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EFFECT OF RESIDUAL RENAL FUNCTION
ON MINIMUM DIALYSIS REQUIREMENTS

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Summary

In two groups of haemodialysis patients, the effect of residual renal function (RRF) on motor nerve conduction velocity (MNCV) was prospectively studied. Patients belonging to Group I had stable GFR of > 1 ml/min while Group II patients had gradually declining GFR. As a result, the dialysis index for middle molecules, $D_I(MM)$, remained above 1.0 in Group I despite dialysis schedules as short as 6 hr/wk. $D_I(MM)$ in Group II fell gradually below 1.0 as renal function deteriorated on equally short dialysis schedules. None of the five patients in Group I developed neuropathy during 1.2—4.1 years of reduced dialysis. However, all four patients belonging to Group II developed significant ($p < .01$) slowing of MNCV when their GFR declined below 0.5 ml/min. Neuropathy in this group was arrested or reversed by increasing $D_I(MM)$. It is, therefore, proposed that residual renal function is a major determinant of dialysis requirements.

Introduction

In 1974, we postulated that seemingly insignificant levels of RRF (GFR 1—3 ml/min) might prevent uraemic neuropathy by the removal of significant amounts of middle molecules, (MM) [1]. This postulate explained why one of our three original dialysis patients, who maintained a GFR > 1.0, failed to develop neuropathy despite totally inadequate amounts of dialysis [2].

In order to test this theory prospectively, we selected two groups of stable chronic dialysis patients. In one group, all of whom had stable GFRs >1.0ml/min, dialysis time was reduced in proportion to their residual GFR without apparent ill effect. In a second group, when dialysis time was similarly reduced in the face of declining GFR, neuropathy developed and was reversed by increasing MM clearance.
Patients and Methods

In this study, weekly dialysis times were determined by calculation of the \( D_f(MM) \) [3]. RRF (GFR) was measured at least every three months using a creatinine clearance method [4].

The patients studied were selected as follows: 1) clinically stable on thrice-weekly haemodialysis for a minimum of three months; 2) without severe hypertension, diabetes, cardiovascular disease, or requiring blood transfusions; 3) free of neuropathy, with stable peroneal nerve conduction velocities greater than 35 m/sec and an M response with adequate wave form characteristics to measure accurately the take-off point. The patients selected were divided into two groups: Group I consisted of five patients with stable GFR of greater than 1 ml/min (mean 3.2). During the induction phase, the dialysis time of these patients was reduced each week to a minimum while still maintaining a \( D_f(MM) \) > 1.0. Group II consisted of four patients with a GFR of < 1.3 ml/min and gradually declining at the start of the study. The dialysis time in this group also was shortened to achieve a \( D_f(MM) \) about equal to 1.0. Thereafter, the shortened dialysis time was maintained despite a declining GFR. When motor nerve conduction velocity (MNCV) was significantly reduced, a recovery phase (\( D_f(MM) > 1.0 \)) was initiated by either increasing the dialysis time or using a dialyser with high permeability to MM. MNCV was measured using a TECA model electromyograph. Both peroneal nerves were measured every seven to 21 days. Induction of neuropathy was defined as a statistically significant negative slope of the regression line of MNCV on time at \( p < 0.01 \) in both peroneal nerves.

Results

In Group I patients, dialysis time was reduced from 12–24 hr/wk (mean 16.4 hrs) to 5–9.0 hr/wk (mean 6.7) for a period of 1.2–4.1 years. Despite a slight elevation in serum creatinine and SUN (Table I), these patients remained well without any complications; dry weight was maintained and blood pressure and haematocrit did not change. Despite marked reduction (70%) in dialysis time, the MNCV did not decline in this group (Figure 1). In a sixth patient, GFR declined below 1 ml/min during the study and the patient developed a reduction in MNCV. This patient's course has been depicted separately in Figure 2.

With similar reduction in dialysis time, patients in Group II lost FFR over time resulting in a fall in \( D_f(MM) \). This group developed significant reduction in MNCV (Table I and Figure 1). One patient also developed sensory symptoms and temporarily lost ankle jerks. Increasing \( D_f(MM) \) to > 1, by switching to dialysis membranes highly permeable to middle molecules, caused improvement in MNCV in three patients and stabilisation of MNCV in the fourth patient.
TABLE I. Values on Five Patients with Stable GFR and Four Patients with Declining GFR

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 5)</th>
<th></th>
<th>Group II (n = 4)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Induction</td>
<td>Control</td>
<td>Induction</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>-0.7 ± 0.2*</td>
<td>2.3 ± 0.4</td>
<td>-0.6 ± 0</td>
<td>0.5–1.4</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>3.3 ± 0.6</td>
<td>2.6 ± 0.5</td>
<td>0.8 ± 0.2</td>
<td>0.17 ± 0.6</td>
</tr>
<tr>
<td>Dialysis time (hr/wk)</td>
<td>16.8 ± 2.2</td>
<td>6.5 ± 0.7</td>
<td>18.3 ± 0.9</td>
<td>10.2 ± 2.1</td>
</tr>
<tr>
<td>Dialysis Index (MM)</td>
<td>1.9 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>1.1 ± 0.02</td>
<td>0.7 ± 0.03</td>
</tr>
<tr>
<td>Serum creat. (mg/dl)</td>
<td>10.1 ± 1.1</td>
<td>13.4 ± 1.4</td>
<td>13.0 ± 1.0</td>
<td>15.5 ± 1.0</td>
</tr>
<tr>
<td>SUN (mg/dl)</td>
<td>67 ± 8.1</td>
<td>99.6 ± 5.5</td>
<td>82.6 ± 17.1</td>
<td>111.6 ± 13.3</td>
</tr>
<tr>
<td>Slope of MNCV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>↓, p&lt;0.01</td>
</tr>
</tbody>
</table>

* ± S.E.M.

Control period  –  Prior to study
Induction period –  Study period with reduced dialysis time
Recovery period  –  Study period with readjusted dialysis time

Discussion

Both groups in our study received the same shortening of dialysis hours; one group developed neuropathy while the other group did not. Loss of RRF was the only major difference between the two groups. In Group I, whose average dialysis time was shorter than Group II, residual GFR of greater than 1.0 ml/min maintained the $D_1$ (MM) $> 1.0$ and, therefore, provided enough clearance of middle molecules to prevent neuropathy. In contrast, the four patients of Group II lost their RRF and the removal of MM by the patients' own kidneys was sharply curtailed, resulting in a drop of $D_1$ (MM) to a value below one, with resultant neuropathy. This deterioration was stabilised and later reversed by increasing the $D_1$ (MM) to a value above one. The $D_1$ concept assumes that clearance of MM by the native kidney is at least equal to the GFR. This assumption has been confirmed by Fürst et al [5].

The results reported here provide additional support for the middle molecule hypothesis. This hypothesis states that substances in the molecular weight range 500–2000 daltons/molecule are uraemic neurotoxins. However, as in our earlier report [6], the synergistic role of elevated small molecule levels cannot be excluded. Several points bear on this issue:

1. During recovery in the four subjects (Table I, Figure 1), decreases in the levels of small molecules are of the order of 20%, whereas decreases in the predicted levels of MM are of the order of 70%, as calculated from $D_1$.  

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Figure 1. Effect of RRF on MNCV in two groups of patients. Despite similar dialysis clearance as GFR declined in Group II (●–●), the $D_1(MM)$ as well as MNCV declined. In Group I (○—○) the GFR, $D_1(MM)$, and MNCV remained unchanged.

2. Three patients of Group I had $D_1$ for creatinine (small molecule) below one with a $D_1(MM) > 1$ and none of these patients showed reduction in MNCV (Figure 2), whereas the patient belonging to Group I who had a reduction in his GFR, had a reduction in MNCV associated with $D_1(MM) < 1$, despite a $D_1$ for creatinine of $> 1$ (Figure 2).

3. Bergström et al [7] reported on 12 patients with severe renal insufficiency treated conservatively by a low protein diet which stabilised or improved MNCV. In these studies, the average BUN and serum creatinine (20–25mg/dl) levels exceeded those seen in our four patients. At the same time, we can assume that Bergström’s patients had sufficient RRF to maintain life without dialysis and, therefore, had good MM clearance by their own kidneys. Bergström’s results,
Figure 2. In three patients with stable GFR (o—o) the $D_f(MM)$ remained greater than one and no slowing of MNCV was noted despite $D_f(creat.)$ (small molecule) declining below one. In another patient (●—●), as $D_f(MM)$ declined below one, the reduction in MNCV was noted despite $D_f(creat.)$ remaining above one.

Together with those reported in this study, tend to exclude the possibility that elevations of small molecules alone will cause a decrease in MNCV.

Two additional studies provide support for the middle molecule hypothesis and the importance of RRF in middle molecule removal. Kiley [8] has reported that when RRF drops below one ml/min and $D_f(MM) < 1$, there is a deterioration in the E.E.G. This effect is reversed by increasing dialysis time to give a $D_f(MM) > 1.0$.

In a group of patients on chronic peritoneal dialysis [9], as RRF declined, the calculated dialysis time to achieve a $D_f$ of one for MM markedly increased. After RRF had dropped below 1.8 ml/min, the actual dialysis provided to
patients continuously lagged behind the calculated dialysis requirements, resulting in underdialysis and requiring conversion to haemodialysis.

As discussed elsewhere in this volume [10], RRF must be factored into the research on dialysis technique. For example, the only theoretical advantage of haemofiltration over haemodialysis is increased clearance of MM. Most studies which compare haemodialysis with haemofiltration have been carried out on subjects with RRF > 2.0 ml/min. Since this amount of RRF is nearly sufficient to control MM levels without any dialysis, it would be difficult to demonstrate significant benefit from switching from haemodialysis to haemofiltration. Quite clearly, such studies should be repeated using anuric subjects.

We conclude with a word of caution. If the clinician chooses to reduce weekly dialysis time in his patients with stable residual GFR < 1.0, several precautions are advisable:

1. Use potassium-free dialysate.
2. Increase dose of phosphate binders.
4. In the case of intercurrent illness, the dialysis time must be increased temporarily until the condition again stabilises.
5. As the patient's GFR decreases with time, appropriate increments in dialysis time will be required in order to avoid the development of neuropathy and possibly other complications of underdialysis. The dialysis index facilitates this decision. A nomogram for calculating this index is available [12].

Acknowledgments

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References

Open Discussion

OREOPOULOS (Toronto) The last graph you showed referred only to patients on intermittent peritoneal dialysis (PD). Most of these patients can be converted to CAPD and stay on PD for long periods. Have you noticed any difference between patients maintained on haemodialysis or peritoneal dialysis?

SCRIBNER Absolutely right. These are all patients on regular thrice weekly peritoneal dialysis. The effect of loss of renal function on CAPD must be determined in the future. I am hopeful that it will not be as bad as I have shown for regular peritoneal dialysis.

GOTCH (San Francisco) You quoted a lot of non specific data, supporting the concept of middle molecules in residual renal function. I am wondering what you think these materials might be, now that Bergström and Furst have shown that there is no difference in the clearance of the highest flux membranes namely the PAN membranes and Cuprophan, that none of those materials that can be biologically measured correlate with the dialysis index and that the correlation between excretion of these materials and residual renal function is really a pretty loose correlation. I am wondering what you think you are actually modelling now with the dialysis index in view of these measurements on the only identified biological compounds of this type?

SCRIBNER Well we presume we are modelling substances that are cleared at least as well as the GFR and unless you know something I do not know, I believe that it is still the case. Did you say that the substances that Bergström and Furst are finding have clearances less than GFR?

GOTCH No I said that the correlation is a very loose one. You can get a correlation coefficient of 0.8, but if you try to relate that and get a confidence band on it, it is a very broad confidence band. But even more troublesome is the clearance of the PAN membrane and Cuprophan being the same for peak 7–C. You know they give the same number, and the Cordis Dow model 5 which has a thick membrane has the highest clearance for peak 7–C. So the biological material now available, just doesn’t fit with the concept of a measurable toxic middle molecule.

SCRIBNER O.K. I’ll have to accept that.

ZAZGORNIK (Vienna) How was the frequency of hypertension in patients with residual renal function compared with those with oligo-anuria?

SCRIBNER I cannot answer that, except to say that it is usual that patients with residual renal function excrete quite a bit of sodium, and I would guess the hypertension is better in that group. I cannot answer it positively.

BERGSTROM (Stockholm) As a comment to Dr Frank Gotch, I would like to
point out that our clearance data comparing cuprophan and PAN membranes were obtained only with one middle molecule fraction, peak 7–C and that the methodological difficulties were considerable. We now know that our middle molecule fraction contains at least 12 different peptides, and we do not have any clearance data for most of them; I can mention that we have seen a negative correlation between plasma concentration and dialysis index for some of these fractions, but not for others.