Submaximal oxygen uptake kinetics, functional mobility, and physical activity in older adults with heart failure and reduced ejection fraction

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Abstract

Background   Submaximal oxygen uptake measures are more feasible and may better predict clinical cardiac outcomes than maximal tests in older adults with heart failure (HF). We examined relationships between maximal oxygen uptake, submaximal oxygen kinetics, functional mobility, and physical activity in older adults with HF and reduced ejection fraction. **Methods**   Older adults with HF and reduced ejection fraction ($n = 25$, age 75 ± 7 years) were compared to 25 healthy age- and gender-matched controls. Assessments included a maximal treadmill test for peak oxygen uptake (VO_{2peak}), oxygen uptake kinetics at onset of and on recovery from a submaximal treadmill test, functional mobility testing [Get Up and Go (GUG), Comfortable Gait Speed (CGS), Unipedal Stance (US)], and self-reported physical activity (PA). **Results**   Compared to controls, HF had worse performance on GUG, CGS, and US, greater delays in submaximal oxygen uptake kinetics, and lower PA. In controls, VO_{2peak} was more strongly associated with functional mobility and PA than submaximal oxygen uptake kinetics. In HF patients, submaximal oxygen uptake kinetics were similarly associated with GUG and CGS as $VO_{2peak,}$ but weakly associated with PA. **Conclusions**   Based on their mobility performance, older HF patients with reduced ejection fraction are at risk for adverse functional outcomes. In this population, submaximal oxygen uptake measures may be equivalent to VO_2 peak in predicting functional mobility, and in addition to being more feasible, may provide better insight into how aerobic function relates to mobility in older adults with HF.

1   Introduction

Heart failure (HF) affects over 5 million Americans, 70% of which are over the age of 60. The aging of the population and increased prevalence of HF risk factors has translated into an overall increase in the prevalence of older adults living in the community with HF. Over the last several decades, major outcomes (such as mortality and rehospitaliza-tion) have improved only modestly in older adults with HF, possibly related to the impact of concurrent frailty and multimorbidity.[1,2] A key contributor to frailty, mobility disability, is a key risk factor for mortality in older adults with HF.[3,4] Physical activity is reduced and sedentary behavior is increased in individuals with cardiovascular disease, particularly in those with HF.[5]

Decreased peak oxygen consumption (VO_{2peak}) is a strong prognostic indicator for mortality in HF patients.[6] However, the relationship between VO_{2peak} and self-reported measures of functional disability and physical activity in older HF patients is not strong.[7] Most daily mobility tasks performed by older adults require submaximal, rather than maximal, oxygen uptake. In physically impaired older adults, submaximal testing is less demanding, carries lower risk, and may be less dependent on participant motivation.

In mobility-impaired older adults without HF, oxygen uptake kinetics during the onset of and recovery from submaximal exercise are more predictive of functional mobility than VO_{2peak}.[8,9] Compared to healthy controls, HF patients' time constants of oxygen uptake kinetics are increased before and after submaximal as well as after maximal exercise.[10,11] These time constants predict key measures and outcomes in HF, including neurohormonal activation,[12] cardiac output,[13] functional class,[14] hospitalization[15] and survival,[16] the latter better than VO_{2peak}.[17]

The purpose of this study was to examine the relationships between VO_{2peak}, submaximal oxygen uptake kinetics, functional mobility, and self-reported physical activity in older adults with HF. To our knowledge, there are no studies that evaluate the relationships of submaximal oxygen uptake kinetics to functional mobility or self-reported physical activity in HF. Based on previous studies and compared to healthy age-and gender-matched controls, we expected older adults with HF to have slower oxygen uptake kinetics, poorer functional mobility and lower self-reported physical activity. The key hypothesis of the present study was that functional mobility and reported physical activity would correlate more strongly with submaximal oxygen uptake kinetics than $VO2_{peak}$, and that this relationship would be stronger in older adults with HF than in healthy controls.

2　Methods

2.1　Participants

Two groups of community dwelling volunteers aged 65 or older, one with HF and reduced ejection fraction and the other healthy controls, were screened by a nurse practitioner for an aerobic exercise trial focusing on functional mobility outcomes. HF participants were referred from HF clinics to the study nurse practitioner, who reviewed the medical record and recent diagnostic tests and then performed a focused history and physical examination to determine inclusion into the study. All participants signed informed consent forms approved by the University of Michigan Institutional Review Board.

HF inclusion criteria were: left ventricular ejection fraction < 40%; New York Heart Association (NYHA) Class II-III symptom duration greater than 3 months; on ACC/AHA guideline medications for 3 months with stable/optimal dosing for at least one month. HF group exclusion criteria were: exercise-induced sustained arrhythmia or myocardial ischemia (symptoms or ischemic changes on EKG); symptomatic arrhythmia that had not been addressed with the use of a pacemaker or implantable defibrillator if appro-

priate; atrial fibrillation with poor rate control; high-grade AV block; symptomatic obstructive valvular disease; and severe renal (serum creatinine > 3.0) or hepatic (transaminases > 4 × normal) disease. Exclusion criteria for HF and controls were: alcohol intake > 3 ounces/day; recent (within the past six months) myocardial infarction, coronary artery bypass graft surgery or stroke; uncontrolled hypertension; substantial dementia [Mini-Mental Status Examination (MMSE) < 24/30]; hemiplegia or lower limb amputation; current participation in intensive aerobic exercise program or physical therapy more than 30 min three times per week; severe orthopedic or musculoskeletal conditions that limited weight bearing; and other acute medical conditions.

Age- and gender-matched healthy controls had no significant cardiopulmonary, musculoskeletal, or neurological findings, and took no beta blocker or nitrate medications.

2.2　Assessments

2.2.1　Self-reported function

Self-reported disability was assessed using the Established Populations for the Epidemiologic Study of the Elderly (EPESE) questionnaire which includes 15 activities of daily living and the Rosow-Breslau and Nagi mobility-relevant items (including walking one half mile, walking up and down a flight of stairs, and moving heavy objects such as carrying a bag of groceries). Items were scored and summed on a scale of disability or difficulty present (1) or absent (0). Total EPESE score could range from 0–15 with a higher score representing greater self-reported disability.[18,19]

The HF group was further evaluated by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ included items assessing physical limitations (amount of limitation of basic activities such as dressing, walking, yard work); symptoms (frequency and severity of symptoms such as shortness of breath or foot swelling); social interference (limitation of social activities such as hobbies or visiting family and friends); and quality of life (enjoyment, discouragement and satisfaction living with HF symptoms). Functional status (combination of physical limitation and symptom domains) and clinical (combination of physical limitation, symptom, social interference and quality of life domains) scores were calculated for the present study. The KCCQ is scored from 0–100 with greater scores indicating higher levels of function and lower symptom burden.[20]

2.2.2　Physical activity

The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire was used to measure physical activity.[21] Participants rated their participation (i.e.,

frequency and duration) in light, moderate and vigorous physical activities during a typical week over the past four weeks. The estimated kilocalories expended per week in moderate (and greater) intensity and total activities were calculated. Moderate intensity physical activity included activities with an intensity of three or more metabolic equivalents (METs) such as brisk walking, jogging, golfing without a cart, tennis, heavy household chores and gardening.[19] Total activities score included the aforementioned moderate to vigorous activities as well as lower intensity physical activities such as light housework, yoga, stretching/flexibility exercises, and leisure walking. The CHAMPS has adequate test-retest reliability (ICC ranging from 0.67 to 0.76) and excellent established construct validity.[21,22]

2.2.3 Treadmill tests

Participants first practiced walking on the treadmill and with a face mask to assess oxygen uptake. Oxygen uptake (VO_2) was assessed breath by breath using a SensorMedics Vmax Cardiopulmonary Exercise System (Yorba Linda, CA).

Submaximal test: participants exercised at a submaximal load [1mph (miles per hour), 0 grade] to determine their submaximal test VO_{2peak} and submaximal oxygen uptake kinetics. Prior to walking on the treadmill, participants stood on a platform immediately above the treadmill belt for 3 min to determine their baseline oxygen consumption. Participants then stepped off the platform onto the moving treadmill and performed a 6-min walk, and then stood quietly for the 3-min recovery period.

Maximal test: following the submaximal testing and rest period, a symptom-limited maximum-exercise tolerance test was performed to determine maximal test VO_{2peak}. Due to our experience in maximal exercise testing of mobility-impaired older adults, a modified Balke treadmill test was utilized, starting at participants' selected comfortable walking speed and 0 grade and then increasing the grade by 2% every 2 min until exhaustion.[11] Of note, the meananaerobic threshold (AT) for the HF group was 11.0 with percent AT (AT divided by VO_{2peak}) 74.1%, suggesting that the low HF group VO_{2peak} shown below did not represent a true VO_{2max}.

2.2.4 Functional mobility assessments

A series of functional mobility assessments were performed during a second laboratory visit. These tasks were chosen because of the likelihood that they reflected aspects of daily walking and standing balance needs. Get-up-and-go test (GUG). Participants rose from a standard chair, walked

3 m, turned around, walked back 3 m, and sat back in the chair.[23] The maximum time allowed was set at 30 s. One practice trial preceded the actual trial analyzed. Unipedal stance (US). Participants stood, up to a maximum of 30 s, with arms crossed over chest and foot of choice on the floor with the other leg at least two inches from the weight bearing leg and from the floor. Three trials were performed, alternating the weight bearing foot, with the best time used for the data analysis. Comfortable gait speed (CGS, m/s) was determined by having participants walk at their usual pace over 10 m. The actual timed portion was 6.1 m, with a section before and after the timed portion to reduce the effects of acceleration upon starting and deceleration upon stopping.

2.3 Data analysis

The HF group was compared to controls in self-reported function, physical activity, functional mobility and oxygen uptake using independent *t*-tests. Pearson's correlation was used to evaluate the relationships between these variables according to group (HF and controls). Since body mass index (BMI) can affect exercise capacity, all of the HF-control group relationships were further explored using ANOVA to control for BMI.

Submaximal oxygen uptake kinetics: the 3-min (baseline) values for oxygen uptake during rest were defined as the average values obtained from 120 s to 180 s during the period when the participant was standing on the elevated platform. The 6-min (end-exercise) values for oxygen uptake during the submaximal walk on the treadmill were defined as the average values obtained from 300–360 s during the exercise period. The 3-min recovery values were also determined as the average values obtained from 120–180 s of the recovery period. The time constant of oxygen uptake kinetics at the onset of exercise, $tc_{deficit}$, was determined by fitting a monoexponential function to the oxygen uptake response using the value at rest as the baseline.[9] The general form of this equation can be written as $Y(t) = \Delta Y(\text{steady state})(1-e^{-(kt)})$ where $Y(t)$ is the VO_2 above baseline at any time (t), ΔY is the steady state increase in Y for VO_2, and k is the rate constant of the reaction with the dimension of t^{-1}. The monoexponential model with delay is appropriate to characterize the parameters of the kinetic response in older participants.[24] The time constant of oxygen uptake kinetics upon recovery from the exercise, the excess post-exercise oxygen consumption (tc_{EPOC}), was determined using the same method. This method appropriately models the submaximal oxygen uptake kinetics following exercise in older cardiac patients.[25] Test-retest reliability

for two separate determinations of oxygen uptake kinetics is excellent ($r = 0.96$) for maximal graded exercise testing.[26]

3 Results

3.1 Participant description

Participant characteristics for the HF group ($n = 25$) and controls ($n = 25$) appear in Table 1. The mean age for both groups was 75 ± 7 with 92% males. The HF group had higher BMI and disability scores (EPESE), and higher total number of chronic conditions such as hypertension and diabetes. The HF group mean KCCQ functional status and clinical scores (67 and 68, respectively) were analogous to a stable outpatient HF cohort reported previously.[22] The HF patients were well-managed medically according to treatment guidelines: nearly all were taking both β-blockers (88%) and angiotension-converting enzyme inhibitor (88%), and 44% were taking aldosterone inhibitors. Most of the HF patients reported a history of coronary artery disease (88%), hypertension (88%), and arrhythmias (76%), while a smaller percentage (48%) reported a history of diabetes.

3.2 VO$_{2peak}$ and submaximal oxygen-uptake kinetics

The mean VO$_{2peak}$ of 12.9 was 43% lower in the HF group than the control group (see Table 2). The time constant at onset of exercise, tc$_{deficit}$, was twice as high in HF as in controls ($P = 0.002$). The time constant upon recovery from exercise, tc$_{EPOC}$, was 55% higher in HF compared to controls ($P = 0.001$).

3.3 Functional mobility performance and physical activity

Compared to controls, the HF group had significantly worse performance on GUG, CGS, and US tests (See Table 3).

Table 1. Group characteristics.

Characteristics	Control, $n = 25$	HF, $n = 25$	P value
BMI	27.2 ± 0.7	32.3 ± 1.4	0.002
EPESE	1.6 ± 03	4.7 ± 0.9	0.005
Total chronic conditions	1.0 ± 0.2	3.3 ± 0.3	0.03
Etiology HF, ischemic/ non-ischemic		72%/28%	
Left ventricular ejection fraction		25 ± 2	
KCCQ functional status score		67 ± 2.8	
KCCQ clinical score		68 ± 2.7	

Data are presented as mean ± SE unless other indicated. BMI: body mass index; EPESE: established populations for the epidemiologic study of the elderly (higher score indicates more disability); HF: heart failure; KCCQ: Kansas City cardiomyopathy questionnaire (higher score indicates higher levels of function and fewer symptoms).

Table 2. Peak oxygen uptake and oxygen uptake kinetics for peak and submaximal treadmill test.

Variable	Control ($n = 25$)	HF ($n = 25$)	P-value
Maximal treadmill test			
VO$_{2peak}$, mL/kg per min	22.5 ± 1.2	12.9 ± 0.7	0.0001
Submaximal treadmill test			
VO$_{2peak}$, mL/kg per min	7.4 ± 0.3	7.2 ± 0.3	0.57
tc$_{deficit}$	29.9 ± 3.6	60.0 ± 8.3	0.002
tc$_{EPOC}$	33.8 ± 3.1	52.2 ± 3.8	0.001

Data are presented as mean ± SE. tc$_{deficit}$: lag in oxygen uptake at the beginning of exercise (oxygen deficit); tc$_{EPOC}$: excess oxygen uptake above rest following exercise (excess post-exercise oxygen consumption); VO$_{2peak}$: peak oxygen uptake.

In addition, the HF group reported much lower total physical activity, particularly moderate or greater intensity physical activity, compared to control. Table 4 shows the relationships between VO$_{2peak}$, submaximal oxygen uptake kinetics, functional mobility, and physical activity. In controls, VO$_{2peak}$ was more strongly associated with functional mobility and physical activity ($r = 0.48–0.72$) than were measures of submaximal oxygen uptake kinetics, tc$_{deficit}$ and tc$_{EPOC}$ ($r = 0.14–0.39$). Among the HF, tc$_{deficit}$ and tc$_{EPOC}$ correlations ($r = 0.48–0.57$) with GUG and CGS were similar to those with VO$_{2peak}$ ($r = 0.45–0.59$). Therefore, in HF, submaximal oxygen kinetics were as strongly related to functional mobility measures as VO$_{2peak}$. However, in HF, neither VO$_{2peak}$ nor the submaximal oxygen kinetics measures were strongly related to self-reported total or moderate

Table 3. Functional mobility and self reported physical activity.

Variable	Control ($n = 25$)	HF ($n = 25$)	P value
Functional mobility			
GUG, s	10.4 ± 0.4	14.3 ± 1.7	0.03
CGS, m/s	1.2 ± 0.1	0.9 ± 0.1	0.0001
Impaired US (% of group able only < 5 s)	22% (5/23)	71% (15/21)	0.002*
Self-reported physical activity			
CHAMPS (kcal/day, total)	3421 ± 428	1893 ± 353	0.01
CHAMPS (kcal/day, ≥ moderate)	2024 ± 296	796 ± 219	0.004

Data are presented as mean ± SE unless other indicated. *Fisher's exact test. CGS: comfortable gait speed; EPESE: established populations for the epidemiologic study of the elderly (higher score indicates more disability); CHAMPS: community healthy activities model program for seniors (daily physical activity reported as expenditure of total kilocalories and kilocalories for intensity of activity at a level of moderate or more); GUG: get up and go; US: unipedal stance.

Table 4. Relationships between VO_{2peak} on peak treadmill, submaximal oxygen uptake kinetics, functional mobility, and physical activity.

Variable	VO_{2peak}	$tc_{deficit}$	tc_{EPOC}
Controls			
VO_{2peak}		–0.55	–0.47
Functional mobility			
GUG	–0.57*	0.37	0.30
CGS	0.54*	–0.39	–0.30
US	0.48*	–0.14	–0.04
Physical activity			
CHAMPS (total)	0.63*	–0.21	–0.11
CHAMPS ($\geq$ moderate)	0.72*	–0.29	–0.22
CHF			
VO_{2peak}		–0.37	–0.40
Functional mobility			
GUG	–0.45*	0.48*	0.11
CGS	0.59*	–0.57*	–0.58*
US	0.32	0.25	0.20
Physical activity			
CHAMPS (total)	0.04	0.1	–0.05
CHAMPS ($\geq$ moderate)	0.13	0.19	–0.03

*$P < 0.05$. CHF: congestive heart failure; CHAMPS: community healthy activities model program for seniors; CGS: comfortable gait speed; GUG: get up and go; $tc_{deficit}$: lag in oxygen uptake at the beginning of exercise (oxygen deficit); tc_{EPOC}: excess oxygen uptake above rest following exercise (excess post-exercise oxygen consumption); US: unipedal stance; VO_{2peak}: peak oxygen uptake.

intensity physical activity. Despite the significantly greater BMI in HF than controls (see Table 1), all of the HF-control group differences cited below remained significant after using ANOVA to control for the covariate BMI.

4 Discussion

The HF participants, as expected, demonstrated significant impairments in VO_{2peak}, submaximal oxygen uptake kinetics, and functional mobility compared with age and gender-matched controls. In controls, VO_{2peak} was more strongly related to functional mobility and physical activity than submaximal oxygen kinetics. In the HF group, submaximal oxygen uptake kinetics were as strongly related to functional mobility as VO_{2peak}. These data are consistent with previous findings by our group that submaximal oxygen kinetics are as strongly related to functional mobility as VO_{2peak} in mobility-impaired individuals without heart failure.[9] The present study now provides vital data in HF patients who as well.

Aside from the practical advantages in using a submaxi-

mal test instead of a maximal test, submaximal oxygen kinetics may also provide a better mechanistic link to determine the relationship between aerobic function and daily mobility in HF. A delay in oxygen kinetics in HF (specifically in $tc_{deficit}$) reflects a delay in muscular oxygen uptake,[27] and muscular function is considered the key factor in performing daily mobility tasks. Furthermore, the calculation for oxygen uptake kinetics on recovery adds additional information, addressing the oxygen debt that needs to be repaid after exercise and that reflects oxygen delivery and oxygen utilization to muscles and changes in muscle composition from type I to less efficient type IIb fiber type.[28] Finally, in addition to prognostic value in HF (see introduction), oxygen uptake kinetics may be a key outcome for training in HF because of these skeletal muscle oxygen utilization issues.[29]

Given their poor performance in maximal treadmill and functional mobility tests, HF patients are at high risk of adverse functional outcomes. In particular, disability, hospitalization, and institutionalization are more likely to occur in older adults with mean VO_{2peak} < 18 mL/kg per min, and mean CGS <1 m/s.[18,30] Moreover, with a mean GUG > 13.5 and the majority of the HF group only able to stand < 5 s in US, patients with HF are at high risk for falls,[31] and injurious falls in particular.[32] Compounding this issue is that patients with HF commonly have gait abnormalities, such as in step variability,[33] increasingly recognized as a significant predictor of falls.[34] A recent paper linked HF to an increased incidence of hip fractures,[35] but did not consider impaired postural control and gait disturbances as potential underlying causes.

In the present study, a self-report instrument was administered according to American Heart Association (AHA) statement algorithms for physical activity measurement.[36] There are advantages and disadvantages of different physical activity measurement techniques, as recently reviewed in an AHA scientific statement.[36] Physical activity in HF as evaluated by self-reported questionnaire relates to VO_{2peak}, especially with activities greater than 3 METs.[37,38] Similarly, accelerometric measures associate with VO_{2peak}, 6-min walk distance, and subsequent morbid events.[39,40]

The HF group in this study reported low physical activity, expending only 796 kcal/week in moderate and vigorous activity and 1893 total kcal/week. Nevertheless, a number of HF participants with very low self-reported physical activity paradoxically had relatively higher VO_{2peak}. The reason for this is not entirely clear but may reflect the gap between usual activity, where patients tend to restrict their activity to manage symptoms, and residual capacity, where patients are willing work harder and endure more symptoms under supervised maximal treadmill conditions.[41]

Alternatively, the lack of correlation may indicate a limitation in use of self reported physical activity measures, and suggests that future studies might also utilize more objective measures of physical activity such as accelerometers. Based on a recent comparison,[42] self-report of physical activity was reasonably successful in classifying HF patients with minimal symptoms (NYHA class I) and those with symptoms during less than usual activity (NYHA class III), whereas accelerometry independently predicted VO2$_{peak}$ and was better at identifying NYHA class III patients. Advantages and disadvantages of both measures continue to be identified, although the CHAMPS questionnaire used in the present study is well-established and recommended for older adults.[43] The present study reports baseline data for an exercise intervention to improve mobility as well as physical activity, and thus self-reported physical activity was important for customization of the intervention and a primary focus for repeated assessment. Future studies in older adults should consider using both CHAMPS and accelerometry, as providing complementary information.[44]

Finally, other factors may account for more modest relationships between measured aerobic function and physical activity in HF. Of the oxygen uptake and kinetics measures, only VO2$_{peak}$ correlated significantly with KCCQ, and only with the overall clinical summary score ($r = 0.54$, $P < 0.05$). The clinical summary score reflects a number of behavioral and health status assessments, including self-reported physical limitations, symptoms, social interference and quality of life. Other studies confirm that behavioral measures, such as self efficacy, predict physical activity in HF better than VO2$_{peak}$.[45] Given modest associations between health and functional status in HF and VO2$_{peak}$, laboratory exercise tolerance may not be a good reflection of how patients perceive their capacity to undertake daily activities.[7]

One other possible explanation of the relationship between aerobic function and physical activity relates to the workload of the maximal and submaximal tests. The submaximal test at 1 mph presents a minimal load to the controls but a more substantial load to the HF, particularly those with more advanced HF,[46] and thus the VO2 levels measured in the HF are more physiologically (and functionally) meaningful. Daily tasks require more effort and oxygen uptake for HF than healthy controls.[47] Reproducibility for submaximal oxygen uptake kinetics may decrease at lower loads, particularly for healthy adults.[10] Recent work highlights the use of six minute walk distance as a predictor for HF mortality and hospitalization.[48] The six minute walk test has been used with accelerometry to provide additional telehealth information about step count and overall activity level,[49] and with oxygen kinetics analysis using a portable gas analyzer as a predictor of HF adverse outcomes.[50] In both these situations, the distance covered during the six minute walk (and thus the work accomplished) can vary, making these outcomes somewhat difficult to interpret.

Other measures of submaximal oxygen uptake that relate to important clinical outcomes may also be considered. Individualization of submaximal load based on other measurements such as anaerobic threshold may be more physiologically meaningful but may be difficult to obtain in older HF patients.[51] Using portable measurement devices, others have reported that percent of peak VO2 utilized during activities of daily living, even when self-paced, is higher in HF patients than controls.[47] Finally, estimation of the oxygen uptake efficiency slope uses an extrapolation of oxygen utilization at certain percentages of maximal testing, and holds promise in use with HF patients,[52] and in predicting HF patient survival.[53] Whether the oxygen uptake efficiency slope is a better predictor of mobility function and physical activity than oxygen uptake kinetics remains to be determined.

Limitations of these data include the modest sample size of self-selected volunteers for this pilot exploratory study. A larger sample size of more representative participants should be considered in future study replication.

In conclusion, based on their mobility task performance, older HF patients with reduced ejection fraction are at risk for adverse functional outcomes. In this population, submaximal oxygen uptake measures may be equivalent to VO2$_{peak}$ in predicting functional mobility, and in addition to being more feasible, may provide better insight into how aerobic function relates to mobility in older adults with HF.

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