Rapid and Highly Accurate Prediction of Poor Loop Diuretic Natriuretic Response in Patients With Heart Failure

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Background—Removal of excess sodium and fluid is a primary therapeutic objective in acute decompensated heart failure and commonly monitored with fluid balance and weight loss. However, these parameters are frequently inaccurate or not collected and require a delay of several hours after diuretic administration before they are available. Accessible tools for rapid and accurate prediction of diuretic response are needed.

Methods and Results—Based on well-established renal physiological principles, an equation was derived to predict net sodium output using a spot urine sample obtained 1 or 2 hours after loop diuretic administration. This equation was then prospectively validated in 50 acute decompensated heart failure patients using meticulously obtained timed 6-hour urine collections to quantify loop diuretic-induced cumulative sodium output. Poor natriuretic response was defined as a cumulative sodium output of <50 mmol, a threshold that would result in a positive sodium balance with twice-daily diuretic dosing. Following a median dose of 3 mg (2–4 mg) of intravenous bumetanide, 40% of the population had a poor natriuretic response. The correlation between measured and predicted sodium output was excellent (r=0.91; P<0.0001). Poor natriuretic response could be accurately predicted with the sodium prediction equation (area under the curve =0.95, 95% confidence interval 0.89–1.0; P<0.0001). Clinically recorded net fluid output had a weaker correlation (r=0.66; P<0.001) and lesser ability to predict poor natriuretic response (area under the curve =0.76, 95% confidence interval 0.63–0.89; P=0.002).

Conclusions—In patients being treated for acute decompensated heart failure, poor natriuretic response can be predicted soon after diuretic administration with excellent accuracy using a spot urine sample. (Circ Heart Fail. 2016;9:e002370. DOI: 10.1161/CIRCHEARTFAILURE.115.002370.)

Key Words: diuretic resistance ▪ diuretics ▪ heart failure ▪ poor natriuretic response ▪ sodium

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cutdecompensated heart failure (ADHF) is the most common hospital discharge diagnosis among Medicare beneficiaries and accounts for more than half of all heart failure–related expenditures.1-3 On a population level, ADHF is primarily a disease of congestion, making removal of excess fluid and sodium the primary therapeutic objective in the majority of ADHF hospitalizations.4-7 As a result, accurately monitoring the progress and success of diuretic therapy is of critical importance. Serial changes in weight and fluid balance are measures nearly universally used to monitor decongestion, with their use endorsed by major cardiovascular society guidelines.8-10 However, it is widely believed that net fluid output and serial changes in weight are difficult to obtain accurately in practice.9,11-13 To that end, we have recently documented in several ADHF populations, including a prospective National Institutes of Health trial of diuretic strategies, that fluid and weight loss are frequently not collected and when available are surprisingly inaccurate.11 Even if these metrics could be consistently and accurately obtained, there is a significant delay between administration of the diuretic and availability of the data (ie, daily weights are generally obtained only once daily). Between the inconsistent collection, low fidelity, and inherent delay in data availability, diuretics are often titrated only once daily, resulting in wasted hospital days before inadequate diuretic response is identified and acted upon.

See Clinical Perspective

Adding further complexity to the above uncertainty is the fact that the primary pathophysiology responsible for extracellular volume expansion is sodium retention.14,15 However, net fluid and weight loss are almost entirely the result of changes in water balance because water accounts for the vast majority of the fluid shift.16 Computational models of fluid and electrolyte balance suggest that sodium balance is an unknown but important determinant of fluid output.17-20

See Table for the key results. The sodium prediction equation is available at http://circheartfailure.ahajournals.org.
The majority of the weight/volume of even isotonic fluid (ie, ≈9 g of NaCl are in 1000 g or milliliters of normal saline). As such, if the goal of diuretic therapy is to correct the underlying pathophysiology of sodium overload, the monitoring parameter should ideally predict not only water but also sodium removal. The limited data available in patients with heart failure suggests that significant variability between patients may actually be present in the sodium content of diuretic-induced urine. Furthermore, even within patients, the sodium content of diuretic-induced urine seems to vary considerably over time and with the type of diuretic administered. Additionally, there seems to be significant prognostic importance of the quantity of sodium in the urine, whereas neither weight nor fluid loss have consistently been linked to outcomes. Unfortunately, performing timed urine collections is not practical in routine clinical practice and would be expected to suffer from many of the same difficult to overcome limitations inherent to monitoring urine output.

Currently, tools that allow early prediction of natriuretic response shortly after administration of a loop diuretic are unavailable. Given the well-understood pharmacokinetics and pharmacodynamics of the loop diuretics, and existing well-validated metrics to query renal filtration and urinary concentration, net sodium and urine output from a dose of diuretic should be accurately predictable from a spot urine sample obtained early after diuretic administration. Glomerular filtration rate (GFR) estimation equations have largely replaced and are generally thought to be more accurate than measurement of 24-hour creatinine clearance, because of the difficulty of accurately conducting timed urine collections. Similar to the above example, the ability to rapidly estimate sodium output from a dose of diuretic using an estimating equation could also provide significant value to clinicians and researchers. The goal of the current investigation was to determine whether sodium output from a loop diuretic can be rapidly and accurately predicted using well established physiological principals in conjunction with inexpensive widely available laboratory tests.

Methods

Equations
The equations on which this article is based are not derived from study data, but rather were derived before study initiation based entirely on the well-established tools and physiological principals available to query renal physiology and diuretic pharmacology. The underlying concept behind the equations is that the instantaneous rate of urine formation at any moment (ie, milliliters of urine produced per minute) can be described as the GFR adjusted for the degree of urinary concentration/dilution occurring in the renal tubule. There is a vast body of literature that has optimized and validated equations for the accurate estimation of GFR, which are used here in the form of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Because creatinine undergoes limited reabsorption in the kidney (the basis for the use of creatinine to estimate GFR), the ratio of serum creatinine to urine creatinine reflects the degree of concentration occurring in the tubules. As a result, the instantaneous rate of urine formation (mL/min) can be derived from the product of estimated GFR and the ratio of serum to urine creatinine. Multiplication of this parameter by the urine sodium concentration allows conversion from the instantaneous rate of urine formation to sodium excretion (mmol/min). Because the majority of natriuresis occurs shortly after bolus intravenous loop diuretic administration, and natriuresis is completed within 6 hours, the instantaneous rate of sodium excretion can be converted into a cumulative sodium output by multiplying by a time constant. The predicted total sodium output was calculated using Equation 1:

\[
\text{Na output (mmol)} = \frac{\text{eGFR} \times (\text{BSA}/1.73) \times \left(\frac{C_{\text{U,serum}}}{C_{\text{U,urine}}}\right)}{60 \text{ min} \times 2.5 \text{ h} \times \left(\frac{\text{Na}_{\text{urine}}}{1000 \text{ ml}}\right)}
\]

Cr represents creatinine in the serum or urine. Body surface area was calculated using the Du Bois formula. The CKD-EPI estimated GFR was unindexed to 1.73 m² because absolute sodium output rather than sodium output per 1.73 m² is the parameter of interest. In patients with extreme obesity (body mass index >40 kg/m²), ideal body weight (Robinson formula) was used to calculate body surface area.

\[
\text{Predicted fluid output was calculated using Equation 2:}
\]

\[
\text{Urine output (mL)} = \frac{\text{eGFR} \times (\text{BSA}/1.73) \times \left(\frac{C_{\text{U,serum}}}{C_{\text{U,urine}}}\right)}{60 \text{ min} \times 2.5 \text{ h}}
\]

Population
Patients admitted to the general cardiology and advanced heart failure services at Yale New Haven Hospital were eligible for enrollment. Selection criteria were intentionally broad to attempt to capture a generalizable population of patients undergoing diuresis. Eligibility required a diagnosis of heart failure and a plan by the treating physician for diuresis with intravenous loop diuretics. Exclusion criteria were known bladder dysfunction/incontinence or an inability to comply with the timed urine collection protocol. Enrollment could occur at any time during the hospitalization at which they met the above criteria. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Yale University. All patients provided written informed consent, and the study was approved by the Yale Institutional Review Board.

Urine Collection Protocol
Before the morning diuretic dosing, the patient was asked to completely empty their bladder. Next, a dose of intravenous loop diuretic was administered. The dose was determined by the treating physician, but all patients in this proof of concept study received bumetanide because of the reproducible pharmacokinetics of this agent. Next, a timed 6-hour urine collection with intense supervision by study staff began. This supervision consisted of study personnel stationed outside of the patient’s room for the duration of the study with frequent transfer of urine into study collection containers and frequent reinforcement with the patient of the importance of complete collection. Additionally, signs were placed on the door of the patient’s room, the bathroom door, and over the toilet reminding patient and staff that all urine was to be saved. A spot urine sample was obtained at hour 1 and hour 2 after the intravenous diuretic, and the cumulative urine output was also collected, terminating with a forced void at hour 6. A 6-hour time period was chosen because it has been well documented that natriuresis from a dose of intravenous furosemide or bumetanide is completed within 6 hours.

Assays
Serum creatinine, from the patients’ routine morning clinical laboratory, was obtained from the medical record. Urine creatinine and sodium were determined using a fully automated RxDaytona Clinical Chemistry Analyzer (Randox Laboratories, Ireland, UK). Urine creatinine was determined using a modified Jaffe method and sodium by direct measurement with ion selective electrodes. In the case where urine sodium

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was below the lower limit of detection, samples were diluted 1:1 with normal saline and reanalyzed. The calibrators, reagents, and urine level 2 and level 3 controls were purchased from Randox Laboratories. The interassay coefficient of variation for the controls were 4.76% and 4.9% for creatinine and 4.4% and 3.71% for sodium. Assays were conducted using deidentified aliquots of urine, blind to the clinical data from the urine collection protocol (ie, volume of urine output), and by different study personnel than those who obtained the clinical data.

**End Points**

The primary end point was the ability of Equation 1 to predict a poor loop diuretic natriuretic response, defined as a measured cumulative sodium output of ≥50 mmol in the 6 hours after the dose of diuretic. The threshold of ≤50 mmol was selected because twice daily dosing of the same dose of diuretics would result in ≤100 mmol daily Na output. Because the standard cardiac diet at Yale is a 3 g/130 mmol sodium diet, ≤100 mmol Na would result in a positive sodium balance. Primary focus was on calculations from the 2-hour spot urine sample because this was hypothesized to be the more accurate of the 2 time points as a result of the delay from urine production to availability for collection introduced by the bladder. Secondary end points were (1) a suboptimal natriuretic response and (2) an excellent natriuretic response. A suboptimal natriuretic response was defined as ≤100 mmol of sodium output from the diuretic which would result in a maximum net sodium deficit of only 70 mmol per day with twice daily diuretic dosing. This is equivalent to a maximum of ≤0.5 L of isotonic fluid or <1.1 lb per day of weight loss with twice daily dosing, which we feel would be a threshold below which up titration of diuretics should be considered in patients with significant volume overload. An excellent response was defined as >150 mmol of sodium output in response to the loop diuretic. This would result in >1 L of isotonic fluid loss or >2 lbs with twice daily dosing of diuretics.

**Statistical Analysis**

Values reported are mean±SD, median (quartile 1–quartile 3), and percentile. Independent Student’s t test or the Wilcoxon rank-sum test was used to compare continuous variables. The χ² test was used to evaluate associations between categorical variables. Correlation coefficients reported are Pearson’s. Receiver operating characteristic curves with calculation of the area under the curve (AUC) for clinically relevant thresholds of sodium and fluid output (see end points section above) were performed. Although the time constant used in the equations does not influence the correlation or AUC because it is a linear constant, it will influence the absolute accuracy of the equation particularly at higher sodium outputs. As such, sensitivity analysis was undertaken to determine whether the empirically derived constant of 2.5 hours could be improved upon. Sodium output prediction equations with time constants ranging from 2 to 4 hours in 0.25 hour increments were computed. The proportionality of the bias of the equation over the range of sodium output was determined by subtracting the measured sodium output from the predicted sodium output with each time constant and evaluating the correlation with measured sodium output. The time constant resulting in the smallest correlation coefficient was considered the best data-driven time constant. Statistical analysis was performed with IBM SPSS Statistics version 21 (IBM Corp, Armonk, NY) and Stata version 13.1 (StataCorp, College Station, TX), and statistical significance was defined as 2-tailed P<0.05.

**Results**

Overall, 50 patients completed the 6-hour urine collection protocol and were included in the analysis (Figure I in the Data Supplement for cohort assembly details). The median time from hospital admission to enrollment was 4 days (1–7 days). Baseline characteristics of the population are presented in Table 1. Notably, the population consisted predominantly of patients with heart failure with reduced ejection fraction of nonischemic pathogenesis. Hypertension, diabetes mellitus, hyponatremia, and renal dysfunction were common. On average, enrolled patients were receiving relatively high doses of loop diuretics with a median diuretic dose of 100 mg/24 hours of intravenous furosemide equivalents the day before the study (Table 1).

The median dose of intravenous bumetanide administered was 3 mg (quartile 1–quartile 3: 2–4 mg), resulting in a mean cumulative sodium output of 85.5±73 mmol and a mean cumulative urine output of 979±589 mL over the ensuing 6-hour period. The median diuretic efficiency in this population was 257 mL/mg bumetanide (164–486 mL/mg), similar to previously reported ADHF populations.Overall, the correlation between the actual cumulative sodium output and the predicted sodium output from Equation 1 was excellent for both the 2-hour sample (Figure A and Table 2) and the 1-hour sample (Table 2). The correlation between measured sodium output and the clinically recorded net fluid output for the corresponding 7 AM to 3 PM nursing shift (ie, what the physician would otherwise be making same day dose titration decisions upon) was substantially worse (Table 2 and Figure B). The correlation between measured sodium output and parameters such as 24-hour net fluid output, weight change, urine sodium

**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58.9±13.9</td>
</tr>
<tr>
<td>White race</td>
<td>72.0%</td>
</tr>
<tr>
<td>Male</td>
<td>64.0%</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>59.6%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42.9%</td>
</tr>
<tr>
<td>Gout</td>
<td>16.3%</td>
</tr>
<tr>
<td>Ischemic heart failure pathogenesis</td>
<td>26.5%</td>
</tr>
<tr>
<td><strong>Medications (baseline)</strong></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor or receptor blocker</td>
<td>93.9%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>76.0%</td>
</tr>
<tr>
<td>Thiazide type diuretic</td>
<td>24.0%</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>48.0%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>20.4%</td>
</tr>
<tr>
<td>Loop diuretic dose before study (mg furosemide equivalents)</td>
<td>100 (80 - 160)</td>
</tr>
<tr>
<td><strong>Laboratory value</strong></td>
<td></td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>135.2±3.7</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>37 (23.8–64.2)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.4 (1–2.1)</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min/1.73 m²</td>
<td>55 (30–76)</td>
</tr>
<tr>
<td>Glomerular filtration rate ≤60 mL/min/1.73 m²</td>
<td>60.0%</td>
</tr>
<tr>
<td>Glomerular filtration rate &gt;60 mL/min/1.73 m²</td>
<td>24.0%</td>
</tr>
<tr>
<td><strong>Functional status/ejection fraction</strong></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>29.2±17.7</td>
</tr>
<tr>
<td>Ejection fraction &gt;40%</td>
<td>20.9%</td>
</tr>
</tbody>
</table>
Table 2. Correlations With Measured Sodium Output

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation With Measured Cumulative Sodium Output</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Predicted sodium output (2-h sample)</td>
<td>0.91</td>
</tr>
<tr>
<td>Predicted sodium output (1-h sample)</td>
<td>0.85</td>
</tr>
<tr>
<td>Clinically recorded net fluid balance from corresponding nursing shift*</td>
<td>0.66</td>
</tr>
<tr>
<td>24-h clinically recorded net fluid balance</td>
<td>0.72</td>
</tr>
<tr>
<td>24-h clinically recorded weight loss</td>
<td>0.41</td>
</tr>
<tr>
<td>Bumetanide dose</td>
<td>0.11</td>
</tr>
<tr>
<td>Urine sodium (1 h)</td>
<td>0.70</td>
</tr>
<tr>
<td>Urine sodium (2 h)</td>
<td>0.71</td>
</tr>
<tr>
<td>Fractional excretion of sodium (1 h)</td>
<td>0.66</td>
</tr>
<tr>
<td>Fractional excretion of sodium (2 h)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

*Represents the 7 AM to 3 PM nursing shift that fluid balance is calculated by the clinical staff as part of usual care and the parameter that same day diuretic dosing decisions are generally made on.

concentration, fractional excretion of sodium, and diuretic dose, also tended to have a weaker correlation than predicted sodium from Equation 1 (Table 2). Similar to prior reports, the correlation between clinically obtained 24-hour net fluid balance and clinically obtained 24-hour weight loss was modest (r=0.58; P=0.001). The time from hospital admission to diuretic administration did not influence the accuracy of the prediction equation because nearly identical correlations between predicted and measured sodium output were observed (r=0.90, P=0.001 versus 0.91, P=0.001) in patients studied within 48 hours of admission (n=21, median time to study =1 day) and in patients studied >48 hours after admission (n=29, median time to study =6 days). Additionally, in receiver operating curve analysis of subgroups defined by patients studied within 48 hours of admission or >48 hours after admission, AUC values for prediction of poor natriuretic response (sodium output <50 mmol) were similar for both subgroups (AUC=1.0, P<0.001, 95% CI 1.0–1.0 versus 0.95, P<0.001, 95% CI 0.87–1.0).

Poor diuretic natriuretic response (≤50 mmol sodium output in the 6 hours after the diuretic) occurred in 40% of the population. In patients with poor natriuretic response, the average cumulative sodium output was 24.3±12 mmol after a median bumetanide dose of 2.75 mg (2–4 mg). A suboptimal natriuretic response (≤100 mmol of sodium output) occurred in 68% of the population. These patients received a median of 3 mg (interquartile range 2–4 mg) of bumetanide and excreted 45.0±28.8 mmol of sodium. In the 16% of patients who had an excellent natriuretic response (>150 mmol), mean sodium output was 221.1±52.2 mmol with a bumetanide dose of 3.5 mg (2–4 mg). Particularly with the 2-hour time point, Equation 1 performed remarkably well in predicting which patients would have a poor natriuretic response (Figure C). A predicted sodium output from Equation 1 of ≤50 mmol was 95% sensitive and 73% specific in predicting a poor natriuretic response. A predicted sodium output <25 mmol was 100% specific, and a predicted sodium output <75 mmol was 100% sensitive in predicting a poor diuretic natriuretic response. Overall, Equation 1 had excellent accuracy in predicting all natriuretic thresholds ranging from 50 to 150 mmol, with AUC values ≥0.95 using the 2-hour spot urine and AUC values ≥0.86 for the 1-hour spot urine time point (Table 3). Operating characteristics of the clinically recorded net fluid output for the corresponding nursing shift were inferior to Equation 1 (Figure D) as were those of 24-hour fluid and weight loss, particularly at lower sodium output thresholds (Table 3).

Time Constant Sensitivity Analysis

The a priori chosen 2.5 hour time constant appeared to lead to an underestimation of sodium output with progressively higher sodium outputs (Figure A; Figure I in the Data Supplement; P<0.001). Analyzing time constants ranging from 2 hours to 4 hours in 0.25 hour increments revealed that the best fit in the current 50 patients was using a constant of 3.25 hours, which resulted in stable prediction with progressively larger sodium outputs, as demonstrated by the lack of correlation between observed sodium output and the difference between predicted and observed sodium output (r=−0.05; P=0.74).

Prediction of Fluid Output

The correlation between measured fluid output in the 6 hours after a dose of loop diuretic and that predicted by Equation 2 was r=0.81, P<0.001, for the one hour equation and r=0.84, P<0.001, for the 2-hour equation. AUC values for

Table 3. Receiver Operating Curve Analysis Results for Prediction of Various Measured Cumulative Sodium Output Thresholds

<table>
<thead>
<tr>
<th>Measured Sodium Output</th>
<th>Predicted Sodium Output (2-h Sample)</th>
<th>Predicted Sodium Output (1-h Sample)</th>
<th>Clinically Recorded Net Fluid Balance (Corresponding Nursing Shift*)</th>
<th>Clinically recorded net fluid balance (24-h)</th>
<th>Clinically recorded weight change (24-h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>95% CI</td>
<td>P Value†</td>
<td>AUC</td>
<td>95% CI</td>
</tr>
<tr>
<td>≤50 mmol</td>
<td>0.95</td>
<td>0.89–1.0</td>
<td>&lt;0.001</td>
<td>0.76</td>
<td>0.63–0.89</td>
</tr>
<tr>
<td>75 mmol</td>
<td>0.97</td>
<td>0.92–1.0</td>
<td>&lt;0.001</td>
<td>0.77</td>
<td>0.64–0.90</td>
</tr>
<tr>
<td>100 mmol</td>
<td>0.97</td>
<td>0.93–1.0</td>
<td>&lt;0.001</td>
<td>0.75</td>
<td>0.60–0.91</td>
</tr>
<tr>
<td>125 mmol</td>
<td>0.99</td>
<td>0.98–1.0</td>
<td>&lt;0.001</td>
<td>0.90</td>
<td>0.78–0.99</td>
</tr>
<tr>
<td>150 mmol</td>
<td>0.99</td>
<td>0.97–1.0</td>
<td>&lt;0.001</td>
<td>0.92</td>
<td>0.81–1.0</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; and CI, confidence interval.

*Represents the 7 AM to 3 PM nursing shift that fluid balance is calculated by the clinical staff and the parameter that same day diuretic dosing decisions are frequently made on.

†P value for comparison to 2-h prediction.
predicting various levels of measured urine output are presented in Table 4. Overall, prediction of urine output was inferior to prediction of sodium output; however, prediction of urine output by the equation was similar to or better than results achieved using the clinically recorded net fluid output during the corresponding nursing shift in the majority of cases (Table 4).

A web-based calculator for Equations 1 and 2 can be found at www.CardioRenalResearch.net.

Discussion

The primary finding of the current analysis is that cumulative sodium output from a dose of loop diuretic can be predicted rapidly and with excellent accuracy from a spot urine sample collected 1 to 2 hours after the dose of loop diuretic. Importantly, derivation of the equations used in this study was not data driven. Rather, the equation was derived from well-established physiological and pharmacological principals and then validated in this real world ADHF population receiving loop diuretics. In addition to the fact that application of this equation allows the possibility of diagnosis and thus provider response to poor diuretic natriuretic response within hours of diuretic administration, it was significantly more accurate in predicting a poor diuretic response than currently available clinical parameters, such as net fluid output or weight loss. Although additional research is necessary to understand the appropriate application of these findings, this represents the first description of a new tool to monitor diuretic response with potential use in both research and clinical care in heart failure.

The use of sodium output as a metric of diuretic response is intuitive because physiologically sodium is the principal determinant of extracellular fluid volume and diuretics function primarily via effects on renal sodium channels. Furthermore, from a practical standpoint measuring sodium rather than fluid balance in hospitalized patients offers several theoretical advantages. Controlling and accounting for actual fluid intake in ADHF patients, who commonly have increased thirst, is a labor-intensive task with many pitfalls because these patients often have free access to water. However, most hospitalized patients’ primary source of dietary sodium should be the diet delivered by the hospital nutrition service, making assumptions about intake much simpler. Unfortunately, formally measuring sodium output in clinical practice with standard approaches is burdensome because it requires timed urine collections and obligatorily suffers from the same challenges limiting the accuracy of measuring cumulative fluid output. Notably, in the current study, despite (1) the patient and staff knowing they were in a study and needed optimal collection of urine for 6 hours, (2) not enrolling patients unlikely to be able to comply with complete urine collection, (3) placing signs in the room and bathroom reminding patient/staff that urine was to be saved, (4) a coordinator intensely supervising the timed urine collection, and (5) compensating both patient and the nursing staff during the latter part of the study for the inconvenience of the above interventions, 12% of patients still had issues with the timed urine collection leading to study cancellation (Figure 1 in the Data Supplement). However, a spot urine specimen was obtainable in all patients. As such, the use of a spot urine sample to guide natriuretic therapy provides the advantage of monitoring sodium rather than fluid output and provides this information much more rapidly, accurately, and easily than would be possible with a timed urine collection. Furthermore, given the labor-intensive nature of monitoring fluid intake and output, and the low cost of urine sodium and creatinine, this approach may additionally prove to be more cost-effective.

There are several potential direct applications of the current findings to clinical care and research. First, the capability to detect an inadequate natriuresis shortly after diuretic administration offers significant potential opportunity. Given the low fidelity and delay inherent to collection of net fluid balance and weight change in weight, diuretics are often titrated only once daily. By identifying patients who are responding suboptimally to diuretics just an hour or 2 after a loop diuretic is given, repeat dosing could occur much more rapidly, offering advantage with respect to outcomes ranging from more rapid symptom relief to possibly a reduction in length of stay or improved overall decongestion. Second, in many patients and on many clinical wards, it is extremely challenging to accurately monitor diuresis with fluid balance and weight loss. The current findings provide a tool to allow the clinician to interrogate diuretic responsiveness where otherwise it would be very difficult. Finally, enrollment into ADHF trials of decongestive therapies should occur early into ADHF therapy. As a result, waiting days to determine that the patient is definitively diuretic resistant by traditional metrics (ie, failure to lose weight) is suboptimal. However, enrollment of patients who are not diuretic resistant into trials of diuretic adjuvant therapy can bias the trials toward the null. For example, in the Renal Optimization Strategies Evaluation (ROSE) trial, the placebo group produced 8.3 L of urine with standard...
therapy, a result difficult to improve upon. Rapidly identifying responders and nonresponders to decongestive therapy will allow more selective enrollment of patients who will not respond adequately to standard therapy into trials of novel therapies.

Limitations

There are several limitations that warrant discussion. Although the equations used to predict sodium and fluid output were derived from well-established physiological principals and validated in this cohort, the validation cohort is still a small single-center study and, thus, should undergo additional external validation. Importantly, several parameters in this cohort, such as high incidence of hyponatremia, significant renal impairment, and younger age than found in registry studies, reinforces that these were a highly selected patients at a tertiary care center and that validation is required. Furthermore, despite extraordinary efforts to ensure highly accurate timed urine collection in these patients, 12% had overt errors leading to study termination, and likely many more had errors that were not reported or detected by the study staff. As a result, the gold standard used here of a 6-hour urine collection is likely less than perfect, and the results may have been different if all patients had indwelling urinary catheters. As a result, multicenter external validation of the sodium prediction equation will likely need to use outcomes such as improved length of stay or readmission rates with care guided by predicted sodium versus usual care. Furthermore, because of the capacitance introduced into the urinary system by the bladder, incomplete bladder emptying before and at the last urination during the 6-hour collection will decrease precision of results of both the timed urine collection and the spot urine samples. Intravenous bumetanide was chosen for this proof-of-concept study because of its highly reproducible pharmacokinetics. Given the variable duration half-life of furosemide and the unpredictable rate of absorption of many oral diuretics, further research will be necessary to determine whether the current results are applicable to diuretics other than intravenous bumetanide. Although the goal of the current study was proof of concept that sodium output could be accurately predicted,
additional research will be necessary to evaluate the association with clinical outcomes and compare predicted sodium output with simpler metrics of sodium excretion, such as sodium concentration and fractional excretion of sodium. Finally, substituting the a priori time constant of 2.5 hours with 3.25 hours in Equation 1 improves the accuracy of the equation at higher sodium outputs. However, this was a data-driven finding and will require validation in additional subjects before it should be applied. Nevertheless, despite the limitations described above, given the known substantial limitations of monitoring diuresis with fluid and weight loss, we feel that judicious but immediate application of these findings to research and clinical care remains warranted.

Conclusions

Early prediction of the cumulative natriuretic response to a dose of intravenous bumetanide is possible with high accuracy using inexpensive laboratory tests performed in a spot urine sample and an equation derived from well-established renal physiological principles. This new tool provides the opportunity for rapid diagnosis of poor diuretic natriuretic response and may facilitate improved therapy and enrollment into clinical trials. Future research will be necessary to validate these findings and explore the ideal application of this tool.

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Disclosures

None.

References


**Clinical Perspective**

The primary goal in most hospitalizations for acute decompensated heart failure is the treatment of volume overload. As a result, accurately monitoring the progress and success of diuretic therapy is of critical importance. Currently, fluid and weight loss are the most commonly used monitoring parameters, but these metrics are notoriously inaccurate/not collected and require significant delay between administration of the diuretic and availability of the data. Given the well-described pharmacokinetics of the loop diuretics, we hypothesized that the cumulative sodium output should be predictable from a spot urine sample obtained shortly after diuretic administration. We prospectively enrolled 50 acute decompensated heart failure patients undergoing diuresis with intravenous loop diuretics and performed supervised 6-hour timed urine collections after intravenous bumetanide administration. Using a sodium prediction equation and urine sodium and creatinine obtained from a spot urine 1 or 2 hours after diuretic administration, we found an excellent ability to predict a poor diuretic response (area under the curve =0.95, 95% confidence interval 0.89–1.0; *P*<0.0001). The sodium prediction equation significantly outperformed net fluid output and change in weight obtained by hospital staff for clinical care of the patient. Although additional validation is required, these findings suggest that monitoring of diuretic response can be performed with improved accuracy and much more rapidly using a spot urine sample and a sodium prediction equation.
Rapid and Highly Accurate Prediction of Poor Loop Diuretic Natriuretic Response in Patients With Heart Failure

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Supplementary Figure 1: CONSORT diagram depicting assembly of the study cohort

- Consented and began the 6-hour urine collection protocol N=57
  - Withdrew consent N=1
  - Large volume of urine contaminated with loose stool N=1
  - Urine discarded by clinical staff N=2
  - Study interrupted by testing or procedure N=4
  - Unable to produce urine at both 1 and 2 hour time points N=6

- Completed the 6-hour urine collection protocol N=53
  - Serum creatinine unavailable N=1
  - Received additional intravenous diuretics during study period N=2

- Analyzed N=50
Supplementary Figure 2: Predicted sodium output vs. measured sodium output using time constants ranging from 2 to 4 hours.