A Simple Equation to Estimate Urinary Flow Rate Using Urine Creatinine

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Keywords

Urine volume · Kidney disease · Prediction · Creatinine

Abstract

Background: Accurate assessment of urine flow remains challenging in both inpatient and outpatient settings. We hypothesized we could derive an equation that would accurately estimate urine flow rate (eV) through derivation from other existing equations commonly used in nephrology clinical practice. **Methods:** The eV equation was derived using the Cockcroft-Gault and the measured creatinine clearance ($CrCl = U_{Cr}V/P_{Cr}$) equations. Within the African American Study of Kidney Disease and Hypertension (AASK; $n = 570$) and COMBINE ($n = 133$) clinical trials, we identified participants with concordant estimated and measured creatinine excretion rates to define a subset with highly accurate 24-h urine collections, to assure a reliable gold standard. We then compared eV to measured 24-h urine flow rates in these trials. **Results:** In AASK, we found a high correlation between

eV and measured urine flow rate (V ; $r = 0.91$, $p < 0.001$); however, Bland-Altman plots showed that eV was 9.5 mL/h lower than V , on average. Thus, we added a correction factor to the eV equation and externally validated the new equation in COMBINE. eV and V were again highly correlated ($r = 0.91$, $p < 0.001$), and bias was improved (mean difference 5.3 mL/h). Overall, 80% of individuals had eV that was within 20% of V . **Conclusions:** A simple equation using urine creatinine, demographics, and body weight can accurately predict urine flow rate and may have clinical utility in situations where it is difficult to accurately measure the urine flow rate.

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Introduction

Accurate assessment of urine flow rate (volume per unit time) is a common clinical necessity in both inpatient and outpatient settings and is essential for evaluating volume status; excretion of a myriad of nutrients, minerals,

and hormones; and measurement of kidney function and proteinuria. Yet its assessment remains challenging. In outpatients, assessment requires detailed patient instructions that are difficult for many to perform, and even when done accurately, the clinician is often uncertain whether an individual patient may have over- or under-collected their timed urine collection. In inpatients, urine may be discarded without knowledge of staff, and often the estimated daily intake and output provided by the nursing staff correlate poorly with body weight changes. These factors lead to considerable uncertainties in clinicians who rely on these data for clinical decision making. Novel methods to estimate urine flow rate (eV) that are safe, easy to implement, accurate, readily available, and reproducible would have immediate clinical utility.

We noted that the measured creatinine clearance (CrCl; UV/P) and the Cockcroft-Gault formulas [1] could be combined and rearranged to provide an estimate of urine flow rate. We sought to derive an equation using a single measurement of urine creatinine and demographics and test its accuracy.

Materials and Methods

We began with the equation for measured CrCl (urine creatinine [U] $\times$ urine flow rate [V]/plasma creatinine [P]) and the Cockcroft-Gault equation [1] and derived an equation to eV. The equation was validated by applying it to African American Study of Kidney Disease and Hypertension (AASK), and COMBINE trial participants. The participant characteristics and methods of these trials have been described previously [2–4]. The present study uses data from the run-in phase of these studies, prior to randomization. In each case, participants were provided detailed instructions on voiding to an empty bladder and asked to collect all urine generated over 24 h, maintain in refrigeration, and return it to study personnel subsequently. Participants' 24 h urine specimens served as our gold standard for comparison, but in order to minimize inherent errors induced during collection, we used a previously validated equation to estimate creatinine excretion rate [5]. We compared the measured creatinine excretion in the timed urine specimens versus estimated creatinine excretion rate, and subjects with discordant estimated and measured levels by >20% were excluded. We developed scatter plots comparing estimated to measured urine flow rates and calculated pairwise correlations and Bland-Altman plots [6]. The mean difference between these variables serves as the primary indicator of bias. We multiplied the SD of the mean difference by ± 1.96 to define the 95% limits of agreement (LoA), which served as the primary estimate of precision. Finally, we calculated the percent of estimated flow rates that fell within 10, 20, and 30% of measured urine flow rates; these percentages served as the primary indicator of overall accuracy. After completing this evaluation in AASK, we noted a moderate bias in the eV leading to a post hoc correction. This new equation was then tested in the COMBINE trial. All participants provided written informed consent. All

analyses were conducted in Stata/SE version 11.2 (Stata Corporation, College Station, TX, USA). Additional information on materials and methods are available in online supplementary Materials (see www.karger.com/doi/10.1159/000506728).

Results

Equation Derivation

We began with the standard equation to measure CrCl as depicted in equation A below, where CrCl = creatinine clearance (mL/min), UCr = urine creatinine concentration (mg/dL), V = urine flow rate (mL/min), and PCr = plasma creatinine concentration (mg/dL). While this equation is traditionally used as an estimate of glomerular filtration rate, it contains a term for urine flow rate (V). Thus, if other inputs were known, the equation could be repurposed to estimate V.

$$\text{CrCl} \left(\frac{\text{mL}}{\text{min}} \right) = \frac{\text{UCr} \times \text{V}}{\text{PCr}} \quad (\text{A})$$

CrCl can also be estimated by the Cockcroft-Gault equation (equation B)

$$\text{CrCl} \left(\frac{\text{mL}}{\text{min}} \right) = \frac{[(140 - \text{age}(\text{years})) \times \text{wt}(\text{kg}) \times (0.85 \text{ if female})]}{72 \times \text{PCr} \left(\frac{\text{mg}}{\text{dL}} \right)} \quad (\text{B})$$

Substituting the Cockcroft-Gault equation into equation A provides equation C, below. Note that urine flow rate (V) has been renamed “eV” in equation C, as urine flow rate is now estimated rather than directly measured:

$$\frac{\text{UCr} \left(\frac{\text{mg}}{\text{dL}} \right) \times \text{eV} \left(\frac{\text{mL}}{\text{min}} \right)}{\text{PCr} \left(\frac{\text{mg}}{\text{dL}} \right)} = \frac{[(140 - \text{age}) \times \text{wt}(\text{kg}) \times (0.85 \text{ if female})]}{72 \times \text{PCr} \left(\frac{\text{mg}}{\text{dL}} \right)} \quad (\text{C})$$

Solving for urine flow rate (eV) provides equation D:

$$\text{eV} \left(\frac{\text{mL}}{\text{min}} \right) = \frac{\text{PCr} \left(\frac{\text{mg}}{\text{dL}} \right) \times [(140 - \text{age}) \times \text{wt}(\text{kg}) \times (0.85 \text{ if female})]}{\text{UCr} \left(\frac{\text{mg}}{\text{dL}} \right) \times \text{PCr} \left(\frac{\text{mg}}{\text{dL}} \right) \times 72} \quad (\text{D})$$

Plasma creatinine is now found in the numerator and denominator and can be cancelled, thereby eliminating the need for serum creatinine measurement for

Table 1. Baseline characteristics of AASK and COMBINE trial participants stratified by median urine flow rates

	AASK		COMBINE	
	urine flow rate < median (<i>n</i> = 289)	urine flow rate ≥ median (<i>n</i> = 281)	urine flow rate < median (<i>n</i> = 62)	urine flow rate ≥ median (<i>n</i> = 61)
Age, years, mean ± SD	55±11	54±11	71±9	64±11
Gender, female, <i>n</i> (%)	113 (39)	102 (36)	24 (40)	21 (34)
Black, <i>n</i> (%)	289 (100)	281 (100)	15 (24)	15 (25)
Weight, kg, mean ± SD	86±19	93±21	84±19	95±23
Height, cm, mean ± SD	170±10	172±10	169±9	172±8
BMI, kg/m ² , mean ± SD	29.6±6.2	31.4±6.7	29.3±5.6	32.0±6.8
CKD etiology, <i>n</i> (%)				
Diabetes	0	0	19 (31)	26 (43)
Hypertension	289 (100)	281 (100)	15 (24)	9 (15)
Glomerulonephritis	0	0	3 (5)	5 (8)
Other	0	0	25 (40)	21 (34)
eGFR, mL/min/1.73 m ² , mean ± SD	49±15	45±15	36±7	32±8
Urine ACR, mg/g, median (IQR)			57 (16–360)	95 (20–442)
Urine protein, mg/day, median (IQR)	71 (33–282)	212.4 (67.3–1,000.9)		
24-H urine volume, mL/h, mean ± SD	70±15	121.0±28.2	60±12	111±25

AASK, African American Study of Kidney Disease and Hypertension; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ACR, albumin to creatinine ratio.

eV estimation. Next, since eV is expressed in milliliters per minute in equation D and urine flow rate is more commonly utilized in milliliters per hour in clinical practice, we multiplied by 60 as depicted in equation E:

$$eV \left(\frac{\text{mL}}{\text{h}} \right) = \frac{[(140 - \text{age}) \times \text{wt} (\text{kg}) \times (0.85 \text{ if female}) \times 60]}{UCr \left(\frac{\text{mg}}{\text{dL}} \right) \times 72} \quad (\text{E})$$

Simplifying the fraction of the 2 constants on the right-hand side (60 and 72) gives our equation for eV in equation F:

$$eV \left(\frac{\text{mL}}{\text{h}} \right) = \frac{[(140 - \text{age}) \times \text{wt} (\text{kg}) \times (0.85 \text{ if female}) \times 0.833]}{UCr \left(\frac{\text{mg}}{\text{dL}} \right)} \quad (\text{F})$$

This equation was carried forward for validation in the AASK trial.

Equation Validation in AASK

Among 1,090 individuals within AASK with available urine collections, 570 (52%) had concordant measured and estimated creatinine excretion rates within 20% and were included in this analysis. These participants had

mean age of 55 years, 62% were male, all were African-American, and none had diabetes by trial design (Table 1). The mean measured urine flow rate (*V*) in AASK was 94.9 ± 34.2 mL/h, and mean estimated urine flow using equation F was 85.3 ± 34.9 mL/h. These 2 measures were highly correlated with one another (*r* = 0.91, *p* < 0.001; Fig. 1). Bland-Altman analysis demonstrated that eV was systematically lower than *V* by 9.5 mL/h, on average, and the 95% LoA were ±29.0 mL/h (Fig. 2). We evaluated the percentage of eV values that were within percentiles of *V*, as an indication of overall accuracy, and found that 36, 71, and 93% of eVs were within 10, 20, and 30% of *V*, respectively.

Post hoc, we added a correction factor to the eV equation to account for the 9.5 mL/h mean bias in AASK. The resulting equation G is shown below:

$$eV \left(\frac{\text{mL}}{\text{h}} \right) = 9.5 + \frac{[(140 - \text{age}) \times \text{wt} (\text{kg}) \times (0.85 \text{ if female}) \times 0.833]}{UCr \left(\frac{\text{mg}}{\text{dL}} \right)} \quad (\text{G})$$

Had this equation been used, the mean bias would be zero, by definition, in AASK, the 95% LoA would remain unchanged (±29 mL/h), but overall precision was improved with the percentage of eVs within 10, 20, and 30% of *V*s are 46, 79, and 92%, respectively.

Fig. 1. Correlation of measured vs. estimated urine flow rate (eV) using equation F in AASK. Figure shows the correlation of measured flow rate vs. estimated flow rate using equation F in AASK trial participants who had measured creatinine excretion rates within 20% of estimated creatinine excretion rates ($n = 540$). $r = 0.91$, $p < 0.001$. AASK, African American Study of Kidney Disease and Hypertension.

Fig. 2. Bland-Altman plot of estimated urine flow rate (eV) using equation F vs. measured urine flow rate in AASK. Figure shows the mean bias (-9.5 mL/h) and 95% LoA (-38.2 , $+19.2$ mL/h) of equation F relative to measured urine flow rate in AASK trial participants who had measured creatinine excretion rates within 20% of estimated creatinine excretion rates ($n = 540$). AASK, African American Study of Kidney Disease and Hypertension.

External Equation Validation in the COMBINE Trial

One hundred twenty-three (60%) of the 205 COMBINE trial participants had measured and estimated creatinine excretion rates within 20% of one another. These participants had mean age of 68 years, 63% were male, and 25% were African-American (Table 1). We evaluated equation G in COMBINE, incorporating the correction factor derived in AASK. Using this equation, the correlation between eV and V was once again very high ($r = 0.91$; Fig. 3); however, the mean bias was diminished; eV was 5.3 mL/h lower, on average, than V, with 95% LoA ± 26.1 mL/h in COMBINE (Fig. 4). The overall accuracy was improved with equation G with 43, 80, and 93% of eVs falling within 10, 20, and 30% of Vs, respectively.

The purpose of limiting the study sample to the subsets with highly correlated estimated and measured creatinine excretion rates was to define a subset of individuals with highly accurate 24 h urine collections to provide a reliable gold standard. Without this exclusion, we anticipated that bias (mean difference between eV and V) would be similar, but that accuracy (the 95% LOAs) would be wider, due to added variability in the gold stan-

dard by over- and under-collected 24 h urine collections. To test this, we reevaluated the performance of equation G in COMBINE including all 205 study participants without any exclusions based on creatinine excretion. In this analysis, eV was 2.3 mL/h lower than V, thus slightly better than in the main restricted analysis. However, accuracy was much worse, with 95% LoA of 63.6 mL/h, likely due to greater variability in over- and under-collected urine collections included in the gold standard.

The final equation G for urine creatinine in both mg/dL and $\mu\text{mol/L}$ are shown in Figure 5.

Discussion

We derived a simple equation to estimate urine flow, eV. Due to the nature of the inputs, plasma creatinine could be eliminated, such that the new equation requires only urine creatinine measurement and age, gender, and body weight. The eV estimates were highly correlated with measured urine flow rates in AASK participants, but under-estimated urine flow rate by 9.5 mL/h. We there-

Fig. 3. Correlation of measured vs. estimated urine flow rate (eV) using equation G in COMBINE. Figure shows the correlation of measured flow rate relative to estimated flow rate using equation G in COMBINE trial participants who had measured creatinine excretion rates within 20% of estimated creatinine excretion rates ($n = 123$). $r = 0.91$, $p < 0.001$.

Fig. 4. Bland-Altman plot of estimated urine flow rate (eV) using equation G vs. measured urine flow rate in COMBINE. Figure shows the mean bias (-5.3 mL/h) and 95% LoA (-31.4 , $+20.8$ mL/h) of equation G relative to measured urine flow rate in COMBINE trial participants who had measured creatinine excretion rates within 20% of estimated creatinine excretion rates ($n = 123$).

fore applied a post hoc correction, adding back the 9.5 mL/h underestimate, and validated the new equation in the COMBINE trial. The equation remained highly correlated with measured urinary flow rates and underestimated urine flow rate by 5.3 mL/h in COMBINE. With this equation, 80% of eV estimates fell within 20% of the measured flow rates, and nearly half were within 10%. Thus, we put forward the equations shown in Figure 5 (using urine creatinine in mg/dL or $\mu\text{mol/L}$) as a simple method to estimate urine flow rate when urine collections are not possible, impractical, or of uncertain accuracy.

We envision that this new tool may be useful in several different clinical scenarios. For example, increasing fluid intake is a common treatment recommendation for nephrolithiasis. Monitoring eV at sequential clinic visits could allow assessment of adherence. Clinical trials are evaluating fluid intake to prevent chronic kidney disease (CKD) progression, and eV may provide a simple way to monitor adherence and separation of randomized treatment arms. Outpatient hydration protocols are frequently used in patients undergoing radiocontrast imaging studies and chemotherapy to prevent acute kidney injury. How often, and how well, these protocols are followed by patients is uncer-

	For urine creatinine in mg/dL
a	$\text{eV} \left(\frac{\text{mL}}{\text{h}} \right) = 9.5 + \frac{[(140 - \text{age}) \times \text{wt (kg)} \times (0.85 \text{ if female}) \times 0.833]}{\text{UCr} \left(\frac{\text{mg}}{\text{dL}} \right)}$
	For urine creatinine in $\mu\text{mol/L}$
b	$\text{eV} \left(\frac{\text{mL}}{\text{h}} \right) = 9.5 + \frac{[(140 - \text{age}) \times \text{wt (kg)} \times (0.85 \text{ if female}) \times 73.3]}{\text{UCr} \left(\frac{\mu\text{mol}}{\text{L}} \right)}$

Fig. 5. Equations to estimate urine flow rate (eV) using urine creatinine in mg/dL (**a**) or $\mu\text{mol/L}$ (**b**). Equations are identical and correspond to “equation G” for urine creatinine in mg/dL (**a**), and the same equation after conversion of units to accommodate urine creatinine concentrations in $\mu\text{mol/L}$ (**b**). UCr, urine creatinine concentration.

tain. eV could be measured on presentation, and those with low eV may benefit from additional fluids before performing the procedure. Future studies are needed to evaluate these uses of the eV equation. This study has important limitations. While estimated and measured flow rates

were highly correlated, our first equation underestimated urine flow by 9.5 mL/h. A correction factor was added and resulted in less, but still evident, systematic bias (5 mL/h), in an external validation sample. We validated the equation in persons with CKD. While assessment of urine flow rate is particularly common in CKD, the eV equation will likely also have utility in non-CKD patients. Future studies are needed to validate the eV equation in other settings.

In conclusion, we have derived and validated a simple equation that estimates urine flow rate using only urine creatinine concentration and several readily available demographic variables. The equation may have utility to facilitate clinical decision making by overcoming ambiguity about the accuracy of timed urine volumes.

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Disclosure Statement

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Author Contributions

Dr. Joachim H. Ix is the primary investigator for this project; he assisted in project development, result analysis, manuscript preparation, and editing. Dr. Luke Webster, as a lead author of this project, assisted with data collection, data analysis, result analysis, manuscript preparation, and editing. Brett Larive was the lead statistician on this project and assisted with statistical analysis, table formulation, and manuscript editing. Drs. Jennifer Gassman, Alexander Bullen, Steven D. Weisbord, Paul M. Palevsky, Linda F. Fried, Kalani Raphael, and Tamara Isakova all assisted with manuscript preparation and editing. The results presented in this paper have not been published previously in whole or part, except in abstract form.