Baseline Albumin Is Associated with Worsening Renal Function in Patients with Acute Decompensated Heart Failure Receiving Continuous Infusion Loop Diuretics

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Study Objectives To identify baseline predictors of worsening renal function (WRF) in an acute decompensated heart failure (ADHF) patient population receiving continuous infusion loop diuretics

Design Retrospective observational analysis.

Setting Academic tertiary medical center.

Patients A total of 177 patients with ADHF receiving continuous infusion loop diuretics from January 2006 through June 2009.

Measurements and Main Results The mean patient age was 61 years, 63% were male, ~45% were classified as New York Heart Association functional class III, and the median length of loop diuretic infusion was 4 days. Forty-eight patients (27%) developed WRF, and 34 patients (19%) died during hospitalization. Cox regression time-to-event analysis was used to determine the time to WRF based on different demographic and clinical variables. Baseline serum albumin 3 g/dl or less was the only significant predictor of WRF (hazard ratio [HR] 2.87, 95% confidence interval [CI] 1.60–5.16, p=0.0004), which remained significant despite adjustments for other covariates.

Conclusion Serum albumin 3 g/dl or less is a practical baseline characteristic associated with the development of WRF in patients with ADHF receiving continuous infusion loop diuretics.

Key Words bumetanide, furosemide, heart failure, albumin, renal function.

(Pharmacotherapy 2013;33(6):583–588) doi: 10.1002/phar.1241

Worsening renal function (WRF) occurs in 30–50% of patients hospitalized for decompensated heart failure[1–3] and is as prevalent as WRF in patients with circulatory shock, hypotension, cardiac arrest, sepsis, or acute coronary syndrome.[1, 2] WRF in patients with heart failure (HF) is associated with increased mortality,[1, 2, 4] increased length of hospital stay,[1, 2] higher in-hospital cost,[2] and re-hospitalization.[1, 2, 4] The development of WRF in patients with HF limits the use of survival-impacting therapies such as angiotensin-converting enzyme (ACE) inhibitors or spironolactone. Renal dysfunction activates the renin-angiotensin-aldosterone system to preserve renal perfusion and circulatory homeostasis, both of which can contribute to the pathophysiology of HF.[5]

Serum creatinine,[1, 2] pulmonary edema,[1] female gender, rales, tachycardia (pulse higher than > 100 bpm), systolic blood pressure higher than 200 mm Hg,[2] chronic kidney disease, loop diuretic dose upon hospital admission, New

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York Heart Association (NYHA) functional class, and left ventricular ejection fraction (LVEF) less than 30%[3] are independent predictors of WRF in patients with HF. In a retrospective analysis of the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH) study (n = 1023) age, type 2 diabetes, and anemia were independent predictors of WRF over 18 months (including in- and out-of-hospital WRF).[4] In the COACH study, WRF significantly increased the number of unfavorable days (i.e., days in the hospital or dead). Because WRF may contribute to increased hospital stay as well as increased morbidity, it is important to understand predictors of WRF.[1, 2, 4] To our knowledge, no studies have evaluated baseline predictors of WRF associated with continuous infusion of loop diuretics. Patients treated with continuous infusion loop diuretics are a unique patient population. Typically these patients are diuretic resistant or unable to tolerate the hypotension secondary to fluid shifts associated with loop diuretics infused on an intermittent schedule. Continuous infusion of loop diuretics increases the risk of WRF and can increase the length of hospital stay.[1, 2] Furosemide is the loop diuretic most often used in continuous-infusion regimens. Use of bumetanide is less common. Therefore, the aim of this study was to identify baseline predictors of WRF in patients with acute decompensated heart failure (ADHF) receiving continuous infusions of the loop diuretics furosemide and bumetanide.

Methods

Design Overview

We conducted a retrospective review of patient records to determine predictors of WRF in patients with ADHF receiving continuous infusions of loop diuretics. The study was approved by the University of Michigan institutional review board.

Patient Population

All patients admitted to the University of Michigan Health System with ADHF, receiving continuous infusion of loop diuretics from January 2006 through June 2009, were included. Exclusion criteria were incomplete medical records, less than 24 hours of loop diuretic infusion treatment, concurrent nephrotoxic agents (aminoglycosides, tacrolimus, cyclosporine, and sirolimus), dialysis, prior infusions of loop diuretics at an outside hospital, and age younger than 18 years. The most common reason for exclusion was loop diuretic infusion treatment for less than 24 hours. For patients with multiple admissions during the study, only index hospitalization was included in the analysis.

Outcome Measures

The primary goal of this study was to identify baseline predictors of time to WRF in patients with ADHF who were receiving continuous infusion loop diuretics. Worsening renal function was defined as any increase in baseline serum creatinine of 0.3 mg/dl or more during continuous infusion of loop diuretic. This rise in serum creatinine is consistent among other studies of WRF.[6, 7] In-hospital mortality, defined as in-hospital death, was also collected.

Statistical Analysis

Cox regression was performed as a time-to-event analysis to determine the time to WRF based on different baseline variables. Clinical characteristics were then associated with time to WRF. Baseline variables were dichotomized when data for continuous variables were not normally distributed. Patients were evaluated until discharge or in-hospital death. Each variable was tested univariately and then retested after adjustments for other possible cofounders in the Cox model. Variables with $p<0.1$ in the univariate Cox regression analysis were used in the multivariable Cox model.

The following baseline clinical characteristics were considered in the analysis (Table 1): age, gender, weight, height, specific loop diuretic infused, primary etiology of HF (ischemic versus nonischemic, systolic versus diastolic), NYHA functional class, LVEF (less than 40%), history of diabetes mellitus, hypertension, or peripheral vascular disease, atrial fibrillation, chronic kidney disease, automatic implantable cardioverter-defibrillator, dose of preinfusion loop diuretic, systolic blood pressure, serum creatinine, serum sodium, aspartate amino transferase (more than three times the upper limit of normal [ULN]), alanine amino transferase (more than three times the ULN), alkaline phosphatase (higher than our laboratory ULN), serum albumin and total protein (lower than our laboratory cut-off for normal), and B-type natriuretic peptide (BNP) (divided into quartiles). For purposes of this study, baseline was defined as the start of loop

Table 1. Baseline Characteristics

Variables	Overall Cohort (n=177)	No WRF (n=129)	WRF (n=48)	HR (95% CI)	p Value
Age (yrs)	60.8 ± 15.2	60.4 ± 15.1	62.1 ± 15.4	1.01 (0.99–1.01)	0.50
Weight (kg)	94.3 ± 28.8	95.7 ± 30.5	90.7 ± 23.5	1.00 (0.99–1.01)	0.37
Height (in.)	67.6 ± 4.4	67.4 ± 4.5	68.1 ± 4.7	1.03 (0.97–1.1)	0.36
Male	111 (62.7)	77 (59.7)	34 (70.8)	0.57 (0.30–1.07	0.08
White	127 (71.8)	92 (71.2)	35 (72.9)	0.83 (0.43–1.07	0.57
Loop diuretic infusion					
Bumetanide	137 (77.4)	96 (74.2)	41 (85.4)	1.6 (0.72–3.57)	0.25
Furosemide	40 (22.6)	33 (25.6)	7 (14.6)		
Comorbidities					
Diabetes	81 (45.8)	59 (45.7)	22 (45.8)	0.98 (0.55–1.75)	0.95
Hypertension	91 (51.4)	56 (51.1)	25 (52.1)	1.14 (0.64–2.02)	0.65
Atrial fibrillation	83 (46.9)	62 (48.1)	21 (43.8)	0.73 (0.41–1.31)	0.29
ICD present	89 (50.3)	69 (53.5)	20 (41.7)	0.72 (0.40–1.28)	0.26
CKD	100 (56.5)	75 (58.1)	25 (52.1)	0.69 (0.39–1.23)	0.21
PVD	18 (10.2)	10 (7.8)	8 (16.7)	2.02 (0.94–4.36)	0.07
Heart failure characteristics					
ICM	84 (51.9)	58 (48.7)	26 (60.5)	1.44 (0.81–2.58)	0.22
NICM	78 (48.1)	61 (51.3)	17 (39.5)		
Systolic dysfunction	125 (71.2)	95 (79.9)	30 (69.8)	1.62 (0.81–3.24)	0.17
Diastolic dysfunction	34 (21.0)	23 (19.3)	11 (25.6)		
PHTN with RHF	40 (22.6)	29 (22.5)	11 (22.9)	0.92 (0.47–1.81)	0.81
Ejection fraction < 40%	118 (67.1)	87 (67.8)	31 (64.6)	1.15 (0.63–2.10)	0.64
NYHA class					
II	41 (23.2)	28 (21.7)	13 (27.1)	1.1 (0.53–2.27)	0.80[b]
III	79 (44.6)	62 (48.1)	17 (35.4)	0.74 (0.38–1.45)	0.38[c]
IV	57 (32.2)	39 (30.2)	18 (37.5)	–	–
SBP (mm Hg)	109.9 ± 20.7	110.1 ± 20.8	109.6 ± 20.5	1.00 (0.99–1.01)	0.99
Baseline laboratory values					
Serum sodium	135.7 ± 4.9	135.4 ± 5.0	136.6 ± 4.5	1.04 (0.97–1.10)	0.25
Serum creatinine	1.8 ± 0.8	1.9 ± 0.9	1.6 ± 0.7	0.72 (0.49–1.06)	0.1
AST > 90 IU/L	89 (51.2) (n=173)[a]	63 (49.6) (n=127)[a]	26 (55.3) (n=47)[a]	1.47 (0.82–2.64)	0.20
ALT > 105 IU/L	63 (36.2) (n=173)[a]	43 (33.9) (n=127)[a]	20 (42.6) (n=47)[a]	1.33 (0.74–2.40)	0.34
Alk Phos > 130 IU/L	56 (32.2) (n=173)[a]	40 (31.5) (n=127)[a]	16 (34.0) (n=47)[a]	0.97 (0.52–1.79)	0.92
Serum albumin ≤ 3 mg/dl	34 (19.8) (n=172)[a]	15 (12.0) (n=125)[a]	19 (40.4) (n=47)[a]	2.86 (1.59–5.13	0.0004
Total protein < 6 g/dl	63 (38.0) (n=166)[a]	40 (33.0) (n=121)[a]	23 (51.1) (n=45)[a]	1.71 (0.95–3.10)	0.07
BNP (pg/ml)	(n=164)[a]	(n=120)[a]	(n=44)[a]		
< 470	41 (25.0)	28 (23.3)	13 (29.6)	1.25 (0.55–2.84)	0.60[d]
470–952	40 (24.4)	30 (25.0)	10 (22.73)	0.99 (0.41–2.38)	0.98[e]
953–1899	24 (25.6)	31 (25.8)	11 (25.0)	1.03 (0.44–2.42)	0.95[f]
> 1899	41 (25.0)	31 (25.8)	10 (22.7)	–	–
Baseline medications					
ACEI or ARB	47 (26.6)	39 (30.2)	8 (16.7)	0.64 (0.30–1.39)	0.26
β-Blocker	77 (43.5)	61 (47.3)	16 (33.3)	0.59 (0.32–1.07)	0.08
Digoxin	53 (30.0)	41 (31.8)	12 (25.0)	0.82 (0.43–1.58)	0.56
Spironolactone	46 (26.0)	36 (27.9)	10 (20.8)	0.69 (0.34–38)	0.29
Inotropes/vasopressors	59 (33.3)	41 (31.2)	18 (37.5)	1.21 (0.67–2.20)	0.53
Thiazide diuretic	41 (23.2)	27 (20.9)	14 (29.2)	1.14 (0.60–2.14)	0.69

Values are represented as means ± SD or n (%).
The p values were calculated by the Student *t* test or χ^2 or Fisher exact test.
WRF = worsening renal function; HR = hazard ratio; CI = confidence interval; ICD = implantable cardioverter-defibrillator; CKD = medical record diagnosis of chronic kidney disease; PVD = peripheral vascular disease; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; PHTN = pulmonary hypertension; RHF = right heart failure; NYHA = New York Heart Association; SBP = systolic blood pressure; AST = aspartate amino transferase; ALT = alanine amino transferase; Alk Phos = alkaline phosphatase; BNP = b-type natriuretic peptide; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.
[a]Laboratory values not available for all patients.
[b]NYHA class II vs IV.
[c]NHYA class III vs IV.
[d]< 470 pg/ml vs > 1899 pg/ml.
[e]470–952 pg/ml vs > 1899 pg/ml.
[f]953–1899 pg/ml vs > 1899 pg/ml.

diuretic infusion during hospitalization. The following medications were adjusted for as dichotomous variables, indicating the use or nonuse of the medication at the time of loop infusion initiation: digoxin, β-blockers, ACE inhibitors, angiotensin II receptor blockers, thiazide diuretics, and spironolactone. Regression analysis also adjusted for intravenous inotropic and vasopressor therapy. Bumetanide doses were converted to furosemide equivalents (i.e., 1 mg intravenous bumetanide = 40 mg intravenous furosemide). All statistical analyses were performed using SAS software v.9.2 (SAS Institute, Cary, NC, USA).

Results

Of the 384 records reviewed, 177 patients met the inclusion and exclusion criteria. Overall the population was predominantly male (63%) and white (72%), with a mean age of 61 plus or minus 15 years. Approximately 50% of the patients had diabetes, chronic kidney disease, or atrial fibrillation, and the mean LVEF was 31%. Patients received continuous infusions of loop diuretic for a median of 4 days (range 1–12 days). Bumetanide was the most common agent used (77%). There were no significant differences in patient demographics, HF characteristics, NYHA functional class, baseline blood pressure, or baseline medication use. Most patients (44.6%) were categorized as NYHA functional class III, and ~30% were receiving intravenous inotropic or vasopressor agents. Table 1 presents the baseline demographic characteristics and clinical features of patients who developed WRF versus those who did not develop WRF.

Time to Worsening Renal Function

Forty-eight patients (27%) experienced WRF during continuous infusion loop diuretic. The median time to WRF was 2 days. Variables with $p<0.1$ in the univariate Cox regression analysis that were used in the multivariable Cox model were peripheral vascular disease, baseline total protein, baseline serum creatinine, baseline β-blocker use, and baseline serum albumin. Univariate analysis demonstrated that baseline albumin (3 g/dl or less, hazard ratio [HR] 2.87, 95% confidence interval [CI] 1.60–5.16, p=0.0004) was the only characteristic that predicted WRF (Figure 1). Serum albumin 3 g/dl or less remained a significant predictor of WRF during multivariate analysis. The furosemide-equivalent infusion dose on day 1 was not different between the two groups (more than 685 mg in furosemide equivalents, 48% of patients without WRF and 54% with WRF, HR 0.86, 95% CI 0.64–1.19, p=0.50). Day 1 urine output for patients who developed WRF during hospitalization (−825 ± 1384 ml) was lower than in patients who did not develop WRF (−1512 ± 1824 ml, p=0.0089).

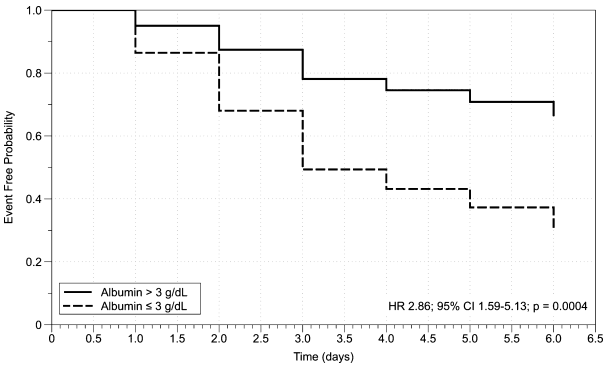

Figure 1. Event-free time to worsening renal function probability curves with data represented as a Cox regression model according to baseline albumin > 3 g/dl versus ≤ 3 g/dl. The p values <0.05 are considered significant. CI = confidence interval; HR = hazard ratio.

In-Hospital Mortality

Patients with WRF were more likely to die during the index hospitalization than were patients who did not develop WRF (35.4% versus 13.2%, respectively; odds ratio 3.61, 95% CI 1.65–7.89, p=0.0008). An association was also shown with albumin 3 g/dl or less and in-hospital mortality (35.3% WRF versus 15.9% no WRF; odds ratio 2.86, 95% CI 1.24–6.65, p=0.011).

Discussion

The purpose of this study was to identify patient characteristics that could enable clinicians to identify risk of renal dysfunction during continuous infusion of loop diuretics. The characteristic that predicted WRF was baseline serum albumin level of 3 g/dl or less, which we view as a clinically low value. WRF was not associated with typical predictors for WRF including baseline serum creatinine, the amount of diuretic received during the study period, or net urine output over the first 24 hours. Worsening renal function was also associated with increased rates of in-hospital mortality, which were 2-fold higher in patients with low serum albumin levels.

The patients in this study represent a real-world acutely ill population seen in a tertiary care academic medical center with a heart transplant/ventricular assist device program. These patients tended to have severe HF with low serum sodium, elevated serum creatinine, inotropic therapy, elevated BNP (more than 50% of patients had BNP higher than 1000 pg/ml), and high rates of in-hospital mortality. Patients who developed WRF, had significantly lower serum albumin (albumin 3 mg/dl or less in 40% of patients in the WRF group versus 12% of patients in the group that did not develop WRF; p=0.0004). Although not significant in the multivariable model, patients with WRF had lower body weight, lower serum creatinine, and lower total protein (total protein less than 6 g/dl in 51% of the WRF group versus 33% in the group that did not develop WRF; p=0.07) (Table 1). Interestingly, in a post-hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, patients who developed WRF[8] had similar baseline features as the patients in the current study (significantly lower serum albumin, total protein, and serum creatinine levels; p<0.011). In the ESCAPE trial, intravascular volume contraction determined by hemoconcentration (based on changes in hematocrit, serum albumin, total protein) induced by aggressive in-hospital diuresis was associated with WRF. The net urine output was significantly greater and diuretic dose was significantly higher in the patients with hemoconcentration.[8] In contrast, we found net urine output was significantly lower in patients with WRF than in patients who did not develop WRF. Our findings suggest that low serum albumin is associated with WRF and not related to aggressive diuresis measured by net urine output and diuretic dose.

The reason why patients with low serum albumin may be more likely to develop WRF is not certain, but it may relate to the degree of intravascular volume depletion. When fluid is lost from the intravascular compartment via diuretic-induced diuresis, it needs to be replaced by the fluid in the extravascular space (i.e., peripheral edema). If fluid is not replaced rapidly enough, intravascular volume contraction may occur and contribute to WRF.[8, 9] Physiologically, a factor that contributes to the movement of fluid between the extravascular and intravascular spaces is oncotic pressure. Theoretically, patients with lower serum albumin (and overall total protein) may be at higher risk for developing WRF due to lower intravascular oncotic pressure (and associated slower refill rates of the intravascular volume) as compared with patients with normal serum albumin (and higher oncotic pressure).[9–11] Similar to the ESCAPE study, we found that patients who developed WRF had lower serum albumin and total protein (total protein not statistically significant in our results for unclear reasons) at baseline.

Another consideration why patients with low serum albumin levels may be at risk for developing WRF is that low serum albumin levels may be a marker for a more "sick" patient population as alluded to in the ESCAPE trial.[8] In fact, studies in patients with HF have shown that hypoalbuminemia is a predictor of poor outcomes including mortality.[12, 13] Our mortality data reflect these findings. Hypoalbuminemia may also represent a set of patients who are highly congested. It has been suggested that patients with elevated filling pressures or patients who are discharged while still congested may have poorer outcomes and may contribute to HF progression.[8, 14, 15] A recent study showed that patients discharged with persistent congestion had a higher risk of death or acute HF readmission.[14] These findings included patients with and without WRF. If low serum albumin does represent patients that are highly congested, these patients may be a high-risk population for poor outcomes including developing WRF.

An important aspect to consider from our study is the finding that both groups received a similar initial diuretic dose during the hospitalization. These are important findings because previous studies have associated WRF with either diuretic dose or diuretic response (i.e., excessive diuresis).[3, 8] Because both groups in our study had a similar diuretic course, our findings that baseline low serum albumin predicted WRF becomes more valuable to the clinician in assessing risk of WRF in patients with ADHF. How to prevent WRF in high-risk patients is not known. It appears that the degree of diuresis or the modes of administration are not factors in developing WRF in patients with low serum albumin levels. It is not known if alternative methods for diuresis may help prevent in-hospital WRF. For example, ultrafiltration enables a more controlled diuresis and may theoretically be of benefit.[16] Whether or not ultrafiltration is associated with less neurohormonal activation than loop diuretic therapy is not certain. Another option may be vasopressin

antagonist-induced diuresis, which may allow for very low doses of loop diuretics. The acute use of both vasopressin antagonists and loop diuretics appears not to worsen renal function in HF patients.[17] However, it is not known if the plasma refill rate would be any different between the use of vasopressin antagonists and diuretics versus diuretics alone. Although low serum albumin and protein levels in our study were likely due to excess fluid volume, evaluation for malnutrition and cachexia may be another consideration. Nutritional consultation in these patients may be of benefit over the long term. Finally, it is not known if albumin infusions would prevent worsening renal function in this patient population.

A limitation of the study is that we do not know the exact mechanism(s) for WRF during diuresis in patients with low serum albumin. As such, we do not know the best approach to preventing WRF. However, this study does provide data to target a specific type of patient for evaluation and testing. Obvious concerns with the study also include the relatively small number of patients, the retrospective design, and lack of more details regarding inpatient clinical course that may provide more information about potentially confounding clinical features. The patients in this study were seriously ill, both acutely in terms of decompensated HF, but also chronically. We do not know if our findings would be the same in a less critically ill population.

Overall, this study found that baseline serum albumin concentration of 3 mg/dl or less predicted WRF in patients with ADHF who received continuous infusion loop diuretics. Patients presenting with hypoalbuminemia and ADHF may represent an at-risk population. Further investigation regarding this subset of patients is warranted.

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