ORIGINAL ARTICLE

Clinical Safety and Parameters of Maximum Oxygen Uptake (VO_2 Max) Testing in Pakistani Patients With Heart Failure

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ABSTRACT

Objective: To determine the parameters of maximum oxygen uptake (VO_2 max) in a Pakistani systolic heart failure cohort and its safety in a clinical setting.

Study Design: Descriptive study.

Place and Duration of Study: Armed Forces Institute of Cardiology, National Institute of Heart Diseases, Rawalpindi, from June 2011 to January 2013.

Methodology: Maximum oxygen uptake test was performed in patients with severe heart failure, who could perform the VO_2 max treadmill test. Age, Body Mass Index (BMI) ejection fraction, VO_2 max and respiratory exchange ratios and their correlations were determined.

Results: Out of 135 patients, 77% (n=104) were males, with a mean age of 45.9 ± 15.7 years. Weight of patients ranged from 30 kg to 107 kg (mean 63.29 ± 13.6 kg); mean BMI was 23.16 ± 4.56 kg/m^2. All patients presented with either NYHA class of III (50.3%; n=68) or IV (49.7%; n=67); mean ejection fraction was 22.54 ± 5.7% (10 - 35%, IQ:20 - 25). The VO_2 max of the patients ranged from 3 to 32 ml/kg/minute (mean 12.85 ± 4.49 ml/kg/minute). Respiratory exchange ratio was over 1 for all patients (1.12 - 1.96, mean = 1.36 ± 0.187). There was a negative correlation with age (r = -0.204; p = 0.028) whereas a positive correlation was found with exercise time (r = 0.684; p = 0.000), hemoglobin (r = 0.190; p = 0.047) and ejection fraction (r = 0.187 ; p = 0.044).

Conclusion: Cardiopulmonary exercise testing in a high-risk heart failure cohort is safe and provides information beyond the routine clinical evaluation of heart failure patients.

Key Words: *VO_2 max. Heart failure. Peak oxygen uptake. VCO_2.*

INTRODUCTION

Heart Failure (HF) is a clinical syndrome with considerable morbidity and mortality and incurs significant expense on any healthcare system.[1] In 2008 the prevalence of HF in American males and females aged ≥ 20 years was 3% and 2% respectively. The incidence of HF in males and females aged ≥ 45 years was 350,000 and 320,000 respectively. There were a total of 56,830 deaths due to heart failure in 2008. The total number of hospital discharges admitted initially as heart failure was 1,094,000 in 2009.[2]

Risk stratification and prognosis assignment is an integral part of the management of heart failure so that these patients may be counseled about their prognosis and referred appropriately for advanced therapies such as cardiac resynchronization Therapy (CRT), Implantable Cardioverter Defibrillators (ICDs) and eventually Heart Transplantation (HT). Different prognostic calculating systems have been devised for this population. Testing the patients for maximum oxygen uptake (VO_2 max) is one of the methods for risk stratifying the patients and explanation of prognosis to these patients. VO_2 max testing is an expensive enterprise; however, it is the way forward in the management of systolic heart failure.

The aim of this study was to determine the parameters of VO_2 max in systolic heart failure patients as well as its safety in a clinical setting in Pakistan.

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Received: November 16, 2013; Accepted: August 07, 2015.

METHODOLOGY

A descriptive study was conducted at The Armed Forces Institute of Cardiology-National Institute of Heart Diseases, Rawalpindi, from June 2011 to January 2013 after formal approval from the Ethical Review Board of the Hospital. The study population consisted of all heart failure patients referred to heart failure clinic and willing to participate in study. Heart failure was defined as documented Ejection Fraction of less than or equal to 40% with sign and symptoms of heart failure. Complete history (including age, gender, NYHA class, diagnosis) and relevant cardiovascular examination was recorded. Blood samples were taken and hemoglobin estimation was done for every patient. A detailed echocardiography was done and Ejection Fraction (EF) was calculated using modified Simpson's method and M-mode measurements on an IE-33 echocardiography machine.

Informed consent of patients was obtained prior to the start of the test. The cardiopulmonary exercise testing using ergocard treadmill (Medisoft-CE) using Modified McNaughton protocol was conducted.

The test was not conducted on patients who were in acute heart failure or who could not perform the test because of non-cardiac physical disability. To conduct the test, the patients were physically prepared and instructed as would be for a standard treadmill exercise test. In addition, patients were made to wear a tight fitting mask which has breathing in and out circuits leading to a gas analyzer unit. The inhaled and exhaled gases are analyzed within this unit while the patient is exercising. The patients were required to achieve an adequate level of exertion which was ensured by achieving the Anaerobic Threshold (AT), and a heart rate of ≥ 85% of the age calculate target heart rate (220 - age in years). Emergency cart with requisite equipment to execute Advanced Cardiac Life Support (ACLS) was kept at hand. The test was stopped when above parameters were achieved or if patient became symptomatic.

The acquired data was entered in SPSS version 19. Frequencies and percentages were obtained for qualitative variables (gender, NYHA class, diagnosis) whereas range and mean value with standard deviation was described for quantitative variables (age, weight, body mass index, ejection fraction, VO_2 max, RER, max heart rate,). Pearson Correlation was applied to demonstrate the relationship of age, weight, Hemoglobin (Hb), EF, maximum heart rate, RER value, maximum ventilation and max O_2 and CO_2 consumption with VO_2 max measurement.

RESULTS

Test was performed in a total of 135 patients who were referred for evaluation of heart transplant. Out of them, 76% (n=104) were males and 23% (n=31) were females. The age ranged from 12 to 79 years with a mean of 45.90 ± 15.7 years (IQ=34 - 56 years). Weight of patients ranged from 30 to 107 kg (mean 63.29 ± 13.6 kg; median 63 kg) whereas mean body mass index was 23.16 ± 4.56 kg/m^2. All patients presented with either NYHA class III (50.3%; n=68) or IV (49.7%; n=67). Hemoglobin estimation showed a minimum of 8.7 g/dl and maximum of 17.4 g/dl and a mean of 13.09 ± 1.87 g/dl. The echocardiography showed mean ejection fraction of 22.54 ± 5.7% (maximum 35; minimum 10%).

The VO_2 max of the patients ranged from minimum of 3 to maximum of 32 and mean of 12.85 ± 4.49 ml/kg/minute. Respiratory exchange ratio was over 1.12 for all patients (maximum 1.96; minimum 1.12, mean=1.36 ± 0.187). The correlations of different cardiopulmonary test variables with VO_2 max are shown in Table I.

There was a weak negative correlation with age (r = -0.204; p=0.028), a moderate positive correlation with exercise time (r = 0.684; p < 0.0001), and weak positive correlation with hemoglobin (r = 0.190; p = 0.047) and ejection fraction (r = 0.187; p = 0.044).

Table I: Correlation between VO_2 max and patient parameters.

	VO_2 max	Age	BMI 1 (kg/m^2)	Ejection fraction	VO_2 Exercise time in min.	Hb
VO_2 max						
Pearson correlation (r)	1	-.204*	-.301**	.185*	.685**	.190*
p-value	-	.028	<.001	.046	<.001	.047
n	117	117	113	116	115	110
Age						
Pearson correlation (r)	-.204*	1	.189*	.007	-.152	.121
p-valve	.028	-	.031	.938	.081	.175
n	117	135	130	134	133	127
BMI 1 (kg/m^2)						
Pearson correlation (r)	-.301**	.189*	1	.102	-.408**	.018
p-value	.001	.031	-	.250	<.001	.848
n	113	130	130	129	130	122
Ejection fraction						
Pearson correlation (r)	.187*	.007	.102	1	.108	-.088
p-value	.044	.938	.250	-	.220	.328
n	116	134	129	134	132	127
VO_2 Exercise time in minutes						
Pearson correlation (r)	.684**	-.152	-.408**	.108	1	.085
p-value	<.001	.081	<.001	.220	-	.347
n	115	133	130	132	133	125
Hb						
Pearson correlation (r)	.190*	.121	.018	-.088	.085	1
p-value	.047	.175	.848	.328	.347	-
n	110	127	122	127	125	127

Table II: Correlations between VO_2 max and VO_2 max variables.

	VO_2 max	Exercise Time (min.)	Target heart rate %	RER value	Ventilation	VCO_2	VO_2	Ve / VCO_2	Ve / VO_2	VO_2/ HR
VO_2 Max										
Pearson correlation (r)	1	.685**	.220*	.119	.650**	.834**	.868**	-.583**	-.455**	.503**
p-value	-	<.001	.018	.200	<.001	<.001	<.001	<.001	<.001	<.001
n	118	116	116	117	117	117	117	117	117	115
Exercise time (min.)										
Pearson correlation (r)	.685**	1	.126	.234**	.473**	.604**	.574**	-.363**	-.195*	.228**
p-value	<.001	-	.147	.007	<.001	<.001	<.001	<.001	.024	.008
n	116	134	134	134	134	134	134	134	134	133
Target heart rate (%)										
Pearson correlation (r)	.220*	.126	1	.014	.168	.234**	.221*	-.183*	-.138	-.108
p-value	.018	.147	-	.875	.052	.006	.010	.034	.111	.215
n	116	134	134	134	134	134	134	134	134	133
RER value										
Pearson correlation (r)	.119	.234**	.014	1	.501**	.322**	.090	.170*	.523**	.220*
p-value	.200	.007	.875	-	<.001	<.001	.298	.048	<.001	.011
n	117	134	134	135	135	135	135	135	135	133
Ventilation										
Pearson correlation (r)	.650**	.473**	.168	.501**	1	.874**	.773**	-.155	.139	.478**
p-value	<.00	<.001	.052	<.001	-	.000	<.001	.073	.107	<.001
n	117	134	134	135	135	135	135	135	135	133
VCO_2										
Pearson correlation (r)	.834**	.604**	.234**	.322**	.874**	1	.953**	-.528**	-.278**	.532**
p-value	<.001	<.001	.006	<.001	<.001	-	<.001	<.001	.001	<.001
n	117	134	134	135	135	135	135	135	135	133
VO_2										
Pearson correlation (r)	.868**	.574**	.221*	.090	.773**	.953**	1	-.593**	-.453**	.592**
p-value	<.001	<.001	.010	.298	<.001	<.001	-	<.001	<.001	<.001
n	117	134	134	135	135	135	135	135	135	133
Ve / VCO_2										
Pearson correlation (r)	-.583**	-.363**	-.183*	.170*	-.155	-.528**	-.593**	1	.751**	-.220*
p-value	<.001	<.001	.034	.048	.073	<.001	<.001	-	<.001	.011
n	117	134	134	135	135	135	135	135	135	133
Ve / VO_2										
Pearson correlation (r)	-.455**	-.195*	-.138	.523**	.139	-.278**	-.453**	.751**	1	-.254**
p-value	<.001	.024	.111	<.001	.107	.001	<.001	<.001	-	.003
n	117	134	134	135	135	135	135	135	135	133
VO_2/ HR										
Pearson correlation (r)	.503**	.228**	-.108	.220*	.478**	.532**	.592**	-.220*	-.254**	1
p-value	<.001	.008	.215	.011	<.001	<.001	<.001	.011	.003	-
n	115	133	133	133	133	133	133	133	133	133

***Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed).*

Table III: McNaughton protocol.

0	1.0 mph	0% grade	2 minutes	1.6 Mets
I	2.0 mph	0% grade	2 minutes	2 Mets
II	2.0 mph	3.5% grade	2 minutes	3 Mets
III	2.0 mph	7% grade	2 minutes	4 Mets
IV	2.0 mph	10.5% grade	2 minutes	5 Mets
V	2.0 mph	14% grade	2 minutes	6 Mets
VI	2.0 mph	17.5% grade	2 minutes	7 Mets

There was a moderate positive correlation with ventilation ($r = 0.653$; $p < 0.001$) and VCO_2/HR ($r = 0.545$; $p = 0.004$), a strong positive correlation with VCO_2 ($r = 0.835$; $p < 0.001$) and VO_2 ($r = 0.87$; $p < 0.001$), and weak negative correlation with Ve/VO_2 ($r = -0.454$; $p < 0.001$), Ve/VCO_2 ($r = -0.58$; $p < 0.001$) whereas Heart Rate (HR) showed strong positive correlation with a non-significant association ($r = 0.73$; $p = 0.591$) as seen in Table II.

DISCUSSION

Heart failure is a chronic syndrome of cardiovascular decompensation with detrimental systemic effects. Different trials of beta blockers,[3] angiotensin converting enzyme inhibitors and angiotensin receptor blockers have shown an improvement in the quality of life and reduction in mortality.[4-6] Cardiac resynchronization therapy also improves the quality of life and reduces mortality in these patients.[7]

Two commonly used scoring systems to predict mortality, survival and risk include the Seattle Heart Failure Model (SHFM) and the Heart Failure Scoring System (HFSS). Both these models are computer based calculators that use patients' clinical and laboratory variables to generate a composite score and predict risk. Although most centers employ both models, and combining the HFSS and SHFM has been shown to improve predictive ability,[8] the SHFM is more commonly used for its ease of use in the out-patients setting. When the 1-year predicted mortality for the patient on SHFM exceeds 20% the patient is referred for heart transplantation. The HFSS uses the VO_2 max of the patient as one of the variables which need to be measured in order to finally calculate everything.

Maximum oxygen uptake is the highest value for oxygen uptake which can be attained and measured during an incremental exercise protocol for a specific exercise mode. Attainment of VO_2 max generally needs the use of large muscle groups over a 5 - 15 minutes period in aerobic exercise. VO_2 max is dependent upon the presence of effective external and internal respiration.[9] External respiration means the process of pulmonary ventilation and pulmonary diffusion or the exchange of O_2 and CO_2 between alveoli and the blood. Internal respiration means the transport of O_2 and CO_2 in the blood and the capillary gas between blood and the working muscle. Thus, an effective perfusion and oxygen uptake is related to the presence of effective ventilation and a normal cardiac output. One of the hall marks of the chronic heart failure syndrome is the failure to increase this oxygen delivery to muscles due to a low cardiac output, and the ventilation must increase disproportionately to the metabolic needs to compensate for the inadequate perfusion. Indeed, there is also impaired oxygen uptake by the exercising muscle.[10] The method of measuring this capacity is to put the patients through Cardio Pulmonary Exercise (CPX) testing in which the patient is subjected to incremental aerobic workload either on a treadmill or an exercise cycle. Selection of the appropriate exercise protocol is essential. It is essential that the patient be subjected to a constantly increasing workload. Subjecting the patient to steep workloads leads to earlier achievement of the anaerobic threshold and a test value that may not be correct. For this reason the Balke, McNaughton and other similar protocols with moderate increases in exercise capacity are recommended for these assessments.[11,12] In these patients, the modified McNaughton exercise protocol was selected (Table III). Since the test population is one at high risk of events due to the severity of disease the test needs to be conducted under close medical supervision ready to deal with any cardiac emergencies and events. The event rate for heart failure patients undergoing the test is very low at < 1 to < 5 in 10,000 tests and death at approximately 0.5 in 10,000 tests.[13] In the HF-ACTION study the event rate for non-fatal cardiac events was < 0.5 per 1000 tests.[14] In this case series, there were no adverse events during the conduct of the test, the probable reason being the small sample size.

A comprehensive technical discussion of performance of VO_2 test is beyond scope of this article. The patient is instructed and prepared for a standardized exercise test either on a treadmill or an exercise bicycle. The addition is a breathing face mask which is connected to a gas analyzer at the other end.

It should be remembered that meticulous gas and volume calibration, temperature maintenance has to be ensured.[9] Close attention also needs to be paid to the ambient temperature as well as humidity levels in the room where the test is being performed. It should be ensured that the face mask is tight but a comfortable fit without any air leaks; the warning messages about the system performance on the computer should not be ignored. This study showed mean VO_2 max of 12.85 ± 4.49 ml/kg/minute. Respiratory exchange ratio was over 1.12 for all patients whereas a study in United Kingdom showed a mean VO_2 max of 18.4 ± 5.5 ml/kg/minute.[15] In Iran, a study on 22 patients with severe heart failure showed O_2 mean consumption was 6.27 ± 4.9 ml/kg/minute at rest and 9.48 ± 3.38 at Anaerobic Threshold (AT) exceeding 13 ml/kg/minute in maximum which was significantly more than the expected levels. Respiratory Exchange Ratio (RER) was over 1 for all patients. This study could not find any statistical correlations between VO_2 max and participants' ergonomic factors such as age, height, weight, BMI, as well as EF. This study showed no significant correlation between VO_2 max and maximum Heart Rate (HR max), although O_2 maximum consumption was rationally correlated with expiratory ventilation.[16] However, this study found weak negative correlation with age, a moderate positive correlation with exercise time and a weak positive correlation with hemoglobin and ejection fraction.

The VO_2 max test is a comprehensive Cardiopulmonary Exercise (CPX) test and generates far more information beyond the VO_2 reading itself. The other important variable which needs consideration is the VE/VCO_2 slope. The minute ventilation-carbon dioxide output relationship (VE/VCO_2 slope) reflects the relationship between ventilation and the level of work. Although this variable is used to assess ventilatory efficiency, it essentially reflects a change in the ventilation perfusion mismatch as well as changes in central chemoreceptor and baroreceptor sensitivity in response to exercise. This variable has also been correlated with reduced cardiac output, elevated pulmonary pressures and reduced heart rate variability. Disease severity continues to increase with increases of VE/VCO_2 slope (> 30) with values > 60 indicating severe disease.[17] The present data showed a minimum value of 30.28 and a maximum of 100 with a mean value of 54.59 ± 14.91 and there was a strong correlation between VO_2 max and VE/VCO_2.

The heart rate is another variable which is important to consider during the CPX testing. It not only indicates adequacy of exercise but also gives info about chronotropic incompetence (Failure to achieve ≥ 85% of the age predicted maximum heart rate) in response to exercise. Chronotropic incompetence in response to exercise is also a predictor of increased mortality and adverse outcomes. However, this measurement may be confounded by drugs reducing the heart rate such as beta-blockers.

As a general rule exercise induced hypotension is associated with adverse outcomes. CPX testing also provides important information about the development of chest discomfort, arrhythmia and ischemic ECG changes.

The two major pitfalls in performing a CPX test are machine calibration and failure to achieve the anaerobic threshold. Volume calibration for the machine needs to be done before every test using a standard 3-Liter canister (provided with the machine by the manufacturer); gas calibration needs to be done every 3 or 6 months depending upon the requirement set forth by the manufacturer. In order for the test to be successful the patient effort needs to be adequate indicated by achievement of the AT or 85% of the predicted maximum heart rate. Failure to prevent the pitfalls mentioned above will lead to erroneous reports.

Studies show that patients with a low VO_2 have higher mortality as compared to the normal population.[18] This is the reason that VO_2 is used to set up cut off lines for referring patients for heart transplant. For heart transplant, these lines have been set at VO_2 max < 12 ml/kg/ minute if on ß-blockade, < 14 ml/kg/minute if not on β-blockade, ensuring an RER of 1.05.[19] These values may differ in the US guidelines.[9] The efficacy of VO_2 max testing to guide the intensity of exercise prescription in patients with heart failure as well as other advanced cardiopulmonary diseases has also been well established.[20,21]

CONCLUSION

Cardiopulmonary exercise testing in a high-risk heart failure cohort in Pakistan is safe and provides information beyond the routine clinical evaluation of heart failure patients.

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