Fractional uptake rate revisited -
theory and clinical validation

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Fractional uptake rate (FUR)

= fraction of injected activity entering the kidney per unit time

Rutland M.
Glomerular filtration rate without blood sampling.
*Nucl Med Commun* 1983; 4:425-433

Rutland M., Que L., Hassan I.M.
"FUR" - one size suits all.
Fractional uptake rate (FUR)

= fraction of injected activity entering the kidney per unit time

\[ FUR = \frac{kP(0)}{D} \quad [s^{-1}] = [s^{-1}][cps]/[cps] \]
Fractional uptake rate (FUR)

\[ FUR = kP(0) / D \quad [s^{-1}] = [s^{-1}][cps]/[cps] \]

\( k \) = slope of Patlak-Rutland plot
**Fractional uptake rate (FUR)**

= fraction of injected activity entering the kidney per unit time

\[
FUR = \frac{kP(0)}{D} \quad \left[ s^{-1} \right] = \left[ s^{-1} \right][cps]/[cps]
\]

- \( k \) = slope of Patlak-Rutland plot
- \( P(0) \) = precordial curve extrapolated to \( t = 0 \)
Fractional uptake rate (FUR)

= fraction of injected activity entering the kidney per unit time

\[ FUR = \frac{kP(0)}{D} \quad \text{[s}^{-1}\text{]} = \text{[s}^{-1}\text{]} \text{[cps]} / \text{[cps]} \]

- \( k \) = slope of Patlak-Rutland plot
- \( D \) = administered activity
- \( P(0) \) = precordial curve extrapolated to \( t = 0 \)
Alternative interpretation of FUR

\[ \frac{dR(t)}{dt} = Zc(t) \]

**Stewart-Hamilton principle**
 uptake rate in an organ is proportional to plasma concentration, constant of proportionality is the organ clearance
Alternative interpretation of FUR

\[ \frac{dR(t)}{dt} = Zc(t) \]

Stewart-Hamilton principle

- uptake rate in an organ is proportional to plasma concentration, constant of proportionality is the organ clearance

\[ \frac{dR(t)}{dt} \] = uptake rate in the kidney

\[ R(t) \] = depth-corrected kidney counts after tissue and vascular background subtraction
Alternative interpretation of FUR

\[ \frac{dR(t)}{dt} = Zc(t) \]

Stewart-Hamilton principle: uptake rate in an organ is proportional to plasma concentration, constant of proportionality is the organ clearance

\[ Z = \text{renal clearance} \]

\[ \frac{dR(t)}{dt} = \text{uptake rate in the kidney} \]

\[ R(t) = \text{depth-corrected kidney counts after tissue and vascular background subtraction} \]
Alternative interpretation of FUR

\[ \frac{dR(t)}{dt} = Zc(t) \]

**Stewart-Hamilton principle**
- uptake rate in an organ is proportional to plasma concentration, constant of proportionality is the organ clearance

**c(t)** = plasma concentration

**Z** = renal clearance

\[ \frac{dR(t)}{dt} = \text{uptake rate in the kidney} \]

\[ R(t) = \text{depth-corrected kidney} \]

\[ \text{counts after tissue and vascular background subtraction} \]
Alternative interpretation of FUR

\[
dR(t) / dt = Z c(t)
\]

Stewart-Hamilton principle

\[
dR(0) / dt = Z D / V_P
\]

\[c(0) = D / V_P\]

\[D = \text{injected activity}\]

\[V_P = \text{total plasma volume}\]
Alternative interpretation of FUR

\[
d\frac{R(t)}{dt} = Zc(t)
\]

\[
d\frac{R(0)}{dt} = \frac{ZD}{V_P}
\]

\[c(0) = \frac{D}{V_P}\]

\[D = \text{injected activity}\]

\[V_P = \text{total plasma volume}\]

\[\text{d}R(0)/\text{dt cannot be measured reliably}\]
Alternative interpretation of FUR

\[ \frac{dR(t)}{dt} = Zc(t) \]  
\[ \frac{dR(0)}{dt} = \frac{ZD}{V_P} \]  
\[ kP(0) = \frac{ZD}{V_P} \]

Stewart-Hamilton principle

\[ c(0) = \frac{D}{V_P} \]

\[ \frac{dR(0)}{dt} = kP(0) \]
tracer entering the kidney at \( t = 0 \)

\( k \) = uptake constant

\( P(0) \) = precordial curve extrapolated to \( t = 0 \)
Alternative interpretation of FUR

\[ \frac{dR(t)}{dt} = Zc(t) \]
\[ \frac{dR(0)}{dt} = \frac{ZD}{V_P} \]
\[ kP(0) = \frac{ZD}{V_P} \]
\[ FUR = \frac{kP(0)}{D} = \frac{Z}{V_P} \]

Stewart-Hamilton principle

\[ c(0) = \frac{D}{V_P} \]
\[ \frac{dR(0)}{dt} = kP(0) \]
**Alternative interpretation of FUR**

\[
\frac{dR(t)}{dt} = Zc(t) \quad \text{(Stewart-Hamilton principle)}
\]

\[
\frac{dR(0)}{dt} = \frac{ZD}{V_p}
\]

\[
kP(0) = \frac{ZD}{V_p}
\]

\[
FUR = \frac{kP(0)}{D} = \frac{Z}{V_p}
\]

\[
\frac{dR(0)}{dt} = kP(0)
\]

= fraction of injected dose entering the kidney per unit time
Alternative interpretation of FUR

\[ \frac{dR(t)}{dt} = Zc(t) \]  
\[ \frac{dR(0)}{dt} = ZD/V_p \]  
\[ kP(0) = ZD/V_p \]  
\[ FUR = \frac{kP(0)}{D} = \frac{Z}{V_p} \]

Stewart-Hamilton principle

\[ c(0) = \frac{D}{V_p} \]

\[ \frac{dR(0)}{dt} = kP(0) \]

= fraction of total plasma volume cleared by the kidney per unit time

= fraction of injected dose entering the kidney per unit time
Alternative model of renal uptake

\[ k_L \int P(t)dt + k_R \int P(t)dt + k_E \int P(t)dt + k_P P(t) = D \]

- left kidney
- right kidney
- elsewhere
- plasma = total
Alternative model of renal uptake

\[ D = k_{\text{lumped}} \int_{0}^{t} P(t) \, dt + k_P P(t) \]

amount removed from plasma up to time \( t \)
Alternative model of renal uptake

\[ D = k_{lumped} \int_0^t P(t) \, dt + k_P P(t) \]

- residue in plasma at time \( t \)
- amount removed from plasma up to time \( t \)
Alternative model of renal uptake

\[ D = k_{lumped} \int_{0}^{t} P(t) dt + k_P P(t) \]

- \( k_{lumped} \) = the sum of uptake constants \( k_L + k_R + k_E \)
- Residue in plasma at time \( t \)
- Amount removed from plasma up to time \( t \)
Alternative model of renal uptake

\[ k_{\text{lumped}} = \text{the sum of uptake constants } k_L + k_R + k_E \]

\[ D = k_{\text{lumped}} \int_0^t P(t) dt + k_P P(t) \]

\[ k_P = V_P / V_H = \text{constant scaling plasma volume in the heart ROI } (V_H) \text{ to total plasma volume } (V_P) - \text{how many times } V_H \text{ included in } V_P \]
Alternative calculation of FUR

\[ k_{lumped} \left[ \int \frac{P(t) \, dt}{P(t)} \right] + k_p = \frac{D}{P(t)} \]

\( k_p \) is obtained from direct solution of an alternative model or as an intercept of a straight line after dividing both sides of model equation by \( P(t) \)
Alternative calculation of FUR

\[ k_{\text{lumped}} \left[ \int P(t) \, dt / P(t) \right] + k_P = D / P(t) \]

\[ R(t) = Z \int_0^t c(t) \, dt = Zk_P \int_0^t P(t) / V_P \]

Using \( k_P \) and Stewart-Hamilton principle, pure \( R(t) \) can be written in terms of renal clearance \( Z \) and plasma concentration \( k_P \int P(t) / V_P \)
Alternative calculation of FUR

\[ k_{\text{lumped}} \left[ \int P(t)dt / P(t) \right] + k_P = D / P(t) \]

\[ R(t) = Z \int_0^t c(t)dt = Zk_P \int_0^t P(t) / V_P \]

\[ R(t) / \int_0^t P(t) = k = k_P Z / V_P \]
Alternative calculation of FUR

\[ k_{\text{lumped}} \left[ \int P(t) dt / P(t) \right] + k_P = D / P(t) \]

\[ R(t) = Z \int_0^t c(t) dt = Zk_P \int_0^t P(t) / V_P \]

\[ R(t) / \int_0^t P(t) = k = k_P Z / V_P \]

\[ Z / V_P = k / k_P \]

simple expression for renal clearance as fraction of plasma volume per unit time

\[ k = \text{uptake const.}, \text{either } k_L, k_R, \text{ or } (k_L+k_R), \]

\[ k_P = \text{scaling const. of plasma volumes} \]

\[ V_P / V_H \text{ from alternative model} \]
Alternative calculation of FUR

\[ k_{\text{lumped}} \left[ \int P(t) \, dt / P(t) \right] + k_P = D / P(t) \]

\[ R(t) = Z \int_0^t c(t) \, dt = Z k_P \int_0^t P(t) / V_P \]

\[ R(t) / \int_0^t P(t) = k = k_P Z / V_P \]

\[ Z / V_P = k / k_P \]

\[ k_P = D / P(0) \]
Alternative calculation of FUR

\[ k_{_\text{lumped}} \left( \int P(t) \, dt / P(t) \right) + k_p = D / P(t) \]

\[ R(t) = Z \int_0^t c(t) \, dt = Z k_p \int_0^t P(t) / V_p \]

\[ R(t) / \int_0^t P(t) = k = k_p Z / V_p \]

\[ Z / V_p = k / k_p \]

\[ k_p = D / P(0) \]
Alternative calculation of FUR

\[ k_{\text{lumped}} \left[ \int P(t) \, dt / P(t) \right] + k_p = D / P(t) \]

\[ R(t) = Z \int_0^t c(t) \, dt = Zk_p \int_0^t P(t) / V_p \]

\[ R(t) / \int_0^t P(t) = k = k_p Z / V_p \]

\[ \frac{Z}{V_p} = \frac{k}{k_p} \]

\[ \frac{Z}{V_p} = \frac{k P(0)}{D} = \text{FUR} \]
\[ FUR = \frac{Z}{V_P} = \frac{kP(0)}{D} = \frac{P_s(0)}{D} \quad [\%V_p/\text{min}] \]

\[ V_P = 1645 \times BSA \quad \text{Dissmann et al, Klin Wschr, 1971} \]

\[ Z = V_P \times FUR = 1645 \times BSA \times FUR \quad [\text{ml/min}] \]

\[ Z_{\text{norm}} = Z \times 1.73 / BSA \]

\[ Z_{\text{norm}} = 1.73 \times 1645 \times BSA \times FUR / BSA \]

\[ Z_{\text{norm}} = 2846 \times FUR \quad [\text{ml/min}] \quad \text{- implicitly normalized for body size} \]
Motivation of the study

• is it possible to estimate total (absolute) renal MAG3 clearance in dynamic renal scintigraphy with better accuracy than that provided by current gamma-camera methods (though not as good as that provided by multiple samples)?

• is it possible to perform better when exploiting better detection techniques and data processing methods?
The aim of the study

• clinical validation of fractional uptake rate (FUR) in a clinical setting (routine clinical practice)
• comparison of FUR with currently used methods for measurement of renal function (MAG3 clearance)
• assessment of accuracy of measurement using data acquisition in two opposite projections, data analysis in the geometric-mean image, and application of image-processing procedures minimizing the user's interaction
Patients

- 111 patients (47 men and 64 women)
- age 53 ± 18 (15 - 86) years
- weight 78 ± 19 (45 - 143) kg
- height 168 ± 10 (145 - 192) cm
- BMI 27.7 ± 5.93 (17.36 - 51.89)
- Cr clearance 46 ± 36 (3 - 155) ml/min
- Cr clearance 42 ± 33 (2 - 155) ml/min/1.73m²
- <15 (11), 15-30 (11), 30-60 (16), 60-90 (5), 90< (7)
Methods

• MAG3
  198 ± 26 (145 - 301) MBq
  2.62 ± 0.45 (1.75 - 3.96) MBq/kg

• EDTA
  ≤ 3 MBq (n = 58)

• blood sampling
  40 - 50, 120, and 240 min

• dynamic renal study
  30 min (10" frames)

• images 128 x 128

• posterior + anterior proj.

• $^{57}$Co - flood source (n = 80)
Transmission measurement

\[ D = \ln\left(\frac{I_1 f}{I_2}\right) / -\mu \]

detector 2

detector 1
Methods

• laboratory data (SCr, 24-hrs creatinine clearance)
• Cockcroft-Gault & MDRD-abbreviated equations
• MAG3 - Russell et al 1989
• Taylor et al (JNM 1995, Radiology 1997)
• fractional uptake rate (FUR) [ml/min]
• criteria of agreement - correlation coefficient, regression coefficients, prediction errors calculated by cross validation
Prediction of creatinine clearance by $^{51}$Cr-EDTA and prediction equations

- 1st sample (120 min) $r = 0.82$  MAE = 15 ml/min
- 2nd sample (240 min) $r = 0.89$  MAE = 12 ml/min
- 1+2 samples $r = 0.94$  MAE = 9 ml/min
- Cockcroft-Gault $r = 0.94$  MAE = 9 ml/min
- MDRD - abbrev. $r = 0.91$  MAE = 10 ml/min

$r$ = correlation coefficient
MAE = mean absolute error of prediction [ml/min] obtained by cross-validation
Prediction of creatinine clearance by $^{51}$Cr-EDTA and prediction equations

<table>
<thead>
<tr>
<th>24-HRS CR CLEARANCE</th>
<th>&lt; 15 ml/min</th>
<th>≥ 15 ml/min</th>
<th>&lt; 30 ml/min</th>
<th>≥ 30 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>correlation</td>
<td>r</td>
<td>MAE [ml/min]</td>
<td>r</td>
<td>MAE [ml/min]</td>
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<tr>
<td>prediction error</td>
<td></td>
<td></td>
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<tr>
<td>EDTA (2 SAMPLES)</td>
<td>0.30</td>
<td>3.86</td>
<td>0.95</td>
<td>8</td>
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<tr>
<td></td>
<td>0.48</td>
<td>6.81</td>
<td>0.94</td>
<td>9</td>
</tr>
<tr>
<td>COCKFROFT - GAULT</td>
<td>0.45</td>
<td>3.03</td>
<td>0.92</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>0.76</td>
<td>4.39</td>
<td>0.88</td>
<td>12</td>
</tr>
<tr>
<td>MDRD (ABBREVIATED)</td>
<td>0.59</td>
<td>2.75</td>
<td>0.88</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>0.74</td>
<td>4.42</td>
<td>0.82</td>
<td>14</td>
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</tbody>
</table>

r = correlation coefficient
MAE = mean absolute error of prediction obtained by cross-validation [ml/min]
Prediction of creatinine clearance by MAG3 in-vitro and camera clearance

- Russell et al 1989 \( r = 0.86 \) \( \text{MAE} = 12 \text{ ml/min} \)
- Taylor et al 1995 \( r = 0.79 \) \( \text{MAE} = 14 \text{ ml/min} \)
- Taylor et al 1995 -vbg \( r = 0.86 \) \( \text{MAE} = 12 \text{ ml/min} \)
- FUR [ml/min] \( r = 0.85 \) \( \text{MAE} = 12 \text{ ml/min} \)
- plasma clearance \( r = 0.83 \) \( \text{MAE} = 13 \text{ ml/min} \)

\( r = \) correlation coefficient
\( \text{MAE} = \) mean absolute error of prediction [ml/min] obtained by cross-validation
Prediction of MAG3 one-sample clearance (Russell et al 1989) by Taylor's method

<table>
<thead>
<tr>
<th>TAYLOR et al 1995</th>
<th>POSTERIOR PROJECTION</th>
<th>GEOMETRIC MEAN</th>
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</thead>
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<tr>
<td></td>
<td>n</td>
<td>r</td>
</tr>
<tr>
<td>no bg subtraction</td>
<td>111</td>
<td>0.83</td>
</tr>
<tr>
<td>KD &amp; BT estimated</td>
<td></td>
<td></td>
</tr>
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<td>T &amp; V bg subtracted</td>
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<td>KD &amp; BT estimated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T &amp; V sub. Middleton</td>
<td>111</td>
<td>0.90</td>
</tr>
<tr>
<td>KD estim., BT meas.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prediction of MAG3 one-sample clearance (Russell et al 1989) by Taylor's method

- geometric mean tissue (lateral) and vascular background subtracted
- body thickness estimated
- $n = 111, r = 0.92, MAE = 27 \text{ ml/min}$

- geometric mean tissue and vascular background subtracted (Middleton)
- body thickness measured (flood)
- $n = 80, r = 0.95, MAE = 23 \text{ ml/min}$
Prediction of MAG3 one-sample clearance (Russell et al 1989) by FUR [ml/min]

<table>
<thead>
<tr>
<th>FUR [ml/min]</th>
<th>POSTERIOR PROJECTION</th>
<th>GEOMETRIC MEAN</th>
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<tr>
<td></td>
<td>n</td>
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<td>no bg subtraction KD &amp; BT estimated</td>
<td>111</td>
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<td>T &amp; V bg subtracted KD &amp; BT estimated</td>
<td>109</td>
<td>0.89</td>
</tr>
<tr>
<td>T &amp; V sub. Middleton KD estim., BT meas.</td>
<td>111</td>
<td>0.89</td>
</tr>
</tbody>
</table>
Prediction of MAG3 one-sample clearance (Russell et al 1989) by FUR [ml/min]

geometric mean tissue (lateral) and vascular background subtracted
body thickness estimated
n = 109, r = 0.92, MAE = 26 ml/min

geometric mean tissue and vascular background subtracted (Middleton)
body thickness measured (flood)
n = 80, r = 0.94, MAE = 25 ml/min
Distribution of absolute and relative errors of prediction
Prediction of MAG3 gamma-camera clearance (Taylor et al 1995) by FUR [ml/min]

\[ FUR [\text{ml/min}] \]

\[ \text{Taylor} [\text{ml/min}] \]

\[ n = 80, r = 0.9878, y = 17.926 + 0.933x \]

\[ m_x = 218.861, s_x = 126.485 (21.062 - 576.285) \]

\[ m_y = 222, s_y = 119 (21 - 504) \]

\[ \text{MAE} = 10 \text{ ml/min} \]

\[ \text{md} = 0, \text{sd} = 0.16 \]

\[ \text{normalized (x + y) / 2} \]

\[ \text{normalized y - x} \]
Prediction of MAG3 gamma-camera clearance (Taylor et al 1995) by FUR [ml/min]

- **Taylor et al 1995** - regression equation

\[
Z(1-2\text{min}) = 17.6 \left(100 \frac{R(1-2\text{min})}{D}\right) \left(\text{BSA}/1.73\right)+2.5
\]

- validated in 69 patients (Taylor et al 1997) in comparison with multiple sample MAG3 plasma clearance \((r = 0.80 - 0.98)\)

- agreement with one-sample plasma clearance (Russell et al 1989) was significantly improved by using geometric-mean data, measured transmission factors for AC, and vascular background subtraction
Prediction of MAG3 gamma-camera clearance (Taylor et al 1995) by FUR [ml/min]

- **Taylor et al 1995** - regression equation
  \[ Z(1-2\text{min}) = 17.6 \left(100 \frac{R(1-2\text{min})}{D}\right) \frac{\text{BSA}/1.73}{1.73} + 2.5 \]

- **FUR (Rutland 1983, 2000, modification 2007)** - physiological model
  \[ Z(\text{uptake}) = k \frac{P(0)}{D} = \frac{P_s(0)}{D} \]
  \[ P_s(0) = \text{proportional to the integral of } P_s(\text{uptake}) \]
  \[ \text{integral of } P_s(\text{uptake}) = R(1-2\text{min}) \]
Conclusions

• mean absolute error of prediction of MAG3 plasma clearance estimated by one-sample method (Russell et al 1989) was
  23 ml/min (r=0.95) - Taylor 1995, 1997
  24 ml/min (r=0.94) - FUR 1983, 2000, modif. 2007

Possible sources of error:
- combined inaccuracy of both types of methods
- higher absolute errors of high clearance values
Conclusions

• mean absolute error of prediction of MAG3 plasma clearance estimated by a gamma-camera method (Taylor et al 1995, 1997) was 10 ml/min ($r=0.99$) - FUR(1983,2000,modif. 2007)

Accuracy of both Taylor's method and FUR can be significantly improved by using geometric mean data, measured transmission factors for AC, and vascular background subtraction.
Conclusions

• measurement of MAG3 renal clearance using gamma camera methods by Taylor 1995 and FUR is sufficiently accurate to provide reliable estimation of total MAG3 renal clearance
• both methods perform equally well
• technical and time requirements for introduction and using either or both the methods in clinical practice including necessary additions (transmission measurements) are minimal