

# Echocardiographic predictors of change in renal function with intravenous diuresis for decompensated heart failure

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**Aims** The aim of this study was to identify echocardiographic predictors of improved or worsening renal function during intravenous diuresis for decompensated heart failure. Secondary aim included defining the incidence and clinical risk factors for acute changes in renal function with decongestion.

**Methods and results** A retrospective review of 363 patients admitted to a single centre for decompensated heart failure who underwent intravenous diuresis and transthoracic echocardiography was conducted. Clinical, echocardiographic, and renal function data were retrospectively collected. A multinomial logistic regression model was created to determine relative risk ratios for improved renal function (IRF) or worsening renal function (WRF). Within this cohort, 36% of patients experienced WRF, 35% had stable renal function, and 29% had IRF. Patients with WRF were more likely to have a preserved left ventricular ejection fraction compared with those with stable renal function or IRF ( $P = 0.02$ ). Patients with IRF were more likely to have a dilated, hypokinetic right ventricle compared with those with stable renal function or WRF ( $P \leq 0.01$ ), although this was not significant after adjustment for baseline characteristics. Left atrial size, left ventricular linear dimensions, and diastolic function did not significantly predict change in renal function.

**Conclusions** An acute change in renal function occurred in 65% of patients admitted with decompensated heart failure. WRF was statistically more likely in patients with a preserved left ventricular ejection fraction. A trend towards IRF was noted in patients with global right ventricular dysfunction.

**Keywords** Echocardiography; Heart failure; Cardiorenal syndrome

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## Introduction

Heart failure and renal dysfunction are frequent co-morbid conditions in the acute and chronic settings. Numerous studies have established a relationship between impaired renal function and poor heart failure outcomes.<sup>1–4</sup> Worsening renal function (WRF) develops in 18–40% of patients hospitalized for decompensated heart failure and has been associated with higher morbidity and mortality.<sup>2,3,5–10</sup> Similar findings have been observed with chronic kidney disease and heart failure.<sup>11</sup> Risk factors for the development of WRF have been previously identified and include renal dysfunction on admission,<sup>2,4,5,12</sup> diabetes mellitus,<sup>2,4,12</sup> hypertension,<sup>2,12</sup> pulmonary oedema,<sup>5</sup> diastolic dysfunction by echocardiography,<sup>4</sup> and the presence of atrial fibrillation.<sup>5</sup>

Paradoxically, a proportion of patients admitted with decompensated heart failure experience improved renal function (IRF).<sup>13</sup> Improvement in renal function was described by Testani *et al.* in patients with lower baseline estimated glomerular filtration rate (eGFR), lower serum sodium on presentation, severely decreased left ventricular ejection fraction (LVEF), lower systolic blood pressure, and higher B-type natriuretic peptide levels. Patients with IRF do not necessarily experience a benefit in survival; in fact, there is evidence to the contrary.<sup>14</sup>

Echocardiography remains the mainstay of non-invasive haemodynamic and cardiac function assessment in heart failure, but its role in defining patients at risk for improvement or deterioration in renal function remains uncertain. Results regarding systolic function have been inconsistent; however, there may be a trend towards stable renal function or IRF

in patients with a severely reduced LVEF and/or evidence of right-sided volume overload.<sup>2,4,14,15</sup> The aim of the present study was to identify echocardiographic predictors of either IRF or WRF during inpatient diuresis for decompensated heart failure.

## Methods

### Study population

We studied patients admitted to Beth Israel Deaconess Medical Center (Boston, MA) from January 2011 to November 2014 for decompensated heart failure who received intravenous loop diuretics and underwent inpatient transthoracic echocardiography. Patients were identified using a searchable clinical data warehouse with corresponding International Classification of Diseases, Ninth Revision codes.<sup>16</sup> A primary diagnosis of heart failure was verified by clinical chart review and identification of at least one symptom of heart failure (dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea, lower extremity swelling, or chest discomfort attributed to heart failure) and one objective measure or sign of heart failure (elevated jugular venous pressure, bilateral crackles, pitting peripheral oedema, cardiogenic shock, pulmonary oedema on chest radiograph, or N terminal pro brain natriuretic peptide > 1000 pg/mL). Only patients with a length of stay between 2 and 14 days were included as to provide sufficient renal function data and to exclude those with complicated hospital courses with competing causes of renal dysfunction. Patients undergoing renal replacement therapy or with a history of cirrhosis were excluded. This study was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center.

### Period of diuresis

The period of diuresis was defined as the time of first intravenous diuretic administration to 12 h after the last dose of intravenous diuretic administration. Identification of this period was felt to be important to capture the change in renal function specific to the period of decongestion. Chemistry panels, fluid balances, and weights corresponding to the diuresis period were recorded separately from the admission and discharge data.

### Two-dimensional and Doppler echocardiography

Echocardiographic data were retrospectively collected from inpatient transthoracic echocardiograms. Left ventricular (LV), left atrial, and right atrial linear dimensions were

documented. LVEF was recorded as assessed by the primary reading physician. Valvular stenosis and regurgitation severity were classified according to current guidelines.<sup>17,18</sup> A comprehensive diastolic function examination was completed including mitral inflow patterns and mitral annular tissue velocities. Right ventricular (RV) size and systolic function were determined based on a combination of visual assessment, RV basal diameter, and tricuspid annular plane systolic excursion. Estimation of right atrial pressure was based on inferior vena cava size and collapsibility. Missing data were obtained by a blinded review of echocardiographic images by a board-certified cardiologist.

### Outcomes

Change in renal function as measured by change in eGFR during the period of diuresis was the primary study outcome. The chronic kidney disease epidemiology collaboration equation was used to calculate eGFR.<sup>19</sup> WRF was defined as a decrease in eGFR of  $\geq 10\%$ . IRF was defined as an increase in eGFR of  $\geq 10\%$ .

### Statistical analysis

Study data were collected and managed using the REDCap (Research Electronic Data Capture) electronic data tool.<sup>20</sup> The goal of the primary analysis was to describe echocardiographic parameters associated with either WRF or IRF during diuresis. A multinomial logistic regression model with robust standard errors was created to determine relative risk ratios for WRF or IRF relative to stable renal function with adjustment for age, sex, race, admission serum sodium, admission eGFR, initial systolic blood pressure, and the presence of coronary artery disease, diabetes mellitus, or hypertension. Repeated hospitalizations were accounted for as well. We then used fractional polynomial smoothing to explore dose-response relationships with covariates significantly associated with WRF or IRF. Continuous variables were subject to a standard ANOVA test and categorical variables to Fisher's exact test. All analyses were performed using STATA version 12 (Stata Corp., College Station, Texas).

## Results

### Study population

Overall, 363 patient admissions met eligibility criteria. Three patients had repeat admissions, which were included in the study population.

## Incidence of worsening or improved renal function

Within our study population, 36% of patients experienced a decrease in eGFR by at least 10% during the diuresis period, 35% had stable renal function, and 29% had an improvement in eGFR by at least 10%. Estimated GFR in patients with WRF declined by a mean of  $23 \pm 11\%$ . Of the patients who experienced IRF, the mean improvement was  $35 \pm 37\%$ .

## Patient characteristics

Baseline patient characteristics are presented in *Table 1*, subdivided based on renal function outcome. There were no significant differences in baseline characteristics between patients with IRF, stable renal function, and WRF.

## Hospitalization data

Clinical data are presented in *Table 2* subdivided based on renal function outcome. We observed a highly significant correlation between fluid balance and weight change at discharge (Pearson  $r$  0.64;  $P < 0.001$ ). Initial systolic blood pressure and serum sodium tended to be lower in those with IRF. On admission, 92% of patients complained of dyspnoea, 33% noted worsening oedema, and 72% had evidence of pulmonary oedema or congestion on chest imaging. Continuous loop diuretic infusions were utilized in 19% of patient admissions. There were no statistically significant differences between groups in terms of N terminal pro brain natriuretic peptide levels, diuresis volumes, or incidence of contrast exposure.

**Table 1** Patient characteristics according to change in renal function

Demographics	Improved N = 105	Stable N = 126	Worsening N = 132
Age, years	73 [15]	73 [13]	76 [14]
Female	52 (50)	47 (37)	62 (47)
White	80 (76)	99 (79)	97 (73)
Medical history			
Hypertension	81 (77)	104 (83)	115 (87)
Coronary artery disease	39 (37)	52 (41)	45 (34)
Prior heart failure	56 (53)	72 (57)	63 (48)
Diabetes mellitus	43 (41)	52 (41)	47 (36)
Current smoking	46 (44)	52 (41)	52 (39)
BMI	30 [15]	30 [8]	31 [9]
Initial eGFR, mL/min/1.73 m <sup>2</sup>	48 [20]	54 [28]	54 [24]

BMI, body mass index; eGFR, estimated glomerular filtration rate. Continuous variables presented as mean [standard deviation]. Categorical variables presented as number (%).

## Echocardiographic parameters

Echocardiographic data from the study population are presented in *Table 3*. Patients with WRF were more likely to have a preserved ejection fraction compared with those with stable renal function or IRF ( $P = 0.02$ ). After adjustment for baseline and RV characteristics, this association remained significant, RR 0.55 [0.32–0.97],  $P = 0.04$ . The roughly linear association of LVEF with risk of WRF is presented in *Figure 1*.

Patients with IRF were more likely to have a dilated, hypokinetic RV compared with those with stable renal function or WRF ( $P = 0.008$ ), although this was not significant after additional adjustments for baseline characteristics and LVEF. Right atrial enlargement tended to be associated with IRF with a  $P$ -value of 0.09 even after adjustment.

Left atrial and LV linear dimensions were not related to change in renal function. Mitral inflow patterns and mitral annular velocities were not associated with IRF or WRF. Predicted right atrial pressure and tricuspid regurgitation gradient were not significantly different between groups.

## Discussion

The current investigation adds to the expanding body of evidence that most patients admitted for decompensated heart failure experience acute changes in renal function. The main findings of the study include 36% of patients had a decrease in eGFR by  $\geq 10\%$ , 29% experienced an increase in eGFR by  $\geq 10\%$ , and WRF was statistically more likely in patients with a preserved LVEF. A trend towards IRF was noted in patients with a dilated, hypokinetic RV and dilated right atrium.

The proportions of patients with WRF and IRF in our study are slightly higher than those reported previously, although this likely reflects the lower cut-off for a significant change in renal function. Prior studies have reported the incidence of WRF to be 18–40%.<sup>2,3,5–10</sup> IRF was noted by Testani *et al.* in 31% of patients at any point during their hospitalization and 18% of patients at discharge.<sup>14</sup> Most early reports used an increase in creatinine of  $\geq 0.3$  mg/dL to define WRF. This definition, however, does not take into account the non-linear relationship between serum creatinine and eGFR.<sup>21</sup> Notably, adverse outcomes have been associated with even minimal changes in renal function (0.1 mg/dL increase in serum creatinine or 10 mL/min decrease in eGFR).<sup>3,22</sup> More recent studies have used a percent change in eGFR to define WRF and IRF. A cut-off of 10% change in eGFR was used in this study to maximize the study's power and maintain clinical significance.

A number of investigators have analysed the relationship between LV systolic function and change in renal function with treatment of decompensated heart failure. Results have varied, with some studies reporting no difference in the

**Table 2** Clinical factors according to change in renal function

	Improved N = 105	Stable N = 126	Worsening N = 132	P-value
Length of stay, days	6.5 [2.8]	5.8 [2.6]	5.9 [2.5]	0.11
Diuresis days	4.3 [2.3]	3.9 [2.0]	4.4 [2.3]	0.15
Initial systolic blood pressure	128 [24]	136 [28]	143 [29]	<0.001
Initial serum sodium	137.0 [5.0]	137.9 [4.8]	138.7 [4.6]	0.03
Initial serum bicarbonate	25.3 [4.6]	25.9 [4.8]	25.0 [4.4]	0.31
Loop diuretic infusion	16 (15)	24 (19)	30 (23)	0.35
Iodinated contrast exposure	31 (30)	41 (33)	29 (22)	0.15
NT-proBNP	5869 (2392–13 117)	4981 (2160–12 185)	4435 (2096–8899)	0.39
Fluid balance at discharge	4232 (2090–7980)	3886 (1656–7231)	3530 (1517–6791)	0.56
Weight change at discharge	3.9 (1.7–7.0)	3.4 (1.8–6.1)	3.4 (1.8–6.2)	0.37

NT-proBNP, N terminal pro brain natriuretic peptide.

Continuous variables presented as mean [standard deviation].

Categorical variables presented as number (%).

Skewed variables presented as median (interquartile range).

**Table 3** Echocardiographic parameters according to change in renal function

	Improved N = 105	Stable N = 126	Worsening N = 132	P-value
Left atrial size (cm)	6.1 [1.0]	5.8 [0.9]	5.8 [1.0]	0.83
Right atrial size (cm)	5.8 [1.0]	5.5 [0.9]	5.6 [0.9]	0.14
Left ventricular diastolic diameter (cm)	5.1 [1.2]	5.0 [0.9]	4.9 [1.0]	0.18
Left ventricular septal wall thickness (per 0.1 cm)	1.2 [0.2]	1.2 [0.2]	1.2 [0.2]	0.73
Tricuspid regurgitation gradient (per 5 mmHg)	39 [15]	38 [11]	39 [14]	0.85
Reduced LVEF ( $\leq 40\%$ )	58 (55)	67 (54)	51 (39)	<b>0.02</b>
Normal septal tissue Doppler ( $\geq 0.08$ m/s)	14 (16)	23 (22)	28 (24)	0.33
Mitral E/A normal (0.75–1.5)	30 (43)	39 (44)	38 (43)	0.99
Mitral E/E' normal ( $< 13$ )	26 (29)	30 (29)	30 (25)	0.78
Mitral deceleration time normal ( $< 220$ ms)	75 (76)	92 (78)	96 (77)	0.93
Estimated right atrial pressure				
0–5 mmHg	24	25	35	0.17
5–10 mmHg	25	41	30	
>15 mmHg	28	21	28	
Global RV dysfunction	40 (39)	32 (26)	27 (21)	<b>&lt;0.01</b>

LVEF, left ventricular ejection fraction; RV, right ventricular.

Continuous variables presented as mean [standard deviation].

Categorical variables presented as number (%).

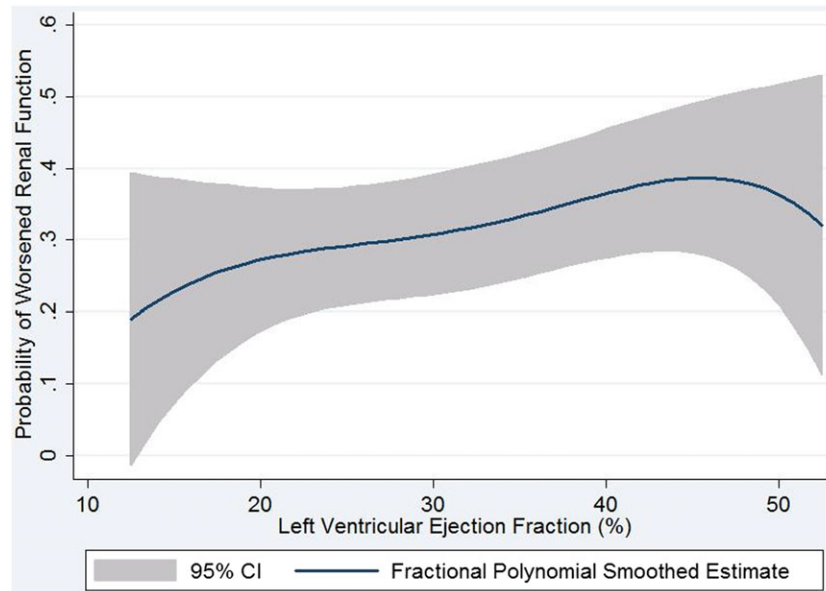
incidence of WRF between patients with reduced and preserved LVEF<sup>2,4</sup> and others reporting a lower incidence of WRF in patients with a severely reduced LVEF.<sup>13,15</sup> We report a near linear relationship between LVEF and the probability of WRF. The notion that WRF is purely the result of low cardiac output and poor renal perfusion represents an oversimplification. While reduced cardiac output may play a role in WRF in patients with severely decreased LV function, multiple studies using invasive haemodynamic techniques have been unable to directly implicate alterations in cardiac output in WRF.<sup>13,23</sup> Additional haemodynamic considerations include elevation in renal venous pressure, further reducing renal perfusion, and elevated intraabdominal pressure.<sup>24,25</sup>

Testani *et al.* identified a higher incidence of IRF in patients with evidence of venous congestion and RV dysfunction. Interestingly, right heart catheterization pressures were not significantly different between patient groups suggesting a

distinction between pressure and volume overload.<sup>14</sup> In the present study, we identified a trend towards IRF in patients with a dilated, hypokinetic RV. There are likely several explanations for this observation including ventricular interaction, wherein right-sided volume unloading improves LV performance, and improved microvascular perfusion secondary to decreased neurohormonal activation. In the volume overloaded state, ventricular interaction results in leftward displacement of the interventricular septum decreasing LV filling and decreased effective LV distending pressure from higher surrounding pressures in the RV and pericardium.<sup>26,27</sup>

Acute RV unloading has been observed in human and animal models to lead to an increase in LV distending pressure, volume, stroke volume, and stroke work.<sup>26,28,29</sup> Lauten *et al.* demonstrated improved microvascular tissue perfusion with medical treatment for acute decompensated heart failure. Those patients with RV failure likely have more advanced

**Figure 1** Local regrESSion (LOESS) smoothing curve depicting the relationship between left ventricular ejection fraction and probability of worsening renal function. CI, confidence interval.



heart failure, a higher degree of sympathetic and neurohormonal activation, and a more favourable response to ventricular unloading.<sup>30</sup>

Additional parameters of LV geometry, diastolic function, and filling pressures were assessed by 2D echocardiography. We did not note any statistically significant between-group differences for these additional measurements. Finally, our study supports previous findings of lower presenting serum sodium for patients with IRF<sup>14</sup> and higher presenting systolic blood pressure for patients with WRF.<sup>2,8,12</sup> The pathophysiology behind these findings has not been defined.

In conclusion, this retrospective cohort study demonstrates that a majority of patients admitted with decompensated heart failure experience a significant change in renal function with treatment. WRF was statistically more prevalent in those with preserved LV function. A trend towards IRF was noted in those with a dilated, hypokinetic RV and larger RA size. This study adds to the cardiorenal literature, which enables tailored diuresis among heart failure patients to optimize clinical outcomes.

The single centre, retrospective design of this analysis results in several limitations, including the potential for

uncontrolled confounding. Available information was limited to that recorded in the electronic medical record or interpreted from archived echocardiographic studies. Additionally, echocardiograms were performed at various times during patient hospitalizations potentially representing various loading conditions. Choice of in-hospital therapy was certainly influenced by many clinical data points, including daily renal function and vital signs. Multiple inclusion and exclusion criteria likely limit the overall generalizability.

## Conflict of interest

None declared.

## Funding

None.

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