Clinical Characteristics and Outcomes of Patients With Improvement in Renal Function During the Treatment of Decompensated Heart Failure

JEFFREY M. TESTANI, MD,[1] BRIAN D. McCAULEY, MPH,[1] JENNIFER CHEN, MD,[1] STEVEN G. COCA, DO, MS,[3] THOMAS P. CAPPOLA, MD, ScM,[1] AND STEPHEN E. KIMMEL, MD, MSCE, FACC[1,2]

Philadelphia, Pennsylvania; and New Haven, Connecticut

ABSTRACT

Background: In the setting of acute decompensated heart failure, worsening renal function (WRF) and improved renal function (IRF) have been associated with similar hemodynamic derangements and poor prognosis. Our aim was to further characterize IRF and its associated mortality risk.

Methods and Results: Consecutive patients with a discharge diagnosis of congestive heart failure at the Hospital of the University of Pennsylvania were reviewed. IRF was defined as a ≥20% improvement and WRF as a ≥20% deterioration in glomerular filtration rate. Overall, 903 patients met the eligibility criteria, with 31.4% experiencing IRF. Baseline venous congestion/right-side cardiac dysfunction was more common ($P \leq .04$) and volume of diuresis ($P = .003$) was greater in patients with IRF. IRF was associated with a greater incidence of preadmission (odds ratio [OR] 4.2, 95% confidence interval [CI] 2.6−6.7; $P < .0001$) and postdischarge (OR 1.8, 95% CI 1.2−2.7; $P = .006$) WRF. IRF was associated with increased mortality (adjusted hazard ratio 1.3, 95% CI, 1.1−1.7; $P = .011$), a finding largely restricted to patients with postdischarge recurrence of renal dysfunction (P interaction = .038).

Conclusions: IRF is associated with significantly worsened survival and may represent the resolution of venous congestion−induced preadmission WRF. Unlike WRF, the renal dysfunction in IRF patients occurs independently from the confounding effects of acute decongestion and may provide incremental information for the study of cardiorenal interactions. (*J Cardiac Fail 2011;17:993−1000*)

Key Words: Cardiorenal syndrome, worsening renal function, venous congestion.

Worsening renal function (WRF) during the treatment of acute decompensated heart failure has been associated with adverse outcomes, such as death, in multiple recent studies.[1−8] However, despite significant study of this phenomenon, little progress has been made toward a mechanistic or therapeutic understanding of cardiorenal interactions through the study of WRF. This limited success may relate to the fact that, in the setting of aggressive decongestion, some decreases in glomerular filtration may represent a normal physiologic response to intravascular contraction and be free of adverse prognostic significance.[9] Because decongestion is the primary goal of most decompensated heart failure admissions, the confounding effects of treatment make WRF a complex entity to study. Further progress toward an understanding of cardiorenal syndrome (CRS) could likely be accomplished by identifying CRS at a time before, or in the absence of, the physiologic derangements induced by acute treatment.

We have recently reported that patients experiencing improved renal function (IRF) during the treatment of decompensated heart failure have an increased rate of mortality similar to patients that develop WRF.[10] A possible explanation for the increased mortality in patients with IRF could be that WRF occurred before admission and/or they have a recurrence of renal dysfunction after discharge. The primary aim of the present study was to validate our previous observation that IRF is associated with

From the [1]Cardiovascular Division, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [2]Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania and [3]Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Manuscript received March 25, 2011; revised manuscript received July 21, 2011; revised manuscript accepted August 16, 2011.

Reprint requests: Jeffrey M. Testani, MD, Hospital of the University of Pennsylvania, 3400 Spruce Street, 8 Gates Pavilion, Philadelphia, PA 19104. Tel: 215-662-7355; Fax: 215-349-5734. E-mail: jeffrey.testani@uphs.upenn.edu

Funding: National Institutes of Health grant no. 5T32HL007843-15.
See page 1000 for disclosure information.
1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2011.08.009

significantly increased mortality and to further investigate the clinical profile of these patients. Additionally, we sought to test the hypothesis that patients with IRF likely experienced WRF as an outpatient before admission. We further hypothesized that the improvement in renal function is likely transient, possibly driving the adverse prognosis observed in these patients.

Methods

Consecutive admissions from 2004 to 2009 to the cardiology and internal medicine services at the Hospital of the University of Pennsylvania with a primary discharge diagnosis of congestive heart failure were reviewed. Inclusion required an admission B-type natriuretic peptide level of >100 pg/mL within 24 hours of admission, a length of stay of 3−14 days, and measurement of serum creatinine levels at admission and discharge. Exclusion criteria included renal replacement therapy or admission to interventional cardiology services (to avoid confounding from contrast nephropathy). In the event of multiple hospitalizations in a single patient, the first admission in which the patient underwent right-side heart catheterization (RHC) was given priority to maximize available RHC data. If RHC did not occur, the first admission was retained. The primary analyses investigating the direct association between IRF and mortality were conducted in first admissions only (without preference for RHC) to ensure that the RHC enrollment criteria did not introduce bias into the survival analyses. Results of the same analyses in the RHC-enriched population can be found in Supplemental Table 1. Values for echocardiographic and RHC-derived variables were obtained from their respective clinical reports.

Estimated glomerular filtration rate (GFR) was calculated using the Modified Diet and Renal Disease equation.[11] IRF was defined as a ≥20% increase in GFR, as consistent with published literature investigating IRF.[9,10,12] Given the nonlinear relationship between serum creatinine and renal function, and to maintain consistency with the IRF definition, WRF was defined as a ≥20% decrease in GFR.[13] Changes occurring at any time during the hospitalization were evaluated unless specifically stated otherwise. Transient IRF was defined as the occurrence of IRF at any time during hospitalization but deterioration in GFR before discharge leaving the admission-to-discharge improvement in GFR <20%. Persistent IRF was defined as a continued ≥20% improvement in GFR at discharge. All-cause mortality was determined via the Social Security Death Index.[14] Pre- and postdischarge creatinine values were obtained by searching electronic medical records that provided access to data for the University of Pennsylvania health system, which includes 3 hospitals in the Philadelphia area and the majority of the associated outpatient facilities. In an attempt to capture the patients' pre- and postdischarge compensated renal function, creatinine values were collected if they were within 1 year of admission, >7 days before or after the hospitalization, and obtained when the patient was an outpatient. Loop diuretic doses were converted to furosemide equivalents with 1 mg bumetanide = 20 mg torsemide = 80 mg furosemide for oral diuretics, and 1 mg bumetanide = 20 mg torsemide = 40 mg furosemide for intravenous diuretics. Data on net fluid output (total fluid out− total fluid in) was obtained by summing the daily fluid in/out flow sheets on all days of hospitalization. The present study was approved by the Institutional Review Board of the Hospital of the University of Pennsylvania.

Statistical Methods

The primary analyses in this study focused on: 1) description of the clinical characteristics associated with IRF; 2) evaluation of the relative change in preadmission-to-admission GFR; 3) evaluation of the relative change in GFR occurring post discharge; and 4) investigation of the risk of mortality associated with IRF and its interaction with post-IRF changes in renal function. Values reported are mean ± SD, median (quartile 1−quartile 4) and percentile. Independent Student t test or the Mann-Whitney U test was used to compare continuous parameters. The Wilcoxon signed ranks test was used to evaluate paired data associations. Pearson chi-square was used to evaluate associations between categorical variables. Proportional hazards modeling was used to evaluate time-to-event associations with all-cause mortality. Candidate covariates for multivariable models adjusting for baseline characteristics were obtained by screening all baseline variables with missing data <5% and a univariate association with mortality ($P \leq .2$). Covariates were removed using backward elimination (likelihood ratio), and variables with $P < .2$ were retained.[15] Covariates for other multivariable models were entered using forced entry of theoretically relevant variables. Given that the primary hypothesis was that IRF represents baseline cardiorenal dysfunction, discharge rather than baseline indices of renal function (ie, GFR and blood urea nitrogen) were used to control for the potential influence of chronic renal insufficiency. Survival curves for death from any cause were plotted for patients that did not experience IRF, patients with transient IRF, and patient with persistent IRF. Additional survival curves were plotted for the 4 combinations of groups between yes/no IRF and yes/no deterioration in renal function after discharge. Given that the focus of these plots was change in GFR rather than absolute GFR, all survival curve plots were adjusted for discharge GFR. The x axis was terminated when the remaining number at risk was <10%. Proportional hazard models for the primary analysis were subjected to 1,000 bootstrap replications (with replacement) to derive P values and 95% confidence intervals (CIs). Significance was defined as 2-tailed $P < .05$ for all analyses, excluding tests of interaction, where P values of <.1 were considered to be significant. Statistical analysis was performed with PASW Statistics version 18.0 (SPSS, Chicago, Illinois).

Results

Overall, 903 patients met the eligibility criteria. Baseline characteristics are presented in Table 1. In total, 31.4% of the population experienced IRF during hospitalization and 18.1% still met criteria for IRF at the time of discharge. Patients experiencing IRF had a mean improvement in GFR of 43.7 ± 27.1% compared with the remainder of the cohort, which experienced only a 5.3 ± 6.7% improvement in GFR from admission to the highest GFR during hospitalization. At the time of discharge, IRF patients had a 25.4 ± 29.6% mean improvement in GFR compared with a 9.6 ± 14.8% deterioration in GFR in the remainder of the cohort.

Characteristics of patients experiencing IRF and comparisons with the remainder of the cohort are presented in Table 1. Notably, the IRF group had multiple baseline indices consistent with a higher heart failure disease