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The Role of Three-Month Program of Rehabilitative Exercise after Heart Transplantation: The Effects of the Recipient's and Donor's Risk Factors on the Exercise Capacity Early after Heart Transplantation

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Abstract

Introduction: Although previous studies have shown that the recipients exhibit improvements in exercise capacity and performance after heart transplantation (HTx), the recipients often have a lower exercise capacity than normal healthy age and gender-matched controls in the early period or long after HTx. The purpose of this study is to elucidate the effects of the recipient and donor risk factors on the patient's exercise capacity early after HTx.

Methods: We retrospectively reviewed the medical records of 50 HTx recipients transplanted from April 2010 to November 2016 at National Cerebral and Cardiovascular Center (NCVC) in Japan. Patients' medical records were reviewed retrospectively for clinical parameters, including demographics of the recipient, recipient nutritional risk factors, demographics of the his/her donor and other risk factors for the donor heart. Three weeks after HTx, if patients have no episode of rejection or other adverse events, three-month program of rehabilitative exercise under the supervision of experienced personnel was initiated. Each recipient underwent symptom-limited cardiopulmonary exercise test at the entry and the end of 3-month program.

Results: The peak VO_2 was significantly increased after 3-months program in patient irrespective of recipient risk factors, such as recipient age, underlying heart disease, type of LVAD implanted for bridge to transplant, cerebrovascular complications during awaiting HTx, and several nutritional factors, such as serum choline esterase, serum albumin, blood lymphocyte counts and Geriatric Nutritional Risk Index as well as donor risk factors, such as donor age, history of cardiopulmonary resuscitation, total ischemic time, low left ventricular ejection fraction of the donor heart, and inotrope dosage prior to procurement surgery.

Discussion: Younger recipient age, higher serum choline esterase and higher blood lymphocyte counts at the entry were significantly associated with higher peak VO_2 at the entry and end of 3-momths program.

Conclusion: 3-months rehabilitation exercise increased peak VO_2 irrespective of main recipient or donor risk factors predictive on heart recipient survival, which included the type of LVAD and marginal donor heart factors. Only recipient age and several nutrition factors at the entry of 3-months exercise were associated with peak VO_2 at the entry or the end of 3-months program, and these data suggested that nutrition management and rehabilitation at bedside between the time of HT and the entry of 3-months program play a significant role in increasing peak VO_2 at the entry of rehabilitation program.

Keywords: Heart transplantation; Rehabilitation; Exercise capacity; Left ventricular assist device; Recipient and donor risk factors; Nutrition

Introduction

Since the 1980s, heart transplantation (HTx) has been an established treatment for patients with end-stage heart failure to extend their life and improve quality of their life and previous studies have shown that the recipients exhibit improvements in exercise capacity and performance after HTx [1]. However, the recipients often have a lower exercise capacity than normal healthy age and gender-matched controls in the early period or long after HTx [2,3]. This persistently abnormal exercise capacity and skeletal muscle performance may be attributed to prolonged deconditioning prior to HTx, a denervated heart and muscle wasting from anabolic resistance or the prescribed immunosuppressive regimen [3-5].

Because of extraordinarily severe organ shortage in Japan, most HTx candidates had required an implantation of left ventricular assist device (LVAD) during awaiting HTx (bridge to transplant; BTT) and

bridging periods for initial 263 recipients by the end of June 2016, ranged from 21 to 1,738 days, with an average of 936 days, which was much longer than that in USA and European countries [6]. Until use of implantable continuous flow VADs (cf-LVADs) was covered by medical insurance as BTT in April 2011, the paracorporeal Nipro-Toyobo LVAD (p-LVAD) had been the most commonly used for BTT. However, the survival rate in patients who underwent HTx by the end of June 2016 was not significantly different between patients bridged with p-LVAD (N=106) and implantable LVAD (N=157). As the patients implanted with p-LVAD stayed in hospital with less active daily life, underwent less degree of exercise training and had more neurological complications than those implanted with cf-LVAD during prolonged period awaiting HTx, post-transplant exercise capacity and performance in patients bridged with p-LVAD seemed to be less than those bridged with cf-LVAD due to prolonged decondition during awaiting HTx. But the effect of the type of LVAD for BTT on exercise capacity after HTx has not been fully elucidated.

To increase heart availability, special strategies to assess and manage donors have been established since 2002 [7]. Briefly, special cardiac transplant surgeons or physicians are sent to a procurement hospital to evaluate whether the heart can be transplanted and to stabilize hemodynamics and respiratory function using antidiuretic hormone and frequent bronchofiberoscopy in collaboration with physicians in the procurement hospital. By these efforts, 287 (75%) of 384 donor hearts (including 3 heart-lung transplantations) were transplanted [6]. Although 20 heart grafts from donors aged 60 or older at the time of the procedure were transplanted, there was no significant difference in patient survival by donor age group. The most common cause of brain death of the donor was subarachnoid hemorrhage (95), followed by anoxia (58), head trauma (53), cerebral hemorrhage (29), post-resuscitation (19), cerebral infarction (5) and others. Interestingly, there was no significant difference in patient survival by cause of brain death of the donor. Although these donor risk factors for post-transplant outcomes had no significant impacts on patient survival rate after HTx in Japan, these factors seemed to affect exercise capacity and performance after HTx. However, the effects of use of marginal donor hearts on exercise capacity after HTx have not been fully elucidated.

The purpose of this study is to elucidate the effects of the recipient and donor risk factors on the patient's exercise capacity early after HTx.

Methods

Patient population

We retrospectively reviewed the medical records of 65 consecutive HTx recipients transplanted from April 2010 to November 2016 at National Cerebral and Cardiovascular Centre (NCVC) in Japan. Of these, one recipient who was younger than 16 years old and 23 adult patients who did not undergo cardiopulmonary exercise test (CPET) either at the entry or the end of three-month program of rehabilitative exercise early after HTx were excluded. Finally, 41 recipients were included in this study. Data collection, analysis, and reporting were approved by the National Cerebral and Cardiovascular Centre Institutional Review Board.

Clinical parameters

Patients' medical records were reviewed retrospectively for clinical parameters, including demographics of the recipient (age, sex, body weight, aetiology of underlying disease, and type of implanted VAD), recipient nutritional risk factors, such as serum choline esterase, serum albumin, blood lymphocyte counts and Geriatric Nutritional Risk Index (GNRI), demographics of the his/her donor (age, sex, body weight, aetiology of brain death, and history of cardiopulmonary resuscitation) and other risk factors for the donor heart, such as total ischemic time, low LV ejection fraction (LVEF), and inotrope dosage prior to procurement surgery.

In the present study, marginal donor criteria included age greater than 50 years, LVEF less than 55%, history of cardiopulmonary resuscitation, donor/ recipient body weight ratio of less than 0.8, total ischemic time greater than 240 minutes and total inotrope dosage prior to procurement surgery of greater than 10 μg/min/ml.

Immunosuppressive regimen early after HTx

All patients were treated with triple-drug immunosuppression, including tacrolimus, mycophenolate mofetil and prednisone. The dosage of prednisone was initially 1 mg/kg/day, given in divided doses, and was reduced by 0.125 mg/kg/day every 2 days until 20 mg/day was achieved, and gradually reduced to 10 to 15 mg/day at 3 months after HTx. Patients were excluded from the study if they had moderate or severe rejection episode diagnosed by the International Society for Heart and Lung Transplantation (ISHLT) grade 2R or 3R, or they had any difficulty in exercise capacity test, including postoperative infection or cerebrovascular disease.

Three-month rehabilitative exercise program

Because of the strong immunosuppressive therapies at early phase, the HTx recipients cannot go out freely from the ward specialized for advanced heart failure care within 3 weeks after HTx in our centre. Therefore, exercise training at early phase after HTx consists of standing and walking inside the ward which is tailored for each patient's exercise capacity.

Three weeks after HTx, if patients have no episode of rejection or other adverse events, three-month program of rehabilitative exercise (3-months program) under the supervision of experienced personnel was initiated at the cardiac rehabilitation centre. At the time of entry into the structured, three-month supervised program of rehabilitative exercise, patients were evaluated by a physical therapist for overall muscle strength, joint flexibility, and aerobic endurance. They underwent 40 to 60-minutes aerobic exercises three times weekly, which consisted of walking on a 60-meter round track or pedaling on a bicycle ergometer, as well as arm movements on an ergometer. The duration and intensity of aerobic-exercise sessions were increased to meet the patient's tolerance, with a goal of at least 30 min of continuous exercise at a moderate intensity, such as Borg scale 6 to 20. All patients also underwent the low-grade resistance training (RT) consisted of a body weight half-squat and a calf-raise training using body mass at the rehabilitation centre.

Cardiopulmonary exercise test

Each recipient underwent symptom-limited CPET using a cycle ergometer, with continuous electrocardiographic and respiratory gas exchange monitoring (AE-300S; Minato Medical Science, Osaka, Japan) at the entry and the end of 3-months program early after HTx. The CPET consisted of an initial 2 min of rest, one minute of warm-up (0 W load), and full exercise using an individualized ramp protocol, with increments of 10-20 W/min until symptoms limited patient

performance. We concurrently analysed expired gas through breath-by-Breath testing. We obtained minute ventilation (VE), VO_2, and carbon dioxide production (VCO_2) data at 6-second intervals throughout testing duration.

Variables of interest were peak respiratory exchange ratio, peak VO_2, peak work rate, and the VE-VCO_2 slope. Peak VO_2 was determined as the higher value of either the greatest VO_2 during exercise or the average VO_2 in the final 18 seconds of exercise. We adjusted this measure for age, sex, and body weight to derive a percent-predicted peak VO_2. We determined the VE-VCO_2 slope, an index of ventilation efficiency during exercise, through linear regression analysis of VE and VCO_2 from the beginning of exercise until the respiratory compensation point.

Statistical analysis

Continuous variables are expressed as mean and standard deviation. All results were analyzed using JMP for Macintosh (Version 14.0, SAS Institute Inc., Cary, NC, USA) with P<0.05 indicating statistical significance. The chi-squared test was used to test for differences in categorical variables between groups. Comparisons between the baseline and the end of rehabilitation exercise peak VO_2 were determined with paired t-tests or Wilcoxon signed rank tests within each category group.

Results

Clinical demographics at the time of HTx

The subjects compromised 36 males and 5 females, aged 37.4 ± 13.8 (mean ± standard deviation) years. The underlying disease were dilated cardiomyopathy (DCM) in 21 patients (51.2%), dilated phase hypertrophic cardiomyopathy (dHCM) in 10 patients (24.4%) and others in 10 patients. Of 41 patients, only one patient was receiving intensive care with continuous intravenous infusion of inotropes. The other 40 cases were on BTT with a p-LVAD (N=16; all Nipro-Toyobo LVAD) and an implantable cf-LVAD (N-24; DureHeart in 3, EVAHEART in 9, HeartMate-II in 11 and Jarvik2000 in 1). The Status 1 waiting time in days was 1085 ± 224 days.

Valuable	at baseline	at three-month follow-up	p-value
Peak VO_2 (ml/kg/min)	18.1 ± 4.2	22.7 ± 5.5	P<0.01
%predict peakVO_2()	49.2 ± 9.9	61.5 ± 12.8	p<0.01
Workload (W)	90.7 ± 22.1	115.2 ± 29.5	P<0.01
VE/VCO_2 slope	33.5 ± 5.0	33.4 ± 6.4	P=0.38
Duration of exercise(min)	7.5 ± 1.3	8.1 ± 1.6	P<0.01
AT (ml/kg/min)	10.0 ± 1.9	11.5 ± 2.6	P<0.01
Heart rate at rest (beats/min)	99.4 ± 9.9	95.5 ± 12.4	P<0.01
Peak heart rate (beats/min)	119.5 ± 16.4	129.5 ± 18.1	P<0.01
Systolic blood pressure at rest (mm Hg)	109.0 ± 13.0	113.3 ± 15.7	P<0.01
Peak systolic blood pressure (mm Hg)	144.8 ± 21.9	161.4 ± 26.5	P<0.01
Body weight (Kg)	56.5 ± 8.3	57.8 ± 8.5	P=0.88

Table 1: Changes from baseline to the three-month follow-up in cardiopulmonary exercise-test measurements results (Peak Vo_2; Peak oxygen consumption, VE/VCO_2 slope; Ventilatory equivalent for carbon dioxide, VE/VO_2slope; Ventilatory equivalent for oxygen, AT; Time to estimated lactic acidosis threshold, Resting heart rate (beats/min)).

The durations between HTx and the entry of 3-months exercise program (baseline) and between the entry and the end of 3-months program were 35 ± 12 and 95 ± 12 days, respectively. In all 41 enrolled patients, the changes in parameters of cardiopulmonary exercise-test measurements (peak VO_2 and %predict peak VO_2) from the entry to the end of 3-months program revealed improvements in peak VO_2 as shown in Table 1.

Recipient risk factors at the time of HTx, predictive on survival in heart transplant recipients

Changes in CPEX from the entry to the end of 3-months program results compared by recipient risk factors at the time of HTx were shown in Table 2. Comparisons analysis of peak VO_2 between the entry and the end of 3-months program showed that the peak VO_2 was significantly increased at the end of 3-months program in patient irrespective of recipient risk factors, such as the recipient age (50 or <50 years), underlying heart disease (DCM, dHCM or others), the type of LVAD implanted for BTT (p-LVAD or cf-LVAD), cerebrovascular complications during awaiting HTx, and several nutritional factors (serum choline esterase, serum albumin, blood lymphocyte counts and GNRI.

Recipient risk factor	N		Recipient Age (years)	Donor Age (years)	At baseline (ml/kg/min)	At 3-months follow-up (ml/kg/min)	p-value between baseline and 3-mo f/u
Recipient age (years)	<50	30	30.5 ± 8.7	38.2 ± 12.2	19.1 ± 4.0	24.2 ± 5.4	<0.01
	50	11	56.3 ± 3.5	44.2 ± 14.7	15.4 ± 3.2	18.6 ± 3.5	P=0.019
	p-value between two groups		<0.01	0.19	<0.01	<0.01	
Underlying heart disease	DCM	21	37.1 ± 13.1	36.8 ± 14.3	18.6 ± 4.0	23.0 ± 5.9	<0.01
	dHCM	10	39.1 ± 14.4	46.8 ± 9.0	17.8 ± 4.2	21.8 ± 6.2	<0.01

	Others	10	36.5 ± 16.1	39.1 ± 12.0	17.4 ± 3.3	22.8 ± 4.4	P=0.05
	p-value between two groups		0.91	0.13*	0.72	0.85	
	p-LVAD	16	27.8 ± 8.7	40.3 ± 13.5	19.4 ± 4.8	25.6 ± 5.9	<0.01
	cf-LVAD	24	44.2 ± 13.0	39.9 ± 13.1	17.3 ± 3.6	20.6 ± 4.3	P=0.019
LVAD type	p-value between two groups		<0.01	0.75	0.3	0.011	
Cerebrovascular complications	Yes	21	37.2 ± 14.2	39.5 ± 14.2	17.5 ± 3.2	21.9 ± 4.0	<0.01
	None	20	37.7 ± 13.8	40.1 ± 12.0	18.8 ± 5.0	23.5 ± 6.8	<0.01
	p-value between two groups		0.91	0.88	0.3	0.36	
	M>245,F >198	28	39.0 ± 12.6	40.0 ± 14.1	18.2 ± 4.2	22.2 ± 5.3	<0.01
	M 245, F 198	13	34.1 ± 16.2	39.2 ± 10.8	17.9 ± 4.2	23.7 ± 6.0	<0.01
Choline Estelase (U/L)	p-value between two groups		0.29	0.86	0.81	0.42	
	3.8	38	37.6 ± 13.9	40.4 ± 12.7	18.0 ± 4.3	22.5 ± 5.7	<0.01
	3.8	3	35.3 ± 15.9	31.3 ± 17.2	19.5 ± 1.6	24.8 ± 0.6	P=0.29
Albumin (g/dl)	p-value between two groups		0.79	0.25	0.55	0.5	
	1200	16	34.8 ± 11.6	39.8 ± 11.8	18.1 ± 2.5	22.3 ± 4.9	<0.01
	<1200	25	39.1 ± 15.1	39.8 ± 14.0	18.2 ± 5.0	22.9 ± 6.1	<0.01
Lymphocyte counts/ (µl)	p-value between two groups		0.33	0.99	0.96	0.71	
	99	30	39.1 ± 13.7	42.0 ± 12.8	17.6 ± 3.9	21.8 ± 5.6	<0.01
	<99	11	33.0 ± 13.9	33.8 ± 12.1	19.4 ± 4.6	25.1 ± 4.6	<0.01
Geriatric Nutritional Risk Index (GNRI)	p-value between two groups		0.22	0.07	0.22	0.09	

Table 2: Changes from baseline to the three-month follow-up in cardiopulmonary exercise-test measurements results compared by recipient risk factors at the time of heart transplantation (f/u; follow-up, DCM; dilated cardiomyopathy, dHCM; dilated phase hypertrophic cardiomyopathy, p-LVAD; paracorporeal left ventricular assist device, cf-LVAD; continuous flow LVAD, M; male, F: female, *; p<0.05 DCM *vs* dHCM).

While there was no significant differences in donor age between patients aged <50 years (N=30) and 50 years (N=11) at HTx38.2 ± 12.2 *vs.* 44.2 ± 14.7 years, p=0.19, the peaks VO_2 at both the entry and the end of 3-months program in patients aged <50 years were significantly higher than those in patients aged 50 years (19.1 ± 4.0 *vs.* 15.4 ± 3.2 ml/kg/min; p<0.01 and 24.2 ± 5.4 *vs* 18.6 ± 3.5 ml/kg/min; p<0.01).

Among patients with DCM (N=21), dHCM (N=10), and other (N=10), there were no significant differences in recipient age (37.1 ± 13.1 *vs.* 39.1 ± 14.4 *vs.* 36.5 ± 16.1 years, p=0.91), donor age (36.8 ± 14.3 *vs.* 46.8 ± 9.0 *vs.* 39.1 ± 12.0 years, p=0.13) or peak VO_2 at either the entry or the end of 3-months program among these three groups.

Recipient risk factor		N	Recipient Age (years)	Donor Age (years)	At baseline (ml/kg/min)	At 3-months follow-up (ml/kg/min)	p-value between baseline and 3-mo f/u
Choline Estelase (U/L)	M>245, F >198	12	33.9 ± 10.8	40.5 ± 12.2	20.4 ± 5.2	24.5 ± 6.8	<0.01
	M 245 F 198	29	38.9 ± 14.8	39.5 ± 13.5	17.2 ± 3.2	21.9 ± 4.9	<0.01
	p-value between two groups		0.3	0.82	0.019	0.18	
Albumine (g/dl)	3.8	34	36.4 ± 13.5	38.8 ± 12.5	18.3 ± 4.2	23.1 ± 5.6	<0.01
	3.8	7	42.4 ± 15.6	44.7 ± 15.9	17.2 ± 4.1	20.6 ± 5.2	P=0.02
	p-value between two groups		0.3	0.28	0.53	0.3	

Lymphocyte counts/ (μl)	1200	16	32.1 ± 11.6	35.9 ± 11.6	20.2 ± 4.5	25.1 ± 5.7	P=0.01
	<1200	25	40.8 ± 14.3	42.3 ± 13.5	16.8 ± 3.4	21.1 ± 4.9	P=0.02
	p-value between two groups		0.047	0.13	<0.01	0.021	
Geriatric Nutritional Risk Index (GNRI)	99	19	37.3 ± 12.9	39.2 ± 13.2	17.8 ± 4.3	22.7 ± 6.1	<0.01
	< 99	22	37.6 ± 14.9	40.3 ± 13.2	18.4 ± 4.1	22.6 ± 5.1	<0.01
	p-value between two groups		0.94	0.8	0.68	0.97	

Table 3: Changes from baseline to the three-month follow-up in cardiopulmonary exercise-test measurements results compared by recipient risk factors at the initiation of three-months exercise program (f/u; follow-up, DCM; dilated cardiomyopathy, dHCM; dilated phase hypertrophic cardiomyopathy, p-LVAD; paracorporeal left ventricular assist device, cf-LVAD; continuous flow LVAD, M; male, F: female, *; p<0.05 DCM *vs* dHCM).

While recipient age in patients with p-LVAD was significantly lower than that in patients with cf-LVAD (27.8 ± 8.7 *vs.* 44.2 ± 13.0 years, respectively; p<0.01), there was no differences in peak VO_2 at the entry between patients with p-LVAD (N=16) and cf-LVAD (N=24) (19.4 ± 4.8 *vs.* 17.3 ± 3.6 ml/kg/min, respectively) , but that at the end of 3-months program in patients with p-LVAD was significantly higher than that in patients with cf-LVAD (25.6±5.9 *vs.* 20.6±4.3 ml/kg/min, respectively; p=0.011). Between patients with and without cerebrovascular complication during awaiting HTx, there was no significant difference in recipient age, donor age, or the peaks VO_2 at ether the entry or the end of 3-months program.

There were no significant differences in peaks VO_2 at either the entry or at the end of 3-months program between nutritional recipient risk factors at the time of HTx, such as serum choline esterase, serum albumin, blood lymphocyte counts, or GNRI.

Recipient risk factors at the entry of 3-months program, predictive on survival in heart transplant recipients

There were no significant differences in peaks VO_2 at either the entry or at the end of 3-months program between nutritional recipient risk factors at the entry, such as serum albumin or GNRI. However, peak VO_2 at the entry in patients with serum choline esterase >245 U/L in male and >198 U/L in female at the entry was significantly higher than that in patients with serum choline esterase 245 U/L in male and 198 U/L in female at the entry (20.4 ± 5.2 *vs* 17.2 ± 3.2 ml/kg/min, respectively; p=0.019) and peaks VO_2 at both the entry and the end of 3-months program in patients with blood lymphocyte counts 1200 μl at the entry was significantly higher than that in patients with patients with blood lymphocyte counts < 1200 μl at the entry (20.2 ± 4.5 *vs.* 16.8 ± 3.4 ml/kg/min, p<0.01 and 25.1 ± 5.7 *vs* 21.1 ± 4.9 ml/kg/min, p=0.021, respectively)(Table 3).

Donor risk factors predictive on survival in heart transplant recipients

Changes from the entry to the end of 3-months program in CPEX results compared by donor risk factors were shown in Table 4. Comparisons analysis of peak VO_2 between the entry and the end of 3-months program showed that the peak VO_2 was significantly increased at the end of 3-months program irrespective of donor risk factors, such as the donor age (50 or <50 years), left ventricular ejection fraction (LVEF) of the donor heart (<55 or 55%), history of cardiopulmonary resuscitation, donor/recipient weight ratio (<0.8 or 0.8), total ischemic time during HTx (240 or <240 min) and inotrope dosage prior to procurement surgery (10 or <10 μg/ml/min).

Donor risk factor	N		Recipient Age (years)	Donor Age (years)	At baseline (ml/kg/min)	At 3-months follow-up (ml/kg/min)	p-value between baseline and 3-mo f/u
Donor age (years)	50	13	41.3 ± 14.6	55.4 ± 4.0	16.6 ± 3.3	20.8 ± 4.8	<0.01
	<50	28	35.6 ± 13.4	32.5 ± 8.5	18.8 ± 4.4	23.5 ± 5.7	<0.01
	p-value between two groups		0.23	<0.01	0.12	0.14	
LVEF (%)	<55	5	40.4 ± 14.3	32.4 ± 8.5	20.8 ± 5.9	28.2 ± 5.7	<0.01
	55	36	37.0 ± 13.9	40.8 ± 13.3	17.8 ± 3.8	21.9 ± 5.1	<0.01
	p-value between two groups		0.62	0.18	0.13	0.015	
History of cardiopulmonary resuscitation	Yes	25	40.7 ± 13.4	37.8 ± 13.0	17.9 ± 4.0	21.5 ± 4.5	<0.01
	None	16	32.4 ± 13.4	42.8 ± 12.8	18.4 ± 4.6	24.5 ± 6.5	<0.01

	p-value between two groups		0.06	0.23	0.73	0.09	
Donor/Recipient weight ratio	<0.8	8	32.4 ± 16.7	30.6 ± 9.8	18.9 ± 7.1	23.6 ± 8.4	<0.01
	0.8	33	38.7 ± 13.0	42.0 ± 12.9	17.9 ± 3.2	22.4 ± 4.7	<0.01
	p-value between two groups		0.25	0.03	0.59	0.6	
TIT (min)	240	2	38.5 ± 9.9	57.5 ± 0.7	16.6 ± 0.2	23.2 ± 6.9	<0.01
	<240	39	37.4 ± 2.2	38.9 ± 12.7	18.2 ± 4.2	22.6 ± 5.5	<0.01
	p-value between two groups		0.91	0.047	0.59	0.88	
High dose requirement of inotropes	Yes	4	34.3 ± 7.0	29.3 ± 6.3	16.2 ± 1.4	22.1 ± 2.8	P=0.022
	None	37	37.8 ± 2.3	40.9 ± 2.1	18.3 ± 4.3	22.7 ± 0.9	<0.01
	p-value between two groups		0.63	0.09	0.34	0.85	

Table 4: Changes from baseline to the three-month follow-up in cardiopulmonary exercise-test measurements results compared by donor risk factors.

While there was no significant differences in peaks VO_2 at either the entry or the end of 3-months program between the donor age 50 years (N=13) or <50 years (N-28), positive or negative history of cardiopulmonary resuscitation, donor/recipient weight ratio <0.8 (N=8) or 0.8 (N=33), total ischemic time during HTx 240 min (N=2) or <240 min (N=39), or inotrope dosage prior to procurement surgery 10 μg/ml/min (N=4) or <10 μg/ml/min (N=37), or in peak VO2 at the entry between patients transplanted with the donor heart of LVEF <55% (N=5) and 55 % (N=55), peak VO_2 at the end of 3-months program in patients transplanted with the donor heart of LVEF <55% was significantly higher than that in patients with the donor heart of LVEF 55 % (28.2 ± 5.7 *vs.* 21.9 ± 5.1 ml/kg/min, p=0.015) (Table 4).

Discussion

Although physical exercise is clearly warranted for patients after bypass surgery or after acute myocardial infarction, the role of exercise in the treatment of patients who have undergone cardiac transplantation is less well defined, because in recipients of cardiac transplants, exercise capacity is influenced by the denervation that occurs during transplantation surgery, which reduces the overall response to exercise as compared with that of normal volunteers [2-5].

Savin et al. [7] initially reported that five heart-transplant recipients undergoing a four-month exercise program of stationary cycling increased their peak work output by 45 percent and their peak oxygen consumption by 18 percent. Kavanagh et al. [8] selected 36 patients a mean of 7 months after HTx to participate in a program of walking and jogging that lasted 16 ± 7 months and showed that patients progressed to walking or jogging an average distance of 24 km per week at an average pace of 8.5 min/km. The first prospective, randomized study of heart-transplant recipients, initiated early in the postoperative period reported by Kobashigawa et al. [1] demonstrated that the exercise group had significantly greater increases in peak oxygen consumption (mean increase, 4.4 ml/kg/min (49%) *vs.* 1.9 ml/kg/min [18%]; P=0.01) and workload (mean increase, 35 W (59%) *vs.* 12 W (18%); P=0.01) and a greater reduction in the ventilatory equivalent for carbon dioxide (mean decrease, 13 (20 %) *vs.* 6 (11 %); P=0.02). Although many investigators [9,11] revealed the benefit of rehabilitation exercise on peak VO_2 early after HTx as shown above and many reviews supported these results [12,13], the effects of recipient or donor risk factors predictive on patient survival after HTs on exercise capacity of the patents early after HTx have not been fully elucidated.

In the present study, we retrospectively reviewed the medical records of 50 heart transplant recipients and analysed the relationship between peak VO_2 at the entry and the end of 3-months rehabilitation program and several recipient or donor risk factors. This study showed that the peak VO_2 was significantly increased after 3-months program in patient irrespective of recipient risk factors, such as recipient age, underlying heart disease, type of LVAD implanted for BTT, cerebrovascular complications during awaiting HTx, and several nutritional factors, such as serum choline esterase, serum albumin, blood lymphocyte counts and GNRI as well as donor risk factors, such as donor age, left ventricular ejection fraction (LVEF) of the donor heart, history of cardiopulmonary resuscitation, donor/recipient weight ratio, total ischemic time during HTx and inotrope dosage prior to procurement surgery. Therefore, almost every heart transplant recipient can improve their physical work capacity by exercise training initiated early after HTx.

Regarding recipient risk factors at the time of HTx, only age was significantly associated with peak VO_2 at the entry and the end of 3-momths program. Although post-transplant exercise capacity and performance in patients bridged with p-LVAD seemed to be less than those bridged with cf-LVAD due to prolonged decondition during awaiting HTx, there was no significant differences in peak VO_2 at the entry of 3-months program between patients with p-LVAD and cf-LVAD. Interestingly, the peak VO_2 at the end of 3-months program in patients with p-LVAD was significantly higher than that in those with cf-LVAD. Although the patients with p-LVAD were significantly younger than those with cf-LVAD, post-transplant rehabilitation seemed to be more effective in patients with prolonged decondition in hospital during awaiting HTx than those with active daily life at home.

Regarding recipient nutrition risk factors, there were no significant differences in peaks VO_2 at either the entry or at the end of 3-months program between nutritional recipient risk factors at the time of HTx, such as serum choline esterase, serum albumin, blood lymphocyte counts, or GNRI. However, peak VO_2 at the entry in patients with higher serum choline esterase at the entry was significantly higher than that in patients with serum choline esterase at the entry and peaks VO_2 at both the entry and the end of 3-months program in patients with higher blood lymphocyte counts at the entry was significantly higher than that in patients with patients with lower blood lymphocyte counts. These data suggested that nutrition management and rehabilitation at bedside between the time of HT and the entry of 3-months program play a significant role in increasing peak VO_2 at the entry of rehabilitation program as previously reported [10].

Regarding donor risk factors, there was no significant differences in peaks VO_2 at either the entry or at the end of 3-months by the donor age, history of cardiopulmonary resuscitation, donor/recipient weight ratio, total ischemic time, or inotrope dosage prior to procurement surgery, or in peak VO_2 at the entry by LVEF of the donor heart, but peak VO_2 at the end of 3-months program in patients transplanted with the donor heart of LVEF <55% was significantly higher than that in patients with the donor heart of LVEF 55 % . Although peak VO_2 increased in patients with the donor heart of LVEF <55%, but there was no significant differences in LVEF between prior to procurement surgery and at the end of 3-months program '(50.2 ± 1.5 *vs* 58.0 ± 2.7 ml/kg/min, respectively; p=0.31) probably due to small number of patients with the donor heart of LVEF <55%. These data suggested that if the donor heart was meticulously assessed for indication and the donor was intensively managed, exercise capacity of the patients even transplanted with a marginal donor heart was satisfactory and improved by rehabilitation exercise early after HTx.

Considering exercise prescription and future guidelines, the study of Yardley et al. [14]. Suggest that high-intensity interval training (HIT) is a feasible and efficient modality of exercise among maintenance HTx recipients moderate levels of exercise and intensity are insufficient to maintain the improved VO_2 peak achieved after a HIT intervention. Thus, intermittent periods of HIT are likely to be necessary. Also, the number and length of HIT intervals needed in a HIT session should be further investigated. If a modified HIT protocol with shorter and fewer intervals has comparable effect to a 4 × 4 protocol, it could probably increase the patients' motivation and adherence to exercise in the long-term. When considering other long-term effects, the benefit from a tough and intense HIT-intervention showed a positive effect on the development of anxiety symptoms. The exercise prescription in de novo HTx recipients is still conservative, consisting mainly of moderate-intensity continuous training exercise, but this traditional guideline might change when the ongoing High-intensity Interval Training in de novo Heart Transplant Recipients (HITTS) study is completed. Existing gaps in knowledge are briefly mentioned in this study, and the results from the HITTS study [15] will contribute to fill some of these gaps, and may also have the potential to update, optimize and possibly include HIT as a safe exercise modality in future guidelines.

Bachmann et al. [16] report on 2,531 HT patients studied in the United States in 2013, specifically examining 595 (24%) under Medicare coverage. The authors found that 55% of patients participated informal cardiac rehabilitation programs, with higher use in the Midwest and increasing rates overtime from 2008 to 2013. Although they "spin" this as a disappointment, noting "only half of HTx recipients participate in cardiac rehabilitation programs in the US," the 55% participation is actually extremely high compared with most assessments of patients with congenital heart disease and heart failure. More importantly, hospital re-admissions at 1-year decreased by 29 % in those who participated informal rehabilitation program compared with non-participants.

Limitations

Our study had several limitations. First, it was retrospective and conducted at a single center, included small number of patients. Second other factors influencing exercise capacity in transplant recipients, such as hemodynamic were not evaluated.

Conclusion

In the present study, 3-months rehabilitation exercise increased peak VO_2 irrespective of main recipient or donor risk factors predictive on heart recipient survival, which included the type of LVAD and marginal donor heart factors. Only recipient age and several nutrition factors at the entry of 3-months exercise were associated with peak VO_2 at the entry or the end of 3-months program, and these data suggested that nutrition management and rehabilitation at bedside between the time of HT and the entry of 3-months program play a significant role in increasing peak VO_2 at the entry of rehabilitation program.

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