ORIGINAL ARTICLE

Cardiopulmonary Exercise Test in Advanced Heart Failure Among Heart Transplantation Candidates

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Abstract- Cardiopulmonary exercise test has been raised through recent decades as a brilliant prognostic tool in a wide field of diseases and clinical conditions which makes it valuable to be used in prognostic assessment during the current study among chronic heart failure (CHF) patients. This study recruited 71 patients with severe CHF who were candidates for heart transplantation. Bicycle-protocol Cardiopulmonary Exercise Test was done, and several parameters were measured and compared between four groups of patients based on their VO2/kg to show four grades of the disease from G1 to G4. Total 71 CHF subjects from 18 to 46 year of age enrolled in the study. Statistically significant correlation**s** were determined between HRR, VE/VCO2, VE/VO2, BR and the severity of CHF. VO2max, HRR, VE/VO2, VE/VCO2, BR, and AT were the most prominent factors of CPET which showed their validity and reliability in terms of prognosis of CHF. It seems that combination of CPET and other cardiac prognostic tools like echocardiography and measurement of the pressure in cardiac chambers can improve the prognosis in CHF.

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Keywords: Cardiopulmonary exercise test (CPET); Chronic heart failure (CHF); Prognosis; VO_2max; VE/VCO_2; VE/VO_2; Heart rate reserve (HRR); Breathing reserve (BR)

Introduction

Heart failure is a critical condition disregarding its hereditary or acquisitive base which involves 6-10% of individuals over 65 years of age. Chronic heart failure (CHF) is a serious problem in 5.8 and 15 million people in the US and Europe, respectively (1,2). In Iran, CHF is hitting the record of 3500 in 100,000 of the population in the near future (3,4). The most prominent causes of CHF in the industrial world are undoubtedly cardiovascular diseases (CAD) and arterial hypertension. Through recent decades, Cardiopulmonary Exercise Test (CPET) has been added to conventional studies for CHF like echocardiography, exercise test, electrocardiography and serum biomarkers. This test is now one of the most important strategies of diagnosis and prognosis determination and consequently a valid tool to make plans to manage CHF in Europe and the United States (5,6).

Heart transplantation is a final reliable way to manage CHF which has been also highly focused in Iran through recent decades (7). Heart transplantation is thought as a probable effective solution against conventional conservative therapies, nowadays (8). CPET has fixed its place between many other prognostic and predictive tools to achieve the fact that people with advanced CHF (maximum O_2 consumption >10 ml/Kg/min) have greater chance of survival. CPET shows that heart transplantation in the named group is obviously more successful than conservative therapies (7).

This is worth thinking that pomp incapacitation is not always the main cause of troubles in CHF, while any problems in muscular and/or peripheral circulation, individual ways of breathing during exercise, and also

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anthropometric measures in addition to muscle mass and type of muscular fibers are very important in CPET interpretation.

AT(VAT)

Ventilatory anaerobic threshold or anaerobic threshold (AT) in brief, is a point which the aerobic metabolism fails to consume more oxygen at as the main source of fuel shifting to anaerobic metabolism to produce local lactate in muscles (9-11). AT is calculated by analysis produced CO_2 (VCO_2) and consumed O_2 (VO_2) through their exchanges in the mouth. The v-slop method shows the fact that VO_2/VCO_2 slope is less than 1 in aerobic but rises in anaerobic ventilation to more than 1. Increased CO_2 production after AT is the main cause of increased ventilation to fix the linear correlation between minute ventilation (VE) and VCO_2 and keep CO_2 end-tidal pressure ($P_{ET}CO_2$) still (12,13). AT is almost always considered as the ratio of VO_2/VO_{2max} which is supposed to be 40-60% (14). This ratio would grow even up to 80% in trained athletes (15). All the pathologic conditions resulted from CHF which disturb the chain of O_2 transportation obviously lower the AT even by 40%. (16). Most of the time, there is an undetermined AT in CPET due to limited exercise capacity in addition to fluctuated VE in the majority of CHF subjects.

VO_2max or in other words “aerobic power” is defined as the maximum energy which is available during aerobic metabolism. Minute ventilation (VE)and VO_2 max are usually affected by cardiac output, arterial O_2 content, distribution of cardiac output in the muscles, the ability of muscles to consume O_2, and finally some features in the central nervous system (17). VO_2max, in other words, is the point that VO_2 fails to rise in spite of increasing load of exercise (18). Age, sex, BMI, ordinary daily activity and genetic features usually affect VO_2max (19,20). VO_2max starts to reduce 10% on average for every 10 years of age after 30. This is mainly because of decreased maximum heart rate, stroke volume, musculoskeletal blood flow and the capacity of aerobic metabolism in skeletal muscles (21). Decreased capacity of aerobic exercise is obviously the key point of CHF pathophysiology which is led by changes in peripheral organs such as skeletal muscles, endothelium, local blood flow, and cardiovascular reflex control systems in addition to central organs like lungs, heart, and arterial blood hemoglobin content (22,23).

VE, simply as the amount of the air which individuals take O_2 from, is always increased when compared with healthy people at the same age. This means the fact that CHF patients lose their competence in taking enough O_2 from the air (24).

This study was designed and conducted based on pretesting cases of heart transplantation to separate CHF cases from other situations like deconditioning which are usually treated via rehabilitation and training instead of invasive ways like transplantation.

Materials and Methods

Through a cross-sectional study, we recruited patients who referred to CPET department at a tertiary hospital in Tehran before heart transplantation to recheck their indications for the operation. Patients over 14 years of age enrolled the study if were metabolically stable and cooperated the test. Individuals who did not meet maximum effort criteria (RER<1.15; HR peak <85% of the predicted; Borg score <8.10) or had respiratory disease, orthopedic issues or aortic valve stenosis quitted the study. After giving their informed consent, the participants were checked for demographics, comorbidities, current medications, and echocardiography and spirometry.

Bicycle CPET protocols

For CHF subjects, both treadmill and bicycle CPET protocols are suitable among which the second protocol was used by the current study. The starting load is usually 20-25 W increasing 15-25 W every two minutes to achieve the maximum load of exercise. Electronic ergometer, which was utilized by this study, could estimate the starting load and establish a 10 W/min-ramp-protocol. Bicycle CPET seems to have obviously less false results than the treadmill because of less noise in addition to lower metabolic expenditure for patients. Furthermore, the bicycle is not as expensive as treadmill and needs smaller space.

RER

The ratio of VCO_2/ VO_2 is named as respiratory exchange ratio (RER) which is naturally an index of metabolism in body tissues.

CPET contraindications

There is a wide range of medical conditions in this regard that the most serious ones are myocardial ischemia, unstable angina, syncope, acute endocarditis, and uncontrolled asthma.

CPET ending indications

Chest pain, ischemic ECG pattern, heart blocks, hypertension (>250 mm Hg systolic; >120 mm Hg diastolic), >20 mm Hg fall in systolic blood pressure, severe desaturation ($Spo_2 \leq 80\%$) along with symptoms and signs of hypoxemia, sudden pallor, dizziness and finally mental confusion is the most known indications of putting the test an end. In these cases, the patient was monitored for recovery at rest to make sure of stable and safe condition.

CPET procedure

After selecting a suitable mask the patient placed on a medical electronically braked bicycle and started the test with 10 W/min-ramp protocol with 10-15 W based on the patient's ability. For three minutes the patient sat on the bicycle for a short relax before starting to steal for 2 minutes without load. Before starting the test, the patient was asked to breathe fast and deep for 12-15 seconds to calculate MVV. Throughout the test, exhaled gases were measured "breath by breath" through exhalation airflow analysis. At the same time, heart rate, O_2 saturation, and electrocardiography were monitored and recorded.

All the participants were divided into four groups regarding their VO_2/kg to separate different CHF severity as follows:

Group 1: VO_2/kg>20

Group 2: 16< VO_2/kg<19.99

Group3: 10< VO_2/kg<15.99

Group4: VO_2/kg≤9.99

Group1 (G1) had the best condition with less severity of CHF while G4 had the most severe disease regarding the "West" method.

Statistics

This study recruited patients considering simple sample selection, and no randomization was done. All collected data were checked for normal distribution, firstly. There was no need to use nonparametric tests. Central tendency indices were reported for quantitative data by using means, modes, medians, and standard deviations. The confidence interval (CI) was defined as 95% along with a type 1 error (α) of 0.05 and the significance of 0.05. Chi-square test was used when qualitative data were compared while t-test was used for quantitative comparative issues.

Ethics

The current study considered the "Helsinki Statement" in terms of ethical issues. All the patients were free to participate in the study regarding the inclusion and exclusion criteria with no facilitation or advantage while nobody was limited to continue getting medical supports due to regret to participate. All the participants were able to quit the study with no penalty or permission whenever they wished.

Results

Total 71 patients including 58 males (81.6%) and 13 females (18.4%) enrolled the current study regarding the inclusion and exclusion criteria. The mean age±SD was 32.8±12.12 years containing 18-46-year-old patients. The patients were divided into four groups based on their VO_2/kg as defined before in methods. Table 1 shows the frequency and percentage of the participants in each group.

Table 1. Grouping of the participants regarding their VO_2/kg. AT and gender information are also provided

Grade	Cases (%)	Sex		VO_2/kg					AT(mean±SD)
		M	F	Mean±SD	Median	Mode	min	Max	
G1	7 (9.9)	6	1	23.47±3.22	22.1	20.5	20.5	28.8	48.86±21.46
G2	10 (14.1)	7	3	17.9±1.2	17.8	18.9	16.2	19.5	37.2±12.27
G3	37 (52.1)	28	9	12.62±1.53	12.5	12.5	10	15.7	28.11±9.21
G4	17 (23.9)	13	4	7.86±1.6	8.1	6.1	4.6	9.8	17.06±5.85

There was no relationship between sex and severity of CHF among the subjects (*P*=0.528). On the contrary, there was a strong correlation between AT and VO_2/kg (*P*=0.001) which is summarized in table 2 that shows the most AT (48.86) in group 1 as expected. The most significant difference was found between G1 and G4 in terms of AT although G2 had no prominent difference with G1 and G3 (*P*=0.92 and *P*=0.133, respectively).

Table 2. PostHoc table for the Tukey test for AT in groups of participants. The most predominant differences were seen between G4, G2, and G1

Tukey HSD						
vo2/kg	vo2/kg	Mean Difference	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
G4	G3	-11.049*	3.145	.004	-19.34	-2.76
	G2	-20.141*	4.278	.000	-31.41	-8.87
	G1	-31.798*	4.821	.000	-44.50	-19.10
G3	G4	11.049*	3.145	.004	2.76	19.34
	G2	-9.092	3.826	.092	-19.17	.99
	G1	-20.749*	4.425	.000	-32.41	-9.09
G2	G4	20.141*	4.278	.000	8.87	31.41
	G3	9.092	3.826	.092	-.99	19.17
	G1	-11.657	5.290	.133	-25.60	2.28
G1	G4	31.798*	4.821	.000	19.10	44.50
	G3	20.749*	4.425	.000	9.09	32.41
	G2	11.657	5.290	.133	-2.28	25.60

*. The mean difference is significant at the 0.05 level

The mean±SD for VO_2/kg was 13.292±4.87 lit/kg for all 71 subjects with the range of 4.6-28.8 lit/kg. Table 3 shows central tendencies and the range of the most important parameters this study measured. Heart rate reserve (HRR) was significantly higher in group 4 (63.53). ANOVA found an obvious direct significant correlation between HRR and the severity of CHF which grew from G1 to G4 (*P*=0.019).

Table 3. Central tendency indices of CPET for some key parameters regarding patients' gender

Parameter	Sex	Mean	Std. Deviation	Std. Error Mean
LoadMax	**Male**	40.80	17.549	2.588
	Female	40.09	22.385	6.749
HRmax	**Male**	71.63	11.880	1.752
	Female	71.27	11.306	3.409
HRR	**Male**	51.04	22.443	3.309
	Female	53.00	21.753	6.559
o2pulse%	**Male**	56.61	19.840	2.925
	Female	57.09	13.502	4.071
VO2max	**Male**	1.0654	.40310	.05943
	Female	.6864	.20190	.06088
AT	**Male**	29.83	14.879	2.194
	Female	28.55	12.275	3.701
VE.VCO2	**Male**	35.552	8.3881	1.2368
	Female	37.127	6.2102	1.8724
VElitr	**Male**	45.57	12.927	1.906
	Female	32.00	9.241	2.786
BRmax	**Male**	82.865	24.9136	3.6733
	Female	67.509	24.0766	7.2594

Figure 1 illustrates the linear correlation between HRR and severity of the disease in which a steep slope is seen between the groups in this regard except between G2 and G3.

Concerning VE/VO_2 and VE/VCO_2, a significant correlation was seen between the groups of participants to show obviously higher amounts in group 4 (*P*<0.001) as seen in figure 2. Groups 1 and 3 had no statistical difference in terms of VE/VO_2 differential (*P*=0.597).

VE/VCO_2 had the most prominent difference between G1 and G4 as expected (13.71) (*P*<0.001). Although G2 had no difference with G1 and G3 (*P*<0.551 and 0.539, respectively) G4 differed with other groups in this matter. The relevant negative coefficients demonstrate the indirect correlation of VE/VO_2 and VE/VCO_2 with VO_2/kg (Figure 3).

A parameter named VE% is defined as the ratio of VE/MVV multiplication by 100 which is actually the rate of O_2 consumption and aerobic exercise against the predicted rate for each participant. ANOVA showed a significant relationship between the named parameter (VE%) and the severity of CHF, directly (*P*<0.001). when compared using the "Tukey" test, G2 and G4 had the most prominent correlation with VE%, and G1 failed to show any valuable correlation as illustrated by figure 4.

Breathing reserve (BR: MVV-VEmax) increased from G1 to G4 to show indirect significant linear correlation with VO_2/kg. The highest amount of it was 141.3 in G3 whilst its least amount of 22.6 in the same group (*P*=0.011).

For VO_2 max, G1 and G2 had higher levels than the other which is reasonable since the current study divided the participants based on VO_2/kg. Post Hoc test endorsed the mentioned indirect relationship with the groups (*P*<0.001), and the means plot is seen in figure 5.

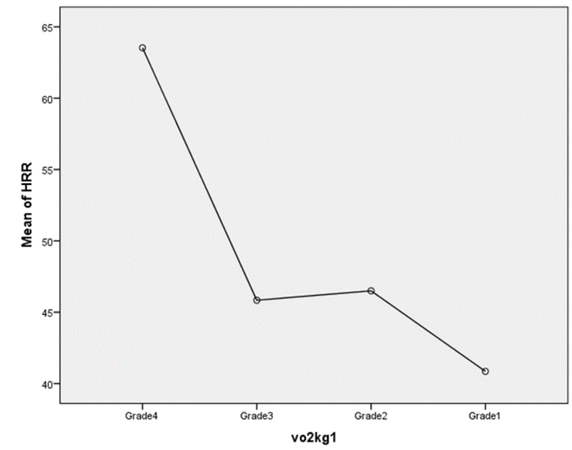

Figure 1. The linear correlation between HRR and CHF severity in four groups of the study. Group 4 had the least amounts of VO_2/kg. The diagram illustrates the indirect strong correlation between HRR and VO_2/kg

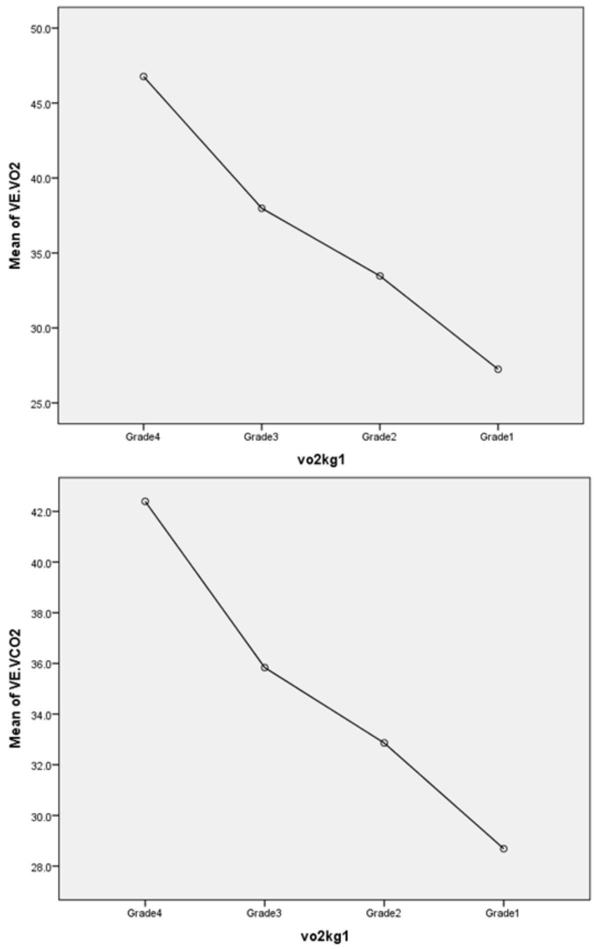

Figure 2. Correlation diagrams of VO_2/kg with VE/VO_2 (above) and VE/VCO_2 (below). Indirect strong correlation was obviously found

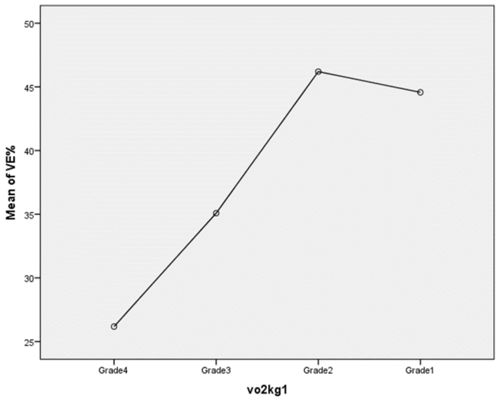

Figure 3. The diagram shows direct correlation between the VE% and VO_2/kg but groups 2 and 1 had a faded correlation of the named items as can be seen which may be resulted due to low sample size in group 1

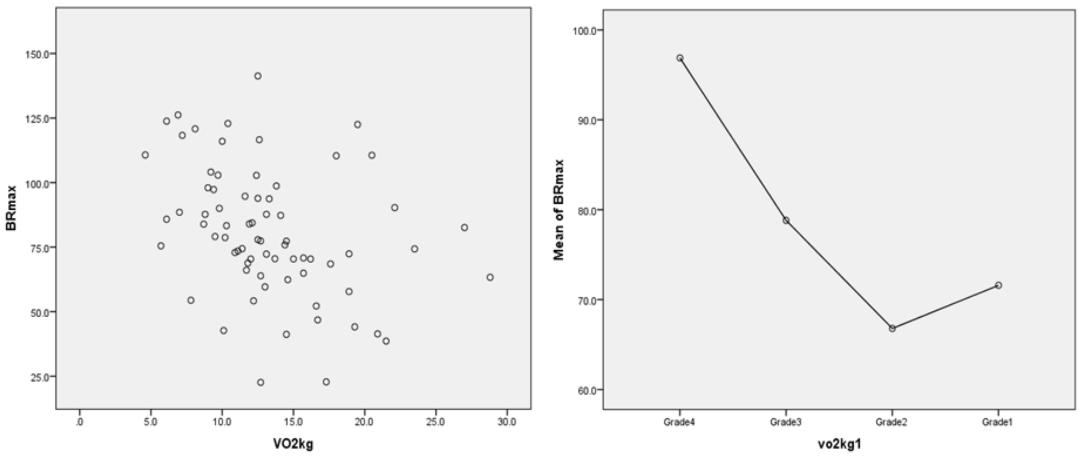

Figure 4. A regression test showed indirect correlation between BRmax and VO_2/kg. The means plot is seen on the right side. The relationship is faded between group 2 and 1 mainly due to the low number of participants in the latter

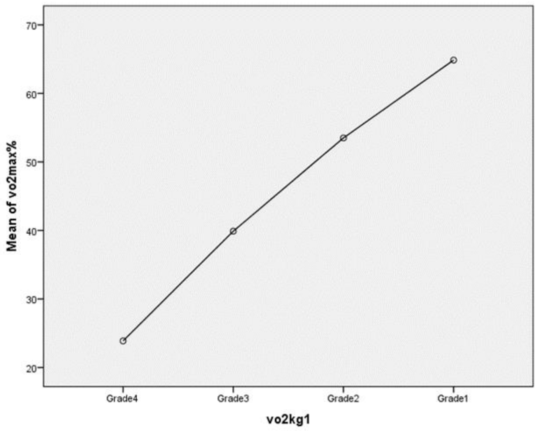

Figure 5. As expected, VO2max had a very strong linear correlation with VO_2/kg of the participants

Discussion

The main aim of the current study was the assessment of key parameters of Ergospirometry in CHF patients who were candidate for heart transportation, and it found some valuable correlation in terms of the mentioned parameters and the severity of the disease.

As can be seen in table 1, the groups had different numbers of patients which are usually expected in cross-sectional clinical studies, and it had no effect on the results due to the power of the correlation except some issues for the group 1 because of containing only 7 subjects. The oldest participant was in his/her 40's which is very lower age than many other studies. This may be mainly because of less referral to CPET in advanced age by Iranian physicians based on musculoskeletal limitations or higher risk of comorbidities which make exercise test more difficult (25). The number of patients to be studied in the current research was enough comparing with many other works to get an acceptable power of the study. (26-29).

It was expected to witness a direct correlation between AT and VO_2/kg in CPET and the current study determined the highly strong result in this regard between G1 and G4 despite non-significant differences in G1 to G3.

The mean of VO_2 was just more than 13 ml/kg/min which was expectedly lower than individuals with heart failure with preserved ejection fraction (HFPEF) in a study conducted by Garcia *et al*., in 2015 who reported VO_2 mean of 17 ml/kg/min (25). HFPEF patients have the naturally better condition than the patients we studied, but they probably have growth in hospitalization rate up to 32% for each 10% fall in peak VO_2 (27). However, the current study did not follow up patients, and there is nothing to conclude or compare about outcome or prognosis of CHF among our participants.

Grazzi *et al*., working on a population-based study in 2017, determined that the ratio of actual peak VO_2/predicted VO_2 correlated indirectly with the survival rate in 1400 participants. (30)

The current study was not trying to assess the effects of comorbidities on CPET results; so, all the patients with BMI>30, anemia, lung or kidney disease, diabetes, malignancies, depression, psychological disorders and musculoskeletal problems even knee arthrosis and rheumatoid arthritis were excluded (31).

We also disclosed a rather strong indirect correlation between HRR and VO_2 /kg among our CHF patients, especially between G1 and G2; likely, between G3 and G4. Groups 2 and 3 had a weaker correlation and G1, despite the limited number of participants, had a good prominent result in this regard.

In a study by Czubaszewski *et al*., in 2017, 132 men with heart failure were followed up for 2 years using CPET to disclose that HR indices, although not of the quality of VE/VO_2, are valuable in terms of the determination of prognosis in CHF patients. These parameters are obviously weaker than respiratory parameters in this regard but are key prognostic determinants, especially in the absence of the relevant facilities of exercise test in distant areas (29). They concluded that individuals with weak prognosis of HF had LVEF <45%, lower HR max (122/min), lower chronotropic index (CHI), lower peak VO_2 and higher VE/VCO_2 at AT which correlated indirectly with VO_2/kg through the current study to show the most severity of disease by its higher amounts as also shown before (32).

Increased ventilatory response to exercise metabolic demand, named VE/ VCO_2, as Rocha *et al*., expressed in 2017, is a very common finding in COPD subjects with coincident heart failure. A destructive disease like COPD could increase the respiratory effort to reach an accepted supply compared to healthy lungs due to a V/Q mismatch which wastes patient's attempts to access enough O2 (28).

At weaker level, VE/VO_2 may help in terms of determining prognosis and life quality and other kinds of approach to HF patients. The current study showed a significant difference between G4 and other groups of participants to endorse the efficacy of VE/VO_2 as a key parameter of CPET in HF subjects.

VE% (VE/MVV×100) correlated indirectly with the severity of CHF in our participants, especially in group 4; but there was no previous work, as far as our knowledge, to compare the findings within this matter.

In healthy individuals, BR is 10-40% of MVV which could be around 11 lit/min in raw form. Lower amounts of BR figures a respiratory and ventilatory problem resulted from primary lung disease and its least amounts occur in obstructive lung diseases. On the contrary, higher amount of BR is an index of cardiovascular problems (5). Our study obtained higher measures of BR in more severe cases of heart failure. Toma *et al*. preferred to express that in heart failure, BR could be usually in the normal range just to rule out respiratory cases (5). Concerning the pathophysiology of O_2 consumption at the tissue level, two things are important including capillary density in tissues and especially muscles, secondly, mitochondrial density in muscular ultrastructure. These factors absolutely help obtain much more energy from O_2 at the best way of metabolism (33).

VO_2 max was the last parameter to report which differed from group to group despite low number of cases in G1 and G2. Hussain *et al*., showed in Pakistan that VO_2 max indirectly correlated with age of CHF patients who had LVEF 10-35% but was directly in a relationship with CPET duration, blood hemoglobin level and LVEF (34). Unlikely, Malek-Mohammad *et al*., found no correlation between VO_2 max and age, height, weight, BMI and LVEF in 2012 among 22 cases of severe heart failure with LVEF<30%. (35)

Unjustified dyspnea is indeed a common condition needing several diagnostic techniques to determine and manage. Ergospirometry is only one of the wide ranges of those diagnostic ways in recent decades (36). Ergospirometry along with myocardial perfusion imaging (MPI) has shown that patients with normal MPI and abnormal CPET results should be focused for respiratory issues instead of cardiovascular ones in a study in 2017 (37). However, CPET can brilliantly put patients in physical exercise situation to manifest their hidden symptoms which are important to diagnose the predisposing disease to dyspnea (32).

Study limitations

Heart transplantation is not actually a common procedure at least in Iran, and this was mainly why we were limited to establish strict inclusion criteria to keep rather suitable sample size.

Due to small sample size, there was no ability to dividing the participants based on age, career, and etiology of HF pushing patients to transplantation, risk factors of HF, and other important factors. Categorization could lessen the number of participants in each group to make analysis much difficult.

However, using statistical tools, the study tried to assess the effects of some crucial factors disregarding other probable confounding factors on CPET parameters. Finally, we decided to categorize the participants based on the severity of HF as well as VO_2/Kg in order to get the most reliable output.

The current study found prominent correlations of CPET parameters and CHF severity to be useful in approach and prognosis determination for CHF despite limitations. It seems to be more useful to involve many other factors including the cause of test termination and some comorbidities as well as echocardiography findings via case-control or clinical trial studies to find much more interesting information among wider range of patients.

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