PLASMA RENIN ACTIVITY BEFORE AND AFTER ALLOGENEIC KIDNEY TRANSPLANTATION IN MAN

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Previous studies (Kountz et al., 1963; Porter et al., 1963; Darmady et al., 1964) have demonstrated that vascular injury plays a prominent role in the rejection of kidneys in dog and man. Such vascular injury may lead to intrarenal vascular stenoses. It is well known that stenosis of the renal artery sometimes causes an increased secretion of renin from the kidney. It is also pointed out (Goldblatt, 1965) that an intrarenal vascular stenosis would give the same effect.

The purpose of this study was to investigate whether renin release increased with rejection in renal-transplanted patients, whether determinations of plasma renin activity (PRA) could contribute to the diagnosis of acute rejection, and whether renin activity might be high in patients who had undergone several rejections.

Material and methods
The study group was composed of fourteen patients with terminal uremia. In ten of the patients PRA was determined before bilateral nephrectomy or kidney transplantation, in nine patients after bilateral nephrectomy, and in ten patients repeated determinations were made after kidney transplantation. The method of Boucher et al. (1964) with slight modifications (Castenfors, 1967) was used to make 93 determinations. Normal values in our hands lie between 0 and 125 nanograms of angiotensin per 100 ml plasma.

Results
Before bilateral nephrectomy PRA varied between 0 and 5725 (Table I). In only three cases of the ten was activity above normal values, in spite of severe hypertension in eight. The hypertension in the five cases with normal renin activities was probably due to other reasons. It is, however, of interest that both normotensive patients had no detectable renin activity in plasma. The diagnoses in the three cases with high renin activities were chronic glomerulonephritis in two and lupus erythematosus in one. This last patient stands out strikingly from the others in the series. A PRA of 5725 was recorded. Renal angiography showed no stenosis in the main renal arteries. On histological study (Fig. 1) of the excised kidneys, the picture was dominated by advanced intrarenal arterial changes with extensive intimal proliferation and an occasional total occlusion of the lumen. The glomeruli were relatively well preserved. These changes were very similar to the arterial changes which are observed in transplanted kidneys. It is possible that the combination of intrarenal, preglomerular arterial stenoses with well preserved glomeruli and juxtaglomerular apparatuses would allow high renin secretion.

After bilateral nephrectomy. In five cases serial determinations of PRA were made immediately after the renal vessels were clamped at bilateral nephrectomy. In two of these, initial values were so low that changes in PRA could not be evaluated. The remaining three cases
are presented in Fig. 2. There was a faster disappearance of PRA with high initial values than with low. In case RE, PRA sank from 5725 to half of that in ten minutes, while in case BAG a corresponding fall to half occurred in approximately 35 minutes. Later post-nephrectomy, no renin activity was demonstrable in five cases of nine, while in the remaining four, low values were recorded.

After renal transplantation. Immediately after revascularization, serial determinations of PRA were made in three cases (Fig. 3). In two of these the ischemic time was relatively short (29 and 30 minutes) and PRA did not rise above normal values. In the remaining case a

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**TABLE I**

*Plasma renin activity prior to bilateral nephrectomy.*

*The values are expressed in nanograms angiotensin per 100 ml plasma.*

*Patients with normal values are below the dotted line.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hypertensive</th>
<th>Normotensive</th>
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<tbody>
<tr>
<td>RE</td>
<td>5725</td>
<td></td>
</tr>
<tr>
<td>BAG</td>
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</tr>
<tr>
<td>EK</td>
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<td>SÖ</td>
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</tbody>
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*Fig. 1. Patient RE. The kidneys were removed prior to transplantation because of severe hypertension. The diagnosis was lupus erythematosus. Plasma renin activity before bilateral nephrectomy was 5725 nanograms angiotensin per 100 ml plasma. Note the extensive changes in the intralobular artery in the center of the picture. The glomeruli are relatively well preserved. Magnification × 150. Htx-cosin-stain.*
“free kidney” was utilized after an ischemic period of 126 minutes. PRA rose to 468 within 75 minutes and returned to normal values within a few hours.

Ten patients were followed in the longer post-transplantation course with repeated determinations of PRA. 3-7 determinations were made on every patient, at varied intervals. In eight of the ten cases, abnormally high PRA was occasionally recorded. A striking correlation between renin activity and the presence of clinical rejection did exist. In six cases, abnormally high PRA was measured during or in the initial phase of rejection. In no case was PRA normal during rejection. In two patients normal values only were recorded and neither underwent rejection during the observation period.

A typical rejection crisis is presented in Fig. 4. The patient developed a rejection on the third day after transplantation. Even before a decrease in renal function was observed, a rise in PRA could be recorded. There was a concomitant increase in blood pressure and a marked decrease in sodium excretion. That this sodium retention was not steroid dependent seems within reason since sodium excretion decreased before steroid medication was initiated. Sodium excretion increased again after prednisone was administered. The blood volume was essentially unchanged during rejection and serum sodium showed a tendency to rise. One week later when kidney function had improved, PRA returned toward normal levels. Three months after transplantation, the patient’s own kidneys were removed because of hypertension. PRA had then risen to around 400 where it remained one week after bilateral nephrectomy. It appears to have been the transplant that secreted the renin. There was no new rejection attack in the interim. A similar increase in renin activity in the longer post-transplantation course was seen in two other patients without evidence of acute rejection.

Discussion

Hypertension in patients with terminal uremia seldom depended on increased PRA in our cases. This is completely in accord with other investigations (Blaufax et al., 1966; Gunnels et al., 1966). It also fits with experience from chronic dialysis centers where it is felt that hypertension can nearly always be controlled by adequate dialysis. Our case, with the highest PRA (5725) was remarkably easy to hold in a normotensive state with hemodialysis after bilateral nephrectomy, although he had previously been highly resistant to therapy. It may
Fig. 3. Serial determinations of plasma renin activity in peripheral blood after revascularization in three patients undergoing allogeneic kidney transplantation.

Therefore be that determination of PRA could be helpful in establishing the need for bilateral nephrectomy as a treatment for hypertension in patients on chronic dialysis.

After bilateral nephrectomy a significantly faster disappearance of PRA was seen with high initial values than with low. It seems plausible that an individual with high renin secretion from the kidneys should have a high capacity for inactivation of renin in order to prevent a continuous rise in PRA.

The amount of renin activity in the blood immediately following revascularization at renal transplantation seemed to be related to the length of the ischemic period (Fig. 3). This could conceivably be caused by anoxia of the juxtaglomerular apparatus leading to cellular injury.

A striking correlation between renin activity and the presence of clinical rejection was observed. This agrees with the observation of Gunnels et al. (1966) who reported a case in which a rise in renin activity could be seen in connection with clinical rejection. Blaufax et al. (1966) found no elevation of renin activity during rejection in one case, while in two others an elevation was present. They attributed the increased renin activity to a concomitant congestive heart failure. An increased PRA conceivably contributes through stimulation of aldosterone (Gunnels et al., 1966) to the increased sodium retention which often occurs with clinical rejection. The gradual rise in PRA with time, observed in our study in three cases without evidence of acute rejection, might depend upon the development in these kidneys of arterial changes of the type described by Porter et al. (1963).

Fig. 4. Plasma renin activity after allogeneic kidney transplantation correlating urine volume (line), creatinine clearance (dotted line), blood pressure, urinary excretion of sodium, prednisone administration, blood volume, serum sodium, and clinical rejection. RT = renal transplantation; R = rejection; BN = bilateral nephrectomy. Note change in scale after 20 days.
Several factors can be conducive to renin secretion in the transplanted kidney. A drop in blood flow during rejection (Kountz et al., 1963), and especially in cortical blood flow (Retik et al., 1967) might be able to stimulate renin secretion through renal baroreceptors. The occurrence of intrarenal arterial stenoses without apparent rejection, could have the same effect. It is also possible that a direct immunological attack on the juxtaglomerular cells can cause an increased renin release. If rapid methods for renin determination are developed in the future, it is possible that repeated determinations of plasma renin activity could be useful in the early detection of rejection.

Summary

Plasma renin activity was studied in uremic patients before bilateral nephrectomy or kidney transplantation, after bilateral nephrectomy and after allogeneic kidney transplantation. Only three of ten uremic patients had elevated values before bilateral nephrectomy in spite of severe hypertension in eight. After bilateral nephrectomy renin activity was not demonstrable in five cases of nine, while in four low values were recorded. Disappearance of renin activity after bilateral nephrectomy was more rapid with high initial values than with low. Serial determinations immediately following revascularization at renal transplantation showed renin activity in the blood, the degree of which seemed to be related to the length of the ischemic time. In the later course following transplantation a striking correlation was observed between increase of renin activity in plasma and occurrence of clinical rejection.

REFERENCES


DEMONSTRATIONS