Journal of Cardiac Failure Vol. 12 No. 6 2006

Association of Functional and Health Status Measures in Heart Failure

JONATHAN MYERS, PhD, NAYMA ZAHEER, MD, SUSAN QUAGLIETTI, RNP, RUPA MADHAVAN, BS, VICTOR FROELICHER, MD, AND PAUL HEIDENREICH, MD

Palo Alto, California

ABSTRACT

Background: A wide variety of instruments have been used to assess the functional capabilities and health status of patients with chronic heart failure (HF), but it is not known how well these tests are correlated with one another, nor which one has the best association with measured exercise capacity.

Methods and Results: Forty-one patients with HF were assessed with commonly used functional, health status, and quality of life measures, including maximal cardiopulmonary exercise testing, the Duke Activity Status Index (DASI), the Veterans Specific Activity Questionnaire (VSAQ), the Kansas City Cardiomyopathy Questionnaire (KCCQ), and 6-minute walk distance. Pretest clinical variables, including age, resting pulmonary function tests (forced expiratory volume in 1 s and forced vital capacity), and ejection fraction (EF) were also considered. The association between performance on these functional tools, clinical variables, and exercise test responses including peak VO_2 and the VO_2 at the ventilatory threshold, was determined. Peak oxygen uptake (VO_2) was significantly related to VO_2 at the ventilatory threshold ($r = 0.76, P < .001$) and estimated METs from treadmill speed and grade ($r = 0.72, P < .001$), but had only a modest association with 6-minute walk performance ($r = 0.49, P < .01$). The functional questionnaires had modest associations with peak VO_2 ($r = 0.37, P < .05$ and $r = 0.26$, NS for the VSAQ and DASI, respectively). Of the components of the KCCQ, peak VO_2 was significantly related only to quality of life score ($r = 0.46, P < .05$). Six-minute walk performance was significantly related to KCCQ physical limitation ($r = 0.53, P < .01$) and clinical summary ($r = 0.44, P < .05$) scores. Among pretest variables, only age and EF were significantly related to peak VO_2 ($r = -0.58$, and 0.46, respectively, $P < .01$). Multivariately, age and KCCQ quality of life score were the only significant predictors of peak VO_2, accounting for 72% of the variance in peak VO_2.

Conclusion: Commonly used functional measures, symptom tools, and quality of life assessments for patients with HF are poorly correlated with one another and are only modestly associated with exercise test responses. These findings suggest that exercise test responses, non-exercise test estimates of physical function, and quality of life indices reflect different facets of health status in HF and one should not be considered a surrogate for another.

Key Words: Heart failure, Exercise testing, Maximal oxygen uptake, Exercise capacity.

Heart failure (HF) is characterized by exercise intolerance, typically from shortness of breath or fatigue. The mechanisms for exercise limitation in HF have been the topic of a great deal of investigation, and include factors such as a diminished cardiac output response to exercise, skeletal muscle metabolic dysfunction, abnormal vasodilatory capacity, and abnormal distribution of blood flow.[1,2] The degree of exercise intolerance is commonly used clinically to assess the severity of the disease and efficacy of therapy. Randomized clinical trials frequently use exercise duration or workload on a standardized exercise test as a primary outcome variable when assessing the efficacy of an intervention. The most accurate expression of exercise tolerance is directly measured peak oxygen uptake (peak VO_2),[1,3] although numerous surrogates for peak VO_2 and other expressions of a patient's functional capabilities have been used, including symptom questionnaires, submaximal walking tests, and various functional classifications.[4–9]

Peak VO_2 is rarely performed in clinical trials among patients with HF because of the added time, equipment, and

From the Cardiovascular Division, Veterans Affairs Palo Alto Health Care System, Stanford University School of Medicine, Palo Alto, California.

Manuscript received January 25, 2006; revised manuscript received April 10, 2006; revised manuscript accepted April 17, 2006.

Reprint requests: Jonathan Myers, PhD, Cardiology, 111-C, VA Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304.

All decisions regarding this manuscript were made by a guest editor.
1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2006.04.004

technical expertise required to use ventilatory gas exchange equipment. Advantages of submaximal tests or health status and symptom questionnaires include that they are quick, inexpensive, and safe. Examples of health status and functional measures commonly used include the Kansas City Cardiomyopathy Questionnaire (KCCQ),[8] Veterans Specific Activity Questionnaire (VSAQ),[6] Duke Activity Status Index (DASI),[5] 6-minute walk distance, and New York Heart Association (NYHA) functional class.[10] Although it has been suggested that these measures can be unreliable because they may provide incomplete or misleading information,[4,11–13] some of these instruments have also been shown to be sensitive to changes in clinical status.[8,13,14] However, it is uncertain how well the commonly used measures of functional status in patients with HF are associated with clinical status measures, quality of life, or directly measured exercise capacity.

In the present study, we evaluated the association between peak VO_2, clinical measures, and commonly used symptom and functional tools in patients with HF. Our objectives were: (1) to evaluate the relationships between these functional assessments and to determine which is most strongly associated with peak VO_2 and (2) to determine the extent to which of these tools could be used to predict peak VO_2.

Table 1. Demographic and Clinical Characteristics

Patient Characteristics	Mean ± SD
Age (years)	68.3 ± 12
Body mass index (kg/m^2)	26.0 ± 3.3
Maximal oxygen uptake (mL·kg·min)	16.1 ± 6.2
Ejection fraction (%)	32.6 ± 9.3
Pulmonary Function	
Forced expiratory volume, 1 s (L)	2.08 ± 0.58
Forced expiratory volume (% of normal)	66.6 ± 16
Forced vital capacity (L)	2.75 ± 0.62
Forced vital capacity (% of normal)	68.6 ± 13
Etiology of congestive heart failure, # subjects (%)	
Ischemic	22 (53)
Nonischemic	20 (49)
Historical Variables, # subjects (%)	
Myocardial infarction	15 (37)
Pulmonary disease	6 (15)
Hypertension	22 (54)
Hyperlipidemia	11 (27)
Diabetes	4 (10)
Obesity	17 (41)
Medications, # subjects (%)	
Digoxin	17 (41)
β-Blocker	25 (61)
Calcium channel blocker	6 (15)
Angiotensin-converting enzyme inhibitor	36 (88)
Diuretics	25 (61)
Others	37 (90)

Methods

Patients

Forty-one male patients with stable HF (mean age 68 ± 12 years) participated in the study. HF was documented by clinical history and diagnosis in outpatient medical records, and an ejection fraction (EF) <40%. Ischemic HF (n = 22) was defined by having a history of myocardial infarction, coronary bypass surgery, or documented angiographic coronary disease. Only patients with stable, compensated HF >30 years of age were included in the study. Written informed consent was obtained from all subjects using a protocol approved by the Stanford Investigational Review Board. Clinical characteristics of the study group are presented in Table 1.

Exercise Testing

Symptom limited maximal exercise tests were performed on a treadmill using an individualized ramp protocol.[15] This test individualizes warm-up and peak walking speeds, along with the ramp rate (rate of change in speed and grade) to yield a test duration of approximately 10 minutes.[6,15] All tests were performed in the morning. Before testing, standard pulmonary function tests were performed, including forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). Ventilatory oxygen uptake was measured using an Orca Diagnostics metabolic system (Santa Barbara, CA). Gas exchange data were acquired breath-by-breath and expressed in 10-s intervals of rolling 30-s averages. Ventilatory oxygen uptake, carbon dioxide production, minute ventilation, and respiratory exchange ratio were calculated online. The percentage of age-predicted normal peak VO_2 was determined for each patient using the equation of Wasserman et al.[16] The ventilatory threshold was determined by 2 experienced, independent reviewers using the V-slope method,[17] and confirmed by ventilatory criteria. Estimated peak VO_2 was determined from the American College of Sports Medicine equations.[18] A 12-lead electrocardiogram was monitored continuously and recorded every minute. Blood pressure was recorded manually every 2 minutes throughout the test. All subjects were encouraged to provide a maximal effort, and the Borg 6 to 20 perceived exertion scale was used to quantify effort.[19]

Symptom Questionnaires

Before undergoing exercise testing, responses to 4 symptom and health status questionnaires were obtained. These included the KCCQ,[8] VSAQ,[6] DASI,[5] and NYHA functional class.[10] The KCCQ is a detailed, disease-specific health status measure that encompasses domains including physical limitations, symptoms, disease severity, change in status over time, self-efficacy, social interference, and quality of life.[8] The DASI is a brief, self-administered questionnaire designed to estimate functional status.[5] The VSAQ was similarly developed by our group and was specifically designed to estimate exercise tolerance before exercise testing to individualize the treadmill protocol for clinical exercise testing. The VSAQ score was age-adjusted.[6] The NYHA Functional Classification is a widely used general (4 categories), provider-derived classification scheme to categorize patients in terms of symptoms associated with daily activities.[10] A description, metric, and ranges for each of the health status measurements is presented in Table 2.

Six-Minute Walk Test

The 6-minute walk test was completed after the exercise test after a minimum 30-minute rest period, and performed as described by Guyatt et al.[7] A 100-foot distance was marked in a hospital corridor, and patients were instructed to walk from end to end at their own pace, attempting to cover as great a distance as possible within 6 minutes. The test was supervised by a technician, who provided verbal encouragement at 30-second intervals. Patients

Table 2. Description, Metric, and Ranges Observed for the Health Status Tools

Measurement	Description	Metric (Range)
NYHA	Functional classification	4-category scale (1 to 4)
VSAQ	Pretest estimation of exercise capacity based on symptoms	13-category scale using METS (3 to 10)
Peak VO_2	Measured oxygen uptake	Continuous variable (6.0–32 mL $O_2 \cdot kg \cdot min$)
Estimated METS	Multiple of RMR estimated from peak speed and grade	Continuous variable (2.4 to 10.4)
KCCQ	HF-specific health status measure with 8 domains	Transformed 0 to 100 scale
DASI	Estimate of exercise tolerance	Transformed continuous variable (7 to 58)
Six-minute walk	Distance walked in 6 minutes	Meters (61 to 507)

NYHA, New York Heart Association functional class; VSAQ, Veterans Specific Activity Questionnaire; RMR, resting metabolic rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; HF, heart failure; DASI, Duke Activity Status Index.

were permitted to stop and rest, and were instructed to continue walking as soon as they felt they were able to do so. Symptoms experienced by the patient were recorded. Distance covered was expressed in meters.

Statistics

Simple univariate linear regression was performed to assess the relationships between peak VO_2 and the various functional and quality of life measures, including 6-minute walk distance, age-adjusted VSAQ score in metabolic equivalents (METS), functional capacity as determined by the DASI, the functional, clinical status, and quality of life domains of the KCCQ (each expressed in 0 to 100 scales), NYHA functional class, VO_2 at the ventilatory threshold, and peak METS estimated from treadmill speed and grade. Using the pretest variables with the strongest univariate associations with peak VO_2 (age, 6-minute walk distance, VSAQ score, FVC, and KCCQ quality of life score), a forward stepwise multiple regression procedure was performed to predict peak VO_2. A second multiple regression procedure was performed to determine predictors of estimated METS achieved (from peak treadmill speed and grade), using the variables with the strongest univariate associations with estimated METS (age, DASI, VSAQ, 6-minute walk distance, and KCCQ physical limitation score).

Results

Exercise Test Responses

Exercise test results are listed in Table 3. The mean maximal perceived exertion was 17.6 ± 2.0, and the mean peak respiratory exchange ratio was 1.14 ± 0.23, suggesting that maximal effort was achieved by most patients. The mean maximal heart rate of 124 ± 28 beats/min was lower than that expected for age (82% of predicted), reflecting that many patients were limited by symptoms associated with HF, that heart rate was limited by the effects of β-blockade, or both. Mean maximal oxygen uptake was 16.1 ± 6.2 mL·kg·min (representing 54 ± 22% of age-predicted peak VO_2), and the ventilatory threshold occurred at 76% of peak VO_2.

Table 3. Exercise Test Responses (Mean ± SD)

	Rest	Ventilatory Threshold	Maximal Exercise
Heart rate (beats/min)	68 ± 13	103 ± 22	124 ± 28
Systolic blood pressure (mm Hg)	119 ± 20	131 ± 25	144 ± 25
Diastolic blood pressure (mm Hg)	72 ± 12	69 ± 13	70 ± 21
Oxygen uptake (mL/min)	—	1166 ± 619	1481 ± 760
Oxygen uptake (mL/kg/min)	—	12.3 ± 4.3	16.1 ± 6.2
Minute ventilation (L/min)		33.2 ± 15.7	53.2 ± 20.6
CO_2 production (mL/min)		1102 ± 676	1493 ± 746
Respiratory exchange ratio	—	0.89 ± 0.05	1.14 ± 0.23
Exercise time (min)	—	2.1 ± 1.1	6.82 ± 3.2
Perceived exertion	—	11.1 ± 2.6	17.6 ± 2.0

Mean values for the various functional and health status measures are presented in Table 4. The mean NYHA functional class was 1.7 ± 0.98. METS from the VSAQ (6.6 ± 2.0) were higher than that achieved on the treadmill expressed as measured peak VO_2 (4.5 ± 1.8, $P < .01$), and METS estimated from peak treadmill speed and grade (5.4 ± 2.2, $P < .05$). Mean 6-minute walk distance was 328 ± 97 meters.

Association Between Functional Measures and Peak VO_2

Correlation coefficients between peak VO_2 and the various functional measures are presented in Table 5. Both estimated METS and VO_2 at the ventilatory threshold were significantly associated with peak VO_2 (r = 0.72 and 0.76, $P < .001$ and $P < .001$, respectively). Among the non-exercise test health status measures, peak VO_2 had

Table 4. Functional and Health Status Measures

Exercise Data	Mean ± SD
NYHA	1.74 ± 0.98
VSAQ (METS)	6.6 ± 2.0
Measured METS	4.5 ± 1.8
Estimated METS	5.4 ± 2.2
KCCQ physical limitation score	74.5 ± 21
KCCQ symptom score	54.5 ± 18
KCCQ symptom frequency score	69.2 ± 26
KCCQ symptom burden score	76.9 ± 18
KCCQ total symptom score	73.9 ± 20
KCCQ self efficacy score	79.0 ± 25
KCCQ quality of life score	65.2 ± 26
KCCQ social limitation score	68.4 ± 29
KCCQ overall summary score	70.7 ± 21
KCCQ clinical summary score	74.2 ± 19
DASI	33.5 ± 15
Six-minute walk distance (meters)	328.4 ± 97

NYHA, New York Heart Association functional class; VSAQ, Veterans Specific Activity Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; DASI, Duke Activity Status Index.

Measured METS = peak METs measured from cardiopulmonary exercise testing.

Estimated METS = peak METs estimated from peak treadmill speed and grade.

Table 5. Correlations Between Functional and Health Status Measures in CHF

	Age	Rest HR	EF	FVC	FEV_1	Estimated METS	VSAQ	VO_2 Peak	VO_2@VT	PE@VT	DASI	NYHA	6MWT	KC Phys Lim	KCQL	KC Sym Tot
Age	1.0															
Rest HR	−0.04	1.0														
EF	−0.19	−0.03	1.0													
FVC	−0.51**	−0.09	0.06	1.0												
FEV_1	−0.48**	−0.11	0.07	0.87***	1.0											
Estimated METS	−0.53***	−0.21	0.18	0.33	0.25	1.0										
VSAQ	−0.41*	−0.09	0.08	0.25	0.23	0.73***	1.0									
VO_2 peak	−0.58***	−0.04	0.46**	0.32	0.29	0.72***	0.37*	1.0								
VO_2@VT	−0.35	−0.15	0.56**	0.45*	0.39*	0.46**	0.36	0.76***	1.0							
PE@VT	−0.01	0.34	−0.08	−0.06	0.01	−0.68***	−0.59**	−0.53*	−0.26	1.0						
DASI	−0.15	−0.04	−0.03	0.35	0.22	0.46**	0.30	0.26	0.40	−0.18	1.0					
NYHA	−0.14	−0.06	0.04	−0.11	−0.12	−0.31	−0.31	−0.14	−0.33	0.26	−0.64***	1.0				
6MWT	−0.46**	0.10	0.28	0.28	0.17	0.59***	0.45**	0.49**	0.39*	−0.29	0.44**	−0.32	1.0			
KC phys Limitation	−0.01	−0.08	0.24	0.12	0.20	0.42*	0.28*	0.25	0.24	−0.63**	0.68***	−0.36	0.53**	1.0		
KCQL	−0.15	0.28	0.54**	−0.02	0.05	0.34*	0.17	0.46*	0.26	−0.25	0.24	−0.11	0.28	0.49**	1.0	
KC SymTot	−0.03	0.23	0.31	−0.27	−0.16	0.32	0.15	0.30	0.21	−0.24	0.41*	−0.33	0.27	0.62***	0.80***	1.0
KC Clin Sum	−0.02	0.08	0.30	−0.08	0.02	0.41*	0.24	0.30	0.25	−0.52*	0.60***	−0.38*	0.44*	0.90***	0.71***	0.90***

HR, heart rate; estimated METS, METS calculated from peak treadmill speed and grade; KCPhyLim, Kansas City Physical Limitation score; EF, ejection fraction; VSAQ, Veterans Specific Activity Questionnaire; NYHA, New York Heart Association functional class; KCQL, Kansas City Quality of Life score; FVC, forced vital capacity; 6MWT, 6-minute walk test; KCSympTot, Kansas City Total Symptom score; FEV_1, forced expiratory volume in 1 s; CClinSum, Kansas City Clinical Summary score; PE, perceived exertion; VT, ventilatory threshold; VSAQ, Veterans Specific Activity Questionnaire; DASI, Duke Activity Status Index.

*$P < .05$.

**$P < .01$.

***$P < .001$.

significant associations with the VSAQ score ($r = 0.37$, $P <$ .05), but not with the DASI ($r = 0.26$) or NYHA class ($r = -0.14$). Among the KCCQ domains, peak VO_2 was significantly associated with quality of life score ($r = 0.46$, $P <$ .05), but not with physical limitation, symptom, or clinical summary scores. Six-minute walk distance was significantly though modestly related to peak VO_2 ($r = 0.49$, $P < .01$), KCCQ physical limitation ($r = 0.53$, $P < .01$), and clinical summary scores ($r = 0.44$, $P < .05$). Among pretest clinical indices (age, heart rate, EF, FVC, FEV_1), only age and EF were related to peak VO_2 (−0.58, $P < .001$ and 0.46, $P < .01$, respectively). The associations between the various functional and health status measures and peak VO_2 were similar when those with nonischemic HF were assessed separately.

Multivariate Predictors of Peak VO_2

Predictors of peak VO_2 by multiple regression are presented in Table 6. Age explained the greatest proportion of variance in peak VO_2 (49%) followed by the KCCQ quality of life score (23%). Six-minute walk performance was not a significant multivariate determinant of peak VO_2. The final regression equation for peak VO_2 was [peak $VO_2 = 28.8 - 0.33$ (age) $+ 0.14$ (KCCQ quality of life score)]. The multiple r from the regression model was 0.85 ($P < .001$).

To compare the current sample of HF patients with our previous results among exercise test referrals (largely non-HF) in which peak estimated METS was the dependent variable,[5,19] a second analysis was performed. Only VSAQ score ($r^2 = 0.34$), age (additional $r^2 = 0.15\%$), and KCCQ physical limitation score (additional $r^2 = 16\%$) were significant predictors of peak estimated METS (multiple r for model $= 0.81$, $P < .001$) (Table 7).

Discussion

The present results suggest that commonly-used functional measures, estimates of quality of life, and symptom tools in patients with HF generally have only modest associations with peak VO_2 and with one another. The clinical implications of these findings are that: (1) each test or instrument targets a specific aspect of clinical status and they should not be considered interchangeable and (2) none of these measures alone is a reliable surrogate for peak VO_2.

Peak VO_2 was used as the dependent variable because it is widely recognized as the standard measure of cardiopulmonary function and has wide applications for risk stratification in HF.[3,16,20,21] It should be noted, however, that not all the independent variables employed in the present study were designed specifically to estimate maximal cardiopulmonary function, even though many of them have been used to quantify functional changes in clinical trials. The lack of strong associations between the various functional measures is likely explained in part by the fact that they

Table 6. Explanation of Variance in Peak VO_2 by Stepwise Multiple Regression Analysis

Variables Entered	r	r^2	New Variance Explained (%)	P value
Age	0.70	0.49	49	<.001
KCCQ quality of life score	0.85	0.72	23	.001

Regression equation: Peak VO_2 = 28.8 − 0.33 (age) + 0.14 (KCCQ quality of life score).
KCCQ, Kansas City Cardiomyopathy Questionnaire.

Table 7. Explanation of Variance in Estimated METS Achieved by Stepwise Multiple Regression Analysis

Variables Entered	r	r^2	New Variance Explained (%)	P value
VSAQ	0.58	0.34	34	<.05
Age	0.70	0.49	15	<.01
KCCQ physical limitation score	0.81	0.65	16	<.05

Regression equation: Estimated METs = 5.1 − 0.07 (age) + 0.37 (VSAQ score) + 0.03 (KCCQ physical limitation score).
VSAQ, Veterans Specific Activity Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire.

assess different aspects of functional status. These observations also highlight the complexity of HF; many factors interact to underlie exercise intolerance in a given patient,[1,2,16,20] symptoms can vary from day to day, and progression of the disease can be unpredictable, leading to a divergence in physiologic function, clinical status, and quality of life.

None of the symptom tools had a strong association with peak VO_2; correlation coefficients between peak VO_2 and these instruments were in the order of 0.20 to 0.40 (Table 5). The relationship between peak VO_2 and the VSAQ (r = 0.37) is similar to what we previously observed using this measure in a more heterogeneous sample of patients referred for exercise testing (r = 0.42).[22] In various populations with cardiovascular disease, studies have reported associations between the VSAQ and peak VO_2 in the range of 0.46 to 0.57.[23–26] In general, the functional questionnaires had stronger associations with *estimated* than with measured peak VO_2. Among the questionnaires, the VSAQ had the strongest association with estimated METS (r = 0.73, P < .001). The latter relationship is similar to what we observed previously among treadmill test referrals, largely without HF (r = 0.79).[6]

Association Between Quality of Life and Exercise Tolerance in HF

Although quality of life would be expected to be closely related to one's exercise capabilities, studies associating quality of life and exercise tolerance have been mixed. Arena et al[27] observed that the Minnesota Living with Heart Failure Questionnaire (MLHF) was significantly related to peak VO_2 in patients with HF (r = 0.66, P < .001), though it was poorly related to the VE/VCO_2 slope. Koukouvou and colleagues[28] reported that the MLHF and other quality of life scores closely paralleled improvements in peak VO_2 and other cardiopulmonary exercise test responses before and after 6 months in a rehabilitation program. Conversely, Wilson and colleagues[29] reported poor relationships between perceived exercise tolerance as measured by the MLHF and objective measures of circulatory or ventilatory performance. Grigioni et al[30] observed poor relationships between the majority of objective clinical markers of disease severity (peak VO_2, presence of a third heart sound, signs of fluid retention, electrocardiogram findings, EF, and echocardiographic variables) and the MLHF. Juenger et al[31] reported that the physical function domain of the Medical Outcomes Study (SF-36) was significantly related to peak VO_2 (r = 0.47, P < .001), but the other 7 SF-36 domains were generally poorly associated with peak VO_2 (r = 0.16 to 0.40). In accordance with these studies, peak VO_2 had relatively poor relationships with subjective symptom measures in the present study (r = −0.14 to 0.30), although a significant association was observed between peak VO_2 and KCCQ quality of life score (r = 0.46, P < .05).

Association of 6-Minute Walk Performance With Functional Measures

The 6-minute walk test has been widely used in the evaluation and serial assessment of patients with HF.[7,13,32–35] Our HF patients were similar to those in previous studies in that their mean 6-minute walk distance was 328 ± 93 meters.[32–35] Previous studies have reported correlation coefficients between 6-minute walk performance and peak VO_2 among patients with HF in the range of 0.50 to 0.70.[32,34,36–40] The association we observed between 6-minute walk distance and peak VO_2 (r = 0.49) was comparable to these previous studies. It might be expected that 6-minute walk performance, as a submaximal measure, would be more closely associated with questionnaires designed to reflect symptom limitations during daily activities than peak VO_2. However, although we observed that 6-minute walk distance had a modest association with KCCQ physical limitation score (r = 0.53, P < .01), it was poorly related to KCCQ symptom and quality of life scores. In developing the KCCQ, Green et al[8] originally observed a correlation of 0.48 between the physical limitation score and 6-minute walk distance, which is similar to other studies associating various quality of life instruments to 6-minute walk performance.[30,31] These studies suggest that although 6-minute walk performance may not be an appropriate surrogate for peak VO_2, it is a modest reflection of functional status assessed by questionnaire.

Functional Status Measures and EF

Another potentially useful clinical application relates to whether simple, noninvasive functional measures and exercise test responses are associated with a clinical index such as EF. In previous studies, both 6-minute walk performance and exercise test responses have been shown to relate poorly to EF and other hemodynamic variables in HF.[34,38,39] Although we observed that EF had a stronger relation with peak VO_2 than most previous studies, the relationship was modest ($r = 0.46$, $P < .01$). Among the other functional measures, the highest correlation with EF was for 6-minute walk performance, but the relationship was relatively weak ($r = 0.28$). EF also did not have strong associations with the KCCQ domains, ranging from 0.24 for the physical limitation to 0.54 for the quality of life score. The absence of strong relationships between EF and HF-specific quality of life measures has been observed by other investigators.[31,41,42]

Multivariate Analysis

We observed that the multivariate model explained 72% of the variance in peak VO_2, with age accounting for the greatest amount of variance (49%). That age accounted for the greatest amount of variance in peak VO_2 is not surprising, given the decline in peak VO_2 that occurs with aging regardless of disease presence, and the greater likelihood of comorbidities and more severe disease in older subjects. Interestingly, the KCCQ quality of life score was the only health status measure that contributed significantly to the model, adding 23% to the variance explained. Similar to our previous study among consecutive exercise test referrals (largely without HF) in which the combination VSAQ score and age were the only significant predictors of *estimated* exercise capacity (multiple $r = 0.79$),[6] age and VSAQ score were significant predictors of estimated METS achieved in the present study, along with the KCCQ physical limitation score (multiple $r = 0.81$). These results suggest that when exercise testing is unavailable, exercise capacity might be reasonably estimated multivariately by considering age and a non-exercise test assessment tool.

Limitations

The study sample size was relatively small. We did not employ practice trials for maximal exercise testing or the 6-minute walk test, both of which are known to improve with repetition.[7,32,43] The study was limited to men, and the sample was a heterogeneous group of patients with HF; our findings may not apply to women or specific subgroups of HF. In addition, the sample was a comparatively healthy group of patients with HF, and the results may have differed in patients with more severe HF.

Summary

Health status, including functional capabilities, symptoms associated with daily activities, and physical or psychologic well-being are important indices that are widely used in the assessment of interventions for HF. Accurate and reliable tools that quantify health status are important to appropriately assess responsiveness to therapy in this population. We observed that tools commonly used to assess health and functional status in HF had only modest associations with peak VO_2 and with one-another. In practical terms, this suggests that: (1) laboratory exercise tolerance is not necessarily a good reflection of how patients perceive their capacity to undertake daily activities and (2) cardiopulmonary exercise testing, non-exercise test estimates of physical function, and quality of life measures reflect different facets of health status and one should not be considered a surrogate for another. These findings may have applications for the design and interpretation of clinical trials in which estimates of exercise tolerance are used as efficacy parameters in patients with HF.

References

1. Pina IP, Apstein CS, Balady GJ, et al. Exercise and heart failure: a statement from the American Heart Association committee on exercise, rehabilitation, and prevention. Circulation 2003;107:1210–25.
2. Brubaker PH. Exercise intolerance in congestive heart failure: a lesson in exercise physiology. J Cardiopulmonary Rehabil 1997;17:217–21.
3. Myers J. Essentials of cardiopulmonary exercise testing. Champaign: Human Kinetics; 1996.
4. Anand IS, Florea VG, Fisher L. Surrogate end points in heart failure. J Am Coll Cardiol 2002;39:1414–21.
5. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). Am J Cardiol 1989;64:651–4.
6. Myers J, Do D, Herbert W, Ribisl P, Froelicher VF. A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. Am J Cardiol 1994;73:591–6.
7. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919.
8. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–55.
9. European Heart Failure Training Group. Experience from controlled trials of physical training in chronic heart failure; protocol and patient factors in effectiveness in the improvement in exercise tolerance. Eur Heart J 1998;19:466–75.
10. Criteria Committee of the New York Heart Association (Kossman CE, Chairman). Diseases of the heart and blood vessels: Nomenclature and criteria for diagnosis. 6th ed. Boston: Little Brown; 1964. p. 110–4.
11. Sobel BE, Furberg CD. Surrogates, semantics, and sensible public policy. Circulation 1997;95:1661–3.
12. Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 1999;282:790–5.
13. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JGF. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. Eur Heart J 2005;26:778–93.
14. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;150:707–15.
15. Myers J, Buchanan N, Walsh D, et al. Comparison of the ramp versus standard exercise protocols. J Am Coll Cardiol 1991;17:1334–42.
16. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. 3rd ed. Baltimore: Lippincott, Williams & Wilkins; 1999.
17. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.

18. American College of Sports Medicine. Guidelines for exercise testing and exercise prescription. 7th ed. Baltimore: Lippincott, Williams & Wilkins; 2005.
19. Borg GAV. Borg's perceived exertion scales. Champaign: Human Kinetics; 1998.
20. Myers J. Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. Int J Sports Med 2005;26:S49–55.
21. Myers J, Gullestad L. The role of exercise testing and gas-exchange measurement in the prognostic assessment of patients with heart failure. Curr Opin Cardiol 1998;13:145–55.
22. Myers J, Bader D, Madhavan R, Froelicher VF. Validation of a specific activity questionnaire to estimate exercise tolerance in patients referred for exercise testing. Am Heart J 2001;142:1041–6.
23. McAuley P, Myers J, Abella J, Froelicher V. Evaluation of a specific activity questionnaire to predict mortality in men referred for exercise testing. Am Heart J 2005;128:e1–7.
24. Maeder M, Wolber T, Atefy R, et al. Impact of the exercise mode on exercise capacity: bicycle testing revisited. Chest 2005;128:2804–11.
25. Pierson LM, Norton HJ, Herbert WG, et al. Recovery of self-reported functional capacity after coronary artery bypass surgery. Chest 2003; 123:1367–74.
26. Rankin SL, Briffa TG, Morton AR, Hung J. A specific activity questionnaire to measure the functional capacity of cardiac patients. Am J Cardiol 1996;77:1220–3.
27. Arena R, Humphrey R, Peberdy MA. Relationship between the Minnesota Living with Heart Failure Questionnaire and key ventilatory expired gas measures during exercise testing in patients with heart failure. J Cardiopulm Rehabil 2002;22:273–7.
28. Koukouvou G, Kouidi E, Lacovides A, Konstantinidou E, Karinis G, Deligiannis A. Quality of life, psychological and physiological changes following exercise training in patients with chronic heart failure. J Rehabil Med 2004;36:36–41.
29. Wilson JR, Rayos G, Yeoh TK, Gothard P, Bak K. Dissociation between exertional symptoms and circulatory function in patients with heart failure. Circulation 1995;92:47–53.
30. Grigioni F, Carigi S, Grandi S, et al. Distance between patient's subjective perceptions and objectively evaluated disease severity in chronic heart failure. Psychother Psychosom 2003;72:166–70.
31. Juenger J, Schellberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart 2002;87: 235–41.
32. Sadaria KS, Bohannon RW. The 6-minute walk test: a brief review of literature. Clin Exerc Physiol 2001;3:127–32.
33. Bitner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. JAMA 1993;270:1702–7.
34. Opasich C, Pinna GD, Mazza A, et al. Six-minute walking performance in patients with moderate-to-severe heart failure. Is it a useful indicator in clinical practice? Eur Heart J 2001;22:488–96.
35. Opasich C, De Feo S, Pinna GD, et al. Distance walked in the 6-minute test soon after cardiac surgery: Toward an efficient use in the individual patient. Chest 2004;126:1796–801.
36. Delahaye N, Cohen-Solal A, Faraggi M, et al. Comparison of left ventricular responses to the six-minute walk test, stair climbing, and maximal upright bicycle exercise in patients with congestive heart failure due to idiopathic dilated cardiomyopathy. Am J Cardiol 1997;80: 65–70.
37. Cahalin LP, Mathier MA, Semigran MJ, Dec W, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 1996;110:325–32.
38. Rostagno C, Galanti G, Comeglio M, et al. Comparison of different methods of functional evaluation in patients with chronic heart failure. Eur J Heart Fail 2000;3:273–80.
39. Zugck C, Kruger C, Durr S, et al. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? Eur Heart J 2000;21:540–9.
40. Lucas C, Stevenson LW, Johnson W, et al. The 6-min walk and peak oxygen consumption in advanced heart failure: Aerobic capacity and survival. Am Heart J 1999;138:618–24.
41. Gorkin L, Norvell NK, Rosen RC, et al. Assessment of quality of life as observed from the baseline data of the studies of left ventricular dysfunction (SOLVD) trial quality-of-life substudy. Am J Cardiol 1993;71:1069–73.
42. Dracup K, Walden JA, Stevenson LW, et al. Quality of life in patients with advanced heart failure. J Heart Lung Transplant 1992; 11:273–9.
43. Sullivan M, Genter F, Savvides M, Roberts M, Myers J, Froelicher V. The reproducibility of hemodynamic, electrocardiographic, and gas exchange data during treadmill exercise in patients with stable angina pectoris. Chest 1984;86:375–83.