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Lack of Concordance in Defining Worsening Renal Function by Rise in Creatinine Versus Rise in Cystatin C

Matthias Dupont, MD¹, Kevin Shrestha, AB², Dhssraj Singh, MD², Michael Finucan, BS², and W. H. Wilson Tang, MD²

¹Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium.

²Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Ohio.

³Division of Cardiovascular Diseases, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas.

Abstract

Worsening renal function (WRF) during treatment of acute decompensated heart failure (ADHF) is generally associated with adverse outcomes. A 0.3 mg/dl creatinine rise is widely used as the definition of WRF. We sought to determine the level of agreement between WRF, based on changes in creatinine and changes in cystatin C (CysC) by analyzing data from 121 ADHF patients with available admission and day 3 creatinine and CysC levels. Admission creatinine and CysC were 1.39 (0.98–2.11) mg/dl and 1.95 (1.42–2.69) mg/L respectively and correlated well ($r=0.81$). On average, creatinine (-0.04 ± 0.40 mg/dl) and CysC (0.001 ± 0.34 mg/L) changed minimally from admission to day 3. Although the correlation between both markers on day 3 was still good ($r=0.79$), the correlation between changes therein was only modest ($r=0.43$). From the 14 and 15 patients who had WRF based on a 0.3 mg/dl rise in creatinine and 0.3 mg/L rise in CysC respectively, only 4 (about 30%) met both definitions. These observations, together with recent insights in the inconsistencies of creatinine-defined concept of worsening renal function and outcomes, raises the need to sought for more reliable measures of renal function during treatment of ADHF.

Keywords

Acute decompensated heart failure; Cardio-renal syndrome; Cystatin C; Worsening Renal Function

INTRODUCTION

The interaction between the heart and the kidney has received considerable attention in recent years and has been labeled and subdivided as the cardio-renal syndrome types 1–5¹. In the management of acute decompensated heart failure (ADHF), Type 1 cardio-renal syndrome, also called worsening renal function (WRF), is of particular importance because its occurrence has most often been associated with a poor prognosis^{2–5}. Nevertheless, certain subgroups of patients with WRF do not appear to have this adverse prognosis^{6–10}.

Address for Correspondence: W.H. Wilson Tang, MD, Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk J3-4, Cleveland, OH 44195, Phone: 216-444-2121 / Fax: 216-445-6165 / tangw@ccf.org.

DISCLOSURE

The other authors have no relationships to disclose.

Part of the explanation for this finding might have to do with the way WRF is defined. Whereas clinicians originally referred to WRF as the clinical scenario whereby renal function deteriorated in the setting of (escalating) diuretic use accompanied by a less than expected diuretic response (“diuretic resistance”), it is now almost invariably defined as a 0.3 mg/dl increase in serum creatinine. This definition is convenient in clinical studies and was originally chosen because of its favorable sensitivity and specificity¹¹. However, it lacks a clinical scenario or information about urine output. A second potential hazard of this definition is that it solely relies on a change in creatinine as a reliable marker of a change in glomerular filtration rate (GFR).

In recent years, cystatin C (CysC) has emerged as a better marker of GFR with higher prognostic ability due to its larger independence of diet, muscle mass and tubular secretion^{12–16}. However, in theory both CysC and creatinine are not ideal as markers of GFR outside a steady state situation¹⁷. This study had the simple aim to determine the degree of concordance between WRF defined either on the base of an increase in creatinine or an increase in CysC.

METHODS

Study Population

We analyzed data from 121 patients admitted to a tertiary care hospital with a primary diagnosis of acute decompensated heart failure and with available admission and day 3 creatinine and CysC levels. The 121 patients stem from 2 different datasets containing prospectively enrolled patients for other studies in the domain of ADHF. There was no treatment intervention in both datasets and thus medical treatment was up to the discretion of the attending physician. The first dataset (n=75) included patients aged ≥ 18 years admitted to the heart failure intensive care unit for hemodynamically tailored therapy between January 2006 and June 2007. They all had elevated filling pressures defined as a pulmonary capillary wedge pressure ≥ 18 mmHg or central venous pressure ≥ 8 mmHg. The second dataset (n=46) contained patients aged ≥ 18 years admitted with ADHF to a regular nursing floor or the intensive care unit between October 2009 and April 2010. In this population, fluid overload was evident by either $\geq 2+$ lower extremity edema, pulmonary rales, jugular venous distention, ascites or increase in body weight from baseline. Patients with a congenital cardiomyopathy, acute coronary syndromes, on mechanical ventilatory support or on renal replacement therapy were excluded in both datasets. The Cleveland Clinic Institutional Review Board approved both studies that generated the datasets for this analysis.

Data Synthesis

All demographic, clinical, laboratory and echocardiographic data were abstracted from the electronic medical record. For the purpose of this study, WRF was defined in two different ways. First, it was defined as a ≥ 0.3 mg/dl increase in creatinine from admission to day 3. Second, it was defined as a ≥ 0.3 mg/L increase in CysC in the same time interval. Both are in agreement with previously proposed definitions^{11, 18}. The primary outcome of this study was the level of concordance between changes in creatinine and changes in CysC and subsequently the level of agreement between the 2 WRF definitions.

Assays of Renal Indices

Creatinine and CysC were measured on simultaneously collected serum samples, on the day of admission and on day 3. After samples were collected, they were centrifuged at 4°C for 15 minutes at $1500 \times g$ and stored at -80°C until assayed. Creatinine and CysC test were measured on the Abbott ARCHITECT ci8200 platform (Abbott laboratories, Abbott Park,

Illinois, USA). Within-run coefficients of variation were 0.76% and 3.% for creatinine and CysC respectively. Between day coefficients of variation were 4.83% and 6% for creatinine and CysC respectively.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation if normally distributed or as median and interquartile range for non-normally distributed data. Categorical data were summarized as frequencies. Spearman's correlation coefficient was used to correlate creatinine and CysC levels (non-normally distributed). Pearson's coefficient was used to correlate changes in creatinine and CysC. Statistical significance was set at a 2-tailed probability level <0.05 . All statistical analyses were performed using JMP 9 (SAS Institute, Cary, NC). All authors have read and agree to the manuscript as written.

RESULTS

Table 1 demonstrates the baseline characteristics for all 121 patients included in this study. The two original datasets differed somewhat from each other. Patients admitted for hemodynamically tailored therapy ($n=75$) had lower blood pressure on admission (109 ± 15 vs. 119 ± 23 , $p=0.01$), were younger (56 ± 14 vs. 63 ± 14 years, $p=0.002$), had less frequent history of hypertension (36 vs. 67%, $p=0.001$) and had higher B-type natriuretic peptide levels ($1,734\pm1,703$ vs. $1,225\pm1,174$ pg/mL, $p=0.03$). Baseline and changes in renal function however, were similar for both datasets and so the baseline characteristics are presented for the overall study population.

The baseline creatinine was 1.39 (0.98 – 2.11) mg/dl and baseline CysC was 1.95 (1.42 – 2.69) mg/L. There was a good correlation ($r=0.81$) between both markers of GFR (figure 1). On day 3 median creatinine was 1.4 (0.98 – 1.96) mg/dl and median CysC was 1.97 (1.42 – 2.60) mg/L, still demonstrating a good correlation ($r=0.79$) between both markers (figure 1). On average, there was only a minimal change in creatinine (-0.04 ± 0.40 mg/dl) and CysC (0.001 ± 0.34 mg/L) from day 1 till day 3.

Figure 2 depicts the percentage of patients with an increase of creatinine (mg/dl) or CysC (mg/L) above certain cut-off values. The distribution of these changes is similar for creatinine and CysC. 14 (12%) patients experienced WRF as defined by a ≥ 0.3 mg/dl rise in creatinine, whereas 15 (12%) patients had WRF based on a ≥ 0.3 mg/L rise in CysC. However, the correlation between changes in creatinine and changes in CysC is only modest ($r=0.43$, figure 3), resulting in only 4 patients meeting both definitions. These 4 patients had an average increase in creatinine of 0.77 mg/dl and in CysC of 0.75 mg/L. This increase was higher than other patients with WRF based on either creatinine increase (0.53 mg/dl, $p=0.09$) or CysC increase (0.42 mg/L, $p=0.001$).

DISCUSSION

In the setting of ADHF, the assessment of renal function almost invariably occurs through the estimation of GFR by readily measured blood markers. Creatinine is the classic marker of GFR and changes in its serum levels are thought to reflect changes in GFR. As there is increasing recognition that CysC may be a more sensitive marker for impaired renal function, the new finding of this study is that changes in these 2 biomarkers may correlate only modestly in the setting of ADHF. In other words, only a minority of patients ($\approx 30\%$), who have WRF as defined by a ≥ 0.3 mg/dl rise in creatinine, also have WRF as defined by a ≥ 0.3 mg/L rise in CysC and vice versa. Such discrepancy adds to the difficulty in deciding how to best define WRF in the setting of ADHF, and may explain why treatment that utilizes changes in creatinine or CysC as selection criteria or endpoints may be challenged.

We see a couple of potential explanations. First, there might be a mathematical explanation. All laboratory tests come with a certain variability, expressed as a coefficient of variation ($= \text{standard deviation/mean value} \times 100$). The between run CV is in the order of 5% for both the creatinine and the CysC assay. Especially at higher baseline values of creatinine and CysC, this results in considerable absolute changes between measurements even when they have not changed from day 1 to day 3. Under the assumption that the markers of GFR are normally distributed after logarithmic transformation, certain formulas allow to predict the chance of having a ± 0.3 change only due to assay variability¹⁹. For example, when baseline creatinine or CysC are around 3 mg/dl or 3mg/L respectively, this chance equals 18% (assuming a coefficient of variation of 5%). This chance drops to 5% with baseline values around 2 mg/dl (creatinine) or 2mg/L (CysC) and does almost not exist ($<1\%$) with baseline values around 1mg/dl (creatinine) or 1mg/L (CysC). The imprecision (variability) of the tests has a greater impact on the correlation between the changes of both markers than on the correlation between their absolute values. Another consequence of test variability is that patients with, in reality, only minimal change in creatinine or CysC, may nevertheless be classified as having WRF.

A second reason for the somewhat lower-than-expected correlation might have to do with the non steady-state situation which is characteristic for ADHF. Classical teaching learns that endogenous markers of filtration should only be used in steady-state, i.e. stable production and excretion of the marker^{17, 20, 21}. During treatment for ADHF, both processes may affect creatinine levels particularly in the setting of altered in-hospital diet and immobilization¹⁷. As a consequence, both markers require some time to accumulate or decrease when GFR alters. There have been reports in non heart failure settings pointing to CysC as an earlier marker of acute kidney injury^{21–23}. This finding could also explain a lower-than-expected correlation between changes in both markers of GFR. However, in our study, the amount of patients with proportional increases and decreases in creatinine and CysC was similar (figure 2). In addition, the volume of distribution (total body water) influences creatinine and CysC concentrations. In a similar way as rapid plasma volume expansion decreases serum levels, large volume diuresis might increase creatinine and CysC levels¹⁷. How their levels rise relative to each other in the setting of hemoconcentration is unknown.

Finally, the finding that CysC is a better marker of GFR (at least in patients with normal or mildly reduced GFR) as compared to creatinine in stable conditions^{12, 24}, might extend to the acute setting. This would mean that changes in CysC maybe more sensitive and therefore more reliably reflect changes in GFR. Whether or not such improved sensitivity can ultimately translate in a higher prognostic ability remains unclear.

The recent reports demonstrating equal and sometimes even improved outcomes in certain subgroups of patients with WRF make the discussion about the definition of WRF (or Type 1 cardio-renal syndrome) very relevant. Likely, several different mechanisms with different prognostic value may lead to WRF as presently defined. New therapies, developed with the aim to improve outcomes in patients with WRF should focus on those patients in whom WRF is closely associated with adverse outcomes. To identify that target population, the incorporation of a clinical scenario in the definition of WRF, in addition to the use of the most sensitive marker of change in GFR (creatinine or CysC), might be useful. This strategy was for example applied in the recently completed CARRESS-HF trial, which necessitated either escalating doses of loop diuretics before hospitalization or persistent volume overload during hospitalization, in addition to a ± 0.3 mg/dl rise in creatinine, to be included in the study²⁵. It remains to be seen whether avoiding WRF and improving outcomes necessarily go hand in hand.

To our knowledge, there was one prior study that has directly compared between changes in creatinine and CysC and found a higher correlation between changes in both markers ($r=0.77$) when compared to our study. Nevertheless, only 44% of patients with WRF based on a CysC definition had WRF according to a creatinine-based definition¹⁸, which is somewhat consistent with our findings.

Study Limitations

A few limitations of this study should be pointed out. This is a rather small study that was not powered for the evaluation of outcome data. Hence, whether there is a difference in prognostic ability between creatinine and CysC-based definitions of WRF remains to be determined. There is no direct measurement of GFR which makes it impossible to say which marker of GFR performs best. Finally, only two time points (admission and day 3) were studied. We did not have dosing information for furosemide nor detailed information about mode and adjunctive diuretic therapy during admission to determine if dose of furosemide may impact creatinine (but not CysC) levels via competition to cotransporter at the level of proximal tubular secretion. This explains the relative low incidence of WRF in this study. Nevertheless, as we observed some discrepancies between acute changes in 2 markers of glomerular filtration rate (creatinine and CysC) during the treatment of ADHF, we caution the reliability of these markers to reflect acute changes in GFR that may further complicates how to best define WRF. Future research is required to elucidate the different mechanisms that result in WRF and their prognostic significance.

CONCLUSION

In our study cohort of patients with ADHF, there were modest and somewhat discordant changes in creatinine versus changes in CysC, which raises the question regarding reliability of either marker to reflect true changes in renal function during treatment of ADHF.

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Figure 1.
Correlation between creatinine and cystatin C on day 1 and day 3.

Figure 2.
Incidence of increase in creatinine and cystatin C from day 1 to day 3.

Figure 3.
Correlation between change in creatinine and cystatin C.

Table 1

Baseline Characteristics.

	Total cohort (n=121)
Age (years)	60 ± 14
Male (%)	74
African American (%)	24
Hypertension (%)	55
Ischemic (%)	48
Ejection fraction (%)	25 (20 – 40)
Atrial fibrillation (%)	37
Heart Rate (/min)	81 ± 16
Systolic Blood Pressure (mmHg)	115 ± 21
BNP (pg/ml)	1462 ± 1386
Baseline Creatinine (mg/dl)	1.39 (0.98 – 2.11)
Baseline Cystatin C (mg/L)	1.95 (1.42 – 2.69)
Baseline BUN (mg/dl)	31 (21 – 59)
eGFR MDRD (ml/min/1.73m ²)	53 (32 – 85)
ACE-I or ARB (%)	40
Beta blocker (%)	60
Aldosterone antagonists (%)	29
Loop diuretics (%)	68
Digoxin (%)	28
Aspirin (%)	50
Statin (%)	45

Abbreviations:

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.