J. Physiol. (1979), **287**, *pp.* 455–466
With 5 text-figures
Printed in Great Britain

LEFT VENTRICULAR INOTROPIC RESPONSES TO STIMULATION OF CAROTID BODY CHEMORECEPTORS IN ANAESTHETIZED DOGS

BY R. HAINSWORTH, F. KARIM AND O. A. SOFOLA
From the Departments of Cardiovascular Studies and Physiology, University of Leeds, Leeds LS2 9JT

(*Received 7 July 1978*)

SUMMARY

1. Dogs were anaesthetized with chloralose and artificially ventilated. The regions of both carotid bifurcations were vascularly isolated and perfused at constant pressure with arterial blood or with venous or hypoxic blood.

2. Inotropic responses were assessed by measuring the maximum rate of change of left ventricular pressure (dP/dt_{max}) with aortic pressure and heart rate held constant.

3. Stimulation of the chemoreceptors with venous blood from the inferior vena cava resulted in a decrease in dP/dt_{max} from 510 ± 27 kPa.s^{-1} to 418 ± 21 kPa.s^{-1} (mean $\pm$ S.E.): a change of 17.9 ± 1.0 %

4. In experiments in which the oxygen tension of the blood perfusing the carotid chemoreceptors was decreased in steps between 10 and 3 kPa, by use of an oxygenator, graded responses of dP/dt_{max} were obtained at each step.

5. The inotropic responses to chemoreceptor stimulation were abolished by raising carotid pressure.

6. The inotropic responses were abolished either by crushing both carotid bodies or both ansae subclaviae, indicating that the reflex originates from the carotid bodies and that the efferent pathway is in the cardiac sympathetic nerves.

INTRODUCTION

In anaesthetized dogs, when ventilation is held constant or the lung is denervated, stimulation of the carotid body chemoreceptors results in reflex bradycardia (Daly & Scott, 1958). However, the effect of stimulation of carotid chemoreceptors on the inotropic state of the heart is not yet certain. The results of previous studies are conflicting, probably as a result of inadequate localization of the stimulus (e.g. Salem, Penna & Aviado, 1964; Stern & Rapaport, 1967; Pace, 1970) or inadequate control of variables such as heart rate and aortic blood pressure which secondarily influence the inotropic state of the heart (e.g. Kahler, Goldblatt & Braunwald, 1962).

In the present investigation, the stimulus to the carotid bodies was localized by vascularly isolating the regions of the carotid bifurcations and perfusing them at constant pressure with venous blood or blood of various oxygen tensions. The inotropic state of the heart was assessed by measuring the maximum rate of change of left ventricular pressure (dP/dt_{max}), with heart rate and aortic pressure held constant. Furnival, Linden & Snow (1970) have shown that, under these conditions,

dP/dt_{max} provides a sensitive and quantitative index of the inotropic state of the heart. The interaction of carotid baroreceptors and chemoreceptors was also examined.

METHODS

Dogs of weight 24–39 kg were anaesthetized with chloralose (0·1 g.kg^{-1}, Cambrian Chemicals Ltd., Croydon) infused through a catheter passed under local anaesthesia (2% amethocaine), through a saphenous vein into the inferior vena cava. The chloralose was dissolved in 0·15 M-NaCl to make a solution of 0·01 g.ml.$^{-1}$. Light surgical anaesthesia was maintained throughout the experiment by infusions of chloralose of 0·01 g.kg^{-1} every 15–20 min. The neck was opened in the mid line and the trachea cannulated. The lungs were ventilated by positive pressure, with air enriched to contain 40% oxygen using a Starling 'Ideal' pump at a rate of 18 strokes.min^{-1} and tidal volume of about 17 ml.kg^{-1}. On opening the chest, a resistance to expiration of 0·3 kPa was inserted.

Both vagus nerves were exposed in the neck. The regions of both common carotid bifurcations were vascularly isolated by tying the external carotid, internal carotid, occipital, ascending pharyngeal and muscular arteries and any other small branches.

In twelve dogs the chest was opened by splitting the sternum in the mid line. The pericardium was opened and two small silver ring electrodes were sewn on to the right atrial appendage for pacing the heart. A short stainless-steel cannula with side holes (length 5 cm, bore 1·5 mm) was inserted into the left ventricle through the apical dimple, tied in place by means of a purse string suture and firmly clamped in position. In the remaining five dogs, the chest was opened in the third left intercostal space, electrodes were sewn on to the right atrial appendage and an implantable catheter tip transducer (Model P13, Konnigsberg Instruments Inc., Pasadena) was passed through the left atrial appendage into the left ventricle and secured in place by a tie round the base of the appendage.

The dogs were given heparin, 500 i.u. kg^{-1} followed by 50 i.u. kg^{-1} every $\frac{1}{2}$ hr, and the perfusion circuit, capacity about 300 ml., was filled with dextran solution (Dextraven 150, Fisons Pharmaceuticals Ltd., Loughborough).

The central ends of both femoral arteries were cannulated and connected to an arterial reservoir. This reservoir was connected to a pressure bottle (Fig. 1). Systemic arterial pressure was measured in the aortic arch through a cannula which was passed through either a brachial or a common carotid artery. The distal ends of both common carotid arteries were cannulated and perfused at constant pressure with blood from a small reservoir which was connected to a pressure bottle. The blood for perfusion was either arterial from the arterial reservoir or venous from the inferior vena cava. Polyethylene cannulae were inserted into both lingual arteries to drain blood perfusing the area through an oxygen electrode system (Electronic Instruments Ltd., Chertsey, Surrey), then into a vein. Samples of blood were withdrawn from the cannulae to measure P_{O_2}, P_{CO_2} and pH of the blood perfusing the chemoreceptors using a blood gas electrode system (Corning model 165, Corning Medical, Halstead, Essex). The vascular isolation of the carotid bifurcations was tested by stopping the perfusion and noting the pressure. It was considered adequate when the pressure fell below 4 kPa despite a systemic arterial pressure of over 20 kPa. The temperature of the blood perfusing the carotid bifurcation areas was maintained at 37 °–38 °C by means of a heat exchanger.

In five of the dogs the carotid chemoreceptors were perfused with blood from an oxygenator (modified 'Temptrol' Pediatric, Bentley Laboratories). The oxygenator was filled with about 400 ml. blood from the dog and the dog's blood volume replaced by a similar volume of Dextran 150 (Fisons Pharmaceuticals Ltd.). The oxygen tension of this blood was adjusted to desired levels by adjusting the flow of the gas mixtures from two cylinders; one containing 5% CO_2 in nitrogen and the other 5% CO_2 in air. The oxygen content of the gas mixture ranged from 19% to 0%. The P_{CO_2} was constant at 5·3 ± 0·1 kPa (range 4·7–5·9 kPa), and the pH was adjusted to 7·39 ± 0·01 units by addition when necessary of molar sodium bicarbonate.

Pressures were recorded using Statham strain gauges (Model P23 Gb) attached to cannulae in the common carotid arteries, aorta and left ventricle. After amplification by carrier amplifiers (S.E. Laboratories Ltd., Feltham, Middlesex), the pressure signals were recorded on photographic paper by a direct writing ultraviolet light recorder (S.E. Laboratories). The mean pressure in the common carotid arteries was recorded by passing the output from the strain gauge through

an RC network with a time constant of 2 s incorporated in the amplifier. The output from the amplifier used for the left ventricular pressure transducer was distributed in three ways: (*a*) directly to a galvanometer to record left ventricular end-diastolic pressure at a high sensitivity (1 kPa = 10 mm paper), (*b*) through a variable series resistance to a galvanometer to measure left ventricular pressure at a lower sensitivity and (*c*) to an analogue differentiator to provide a signal of dP/dt which was amplified and recorded. The differentiator was calibrated according to the method of Neal, Halpern & Reeves (1960). The frequency response of the cannula and transducer system was flat ($\pm 5\%$) to better than 80 Hz in the case of the apical cannula and better than 200 Hz for the catheter tip transducer.

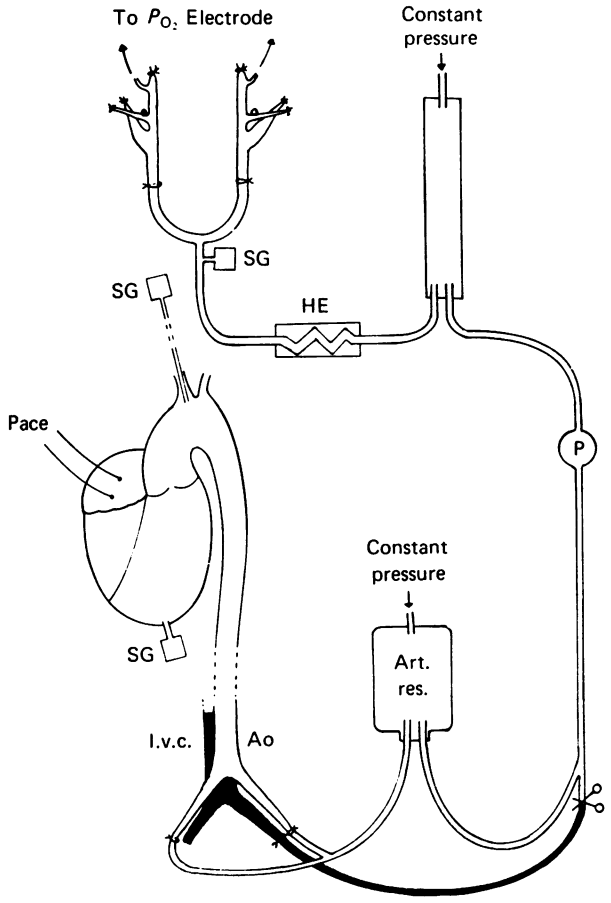

Fig. 1. Diagram of the experimental preparation. Blood from the arterial reservoir or the inferior vena cava was pumped at constant pressure into the regions of the carotid bifurcations and was drained from the lingual arteries into an external jugular vein via a P_{O_2} electrode assembly. SG, strain gauge; HE, heat exchanger; P, roller pump; Ao, aorta; I.v.c., inferior vena cava; Art. res, arterial reservoir connected to both femoral arteries.

The electrocardiogram was recorded from the left hind limb and right forelimb. Heart rate was recorded on a display cardiotachometer triggered by the systemic arterial pressure pulse and was held constant by electrical pacing of the right atrium using a Grass stimulator (Model S4). A thermistor probe (Yellow Springs Instruments Inc.) was used to record oesophageal temperature which was maintained at 37 °–39 °C using electrical heaters under the operating table. The

systemic arterial P_{O_2}, P_{CO_2} and pH were determined frequently. P_{CO_2} was adjusted by altering the stroke of the pump and acidaemia corrected when necessary by infusions of molar sodium bicarbonate. Since the dogs breathed air enriched with oxygen, the arterial P_{O_2} was greater than 15 kPa.

Experimental procedure

At the beginning of each experiment, the carotid bifurcations were perfused with arterial blood and the perfusion pressure gradually increased until there was a noticeable reduction in dP/dt_{max}. The pressure was then controlled at this level (16·5 ± 0·6 kPa) during the tests of chemoreceptor stimulation. Systemic arterial pressure was set to approximately the same level as that obtained before connecting the perfusion circuits and was held constant during tests by adjustments, when necessary, of the pressure of air in the arterial reservoir. Heart rate was held constant by electrical pacing of the right atrium. When all measured variables were steady, control records were taken. The pacing stimulator was then switched off to record free heart rate. The carotid chemoreceptors were then perfused with venous blood from the inferior vena cava and when the measured variables had again reached steady states, usually 2–4 min after changing the perfusion, the pacing stimulator was switched on again and records were again taken. The area was then perfused again with arterial blood and second control values obtained. The values of dP/dt_{max} obtained during perfusion of the chemoreceptors with venous blood were compared with the means of the values obtained during perfusion with arterial blood.

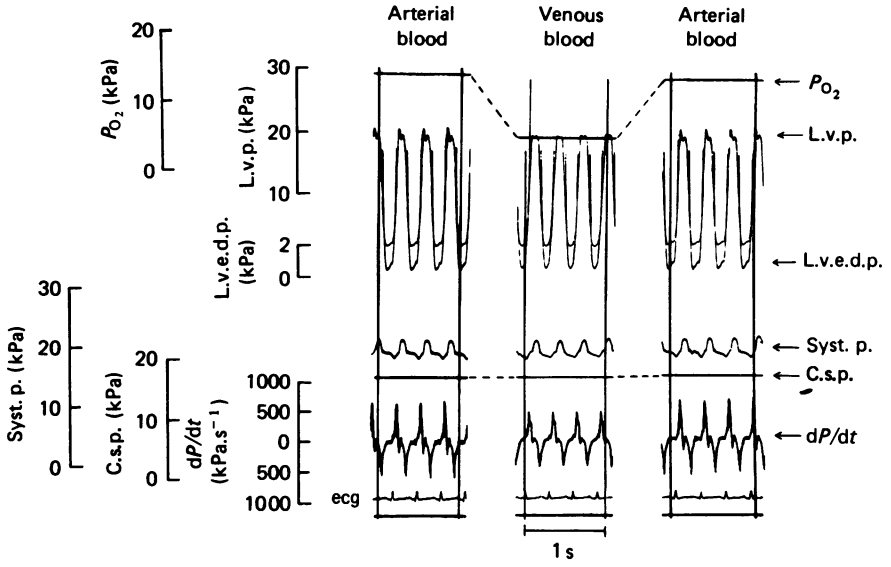

Fig. 2. Records showing the effects of perfusing the carotid chemoreceptors with arterial and venous blood. Both vagus nerves were cut and the heart was paced at 210 beats min^{-1}. P_{O_2}, oxygen tension of perfusate. L.v.p. left ventricular pressure. L.v.e.d.p., left ventricular end-diastolic pressure. Syst. p, systemic arterial pressure. C.s.p., carotid sinus pressure. dP/dt, rate of change of left ventricular pressure. During perfusion with venous blood, dP/dt max decreased (heart rate, carotid and systemic pressures constant). On re-establishing arterial perfusion, dP/dt_{max} returned to control value.

RESULTS

Values reported are of means ± standard errors of the means.

Inotropic responses from perfusion of the carotid chemoreceptors with venous blood

Forty-five tests were done in seventeen dogs. In the arterial perfusate P_{O_2} was 16·2 ± 1·1 kPa, P_{CO_2} 5·25 ± 0·16 kPa and pH 7·36 ± 0·01 units. In the venous

perfusate P_{O_2} was 4·8 ± 0·2 kPa, P_{CO_2} 6·79 ± 0·18 kPa and pH 7·27 ± 0·01 units. Carotid perfusion pressure was 16·5 ± 0·6 kPa, mean systemic arterial pressure 16·6 ± 0·7 kPa and heart rate 189 ± 6 beats.min^{-1}.

When the heart was not paced a change of perfusion of the chemoreceptors from arterial to venous blood resulted in a reduction of the heart rate of 55 ± 8 beats.min^{-1} ($P < 0·001$) from 187 ± 7 beats.min^{-1}. When the heart was paced, chemoreceptor stimulation resulted in a decrease in dP/dt_{max} of 92 ± 7·9 kPa.s^{-1} from 510 ± 27 kPa.s^{-1} ($P < 0·001$); a reduction of 17·9 ± 1·0%. Peak left ventricular pressure also decreased by 1·0 ± 0·2 kPa from 18·4 ± 0·8 kPa ($P < 0·001$) but left ventricular end-diastolic pressure did not change significantly. Table 1 gives the averages of the responses obtained from each dog and Fig. 2 shows an example of records obtained during perfusion of the chemoreceptors with arterial blood, venous blood and again with arterial blood.

TABLE 1. Inotropic responses from perfusion of the regions of the carotid bifurcations with venous blood

Dog no.	C.s.p. (kPa)	L.v.e.d.p. (kPa) A	L.v.e.d.p. (kPa) V	L.v.p. (kPa) A	L.v.p. (kPa) V	dP/dt_{max} (kPa.s^{-1}) A	dP/dt_{max} (kPa.s^{-1}) V	dP/dt_{max} (kPa.s^{-1}) % change
1	18·6	0·50	0·70	17·3	16·6	495	394	20·4
2	16·0	0·20	0·30	15·2	14·6	463	378	18·3
3	12·6	0·65	0·60	19·9	19·2	443	363	18·1
4	13·0	0·70	0·75	14·0	13·3	379	286	24·5
5	18·6	0·70	0·55	16·0	15·0	426	359	15·7
6	19·0	0·85	1·05	19·2	18·3	494	412	16·6
7	17·3	0·85	0·70	19·9	18·6	592	492	16·9
8	13·3	0·35	0·65	18·6	17·3	492	366	25·6
9	15·5	0·40	0·45	25·6	22·5	635	512	19·4
10	20·4	0·50	0·70	25·6	23·3	838	652	22·2
11	14·6	1·00	1·10	17·9	17·9	512	426	16·8
12	16·0	0·60	0·50	19·2	18·6	555	452	18·6
13	17·3	—	—	15·7	14·6	505	412	18·4
14	16·0	—	—	15·3	15·3	585	505	13·7
15	18·6	—	—	16·0	14·3	359	306	14·8
16	16·0	—	—	16·5	15·7	412	346	16·0
17	18·6	—	—	21·3	20·0	492	452	8·1
Mean	16·5	0·61	0·67	18·4	17·4	510	418	17·9
S.E. of mean	0·6	0·07	0·07	0·8	0·7	27	21	1·0
P	—	> 0·1		< 0·001		< 0·001		—

Values listed are the averages obtained from each dog during perfusion of carotid bifurcation areas with arterial (A) and venous (V) blood at constant carotid sinus pressure. C.s.p., carotid sinus pressure; L.v.e.d.p., left ventricular end-diastolic pressure; L.v.p., left ventricular systolic pressure; dP/dt_{max}, maximum rate of change of left ventricular pressure. Aortic blood pressure was held constant at 16·6 ± 0·7 kPa and heart rate at 189 ± 6 beats.min^{-1}. In arterial blood P_{O_2} was 16·2 ± 1·1 kPa, P_{CO_2} 5·25 ± 0·16 kPa and pH 7·36 ± 0·01 units. In venous blood, P_{O_2} was 4·8 ± 0·2 kPa, P_{CO_2} 6·79 ± 0·18 kPa and pH 7·27 ± 0·01 units.

Inotropic responses from graded changes in P_{O_2} of the carotid perfusate

In five dogs, the carotid bifurcation regions were perfused with blood from an oxygenator. P_{CO_2} and pH of the perfusate blood were held constant and P_{O_2} was decreased in steps by reducing the flow of oxygen through the oxygenator (see Methods).

A change of dP/dt_{max} was obtained when P_{O_2} decreased by the first step tested, to $9{\cdot}9 \pm 0{\cdot}9$ kPa, and further graded changes in dP/dt_{max} were obtained for all values of oxygen tension which were tested, down to 3·0 kPa. No lower limit was found. An example of records from one of the experiments is shown in Fig. 3 and the values from all the dogs are plotted in Fig. 4.

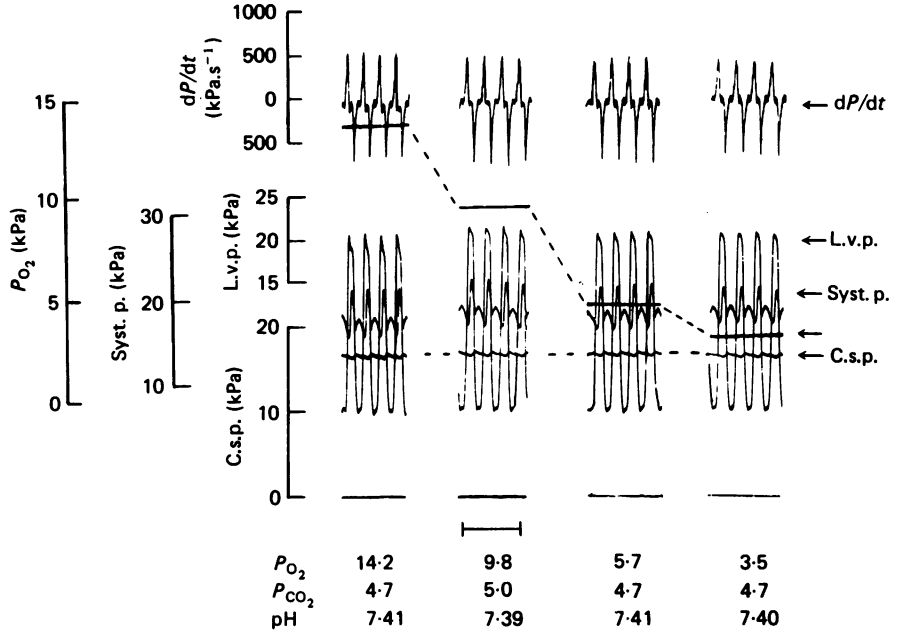

Fig. 3. Inotropic responses to varying the oxygen tension in the carotid perfusate in steps. Both vagus nerves were cut and P_{CO_2} and pH were held nearly constant. Abbreviations are the same as in Fig. 2. Note that responses were obtained at the first step decrease in P_{CO_2} from the arterial value of 14·2 to 9·8 kPa.

Effect of setting carotid perfusion presure at different levels on the inotropic response to chemoreceptor stimulation

In six of the dogs, the responses to stimulation of the carotid chemoreceptors were examined with carotid pressure held steady at different levels.

At a carotid perfusion pressure of $16{\cdot}9 \pm 0{\cdot}7$ kPa, stimulation of the chemoreceptors with venous blood resulted in a decrease in dP/dt_{max} of 64 ± 8 kPa.s^{-1} from a control value of 454 ± 36 kPa.s^{-1}. At a perfusion pressure of $8{\cdot}9 \pm 0{\cdot}2$ kPa stimulation with venous blood resulted in very little response in three of the dogs, but in two of the dogs the response was similar to that observed at medium carotid pressure. However, when the perfusion pressure was raised to $29{\cdot}9 \pm 1{\cdot}2$ kPa, the response to chemoreceptor stimulation was abolished.

An example of records showing the effects on the inotropic responses of setting the carotid pressure at three levels is given in Fig. 5, and Table 2 gives the results obtained from each dog.

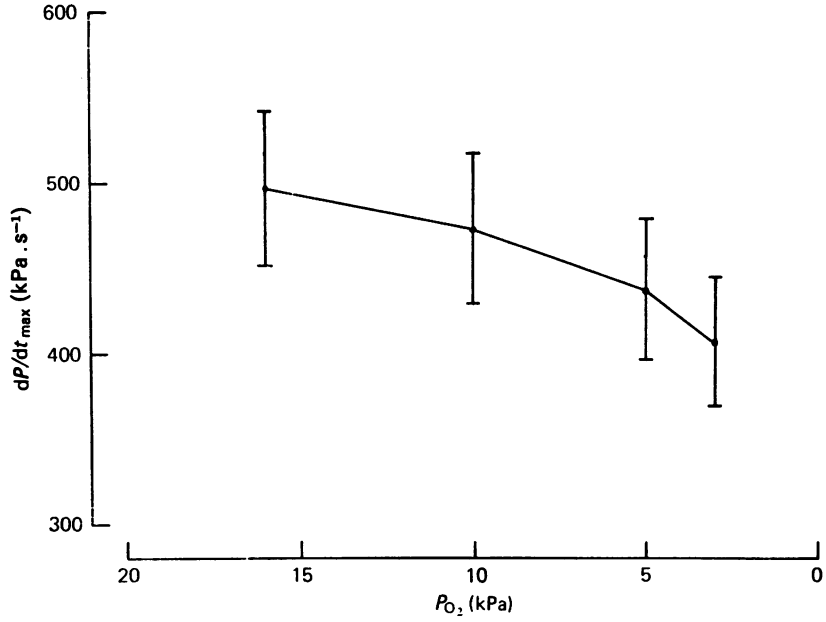

Fig. 4. Inotropic responses at different oxygen tensions of carotid perfusate in five dogs. Values are shown of means ± 1 S.E. P_{CO_2} and pH were 5·3 ± 0·1 kPa and 7·39 ± 0·01 units respectively. Heart rate, aortic and carotid pressures were all held constant throughout each series of observations.

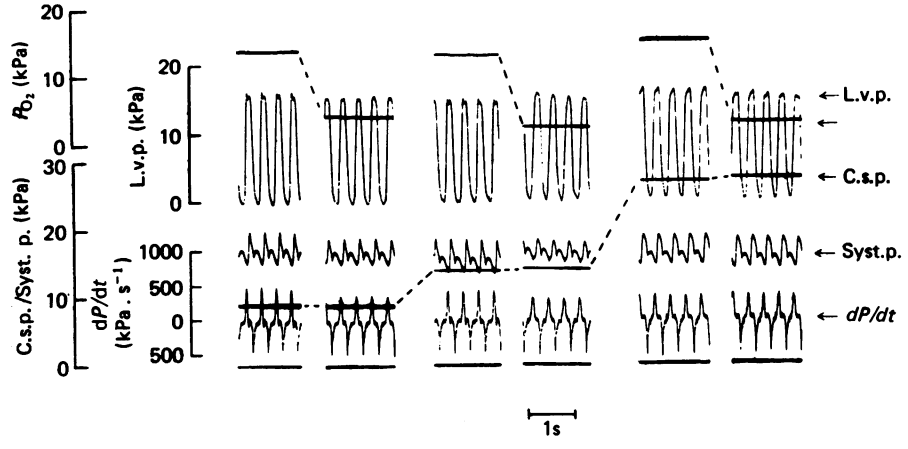

Fig. 5. Records showing the inotropic responses to changing carotid perfusion from arterial to venous blood at three levels of carotid sinus pressure in one dog. Abbreviations are as in Fig. 2. Heart rate and aortic pressure were held constant. In this example, the inotropic responses obtained at low (8·8 kPa) and medium (13·9 kPa) carotid pressures were similar. However, at high carotid pressure (27·8 kPa), there was no response to chemoreceptor stimulation.

Effect of cervical vagotomy on the inotropic responses

In six of the dogs the inotropic responses were assessed before and after cutting both cervical vagosympathetic trunks. Neither the control values nor the responses were significantly altered by vagotomy. Before vagotomy, stimulation of the chemoreceptors with venous blood caused a decrease in dP/dt_{max} of $99{\cdot}7 \pm 5{\cdot}7$ kPa.s^{-1} from a control value of 488 kPa.s^{-1}, and after vagotomy it decreased by $92{\cdot}6 \pm 8{\cdot}0$ kPa.s^{-1} from a control value of 480 kPa.s^{-1}.

TABLE 2. The inotropic responses to stimulation of carotid chemoreceptors at various levels of carotid sinus pressure

	Carotid sinus pressure					
	$8{\cdot}9 \pm 0{\cdot}2$ kPa		$16{\cdot}9 \pm 0{\cdot}7$ kPa		$29{\cdot}9 \pm 1{\cdot}2$ kPa	
Dog no.	Control dP/dt_{max} (kPa.s^{-1})	Change	Control dP/dt_{max} kPa.s^{-1})	Change	Control dP/dt_{max} (kPa.s^{-1})	Change
5	399	+7	372	−53	—	—
13	—	—	505	−93	372	+3
14	628	−3	585	−80	362	−3
15	445	−46	359	−53	295	−2
16	425	−53	412	−66	336	−3
17	505	+4	492	−40	385	−3
Mean	480	−18	454	−64	350	−2
S.E. of mean	41	13	36	8	16	1
Perfusate	A	V	A	V	A	V
P_{O_2} (kPa)	$14{\cdot}0 \pm 1{\cdot}1$	$4{\cdot}4 \pm 0{\cdot}5$	$13{\cdot}6 \pm 0{\cdot}3$	$4{\cdot}9 \pm 0{\cdot}5$	$13{\cdot}4 \pm 0{\cdot}7$	$4{\cdot}7 \pm 0{\cdot}2$
P_{CO_2} (kPa)	$5{\cdot}6 \pm 0{\cdot}2$	$6{\cdot}9 \pm 0{\cdot}3$	$5{\cdot}2 \pm 0{\cdot}5$	$6{\cdot}9 \pm 0{\cdot}4$	$5{\cdot}6 \pm 0{\cdot}4$	$6{\cdot}4 \pm 0{\cdot}2$
pH	$7{\cdot}40 \pm 0{\cdot}02$	$7{\cdot}33 \pm 0{\cdot}02$	$7{\cdot}39 \pm 0{\cdot}02$	$7{\cdot}31 \pm 0{\cdot}02$	$7{\cdot}39 \pm 0{\cdot}01$	$7{\cdot}33 \pm 0{\cdot}02$

Results are average values from each dog. Control values of dP/dt_{max} were obtained when the carotid bifurcation areas were perfused with arterial blood (A) and changes were obtained when the areas were perfused with venous blood (V).

Effect of crushing the cardiac sympathetic nerves on the inotropic responses

In three of the dogs, the responses to chemoreceptor stimulation were determined before and after crushing both ansae subclaviae. The results, listed in Table 3, show that after crushing the ansae the responses were abolished or greatly reduced.

Effect of crushing the carotid bodies on the inotropic responses

In three of the dogs the responses to chemoreceptor stimulation were determined before and after both carotid bodies were crushed with fine forceps (Schmidt, 1932). Before crushing the carotid bodies, stimulating the chemoreceptors with venous blood resulted in an average change in dP/dt_{max} of 108 kPa.s^{-1}, whereas after the carotid bodies had been crushed the response was only 12 kPa.s^{-1}. The responses in the individual dogs are listed in Table 3.

The inotropic responses to changing carotid sinus pressures were not affected by crushing the carotid bodies. Before crushing, an increase in carotid sinus pressure

from 11·6 to 22·6 kPa resulted in a decrease in dP/dt_{max} of 133 kPa.s^{-1} and, after crushing the bodies, the response to the same change in carotid pressure was 163 kPa.s^{-1}.

TABLE 3. Inotropic responses to stimulation of carotid chemoreceptors before and after crushing the ansae subclaviae and carotid bodies

		Before crushing		After crushing	
Dog no.	Crushing of	Control dP/dt_{max} (kPa.s^{-1})	Change	Control dP/dt_{max} (kPa.s^{-1})	Change
1	Ansae	495	−101	293	0
2	Ansae	532	−160	479	−27
14	Ansae	638	−67	346	0
10	Carotid bodies	838	−186	1017	+21
11	Carotid bodies	512	−86	678	+14
15	Carotid bodies	359	−53	319	0

DISCUSSION

Perfusion of the vascularly isolated regions of the carotid bifurcations with venous or hypoxic blood consistently resulted in a negative inotropic response of the left ventricle and a decrease in heart rate. These responses were the reflex effects of stimulation of chemoreceptors and not due to a change in the activity of baroreceptors or other afferent nerves for several reasons. (1) The pressure perfusing the carotid baroreceptors was held constant throughout each test. (2) Responses could not have been due to hypoxic inactivation of baroreceptors because the changes in both heart rate and dP/dt_{max} were opposite to those which would have resulted from a decrease in baroreceptor activity. (3) The flow of blood into the perfused region was too low (2 ml.min^{-1}) for any effect on adjacent structures to have been likely. (4) Responses were abolished by crushing the carotid bodies whereas responses from baroreceptors remained unaltered.

Furnival *et al.* (1970) reported that the maximum rate of change of left ventricular pressure (dP/dt_{max}) provides a sensitive and quantitative index of the inotropic state of the heart provided that heart rate and mean aortic pressure are held constant. It is insensitive to moderate changes in end-diastolic pressure and, in our experiments, although we did not attempt to control end-diastolic pressure there was no significant change during chemoreceptor stimulation.

By use of an oxygenator we were able to determine the responses to perfusion of chemoreceptors with blood of various oxygen tensions. It was thus possible to grade the responses. However, we were not able to determine the oxygen tensions at which responses were first obtained or the tensions at which responses were maximal. Small changes in dP/dt_{max} were obtained when oxygen tension was reduced by the first step tested, to about 10 kPa, and responses were obtained at the last step tested, to about 3 kPa. Similar tensions have been reported by Pelletier (1972) to result in graded vasomotor responses, and by Schmidt & Comroe (1940) for respiratory responses. Biscoe, Purves & Sampson (1970) showed that changes in afferent impulse traffic occurred over a similar range.

The efferent path of the reflex inotropic change was shown to be in the cardiac sympathetic nerves because there was no change in dP/dt_{max} during chemoreceptor stimulation after both ansae subclaviae had been crushed. Abolition of the responses by cutting the cardiac sympathetic nerves also rules out a significant effect due to possible decreases in concentration of circulating catecholamines. Also, catecholamine concentration would have been expected to increase during chemoreceptor stimulation (Anichkov, Malyghina, Poskalenka & Ryzhenkov, 1960), which would have increased the inotropic state of the heart.

The vagus nerves played no significant part in the inotropic responses to carotid chemoreceptor stimulation; in six dogs tested we obtained almost identical results before and after cutting both cervical vagosympathetic trunks. This is in direct contradiction to the findings of De Geest, Levy & Zieske (1965) who reported usually a small negative inotropic response before vagotomy and no change or a positive response after vagotomy. It is difficult to explain their findings since, in dogs, the vagus nerves do not innervate the ventricular myocardium (Nonidez, 1939) and vagal stimulation has been shown to have little or no effect on the left ventricular inotropic state (Sarnoff, Brockman, Gilmore, Linden & Mitchell, 1960; Furnival, Linden & Snow, 1973).

Other previous work on the inotropic responses from chemoreceptor stimulation can be criticized on various counts. Downing, Remensnyder & Mitchell (1962) measured ventricular function curves in vagotomized dogs and reported variable shifts of the curves. The variable results could be explained by the variations in arterial blood pressure which would have affected the inotropic state of the heart even when the activity in cardiac sympathetic nerves remained unchanged (Furnival *et al.* 1970). An increase in arterial blood pressure during chemoreceptor stimulation could also explain the positive inotropic responses reported by Kahler *et al.* (1962). Other reports can be criticized because the area stimulated was not well localized. Stern & Rapaport (1967) used the technique of injecting nictoine into the brachiocephalic artery and failed to obtain any responses of left ventricular contractile force as recorded using a strain gauge sutured to the myocardium. Pace (1970) however, reported a small decrease in right ventricular contractile force when nicotine was injected into the brachiocephalic artery of the dog.

In our experiments we attempted to examine the interaction between carotid chemoreceptors and baroreceptors by perfusing the chemoreceptors with hypoxic blood at various perfusion pressures. We found that responses were greatest at the intermediate carotid pressure tested which was approximately equal to systemic arterial pressure. When carotid pressure was increased, there was no inotropic response to chemoreceptor stimulation. This effect can readily be explained because raising carotid pressure reduces the activity in efferent sympathetic nerves to near zero (Trzebski, Lipski, Majcherczyk, Szulczyk & Chruscielewski, 1975; Hainsworth & Karim, 1976), so it is not possible to obtain any further decrease by stimulation of chemoreceptors. However, this observation is also consistent with that of Heistad, Abboud, Mark & Schmid (1974) and Mancia (1975), who reported inhibition at high carotid sinus pressure of the vasoconstrictor responses in the hind limb and skeletal muscle to hypoxic and hypercapcnic stimulation of the chemoreceptors. At carotid pressures below the baroreceptor thresholds, the responses to perfusion with venous

blood were abolished in three out of five dogs tested, but were unaffected in the other two.

Mancia (1975) showed that the vasoconstrictor responses to carotid chemoreceptor stimulation were also small when the perfusion pressure was low. These findings might be interpreted to imply that reflex chemoreceptor responses can only occur when the pressure perfusing the baroreceptors is approximately equal to the systemic arterial pressure. However, at low pressures we cannot be certain that the chemoreceptors are adequately perfused and the change in the response may have occurred because the stimulus was different.

Stimulation of carotid chemoreceptors has thus been shown to result in a differential effect on the efferent sympathetic nerves. Daly & Scott (1962) showed that there was an increase in activity in vasomotor nerves whereas, in the present study, we have shown evidence of a decrease in the activity of the cardiac sympathetic nerves.

The authors are grateful to Mrs M. Lindley and Mr B. Griffiths for technical assistance. This work was supported by a grant from the Medical Research Council.

REFERENCES

ANICHKOV, S. V., MALYGHINA, E. I., POSKALENKO, A. N. & RYZHENKOV, V. E. (1960). Reflexes from carotid bodies upon the adrenals. *Archs int. Pharmacodyn. Thér.* **129**, 156–165.

BISCOE, T. J., PURVES, M. J. & SAMPSON, S. R. (1970). The frequency of nerve impulses in single carotid body chemoreceptor afferent fibres recorded *in vivo* with intact circulation. *J. Physiol.* **208**, 121–131.

DALY, M. DE B. & SCOTT, M. J. (1958). The effects of stimulation of the carotid body chemoreceptors on heart rate in the dog. *J. Physiol.* **144**, 148–166.

DALY, M. DE B. & SCOTT, M. J. (1962). An analysis of the primary cardiovascular reflex effects of stimulation of the carotid body chemoreceptors in the dog. *J. Physiol.* **162**, 555–573.

DE GEEST, H., LEVY, M. N. & ZIESKE, H. (1965). Carotid chemoreceptor stimulation and ventricular performance. *Am. J. Physiol.* **209**, 564–570.

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

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

FURNIVAL, C. M., LINDEN, R. J. & SNOW, H. M. (1973). The inotropic effect on the heart of stimulating the vagus in the dog, duck and toad. *J. Physiol.* **230**, 155–170.

HAINSWORTH, R. & KARIM, F. (1976). Responses of abdominal vascular capacitance in the anaesthetized dog to changes in carotid sinus pressure. *J. Physiol.* **262**, 659–677.

HEISTAD, D. D., ABBOUD, F. M., MARK, A. L. & SCHMID, P. G. (1974). Interaction of baroreceptor and chemoreceptor reflexes. Modulation of the chemoreceptor reflex by changes in baroreceptor activity. *J. clin. Invest.* **53**, 1226–1236.

KAHLER, R. L., GOLDBLATT, A. & BRAUNWALD, E. (1962). The effects of acute hypoxia on the systemic venous and arterial systems and on myocardial contractile force. *J. clin. Invest.* **41**, 1553–1563.

MANCIA, G. (1975). Influence of carotid baroreceptors on vascular responses to carotid chemoreceptor stimulation in the dog. *Circulation Res.* **36**, 270–276.

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.

NONIDEZ, J. F. (1939). Studies on innervation of the heart. 1. Distribution of the cardiac nerves with special reference to the identification of the sympathetic and parasympathetic postganglionics. *Am. J. Anat.* **65**, 361–413.

PACE, J. B. (1970). Influence of carotid chemoreceptor stimulation on ventricular dynamics. *Am. J. Physiol.* **218**, 1687–1696.

PELLETIER, C. L. (1972). Circulatory responses to graded stimulation of the carotid chemoreceptors in the dog. *Circulation Res.* **31**, 431–443.

SALEM, H., PENNA, M. & AVIADO, D. M. (1964). Mechanism for bradycardia arising from stimulation of carotid bodies. *Archs int. Pharmacodyn. Thér.* **150**, 249–258.

SARNOFF, S. J., BROCKMAN, S. K., GILMORE, J. P., LINDEN, R. J. & MITCHELL, J. H. (1960). Regulation of ventricular contraction. Influence of cardiac sympathetic and vagal nerve stimulation on atrial and ventricular dynamics. *Circulation Res.* **8**, 1108–1122.

SCHMIDT, C. F. (1932). Carotid sinus reflexes to the respiratory centre. 1. Identification. *Am. J. Physiol.* **102**, 94–118.

SCHMIDT, C. F. & COMROE, J. H. JR. (1940). Functions of the carotid and aortic bodies. *Physiol. Rev.* **20**, 115–157.

STERN, S. & RAPAPORT, E. (1967). Comparison of reflexes elicited from combined or separate stimulation of the aortic and carotid chemoreceptors on myocardial contractility, cardiac output and systemic resistance. *Circulation Res.* **20**, 214–227.

TRZEBSKI, A., LIPSKI, S., MAJCHERCZYK, S., SZULCZYK, P. & CHRUSCIELEWSKI, L., (1975). Central organization and interaction of the carotid baroreceptor and chemoreceptor sympathetic reflex. *Brain Res.* **87**, 227–237.