Radionuclide method for evaluating the performance of hemodialysis in vivo

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Background. Specifications of dialyzer performance are generally based on in vitro measurements. There is, however, a shortage of data on dialyzer performance in vivo. The aim of this study was to use continuous measurement of technetium-99m-diethylenetriaminepentaacetic acid (Tc-99m-DTPA) blood concentration as a means of continuously monitoring dialyzer function in vivo in patients undergoing routine hemodialysis.

Methods. The study population comprised 15 patients (45 to 80 years old; 13 males). Tc-99m-DTPA was administered intravenously 90 minutes before obtaining a blood sample and starting dialysis. Blood Tc-99m-DTPA activity was continuously monitored by passing the line carrying blood from the patient to the dialyzer close to a scintillation probe mounted in a shielded housing. At the end of hemodialysis, lasting 180 to 300 minutes, chromium-51-ethylenediaminetetraacetic acid (Cr-51-EDTA) was given intravenously and a blood sample taken 90 minutes later. Baseline dialyzer blood flow (Q_b) and dialysate flow (Q_d) were 250 to 350 mL/min and 500 mL/min, respectively. The rate constant, α, of the decrease in blood Tc-99m-DTPA activity was used as the measure of moment-to-moment dialyzer function. Pre- and postdialysis extracellular fluid volumes were calculated from the blood Tc-99m-DTPA and Cr-51-EDTA concentrations (V_{DTPA} and V_{EDTA}) before and after dialysis. Tc-99m-DTPA clearance was measured as the product of α and V_{DTPA}. Dialyzer urea clearance was calculated from pre- and postdialysis urea nitrogen concentrations and the time of dialysis. The effects of brief changes in Q_b and Q_d on dialyzer function were assessed from the associated changes in α.

Results. The Tc-99m-DTPA clearance profile was biexponential, becoming monoexponential about 1 hour after starting hemodialysis, with α remaining constant for as long as dialysis continued in five patients in whom Q_b and Q_d were left unaltered. Mean (SEM) plasma Tc-99m-DTPA clearance averaged over the entire period of dialysis in all 15 patients was 110 (3.1) mL/min. It correlated with urea clearance (r = 0.71) (P < 0.01) which was 225 (9.5) mL/min based on a total body water of 2.5 that of V_{DTPA} and 212 (13) mL/min scaled to 40 L/1.73 m². Extracellular fluid volume decreased by 1.73 (0.74) L over dialysis, which was comparable to the change in weight (1.48 (0.57) kg). The extraction fraction of Tc-99m-DTPA across the artificial kidney, directly measured from afferent and efferent blood samples under baseline Q_b and Q_d, was 0.5 (0.013). Average extraction fraction indirectly estimated from Tc-99m-DTPA blood clearance and Q_b was 0.54 (0.019). These two measurements of extraction fraction correlated with each other under conditions of varying Q_b and Q_d (r = 0.74) (N = 27) (P < 0.001). Changes in α resulting from changes in Q_b and Q_d were similar to changes predicted from computerized modeling. The ratio of mass transfer coefficients of urea and Tc-99m-DTPA with respect to the dialyzer, calculated as if they were permeability-surface area products, was 3.3, similar to the ratio, obtained from the literature, in continuous capillary endothelium.

Conclusion. Tc-99m-DTPA is a useful agent for continuously monitoring dialyzer function in vivo and provides a platform for the use of other radio-pharmaceuticals of different molecular sizes that could be used in an analogous fashion.

The conventional benchmark by which to assess the effectiveness of a single session of haemodialysis is urea removal [1], which is conventionally expressed as the quotient, Kt/V, where K is blood urea clearance, t is time of dialysis, and V is urea distribution volume. A major performance specification of a dialyzer is the mass transfer area coefficient of urea which is the urea flux per unit concentration gradient. Mass transfer area coefficient is analogous to permeability-surface area (PS) product which is similarly defined as the solute flux (mg.min⁻¹) per unit concentration gradient (mg.mL⁻¹) across capillary endothelium in vivo in a specific capillary vascular bed and which has units of mL.min⁻¹. Dialysis removes many other soluble substances with a range of molecular sizes, and therefore a range of permeability coefficients, toward the top end of which is urea. Insofar as urea is a relatively small and relatively highly diffusible molecule,
its transport in a dialyzer is blood flow-dependent at standard levels of dialyzer blood flow ($Q_b$). It provides, therefore, an overrepresentation of dialyzer function, in that clearance of larger molecules would be expected to be less blood flow-dependent at the levels of flow used.

Measurement of dialyzer permeability coefficients in vivo have been difficult because of uncertainties about constancy of dialyzer function over time especially in relation to membrane fouling by plasma proteins which may alter transport properties [2, 3]. Technetium-99m-diethylenetriaminepentaacetic acid (Tc-99m-DTPA) is an inert diffusible hydrophilic solute of molecular weight 492 D. It has been widely used over many years for gamma camera renography [4] and, as it shares essentially the same properties as chromium-51-ethylenediaminetetraacetic acid (Cr-51-EDTA) (360 D), is also a useful radiotracer for measuring glomerular filtration rate (GFR) [5, 6]. Because Tc-99m-DTPA is an excellent gamma emitter, we decided to explore the value of Tc-99m-DTPA for “real-time” monitoring of dialysis performance in a manner analogous to the way it has previously been used for “real-time” monitoring of GFR, including immediate responses of GFR to interventions such as adenosine infusion [7] and administration of potentially nephrotoxic agents like radiologic contrast media [8]. Exploitation of it in this way relies on the fact that the rate constant ($\alpha$) of disappearance from its distribution volume ($V_{DTPA}$) is very close to the ratio of its clearance (almost identical to that of inulin) and distribution volume. Any change in clearance without a change in distribution volume is reflected in a change in $\alpha$. The efficiency with which the signal emitted by Tc-99m-DTPA is detected following intravenous injection can be improved in the dialysis setting by placing the detector in close proximity to one of the vascular lines exchanging blood between the patient and the dialyzer. Using multichannel detectors it would be possible moreover to monitor more than one gamma-emitting radiotracer continuously but in this preliminary study we have focused exclusively on Tc-99m-DTPA.

The aims of the study, therefore, were first to determine if dialyzer performance displayed any evidence of deterioration toward the end of a dialysis session, which would be indicated by a steady decrease in $\alpha$; second, to compare Tc-99m-DTPA clearance kinetics with those of urea; and third, to see if we could detect and quantify changes in Tc-99m-DTPA clearance in response to changes in machine parameters, namely $Q_b$, and dialysate flow rate ($Q_d$). Because Tc-99m-DTPA is an efficient gamma emitter, it is also feasible to make parallel physiologic measurements of dialyzer performance by obtaining simultaneous blood samples from either side of the dialyzer and measuring extraction fraction ($E$). By comparing clearance measured as the product of $E$ and $Q_b$ with clearance measured as the product of $V_{DTPA}$ and $\alpha$, we were able to assess the robustness of Tc-99m-DTPA for continuous real-time measurement of dialyzer function.

### METHODS

#### Patients

Fifteen patients on long-term hemodialysis were recruited (Table 1). Thirteen were males and the age range was 48 to 80 years (median 66 years). They were all essentially anephric with GFRs less than 5 mL/min/1.73 m$^2$. The study was approved by the Local Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee of the United Kingdom.

### Table 1. Clinical details

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<th>Height cm</th>
<th>Weight kg</th>
<th>Pre-</th>
<th>Post-</th>
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<th>ln $R_{DTPA}$</th>
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R is the ratio of concentrations of respective indicator in the blood samples taken before dialysis started and immediately before its termination. $Kt/V$ for urea is a conventional measure of delivered dialysis calculated using the formula of Daugirdas [10]: $Kt/V = \ln(R_{urea} - 0.008 + T)) + [(4 – 3.5 + R) + UF/W]$, where $t$ is time of dialysis in minutes and $T$ in hours, and $UF/W$ is weight difference/predialysis weight. “Equilibrated” $Kt/V$ ($eKt/V$) has been corrected for rebound using a further formula [10]: $eKt/V = Kt/V – (0.46 \ast [Kt/V]/T) + 0.02$. Urea rebound is the% difference between $Kt/V$ and $eKt/V$.
Radiopharmaceuticals

Tc-99m-DTPA and Cr-51-EDTA were obtained from Amersham Healthcare (Bucks, UK) and dispensed according to the manufacturer’s instructions.

Procedures

Prior to dialysis, patients were injected intravenously with 150 to 200 mBq of Tc-99m-DTPA. After 90 minutes, a venous blood sample was taken to estimate the distribution volume (V_DTPA) of this radiotracer. Dialysis was then started and continued for 3 to 5 hours. Another blood sample was taken from the line carrying blood from the patient to dialyzer immediately before the termination of dialysis and between 15 seconds and 2 minutes after slowing dialyzer blood flow down to 50 mL/min (in two patients, this blood sample was omitted). In six patients, Cr-51-EDTA (2 mBq) was also given immediately after the termination of dialysis, and, after a further period of 90 minutes, a final blood sample was taken to estimate the postdialysis distribution volume (V_EDTA) of this radiotracer. Tc-99m-DTPA and Cr-51-EDTA, being crystalloids of similar molecular size (492 and 360 D, respectively), have essentially identical distribution volumes (~15 L in normal subjects) [5, 6]. Additional blood samples were obtained during dialysis to estimate the dialyzer Tc-99m-DTPA extraction fraction (see below). Patients were weighed immediately before and after dialysis.

A shielded housing was built through which the plastic line taking blood from the patient to the dialyzer was fed and in which a 5 cm sodium iodide scintillation detector was placed. The housing was designed so that the line passed across the face of the detector, which was connected to a PC-based Multi-Channel Analyzer (MCA) system (Ortec Maestro, Oak Ridge, TN, USA) set to dynamically acquire counts in 1-minute bins, thereby enabling the blood concentration of Tc-99m-DTPA to be plotted continuously as a function of time throughout dialysis.

Plasma from the blood samples was counted for Cr-51-EDTA and Tc-99m-DTPA in an automatic gamma counter (Wallac-Wizard, Turku, Finland). Where both radionuclides were present in the sample, correction was made for the cross-talk between the Cr-51-EDTA and Tc-99m-DTPA windows. The dialysis machine was a Fresenius 4008 and two different types of dialyzer were used (Althlin A-18 in seven patients and Fresenius F-8 in eight patients) (Fresenius, Bad Homburg, Germany). The initial blood flow rate dialed into the dialyzer machine was usually 300 mL/min (12/15 patients), although it ranged from 250 to 350 mL/min. The initial dialysate flow rate was 500 mL/min in all patients. In five patients, these baseline flow rates were left unaltered throughout dialysis while in ten patients Q_b and Q_d were changed in isolation for periods of 20 minutes starting 1 hour after the onset of dialysis. The flow rates were returned to their respective baseline values for at least 15 minutes before making another change. The changes comprised a 33% reduction in Q_b, a 60% increase in Q_d (to 800 mL/min) and a 40% decrease in Q_d (to 300 mL/min).

Data analysis

Volumes of distribution. The volumes of distribution of Tc-99m-DTPA (V_DTPA) and Cr-51-EDTA (V_EDTA) were, respectively, calculated from the blood samples taken just before the start of dialysis and, in six patients, 90 minutes after the termination of dialysis by simple dilution analysis. These volumes are close to extracellular fluid volume. In order to calculate the Tc-99m-DTPA "rebound," the Tc-99m-DTPA concentration in the sample taken 90 minutes after the finish of dialysis was compared with that in the sample taken just before the termination of dialysis from which postdialysis urea concentration was measured.

Tc-99m-DTPA clearance. Ignoring the first 60 minutes after the start of dialysis, during which reequilibration of Tc-99m-DTPA takes place (see Fig. 1 and Appendix 1), a least squares exponential fit was applied to the entire disappearance curve (or segments of it in the patients in whom flow rates were altered; see below) to give the rate constant, a. This rate constant is close to the ratio of plasma Tc-99m-DTPA clearance (plasmaK_DTPA) and V_DTPA. In fact, a is slightly less than this ratio by an amount that is dependent on a [9]. It was therefore...
subjected to a correction, to give \( \alpha_{\text{corr}} \) using a previously published formula that is itself a function of the recorded value of \( \alpha \) [9]. \( \text{plasma}K_{\text{DTPA}} \) was therefore calculated as the product of \( \alpha_{\text{corr}} \) and \( V_{\text{DTPA}} \). Although \( V_{\text{DTPA}} \) changed slightly over the course of dialysis, the predialysis value, determined with Tc-99m-DTPA, was used to calculate \( \text{plasma}K_{\text{DTPA}} \). Urea distributes between plasma and red cells so blood clearance is the appropriate expression for urea clearance but Tc-99m-DTPA does not enter red cells so plasma clearance is usually used. Nevertheless, \( \text{plasma}K_{\text{DTPA}} \) was converted to blood clearance (\( \text{blood}K_{\text{DTPA}} \)) by dividing it by \( (1 – \text{hematocrit}) \).

\( \text{blood}K_{\text{DTPA}} \) averaged out for the whole period of dialysis (except the first 60 minutes) was based on the value of \( \alpha_{\text{corr}} \) that was obtained by performing a least squares fit to the time-dependent blood Tc-99m-DTPA concentration from 60 minutes after the start of dialysis to the termination of it (ignoring the brief periods during which changes in \( Q_b \) and \( Q_d \) were made). The average extraction fraction of Tc-99m-DTPA by the dialyser was then taken as the quotient, \( \text{blood}K_{\text{DTPA}} \), divided by baseline \( Q_b \).

**Urea clearance.** \( K_t/V \) for urea (\( K_{\text{urea}}t/V_{\text{urea}} \)) was calculated from urea levels in blood samples obtained from the patient before the start of dialysis and at its termination using a previously published formula (see Table 1) [10]. The value of \( K_{\text{urea}}t/V_{\text{urea}} \) calculated from the pre- to posturea concentration ratio was then corrected for rebound using another previously published formula [10]. The ratio of ultrafiltration to weight was taken as the weight difference divided by predialysis weight. \( K_{\text{urea}}t/V_{\text{urea}} \) was divided by duration of dialysis (in minutes) and multiplied by an estimate of total body water (i.e., \( Q_b \) and \( Q_d \) were modified) over the course of dialysis, plus a contribution related to ultrafiltration (\( Q_f \)).

\[
\text{blood}K_{\text{DTPA}} = Q_b \times (1 - [C_{\text{out}}/C_{\text{in}}]) + Q_f (C_{\text{out}}/C_{\text{in}})
\]

(1)

where \( E = 1 - (C_{\text{out}}/C_{\text{in}}) \) and \( C \) is blood Tc-99m-DTPA concentration.

\( Q_f \), the net rate of fluid loss through the dialyzer, can be assessed from the patient’s weight loss. The blood clearance component resulting from ultrafiltration, given by the final term in equation 1, was small compared with the first term (see **Results** section) and therefore ignored. No corrections were made for access recirculation.

Tc-99m-DTPA clearance in the setting of dialysis was subjected to a computerized simulation based on a two-compartmental model, as described in Appendix 1. Dialyzer function was modeled as shown in Appendix 2, from which changes in Tc-99m-DTPA clearance were predicted from changes in model variables.

**Statistics**

Results are expressed as the mean (SEM). Levels of association between variables were assessed by Pearson’s correlation coefficient. A \( P \) value of less than 0.05 was considered to represent significance.

**RESULTS**

**Tc-99m-DTPA clearance**

In the five patients in whom the machine parameters (i.e., \( Q_b \) and \( Q_d \qquad \)) were left unaltered over the entire period of dialysis, the Tc-99m-DTPA clearance curve followed a consistent pattern. When plotted on a logarithmic scale, it was biexponential. After about 60 minutes, it became monoexponential and remained as such for as long as dialysis continued for both types of dialyzer (Fig. 1). Two of these five patients were dialysed with A-18 and 3 with F-8. \( \text{blood}K_{\text{DTPA}} \) (and in parentheses \( \text{plasma}K_{\text{DTPA}} \) values based on data acquired from 1 hour after the onset of dialysis were similar between the two dialyzers: 165 (104) and 176 (105) mL/min for A-18 and 154 (109), 173 (119), and 175 (121) mL/min for F-8. Ignoring the influence of changes in \( Q_b \) and \( Q_d \), the overall mean \( \text{blood}K_{\text{DTPA}} \) recorded from 1 hour in seven patients dialysed with A-18 was 153 (6.4) mL/min and in eight patients dialysed with F-8, 168 (6.0) mL/min (\( P > 0.05 \)). Corresponding values for \( \text{plasma}K_{\text{DTPA}} \) were 106 (2.9) and 113 (5.1) mL/min (\( P > 0.05 \)). Because the two dialyzers were not significantly different with respect to Tc-99m-DTPA clearance, data from them were pooled, giving mean \( \text{plasma}K_{\text{DTPA}} \) values based on the entire dialysis period from 60 minutes of 110 (3.1) mL/min and 161 (4.7) mL/min, respectively. Mean extraction fraction based on the
Fig. 2. Relation between the rate constant of technetium-99m-diethyltriaminepentaacetic acid (Tc-99m-DTPA) disappearance from blood, \( a \), and predialysis volume of distribution of (V\text{DTPA}). An exponential fit has been used as \( a \) is asymptotic to the x axis. The inset shows the similar relation between \( a \) and body surface area.

The dependence of \( a \) on V\text{DTPA} (and on body surface area) is illustrated by a close correlation between them of \( r = 0.82 \) (Fig. 2). As predicted by the simulated model, there was a rebound in Tc-99m-DTPA concentration after termination of dialysis. In the six patients in whom it was measured, it amounted to 12.7% (2.9). As would be expected, this rebound tended to correlate with \( a \) (\( r = 0.79; P \sim 0.06 \)). Moreover, it was similar in magnitude to urea rebound, calculated from dialysis rate (\( K\text{urea}/V\text{urea} \)) using the equation of Daugirdas [10], which was 13.2% (0.7).

Urea clearance

The similarity between the performances of the two dialyzers with respect to \( \text{blood} K\text{DTPA} \) was also seen with \( \text{blood} K\text{urea} \) with respective values for A-18 and F-8 of 212 (11) and 235 (14) mL/min (\( P > 0.05 \)) based on \( V\text{urea} = 2.5 \times V\text{DTPA} \) and 198 (11) and 224 (7.5) mL/min (\( P > 0.05 \)) based on \( V\text{urea} = 40 \text{ L}/1.73 \text{ m}^2 \). Data from the two dialyzers were therefore again pooled for the entire patient group. Mean “average” urea clearance was then 225 (9.5) mL/min based on an estimate of total body water of 2.5 that of V\text{DTPA}, and 212 (13) mL/min based on total body water of 40 L/1.73 m\(^2\). The corresponding estimates of urea extraction fraction, using baseline \( Q_b \), were 0.76 (0.03) and 0.72 (0.03). Average urea clearance (with \( V\text{urea} \) taken as \( 2.5 \times V\text{DTPA} \)) correlated with both average plasma and blood Tc-99m-DTPA clearances (\( r = 0.71 \) (\( N = 13 \)) (\( P < 0.01 \)) and (\( r = 0.60 \) (\( N = 13 \)) (\( P < 0.05 \)), respectively (Fig. 3A). A closer correlation was
observed, however, between the respective ratios of urea and Tc-99m-DTPA concentrations in the blood samples obtained before dialysis and at the termination of dialysis \((r = 0.88)\) (\(N = 13\)) (\(P < 0.001\)) (Fig. 3B).

**Volumes of distribution of radiotracers and ultrafiltration rate**

The volume of distribution of Tc-99m-DTPA (\(V_{DTPA}\)) prior to dialysis was 18.9 (1) L (or 17.1 [0.6] L/1.73 m\(^2\)). Mean weight reduction after dialysis was 1.68 (0.27) kg. Postdialysis volume of distribution of Cr-51-EDTA was measured in only six patients. In these six patients, \(V_{EDTA}\) was less than \(V_{DTPA}\) by an average of 1.73 (0.74) L but they showed good correlation with each other (Fig. 4) consistent with previous claims [5, 6] that they are interchangeable for measurement of extracellular fluid volume. The reduction in body weight in these six patients was 1.48 (0.57) kg which is well matched to the reduction of 1.73 L in extracellular fluid volume, confirming that weight loss over the period of dialysis is almost exclusively the result of loss of fluid from the extracellular fluid compartment. Taking 1.5 L as representative of the average fluid loss, \(Q_f\), amounted to less than 10 mL/min (i.e., 1500 mL/240 min) and could therefore be considered negligible compared with \(Q_b\).

**Effects of flow changes on Tc-99m-DTPA kinetics**

Tc-99m-DTPA extraction fraction by the dialyzer (E) was measured directly under varying conditions of \(Q_b\) and \(Q_d\) in ten patients. Measured in six patients in whom \(Q_b\) was 250 to 350 mL/min and \(Q_d\) was 500 mL/min, mean E was 0.50 (0.013), similar to extraction fraction averaged out for the entire dialysis period (see above).

Measured under varying conditions of \(Q_d\) and \(Q_b\), E showed a good correlation with extraction fraction (\(E_K\)) based on \(\text{blood} K_{DTPA}\) and \(Q_b\): \(E_K = 1.14E + 0.057\) (\(r = 0.74\)) (\(N = 27\)) (\(P < 0.001\)) (Fig. 5).

Table 2 compares changes in \(\text{blood} K_{DTPA}\) in response to changes in (1) \(Q_b\) at baseline \(Q_d\) (= 500 mL/min) and (2) to changes in \(Q_d\) at baseline \(Q_b\) (250 to 350 mL/min) with the corresponding changes predicted from the model in Appendix 2. The relations between \(\text{blood} K_{DTPA}\) and \(Q_b\) and \(Q_d\) are illustrated in Figure 6. In these experiments, \(\text{blood} K_{DTPA}\) was calculated as described above as the product of \(a_{corr}\) and \(V_{DTPA}\) and also as the product of E (directly measured) and \(Q_b\). These two expressions of \(\text{blood} K_{DTPA}\) agreed reasonably well with each other (Fig. 7). Based on \(a_{corr}\) and \(V_{DTPA}\), \(\text{blood} K_{DTPA}\) was 169 (9.1) at a \(Q_b\) of 300 to 350 mL/min compared to 157 (8.8) mL/min at a \(Q_b\) of 200 to 230 mL/min (\(P > 0.05\))
Table 2. Measured changes in technetium-99m-diethyltriaminepentaacetic acid (Tc-99m-DTPA) blood clearance (blood\textsuperscript{K\textsubscript{DTPA}}) in responses to changes in dialyzer blood flow (Q\textsubscript{b}) and dialysate flow (Q\textsubscript{d}) compared with changes predicted from the model described in Appendix 2

<table>
<thead>
<tr>
<th>Change in Q\textsubscript{b} or Q\textsubscript{d}</th>
<th>% Change in Tc-99m-DTPA clearance (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q\textsubscript{b} reduction from 500 to 300 mL/min</td>
<td>Predicted Based on E, V\textsubscript{DTPA} Based on E</td>
</tr>
<tr>
<td>33% reduction in Q\textsubscript{b}</td>
<td>−13.6</td>
</tr>
<tr>
<td>Q\textsubscript{d} reduction from 500 to 800 mL/min</td>
<td>−6.0</td>
</tr>
<tr>
<td>Q\textsubscript{d} increase from 300 to 800 mL/min</td>
<td>+3.5</td>
</tr>
</tbody>
</table>

The volume of distribution of Tc-99m-DTPA is denoted V\textsubscript{DTPA}, the rate constant of decrease in blood Tc-99m-DTPA concentration is denoted \(\alpha\) and the fraction of Tc-99m-DTPA extracted by the dialyzer, measured from samples simultaneously collected in blood entering and leaving the dialyzer, is denoted E

\(\alpha_{\text{corr}} \times V_{\text{DTPA}}\). Measured changes in Tc-99m-DTPA clearance during changes in Q\textsubscript{b} or Q\textsubscript{d} compared with changes predicted from the model described in Appendix 2.

DISCUSSION

The differences between Tc-99m-DTPA and urea with respect to their distribution volumes and red cell penetration characteristics introduced some difficulties in comparing them in the dialysis settings described in this study. The most difficult of these is the dependence of Tc-99m-DTPA clearance on hematocrit. This radiotracer is excluded from red cells and so, in the setting of flow-limited transport, its clearance across the dialyzer is dependent on plasma flow rather than blood flow and therefore dependent also on hematocrit. In contrast, for urea, which freely enters red cells, plasma and blood clearances can be regarded as identical. It therefore makes sense to use blood clearance rather than plasma clearance when comparing Tc-99m-DTPA with urea. When hematocrit is high then for a given blood flow, plasma flow will tend to be low. For a given dialyzer mass transfer area coefficient, Tc-99m-DTPA transport will therefore tend to be low. Expressing Tc-99m-DTPA clearance as blood rather than plasma clearance tends to compensate for this disadvantage of Tc-99m-DTPA, but not entirely, so we are to some extent still comparing apples with oranges when we compare urea with Tc-99m-DTPA.

Kt/V is the variable conventionally used to quantify the effectiveness of dialysis [1]. Urea is a small highly diffusible molecule with a large volume of distribution but Kt/V for urea is assumed to be representative of the handling by the dialyzer of a range of molecules of varying size. An attraction of Tc-99m-DTPA is that, as a radiotracer, it can be used for continuous, real-time, monitoring of dialysis performance. This gives a robust measurement of clearance per unit distribution volume, unlike Kt/V for urea which depends critically on the technique of sampling at the end of dialysis and requires a correction for rebound based on an historic formula. The imprecision of these corrections can be appreciated from the poorer correlations observed between urea and Tc-99m-DTPA clearances compared with the strong correlation between the "raw" post- to predialysis ratios of urea and Tc-99m-DTPA (Fig. 3), neither of which are subjected to any correction procedure but both more or less equally affected by the venoarterial gradient (so-called cardiopulmonary recirculation, the tissue-blood gradient from which rebound originates) and by access recirculation. Although on-line measurement of urea concentration has recently been described for continuous assessment [12], it is obtained from dialysate concentration and is unlikely to have the temporal resolution of Tc-99m-DTPA. Thus, it was possible to show in this study that in the absence of interventions, and after a period during which an interstitial fluid/plasma concentration gradient is established, Tc-99m-DTPA clearance remained absolutely constant throughout dialysis for periods of up to 5 hours. As for urea, the rebound in plasma Tc-99m-DTPA concentration is the result of the normalization of the concentration gradient established between interstitial fluid (total body water for urea) and plasma during dialysis. This gradient is fully established from about 60 minutes after injection of any filtration marker, and, in the presence of normal GFR, is about 15\% for Tc-99m-DTPA [13], consistent with the rebound observed here of 13\%. The rebound tended to correlate with \(\alpha\), which is to be expected as the concentration gradient generated in the first place is dependent on \(\alpha\), just as urea rebound is dependent on \(K_{\text{urea}}/V_{\text{urea}}\). Rebound for Tc-99m-DTPA was similar to that for urea. This was in spite of their different distribution volumes and clearances because their ratio of distribution volumes was similar to their ratio of clearances. Rebound has also been quantified for iohexol [12].

Tc-99m-DTPA also allows extracellular fluid volume to be measured, at least prior to dialysis, and, combined with the handling by the dialyzer of a range of molecules of varying size. An attraction of Tc-99m-DTPA is that, as a radiotracer, it can be used for continuous, real-time, monitoring of dialysis performance. This gives a robust measurement of clearance per unit distribution volume, unlike Kt/V for urea which depends critically on the technique of sampling at the end of dialysis and requires a correction for rebound based on an historic formula. The imprecision of these corrections can be appreciated from the poorer correlations observed between urea and Tc-99m-DTPA clearances compared with the strong correlation between the "raw" post- to predialysis ratios of urea and Tc-99m-DTPA (Fig. 3), neither of which are subjected to any correction procedure but both more or less equally affected by the venoarterial gradient (so-called cardiopulmonary recirculation, the tissue-blood gradient from which rebound originates) and by access recirculation. Although on-line measurement of urea concentration has recently been described for continuous assessment [12], it is obtained from dialysate concentration and is unlikely to have the temporal resolution of Tc-99m-DTPA. Thus, it was possible to show in this study that in the absence of interventions, and after a period during which an interstitial fluid/plasma concentration gradient is established, Tc-99m-DTPA clearance remained absolutely constant throughout dialysis for periods of up to 5 hours. As for urea, the rebound in plasma Tc-99m-DTPA concentration is the result of the normalization of the concentration gradient established between interstitial fluid (total body water for urea) and plasma during dialysis. This gradient is fully established from about 60 minutes after injection of any filtration marker, and, in the presence of normal GFR, is about 15\% for Tc-99m-DTPA [13], consistent with the rebound observed here of 13\%. The rebound tended to correlate with \(\alpha\), which is to be expected as the concentration gradient generated in the first place is dependent on \(\alpha\), just as urea rebound is dependent on \(K_{\text{urea}}/V_{\text{urea}}\). Rebound for Tc-99m-DTPA was similar to that for urea. This was in spite of their different distribution volumes and clearances because their ratio of distribution volumes was similar to their ratio of clearances. Rebound has also been quantified for iohexol [12].

Tc-99m-DTPA also allows extracellular fluid volume to be measured, at least prior to dialysis, and, combined
with a postdialysis measurement of the same (or very similar) volume using Cr-51-EDTA, enables measurement of the change in extracellular fluid volume resulting from dialysis. The recorded patient weight changes were very similar to the changes in extracellular fluid volume confirming that weight lost over dialysis is almost exclusively accounted for by loss of extracellular fluid, with no apparent change in intracellular fluid volume.

Taking baseline Tc-99m-DTPA extraction fraction as 0.52, which, using the modeling approach described in Appendix 2, gives an in vivo value for what is effectively the dialyzer PS product of 178 mL/min. Based on a urea extraction fraction of 0.74, the model gave a “PS product” for urea of 579 mL/min. The ratio of these two PS values (urea/Tc-99m-DTPA) was 3.3, similar to ratios of PS products in continuous vascular endothelium in vivo for urea and for solutes of a similar molecular size to Tc-99m-DTPA [14], suggesting that the relative diffusion rates of the 2 molecules through the dialyzer are similar to those through continuous vascular endothelium in

![Fig. 6. Relations between $Q_b$ (A and B) and $Q_d$ (C and D) and technetium-99m-diethyltriaminepentaacetic acid (Tc-99m-DTPA) blood clearance ($\text{blood}_{\text{Tc-99m-DTPA}}$) shown for individual patients. In (A and C) $\text{blood}_{\text{Tc-99m-DTPA}}$ was calculated by dividing ($\alpha_{\text{corr}}V_{\text{DTPA}}$) by (1 − hematocrit) while in (B and D) it was calculated as the product of $E$ and $Q_b$. The bold squares are the mean values at particular levels of $Q_b$ (180 to 200 mL/min and 270 to 350 mL/min) (A and B) and $Q_d$ (300 mL/min, 500 mL/min, and 800 mL/min) (C and D) and the error bars represent SEM.]
vivo. Using the same baseline extraction fractions, the model also enables the calculation of theoretically predicted changes in Tc-99m-DTPA clearance and extraction fraction in response to the changes in \( Q_b \) and \( Q_d \) that were applied and to compare them with the changes actually recorded. Agreements were reasonable, with the predicted values falling within the limits of error of the recorded values (Table 2).

Extraction fraction is critical in the dependence of solute transfer on blood flow. Urea extraction fraction is high, making its transfer blood flow–dependent, whereas larger solutes that have lower extraction fractions will display less blood flow–dependence. This explains, for example, why the transferred mass of iohexol (molecular weight 821 D), but not urea, was significantly greater after long dialysis (6 hours) at low \( Q_b \) (118 mL/min) than after short dialysis (3 hours) at high \( Q_b \) (296 mL/min) \[12\].

A potential source of error in the comparisons of clearance parameters respectively based on directly measured extraction fraction (E) and on \( \alpha_{corr} \) is the fact that the latter but not the former will be influenced by any residual filtration function that the patient may have. Nevertheless, provided this remains unchanged, it will have little impact on the interpretation of changes in \( \alpha_{corr} \), or lack of them as the case may be. In any event, residual natriuretic filtration function was negligible compared with the equivalent GFR that is established during dialysis.

Reducing \( Q_d \) from 500 to 300 mL/min had the effect of significantly reducing Tc-99m-DTPA clearance but increasing it from 500 to 800 mL/min had no clear effect. An increase in \( Q_d \) could increase clearance through two mechanisms; first, by increasing the mean concentration difference between plasma and dialysate and second, by increasing the effective mass transfer coefficient or surface area for exchange \[15, 16\]. Even if \( Q_d \) was at a sufficiently high level to render Tc-99m-DTPA transfer independent of it, an increase in effective surface area for exchange should have increased clearance. The failure to record an increase suggests that this effect of increasing \( Q_d \) is not important, at least for molecules like Tc-99m-DTPA, or that alternatively flow becomes turbulent at high rates \[17\]. The effect on clearance of a 33% reduction in \( Q_b \) was somewhat ambiguous, although a reduction would have been expected on the basis of the modeling data. Moreover, \( \text{Plasma}_{K_{DTPA}} \) based on E and dialyzer plasma flow, but not based on \( \alpha_{corr} \) and \( V_{DTPA} \), showed a significant positive correlation with dialyzer plasma flow.

**CONCLUSION**

The technique detailed in this study using the online clearance of Tc-99m-DTPA is an accurate, reliable, and reproducible technique, uninfluenced by cardiopulmonary recirculation, access recirculation, or the rebound phenomenon, for the in vivo determination of dialyzer function, knowledge of which may allow the nephrologist to accurately assess and modify the dialysis prescription with the assurance that the dialyzer fully maintains function throughout the dialysis session. It provides a technique with the potential to monitor dialysis in real-time for a range of molecules for which radioactive labels are readily available and to assess the effects of alterations in dialysis parameters on dialyzer performance.

**APPENDIX 1. COMPUTERIZED SIMULATION**

A simulation of tracer clearance in the dialysis situation was performed to give an idea of the expected pattern of change in plasma concentration with time. A two-compartment model was used (Fig. 9). Suitable parameters were chosen on the basis of previous multisample plasma clearance measurements in subjects with varying levels of native renal function. In the simulation, the tracer is introduced to compartment 1 at time zero. After a period of 90 minutes, during which there is no clearance from the system, the tracer is assumed to equilibrate between the two compartments. When dialysis is commenced, clearance begins from compartment 1, is allowed to continue for 4 hours and then stopped. In this two-compartment model, compartment 1 does not simply represent the plasma volume but is in fact considerably larger \[17, 18\]. Although a two-compartment model does not accurately simulate the clearance curve within the first few minutes after introduction of the tracer, for which a three-compartment model should be used, the system nevertheless behaves as a two-compartment model after about 20 minutes.

A biexponential disappearance curve is predicted on the basis of the model (Fig. 10). The first exponential corresponds to the generation
Fig. 8. Relation between plasma technetium-99m-diethyltriaminepentaacetic acid (Tc-99m-DTPA) clearance (\(K_{DTPA}\)) and dialyzer plasma flow [calculated as the product of \(Q_b\) and (1 – hematocrit)]. Left panel, \(K_{DTPA}\) has been calculated as the product of \(E\) and \(Q_b\) (1 – hematocrit). Right panel, \(K_{DTPA}\) is the product of \(a_{corr}\) and \(V_{DTPA}\). The continuous line in the left panel is the regression line.

Fig. 9. Compartmental model depicting the distributions of technetium-99m-diethyltriaminepentaacetic acid (Tc-99m-DTPA) and chromium-51-ethylenediaminetetraacetic acid (Cr-51-EDTA).

of a concentration gradient between the two functional volumes at the onset of dialysis, a gradient which is predicted to take about 60 minutes to become constant relative to plasma concentration. The model also predicts a rebound of the plasma Tc-99m-DTPA concentration when dialysis is terminated that is due to reequilibration of concentrations between the two functional volumes.

APPENDIX 2. DIALYSIS MODEL

A computerized simulation was written to model the concentrations within a dialyzer arranged such that dialysate and blood are flowing in opposite directions and that the dialysate entering the dialyzer is across the membrane from blood just before it leaves the dialyzer. The concentration of the solute to be modeled is assumed to be zero in the dialysate entering the dialyzer. The dialyser is then considered to be divided into a finite number of cells (100) on each side of the dialysis membrane and the concentration within any one cell is assumed to be constant (Fig. 11). The simulation models unit time intervals during which the solute flows between adjacent cells on the same side of the membrane while at the same time crossing the membrane as a result of diffusion. The simulation is run until a steady state is reached, at which point there is a concentration gradient in blood and dialysate along the length of the membrane. The simulation was then used to find a mass transfer coefficient that gives a particular extraction fraction at standard blood and dialysate flow rates [0.52 for Tc-99m-DTPA and 0.74 for urea (see Results section)] and then to model how changes in dialysate or blood flow rates would affect the extraction fraction. The effect of ultrafiltration was ignored. For Tc-99m-DTPA, the hematocit
was assumed to be 0.3 so that plasma flow rather than blood flow was used. It was assumed that urea moves freely between plasma and red cells within which concentrations would then be identical.

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