



## The Relation Between Physiological Markers of Cardiovascular Health and Quality of Life in Heart Failure

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### ABSTRACT

**Acree LS, Porter CB, Godard MP.** The Relation Between Physiological Markers of Cardiovascular Health and Quality of Life in Heart Failure. **JEPonline** 2012;15(6):13-22. This cross-sectional study examined the associations among functional capacity, ejection fraction, and health-related quality of life (HRQoL) in stable heart failure patients. Twenty-one stable NYHA Class II and III heart failure patients (mean age =  $56.9 \pm 11.1$  yrs; BMI =  $28.9 \pm 4.2$  kg·m<sup>-2</sup>) participated in this study. The subjects underwent cardiopulmonary treadmill testing to determine peak oxygen consumption ( $VO_2$  peak =  $16.9 \pm 5.3$  mL·kg<sup>-1</sup>·min<sup>-1</sup>) and ventilatory threshold ( $961.9 \pm 308.4$  ml). The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess HRQoL. Ejection fraction was assessed by echocardiogram (EF =  $28.9 \pm 8.03\%$ ). HRQoL was non-significantly ( $P > 0.05$ ) related to  $VO_2$  peak ( $r = 0.221$ ), EF ( $r = 0.204$ ), and ventilatory threshold ( $r = 0.108$ ). However, the physical limitation domain of the KCCQ was independently related ( $P < 0.05$ ) to  $VO_2$  peak ( $r = 0.621$ ) and ventilatory threshold ( $r = 0.555$ ). The physiological markers of cardiovascular health were specifically related to the physical limitations domain of the KCCQ. These same markers, however, were not associated with overall HRQoL, which suggest that both quantitative and qualitative measures may be used to better assess cardiovascular health in heart failure patients.

**Key Words:** Exercise,  $VO_2$  Peak, Ejection Fraction, Echocardiogram

## INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from impaired ability of the heart to distribute blood, either from insufficient ventricular filling or the insufficient ability to eject blood. Individuals with HF may demonstrate dyspnea and fatigue (limiting exercise tolerance) and fluid retention (leading to pulmonary congestion and edema), which may ultimately lead to a reduction in functional status. Preventing the physiological progression of the disease in addition to maintaining the functional capability (i.e., exercise capacity and ventricular function) is a major priority in the management of HF. However, alleviating the symptoms and patient suffering is another area of primary concern in the treatment of HF that cannot be overlooked.

Functional capacity (peak oxygen consumption,  $VO_2$  peak) and cardiac function (i.e., ejection fraction) have long been accepted by allied healthcare professionals as the primary physiological parameters used to assess and monitor the progression of HF (11-13,16,24). From a traditional perspective, in order to classify and determine functional status based on symptoms, the New York Heart Association (NYHA) classification has been used (1). This classification (Class I – IV) has provided a simple, generic means for relating the patient's symptoms to disease progression. Furthermore, health-related quality of life (HRQoLs) instruments are becoming more accepted, standardized, and precise as measures for a subjective measurement on health status (4,5,9,22). Given that improving quality of life for individuals has continued to gain momentum as a primary goal for exercise physiologists and medical professionals, it is imperative that we understand it thoroughly.

Some consensus exists in that physiological domains and symptoms have been related to HRQoL in clinical populations (5,9). Green et al. (9) determined a significant relationship between distance walked in a 6-min walk test to the HRQoL scores ( $r^2 = 0.48$ ,  $P < 0.001$ ), yet a gap remains in what is known about physiological function and how it affects the HRQoL in HF patients. Therefore, the purpose of this investigation was to determine if physiological function (i.e., functional capacity and cardiac function) are related to HRQoL, as assessed by the KCCQ, in NYHA class II and III HF patients.

## METHODS

### Subjects

This was a cross-sectional study involving 21 individuals (12 males and 9 females,  $56.9 \pm 11.1$  yrs of age) who were outpatients at a Medical Center in the Midwestern United States. All patients were clinically diagnosed as having stable ( $\geq 3$  months) NYHA class II or class III HF (as determined by a board certified cardiologist) with a documented ejection fraction of less than 40%. Individuals with insulin dependent diabetes or with pulmonary dysfunction or disease (i.e., COPD) were excluded from participation in the study. Prior to the initiation of any testing, the subjects were informed of the procedures and risks associated with the study. The participants then signed an informed consent in accordance with the Institutional Review Board.

### Procedures

#### ***Determining Heart Function: Echocardiography***

Left ventricular ejection fraction (LVEF) was determined from a two-dimensional echocardiogram (Acuson, Aspen; Malvern, PA). The left ventricular systolic and diastolic function was assessed with the subjects in the left lateral position in a resting state. Specifically, left ventricular endocardial and epicardial borders in the left parasternal short-axis view and the apical four-chamber view, from at least five high quality frozen end-diastolic (onset of QRS complex) and end-systolic (aortic valve

closure) frames were captured for analysis. The LVEF was calculated using the end-systolic volume (ESV) and the end-diastolic volume values (EDV) via the Simpson's rule algorithm.

### ***Cardiopulmonary Exercise Testing: VO<sub>2</sub> Peak Testing***

In order to accurately determine the gases exchanged during the cardiopulmonary exercise testing (CPET), a metabolic cart (CardiO<sub>2</sub>/CP, MedGraphics; St. Paul, MN) was used. After a warm-up for approximately 30 min, the pneumotach and gas analyzers were calibrated before testing each subject. Then, each subject was fitted with a nose clip to seal the nostrils allowing air to only escape from the mouth to the metabolic cart for analysis. The subject was required to remain relaxed in a seated position with minimal movements for 2 min so that baseline oxygen consumption (VO<sub>2</sub>) and carbon dioxide production (VCO<sub>2</sub>) values could be obtained. The laboratory tester responsible for conducting the CPET was blinded to the HRQoL status and LVEF values of each subject.

The CPET was conducted using a Modified Bruce Protocol to exhaustion on a treadmill (Trackmaster, MedGraphics; St. Paul, MN) during continuous electrocardiographic monitoring. At the start of the test, the subject was asked to start walking at a comfortable pace completing a brief warm-up. Each subject was encouraged to exercise until exhaustion. The highest VO<sub>2</sub> value was recorded as the VO<sub>2</sub> peak value in mL·kg<sup>-1</sup>·min<sup>-1</sup>. Throughout the duration of the protocol, heart rate (HR) was recorded every minute while blood pressure (BP) and the Rating of Perceived Exertion (RPE) was recorded only once during each stage (at ~2:30 of each 3-min stage). RPE was assessed using the Borg rating scale ranging from 6 (lightest level of exertion) to 20 (absolute most difficult level of exertion) (6). At the end of the test, the highest of all of the monitored values (HR, BP, and RPE) was determined to be the peak value. All of the tests were terminated due to fatigue. There were no additional clinical symptoms that limited the test for any of the HF subjects.

### ***Anaerobic Threshold***

After the functional capacity test was completed, anaerobic threshold (AT) was calculated from the test data. Using the metabolic cart (CardiO<sub>2</sub>/CP, MedGraphics; St. Paul, MN), the values for the gas exchange ratio (VCO<sub>2</sub>/VO<sub>2</sub>) every 10 sec averaged throughout the test were charted on a scatter-plot graph. The point at which the curve changed from flat or gently rising to a steeper slope was determined to be the AT. The same experienced reviewer made the visual determination of the AT for all of the subjects.

### ***Kansas City Cardiomyopathy Questionnaire***

To assess the HRQoL, each subject completed the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is a self-administered 23-item questionnaire (9), prior to the VO<sub>2</sub> testing. As previously defined, the KCCQ quantifies physical limitation, symptoms, quality of life, social interference, and self-efficacy in a heart failure population (9). Responses were ordered on an adjectival (Likert) scale and transformed to a score ranging from 0 to 100, as described by Green et al. (9) to better facilitate interpretability and clinical gradation. The questionnaire was scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning and summing items within each domain (9).

A clinical summary score is calculated by combining the functional status (physical limitations and symptom domains) with the quality of life and social limitation domains. For our analysis, we use the clinical summary score to represent overall HRQoL. The Kansas City Cardiomyopathy Questionnaire (KCCQ) has demonstrated to be a reliable (Clinical summary,  $\alpha = 0.95$ ) and valid (clinical summary,  $r^2 = 0.55$ ,  $P < 0.001$ ) HRQoL instrument for HF patients, and has served as a clinically meaningful outcome measure in patient management and quality assessment (7).

## Statistical Analyses

Means and standard deviations (SD) were calculated for all variables ( $VO_2$  peak, LVEF, and HRQoL). Independent t-tests were conducted among all variables to detect significant differences in a gender comparison. Additionally, Pearson correlation coefficients were calculated to assess the relationships among  $VO_2$  values, LVEF, and HRQoL domains. In an attempt to control for possible influential variables on HRQoL (i.e., age), a partial correlation was used to further examine the relationship between the physiological parameters and HRQoL. The overall significance level was set at  $P < 0.05$ .

## RESULTS

Baseline physical and clinical characteristics for the group are presented in Table 1. As mentioned in the inclusion criteria, all subjects were classified as NYHA Class II or III HF (Class II,  $n = 16$ ; Class III,  $n = 4$ ). Hemodynamic, metabolic, and echocardiographic results for the subjects are presented in Table 2. The scores and domains scored on the KCCQ are depicted in Table 3. Lastly, an independent t-test revealed that there were no differences between genders ( $P > 0.05$ ) for all of the measured variables.

**Table 1.** Mean and Standard Deviation Values of the Baseline Physical Characteristics for the Whole Group ( $n = 21$ ) and the Number of Subjects Taking Each Type of Cardiovascular Medication in this Study.

	<b>Mean</b>	
<b>Height (cm)</b>	$171.8 \pm 8.8$	
<b>Weight (Kg)</b>	$85.3 \pm 14.0$	
<b>Age (yrs)</b>	$56.9 \pm 11.1$	
<b>Body-Mass Index (BMI)</b>	$28.9 \pm 4.2$	
<b>Medication Use</b>	<b>Total Number (n)</b>	<b>% of Total Sample</b>
ACE Inhibitor	19	90%
ATII Antagonist	1	5%
Beta Blocker	21	100%
Diuretic	19	90%
Calcium Channel Blocker	2	10%
Nitrate	8	38%
Anti-Coagulant	15	71%
Antiarrhythmic	13	62%

ACE = Angiotensin Converting Enzyme; ATII = Angiotensin Two.

**Table 2.** Mean and Standard Deviation Values for all Measured Variables in the Functional Capacity and Hemodynamics Testing for the Total Sample (n = 21).

	<b>Mean</b>
<b>Functional Capacity Component</b>	
<b>Relative VO<sub>2</sub> peak</b> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	16.9 ± 5.3
<b>Absolute VO<sub>2</sub> peak</b> (mL·min <sup>-1</sup> )	1440.8 ± 517.8
<b>Anaerobic Threshold</b> (mL·min <sup>-1</sup> )	961.9 ± 308.4
<b>% of Peak VO<sub>2</sub></b>	64.9 ± 8.8
<b>Heart Rate at Peak Exercise</b> (beats·min <sup>-1</sup> )	125 ± 22
<b>Systolic Blood. Press. at Peak Ex</b> (mmHg)	149 ± 28
<b>Diastolic Blood Press. At Peak Ex</b> (mmHg)	66 ± 10
<b>Rating of Perceived Exertion at Peak</b>	17 ± 2
<b>Time of Exercise</b> (sec)	659.8 ± 213.5
<b>Cardiac Function</b>	
<b>Ejection Fraction</b> (%)	28.9 ± 8.0

**Table 3.** Mean and Standard Deviation Values for the Health-Related Quality of Life (HRQoL) Summary Scores from the Kansas City Cardiomyopathy Questionnaire (KCCQ) for the Total Sample (n = 21).

<b>HRQoL (KCCQ)</b>	<b>Mean</b>
<b>Clinical Score</b>	70.2 ± 17.9
<b>Physical Limitations</b>	68.7 ± 18.8
<b>Self-Efficacy</b>	84.6 ± 20.1
<b>Combined Symptoms</b>	72.0 ± 20.9
<b>Social Limitations</b>	63.5 ± 27.0
<b>Quality of Life</b>	66.2 ± 22.9

Pearson correlation coefficients among the physiological measures and the quality of life domains are presented in Table 4. Left ventricular ejection fraction and relative VO<sub>2</sub> peak demonstrated non-significant (P>0.05) correlations with each of the quality of life domains. However, the physical limitation domain did demonstrate a significant correlation with absolute VO<sub>2</sub> peak (r = 0.45, P=0.039) and anaerobic threshold (r = 0.467, P=0.044). Additionally, left ventricular ejection fraction demonstrated non-significant relationships (P>0.05) with VO<sub>2peak</sub> values and anaerobic threshold.

**Table 4.** Correlations Among VO<sub>2</sub> Variables, EF, and QoL Domains in Heart Failure Patients.

<b>Variables</b>	<b>Relative VO<sub>2peak</sub></b>	<b>Absolute VO<sub>2peak</sub></b>	<b>Anaerobic Threshold</b>	<b>Ejection Fraction</b>
<b>Clinical Score</b>	0.010	0.236	0.245	0.257
<b>Physical Limitations</b>	0.260	0.453*	0.467*	0.211
<b>Self-Efficacy</b>	0.159	0.052	-0.009	-0.096
<b>Combined Symptoms</b>	0.202	0.002	0.009	0.254
<b>Social Limitations</b>	-0.010	0.028	0.042	0.367
<b>Quality of Life</b>	0.221	0.067	0.108	0.204
<b>Ejection Fraction</b>	0.316	0.328	0.030	--

\*Denotes a significant correlation between variables (P<0.05).

An age-adjusted correlation was used to examine the relationship between functional capacity, EF, and HRQoL among the subjects. The results are presented in Table 5. The relationship between the EF and the quality of life domains remained non-significant (P>0.05). The relative VO<sub>2peak</sub> was found to significantly correlate with the physical limitations domain (r = 0.483, P=0.042). Additionally, adjusting for age strengthened the correlations between the physical limitations and absolute VO<sub>2peak</sub> (r = 0.621, P=0.006) and anaerobic threshold (r = 0.555, P=0.012).

**Table 5.** Age-Adjusted Correlations Among VO<sub>2</sub> Variables, EF, and QoL Domains in HF Patients.

<b>Variables</b>	<b>Relative VO<sub>2peak</sub></b>	<b>Absolute VO<sub>2peak</sub></b>	<b>Anaerobic Threshold</b>	<b>Ejection Fraction</b>
<b>Clinical Score</b>	0.246	0.431	0.381	0.296
<b>Physical Limitations</b>	0.483*	0.621**	0.555*	0.227
<b>Self-Efficacy</b>	0.263	0.042	0.079	0.053
<b>Combined Symptoms</b>	0.006	0.171	0.131	0.306
<b>Social Limitations</b>	0.013	0.027	0.094	0.351
<b>Quality of Life</b>	0.131	0.008	0.006	0.169
<b>Ejection Fraction</b>	0.095	0.114	0.012	--

\*Denotes a significant correlation between variables (P<0.05). \*\*Denotes a significant correlation between variables (P<0.01).

## DISCUSSION

In this investigation, we examined the relations between peak functional capacity, cardiac function and HRQoL in a stable HF population with advanced symptoms and specifically determined the contribution of the hemodynamic and metabolic parameters to the patient's HRQoL. The primary findings revealed that: (1) the functional capacity ( $\text{VO}_2$  peak) and HRQoL were not significantly related in this HF population; and (2) the cardiac function, as measured by the echocardiographic EF, was not related to HRQoL or peak functional capacity as measured by the peak oxygen consumption method.

The functional capacity values obtained in this study were not unexpected with the average  $\text{VO}_2$  peak ( $16.9 \pm 5.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) values reported earlier (1). The anaerobic threshold, which defines when ventilation demands exceed what is produced aerobically (12,20), was measured to ensure that the termination of the exercise test was because of exhaustion instead of a motivational influence. In the current study, the anaerobic threshold was obtained from 90% of the sample and averaged  $11.2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (64% of the average  $\text{VO}_2$  peak), which accurately reflects previously reported values (12,15,16,24). The anaerobic threshold may represent metabolic efficiency (ability to exercise) at a given intensity of physical activity more appropriately in HF patients, since a true  $\text{VO}_2$  max cannot be achieved due to lack of motivation or physical limitations (16). The anaerobic threshold may be used to assess disease progression and/or severity, as it provides a useful index of change after an intervention (13) with low inter-observer variability and good reproducibility (17,20,22).

The direct assessment of  $\text{VO}_2$  peak during exercise allows for a more accurate measurement of work performed and capacity to do work in a setting where the work intensity of a patient is pushed beyond levels of personal comfort (16). In the present study, using maximal force work capacity with graded exercise in conjunction with the KCCQ, the correlation seen between the voluntary maximal performance defined by the 6-min walk (i.e., voluntary functional capacity) and the KCCQ (9) could not be established. However, the significant relationship between the physical limitation domain and the anaerobic threshold ( $r = 0.555$ ,  $P=0.012$ ) offers a new, physiologically objective, parameter of functional capacity reflected by the KCCQ questionnaire. Therefore, this revelation could add an advantage to the employment of the KCCQ in the management of HF, as the anaerobic threshold has been shown to have a high prognostic value for increasing risk of early death in HF patients (8).

Although the subjects' LVEF responses were low ( $28.9 \pm 8.0\%$ ), they were typical for the HF patient population (7,11,13). As hypothesized, the LVEF did not correlate significantly with the subjects' functional capacity ( $P=0.16$ ). Interestingly, previous reports also failed to demonstrate a relationship between maximal exercise capacity and EF at rest (2,3,7,21) or between the response in EF to exercise of different intensities (7). Collectively, these findings support the concept that functional capacity and central hemodynamics are not dependent upon one another.

Like the functional capacity values, the cardiac function was not correlated with HRQoL scores from the KCCQ ( $P=0.37$ ). Although we had hypothesized that a significant correlation would be established, HF patients have demonstrated a poor correlation between symptomatic status (i.e., HRQoL) and left ventricular EF. This finding suggests that the influence of HRQoL may not depend strongly upon the most easily obtained clinical marker of ventricular function (EF), but may be dependent on more complex or less easily measured set of physiologic or psychological parameters.

The KCCQ prognostic value has recently been confirmed in a population of patients with ACE inhibitors and beta blockers with or without aldosterone blockade who were not subjected to graded or voluntary peak exercise studies (19). The prognostic value of the  $\text{VO}_2$  peak test in congestive HF

was initially established in patients without beta blocker therapy. The presence of beta blocker therapy has been postulated to have a confounding effect upon the prognostic value of the  $\text{VO}_2$  peak result in patients with HF (18).

Relative to this clinical population, these results provide pertinent insight regarding the relationships among these parameters in health assessment. It should also be noted that the relationship between the physiological parameters and the HRQoL persists after adjusting for the wide age range in this group of HF patients. While physical activity levels could have also produced a confounding influence, all subjects were for the most part inactive. Furthermore, in an attempt to stabilize the degree of severity in HF, only NYHA class II and III patients participated in the study. Perhaps, the relations would have been more robust if NYHA classes I and IV had been included in this study.

## CONCLUSIONS

In summary, this investigation found that HRQoL was not associated with forced peak functional capacity or with a measure of resting cardiac function. Furthermore, peak forced functional capacity was not significantly correlated to the resting EF (i.e., an indicator of myocardial dysfunction). The difference between the peak oxygen capacity, which forces the subject to walk at increasing speed and grade, and the previously correlated 6-min walk test (9) that allows the subject to select a comfortable increase in speed or grade may be the factor that influences the correlation between the exercise result and the HRQoL score.

This discordance underscores the importance of assessing and managing cardiovascular health through a holistic approach, which should incorporate objective evaluations of functional capacity and myocardial function in addition to patient centered HRQoL to obtain a comprehensive assessment of functional status and prognosis.

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