4100	5000	22	67	103	131	200
13	257	67	4083	5780	42	65	153	124	237
14	220	60	4200	7000	67	67	134	127	250
15	254	80	2800	5060	80	137	157	127	207
16	256	50	3500	4150	18	76	115	125	204
17	306	64	3600	6400	78	219	164	142	240
19	308	72	3800	5150	35	11	135	166	216
20	222	72	2240	3250	44	36	155	133	200
21	256	60	2500	3000	20	52	128	131	210
Mean	241	67	3330	4784	45	59	132	129	214
P	—	—	—	—	< 0·0005	< 0·0005	—	—	—

A, average of values at high carotid sinus pressures before and after lowering pressure; *B*, average value at low carotid sinus pressure; C.S.P., carotid sinus pressure; dP/dt max, maximum rate of change of left ventricular pressure; V.R., percent increase in calculated vascular (resistance; C.P., cerebral perfusion pressure; Ao.P., mean aortic pressure;. H.R., heart rate. P denotes level of significance for paired observations.

In the five dogs in which we had recorded the responses to stepwise changes in carotid sinus pressure with cerebral perfusion pressure held constant, we also recorded the responses to similar stepwise changes in cerebral perfusion pressure with carotid sinus pressure held constant. The results, plotted in Fig. 3*A* and *B*, show that decreasing cerebral perfusion pressure to 60 mm Hg in these experiments resulted in little or no responses of either d*P*/d*t* max or vascular resistance. This lack of response to cerebral pressure changes contrasts with the large responses in these dogs to carotid sinus pressure changes (Fig. 3*C*, *D*).

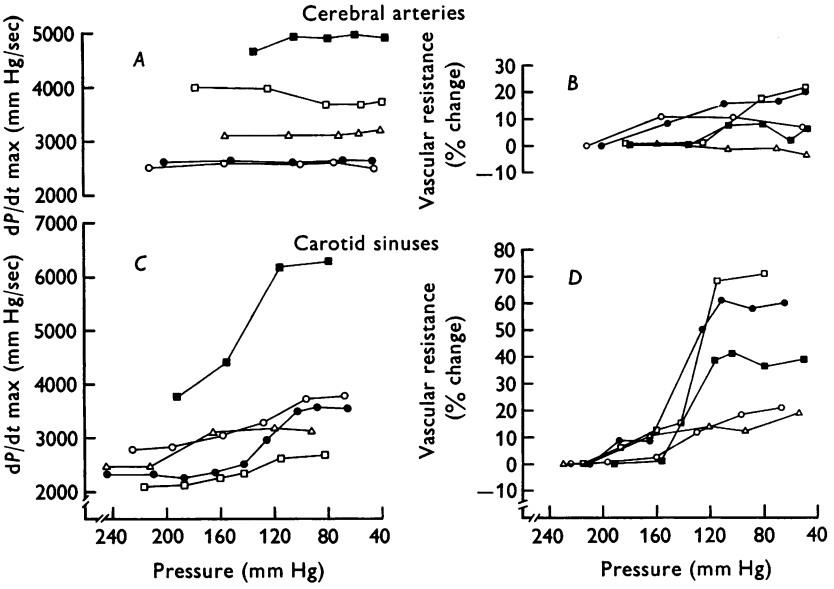

Fig. 3. Effects on d*P*/d*t* max and vascular resistance of stepwise changes in cerebral perfusion pressure (*A*, *B*) and carotid sinus pressure (*C*, *D*) in five dogs. Each symbol represents results obtained from one experiment, $P_{a,O_2} > 147$ mm Hg in all cases. Mean aortic pressure and heart rate constant during each series of pressure changes. For carotid sinus pressure changes, cerebral perfusion pressure constant. For cerebral perfusion pressure changes, carotid sinus pressure constant. Vascular resistance changes expressed as percent of values at the highest carotid or cerebral pressure.

Effects of lowering cerebral pressure with P_{a,O_2} 87–120 *mm Hg and* 30–60 *mm Hg*

The absence of large inotropic or vasomotor responses to lowering cerebral perfusion pressure in the experiments described above may have been due to an abnormally high arterial oxygen tension and a cerebral perfusion pressure which although low was still high enough to provide an

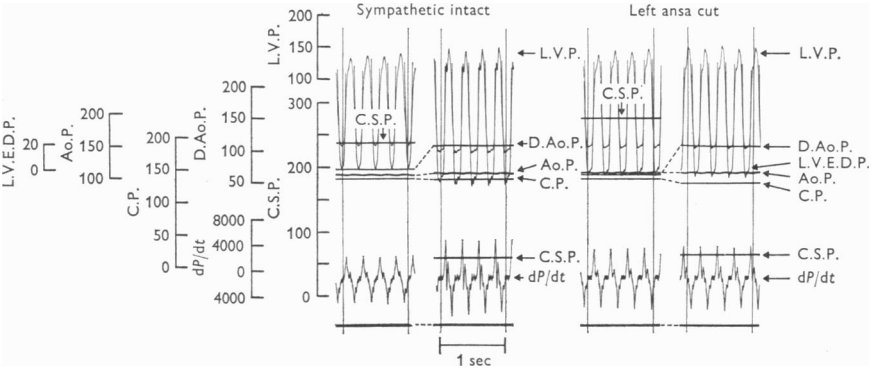

Fig. 4. Effect of reduction in carotid sinus pressure on the inotropic state of the heart before and after section of the left ansa subclavia (dog no. 10). In this dog vasomotor responses were measured as changes in descending aortic pressure (D.Ao.P.) at constant flow. Other conventions as in Fig. 2. Before cutting left ansa subclavia, reducing carotid sinus pressure resulted in large increases in dP/dt max and descending aortic perfusion pressure (aortic cannula pressure, cerebral perfusion pressure and heart rate constant). After cutting left ansa, cardiac response abolished but vasomotor response persisted.

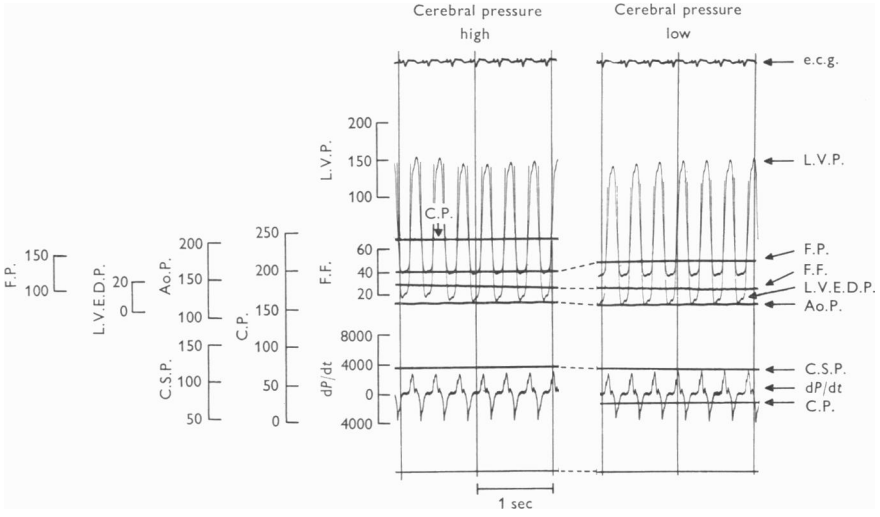

Fig. 5. Effects of large step change in cerebral perfusion pressure (dog no. 3). Conventions as in Fig. 2. Heart rate paced at 200 beats/min. P_{a,O_2} 160 mm Hg. Records obtained from same dog as in Fig. 2. Note that whereas changes in carotid sinus pressure resulted in large inotropic and vasomotor responses (Fig. 2) a large change in cerebral perfusion pressure resulted in very small inotropic and vasomotor responses.

adequate cerebral circulation. We, therefore, did further experiments in which we decreased cerebral perfusion pressure to even lower levels with different arterial oxygen tensions in an attempt to define the values of P_{a,O_2} and cerebral perfusion pressure required to induce inotropic and vasomotor changes.

TABLE 2. Inotropic responses of the left ventricle and vasomotor responses to changes in cerebral perfusion pressure with carotid sinus pressure, mean aortic pressure and heart rate held constant. $P_{a,O_2} > 147$ mm Hg. Values are means of responses obtained from each dog

Dog no.	C.P. (mm Hg) A	C.P. (mm Hg) B	dP/dt max (mm Hg/sec) A	dP/dt max (mm Hg/sec) B	% change in dP/dt max	V.R. % change	C.S.P. (mm Hg)	Ao.P. (mm Hg)	H.R. (beats/min)
2	126	47	3800	3950	+3·9	—	120	145	180
3	202	48	2770	2800	+1·1	—	114	120	195
4	162	74	4050	4000	−1·2	+5·5	114	120	240
5	170	64	2620	2700	+3·0	+5·6	255	82	210
6	108	42	3160	3328	+5·3	−5·0	155	138	168
8	132	40	3519	3463	−1·6	+7·4	212	104	230
9	120	61	3715	3950	+5·9	+13·7	150	124	228
10	132	41	4750	4750	0·0	+6·3	146	117	200
11	214	46	3150	3200	+1·6	+1·0	132	131	210
12	130	70	3900	4300	+10·2	0·0	102	132	200
13	161	47	4660	4560	−2·1	+6·8	197	124	240
15	131	77	3390	3570	+5·0	+12·6	141	126	210
16	158	56	4000	4250	+6·2	+4·7	100	142	204
18	147	44	4570	4775	+4·5	+2·7	141	133	190
19	169	60	4300	4350	+1·2	−13·2	141	166	216
21	138	70	3020	2950	−2·5	+5·8	114	141	210
Mean	150	55	3711	3806	+2·3	+3·8	146	128	208
P	—	—	—	—	< 0·05	< 0·05	—	—	—

Conventions as in Table 1. *A*, average of values at high cerebral perfusion pressures before and after lowering pressure. *B*, average value at low cerebral perfusion pressure.

In six dogs the responses to stepwise lowering of cerebral perfusion pressure were compared at two different oxygen tensions. Parts of the original records obtained from one dog are shown in Fig. 6. The results from all six dogs, plotted in Fig. 7, show that at the higher oxygen tensions inotropic and vasomotor responses were small even at cerebral perfusion pressures of about 40 mm Hg. At the lower oxygen tensions, however, decreasing cerebral perfusion pressure did result in positive inotropic and vasomotor responses. In some dogs responses occurred as cerebral pressure was changed within the range of normal arterial pressures and in all experiments responses occurred when cerebral pressure was lowered below about 80 mm Hg.

In all experiments in which responses were obtained with cerebral hypotension, values of dP/dt max and vascular resistance returned to near control levels after increasing cerebral perfusion pressure.

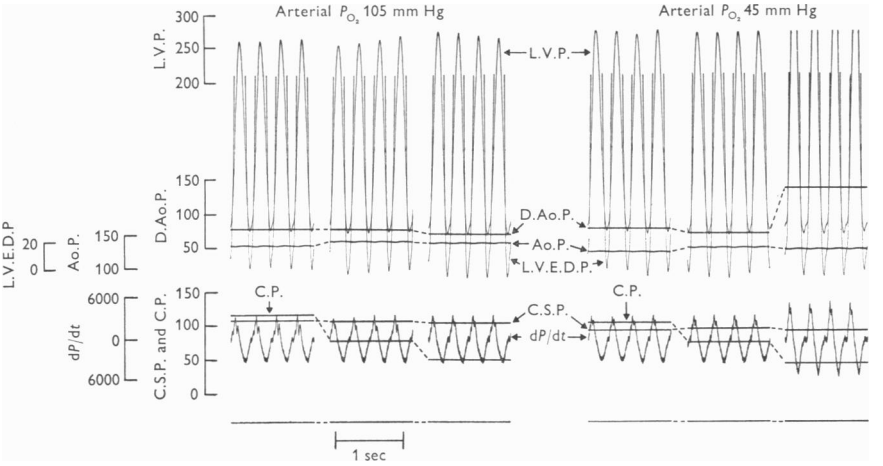

Fig. 6. Effects of reducing cerebral perfusion pressure in steps at two levels of arterial oxygen tension (dog no. 20). Heart paced at 200 beats/min. L.V.P., left ventricular pressure (mm Hg); L.V.E.D.P., left ventricular end-diastolic pressure (cm H_2O); Ao.P., aortic pressure, measured in aortic cannula (mm Hg); D.Ao.P., descending aortic perfusion pressure (mm Hg) with constant flow perfusion throughout; C.P., cerebral perfusion pressure (mm Hg); C.S.P. carotid sinus pressure (mm Hg); dP/dt, first differential of left ventricular pressure (mm Hg/sec). Records show responses only when cerebral perfusion pressure reduced to 50 mm Hg and P_{a,O_2} 45 mm Hg.

DISCUSSION

Method used to assess inotropic responses

In the present study, inotropic responses were assessed by measuring changes in the maximum rate of change of left ventricular pressure (dP/dt max) in preparations in which heart rate and mean aortic pressure were held constant. Under these conditions dP/dt max has been shown to provide a sensitive and quantitative index of changes in the inotropic state of the heart due to changes in cardiac sympathetic nerve activity or circulating catecholamine concentration (Furnival, Linden & Snow, 1968, 1970, 1971).

Since changes in heart rate or in arterial blood pressure can result in changes in the inotropic state of the heart in the absence of any direct reflex effects on the myocardium, the results from experiments in which these variables were not controlled cannot easily be interpreted. Thus the experiments of Sarnoff, Gilmore, Brockman, Mitchell & Linden (1960),

Lindgren & Manning (1965), Manning & Lindgren (1966) and most of those of De Geest *et al.* (1964) cannot be regarded as conclusive.

Furnival *et al.* (1970) have shown that measurements of dP/dt max provide a more sensitive index of inotropic changes in the heart than measurements of peak left ventricular pressure, which were used to assess the myocardial responses to carotid sinus pressure changes by De Geest *et al.* (1964) and Salisbury, Cross & Rieben (1962). Measurements of dP/dt max in an isovolumetric left ventricular balloon were made by

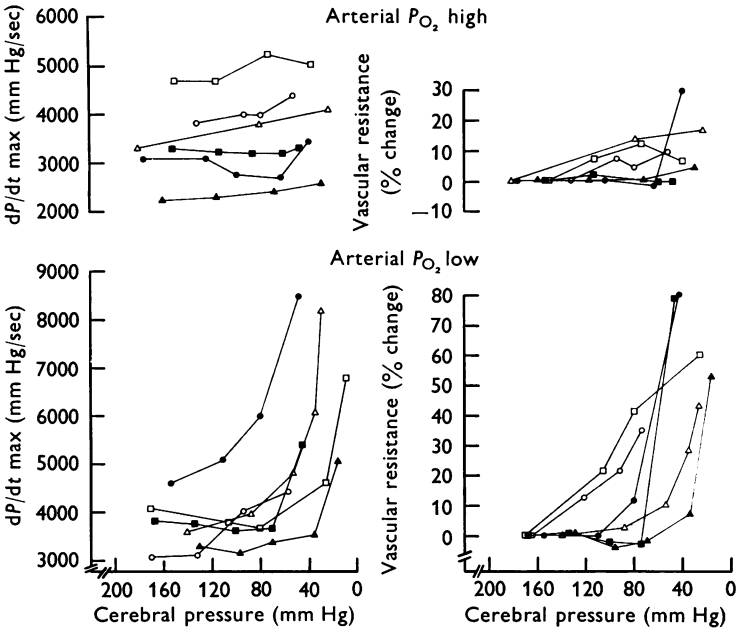

Fig. 7. The effect of stepwise changes in cerebral perfusion pressure on dP/dt max and vascular resistance at two levels of arterial oxygen tension. Mean ascending aortic and carotid sinus pressures and heart rate held constant throughout each series of steps. Each symbol denotes results obtained from one dog. Values of P_{a,O_2}, high and low respectively in mm Hg are: □—□ 120, 30; ○—○ 87, 60; △—△, 120, 35; ■—■ 105, 45; ●—● 90, 60; ▲—▲ 102, 45.

Glick (1971) but in these experiments the values of dP/dt max were all abnormally low and the responses small. This is possibly due in part to the low aortic pressure in these experiments. Downing & Gardner (1968) measured left ventricular dP/dt max in response to carotid occlusion in anaesthetized cats, but did not obtain any definite responses; the possible explanations for this are discussed below.

Responses from changing pressures in bilateral isolated carotid sinuses

In the present experiments we obtained consistent responses of dP/dt max from changing pressure in isolated carotid sinuses. Mean aortic pressure was held constant at 129 mm Hg (mean) and, at high carotid pressures, values of dP/dt max were obtained which were not greatly dissimilar to those found by Furnival *et al.* (1971) with denervated hearts.

We did not rigidly control left ventricular end-diastolic pressure in these experiments, and despite flow from the atrial reservoir, end-diastolic pressure usually fell as the result of a positive inotropic response. However, this is unlikely to have greatly reduced the responses of dP/dt max (Furnival *et al.* 1970).

The increase in dP/dt max which we consistently obtained on decreasing carotid sinus pressure was due predominantly to a decrease in the stimulus to carotid sinus baroreceptors. It is unlikely that an increased stimulus to carotid body chemoreceptors contributed significantly to the responses because P_{a,O_2} was always high ($>$ 147 mm Hg) and P_{a,CO_2} and pH within normal limits. Under these conditions, chemoreceptors are relatively inactive even at low perfusion pressures (Lee, Mayou & Torrance, 1964; Landgren & Neil, 1951), also, the absence of large responses as carotid sinus pressure was reduced in steps between 100 mm Hg and 60 mm Hg makes any significant contribution by carotid chemoreceptors unlikely.

The results of this study are entirely at variance with those reported by Salisbury *et al.* (1962) and Downing & Gardner (1968). Salisbury *et al.* (1962) compared responses to carotid occlusion and aortic constriction and concluded that the responses from carotid occlusion could be explained entirely as the result of the concomitant change in aortic pressure. However, with their technique, it is uncertain that they would have been able to recognize inotropic responses if they had occurred. Also, carotid occlusion is an unsatisfactory way of studying responses from carotid baroreceptors because the extent to which the pressure in the sinuses falls is variable and depends on anastomoses, particularly with the vertebral arteries. The reflex responses depend on the degree of stimulation of the baroreceptors at the animal's existing blood pressure. The responses might also be impaired because of the use of pentobarbital anaesthesia (Brown & Hilton, 1956; Armstrong, Porter & Langston, 1961; Van Citters, Franklin & Rushmer, 1964). However, in a recent report, Vatner, Higgins, Franklin & Braunwald (1972) were able to produce inotropic responses to carotid sinus nerve stimulation only after their dogs had been anaesthetized with pentobarbitone and bled; little or no responses were obtained in unanaesthetized dogs.

Downing & Gardner (1968) also studied responses from carotid occlusion

in cats under pentobarbital anaesthesia and their results are thus open to some of the same criticisms as those of Salisbury *et al.* (1962). Downing & Gardner gave no information on the arterial blood gas and pH state of their animals. Indeed, from the magnitude of the responses to cerebral hypotension it is possible that the animals were hypoxic (*vide infra*). If this is so, carotid clipping would likely cause a significant increase in the activity from carotid chemoreceptors. Since carotid chemoreceptor stimulation may cause a reflex negative inotropic response (Downing, Remensnyder & Mitchell, 1962) the absence of definite myocardial responses to carotid occlusion may be the result of the opposing influences of a reduced stimulus to carotid sinus baroreceptors and an increased stimulus to carotid body chemoreceptors. A decreased stimulus to baroreceptors and an increased stimulus to chemoreceptors both result in vasoconstriction and thus a rise in blood pressure.

In the present experiments the cardiac responses were due predominantly to changes in cardiac sympathetic nerve activity. It is unlikely that changes in circulating catecholamine concentration were very important in producing responses since in two dogs inotropic responses were abolished by cutting the left cardiac sympathetic nerves (the left ansa subclavia contains most of the fibres responsible for inotropic responses (Randall & Rohse, 1956; Furnival *et al.* 1968)). Furthermore, the onset of the changes was much more rapid than could have occurred from changes in catecholamine level in the large circuit volume.

There was a wide variation in responses to changing carotid sinus pressure (Table 1). It is possible in some experiments that surgical interference in the region of the sinuses may have resulted in some damage to the sinus or its nerve. However, a similar variation in responses was also found in experiments in which the pressure in the entire brachiocephalic and subclavian arterial system was changed without dissecting near the carotid sinuses (Hainsworth & Karim, 1972), so the variability is more likely to be due to different sensitivity in different dogs, due amongst other things perhaps to different levels of anaesthesia.

It is likely that responses would have occurred at lower carotid perfusion pressures if these had been pulsatile instead of steady (Ead, Green & Neil, 1952; Scher & Young, 1963). However, since the carotid sinus pressure was changed over its entire range, i.e. further increases or decreases did not induce further changes in dP/dt max or vascular resistance, it is unlikely that the over-all responses would have been greatly affected by using pulsatile pressures.

Responses from changing pressures in cerebral arteries

In the present study the cerebral arteries were perfused predominantly through both vertebral arteries through the brachiocephalic and left subclavian arteries. In preparing the isolated carotid sinuses, both internal and external carotid arteries were tied. This, however, is unlikely to be of great importance since in the dog the vertebral arteries are large and can maintain cerebral perfusion after carotid occlusion (Chungcharoen, Daly, Neil & Schweitzer, 1952; Bonakdarpour, Lynch & Turner, 1967; Fukuyama & Himvich, 1970). Also the lack of responses from moderate degrees of brachiocephalic and left subclavian hypotension suggest that cerebral perfusion was not grossly impaired by ligation of the carotid arteries.

There is good evidence that gross cerebral hypoxia or ischaemia results in vasoconstriction and a positive inotropic response (Sagawa *et al.* 1961; Downing *et al.* 1963; De Geest *et al.* 1965) and we are generally in agreement with those conclusions. However, apart from the study of Sagawa *et al.* no attempt was made to gradate the cerebral ischaemia or hypoxia to determine the levels at which responses were obtained. Sagawa *et al.* obtained vasomotor responses when cerebral perfusion pressure was lowered to 40–60 mm Hg. However, they gave no values for oxygen tension of the perfusing blood and the control levels of arterial blood pressure in their 'debuffered' preparations were abnormally low. In the present experiments we did not determine the maximum responses obtainable from cerebral ischaemia but attempted to determine the values of cerebral perfusion pressure and arterial oxygen tension at which inotropic and vasomotor responses become apparent. We found that with a high P_{a,O_2} there were only very small inotropic or vasomotor responses even when cerebral perfusion pressure was reduced to a very low level (about 40 mm Hg). However, at lower arterial oxygen tensions the brain was much more sensitive to hypotension. Responses occurred in most dogs when cerebral perfusion pressure was decreased below about 80 mm Hg. The results at low oxygen tension are comparable with those reported by Downing & Gardner (1968) in which the oxygen was not specified.

Carotid sinus baroreceptor activity versus cerebral ischaemia in the control of the inotropic state of the heart and vasomotor tone

Our conclusions are diametrically opposed to those of Downing & Gardner (1968). We found that, unless P_{a,O_2} was abnormally low, carotid sinus hypotension was very much more important than cerebral ischaemia in the control of the inotropic state of the heart and of vascular resistance. We believe that the methodological inadequacies of Downing & Gardner's preparation, as discussed above, are sufficient to account for the dis-

crepancy. We have confirmed that a reduction in the perfusion pressure of the blood perfusing the brain does result in an augmented sympathetic activity, but unless the animal was hypoxic the responses were small and the levels of cerebral perfusion required to cause inotropic or vasomotor responses were below the level at which most sinus baroreceptors would be inactive (Landgren, 1952). In the physiological situation when carotid and cerebral pressures are lowered simultaneously the resulting responses would be due predominantly, if not entirely, to a change in the stimulus to the sinus baroreceptors. This conclusion is further supported by the fact that the inotropic responses from decreasing carotid sinus pressure alone, reported in this paper, were quantitatively very similar to the responses reported in a recent paper (Hainsworth & Karim, 1972) from decreasing both carotid and cerebral pressures simultaneously to a similar level.

These results therefore suggest that the carotid sinus baroreceptor reflex is of primary importance in control of the heart and blood vessels and that cerebral ischaemia and hypoxia are normally of secondary importance and produce large effects only in conditions of severe hypotension and hypoxia.

The authors are grateful to Mr B. Griffiths, Miss A. Jarrett, and Mrs M. Lindley for technical assistance.

This work was supported by grants from the British Heart Foundation, the Medical Research Council and the Wellcome Trust.

REFERENCES

ARMSTRONG, G. C., PORTER, H. JR. & LANGSTON, J. B. (1961). Alteration of carotid occlusion response by anaesthesia. *Am. J. Physiol.* **201**, 897–900.

BONAKDARPOUR, A., LYNCH, P. R. & TRUEX, R. C. (1967). Comparative angiographic and corrosion cast studies of the cervicocerebral arteries in the dog. *Invest. Radiol.* **2**, 290–303.

BROWN, R. V. & HILTON, J. G. (1956). The effectiveness of the baroreceptor reflexes under different anaesthetics. *J. Pharmac. exp. Ther.* **118**, 198–203.

CHUNGCHAROEN, M., DALY, M. DE B., NEIL, E. & SCHWEITZER, A. (1952). The effect of carotid occlusion upon the intrasinusal pressure with special reference to vascular communications between the carotid and vertebral circulations in the dog, cat and rabbit. *J. Physiol.* **117**, 56–76.

DE GEEST, H., LEVY, M. N. & ZIESKE, H. JR. (1964). Carotid sinus baroreceptor reflex effects upon myocardial contractility. *Circulation Res.* **15**, 327–342.

DE GEEST, H., LEVY, M. N. & ZIESKE, H. JR. (1965). Reflex effects of cephalic hypoxia, hypercapnia, and ischemia upon ventricular contractility. *Circulation Res.* **17**, 349–358.

DOWNING, S. E. & GARDNER, T. H. (1968). Cephalic and carotid reflex influences on cardiac function. *Am. J. Physiol.* **215**, 1192–1199.

DOWNING, S. E., MITCHELL, J. H. & WALLACE, A. G. (1963). Cardiovascular responses to ischemia, hypoxia and hypercapnia of the central nervous system. *Am. J. Physiol.* **204**, 881–887.

DOWNING, S. E., REMENSNYDER, J. P. & MITCHELL, J. H. (1962). Cardiovascular responses to hypoxic stimulation of the carotid bodies. *Circulation Res.* **10**, 676–685.

EAD, H. W., GREEN, J. H. & NEIL, E. (1952). A comparison of the effects of pulsatile and non-pulsatile blood flow through the carotid sinus on the reflexogenic activity of the sinus baroreceptors in the cat. *J. Physiol.* **118**, 509–519.

FUKUYAMA, G. S. & HIMVICH, W. A. (1970). Canine basilar arterial flow and effects of common carotid occlusion. *Am. J. Physiol.* **219**, 525–527.

FURNIVAL, C. M., LINDEN, R. J. & SNOW, H. M. (1968). Response to stimulation of the cardiac sympathetic nerves. *J. Physiol.* **197**, 74–75*P*.

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

FURNIVAL, C. M., LINDEN, R. J. & SNOW, H. M. (1971). Inotropic and chronotropic effects of catecholamines on the dog heart. *J. Physiol.* **214**, 15–28.

GLICK, G. (1971). Importance of the carotid sinus baroreceptors in the regulation of myocardial performance. *J. clin. Invest.* **50**, 1116–1123.

HAINSWORTH, R. & KARIM, F. (1972). Inotropic responses of the left ventricle to changes in aortic arch pressure in anaesthetized dogs. *J. Physiol.* **223**, 213–228.

HEYMANS, C. & NEIL, E. (1958). *Reflexogenic Areas of the Cardiovascular System.* London: Churchill.

LANDGREN, S. (1952). On the excitation mechanism of the carotid baroreceptors. *Acta physiol. scand.* **26**, 1–34.

LANDGREN, S. & NEIL, E. (1951). Chemoreceptor impulse activity following haemorrhage. *Acta physiol. scand.* **23**, 158–167.

LEE, K. D., MAYOU, R. A. & TORRANCE, R. W. (1964). The effect of blood pressure upon chemoreceptor discharge to hypoxia, the modification of this effect by the sympathetic adrenal system. *Q. Jl exp. Physiol.* **49**, 171–183.

LINDGREN, P. & MANNING, J. (1965). Decrease in cardiac activity by carotid sinus baroreceptor reflex *Acta physiol. scand.* **63**, 401–408.

MANNING, J. & LINDGREN, P. (1966). Sinus baroreceptor reflex and ouabain interaction on cardiac contractility. *Cardiologia* **49**, 345–358.

NEAL, T. J., HALPERN, W. & REEVES, T. J. (1960). Velocity and acceleration of pressure changes in heart and arteries. *J. appl. Physiol.* **15**, 747–749.

NORMAN, J., LEDSOME, J. R. & LINDEN, R. J. (1965). A system for the measurement of respiratory and acid base parameters in blood. *Br. J. Anaesth.* **37**, 466–479.

RANDALL, W. C. & ROHSE, W. G. (1956). The augmentor action of the sympathetic cardiac nerves. *Circulation Res.* **4**, 470–475.

SAGAWA, K., ROSS, J. M. & GUYTON, A. G. (1961). Quantitation of cerebral ischaemia pressor response in dogs. *Am. J. Physiol.* **200**, 1164–1168.

SALISBURY, P. F., CROSS, C. E. & RIEBEN, P. A. (1962). Regulation of ventricular and atrial contraction by carotid sinus. *Circulation Res.* **11**, 53–62.

SARNOFF, S. J., GILMORE, J. P., BROCKMAN, S. K., MITCHELL, J. H. & LINDEN, R. J. (1960). Regulation of ventricular contraction by the carotid sinus its effects on atrial and ventricular dynamics. *Circulation Res.* **8**, 1123–1136.

SCHER, A. M. & YOUNG, A. C. (1963). Servo analysis of carotid sinus reflex effects on peripheral resistance. *Circulation Res.* **12**, 152–162.

VAN CITTERS, R. L., FRANKLIN, D. L. & RUSHMER, R. F. (1964). Left ventricular dynamics in dogs during anaesthesia with alpha-chloralose and sodium pentobarbital. *Am. J. Cardiol.* **13**, 349–354.

VATNER, S. F., HIGGINS, C. B., FRANKLIN, D. & BRAUNWALD, E. (1972). Extent of carotid sinus regulation of the myocardial contractile state in conscious dogs. *J. clin. Invest.* **51**, 995–1008.