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Six-Minute Walk Test Among Heart Transplant Recipients

S.-Y. Chen, P.-C. Lu, C. Lan, N.-K. Chou, Y.-S. Chen, J.-S. Lai, and S.-S. Wang

ABSTRACT

Objective. Six-minute walk test (6MWT) is an important measure to assess the exercise capacity of cardiac patients. This study aimed to evaluate the correlations of 6MWT with findings of cardiopulmonary exercise testing (CPET), health-related quality of life (HRQoL), and obesity among heart transplantation recipients (HTR) at least 1 year after transplantation.

Method. Clinically stable HTR were recruited for this study from the National Taiwan University Hospital, Taipei, Taiwan. The 6MWT was performed by a physical therapist following the American Thoracic Society standard. Each subject underwent a symptom-limited CPET to evaluate cardiorespiratory fitness and bioelectrical impendence analysis for determination of body composition. The HRQoL of study subjects was evaluated by the Medical Outcomes Trust 36-item health survey (SF-36).

Results. The study subjects included 43 HTR (age: 47.8±11.1 years; 37 men, 6 women) at 4.8±3.2 years after transplantation. The 6MWT distance was 539±108 m (89.9±18.2% of the predicted value). The peak oxygen uptake was 19.3±4.7 mL/kg/min. The body composition analysis showed body fat percentage 25.2±7.9%, body mass index 26.5±4.8, and waist circumference 94.8±13.3 cm. The 6MWT distance was significantly positively correlated with peak oxygen uptake, peak heart rate, peak work rate, and peak systolic blood pressure during CPET, and significantly negatively correlated with body fat percentage, body mass index, and waist circumference. The 6MWT distance was also significantly positively correlated with SF-36 HRQoL parameters including general health perception and standardized physical component scale. The peak HR during CPET and standardized physical component scale was significantly correlated with 6MWT distance in multivariate analysis.

Conclusions. Our findings indicate that 6MWT is a simple and useful measure to assess the exercise capacity of clinically stable HTR. The 6MWT distance is positively correlated with HRQoL and negatively correlated with obesity among HTR. The prognostic significance of 6MWT for HTR requires further investigation.

HEART transplant recipients (HTRs) were reported to have persistent impairment in exercise capacity after transplantation [1]. Health-related quality of life (HRQoL) has emerged as an important measurement in both clinical and research settings corresponding with the increased life expectancy of HTRs [2]. Low exercise capacity may lead to exercise intolerance, poor clinical outcome, and prevention of patients from performing daily activities. Low exercise capacity is also considered as one of the key determinants of impaired HRQoL [3]. HRQoL measures may be disease specific or generic. Our previous study has demonstrated that a common generic measure of HRQoL, the short form 36 (SF-36), showed the improvement of HRQoL during an early outpatient cardiac rehabilitation program for HTRs [4].

Measurement of oxygen uptake ($\dot{V}O_2$) during cardiopulmonary exercise testing (CPET) is the gold standard for determining exercise capacity in cardiac patients [5]. The

From the Department of Physical Medicine and Rehabilitation (S.-Y.C., P.-C.L., C.L., J.-S.L.), National Taiwan University Hospital; National Taiwan University College of Medicine (S.-Y.C., C.L., N.-K.C., Y.-S.C., J.-S.L., S.-S.W.); and the Department of Surgery (N.-K.C., Y.-S.C., S.-S.W.), National Taiwan University Hospital, Taipei, Taiwan.

Address reprint requests to Shoei-Shen Wang, MD, PhD, Department of Surgery, National Taiwan University Hospital, 7 Chun-Shan South Road, Taipei 10002, Taiwan. E-mail: wangp@ntu.edu.tw

0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.11.015

CPET involves complex equipment, technical support, and personnel who are proficient in the administration and interpretation of the test [6]. Owing to its complexity, CPET is not widely available in all settings of clinical practice. On the other hand, the 6-minute walk test (6MWT), a popular and commonly used submaximal exercise test, requires minimal equipment and technical support. Because 6MWT is easy to perform, it has been applied to evaluate the exercise capacity of patients with chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung disease, and congestive heart failure and in the presurgical evaluation of patients [7,8].

The distance walked at 6MWT showed variable degrees of correlation with peak oxygen uptake ($\dot{V}O_2$ peak) or $\dot{V}O_2$ at ventilator threshold (VeT) obtained during CPET in different studies, in particular due to the characteristics of each group under investigation [9]. Previous studies showed negative correlation between $\dot{V}O_2$peak and obesity in HTRs [10,11]. By the way, scarce small sample studies have used the 6MWT to evaluate the exercise capacity of HTRs [12,13]. The reported 6MWT distance included 516.5 ± 12.8 m (85.3% ± 2.5% of the predicted) from 22 male HTRs at 5 years after transplantation, 486 ± 55 m (88.4% of the predicted) from 14 HTRs (12 males and 2 females) at 4 years after transplantation [12,13]. The purpose of this study was to evaluate the correlations of 6MWT distance with findings of CPET, HRQoL, and body composition among HTRs at least 1 year after transplantation.

METHODS

This cross-sectional study invited clinically stable adult HTRs at least 1 year after transplantation during their follow-up at the Department of Surgery, National Taiwan University Hospital in 2012. The subjects were excluded if they had: (1) active congestive heart failure, (2) active rejection or recent infection, (3) unstable dysrhythmias, (4) exercise limited by neurological or orthopedic disease, and (5) uncontrolled diabetes and/or hypertension. All procedures were fully explained to the patients, and written consents were obtained. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital.

Body Composition Analysis

Body composition was measured using the anthropometric method and bioimpedance analysis. The body mass index (BMI) was calculated as body weight (kg) divided by height in meters squared (kg/m^2). The waist circumference was measured at a level midway between the lowest rib and the iliac crest with a tape. Body fat percentage was measured using a bioelectrical impedance analyzer (BioScan 920, Maltron International Ltd., Essex, United Kingdom).

6MWT

The 6MWT was performed according to the American Thoracic Society standards to measure the distance that the study subjects were able to walk within a 6-minute period [7]. The study subjects were asked to walk as far as possible at a self-determined speed. No other advice was provided. The test was performed by an experienced physical therapist. The percentage predicted 6MWT distance was calculated considering gender, age, height, and weight of each subject based on the equation by Enright et al [14].

CPET

Each subject underwent the CPET using a bicycle with continuous electrocardiographic monitoring and analysis of expired gases by an automated system (MetaMax 3B, Cortex Biophysik GmbH, Leipzig, Germany) until intolerable dyspnea or muscular fatigue occurred. The work rate was 10 watts for the first 3 minutes (familiarization period) and was then increased by 10 watts every minute. The pedaling cadence was maintained between 50 and 70 rpm. Automated blood pressure (BP) monitor (TANGO, SunTech Medical Instruments, Inc., Morrisville, North Carolina, United States) was used for BP measurement before the test, during exercise, and during recovery. The cardiorespiratory variables including heart rate (HR), $\dot{V}O_2$, and carbon dioxide production ($\dot{V}CO_2$) were continuously measured. The data were averaged every 30 seconds for further analysis. The $\dot{V}O_2$ peak was defined as the highest $\dot{V}O_2$ attained during CPET.

The VeT was determined by using at least 2 of the following criteria: (1) the ventilatory equivalent for oxygen began to increase systematically without a corresponding increase in the ventilatory equivalent for CO_2, (2) the end tidal PO_2 began to increase without a decrease in the end tidal PCO_2, or (3) the departure from linearity for minute ventilation [6,15]. Two independent observers with experience in CPET reviewed each determination of the VeT.

Quality of Life

HRQoL was evaluated using the Chinese version of the 36-item Short-Form Health Survey (SF-36) [16]. The SF-36 comprises 36 items that cover the domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Individual subscales scores and 2 summary scores, defined as physical component score (PCS) and mental component score (MCS), were computed. PCS is an overall assessment of physical health, including both actual function and the patient's evaluation of the ability to perform an activity. MCS is an overall measurement of mental health, role-emotional, social functioning, and overall vitality.

Data Analysis

All analyses were performed using the SAS System for Microsoft Windows (Version 9.2, SAS Institute Inc., Cary, NC, United States). The summary of the observed continuous variables was expressed as means ± standard deviation. Pearson product-moment correlation analysis was performed to evaluate the linear correlation between 6MWT distance and the other interested variables. Stepwise multiple linear regression models were applied for multivariate analysis of associations with 6MWT distance. Only variables with $P < .10$ were kept in the final models. A 2-tailed $P < .05$ was considered to be indicative of statistical significance.

RESULTS

The study included 43 clinically stable HTRs (age, 47.8 ± 11.1 years; 86% were men and 14% were women) at 4.8 ± 3.2 years after transplantation. The reason for heart transplantation included 26 dilated cardiomyopathy, 13 ischemic cardiomyopathy, and 4 other causes. All participants were treated according to immunosuppressive protocols with tacrolimus, cyclosporine, corticosteroid, rapamycin, or

mycophenolate mofetil. Table 1 lists the demographic, clinical characteristics, CPET variables, and HRQoL parameters based on administration of SF-36 to the study subjects. The 6MWT distance was 539 ± 108 m (range, 287–730), as 89.9% ± 18.2 % (range, 53.1–129.8) of the predicted value.

Table 2 lists the findings of Pearson correlations of 6MWT distance with clinical characteristics, CPET variables, and HRQoL parameters. The 6MWT distance was significantly positively correlated with $\dot{V}O_2$ peak, peak HR, peak work rate, and peak systolic BP during CPET ($P < .05$), and was significantly negatively correlated with body fat percentage, BMI, and waist circumference ($P < .05$). Figure 1 demonstrates that the 6MWT distance had modest positive correlation with $\dot{V}O_2$ peak. In contrast with variables at peak exercise, the positive correlation of 6MWT distance with $\dot{V}O_2$ or work rate at VeT was of borderline significance ($\dot{V}O_2$: $r = 0.29$; $P = .060$; work rate: $r = 0.25$; $P = .010$). The 6MWT distance was also significantly positively correlated with HRQoL parameters including general health perception and PCS ($P < .05$). Negative correlation of $\dot{V}O_2$ peak with BMI ($r = -0.49$; $P < .001$), body fat percentage ($r = -0.65$; $P < .001$), and waist circumference ($r = -0.49$; $P < .001$) was also observed. Findings from multivariate analyses are reported in Table 3. Model 1 included body composition variables, model 2 recruited additional CPET variables, and model 3 further added HRQoL parameters. Model 3 showed significant correlations of 6MWT distance with duration after heart transplantation, peak HR during CPET, and PCS in SF-36 ($P < .05$).

Table 1. Demographic and Clinical Characteristics of HTRs

	N = 43
Age (y)	47.8 ± 11.1
Gender (male/female)	37/6
Duration after heart transplantation (y)	4.8 ± 3.2
6MWT	
6-min walk distance (m)	539 ± 108
Predicted percentage of 6-min walk distance (%)	89.9 ± 18.2
Body composition analysis	
Body height (cm)	168.7 ± 8.7
Body weight (kg)	75.6 ± 16.0
BMI (kg/m^2)	26.5 ± 4.8
Percentage of body fat (%)	25.2 ± 7.9
Waist circumference (cm)	94.8 ± 13.3
CPET	
Peak WR (watt)	103 ± 34
Peak HR (beats·min^{-1})	137 ± 24
Peak SBP (mm Hg)	178 ± 26
Peak DBP (mm Hg)	84 ± 14
Peak $\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	19.3 ± 4.7
Peak respiratory exchange ratio	1.15 ± 0.08
VeT WR (watt)	56 ± 20
VeT HR (beats ·min^{-1})	108 ± 18
VeT $\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	13.2 ± 2.8
SF-36	
Physical functioning	92.2 ± 8.0
Role- physical	78.5 ± 38.4
Bodily pain	84.6 ± 21.3
General health	68.6 ± 14.4
Vitality	72.4 ± 13.1
Social functioning	88.9 ± 13.4
Role-emotional	79.1 ± 41.2
Mental health	79.5 ± 13.5
Standardized PCS	51.2 ± 7.2
Standardized MCS	52.0 ± 8.6

Note: Data are listed as mean ± SD.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; WR, work rate.

Table 2. Pearson Correlations of 6MWT Distance With Clinical Characteristics

Variables	Correlation Coefficient	*P*
Age (y)	−0.29	.056
Duration after heart transplantation (y)	−0.34	.028*
Body composition analysis		
Body height (cm)	0.22	.150
Body weight (kg)	−0.16	.310
BMI (kg/m^2)	−0.30	.048*
Percentage of body fat (%)	−0.36	.017*
Waist circumference (cm)	−0.37	.013*
CPET		
Peak WR (watt)	0.41	.006*
Peak HR (beats ·min^{-1})	0.42	.005*
Peak SBP (mm Hg)	0.34	.025*
Peak DBP (mm Hg)	0.06	.683
Peak $\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	0.41	.006*
VeT WR (watt)	0.25	.100
VeT HR (beats ·min^{-1})	0.20	.191
VeT $\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	0.29	.060
SF-36		
Physical functioning	0.12	.423
Role-physical	0.29	.059
Bodily pain	0.22	.149
General health	0.34	.028*
Vitality	0.14	.368
Social functioning	0.20	.191
Role-emotional	0.18	.258
Mental health	−0.15	.334
Standardized PCS	0.44	.004*
Standardized MCS	0.03	.812

*$P < .05$, indicating a significant variable in the 2-tail Pearson correlation test.

Compared with our previous study of HTRs within 1 year of transplantation [4], the HTRs in this study had a little higher $\dot{V}O_2$ peak (19.3 ± 4.7 vs 18.5 ± 4.7 mL/kg/min). In addition, they had higher HRQoL scores in physical functioning (92.2 ± 8.0 vs 77.0 ± 14.0), role-physical (78.5 ± 38.4 vs 38.3 ± 37.9), social functioning (88.9 ± 13.4 vs 72.8 ± 22.1), mental health (79.5 ± 13.5 vs 73.4 ± 14.6), and PCS (51.2 ± 7.2 vs 43.2 ± 8.9).

DISCUSSION

The main results of this study performed on HTRs at 4.8 ± 3.2 years after transplantation are the following: (1) the 6MWT distance is significantly positively correlated with $\dot{V}O_2$ peak, peak HR, peak work rate, and peak systolic BP during CPET; (2) the 6MWT distance is significantly positively correlated with HRQoL parameters including general health perception

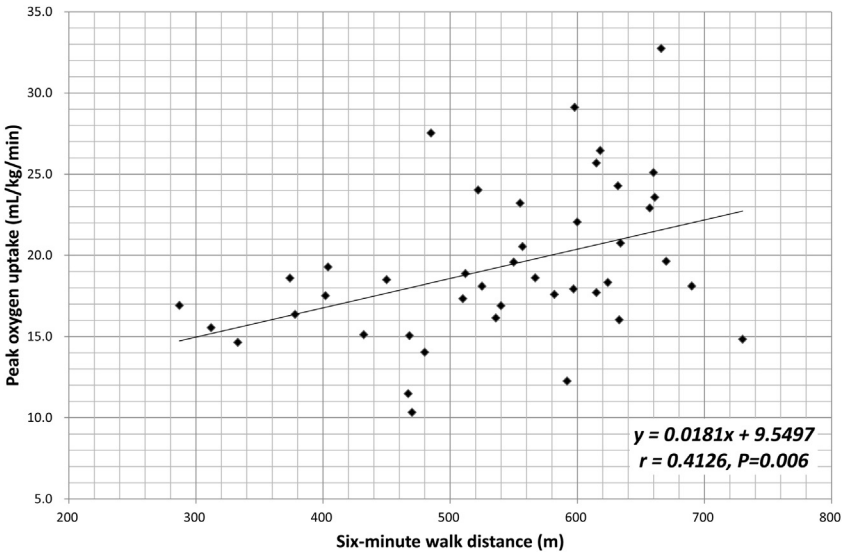

Fig 1. The linear relationship between 6MWT distance and $\dot{V}O_2$ peak among 43 HTRs.

and PCS; (3) the 6MWT distance is significantly negatively correlated with body fat percentage, BMI, and waist circumference; (4) the 6MWT distance is significantly correlated with duration after heart transplantation, peak HR during CPET, and PCS in multivariate analysis; (5) the HRQoL continues to improve 1 year after transplantation despite persistent impairment in exercise capacity.

The 6MWT is a low cost, simple test that measures exercise capacity and shows good to excellent test-retest reliability [17]. In this study, the 6MWT distance was significantly positively correlated with $\dot{V}O_2$ peak ($r = 0.41$; $P = .006$). Similar findings were reported in a study performed on 22 HTRs at 5 years after transplantation ($r = 0.46$; $P < .02$) [12]. In patients with chronic heart failure, the 6MWT distance is significantly correlated with $\dot{V}O_2$ peak in different studies ($r = 0.24 \sim 0.98$) [9,17]. Such correlations would be stronger when the 6MWT distance results were less than 300 ~ 490 m as reported in different studies [17]. The 6MWT distance of our HTRs was farther than 490 m and it might explain why only weak correlation with $\dot{V}O_2$ peak was observed. In addition, the 6MWT distance was significantly correlated with $\dot{V}O_2$ at VeT ($r = 0.40 \sim 0.54$) in HTRs and patients with chronic heart failure [9,12]. However, the correlation of 6MWT distance with $\dot{V}O_2$ at VeT was of borderline significance ($r = 0.29$; $P = .060$) among our HTRs.

To our knowledge, the correlation of 6MWT distance with HRQoL among HTRs has not been previously reported in the literature. In this study, the 6MWT distance was significantly positively correlated with general health perception and PCS of HRQoL. It seems plausible as exercise capacity of HTR increases, the PCS improves. Interestingly, a positive correlation of 6MWT distance and MCS but not PCS was ever reported in patients with chronic heart failure [18]. Further studies are required to explore and clarify the correlations of 6MWT distance with HRQoL among different populations.

Previous studies confirmed the negative correlation between exercise capacity and obesity in HTRs [10,11]. The $\dot{V}O_2$ peak was reported to be significantly negatively correlated with BMI among 95 HTRs at 1 year after transplantation ($r = -0.39$; $P < .001$) [10]. Negative correlation between $\dot{V}O_2$ peak and body fat percentage was observed among 51 HTRs at 4.1 year after transplantation [11].

Table 3. Multivariate Models Correlating 6MWT Distance With Clinical Characteristics

	Model 1			Model 2			Model 3		
	β	SE (β)	*P*	β	SE (β)	*P*	β	SE (β)	*P*
Duration after heart transplantation	−8.96	4.96	.079	−12.39	4.52	.009*	−11.53	4.40	.013*
Waist circumference	−2.54	1.18	.038*						
Peak HR during CPET				2.02	0.61	.002*	1.46	0.64	.027*
PCS in SF-36							4.60	2.10	.034*
Intercept	822.66	109.79	.001*	321.26	86.05	.001*	156.67	111.90	.170
R^2	0.20			0.30			0.38		
Adjusted R^2	0.17			0.27			0.33		

Abbreviations: β, the unstandardized coefficients of the independent variable; SE, standard error; R^2, coefficient of determination.
*$P < .05$.

Similarly, our HTRs had significantly negative correlations of exercise capacity (either 6MWT distance or $\dot{V}O_2$ peak) with body fat percentage, BMI, and waist circumference.

In this study, HTRs had higher HRQoL scores of physical functioning, role-physical, social functioning, mental health, and PCS than our previous findings from HTRs within 1 year of transplantation [4]. However, their exercise capacity in terms of $\dot{V}O_2$ peak did not increase accordingly [4]. Such observations are in accordance with previous studies and imply HTRs have a persistent impairment in exercise capacity despite continuous improvements in HRQoL after 1 year of transplantation [19].

There were some limitations in this study. First, we included a relatively low number of HTRs without acute rejection, cardiac allograft vasculopathy, and mobility problems. The low subject number confined the applications of multivariate analysis. Second, the cross-sectional study design limited the causal inference of correlated factors. However, among the available 6MWT studies in HTRs, our study had the largest subject number.

In conclusion, 6MWT is a simple and useful measure to assess the exercise capacity of clinically stable HTRs. The 6MWT distance is positively correlated with HRQoL and negatively correlated with obesity among HTRs. The prognostic significance of 6MWT for HTRs requires further investigation.

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