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Diagnostic and Prognostic Value of Lactate Threshold and pH - Threshold Determination during Cardiopulmonary Testing in Patients with Chronic Heart Failure

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TAL and MYS were responsible for the study design, data analysis, and manuscript preparation. Author TAL wrote the first draft of the manuscript, managed the analyses of the study and the literature searches. Author EVS supervised the work and contributed methodical instructions. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Objective: lactate threshold and pH-threshold determination during cardiopulmonary testing (CPET) and evaluate their diagnostic and prognostic value in patients with chronic heart failure.
Methods: The study included 58 HF patients with NYHA class II-IV, who have performed CPET on treadmill using equipment «Oxycon PRO», Jaeger, Germany. Individual exercise test protocol (ramp protocol) was created for every participant. The cubital venous catheter was installed in all subjects before exercise test. Blood samples were taken at baseline and at 1-minute intervals during test. PH, lactate and HCO_3- concentration were estimated using analyzer i-STAT, cartridge CG4 (Abbot, USA). Lactate threshold (LT) and pH-threshold (pH-T) were determined by changes in pH and lactate levels in correlation with dynamics of oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (V_E), ventilatory equivalent of carbon dioxide (V_E/VCO_2), respiratory exchange ratio (RER). Respiratory compensation point (RCP) was determined, when ventilation

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dramatically increase relative V_E/VCO_2.
Results: In HF patients with NYHA class II level of physical performance was significantly higher than in patients NYHA class III and IV. However, during exercise in all HF patients were observed similar physiological stages and compensatory mechanisms of regulation of homeostasis, but with varying of exercise intensity. In HF patient with NYHA class IV, exercise was stopped before reaching of RCP in connection with the development shortness of breath, weakness, tiredness, fatigue in the legs 8-9/10 Borg scale. Among HF patients with NYHA class III RCP reached 12 (36%) of people, among patients with class II - 14 (82%). The 95% confidence intervals (CI) for the VO_2 peak, RCP, pH-T and LT in II, III and IV NYHA class are follows: in HF patients with NYHA class II - 17.4 to 18.2, 16.3 to 17.2, 14.7 to 15.3 and 9.7 to 10.1; NYHA class III - 13.5 to 14.3, 12.2 to 12.8, 11.4 to 11.8 and 8.2 to 8.6; NYHA class IV - 8.6 to 10.6 for VO_2 peak, 8.1 to 9.7 for VO_2 pH-T, 5.7 to 7.5 for VO_2 LT. HF NYHA class correlated with VO_2 LT, VO_2 pH-T and VO_2 RCP, r=-0.7, p<0.01, r=-0.5, p<0.01 and r=-0.4, p<0.01, respectively. Patients were observed in the average 21.4 of +/ - 1.5 months (6-48). For the specified period in the study group died 15 HF patients (25%) with III-IV FC. We observed the following correlations: the survival and VO_2 LT - r=0.8, p<0.05; survival and VO_2 pH-T - r=0.5, p<0.05; survival and VO_2 RCP - r=0.2, p<0.07.
Conclusion: In HF patients with NYHA class II-IV significant diagnostic and prognostic markers are content VO_2 at lactate threshold and pH-threshold, especially at the lactate threshold.

Keywords: Lactate threshold; pH-threshold; cardiorespiratory testing; heart failure.

1. INTRODUCTION

Chronic heart failure (HF) is the final stage syndrome of cardiovascular diseases [1]. Patients with heart failure note a progressive decrease in exercise tolerance up to the point where the activities of daily living become unbearable and HF symptoms (shortness of breath, weakness, etc.) occur even at rest. This state is the evidence that the organisms' spare capacities are almost completely exhausted, and even the state of basal metabolism in itself is excessive load to the body. In this case, heart transplantation is the only outcome for such patient.

«Gold standard» for determining the exercise capacity in HF patients is cardiopulmonary exercise testing (CPET) [2-5]. Achieving a clear plateau in VO_2 has traditionally been used as the best evidence of VO_2max. VO_2max is the best index of aerobic capacity and the gold standard for cardiorespiratory fitness. It represents the maximal achievable level of oxidative metabolism involving large muscle groups. However, in patients with HF a VO_2plateau may not be achieved before symptom limitation of exercise [6-8]. Consequently, VO_2peak is often used. But the VO_2peak depends on the motivation of the patient, experience of the physician performing the CPET, and do not always reflect the true exercise capacity.

In previous work [9] we have proposed a method of evaluating biological reserves adaptation to physical exercise based on the definition of four compensatory-adaptive stages physical efficiency during CPET in healthy individuals: lactate threshold (LT), pH-threshold (pH-T), respiratory compensation point (RCP) and aerobic limit. Until now, such an assessment in HF patients has not been performed. We propose that VO_2 at the level of pH-T (VO_2pH-T) and VO_2 at the level of LT (VO_2LT) may reflect the true exercise capacity even in weak HF patients performing little effort.

1.1 Objective

To determine lactate threshold and pH-threshold during cardiopulmonary exercise testing and evaluate their diagnostic and prognostic value in HF patients with NYHA class II-IV.

2. METHODS

2.1 Patients' Population

We examined 58 HF patients with NYHA class II-IV (8 of them are women) under observation in Federal Research Centre named after V.A. Almazov. The inclusion criteria in the study were the availability of NYHA class II-IV, the clinical state stability for at least 2 weeks, the ability to perform CPET. Exclusion criteria were myocardial infarction within last three months; acute cerebrovascular accident within last six months; significant mental abnormalities, contraindications to perform CPET.

Clinical and instrumental data on patients under study are given in Tables 1 and 2.

Patients received standard therapy, including ACE inhibitors or antagonists of type 1 angiotensin I, β- blockers, diuretics, spironolactone and nitrates as indicated.

Table 1. Clinical data on patients

NYHA class Characteristic	NYHA class II	NYHA class III	NYHA class IV
Demographic profile			
Total number of HF patients, n(%)	17 (29)	33 (57)	8 (14)
Men, n (%)	17 (100)	27 (82)	6 (75)
Cause of CHF			
ICM, n (%)	12 (70)	17 (53)	4 (50)
DCM, n (%)	5 (30)	16 (47)	4 (50)

ICM – Ischemic Cardiomyopathy, DCM – Dilated Cardiomyopathy

The study was performed in accordance with standards of Good Clinical Practice and principles of the Helsinki's Declaration. All study participants signed informed consent which was approved by the Ethics Committee of the Federal Research Centre.

The following parameters were initially evaluated: clinical status, echocardiography data, indicators of ventilation, gas exchange parameters during CPET. 5 days prior to the main study patients became familiar with the procedure, they performed preliminary cardiopulmonary testing, and then - diagnostic CPET. After that all patients were observed were observed for 21.4+/-1.5 (6-48) months.

2.2 Cardiopulmonary Testing

CPET was performed using equipment «Oxycon Pro» (Jeger, Germany). Exercise ramp protocols were personified so that each participant reached submaximal effort within 8-10 minutes. CPET was stopped due to breathlessness or fatigue or legs' pain (at the level of 8 out of 10 points on a Borg scale), development of severe weakness, faintness.

During the test 12 - lead ECG was continuously recorded, blood pressure was measured every 2 minutes. In evaluation respiratory cycle mode «breath by breath» with automatic averaging data within 10 sec the following parameters were continuously recorded and comprehensively evaluated: the amount of minute ventilation (V_E), breathing reserve (BR), dead space to tidal volume ratio (V_d/V_t), carbon dioxide equivalents (V_E/VCO_2), $PETCO_2$, volume of oxygen uptake (VO_2).

The cubital venous catheter was installed in all subjects before exercise test. Blood samples were taken at baseline and at 1-minute intervals during test. PH, lactate and HCO_3- concentration were estimated using analyzer i-STAT, cartridge CG4 (Abbot, USA). The decision to take venous blood samples, was taken on the basis of results of recent studies showing high identity of the content of lactate and hydrogen carbonate in arterial and venous blood [10,11].

Physiological stages of involving compensatory reactions were determined by changes in pH and lactate levels in correlation with dynamics of oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (V_E), ventilatory equivalent of carbon dioxide (V_E/VCO_2), respiratory exchange ratio (RER). Lactate threshold was determined at the moment when blood lactate level began to increase. pH-threshold was determined at the moment when blood pH level began to decrease. Respiratory compensation point (RCP) was determined, when ventilation dramatically increase relative to carbon dioxide output (V_E/VCO_2).

2.3 The Statistical Data Analysis

The statistical analyses were performed with the use of the Statistika PC (version 6.0, Windows). Sample size calculation: Step 1. Finding standardized difference/ Standardized difference = target difference: standard deviation = 3, 21:3, 83= 0,838. Step 2. The definition of the sample size by the Altman nomogram [12] (Fig. 1).

The total sample size for this study that is capable of detecting a 0.838 standardized difference with 85% power using a cutoff for statistical significance of 0.05 is approximately 60. Continuous variables are expressed in Median, Lower Quartile (Q1), Upper Quartile (Q3) and inter-quartile range (IQR). Comparison of means of sample was performed using CI. Statistical relationships between variables was determined using correlation analysis.

3. RESULTS AND DISCUSSION

In patients with NYHA class II physical performance level was significantly higher than in patients with NYHA class III and IV. The Median, Lower Quartile (Q1), Upper Quartile (Q3) and inter-quartile range (IQR) for VO_2peak, RCP, pH-T and LT in HF patients with II, III and IV NYHA class are presented in Table 3.

Table 2. Clinical and instrumental data on patients

Characteristic NYHA class	Median			Q1			Q3			IQR		
	II	**III**	**IV**	**II**	**III**	**IV**	**II**	**III**	**IV**	**II**	**III**	**IV**
Age, years old	53	54	43	48	48	38	60	58	47	12	10	9
BMI, kg/m^2	27	26	22	25	24	19	30	30	23	5	6	4
LVEF, %	37	31	20	31	26	19	43	35	22	12	9	3

Q1- Lower Quartile, Q3 - Upper Quartile, IQR - inter-quartile range. II - HF patients with NYHA class II, III - HF patients with NYHA class III, IV - HF patients with NYHA class IV. BMI – body mass index, LVEF – left ventricular ejection fraction

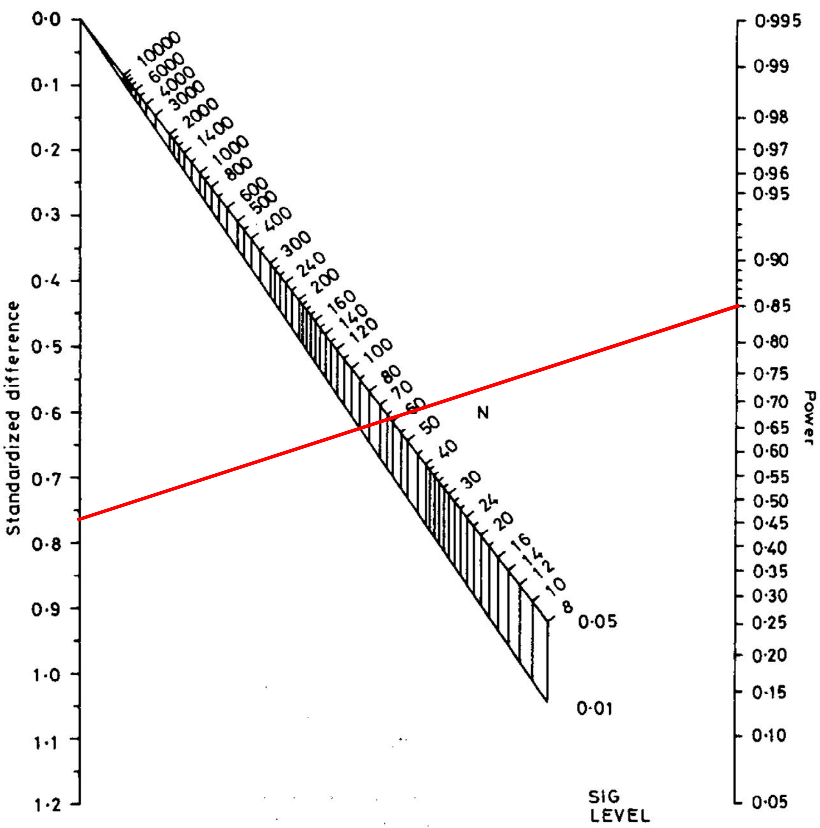

Fig. 1. Sample size calculation using Altman nomogram

Table 3. CPET results

Characteristic NYHA class	Median			Q1			Q3			IQR		
	II	**III**	**IV**	**II**	**III**	**IV**	**II**	**III**	**IV**	**II**	**III**	**IV**
VO_2peak, ml/min/kg	17.8	14.0	9.8	17.1	12.9	8.8	18	14.2	10.2	1	1.3	1.4
VO_2RCP, ml/min/kg	17	12.7		16.4	12		17.5	13		1.1	1	
VO_2pH-T, ml/min/kg	15	11.8	9.3	14.7	11.3	8.8	15.2	11.8	9.5	0.5	0.5	0.7
VO_2LT, ml/min/kg	10	8.4	6.3	10.2	8.6	7.0	9.6	8.1	5.7	0.6	0.5	1.3

Q1- Lower Quartile, Q3 - Upper Quartile, IQR - inter-quartile range. II - HF patients with NYHA class II, III - HF patients with NYHA class III, IV - HF patients with NYHA class IV. VO_2peak - VO_2 at the peak exercise, VO_2RCP - VO_2 at the respiratory compensation point, VO_2pH-T - VO_2 at the level of pH-T, VO_2LT - VO_2 at the level of LT

All patients under physical load showed the similar physiological stages of compensatory mechanisms of homeostasis regulation, but with different physical exercises' intensity and different volume of O_2 (Figs. 2-5). It should be noted that none of the patients under the study reached the fourth stage of the compensatory-adaptive stage - aerobic limit (plateau of VO_2). 28 (48%) patients reached the respiratory compensation point (Fig. 3). 100% of patients during CPET reached lactate threshold and pH threshold.

None of HF patients with IV NYHA class during CPET reached the respiratory compensation point, CPET was stopped earlier due to the fact that patients developed severe shortness of breath, weakness, fatigue 8-9/10 on Borg scale. Among HF patients with NYHA class III RCP was reached by 12 (36 %), NYHA class II - 14 (82%).

The 95% confidence intervals (CI) for the VO_2peak, RCP, pH-T and LT in HF patients with II, III and IV NYHA class are presented in Table 4.

Patients were observed for 21.4+/-1.5 months (6-48) on the average. During this period in the study group 15 (25%) CHF FC III-IV patients, who were considered as candidates for heart transplantation, died. We observed the following correlations: the patients survival and VO_2LT - r=0.8, $p<0.05$;patients survival and VO_2pH-T - r=0.5, $p<0.05$; patients survival and VO_2RCP - r=0.2, p<0,07. Thus, this study demonstrates significant relationship between VO_2LT and VO_2pH-T on the one hand and the severity of heart failure and survival in patients with chronic heart failure on the other hand.

Classification of severity of heart failure, prognosis, and selection for transplantation is based on VO_2max [13-17]. But none of the patients in this study reached a plateau VO_2max and only 45% of patients reached the RCP. However, all the studied reached LT and pH-T. Perhaps in the future it will be advisable to use VO_2LT and VO_2pH-T to assess the severity of CH and prognosis of patients with HF.

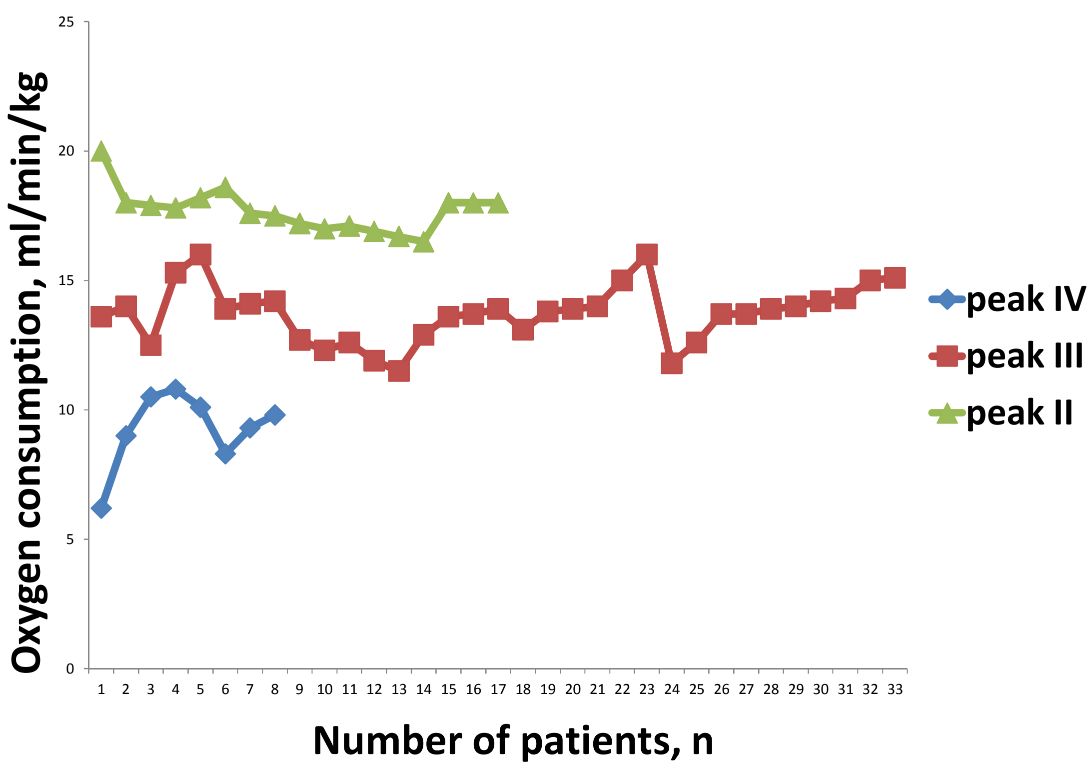

Fig. 2. Oxygen consumption in heart failure patients at exercise peak

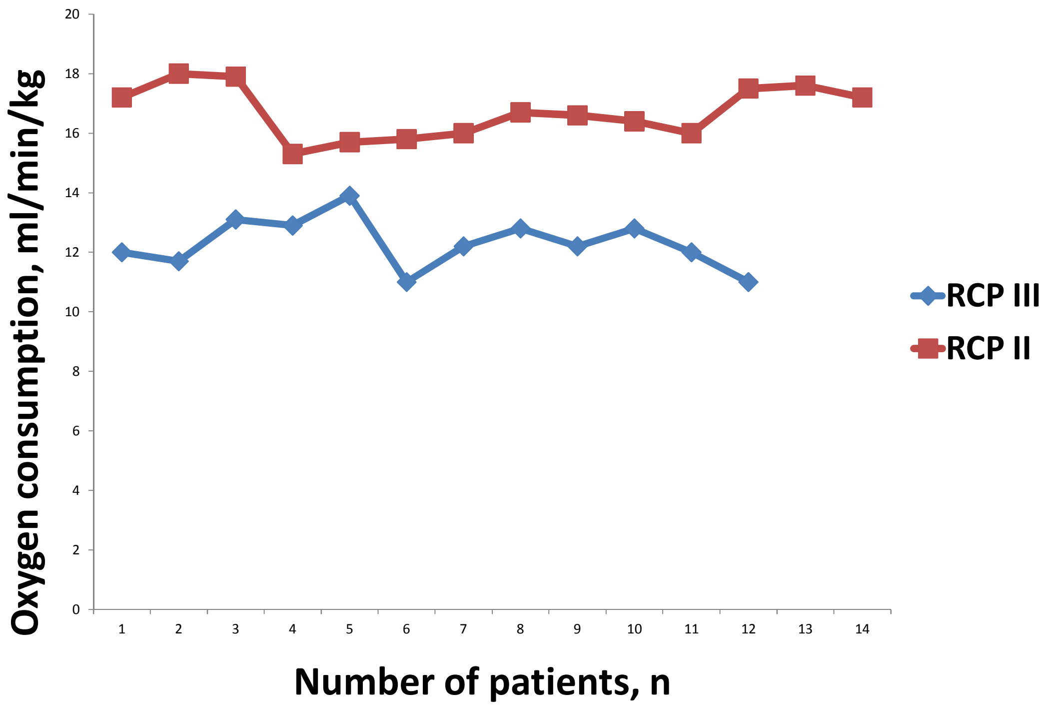

Fig. 3. Oxygen consumption in heart failure patients at respiratory compensation point

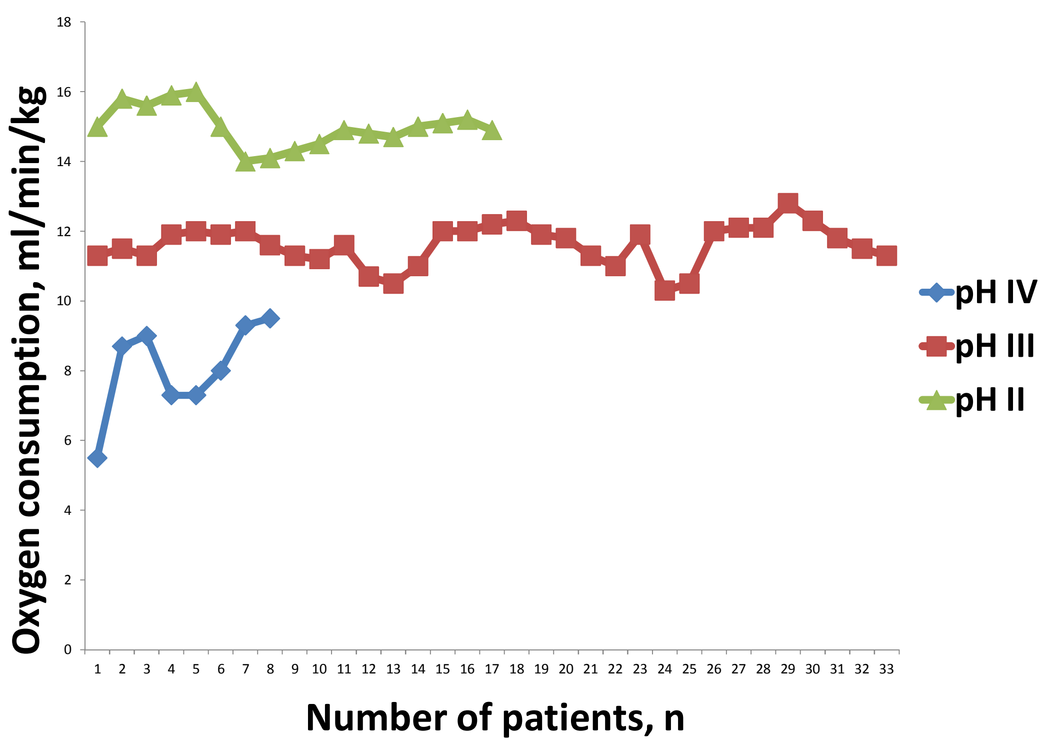

Fig. 4. Oxygen consumption in heart failure patients at pH-threshold

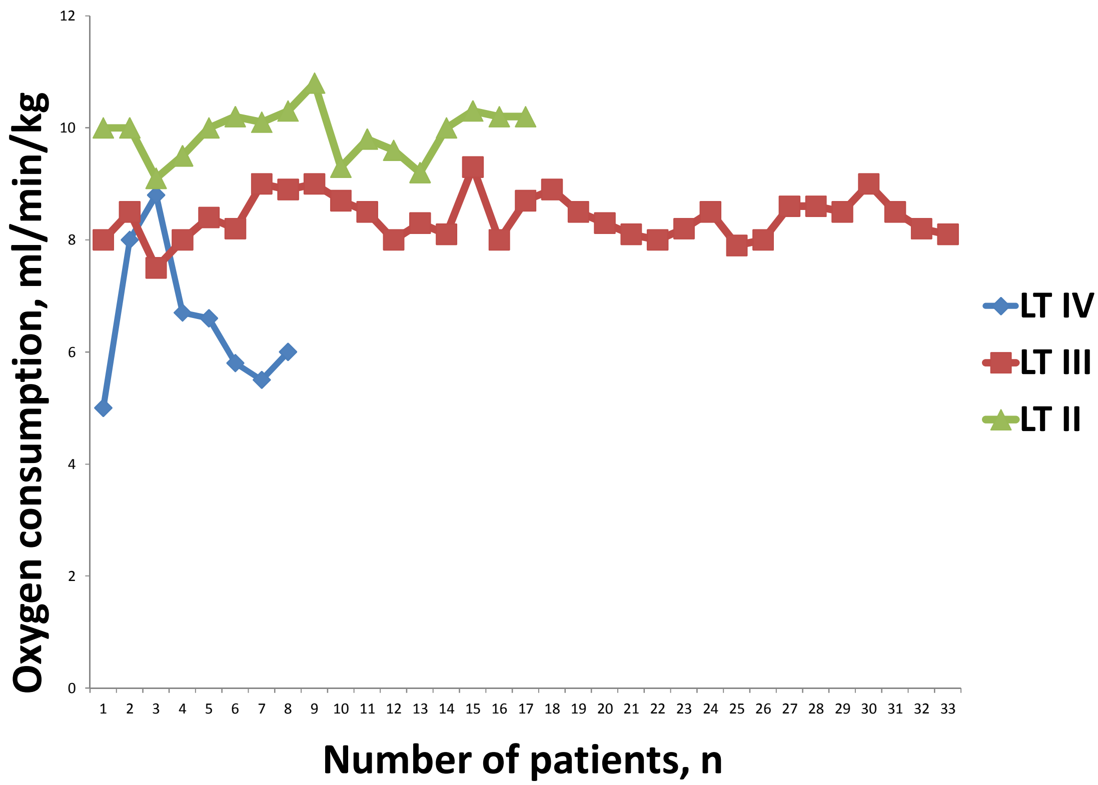

Fig. 5. Oxygen consumption in heart failure patients at LT-threshold

Table 4. 95% confidence intervals (CI) for the VO_2peak, RCP, pH-T and LT in HF patients

Characteristic NYHA class	The 95% confidence interval		
	NYHA class II	NYHA class III	NYHA class IV
VO_2peak, ml/min/kg	17.4 to 18.2	13.5 to 14.3	8.6 to 10.6
VO_2RCP, ml/min/kg	16.3 to 17.2	12.2 to 12.8	
VO_2pH-T, ml/min/kg	14.7 to 15.3	11.4 to 11.8	8.1 to 9.7
VO_2LT, ml/min/kg	9.7 to 10.1	8.2 to 8.6	5.7 to 7.5

During the correlation analysis, strong feedback was revealed 1) between NYHA class and VO_2-level at the LT and pH-T, $r_{LT} = -0.7$, $p < 0.01$; $r_{pH-T} = -0.5$, $p < 0.01$; 2) between HF duration and VO_2 at LT and pH-T, $r_{LT} = -0.5$, $p < 0.05$; $r_{pH-T} = -0.5$, $p < 0.05$

3.1 Study Limitations

The relatively small sample size of the present study is a limitation. The fact there only 8 of the subjects were NYHA class IV may also limit application of our findings to group with more severe CHF. Future research should investigate the diagnostic and prognostic value of VO_2 at lactate threshold and pH-threshold.

4. CONCLUSION

In HF patients with NYHA class II-IV significant diagnostic and prognostic markers are VO_2 at lactate threshold and pH-threshold, especially at the lactate threshold.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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