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RAPID RESETTING OF RABBIT AORTIC BARORECEPTORS AND REFLEX HEART RATE RESPONSES BY DIRECTIONAL CHANGES IN BLOOD PRESSURE

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SUMMARY

1. In both anaesthetized and conscious rabbits, perivascular balloon inflations slowly raised or lowered mean arterial pressure (M.A.P.), at 1–2 mmHg/s, from resting to various plateau pressures. Deflations then returned the M.A.P. to resting. 'Steady-state' curves relating M.A.P. to (i) unitary aortic baroreceptor firing, (ii) integrated aortic nerve activity and (iii) heart rate were derived during the primary and return pressure changes and they formed typical hysteresis loops.

2. In single units, return M.A.P.–frequency curves were shifted in the same direction as the primary pressure changes by an average 0·37 mmHg per mmHg change in M.A.P. Shifts were linearly related to the changes in M.A.P. between resting and plateau levels for all pressure rises and for falls less than 30 mmHg. They were established within 30 s and were quantitatively similar to the rapid resetting of baroreceptor function curves found 15 min–2 h after a change in resting M.A.P. (Dorward, Andresen, Burke, Oliver & Korner, 1982). Unit threshold pressures were shifted within 20 s to the same extent as the over-all curve shift to which they contributed.

3. In the whole aortic nerve, return M.A.P.–integrated activity curves were shifted to same degree as unit function curves in both anaesthetized and conscious rabbits. Simultaneous shifts of return reflex M.A.P.–heart rate curves were also seen in conscious rabbits within 30 s. During M.A.P. falls, receptor and reflex hysteresis was similar, but during M.A.P. rises, reflex shifts were double baroreceptor shifts, suggesting the involvement of other pressure-sensitive receptors.

4. We conclude that hysteresis shifts in baroreceptor function curves, which follow the reversal of slow ramp changes in blood pressure are a form of rapid resetting. They are accompanied by rapid resetting of reflex heart rate responses. We regard this as an important mechanism in blood pressure control which produces relatively high-gain reflex responses, during slow directional pressure changes, over a wider range of absolute pressure levels than would otherwise be possible.

INTRODUCTION

In chronic human and experimental hypertension arterial baroreceptor thresholds are 'reset' in the direction of the elevated blood pressure, accompanied by a shift in their mean arterial pressure (M.A.P.)– activity curves which now operate over

a higher pressure range (Kezdi, 1962; Aars, 1968; Angell-James, 1973; Brown, Saum & Tuley, 1976; Sleight, Robinson, Brook & Rees, 1977). More recently, resetting has been shown to occur within 10–20 min of a 'steady-state' rise or fall in resting M.A.P. (Salgado & Krieger, 1978; Coleridge, Coleridge, Kaufman & Dangel, 1981; Dorward, Andresen, Burke, Oliver & Korner, 1982; Munch, Andresen & Brown, 1983; Coleridge, Coleridge, Poore, Roberts & Schultz, 1984; Heesch, Thames & Abboud, 1984); once established, it is stable for at least 1–2 h (Dorward *et al.* 1982; Munch *et al.* 1983). Receptor resetting appears to be largely responsible for the resetting of baroreflex responses, which also occurs over a similar time span (Kunze, 1981; Dorward *et al.* 1982; Dorward, Riedel, Burke, Gipps & Korner, 1985).

Estimates of the minimum time required to produce baroreceptor resetting have been restricted to analysis of unitary activity following step changes in pressure in the vascularly isolated carotid sinus or the *in vitro* aortic arch and these vary from 30 s to 15 min (Landgren, 1952; Bergel, Anand, Brooks, MacDermott, Peveler, Robinson & Sleight, 1980; Munch *et al.* 1983). However, the hysteresis loops in baroreceptor M.A.P.–activity curves constructed when arterial pressure is initially changed away from resting level and then returned to resting (Coleridge *et al.* 1981) are in fact formed by shifts in the baroreceptor function curves which are directionally in accord with curve shifts accompanying changes in resting M.A.P. and attributed to rapid resetting (Dorward *et al.* 1982).

In the present study we have quantified the hysteresis shift between pairs of baroreceptor M.A.P.–unitary activity curves approximately 30 s apart and compared this measurement with our previous estimate of the magnitude of acute baroreceptor resetting, using similar slow balloon-induced ramp changes in M.A.P. to construct the receptor function curves (Dorward *et al.* 1982). Hysteresis shifts were then compared with shifts in unit threshold pressures occurring within 20 s. Secondly, we have measured shifts between pairs of M.A.P.-integrated aortic nerve activity curves obtained both under anaesthesia and when the rabbits were conscious. Lastly, we have measured similar curve shifts in M.A.P.–heart rate loops in conscious rabbits to determine the functional significance of baroreceptor hysteresis in reflex cardiovascular control.

METHODS

Experiments were performed on eighteen cross-bred rabbits weighing 2·4–3·4 kg. Silastic perivascular balloons were implanted around the inferior vena cava, the thoracic aorta and in some rabbits around the abdominal aorta, at two preliminary operations under halothane anaesthesia, 1–2 weeks apart (Korner, Shaw, West & Oliver, 1972).

Studies on single baroreceptor units. Eight rabbits were anaesthetized with sodium pentobarbitone (Sagatal, May and Baker; 35–45 mg/kg bolus, then by infusion at 0·15 mg/kg . min.) After surgery, animals were artificially ventilated with 32% oxygen at 0·8–1·0 l/min (to maintain P_{CO_2} between 25 and 30 mmHg and P_{O_2} between 85 and 110 mmHg) and paralysed with succinyl choline (Scoline, Glaxo; 50 mg bolus, then 0·78 mg/min infusion). Pulsatile arterial pressure was measured from the carotid artery using a Statham P23D strain gauge, the undamped frequency of the catheter–manometer system being about 30 Hz. Baroreceptor activity was recorded in filaments isolated from the left aortic nerve using a differential amplifier (band width 50 Hz–3 kHz). Balloon-induced pressure ramps together with their preceding 1 min resting period were stored on magnetic analogue tape (Hewlett–Packard model 3968A) for subsequent analysis.

Slow balloon inflation changed pressure, from resting to various plateau pressures, at 1–2 mmHg/s (Fig. 1). In most units, four to five inflations were used to reach different plateau levels above or below resting (change for all units studied, 5–70 mmHg). In some units similar plateau levels were maintained for different time intervals (2–23 s). Slow balloon deflation returned M.A.P. to resting level. Primary and return M.A.P.–unitary activity curves were constructed by plotting firing frequency (expressed as spikes/beat and spikes/s) against the mid-point of the pressure range over which this level of activity occurred. With heart rates of 3–5 beats/s, this involved scanning up to 300 cardiac cycles (with 1–15 spikes/cycle) per balloon inflation.

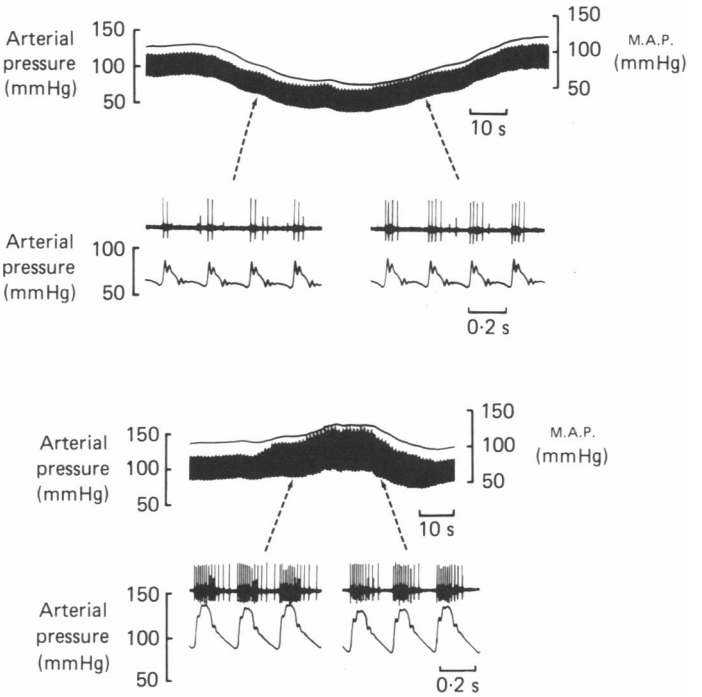

Fig. 1. Upper records show M.A.P. (mmHg) and pulsatile arterial pressure, which has been offset to a lower level for clarity. The caval balloon was slowly inflated, held for a pre-determined length of time then slowly deflated. Insets are short segments of the pressure ramps, recorded on an expanded time scale, which show unit activity and the arterial pressure wave form at points indicated by the arrows. Lower panels are similar records obtained during the aortic balloon inflation.

Baroreceptor resetting was estimated as the shift in mmHg (Fig. 2, labelled 'Shift') between primary and return M.A.P.–activity curves divided by the change between resting and plateau pressures (labelled 'ΔM.A.P.'). Shift was measured at regular activity levels along each pair of curves (e.g. 2, 3,..7 spikes/beat, dashed lines in Fig. 2) and the average value calculated, excluding levels near resting and plateau pressures. For a given type of balloon inflation, a linear regression was fitted to the set of data points (curve shift/M.A.P.) which was pooled from all units (e.g. Figs. 4 and 6). Data from different types of inflations were compared by covariance regression analysis (Snedecor & Cochran, 1980). For each set of data the intercept a of the regression equation ($y = a + bx$), was not significantly different from zero, so the regression was refitted to pass through the origin, and the slope b of this regression line gave the average estimate of resetting (values given in Tables 1 and 2).

Recording of aortic nerve activity. An electrode for chronic recording was implanted around the aortic nerve under Alfathesin anaesthesia (alphaxalone: alphadolone acetate, 3:1 mixture, Glaxo; 0·2 mg Alfathesin/kg . min I.V. infusion) in ten rabbits (Dorward *et al.* 1985). Anaesthesia was then

lightened (Alfathesin infused at 0·1 mg/kg.min) for nerve recording. Whole-nerve activity was rectified and integrated over 1 s periods. Noise was excluded by immersing the electrode wires in saline during implantation and setting the integrator to give 'zero' reading at this level.

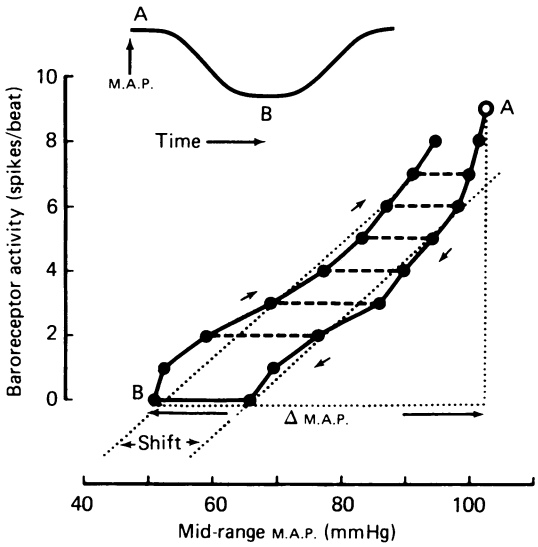

Fig. 2. Diagram to illustrate method of determining average curve shift (during a balloon-induced pressure change) from individual measurements of shift at different activity levels along the pressure–activity loop (dashed lines at 2–7 spikes/beat). The pressure change produced by the inflation was the difference between resting (A) and plateau (B) levels.

Experiments in conscious rabbits. Rabbits were studied again 1–2 days after implanting the electrode, sitting in a rabbit box without restraint. An arterial cannula was inserted for pressure and heart rate measurements and the electrode plugs retrieved under local anaesthesia with 0·5% lidocaine. Simultaneous measurements of aortic nerve activity and heart rate were obtained during sinusoidal changes in M.A.P. produced by consecutive use of the venous and aortic balloons. The average M.A.P. and heart rate corresponding to each 1 s whole-nerve integration period were calculated and used to construct M.A.P.–baroreceptor activity and M.A.P.–heart rate curves. Data points from the aortic balloon part of follow-on inflations were similar to those derived from individual inflations that raised M.A.P. from a steady resting level. The shift between primary and return curves was measured after binning ramp M.A.P. over 5 mmHg pressure steps above and below resting, and then calculating average nerve activity and heart rate for each bin. Shift was taken as the average difference in M.A.P. at various response levels along the binned curves, excluding levels close to the M.A.P. plateaus.

RESULTS

Hysteresis shifts in aortic baroreceptor units

Pressure–activity curves were constructed in fourteen baroreceptor units by combining measurements from venous and aortic balloon inflations. The continuous lines in Fig. 3 show the curvilinear primary relationship between M.A.P. and firing frequency, obtained as pressure changed away from the prevailing resting levels, at 1–2 mmHg/s. The high-gain region of these curves straddled resting M.A.P. (range

50–115 mmHg) in ten of the units studied (e.g. Fig. 3*A*). In the other four units, maximum gain was found as pressure fell from a high resting level (range 103–135 mmHg; e.g. Fig. 3*B*). The dashed lines in Fig. 3 give the return pressure–activity curves, which were displaced from the primary curve in the direction of the primary pressure change to produce typical hysteresis loops. The primary and return

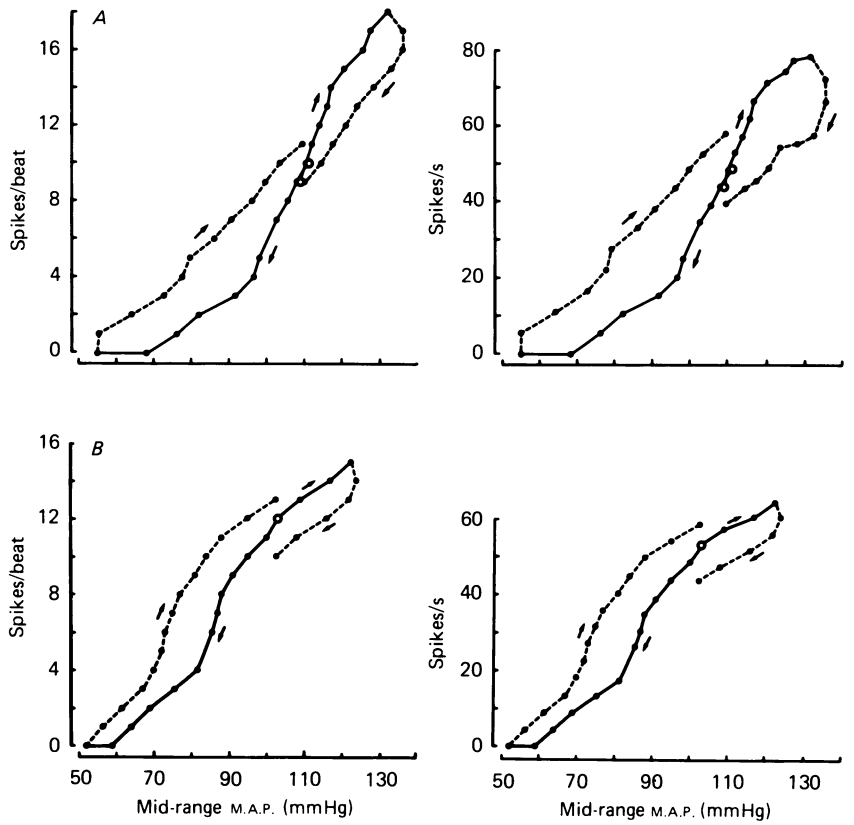

Fig. 3. *A* and *B* show relationship between mid-range M.A.P. (mmHg) and unitary activity in two baroreceptor units, in which firing is expressed both as spikes/beat (left) and spikes/s (right). Pressure changes in the direction of the arrows were induced by inflation and deflation of balloons around the vena cava and aorta. The continuous lines show the curves derived as pressure changed away from resting levels (○) while the dashed lines are the curves obtained as pressure returned to resting.

curves were parallel over certain sections, although there was a reduction in displacement near resting and plateau pressure levels. Curve shifts were reversible: when resting M.A.P. returned to the same level after the first inflation, resting activity returned to the same frequency (Fig. 3).

The size of the hysteresis shifts was related to the change in M.A.P. between resting and plateau levels (Fig. 4). The relationship was linear for falls in M.A.P. down to about 30 mmHg, but for greater falls there was little further increase in shift. By contrast,

linearity was maintained for rises in M.A.P. up to 55–60 mmHg. The magnitude of the hysteresis shift for both rises and moderate falls in M.A.P. was similar (averaging 0·37 mmHg/mmHg ΔM.A.P.) whether unitary activity was expressed as spikes/beat or spikes/s (Fig. 4, upper graph; Table 1). There was no relationship between the size of the curve shift and the level of resting M.A.P. prevailing immediately before balloon inflation.

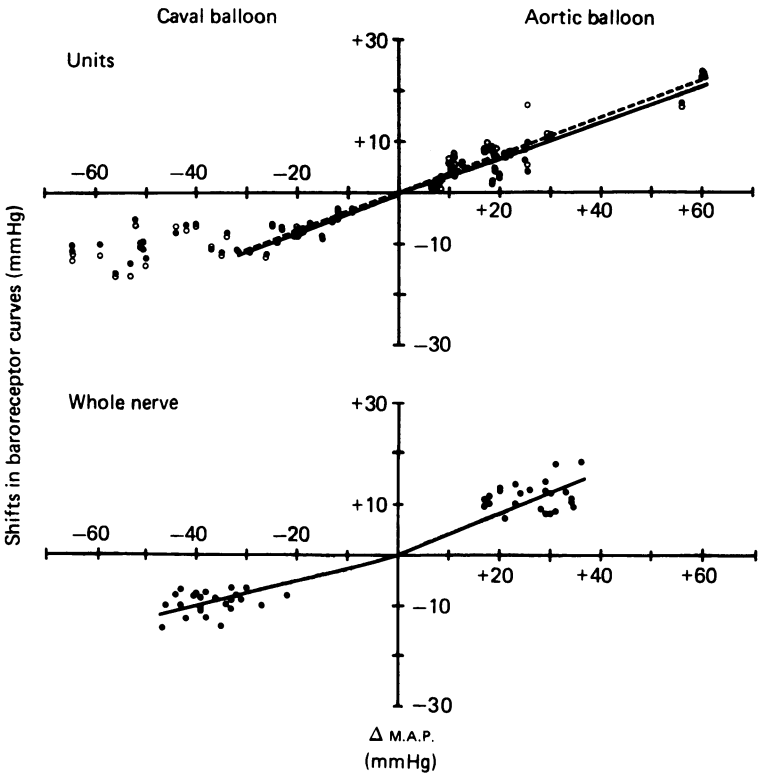

Fig. 4. Relationship between ΔM.A.P. (mmHg) from resting to plateau pressures and shifts (mmHg) in baroreceptor pressure–activity curves during caval (left) and aortic (right) balloon inflation, in anaesthetized rabbits. Upper graph gives pooled data from sixty-three balloon inflations performed in fourteen baroreceptor units isolated from eight rabbits, with activity expressed both as spikes/beat (●, continuous regression line) and spikes/s (○, dashed regression line). Lower graph gives pooled data from forty-eight inflations in ten rabbits in which integrated aortic nerve activity (μV/s) was recorded.

Changes occurred in pulsatile arterial pressure (as in Figs. 1 and 5) during inflation of the caval and thoracic aortic balloons. During venous balloon inflation, the pulse pressure was 2·6 ± 0·6 mmHg higher (difference ± standard error of difference; $n = 17$) during the return pressure–activity curve than at equivalent levels of M.A.P. during the primary curve, although resting and plateau pulse pressure were similar. During inflation of the thoracic aortic balloon, pulse pressure was 3·1 ± 0·9 mmHg ($n = 28$) lower during the return curve compared to the primary

curve, and plateau pulse pressure was increased by 13·5 ± 3·2 mmHg. Inflation of the abdominal aortic balloon had no consistent effect on pulse pressure. The M.A.P. shift relationships derived with these three balloons however were not significantly different (Table 1).

TABLE 1. Average shifts (mmHg) between primary and return M.A.P.–baroreceptor activity curves per mmHg change in M.A.P. (ΔM.A.P.) (regression coefficient, $b \pm$ standard error of b, S.E. b) derived from repeated inflations of different perivascular balloons. n gives the number of inflations performed in fourteen units isolated from eight rabbits. Left-hand column gives shifts calculated when unitary activity was expressed as spikes/beat; right-hand column gives shifts when activity was expressed as spikes/s

		Curve shift (mmHg/mmHg ΔM.A.P.)	Curve shift (mmHg/mmHg ΔM.A.P.)
Thoracic aortic balloon	28	0·35 ± 0·015	0·36 ± 0·019
Abdominal aortic balloon	21	0·37 ± 0·013	0·39 ± 0·021
Vena caval balloon (M.A.P. falls < 32 mmHg)	17	0·38 ± 0·017	0·38 ± 0·017

Estimate of time required for hysteresis shifts

All pressure rises and pressure falls less than 30 mmHg were completed within 17·2 ± 0·94 s ($n = 66$) and plateau pressures in most units were maintained for 10·9 ± 0·71 s ($n = 59$). Hence the estimated curve shift of 0·37 mmHg/mmHg ΔM.A.P. occurred in about 30 s (range 15–50 s). In twelve units, venous balloon inflation reduced M.A.P. to plateau pressures below unitary thresholds. As M.A.P. fell, firing ceased at a significantly higher pressure level than the pressure at which it started again as M.A.P. rose during balloon deflation (Δthreshold, 7·5 ± 1·14 mmHg, $n = 16$, Student's t value = 6·58, $P < 0·001$). This was due to a shift in threshold which formed part of the general shift in the M.A.P.–activity curve. In these units, plateau pressures were held for varying lengths of time. When the plateau time averaged 17·9 ± 1·2 s (range 14–23 s), threshold shift was 96% of the general curve shift (difference 0·5 ± 1·5 mmHg, $n = 7$, $t = 0·33$, $P > 0·05$), indicating that the hysteresis shift was virtually complete within the time interval between the two threshold measurements (21·2 ± 3·7 s). However, threshold shifts were significantly less than the curve shift, averaging 61% (difference 3·7 ± 1·4 mmHg, $n = 9$, $t = 2·6$, $P < 0·05$), when plateau pressures were held for shorter periods of time (6·6 ± 1·2 s, range 2–10 s).

Hysteresis shifts in the whole aortic nerve and in the baroreceptor–heart rate reflex

In ten anaesthetized rabbits, M.A.P.–integrated aortic activity curves were obtained from slow sinusoidal M.A.P. fluctuations produced by follow-on caval–aortic balloon inflations (see Methods and Fig. 5). 1–2 days later, simultaneous reflex M.A.P.–heart rate curves and M.A.P.–aortic activity curves were constructed when the rabbits were conscious. The gain of the baroreceptor function curves was not affected by anaesthesia. As in single baroreceptor units, both the return whole-nerve function curves and the reflex heart rate curves following a pressure fall were shifted to a lower

pressure range, with more integrated activity and less tachycardia at any given M.A.P. level (Fig. 5). Following pressure rises, both return curves were shifted to a higher M.A.P. range. These hysteresis shifts were established in about 30 s. If faster venous inflations were used (reducing M.A.P. at approximately 4 mmHg/s), the reflex response lagged behind the pressure change, resulting in a return function curve shifted to higher pressures, i.e. in the opposite direction to the shift seen during slow inflations.

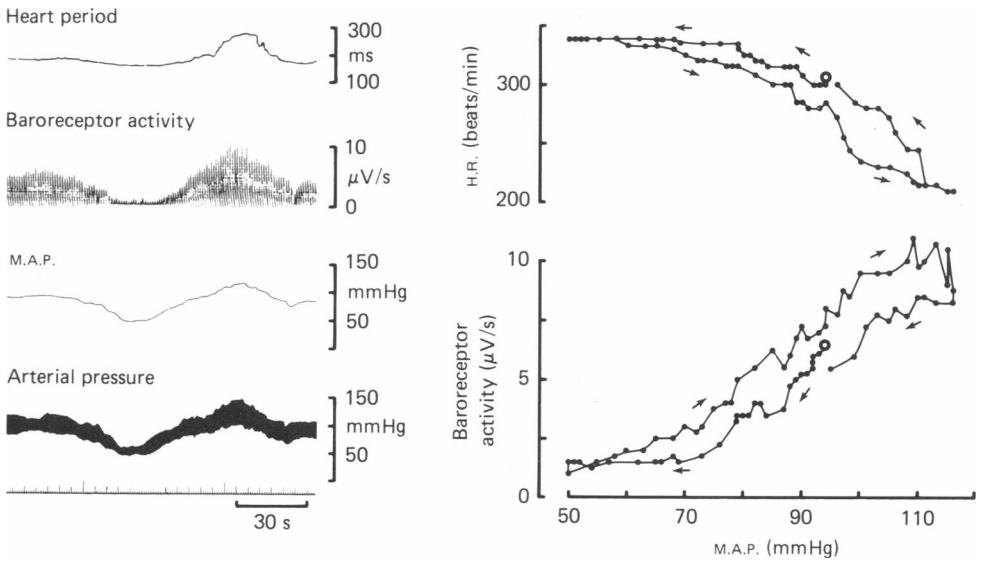

Fig. 5. Left: records show simultaneous recordings of heart period (ms), integrated aortic nerve activity (μV/s), M.A.P. (mmHg) and pulsatile arterial pressure (mmHg) during a follow-on caval–aortic balloon inflation in a conscious rabbit. Right: graphs show relationship between M.A.P. and (i) heart rate (H.R., beats/min, upper), (ii) integrated aortic nerve activity (μV/s, lower) derived from these records. Arrows indicate the direction of the pressure changes.

TABLE 2. Average curve shifts (mmHg) between various primary and return M.A.P.–response curves per mmHg change in M.A.P. (ΔM.A.P.) (regression coefficient, $b \pm$ S.E. b) derived from caval and aortic balloon inflations. n gives the number of inflations performed. Unitary data were obtained from fourteen units isolated from eight rabbits; whole aortic nerve and heart rate data were derived from ten rabbits

M.A.P.–response curve	Caval balloon		Aortic balloon	
	n	Shift (mmHg/mmHg ΔM.A.P.)	n	Shift (mmHg/mmHg ΔM.A.P.)
Anaesthetized rabbits				
Baroreceptor units	35	0·24 ± 0·014	28	0·36 ± 0·019
Aortic nerve activity	24	0·25 ± 0·013	24	0·41 ± 0·026
Conscious rabbits				
Aortic nerve activity	16	0·26 ± 0·022	23	0·30 ± 0·023
Heart rate	16	0·25 ± 0·062	23	0·76 ± 0·061

The size of the hysteresis shifts was again significantly related to the changes in pressure from resting to plateau levels (Fig. 6). With aortic balloon inflation, shifts in unit and whole-nerve baroreceptor function curves were not significantly different (Table 2). However, shifts in reflex heart rate curves were about twice the corresponding shifts in receptor function curves. With caval balloon inflation, the average shift in

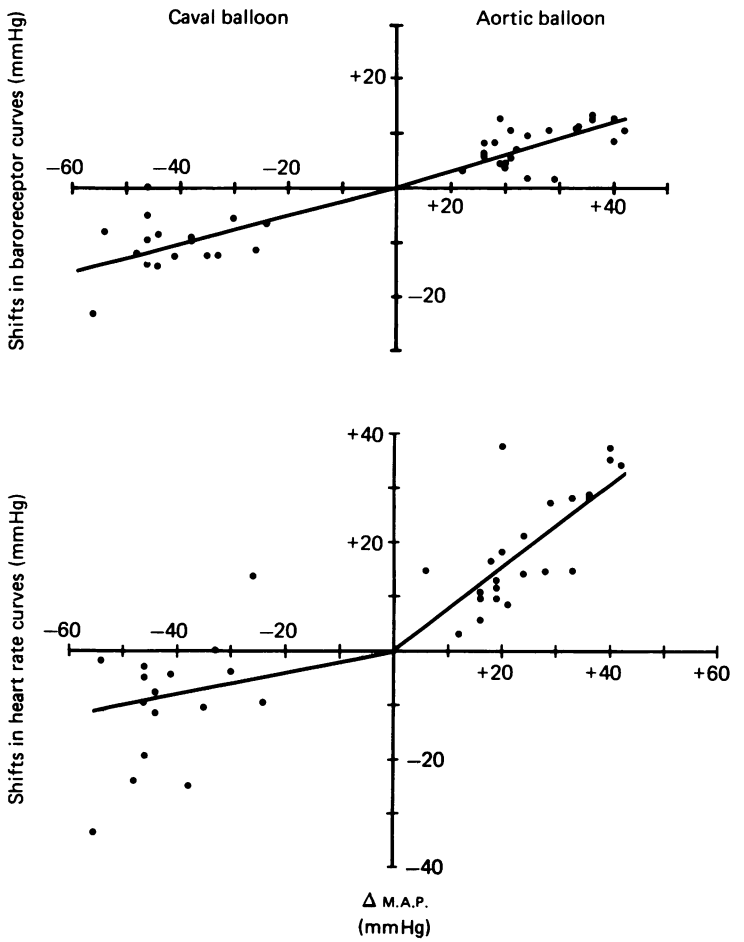

Fig. 6. Relationship between ΔM.A.P. (mmHg) and simultaneous shifts (mmHg) in integrated aortic nerve pressure–activity curves (upper) and the pressure–heart rate curves (lower) derived from thirty-nine inflations in ten conscious rabbits.

the whole-nerve function curves of 0·25 mmHg/mmHg ΔM.A.P. was less than that obtained from individual units during falls in M.A.P. of under 30 mmHg. However, if a linear regression function was fitted to all the unitary caval data, including that from pressure falls greater than 30 mmHg, the shift averaged $0{\cdot}24 \pm 0{\cdot}014$ mmHg/mmHg ΔM.A.P. Hysteresis shifts of similar size were found in the reflex heart rate curves, although the scatter in the data appeared to be somewhat greater.

DISCUSSION

Resetting of the arterial baroreceptors

Hysteresis shifts between primary baroreceptor pressure–activity curves and return curves constructed 30 s later have been characterized and quantified. We restricted the study to 'steady-state' curves derived during slow changes in mean pressure which produced 'adapted' receptor responses with little or no dynamic, rate-sensitive component (Andresen, Kuraoka & Brown, 1979; Dorward *et al.* 1982). In constrast to our earlier study, small changes in pulse pressure were found during the return pressure ramps used to construct the 'reset' function curves, which may have caused or contributed to the hysteresis shift. It is possible they were accompanied by small changes in dP/dt, in the same direction, which were above the frequency response of our catheter–manometer system. However, these changes occurred in opposite directions during vena caval and thoracic aortic balloon inflations and were undetectable when the abdominal aortic balloon was used. As all three balloons yielded the same estimate of resetting, we concluded that changes in pulse pressure were not responsible for the phenomenon. The predominant cause of hysteresis shift following reversal of slow ramp rises or falls in M.A.P. was therefore the change in mean pressure between the resting and plateau levels.

Hysteresis shifts show many features in common with the rapid resetting of baroreceptor function curves over a 15 min–2 h period following a change in resting pressure (Dorward *et al.* 1982). For example, both kinds of curve shift were rapidly reversible, the same size for moderate pressure changes occurring in either direction and were not related to the resting M.A.P. level before displacement. Most importantly, the size of the hysteresis shifts (0·37 mmHg/mmHg ΔM.A.P.) was the same as our earlier estimate of acute resetting (0·4 mmHg/mmHg ΔM.A.P.). The main difference in our current experiments was that falls in M.A.P. greater than 30 mmHg produced no further shifts in the return function curves. However, in our earlier studies the size of the falls in M.A.P. were limited to the extent of the hypotensive response to nitroprusside infusion or haemorrhage, resulting in few data points for M.A.P. falls greater than 30 mmHg. Heesch *et al.* (1984) also report reduced resetting after a very large pressure increase (+90 mmHg) applied to the carotid sinus. We therefore conclude that the hysteresis shift seen after a change in the direction of a slow pressure ramp was an example of acute 'steady-state' resetting.

The minimum time required to establish acute resetting was 20 s. Unit thresholds shifted by 96 % of the whole curve shift of which they formed a part, within this time interval. This is the most rapid estimate of resetting to date and brings it into the time scale of receptor adaptation. Estimates of the speed of adaptation vary: steady firing levels are reported as occurring 30 to 60 s–4 min following a square-wave pressure increase applied to the carotid sinus (Landgren, 1952; Sleight *et al.* 1977; Bergel *et al.* 1980; Bell, Seagard, Hopp & Kampine, 1982). However, Munch *et al.* (1983) report a further reduction in aortic baroreceptor firing *in vitro*, lasting up to 15 min. They estimated a 'resetting time constant' of 3–5 min which they stress is a full order of magnitude slower than the previously reported time constants of adaptation. *In vivo*, we found no evidence of incomplete resetting over this period. An obvious difference between the two preparations is the ongoing pressure fluctuations of the

arterial pulse superimposed on the slow pressure ramps in our study. Under these conditions, the arterial baroreceptors appear to be 'reset' by the time the 'adaptive' changes are complete.

Resetting in baroreceptor units accounted for resetting of integrated aortic nerve activity in both anaesthetized and conscious rabbits. The average shift in whole-nerve function curves was similar to the value we observed in our units when we ignored the curvilinearity and fitted a single regression to all data points. The lack of curvilinearity in the whole-nerve shift–M.A.P. relationship was explained by the use of pressure falls greater than 20 mmHg.

Resetting of the baroreceptor–heart rate reflex

Resetting of reflex function curves within 15 min of a change in resting pressure has been reported in the carotid sinus–systemic M.A.P. reflex, the baroreceptor–heart rate reflex and the renal sympathetic baroreflex (Kunze, 1981; Dorward *et al.* 1982, 1985). We have now found it to occur, within 30 s, whenever there is a reversal in the direction of a slow pressure rise or fall. This produces a larger reflex response, appropriate to the new direction of pressure change, than could occur if the initial reflex curve had been retraced without resetting.

With caval balloon inflation, the average reflex curve shift was similar to that observed in the aortic baroreceptors. Assuming similar effects in the carotid sinus, arterial baroreceptor resetting appears largely responsible for resetting of the heart rate reflex during falls in blood pressure. This is different from our earlier results where reflex resetting was larger than receptor resetting during nitroprusside-induced pressure falls (Dorward *et al.* 1982). Possibly additional pressure-sensitive receptors contributed to the reflex response in these experiments due to drug-induced alteration of other intravascular pressures. With aortic balloon inflation, the average shift in the reflex curves was double that observed in the aortic baroreceptors. Balloon inflation alters the discharge of other pressure-sensitive receptors including those in the heart, which may explain this result (Korner *et al.* 1972; Paintal, 1973; Thoren, 1979; Ludbrook, 1984).

In conclusion, rapid resetting of arterial baroreceptors and their reflex responses occurs continuously during gradual changes in blood pressure and the magnitude of the response at any moment (either receptor or reflex) is influenced both by the direction of the pressure change and the current absolute pressure level. This enables optimum reflex responses to be maintained on a minute-to-minute basis.

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