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THE CAROTID SINUS BARORECEPTOR REFLEX IN CONSCIOUS RABBITS

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SUMMARY

1. A method is described for altering the pressure across the wall of the carotid sinus in conscious rabbits by enclosing the carotid bifurcation in a rigid, fluid-filled capsule. The extracapsular arterial baroreceptors were denervated.

2. The baroreceptor–heart rate reflex, elicited by injecting vasoactive drugs or inflating aortic and vena caval cuffs, was used to test the new method. The function of the carotid sinus was shown to be unaffected by enclosure in the capsule. Denervation of the extracapsular baroreceptors reduced the gain of the baroreceptor–heart rate reflex two- to threefold.

3. The characteristics of the carotid baroreceptor reflex were studied in sixteen animals by the capsule method. Median estimates of maximum gain, and the range over which blood pressure changed, were 1·1 mmHg/mmHg and 57 mmHg respectively. There was good agreement between duplicate estimates made 1–20 days apart.

4. There was only a weak association between the effects on blood pressure and heart rate of altering carotid sinus transmural pressure. Autonomic blockade of the heart, so that its rate was fixed, did not reduce the gain or range of blood pressure change.

INTRODUCTION

The properties of the carotid baroreceptor reflex have been studied mostly by a variant of the Moissejeff (1927) technique in which pressure is varied within the vascularly isolated carotid sinus. However, this requires general anaesthesia which alters the characteristics of the reflex and modifies its interactions with neural inputs that originate from, or have synaptic relays in, supramedullary brain centres (Korner, 1971; Kirchheim, 1976).

An indirect method used for measuring the sensitivity of the baroreceptor reflexes in the conscious state has been to alter systemic blood pressure and study the evoked changes in heart rate. Blood pressure has been altered by inflating cuffs placed around the aorta or inferior vena cava (Scher & Young, 1970; Korner, Shaw, West & Oliver, 1972), or by injecting pressor and depressor drugs which are believed to have no direct chronotropic action (Pickering, Gribbon & Sleight, 1972; Korner & Shaw, 1971; Korner, West, Shaw & Uther, 1974). While this approach can give precise information about the control of heart rate, this is not necessarily correlated with the ability of the reflex to control blood pressure.

The present paper describes a method for enclosing the carotid bifurcation in a

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surgically implanted, rigid capsule, the fluid contents of which are in equilibrium with tissue fluid and accessible to needle puncture, so permitting induction of changes in carotid sinus transmural pressure. We report here comparisons between baroreceptor reflex control of blood pressure and heart rate. A preliminary communication has been made to the Australian Physiological and Pharmacological Society (Jamieson, Faris, Iannos & Ludbrook, 1978).

METHODS

Seven Waite Institute semi-lopeared and nine NZW rabbits were used in these experiments. Their ages ranged from 4 to 6 months and their weights from 2·0 to 3·3 kg. Operations were performed under halothane anaesthesia, with full aseptic precautions.

Capsules were implanted in all sixteen animals, with equal frequency on the two sides. They were machined from polymethylmethacrylate and consisted of two chambers separated by a waist. The interior surface was polished and the exterior was covered with lightweight knitted nylon fabric so that it would adhere to surrounding tissues. The ventral chamber enclosed the carotid bifurcation, the tubular waist was inserted between the wing of the atlas and the base of the skull, and the dorsal chamber lay in the subcutaneous tissue behind the ear (Fig. 1). The carotid vessels were inserted into the ventral, rectangular chamber by way of slots in its end walls, which were converted into elliptical orifices when the lid was applied. The common carotid artery entered through the caudal orifice. The rostral orifice accommodated the external and internal carotid arteries, together with the tissues lying in the angle between them which included the sinus nerve and one or more veins draining the carotid body. The open end of the dorsal cylindrical chamber was covered by a continuation of the nylon fabric so that the interior of the capsule was accessible to needle puncture and its contents were in communication with the tissue fluid.

The branches of the carotid bifurcation to surrounding structures were individually ligated and divided. Special attention was paid to preserving the venous drainge of the carotid body (Chungcharoen, Daly & Schweitzer, 1952). The fine connexions between the carotid sinus and the nodose ganglion of the vagus were divided, as were its more substantial nervous and vascular connexions with the superior cervical sympathetic ganglion. The common carotid artery was dissected free in a caudal direction to where it emerges from beneath the sternothyroid muscle. The muscles between the occiput and the wing of the atlas were divided so as to create a tunnel which led back to the subcutaneous tissue behind the ear cartilage, and into which the capsule was inserted. The vagus and sympathetic nerves ran on the medial side of its waist. The carotid vessels were lifted into the slots in the end walls of the ventral chamber, the capsule was filled with Ringer (U.S.P.) solution and the lid was applied. The nylon fabric was sewn over the lid, and as sleeves around the vessels, so that fibrous reaction would create a watertight seal. The capsule was locked in place by suturing the ventral chamber to the wing of the atlas and the base of the skull. A 5 mm length of each aortic nerve was excised. The opposite carotid sinus was denervated by dividing all structures in the intercarotid angle, stripping its adventitia, and painting its wall with 1 % aqueous phenol. In seven animals the denervations were performed at a separate, earlier, operation in order to be able to test whether encapsulation of the carotid sinus had affected its function. In all animals the carotid sinus within the capsule was destroyed at a final operation, so that the presence of unwanted extracapsular baroreceptors could be detected.

The baroreceptor reflexes were tested while the rabbit sat quietly within a restraining box. Preliminary cannulations were performed under local analgesia (1 % lignocaine HCl) and recording was made on a Grass model 7 Polygraph using Statham P23Dc strain gauges for recording pressure. Zero was set at a level 50 mm above the floor of the animal's box, close to the level of the carotid sinus. Arterial pressure was measured by connecting the manometer through a polyvinyl tube (50 cm long, 0·9 mm i.d.) to a thin-walled nylon catheter (10 cm long, 0·5 mm i.d.) which was inserted into the central artery of the ear on the side opposite to the capsule and advanced so that its tip lay at the root of the ear. When simultaneous comparison was made between blood pressure in the ear artery and that at the origin of the contralateral external carotid artery, the difference in mean or pulse pressures was never more than 3 mmHg. Heart rate was determined by a tachometer triggered from the arterial pressure pulse. Mean

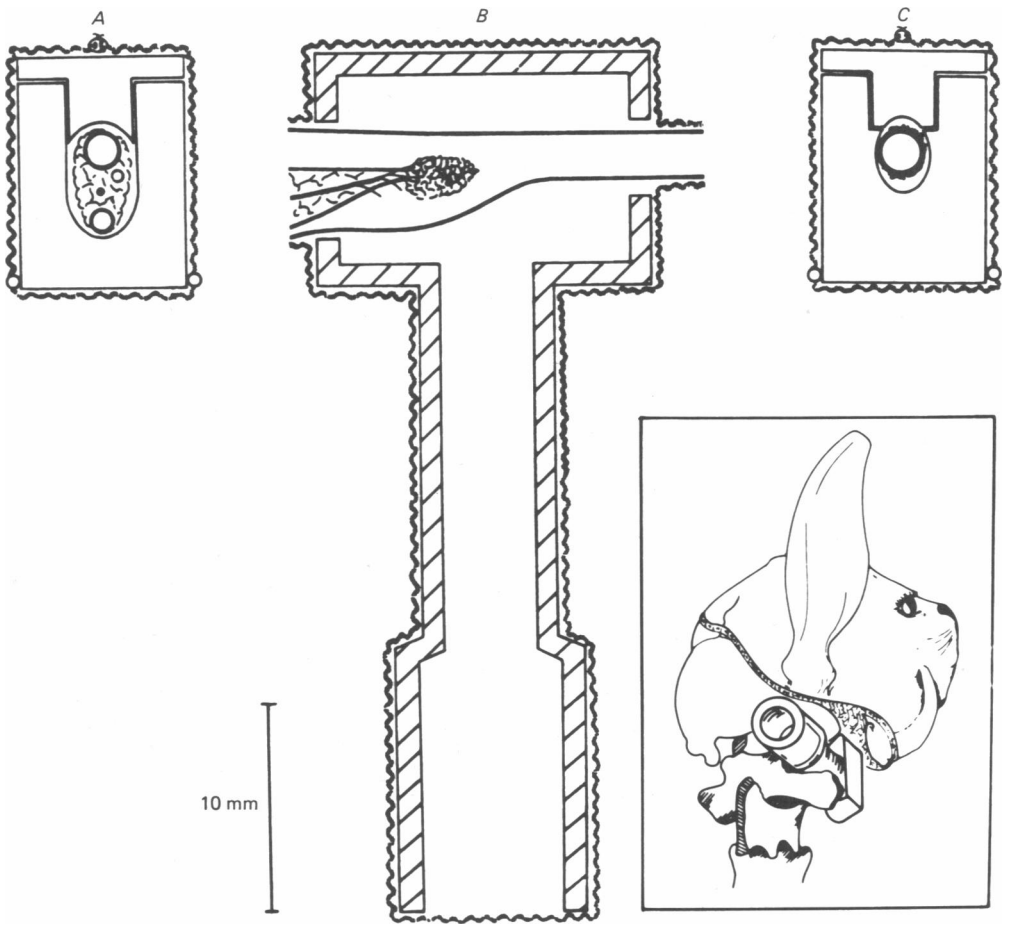

Fig. 1. Scale drawing of the carotid sinus capsule with its ventral chamber uppermost. *A*, end-on view of the rostral wall of the ventral chamber. The elliptical orifice accommodates the internal and external carotid arteries, the sinus nerve, and a small vein from the carotid body. *B*, longitudinal section showing the location of the carotid bifurcation in the ventral chamber and the disposition of the external covering of nylon fabric (irregular line). *C*, end-on view of the caudal wall of the ventral chamber with the orifice through which the common carotid artery enters. Inset: the disposition of the capsule in relation to the occipital bone and the wing of the atlas.

arterial pressure in mmHg and mean heart rate in beats/min were derived each 2 sec by integration of the corresponding signals. Mean heart interval in msec was calculated as 60,000 per mean heart rate. Respiratory movements were monitored by means of a mercury-in-Silastic strain gauge placed around the rabbit's thorax. This also served as a sensitive indicator of other movements made by the animal.

A hypodermic needle (0·8 mm i.d.) was inserted into the dorsal chamber of the capsule by percutaneous puncture and connected to a variable-pressure saline reservoir and manometer. This system was used to alter pressure within the capsule. Stimuli took the form of damped square waves of pressure of up to $\pm$ 150 mmHg. There was no leakage of fluid from the capsule even after it had been implanted for only 5 days. Transmission of pressure to the carotid sinus was confirmed by the persistence in the trace of a pulse of about 5 mmHg amplitude. Negative

and positive pressures were applied to the capsule each for 15–30 sec, long enough for blood pressure and thus carotid sinus transmural pressure to have raeched a steady plateau and to have maintained it for 6–10 sec (Fig. 2). Stimulus–response curves were constructed from twelve to thirty square wave changes of pressure of varying magnitude and direction applied in random order. The animals did not indicate by movement or change in respiration that they were aware of these changes, except when the pressure applied was close to or exceeded the level of systolic blood pressure when hyperventilation commonly occurred (see Fig. 3 and Results). Such results were excluded from the calculation of stimulus–response curves. Carotid sinus transmural pressure was calculated as the difference between mean arterial pressure and the level of pressure within the capsule. In all animals the carotid sinus reflex was studied on at least two occasions: 7–24 days after the capsule had been implanted, and 1–20 days later. In five animals the reflex was also studied during autonomic blockade of the heart by I.V. infusion of DL-propranolol HCl at 5–10 μg/kg per min after a loading dose of 250 μg/kg (Anderson, Korner, Bobik & Chalmers, 1977), and I.V. injection of L-hyoscine methyl bromide, 50 μg/kg followed by 25 μg/kg each 30 min.

In most animals the sensitivity of the baroreceptor–heart rate reflex was estimated independently by inducing changes in blood pressure by one or both of two methods. In the first method (Korner & Shaw, 1971; Korner *et al.*, 1974) aqueous solutions of phenylephrine (phenylephrine HCl 0·1 g/l., NaCl 9·0 g/l·, ascorbic acid 0·05 g/l.) and glycerol trinitrate (0·1 g/l., NaCl 7·0 g/l., ethanol 3·8 g/l.) were injected through an ear vein catheter in doses of 3–30 μg (0·03–0·3 ml.). The drugs were given by brief infusions so as to maintain changes in blood pressure and heart rate at a plateau for 6–10 sec. The changes in blood pressure ranged from -40 to $+60$ mmHg. Six to eleven infusions of each drug were made during an experiment. The second method was that of Korner *et al.* (1972). At preliminary thoracotomies inflatable cuffs were placed around the descending aorta and the inferior vena cava. The reflex was tested by inflating the cuffs alternately for 15–30 sec, until blood pressure and heart rate were maintained at a plateau for 6–10 sec. The changes in blood pressure ranged from -60 to $+48$ mmHg. Twelve to twenty-four observations were made during each experiment.

For the capsule experiments stimulus–response curves were calulated as follows. Changes in values of mean arterial pressure, mean heart rate and carotid sinus transmural pressure were taken as the differences between the average over the 6–10 sec plateau of change which followed imposition of the stimulus and the average during the 10 sec which preceded it. The equation $y=a+b(1+e^{\alpha+\beta x})^{-1}$, with properties of a normal probability cumulative function, was employed to describe the relation of response to stimulus, as has been done successfully in anaesthetized animals (Koch, 1930; Kumada, Schramm, Altmansberger & Sagawa, 1975). The constants for the equation were calculated by an iterative method, in such a way that the residual variance was reduced to a minimum, using a specially developed computer programme (Leppard, Faris, Jamieson & Ludbrook, 1979). In this manner best estimates and the corresponding variances were obtained for the upper and lower limits of the response, and for the interval between these limits (range). By differentiating the equation the best estimate and variance were obtained for the maximum slope of the curve, which with the sign omitted is referred to as gain_{max}. The threshold and saturation of the reflex were calculated as the levels of carotid sinus transmural pressure at which the change in mean arterial pressure had reached 95 % of its upper and lower limits respectively, or at which the change in heart interval had reached 95 % of its lower and upper limits respectively. The same method was used to calculate the relationship between changes in mean arterial pressure and heart rate in the baroreceptor–heart rate reflex. Resting blood pressure and heart rate for each experiment were taken as the respective medians of the values recorded during the 10 sec periods before the stimuli.

Distribution-free methods have been used to describe and compare sets of animals, because of the small size of the samples. The central tendency of sample values has been expressed as the median, with the range in parentheses. The two-sided probability that population medians are identical has been arrived at by calculating the Wilcoxon T statistic for matched or independent samples. Closeness of association has been examined by calculating the Spearman rank order correlation coefficient (r_s) and the corresponding two-sided probability that $r_s=0$.

RESULTS

Effects of carotid encapsulation

Eleven animals were studied before, and 7–20 days after, a capsule had been implanted. Median resting blood pressure and heart rate changed insignificantly, from 78 to 79 mmHg and from 216 to 224 beats/min. The baroreceptor–heart rate reflex was tested in all eleven by the vasoactive drug method, and in six by inflatable cuffs. Paired comparison of the two methods showed that the values for $\text{gain}_{\max}$ were well correlated ($n = 12$; $r_s = 0{\cdot}860$; $P < 0{\cdot}01$), but that $\text{gain}_{\max}$ obtained by the inflatable cuff method was consistently greater ($n = 12$; $T = 2$; $P < 0{\cdot}01$). Implantation of the capsule and the associated partial baroreceptor denervation caused median $\text{gain}_{\max}$ estimated by the vasoactive drug technique to fall from 5·4 to 2·7 msec/mmHg ($n = 11$; $T = 1$; $P < 0{\cdot}01$), and as estimated by the inflatable cuff method from 9·8 to 3·4 msec/mmHg ($n = 6$; $T = 0$; $P < 0{\cdot}05$).

In seven animals the baroreceptor–heart rate reflex was tested by the vasoactive drug method 3–16 days after a first-stage operation in which both aortic nerves were sectioned and one carotid sinus denervated, and again 7–20 days after a capsule had been implanted around the intact carotid sinus. The median estimates of $\text{gain}_{\max}$ before and after were respectively 3·8 msec/mmHg and 3·3 msec/mmHg ($T = 15$; $P > 0{\cdot}10$).

The carotid sinus baroreceptor reflex

The application of negative pressure to the capsule (Fig. 2) caused heart rate to fall sharply, to reach a trough after about 1·5 sec. It then rose to a steady level which was sometimes not far below the resting value. Blood pressure fell more slowly, and with little or no undershoot, to reach a steady level after 7 sec (5–16). When positive pressure was applied to the capsule (Fig. 2) the time course of the changes in heart rate and blood pressure was slower. It was about 2 sec before the heart rate and blood pressure began to rise, in parallel, to reach a sustained plateau after 11 sec (5–18).

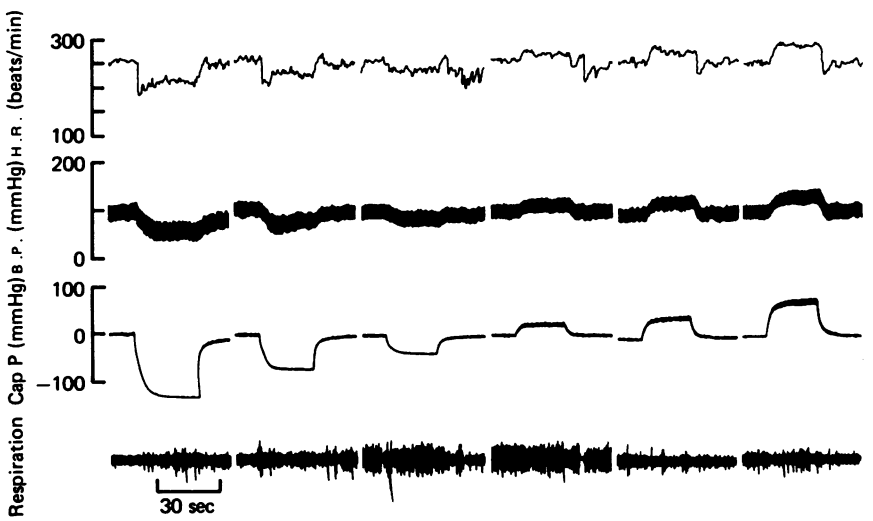

Fig. 2. The effects in a conscious rabbit of changes in pressure within the carotid capsule (Cap P) on blood pressure (B.P.), heart rate (H.R.) and thoracic excursion (respiration).

When the capsule pressure was increased to a level above systolic blood pressure, the usual tachycardia and hypertension were replaced by profound bradycardia and hypotension, followed after 4–16 sec by progressive augmentation of the respiratory excursions (Fig. 3*C*). In some cases raising the capsule pressure to just below the systolic level produced a different sequence of events (Fig. 3*B*): there was first the usual rise in blood pressure and heart rate, then hyperventilation, and finally a secondary rise in blood pressure.

Relationship between carotid sinus transmural pressure and systemic blood pressure (Fig. 4*A*). In every case it was possible to fit a satisfactory sigmoid curve to the relationship between change in mean arterial pressure and that in carotid sinus transmural pressure, the standard deviations always being less than 12 % of the best estimates of gain_{max} and range. Resting blood pressure and heart rate were 82 mmHg (72–101) and 227 beats/min (192–270) respectively. Gain_{max} was 1·11 mmHg/mmHg (0·64–3·14). The upper and lower limits of change in blood pressure were + 30 (17–46) and − 28 (− 16 to − 45) mmHg, the range being 57 mmHg (47–80). The threshold and saturation values for carotid sinus transmural pressure were 38 (− 10 to 63) and 134 (96–185) mmHg.

In none of the animals could the baroreceptor–heart rate reflex be elicited after destruction of the encapsulated carotid sinus. There are excluded from this report six other animals in whom reflex activity could still be demonstrated after destruction of the carotid sinus (and in whom gain_{max} for the carotid sinus reflex was always less than 0·44 mmHg/mmHg).

On repeated testing, there was a close association between the estimates of gain_{max}

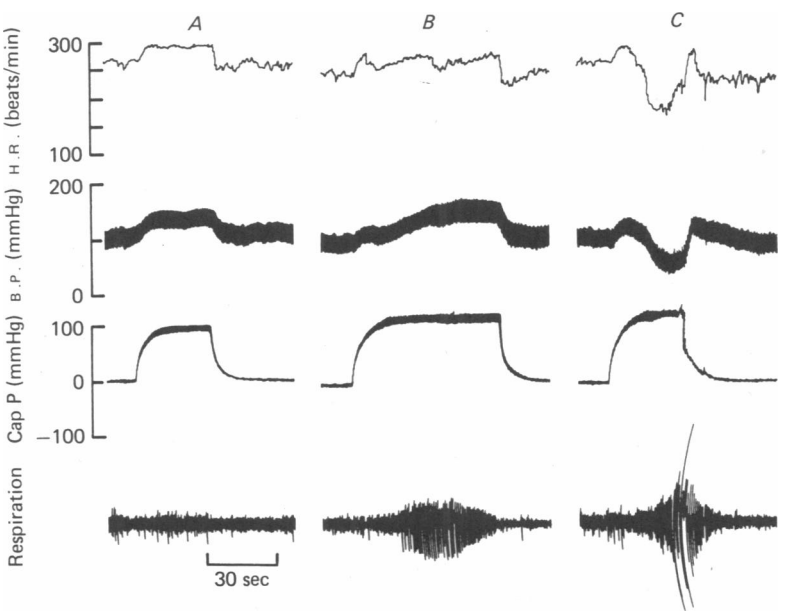

Fig. 3. The effects in a conscious rabbit of pressure increases within the carotid capsule to levels that were just less than (*A*), approximately the same as (*B*), and just greater than (*C*), resting systolic blood pressure. Symbols otherwise as in Fig. 2. Note that in *B* a secondary rise in B.P. coincided with an increase in amplitude of respiration, while in *C* the secondary fall in B.P. and H.R. preceded the change in respiration.

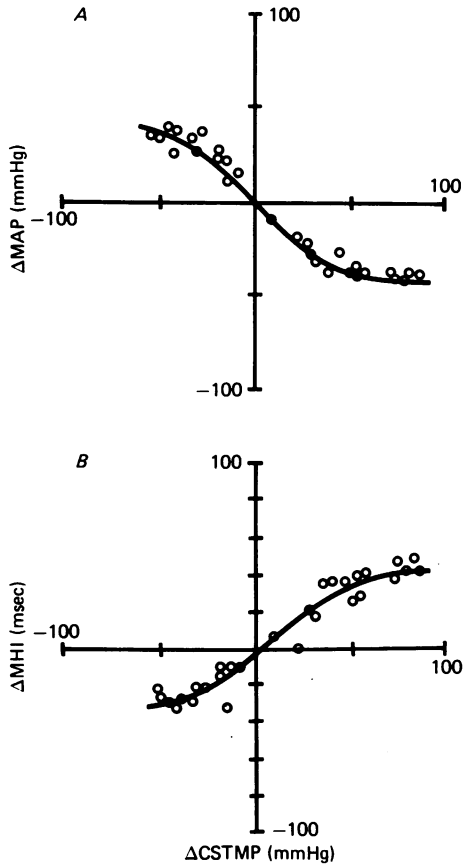

Fig. 4. Experimental points (○) and fitted curves (——) describing the characteristics of the carotid baroreceptor reflex in a conscious rabbit. Abscissae: deviations of carotid sinus transmural pressure from the resting level (△CSTMP). *A*: the carotid baroreceptor –blood pressure reflex. Ordinate: change in mean arterial pressure from the resting level (△MAP). *B*: the carotid baroreceptor–heart interval reflex. Ordinate: change in mean heart interval from the resting level (△MHI).

($r_s = 0{\cdot}868$; $P < 0{\cdot}001$), but a less close correlation for range ($r_s = 0{\cdot}644$; $P < 0{\cdot}02$). No differences of central tendency were revealed between the two sets of values for $\text{gain}_{\max}$ ($T = 49$; $P > 0{\cdot}10$) or for range ($T = 71$; $P > 0{\cdot}10$). In three animals a third set of measurements were made 61–81 days after the capsule had been implanted. In one case $\text{gain}_{\max}$ was unchanged but in the other two it had diminished by about one half.

Relationship between carotid sinus transmural pressure and heart interval (Fig. 4*B*). The relationship of changes in carotid sinus transmural pressure to changes in mean heart interval was less predicable than its relationship to mean arterial pressure. In fourteen of the sixteen animals curves could be fitted, for twenty-five out of the twenty-eight sets of observations, although the confidence intervals (especially those for the limits) were wider than in the case of the blood pressure curves. In these fourteen animals the $\text{gain}_{\max}$ for heart interval was 1·1 msec/mmHg (0·6–4·7). The

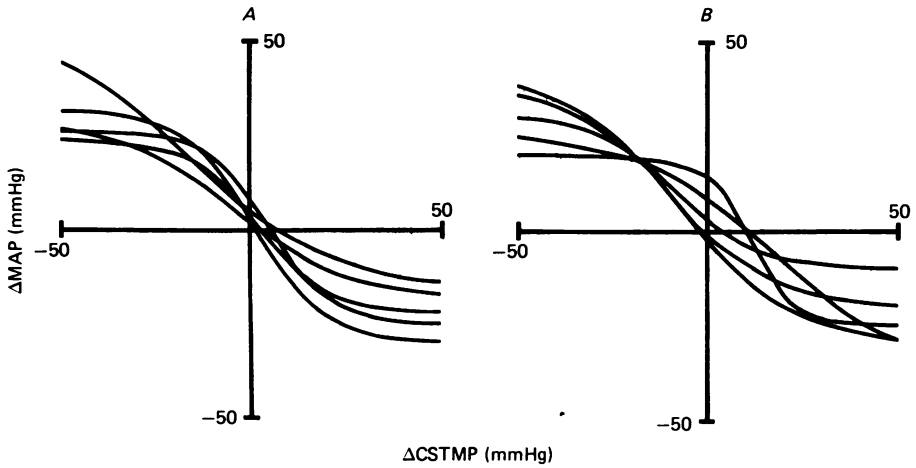

Fig. 5. Fitted curves describing the characteristics of the carotid sinus baroreceptor–blood pressure reflex in five conscious rabbits before (*A*) and after (*B*) autonomic blockade of the heart with propranolol and hyoscine methyl bromide, so that heart rate did not vary by more than 5 beats/min when carotid sinus transmural pressure was changed. Symbols as in Fig. 4*A*.

range of change in heart interval was 60 msec (24–188), symmetrically disposed around the resting value. The estimated threshold for the reflex was a carotid sinus transmural pressure of 29 mmHg (−38 to 64) and saturation occurred at 136 mmHg (95–218).

There was only a weak association between $\text{gain}_{\max}$ for heart interval and for blood pressure ($r_s = 0{\cdot}385$; $P > 0{\cdot}10$), and an equally weak assocation between the ranges of the responses ($r_s = 0{\cdot}395$; $P > 0{\cdot}10$).

Effect of cardiac autonomic blockade. The carotid sinus reflex was studied before and after cardiac autonomic blockade in five animals. The administration of propranolol and hyoscine methyl bromide caused only a small and inconstant change in blood pressure but a fall in heart rate of 16 beats/min (5–30). Heart rate did not vary by more than 5 beats/min when carotid sinus transmural pressure was altered. The rate of change of blood pressure was slowed by autonomic blockade, but there was no consistent alteration in the final magnitude of the change or in the maximum gain (Fig. 5). Before and after blockade the values for $\text{gain}_{\max}$ were 1·35 mmHg/mmHg (0·80–1·67), and 1·09 mmHg/mmHg (0·91–2.06) and for the range of blood pressure change 49 mmHg (47–71) and 59 mmHg (41–72). The range of heart interval change fell from 70 msec (24–117) to 7 msec (4–10).

DISCUSSION

The technique which we have described has certain advantages as a method with which to study the carotid sinus baroreceptor reflex in the conscious animal. The stimulus to the reflex is a change in pressure across the wall of the carotid sinus in which the natural pulse amplitude, frequency and wave form are preserved. The behaviour of the carotid sinus baroreceptors appears to be unaffected by the sur-

rounding capsule. The full range over which the carotid baroreceptors exercise reflex control of blood pressure can be examined. It is not likely that the input from the carotid baroreceptors is confused by unwanted alterations of input from other receptor areas, including the carotid chemoreceptors, except when carotid transmural pressure is close to zero The characteristics of the reflex can be quantified and are reproducible within the same animal for a period of time which is sufficient to allow repeated observations to be made. There are also certain limitations to the method. Surgical implantation of the capsule is technically demanding. It is also important that great care be taken to denervate all extracapsular baroreceptors, otherwise the carotid sinus reflex is buffered and the gain appears falsely low. It must be presumed that the method underestimates the capacity of the arterial baroreceptor reflex to control blood pressure in the intact animal because only that part of the reflex which emanates from one carotid sinus can be evoked. The loss of blood pressure control cannot be exactly quantified, but the change in the baroreceptor–heart rate reflex suggests that it may be as much as two- or threefold.

The characteristics of our stimulus–response curves for blood pressure are very similar to those derived from preparations of an isolated carotid sinus in anaesthetized rabbits by Koch (1929, 1931) and Humphreys & Joels (1977). Humphreys and Joels' data suggest a maximum gain of just less than 1 mmHg/mmHg and a range of 68 mmHg, and similar values can be inferred from Koch's work. Their values for carotid sinus pressure at the threshold and saturation points of the reflex are also close to ours, as are those of Bronk & Stella (1932, 1935) for carotid baroreceptor discharge. A similar phenomenon to the anomalous response of heart rate and blood pressure which occurred when we applied suprasystolic pressure to the capsule (Fig. 3*C*) was observed by Heymans, Bouckaert & Dautrebande (1931) and Landgren (1952) when the isolated carotid sinus was exposed to very low distending pressures, and is attributable to distortion of the sinus wall. As pressure in the capsule approaches the level of systolic blood pressure, perfusion pressure through the carotid body must approach zero. The hyperventilation visible in Fig. 3 may well be attributable to carotid chemoreceptor stimulation, which occurs in the rabbit only when perfusion pressure falls below 6–18 mmHg (Ott, Kiwull & Wiemer, 1971).

Our study of the carotid sinus reflex after autonomic blockade of the heart shows that change in heart rate is not essential to a full measure of blood pressure control by the carotid sinus, but only speeds up its attainment. There is other evidence for this conclusion. We found only a weak association between maximum gain of the carotid sinus reflex for blood pressure and that for heart interval. Gross & Kirchheim (1972) showed in the conscious dog that cardiac pacing did not alter the magnitude of the pressor response to common carotid artery occlusion. Humphreys & Joels (1977) demonstrated that in the anaesthetized rabbit cardiac output (and thus heart rate) contributed much less than peripheral resistance to reflex alteration of blood pressure by the carotid sinus. This suggests that a change in the sensitivity of baroreceptor control of heart rate may not always be associated with a corresponding change in the control of blood pressure. Indeed we have previously demonstrated just such a dissociation between the control of heart rate and blood pressure by the carotid sinus during isometric exercise in man (Mancia, Iannos, Jamieson, Lawrence, Sharman & Ludbrook, 1978; Ludbrook, Faris, Iannos, Jamieson & Russell, 1978).

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