The Cockroft and Gault formula for estimation of creatinine clearance: a friendly deconstruction

J Alasdair Millar

Abstract

Aims To review the derivation of the Cockroft and Gault formula for estimating creatinine clearance from serum creatinine in a historical context.

Method The derivation described by Cockroft and Gault was reviewed, and an alternative formula was sought using the data reported in the paper.

Results Cockroft and Gault used 24 hour urine creatinine data expressed as mg/kg body weight and mathematical manipulation of a linear regression equation which introduced body weight as an independent variable into the formula. This involved a circular logic and may have been mathematically invalid. A more logical equation not containing body weight was derived from the data.

Conclusion The Cockcroft and Gault formula has been validated by long usage but the derivation appears logically insecure. Nevertheless, its role in estimating renal function at the bedside is established.

The Cockroft and Gault formula for estimating creatinine clearance (C\textsubscript{Cr}) as a proxy for glomerular filtration rate (GFR) has been in use for clinical and research purposes since its derivation in 1976.\textsuperscript{1} Recently it has been largely superceded by the eGFR, based on the MDRD formula\textsuperscript{2} $\frac{203.0154.12}{Cr^{1.73} \times \frac{1}{\sqrt{age}}}$ (omitting factors for sex and race) but remains a valuable bedside tool for estimating the need to adjust the doses of drugs that are cleared by the kidney in patients with renal dysfunction.

In this paper I review the derivation of the Cockcroft and Gault formula from a historical perspective and comment on its use at the bedside.

Methods

This work is based on an analysis of the paper by Donald W Cockroft and M Henry Gault in Nephron (1976)\textsuperscript{1} and some extrapolations therefrom. The formula as published was

$$C_{Cr} = \frac{(140 - \text{age})(\text{wt kg})}{72 \times S_{Cr} (\text{mg/100ml})}$$

or using molar units, $C_{Cr} = \frac{1.23 \times (140 - \text{age})(\text{wt kg})}{S_{Cr} (\mu\text{mol}/\text{L})}$

(Equation 1). An alternative formula without weight as a dependent variable was derived from the paper after calculating total 24 hr creatinine excretion, following the method described by Cockroft and Gault.

Derivation of the formula:

Cockroft and Gault studied 534 consecutive patients in whom creatinine clearance was measured on 2 or more occasions using serum and 24-hour urine creatinine concentrations. Ninety six percent of the patients were male. Patients (n = 29) were excluded if not in steady state (blood creatinine values differed by > 20%). A sub-group (“Group II”) used for the derivation of the formula (n = 236) was formed from “Group I” by further excluding patients whose 24-hr urine creatinine values differed by...
more than 20% (n = 173) or was < 10 mg/Kg (n = 31) or where the records were inadequate (n = 65).

Group II was augmented by re-inclusion of 23 patients who satisfied the second criteria but whose 24-
hour urine volume was > 500 ml (final n = 249).

The steps in deriving the formula were:

Step 1. The relationship between creatinine excretion expressed as mg/kg/24h (as the dependent
variable) (CrUV24/kg) was plotted against age (independent variable) after aggregating data into age
bands of 10 years (data given as table II in their paper).

Step 2. The equation for the curve was obtained by linear regression:

\[ CrUV_{24/kg} = 28 - 0.2 \times age \] (Equation 2)

Step 3. Both sides of the equation were multiplied by weight, to give

\[ CrUV_{24} (mg) = 28 - 0.2 \times age \times wt \ kg \] (Equation 3)

Step 4. Equation 3 for CrUV24 (mg) was inserted into the expression for creatinine clearance and
hence the final equation was derived:

\[ C_cr_{24} = \frac{CrUV_{24} \times 100}{1440 \times S_{cr}} = \frac{(28 - 0.2 \times age \times wt \ kg)}{72 S_{cr} \ mg/100ml} = \frac{(140 - age \ wt \ kg)}{72 S_{cr} \ mg/100ml} \]

Cockcroft and Gault validated their formula by comparing it to three other formulae3-5 for creatinine
clearance and against a nomogram published from Denmark,6 which contained body weight. Cockroft
and Gault noted that as the average weight in their Group II was 72 kg, their formula simplified to

\[ C_{cr} = \frac{(140 - age)}{Cr} \] for patients of average weight.

Comment and discussion

From a modern perspective, several aspects of the derivation of the Cockroft and
Gault formula require comment.

- The total number of patients studied (n= 249) was low by modern standards,
  though it represents a prodigious amount of clinical and laboratory work. By
  comparison, the derivation of the MDRD equation used data from 1070
  patients7 from the Modification of Diet in Renal Disease Study.8

- A modern analysis (of which the derivation of the MDRD equation is an
  example) would not have aggregated data into bands of age. This is
  statistically suspect since it decreases the degrees of freedom in the regression
  analysis. I believe the reason was the absence of computing power using
  statistical software packages that we now take for granted.

- In order to express urine creatinine data as mg/kg, Cockroft and Gault must
  have taken the measured 24 hour creatinine and divided by body weight. Thus
  the development of the formula uses circular logic because in Step 3 the
  regression equation is multiplied throughout by weight to re-express the
  dependent variable as 24 hr creatinine (mg) and thereby create a variable for
  weight on the right side of the equation and hence in the final formula.
  Furthermore, it is not clear whether the multiplication is by body weight as a
  measured variable or by ‘weight” (mass) as a dimension; either is
  mathematically suspect in this context.

- Note that the weight used throughout is the actual body weight, not some other
  measure of weight such as lean body mass.
It is possible to derive a valid equation from the Cockroft and Gault data that does not depend on weight, by calculation of the 24 hr urine creatinine according to each age group assuming that the average weight applies throughout, and using these data to follow the stepwise procedure used by the authors.

The new data are:

<table>
<thead>
<tr>
<th>Age</th>
<th>CrUV (mg/kg/24 h)</th>
<th>Wt (kg)</th>
<th>CrUV (mg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.6</td>
<td>23.6</td>
<td>72</td>
<td>1699</td>
</tr>
<tr>
<td>34.6</td>
<td>20.4</td>
<td>72</td>
<td>1469</td>
</tr>
<tr>
<td>46.2</td>
<td>19.2</td>
<td>72</td>
<td>1382</td>
</tr>
<tr>
<td>54.4</td>
<td>16.9</td>
<td>72</td>
<td>1217</td>
</tr>
<tr>
<td>64.6</td>
<td>15.2</td>
<td>72</td>
<td>1094</td>
</tr>
<tr>
<td>74.4</td>
<td>12.6</td>
<td>72</td>
<td>907</td>
</tr>
<tr>
<td>85.1</td>
<td>12.1</td>
<td>72</td>
<td>871</td>
</tr>
</tbody>
</table>

Regressing CrUV (mg/24 h) on weight gives the linear equation

\[ CrUV/24(mg) = -13.9 \times \text{age} + 1997 \] (Compare with equation 2 above). When this equation is substituted into the equation for creatinine clearance, the result after collection of terms becomes

\[ C_{cr} = \frac{144 - \text{age}}{S_{cr}}, \text{ or in SI units, } C_{cr} = \frac{85 \times (144 - \text{age})}{S_{cr}} \]

(Equation 4). This is almost identical to the Cockroft and Gault formula when it is applied to patients of average weight, but this is to be expected since the derivation involved using the constant factor, equal to average weight, of 72. I did not study the performance of this formula in detail and mention it here only to emphasize the circumstances surrounding the inclusion of body weight in the Cockroft and Gault formula. However, it is of interest that body weight was not a significant independent variable in the derivation of eGFR using the MDRD Study patients.

Because 96% of Cockroft and Gault’s patients were male, the original formula applies only to male patients. The creatinine clearance in females is about 85% of males. Hence the use of the formula at the bedside is greatly simplified if the factor of 1.23 in equation 1 is ignored and the result is regarded as the value of \( CL_{Cr} \) in females. For a male patient, simply add 20%.

**Conclusion**

The Cockroft and Gault formula has stood the test of time and hence may be said to have been validated by usage. However, its derivation was unusual and involved circular logic. The introduction of the weight variable appears to have come from an arbitrary regression of 24 hr creatinine excretion (as mg/kg) on age, with a subsequent manipulation that caused body weight to appear as an independent variable in the published formula.

With the possible exception of formula III, all the pre-existing formulae for creatinine clearance listed by Cockroft and Gault gave usable values, as does Equation 4 above (results not shown). Thus it appears that there are a range of potentially usable formulae for CCr that are reciprocal functions of serum creatinine.
but vary in the other dependent variables and scaling factors. This is confirmed by the example of the eGFR equation in which the term $Cr^{-1.154} = \frac{1}{Cr^{1.154}} \approx \frac{1}{Cr}$.

**Historical note**

Professor Cockroft graduated in medicine at the University of British Columbia in 1950. He now works as a researcher in asthma at the Department of Medicine, University of Saskatchewan in Saskatoon. His career has taken him there via San Jose, Montreal, Vancouver and Hamilton (Ontario).

This author approached Professor Cockcroft at his place of work and requested clarification on the reason for including weight in the regression equation. Professor Cockcroft replied that the primary interest of the work was effectively to validate the values for CL\textsubscript{Cr} obtained from the Danish nomogram, which contains weight, but he could not recall the specific reason for the choice of regression. In the event, his objective was secured (see Cockroft and Gault, Table III).

Professor Gault died in May 2003. His obituary from the University of Newfoundland describes him as a pioneer in the field of nephrology. As a young man he survived 31 wartime bombing missions over Germany with the Royal Canadian Air Force. His subsequent nephrology career was in Montreal and Newfoundland.

**Competing interests:** None declared.

**Author information:** J Alasdair Millar, Consultant Physician and Clinical Director, Medical Department, Southland Hospital, Invercargill.

**Correspondence:** J Alasdair Millar, Consultant Director Acute Care Services, Albany Regional Hospital, Warden Ave, Albany, WA 6330, Australia. Email Alasdair.millar@health.wa.gov.au

**References:**