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Effect of Elevated Admission Serum Creatinine and Its Worsening on Outcome in Hospitalized Patients With Decompensated Heart Failure

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Renal insufficiency (RI), as represented by elevated serum creatinine (>1.5 mg/dl) on admission, is common and found in almost half of patients hospitalized with decompensated heart failure. This finding is associated with prolongation of length of stay and rate of rehospitalizations after discharge and also has an independent unfavorable effect on 6-month mortality. Similarly, an increase in serum creatinine (>0.5 mg/dl) in the hospital results in a significantly longer length of stay and has an independent effect on long-term mortality. ©2004 by Excerpta Medica, Inc.

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Recent studies have shown that impaired renal function is a strong and independent predictor of mortality in patients with chronic congestive heart failure (CHF) regardless of symptom severity.¹⁻³ Furthermore, worsening of renal function in hospitalized patients with CHF has been associated with a significantly worse outcome.^{4,5} We evaluated the relation between elevated serum creatinine at the time of hospital admission, as well as its worsening during hospitalization, and the outcome of a large number of patients hospitalized for decompensated CHF who were enrolled in a recent Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial.⁶

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The VMAC study was a prospective, multicenter trial designed to compare the effects of a 24-hour

infusion of nesiritide with those of intravenous nitroglycerin on symptoms and hemodynamics in hospitalized patients with decompensated CHF. The study was conducted in 55 centers in the United States and included patients with dyspnea at rest caused by CHF that was severe enough to require hospitalization and intravenous vasoactive therapy, regardless of their baseline creatinine level.⁶

Baseline creatinine values were obtained in 481 of 489 patients after admission to the hospital and before the initiation of the study. Renal insufficiency (RI) was defined as a serum creatinine level >1.5 mg/dl, which was based on the baseline levels of serum creatinine in the control cohort of the Framingham Study⁷ and the hypertensive cohort in the hypertension detection and follow-up program cooperative study that showed a level of 1.5 mg/dl to represent the upper limit of the 95th percentile of normal.⁸ Of 481 patients in this study, 215 had RI and 266 did not. Worsening renal function was defined by a >0.5 mg/dl increase of serum creatinine from baseline at any time during hospitalization. Such an increase has been shown in a recent retrospective review of 1,002 patients admitted with a diagnosis of CHF to have the highest specificity for mortality (81%).⁴ Of 480 patients with available information, 119 (25%) showed an increase of serum creatinine of >0.5 mg/dl and 361 did not.

Two subgroup analyses were performed, 1 comparing patients with and without an elevated baseline serum creatinine and the second comparing patients with and without worsening of renal function. Baseline characteristics were summarized for all 489 randomized patients and each patient subgroup. Student's *t* tests were used to compare the continuous variables, and a Fisher's exact test was used to compare the categorical variables. Patient outcomes, including length of hospitalization, 30 days readmission rate as well as 30-day and 6-month mortality, were summarized and compared in each subgroup analysis. Mor-

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Characteristic	Serum Creatinine	Serum Creatinine	p Value
	<1.5 mg/dl (n = 266)	≥1.5 mg/dl (n = 215)	
Age (yrs)	59 ± 14	65 ± 13	<0.0001
Men	64%	75%	<0.01
Body surface area (m ²)	2.0 ± 0.3	1.9 ± 0.3	0.274
Sinus rhythm	71%	63%	0.063
Atrial fibrillation	12%	12%	0.136
Diabetes mellitus	42%	53%	0.027
New York Heart Association functional class III and IV	80%	88%	0.116
Myocardial ischemic etiology	48%	59%	0.029
Left ventricular ejection fraction	27 ± 14%	27 ± 13%	0.904
Coronary artery disease	61%	71%	0.034
Systemic hypertension	68%	73%	0.230
Automatic implantable cardiac defibrillator/pacemaker	20%	30%	0.014
Previous myocardial infarction	41%	53%	0.008
Coronary bypass or angioplasty	32%	44%	0.010
Mean right atrial pressure (mm Hg)*	14 ± 7	16 ± 7	<0.05
Mean pulmonary capillary wedge pressure (mm Hg)*	27 ± 6	28 ± 7	0.280
Cardiac index (L/min/m ²)*	2.2 ± 0.7	2.2 ± 0.7	0.993

*In patients who underwent hemodynamic monitoring.

Outcome	Renal Insufficiency		p Value
	+ (n = 266)	0 (n = 215)	
Mortality (95% CI) at 30 d	5.3% (3.0%–8.5%)	8.8% (5.4%–13.2%)	0.149
Mortality (95% CI) at 6 mo	12.3% (8.6%–16.7%)	37.4% (30.8%–43.9%)	<0.0001
Length of hospitalization (d)	8.2 ± 7.1 (6)*	10.3 ± 8.4 (7)*	0.003
Readmission within 30 d of discharge	17%	27%	0.016

*Numbers in parenthesis represent medium length of stay.
CI = confidence interval.

Covariate	Comparison	Risk Ratio	95% CI of Risk Ratio	p Value
Serum creatinine (mg/dl)	≥1.5 vs <1.5	2.72	1.76–4.21	0.0001
Ventricular tachyarrhythmia/ventricular fibrillation	Yes:no	1.83	1.22–2.75	0.0035
Diabetes mellitus	Yes:no	1.45	0.98–2.14	0.0641
Digoxin (long-term use)	Yes:no	1.56	0.99–2.44	0.0539
Aspirin (long-term use)	Yes:no	1.41	0.95–2.09	0.0907
Ejection fraction	Per 10% decrease	1.13	0.95–1.34	0.1701
Age	Per 5-year increase	1.14	1.05–1.24	0.0031
Gender	Men:women	0.97	0.60–1.55	0.8961
Ischemic etiology	Yes:no	0.72	0.47–1.11	0.1388

Abbreviation as in Table 2.

tality was estimated by Kaplan-Meier analysis and group difference was tested using a log-rank test. Statistical means and medians were calculated for the length of hospitalization, and the group differences were tested by Wilcoxon rank test. Proportions of readmissions were also calculated, and a Fisher's exact test was used for the group comparison. Effect of RI on admission and worsening in renal function during hospitalization on 6-month mortality was analyzed using a stratified Cox proportional hazard model adjusting for demographics and other baseline risk factors. The risk ratios along with 95% confidence

intervals, and a p value (Wald chi-square test) are presented.

Elevated serum creatinine levels were found in 215 cases (45%). There were significant differences between patients with and without RI in age, gender, history of diabetes mellitus, coronary artery disease, acute myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, and implantation of automatic implantable cardioverter defibrillators or pacemakers (Table 1). Other baseline parameters did not differ between patients in both groups.

The presence of elevated baseline serum creatinine

TABLE 4 Comparison in Outcome Between Patients With and Without a >0.5 mg/dl Increase in Serum Creatinine at Any Time During Hospitalization

Outcome	With Increase (n = 119)	Without Increase (n = 361)	p Value
Mortality (95% CI) at 30 d	9.5% (4.8%–15.4%)	6.1% (3.9%–8.9%)	0.284
Mortality (95% CI) at 6 mo	37.9% (29.2%–46.7%)	18.8% (14.8%–23.1%)	<0.001
Mean ± SD (median) length of hospitalization (d)	11.8 ± 9.1 (8)*	8.3 ± 7.1 (6)*	<0.001
Readmission within 30 d of discharge	26%	20%	0.227

*Numbers in parentheses represent medium length of stay. Abbreviation as in Table 2.

had a significant effect on length of hospital stay, which increased from a median of 6 days to a median of 7 days ($p = 0.003$) and from a mean of 8.2 ± 7.1 to 10.3 ± 8.4 days, respectively (Table 2). RI was also associated with a 59% increase in the number of 30-day readmissions to the hospital after discharge (17% vs 27%, $p = 0.016$). Approximately half of the admissions were for decompensated CHF (8% vs 12%). Finally, an elevated baseline serum creatinine on hospital admission was associated with a significant impact on both morbidity and mortality (Table 2). All-cause mortality at 6 months increased approximately threefold (37.4% vs 12.3%, $p < 0.0001$) and 30-day mortality was also substantially higher (8.8% vs 5.3%), although the difference was not statistically significant. A multivariate analysis using a stratified Cox proportional hazard model adjusting for baseline differences revealed baseline RI to be an independent and the most significant predictor of 6-month mortality (Table 3), with a risk ratio of 2.72 (95% confidence interval 1.76 to 4.21, $p = 0.0001$). In addition, both a history of ventricular tachycardia and/or fibrillation (risk ratio 1.83, $p = 0.003$) and age (risk ratio 1.14 per 5-year increase, $p = 0.003$) were shown to be independent predictive risk factors for 6-month mortality.

A comparison of characteristics between patients with and without a >0.5 mg/dl increase in serum creatinine during their hospitalization showed a statistically significant difference in baseline serum creatinine levels between the 2 groups (1.8 ± 0.8 vs 1.6 ± 1.0 mg/dl, $p = 0.05$). In contrast, there was no difference in age, gender, cardiac rhythm, presence of diabetes mellitus, baseline systolic blood pressure, or change in blood pressure 3 hours after initiation of the infusion therapy. Table 4 shows the significant effect of worsening renal function on length of hospital stay, rehospitalizations, and mortality. A >0.5 mg/dl increase in serum creatinine resulted in a significantly longer hospital stay and 6-month mortality. The median hospital stay was longer in these patients (8 vs 6 days, $p < 0.001$), and the mean number of hospital days increased from 8.3 ± 7.1 to 11.8 ± 9.1 . There was also an increase in 30-day rehospitalization and mortality, which did not reach statistical significance. Using a stratified Cox proportional hazard model adjusting for baseline differences showed that in-hospital worsening of renal function was an independent risk factor of 6-month mortality (risk ratio 1.61, 95% confidence interval 1.09 to 2.37, $p = 0.02$).

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The results of this study show that the presence of RI as manifested by serum creatinine level of >1.5 mg/dl on admission and worsening of renal function (>0.5 mg/dl) during hospitalization are powerful predictors of prolongation of hospital stay as well as worse outcome in patients hospitalized for decompensated CHF. Our findings show that RI is common in patients with decompensated CHF and is found on admission in almost half of the patients. This finding was associated with older age, male gender, a higher incidence of diabetes mellitus and coronary artery disease, and a history of myocardial infarction. An adjustment for these variables identified the finding of RI on presentation to the hospital as a powerful and independent predictor of poor outcome. Furthermore, the presence of RI on admission was a stronger predictor of 6-month mortality than the other risk factors examined, such as age, history of ventricular arrhythmias, left ventricular ejection fraction, diabetes mellitus, and ischemic etiology of CHF. The strong association between admission RI and mortality shown in our study in hospitalized patients with decompensated CHF is similar to a recently published association between renal function and outcome in patients with chronic CHF. An analysis of New York Heart Association class I and II patients enrolled in the Studies of Left Ventricular Dysfunction² showed that even a moderate degree of RI was independently associated with increased mortality, largely explained by an increased risk of CHF progression. Similar findings were reported by Hillege et al,¹ who studied 1,906 patients with chronic CHF and New York Heart Association class III and IV symptoms who were enrolled into the second prospective, randomized study evaluating the effect of ibopamine. In this study, RI was the most powerful predictor of mortality and was not related to the degree of left ventricular ejection fraction. This finding may suggest that impaired renal function may not be caused directly by cardiac disease and that both renal and cardiac function could represent separate prognostic entities in patients with CHF.

An increase in serum creatinine of ≥ 0.5 mg/dl during hospitalization occurred in 25% of patients in this study and was associated with a striking effect on morbidity and mortality, including over a 3-day longer mean length of stay, a 40% increase in the number of hospital days, approximately 50% increase in 30-day mortality, and a twofold increase

in 6-month mortality. Although increase of serum creatinine during hospitalization was more likely in patients with baseline RI, a correction for baseline variables showed worsening renal function to provide independent information on long-term mortality. The results of our study are supported by a recent report by Krumholz et al,⁹ who reviewed the hospital records of 1,681 patients aged >65 years discharged with the diagnosis of CHF. Worsening renal function, defined as >0.3 mg/dl increase in serum creatinine, occurred in 28% of patients and was associated with longer length of stay, higher in-hospital cost, and an almost twofold increase in hospital mortality. In a smaller study, Weinfeld et al⁵ reviewed the experience of 48 consecutive patients hospitalized for treatment of advanced chronic CHF. Worsening of renal function was defined as a >25% increase in serum creatinine, to a value of >2 mg/dl, and was associated with a longer hospital stay (median 14 vs 9 days) and a fivefold increased risk of death after hospital discharge.

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Usefulness of Spatial Dispersion of QRS Duration in Predicting Mortality in Patients With Mild to Moderate Chronic Heart Failure

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To prospectively evaluate the prognostic significance of spatial dispersion of QRS duration (S-QRSd) on a signal-averaged electrocardiogram in patients with chronic heart failure (CHF), we studied 114 consecutive stable outpatients with radionuclide left ventricular ejection fraction <40%. Cardiac and sudden deaths were significantly more often observed in patients with than without abnormal S-QRSd. S-QRSd is a powerful prognostic marker of the mortality in patients with mild to moderate CHF. ©2004 by Excerpta Medica, Inc. (Am J Cardiol 2004;94:960–963)

Chronic heart failure (CHF) is common and has a high mortality.¹ It is clinically valuable to identify patients with CHF at risk for cardiac death. It has been reported that interlead dispersion of the QRS complex

measured on the standard 12-lead electrocardiogram (ECG) was related to poor outcome in patients with advanced CHF.² However, the excessive overlap of QRS dispersion on the standard 12-lead ECG between survivors and nonsurvivors has limited the predictive value of mortality. In contrast, the signal-averaging technique can detect low-amplitude electrocardiographic potentials that are not detectable by the standard ECG.^{3,4} No data are available regarding the possible predictive value of spatial dispersion of QRS duration (S-QRSd) on a signal-averaged ECG in patients with CHF. We sought to prospectively evaluate the prognostic significance of S-QRSd in patients with CHF, using body surface mapping of the signal-averaged ECG.

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We studied 114 consecutive outpatients with CHF with radionuclide left ventricular ejection fraction <40%. Patients were required to be stable for ≥ 3 months and receiving conventional therapy of angiotensin-converting enzyme inhibitors, diuretics, and digoxin. There were 92 men and 22 women (mean age 64 ± 11 years; range 28 to 85). Sixty-two (54%) of them had coronary heart disease, and the remaining 52 patients

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