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4-1-2011

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Citation of this paper:
Fille, Guido and Huang, Shih Han, "A simple estimate for extracellular volume: Too simple?" (2011). *Paediatrics Publications*. 1282.
https://ir.lib.uwo.ca/paedpub/1282

# A Simple Estimate for Extracellular Volume: Too Simple?

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*Clin J Am Soc Nephrol* 6: 695–696, 2011. doi: 10.2215/CJN.01340211

Extracellular volume (ECV) is the body water outside cells. It is also the volume of distribution of endogenous markers used for measuring GFR. Traditionally, GFR is calculated in children in relation to body surface area (BSA). Among the various BSA formulas used in most countries, the DuBois formula [BSA = $0.007184 \times H^{0.725} \times W^{0.425}$] is the standard (1). This complicated formula requires a scientific calculator; therefore, many clinicians use the much more simple Mosteller formula [BSA = $\sqrt{(H \times W/3600)}$] instead (2), which can be calculated using simple calculators.

The use of BSA for the estimation of GFR has been criticized for leading to inaccurate estimates, especially in children. Several other variables correlate to GFR and have been considered instead of BSA, including weight (3,4), the square of height (4), lean body mass (5,6), total body water (7), and plasma volume (8). However, several groups, particularly Dr. Peter's group from Cambridge, proposed normalizing GFR to ECV instead (9). Interestingly, pediatric studies in this area are rare. These methods require adequate calculations based on the volume of distribution of the isotope injected, using appropriate nonlinear two-compartment models. In Europe, $^{51}$chromium-ethylenediamine tetra-acetic acid ($^{51}$Cr-EDTA) is the most commonly used method, whereas in North America, the $^{99}$m-technetium diethylene triamine penta-acetic acid ($^{99}$mTc-DTPA) is used most commonly, but iohexol can be used instead. When conducted carefully, ECV can be measured directly during the GFR scan (10,11).

Recently, the large pediatric National Institutes of Health–funded study assessed children with mild to moderate chronic kidney disease (CKD; Chronic Kidney Disease in Children [CKiD] Study; GFR range 30 to 90 ml/min per 1.73 m$^2$) in 43 participating centers (12). In that study, GFR was measured carefully with appropriate plasma disappearance curves using a two-compartment model after iohexol injection. Abraham *et al.* (13) used these 790 iohexol studies from the CKiD Study to determine the volume of distribution from the GFR scan. ECV was in the expected range (interquartile range 5.9 to 12.2 L). They elegantly showed that ECV could be simply calculated on the basis of square root of weight (kg) multiplied by the height (m). As expected, ECV strongly correlated with BSA on the log scale. This formula is certainly more applicable than the older ECV formulas (14).

Not only is the study by Abraham *et al.* (13) very helpful for the easy determination of ECV, but also the practicing pediatric nephrologists cannot overemphasize the importance of estimating the ECV. Even though the study by Abraham *et al.* (13) failed to demonstrate an association between ECV and BP, volume-overloaded patients tend to have higher BP, especially those with advanced CKD with or without dialysis. BP may also be related to renin and angiotensin activation in patients with CKD, which may be independent of volume status. There may also be third-spacing of fluid. Another kidney disease associated with alteration of the ECV, either over- or underfill, is frequently seen in patients with nephrotic syndrome.

Another potential advantage is the hope to have a better normalization of GFR. Any biomarker of GFR demonstrates considerable scatter when plotted against the measured GFR, especially in the high GFR range. There is always the question of what causes this. We recently demonstrated that the effect of hyperfiltration is significant but small when creatinine is used (15), rendering creatnine an inferior marker of GFR estimation. On the other hand, the concentration of markers such as cystatin C (small volume of distribution mainly in ECV) varies substantially and can increase in a dialysis session if a substantial amount of ultrafiltration occurs with a reduction of the ECV (16), which reduces the feasibility of cystatin C as a GFR marker independent of ECU. It is hoped that investigators study the question of whether the scatter can be reduced when normalizing GFR to ECV rather than BSA.

To date, only a few other formulas for the estimation of ECV exist, such as the Bird's ECV formula ($ECV = weight^{0.6469} \times height^{0.7236} \times 0.02154$) (14) or the older Friis-Hansen estimate (17). They also use height and weight but require a scientific calculator for their calculation. By contrast, Abraham's ECV formula provides a relatively simple approach to calculate ECV. So why does ECV estimation matter? Peters *et al.* (9) suggested that GFR should be normalized to ECV. Using this simple estimation may allow further study of the question of whether normalizing GFR to ECV rather than BSA is more feasible. Moreover, the volume of distribution can now be assessed more accurately and may assist in the determination of dry weight and diuretics prescription. It is hoped that the scatter of endogenous

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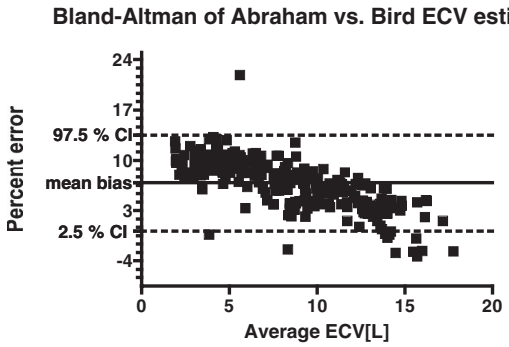


**Figure 1. | Bland-Altman plot: Bias of individual estimated ECV equations**.

markers, especially in the high GFR range, can be reduced if it is normalized to ECV (18).

It would be important to validate these findings against different measures of volume status, such as bioimpedance, inferior vena cava diameter, and other tools (19). For similar validations purposes, the authors could have been randomly split the group into a two-thirds data generation set and a one-third data validation set for internal validation of the formula, as is frequently done for similar questions (20). A comparison with other equations would also have been helpful.

Using our own data set, we compared the Bird's ECV formula with the proposed Abraham's ECV formula. We found a good correlation using Spearman rank correlation with coefficient of 0.9988 (95% confidence interval 0.9985 to 0.9991). However, the agreement (Bland-Altman analysis) was less than perfect with a systematic overestimation of the new Abraham formula (Figure 1). The percentage bias was 6.83% [100 × (Abraham's ECV − Bird's ECV)/average ECV] with a 95% confidence interval between 0.119 and 13.543%. It is important to note that without having the gold standard ECV measurements, Bland-Altman analysis studies only the agreement between formulas but does not assist with determining which is correct.

It will remain to be established how robust this new formula will be when validated in future studies, adult populations, and dialysis patients. An assessment in special populations such as hyperfiltering patients who have diabetes and are early in the course of diabetic nephropathy or obese patients who have normal ECV would also be helpful. Intuitively, using lean body weight may serve as a better parameter for ECV estimation when compared with total body weight.

Nonetheless, 95 years after Dubois and Dubois published the standard BSA formula, Abraham's formula derived from the carefully conducted CKiD Study provides a simple tool for estimation of ECV that has previously been missing.

**Acknowledgments**

We thank Dr. Ajay Sharma, University of Western Ontario, and Professor Jochen Ehrich, Hanover Medical School, for critical review of the manuscript.

**Disclosures**

None.

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See related article, "Extracellular Volume and Glomerular Filtration Rate in Children with Chronic Kidney Disease," on pages 741–747.