

Indexing Glomerular Filtration Rate to Suit Children

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In order to be able to compare individuals of differing size, glomerular filtration rate (GFR) is conventionally indexed to body surface area (BSA). This does not, however, suit children because they naturally have a relatively high BSA simply because of their small size. The aim of the study was to identify an appropriate simple whole-body variable based on height and weight suitable for indexing GFR that would be simultaneously appropriate for both children and adults. **Methods:** A database of 532 routine clinical GFR measurements, each based on 3 venous blood samples obtained between 2 and 4 h after injection of ⁵¹Cr-ethylenediaminetetraacetic acid, was analyzed to give GFR and, using only the half-time of the slope of the clearance curve, the quotient GFR to extracellular fluid volume (ECV). BSA was obtained from the Haycock formula, which is based on height and weight raised to indices to give units of area. Both GFR and GFR/ECV were corrected for the 1-compartment assumption using previously published empiric correction formulas. ECV was obtained by dividing GFR by GFR/ECV. An equation analogous to Haycock's was derived in which the indices of height and weight were varied to give an iterative best fit to ECV instead of BSA. **Results:** GFR, ECV, and BSA increase as functions of age until about age 13 y, corresponding to a BSA of about 1.35 m², which was taken as the cutoff point between children and adults. As humans grow, their ratio of height to effective radius changes as a nonlinear function of surface area. Humans must therefore change shape as they grow. Moreover, the ECV-to-weight ratio decreases as a function of body size, suggesting that humans also change body composition as they grow. The new equation, giving an iterative best fit to ECV, was $ECV = \text{weight}^{0.6469} \times \text{height}^{0.7236} \times 0.02154$. ECV, either measured or estimated from the new equation, corresponding to a BSA of 1.73 m², was 12.9 L. Expressed as values normalized to the corresponding average adult values, the new equation and the second-order polynomial fit to ECV were superimposed as they increased as functions of BSA or weight. In contrast, normalized BSA and normalized weight were respectively larger and smaller than normalized ECV in children. GFR indexed to the new equation correlated more closely with GFR indexed to ECV than did GFR indexed to BSA and, along with GFR/ECV, showed a greater fall as a function of age than did GFR/BSA. **Conclusion:** When required in absolute

units rather than as a rate of turnover of ECV, GFR is appropriately indexed to indices of height and weight as defined by this new equation, which avoids disadvantages to children from indexing to BSA. This unmasks higher values of filtration function in children than have hitherto been recognized.

Key Words: glomerular filtration rate; ⁵¹Cr-EDTA; renal clearance

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Glomerular filtration rate (GFR) is conventionally indexed to body surface area (BSA). However, the use of BSA for this purpose has been criticized, not only in relation to GFR but also to other hemodynamic variables (1). Alternative variables have been suggested, including body weight (2–4), the square of height (5), lean body mass (6,7), total body water (8), plasma volume (9), and especially extracellular fluid volume (ECV) (2–4,10–14). Apart from physiologic advantages over BSA, GFR/ECV is technically simpler to obtain insofar as it is based only on the slope of the terminal exponential of the conventional biexponential plasma clearance curve (“slope-only” method). We have previously compared BSA and ECV as variables for indexing GFR, contrasting children with adults (2,15,16). BSA has the intrinsic disadvantage, especially relevant to children, that the volume (or weight) of an object of any specific shape, as a quotient of its surface area, increases as surface area increases, that is, as the object increases in size. Since the function of GFR is to regulate ECV and indirectly turn over total body water, it seems intuitively evident that it should be indexed to a volume-based whole-body variable rather than one based on area.

Under some clinical circumstances, such as in the titration of doses for cancer chemotherapy, it is preferable to express GFR in absolute units (mL × min⁻¹) rather than as a turnover rate (min⁻¹). Moreover, the slope-only method for measuring GFR has recently been criticized as inferior to the conventional “slope-intercept” method (which generates GFR in absolute units) because it is less robust (17). It would be worthwhile, therefore, to find a simple indexation variable equally applicable to children and adults that avoids the geometric disadvantage of BSA. Weight, which

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is widely used for indexing GFR in veterinary practice (3,4), is influenced by body fat content, which is a reason that BSA gained preference for humans in the first place. A variable for which there is good evidence for indexing GFR, at least in children, is total body water (8), but it is clearly not practical to measure this every time GFR is measured, nor its surrogate, lean body mass. There are, however, good physiologic reasons for indexing GFR to ECV. In this article, therefore, we modified the indices to which weight and height are raised to generate a new equation, similar in form to those of Haycock et al. (18) and Du Bois and Du Bois (19), to estimate ECV instead of BSA. Since ECV, in contrast to BSA, is 3-dimensional, the modified indices would be expected to summate to give units of volume rather than area.

MATERIALS AND METHODS

Patients

Data are based on 577 consecutive GFR measurements in 517 patients (aged 1–87 y) routinely referred for measurement of GFR as part of their clinical management. The clinical indications varied but were mainly in the management of a nephrourologic disorder or for monitoring of cancer chemotherapy.

Data Acquisition

The bolus-injection single-compartment technique was used, in which it is assumed that the tracer mixes throughout its volume of distribution (the single compartment) instantaneously. In fact, mixing takes about 2 h, producing a multiexponential plasma clearance curve that reduces to a single exponential, with rate constant α_2 , within about 2 h of injection. Antecubital venous blood samples were therefore obtained 2, 3, and 4 h after intravenous injection of 3 MBq of ^{51}Cr -ethylenediaminetetraacetic acid (EDTA) (Mallinckrodt) per 70 kg of body weight. ^{51}Cr counts in each sample were compared with those in a standard. The height and weight of each patient was measured, and BSA was calculated using the equation of Haycock et al. (18), which is based on height (in centimeters) and weight (in kilograms) of the subject and is BSA (in square meters) = $\text{weight}^{0.5378} \times \text{height}^{0.3964} \times 0.024265$.

Data Analysis

The plasma ^{51}Cr -EDTA clearance was expressed logarithmically and a least-squares fit applied to the 3 data points to generate the rate constant, α_2 (min^{-1}), of the terminal exponential. GFR was then measured from the standard equation $\text{GFR} = [D \times \alpha_2]/B$, where D is administered activity, B is the zero time intercept of the exponential fit, and volume of distribution (V_d) is the ratio D/B.

In our previous studies (15,16), the correlation coefficient of the least-squares fit to the 3 data points was arbitrarily considered unsatisfactory when it was less than 0.99. This was the case in 45 current studies, leaving 532 measurements in which the fit was better than 0.99 and on which the current analysis is based. The study was performed in 2 phases: data from the first phase (411 studies) were used to derive the new equation, which was then prospectively tested on 121 studies in the second phase.

GFR needs to be corrected to account for the overestimation that results from the assumption of a single compartment. Of several published in the literature, 2 algorithms were considered. The first, derived by Blake et al. (20), is based on GFR indexed to BSA; the second, derived by Peters et al. (21), is based on α_2 and

does not therefore require prior scaling of GFR for body size. Using a factor of 25 (which is higher than published by Peters et al. as a result of further unpublished work) with which to multiply α_2 and a factor of 0.00155 (as used by Blake et al.) with which to multiply $\text{GFR}/1.73 \text{ m}^2$, the 2 correction methods showed very close agreement with respect both to absolute GFR ($r = 0.998$) and to GFR indexed to 1.73 m^2 ($r = 0.997$). Since the philosophy behind the current study was to move away from BSA as an indexation variable, we chose to correct for the 1-compartment assumption using the algorithm of Peters et al. and specifically a correction factor with which to multiply α_2 of 25; that is, corrected $\text{GFR} = \text{raw GFR}/(1 + [25 \times \alpha_2])$.

The rate constant, α_2 , of the exponential fitted to the 3 data points is a close approximation to GFR per unit volume of distribution of indicator (13). Because the volume of distribution of ^{51}Cr -EDTA represents ECV, α_2 is also a close approximation to $\text{GFR}/\text{L ECV}$, systematically slightly underestimating it. The rate constant α_2 was therefore also corrected to give $\text{GFR}/\text{L ECF}$ (i.e., GFR/ECV) using a previously described formula (13). Note that GFR/ECV is already indexed for body size. To obtain ECV ("measured" ECV), GFR (corrected for the 1-compartment assumption) was divided by $\text{GFR}/\text{L ECV}$.

Using the data from the first phase, an equation of the same form as those of Haycock et al. (18) and Du Bois and Du Bois (19)—that is, $y = a \times \text{weight}^b \times \text{height}^c$ —was optimized for estimating ECV (rather than BSA). Thus, a, b, and c were iteratively varied to minimize the sum of squares of error; that is, $\Sigma[(\text{ECV}) - (a \times \text{weight}^b \times \text{height}^c)]^2$. This modified equation gives an indexation variable that is based on ECV rather than BSA. Corrected for the 1-compartment assumption, the unscaled GFR was then indexed to the new equation and normalized to 12.9 L, which is the ECV corresponding to a BSA of 1.73 m^2 , as is described in the Results. For comparison with other indexed values of GFR, $\text{GFR}/\text{L ECV}$ was also multiplied by 12.9 L. Having derived our new equation, it was prospectively tested in comparison with the original equation of Haycock et al. in patients from phase 2.

Finally, measured ECV, BSA, and the value of ECV based on the new equation were normalized to the corresponding average for the adult population (as defined below) and given the prefix n (i.e., nECV and nBSA).

RESULTS

Notwithstanding that this was not a normal population, BSA, measured ECV, and GFR all increased broadly exponentially during the first 13–15 y of life, after which they remained essentially constant (Fig. 1A). A BSA of 1.35 m^2 was taken as the cutoff point between small and large individuals (Fig. 1B); all but 5 children (<13 y old) were included in the population with a BSA of less than 1.35 m^2 ($n = 131$), and all but 3 adults (>13 y old) were included in the population with a BSA of more than 1.35 m^2 ($n = 401$).

If human shape is considered to be cylindric, then the shape of any individual can be expressed as the ratio of height to effective radius, in the same way that the specific shape of a cylinder can be expressed as the length-to-radius ratio. Equating weight with volume, effective radius is equal to the square root of ($\text{weight}/[\pi \times \text{height}]$), where weight is in grams and height is in centimeters. As illustrated in

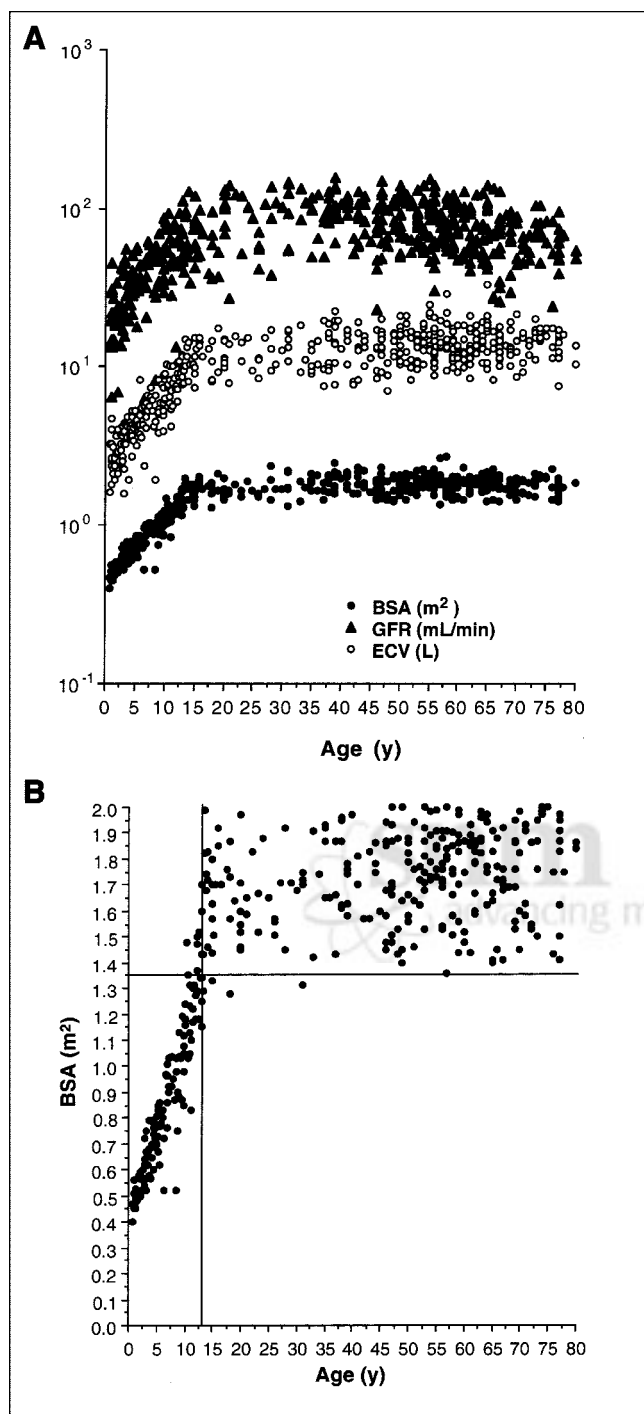


FIGURE 1. (A) Increase in GFR, measured ECV, and BSA as function of age. All increase broadly exponentially until about age 13 y, when they all stop increasing fairly abruptly. (B) Population with BSA above cutoff value of 1.35 m² (horizontal line) includes only 5 (of 131) children (<13 y old; vertical line), and population below cutoff value of 1.35 m² includes only 3 (of 401) adults.

Figure 2A, the plot of height to effective radius as a function of BSA in the entire population initially increases and then, above 1.35 m², decreases, confirming that human shape changes as a complex and nonlinear function of size. This

change in shape suggests that small infants have essentially a similar shape to large adults, whereas children in an intermediate BSA range have a relatively higher surface area, although changes in body composition will also affect this relationship. The importance of body composition is underlined by the decrease in the ECV-to-weight ratio as a function of BSA (taken as a marker of size; Fig. 2B). A similar correlation with BSA was recorded when normalized V_d (i.e., ECV uncorrected for the 1-compartment assumption) was used in place of ECV, excluding a spurious correlation generated by the 1-compartment correction procedure.

Children in the entire patient population had a higher mean GFR/ECV than adults, but there was no difference with respect to GFR/BSA, whether or not corrections were applied for the 1-compartment assumption (Table 1).

The new equation predicting ECV (in liters), derived from phase 1 studies, is $y = \text{weight}^{0.6469} \times \text{height}^{0.7236} \times 0.02154$, where the units of weight and height are kilograms and centimeters, respectively. This equation for y was essentially superimposed on the second-order polynomial fit to ECV (as a function of BSA) derived from phase 2 (Fig. 3). The value of ECV corresponding to a BSA of 1.73 m², based either on the second-order polynomial fit to measured ECV as a function of BSA or on the new equation, was 12.9 L, which was therefore taken as the ECV of standard man and used to convert GFR per liter of ECV to GFR indexed to ECV (i.e., GFR/12.9 L).

When phase-2 values of measured ECV, BSA, body weight, and ECV generated by the new equation were all expressed as values normalized against the corresponding average adult values and plotted as functions of BSA (Fig. 4) or weight (data not shown), as markers of growth, the normalized value given by the new equation was essentially superimposed on the second-order polynomial least-squares fit of nECV on BSA or weight through the full range of body size. The same result was obtained when normalized V_d was used in place of nECV, indicating that this is not a spurious result generated by the 1-compartment correction procedure. In contrast, although nBSA was clearly above nECV and nweight was below nECV during childhood, the reverse was seen in larger adults. In other words, throughout growth, the new equation, but not BSA or weight, closely shadows measured ECV. This was reflected in Bland-Altman plots (22) (not shown) of the differences between nBSA, nweight, or the normalized new equation and nECV against the corresponding averages in which the individual data points in the childhood range (up to age 13 y) were grouped around the zero baseline with respect to the new equation (mean difference, -0.018 [0.052]; $P > 0.05$ compared with zero), in contrast to nBSA (mean difference, -0.11 [0.033]; $P < 0.001$ vs. zero) and nweight (0.034 [0.059]; $P < 0.01$ vs. zero).

In children, BSA is relatively high, but measured ECV and ECV given by the new equation are relatively lower, giving higher indexed GFR values; about 60% higher in small infants (Fig. 5; data from both phases).

With respect to phase-2 data, the differences between GFR/BSA and GFR/ECV and between GFR/height² and GFR/ECV both increased as functions of BSA. Indexing to 1.73 m² (BSA), 3 m² (height²), and 12.9 L (ECV), GFR/BSA – GFR/ECV increased at a rate of 21 mL/min per square meter of BSA ($r = 0.56$; $n = 121$; $P \ll 0.001$) whereas GFR/height² – GFR/ECV increased at a rate of 27

mL/min per square meter of BSA ($r = 0.64$; $n = 121$; $P \ll 0.001$). The difference, however, between GFR indexed using the new equation and GFR/ECV showed no dependence on BSA ($r = 0.07$). Moreover, unlike GFR/BSA, both GFR/ECV and GFR indexed using the new equation clearly fall as functions of age (Fig. 6). Indeed, GFR/BSA increases as a function of age in small children.

Although the overall correlation between GFR/ECV and GFR/BSA in patients from phase 2 ($n = 121$) was moderately close (0.76; Fig. 7A), indexation of GFR to the new equation (derived from phase 1) instead of BSA generated a closer correlation with GFR/ECV (0.86; Fig. 7B). The scattergram illustrating the relationship between the new equation and the original equation of Haycock et al. (18) (Fig. 7C), although showing very close agreement for adults, highlights their divergence in children.

DISCUSSION

The point at which growth ceases is fairly well defined in the current database, relevant variables reaching relatively constant adult values at age 13–15 y. The whole-body variable against which to index GFR in adults seems not to be critical, but in children younger than 13 y, geometric considerations, in particular the changing shape of children as well as the simple fact that small objects have relatively high surface areas, makes the choice of the most suitable indexation variable more problematic. Thus, notwithstanding that this was not a normal population, filtration function in children appeared to be better than that in adults when indexed to ECV but not when indexed to BSA (Table 1). The situation was compounded by a changing body composition as a function of size, as suggested by the finding that the ECV-to-weight ratio decreased significantly as a function of BSA (Fig. 2B).

Seminal work performed decades ago by McCance and Widdowson (8) concluded that, in children, total body water is the optimal variable against which to index GFR. It is of course impractical to measure total body water or its contemporary surrogate, lean body mass (by dual-energy x-ray absorptiometry), every time GFR is measured. Neverthe-

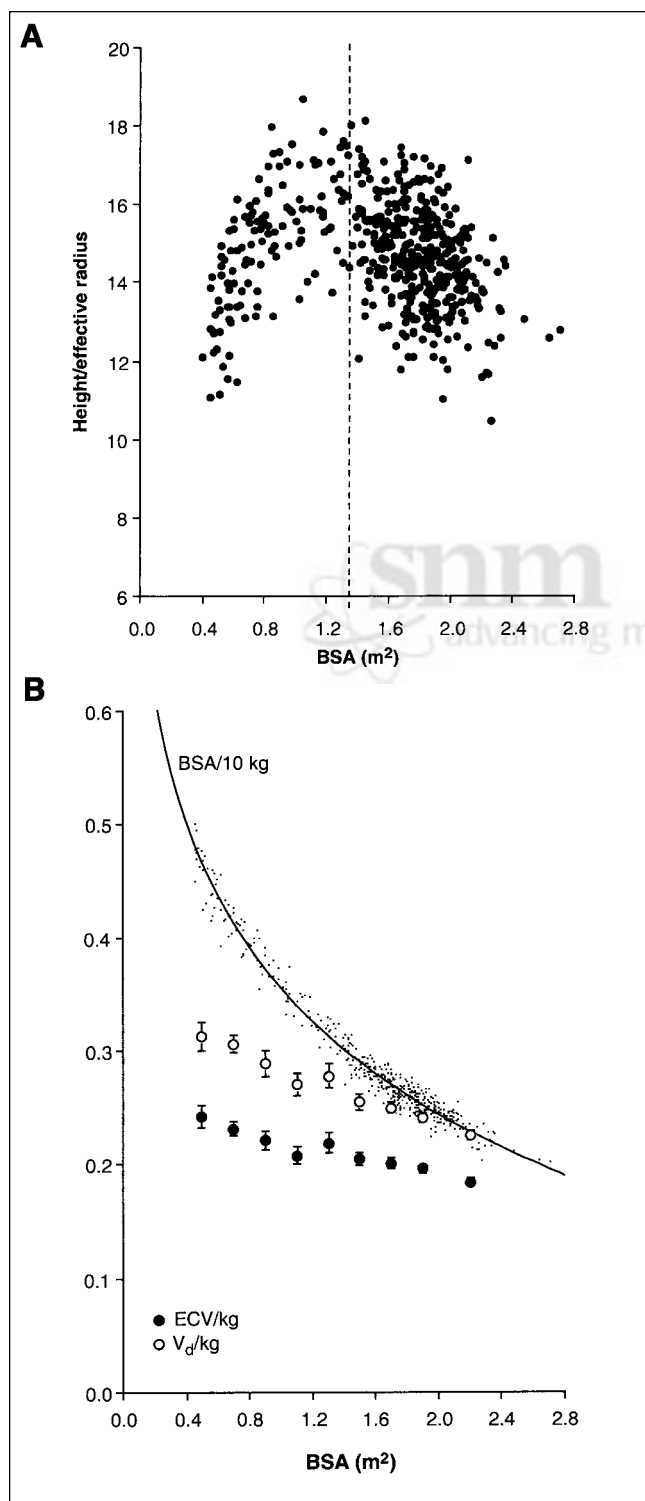


FIGURE 2. (A) Relationship between BSA and ratio of height to effective radius. Dashed line corresponds to BSA of 1.35 m². Children display increasing ratio of height to effective radius as they grow, but in adults, relationship between BSA and ratio of height to effective radius is inverse. Height-to-radius ratio defines shape of cylinder, so humans must change shape as they grow. (B) Ratios of BSA (dots) and measured ECV to body weight shown as functions of BSA. ECV-to-weight ratio decreases significantly as approximate linear function of BSA, whereas decrease in BSA-to-weight ratio is logarithmic. V_d -to-weight ratio is shown for comparison and, with ECV-to-weight ratio, is shown as SEM of groups of patients stratified for BSA (0.4–0.59, 0.6–0.79, 0.8–0.99, 1.00–1.19, 1.20–1.39, 1.40–1.59, 1.60–1.79, 1.80–1.99, and >1.99 m²). Line is logarithmic fit to BSA/10 kg data points.

TABLE 1
GFR Indexed to BSA Compared with GFR Indexed to ECV in Patients with BSA of, Respectively,
Less than ($n = 131$) or Greater than ($n = 401$) 1.35 m^2

Patient size (BSA)	Uncorrected		<i>P</i>	Corrected*		<i>P</i>
	<1.35 m^2	>1.35 m^2		<1.35 m^2	>1.35 m^2	
GFR/BSA ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	91 (31)	89 (32)	>0.1	77 (24)	78 (25)	>0.1
GFR/ECV ($\text{mL}/\text{min}/\text{L}$)	7.0 (1.8)	5.5 (1.7)	$\ll 0.001$	7.7 (2.1)	6.0 (1.9)	$\ll 0.001$

*For 1-compartment assumption.
Data are mean (SD).

less, it is intuitively compelling to use an alternative fluid volume, ECV being the most convenient, as a surrogate for total body water. It is therefore reasonable, at least in the current work, to consider ECV as the gold standard for indexing GFR, and support for this has already been published elsewhere (2–4,12–15).

In circumstances in which GFR is nevertheless required in units of $\text{mL} \times \text{min}^{-1}$ rather than min^{-1} , or if it is accepted that the slope-intercept method for measuring GFR is superior to the slope-only method on grounds of greater robustness (17), then the problem of a suitable whole-body indexation variable remains. The current data show that the problem can be solved by using an equation, with weight and height raised to different indices, that essentially predicts ECV, instead of BSA, and that is therefore a more appropriate indexation variable than BSA, especially for children. As with ECV as an indexation variable, this new equation gives children levels of GFR that are higher than

have hitherto been recognized and that match the relatively high values of BSA that inevitably exist in childhood. The indices of our new equation do not, however, quite add up to 3, which they would if the equation predicted a truly 3-dimensional value. The indices of the original equation of Haycock et al. (18), in which weight is raised to about 0.54 and height to 0.4, do add up to 2 (i.e., $[3 \times 0.54] + 0.4 \sim 2$), as would be expected if the equation yields area, whereas in the modified equation they add up to about 2.7. That this

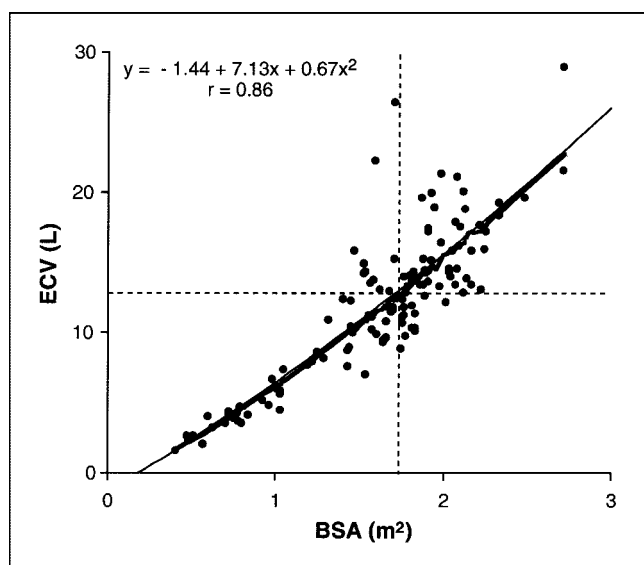


FIGURE 3. Measured ECV (●) increases nonlinearly as function of BSA (second-order polynomial fit shown, i.e., $y = a + bx + cx^2$). ECV based on new equation derived from phase-1 data (bold line) is virtually superimposed on second-order polynomial fit (fine line) to measured ECV based on phase-2 data. Vertical and horizontal dashed lines correspond to 1.73 m^2 and 12.9 L , respectively.

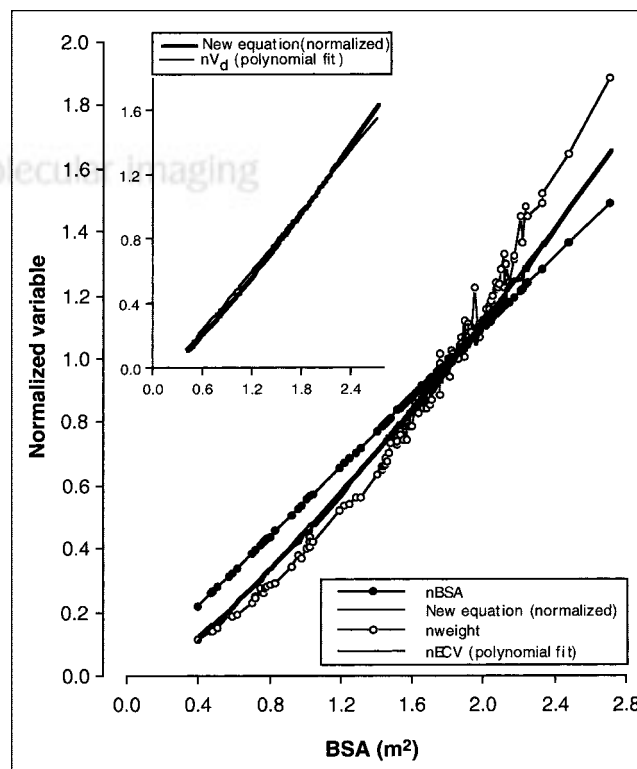


FIGURE 4. New equation is compared with individual values of BSA and weight normalized to corresponding mean values for patients $> 1.35 \text{ m}^2$ (nBSA and nweight) and with second-order polynomial fit of normalized measured ECV (nECV), all shown as functions of BSA. Data from second-phase nECV and normalized new equation are virtually superimposed on each other, whereas nBSA and nweight are respectively higher and lower than nECV in children, reversing in larger adults. Note that all plots converge at BSA of about 1.8 m^2 . Inset shows effect of substituting nECV with nV_d .

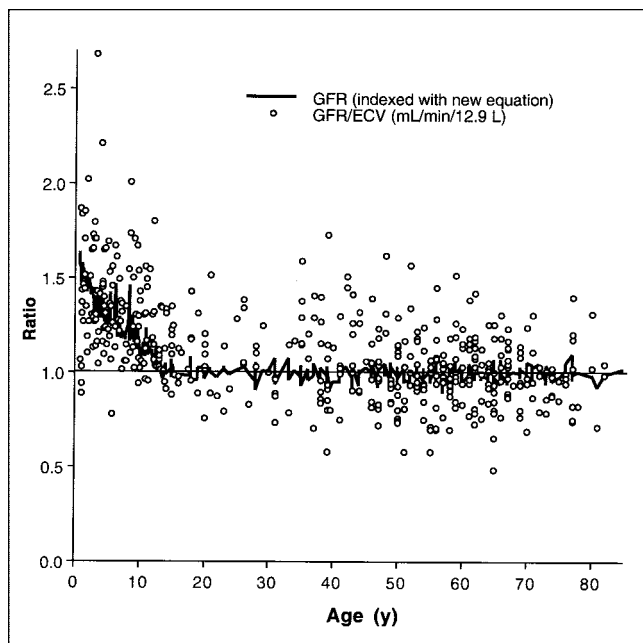


FIGURE 5. Quotients of GFR indexed to new equation and GFR/ECV, respectively, to GFR/BSA shown as functions of age in entire population ($n = 532$). Use of both new equation and measured ECV give indexed GFR values about 60% higher than GFR/BSA in small infants. Discrepancy decreases linearly as function of age, essentially disappearing at age 13–15 y.

is slightly less than 3 is probably related to the changing shape of humans as well as a changing body composition.

A difficult question in relation to GFR in children is whether the published equations for correcting the error arising from the assumption of a single distribution compartment (the 1-compartment assumption) are valid for children. As none have been published for children, we cannot answer this question and we cannot therefore be certain that our calculations of ECV in children are valid. Nevertheless, whenever we substituted V_d for ECV, a qualitatively similar result was obtained, making it unlikely that we were misled by an invalid measurement of ECV.

An attraction of this new equation is its versatility and applicability to all comers. This is in contrast to height^2 , for example, which, although it addresses the problem of obesity in adults (5), is not useful for children. Body weight, on the other hand, is well suited to indexing GFR in very small children (23) and has even been proposed as the sole predictor of BSA in children (24) but is entirely unsuitable for adults because of the problems posed by obesity (25), with BSA inevitably changing as a result of an isolated change in weight. The new equation, while not eliminating the problem of obesity, is nevertheless less sensitive to weight and more to height, as can be appreciated by comparing the indices to which weight and height are raised.

CONCLUSION

The current data suggest that, instead of having immature filtration function until several years of age, children have

high levels of filtration function that steadily decline throughout life from a very early age. It is suggested that for a truer reflection of filtration function in children and to redress the apparent difference between children and adults

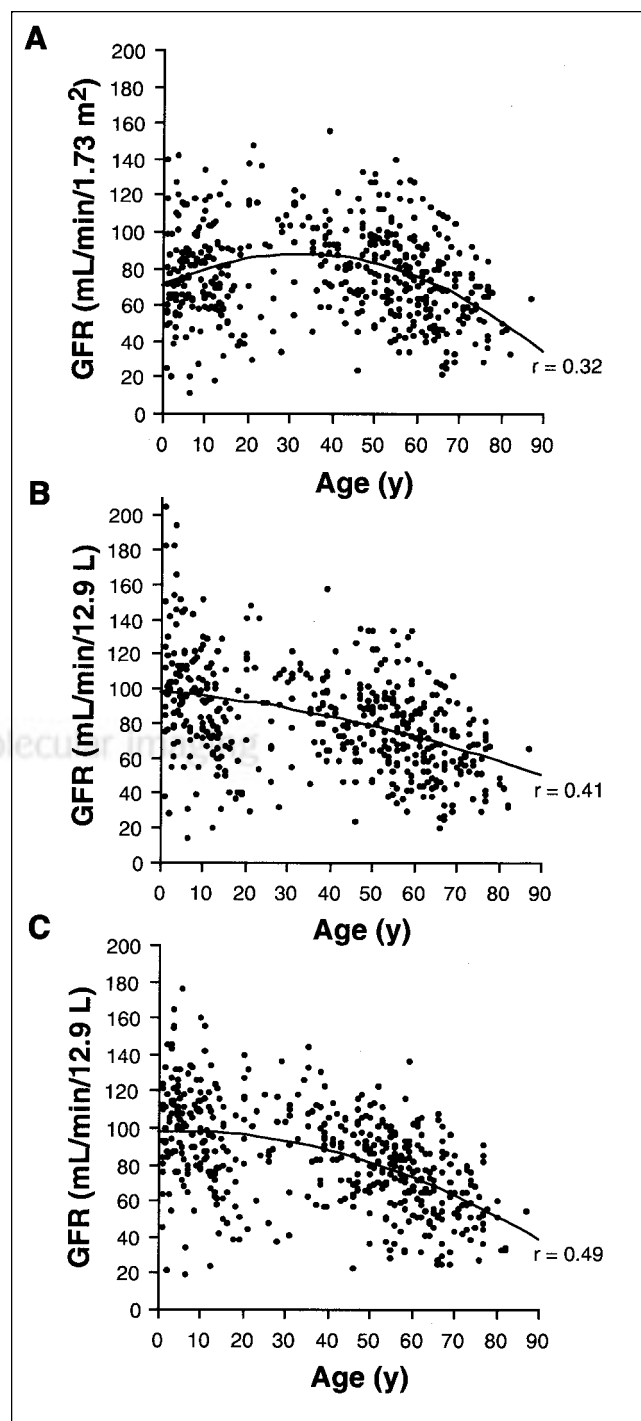


FIGURE 6. GFR indexed to BSA (A), ECV (B), and new equation (C) shown as functions of age in entire patient population. Second-order polynomial functions (i.e., of form $y = a + bx + cx^2$) have been fitted to each regression, with corresponding correlation coefficients shown. Note relatively high values of GFR/ECV and GFR based on new equation in the very young, in contrast to GFR/BSA, which shows tendency to increase in children.

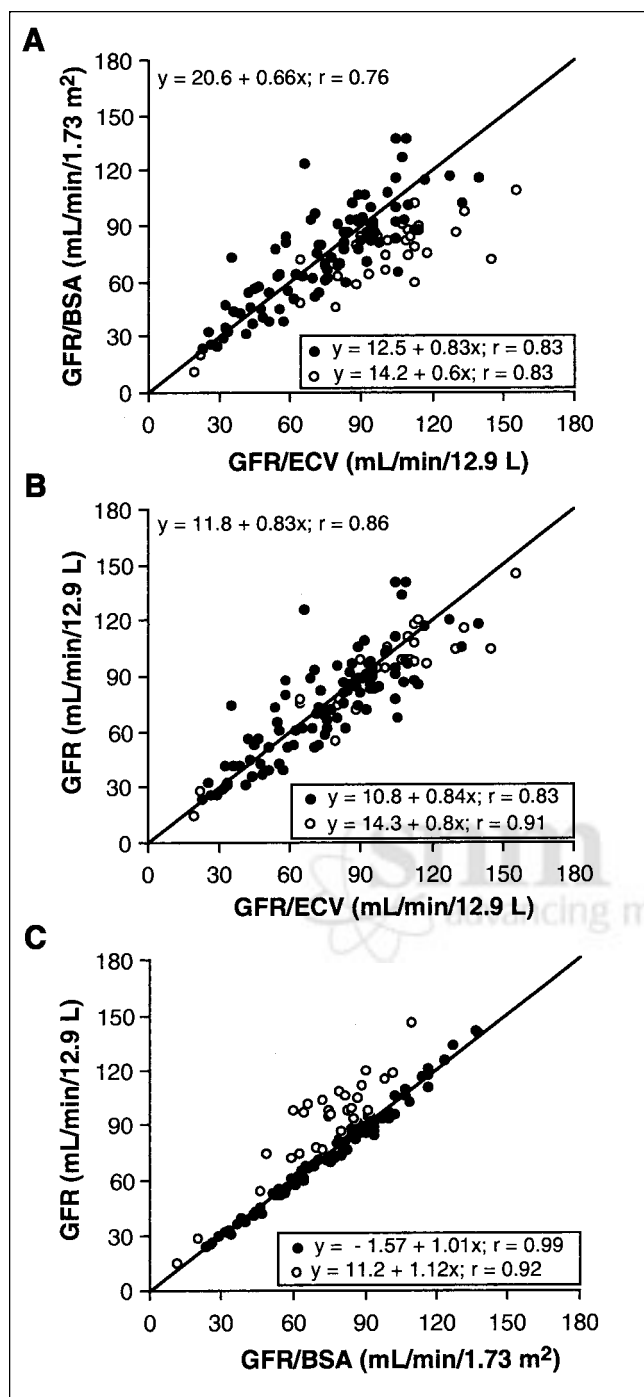


FIGURE 7. Relationships between GFR/ECV and GFR/BSA (A) and between GFR/ECV and GFR indexed to new equation (B). Coefficient of correlation with GFR/ECV is higher for GFR indexed to new equation than indexed to BSA. (C) Comparison of new equation with original equation of Haycock et al. (18). Data are based on second phase of patients (new equation having been calculated from first phase) and are shown separately for patients with BSA < 1.35 m² (○) and > 1.35 m² (●). Lines are lines of identity. Overall regression equations (for patients of all sizes) are shown in top left corner of each panel, and regression equations for each size-based group are shown in bottom right corner.

when BSA is used as the indexation variable, GFR should be indexed using the new equation developed in this study. This equation is equally suited to both children and adults and, moreover, is applicable to the increasing practice of estimating GFR from a single postinjection blood sample.

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