Effect of Renal Function on Prognosis in Chronic Heart Failure

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Renal dysfunction (RD) is associated with increased mortality in heart failure (HF). The aim of this study was to identify whether worsened or improved renal function during mid-term follow-up is associated with worsened outcomes in patients with chronic HF. A total of 892 participants from a multicenter cohort study of chronic HF were followed over 3.1 ± 1.9 years of enrollment. Worsened and improved renal functions were tested with multivariate models as independent predictors of HF hospitalization and mortality. Although 12% of subjects experienced a ≥25% decrease in estimated glomerular filtration rate (eGFR), 17% experienced a ≥25% increase in eGFR, and there was stability of kidney function observed in the cohort as a whole. The quartile with the worst RD at any point in time had increased risk of HF hospitalization and mortality. Worsened eGFR was associated with HF outcomes in the unadjusted (hazard ratio = 1.71, 95% confidence interval 1.04 to 2.81, p = 0.035), but not the adjusted analysis. Improvement in eGFR was not associated with outcome (p = 0.453). In chronic HF, the severity of RD predicts risk of poor outcome better than changes in renal function during mid-term follow-up. This suggests that in patients with appropriately treated chronic HF, worsening renal function in itself does not yield useful prognostic information and may not reflect poor outcome. **(Am J Cardiol 2015;115:62−68)**

Heart failure (HF) affects approximately 6 million people in the United States.[1] Co-morbidities clearly impact HF prognosis. Over the last 2 decades, the number of co-morbidities and medications in the average patient with HF has increased substantially, renal failure being among those.[2] Given the high cost of HF hospitalization, identifying risk factors that increase its likelihood is useful. Renal function is considered to be a sensitive marker of decreased organ perfusion and is commonly believed to deteriorate in HF because of chronic hypoperfusion.[3] Recently, several studies have reported an association between worsening renal function (WRF) during inpatient treatment for acute decompensated HF and poor clinical outcomes.[4−11] In chronic HF, reduced renal perfusion may occur over a long period, and patients may experience few symptoms related to the declining renal function.[3] Several studies have found an association of WRF with mortality in the ambulatory setting.[12−17] Most studies have included only patients with HF with reduced ejection fraction (HFrEF), and follow-up has typically been short, investigating changes in renal function over no more than a 6-month interval from baseline. Our aim was to assess how kidney function changed during mid-term follow-up in patients with HF, and whether WRF predicts all-cause mortality and HF hospitalization in patients medically treated for chronic HF. We also examined risk factors for WRF and whether improvement in renal function was associated with improved outcomes.

Methods

Subjects were enrolled in the multicenter Penn Heart Failure study. The Penn Heart Failure study began in 2003 at the University of Pennsylvania and subsequently expanded into a multicenter study. This is a prospective observational cohort study of more than 2,000 subjects with HF followed in HF specialty clinics. The study was approved by institutional review committees, and the subjects gave informed consent. Detailed patient information was collected at baseline and patients were followed every 6 months to measure predefined end points (hospitalization, change in therapy, and death). Patients were either seen in clinic or called at intervals of 6 months. Inclusion criteria in this analysis were an available baseline measurement of creatinine (at time of enrollment) and at least 1 follow-up value. At the beginning of the study follow-up kidney function was not routinely collected, and therefore only the subset of patients in whom this information was available was included in this analysis. The primary outcome measures were death or HF hospitalization (primary composite outcome) and death alone. Ten subjects underwent heart transplantation and were counted in the death end point. This was done because the assumed outcome without transplantation is death. HF hospitalization was based on primary discharge diagnosis. Patients with a clinical diagnosis of HF were considered to have HFrEF based on an EF ≤40% as defined in current guidelines.[18] The remaining patients were classified as HF with preserved EF (HFpEF).

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Table 1
Baseline characteristics by baseline eGFR quartiles

Variable	Quartile					P
	1 (n=223)	2 (n=223)	3 (n=223)	4 (n=223)	Total Cohort (n=892)	
eGFR ($mL*min^{-1}*1.73m^{-2}$) median (minimum, maximum)	95 (85, 628)	76 (69, 84)	62 (53, 69)	40 (6, 53)	69 (6, 628)	…
Age (years)	48 (14)	54 (13)	59 (14)	64 (12)	56 (15)	< 0.01
Male	154 (69%)	138 (62%)	135 (61%)	128 (57%)	555 (62%)	0.07
White Race	155 (71%)	165 (76%)	182 (83%)	151 (70%)	653 (73%)	< 0.01
Black Race	58 (27%)	50 (23%)	32 (15%)	58 (27%)	198 (22%)	
Ischemic origin	33 (15%)	47 (21%)	70 (32%)	78 (36%)	228 (26%)	< 0.01
Systolic heart failure	114 (52%)	130 (58%)	121 (55%)	121 (55%)	486 (55%)	0.57
Hospitalization in prior 12 months	68 (30%)	83 (37%)	84 (38%)	91 (41%)	326 (37%)	0.14
Diabetes mellitus	44 (20%)	49 (22%)	49 (22%)	86 (39%)	228 (26%)	< 0.01
Hypertension	11 (50%)	121 (54%)	131 (59%)	166 (74%)	529 (59%)	< 0.01
Stroke	3 (1%)	16 (7%)	10 (4%)	21 (9%)	50 (6%)	< 0.01
Follow-up time, years, median (IQR)	3.0 (1.6, 5.0)	2.9 (1.8, 4.8)	3.0 (1.7, 4.4)	2.5 (1.3, 3.7)	2.9 (1.5, 4.5)	< 0.01
New York Heart Association Class						
II	122 (55%)	123 (55%)	116 (52%)	113 (52%)	472 (53%)	
III	31 (14%)	43 (19%)	45 (20%)	71 (33%)	190 (22%)	< 0.01
IV	1 (0%)	0 (0%)	6 (3%)	6 (3%)	13 (1%)	
Ejection Fraction (%)	37 (16)	36 (17)	38 (17)	39 (18)	37 (17)	0.53
Body Mass Index (kg/m^2)	30 (7)	30 (8)	31 (7)	32 (9)	31 (8)	0.11
Heart rate (beats per minute)	73 (13)	72 (13)	73 (14)	72 (13)	72 (13)	0.78
Systolic blood pressure (mm Hg)	117 (21)	116 (21)	117 (22)	119 (25)	118 (22)	0.59
MLHFQ* score, median (IQR)	19 (2, 51)	18 (4, 45)	24 (6, 50)	34 (9, 59)	24 (4, 52)	0.01
Serum creatinine (mg/dL)	0.9 (0.1)	1.0 (0.1)	1.2 (0.2)	2.1 (1.4)	1.3 (0.9)	< 0.01
Serum sodium (mEq/L)	139 (3)	140 (2)	139 (3)	139 (4)	139 (3)	0.19
Potassium-sparing diuretics	2 (1%)	3 (1%)	7 (3%)	2 (1%)	14 (2%)	0.25
Loop diuretics	118 (53%)	135 (61%)	138 (62%)	168 (75%)	559 (63%)	< 0.01
ACE inhibitors	161 (72%)	163 (73%)	149 (67%)	138 (62%)	611 (68%)	0.04
Aldosterone antagonist	59 (26%)	64 (29%)	61 (27%)	87 (39%)	271 (30%)	0.01
Angiotensin receptor blockers	48 (22%)	50 (22%)	59 (26%)	56 (25%)	213 (24%)	0.58
Aspirin	114 (51%)	122 (55%)	123 (55%)	145 (65%)	504 (57%)	0.02
β-Blockers	195 (87%)	198 (89%)	194 (87%)	198 (89%)	785 (88%)	0.91
Digoxin	63 (28%)	58 (26%)	57 (26%)	70 (31%)	248 (28%)	0.5
Hydralazine	14 (6%)	9 (4%)	9 (4%)	36 (16%)	68 (8%)	< 0.01
Long acting nitrate	19 (9%)	21 (9%)	21 (9%)	54 (24%)	115 (13%)	< 0.01
Statin	89 (40%)	127 (57%)	128 (57%)	143 (64%)	487 (55%)	< 0.01

Continuous variables are reported as mean (SD) unless otherwise noted.
Categorical variables are reported as frequency (%).
P-values for continuous variables are from one-way ANOVA or Kruskal-Wallis tests.
P-values for categorical variables are from Pearson chi-square test or Fisher's exact test.
* Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation.[19] Change in eGFR was calculated by subtracting the most recent follow-up eGFR from baseline eGFR. For patients with a primary outcome, the most recent eGFR before reaching the primary outcome was used. We used previously defined criteria for WRF: a ≥25% decrease in eGFR[20,21] or an increase in serum creatinine (SCr) ≥0.3 mg/dl.[22–24] Improvement in renal function was defined as a ≥25% increase in eGFR or a decrease in SCr ≥0.3 mg/dl.

Participants were divided into quartiles of baseline eGFR. Comparisons between baseline eGFR groups were made with 1-way analysis of variance, Kruskal-Wallis tests, or chi-square tests based on distribution and normality assumptions. Univariate Cox proportional hazards models were used to assess the relation between time to a primary outcome and baseline or follow-up eGFR and/or SCr. WRF status and time to primary composite outcome were also assessed with univariate Cox proportional hazards model. Similarly, univariate Cox models were used for the mortality outcome. To assess for linearity in the coefficients of the Cox model over the entire range of follow-up SCr and eGFR, each group was divided into quartiles and hazard ratios (HRs) calculated using the lowest SCr quartile and highest eGFR quartile as the reference.

Multivariate Cox proportional hazards models were developed by compiling a list of 39 baseline variables of clinical importance and that did not have large numbers of missing values. Univariate Cox models of each baseline variable were created for time to primary composite outcome. Candidate variables were considered to be baseline variables that had chi-square p values >0.05. Backward and forward stepwise models of the candidate variables