Interaction Between Worsening Renal Function and Persistent Congestion in Acute Decompensated Heart Failure

Malak Wattad[a], Wisam Darawsha, MD[a], Amir Solomonica, MD[a], Maher Hijazi, MD[b], Marielle Kaplan, PhD[c], Badira F. Makhoul, MD[d], Zaid A. Abassi, PhD[e], Zaher S. Azzam, MD[d,e], and Doron Aronson, MD[a,*]

Worsening renal function (WRF) and congestion are inextricably related pathophysiologically, suggesting that WRF occurring in conjunction with persistent congestion would be associated with worse clinical outcome. We studied the interdependence between WRF and persistent congestion in 762 patients with acute decompensated heart failure (HF). WRF was defined as ≥0.3 mg/dl increase in serum creatinine above baseline at any time during hospitalization and persistent congestion as ≥1 sign of congestion at discharge. The primary end point was all-cause mortality with mean follow-up of 15 ± 9 months. Readmission for HF was a secondary end point. Persistent congestion was more common in patients with WRF than in patients with stable renal function (51.0% vs 26.6%, p <0.0001). Both persistent congestion and persistent WRF were significantly associated with mortality (both p <0.0001). There was a strong interaction (p = 0.003) between persistent WRF and congestion, such that the increased risk for mortality occurred predominantly with both WRF and persistent congestion. The adjusted hazard ratio for mortality in patients with persistent congestion as compared with those without was 4.16 (95% confidence interval [CI] 2.20 to 7.86) in patients with WRF and 1.50 (95% CI 1.16 to 1.93) in patients without WRF. In conclusion, persisted congestion is frequently associated with WRF. We have identified a substantial interaction between persistent congestion and WRF such that congestion portends increased mortality particularly when associated with WRF. **(Am J Cardiol 2015;115:932−937)**

Worsening renal function (WRF), currently defined as acute (type 1) cardiorenal syndrome (CRS),[1] is common in hospitalized patients with acute decompensated heart failure (ADHF) and is associated with increased risk of hospital readmission and mortality.[2−5] The main reason for hospitalization due to worsening heart failure (HF) is related to the symptoms of congestion.[6,7] However, many patients have only partial relief of congestion during admission,[8−10] with potential unfavorable effects on the kidneys.[11,12] Current definitions of WRF are based on an absolute increase in serum creatinine or estimated glomerular filtration rate[13−15] but ignore the volume status of the patients developing WRF. Alternatively, the acute CRS may be defined in the context of treatment success. Some patients develop WRF concomitantly with a clinically significant improvement in congestion. In others, WRF occurs when congestion has not been satisfactorily alleviated. In such cases, further treatment to relieve congestive symptoms is limited by the risk of further decrease in renal function. The later clinical scenario is likely to be different from WRF that occurs after successful decongestion, both from the mechanistic standpoint, treatment complexity, and with regard to its prognostic implications. We therefore hypothesized that WRF occurring in conjunction with persistent congestion would be associated with worse clinical outcome.

Methods

From January 2008 to October 2013, patients admitted to the Rambam Medical Center, Haifa, Israel, with the primary diagnosis of ADHF entered a prospective registry.[16,17] Eligible patients were those hospitalized as with new-onset or worsening preexisting HF as primary cause of admission or those with significant HF symptoms that developed during the hospitalization where HF was the primary discharge diagnosis. In addition, patients were required to have at least 1 sign of congestion and a brain natriuretic peptide (BNP) level >400 pg/ml at admission, using the AxSYM BNP microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, Illinois). The study was approved by the local institutional review committee on human research.

Departments of [a]Cardiology, [b]Internal Medicine D, and [d]Internal Medicine B, Rambam Medical Center, Haifa, Israel; [c]The Laboratory of Clinical Biochemistry, Department of Physiology and Biophysics, Rambam Medical Center, Haifa, Israel; and [e]Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel. Manuscript received November 15, 2014; revised manuscript received and accepted January 3, 2015.

See page 936 for disclosure information.

*Corresponding author: Tel: (972) 4-7772790; fax: (972) 4-7772176.
E-mail address: daronson@tx.technion.ac.il (D. Aronson).

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Table 1
Baseline clinical characteristics according to worsening renal function-persistent congestion category

Worsening renal function Congestion	0 0 **(n = 408)**	+ 0 **(n = 101)**	0 + **(n = 148)**	+ + **(n = 105)**	***P* value**	***P*** value (WRF vs. No WRF)	***P*** Value (Pcong vs. no Pcong)
Age (years)	77 ± 10	77 ± 11	77 ± 11	78 ± 11	0.73	0.81	0.87
Female gender	215 (53%)	50 (50%)	70 (47%)	47 (45%)	0.88	0.95	0.66
Hypertension	358 (88%)	85 (84%)	133 (90%)	92 (88%)	0.61	0.37	0.45
Diabetes mellitus	202 (50%)	55 (54%)	82 (55%)	54 (51%)	0.59	0.65	0.40
Chronic lung disease	60 (15%)	23 (23%)	26 (18%)	24 (23%)	0.10	0.02	0.24
Coronary Artery Disease	270 (66%)	73 (72%)	89 (60%)	69 (66%)	0.26	0.26	0.18
Systolic blood pressure (mm Hg)	140 ± 28	141 ± 31	140 ± 25	141 ± 29	0.98	0.72	0.87
Baseline creatinine (mg/dL)	1.3 [1.0-1.7]	1.6 [1.1-2.3]	1.4 [1.1-1.9]	1.5 [1.0-2.3]	0.0006	0.0004	0.04
Baseline eGFR ($ml \cdot min^{-1}/1.73\ m^{-2}$)	51 [37-65]	39 [26-58]	44 [32-60]	41 [29-59]	0.0003	0.0002	0.03
Discharge eGFR ($ml \cdot min^{-1}/1.73\ m^{-2}$)	54 [40-68]	35 [25-501]	51 [36-65]	35 [25-48]	0.0001	<0.0001	0.0006
Baseline BUN (mg/dl)	27 [19-38]	34 [22-46]	30 [20-47]	31 [21-49]	0.001	0.002	0.017
Discharge BUN (mg/dl)	28 [20-42]	41 [29-55]	29 [23-44]	49 [32-71]	<0.0001	<0.0001	<0.0001
Serum sodium (mmole/l)	137 ± 8	136 ± 5	137 ± 4	137 ± 6	0.18	0.04	0.88
Baseline hemoglobin (g/dl)	11.7 ± 1.8	11.6 ± 2.0	11.4 ± 1.9	11.4 ± 1.7	0.30	0.81	0.06
Discharge hemoglobin (g/dl)	11.6 ± 1.9	11.5 ± 2.0	11.4 ± 1.8	10.9 ± 1.8	0.009	0.03	0.005
Hemoconcentration	134 (33%)	35 (35%)	54 (37%)	32 (30%)	0.76	0.74	0.83
BNP (ng/ml)	952 [636-1602]	1200 [749-1813]	852 [606-1447]	905 [646-1570]	0.02	0.11	0.03
Cardiac troponin I elevation (%)	75 (18%)	21 (21%)	19 (13%)	15 (14%)	0.27	0.85	0.06
Atrial fibrillation	197 (48%)	33 (33%)	75 (50%)	54 (51%)	0.02	0.11	0.16
LVEF <45%	46 ± 18	43 ± 17	47 ± 17	47 ± 17	0.23	0.34	0.14
Medications							
Beta blockers	330 (81%)	82 (81%)	11 (84%)	81 (77%)	0.54	0.40	0.87
ACE inhibitors/ARBs	302 (74%)	71 (70%)	102 (69%)	66 (63%)	0.13	0.10	0.05
Spironolactone	92 (23%)	20 (20%)	40 (27%)	15 (14%)	0.10	0.05	0.93
Digoxin	43 (11%)	6 (6%)	19 (13%)	8 (8%)	0.26	0.08	0.65

Values are expressed as number (%) of patients, mean value ± SD, or Median [Interquartile Range].

ACE = angiotensin converting enzyme; ARB = Angiotensin receptor blocker; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; LVEF = left ventricular systolic function.

The definition of WRF was based on absolute changes in serum creatinine. For the main analysis, WRF was defined on the basis of the maximal increase of ≥0.3 mg/dl in serum creatinine from admission value at any time during hospital stay, as used in most previous studies.[13,15] Sensitivity analyses were performed using an alternative definitions of WRF (maximal increase of ≥0.5 mg/dl and >25% in serum creatinine).[18] Transient WRF was defined as peak creatinine ≥0.3 mg/dl higher than admission creatinine, which later decreased to a level that was <0.3 mg/dl higher than admission creatinine.[18] Estimated glomerular filtration rate (eGFR) was derived from the abbreviated Modification of Diet in Renal Disease study equation.

The degree of congestion at discharge was evaluated on the basis of a combination of several signs and symptoms before hospital discharge. These included raised JVP (≥8 cm water), hepatomegaly, presence of peripheral edema (>trace), pulmonary rales, and third heart sound.[19] Persistent congestion was defined when ≥1 of the aforementioned signs and symptoms were present. Hemoconcentration was defined as an increase in both hemoglobin and hematocrit levels between baseline and predischarge.[20,21] After hospital discharge, mortality data were acquired by reviewing the national death registry and by independently reviewing the hospital course for major clinical events if the patient had been rehospitalized.

Continuous variables are presented as mean (SD) or medians (interquartile ranges) and categorical variables as numbers and percentages. Baseline characteristics of the groups were compared using analysis of variance (ANOVA) for continuous variables and by the chi-square statistic for noncontinuous variables. When continuous data were not normally distributed, groups were compared with the nonparametric one-way ANOVA (Kruskal−Wallis test).

Event-free survival was estimated by the Kaplan−Meier method, and curves were compared with the log-rank test. Stepwise Cox proportional hazards models with backward selection were used to determine which variables were significantly related to all-cause mortality. Each variable was tested univariately and then (Wald test; $p < 0.10$) retested after adjustments for other possible cofounders in the Cox model. The following baseline clinical characteristics were considered in the multivariate procedure: age, gender, baseline systolic blood pressure, baseline and discharge eGFR, baseline and discharge blood urea nitrogen (BUN), baseline and discharge hemoglobin levels, BNP levels, history of diabetes mellitus and hypertension, atrial fibrillation, elevated troponin level at admission, and left ventricular ejection fraction. Skewed variables were logarithmically transformed and evaluated as "per 1 − SD greater" in the model.

We assessed whether the effect of persistent congestion on mortality varied according to WRF status using interaction testing and stratified analyses. The existence of an interaction was formally evaluated with the use of a Cox regression model incorporating terms for the main effect of WRF, the main effect of persistent congestion, and the