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Hemoconcentration of creatinine minimally contributes to changes in creatinine during 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 non-filtration 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 (Crobserved) were compared to predicted changes in creatinine after accounting for alterations in VD and non-steady state conditions using a kinetic GFR equation (Cr72HR Kinetic). Results: When considering only change in VD, the median diuresis to elicit a \( \geq 0.3 \) mg/dL rise in creatinine was -7526 mL (IQR, -5932, -9149). After accounting for stable creatinine filtration during diuresis, a change in VD alone was insufficient to elicit a \( \geq 0.3 \) mg/dL rise in creatinine. Larger estimated decreases in VD were paradoxically associated with improvement in Crobserved \((r=-0.18, p=.003)\). Overall, -3.3% of the change in Cr72HR Kinetic was attributable to the change in VD. A \( \geq 0.3 \) mg/dL rise in Cr72HR Kinetic was not associated with worsening of KIM-1, NGAL, NAG, or post discharge survival \((p>.05 for all)\). Conclusions: During ADHF therapy, increases in serum creatinine are driven predominantly by changes in filtration with minimal contribution from change in VD.
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Hemoconcentration of creatinine minimally contributes to changes in creatinine during the treatment of decompensated heart failure

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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 ($Cr_{\text{observed}}$) were compared to predicted changes in creatinine after accounting for alterations in VD and non-steady state conditions using a kinetic GFR equation ($Cr_{72HR \, \text{Kinetic}}$).

Results: When considering only change in VD, the median diuresis to elicit a $\geq 0.3$ mg/dL rise in creatinine was -7526 mL (IQR, -5932, -9149). After accounting for stable creatinine filtration during diuresis, a change in VD alone was insufficient to elicit a $\geq 0.3$ mg/dL rise in creatinine. Larger estimated decreases in VD were paradoxically associated with improvement in $Cr_{\text{observed}}$ ($r=-0.18$, p=.003). Overall, -3.3% of the change in $eCr_{72HR \, \text{Kinetic}}$ was attributable to the change in VD. A $\geq 0.3$ mg/dL rise in $eCr_{72HR \, \text{Kinetic}}$ was not associated with worsening of KIM-1, NGAL, NAG, or post discharge survival (p>.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).\textsuperscript{1} Worsening renal function (WRF), as it is termed in cardiovascular literature, is often considered a negative prognostic indicator.\textsuperscript{2-5} However, contemporary data has found that clinical context of WRF largely determines its prognostic impact.\textsuperscript{6} Notably, if WRF occurs in an otherwise beneficial clinical context, such as aggressive decongestion or titration of renin-angiotensin-aldosterone (RAAS) 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.\textsuperscript{8} Alternatively, non-filtration 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 glomerular filtration rate (kGFR) equations provide a more dynamic method of estimating acutely changing renal filtration during rapid fluctuations in serum creatinine and the VD of creatinine.\textsuperscript{9,10} Our goal was to apply kGFR and other modeling 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.
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 was previously described.\textsuperscript{11, 12} The study was composed of 360 patients with ADHF with 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 endpoints of change in cystatin C or diuresis.\textsuperscript{12} Importantly, all patients received aggressive open label diuretics equivalent to 2.5 times their daily home loop diuretic dose. Moreover, this dosing of furosemide comprised the randomized high-dose arm of the DOSE trial that significantly increased the incidence of WRF.\textsuperscript{13} A consort diagram is provided in supplementary 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 NHLBI BioLINCC.

Modeling of Renal Function

Chart 1: Definitions of calculated creatinines

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{C}_r^{\text{observed}}$</td>
<td>Difference in the measured serum creatinine at 72 hours and baseline serum creatinine</td>
<td>Patients with a $\text{C}_r^{\text{observed}} \geq 0.3 \text{mg/dL}$ were considered to have “worsening renal function”</td>
</tr>
<tr>
<td>$\text{eC}_r^{\text{instant VD}}$</td>
<td>Calculated creatinine value comprised of the product of baseline measured serum creatinine and the percent change in volume of distribution (VD) from baseline to 72 hours</td>
<td>“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. Since it is calculated instantaneously, increased renal excretion of creatinine over the 72 hours is unaccounted for.</td>
</tr>
<tr>
<td>$\text{eC}_r^{72\text{HR VD}}$</td>
<td>Calculated similarly to $\text{eC}_r^{\text{instant VD}}$ but with an assumed stable creatinine production and</td>
<td>Estimates the impact of VD after accounting for the increased elimination</td>
</tr>
</tbody>
</table>
renal elimination over 72 hours of creatinine during that time when hemoconcentration of creatinine increases concentration, and thus the gradient for renal elimination, over the 72-hour period

| eCr_{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 | 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 |

Chart 1 defines the study metrics of creatinine. Further discussion of the concept underlying and derivation of kinetic GFR equations have been previously reviewed, and all equations utilized for this analysis are located in appendix 1. 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. Due to the absolute mass balance of creatinine, we can calculate the resulting concentration of creatinine through the following equation:

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

Cr_{0} is the initial measured creatinine concentration. V_{0} represents the initial VD of creatinine, which was conservatively estimated to comprise 50% of the participant’s initial weight on presentation (lower assumed % body water would bias toward larger diuresis-induced changes making these analyses more sensitive). V_{t} was calculated by subtracting the net intake and urine output over the 72-hour study period from V_{0}. We performed sensitivity analysis calculating creatinine’s VD as 60% - 80% percent of initial weight. The above thought experiment reflects a worst case, non-physiologic process that does not account for increased renal excretion throughout the 72-hour period as 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.

\[
[eCr]_{72HRVD} = [Cr_{observed}]_0 + \left[ 1 - \left( \frac{V_0}{V_0 + \frac{AV}{\Delta t}} \right) \left( \frac{1 + \frac{GFR}{\Delta V}}{\frac{GFR + \Delta V}{\Delta t}} \right) \right] \cdot \left( \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [Cr_{observed}]_0 \right)
\]

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 estimated GFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). This creatinine generation value was used to calculate the expected serum creatinine based on 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 $Cr_{observed}$. 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 $Cr_{observed}$ by applying a kinetic GFR equation. The kinetic GFR value was calculated using Newton’s method.

\[
k_{GFR_{n+1}} = k_{GFR_n} + \left[ Cr_0 + \left[ 1 - \left( \frac{V_0}{V_0 + \frac{AV}{\Delta t}} \right) \left( \frac{1 + k_{GFR_n}}{\frac{AV}{\Delta t}} \right) \right] \cdot \left( \frac{CreGen}{k_{GFR_n} + \frac{AV}{\Delta t}} - [Cr]_0 \right) - [Cr]_t \right]
\]

\[
\left( \frac{V_0}{V_0 + \frac{AV}{\Delta t}} \right) \left( \frac{1 + k_{GFR_n}}{\frac{AV}{\Delta t}} \right) \cdot \frac{1}{\frac{AV}{\Delta t}} \ln \left( \frac{V_0}{V_0 + \frac{AV}{\Delta t}} \right) \cdot \left( \frac{CreGen}{k_{GFR_n} + \frac{AV}{\Delta t}} - [Cr]_0 \right) + \left[ 1 - \left( \frac{V_0}{V_0 + \frac{AV}{\Delta t}} \right) \left( \frac{1 + k_{GFR_n}}{\frac{AV}{\Delta t}} \right) \right] \cdot \frac{CreGen}{\left( k_{GFR_n} + \frac{AV}{\Delta t} \right)^2}
\]
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 kinetic GFR were allowed to achieve a new steady state, the future creatinine value can be calculated with a rearranged MDRD equation.

$$[eCr]_{72HR\ Kinetic} = \left( \frac{kGFR \cdot Age^{0.203}}{175 \cdot \text{race, gender factor(s)}} \right)^{-1.154}$$

**Statistical Analysis**

Baseline characteristics are presented with continuous variables presented as a mean +/- SD or median and interquartile range (IQR 1-3), with categorical variables presented as n %. To maintain consistency with prior publications, WRF was defined as a ≥ 0.3 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 ρ. To estimate contribution to changes in calculated creatinine by VD alone, the estimated change in eCr_{72HR\ VD} was subtracted from eCr_{72HR\ Kinetic}. This was then expressed as a percentage of the change in eCr_{72HR\ Kinetic}. Independent Student 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 2-tailed value of P<0.05 for all analyses.
Results

Baseline characteristics of the study population are described in table 1. This group closely mirrored the overall ROSE-AHF trial. Patients in the current study population underwent an aggressive diuretic regimen, with a mean of 645 ± 443 mg furosemide equivalents administered, resulting in a median net fluid output of 4394 mL (IQR, 2678 – 6426) over the 72-hour trial period. The mean change in Cr observed was 0.0 ± 0.39 mg/dL from baseline to 72 hours, with 17.4% (47/270) having a ≥ 0.3 mg/dL increase in Cr observed.

Isolating contribution of change in volume of distribution

Utilizing a simple dilution equation to evaluate a “worst case” look wherein the 72 hours of net fluid output of each patient was modeled as if it were an instantaneous diuresis, 19.3% (52/270) of the study population had sufficient diuresis to elicit a ≥0.3 mg/dL worsening of eCr Instant VD based purely on a change in VD. The median net fluid output required to elicit an increase of ≥0.3 mg/dL eCr Instant VD was 13.3% of the patient’s TBW, which translated to a median -7526 mL (IQR, -5933, -9150) of fluid loss. Trend in Cr observed across deciles of net output are shown in (Figure 1, Panel A). Comparatively, the trend in calculated eCr Instant VD in this scenario across deciles of net output are shown in (Figure 1, Panel B), which demonstrates rising eCr Instant VD with increasing net output. However, very few of the aggressively diuresed patients predicted to have an increase in eCr Instant VD ≥ 0.3mg/dL had an increase in Cr observed ≥ 0.3 mg/dL (N=4/52). To the contrary, 69.2% (N=36/52) of these patients had an improvement in Cr observed over the 72-hour period. Sensitivity analyses varying the assumed VD of creatinine by percent of body weight showed decreasing number of participants developing WRF with increasing assumed percentage TBW (Supplementary 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, eCr72HR VD. Incorporating these factors, the magnitude of increase in creatinine was muted and now zero participants had a resulting calculated
eCr\textsubscript{72HR VD} rise $\geq 0.3$ mg/dL (Figure 1, Panel C) purely from a change in volume of distribution. Notably, there was an inverse correlation between eCr\textsubscript{72HR VD} and change in Cr\textsubscript{observed} ($r=-0.18$, $p=0.003$), indicating that changes in renal filtration dominated the change in Cr\textsubscript{observed}. Findings were similar in sensitivity analyses varying the assumed VD of creatinine (Supplementary table 1).

*Accounting for both change in VD, non-steady state conditions, and change in GFR*

The median change in eCr\textsubscript{72HR Kinetic} was 0.05 mg/dL (IQR, -0.17 – 0.30) from baseline to 72 hours. On a population level, the mean eCr\textsubscript{72HR Kinetic} (1.84±0.76 mg/dL) was statistically significantly different from the 72-hour Cr\textsubscript{observed} (1.72±0.63 mg/dL $p < 0.05$). Similarly, the difference in mean 72-hour change in Cr\textsubscript{observed} (0.00±0.39) and eCr\textsubscript{72H kinetic} (0.11±0.50) was statistically significantly different, $p <0.05$. The median change in creatinine attributable to the change in VD was 2.84% (IQR-20.74 – 15.04). On the individual level, 25% (68/270) of patients had a $\geq 0.3$ mg/dL increase in eCr\textsubscript{72HR Kinetic}, with 65% (44/68) also having a $\geq 0.3$ mg/dL increase in Cr\textsubscript{observed}. Conversely, 94% (44/47) of patients with a $\geq 0.3$ mg/dL increase in Cr\textsubscript{observed} also had an increase eCr\textsubscript{72HR Kinetic}. Trend in eCr\textsubscript{72HR Kinetic} across deciles of net output are shown in (Figure 1, Panel D).

*Association with kidney tubular injury markers and survival*

We previously reported an absence of meaningful association between change in Cr\textsubscript{observed} with NAG, KIM-1, and NGAL in the ROSE-AHF population. Including the influence of the change in VD on serum creatinine using the kinetic GFR formula, we found a similar lack of association between tubular injury markers and $\geq 0.3$ mg/dL increase in eCr\textsubscript{72H 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 $\geq 0.3$ mg/dL increase in eCr\textsubscript{72HR Kinetic} (HR= 0.87, 95% CI 0.5 – 1.7, $p=0.67$).
Discussion

In the current study we evaluated the contribution of hemoconcentration of creatinine to the commonly observed worsening in serum creatinine during the aggressive diuresis of HF patients. Our first observation was 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 levels rise) a median of 7.5 L of fluid removal was required to produce a 0.3 mg/dL change in creatinine. Even in this non-physiologic, worst-case experiment, less than 20% of the population had a large enough fluid loss over 72 hours to potentially induce WRF. Accounting for continued creatinine production/filtration over the 72 hours, the change in VD alone was incapable of producing a ≥0.3 mg/dL increase in creatinine in any participant. After accounting for both changes in VD and changes in GFR with a kinetic GFR equation, the change in GFR 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_{Kinetic} and Cr_{observed} correlated inversely with the volume of diuresis, indicating that an improvement in glomerular filtration with effective decongestion outweighed any effect of hemoconcentration of creatinine. The above results would suggest that, in hospitalized HF patients undergoing aggressive diuresis, the observed changes in serum creatinine are primarily driven by true changes in glomerular filtration with minimal influence from hemoconcentration 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.\(^7,24\) The above data thus indicated a
benign cause for the changes in creatinine such as 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 ADHF patients is driven by a true change in GFR.

Aberrations in GFR have traditionally been thought as predominantly hemodynamic and neurohormonal in origin. Notably, reduced renal perfusion, venous congestion, increased intra-abdominal pressure, neurohormonal activation, RAAS antagonism, adverse renal effects of loop diuretics, and volume depletion have been highlighted as mechanisms driving cardio-renal interactions.\textsuperscript{15, 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 kGFR 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.\textsuperscript{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 that the principles of the kinetic 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 impact on GFR estimation.
Limitations:

The equations used in this study use mathematics to model complex physiology. While 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 CKD-EPI 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 kGFR would require frequent sampling of serum creatinine and net output. Lastly, the effect of acute changes in creatinine generation, non-renal creatinine elimination, and renal creatinine secretion are not accounted for in the present analyses. While the above limitations should caution the reader on quantitative interpretation of the results, it is unlikely these limitations would change the qualitative findings of the study that hemoconcentration of creatinine plays a limited role in changes in creatinine.

Conclusion:

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.
Disclosures:

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Author Contributions:
Christopher Maulion: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review and editing. Sheldon Chen: Formal analysis; Methodology; Writing - review and editing. Veena Rao: Data curation; Writing - review and editing. Juan Ivey-Miranda: Data curation; Formal analysis; Methodology. Zachary Cox: Visualization; Writing - review and editing. Devin Mahoney: Writing - review and editing. Steven Coca: Writing - review and editing. Dan Negoianu: Writing - review and editing. Jennifer Asher: Writing - review and editing. Jeffrey Turner: Writing - review and editing. Lesley Inker: Writing - review and editing. Francis Wilson: Writing - review and editing. Jeffrey Testani: Conceptualization; Formal analysis; Supervision; Visualization; Writing - review and editing.

Data Sharing Statement:
All data is included in the manuscript and/or supporting information.

Supplemental Data:
Supplementary Figure 1: Consort Diagram
Supplementary Table 1: Sensitivity Analysis Total Body Water
Appendix 1
References


29. Testani JM, McCauley BD, Chen J, Shumski M, Shannon RP: Worsening renal function defined as an absolute increase in serum creatinine is a biased metric for the study of cardio-renal interactions. Cardiology, 116: 206-212, 2010 10.1159/000316038

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall Cohort (N=270)</th>
<th>No WRF&lt;sub&gt;kinetic&lt;/sub&gt; (N=202)</th>
<th>WRF&lt;sub&gt;kinetic&lt;/sub&gt; (N=68)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>70±12</td>
<td>69±12</td>
<td>72±11</td>
<td>0.095</td>
</tr>
<tr>
<td>Male Sex</td>
<td>200 (74)</td>
<td>149 (74)</td>
<td>51 (75)</td>
<td>0.660</td>
</tr>
<tr>
<td>Race White</td>
<td>208 (77)</td>
<td>153 (76)</td>
<td>55 (81)</td>
<td>0.424</td>
</tr>
<tr>
<td>Clinical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>116±18</td>
<td>115±17</td>
<td>120±18</td>
<td>0.033</td>
</tr>
<tr>
<td>Baseline Weight (kg)</td>
<td>94.5±24.9</td>
<td>92.8±24.1</td>
<td>99.7±26.5</td>
<td>0.047</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>33 (21,52)</td>
<td>30 (20, 54)</td>
<td>33 (25, 46)</td>
<td>0.748</td>
</tr>
<tr>
<td>DM Type 2</td>
<td>146 (54)</td>
<td>106 (53)</td>
<td>40 (59)</td>
<td>0.286</td>
</tr>
<tr>
<td>ICD</td>
<td>117 (43)</td>
<td>86 (43)</td>
<td>31 (46)</td>
<td>0.783</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>212 (79)</td>
<td>153 (76)</td>
<td>59 (87)</td>
<td>0.064</td>
</tr>
<tr>
<td>Laboratory Values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Creatinine (mg/dL)</td>
<td>1.73 ± 0.53</td>
<td>1.69 ± 0.49</td>
<td>1.83 ± 0.63</td>
<td>0.095</td>
</tr>
<tr>
<td>72hr Creatinine Change (mg/dL)</td>
<td>0.00±0.39</td>
<td>-0.15±0.29</td>
<td>0.44±0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline Cystatin C (mg/dL)</td>
<td>1.82 ± 0.56</td>
<td>1.76 ± 0.54</td>
<td>1.99 ± 0.60</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline GFR CKD EPI (ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>42±14</td>
<td>43±14</td>
<td>39±13</td>
<td>0.044</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>42±22</td>
<td>43±23</td>
<td>41±20</td>
<td>0.601</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>5258 (2331, 10120)</td>
<td>5215 (2455, 9748)</td>
<td>6149 (1988, 11349)</td>
<td>0.996</td>
</tr>
<tr>
<td>NGAL (ng/mg)</td>
<td>68.7 (13.6, 503.7)</td>
<td>66.9 (13.2, 538.0)</td>
<td>81.5 (21.4, 412.8)</td>
<td>0.491</td>
</tr>
<tr>
<td>NAG (mU/mg)</td>
<td>8.9 (5.1, 17.1)</td>
<td>8.8 (5.2, 17.7)</td>
<td>9.0 (4.7, 16.9)</td>
<td>0.979</td>
</tr>
<tr>
<td>KIM-1 (pg/mg)</td>
<td>964.5 (334.1, 3219.6)</td>
<td>886.6 (303.1, 3226.0)</td>
<td>1032.4 (377.0, 3726.0)</td>
<td>0.440</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>89 (33.0)</td>
<td>66 (32.7)</td>
<td>23 (33.8)</td>
<td>0.987</td>
</tr>
<tr>
<td>Dopamine</td>
<td>91 (33.7)</td>
<td>67 (33.2)</td>
<td>24 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Nesiritide</td>
<td>90 (33.3)</td>
<td>69 (34.2)</td>
<td>21 (30.9)</td>
<td></td>
</tr>
<tr>
<td>72 Hr Total IV Furosemide Equivalent (mg)</td>
<td>645 ± 443</td>
<td>641 ± 446</td>
<td>665 ± 436</td>
<td>0.703</td>
</tr>
<tr>
<td>72 Hr Net output (mL)</td>
<td>-4394 (-2678, -6426)</td>
<td>-4688 (-2914, -6956)</td>
<td>-3638 (-2113, -5488)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are median (interquartile range), Mean ± standard deviation, or n (%). SBP indicates systolic blood pressure; LVEF, left ventricular ejection fraction; DM, diabetes mellitus; ICD, implantable cardioverter defibrillator; HLD, hyperlipidemia; GFR, glomerular filtration rate; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; BUN, blood urea nitrogen; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-Glucosaminidase; KIM-1, Kidney Injury Molecule-1. No WRF<sub>kinetic</sub> includes participants with eCr<sub>72HR Kinetic</sub> < 0.3 mg/dL. WRF<sub>kinetic</sub> includes participants with eCr<sub>72HR Kinetic</sub> ≥ 0.3 mg/dL.
Figure 1: Change in baseline to 72-hour creatinine by deciles of net fluid output

ΔCr\text{Observed}: Observed change in creatinine over the 72-hour treatment period in ROSE-AHF. ΔCr\text{Instant VD}: Estimated change in creatinine that would occur if 72 hours of diuresis were to occur instantaneously with no filtration of creatinine as the serum concentration rose. ΔCr\text{72HR VD}: Estimated change in creatinine with 72 hours of diuresis assuming a constant steady glomerular filtration rate over those 72 hours. ΔCr\text{72HR Kinetic}: Estimated change in creatinine accounting for both change in volume of distribution and non-steady state during creatinine measurement.
Figure 2: Baseline and 72-hour urinary kidney injury biomarkers between patients with and without WRF\textsubscript{Kinetic}

No WRF\textsubscript{Kinetic} includes participants with Cr\textsubscript{72-Hours} < 0.3 mg/dL. WRF\textsubscript{Kinetic} includes participants with Cr\textsubscript{72-Hours} ≥ 0.3 mg/dL. N-terminal prohormone brain natriuretic peptide; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-Glucosaminidase; KIM-1, Kidney Injury Molecule-1.
Supplemental Material Table of Contents

**Supplementary Figure 1:** Consort Diagram

**Supplementary Table 1:** Sensitivity Analysis Total Body Water

**Appendix 1**
Supplementary Figure 1: Consort Diagram

Consort diagram of patient selection into the study cohort. GFR indicates glomerular filtration rate; CKD Epi, Chronic Kidney Disease Epidemiology Collaboration; KIM-1, kidney injury molecule 1; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; and ROSE-AHF, Renal Optimization Strategies Evaluation.
Supplementary Table 1.

<table>
<thead>
<tr>
<th>Sensitivity Analysis Total Body Water</th>
<th>Cr&lt;sub&gt;Instant VD&lt;/sub&gt;</th>
<th>Cr&lt;sub&gt;72HR VD&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% TBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Change</td>
<td>0.16 (0.10, 0.27)</td>
<td>0.04 (0.02, 0.07)</td>
</tr>
<tr>
<td>WRF</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>no WRF</td>
<td>218</td>
<td>270</td>
</tr>
<tr>
<td>60% TBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Change</td>
<td>0.13 (0.08, 0.22)</td>
<td>0.04 (0.02,0.06)</td>
</tr>
<tr>
<td>WRF</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>no WRF</td>
<td>235</td>
<td>270</td>
</tr>
<tr>
<td>70% TBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Change</td>
<td>0.11 (0.07, 0.18)</td>
<td>0.04 (0.02, 0.06)</td>
</tr>
<tr>
<td>WRF</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>no WRF</td>
<td>254</td>
<td>270</td>
</tr>
<tr>
<td>80% TBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Change</td>
<td>0.10 (0.06, 0.16)</td>
<td>0.03 (0.02, 0.06)</td>
</tr>
<tr>
<td>WRF</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>no WRF</td>
<td>263</td>
<td>270</td>
</tr>
</tbody>
</table>

Sensitivity analysis with varying estimations of total body water based on body weight. WRF includes 72-hour changes in calculated creatinine ≥ 0.3 mg/dL. No WRF includes 72-hour changes in calculated creatinine < 0.3 mg/dL. TBW = total body water; WRF = worsening renal function.
Appendix 1

Abbreviations
Cr = Creatinine
VD = Volume of distribution
CreGen = Creatinine generation
GFR = Glomerular filtration rate calculated with CKD-EPI
kGFR = Kinetic GFR

Calculating estimated volume of distribution & CreGen

\[ V_{Baseline} = Weight_{Baseline} \times 0.5 \]

Calculating changes in estimated total body water, volume of distribution, based on measured intake and urine output

\[ \Delta V_t = IV \ln_t + Oral \ln_t - UrineOutput_t \]

\[ CreGen = Cr_{Baseline} \times GFR_{Baseline} \]

Derivation of the equations

To compare the cases below, we calculate the [Cr] that would result from each manipulation.

Instant hemoconcentration (Cr_{Instant VD}): If only the volume changes, then the creatinine mass stays the same. Therefore, the amount of creatinine before equals the amount of creatinine after, or

\[ [Cr]_0 \cdot V_0 = [eCr_{Instant VD}]_t \cdot V_t \]

\[ [eCr_{Instant VD}]_t = [Cr]_0 \cdot \frac{V_0}{V_t} \]  \hspace{1cm} (1)

Realistic hemoconcentration, stable GFR (Cr_{VD}): Volume change does not occur instantly, as above, but rather is spread over the time interval between [Cr] measurements. During that time, the kidneys continue to clear creatinine, which attenuates the rise in [Cr] due to hemoconcentration. To simplify the modeling, we assume that the volume changes at a constant rate, obtainable by dividing the net of the input/output volumes by the time interval (24 h), giving \( \frac{\Delta V}{\Delta t} \). Then, for a constant \( \frac{\Delta V}{\Delta t} \) rate and a renal clearance (GFR) that stays at baseline, the new [Cr] would be:
\[
[eCr_{VD}]_t = [Cr]_0 + \left[ 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}} \right)^{1+\frac{GFR}{\Delta V}} \right] \cdot \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} \cdot [Cr]_0
\] (2)

In other words, the [Cr] in the future equals the [Cr] at the start plus an adjustment fraction times the gradient between the eventual [Cr] if allowed to reach steady state and the starting [Cr].

For a baseline (i.e., preserved) GFR, the realistic hemoconcentration will not increase the [Cr] as much as the instant hemoconcentration, which admittedly is a worst-case scenario.

Equation (2) can replicate the instant hemoconcentration, by letting the time interval go to zero. Turning \( t \) into \( \Delta t \) and letting \( \Delta t \) approach zero, we can solve the limit as follows:

\[
\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 + 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}} \right)^{1+\frac{GFR}{\Delta V}} \right\} \cdot \left( \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [Cr]_0 \right)
\]

\[
\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 + 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}} \right)^{1+\frac{GFR}{\Delta V}} \right\} \cdot \left( \frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}}^{-\infty} - [Cr]_0 \right)
\]

\[
\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 \right\} \cdot [0 - [Cr]_0]
\]

\[
\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 \right\} \cdot \left( 1 - \left( \frac{V_0}{V_0 + \Delta V} \right)^{1+0} \right) \cdot (-[Cr]_0)
\]

\[
\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 \right\} \cdot \left( -[Cr]_0 + [Cr]_0 \cdot \left( \frac{V_0}{V_t} \right) \right)
\]

\[
\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 \right\} \cdot \left( [Cr]_0 - [Cr]_0 + [Cr]_0 \cdot \frac{V_0}{V_t} \right)
\]

\[
\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 \right\} \cdot \left( \frac{V_0}{V_t} \right)
\]

Thus, if the volume could change instantaneously, then Equation (3) replicates Equation (1).
Realistic hemoconcentration, kinetic GFR (CrKinetic): If realistic hemoconcentration accounts for only part of the [Cr] rise, then the rest must be explained by a change in clearance. But, $k_{GFR}$ cannot be isolated and solved for in Equation (2). Rather, using a root-finding technique, like Newton’s method is required to calculate an accurate value for kGFR.

$$k_{GFR,n+1} = k_{GFR,n} + \left[ \frac{1 - \left( \frac{V_o}{V_o + \Delta V} \right)^{\left(1+k_{GFR,n}\right)}}{\Delta t} \ln \left( \frac{V_o}{V_o + \Delta V} \right) \cdot \left( \frac{\text{CreGen}}{k_{GFR,n} + \Delta V} - [Cr]_t \right) - [Cr]_0 \right] \cdot \frac{\text{CreGen}}{\left( k_{GFR,n} + \frac{\Delta V}{\Delta t} \right)^2}$$

(4)

If this Newton’s $k_{GFR}$ were allowed to drive the [Cr] trajectory all the way to a new steady state, and ignoring hemoconcentration effects, the [Cr] would eventually be

$$[eCr]_{Steady\ State} = \frac{\text{CreGen}}{k_{GFR,Newton}}$$

(5)

For a slightly different answer, the 4-factor MDRD equation (2006) can be rearranged to yield a steady state [Cr] for the calculated $k_{GFR}$.

$$[eCr]_{Steady\ State} = \left( \frac{k_{GFR,Newton} \cdot \text{Age}^{0.203}}{175 \cdot \text{race,gender factor(s)}} \right)^{-1}$$

(6)

Example application

Two hypothetical subjects are provided with identical weight, baseline creatinine, and simplified changes in creatinine and urine output to illustrate the application of the various equations. Subject 1 has minimal net output over a 72-hour period of only 300 mL, but with an observed increase in creatinine from 1.0 to 1.3 mg/dL. Subject 2 has significantly more net output of 3L, however without changes in observed creatinine.
### Subject 1

\[ V_0 = 75 \times 0.5 = 37.5 \]

\[ V_{72HR} = 37.5 - 0.3 = 37.2 \]

**eCrInstant VD**

\[ 1.01 = 1.0 \cdot \frac{37.5}{37.2} \]

**eCr\textsubscript{72HR VD}**

\[
1.0 = [1.0]_0 + \left[ 1 - \left( \frac{37.5}{37.5 + \frac{-0.3}{72}} \right)^{\frac{1+87.37}{72}} \right] \cdot \left( \frac{87.37}{87.37 + \frac{-0.3}{72}} - 1.0 \right)
\]

**eCr\textsubscript{72HR Kinetic}**
\[ k_{GFR_{n+1}} = k_{GFR_n} \]
\[
1.0 + \left[ 1 - \left( \frac{37.5}{37.5 + \frac{3}{72}} \right)^{\left( 1 + \frac{k_{GFR_n}}{37.5} \right)} \right] \cdot \frac{87.37}{k_{GFR_n} + \frac{3}{72}} - 1.0 - \frac{3}{72}
\]

\[ k_{GFR} = 66.86 \]
\[
1.22 = \left( \frac{66.86 \cdot 50^{0.203}}{175 \cdot \text{race, gender factor(s)}} \right)^{-1} = 1.154
\]

**Subject 2**

\[ V_0 = 75 \times 0.5 = 37.5 \]
\[ V_{72HR} = 37.5 - 3.0 = 34.5 \]

\[ eCr_{\text{Instant VD}} = 1.09 = 1.0 \cdot \frac{37.5}{34.5} \]

\[ eCr_{72HR \text{ VD}} = 1.01 = 1.0 + \left[ 1 - \left( \frac{37.5}{37.5 + \frac{3}{72}} \right)^{\left( 1 + \frac{87.37}{37.5} \right)} \right] \cdot \frac{87.37}{\frac{87.37 + \frac{3}{72}}{175} - 1.0} \]

\[ eCr_{72HR \text{ Kinetic}} = 1.0 + \left[ 1 - \left( \frac{37.5}{37.5 + \frac{3}{72}} \right)^{\left( 1 + \frac{k_{GFR_n}}{37.5} \right)} \right] \cdot \frac{87.37}{k_{GFR_n} + \frac{3}{72}} - 1.0 - \frac{3}{72}
\]

\[ k_{GFR} = 88.06 \]
0.96 = \left( \frac{88.06 \cdot 50^{0.203}}{175 \cdot race, gender factor(s)} \right)^{-1}