Original Article

Reproducibilities and responses to food intake of GFR measured with chromium-51-EDTA and iohexol simultaneously and independently in normal subjects

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Abstract

Background. The aim was to evaluate the reproducibility of glomerular filtration rate (GFR) measured with iohexol and its response to food in a direct and independent comparison with Cr-51-ethylenediaminetetraacetic acid (EDTA), and examine the influence of two different whole body scaling parameters, body surface area (BSA) and extracellular fluid volume (ECV).

Methods. Fasting and non-fasting GFR were measured in 20 normal volunteers using Cr-51-EDTA and iohexol, simultaneously injected into opposite arms. In 10, the fasting study was repeated. Venous samples obtained bilaterally 20, 40, 60, 120, 180 and 240 min after injection were assayed for indicator injected contralaterally—Cr-51-EDTA by well-counting and iohexol by X-ray fluorescence. GFR scaled to BSA was measured from six samples (GFR/BSA6) and from the last three (GFR/BSA3). GFR scaled to ECV was calculated as the mean transit time of marker using six samples (GFR/ECV6) or the last three (GFR/ECV3).

Results. GFR/BSA3 was reproducible (coefficient of variations of 7.4% for Cr-51-EDTA and 7.6% for iohexol). Using Cr-51-EDTA, GFR/ECV3 (9.1%) and GFR/ECV6 (7.7%) were as reproducible as GFR/BSA6 (both 8.1%). However, GFR/ECV3 measured with iohexol had poorer reproducibility (16.8%). Food resulted in an increase in scaled GFR of about 5 ml/min but this was statistically significant only with respect to GFR/BSA (measured with Cr-51-EDTA or iohexol) and not GFR/ECV.

Conclusions. Measured with Cr-51-EDTA, but not iohexol, GFR/ECV was as reproducible as GFR/BSA. GFR/BSA, measured with Cr-51-EDTA or iohexol, but not GFR/ECV, significantly increased after food.

Keywords: Cr-51-EDTA; extracellular fluid volume; glomerular filtration rate; iohexol; X-ray fluorescence

Introduction

Glomerular filtration rate (GFR) is the best measure of overall renal function. Steady-state urinary clearance of inulin is the gold standard method for measuring GFR but it is a cumbersome and difficult technique to perform and has consequently been replaced as the clinical gold standard by the measurement of plasma clearance following bolus injection of alternative filtration markers, most commonly, at least in Europe, the radioactive compound, Cr-51-ethylenediaminetetraacetic acid (EDTA). Plasma clearance is most accurately measured from multiple blood samples obtained without waiting for complete mixing of the indicator throughout its distribution volume (which is the extracellular fluid space), i.e. the two-compartment approach. Sampling starting from after complete mixing (which takes about 2 h) is almost as accurate (one-compartment approach) and is known as the slope–intercept technique.

In order to compare individuals of different sizes, GFR is conventionally scaled to body surface area (BSA). This, however, has been challenged on several grounds [1] and alternative scaling variables suggested to replace it, including extracellular fluid volume (ECV) [2]. From the viewpoint of technical simplicity, ECV is an attractive option because GFR per unit ECV requires the measurement of only the mean waiting time of the marker in the extracellular fluid space before filtration; i.e. it is a primary variable in its own right and, in the one-compartment scenario, is simply the rate constant of the terminal exponential of the plasma clearance curve. Since it requires knowledge only of this rate constant, this technique for measuring scaled GFR is known as slope-only technique [3]. In contrast, BSA is not always easy to measure or, in some patient groups, appropriate, especially the obese [4] and children [5].

In some circumstances, a technically simple but accurate method of measuring GFR using a non-radioactive indicator would be advantageous. One such circumstance is the remote measurement of GFR by courier or postal transportation of patient blood samples to a specialist centre for analysis, as promoted recently by Niculescu-Duvaz et al.
Iohexol for measuring GFR

An obvious candidate for this approach is iohexol because it is non-radioactive, stable, cheap, easily available and non-toxic in the required doses [7]. Moreover, it has been validated for the measurement of GFR in several comparisons with Cr-51-EDTA [7–14] or inulin clearance [15,16]. The slope-only technique based on iohexol would be a particularly advantageous approach for a postal service because the amount of administered indicator would not need to be known, significantly simplifying the procedure.

To be described as near-ideal, it is essential to show that a filtration marker is reproducible in its measurement of GFR and is easily able to show changes in GFR that follow physiological stimuli, such as a meal [17–19]. Whilst the reproducibilities of GFR based on both iohexol [20,21] and Cr-51-EDTA [22,23] have previously been separately determined, head-to-head comparisons of these two indicators have generally been restricted to correlation analysis of simultaneously measured GFR in patient cohorts with wide ranges of renal function.

With the aim of further testing the reliability of not only iohexol for measuring GFR but also the alternative scaling variable, ECV, we simultaneously and independently compared the reproducibilities of GFR measured with iohexol and scaled to BSA and ECV against the corresponding values measured with Cr-51-EDTA. Because of the potential advantages of ECV as a whole body scaling parameter for GFR, we also examined the reproducibility of GFR scaled to ECV in both one-compartment and two-compartment scenarios.

Methods

Subjects

Twenty healthy volunteers [7 male, 13 female; age range 30–59 (median 45); body mass index 18–34 (22) kg/m²] with no history of allergy were included. Age range 30–59 (median 45); body mass index 18–34 (22) kg/m². Twenty healthy volunteers [7 male, 13 female; age range 30–59 (median 45); body mass index 18–34 (22) kg/m²] with no history of allergy were included.

Administration of markers

The markers were injected i.v. in close sequence in separate arms. The time half way through injection was noted as the time of injection. The Cr-51-EDTA usually took <5 s to administer but the larger volume of viscous iohexol took up to 30 s to inject. The volume of administered Cr-51-EDTA was measured from the total weight drawn up into the syringe assuming no post-injection residue and a density of the Cr-51-EDTA solution of 1 g/ml. The syringes containing the marker were flushed several times with saline to ensure complete administration of the weighed amount.

Blood sampling

In addition to a baseline sample, 10-ml blood samples were taken from both lines nominally at 20, 40, 60, 120, 180 and 240 min after marker administration. Approximately 3 ml of liquid was withdrawn from the line and discarded prior to the collection of each blood sample. The mid-time point time of sampling was taken as the sampling time. Line patency was maintained with heparin-saline. The samples were transferred from the syringe into heparinized glass tubes, centrifuged at 800–1000 g for 15 min and plasma separated.

Sample analysis

Each marker was assayed in samples contralateral to the side of injection.

Cr-51-EDTA. For each stock solution of Cr-51-EDTA, 1:1000 diluted standards were prepared. Aliquots of plasma, standards and water (as a blank) were counted in an automatic gamma counter (Wallac 1480 ‘Wizard 3’, Turku, Finland) for 1000 s with an energy window suitable for Cr-51. Appropriate corrections were made for counter dead-time and background.

Iohexol. Iohexol was assayed by X-ray fluorescence. In order to calibrate the analyser (Oxford Instruments; Lab-X3500; www.oxinst.com), a series of seven plasma standards were prepared containing iohexol concentrations of 0, 0.34, 0.69, 1.03, 1.36, 1.72 and 3.39 g/l (Figure 1). For each sample, a holder was assembled in which the sample is separated from the irradiation beam and the detector by a taut piece of 6 µm thick film. Three millilitres of the sample was transferred to the sample holder immediately prior to analysis. Once the sample was inside the analyser, air was displaced from the measuring chamber by helium gas to prevent emission of characteristic X-rays from argon in the air or absorption of the characteristic X-rays from the iodine by argon. The sample was irradiated for 300 s, the X-ray target being palladium, the voltage 9 kV and the tube current 100 µA. The average counts per second (cps) was reported using an energy window that was optimized for the L-characteristic X-rays from iodine at ~4–5 keV.
For each sample, the irradiation was repeated three times to confirm the reproducibility of the measurement, the average of the three being used. For each subject, the cps from the baseline blood sample from that subject on that day was used to correct the other sample measurements before using the calibration to obtain an absolute concentration of iohexol. The effective precision of the iohexol assay (i.e. in the range of plasma concentrations encountered; Figure 1) was estimated to be 4.9%.

**Data analysis**

**Curve fitting.** The plasma time–concentration curves for both markers were bi-exponential between 20 and 240 min. No samples were obtained before 20 min; otherwise the clearance curve would have been a triple exponential [24]. A bi-exponential fit to the six-sample curve was therefore performed using firstly a two-stage curve-stripping procedure and secondly iterative fitting. In the two-stage curve stripping procedure, the fast and slow exponentials were stripped in the conventional way. The fast exponential was then subtracted from the last three sample concentrations and a second slow exponential fitted to the resulting values. This was then subtracted from the initial three sample concentrations to give a second fast exponential. The zero-time intercepts of fast and slow exponentials extracted by these two curve-fitting procedures were denoted by $A$ and $B$, respectively, and the corresponding rate constants by $\alpha_1$ and $\alpha_2$.

**Measurement of GFR based on all six samples.** GFR was calculated from $A$, $\alpha_1$, $B$ and $\alpha_2$ using the following conventional formula that equates clearance to the quotient of injected marker divided by the area under the clearance curve between times zero and infinity:

\[
\text{GFR} = \frac{\text{injected activity or dose}}{(A/\alpha_1) + (B/\alpha_2)}.
\]

Using the equation of Du Bois and Du Bois [25] to compute BSA from subject height and weight, GFR was then scaled to 1.73 m$^2$ to give GFR/BSA6.
Measurement of GFR based on the final three samples. A single exponential with intercept $B'$ and rate constant $\alpha_2'$ (to be distinguished from $B$ and $\alpha_2$ based on six-sample fitting) was fitted to the last three sample points. The reciprocal of $B'$ is the one-compartment distribution volume, $V_d$. Slope–intercept GFR was then calculated as the product of $\alpha_2'$ and $V_d$ and scaled to 1.73 m$^2$. It was corrected for the one-compartment assumption using second-order polynomials (of the form $y = A + Bx + Cx^2$) based on the relations between one-compartment and two-compartment GFR to give GFR/BSA3. The formula for iohexol (in which $A = 0$, $B = 1.0022$ and $C = -0.00131$) was derived from our own database of 110 six-sample iohexol clearances. With respect to Cr-51-EDTA data, three-sample GFR was corrected for the one-compartment assumption using the second-order polynomial formula of Brochner-Mortensen [26].

Measurement of mean marker residence time in the ECV using six samples. Any individual molecule of indicator within the extracellular fluid (assumed to be the same as the indicator’s distribution volume) will wait a certain amount of time before undergoing glomerular filtration. The mean waiting time of all the molecules, i.e. transit time ($T$), can be calculated from the following equation [27]:

$$T = \frac{(A/\alpha_1^2) + (B/\alpha_2^2)}{(A/\alpha_1) + (B/\alpha_2)}.$$  \hspace{1cm} (2)

The reciprocal of $T$ is the rate at which the ECV is ‘turned over’ by GFR and is therefore a measure of GFR that is already scaled to ECV. This scaled version of GFR is denoted by GFR/ECV or, as it was based on six samples, GFR/ECV6. Multiplication of GFR (ml/min) by $T$ (min) gives ECV (ml). ECV was then scaled to a BSA of 1.73 m$^2$.

Measurement of mean marker residence time in the ECV using the last three samples. The variable $\alpha_2'$ (with units of min$^{-1}$) is also an estimate of GFR/ECV (ml/min/ml = min$^{-1}$), which, as it was based on the three samples between 2 and 4 h, was denoted by GFR/ECV3. As for GFR/BSA3, GFR/ECV3 also needs correcting for the one-compartment assumption. For iohexol data, GFR/ECV3 was therefore corrected using a second-order polynomial derived from our own database of 110 iohexol clearances in which $A = 0$, $B = 1.0526$ and $C = 5.17$. With respect to Cr-51-EDTA, correction for the one-compartment assumption was based on $\alpha_2'$ using a formula in which $A = 0$, $B = 1$ and $C = 15.4$, similar to that reported by Peters et al. [28].

Statistics

Reproducibility. Estimates of repeatability were made from within-subject variance for the volunteers who had repeat fasting measurements. The within-subject variance (CV) was calculated from the residual mean square from one-way analysis of variance [29]:

$$CV = \left[\frac{\Sigma(x_1 - x_2)^2/2n}{\Sigma x_1 + \Sigma x_2}/2n\right]^{0.5}$$  \hspace{1cm} (3)

where $x_1$ and $x_2$ refer to first and second measurements and $n$ is number of paired measurements.

Comparison of repeatability between different methods and markers was made from the $F$-test on the variance of the differences between repeat measurements.

The standard deviation (SD) of the differences between repeat measures of GFR approximates to $[(SD \text{ of the real differences})^2 + 2 \text{ (measurement error)}^2]^{0.5}$.

Effect of food intake. The difference between fasting and non-fasting GFR was evaluated for all measures of GFR using the paired Student $t$-test. For volunteers with two fasting measurements, the difference was based on the first of the two.

Results

Curve stripping versus iterative fitting

Six-sample GFR based on iterative fitting was less reproducible than six-sample GFR based on two-stage curve fitting, whether scaled to BSA or ECV (results not shown). Six-sample GFR and ECV values are therefore reported only for two-stage curve stripping.

Scaling ECV

ECV showed a marginally better correlation with BSA than with its more traditional scaling parameter, body weight (results not shown). Mean fasting ECV/BSA was 13.5 (SD 1.0) L for Cr-51-EDTA and 13.2 (1.7) L for iohexol. Mean non-fasting ECV/BSA was 13.7 (1.5) for Cr-51-EDTA and 13.6 (1.7) for iohexol, not significantly different from fasting values. To obtain GFR/ECV numerically comparable with GFR/BSA, GFR/ECV (measured with either Cr-51-EDTA or iohexol) was therefore multiplied by 13.500.

Reproducibility

Measured with Cr-51-EDTA, there were no significant differences between the reproducibilities of GFR/BSA3, GFR/BSA6, GFR/ECV3 and GFR/ECV6 (Table 1). For iohexol, however, the within-subject variances of GFR/ECV3 and GFR/ECV6 were both significantly higher ($P < 0.05$) than GFR/BSA3, but not GFR/BSA6. The within-subject variances of GFR/ECV3 and GFR/ECV6 based on iohexol were both significantly higher than the corresponding variances recorded with Cr-51-EDTA, but there were no significant differences between the two markers with respect to GFR/BSA3 and GFR/BSA6.

The changes between the two separate, simultaneous and independent measurements of fasting GFR values based respectively on Cr-51-EDTA and iohexol correlated with each other (Figure 2), although not significantly with respect to GFR/ECV3, indicating that the variation between the two measurements partly reflects real changes in filtration function.

Effect of a light meal

Food intake consistently resulted in small increases in GFR values but these were significant only when scaled to BSA (Table 2). The corresponding food-induced changes in GFR
Table 1. Reproducibilities of fasting GFR/BSA (ml/min/1.73 m²) and GFR/ECV (ml/min/13.5 l) measured on two separate occasions in 10 normal subjects with Cr-51-EDTA and iohexol

<table>
<thead>
<tr>
<th></th>
<th>Mean difference between replicates</th>
<th>SD of differences</th>
<th>Within subject standard deviation</th>
<th>CV%</th>
</tr>
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<tr>
<td><strong>Cr-51-EDTA</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>GFR/BSA3</td>
<td>88.2</td>
<td>0.4</td>
<td>9.7</td>
<td>7.4</td>
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<tr>
<td>GFR/BSA6</td>
<td>89.9</td>
<td>2.4</td>
<td>10.6</td>
<td>8.1</td>
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<tr>
<td>GFR/ECV3</td>
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<td>5.8</td>
<td>10.4</td>
<td>9.1</td>
</tr>
<tr>
<td>GFR/ECV6</td>
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<td>5.4</td>
<td>8.9</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>Iohexol</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GFR/BSA3</td>
<td>83.8</td>
<td>0.6</td>
<td>9.5</td>
<td>7.6</td>
</tr>
<tr>
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<td>1.9</td>
<td>12.9</td>
<td>10.4</td>
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<tr>
<td>GFR/ECV3</td>
<td>87.5</td>
<td>5.9</td>
<td>21.1a</td>
<td>16.8b</td>
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<tr>
<td>GFR/ECV6</td>
<td>87.8</td>
<td>5.4</td>
<td>17.0a</td>
<td>13.2b</td>
</tr>
</tbody>
</table>

*aSignificantly different compared with corresponding variable measured with Cr-51-EDTA.

*bSignificantly different compared with GFR/BSA3 (iohexol).

Fig. 2. Relations between corresponding individual fractional changes in GFR values simultaneously measured with Cr-51-EDTA and iohexol between the first and second fasting measurements in 10 normal subjects.

Table 2. Fasting (first in those having two fasting studies) and non-fasting values of GFR/BSA (ml/min/1.73 m²) and GFR/ECV (ml/min/13.5 l) measured in 20 normal subjects with Cr-51-EDTA and iohexol

<table>
<thead>
<tr>
<th></th>
<th>Mean fasted</th>
<th>Mean increase after food intake</th>
<th>P value</th>
</tr>
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<tr>
<td><strong>Cr-51-EDTA</strong></td>
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<tr>
<td>GFR/BSA3</td>
<td>87.9</td>
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<td>89.3</td>
<td>4.6</td>
<td>0.0067</td>
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<tr>
<td>GFR/ECV3</td>
<td>88.4</td>
<td>2.9</td>
<td>0.086</td>
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<tr>
<td>GFR/ECV6</td>
<td>92.2</td>
<td>3.2</td>
<td>0.052</td>
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<tr>
<td><strong>Iohexol</strong></td>
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<tr>
<td>GFR/BSA3</td>
<td>85.1</td>
<td>3.8</td>
<td>0.023</td>
</tr>
<tr>
<td>GFR/BSA6</td>
<td>83.8</td>
<td>5.7</td>
<td>0.011</td>
</tr>
<tr>
<td>GFR/ECV3</td>
<td>83.3</td>
<td>5.6</td>
<td>0.10</td>
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<tr>
<td>GFR/ECV6</td>
<td>87.8</td>
<td>5.0</td>
<td>0.092</td>
</tr>
</tbody>
</table>

Fig. 3. Relations between corresponding individual fractional changes in GFR values simultaneously measured with Cr-51-EDTA and iohexol between the non-fasting and fasting measurements in 20 normal subjects (the first in the 10 normal subjects who had two fasting measurements).

Many previous studies assessing the accuracy of GFR measurement against a gold standard have not performed the measurements in a truly independent fashion. The novelty of this study is that complete independence was assured with respect to both the reproducibility and effect of food studies. Although this was a cohort of normal volunteers, average GFR was surprisingly low. We have no reason, however, to suspect any measurement errors as the mean
ratio of slope–intercept GFR, e.g. given by the two indicators in all 50 paired studies was 1.037 (SD 0.063).

Reproducibility

Reproducibility studies of Cr-51-EDTA and iohexol are scarce, and we could find no direct comparisons between them. Since chronic kidney disease (CKD) is slowly progressive, reproducibility is a key element for any clinical measure of its rate of progression. There is an underlying diurnal variation in GFR [30–33] as well as changes in response to external stimuli, e.g. exercise [34] and food intake [9–11]. The diurnal rhythm in GFR, which reflects changes in circulating atrial natriuretic peptide rather than arterial pressure [32], is represented differently by insulin and creatinine clearances [35,36].

Food intake

A protein-rich meal causes an increase in GFR of about 25% [18,19] but in the current study we observed a general increase much less than this because the meal was generally lighter. As our intention was to compare iohexol and Cr-51-EDTA in a paired fashion, there was no need to standardize the meal. Moreover, a light meal, resulting in a more modest increase in GFR, is more discriminatory.

Reliability of iohexol

There have been several previous comparisons between iohexol and Cr-51-EDTA for measuring GFR [7–14], although they have not compared the two markers in a truly independent fashion by basing their clearances on separate sets of blood samples drawn from separate sites after simultaneous administration of markers via separate lines or directly compared their reproducibilities, as we have done here.

In the current study, the coefficients of variation did not differ significantly between the two indicators, at least with respect to the conventional slope–intercept approach (i.e. GFR/BSA). By showing a significant correlation between individual changes in fasting GFR measured by the two markers simultaneously and independently, it is evident that a considerable proportion of the variability between sequential measurements was the result of real changes in GFR.

Other recent studies have assayed iohexol by HPLC [6,7,16,20]. Notably though, Brandstrom et al. [7] recorded correlation coefficients with Cr-51-EDTA that were similar for both XRF (0.95) and HPLC (0.92). They commented on the necessity of a minimum plasma iodine concentration of 0.06 g/l (which corresponds to an iohexol concentration of 0.27 g/l, less than our most dilute standard (see Figure 1). GFR values measured with Cr-51-EDTA showed statistically more significant responses compared with iohexol in response to food. High protein meals act directly on the kidney to cause an increase in GFR, which should therefore correlate inversely with any simultaneous change in ECV. However, we previously observed a positive correlation [37], suggesting that for a light meal, with small increases in GFR, primary changes in ECV play a more important role in the GFR increment. This would explain why the increases in GFR/ECV were not significant.

Three versus six samples

The coefficients of variation did not differ significantly between three- and six-sample GFR measured with Cr-51-EDTA, with respect either to GFR/BSA or GFR/ECV. For iohexol, three-sample GFR was more reproducible when scaled to BSA but the opposite was seen scaled to ECV. There was little difference between three- and six-sample GFR with respect to response to food intake. In terms of both reproducibility and response to food intake, inclusion of the initial three blood samples seemed to offer no improvement. So although not necessarily more accurate than six-sample GFR, three-sample GFR provided good precision. This is presumably because the additional error generated by the inclusion of early samples is greater than the normal variation that exists in the parameters on which the first exponential is based. This may not of course apply to an abnormal population or to the elderly with their reduced muscle mass and possibly therefore also a reduced ECV.

Reliability of scaling to ECV

The mean transit time, T, and its approximation, the reciprocal of the terminal rate constant, represent the mean waiting time of individual molecules of marker in the extracellular fluid space compartment before filtration and are therefore measures of GFR that are already scaled to ECV. In other words, measuring GFR per unit ECV requires measurement only of their ratio, and not of their individual values. BSA for scaling GFR is largely historical and well entrenched but has nevertheless been criticized on several grounds, including sex differences in renal perfusion and gross differences in body size [1,38] and compared unfavourably with several alternatives, including ECV. In addition to technical convenience, ECV as a whole body scaling parameter offers the attraction of physiological validity [39], including an element of dependence of GFR on ECV [39–41]. Further advantages of the exclusive use of the terminal rate constant to measure GFR are the opportunity of the ‘real-time’ measurement of GFR (which allows the detection of instantaneous changes) [42,43] and convenience in the context of the remote measurement of GFR.

The coefficients of variation did not differ significantly between GFR values respectively scaled to BSA and ECV with respect either to three- or six-sample Cr-51-EDTA clearance. The slope–intercept technique, however, exposed a clearer response to food intake than scaling to ECV which could be explained by a simultaneous corresponding increase in ECV [37], limiting an increase in the ratio. Scaling to ECV also impaired reproducibility when iohexol was the marker.
Conclusion

GFR measured with iohexol has similar reproducibility to GFR measured with Cr-51-EDTA using three samples and the slope–intercept approach. Unless the volunteer’s weight changes significantly between paired measurements, reproducibility and response to food intake of unsealed GFR would, of course, be identical to BSA-scaled GFR, and some of the disadvantages of BSA as a scaling parameter, discussed above, would not be apparent in reproducibility and acute response studies such as the current one. When measured with Cr-51-EDTA, GFR/ECV was almost as reproducible as GFR/BSA, thereby in principle validating the slope-only technique. GFR/ECV measured with iohexol, however, was less reliable. A feature of the conventional slope–intercept technique that is usually taken for granted, but which relies on careful attention to technical detail, is the administered amount of indicator, errors in which are impossible to detect retrospectively. As far as a postal service is concerned, therefore, scaling to ECV would be impossible to detect retrospectively. As far as a postal service is concerned, therefore, scaling to ECV would be highly favoured but critically dependent on the accuracy of the iohexol assay. Technology advances rapidly, and although previous experiences with XRF have shown it to be reliable, most authorities would agree that HPLC is the most accurate method for assaying iohexol and its unavailability to the current authors must be seen as a limitation in this study. We believe, however, that the results reported here provide a sound platform from which a postal service with iohexol could be developed. Whether it should be based on three or six samples awaits further work to confirm that three-sample GFR/ECV measured with iohexol and HPLC is as accurate as GFR/ECV measured with Cr-51-EDTA.

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Conflict of interest statement.  None declared.

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