THE SIGNIFICANCE OF DISEQUILIBRIUM BETWEEN BODY COMPARTMENTS IN THE TREATMENT OF CHRONIC RENAL FAILURE BY HAEMODIALYSIS

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Introduction

Regular haemodialysis for chronic renal failure (CRF) is usually carried out for 24–30 hours per week at a urea dialysance of 50–100 ml/min. Faster dialysis has been possible from the start but only through the use of dialysers with high priming volume, wash-in volume and ultrafiltration rate. The side effects of fast dialysis with such dialysers may be more the result of blood volume changes and transfusion reactions than of the speed of removal of solute (Kerr et al., 1966). Recently, however, advances in dialyser design have made possible either an increase in speed of dialysis at a priming volume currently regarded as acceptable or a reduction in priming volume at present rates of dialysis. Both of these propositions are attractive and before choosing between them we need to know how far it is worthwhile increasing dialyser performance.

The blood flow available from the standard A-V shunts and the red cell effect (Grossman et al., 1967) limit the urea dialysance attainable with any dialyser to about 250 ml/min. Theoretical studies (Frost, 1968) show that improvements in dialyser performance up to this point would result in a worthwhile reduction in dialysing time of the order of 70%, provided that the human subject behaved like a single well mixed pool of fluid (Fig. 1). This 'single

![Graph showing variation of treatment time with dialyser standard for a given diet—single pool.](image-url)
pool' model of the human has been used in most published studies of urea dynamics during dialysis but it is known to be an extreme oversimplification. In practice blood urea falls faster during dialysis than would be predicted from a single pool model and it rebounds in the early post-dialysis period (Elliott et al., 1961).

A more accurate representation of the human during dialysis is shown in Figure 2a. In the case of urea the position is further complicated since urea production occurs in only one part of the intracellular pool and it is removed by renal excretion and extrarenal degradation as well as through the artificial kidney. However, Bell et al. (1965) suggested that the human could be represented reasonably accurately by a two-pool model (Fig. 2b) and on this basis they were able to fit observed events during and between dialyses surprisingly closely to the prediction using an analog computer. This simplification takes account of the fact that in patients on RDT renal excretion of urea is negligible and both production and extrarenal removal are small in relation to the rate of removal by the dialyser. It also presupposes that mixing is rapid throughout the extracellular compartment with a negligible delay at the capillary wall, that the main diffusional block is at cell walls and that the whole mass of heterogeneous cells in the body acting together can be represented by a single large cell with a membrane behaving like that of the dialyser. Such assumptions could of course only be made in the case of readily diffusible molecules such as urea and creatinine which are not actively transported across cell boundaries.

![Diagram](image)

Fig. 2. Three models of the patient during haemodialysis: (a) three-pool, (b) two-pool and (c) one-pool.

If this model of the human is realistic, the cell wall barrier will have two important effects in limiting fast dialysis: (a) it will cause the rapid fall and rebound in blood urea already alluded to, and will thereby limit total removal; (b) it will generate an osmotic disequilibrium between ICF and ECF as blood urea falls. This phenomenon is the generally accepted cause of the 'disequilibrium syndrome' associated with fast dialysis in acute renal failure (Kennedy et al., 1964). The first effect (a) will apply to all solutes distributed through ICF and ECF.
while the second \(b\) will be important only in the case of small molecules present in high concentration, notably urea and sodium.

In this study we have set out to test Bell’s two-pool hypothesis and to find the magnitude of these two effects in relation to urea by a detailed analysis of the rebound phase.

**METHODS**

Studies were performed on eight patients with chronic renal failure. Total body water was measured with tritiated water while as a measure of extracellular volume we used bromine, measured with Br\(^{82}\). The corrections for trapping by red cells and for chloride shift were assumed to be the same in the uraemic as in the normal subject.

The day after these estimates were completed, haemodialysis was carried out using coil dialysers with urea dialysance from 90 to 200 ml/min., at constant blood flow. Repeated estimates of blood urea and coil dialysance were carried out through the dialysis. For the last half hour of dialysis and the subsequent 1.5 hours (which included the post-dialysis rebound), arterial blood urea was continuously monitored with a Technicon autoanalyser which was connected by a 1 mm sampling tube to the arterial side of the A-V shunt. Intermittent samples were drawn over the subsequent 12–18 hours to estimate the steady production rate.

![Fig. 3. Continuous monitoring of blood urea during and after haemodialysis.](image)

An autoanalyser write-out is shown in Figure 3; it illustrates the urea rebound immediately after dialysis. The periodic slight fluctuation in the trace was at first thought to be a patient phenomenon but was subsequently found to be due to temperature cycling of the constant temperature bath of the autoanalyser.

**RESULTS**

**a. Body spaces**

The age, sex, body weight, TBW and ECF volumes of the patients are shown in Table I. Most of the patients on RDT were studied early in their career of dialysis; their results are similar to those reported by Comty (1967) in patients at the start of RDT.

**b. Analysis of blood urea levels**

The trace was first smoothed and converted into a direct blood urea concentration vs. time graph (Fig. 4, bottom curve) showing more clearly the three distinct periods of dialysis, rebound and steady production.

During this rebound phase the change in blood urea is the result of \(a\) urea production which is assumed to be the same as that estimated from the blood urea graph after a steady state has been reached and \(b\) the rate of re-equilibration between the ICF and ECF which is determined by the urea ‘dialysance’ of the cell wall KC.

The points for the rebound phase can be replotted against time in such a way that they
TABLE I
Data for CRF patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>TBW* (litres)</th>
<th>ECF** (litres)</th>
<th>%TBW weight</th>
<th>%ECF TBW</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EH</td>
<td>35</td>
<td>37.1</td>
<td>24.8</td>
<td>14.8</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>MJ</td>
<td>30</td>
<td>54.4</td>
<td>35.7</td>
<td>16.9</td>
<td>66</td>
<td>47</td>
</tr>
<tr>
<td>MP</td>
<td>16</td>
<td>32.4</td>
<td>18.0</td>
<td>11.6</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td>KP</td>
<td>29</td>
<td>60.2</td>
<td>32.9</td>
<td>17.6</td>
<td>55</td>
<td>54</td>
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<tr>
<td>Average of 4 females</td>
<td></td>
<td>46.1</td>
<td>27.9</td>
<td>15.2</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td>Average normal***</td>
<td></td>
<td>46.1</td>
<td>23.0</td>
<td>9.7</td>
<td>50</td>
<td>42</td>
</tr>
</tbody>
</table>

b. Males

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>TBW* (litres)</th>
<th>ECF** (litres)</th>
<th>%TBW weight</th>
<th>%ECF TBW</th>
</tr>
</thead>
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<tr>
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<td>77.6</td>
<td>43.6</td>
<td>20.4</td>
<td>56</td>
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<tr>
<td>II</td>
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<td>78.2</td>
<td>38.5</td>
<td>18.1</td>
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<td>47</td>
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<tr>
<td>FSA</td>
<td>44</td>
<td>56.8</td>
<td>38.6</td>
<td>18.5</td>
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<tr>
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<td>70.5</td>
<td>39.4</td>
<td>21.9</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Average of 4 males</td>
<td></td>
<td>70.8</td>
<td>40.0</td>
<td>19.7</td>
<td>57</td>
<td>49</td>
</tr>
<tr>
<td>Average normal***</td>
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<td>70.8</td>
<td>42.4</td>
<td>18.7</td>
<td>60</td>
<td>43</td>
</tr>
</tbody>
</table>

* Columns 3, 4 and 5 have been reduced to one decimal place, 6 and 7 to whole number.
** Measured with tritiated water.
*** Measured with Br**.
**** Of same weight as CRF patients.

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Fig. 4. Variation of pool concentrations during dialysis and immediate post-dialysis period.

K.P.
- D = 158 ml/min.
- KC = 700 ml/min.
- ps = 1.3 mg%/hr
form a straight line, the slope of which is a function of the volumes of the 2 compartments and the urea dialysance KC of the cell membrane (see Section 2, Appendix I).

The value of KC so derived (analysis R) is used to predict the post-dialysis variation in the ICF urea concentration, the concentration difference between the ICF and ECF during steady production being about 0.5 mg%.

In our theory the steady production is assumed to occur in the ICF compartment, an assumption which is open to criticism since urea which is produced in the liver is added to the ECF before it reaches some parts of the ICF. The immediate post-rebound urea production is on average about 2.1 mg%/hour, which is some 25% higher than the pre- and post-dialysis blood urea rise estimated from intermittent sampling.

Having established a value for the cell wall dialysance this value together with the solute production rate (Immediate Post Rebound Value) ICF and ECF volumes, dialysate dialysance and dialysate recirculating volume are now used in a 2 pool model simulation of the patient/dialysate system to predict the variation of ICF and ECF urea concentration during dialysis (Appendix I).

In all cases analysed this gave a lower ICF/ECF concentration difference at the end of dialysis than that predicted from the rebound measurements and a second value of KC is therefore calculated which gives agreement on this criterion as demonstrated on Figure 4 (analysis RD).

![Graph](image)

**Fig. 5.** ICF/ECF membrane urea dialysance as a function of body weight.

The values of KC obtained by these two methods are shown for each patient on Figure 5. The large difference between the two sets of values suggests that either (a) the two pool model is an unrealistic oversimplification of the correct model or (b) our measured spaces do not correspond to the distribution volumes of urea. Since urea space has been shown to correlate well with total body water measured with tritium (Anderson and Robson, 1964; Scholz, 1967) it seems more likely that the ECF distribution, and hence ICF, could be erroneous. Of the 3 standard indicators of extracellular space, bromine gives the largest and insulin the smallest volume. Bell *et al.* did not measure extracellular space but assumed it was 30% of TBW based on patient weight, compared with an average value of 52% for our series using bromine.
Re-analysis of our results indicates that agreement between the two methods of obtaining KC would be obtained if the ECF was reduced arbitrarily to between 15 and 25% of the measured TBW. The level of KC obtained would then be towards the upper level indicated on Figure 5.

Reasonable agreement can also be obtained between measured and predicted plasma urea during dialysis using a reduced ECF volume (Fig. 6) of the same order.

![Graph showing urea concentration over time](image)

**Fig. 6.** Comparison of predicted and measured plasma urea during haemodialysis in one- and two-pool models.

This experience suggests either that the two-pool model may be more realistic if inulin space is used as an index for ECF or alternatively that an arbitrary reduction in the bromide ECF space is an approximate technique for simulating a 3-pool model. We have not yet confirmed either of these postulates experimentally.

c. **Relationship of cell wall dialysance to body size**

It is reasonable to expect that the cell wall dialysance will be related to the surface area of the cells. For simplicity we have used body weight as a measure of body size and obtained trends as expected (Fig. 5). We have taken a mean of the two values for each patient as representing an approximate level of KC. This gives a value of 900 ml/min. for a patient of 60 kg body weight which is about 50% higher than Bell's results.

**IMPLICATIONS IN HAEMODIALYSIS**

Having thus calculated an approximate value for cell wall dialysance we can consider its likely effect on fast dialysis as outlined in the introduction.

**Effect A: Reduced total urea removal.** The total urea removal predicted from the one- and two-pool models can be calculated and compared. The reduction in total removal is proportional to the ratio between dialyser and cell wall dialysance (Fig. 7) and is quite small, e.g. for the average cell wall dialysance in our series (900 ml/min.) and a fast dialyser of 250 ml/min. dialysance, the reduction is less than 2.5% for treatment times of 6 hours or more. This is so small that it will not affect the usefulness of fast dialysers that can be produced in the foreseeable future.
**Fig. 7.** Effect of ICF/ECF membrane on removal of urea during haemodialysis.

**Effect B: Osmotic disequilibrium.** From the theoretical two-pool model we predict that the maximum concentration difference between ICF and ECF occurs during the first hour of dialysis (Fig. 8). This difference expressed as a percentage of the pre-dialysis blood urea concentration correlates with the ratio $D/K_C$ (Fig. 9). Taking representative values of $D = 250 \text{ ml/min.}$ and $K_C = 900 \text{ ml/min.}$ the predicted percentage difference is around 10%, which is equivalent to an osmotic force of about 2 milliosmoles at a pre-dialysis blood urea level of 150 mg%.

The majority of our experiments were performed using a pure recirculation dialysate feed system. The theoretical model predicts that an RSP feed system reduces this maximum

**Fig. 8.** Osmotic disequilibrium between body compartments during haemodialysis. Theoretical two-pool model.
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![Graph showing Maximum ICF-ECF concentration difference](image)

**Fig. 9.** Predicted effect of ICF/ECF membrane on disequilibrium during haemodialysis.

figure of about 10% to about 7.5% under strictly comparable circumstances, owing to the rapid rise in the dialysate urea concentration during the first hour (Frost et al., 1967; Kopp et al., 1967). Other techniques could predictably minimise this osmotic disequilibrium particularly with an RSP system in the initial management of patients with high blood urea levels. How important these osmotic forces will prove to be in practice can only be determined by clinical experiment, preferably with continuous EEG monitoring since these figures are calculated for the whole intracellular compartment and the brain and CSF may well prove to act in a highly individual manner.

CONCLUSIONS

1. The two-pool model of the human, although better than the single pool model, does not fit exactly to events, during and after haemodialysis, if bromide is used as a measure of extracellular space. A better agreement is obtained if ECF is assumed to be considerably smaller. This may indicate that extracellular volume is overestimated by bromide or that a three-pool model (at least) is needed to predict events accurately.

2. Limiting effect of cell wall on total urea removed is unimportant during dialysis, at any urea dialysance which can be obtained with present A-V shunts.

3. In stable chronic renal failure patients, the urea rebound is small, and is of short duration.

4. Osmotic forces can be predicted, and are expected to be small in stable CRF. The clinical significance of these can only be assessed by EEG monitoring during fast dialysis.

5. A similar analysis will be required for each solute of importance in the uraemic syndrome.

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ACKNOWLEDGEMENTS

The authors would like to acknowledge the co-operation of the patients involved in this study and of the staff of The Royal Victoria Infirmary, in particular Professor Farmer, Sister Miller and Mr. Crossley.

Symbols

\begin{itemize}
\item C: pool concentration in mg\%/l
\item V: pool volume in litres
\item t: time in minutes
\item KC: cell wall dialysance in ml/min.
\item D: dialysate dialysance in ml/min.
\item ps: measured solute production rate in the blood in mg%/hour
\item \(\Delta V\): pool volume change in litres/hour
\end{itemize}

Suffices

\begin{itemize}
\item c: intracellular pool
\item b: extracellular pool
\item d: dialysate volume
\item o: start of dialysis
\item t: end of dialysis
\item e: end of rebound
\end{itemize}

REFERENCES


APPENDIX I

Analysis of a two-pool patient/dialyser system during and after dialysis

1. Evaluation of pool concentrations during dialysis (analysis RD)

1.1. Assumptions

1. A pure recirculation dialysate feed system is used with an initial volume of \(V_{do}\).
2. Changes in initial pool volumes \(V_{bo}\) and \(V_{co}\) due to ultrafiltration are assumed to be linear and in proportion to the original ratio of volumes.

Consider change of concentration of the various pools in a small interval of time \(dt\) at time \(t\) from start of dialysis: For the intracellular pool

\[
\frac{dC_e}{dt} = \frac{ps}{60} \left( \frac{V_{bo} + V_{co}}{V_{bo}} \right) + \frac{C_e \Delta V_c}{60} - \left( \frac{C_e}{C_b} \right) \frac{KC}{1000} \left( \frac{KC}{1000} \right) - \frac{V_{co}}{\Delta V_c \times t} \]

(1)

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For the extracellular pool

\[
\frac{dC_b}{dt} = \frac{C_b \times \Delta V_b}{60} + \frac{(C_e - C_b) \times KC}{1000} - \frac{(C_b - C_d) \times D}{1000}
\]

\[\frac{\Delta V_b \times t}{60}\]

For the dialysate pool

\[
\frac{dC_d}{dt} = \frac{C_d \times \Delta V_d}{60} + \frac{(C_b - C_d) \times D}{1000}
\]

\[\frac{\Delta V_d \times t}{60}\]

These equations (1)-(3) were solved to give pool concentrations to any time \( t \) during dialysis by a Runge-Kutta type method on an English Electric KDF9 computer.

2. Evaluation of KC from rebound phase (analysis R)

2.1. Assumptions

1. Pool volumes remain unchanged from values calculated at end of dialysis.

\[i.e. \ V_t = V_0 - \frac{\Delta V \times t}{60}\]

Putting \( D = 0 \), equations (1) and (2) therefore reduce to:

\[
\frac{dC_e}{dt} = \frac{ps}{60} \left( \frac{V_{bo} + V_{eo}}{V_{et}} - (C_e - C_b) \times \frac{KC}{1000} \right)
\]

(4)

\[
\frac{dC_b}{dt} = \frac{(C_e - C_b) \times KC}{V_{bt} \times 1000}
\]

(5)

combining (4) and (5):

\[
\frac{d(C_e - C_b)}{dt} = \frac{ps}{60} \left( \frac{V_{bo} + V_{eo}}{V_{et}} \right) - \frac{K_e (C_e - C_b)}{1000} \left( \frac{1}{V_{et}} + \frac{1}{V_{bt}} \right)
\]

(6)

separating variables and integrating:

\[
-\frac{1000}{KC \left( \frac{1}{V_{et}} + \frac{1}{V_{bt}} \right)} \times \log_e \left\{ \frac{ps}{60} \left( \frac{V_{bo} + V_{eo}}{V_{et}} \right) - \frac{K_e (C_e - C_b)}{1000} \left( \frac{1}{V_{et}} + \frac{1}{V_{bt}} \right) \right\} = t + \text{const.}
\]

\[i.e. \ of \ the \ form: \ m \log_e f = t + \text{constant.} \]

Thus if \( \log_e f \) be plotted against time the points should form a straight line the slope of which is

\[
m = -\frac{1000}{KC \left( \frac{1}{V_{et}} + \frac{1}{V_{bt}} \right)}
\]

(7)

Since \( KC \) occurs in both \( m \) and \( f \) a repetitive calculation is necessary to establish a converged value for \( KC \) as follows:

2.2. Evaluation of \( C_e \)

Experimentally when \( \frac{dC_b}{dt} \) attains a constant value at \( t_e \) the rebound phase has finished, and only steady production persists for \( t > t_e \).

hence

\[
\left( \frac{dC_e}{dt} \right)_{t_e} = \left( \frac{dC_b}{dt} \right)_{t_e}
\]

hence from (4) and (5)

\[
C_{ee} = C_{be} + \frac{ps \times V_{bt} \times 1000}{KC \times 60}
\]

(8)
conservation of diffusing solute between any time $t$ during rebound and $t_e$ gives

$$C_e = C_{ee} + (C_{be} - C_b) \times \frac{V_{bt}}{V_{et}} \times \frac{pe(t_e - t)}{60 \times V_{et}}$$

(9)

Thus the only remaining unknown variable in equations (6)-(9) is $KC$.

2.3. Evaluation of $KC$

The following computerised procedure is followed:

1. Guess a value of $KC_1$ (usually 1000 ml/min.).
2. Evaluate $C_{ee}$ from equation (8).
3. Calculate $C_e$ at various time intervals during rebound phase (usually 5–10) using $C_{ee}$ in (9).
4. Calculate function $\log_{10} f$ at these various time intervals.
5. Using least square technique fit a best straight line to $\log_{10} f v t$.
6. Calculate the slope of this line m and hence $KC_2$ from equation (7).
7. Repeat steps 1–6 with new value of $K_e$ until difference between $KC_1$ and $KC_2$ is of the order of 10 ml/min.