Plasma Renin Activity (PRA) in 89 Patients on Regular Haemodialysis

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It is now widely accepted that haemodialysis will control hypertension in the majority of patients with end stage chronic renal failure (Brown et al, 1971). However, to obtain stable control the progressive ultrafiltration engendered by adequate dialysis must be accompanied by dietary sodium restriction and the restoration of positive nitrogen balance. By applying these principles it has been possible at The Royal Free Hospital to control blood pressure without the need to prescribe antihypertensive drugs (Moorhead et al, 1969).

Other renal units have reported the need to use hypotensive drugs and to resort to bilateral nephrectomy, in selected patients, in order to achieve blood pressure control (Schupak et al, 1963; Seto et al, 1963; Toussaint et al, 1966; Onesti et al, 1968; Gleadle et al, 1969; Vertes et al, 1969; Wilkinson et al, 1970). In 1971 we decided to measure plasma renin activity (PRA) in all our patients on the regular haemodialysis programme. The purpose of this study was to attempt to answer the following questions:

a) Does a single PRA measurement accurately reflect the degree of blood pressure control?

b) Can continual haemodialysis overcome the effect of excess circulating angiotensin on blood pressure and thereby obviate the need to perform bilateral nephrectomy?

c) Do the kidneys of patients on regular dialysis treatment for many years lose the ability to secrete renin?

PATIENTS AND METHODS

Eighty-nine out of a total of 94 patients on maintenance haemodialysis were studied. Of the 5 patients not examined, 2 were recovering from a failed transplant, 1 was a child of 6 years, and 2 declined to cooperate. Seventy of the patients dialysed in the home, and of the 19 hospital based patients, 5 were in training for home dialysis. The duration of regular haemodialysis ranged from 1 to 100 months, with a mean of 35 months.
The criteria used for selection of patients for regular haemodialysis has been described previously (Moorhead et al, 1969) as has the technique of dialysis (Baillod, 1971). In brief, patients upon entering the haemodialysis programme cease all antihypertensive drugs and commence daily periods of short (4-6 hours) dialysis using a Kiil kidney with cuprophan membrane. As most patients are hypertensive (94% in the present study), excess salt and water is removed by a process of ultrafiltration and rigid restriction of salt and water intake between dialyses. A diet providing at least 50 grams of protein and 4,000 calories is prescribed to ensure restoration of positive nitrogen balance. Weight loss is a common finding during the first weeks of dialysis, but once hypertension and fluid overload have been corrected, ultrafiltration is reduced and thereafter most patients gain weight.

All patients were examined in the morning after having fasted from midnight the previous day. The length of time post dialysis ranged from 16-28 hours. Blood samples for plasma renin assay were taken from either the arterial end of a Quinton-Scribner shunt, or from a Cimino-Brescia fistula after the patients had lain supine for one hour. Plasma renin activity was measured using a modification of the radioimmunoassay for Angiotensin I of Haber et al (1969). The percent standard deviation for 'within assay' variability was 6% and 'between assay' 12%. The normal range in our laboratory for the supine position with varying sodium intake is 0.28-2.62 ng/ml/hr (Table I).

Table I. Plasma renin activity (ng/ml/hr) in 13 normal volunteers

| Posture | Supine     |  | Erect      |  |
|---------|------------|  |------------|  |
|         | NORMAL     |  | NORMAL     |  |
| Mean    | 0.94       |  | 1.79       |  |
| SE      | 0.18       |  | 0.19       |  |

(Range: 0.28 - 2.62) (Range: 0.47 - 7.56)

*10 mM of sodium and 55 mM of potassium allowed per day

The 89 patients were subdivided into groups according to the ease of control of blood pressure. As none of the patients was receiving antihypertensive drugs, blood pressure control was assessed by using the following data:

1 Monthly averages of predialysis blood pressure. These were recorded by the nursing staff in the hospital based patients, or by the patient if dialysing at home.
2 Measurement of left ventricular voltage in electrocardiograms performed
on the day that blood was taken for PRA assay and prior to that date.

Good control meant that diastolic blood pressure was consistently below 90 mm Hg, and the ECGs showed no evidence of left ventricular hypertrophy. (Sum of deepest S wave in lead V1 or V2 and tallest R wave in lead V5 or V6, not greater than 35 mm — Friedberg, 1966).

CATEGORIES USED

Group A: Blood pressure easy to control from the outset
Group B: Blood pressure difficult to control at first, but now easy
Group C: Blood pressure not well controlled.

RESULTS

Group A in which blood pressure control was never a problem contained 52 patients — 58% of the total patients studied. Group B, those patients in whom blood pressure at first was difficult to control, but later became easy, was made up of 21 patients — 24% of the total patients studied. Thus, good control was achieved in 82% of all patients.

Table II. Allocation of patients according to blood pressure control and PRA

<table>
<thead>
<tr>
<th>Group</th>
<th>Total number in each group</th>
<th>Plasma renin activity (PRA)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;2.6</td>
</tr>
<tr>
<td>A</td>
<td>52</td>
<td>44 (85%)</td>
</tr>
<tr>
<td>B</td>
<td>21</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>C</td>
<td>16</td>
<td>12 (75%)</td>
</tr>
</tbody>
</table>

*results expressed in ng/ml/hr

Table II shows the allocation of patients into groups according to blood pressure control and PRA. There is no significant difference between the proportion of patients with elevated PRA in groups A and C (15% and 25% respectively; p >0.5). The proportion of patients with raised PRA in group B (43%) is significantly greater than that in group A (chi square 7.56; p>0.05), but not group C (p>0.5).

Group B has the highest percentage of patients who entered the dialysis programme with accelerated (malignant) hypertension (Table III). Of the 26 patients who presented with malignant hypertension, 7 now have elevated PRA and of these patients, 6 are in group B. Also in group B, 6 of the 9 patients with elevated PRA (66%) presented with malignant hypertension.

Table IV lists the clinical details of patients who have been on mainten-
Table III. Patients presenting with malignant hypertension

<table>
<thead>
<tr>
<th>Group</th>
<th>Number with normal PRA</th>
<th>Number with high PRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9 (20%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>B</td>
<td>5 (42%)</td>
<td>1 (67%)</td>
</tr>
<tr>
<td>C</td>
<td>5 (42%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table IV. Clinical details of 15 patients on dialysis for > 5 years

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Months on dialysis</th>
<th>PRA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RH</td>
<td>60/F</td>
<td>GN</td>
<td>61</td>
<td>0.79</td>
</tr>
<tr>
<td>JW</td>
<td>50/M</td>
<td>GN</td>
<td>66</td>
<td>3.25</td>
</tr>
<tr>
<td>KS</td>
<td>40/M</td>
<td>PN</td>
<td>69</td>
<td>1.42</td>
</tr>
<tr>
<td>PW</td>
<td>42/F</td>
<td>GN</td>
<td>75</td>
<td>1.44</td>
</tr>
<tr>
<td>HM</td>
<td>42/M</td>
<td>PN</td>
<td>76</td>
<td>0.60</td>
</tr>
<tr>
<td>DM</td>
<td>31/M</td>
<td>PN</td>
<td>77</td>
<td>6.09†</td>
</tr>
<tr>
<td>AW</td>
<td>39/F</td>
<td>PN</td>
<td>79</td>
<td>1.85</td>
</tr>
<tr>
<td>HR</td>
<td>31/F</td>
<td>GN</td>
<td>80</td>
<td>0.97</td>
</tr>
<tr>
<td>MS</td>
<td>26/M</td>
<td>PN</td>
<td>80</td>
<td>1.89</td>
</tr>
<tr>
<td>RB</td>
<td>44/M</td>
<td>GN</td>
<td>84</td>
<td>1.06</td>
</tr>
<tr>
<td>KH</td>
<td>40/M</td>
<td>GN</td>
<td>87</td>
<td>1.67</td>
</tr>
<tr>
<td>BC</td>
<td>38/M</td>
<td>PN</td>
<td>87</td>
<td>0.56‡</td>
</tr>
<tr>
<td>RJ</td>
<td>42/M</td>
<td>GN</td>
<td>89</td>
<td>0.96</td>
</tr>
<tr>
<td>RB</td>
<td>30/M</td>
<td>GN</td>
<td>91</td>
<td>1.25</td>
</tr>
<tr>
<td>RE</td>
<td>30/M</td>
<td>GN</td>
<td>100</td>
<td>1.09</td>
</tr>
</tbody>
</table>

* ng/ml/hr  
† highest value  
‡ lowest value

ance dialysis for longer than 5 years. Results for PRA range from 0.56 to 6.09 ng/ml/hr (normal range 0.28 to 2.62 ng/ml/hr). The PRA levels in the group as a whole are not significantly different from those of the other 74 patients (p > 0.5).

DISCUSSION

In the majority of patients in the present study, the blood pressure is well controlled by haemodialysis. Recent reviews by Ledingham (1971) and Brown et al (1971) agree that this is the experience of most dialysis centres. However, the minority (those with poor blood pressure control) are not similar to patients with uncontrollable hypertension described by other units in that only 4 of the 16 patients with continued hypertension have raised PRA and only in 1 of these is PRA markedly elevated. Plasma levels of renin, renin activity and Angiotensin II are increased in practically all patients with uncontrollable hypertension reported from other dialysis centres (Toussaint et al, 1966; Onesti et al, 1971).

The reasons for the failure to control blood pressure adequately in these patients are complex but include poor physical tolerance of a lower blood pressure, poor insight into their condition and denial of the seriousness of their illness. All these factors may lead to an excess intake of salt and water between dialyses.

The good blood pressure control in group A contrasts with the poor control in group C. Yet both groups have similar percentages of patients with elevated PRA. Hence, an isolated PRA estimation does not accurately reflect the degree of blood pressure control. This conclusion is reinforced by the results in 9 patients in group B. These patients now have well controlled blood pressure and high levels of PRA.

Perhaps the most interesting group of the three is group B. All of these patients were hypertensive on entering the dialysis programme, 52% with malignant hypertension. In all patients, blood pressure was uncontrollable for the first four months of dialysis or longer. Predialysis diastolic blood pressure readings are now regularly below 90 mm Hg. Also, all the patients have recent electrocardiographs which show either normal left ventricular voltages or a substantial reduction in voltage. Despite evidence of good blood pressure control, 9 patients in this group (43%) have elevated PRA and of these patients with elevated PRA, 6 presented with malignant hypertension. This indicates the severity of the initial hypertension in this group of patients.

As serial determinations of PRA were not carried out, it is not possible to state categorically that since commencing haemodialysis the PRA levels in these 9 patients have always been elevated. This appears likely to have been so in view of the high percentage presenting with malignant hypertension. Plasma levels of renin and angiotensin are usually raised in malignant hypertension, particularly when renal disease is the cause (Brown et al, 1971). Vertes et al (1969) measured plasma renin levels in his patients prior to commencing dialysis and again when the patients had reached 'dry weight'. He found that plasma renin levels remained high in all cases. It seems likely then that persistent haemodialysis can overcome the effect of excess circulating angiotensin on blood pressure and that it is not always necessary to remove the source of renin production to achieve blood pressure control.

The Lancet (1971) queried whether persistent intensive dialysis might destroy the pressor activity of the kidneys. This concept of 'autonephrec-
tomy' had been proposed earlier by Hampers et al (1967) and Eady (1971).

The present study did not lend support to this concept of 'autonephrectomy', as all patients who have been on maintenance dialysis for longer than 5 years have levels of PRA greater than the lower limit of the normal range found in our laboratory.

SUMMARY OF RESULTS

1. No correlation was found between blood pressure control and the level of plasma renin activity.
2. Persistent haemodialysis can overcome the effect of excess circulating angiotensin on blood pressure.
3. The kidneys of patients on regular haemodialysis for many years do not lose the ability to secrete renin.

ACKNOWLEDGMENTS

This work was supported by the Pennwalt Corporation (USA), the Peter Samuel Trust, and The Royal Free Hospital Endowment Funds.

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OPEN DISCUSSION

P MICHIelsen (Leuven, Chairman): Dr Weidmann’s and Dr Craswell’s papers are related at least in some respects and I suggest that we discuss both papers together.

WEIDMANN: Well, I have many questions. Dr Craswell certainly shows a rather different distribution of renin and a different relationship between renin and blood pressure in haemodialysis patients from that which a number of other groups, among them our own, have shown in the last few years. I would like to ask when the blood samples were usually taken: were they taken after dialysis, or one day or two days after dialysis?

CRASWELL: The blood samples were taken under standard conditions in all patients. The patients had dialysed 16–28 hours previously and the blood samples were taken after each patient had lain supine for one hour. We did however try to look at the other variables, as everyone knows: we measured plasma sodium and plasma potassium; we arranged for our dietician to estimate the sodium intake on the day prior to the blood sampling. We have this data and we have looked at it individually, as against plasma renin activity, as against blood pressure and found no correlation. We are going to put the data into a computer using a quadric analysis, but unfortunately I haven’t got the results just yet.

WEIDMANN: Well, I think one of the differences may be that we always take the renin samples after one hour in the supine position, always immediately prior to a haemodialysis which would mean that possibly at least some of our patients would be in a somewhat more hydrated state than some of your patients, because you draw the blood samples between the dialyses.

CRASWELL: Most of these patients are dialysing three times a week. I don’t really think that this would really be a difference.

WEIDMANN: It has been shown that haemodialysis can increase plasma renin activity with fluid removal.
CRASWELL: Yes, but not 16-28 hours after — by this time I think there is a state of reasonable equilibrium.

MICHEILESEN: It seems difficult to come to a general agreement between the two speakers. Dr Craswell, have you another question to put to Dr Weidmann?

CRASWELL: I think if anyone reads the literature on renin and hypertension over the past twenty years there has been a dichotomy of results on blood pressure. There have been units right from the start of haemodialysis in the early 1960s who obtained good blood pressure control with patients, for example Scribner. Other units were having major problems with hypertension. Then from about 1965 onwards everything seemed to settle down, and in the units who were having major problems with hypertension the problems became less. But then over the last five years up to 1972, most units have come to accept that there are a few patients who require bilateral nephrectomy for control of hypertension. In our unit, we have had one patient only who has required bilateral nephrectomy for control of hypertension. I think it may relate to the fact that our dialysis techniques may differ in some way. Our patients, when they start dialysis, commence daily dialysis using relatively short periods of 4-6 hours and there is none of the urgency to control their hypertension that perhaps is present in other units.

WEIDMANN: Perhaps, Dr Craswell, one other difference I should maybe mention is that in Los Angeles we have a majority of black patients and, as you know, these patients have very severe, extremely malignant forms of hypertension. Many of our patients actually had malignant hypertension leading to acute anuric renal failure of very short course, and most of these patients have extremely elevated renin levels, not moderately above the normal limit, but 10, 20, 30 or even 50 times normal. I think that my impression of the four or five nephrology groups which differ is that in the cases studied there was really no possibility, in the first few months of haemodialysis, of achieving a decent control of blood pressure. In each case bilateral nephrectomy brought benefit as evaluated by careful comparison of pre- and post-nephrectomy blood pressure and weight levels.

CRASWELL: I think you must admit that where it is possible not to remove the kidneys in patients on haemodialysis, that this is important.

MICHEILESEN: It will depend also on what you call uncontrollable hypertension. You can bring down nearly every hypertension if you dialyse enough, but the problem is to know if the patient is in a better condition if you take the kidneys out, then if you leave the kidneys in. I am not quite sure that we yet have a
definite answer to this question, but there are many people who want to ask
questions from the audience.

J LEDINGHAM (Oxford): Dr Craswell, I think one of the problems with renin
assays is a difficulty in standardising technique. I understand you use a modi-
fication of Haber's technique for Angiotensin by using radio immunoassay. I
think that your results are really so extraordinary in the light of the literature
that it might be a good thing if we knew whether you have validated the tech-
nique that you used. It is not an easy one to be sure that you are getting it
right. I would be very surprised if you have a group of hypertensives who
are difficult to control, and therefore on a low sodium diet and ultrafiltration
but whose plasma renin levels are not a great deal higher than you report,
even from sodium depletion alone. They are very low by any standards at
10 ng/ml per 3 hours.

CRASWELL: Well, what we used were the kits that are obtainable from
Schwartzmann, Orangeburg, NY, USA. I agree with you that there were
problems; however, each patient's blood sample PRA was estimated twice.
I obtained a coefficient of variation within assays of 6%, and between assays
of 12%, which I think you must agree is reasonable.

WEIDMANN: I would like to mention that for the last six months we have
measured every sample in duplicate by radio immunoassay and using Boucher's
method and find a good correlation between the results.

H J KRAMER (Homburg, Saar): You showed a nice correlation, Dr Weidmann,
between plasma potassium, the degree of hypertension and the plasma renin
and the aldosterone activity. But, since all these patients undergo haemodia-
lysis and ultrafiltration and they lose body weight, I wonder if you have any
data on the plasma sodium, blood volume or extracellular volume which are
very important determinants of aldosterone and renin activity?

WEIDMANN: Did I understand you right that you thought I showed a correla-
tion between potassium and hypertension? I didn't. I did show a correlation
between potassium and aldosterone, and the other slide was the correlation
between renin and aldosterone levels. But to answer your question — we
evaluated carefully the plasma sodium levels and in that relationship too
there was no correlation either with blood pressure or with plasma renin acti-

vity. Furthermore, rather surprisingly, the plasma potassium in all three
groups including those with normal blood pressure and those with so-called
uncontrollable hypertension, was not statistically different.
KRAMER: Have you any data on the extracellular volume changes pre-dialysis?

WEIDMANN: No, we didn't do any space measurements.

K BACZYK (Poznan): Dr Weidmann, your second conclusion seems to be for me, at least, controversial. You have stated that having a normal potassium level, you can use aldosterone levels as a substitute for plasma renin.

WEIDMANN: As an alternative!

BACZYK: But you have patients with terminal renal failure. I think we have to assume that all the patients must have no acid base abnormality because if they have a metabolic acidosis, the potassium levels will be too high. You would then draw false conclusions, so I think besides your assumptions about a normal potassium level, it would be very helpful to know that there was no abnormality in the acid base equilibrium.

WEIDMANN: Well, I think it would be nice to measure acid base balance also. However, we only say from the clinical viewpoint that in these cases with normal potassium there is minimal overlap. I think, to be reasonable, we wouldn't use aldosterone as an additional index to help make the decision for or against nephrectomy unless the patient had a clearly elevated renin level — not moderately, like two or three times, but ten or twenty times as in the cases I showed.

DOTTI (Italy): I should like to ask Dr Craswell whether he controlled the pH of plasma before the assay, taking into account that if you use the method of Haber that the plasma renin activity changes, if you measure it at a different pH. I should like to know at what kind of pH you performed the 3 hours incubation. Have you changed it, corrected it, or have you left it after storage?

CRASWELL: The pH is round about 7, I did not control it — that is I did not measure the pH of the actual plasma samples. The buffers that we used were at pH 7. Does that answer your question?

DOTTI: I didn't say the buffer you have used during the actual assay itself, I meant the pH of plasma during the 3 hours incubation.

CRASWELL: This was not controlled in the sense that I used the Haber's method. Other workers have reported that if you do lower the pH of the plasma, you do get higher PRA results over three hours. Haber's method is supposed to be at a pH of 7, but he didn't control it and I didn't control it.