Hemoconcentration of Creatinine Minimally Contributes to Changes in Creatinine during the Treatment of Decompensated Heart Failure

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Key Points
- Hemoconcentration is a minimal contributor to changes in serum creatinine during treatment of decompensated heart failure.
- Changes in GFR is the primary driver of serum creatinine in treatment of decompensated heart failure.

Abstract
Background Worsening serum creatinine is common during treatment of acute decompensated heart failure (ADHF). A possible contributor to creatinine increase is diuresis-induced changes in volume of distribution (VD) of creatinine as total body water (TBW) contracts around a fixed mass of creatinine. Our objective was to better understand the filtration and nonfiltration factors driving change in creatinine during ADHF.

Methods Participants in the ROSE-AHF trial with baseline to 72-hour serum creatinine; net fluid output; and urinary KIM-1, NGAL, and NAG were included (n=270). Changes in VD were calculated by accounting for measured input and outputs from weight-based calculated TBW. Changes in observed creatinine (Cr_{observed}) were compared with predicted changes in creatinine after accounting for alterations in VD and non-steady state conditions using a kinetic GFR equation (Cr_{72HR Kinetic}).

Results When considering only change in VD, the median diuresis to elicit a $0.3 \text{ mg/dl}$ rise in creatinine was $7526 \text{ ml}$ (IQR, $-5932$ to $-9149$). After accounting for stable creatinine filtration during diuresis, a change in VD alone was insufficient to elicit a $0.3 \text{ mg/dl}$ rise in creatinine. Larger estimated decreases in VD were paradoxically associated with improvement in Cr_{observed} ($r=-0.18$, $P=0.003$). Overall, $-3\%$ of the change in eCr_{72HR Kinetic} was attributable to the change in VD. A $0.3 \text{ mg/dl}$ rise in eCr_{72HR Kinetic} was not associated with worsening of KIM-1, NGAL, NAG, or postdischarge survival ($P>0.05$ for all).

Conclusions During ADHF therapy, increases in serum creatinine are driven predominantly by changes in filtration, with minimal contribution from change in VD.

Introduction Fluctuations in serum creatinine are common in patients undergoing treatment for acute decompensated heart failure (ADHF) (1). Worsening renal function (WRF), as it is termed in the cardiovascular literature, is often considered a negative prognostic indicator (2-5). However, contemporary data have found that clinical context of WRF largely determines its prognostic effect (6). Notably, if WRF occurs in an otherwise beneficial clinical context, such as aggressive decongestion or titration of renin-angiotensin-aldosterone system antagonists, WRF can be associated with neutral or improved survival. In this context, these observations have challenged the notion that changes in creatinine are driven by...
meaningful kidney injury. Rather, they suggest that mechanisms such as functional/hemodynamic changes in glomerular filtration are dominant (7). Alternatively, nonfiltration-related factors may be at play, such as a rapid reduction of the volume of distribution (VD) of creatinine leading to hemoconcentration of creatinine as total body water (TBW) contracts around a fixed mass of creatinine. With this mechanism, an increase in creatinine would be unrelated to GFR and simply a marker of effective diuresis. This could explain the null associations between WRF with urinary tubular injury markers and prognosis.

Changes in VD and filtration during the treatment of ADHF can be isolated and accounted for mathematically. Rooted in the conservation of mass of creatinine, kinetic GFR (kGFR) equations provide a more dynamic method of estimating acutely changing renal filtration during rapid fluctuations in serum creatinine and the VD of creatinine (8,9). Our goal was to apply kGFR and other models of these component factors to an ADHF population that underwent aggressive diuresis to better understand the mechanism underlying the changes in creatinine during ADHF therapy.

Materials and Methods

The multicenter ROSE Acute Heart Failure Randomized Trial (ROSE-AHF) provides an ideal platform to study acute changes in renal function in the setting of aggressive diuresis. The rationale, design, and results of the trial were previously described (10,11). The study was composed of 360 patients with ADHF who had at least one symptom and one sign of volume overload. Patients were randomized to receive dopamine, nesiritide, or placebo, interventions that did not influence the primary end points of change in cystatin C or diuresis (11). Importantly, all patients received aggressive open-label diuretic doses. Moreover, the dosing of furosemide comprised the randomized high-dose arm of the Diuretic Optimization Strategies for Renal Evaluation (DOSE) trial that significantly increased the incidence of WRF (12). A consort diagram is provided in Supplemental Figure 1. Of the 360 total patients included in the ROSE-AHF trial, we excluded patients with missing biomarker data and timed urine outputs, leaving 270 patients remaining for analysis. Data and other research materials for ROSE-AHF were obtained from the National Heart, Lung, and Blood Institute BioLINCC.

Modeling of Renal Function

Table 1 defines the study metrics of creatinine. Further discussion of the concept underlying kGFR and derivation of kGFR equations have been previously reviewed, and all equations used for this analysis are located in Supplemental Appendix 1 (8,9). An initial evaluation of the effects of VD was undertaken using a simple dilution equation. In this experiment, each of the ROSE-AHF patients had their TBW (the VD of creatinine) changed by the amount of net diuresis that occurred over 72 hours, without accounting for increased excretion as serum creatinine levels rose (13,14). Due to the absolute mass balance of creatinine, we can calculate the resulting concentration of creatinine through the following equation:

\[ [eCr]_{\text{Instant VD}} = [Cr]_0 \cdot \frac{V_0}{V_t} \]

where \([Cr]_0\) is the initial measured creatinine concentration, \(V_0\) represents the initial VD of creatinine, and \(V_t\) is the volume of distribution after net diuresis. This represents a worst-case, nonphysiologic process that does not account for increased renal excretion throughout the 72-hour period as

| Table 1. Definitions of calculated creatinine |
|---------------------------------------------|
| **Abbreviation** | **Definition** | **Interpretation** |
| --- | --- | --- |
| \(Cr_{\text{observed}}\) | Difference in the measured serum creatinine at 72 hours and baseline serum creatinine | Patients with a \(Cr_{\text{observed}} \geq 0.3\) mg/dl were considered to have “worsening renal function”  
“Worst-case” effect of 72-hour change in TBW on serum creatinine assuming the 72-hour diuresis resulted in an instantaneous change in TBW contracting around the fixed mass of creatinine. Because it is calculated instantaneously, increased renal excretion of creatinine over the 72 hours is unaccounted for. |
| \(cCr_{\text{Instant VD}}\) | Calculated creatinine value comprising the product of baseline measured serum creatinine and the percent change in VD from baseline to 72 hours | Estimates the effect of VD after accounting for the increased elimination of creatinine during that time when hemoconcentration of creatinine increases concentration, and thus the gradient for renal elimination, over the 72-hour period |
| \(eCr_{\text{72HR VD}}\) | Calculated similarly to \(cCr_{\text{Instant VD}}\) but with an assumed stable creatinine production and renal elimination over 72 hours | Most sophisticated model to predict the 72-hour serum creatinine adjusting the GFR daily over 72 hours to the daily measured serum creatinine and daily change in VD |
| \(eCr_{\text{72HR Kinetic}}\) | Calculated serum creatinine at 72 hours incorporating both sequential changes in VD change in measured serum creatinine over the 72-hour study period |  
VD, volume of distribution; TBW, total body water. |
creatinine concentration rises due to TBW contracting around the fixed mass of creatinine.

To isolate the effect of changes in volume while renal clearance is ongoing, the following equation was developed. Assuming the GFR stays constant at its initial value, the model calculates the expected creatinine concentration due to a change in VD occurring over 72 hours. This gradual volume change is more realistic than the instantaneous hemoconcentration above.

\[
[eCr]_{72HR~VD} = [eCr_{observed}]_0 + 
\left[ 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}} \right)^{\frac{1+kGFR}{kGFR+\frac{\Delta V}{\Delta t}}} \right] \cdot \left( \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [eCr_{observed}]_0 \right)
\]

Initial VD of creatinine is estimated as previously described and the VD at 72 hours was estimated by subtracting net output from the initial VD. A creatinine generation rate was calculated by multiplying the initial creatinine concentration at baseline with its corresponding GFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (15). This creatinine generation value was used to calculate the expected serum creatinine on the basis of a gradual and steady change in VD while the GFR remained stable.

Naturally, the \(eCr_{\text{instant}}\) VD and the \(eCr_{72HR}\) VD are going to differ from the \(eCr_{\text{observed}}\). The actual measured creatinine at 72 hours is the result of the dynamic interplay between volume changes and GFR. Previously, the GFR was held constant at its initial value to calculate \(eCr_{72HR}\) VD. In reality, the GFR can change over time. We ascertain this changed GFR from the \(eCr_{\text{observed}}\) by applying a \(kGFR\) equation (8,16). The \(kGFR\) value was calculated using the Newton method (17).

\[
kGFR_{n+1} = kGFR_n + \frac{[Cr]_0}{\ln \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}} \right)^{\frac{1+kGFR}{kGFR+\frac{\Delta V}{\Delta t}}} \cdot \left( \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [Cr]_0 \right)} {\frac{1}{\ln \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}} \right)^{\frac{1+kGFR}{kGFR+\frac{\Delta V}{\Delta t}}} \cdot \left( \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [Cr]_0 \right)} + \left[ 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}} \right)^{\frac{1+kGFR}{kGFR+\frac{\Delta V}{\Delta t}}} \right] \cdot \left( \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [Cr]_0 \right)}
\]

Initial volume, changes in VD, and creatinine generation were calculated similarly. Sequential changes in measured serum creatinine and volume over the 72-hour study period were used to calculate the corresponding \(kGFR\). If this \(kGFR\) was allowed to achieve a new steady state, the future creatinine value can be calculated with a rearranged Modification of Diet in Renal Disease equation.

\[
[eCr]_{72HR~Kinetic} = \left( \frac{kGFR \cdot \text{Age}^{0.203}}{175 \cdot \text{race, sex factor(s)}} \right)^{\frac{1}{24}}
\]

### Statistical Analyses

Baseline characteristics are presented with continuous variables presented as a mean±SD or median and interquartile range (IQR), with categoric variables presented as \(n\) (%).

To maintain consistency with prior publications, WRF was defined as a \(\geq0.3\) mg/dl increase in creatinine concentration from baseline to 72 hours. Patient characteristics were compared between those participants that developed WRF and those that did not. Linearity of the relationship between changes in creatinine derived from each model and net output was assessed by examining trends across deciles of net output over 72 hours. We performed rank-based correlation between the changes in calculated creatinine and net output and report them as the Spearman \(\rho\). To estimate contribution to changes in calculated creatinine by VD alone, the estimated change in \(eCr_{72HR}\) kinetic was subtracted from \(eCr_{72HR}\) kinetic. This was then expressed as a percentage of the change in \(eCr_{72HR}\) kinetic. The independent \(t\) test or Mann–Whitney test was used to compare continuous variables between groups, as appropriate. Cox proportional hazard regression was used to examine survival between groups. Statistical analysis was performed with SPSS Statistics version 23 (IBM Corp, Armonk, NY), and statistical significance was defined as a two-tailed value of \(P<0.05\) for all analyses.

### Results

Baseline characteristics of the study population are described in Table 2. This group closely mirrored the overall ROSE-AHF trial. Patients in this study population underwent an aggressive diuretic regimen, with a mean of 645±443 mg furosemide equivalents administered, resulting in a median (IQR) net fluid output of 4394 (2678–6426) ml over the 72-hour trial period. The mean change in \(eCr_{\text{observed}}\) was 0.0±0.39 mg/dl from baseline to 72 hours, with 17% (47 of 270) of patients having a \(\geq0.3\) mg/dl increase in \(eCr_{\text{observed}}\).

### Isolating Contribution of Change in VD

Using a simple dilution equation to evaluate a “worst-case” situation in which the 72 hours of net fluid output of each patient was modeled as if it were an instantaneous diuresis, 19% (52 of 270) of the study population had sufficient diuresis to elicit a \(\geq0.3\) mg/dl worsening of \(eCr_{\text{instant}}\) VD purely on the basis of a change in VD. The median net fluid output required to elicit an increase of \(\geq0.3\) mg/dl \(eCr_{\text{instant}}\) VD was 13% of the patient’s TBW, which translated to a median (IQR) –7526 (–5933 to –9150) ml of fluid loss. The trend in \(eCr_{\text{observed}}\) across deciles of net output are shown in Figure 1A. Comparatively, the trend in calculated \(eCr_{\text{instant}}\) VD in this scenario across deciles of net output are shown in Figure 1B, which demonstrates rising \(eCr_{\text{instant}}\) VD with increasing net output. However, very few
of the patients who were aggressively diuresed and predicted to have an increase in $eCr_{\text{Instant} \ VD} \geq 0.3 \ mg/dl$ had an increase in $C_{\text{observed}}$ of $\geq 0.3 \ mg/dl$ (four of 52 patients). To the contrary, 69% (36 of 52) of these patients had an improvement in $C_{\text{observed}}$ over the 72-hour period. Sensitivity analyses varying the assumed VD of creatinine by percent of body weight showed a decreasing number of participants developing WRF with increasing assumed percentage of TBW (Supplemental Table 1).

Given that diuresis cannot happen instantaneously and thus creatinine production and excretion continue during the period of diuresis, we next modeled the expected volume-induced changes in creatinine assuming steady GFR and creatinine production, $eCr_{72HR \ VD}$. Incorporating these factors, the magnitude of increase in creatinine was muted and now zero participants had a resulting calculated $eCr_{72HR \ VD} \ \text{rise} \geq 0.3 \ mg/dl$ (Figure 1C) purely from a change in VD. Notably, there was an inverse correlation between $eCr_{72HR \ VD}$ and change in $C_{\text{observed}}$ ($r = -0.18$, $P = 0.003$), indicating changes in renal filtration dominated the change in $C_{\text{observed}}$. Findings were similar in sensitivity analyses varying the assumed VD of creatinine (Supplemental Table 1).

### Accounting for Both Change in VD, Non–Steady State Conditions, and Change in GFR

The median (IQR) change in $eCr_{72HR \ Kinetic}$ was 0.05 ($-0.17$ to $0.30$) mg/dl from baseline to 72 hours. On a population level, the mean $eCr_{72HR \ Kinetic}$ (1.84±0.76 mg/dl) was statistically significantly different from the 72-hour $C_{\text{observed}}$ (1.72±0.63 mg/dl; $P < 0.001$). Similarly, the difference in mean 72-hour change in $C_{\text{observed}}$ (0.00±0.39 mg/dl) and $eCr_{72HR \ Kinetic}$ (0.11±0.50 mg/dl) was statistically significantly different ($P < 0.001$). The median (IQR) change in creatinine attributable to the change in VD was 3% (−21% to 15%). On the individual level, 25% (68 of 270) of patients had a $\geq 0.3 \ mg/dl$ increase in $eCr_{72HR \ Kinetic}$, with 65% (44 of 68) also having a $\geq 0.3 \ mg/dl$ increase in $C_{\text{observed}}$. Conversely, 94% (44 of 47) of patients with a $\geq 0.3 \ mg/dl$ increase in $C_{\text{observed}}$ also had an increase $eCr_{72HR \ Kinetic}$.
Trend in \( eCr_{72HR \text{ Kinetic}} \) across deciles of net output are shown in Figure 1D.

**Association with Kidney Tubular Injury Markers and Survival**

We previously reported an absence of meaningful association between change in \( Cr_{\text{observed}} \) with N-acetyl-β-D-glucosaminidase, kidney injury molecule 1, and neutrophil gelatinase-associated lipocalin in the ROSE-AHF population (18). Including the influence of the change in VD on serum creatinine using the \( kGFR \) formula, we found a similar lack of association between tubular injury markers and \( \geq 0.3 \text{ mg/dL} \) increase in \( eCr_{72HR \text{ kinetic}} \) (\( P > 0.05 \) for all; Figure 2). Over the 180-day follow-up period, a total of 52 deaths were observed, with no difference in survival in patients with or without a \( \geq 0.3 \text{ mg/dL} \) increase in \( eCr_{72HR \text{ Kinetic}} \) (hazard ratio, 0.87; 95% CI, 0.5 to 1.7; \( P = 0.67 \)).

**Discussion**

In this study, we evaluated the contribution of hemoconcentration of creatinine to the commonly observed worsening in serum creatinine during the aggressive diuresis of patients with heart failure (HF). Our first observation was that very large volumes of diuresis over a short interval of time are required to meaningfully change serum creatinine by this mechanism. Notably, even if the diuresis were to occur instantaneously (not allowing any additional filtration of creatinine as the serum concentration rose), \( \Delta eCr_{72HR \text{ Kinetic}} \), estimated change in creatinine accounting for both change in volume of distribution and non-steady state during creatinine measurement, did not materially provide different information than the actual observed change in creatinine. This was true of both the association with urinary tubular injury markers, and the association with mortality. Notably, both the \( eCr_{\text{Kinetic}} \) and \( Cr_{\text{observed}} \) correlated inversely with the volume of diuresis, indicating an improvement in glomerular filtration with effective decongestion outweighed any effect of hemoconcentration of creatinine. The above results would
sugest that, in hospitalized patients with HF undergoing aggressive diuresis, the observed changes in serum creatinine are primarily driven by true changes in glomerular filtration, with minimal influence from hemocoencentration of creatinine.

The importance of changes in GFR in HF has been well recognized and intensely studied over several decades (4,19–21). Recently, a relatively consistent signal has emerged that context for a change in creatinine heavily modifies the associated prognosis. In the setting of aggressive diuresis, hemoconcentration, or complete decongestion, a small-to-moderate magnitude increase in creatinine does not appear to portend an adverse prognosis (22,23). Furthermore, several studies have looked at the association between changes in serum creatinine and urinary tubular injury markers, suggesting these changes in creatinine are not, in fact, driven by true kidney injury (18,24). The above data thus indicates that a benign cause for the changes in creatinine, with hemodynamic/functional changes in GFR and/or hemoconcentration of creatinine as the two plausible remaining candidate mechanisms. The current analyses strongly indicate that the increase in creatinine during diuresis of patients with ADHF is driven by a true change in GFR.

Aberrations in GFR have traditionally been thought to be predominantly hemodynamic and neurohormonal in origin. Notably, reduced renal perfusion, venous congestion, increased intra-abdominal pressure, neurohormonal activation, renin-angiotensin-aldosterone system antagonism, adverse renal effects of loop diuretics, and volume depletion have been highlighted as mechanisms driving cardiorenal interactions (14,25–28). In mild-to-moderate levels of derangement, these factors would be expected to lead to hemodynamic changes in renal function without structural damage. As such, despite the lack of association with adverse outcomes, the assertion that significant hemodynamically induced changes in GFR are common in HF is not surprising.

One notable finding from this analysis was change in GFR estimated with a $k_{\text{GFR}}$ formula did not give meaningfully different information than observed changes in creatinine. Changes in creatinine are common in ADHF, with some series finding that more than half of patients have at least 20% improvement or worsening during treatment (23,29,30). As such, the assumption of steady state is commonly violated at time of ascertainment of creatinine and thus incorporating the slope of change would be expected to provide useful information. However, it is well described that most changes in creatinine during ADHF therapy are of relatively small magnitude and the sampling interval infrequent. Assuming the principles of the $k_{\text{GFR}}$ approach are correct, these findings would argue that, on a population level, violations of steady state assumptions are not large enough to make a clinically meaningful effect on GFR estimation.

Limitations

The equations used in this study use mathematics to model complex physiology. Although the derivations and calculations are precise, certain limitations involving the inputs should be noted. Most important is the assumption of steady state in the calculation of the initial GFR using the CKD-EPI equation and, subsequently, creatinine generation rate, to which the other equations are grounded. In addition, TBW was estimated to comprise 50% of the total body weight of all patients in the study population. This assumption is mitigated by the fact that 50% likely represents an underestimation in the hypervolemic ADHF patient population. The net fluid balance was assumed to occur in a linear fashion throughout the body compartments over the 72-hour period. In reality, diuresis is often episodic and fluctuating. More accurate measurement of $k_{\text{GFR}}$ would require frequent sampling of serum creatinine and net output. Lastly, the effect of acute changes in creatinine generation, nonrenal creatinine elimination, and renal creatinine secretion are not accounted for in these analyses. Although the above limitations should caution the reader on qualitative interpretation of the results, it is unlikely these limitations would change the qualitative findings of the study, i.e., that hemoconcentration of creatinine plays a limited role in changes in creatinine.

Our data suggest that quantity and rate of diuresis required for serum creatinine to meaningfully increase...
primarily due to hemoconcentration in patients with ADHF are larger than typically encountered in clinical practice. The primary driver of changes in serum creatinine is likely to be a substantive change in GFR. Given the absence of association with tubular injury markers and mortality, these changes in GFR are likely hemodynamic/functional in nature. Additional research is required to better understand the underlying mechanisms.

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Author Contributions

J.L. Asher, S. Chen, S.G. Coca, Z.L. Cox, L.A. Inker, D. Mahoney, C. Maulion, D. Negoiatu, V.S. Rao, J.M. Testani, J.M. Turner, and F.P. Wilson reviewed and edited the manuscript; S. Chen and J.B. Ivey-Miranda were responsible for methodology; S. Chen, J.B. Ivey-Miranda, C. Maulion, and J.M. Testani were responsible for formal analysis; Z.L. Cox and J.M. Testani were responsible for visualization; J.B. Ivey-Miranda, C. Maulion, and V.S. Rao were responsible for data curation; C. Maulion wrote the original draft; C. Maulion and J.M. Testani conceptualized the study; and J.M. Testani provided supervision.

Data Sharing Statement

All data are included in the manuscript and/or supporting information.

Supplemental Material

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Supplemental Appendix 1.

Supplemental Table 1. Sensitivity analysis total body water.

Supplemental Figure 1. Consort diagram.

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