Impact of Reduced Kidney Function on Cardiopulmonary Fitness in Patients with Systolic Heart Failure

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Key Words

Heart failure • Chronic kidney disease • Cardiopulmonary fitness • Glomerular filtration rate • Renal insufficiency • Mortality risk

Abstract

Background: Decreased renal function has been consistently associated with increased mortality among patients with systolic heart failure. The relationship between estimated glomerular filtration rate (eGFR) and other high-risk features including reduced cardiorespiratory fitness has not been previously reported in this patient population. **Methods:** The HF-ACTION trial was a prospective, randomized trial of exercise therapy versus usual care in patients with systolic heart failure. Patients with class 2–4 heart failure and a left ventricular ejection fraction of $\leq 35\%$ were recruited. Serum creatinine was measured up to 1 year prior to entry. The 4-variable modified Modification of Diet in Renal Disease equation was used to calculate eGFR. Peak oxygen consumption (peak VO_2) was directly measured using gas exchange analysis during progressive exercise testing to volitional fatigue or adverse signs/symptoms. **Results:** Of 2,091 subjects (mean age 59 ± 13 years, with serum creatinine

available at baseline), 72% were men, and 61, 33, and 5% were Caucasians, African Americans, and others, respectively. Older age, diabetes, and hypertension were all more frequent with declining eGFR. The Pearson correlation between eGFR and peak VO_2 was 0.22 ($p < 0.0001$). Age was negatively correlated with both eGFR ($r = -0.44$, $p < 0.0001$) and peak VO_2 ($r = -0.27$, $p < 0.0001$). The peak VO_2 tended to decline across decreasing levels of eGFR. Individuals with an eGFR < 30 ml/min/1.73 m² had, on average, 2.1 high-risk features including peak $\text{VO}_2 < 14$ ml/kg/min, age > 75 years, diabetes, and functional class 3–4 symptoms. Conversely, those with an eGFR > 90 ml/min/1.73 m² had relatively few (1.0) high-risk characteristics. **Conclusions:** Reduced renal filtration is associated with impaired cardiorespiratory fitness and a clustering of high-risk features in systolic heart failure patients which portend a more complicated course and higher all-cause mortality.

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The study has previously been published as an abstract.

We are in the midst of concurrent chronic disease epidemics of congestive heart failure (HF) and chronic kidney disease (CKD) worldwide [1, 2]. This is marked by increases in incident and prevalent cases of both diseases over the past several decades driven by rising rates of common risk factors for both CKD and HF including obesity, metabolic syndrome, diabetes, and hypertension [3–6]. Measures of renal function can now be calculated with a reasonable degree of accuracy with the use of multivariate equations based on serum creatinine and other demographic variables including age [7]. Previous studies have consistently reported an association between reduced estimated glomerular filtration rate (eGFR) and increased HF mortality [8]. We sought to more fully explain the risk features clustered in those patients with CKD and HF while adjusting for age, cardiorespiratory fitness, and other baseline variables in a large, multicenter randomized trial.

Methods

Setting

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) was a prospective, randomized trial of exercise training in patients who were medically stable, with New York Heart Association (NYHA) class 2–4 HF and measured left ventricular ejection fraction $\leq 35\%$. Recruitment methods for the HF-ACTION have been published elsewhere [9]. The trial was designed to evaluate the composite end point of all-cause mortality and all-cause hospitalization over a median follow-up of 30 months in patients who underwent medically supervised and home-based exercise training as compared with controls who received usual care [10].

Study Sample

A total of 2,331 subjects were recruited from April 2003 through February 2007 at 82 sites within the United States, Canada, and France; however, the study sample was reduced because 240 subjects had no measured serum creatinine recorded at baseline. The remaining 2,091 HF patients served as the study population, providing complete data for analysis. Major exclusion criteria were comorbidities that could interfere with exercise training (e.g. peritoneal dialysis or hemodialysis) and major cardiovascular events within the last 6 months.

Data Collection

Baseline demographics, clinical history, and objective assessment of clinical signs were gathered by trained research personnel at each site. Subjects underwent peak or symptom-limited cardiopulmonary exercise testing as previously described using a modified Naughton treadmill protocol or a 10 W/min incremental cycle ergometry protocol [11]. Heart rate was measured at rest in the supine and standing positions, during each stage of exercise, and throughout a 6-min recovery. Test termination criteria included: patient request; volitional fatigue; increasing chest or leg pain,

and electrocardiographic (ECG) abnormalities (≥ 2 mm ST segment depression and/or threatening ventricular arrhythmias).

Respiratory variables, heart rate, and perceived exertion were determined at submaximal and peak exercise. The ECG was monitored continuously by oscilloscope, with 3-channel (V_1 , V_5 , and aVF) recordings obtained throughout the exercise test, and 12-lead ECGs (1 mV/10 mm) recorded at the end of each stage and during peak exercise. Perception of the intensity of physical effort at submaximal and peak exercise was obtained using the Borg category scale (6–20) [12].

Metabolic data were gathered from standard cardiopulmonary exercise training systems which include a computer assembly for breath-by-breath and on-line 60-second calculations of oxygen consumption ($\dot{V}O_2$; ml/kg/min or METs), minute ventilation (VE), carbon dioxide production ($\dot{V}CO_2$), and respiratory exchange ratio (RER; $\dot{V}CO_2/\dot{V}O_2$). Before each test, the pneumotachometer was referenced according to manufacturer specifications, and the gas analyzers were calibrated with a certified air mixture representing room air (21% O_2 and balance nitrogen) and certified oxygen/carbon dioxide concentrations.

The V-slope method, used by experienced investigators at the HF-ACTION core lab, was applied to determine the ventilatory-derived anaerobic threshold (i.e. the break point in linearity when $\dot{V}CO_2$ was plotted as a function of $\dot{V}O_2$), expressed as a percentage of the peak $\dot{V}O_2$. This method has been reported to be a sensitive, reliable, noninvasive technique for the detection of the onset of metabolic acidosis [13, 14]. The peak $\dot{V}O_2$ was defined as the highest $\dot{V}O_2$ value for a given 15- or 20-second interval within the last 90 s of exercise or the first 30 s of recovery [11]. We also computed the slopes of the relation between VE and $\dot{V}O_2$, and between VE and $\dot{V}CO_2$, as markers of breathing economy and functional limitations, respectively.

Calculation of Glomerular Filtration Rate

Measurement of serum creatinine was obtained from the recorded serum creatinine (up to 1 year prior to study enrollment) and performed using the central laboratory at each center. eGFRs (ml/min/1.73 m²) were calculated using the Levey modified Modification of Diet in Renal Disease formula [$186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$]; calculated values were multiplied by 0.742 for women and by 1.21 for African Americans [7]. Calculated eGFR values were categorized as <30 , 30–59, 60–89, and ≥ 90 ml/min/1.73 m² based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of kidney function; eGFR values <60 ml/min/1.73 m² were considered abnormal and indicative of moderately reduced kidney function.

Statistical Analysis

Baseline characteristics were reported in counts and proportions or means $\pm$ standard deviations as appropriate. The Pearson correlation coefficient was used for bivariate correlations of continuous variables, and the Spearman correlation coefficient was used for bivariate correlations of continuous variables with eGFR category. The Pearson correlation was used to evaluate the bivariate relationship between eGFR and peak $\dot{V}O_2$ as continuous variables. The Cochran-Mantel-Haenszel test was applied to test for trend of categorical variables across eGFR categories. The general linear model was used to evaluate the relevant predictor variables to eGFR as a dependent variable. A p value <0.05 was considered statistically significant.

Table 1. Baseline characteristics, by CKD stage

Characteristic	CKD level					p value for trend
	all	1 (>90)	2 (89–60)	3 (59–30)	4 (29–15)	
Number	2,091	338	947	728	78	
Demographics						
Age, years	59 ± 13	50 ± 13	57 ± 12	65 ± 11	67 ± 12	<0.0001
Age >75 years, %	11	3	6	19	31	<0.0001
Male, %	72	70	73	74	70	0.33
Caucasian, %	61	42	60	71	71	<0.0001
African American, %	33	53	34	24	26	<0.0001
Other race, %	5	5	5	5	4	0.58
Medical history, %						
Hypertension	61	57	59	63	68	0.02
Diabetes mellitus	33	33	26	40	45	<0.0001
Chronic obstructive pulmonary disease	11	7	11	13	13	0.008
Stable angina	26	25	26	28	22	0.53
Prior myocardial infarction	43	27	42	50	53	<0.0001
Prior coronary artery bypass surgery	26	15	22	35	36	<0.0001
Chronic prescribed medications, %						
Angiotensin-converting enzyme inhibitors	74	81	75	71	65	0.0001
ARB	24	20	23	27	22	0.04
Spironolactone/eplerenone	46	45	48	45	35	0.16
β-Blockers	95	96	95	94	95	0.19
Nitrates	25	18	23	30	32	<0.0001
Calcium channel blockers	7	7	7	7	3	0.77
Loop diuretics	79	70	76	87	88	<0.0001
Digoxin	46	46	45	48	35	0.92

CKD level: based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative stage in eGFR, expressed as ml/min/1.73 m² (figures in parentheses). ARB = Angiotensin II receptor blocker. Please note that CKD stages 1 and 2 were not confirmed by the presence of markers of kidney damage.

Results

Baseline Characteristics

The demographics for the study sample (n = 2,091) were as follows: age 59 ± 13 years (range 19–90); 72% male; 61% Caucasians, 33% African Americans, and 5% others. Of note, those with advanced CKD were more likely to be Caucasians than African Americans, consistent with a multinational population including Canadian and European sites. Risk factors for HF or CKD included: history of hypertension in 61%, diabetes in 33%, and myocardial infarction in 43%. The baseline characteristics stratified by eGFR level are shown in table 1. Those with advanced CKD tended to be older, and more commonly had higher rates of expected risk factors for both HF and CKD, including hypertension and diabetes. In addition, advanced CKD patients were more likely

to have had a prior myocardial infarction or have undergone coronary artery bypass surgery (p < 0.0001 for both).

Clinical Examination Variables

Table 2 summarizes the baseline clinical examination variables. Of note, patients had blood pressures that were in the normal range, averaging 114/70 mm Hg. There were no differences in baseline systolic blood pressures across the CKD groups. The severity of HF symptoms as reflected in the NYHA functional classification and the objective impairment in 6-min walk distance tended to be greater in those with reduced eGFR. The degree of left ventricular systolic impairment and dilation tended to be lower across the groups by declining eGFR.

Table 2. Clinical examination variables, by CKD stage

Characteristic	CKD level					p value for trend
	all	1 (>90)	2 (89–60)	3 (59–30)	4 (29–15)	
Number	2,091	338	947	728	78	
Physical exam						
BMI	31 ± 7	33 ± 9	31 ± 7	30 ± 6	29 ± 7	<0.0001
Heart rate, bpm	71 ± 12	73 ± 12	71 ± 12	70 ± 10	68 ± 10	0.0001
Systolic blood pressure, mm Hg	114 ± 18	116 ± 18	113 ± 18	114 ± 19	115 ± 20	0.26
Diastolic blood pressure, mm Hg	70 ± 11	73 ± 12	71 ± 11	69 ± 11	69 ± 11	<0.0001
Euro QOL	65 ± 20	66 ± 19	66 ± 19	64 ± 20	68 ± 17	0.54
NYHA class (2/3/4), %	63/36/1	70/30/1	67/32/1	56/42/1	52/45/3	<0.0001
CCS class (0/1/2/3+4), %	84/9/6/2	84/9/5/1	82/9/6/2	82/9/7/2	88/4/4/4	0.88
6-Min walk distance, feet	365 ± 105	384 ± 99	376 ± 103	342 ± 104	320 ± 88	<0.0001
Echocardiogram						
LVEF, %	25 ± 7	26 ± 8	25 ± 8	25 ± 7	25 ± 7	0.03
LVIDD, cm	6.6 ± 1.2	6.7 ± 1.2	6.6 ± 1.2	6.6 ± 1.2	6.7 ± 1.3	0.88
Laboratories						
Creatinine, mg/dl	1.3 ± 0.8	0.8 ± 0.1	1.1 ± 0.2	1.6 ± 0.3	3.8 ± 2.8	<0.0001

CKD level: based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative stage in eGFR, expressed as ml/min/1.73 m² (figures in parentheses). BMI = Body mass index; QOL = quality of life; CCS = Canadian Cardiovascular Society angina class; LVEF = left ventricular ejection fraction, LVIDD = left ventricular internal diastolic diameter. Please note that CKD stages 1 and 2 were not confirmed by the presence of markers of kidney damage.

Table 3. Results from cardiopulmonary stress tests

Characteristic	CKD level					p value for trend
	all	1 (>90)	2 (89–60)	3 (59–30)	4 (29–15)	
Number	2,091	338	947	728	78	
Resting HR, bpm	71 ± 11	73 ± 12	71 ± 12	70 ± 10	68 ± 10	0.0001
Exercise duration, min	9.8 ± 4.0	10.6 ± 4.1	10.4 ± 4.0	8.6 ± 3.5	7.7 ± 3.1	<0.0001
HR at peak exercise, bpm	120 ± 22	129 ± 23	123 ± 21	111 ± 20	107 ± 22	<0.0001
Perceived exertion (6–20)	16.6 ± 2.4	16.9 ± 2.3	16.6 ± 2.5	16.5 ± 2.4	15.9 ± 2.5	0.002
Peak respiratory exchange ratio	1.09 ± 0.11	1.08 ± 0.11	1.09 ± 0.11	1.09 ± 0.12	1.11 ± 0.11	0.03
Time to RER = 1.0, min	7.8 ± 3.2	8.5 ± 3.3	8.3 ± 3.1	6.8 ± 3.0	5.9 ± 2.4	<0.0001
Peak VO ₂ , ml/kg/min	14.9 ± 4.7	15.9 ± 4.6	15.7 ± 4.9	13.5 ± 4.1	11.7 ± 3.2	<0.0001
Peak VO ₂ <14.0 ml/kg/min, %	46	37	38	59	78	<0.0001
VO ₂ at anaerobic threshold, ml/kg/min	10.8 ± 2.7	11.3 ± 2.6	11.1 ± 2.7	10.0 ± 2.4	9.0 ± 2.3	<0.0001

CKD level: based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative stage in eGFR, expressed as ml/min/1.73 m² (figures in parentheses). HR = Heart rate; Please note that CKD stages 1 and 2 were not confirmed by the presence of markers of kidney damage.

Fig. 1. Box plot of eGFR and peak VO₂ levels obtained at baseline across CKD groups. IQR = Interquartile range.

Fig. 2. Stacked bar graph showing the cumulative frequency per 1,000 subjects of high-risk features stratified by eGFR category.

Fig. 3. Median number of high-risk features stratified by eGFR category.

Glomerular Filtration Rate and Cardiopulmonary Exercise Test Results

The results of the baseline cardiopulmonary exercise tests, including the mean peak VO₂ values per level of eGFR, are shown in table 3. The mean peak VO₂ was lower in a graded fashion over cohorts of declining eGFR. In those categories with eGFR <60 ml/min/1.73 m², the mean peak VO₂ values were consistently lower than the population (n = 2,091) median (14.3 ml/kg/min). The

mean peak RER was similar across groups, suggesting comparable somatic anaerobiosis and volitional fatigue. The VO₂ at the anaerobic threshold and the time to RER = 1.0, however, were both modestly lower in the cohort with the most severely reduced renal function. Figure 1 displays a box plot of the peak VO₂ results according to the eGFR category. The Pearson correlation between eGFR and peak VO₂ was 0.22 (p < 0.0001). Age was inversely correlated with both eGFR (r = -0.44, p < 0.0001) and peak VO₂ (r = -0.27, p < 0.0001).

Clustering of High-Risk Features

Figure 2 shows the relative cumulative frequency per 1,000 of high-risk features including peak VO₂ <14 ml/kg/min, age >75 years, diabetes, and functional class 3-4 symptoms. The relative proportions of older age and peak VO₂ <14 ml/kg/min increased in a graded fashion over the lower eGFR categories and were the 2 most frequent high-risk characteristics among those with an eGFR <60 ml/min/1.73 m². Figure 3 gives the median number of high-risk conditions in patients according to the eGFR category. Among those with eGFR <30 ml/min/1.73 m², 89% of the subjects had at least 1 high-risk characteristic, and 15% of the subjects had all 4 high-risk features. The highest NYHA class (mean 2.68) characterized those who were in both the lowest peak VO₂ quartile (≤11.3 ml/kg/min) and the eGFR category (<30 ml/min/1.73 m²).

Independent Associations with Significant CKD

Using multiple logistic regression, only age (OR = 1.05 per year increase, 95% CI 1.03–1.08, $p < 0.0001$) and peak VO_2 (OR = 1.18 per 1 ml/kg/min decrease, 95% CI 1.09–1.25, $p < 0.0001$) were independently associated with a baseline eGFR < 30 ml/min/1.73 m² (stage 4 and higher CKD). When eGFR was modeled as a continuous outcome variable, older age, lower peak VO_2 , lower left ventricular ejection fraction, higher NYHA functional class, and African American race were all found to be statistically significant ($p < 0.05$). The overall R^2 for the model was 0.23, which can be interpreted as indicating that 23% of the variability in renal filtration function was explained by differences in baseline variables.

Discussion

We found that reduced renal function was modestly associated with lower peak VO_2 in this baseline analysis. This relationship was highly driven by age as there was a 17-year difference between the highest and the lowest eGFR categories. We believe that cardiac function, more than underlying pulmonary disease, accounted for the severely reduced peak VO_2 values, given that 85% of the subjects had no history of chronic obstructive lung disease and all had symptomatic HF. Holding age constant in the multivariate analysis, peak VO_2 was independently associated with reduced eGFR. The VO_2 at the anaerobic threshold and the time to RER = 1.0 were progressively lower as renal function worsened, suggesting that uremia may be related to insufficient oxygen delivery to activate muscles and the associated lactic acidemia. We do not have published reports of expected cardiopulmonary test results in patients with CKD but normal cardiac function to make comparisons. The categories of eGFR according to the National Kidney Foundation stages of CKD segregated patients into groups with a graded increase in the number and cumulative frequency of combined high-risk features, including older age, diabetes, more severe symptoms, and lower cardiorespiratory fitness. Importantly, significant CKD was independently associated with multiple variables that are associated with increased mortality in patients with HF. We did not have the etiology of CKD recorded and cannot make conclusions on whether one form of CKD is different from another. Nonetheless, these data are consistent with the notion that CKD is a high-risk state for patients with HF and represents a complicated clustering of factors that are related to all-cause mortality [15].

Reduced renal filtration function is associated with salt and water retention and chronic volume overload which may exacerbate HF symptoms. Indeed, those with the most impaired renal function and the lowest peak VO_2 had the highest physician-assigned NYHA class and the worst HF symptoms. These patients may indeed have the presence of a chronic cardiorenal syndrome, where either the HF worsens kidney function (type 2) or vice versa (type 4) [16]. In cardiorenal syndromes, uremia may play an additional role in reducing myocardial contractility and systolic performance [17]. Metabolic acidosis associated with progressive renal failure also plays a role in the impairment of cellular transport of electrolytes and oxygen, which affects cardiovascular and cellular functions [18]. Hormonal anomalies in CKD include reduced levels of 1,25-dihydroxyvitamin D and erythropoietin, both of which have been implicated in left ventricular remodeling and HF [19, 20]. Lastly, CKD is associated with increased markers of inflammation and oxidative stress [21, 22]. Although the clinical significance of these indicators in HF remains unclear, it appears that in those patients with the lowest eGFR, both inflammation and oxidative stress may serve to worsen symptomology and functional capacity. Collectively, these pathologic changes may be responsible, at least in part, for the impaired exercise tolerance in patients with the most compromised eGFR. It has been observed that in end-stage renal disease patients with left ventricular impairment, renal transplantation results in an increase in left ventricular ejection fraction from 32 to 52% and improved functional status, suggesting that CKD is playing a reversible role in the depression of cardiopulmonary performance [23].

We recognize that age is an important confounder for the eGFR measurement (part of the estimating equation) and for peak VO_2 (10% per decade decline seen in normal aging) [24]. Age was correlated with both measures in our study, suggesting that the senescent decline in both cardiorespiratory and renal function may play a role in the progression of adverse left ventricular remodeling and attendant HF symptoms [25, 26]. Importantly, the triad of older age, low functional capacity, and reduced renal filtration may identify a particularly frail population that is more prone to medication adverse events, complications during hospitalizations, and a greater susceptibility to mortality with major adverse events over the natural history of HF [27–29]. The rates of β -blocker use were high (approx. 95%) and similar ($p = 0.019$) across the eGFR groups and, hence, were unlikely to confound the results. Our data support this notion to some degree with lower rates of angiotensin-converting en-

zyme inhibitors and higher rates of myocardial infarction and bypass surgery in those with reduced renal function at baseline.

Our study has all the limitations of a cross-sectional analysis from a large randomized trial. Selection bias for entry into the trial invariably yielded a younger and more robust group of HF patients than those normally seen in clinical practice. Our subjects were further restricted to having systolic HF, thus, we cannot generalize our findings to those with pure diastolic HF. Serum creatinine was obtained from clinical records and not measured in a core lab, hence, differences in assay types and standardization invariably contributed to variation in eGFR. Unfortunately, we did not measure arterial blood gas values, levels of vitamin D, or erythropoietin. Moreover, we did not address the complicated issue of anemia, CKD, and HF severity, and did not include hemoglobin in the present analysis, since it has been reserved for future manuscripts. Lastly, we did not have advanced biologic measures of inflammation and oxidative stress or other bio-

markers to elucidate the pathophysiologic mechanisms relating chronic failure of both the heart and kidneys [30].

Conclusion

Reduced renal filtration function is associated with a markedly impaired functional capacity and a clustering of high-risk features in systolic HF patients which portend a more complicated course and higher all-cause mortality.

Acknowledgements

Gregg C. Fonarow is a consultant/honorarium recipient from Novartis (significant), and a honorarium recipient from Merck-Schering Plough (significant). The study was supported/funded by the National Institutes of Health, National Heart, Lung and Blood Institute.

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