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EFFECTS OF SMALL CHANGES IN CAROTID SINUS PRESSURE ON RENAL HAEMODYNAMICS AND FUNCTION IN DOGS

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SUMMARY

1. In dogs anaesthetized with chloralose and artificially ventilated, the carotid sinuses were vascularly isolated and perfused with arterial blood. Mean aortic pressure was held constant at 111 ± 2 mmHg (mean $\pm$ S.E.M., $n = 18$) by means of a pressure bottle connected to the aorta and a Starling resistance. Both vagus nerves were sectioned in the neck and propranolol hydrochloride (1 mg kg^{-1} h^{-1}) or atenolol (0·5–4 mg kg^{-1} h^{-1}) was administered. The left and right renal blood flows were measured by electromagnetic flowmeters (wrap-round probes), glomerular filtration rate by creatinine clearance, urinary sodium by flame photometry and solute excretion by osmometry.

2. In six dogs decreasing pressure in the isolated carotid sinuses from 119 ± 4 to 78 ± 3 mmHg ($n = 9$) resulted in significant decreases in renal blood flow by $18 \pm 3\%$ ($P < 0.01$), glomerular filtration rate by $41 \pm 9\%$ ($P < 0.01$), filtration fraction by $30 \pm 11\%$ ($P < 0.05$), urine flow by $46 \pm 6\%$ ($P < 0.001$), sodium excretion by $46 \pm 9\%$ ($P < 0.001$) and osmolar excretion by $44 \pm 6\%$ ($P < 0.001$). Fractional sodium excretion did not change significantly. Increasing carotid sinus pressure back to 120 ± 4 mmHg ($n = 6$) resulted in increases in all the variables to values not significantly different from those at initial high carotid pressure.

3. Ligation of left renal nerves at low carotid sinus pressure (83 ± 3 mmHg, $n = 5$) caused significant increases in all of the variables in the left kidney. After ligation, changes in carotid sinus pressure produced no effect on the denervated left kidney, but in the three dogs in which the responses of the right kidney were also tested, the usual responses after denervation of the left kidney were seen.

4. The results show that changes in carotid sinus pressure around the normal range can result in significant reflex effects on renal haemodynamics and function and that these effects are mediated solely by renal sympathetic nerves. The influence of any extrarenal humoral factors seems to be minimal.

INTRODUCTION

In anaesthetized dogs, graded changes in pressure in the vascularly isolated carotid sinuses result in graded changes in renal sympathetic nerve activity (Kezdi

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& Geller, 1968; Linden, Mary & Weatherill, 1981) and renal blood flow (Mancia, Shepherd & Donald, 1976; Karim, Kaufman & Kappagoda, 1982*a*; Karim, Mackay & Kappagoda, 1982*b*). We have recently demonstrated in anaesthetized dogs that single step changes in carotid sinus pressure over the whole range of baroreceptor sensitivity (186 ± 10 to 63 ± 5 mmHg) can reflexly alter, not only renal blood flow, but also glomerular filtration rate, urine flow and sodium excretion, and that the responses were mediated via renal sympathetic nerves (Karim, Poucher & Summerill, 1984). However, this large change in carotid sinus pressure is unlikely to occur under physiological conditions. Blood pressure in conscious animals is subject to diurnal variations and sudden fluctuations. Under normal circumstances blood pressure in intact conscious dogs varies over a 24 h period between the range of 75–125 mmHg (see Cowley, Liard & Guyton, 1973). The magnitude of pressure changes under conditions such as a man changing position from lying to standing is likely to be smaller or similar to that seen following carotid occlusion. However, the latter manoeuvre in conscious dogs was reported to have no effect on renal haemodynamics and function (Gross, Kirchheim & Ruffman, 1981); but, in their preparation the primary reflex effect of carotid occlusion on the kidney was likely to have been masked by its secondary effect from the rise in systemic arterial pressure acting on the aortic baroreceptors and the kidney. Thus, it is not clear whether small changes in carotid sinus pressure around normal value can induce a significant reflex effect on renal haemodynamics and function and whether the renal nerves play a major role in the mechanism. As far as we know there has been no adequate study of the effects on both renal haemodynamics and function of changes in carotid sinus pressure within such a physiological range.

The aim of the present investigation was to study the effect of changes in pressure in vascularly isolated carotid sinuses over a range which might normally be encountered (vide supra). The renal responses were determined in well-controlled anaesthetized dog preparations as described previously (Karim *et al.* 1984; Karim, Poucher & Summerill, 1987). In some of the experiments the effects on both kidneys were studied; the responses of an intact kidney were compared with those of the contralateral denervated kidney. The results of this investigation would explain the primary mechanism involved in the significant changes in renal haemodynamics and function (antinatriuresis and antidiuresis) that occur during head-up tilt in normal man (Mimran & Deschodt, 1983). A preliminary report of these experiments has been given (Karim & Poucher, 1984).

METHODS

Six dogs (22·3–31·8 kg; greyhound and mongrel of both sexes, supplied by Leeds University Animal Services) were anaesthetized with 0·5 g sodium thiopentone (Intraval Sodium, May & Baker), followed by chloralose (0·1 g kg^{-1}, Rentokil) infused through a cannula inserted into the right saphenous vein under local anaesthesia (2% lignocaine hydrochloride, Astra Pharmaceuticals). Surgical anaesthesia was maintained throughout the experiment by a continuous infusion of chloralose (0·5 mg kg^{-1} min^{-1}). The chloralose was dissolved in isotonic saline (0·9% w/v) to achieve a final concentration of 1 g 100 ml^{-1}. The trachea was exposed through a mid-line incision and cannulated. Positive pressure ventilation with 40% oxygen in air was started using a Starling Ideal pump, set at 18 strokes min^{-1} and with a stroke volume of 17 ml kg^{-1}.

The techniques for vascularly isolating and perfusing both carotid sinus regions have been

described previously (Karim *et al.* 1984, 1987). Pressure within the sinuses was controlled by altering the outflow resistance using a screw clamp (see Fig. 1).

In all animals the left renal artery was exposed retroperitoneally and a wrap-round electromagnetic flow probe (3·5 or 4·0 mm i.d., Gould Statham model SP 7515) placed around it; distal to this an occluding snare was placed for determination of zero blood flow. The flow probes

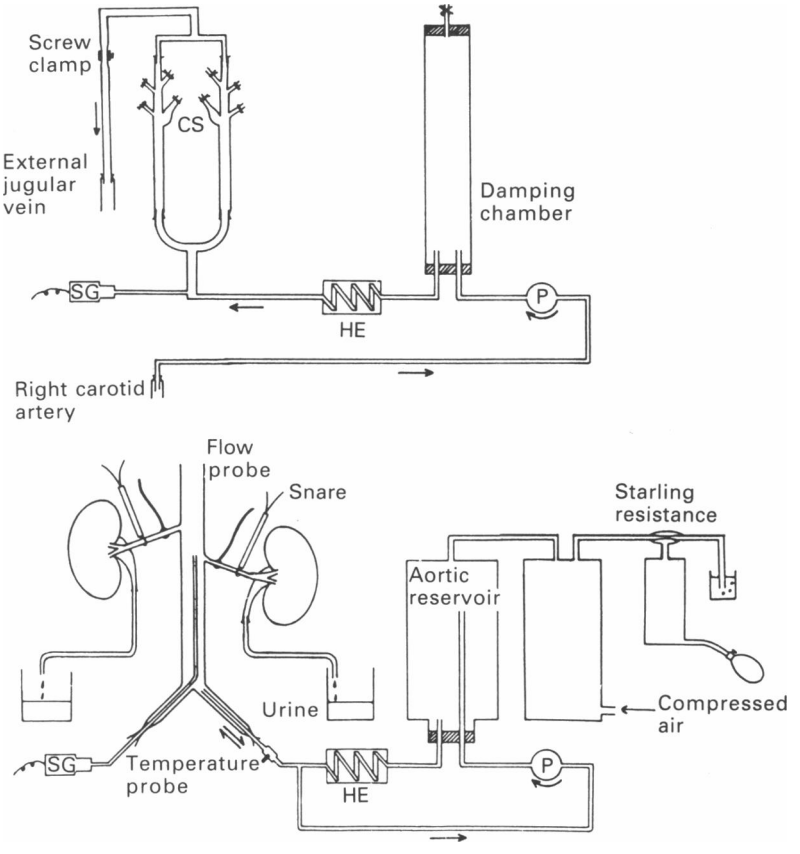


Fig. 1. Diagram of experimental preparation. Vascularly isolated carotid sinuses (CS) were perfused at a constant flow of blood from the right common carotid artery through a reservoir and a heat exchanger (HE) using a roller pump (P). Carotid sinus pressure (CSP) as recorded by a strain gauge (SG) was set at the desired level by regulating the outflow resistance by a screw clamp. Blood from CS returned to an external jugular vein. Renal blood flow was measured using a flow probe. Aortic pressure was held constant by connecting the aorta to a reservoir maintained at a constant pressure. Blood in the circuit was kept warm by circulating it through a heat exchanger by means of a pump. Arrows indicate direction of blood flow.

were calibrated at the end of each experiment by placing them around a common carotid artery and perfusing it with blood at known rates. The left ureter was cannulated and a loose ligature placed around the renal nerves for later ligation. In three of the dogs, the right renal artery and ureter were similarly exposed and the responses of both kidneys studied.

Aortic pressure (renal perfusion pressure) was measured through a cannula inserted into the femoral artery so that its tip lay between the origin of the two renal arteries. Right atrial pressure was also measured through a cannula inserted via an external jugular vein. Pressures were recorded using Statham strain gauges (model P23 ID) connected to the appropriate cannulae. Mean pressure in the abdominal aorta was held constant by connecting it through the other femoral artery to a

reservoir maintained at a constant pressure using a Starling resistance and compressed air (Fig. 1). The vagi were sectioned in the neck, and either propranolol (1 mg kg^{-1} h^{-1}) or atenolol (0·5–4 mg kg^{-1} h^{-1}) infused throughout the experiment. Before connecting any of the perfusion circuits, the animals were given heparin (250 i.u. kg^{-1} I.V.) followed by 25 i.u. kg^{-1} every 30 min. Approximately 50 min prior to the first clearance period, a continuous infusion of creatinine (10 mmol in a solution of 50% dextran, Dextraven 150, Fisons Pharmaceutical Ltd, and 50% isotonic saline solution, 0·9% w/v, Travenol) was started at 2 ml min^{-1} and maintained throughout the experiment for determination of glomerular filtration rate. Creatinine concentration was determined by an autoanalytical method (Technicon II) using the Jaffe reaction. Sodium concentration was determined by flame photometry (Corning–Eel 400). Osmolality was measured by freezing point depression (Osmett, Precision Systems Inc., MA, USA).

Experimental protocol. Before the first clearance period was started, the carotid and aortic pressures were set and maintained constant. Arterial blood gases and pH were within normal range and all other measured variables were steady. Urine was collected for at least two consecutive 10 min periods at each carotid sinus pressure. At the third minute of each collection period, an arterial blood sample was taken from the brachial artery for plasma creatinine determination. Carotid sinus pressure was then reduced to a new level, and after an equilibration period (usually 5 min), still maintaining aortic pressure at its initial level, two further collections of urine were similarly made. The mean values from these two collections were compared with those obtained at initial high CSP setting. In three of the dogs carotid sinus pressure was then raised again; in the remaining three dogs, in which both kidneys were prepared for further experiments, after initial observation the left kidney was first denervated at low carotid sinus pressure and then two further collections were made from the intact and denervated kidneys. Sinus pressure was then raised to the previous level in these three dogs, and two further collections made (see Fig. 4). In two of the three dogs in which only left kidney responses were studied the left renal nerves were ligated and the protocol was repeated. Thus, the total number of denervated kidneys was five.

Statistical methods. The statistical significance of the differences in values was determined using a t test for paired observations. Differences between groups were deemed non-significant at $P > 0·05$. All values quoted are the mean ± S.E. of the mean.

RESULTS

The mean arterial blood pressure was 111 ± 2 mmHg ($n = 6$). The values of arterial pH, P_{O_2}, P_{CO_2} and temperature were 7·42 ± 0·02, 137 ± 14 mmHg, 38·6 ± 1·1 mmHg and 37·9 ± 0·3 °C respectively.

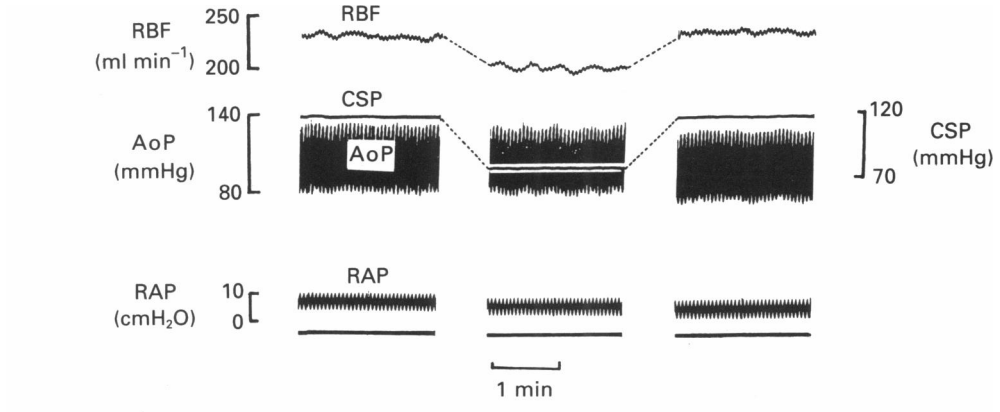
Responses to changes in carotid sinus pressure

Figure 2 shows an example of experimental records and values obtained from one of the tests, and Fig. 3 and Table 1 show the summarized results from nine kidneys in six dogs. In every case, decreasing mean carotid sinus pressure from a pressure corresponding to normal systolic pressure (119 ± 4 mmHg, $n = 9$) to one corresponding to normal diastolic pressure (78 ± 3 mmHg) decreased renal blood flow by 18 ± 3% ($P < 0·01$), glomerular filtration rate by 41 ± 9% ($P < 0·01$), filtration fraction by 30 ± 11% ($P < 0·05$), urine flow by 46 ± 6% ($P < 0·001$), sodium excretion by 46 ± 9% ($P < 0·001$) and osmolar excretion by 44 ± 6% ($P < 0·001$). Raising carotid sinus pressure to 120 ± 4 mmHg ($n = 6$) produced significant increases in all measured variables (see Figs 2 and 3).

In five dogs in which the left kidney was denervated, decreasing carotid sinus pressure from 115 ± 8 to 71 ± 12 mmHg did not produce any significant decreases in the function of this kidney (see Table 2).

Paired kidney responses

Figure 4 shows records and values from both innervated and denervated kidneys in one dog. Both responded normally to lowering the carotid sinus pressure whilst intact. Denervation of the left kidney at low sinus pressure (77 ± 4 mmHg) produced



GFR (ml min^{-1})	38·1	9·4	22·4
$\dot{V}$ (ml min^{-1})	0·17	0·05	0·15
$U_{Na}\dot{V}$ (μmol min^{-1})	1·3	0·3	1·1

Fig. 2. Records and values showing renal responses to a small step-change in carotid sinus pressure (CSP) at a constant aortic pressure (AoP, renal perfusion pressure). RAP, right atrial pressure; RBF, renal blood flow; GFR, glomerular filtration rate; $\dot{V}$, urine flow; $U_{Na}V$, urinary sodium excretion. Each value is from a single collection at each setting of CSP. These results were obtained from dog No. 1. Kidney weight = 60·4 g.

sustained increases in renal blood flow (47 ± 26%), glomerular filtration rate (256 ± 167%), urine flow (468 ± 288%) and sodium excretion (468 ± 284%) whilst the right kidney showed decreases in urine flow and sodium excretion without any change in any of its other variables i.e. renal blood flow and glomerular filtration rate (see Fig. 5). Subsequent increase in carotid sinus pressure to 124 ± 5 mmHg resulted in usual effects on variables from the intact right kidney without any overall change in the function of the denervated left kidney. The summarized results are given in Fig. 5.

DISCUSSION

The results of these experiments clearly show that changes in carotid sinus pressure which would normally be encountered, for example, changing posture from lying to standing, consistently result in reflex changes of renal haemodynamics and function, and that the effects are mediated by renal efferent sympathetic nerves (Figs 2, 3 and 4; Tables 1 and 2). The responses were due predominantly to changes in stimulus to the carotid sinus baroreceptors as previously discussed (Karim *et al.* 1984).

Whilst these experiments were performed in vagotomized animals to prevent any influence of cardiopulmonary receptors, the importance of these receptors upon the responses in the whole intact animal must be considered. The renal blood flow can be altered by stimulation of the left and right atrial receptors (Karim *et al.* 1982*a*, *b*),

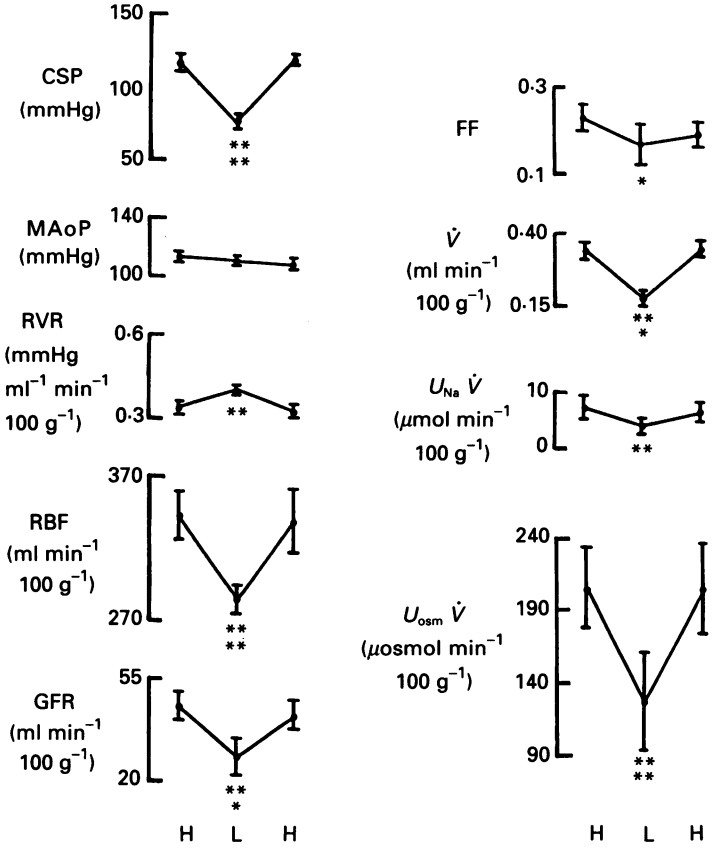


Fig. 3. Effects of small changes in carotid sinus pressure upon function of the intact kidney. Carotid sinus pressure was lowered from 117±6 to 78±5 mmHg and raised to 119±4 mmHg ($n = 6$). Mean aortic pressure (MAoP) at these sinus pressures was 113±3, 110±3 and 108±4 mmHg respectively; these values were not significantly different. Each point is the mean of six values, with standard error bars. The averages of the values at high CSP were statistically compared with the values at low CSP; where no symbol is present, $P > 0{\cdot}05$ and therefore was considered non-significant, otherwise. *, $P < 0{\cdot}05$; **, $P < 0{\cdot}02$; ***, $P < 0{\cdot}01$; ****, $P < 0{\cdot}001$. H, high CSP; L, low CSP; RVR, renal vascular resistance; FF, filtration fraction: U_{osm}, $\dot{V}$, osmolar excretion; other abbreviations as in Fig. 2.

electrical stimulation of cardiopulmonary sympathetic afferent nerves (Purtock, von Colditz, Seagard, Igler, Zuperku & Kampine, 1977), and ventricular distension (Oberg & Thoren, 1973). Two studies by Mancia, Shepherd & Donald (1975, 1976) found that cardiopulmonary receptors discharging afferent impulses into the vagosympathetic trunk had at least an equal and usually greater influence upon renal blood flow than carotid sinus baroreceptors. In a similar canine preparation we

TABLE 1. Effect of changes in carotid sinus pressure on renal haemodynamics and function in intact kidneys

Dog	MAoP (mmHg)		RBF (ml min^{-1} 100 g^{-1})		GFR (ml min^{-1} 100 g^{-1})		$\dot{V}$ (ml min^{-1} 100 g^{-1})		$U_{Na}\dot{V}$ (μmol min^{-1} 100 g^{-1})	
no.	H	L	H	L	H	L	H	L	H	L
1	110	108	414	297	38·9	15·8	0·33	0·15	12·0	6·8
2	101	104	372	312	53·5	29·2	0·39	0·14	2·0	0·6
3a	111	112	310	260	39·4	7·1	0·34	0·09	3·5	1·6
3b	110	111	320	272	28·9	13·9	0·29	0·14	1·9	0·4
4a	112	106	323	239	58·0	37·4	0·27	0·16	4·8	1·9
4b	108	104	303	244	57·6	50·2	0·25	0·19	5·2	4·4
5a	118	112	417	342	36·3	35·6	0·46	0·37	9·2	7·5
5b	110	110	322	287	37·2	16·3	0·39	0·15	10·4	5·3
6	126	125	317	297	46·7	41·7	0·40	0·28	8·9	7·4
Mean	112	110	344	283	44·1	27·5	0·35	0·19	6·4	4·0
S.E.M.	2	2	15	11	3·4	4·9	0·02	0·03	1·3	1·0
P	n.s.		< 0·001		< 0·01		< 0·001		< 0·01	

Values are at high (H, 120±3 mmHg) and low (L, 78±3 mmHg) carotid sinus pressure in experiments with intact kidneys. Since responses were similar in tests in which sinus pressure was set high, then lowered, and finally raised again, to those in which sinus pressure was only lowered (dogs 3a, 4a and 5a), the mean of two values at high CSP in the intact kidney were used. Second high CSPs were maintained in experiments with three intact left kidneys (dogs 1, 2 and 6) and in three intact right kidneys (the left kidneys in these dogs were denervated. Abbreviations as in Fig. 2.

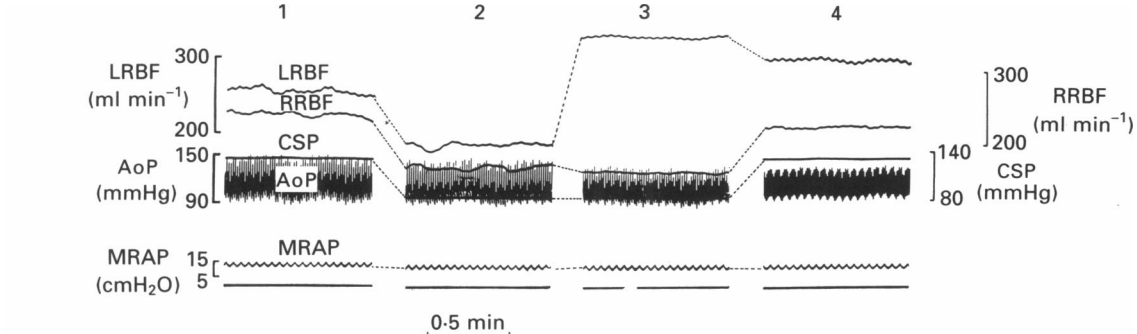
TABLE 2. Effects of changes in carotid sinus pressure on renal function in denervated kidneys

Dog	MAoP		RBF		GFR		$\dot{V}$		$U_{Na}\dot{V}$	
no.	H	L	H	L	H	L	H	L	H	L
2	95	94	366	432	48·1	57·1	1·03	1·03	28·7	49·6
3	108	111	385	495	35·4	49·1	0·60	1·03	12·6	12·5
4	104	104	341	305	63·6	64·6	0·59	0·47	8·2	4·4
5	102	110	401	392	58·4	72·8	0·60	0·99	34·3	91·0
6	124	126	377	408	59·8	64·3	0·83	0·74	40·5	75·0
Mean	107	109	374	406	53·1	61·6	0·73	0·85	24·9	46·5
S.E.M.	5	5	10	31	5·1	3·9	0·09	0·11	6·2	16·9
P	n.s.		n.s.		< 0·05		n.s.		n.s.	

Abbreviations and units as in Fig. 2 and Table 1. Values were obtained at high (H, 115±8 mmHg) and low (L, 71±13 mmHg) CSP. Note that after denervation of the kidney a change in CSP did not produce any significant change in any of the variables except GFR which was now slightly reversed. Ligation of renal nerves was not performed in dog No. 1.

observed that vagotomy can cause a significant reduction in renal blood flow (Karim *et al.* 1987). In the present experiment, therefore, the renal sympathetic nerve activity was likely to be somewhat enhanced. However, under normal conditions when the central venous pressure is low the activities of the receptors in the cardiopulmonary areas, particularly that of the atrial receptors, will be low and hence should cause a minimal inhibition of the renal sympathetic nerve activity.

Since mean renal perfusion pressure was kept constant, the renal blood flow changes must be due to vasoconstriction caused either by direct action of renal efferent nerves upon the vessels, or by a secondary effect due to the release of a humoral factor which acts locally. However, it is unlikely that the responses seen in



	L	R	L	R	L	R	L	R
GFR (ml min^{-1})	26·3	27·4	6·7	8·4	32·4	9·3	24·2	22·2
$\dot{V}$ (ml min^{-1})	0·26	0·28	0·09	0·10	0·70	0·10	0·3	0·28
$U_{Na}\dot{V}$ (μmol min^{-1})	3·4	1·5	1·8	0·3	8·3	0·3	8·4	1·9

Fig. 4. Records and values from a double-kidney experiment showing significant renal responses to changes in CSP in left and right kidneys before (panels 1 and 2) denervation of the left kidney (between 2 and 3), after which only the right kidney showed the usual responses to changes in CSP, the left kidney being unaffected (panels 3 and 4). L and R denote left and right kidneys; MRAP, mean right atrial pressure; LRBF, left renal blood flow; RRBF, right renal blood flow; other abbreviations as in Fig. 2. These results were obtained from dog No. 3. Left kidney weight = 69·1 g and right kidney weight = 67·9 g.

our experiments involve the release of an extrarenal humoral factor, since the responses were completely abolished by renal nerve section. It has been suggested that a reduction of carotid sinus pressure, by carotid occlusion, produces an increased plasma antidiuretic hormone (ADH) level (Share, 1965) and antidiuresis is only observed when the occlusion is applied below the level of the thyrocarotid artery junction (Perlmutt, 1963). But these two studies reported conflicting results. Firstly, Share (1965) found that vagotomy had no effect on ADH levels, yet atrial balloon inflation reduced the circulating levels, which seems paradoxical. Secondly, Perlmutt (1963) found that the antidiuresis was seen only when carotid occlusion was applied below the thyrocarotid junction, but not when the occlusion was applied above the thyrocarotid junction. However, this latter manoeuvre would be expected to increase the general systemic blood pressure, as before, and there would also be an increased pressure at the thyrocarotid junction, which according to the theory of Share (1965) and Perlmutt (1963) would cause a diuresis.

It has also been reported that carotid sinus pressure reduction results in increased adrenaline release in vagotomized dogs (Critchley, Ellis & Ungar, 1980). However, reduction of systemic blood pressure by nitroglycerin injection, although raising plasma catecholamine levels, was not sufficient to alter the pulse rate of a denervated heart (Fater, Dundet, Schultz & Goetz, 1983), indicating that the amount released was not sufficient to have any physiological significance. The lack of renal responses after renal denervation in our experiment would also support an

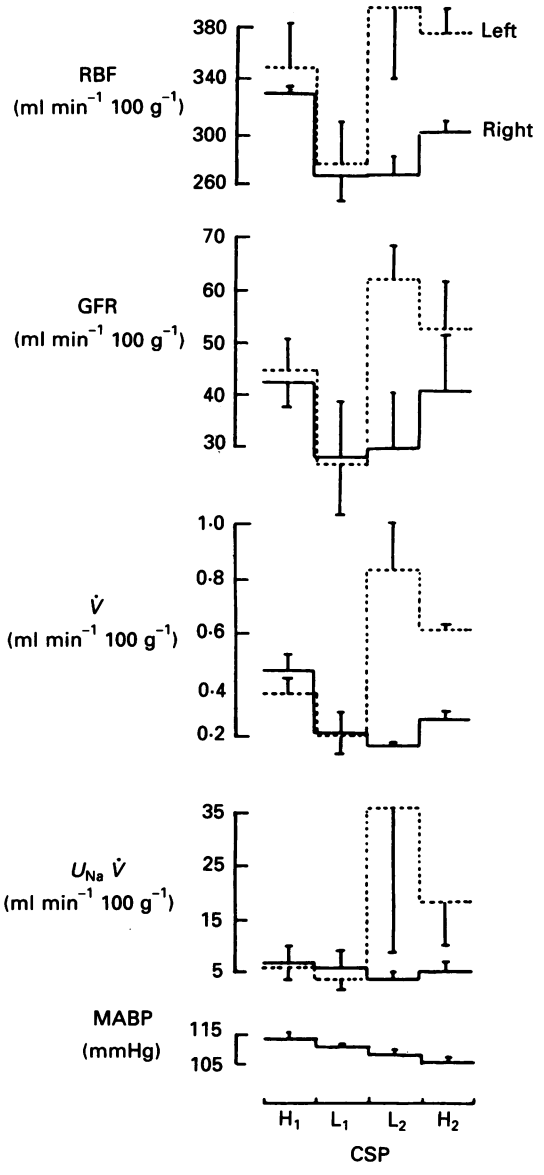


Fig. 5. Effects of denervating the left kidney upon renal responses to small changes in sinus pressure. The responses of the left kidney (dashed line) were abolished after ligation of the nerves running to this kidney (between L_1 and L_2 CSP). However, the responses of the intact right kidney (continuous line) after this procedure were still observed. Abbreviations as in Figs 2 and 3. For high and low CSP (mmHg): $H_1 = 123 \pm 5$, $L_1 = 78 \pm 4$, $L_2 = 77 \pm 5$ and $H_2 = 124 \pm 4$ (mean $\pm$ S.E.M., $n = 3$).

absence of significant change in catecholamine level. This lack of response was not due to deterioration of the preparation as changes in carotid sinus pressure resulted in the usual changes in systemic arterial pressure. More importantly, the paired kidney studies showed that there was still a response in the intact kidney after denervation of the contralateral kidney (Figs 4 and 5).

There is a suggestion that alteration of renal nerve discharge can affect renal function by release of renin (Powis & Donald, 1979). Although we did not measure plasma renin levels it is unlikely that they were affected as we infused the β-adrenergic blockers, propranolol or atenolol, at rates reported to prevent renin release (Powis & Donald, 1979). However, the detailed intrarenal mechanisms of action of the renal nerve in the baroreceptor reflex is not certain. The changes in urine volume and sodium excretion could be largely secondary to changes in renal blood flow and glomerular filtration rate (Kamm & Levinsky, 1965; O'Connor & Summerill, 1979).

Suggestions of a direct tubular action of renal nerves (Prosnitz, Zambraski & DiBona, 1977) must also be considered. Whilst this possibility cannot be ignored, it must be noted that when absolute changes in sodium excretion have been stated (Osborn, Francisco & DiBona, 1981; Kopp & DiBona, 1983) the changes in sodium excretion could be accounted for by a reduction in glomerular filtration rate as little as 0·2 ml min^{-1}. This latter study found that renal nerve stimulation caused a small reduction from 38 ± 3 to 34 ± 3 ml min^{-1} that was associated with a significant reduction in sodium excretion (from 107 ± 32 to 85 ± 25 μequiv min^{-1}). Our own unpublished observations of direct electrical stimulation of renal nerves also reveals that there is a significant decrease in sodium excretion without any change in glomerular filtration rate at frequencies below 1 Hz.

Lowering sinus pressure produced a fall in glomerular filtration rate (41%), urine flow (46%) and sodium excretion (46%), which were all more than twice the fall in renal blood flow (18%) (see Table 1). This suggests, firstly, that the response is due to increased vasoconstriction of the afferent arteriole, and secondly, the decrease in sodium excretion could be accounted for solely due to a reduced tubular delivery.

The normotensive individuals with a mean pressure of about 100 mmHg are expected to be on the most sensitive (high gain) part of the curve relating the activities of the baroreceptor afferents and renal sympathetic efferent (Kezdi & Geller, 1968). A small change in pressure acting on the receptors could cause relatively large changes in the renal efferent nerve activity and hence significant alterations of both renal haemodynamics and function. The responses to small changes between 78 and 120 mmHg (i.e. around normal range) in carotid sinus pressure as seen in the present experiments were not, therefore, greatly different from that seen in the responses to a large change (from 63 to 186 mmHg) in carotid sinus pressure as reported earlier (Karim *et al.* 1984). Our results, therefore, may explain the differences in the renal haemodynamics and function in response to postural changes largely in terms of alterations of baroreceptor activity resulting in a reciprocal change in the sympathetic efferent nerve activity.

In summary, these experiments demonstrate that the kidney can respond to changes in carotid sinus pressure close to the physiological range, which is dependent on renal sympathetic nerves and not on any extra renal humoral factors.

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