Simple and accurate quantification of dialysis in acute renal failure patients during either urea non-steady state or treatment with irregular or continuous schedules

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\section*{Abstract}

\textbf{Background.} The quantification of dialysis in critically ill acute renal failure (ARF) patients requires a unifying expression that can establish kinetic equivalence amongst patients treated with irregular or frequent intermittent haemodialysis (IHD) schedules or with differing renal replacement therapies. EKRJC is a generalized form of the equivalent urea renal clearance (EKRc), and represents the equivalent continuous urea clearance that will result in the given time-averaged concentration of urea, for the given amount of urea removal. The suitability of EKRJC for the measurement of dialysis dose in this setting is examined.

\textbf{Subjects and methods.} 420 weeks of renal replacement therapy (IHD and continuous renal replacement therapy) were simulated in 15 virtual ‘patients’ using a variable volume double pool urea kinetic model. Additional data from eight ARF patients were used to exemplify calculations. 1260 EKRJC values were calculated using both formal urea kinetic modelling, as well as a simplified method that requires input of changes in patient fluid state and blood urea nitrogen concentrations over a period of observation, in addition to an initial estimate of patient post-dialysis urea distribution volume (\(V_T\)).

\textbf{Results.} EKRJC is shown to provide a unifying expression of dialysis dose irrespective of IHD schedule or renal replacement therapy. EKRJC is shown to be independent from the assumption of the urea steady state, and intrinsically normalized to patient urea distribution volume to allow dose comparisons between patients of different size. Residual renal urea clearance is easily incorporated where present. EKRJC is easily calculated using the simplified method without the need for iterative urea kinetic modelling. The accuracy of this simplified method is maintained when the initial estimation of \(V_T\) is both 25\% greater or smaller than the true value. Calculation of EKRJC is exemplified using the clinical data.

\textbf{Conclusions.} EKRJC is the most suitable urea kinetic expression for the quantification of dialysis in critically ill ARF patients.

\textbf{Keywords:} acute renal failure; continuous renal replacement therapy; critical care; EKRJC; equivalent renal urea clearance; intermittent haemodialysis; urea kinetic modelling

\section*{Introduction}

Overwhelming evidence supports a relationship between delivered dose of intermittent haemodialysis (IHD) and overall mortality in end-stage renal disease (ESRD) \cite{1}. The use of urea kinetic modelling (UKM) to measure dialysis dose has become standard practice to enable minimum criteria for adequate dialysis to be met. Reports have recently emerged which support the existence of a similar relationship in critically ill patients with acute renal failure (ARF) \cite{2–4}. However, the clinical application of UKM in this setting is confounded by uncertainty as to the optimal method for dialysis quantification.

Within the literature relating to this topic, the most popular expression for dialysis dose is fractional urea clearance per dialysis treatment (\(K_t/V\)). However, cumulative \(K_t/V\) does not change proportionally with cumulative solute removal when IHD schedules are altered by changes to treatment frequency rather than treatment duration. This expression is therefore unsuitable for comparisons involving patients on different

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EKRjc in ARF

IHD schedules [5,6]. Kt/V is also unsuited for comparisons involving patients on continuous renal replacement therapy (CRRT); the steady state blood urea nitrogen (BUN) levels do not allow for its calculation by either formal UKM or simplified methods such as that by Daugirdas [7].

Alternative expressions for dialysis dose include fractional urea removal per dialysis treatment (SRI) [8], standard Kt/V (stdKt/V) [9], and equivalent renal urea clearance (EKR) [10]. Unlike Kt/V, all can establish kinetic equivalence amongst ESRD patients who are treated with irregular or frequent IHD schedules or with differing renal replacement therapies. All however have properties that give rise to inaccuracy in the critically ill ARF patient. The sources of error are more fully discussed in the Discussion, but include the estimation of urea mass removal during the urea non-steady state, and corrections for the effects of urea generation, multicompartment effects and ultrafiltration during dialysis.

We hypothesized that the ideal urea kinetic expression for renal replacement dose in ARF would be characterized by several key properties. First, it should be able to establish kinetic equivalence amongst critically ill patients who are treated with irregular or frequent IHD schedules or with differing renal replacement therapies. Secondly, it should be independent from the assumption of urea steady state. Thirdly, the expression should be intrinsically normalized to patient urea distribution volume to allow dose comparisons between patients of different size. Fourthly, calculations should be easily undertaken without compromise in accuracy. Formulae that need to be solved iteratively for urea distribution volume (V) and generation (G) are impractical for the clinician, and those that avoid iteration by utilizing empirical rather than determined values for V and G are inaccurate, since these are derived from correlational analysis in ESRD, but not critically ill ARF patients. Finally, the expression should have the capacity to include residual renal urea clearance easily where present.

The clinical role for such an expression will ultimately depend on data that define the conditions under which it correlates with patient outcomes, and the interactions that solute clearance per se might have with other dialytic variables that also affect outcome. However, accurate determination of solute clearance must form the basis for future research in this area. The corrected equivalent renal urea clearance (EKRc) was originally described by Casino and Lopez [10], but only provides a realistic reflection of the effect of dialysis in patients under urea steady state conditions. We propose a new expression for dialysis dose, EKRjc, which will be shown to largely fulfill the above requirements for an ideal expression of dialysis dose in this population. EKRjc is an extension of EKRc and represents the normalized continuous urea clearance that will result in the same time-averaged concentration (TAC) of BUN at steady state for the given amount of urea removal. This unit of measurement (ml/min) is intuitive and practical for clinicians involved in providing renal replacement therapy in the critically ill ARF population.

This article has four aims: to define and describe the derivation of EKRjc; to describe the derivation of simplified methods for the calculation of EKRjc; to analyse error in these simplified methods for determination of EKRjc in the simulated clinical setting; to exemplify calculation of EKRjc in the clinical setting.

Subjects and methods

The derivation and calculation of EKRjc by both reference and simplified methods are described in detail in Appendix 1. A data set of simulated ‘patients’ was used to evaluate the accuracy of the simplified method in comparison with the reference method, and identify and analyse sources of error. A clinical data set was used for the calculation of EKRjc using the simplified method, to illustrate the process and provide an exemplar for clinical practice.

Simulated data

Intracellular (Ci), extracellular (Ce) BUN time-concentration profiles were generated from a variable volume double pool (VVDP) model using the equations previously derived by Depner [11], using an intercompartmental mass transfer area coefficient (KC) of 800 ml/min and an extracellular to intracellular post-dialysis volume ratio of 1 to 2. For each pair of Ci and Ce, a weighted mean (Cwb) was computed as an estimate of the ‘whole-body concentration’, as suggested by Clark et al. [5]. BUN time-concentration profiles were generated for multiple renal replacement regimens in 15 virtual ‘patients’. Initial BUN values were chosen to produce a decreasing TAC and initially negative urea mass balance until steady state was reached. The urea kinetic parameters used for each of the 15 ‘patients’ are provided in Table 1. The index simulation was ‘patient’ 1, and each baseline urea kinetic property was varied individually to constitute the other simulated ‘patients’.

Each ‘patient’ was subjected to a range of dialysis schedules to simulate the clinical prescription of renal replacement therapy in the intensive care unit. Seven different IHD schedules (M/W/F, alternate day, M/W/F/S, M/T/W/F/S, M/T/W/T/F/S, and daily) and one continuous veno-venous haemofiltration (CVVHD) schedule were modelled. The CVVHD schedule is modelled to provide two treatments in the week, with an intradialytic duration of 4320 min and interdialytic duration of 720 min. This is a realistic reflection of practice in the intensive care unit, where operating times very seldom exceed the specified duration, and are never truly continuous [12]. It is to be noted that EKRjc is calculated using measurements of G from the interdialytic rise in BUN, and cannot therefore be calculated in the manner we propose for the hypothetical case of a truly continuous therapy. In practice, the down-time of 12 h is reasonable, although the small amount of post-dialysis urea rebound associated with CVVHD means that an even shorter interdialytic interval can be used for calculations.

BUN profiles were generated over 4 weeks for all simulated regimens. As an example, Table 2 details the dialysis regimens for ‘patient’ 1.
Double pool EKRjc (dpEKRjc) values were calculated for each week of renal replacement therapy using the values for double pool V (dpV) and G provided to the VVDP model, and TAC over the weekly interval (TACWk) calculated using the modelled Cwb. The dpEKRjc values so calculated were considered the gold standard values as calculated by the reference method. For each week, EKRjc values were determined by the simplified method using steps 1–6 as described in Appendix 1.

For the index ‘patient’ simulation, the double pool post-dialysis urea distribution volume (dpVT) was set to 36 000 ml. As for EKRc, EKRjc was normalized to the patient’s own average post-dialysis urea distribution volume (VTM) and then corrected for an arbitrary ‘standard’ V of 40 000 ml for a typical human. This allows comparison of EKRjc amongst patients of different body size. The values of V for our simulated ‘patients’ were deliberately chosen to be different from the normalizing standard, so that EKRjc could be dissociated from its uncorrected form (EKRj) allowing analyses to pertain to the former rather than latter expression. Although modelled ultrafiltration rates were modest and fixed (and hence unrealistic for the critically ill ARF population), this does not affect calculations or the validity of subsequent results.

The calculation of EKRjc requires a clinical estimate of post-dialysis V at the beginning of the weekly interval (VT). The potential impact of error in this estimate was evaluated by using three different values for VT to calculate three

<table>
<thead>
<tr>
<th>'Patient' no.</th>
<th>Parameter Varied</th>
<th>C0 (mg/ml)</th>
<th>dpVT (ml)</th>
<th>G (mg/min)</th>
<th>Kr (ml/min)</th>
<th>b (ml/min)</th>
<th>TD (min)</th>
<th>dpKt/V per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baseline</td>
<td>1</td>
<td>36 000</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>240</td>
<td>4.8</td>
</tr>
<tr>
<td>2</td>
<td>C0 decreased</td>
<td>0.75</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>3</td>
<td>C0 increased</td>
<td>1.25</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>4</td>
<td>dpVT decreased</td>
<td>=</td>
<td>27 000</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>5</td>
<td>dpVT increased</td>
<td>=</td>
<td>45 000</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>6</td>
<td>G decreased</td>
<td>=</td>
<td>=</td>
<td>6</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>7</td>
<td>G increased</td>
<td>=</td>
<td>=</td>
<td>10</td>
<td>=</td>
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<td>=</td>
</tr>
<tr>
<td>8</td>
<td>Kr decreased</td>
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<td>0</td>
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<td>=</td>
<td>=</td>
<td>=</td>
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<tr>
<td>9</td>
<td>Kr increased</td>
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<td>=</td>
<td>=</td>
<td>4</td>
<td>=</td>
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</tr>
<tr>
<td>10</td>
<td>b decreased</td>
<td>=</td>
<td>=</td>
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<td>0.75</td>
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</tr>
<tr>
<td>11</td>
<td>b increased</td>
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<td>12</td>
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<tr>
<td>13</td>
<td>TD increased</td>
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<td>=</td>
<td>300</td>
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<td>14</td>
<td>Kt/Vwk decreased</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>3.6</td>
</tr>
<tr>
<td>15</td>
<td>Kt/Vwk increased</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>6</td>
</tr>
</tbody>
</table>

C0, the initial BUN at the beginning of week 1 (mg/ml); dpVT, the post-dialysis urea distribution volume (ml); b, interdialytic weight gain rate (ml/min); G, the urea generation rate (mg/min); Kr, the residual renal urea clearance (ml/min); TD, the duration of dialysis (min); =, as per the index simulation (‘patient’ 1)

Table 2. UKM variable pertaining to the index simulation of ‘patient’ 1

<table>
<thead>
<tr>
<th>Frequency of treatments (per week)</th>
<th>3</th>
<th>3.5</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>2 CVVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>dpKt/V week</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>dpKt/V session</td>
<td>1.60</td>
<td>1.37</td>
<td>1.20</td>
<td>0.96</td>
<td>0.80</td>
<td>0.69</td>
<td>2.40</td>
</tr>
<tr>
<td>dpVT</td>
<td>36 000</td>
<td>36 000</td>
<td>36 000</td>
<td>36 000</td>
<td>36 000</td>
<td>36 000</td>
<td>36 000</td>
</tr>
<tr>
<td>TD</td>
<td>240</td>
<td>240</td>
<td>240</td>
<td>240</td>
<td>240</td>
<td>240</td>
<td>4320</td>
</tr>
<tr>
<td>b</td>
<td>240</td>
<td>206</td>
<td>180</td>
<td>144</td>
<td>120</td>
<td>103</td>
<td>20</td>
</tr>
<tr>
<td>G</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Kr</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>TI</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

dpVT, the post-dialysis urea distribution volume (ml); TD, the duration of dialysis (min); Kd, the haemodialyser urea clearance (ml/min); b, the interdialytic weight gain rate (ml/min); G, the urea generation rate (mg/ml); Kr, the residual renal urea clearance (ml/min); TI, the interdialytic duration (min).
dialysis regimens. \( V_T \) values were used that were (i) equal to actual \( \text{dp}V_T \), (ii) 0.75 \( \times \) actual \( \text{dp}V_T \) and (iii) 1.25 \( \times \) actual \( \text{dp}V_T \).

Clinical data

The detailed calculation of EKRjc and the dialytic component of this parameter (dEKRjc) is exemplified in using clinical data from eight acute (or acute on chronic) renal failure patients in urea non-steady state treated at Middlemore Hospital, Auckland, New Zealand. Six were male, two female. Median age was 67 years (range 45–83), median body weight 81.5 kg (range 69–111), median ultrafiltration volume 0.71 l (range –0.7 to 3.4), median treatment time 240 min (range 120–270), median blood flow rate 250 ml/min (range 200–400), and dialysate flow rate 500 ml/min. The median number of treatments per week was 5 (range 3–5). All patients were dialysed via central venous catheters using polyamide low-flux haemodialysers (Polyflux 6L or 17L; Gambro AB, Lund, Sweden).

Diagnoses, outcomes and BUN at the beginning and end of the observation period are provided in Table 6. In all patients, \( V_T \) values were estimated empirically using the Watson formula, with empirical adjustment based on clinician intuition in response to the presence of oedema, etc. [13]. EKRjc and dEKRjc were calculated using the algorithms for simplified calculation provided in Appendix 1.

Comparisons and statistical methods

Comparisons were made between paired dpEKRjc and EKRjc values (calculated using the three different input values for \( V_T \)) using simulated data. Agreement was assessed using two statistical tools. The concordance correlation coefficient (CCC) is a measure of the degree to which pairs of observations fall on the line of identity, and is equal to the product of the Pearson correlation coefficient (precision factor) and an accuracy factor to account for systematic bias. CCC values of 1 indicate that pairs of dpEKRjc and EKRjc values are identical, whereas a CCC of zero indicates no relationship. A CCC value of 0.8 or above is an acceptable clinical limit for equivalence [14]. Bias plots involve calculating the mean difference (bias) between dpEKRjc and EKRjc in the same individuals, which is the systematic difference between the methods. The standard deviation (SD) of these differences therefore measure random fluctuations around this mean. The National Committee for Clinical Laboratory Standards (NCCLS) EP9-A procedure defines the range of agreement as the mean difference ± 1.96 SDs, which tell us how far apart dpEKRjc and EKRjc are likely to be for 95% of individuals [15]. Analyses were made using Analyse-It® software (Leeds, UK).

Results

Simulated data

420 weeks of renal replacement therapy were simulated in our 15 ‘patients’, providing 420 dpEKRjc values. For each dpEKRjc, there were three corresponding EKRjc values (each calculated using three different input values for \( V_T \)) providing a total of 1260 EKRjc values.

Figure 2 illustrates the validity of dpEKRjc in the urea non-steady state. dpEKRjc for week 1 is compared with dpEKRjc for week 4 of each of the ‘patient’ simulations. The 105 data points correspond to seven dialysis regimens in each of the 15 simulated ‘patients’ (\( n=105 \)). The dotted line in the lower panel represents the bias between parameters, and the broken lines represent the range of agreement.

Fig. 2. dpEKRjc at week 1 vs dpEKRjc at week 4, for the seven dialysis regimens in each of the 15 simulated ‘patients’ (\( n=105 \)).
Table 3. dpEKRjc per schedule per week for 15 simulated 'patients'

<table>
<thead>
<tr>
<th>Frequency of treatments (per week)</th>
<th>dpEKRjc (ml/min)*</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>17.62 ± 1.55</td>
<td>17.06 ± 1.16</td>
<td>17.06 ± 1.16</td>
<td>17.06 ± 1.16</td>
<td></td>
</tr>
<tr>
<td>3.5b</td>
<td>20.57 ± 2.14</td>
<td>18.73 ± 1.39</td>
<td>18.18 ± 1.26</td>
<td>18.03 ± 1.25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>19.19 ± 1.48</td>
<td>18.19 ± 1.26</td>
<td>18.18 ± 1.26</td>
<td>18.18 ± 1.26</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19.89 ± 1.62</td>
<td>18.82 ± 1.32</td>
<td>18.81 ± 1.32</td>
<td>18.81 ± 1.32</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20.10 ± 1.59</td>
<td>19.25 ± 1.37</td>
<td>19.24 ± 1.37</td>
<td>19.24 ± 1.37</td>
<td></td>
</tr>
<tr>
<td>7b</td>
<td>22.32 ± 1.90</td>
<td>21.34 ± 1.68</td>
<td>20.69 ± 1.54</td>
<td>20.31 ± 1.48</td>
<td></td>
</tr>
<tr>
<td>CVVHDb</td>
<td>21.67 ± 1.62</td>
<td>21.09 ± 1.54</td>
<td>21.03 ± 1.54</td>
<td>21.02 ± 1.54</td>
<td></td>
</tr>
</tbody>
</table>

*Presented as mean ± SD.

bSchedules in which the week contains repeating complete dialysis cycles (i.e. dialysis treatment and following interdialytic period), which are all of identical duration (see symmetric schedules in Appendix 1). dpEKRjc is calculated over a single dialysis cycle instead of over a week.

Fig. 3. EKRjc vs dpEKRjc for each week of the seven dialysis regimens in each of the 15 simulated 'patients' (n=420). EKRjc have been calculated as described in the text, with input \( V_T \) equal to dpVT. The dotted line in the lower panel represents the bias between methods, and the broken lines represent the range of agreement.

Fig. 4. EKRjc vs dpEKRjc for each week of the seven dialysis regimens in each of the 15 simulated 'patients' (n=420). EKRjc have been calculated as described in the text, with input \( V_T \) equal to 0.75 x dpVT. The dotted line in the lower panel represents the bias between methods, and the broken lines represent the range of agreement.
The true value by an average of $-0.14$ ($-0.17$ to $-0.12$) ml/min. The range of agreement is $0.69$ to $0.40$ ml/min. For the input $V_T = 0.75 \times dpV_T$ (Figure 4), CCC is 0.96, and the bias plot comparison indicates that EKRjc overestimates the true value by an average of $1.12$ ($1.08$–$1.17$) ml/min. The range of agreement is $0.28$–$1.97$ ml/min. For the input $V_T = 1.25 \times dpV_T$ (Figure 5), CCC is 0.97, and the bias plot comparison indicates that EKRjc underestimates the true value by an average of $0.90$ ($0.93$ to $0.87$) ml/min. The range of agreement is $-1.53$ to $-0.22$ ml/min. The effect of different input values for $V_T$ on EKRjc during CVVHD is compared with the corresponding effect during IHD in Table 4. It can be seen that the effects of estimation error for $V_T$ on EKRjc are comparable across modalities.

The method for calculating EKRjc assumes a linear rise in BUN between treatments, potentially resulting in overestimation of EKRjc with increasing residual renal urea clearance (Kr). Table 5 compares dpEKRjc (which correctly models the interdialytic BUN rise) with EKRjc (which is based on a linear interdialytic BUN rise) for both the regimen with the shortest interdialytic period (CVVHD), and the regimen with the longest (thrice weekly IHD) across all simulated ‘patients’ with various degrees of Kr. It can be seen that the error is relatively small.

The index simulation is ‘patient’ 1, and each of the other ‘patients’ represents an isolated variation in a single urea kinetic parameter upon this index simulation. The impact of these various changes upon steady state dpEKRjc (week 4) can therefore be assessed. Average dpEKRjc for the index simulation is compared with dpEKRjc for the others in Figure 6. It can be seen that dpEKRjc is independent of isolated changes in $G$, initial BUN at time 0 ($C_0$), rate of interdialytic weight gain ($b$) and dialysis duration ($T_D$). dpEKRjc is however affected by Kr, Kt/V per treatment, and dpV. This last effect is small at $\sim 3$–$5\%$, and of little clinical significance as illustrated by the analyses in Figures 3–5.

**Clinical data**

Results in this section are reported as mean±SD (range) unless stated otherwise. Summary UKM data

<table>
<thead>
<tr>
<th>Treatment schedule</th>
<th>Vsp/Vdp</th>
<th>dpEKRjc</th>
<th>EKRjc</th>
<th>Difference</th>
</tr>
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<tbody>
<tr>
<td>CVVHD</td>
<td>1</td>
<td>21.2±2.0</td>
<td>21.4±1.8</td>
<td>0.2±0.3</td>
</tr>
<tr>
<td>CVVHD</td>
<td>0.75</td>
<td>21.2±2.0</td>
<td>22.5±1.9</td>
<td>1.4±0.5</td>
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<tr>
<td>CVVHD</td>
<td>1.25</td>
<td>21.2±2.0</td>
<td>20.7±1.7</td>
<td>$-0.5±0.4$</td>
</tr>
<tr>
<td>3× week</td>
<td>1</td>
<td>17.2±1.4</td>
<td>17.1±1.4</td>
<td>$-0.1±0.0$</td>
</tr>
<tr>
<td>3× week</td>
<td>0.75</td>
<td>17.2±1.4</td>
<td>18.4±1.6</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>3× week</td>
<td>1.25</td>
<td>17.2±1.4</td>
<td>16.3±1.3</td>
<td>$-0.9±0.2$</td>
</tr>
<tr>
<td>All treatments</td>
<td>1</td>
<td>19.3±2.2</td>
<td>19.0±2.2</td>
<td>$-0.4±0.4$</td>
</tr>
<tr>
<td>All treatments</td>
<td>0.75</td>
<td>19.3±2.2</td>
<td>20.3±2.3</td>
<td>0.9±0.5</td>
</tr>
<tr>
<td>All treatments</td>
<td>1.25</td>
<td>19.3±2.2</td>
<td>18.2±2.1</td>
<td>$-1.1±0.4$</td>
</tr>
</tbody>
</table>

Data are shown for all treatments, and for CVVHD and the thrice weekly IHD schedule.

$^a$Presented as mean±SD.

<table>
<thead>
<tr>
<th>Treatment schedule</th>
<th>Kr</th>
<th>dpEKRjc</th>
<th>EKRjc</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVHD</td>
<td>0</td>
<td>19.0±0.3</td>
<td>19.4±0.2</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>CVVHD</td>
<td>2</td>
<td>21.2±1.9</td>
<td>21.4±1.8</td>
<td>0.2±0.4</td>
</tr>
<tr>
<td>CVVHD</td>
<td>4</td>
<td>23.4±0.4</td>
<td>23.4±0.0</td>
<td>0.0±0.4</td>
</tr>
<tr>
<td>3× week</td>
<td>0</td>
<td>15.0±0.1</td>
<td>14.7±0.1</td>
<td>$-0.3±0.0$</td>
</tr>
<tr>
<td>3× week</td>
<td>2</td>
<td>17.2±1.2</td>
<td>17.1±1.2</td>
<td>$-0.1±0.1$</td>
</tr>
<tr>
<td>3× week</td>
<td>4</td>
<td>19.4±0.6</td>
<td>19.5±0.6</td>
<td>0.1±0.0</td>
</tr>
</tbody>
</table>

$^a$Presented as mean±SD.
for the eight patients are presented in Table 7. An EKRjc of 14.7 ± 3.8 (10.3–21.1) ml/min was delivered over a total interval of 12 563 ± 2371 (7350–14 400) min. Each patient received 4.6 ± 0.7 (3.0–5.0) IHD treatments, and treatment duration was 202 ± 12 (180–222) min. Stepwise calculation of EKRjc and dEKRjc is exemplified in detail for patient 3 in Appendix 2.
Discussion

There is increasing evidence supporting a relationship between dose of renal replacement therapy and clinical outcomes amongst the critically ill ARF patients. As a consequence, initiatives are now underway to establish dosage guidelines to optimize the management of uraemia in this setting and minimize its impact on patient recovery [16]. For both research and clinical practice, an expression of dose should be used that is comparable across all modalities (CRRT vs IHD vs peritoneal dialysis), and accurate across all degrees of schedule (continuous vs frequency of n), interdialytic weight gain, and fluctuations of G and TAC. As shown above, EKRjc can be calculated simply without the need for iterative calculation, knowledge of haemodialyser clearance (Kd), extensive adjustment for double pool urea kinetics, or precise knowledge of $V_T$. We have shown that estimated $V_T$ values that are within 25% of the actual dp$V_T$ provide EKRjc values that are sufficiently close to dpEKRjc to be clinically acceptable.

It is to be emphasized that EKRjc is not simply time-averaged haemodialyser urea clearance. By way of an example, EKRjc would not triple if Kd were to be tripled for a given IHD regimen. EKRjc is a mass balance parameter that accounts for inefficiency of intermittent therapies. We have proposed UKM methods to compute components of this definition, but the determination of urea mass removal could conceivably be achieved by total (or fractional) dialysate collection in addition to any urinary output, and TAC by any means including more formal computed or manual graphical integration.

There are two competing urea kinetic methods for quantifying different renal replacement therapies in this setting. Gotch [9] recently derived an expression termed ‘standard Kt/V’ (stdKt/V), while Keshaviah and Star [8] derived the ‘solute removal index’ (SRI) about a decade ago. Both expressions are similar from a UKM perspective, and each has been argued to provide a superior definition of treatment equivalency in the ESRD setting by being numerically equal for clinically acceptable. EKRjc is normalized to the patient’s state and irregular dialysis schedules, so long as measurements are undertaken for every treatment. This cumbersome requirement can be avoided by the calculation of SRI from blood-sided measurements using a number of formulae, although these variably do not account for G, ultrafiltration during dialysis or multicompartment effects [8,20].

An additional problem lies with the reliance of stdKt/V and SRI on peak urea concentrations. Kinetically equivalent therapy prescriptions will be those that produce the same Jm at the same pre-dialysis BUN. The peak concentration hypothesis defines the peak pre-dialysis BUN for use in calculations as the maximum after the longest interdialytic break [21], although for stdKt/V this peak has been redefined as the average of all pre-dialysis BUN in the week [18]. Urea concentrations may be very asymmetrical and variable in the critically ill ARF population, and these arbitrary definitions may have accordingly less significance. In contrast, EKRjc uses TAC, which has more validity and is easier to define for patients in urea non-steady state or with irregular IHD schedules. The arguments supporting the peak concentration hypothesis in the ESRD setting cannot be extrapolated to the critically ill ARF population, where the rudimentary nature of dose–outcome relationships precludes validation of any one hypothesis over its competitors.

EKRjc has several potential systematic sources of error. It can be seen from Table 3 and Figure 2 that there is a small residual error arising from effects of the urea non-steady state. In the course from weeks 1–4, both TAC and weekly removal decrease. The ratio of urea removal to TAC is affected by the difference between its removal and generation, so that EKRjc is greater for the first week and become less for the following weeks. This error is clinically insignificant, however, and could be accepted for routine purposes. In addition, there is potentially a small error arising from the assumption of a linear rise in urea between treatments, resulting in a small overestimation of EKRjc with increasing Kr. This degree of this error is shown in Table 5, and once again could be accepted for routine purposes.

The manner in which Kr is incorporated into EKRjc warrants comment. Residual renal urea clearance underestimates glomerular filtration rate (GFR), but is more relevant from a urea kinetic perspective and is required for the calculation of urea mass removal in EKRjc. Kr is therefore corrected in the same manner as EKRjc to provide a time-averaged residual renal clearance that can be mathematically resolved within the expression. This seemingly unconventional approach is justifiable in that solute removal by any route must be normalized to body content before the expression is a realistic reflection of removal alone. Using this rationale, it makes sense to normalize Kr to $V_{TM}$—a superior indicator of body urea content—as opposed to body surface area (BSA), which is more likely to be confounded by obesity and gender [22].
from both a theoretical and logistic perspective to a study. An example can be found by way of a recent toxicity should not be considered as fact until a population. Urea may be imprecise as a marker of related to clinical outcomes of the critically ill ARF paradigm in which expressions of urea clearance are not so if it is normalized to the actual body weight, the latter being less tightly bound to the kinetic parameter V. To illustrate this point using our simulations, the effect of a different input V_T on EKRj (i.e. not normalized) when dpEKRjc is 17.4 ml/min is as follows: EKRj = 13.8 ± 1.9 ml/min when V_T/dpVT = 0.75 (~21% error); EKRj = 20.7 ± 3.0 ml/min when V_T/dpVT = 1.25 (~19% error). Thus, it is essential from both a theoretical and logistic perspective to normalize in the manner described in this article.

In practical terms, how should the clinician estimate V_T? There is no doubt that this is a formidable task, but it is certainly made easier by the limits of this requirement (i.e. to within ±25% of the actual dpVT) and the offsetting of errors within these limits such that EKRjc is accurate to ~5%. A variety of options are available, such as anthropometric formulae (Hume-Weyer [23], Watson et al. [13], Chertow et al. [24]), bioimpedence analysis and clinical intuition. There are few data within the literature to rigorously compare these methods in the critically ill ARF population. It is well documented that V_T values in such patients are greater than those estimated by anthropometry [25], and one report has shown that total body water as measured from bioimpedence analysis may in fact be a poor surrogate for urea distribution volume [26]. There is probably no better recommendation than to appraise the patient using anthropometry, bioimpedence analysis, or whatever means available and then alter this value according to clinical intuition. If a clinician estimate of V_T were very deviant, there would be a progressive increase in error. For instance, when V_T/dpVT = 0.5 in our simulations, then EKRJc by the simplified method overestimated dpEKRjc (n = 420) by between 6.3% (Kr = 0 ml/min) and 20.8% (Kr = 4 ml/min). When V_T/dpVT = 1.5, then EKRjc under-estimated dpEKRjc by between −5.8 (Kr = 0 ml/min) and −12.1% (Kr = 4 ml/min).

It is appropriate to comment upon the traditional paradigm in which expressions of urea clearance are related to clinical outcomes of the critically ill ARF population. Urea may be imprecise as a marker of uraemic solute burden or clinical toxicity in this setting, and the relationship between urea kinetics and uraemic toxicity should not be considered as fact until corroborating data emerge from rigorous clinical study. An example can be found by way of a recent comparison of CAPD with CRRT [27], where urea clearance was comparable between therapies but outcomes very different [28].

Moreover, a possibility exists that outcomes of critically ill ARF patients are dependent not on urea clearance, but on the degree of metabolic control per se. For instance, consider two hypothetical patients with the same urea distribution volume and generation rate that are treated with identical renal replacement regimens, with the only difference being that treatment was initiated in one patient at a lower BUN that the other. There are provisional clinical data that suggest this latter strategy would be associated with superior outcomes [4,29]. Although in need of further study, this distinction between dialysis dose and metabolic control may lead to a paradigm shift in this population away from the traditional objectives for solute control that guide the prescription of dialysis in ESRD patients.

Considering these issues, EKRjc is well suited to allow determination of dialysis dose independent of metabolic control. Using the above example, both patients will have the same TAC at steady state despite the different C0. EKRjc will, however, be almost identical for both patients when calculated during their respective urea non-steady states immediately after dialysis initiation, and will not confound analyses of their outcomes by ascribing a higher dialysis dose to the patient who initiates dialysis at a higher BUN.

The purpose of this article is to provide a theoretical and conceptual framework for EKRjc, and provide some clinical examples of its calculation. There is an urgent need for prospective studies that establish dosage guidelines for dialytic therapies in the intensive care unit. For any expression of dialysis dose to be credible, clinical study must verify its value as a correlate of patient outcomes. These data will become available as clinical experience with EKRjc increases. EKRjc is theoretically well suited for use in such studies, as a pure and accurate expression of renal replacement dose, and investigators in the field should give preference to UKM parameters that provide a realistic reflection of the effect of therapy on solute kinetics in such patients.

Conflict of interest statement. None declared.

References
4. Ronco C, Bellomo R, Homel P et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of


18. Gotch F. Is Kt/V urea a satisfactory measure for dosing the newer dialysis regimens? *Semin Dial* 2001; 14: 15–17


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**Appendix 1**

**Core definition of EKR**

EKR is traditionally defined using a form of the clearance equation that is used to determine GFR [clearance = (urine concentration x urine volume/ plasma concentration)/time]. In this way, EKR is expressly analogous to the rate of urea mass cleared by the renal route for patients without ESRD. The general form of this equation utilizes a ‘black box’ approach that relates total removal to the concentration profile, without any reference to other complexities of the dialysis procedure or renal function. This definition of EKR can be described in urea kinetic terms:

\[
J_m/TAC
\]

where \(J_m\) is mean urea removal rate and \(TAC\) the time-averaged urea concentration. This equation should be regarded as a fundamental definition, and all other equations as being derived. The urea kinetic model below is used to provide a framework within which EKR can be related to other urea kinetic variables, and methods for the calculation of EKR derived.

**Derivation of EKRjc**

The following equations arise from consideration of a variable volume single pool (Vvsp) urea kinetic model, as previously described by Sargent and Gotch [30]. Urea is generated within the urea distribution volume \(V\) at rate \(G\), and is assumed to have uniform distribution throughout the compartment with concentration \(C\). Urea is removed by both residual renal clearance \((Kr)\) and haemodialysier clearance \((Kd)\). The principles governing conservation of body urea mass give rise to the equation:

\[
\frac{d(VC)}{dt} = G - (Kr + Kd) 
\]

**core equation 1**
For stable ESRD patients on maintenance dialysis, urea steady state and constant $G$ can be assumed. Under these conditions, the combined total dialysis and residual renal urea clearance ($Kr + Kd$) over a 1 week period is equivalent to EKR, which has been previously defined [10]:

$$EKR = \frac{G}{TAC}$$  \hspace{1cm} \text{core equation 2}

Considering the core definition of EKR, the use of $G$ in the place of $Jm$ in the numerator of this equation requires the presence of urea steady state; i.e., over a given time interval of a week (from $T_0$ to $T_{Wk}$), the urea mass ($V \times C$) at the beginning ($V_0 \times C_0$) and at the end ($V_{Wk} \times C_{Wk}$) of the time interval are identical. Even in steady state, the actual time interval over which this condition is met is critically dependent on the IHD schedule. For regular or symmetric schedules (weekly, alternate day and daily), the interdialytic period is of fixed duration and there will be no change in urea mass over a single complete dialysis cycle (i.e., from the beginning of the dialysis treatment to the end of the following interdialytic period). For irregular or asymmetric schedules (2x, 3x, 4x, 5x, 6x per week), the interdialytic period is of variable duration and the change in urea mass will only equal zero over a weekly cycle. EKR may therefore be calculated over a single dialysis cycle for the former regimens, but only over a week for the latter.

For the patient in urea non-steady state, change in urea mass over the period of observation will preclude the use of $G$ in the place of $Jm$ in the calculation of EKR. To overcome this problem, we revert to the more general parameter, $EKR_j$, which is based on the core definition using urea removal rather than generation. $EKR_j$ is normalized to the patient's average post-dialysis urea distribution volume ($V_{TM}$), which is then normalized to $V_{TM}$ and then corrected for an arbitrary 'standard' $V$ of 40 000 ml for a typical human, to give $EKR_{jc}$.

$$EKR_{jc} = \frac{dEKR_{jc} + Krc}{M_{Wk}}$$  \hspace{1cm} \text{core equation 6}

Simplified calculation of $EKR_{jc}$

The calculation of $EKR_{jc}$ requires knowledge of $M_{Wk}$, $AUC_{Wk}$ and $V_{TM}$. These data could be provided by measurement of $Kd$ using either classic iterative UKM algorithms or by DDQ. These procedures are logistically difficult on a routine basis, particularly in the critical care setting. To avoid these measurements, we devised a simplified calculation method, which, in short, first computes $M_{Wk}$ as a function of an assumed value for $V_{TM}$, and then $AUC_{Wk}$, as the sum of a series of subareas. The ratio of $M_{Wk}$ and $AUC_{Wk}$ provides $EKR_j$, which is then normalized to $V_{TM}$ and then corrected for an arbitrary 'standard' $V$ of 40 000 ml for a typical human, to give $EKR_{jc}$.

To avoid the requirement for measurement of $Kd$, a modified UKM algorithm is used which fixes this parameter and uses $V$ as an input into the VVSP model. The procedures for this calculation have been previously published [31], and it has previously been shown that fixing either $V$ or $Kd$ as an input for UKM calculations provides the same values for $Kt/V$ and $PCRn$ [32]. The utility of such a strategy arises from the property of the VVSP model that results in internal compensation for any error in the estimation of patient $V$ by a proportional change in $G$ and $Kd$. This property does not necessarily result in true values for $G$ and $Kd$, unless the $V$ value used for input is accurate. Irrespective of the inaccuracy of input data, the model provides accurate final values for $Kt/V$ and $PCRn$, and by inference $EKR_{jc}$.

The calculation of $EKR_{jc}$ in practice involves simple algebraic formulae that derive the necessary input data from the BUN time–concentration profile over the weekly interval. It is necessary then to have pre- and post-dialysis BUN and fluid assessments for every IHD treatment, providing a profile such as that illustrated in Figure 1, which can be considered as a series of subareas.
subareas. EKRjc can be calculated over a single dialysis cycle for regular or symmetric schedules (weekly, alternate day and daily), but only over a week for irregular or asymmetric schedules (2×, 3×, 4×, 5×, 6× per week). In clinical practice, a patient may not survive or dialyse for as much as a week, and EKRjc can be calculated over the dialysis cycles that are available.

The steps of a suggested algorithm for the calculation of EKRjc over a weekly interval are as follows, and can be undertaken in any commercial spreadsheet program.

**Step 1.** An estimate is made as to the patient V_T for input into subsequent calculations. For each of the n dialyses and interdialytic periods during the weekly interval, the pre- and post-dialysis V values [V_0(n) and V_T+(n)], respectively are estimated from V_T and serial body weight changes or fluid balance assessments.

**Step 2.** G is calculated for each of the interdialytic periods:

\[ G = \frac{V_0(\text{Next}) \times C_0(\text{Next}) - V_T \times C_{EQ}}{T_I} + Kr \times \frac{C_0(\text{Next}) + C_{EQ}}{2} \]

where \( C_0(\text{Next}) \) is pre-dialysis BUN for the following treatment, \( V_0(\text{Next}) \) is pre-dialysis urea distribution volume for the following treatment, \( C_{EQ} \) is the equilibrated post-dialysis BUN concentration, and \( T_D \) and \( T_I \) are the intradialytic and interdialytic duration, respectively. As with all urea kinetic algorithms, G is extrapolated to the preceding dialytic interval, so that a total net urea generation per cycle (A_Cy) can be computed: \( A_Cy = G \times (T_D + T_I) \). The weekly total generation (A_WK) is then calculated by simple addition: \( A_WK = A_{CY(1)} + A_{CY(2)} + \cdots + A_{LAST(n)} \), which is then time averaged over the weekly interval. \( C_{EQ} \) is estimated using the method of Tattersall et al. [33]:

\[ C_{EQ} = C_0 \times (C_T/C_0)^{T/[T+35]} \]

**Step 3.** AUC for the weekly interval is calculated. For IHD, areas comprised of each of the intradialytic subareas (AUC_I) were calculated using the logarithmic mean of pre- and post-dialysis BUN:

\[ \text{AUC}_D = T_D \times \frac{C_0 - C_{EQ}}{\ln(C_0/C_{EQ})} \]

The logarithmic mean is the analytical expression that averages a parameter undergoing a pure exponential decay. This description fits the decline of BUN during dialysis so long as the ratio of Kd/G is high, as described by the simplified equation \( C(t) = C_0 \times e^{-Kt/V} \). The logarithmic mean is thus the best estimate of time averaged intradialytic BUN concentration during IHD. For CVVHD, the decline of BUN is no longer purely exponential as the ratio of Kd/G is low, and we have found empirically that another formula using an approximation based on parabolic decay provided a better estimate of time averaged intradialytic BUN concentration (TACD) than the logarithmic mean [TACD = C_EQ + (C_0 - C_EQ)/3]. Therefore:

\[ \text{AUC}_D = \left( \frac{C_{EQ} + C_0 - C_{EQ}}{3} \right) \times T_D \]

Areas comprised of each of the intradialytic subareas (AUC_I) for all therapies were calculated using the arithmetic mean for BUN:

\[ \text{AUC}_I = T_I \times \frac{C_0(\text{Next}) + C_{EQ}}{2} \]

The AUC for the entire weekly interval (AUC_WK) was calculated by simple addition:

\[ \text{AUC}_W = \text{AUC}_D(1) + \text{AUC}_I(1) + \text{AUC}_I(2) + \cdots + \text{AUC}_I(n) \]

and TAC_WK calculated by:

\[ \text{TAC}_W = \text{AUC}_W / T_W \]

**Step 4.** M_WK is calculated from a form of (mass balance) core equation 1:

\[ M_WK = A_W - (V_W \times C_W - V_0 \times C_0) \]

**Step 5.** EKRjc is calculated using core equation 4 and then core equation 5, where \( V_{TM} \) is the average post-dialysis urea distribution volume over the weekly interval.

**Step 6.** If desired, dEKRjc may be calculated using core equation 6:

\[ K_{RC} = (Kr \times 40000) / V_{TM} \]

\[ d\text{EKRjc} = \text{EKRjc} - K_{RC} \]

**Appendix 2**

Detailed calculations of EKRjc and dEKRjc over a period of observation are shown for patient 3 of the clinical cohort (Table 8).
<table>
<thead>
<tr>
<th>Clinical data (units)</th>
<th>Symbols</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dialysis urea distribution volume (ml)</td>
<td>V_{0(n)}</td>
<td>43 440</td>
<td>42 640</td>
<td>44 190</td>
<td>45 090</td>
<td>46 590</td>
</tr>
<tr>
<td>Post-dialysis urea distribution volume (ml)</td>
<td>V_{T(n)}</td>
<td>42 700</td>
<td>42 000</td>
<td>44 100</td>
<td>44 000</td>
<td>43 800</td>
</tr>
<tr>
<td>Next pre-dialysis urea distribution volume (ml)</td>
<td>V_{0(next)}</td>
<td>42 640</td>
<td>44 190</td>
<td>45 090</td>
<td>46 590</td>
<td>45 840</td>
</tr>
<tr>
<td>Pre-dialysis BUN (mg/ml)</td>
<td>C_{0(n)}</td>
<td>1.43</td>
<td>1.04</td>
<td>0.77</td>
<td>0.68</td>
<td>0.66</td>
</tr>
<tr>
<td>Equilibrated post-dialysis BUN (mg/ml)</td>
<td>C_{EQ(n)}</td>
<td>0.93</td>
<td>0.66</td>
<td>0.39</td>
<td>0.36</td>
<td>0.32</td>
</tr>
<tr>
<td>Next pre-dialysis BUN (mg/ml)</td>
<td>C_{0(next)}</td>
<td>1.04</td>
<td>0.77</td>
<td>0.68</td>
<td>0.66</td>
<td>0.65</td>
</tr>
<tr>
<td>Native renal urea clearance (ml/ min)</td>
<td>Kr</td>
<td>3.2</td>
<td>2.8</td>
<td>3</td>
<td>2.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Treatment duration (min)</td>
<td>T_{D(n)}</td>
<td>120</td>
<td>180</td>
<td>240</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>Interdialytic duration (min)</td>
<td>T_{I(n)}</td>
<td>1380</td>
<td>3000</td>
<td>3720</td>
<td>2880</td>
<td>2400</td>
</tr>
</tbody>
</table>

**Equations**

\[ TT = T_D + T_I \]
\[ \text{Sum } TT = \Sigma TT \]
\[ G = \frac{(V_{0(next)} \times C_{0(next)} - V_T \times C_{EQ})}{T_I + Kr \times (C_{EQ} + C_{0(next)})/2} \]
\[ nPCR = \frac{(9.35 \times G + 0.294 \times V_T/1000)}{(V_T/580)} \]
\[ A_{CY} = G \times TT \]
\[ \text{Sum } A_{CY} = \Sigma A_{CY} \]
\[ V_{0(next)} \times C_{0(next)} - V_T \times C_0 \]
\[ \text{Sum } V_{0(next)} \times C_{0(next)} - V_T \times C_0 \]
\[ V_T \times TT \]
\[ \text{Sum } V_T \times TT = \Sigma V_T \times TT \]
\[ V_{TM} = V_T \times TT / \Sigma TT \]
\[ \text{EK RJc} = \frac{\text{EK RJc} \times 40000}{V_{TM}} \]
\[ K_{rc} = \frac{K_r \times 40000}{V_{TM}} \]
\[ d\text{EK RJc} = \text{EK RJc} - K_{rc} \]

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