Original Paper

Estimated Glomerular Filtration Rate and 6-Minute Walk Distance in African Americans with Mild to Moderate Heart Failure

Karen M. Vuckovic · Houry Puzantian

Department of Biobehavioral Health Science, University of Illinois at Chicago College of Nursing, Chicago, IL, USA

Keywords

Heart failure · Kidney disease · Functional capacity · Six-minute walk test

Abstract

Background/Aims: The 6-minute walk test is a measure of functional capacity in patients with heart failure (HF) or chronic kidney disease (CKD). The association between estimated glomerular filtration rate (eGFR) and 6-minute walk distance (6MWD) has not been investigated in African-Americans (AA), despite them having a higher incidence of CKD and chronic HF. Thus, our aim was to determine if eGFR was an independent predictor of 6MWD in AA >50 years of age with HF. **Methods:** In this cross-sectional study, we examined the relationship between eGFR and 6MWD in 45 AA patients with HF from an urban outpatient HF clinic, using logistic regression with bootstrapping. **Results:** The sample consisted of 53% females; mean age = 64.8 ± 9 years, mean eGFR = 61.6 ± 20 mL/min/1.73 m², and mean 6MWD = 222 ± 78 m. A decrease in eGFR by 10 mL/min/1.73 m² was associated with 46% higher odds ($p = 0.02$) of a 6MWD ≤ 200 m in an unadjusted model and 39–41% higher odds ($p = 0.03$) of a 6MWD ≤ 200 m in adjusted models. **Conclusion:** A decrease in eGFR significantly predicted a shorter 6MWD in AA patients with HF. Therefore, a reduction in eGFR may be used as an early marker to identify and manage declining functional capacity in these patients.

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Introduction

African-Americans (AA) are more likely to develop severe heart failure (HF) with renal insufficiency or chronic kidney disease (CKD) as a comorbidity [1, 2]. Often chronic HF in AA is not preceded by myocardial infarction; rather HF arises due to hypertension, diabetes, and renal insufficiency [3–5].

Houry Puzantian, PhD, MSc, MTR
University of Illinois at Chicago College of Nursing (MC 802)
845 S. Damen Ave
Chicago, IL 60618 (USA)
E-Mail houry@uic.edu

Patients with either HF or CKD may experience a significant decline in functional capacity, which impacts their ability to perform activities of daily living such as walking [1, 6]. The assessment of functional capacity, as measured by the 6-minute walk test (6MWT), has provided important diagnostic and prognostic information in both the setting of HF and CKD [7–9]. To our knowledge, the relationship between kidney function and functional capacity has not been determined in AA patients with chronic HF. Data support a relationship, in that Stanojevic et al. [10] investigated estimated glomerular filtration rate (eGFR) in relation to functional capacity in 127 HF patients (70% European male, >65 years of age) and found that eGFR correlated with 6-minute walk distance (6MWD; $r = 0.390$, $p < 0.01$). However, in multiple regression, only age significantly predicted 6MWD <300 m [10]. Because of the well-known cardiorenal interaction and high prevalence of CKD among AA patients with HF, it is important to determine if there is an association between eGFR and functional capacity using parameters that are routinely measured and monitored in the clinical setting. Therefore, the aims of this investigation were to (1) examine the association between eGFR and 6MWD in AA patients with HF and (2) determine if eGFR predicts 6MWD. If eGFR is associated with 6MWD in AA patients with stable HF, then eGFR may provide additional information to identify patients with declining functional capacity and guide the development of interventional studies to preserve function.

Material and Methods

The current analysis is a secondary aim of a study which examined activity-induced dyspnea in AA with HF as a primary outcome [11]. This study was approved by the Office of Protection of Research Subjects and the Institutional Review Board. HF was defined by ejection fraction (EF) derived from echocardiographic data (reduced [HF_rEF] <40%; preserved [HF_pEF] >50%). Inclusion and exclusion criteria are reported elsewhere [11]. In short, participants with established stable HF recruited from a single HF clinic performed a 6MWT. Patients were instructed to walk back and forth along a flat 100 foot surface at a self-determined pace for 6 min, according to the American Thoracic Society (ATS) recommendations [12]. Demographics and health information data were obtained from the medical record, collecting values to the date closest to the day of the 6MWT. For the current study, we determined eGFR using the creatinine-based CKD Epidemiology Collaboration equation (CKD-Epi creatinine) [13, 14]. CKD-Epi creatinine-based eGFR values are deemed less biased and more precise than eGFR calculated by the Modified Diet in Renal Disease (MDRD) equation, with a significantly greater percentage of eGFR values found to be within 30% of measured GFR using the CKD-Epi creatinine equation versus the MDRD. CKD-Epi creatinine-based eGFR also outperforms MDRD-based eGFR in risk prediction for adverse outcomes in patients with HF [15].

Data analyses were conducted using IBM SPSS version 22 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics included demographics and clinical characteristics. For continuous variables, means, medians, and standard deviations were determined; for categorical variables, frequencies and percentages were determined. Independent t tests and χ^2 tests were performed to compare characteristics of patients with 6MWD ≤ 200 m and those with 6MWD >200 m, a cut-point previously found to be prognostic in AA with HF [16]. Since males are known to have a greater 6MWD, we also examined the data by sex. Logistic regression modeling was performed to determine the relationship between eGFR and functional capacity; 6MWD was used as a binary outcome (cut-point 200 m). Variables significant at the 0.05 level in bivariate correlations and conceptually related to the 6MWT were used in the adjusted models.

Results

Baseline Characteristics

Baseline characteristics for the total sample and by 6MWD category are shown in Table 1. An equal percentage of males and females participated, ranging from 50 to 88 years in age. All patients were on guideline-directed pharmacotherapy. The majority of patients with a 6MWT >200 m were prescribed diuretics. Systolic blood pressure ranged from 90 to 160 mm

Table 1. Baseline characteristics by distance walked

Characteristics	Total sample (n = 45)	6MWD ≤200 m (n = 18)	6MWD >200 m (n = 27)	p value
Age, years	64.8±9	63±9	67.6±9	0.09
Female gender	24 (53.3)	11 (61.1)	13 (48.2)	0.40
Weight, kg	98.1±27	90.5±23	103±28.1	0.12
Height, cm	169.4±10	167.8±3	170.6±2	0.38
BMI ≥30	27 (60)	10 (55.6)	17 (63)	0.26
Diabetes	14 (31)	6 (33.3)	8 (29.6)	0.80
Current smoking	14 (31)	5 (27.8)	9 (33.3)	0.69
ACE/ARB	38 (84.4)	15 (83.3)	23 (85.2)	0.86
Beta blocker	45 (100)	18 (100)	27 (100)	1.00
Diuretics	33 (73.3)	10 (55.6)	23 (85.2)	0.03
CCB	13 (28.9)	6 (33.3)	7 (25.9)	0.59
Statins	30 (66.7)	15 (83.3)	15 (55.6)	0.53
Sodium, mmol/L	139.7±2	140±2	139±3	0.07
Potassium, mmol/L	4.2±0.5	4.4±0.6	4.2±0.5	0.27
BUN, mg/dL	19±10	22±14	18±6	0.27
Creatinine, mg/dL	1.3±0.4	1.45±0.5	1.26±0.3	0.14
Glucose, mg/dL	119±46	141±58	104±29	0.01
eGFR, mL/min/1.73 m ²				
by CKD-Epi creatinine	61.6±20	53.8±17	66.7±20	0.03
Hb, g/dL	12.7±1.0	12.59±1.6	12.77±1.2	0.67
Mean EF, % (n = 45)	40.8±17	43±18	39±15	0.43
Systolic BP, mm Hg	126±19	129±23	124±17	0.46
Diastolic BP, mm Hg	72±13	71±13	73±13	0.66
Heart rate, beats/min	65±9	67±7	64±10	0.35
FEV ₁ , L	1.6±0.6	1.5±0.6	1.6±0.6	0.33
Respiratory rate, breaths/min	16±2	16±2	16±2	0.86
6MWD, m	222±78	150±39	270±60	0.001
Borg score	0±1.5	0.92±1.3	0.96±1.7	0.92

Data are mean ± SD or n (%). n = 44 for Hb and FEV₁. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FEV₁, forced expiratory volume (in first second after taking a deep breath); Hb, hemoglobin; 6MWD, 6-minute walk distance.

Hg and diastolic blood pressure ranged between 40 and 98 mm Hg. All had hypertension; 40% had atrial fibrillation. The mean EF for patients with HFpEF was 57.5 ± 5% and 27.2 ± 7% for HFrEF patients. There were no differences in eGFR by HF type: eGFR_{HFpEF} = 61.9 ± 23 mL/min/1.73 m² versus eGFR_{HFrEF} = 61.3 ± 18 mL/min/1.73 m². Creatinine values were elevated (1.26 ± 0.5 mg/dL in females vs. 1.43 ± 0.3 mg/dL in males) and 51% of the sample had an eGFR <60 mL/min/1.73 m². Compared to males, females had significantly lower hemoglobin levels (12.3 ± 1 vs. 13.2 ± 1.5 g/dL, p = 0.02), forced expiratory volume in 1 s (1.30 vs. 1.86 L, p = 0.001), and shorter 6MWD (197.6 vs. 250 m, p = 0.03). The only significant group differences by 6MWD (≤200 vs. ≥200 m) were a lower eGFR, less diuretic use, and higher glucose levels in the 6MWD ≤200 m group (Table 1). Walk distance did not differ by HF type (HFpEF = 215.5 ± 81.3 m vs. HFrEF = 226.8 ± 78.1 m, p = 0.63).

Association between eGFR and 6MWD

Age, eGFR, and heart rate significantly correlated with 6MWD. Since the normality of the sampling distribution was uncertain, bootstrapped resampling was applied (as a nonpara-

Fig. 1. Scatter plot of estimated glomerular filtration rate (eGFR) and 6-minute walk distance.

Color version available online

Table 2. Association of estimated glomerular filtration rate (eGFR) and 6-minute walk distance ($n = 45$)

Model	β for eGFR	Standard error	OR	p value	Confidence interval
Unadjusted	−0.038	0.02	0.96	0.02	0.93, 0.98
Model 1	−0.033	0.02	0.97	0.03	0.94, 0.98
Model 2	−0.034	0.02	0.97	0.03	0.93, 0.98

Unadjusted model includes eGFR by CKD-Epi creatinine. Model 1 adjusts for age and gender. Model 2 adjusts for age, gender, and heart rate.

metric approach; $n = 45$) to logistic regression, with $n = 1,000$ [17] and seed number = 2,000,000 for improved accuracy of estimates. In our models, a higher eGFR was associated with greater functional capacity (≥ 200 m; Table 2). More specifically, our analysis indicates that a decrease in eGFR of 10 mL/min/1.73 m² was associated with 46% higher odds of 6MWD ≤ 200 m in an unadjusted model, and 39% (model 1) and 41% (model 2) higher odds of 6MWD ≤ 200 m in adjusted models.

We also examined associations among sex, eGFR, and 6MWD; sex did not moderate the relationship between eGFR and 6MWD. As expected, females who had an eGFR ≥ 60 mL/min/1.73 m² had a shorter 6MWD compared to males within the same eGFR category ($p = 0.04$); however, no sex differences were noted in 6MWD in those with eGFR < 60 mL/min/1.73 m².

Finally, we explored whether there was a nonlinear relationship between eGFR and 6MWD; a sigmoidal curve best represented the nonlinear relationship between eGFR and 6MWD ($R^2 = 0.44$, $p = 0.003$) in patients with a 6MWD ≤ 200 m (see Fig. 1). There was no clear relationship between eGFR and 6MWD among patients who walked 6MWD > 200 m.

Discussion

To the best of our knowledge, this is the first study to conduct an in-depth examination of the relationship of eGFR and 6MWD in AA with stable HF. Our major finding is that a lower eGFR was associated with higher odds of 6MWD < 200 m in AA patients with HF over 50 years

of age. Similarly, Alahdab and colleagues [16] found that AA patients hospitalized with HF who walked a shorter distance were more likely to have an eGFR <60 mL/min/1.73 m² by the MDRD equation and to be female and older (59.4 vs. 50.3 years). European investigators also reported significant correlations between eGFR and 6MWD in patients >65 years of age (mean age = 72.5 ± 5 years); however, contrary to our study, they did not find eGFR to be a predictor of 6MWD [10]. Importantly, our study participants were AA and younger (mean age = 64.8 ± 9 years). Apart from the fact that the study populations differed by race, the observed difference by age suggests that an eGFR-related decrease in 6MWD may be more prominent in younger versus older patients; older patients may already be experiencing an age-related decline in functional capacity. Future studies should examine the association between eGFR and 6MWD across different racial groups of age-matched HF patients.

Patients with early stage CKD are known to have lower functional capacity than healthy individuals [18]. In the subanalysis we conducted on mild to moderate CKD (stage 1–3), only patients with eGFR >30 mL/min/1.73 m² ($n = 44$) were included. A 10 mL/min/1.73 m² decrease in eGFR was associated with 41% higher odds of a 6MWD ≤ 200 m ($\beta = -0.034$, OR = 0.966, $p = 0.05$) in unadjusted analysis. However, eGFR did not predict 6MWD in adjusted models in this subsample. In the subanalysis, one 64-year-old female patient who completed the parent study was excluded. This excluded patient had the highest BMI (51.7), a relatively low hemoglobin level (10.5 g/dL), and the highest EF (67.5%) in the original sample. As eGFR was not a predictor of 6MWD in the above-mentioned subsample (in adjusted models), the results of the subanalysis further support our hypothesis that lower eGFR predicts shorter 6MWD. These findings highlight the need for upcoming studies to include larger numbers of HF patients with eGFR <30 mL/min/1.73 m².

In the total sample of 45 patients, we found no sex differences using the 200-m cut-point for the 6MWD, contrary to Alahdab et al. [16]. However, within the eGFR ≥ 60 mL/min/1.73 m² group, the mean 6MWD was significantly shorter for females than males; anthropomorphic variation (height and skeletal muscle mass) could account for differences [7]. The fact that no sex difference was noted in the eGFR <60 mL/min/1.73 m² group could be due to the overall synergistic adverse effect of CKD and HF on functional capacity in this group.

The exact mechanisms by which eGFR may reduce functional capacity in patients with HF are not clear. Higher eGFR reflects better health status. As eGFR declines and kidney disease progresses, one expects metabolic/catabolic perturbances to interfere with functional capacity [18]. When evaluating the effect of eGFR on functional capacity in this population, one must consider mechanisms related to the cardiorenal crosstalk. In HF, reduced renal perfusion increases norepinephrine release from renal efferents, causing renin release, activation of the renin-angiotensin-aldosterone system (RAAS), and sodium and water retention [19]. At the time of our study, patients were clinically stable, euvolemic, and on guideline-directed therapy for 3 months. The majority of patients who were prescribed diuretics (known RAAS activator) had a 6MWD >200 m. Future research with a larger sample is needed to examine the relationship between diuretic dose and walk distance. In terms of increased afferent nerve firing, an associated increase in central sympathetic drive [19] contributes to increased heart rate and myocardial oxygen consumption. We found that heart rate inversely correlated with 6MWD ($r = -0.3$, $p = 0.05$); all patients were on beta blockers (mean baseline heart rate = 65 ± 9 beats/min).

The underlying pathologies associated with HFpEF and HFrEF differ, but prevalence of kidney dysfunction is similar in both patient groups; there were no differences in mean eGFR by HF type in our study. Notably, HF and CKD share some pathological derangements. Both HF and CKD are associated with molecular processes such as inflammation and oxidative stress, which promote cell injury, endothelial dysfunction, and disease progression. Recently,

mitochondrial dysfunction has been identified as a source of oxidative stress with particular importance in patients with cardiac and kidney disease [20, 21]. Collectively, these processes may damage skeletal muscle and induce limitations in functional capacity [22]. Moreover, patients with HF and CKD experience common comorbidities such as hypertension. In our sample, all participants were known to be hypertensive. Finally, other sample characteristics, such as smoking, asthma, anemia, and atrial fibrillation, could contribute to reduced 6MWD.

This study exhibits several strengths. Our sample was half female and included HFpEF patients. We used the relatively new CKD-Epi creatinine equation in estimating kidney function [15]; others used the MDRD. Also, we used a bootstrapping approach in statistical modeling to improve accuracy of inference.

Limitations of the Study

Certain limitations should be acknowledged relative to our findings. We exclusively recruited a small, convenience sample of AA from one clinic; thus, results are not generalizable. For future studies, larger samples would allow the detection of group differences in multivariate analysis. Moreover, recruitment should include a greater number of patients with severe CKD (stage 4). This was a cross-sectional study, and eGFR reflects a one-time estimate of kidney function. Longitudinal studies will be able to capture how change in eGFR would be associated with 6MWD.

Conclusions

Commonly, HF patients limit physical activity to avoid symptom occurrence; thus, changes in functional capacity may go undetected and untreated. Therefore, eGFR may be an important early objective marker to screen and identify HF patients with declining functional capacity who would benefit from increased physical activity. In addition to routinely monitoring eGFR, health care providers need to promote adherence to long-term renoprotective measures, which may help preserve functional ability in this population. This may require collaborative efforts between healthcare providers in cardiology and nephrology.

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Statement of Ethics

All subjects have given their informed written consent and the study protocol was approved by the PIs institutional review board. The research was ethically conducted in accordance with the World Medical Associations Declaration of Helsinki.

Disclosure Statement

The authors have no conflict of interest to disclose.

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