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The 6-Minute Walk is Associated With Frailty and Predicts Mortality in Older Adults With Heart Failure

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The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure

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Abstract

Introduction—HF may contribute to the development of functional decline and frailty in older adults.

Methods—Sixty HF patients with EF ≤ 40% evaluated in 2004–5 were reevaluated in 2008. Six-minute walk distance (6MW), frailty score, and biomarkers (25-hydroxyvitamin D, C-reactive protein and interleukin-6[IL6]) were measured. Participants were categorized at baseline and follow-up into 3 groups: non-frail/normal endurance (NF/NE), non-frail/low endurance (NF/LE) and frail/low endurance (F/LE). Survival time was assessed according to frailty/endurance status and associated predictors of mortality.

Results—Forty-three men, 17 women (mean age 78±12) were contacted. At follow up 20 died, 20 participated and 20 did not participate. There were no changes in frailty/endurance status over time (McNemar; p=0.19). Deaths occurred in 18% of NF/NE, 45% of NF/LE and 60% of F/LE. NF/NE had greater survival rates than NF/LE (p=.032) and F/LE (p=.014). The 6MW and frailty score were independently predictive of mortality with hazard ratio.82(.72–.94) and 1.64(1.19–2.26) respectively, as was NYHA and IL6. Backward stepwise Cox- regression revealed that 6MW and frailty each were associated with mortality (p=0.005) and highly correlated.

Conclusions—Physical function is an important predictor of mortality in older adults with HF. The 6MW may be useful as a measure of frailty.

Introduction

Heart failure is the most rapidly increasing cardiovascular disease in the US and the primary discharge diagnosis for Medicare recipients. There are approximately 5.7 million people who have the diagnosis of HF in the US.[1] Heart failure constitutes the most common cause for re-hospitalization and has been identified by the Medicare Payment Advisory Commission as the highest cost to the healthcare system.[2, 3] Hospitalizations of older patients can result in functional deterioration leading to dependency and disability.[4, 5] Due to the unpredictable trajectory of heart failure exacerbations it is difficult to discern which

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patients are at the greatest risk for repeat hospitalizations, functional decline and mortality. The frailty syndrome defined as a poor ability to cope with physiological stress, has demonstrated a strong association with a diagnosis of heart failure in observational studies.[5–9] Frail patients with or without heart failure often experience functional decline and have an increased risk of death compared to their more robust counterparts. The difficulty has been to identify patients who are frail in order to increase resources available to these patients in hopes of improving health outcomes. There is no direct clinical test to measure frailty, and the challenge is to identify proxy measures which can serve as an indicator of this vulnerable state. Since heart failure and frailty have an association, patients with heart failure are an ideal population to study to further understand frailty.

We have previously found an association between frailty, poor endurance, vitamin D, and C-reactive protein in a cross-sectional analysis of patients with heart failure.[10] This study is a 4 year follow up of the original cohort of patients to determine if measures of frailty and endurance are useful predictors of outcomes in older patients with heart failure.

Methods

The study was reviewed and approved by the Institutional Review Board at the University of Connecticut Health Center (UCHC). Participants were recruited from UCHC Heart Failure Center. Informed consent was obtained from each participant. Baseline inclusion criteria included patient's age ≥ 60 years with heart failure who received their care in a heart failure program and an ejection fraction (EF) of ≤ 40% measured by echocardiogram, cine angiography, or radionuclide angiography within the preceding year. Patients were excluded at baseline if they had serious end stage disease of another organ system, disorders that greatly affected ambulation, and hormonal therapy known to affect muscle function. Exclusion criteria included: metastatic, active, or advanced cancer, active chemotherapy, radiation treatment, or hormonal therapy, systemic rheumatologic or connective tissue disorders, consumption of more than three alcoholic drinks per day, use of androgen, estrogen, DHEA, or hormone receptor antagonists in the preceding year, or had advanced liver disease, renal disease requiring dialysis, Parkinson's disease, an inability to ambulate, or a myocardial infarction within three months prior to the study.

Frailty Phenotype Score

The Frailty Phenotype score (frailty score)5, a multi-domain research tool to quantify frailty was selected because it was validated in a large population of community dwelling older adults (≥ age 65 years) from the Cardiovascular Health Study. The frailty score was found to overlap measures of disability and co-morbidity but also independently predicted disability, hospitalization and death over 3 years. The frailty score includes self-reported weight loss of ≥ ten pounds in the preceding year, grip strength measured by hand-held Jamar dynamometer, sense of exhaustion as evaluated by two questions from the Center of Epidemiologic Studies-Depression Scale,11 walking speed by an 8-foot walk, and level of physical activity reported in kcals/week from the Physical Activity Scale in the Elderly (PASE).12 The scoring of each measure according to cut-off values to determine the total frailty score is described elsewhere.5 The results of the tests were dichotomized to identify non-frail (NF) with 0–2/5 characteristics, or frail (F) with ≥ 3 characteristics.

6- Minute Walk

The 6-minute walk test protocol was performed as previously published.[13] Participants were permitted to use a walker or cane if needed while the observer recorded symptoms such as chest pain, shortness of breath or leg pain. Participants were categorized into two groups according to the performance on the test. Those walking ≤ 300 meters were classified as

having low endurance (LE), and those walking > 300 meters were classified as normal endurance (NE). The cutoff of 300 meters was chosen because of its use as a cutoff in SOLVD (Studies of Left Ventricular Function) as well as others.[14–16]

Biochemical Measurements

Serum was divided into 0.5 ml aliquots and stored at −70°C. Interleukin-6 was measured with an intra-assay CV of 3.4 % and C-reactive protein with an intra-assay variation of 3.3%. Vitamin D as 25-hydroxyvitamin D (25OHD) measurement was measured by enzyme immunoassay (Immunodiagnostic Systems Inc.,Fountain Hills, AZ), with an intra-assay CV of less than 6.6%. The N-Terminal prohormone B-Type Natriuretic Peptide was measured by ELISA (Alpco Diagnsostics, Windham, NH) with an intraassay CV of 5.3%. Blood urea nitrogen, creatinine and hemoglobin were measured in the clinical laboratory of the University of Connecticut Heath Center, Farmington, CT.

Follow up Assessments

Original participants were contacted in 2008. Subjects were re-contacted by letter or during their routine cardiology appointments to consider further participation in the study. Deaths were confirmed by clinical notes and death records. Of the 60 original participants 20 participated in the second assessment, 20 were deceased, and 20 did not participate. Those who participated underwent a frailty score assessment and 6 minute walk test. Participants were reclassified into frailty and endurance subgroups as described above.

Statistical Analysis

Kaplan-Meier method was used to assess survival time distribution according to frailty/endurance status. Status was defined as the 3 category descriptor of frailty and endurance; nonfrail/normal endurance (NF/NE), nonfrail/low endurance (NF/LE), frail/low endurance (F/LE). F/NE (frail/normal endurance) was excluded from the analysis as only one subject fit this category). The time to event or survival time was calculated as the number of days from the first exam date to the endpoint date. Death was defined as the primary endpoint, while censored events were the dates participants were contacted for follow up assessments. Subjects without follow-up contact were verified as living and a mean date of the participating subjects' dates was added as an endpoint. Log rank pairwise comparison tests were used to detect differences in survival time (days) between each of the 3 frailty/endurance status categories. Univariate Cox regression models, adjusted for age, were used to detect if vitamin D, CRP levels, ischemia, hemoglobin, creatinine, ejection fraction heart history, NTproBNP, NYHA classification and interleukin 6 were associated with survival time. Based only on significant predictors of mortality from the univariate models, we performed a multivariate Cox regression model including age (5 year categories), CRP levels, NYHA classifications, interleukin 6, six minute walk distance (30 meter categories), and frailty score. To adjust for the high collinearity between six minute walk distance and frailty score, each of the latter variables mentioned were included without the other in two separate backwards stepwise Cox regression models. A McNemar test of agreement was used to assess if frailty/endurance status changed from baseline assessments to follow-up. All statistics were evaluated using SPSS 16.0 software (SPSS Inc., Chicago, IL). Significance was noted as p values <0.05.

Results

Twenty deaths were reported of the original 60 heart failure participants prior to study follow-up assessment. Twenty did not participate (4 had serious long term health problems, 3 moved out of state, 13 did not respond to contact). Twenty underwent the 4 year assessment. Individuals who did not participate in the 4 year follow-up visit were not

different in baseline characteristics compared to follow up participants or deceased participants (Table 1). However, non-participants appeared intermediate in frailty score and 6-minute walk distance between deceased subjects compared to 4 year follow-up participants. This did not reach statistical significance.

At baseline, the participants categorized as NF/NE were younger and performed significantly better on all components of the frailty score as well as distance walked in 6 minutes. On average, individuals did not transition from one endurance/frailty category to another (McNemar test; p=0.19; Figure 1).

With regard to mortality, of those characterized as NF/NE at baseline, 18% died, NF/LE 45% died, and F/LE 60% died. (Figure 1) The NF/NE group had significantly longer survival than the other two groups (1481 days; p<.05 for both) by Kaplan Meier analysis. However, the survival time for NF/LE (1219 days) and the F/LE (1222 days) were not different (p = .85) (Figure 2). In univariate analysis, shorter 6-minute walk distance, higher frailty score, higher CRP, higher IL6 levels, and higher NYHA class were significantly associated with higher mortality rates (Table 2). Vitamin D, ischemia, hemoglobin, creatinine, ejection fraction, NTproBNP were evaluated and not associated with mortality. Including only variables that were significant in the univariate analysis, two multivariate backwards stepwise Cox regressions were performed. The 6-minute walk and frailty score were highly negatively correlated, and therefore, collinear in the models (data not shown). In order to account for high collinearity, 6-minute walk and frailty were included in separate models. Increasing one frailty category meant individuals were more than 1.5 times more likely to be deceased (Table 3a). Decreasing walk distance by 30 meters meant individuals were 19% more likely to be deceased. (Table 3b). Each of these factors was important and significant in predicting mortality rates.

Discussion

In this study of 59 older patients with systolic HF, both the frailty score and 6-minute walk distance were independently predictive of mortality. Albeit the HR are small, with the HR for frailty of 1.58 and for the 6-minute walk .84. Many studies in patients with heart failure have shown an association between 6-minute walk distance and mortality.[15, 17, 18] Our work has shown that the frailty score and 6-minute walk were highly correlated (r= −.72), and were in moderate agreement in patients with HF(kappa 0.57, 95% CI = (0.37, 0.77)[19], In Cox regression modeling, the two measures are collinear and likely capture different but overlapping phenomenon. Frailty is a measure of increased vulnerability to adverse outcome and the 6-minute walk is a measure of functional ability and aerobic capacity. These two measures together can theoretically capture the most at risk patients for adverse events and decline in physical function. The Kaplan-Meier curve captures this in the survival analysis; those who are frail combined with low endurance have the highest mortality.

The change over time in this cohort of patients seen in Figure 1 demonstrates that those that remain in the NF/NE at baseline may have the best prognosis. Although 9% of those patients moved to the NF/LE category, our numbers are too small for this to reach statistical significance. Over the 4 year study period we expected more of these patients to decline and move out of the NF/NE category. We were under the assumption that the majority of older patients with heart failure would physically decline. Although, it is unknown if heart failure patients, regardless of age, decline in function over time. Individual specific markers of stability and/or decline may be important in order to design appropriate interventions.

The 6-minute walk distance is a frequently used and easily administered test to assess patients with heart failure. Walk tests are often part of a battery of tests to assess older adults

and have been correlated with multiple domains of function and outcome.[20–22] Interpreting the 6-minute walk with a distance of ≤ 300 meters as a valid measure of frailty may broaden the accessibility of a frailty diagnosis into the cardiologist's office. Recognition of frailty can alert the physician that the patient may benefit from a multidisciplinary geriatric care setting[23] and/or an exercise prescription. To date, exercise is the only accepted frailty "therapy" and may improve the outcome for these patients.[24, 25]

Strategies to reverse the frail state have been an area of intense research. Restoration of physical function through resistance training has shown benefit in frail older adults.24–27 Exercise training in patients with heart failure has been evaluated in multiple small studies[28] and recently in the multi-center HF ACTION trial (A Randomized Controlled Trial Investigating Outcomes of Exercise Training) in 2331 participants. In addition to tolerability and safety of aerobic exercise, the results of the trial included significant improvement in the 6-minute walk distance, and improved health status, but no changes in all cause mortality or hospitalization.[29, 30] Although it is unclear if aerobic exercise has an impact on the frail state, the changes seen early in this study on the 6-minute walk distance are encouraging.

Cross-sectional analysis of this cohort had indicated that the biomarkers CRP and vitamin D were indicative of functional status in patients with heart failure.[10] In longitudinal univariate analysis these measures were predictive of death (as was NYHA class). Although in multivariate analysis, these biomarkers were surpassed by the two functional measures, frailty and the 6-minute walk. This implies that measures of physical function have an important role in predicting outcome in older heart failure patients and should not be forgotten in the wave of serum biomarkers research. This data may suggest that CRP and vitamin D are intermediary markers to the more robust 6-minute walk or frailty markers. Studies of vitamin D in older adults have demonstrated that higher vitamin D levels or repletion with vitamin D are associated with improvement in muscle strength, walking distance, decreased fall frequency and improved balance/body sway.[31–34] Cross-sectional analysis of CRP and functional status established an association between CRP and function, 35 but longitudinal studies of the effects of CRP change on functional status are not available.

Few prospective studies have evaluated frailty in patients with heart failure even though the two syndromes have a well recognized relationship. The majority of frailty research has been in community dwelling older adults, and this research has consistently identified a link between cardiovascular disease and frailty[7, 36]. Caccitore et al. measured frailty in patients with heart failure using the Frailty Staging System. This instrument enlists a multi-domain approach by history and physical exam which can easily be performed in the physician's office. It includes questions to determine ADLs, urinary incontinence, depression, cognitive function and social supports as well as simple physical testing for mobility, vision, and hearing. Although this measure captures multiple domains of function, it does not include any direct measurement of aerobic capacity or endurance. This staging system includes measures that are not routinely used in the cardiologist's office and may be more appropriate in the primary care setting. This frailty measure was found to be a stronger predictive of long term mortality at 9 years in an older cohort of heart failure patients than those without heart failure.[37]

The ability of heart failure participants in the NF/NE group to maintain their function and endurance over the 4 years suggests that this subgroup of individuals may warrant a multi-faceted intervention to maintain physical capacity and reserve. Maintaining and/or restoring physical function through exercise may be the cornerstone of reversing frailty in chronically ill older adults. The challenge will be how to initiate and maintain exercise training in these patients.

A diagnosis of heart failure confers a risk for functional decline and disability. Identification of patients at the highest risk for functional decline remains difficult due to the unpredictable trajectory of chronic heart failure. Measures of function which capture the multi-dimensional features of frailty can provide a valuable clinical tool for the management of older patients with heart failure.

Limitations of the Study

This study has limitations. The sample size is small and these results need confirmation in a larger sample. In addition, a significant number of individuals were not able to be contacted in follow up. The mortality data was not affected by those that could not be contacted, but follow-up information on function would be. The functional status of those lost to follow-up at baseline appears intermediate between those that died and those willing to be reassessed, suggesting functional ability in this subgroup may not be maintained as well as those for which we have data. Further, our sample was too small to evaluate our frailty assessment as an ordinal measure by more then a dichotomy. Future studies will need to address this intermediate group in alternate ways, possibly with home visits or less cumbersome testing.

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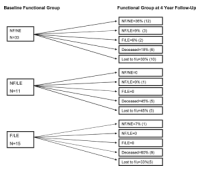

Figure 1.

Functional Group from Baseline to 4 Years

NF/NE = non-frail/normal endurance, NF/LE = non-frail/low endurance, F/LE = frail/low endurance

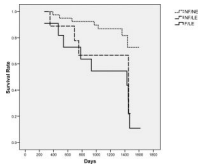

Figure 2.
Kaplan-Meier Survival Curve for 59 Heart Failure Subjects categorized by endurance and frailty followed for 4 years

Table 1

Baseline Characteristics of Participants who Followed-up at 4 Years vs. Lost to Follow-up

	Completed 4 year f/u (n=19)	Deceased (n=20)	Lost to f/u (n=20)	P value comparing all 3 groups	P value comparing all to lost to f/u
Age (yrs)	75 ± 8	79 ± 11	77 ± 10	.37	.76
Body mass index (kg/m^2)	26.4 ± 3.4	28.0 ± 6.1	29.1 ± 5.6	.26	.19
Sex (female)	10% (2)	35% (7)	40% (8)	.10	.17
NYHA class				.07	.31
I or II	79% (15)	45% (9)	50% (10)		
III or IV	21% (4)	55% (11)	50% (10)		
Length of time with HF (yrs)	4.53 ± 3.44	6.25 ± 5.75	6.50 ± 6.48	.47	.47
Six min walk (m)	393.4 ± 71.4	230.1 ± 108.8	299.4 ± 116.8	<.001	.76
8 ft walk time (sec)	2.2 ± 0.6	4.0 ± 1.8	3.1 ± 1.2	<.001	.91
PASE score	1159 ± 1150	409 ± 339	1067 ± 1315	.051	.32
Handgrip (kg)	30.9 ± 7.0	20.1 ± 9.4	25.4 ± 11.6	.003	.99
Frailty Total	0.84 ± 1.1	2.4 ± 1.1	1.6 ± 1.4	.001	.81
NF/NE	90% (17)	30% (6)	50% (10)	.001	.51
NF/LE	5% (1)	25% (5)	25% (5)	.19	.37
F/LE	5% (1)	45% (9)	25% (5)	.017	.96
25OHD (ng/mL)	31.9 ± 15.4	24.1 ± 10.6	24.6 ± 10.3	.09	.34
Hemoglobin (g/dL)	13.3 ± 1.0	12.8 ± 1.6	13.2 ± 1.2	.39	.60
Creatinine (mg/dL)	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.6	.86	.60
hsCRP (mg/dL)	0.29 ± 0.24	2.31 ± 3.67	0.62 ± 0.62	.01	.29
IL-6 (mg/dL)	4.56 ± 2.26	9.16 ± 8.20	5.56 ± 3.19	.024	.40
NT-Pro-BNP (fmol/L)	1137.1 ± 620.2	1114.1 ± 787.6	1066.6 ± 594.3	.95	.75

PASE – Physical Activity Scale in the Elderly

25OHD – 25 hydroxy vitamin D (vitamin D stores)

hsCRP – high sensitivity C-reactive protein

IL-6- Interleukin 6

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Table 2

Univariate predictors of death adjusted for age (yrs)

	Hazard ratio	95% CI	p value
Six min walk distance (30m)	0.82	0.72 – 0.94	.004
Frailty Phenotype score	1.64	1.19 – 2.26	.003
Ejection Fraction	1.003	.945 – 1.064	.926
NYHA Class	2.42	1.16 – 5.07	.019
Ischemia as cause of heart failure	.685	.188 – 2.492	.566
NT-Pro-BNP (fmol/L)	1.00	999 – 1.001	.888
hsCRP (mg/dL)	1.12	0.99 – 1.25	.062
IL6 (mg/dL)	1.06	1.00 – 1.11	.035
Vitamin D (ng/mL)	.99	.969 – 1.004	.123
Creatinine (mg/dL)	1.16	.431 – 3.14	.767
Hemoglobin (g/dL)	.782	543 – 1.126	.186

P values based on cox regression survival analyses

Table 3a

Predictors of Mortality Rate with the Frailty Score

Predictors of Survival	Hazard Ratio	CI 95%	P value	Chi square	−2 Log likelihood
Step 2 model			.029	10.77	132.76
Age (5 yrs)	.93	.69 to 1.27	.66		
hsCRP	1.08	.76 to 1.53	.66		
Interleukin 6	.98	.84 to 1.14	.79		
Frailty score	1.57	1.05 to 2.33	.03		
Step 3 model			.013	10.71	132.83
Age (5 yrs)	.95	.72 to 1.26	.72		
hsCRP	1.04	.90 to 1.20	.63		
Frailty score	1.54	1.05 to 2.25	.03		
Step 4 model			.007	9.94	133.96
hsCRP	1.05	.92 to 1.19	.50		
Frailty score	1.50	1.06 to 2.11	.02		
Step 5 model			.004	8.42	134.39
Frailty score	1.58	1.15 to 2.17	.005		

p values <.05 considered significant

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Table 3b

Predictors of Mortality Rate with the Six Minute Walk

Predictors of Survival	Hazard Ratio	CI 95%	P value	Chi square	−2 Log likelihood
Step 2 model			.032	10.58	132.80
Age (5 yrs)	.94	.70 to 1.25	.65		
hsCRP	1.01	.78 to 1.39	.79		
NYHA codes	1. 27	48 to 3.38	.63		
Six min walk (30m)	.85	.71 to 1.02	.08		
Step 3 model			.018	10.03	132.87
Age (5 yrs)	.93	.70 to 1.23	.60		
NYHA codes	1.32	.51 to 3.42	.58		
Six min walk (30m)	.85	.71 to 1.01	.06		
Step 4 model			.009	9.39	133.14
NYHA codes	1.43	.58 to 3.52	.44		
Six min walk (30m)	.87	.74 to 1.01	.07		
Step 5 model			.003	8.71	133.75
Six min walk (30m)	.84	.74to .94	.005		

p values <.05 considered significant