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THE CONTRIBUTION OF ALTERATIONS IN CARDIAC OUTPUT TO CHANGES IN ARTERIAL PRESSURE REFLEXLY EVOKED FROM THE CAROTID SINUS IN THE RABBIT

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SUMMARY

1. The reflex cardiovascular effects of changes in pressure within the vascularly isolated carotid sinus were examined in seventeen anaesthetized rabbits. The opposite sinus was denervated and both aortic nerves were divided.

2. Comparison of the mean values at sinus pressures of 40 and 200 mmHg showed a large reduction in systemic arterial pressure from 126 to 58 mmHg and a moderate reduction in heart rate, from 287 to 253 beats min^{-1}. Cardiac output, measured by thermal dilution, showed only a small change, a fall from 160 to 148 ml. min^{-1} kg^{-1}.

3. By contrast with this reduction in cardiac output of just over 7%, total peripheral resistance, derived by dividing mean arterial pressure by cardiac output, was halved, falling from 0·84 to 0·41 mmHg $ml.^{-1}$ min kg.

4. Thus in the anaesthetized rabbit changes in cardiac ouput make only a small contribution to the changes in systemic pressure evoked by alterations in carotid sinus pressure. Changes in total peripheral resistance are principally responsible for the effect on systemic pressure.

5. Though the changes in output of the heart were small, there were considerable changes in the work done by the left ventricle which was approximately halved when carotid sinus pressure was raised from 40 to 200 mmHg.

INTRODUCTION

Considerable alterations in systemic arterial pressure can be reflexly engendered by changes in pressure within the vascularly isolated carotid sinus. Arterial pressure is determined by both cardiac output and peripheral resistance and while the participation in this reflex of alterations in

the calibre of resistance vessels in muscle, skin and splanchnic beds is well established (Heymans & Neil, 1958), there have been only a few reports covering the possible contribution to the response of changes in cardiac output. Daly & Luck (1958) raised the pressure within the isolated sinus of the dog by up to 140 mmHg and found an average reduction of 17·6 % in combined superior and inferior caval flow. A similar fall in cardiac output, of about 15 %, was noted by Schmidt, Kumada & Sagawa (1971) when sinus pressure was raised between 50 and 200 mmHg in dogs with vagi intact, but after vagotomy, to eliminate secondary effects from aortic baroreceptors as well as vagal effects on heart rate, the same change in sinus pressure reduced cardiac output by about 60 %. On the other hand, Kumada, Nogami & Sagawa (1975) using comparable techniques in vagotomized cats, found that cardiac output remained virtually unaltered when pressure in the perfused sinus was altered between 60 and 240 mmHg. In view of this considerable species difference we have investigated the effect of changes in carotid sinus pressure on cardiac output and total peripheral resistance in the rabbit, in an attempt to estimate the relative contribution of each of these factors to the over-all reflex change in arterial pressure in this species. A brief account of some of the findings has been presented (Humphreys & Joels, 1976).

METHODS

The experiments were performed on female New Zealand White rabbits anaesthetized with a 3 % solution of pentobarbitone sodium B.P. in 0·9 % NaCl administered through an ear vein. The mean dose required to induce anaesthesia was 51 mg kg^{-1}. Supplementary doses of 0·2–0·5 ml. were given when necessary to maintain a steady plane of anaesthesia as judged principally from the end-tidal value of the airway CO_2. The depth of anaesthesia chosen was sufficient to prevent a withdrawal response to firm squeezing between the toes.

The trachea was cannulated and catheters were introduced into a femoral vein and the left femoral artery, the arterial catheter, which was used for the measurement of systemic arterial pressure, being advanced into the abdominal aorta. A saline-dextrose solution (1 part of 0·9 % NaCl to 4 parts of 5 % dextrose) was infused through the venous cannula at an hourly rate of approximately 1·5 ml. kg^{-1}. Throughout the dissection and experiment the inspired air was slightly enriched with O_2 by passing a gentle stream of the gas over the tracheal cannula. Body temperature was maintained with the aid of heating lamps when necessary.

Isolation of the carotid sinus. The right carotid sinus was partially isolated by tying all the arterial branches arising from the region of the bifurcation with the exception of the external and common carotid arteries. Complete vascular isolation could then be achieved by placing clips on these vessels. The clips were removed between tests to restore the normal pulsatile blood flow to the sinus region. The contralateral sinus nerve was divided and both aortic nerves were cut to minimize compensatory cardovascular changes due to altered activity of baroreceptors in other regions.

After completion of the dissection heparin, 1000 i.u. kg^{-1} (Pularin, Evans Medical

1000 i.u. ml.$^{-1}$) was injected intravenously and a T-cannula inserted in the right common carotid artery. The stem of the T-cannula led to the perfusion apparatus which comprised a small reservoir containing oxygenated saline with an air space above. The reservoir could be placed in communication with the T-cannula by turning a tap. The air space was connected to a much larger tank of compressed air and by altering

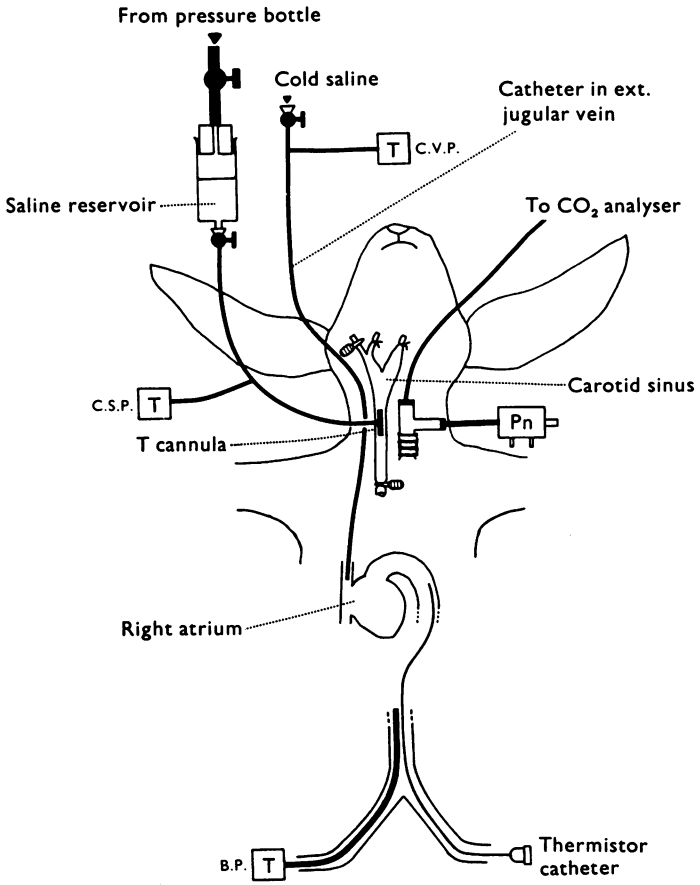

Fig. 1. Diagram of the experimental preparation. Pn, pneumotachograph. T, transducer measuring blood pressure (B.P.), carotid sinus pressure (C.S.P.) or central venous pressure (C.V.P.). For further details see text.

the pressure of this compressed air various non-pulsatile pressures could be applied to the carotid sinus. The pressure within the sinus was measured by an electromanometer connected through a side tube with the inlet to the rabbit (Fig. 1).

Recordings. Systemic arterial pressure, carotid sinus pressure and superior vena caval pressure (see below) were measured by transducers (Consolidated Electrodynamics Type 4-327-L221). The signals were amplified by carrier amplifiers (S.E. Laboratories, Type 423/1) and displayed on a direct writing U.V. recorder (S.E. Laboratories, Model No. 2100). Mean arterial pressure was obtained by passing the

systemic pressure signal through a simple R-C network with a time constant of 1 sec and was recorded by a separate galvanometer. Heart rate was counted from the pressure pulses. Tidal CO_2, measured by an infra-red CO_2 analyser (Hartmann & Braun, Type URAS 4) and tidal volume, measured by an integrating pneumotachograph (Godart NV) were also displayed on channels of the U.V. recorder. These measurements of tidal CO_2 and tidal volume were used primarily, in conjunction with occasional blood gas measurements, to aid the maintenance of a steady state of anaesthesia, but also showed whether or not respiration was altered by the test procedures.

Measurement of cardiac output. Cardiac outputs were determined using the thermal dilution technique (Fegler, 1954). 0·6 or 0·8 ml. 0·9 % saline at room temperature was injected from a calibrated syringe into the right atrium via a catheter passed through the right external jugular vein until its tip lay just above the entry of the superior vena cava into the right atrium (Fig. 1). A side-tube from this catheter led to a manometer which measured central venous pressure and also indicated the time of injection by the sharp pressure peak which this produced. The injectate temperature was measured with a mercury thermometer. Care was taken not to handle the plastic syringe barrel during the injection. The resulting change in aortic temperature was measured by a thermistor probe threaded through the right femoral artery until its tip lay in the thoracic aorta behind the heart (Fig. 1). The probe comprised an ITT type U23US thermistor bead, aged for 2 weeks at 90 °C before being secured at the tip of a 45 cm length of nylon tubing (Portex Nylon 1) using a flexible epoxy resin (Ciba MY750 + Cy208 with HY 956 hardener). The characteristics of the resulting thermistor catheter were determined and a linearizing resistor selected. The output from the thermistor was amplified using a temperature measuring unit designed and built in our department by Mr H. W. Ead and the output signal was displayed on one channel of the U.V. recorder. Cardiac output curves were recorded at a paper speed of 750 mm min^{-1}.

The area of the thermal dilution curve was calculated after a semilogarithmic plot of the down-slope had been drawn. This permitted extrapolation of the curve and also enabled correction to be made for the effects of recirculation of the indicator. Cardiac output was calculated from the formula

$$Q = \frac{60 V_i d_i s_i (T_b - T_i)\, K}{d_b s_b \int_0^{\infty} \Delta T_b(t)\, dt},$$

where Q is the cardiac output (ml. min^{-1}), V_i is the volume of injectate, d_i and d_b are the densities of injectate and blood (i.e. 1·005 and 1·045) respectively, s_i and s_b are the specific heats of injectate and blood (i.e. 0·997 and 0·85) respectively, T_i and T_b are the temperatures of injectate and of aortic blood immediately before the injection of room temperature saline, whilst ΔT_b is the change in aortic blood temperature at any instant. K is a correction factor for loss of thermal indicator between the injectate at room temperature and the warm wall of that part of the injection catheter inside the body which is at body temperature. With 10 cm of catheter inside the body, K is 0·94 (Korner & Hilder, 1974).

Comparison between thermal and dye dilution methods

The validity of the thermal dilution method for the measurement of cardiac output has been widely confirmed in many species ranging from man to rat and including the rabbit (Korner, 1965). But a report by Warren & Ledingham (1974) suggests that a systematic error could arise at low cardiac outputs when the thermal dilution method is used in rabbits. We therefore made simultaneous measurements of cardiac output

by thermal and dye dilution in a group of seven rabbits using indocyanine green (Cardio-green, Hynson, Westcott and Dunning, Inc.). The dye curves were recorded by withdrawing blood from the aorta for a few seconds at a rate of 6 ml. min^{-1} through a Gilford cuvette densitometer model 103 IR using a Harvard withdrawal-infusion pump. The blood was reinfused after each determination and the densitometer was calibrated at the end of the experiment using serial dilutions of indocyanine green in the rabbit's own blood. A variety of procedures was used to obtain a range of cardiac outputs in each animal. These included carotid occlusion, hypoxia, injection of adrenaline and noradrenaline, inhalation of amyl nitrite and haemorrhage. The results of sixty-three simultaneous determinations in the seven rabbits are shown in

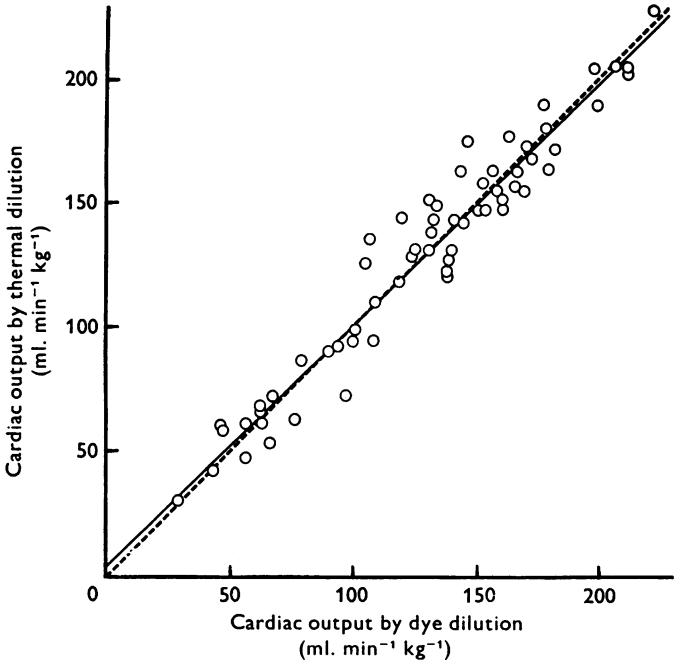

Fig. 2. Comparison of simultaneous cardiac output determinations by thermal dilution and dye dilution. Sixty-three determinations in seven rabbits. The calculated regression line (continuous) has the equation: cardiac output by thermal dilution = 0·97 cardiac output by dye dilution + 3·68 ml. min^{-1} kg^{-1}. The interrupted line represents the line of equality.

Fig. 2. The cardiac outputs cover the range found in the principal studies reported in this paper. The agreement between the two methods is very similar to that shown in Fig. 2 of Korner's (1965) paper, and in common with his findings there is no evidence of alinearity in their correlation at lower cardiac outputs. The correlation coefficient for the values of cardiac output by thermal dilution and dye dilution shown in our Fig. 2 is 0·972. The equation of the regression line is: cardiac output (thermal dilution) 0·97 cardiac output (dye dilution) + 3·68 ml. min^{-1} kg^{-1}.

Test procedure. The procedure used to determine the reflex cardiovascular effects of subjecting the carotid sinus baroreceptors to various non-pulsatile pressures has

been described briefly (Ead, Humphreys & Joels, 1974). Vascular isolation of the sinus was completed by placing clips on the external carotid artery and on the common carotid artery below the T-cannula, then connecting the T-cannula with the saline reservoir which had been set to provide the desired pressure. Generally pressures of 40, 70, 100, 130, 160 and 200 mmHg were used and these were applied in a random sequence. Positioning the clips and turning the reservoir tap could be accomplished in about 2 sec. Immediately prior to placing the clips on the arteries the polyethylene tube connecting the reservoir with the T-cannula was filled with blood by allowing blood to run back into it from the carotid artery. This tube had a capacity of 0·4 ml and during thec ourse of a single test no more than one-quarter of this blood was displaced by saline. Thus the carotid sinus must have remained filled with blood throughout.

The injection of room temperature saline for cardiac output determination was given about 25 sec after applying the selected carotid sinus pressure, by which time heart rate and arterial pressure had reached a new steady level. The test was terminated after completion of the thermal dilution curve. Sometimes the change in carotid sinus pressure itself, without injection of cold saline, led to a transient but consistent change in aortic temperature, presumably due to a redistribution of blood between the vascular beds of the skin and deeper structures. Therefore a control series of tests was always performed in which cardiac output was not determined. This enabled any drift of the thermal base line over the period of the cardiac output determination to be measured and allowed for.

Blood gases. Arterial blood samples (0·7 ml.) were withdrawn into syringes anaerobically and their pH, P_{O_2} and P_{CO_2} measured immediately at 39° C with a Radiometer Type PHM 27b pH meter and Type PHA 927b Gas Monitor using Radiometer electrodes.

Calculation of total peripheral resistance. The measured central venous pressure was in practice at all times close to zero and in no procedure did its mean value change by more than 1–2 mmHg. Consequently total peripheral resistance has been computed as the ratio of mean aortic blood pressure in mmHg to cardiac output in ml. min^{-1} kg^{-1}.

Values. Unless otherwise stated all values are quoted as means ± S.D.

RESULTS

Control values

The effects of changes in carotid sinus pressure on cardiac output were examined in seventeen rabbits. The control values for blood pressure and heart rate, i.e. the means of the values at the beginning of each test, immediately before applying the arterial clips and when the carotid sinus was exposed to pulsatile blood flow at the animal's arterial pressure, were blood pressure 103·9 ± 10·0 mmHg and heart rate 284·1 ± 27·9 beats min^{-1}. An arterial blood sample was withdrawn during each series of tests. The mean P_{CO_2} was 37·6 ± 4·2 mmHg and the mean pH 7·36 ± 0·03. Arterial P_{O_2} was always in excess of 150 mmHg. The mean weight of the rabbits was 3·14 ± 0·48 kg and the mean rectal temperature 38·8 ± 0·97° C.

In eleven of these seventeen rabbits cardiac output was also measured with the sinus exposed to pulsatile blood flow and was found to be 161·5 ±

41·5 ml. min^{-1} kg^{-1}. Calculated total peripheral resistance in these animals was 0·697 ± 0·164 mmHg $ml.^{-1}$ min kg.

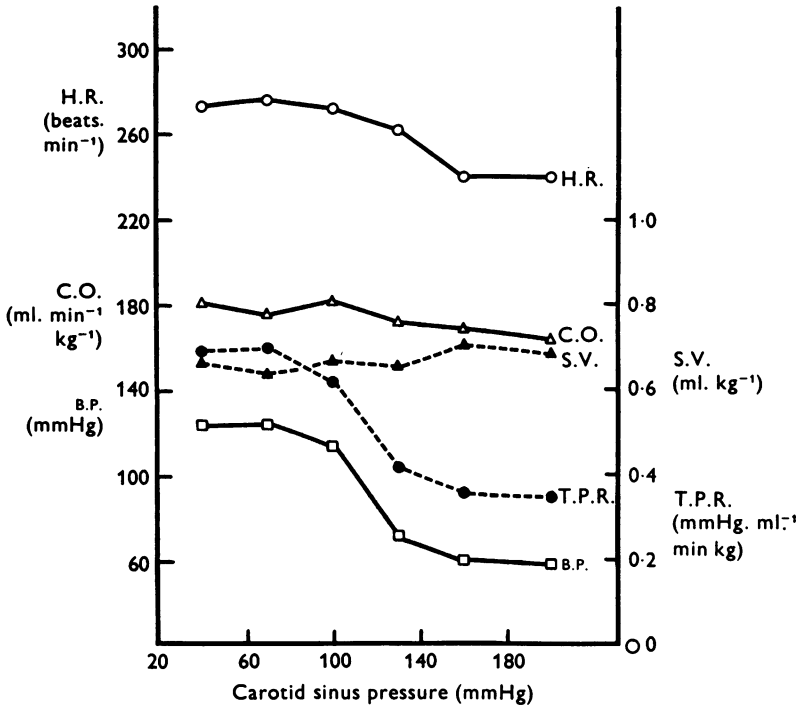

Fig. 3. Measured values for heart rate (H.R. beats min^{-1}), cardiac output (C.O. ml. min^{-1} kg^{-1}) and arterial pressure (B.P. mmHg) and calculated values for stroke volume (S.V. ml. kg^{-1}) and total peripheral resistance (T.P.R. mmHg $ml.^{-1}$ min kg) at different levels of carotid sinus pressure in an anaesthetized rabbit.

Effect of changes in sinus pressure

Fig. 3 illustrates the results of a representative experiment in which arterial pressure, heart rate and cardiac output were measured 25–30 sec after applying each of the series of six non-pulsatile pressures ranging from 40 to 200 mmHg to the vascularly isolated carotid sinus. Also shown are the calculated values for stroke volume and total peripheral resistance.

In the experiment shown in Fig. 3 an increase in sinus pressure from 40 to 200 mmHg was associated with a fall in heart rate from 273 to 240 beats min^{-1}, a fall in arterial pressure from 124 to 58 mmHg and a fall in cardiac ouput from 181 to 164 ml. min^{-1} kg^{-1}. Calculated total peripheral resistance fell from 0·665 to 0·350 mmHg $ml.^{-1}$ min kg, and there was a small rise in stroke volume from 0·665 to 0·690 ml. $kg.^{-1}$

The cardiovascular changes in the individual rabbit illustrated in Fig. 3 are mirrored by the mean findings for all seventeen rabbits in which these cardiovascular effects of alterations in sinus pressure were examined (Fig. 4).

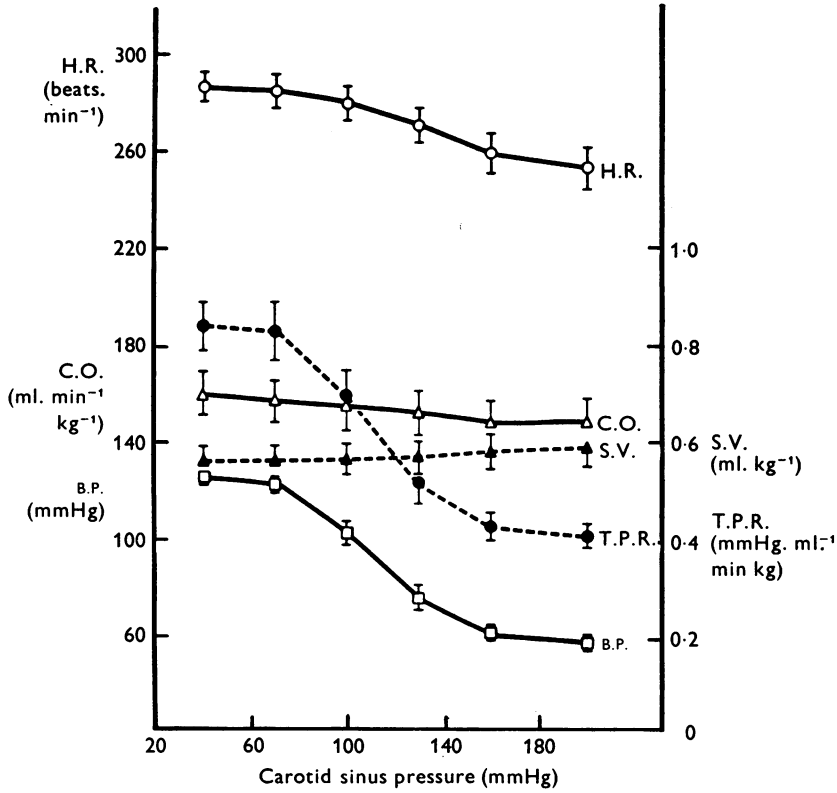

Fig. 4. Mean values (± 1 S.E. of mean) of cardiovascular parameters at different sinus pressures for the series of seventeen rabbits. Abbreviations as for Fig. 3.

In Table 1 the mean values for the various cardiovascular parameters at sinus pressures of 40 and 200 mmHg are listed together with the percentage change in the value of each parameter between the two sinus pressures.

From this Table and Fig. 4 it can be seen that a rise in pressure within the isolated carotid sinus from 40 to 200 mmHg led to a reduction in arterial pressure which exceeded 50 %. This fall in arterial pressure was associated with a fall in cardiac output from 159·2 ± 37·8 to 147·8 ± 40·9 ml. min^{-1} kg^{-1}. Though small, this 7·2 % reduction in cardiac output was statistically significant ($P < 0·05$, paired t-test). However by far the

greater contribution to the fall in arterial pressure must have come from the change in total peripheral resistance, which fell by 51·5%, from 0·836 ± 0·211 to 0·405 ± 0·113 mmHg ml.$^{-1}$ min kg ($P < 0·001$).

TABLE 1. Values (mean ± S.D.) of heart rate (H.R.) arterial pressure (B.P.). cardiac output (C.O.), stroke volume (S.V.) and total peripheral resistance (T.P.R.) at carotid sinus pressures of 40 and 200 mmHg in seventeen rabbits. The P values refer to the mean difference between the measurements at low and high sinus pressures in individual experiments (paired t test)

	Sinus pressure 40 mmHg	Sinus pressure 200 mmHg	% change	P
H.R. beats min^{-1}	287·4 ± 26·4	252·8 ± 36·9	−12·0	< 0·001
B.P. mmHg	126·3 ± 8·4	57·7 ± 11·5	−54·3	< 0·001
C.O. ml. min^{-1} kg^{-1}	159·2 ± 37·8	147·8 ± 40·9	−7·2	< 0·05
S.V. ml. kg^{-1}	0·559 ± 0·142	0·587 ± 0·154	+5·0	< 0·05
T.P.R. mmHg ml.$^{-1}$ min kg	0·836 ± 0·211	0·405 ± 0·113	−51·5	< 0·001

Changes in cardiac performance. The smallness of the change in cardiac output as carotid sinus pressure is varied tends to obscure the fact that these alterations in sinus pressure are accompanied by considerable changes in cardiac performance. An assessment of left ventricular stroke work can be obtained by multiplying together left ventricular stroke volume and arterial pressure; the mean values for the seventeen rabbits are plotted in Fig. 5*A*. When sinus pressure was increased from 40 to 200 mmHg left ventricular stroke work was reduced from 0·97 ± 0·22 to 0·46 ± 0·15 gram-metres kg^{-1}, a fall of 52·3%. Since the alteration in heart rate as sinus pressure is raised is in the same direction as the alteration in stroke work, the corresponding values for left ventricular work, obtained by multiplying left ventricular stroke work by heart rate, show an even greater change with variation in sinus pressure, from 274 ± 61 gram-metres kg^{-1} min^{-1} at a sinus pressure of 40 mmHg, to 118 ± 44 gram-metres kg^{-1} min^{-1} at a sinus pressure of 200 mmHg, a reduction of 56·9% (Fig. 5*B*).

Effects of sinus and aortic nerve section

As described in Methods, the preparation involved section of one sinus nerve and both aortic nerves. To see whether leaving only one sinus nerve intact had appreciably altered the control cardiovascular parameters in which we were interested, two additional experiments were performed in which heart rate, arterial pressure and cardiac output were measured immediately before cutting one sinus and both aortic nerves and again 2–3 hr later, this being the interval which normally intervened between sectioning these nerves and performing the tests. The values for heart

rate, arterial pressure, cardiac output and total peripheral resistance just before and 2–3 hr after cutting both aortic nerves and one sinus nerve in these two rabbits are given in Table 2.

They show that this procedure had no effect on arterial blood pressure, but there was a small rise in total peripheral resistance which was virtually balanced by a reduction in cardiac output of approximately 10%.

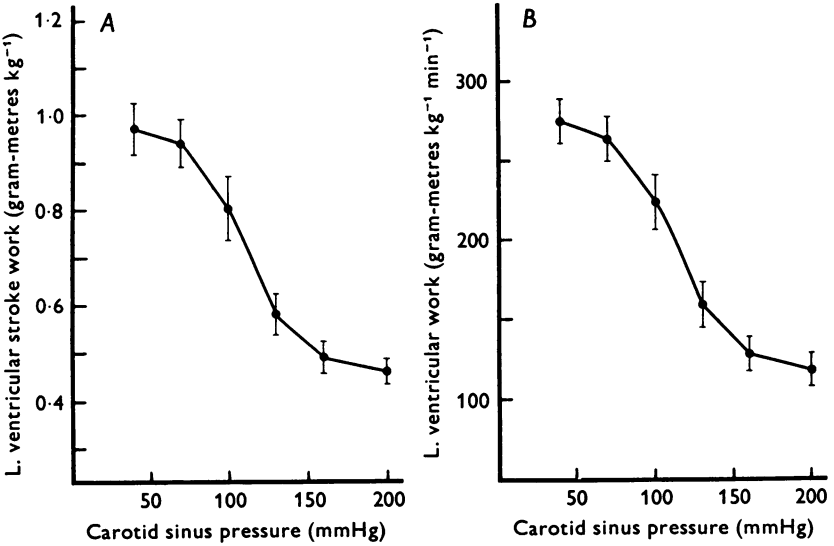

Fig. 5. Mean values (± 1 S.E. of mean) for left ventricular stroke work (on left) and left ventricular work (on right) at different levels of pressure within the isolated carotid sinus.

TABLE 2. Heart rate (H.R.), arterial pressure (B.P.), cardiac output (C.O.) and total peripheral resistance (T.P.R.) before and 2–3 hr after cutting one sinus nerve and both aortic nerves. Each value is the mean of a pair of measurements

	Rabbit 62			Rabbit 66			
	Before	After	% change	Before	After	% change	Mean change (%)
H.R. (beats min^{-1})	266	276	+3·8	321	288	−10·3	− 3·3
B.P. (mmHg)	102	100	−2·0	101	105	+ 4·0	+ 1·0
C.O. (ml. min^{-1} kg^{-1}	202	182	−9·8	153	138	− 9·7	− 9·8
T.P.R. (mmHg ml.$^{-1}$ min kg)	0·503	0·549	+9·1	0·658	0·761	+15·6	+12·4

DISCUSSION

These results establish that in the rabbit alterations in cardiac output make only a small contribution to the changes in blood pressure which result from alterations in pressure within the vascularly isolated carotid

sinus; modification of the total peripheral resistance is clearly the major factor determining the change in blood pressure. Thus, after cutting both aortic nerves and the contralateral sinus nerve to minimize compensatory responses from other baroreceptor zones, raising sinus pressure from 40 to 200 mmHg caused a fall of only 7 % in cardiac output whereas total peripheral resistance fell by more than 50 %. In this respect the behaviour of the rabbit resembles that of the vagotomized cat, in which Kumada *et al.* (1975) found that a rise in isolated carotid sinus pressure from 60 to 240 mmHg had almost no effect on cardiac output but as in the rabbit reduced total peripheral resistance by about 50 %. By contrast, in the dog, when the compensatory effects of aortic baroreceptors had also been eliminated by vagotomy, raising isolated carotid sinus pressure from 50 to 200 mmHg was shown by Schmidt *et al.* (1971) to reduce total peripheral resistance by a very similar 55 %, but this was accompanied by a fall of 60 % in cardiac output. Thus in the vagotomized dog, cardiac output makes a contribution to the fall in arterial pressure evoked by stimulation of the carotid sinus baroreceptors, which is at least as great, and possibly exceeds, that of the reduction in total peripheral resistance.

Changes in the discharge from the carotid sinus baroreceptors were undoubtedly responsible for the alteration in cardiac output observed in our experiments. We were conscious of the possibility that at the lowest sinus pressures used stagnant hypoxia might lead to excitation of the carotid body chemoreceptors (Landgren & Neil, 1951; Biscoe, Bradley & Purves, 1970) and to minimize this risk arterial O_2 tension was always maintained in excess of 150 mmHg. However, it is most unlikely that chemoreceptor stimulation contributed to our findings since there was never any evidence of increased respiration during the 30 sec. test period at low sinus pressure. Ott, Kiwull & Wiemer (1971) have reported a similar absence of respiratory stimulation in the rabbit even when pressure within the isolated carotid sinus was reduced below 20 mmHg.

Attempts have previously been made to estimate the effects of altered baroreceptor stimulation on cardiac output in the rabbit using other methods. However, the techniques employed are open to criticism. Thus Edwards, Korner & Thorburn (1959) found that neither unilateral nor bilateral carotid occlusion had any effect on cardiac output in unanaesthetized rabbits. But carotid occlusion represents merely the withdrawal of baroreceptor activity present before occlusion and therefore the size of the stimulus will depend largely on the control level of blood pressure. Moreover during unilateral carotid occlusion compensatory responses may be mediated from the opposite carotid sinus, while cerebral ischaemia may also contribute to the cardiovascular effects of bilateral carotid occlusion, as has been shown to occur in the cat (Brown, Duke & Joels, 1963). In

our experiments, though it was necessary to interrupt flow through one carotid artery to obtain a vascularly isolated carotid sinus, flow through the contralateral carotid artery was unimpeded throughout. Korner (1965) has assessed the effect of the baroreceptors on cardiac output by comparing the cardiac outputs of unanaesthetized rabbits with those of a group of rabbits whose sinus and aortic nerves had been sectioned a few days earlier. In the denervated rabbits cardiac output, heart rate and arterial pressure were all about 17% above the values for the control animals. This of course represents the combined effect of both carotid and aortic baroreceptor regions. Again in this type of experiment the extent of the difference in baroreceptor stimulus is limited to withdrawal of a normal level of baroreceptor activity.

Perfusion of the vascularly isolated carotid sinus circumvents many of the difficulties presented by these other experimental approaches and allows investigation of the effects of subjecting the carotid sinus baroreceptors to a wide range of known pressures encompassing pressures above as well as below the animal's control arterial pressure. This was also the technique used in the studies on the cat by Kumada *et al.* (1975) and on the dog by Schmidt *et al.* (1971) with which the results of the present investigation have already been compared.

The small size of the changes in cardiac output which we have found in response to alterations in sinus pressure gives a deceptive impression of the changes in left ventricular performance which must be taking place, for the changes in left ventricular work, estimated in the way we have described, were large, more than 50% (Fig. 5). Since cardiac output was little altered these changes in left ventricular performance are largely a reflexion of the changes in peripheral resistance. There were similar alterations in stroke work on altering carotid sinus pressure. However we are unable to say whether there were accompanying inotropic effects on the ventricle as have been reported in other species (Sarnoff, Gilmore, Brockman, Mitchell & Linden, 1960; Furnival, Linden & Snow, 1971), mediated by changes in the sympathetic discharge to the myocardium (Downing & Siegel, 1963; Green & Heffron, 1968).

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