Plasma renin activity following renal transplantation

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Summary

Plasma renin activity (PRA) was studied serially for up to 21 days following transplantation in thirteen patients receiving renal allografts. PRA was measured during fasting and recumbency and its relationship to renal function, diuretic administration, plasma sodium, allograft rejection and blood pressure was examined.

PRA fell steadily as renal function improved and plasma sodium rose following transplantation and when rejection episodes were excluded an inverse relationship between PRA and renal function could be seen. It is not possible to say whether the changes in PRA and function are causally related or whether changes in plasma sodium alone account for the observed changes in PRA. Some rejection episodes were accompanied by an increase in PRA, but this was not sufficiently consistent to be of value in the diagnosis of rejection. PRA also increased in relation to frusemide-induced fluid loss. There was no relationship in these patients between PRA and blood pressure.

Introduction

It has been shown that the recently transplanted kidney can release renin in response to a variety of events including active allograft rejection (Gunnels, Stickel and Robinson, 1966; Roguska, Del Greco and Simon, 1971; Abbrecht, Turcotte and Vander, 1968; West, Turcotte and Vander, 1969), ischaemia (West *et al.*, 1969) and sodium depletion; orthostasis (Greene, Vander and Kowalczyk, 1968; Beckerhoff *et al.*, 1974) may also stimulate release of renin from the graft. The diseased non-functioning kidneys of patients on regular dialysis are also capable of releasing renin in response to sodium depletion (Kotchen *et al.*, 1970; Brown *et al.*, 1969) making interpretation of changes in renin in non-nephrectomized patients difficult.

During acute rejection episodes a close correlation has been found between plasma renin activity (PRA) and blood pressure (Popovtzer *et al.*, 1973) and

acute hypertension has occurred after the transplantation of 'high renin' allografts from donors with hepato-renal syndrome into anephric recipients (MacDonald, Brennan and Turcotte, 1973).

The aims of this study were to assess the value of PRA estimations in the detection of allograft rejection, to delineate other factors causing changes in PRA (whether from the allograft or the diseased kidneys) in transplant recipients and to examine the relationship of PRA to blood pressure in the early transplant period.

Patients

Nine women and four men receiving renal allografts were studied during the first three post-operative weeks. Twelve patients, all of whom retained their own kidneys, received cadaver grafts. The thirteenth, who had previously undergone bilateral nephrectomy received a kidney from his father. Postoperatively five patients received frusemide and one continued hypotensive therapy.

Methods

Following transplantation patients were maintained on an immunosuppressive regime of oral prednisone 40 mg daily and azathioprine 2.5 mg/kg to a maximum of 200 mg daily. Acute rejection episodes were treated by increasing the steroid dosage to 200 mg of prednisone daily for 2 days and gradually returning to baseline therapy over 6 days.

Patients were monitored by 4-hourly pulse, blood pressure and temperature recordings. Central venous pressure was monitored for the first 48 hr post-operatively. Daily measurements of urine volume, plasma creatinine, urea and electrolytes and creatinine clearance were made. Body weight was recorded daily. Each morning, when possible, a blood sample was collected for estimation of plasma renin activity (PRA) after overnight fasting and recumbency. Tubes containing EDTA were used and the sample chilled immediately in an ice bath. Plasma was separated at 4°C and stored at -20°C until assay.

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TABLE 1. Plasma renin activity (PRA) following renal transplantation (the fasting recumbent morning PRA level (ng/l/min) is shown for each patient for up to 21 days after transplantation)

Patients	0	1	2	3	4	5	6	7	8	Days after transplantation											18	19	20	21			
										9	10	11	12	13	14	15	16	17									
F.S.			77	175	330	330	330	330	283	167	167	96	63	58													
D.I.	13	13	5	13	5	10	33	70	65	27	12	6	0	0													
I.K.			330	158	89*	260		151*	265	128	330	330	330	330	330	198	134	165*									
J.B.		62	82	78	24	58*		2		11	10*	8.1	1.3	0	10.2	11.6	51	18.5	57	41	43	140†					
E.M.	28.7	13.8*	4.3	5.3	15.6	14.9	13.5	29.1	20.5	30.5		19.2	11.2	5.4	6.5	4.7	4.8	1.2	4.2	18	21	4					
B.A.					150	136	99	129*	175	64	78	115	269		148	330	135	76	192*	93	198	85					
H.H.		330	138	109	115	138	150	116*	81	138		150	88	117	84	76	61										
M.V.	64	12.3	12.9			4.7	13.2	13.5	10.6	27.7		20.8	46	14.6	17.5	12	25.4	25.1	49.6	37	145†	199					
K.P.		277	29	56		46	69	56	72	52	5.6	131	61	64	37	85	33	33	38	8.2	11.1	12.2					
V.M.	39	148*	51	36	14	333*		6.6	11.7	64	93																
D.H.		110		145*	17	32	13	9.3	14		23	33	24	16.3	36	10	22	30	32								
R.P.		293	239	210	65	151	176	260	303	178*	291																
E.E.		3.3	17			132*	0	5.9	0	5.8	7.8	0		2.7		711	17.5	25	10.7	3.0	3.6						

* Day of clinical rejection or clinical exacerbation of rejection. † Episode of fluid depletion.

FIG. 1. Changes in plasma renin activity (PRA) in relation to fluid balance (indicated by daily weight). A clear rise in renin accompanied fluid depletion. Patient A had undergone bilateral nephrectomy, but in patient B polycystic kidneys were *in situ*.

The diagnosis of acute rejection was based on one or more of the following features:

Fever not explained by infection; hypertension not explained by fluid overload; tenderness and swelling of the graft and in those patients with functioning grafts; reduced urine output or rising serum creatinine. The diagnosis of rejection was usually confirmed by needle biopsy of the graft.

Measurement of PRA

PRA measurements were made by the radioimmunoassay of angiotensin I (AI) in a modification of the method of Skinner (1967). Results were expressed as nanograms of generated AI per litre per minute.

The coefficient of variation of the method was 20% between assays and 9.3% within a single assay. All samples from an individual patient were examined in the same assay.

In the authors' laboratory the normal range for PRA by this method in subjects taking unrestricted diet is 16 ± 7.7 ng/l/min during recumbency at 9.00 a.m.

Results

PRA varied widely from patient to patient and in the same patient during the course of the study (Table 1). These variations can be partly explained

by the renin secretory response to identifiable stimuli.

No significant differences in levels of PRA following transplantation were found between patients whose grafts developed immediate function and those with delayed function. No correlation was found between the initial post-transplant PRA and graft ischaemia times in this group of patients.

The effect of frusemide on PRA

In three patients who received frusemide the loss of weight produced was small. However, in two patients, including the patient with previous bilateral nephrectomy, reductions of body weight of 3.5 kg and 6.0 kg occurred during frusemide administration. In these patients there was a marked rise in PRA (Fig. 1), which returned to baseline levels following fluid replacement.

Changes in PRA in relation to clinical rejection episodes

Fourteen episodes of rejection were studied. In view of the difficulty in determining the exact time of onset of an acute rejection episode PRA levels were examined when available for the 4 days before and after the day on which acute rejection was detected clinically. In order to achieve comparability between patients, PRA values were expressed as percentages

of the values measured on the day of diagnosis of rejection. The means of the values for all patients are plotted in Fig. 2. Although statistically not significant, a peak occurred two days before the day on which rejection became clinically manifest.

FIG. 2. Mean plasma renin activity (PRA) for all patients on the days preceding and following rejection expressed as a percentage of the value on the day of diagnosis of rejection. The mean was increased 2 days before the day of diagnosis, but did not differ significantly from the mean on other days.

However, in five episodes (31%) PRA levels did not exceed the highest levels observed between rejection episodes and only in six (37.5%) were levels 50% greater than the highest non-rejection level. In addition, in the three patients who were free of rejection episodes, the apparently unstimulated PRA levels varied between 58 and 330, 0 and 70 and 5.6 and 277 ng/l/min.

PRA and blood pressure

Blood pressure varied by more than 10 mmHg diastolic or 20 mmHg systolic in association with ten of the fourteen rejection episodes (Table 2). However, in only three of these episodes were rises in blood pressure and PRA synchronous. No significant correlation was found between blood pressure and PRA in individual patients or the group as a whole during rejection episodes or otherwise.

The evolution of non-stimulated PRA levels

For this analysis, PRA levels within 3 days of a

rejection episode or during fluid depletion were excluded. Figure 3 shows the means of the remaining PRA levels together with mean renal function. As the number of values on which means were based was small at some points, statistical analysis was not possible but it is of interest that the peak mean PRA value corresponded with the lowest mean renal function and that PRA fell as renal function improved. Furthermore, in three patients in whom there were sufficient non-stimulated values to allow individual statistical analysis, there existed a significant negative correlation between PRA and renal function (Fig. 4). However, during the period of improving renal function there was a steady rise in serum sodium (see below) which may have been the factor responsible for the observed fall in PRA.

FIG. 3. The relationship of the mean of the daily plasma renin activity (PRA) for all patients, excluding values within 3 days of rejection or dehydration, to creatinine clearance. The apparent inverse relationship is discussed in the text.

Plasma sodium and body weight

On the day of transplantation mean plasma sodium for the group was 127.7 ± 7.0 mmol/l reflecting the low dialysate sodium concentration used in long-term haemodialysis at the time of the study. By the twenty-first postoperative day, plasma sodium had risen significantly ($P < 0.05$) to 136.7 ± 4.5 mmol/l.

There was a reduction in mean body weight for the group, but this may represent loss of lean body mass due to the effects of surgery and corticosteroids on nutrition rather than reduction in body water.

Discussion

A variety of events have been shown to influence PRA during the first 3 weeks following renal transplantation.

An apparent relationship between renal function and PRA was observed in this study. In three

TABLE 2. Blood pressure and rejection. (The maximum blood pressure (in mmHg) reading for each day is shown in relation to the day of diagnosis of rejection.)

Patient	Time in relation to clinical rejection (days)						
	-4	-3	-2	-1	0	+1	+2
D.H.			125/60	135/70	155/80	160/100	165/98
H.H.	145/88	150/94	153/87	152/88	152/82	142/85	148/90
E.E.	160/75	165/80	160/80	160/70	158/84	163/67	136/66
R.P. (i)		185/105	200/100	180/90	162/94	180/112	182/112
(ii)	180/112	180/101	161/93	146/84	166/102	170/98	172/98
V.M. (i)				100/60	105/70	120/70	110/70
(ii)	105/70	120/70	110/70	110/60	151/93	133/73	111/67
E.M.				150/80	150/85	150/97	145/90
J.B. (i)	160/90	170/90	150/105	161/100	168/100	152/95	180/106
(ii)	150/95	180/106	182/107	182/107	170/100	170/96	176/102
M.V.			125/75	125/75	130/70	128/68	143/83
I.K. (i)	150/100	155/100	150/100	140/90	140/100	125/90	132/90
(ii)	140/90	140/100	125/90	132/90	150/98	138/84	140/84
(iii)	150/98	171/114	156/95	140/90	135/78	135/85	140/90
B.A. (i)		116/59	123/66	126/73	114/63	124/73	119/67
(ii)		115/55	144/70	150/83	130/80	99/62	130/78
Mean	149/88	156/89	150/86	146/82	147/85	146/87	148/90

FIG. 4. The relationship between plasma renin activity (PRA) and creatinine clearance in three patients from whom sufficient data were available for individual analysis. There was a significant inverse relationship in each case.

patients there was a significant inverse relationship between PRA and creatinine clearance and following the exclusion of stimulated levels a similar trend was seen for the group as a whole. This may indicate that PRA reflects the severity of ischaemically induced tubular damage, levels falling as recovery occurs. It

is also possible that hypersecretion of renin is the cause of renal failure as has been suggested in non-transplant situations (Brown *et al.*, 1970; Snow *et al.*, 1976). The fall in PRA following transplantation may also be partly explained by the observed increase in plasma sodium concentration. However, this does

not seem likely to be the whole explanation since there was no evidence of water accumulation with the increasing sodium concentration; in fact, body weight fell and blood volume may be more important than sodium concentration in the control of renin secretion (Gordon and Pawsey, 1971).

Following transplantation, rises in PRA were seen during frusemide therapy, but only when significant fluid depletion occurred. This response cannot be attributed solely to the patient's diseased kidneys as it occurred in the patient in whom bilateral nephrectomy had been previously performed and although renin-like activity can be detected in the anephric's plasma, its level does not respond to physiological stimuli (Yu *et al.*, 1972). In the normal kidney, frusemide may stimulate renin release by an action at the macula densa (Nash *et al.*, 1969; Vander and Carlson, 1969; Bailie, Davis and Loutzenhiser, 1973), but in the present situation the absence of effect when fluid depletion did not occur suggests that the response is more likely to have been mediated by changes in renal perfusion, perhaps acting through the afferent arteriolar baroreceptors.

The authors were unable to relate blood pressure changes in the early post-transplant period to PRA levels. Other workers have noted this lack of correlation (West *et al.*, 1969; Beckerhoff *et al.*, 1974), although Popovtzer *et al.* (1973) found a significant relationship between renin and blood pressure during rejection. Glucocorticoids both lower renin production by the kidney (Newton and Laragh, 1968) and increase blood pressure (Knowlton *et al.*, 1952; Clarke, Ashburn and Williams, 1969) and steroid administration may provide the explanation for the lack of relationship between blood pressure and PRA. Although a positive correlation has been shown between diastolic blood pressure and steroid dosage during the three months following transplantation (Popovtzer *et al.*, 1973), the authors were unable to demonstrate this relationship during their much shorter observation period.

Increased plasma renin levels in association with acute rejection episodes have been reported (Gunnels *et al.*, 1966; Roguska *et al.*, 1971; West *et al.*, 1969; Popovtzer *et al.*, 1973), but not in all studies (Beckerhoff *et al.*, 1974). In the authors' patients, mean PRA reached a peak two days before the clinical diagnosis of acute rejection. However, changes in PRA did not occur in a third of rejection episodes and when they did occur their temporal relationship to the clinical episode varied. In addition, apparently spontaneous fluctuations in PRA of similar magnitude were frequently observed between rejection episodes and in patients in whom no rejection episodes occurred. These observations suggest that measurements of PRA have no part to play in the early diagnosis of acute rejection.

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