Clinical Research

Lean Tissue-Adjusted Peak Oxygen Consumption in Chronic Heart Failure Patients

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Objective: Peak oxygen consumption (MVO_2) is a very significant predictor in patients with chronic heart failure (CHF). MVO_2 expresses the amount of oxygen, which is consumed by metabolically active tissues during exercise (especially skeletal muscle). However, it is still expressed in mL/min/kg of body weight (MVO_2-weight). The objective of this study is to evaluate whether the adjustment of this value as to absolute lean mass of muscle tissue (MVO_2-lean) has a further predictive value beyond that of MVO_2-weight in patients with CHF.

Methods and Results: We prospectively evaluated one-hundred and thirty five (135) clinically stable (mean age 61±12 years of age, NYHA stage 2.5±0.9) male patients with CHF, who were subjected to cardiopulmonary exercise testing and evaluation of their body composition by dual-energy X-ray absorptiometry, DEXA. The mean value of MVO_2-weight was 18.0±6.4 mL/min/kg body weight, while the mean MVO_2-lean was 25.5±9.4 mL/min/kg of muscle tissue. During follow-up (mean duration 1398±1038 days), 53 patients died (12 month survival 82 % [95% CI 79-85]). The Cox proportional hazard model showed that, both, MVO_2-weight ($p=0.0004$) as well as MVO_2-lean ($p<0.0001$) are significant predictors of survival. However, the log-likelihood ratio test showed that MVO_2-lean is a statistically more significant prognostic factor than MVO_2-weight ($p=0.0004$). The area under the ROC curve was significantly larger in MVO_2-lean than in MVO_2-weight at 12, 15, 18, 21, 24, 27 and 30 months of follow up ($p<0.05$), while MVO_2-weight progressively lost its predictive value.

Conclusion: MVO_2 adjustment to the absolute lean muscle tissue mass instead of body weight provides a better prognostic marker of survival in patients with CHF. This marker may be of special value in patients with milder forms of CHF as well as in patient subgroups, such as women and the obese patients, in whom the predictive value of conventional MVO_2 is less obvious.

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Chronic heart failure (CHF) is a syndrome characterized by decreased exercise tolerance and low survival rate. The implementation of modern therapeutic methods has somewhat improved the outcome of the disease, but mortality remains high[1,2]. Thus, it is important to have reliable prognostic markers relating to the outcome of the disease as well as to the evaluation of the implemented therapeutic interventions. One such marker, with a continually increasing value, is the peak oxygen consumption (MVO_2), which may accurately predict the outcome in patients with CHF and also direct treatment towards specific interventions[3]. A recent study has shown that in patients with CHF the strongest predictive factor of MVO_2 is the lean skeletal muscle mass, independently of any other clinical or hemodynamic factors[4]. However, MVO_2 is still expressed

in mL/min/kg body weight (MVO_2-weight) which does not seem correct from a physiopathological aspect, since only the metabolically active tissues (skeletal mucles) consume oxygen during physical activity. Thus, another marker is needed, which will take into account the exact mass of the exercised muscles in order to accurately express the amount of oxygen consumed by metabolically active tissue only.

A modern non-invasive method of calculating the total skeletal muscle mass is dual-energy X-ray absorptiometry, DEXA[5]. No study until now has evaluated the predictive value of lean tissue-adjusted peak oxygen consumption (MVO_2-lean) with the use of DEXA in patients with CHF. This study aims at evaluating whether MVO_2-lean is a more accurate predicting factor than conventional MVO_2-weight in a population of ambulatory patients with CHF.

Methods

Study population

The study population consisted of patients who were regularly followed in the period between 1997 and 2001 in the outpatient clinic of Royal Brompton Hospital, London. The study was approved by the Ethics Committee of the Institution and all patients signed an informed consent prior to their inclusion in the study. One hundred and thirty five (135) male patients who fulfilled the following criteria were prospectively studied: diagnosed CHF lasting for at least 6 months, stable clinical condition, capability for maximal exercise testing. Patients with pulmonary or peripheral oedema were excluded from the study because fluid retention would interfere with the evaluation of the body composition[6]. The presence of cardiac cachexia was evaluated as described by Anker *et al*[7].

Body composition

Body composition was assessed by the DEXA method and the use of a Hologic, and Lunar model DPX total body scanner, Lunar Radiation Company, Madison, WI, USA. As the two electron rays pass through the body of the patients, their energy weakens relative to the kind and the mass of the tissue they have penetrated. Based on the changes in this energy decrease, we may assess with high accuracy both, the total mass of the fatty and the muscle tissue, as well as the mass of the muscle tissue in the upper and lower limbs[7]. A series of transverse sections were taken in each patient, from the head to the toes of the feet at 1 cm intervals (total CT scanning time 7-15 min).

Cardiopulmonary exercise test protocol

A treadmill was used (Modified Bruce's protocol, Amis 2000, Odense, Denmark). The patients were encouraged to reach maximal exercise. The VO_2 value at which the expired carbon dioxide (CO_2) increases in a non-linear fashion in relation to the oxygen consumption, was defined as the anaerobic threshold[8]. The highest VO_2 value during maximal exercise was defined as peak oxygen consumption MVO_2 and was expressed in either mL/min/kg body weight (MVO_2-weight) or in mL/min/kg muscle tissue (MVO_2-lean). The curve of the relation between ventilation and carbon dioxide production (VE/VCO_2 slope) was assessed from the exercise variables and its slope was used as a marker of ventilation during exercise[9].

Patient follow-up

The patients were followed-up for at least 6 months in the outpatient clinic of our Hospital. The primary endpoint of the study was all-cause mortality. The patients who underwent heart transplantation were considered survivors during the transplantation procedure.

Statistical analysis

The data is presented as mean values ± standard deviation. In order to make the comparisons between the patient groups, we used t-test and χ^2 testing either. A p value <0.05 was considered statistically significant. Univariate and multivariate Cox proportional hazard analyses were performed in order to assess the effect of the clinical parameters and the cardiopulmonary exercise variables on survival. MVO_2-weight was used both as a quantitative as well as a qualitative variable and the value of 14 mL/min/kg was used as the cut-off point value as described in previous studies[3]. We also calculated the relative risk (RR) with 95% confidence intervals (CI) and the log-likelihood ratio. The comparison of the predictive value of the two variables was performed with the use of the log-likelihood ratio.

In order to compare different prognostic values at specific time-points, the Receiving Operator Cha-

Table 1. Clinical characteristics of study population.

	All patients (n=135)	Survivors (n=82)	Non-survivors (n=53)	p*
Age (years)	61±12	59±13	63±10	0.045
NYHA class, n (%)				<0.0001
I	18 (13)	17 (21)	1 (2)	
II	52 (39)	34 (41)	18 (34)	
III	49 (36)	25 (31)	24 (45)	
IV	16 (12)	6 (7)	10 (19)	
Etiology, n (%)				NS
Ischemic	82 (61)	52 (63)	30 (57)	
Dilated Cardiomyopathy	53 (39)	30 (37)	23 (43)	
ACE inhibitors (%)	124 (92)	76 (93)	48 (90)	NS
Beta-blockers (%)	42 (31)	27 (33)	14 (26)	NS
LVEF (%)	31±14	35±14	25±13	0.0003
BMI (kg/m^2)	25.0±4.5	25.7±4.5	23.9±4.4	0.02
Peak VO_2–weight (mL/min/kg)	18.0±6.4	19.4±6.2	15.8±6.1	0.001
Peak VO_2–lean (mL/min/kg)	25.7±9.1	28.1±8.6	22.0±8.8	0.0001
VE/VCO_2 slope	38.0±14.6	34.2±10.9	43.9±17.4	0.0001

* Survivors vs. non-survivors. Values are presented as mean ± standard deviation or number (% of total). Comparisons are made with Student's t test or chi-square, as appropriate. NS: non significant; NYHA: New York Heart Association; ACE: angiotensin-converting enzyme; LVEF: left ventricular ejection fraction; BMI: body mass index; VO_2: oxygen consumption; VE/VCO_2: relation of minute ventilation to carbon dioxide production.

racteristics (ROC) curve of the true positive events (sensitivity) against the false positive events (1-specificity) was calculated. The statistical differences between the curves were calculated with z statistical analysis. The point at which the sensitivity times specificity product is maximal was defined as the optimal prognostic survival point at a specific timepoint and it was used in order to divide the patients in two subgroups for the analyses according to the Cox proportional hazard and the Kaplan Meier models. Two different statistical programs Statview 5.0 (Abacus Concepts, SAS Institute, Cary, U.S.A.) and MedCalc 5.0 (Mariakerke, Belgium) were used.

Results

The patients' mean age was 61±12 years (range 19-87). The left ventricular ejection fraction (LVEF) was 30±14%. In 82 patients the cause of CHF was coronary heart disease and in 52 patients dilated cardiomyopathy. The clinical characteristics and the results of the cardiopulmonary exercise testing of the patients are summarized in Table 1. During follow-up (1398±1038 days, range 8-3492), 53 patients died. The median follow-up for the survivors was 1281 days (1776±996, range 433-3492). The total survival rate was 89% at 6 months (15 deaths, 95% CI 84-94), 82% at 12 months (24 deaths, 95% CI 76-89), 78% at 24 months (30 deaths, 95% CI 71-85) and 71% at 36 months (36 deaths, 95% CI 62-79).

Age was marginally higher in the patients who died (p=0.045) but the cause of CHF did not differ significantly between the patients who died in comparison to those who survived. The patients who did not survive –as was expected- were at a significantly worse NYHA stage. The value of the Body Mass Index (BMI) and the LVEF were significantly lower in the non-survivors. Similarly, all cardiopulmonary exercise variables were worse in these patients (Table 1).

Survival statistical analysis

In the Cox proportional hazards univariative analysis (Table 2), age (χ^2 8.1), NYHA staging (χ^2 10.1), LVEF (χ^2 10.5) and BMI (χ^2 7.4) were shown to be significant prognostic markers of survival. Amongst the cardiopulmonary exercise testing variables, MVO_2-weight (χ^2 10.7), MVO2-lean (χ^2 14.9) and the VE/VCO_2 curve (χ^2 22.3) were shown to be statistically significant prognostic markers of survival. In the log-likelihood ratio test, MVO_2-lean was shown to be the most significant prognostic factor of survival in comparison to other exercise variables (Table 2). MVO_2-lean predicted the survival in patients with milder forms of CHF (NYHA stage I and II), (p=0.04, RR: 0.93, 95% CI 0.88-0.99, χ^2 4.00)

Table 2. Cox proportional hazard model of predictors of mortality in study population (univariate analysis).

	Relative Risk (95% CI)	Log-likelihood ratio test	p*
Peak VO_2-lean (mL/min/kg)	0.92 (0.88-0.96)	<0.0001	–
Peak VO_2-weight (mL/min/kg)	0.91 (0.86-0.96)	0.0004	0.003
VE/VCO_2 slope	1.04 (1.02-1.05)	<0.0001	0.009
NYHA class	1.69 (1.22-2.33)	0.001	0.003
LVEF (%)	0.96 (0.94-0.98)	0.0005	0.003
Age (years)	1.04 (1.01-1.06)	0.003	0.0003
BMI (kg/m^2)	0.91 (0.85-0.97)	0.005	0.0003
Peak VO_2-lean <24.9 mL/min/kg	4.63 (2.38-9.00)	<0.0001	–
Peak VO_2-weight <14 mL/min/kg	2.09 (1.20-3.66)	0.01	<0.0001
Peak VO_2-weight <15.5 mL/min/kg	2.63 (1.52-4.58)	0.0005	0.0003
VE/VCO_2 slope>37.8	3.56 (2.03-6.25)	<0.0001	0.0005
Cardiac cachexia	3.47 (2.00-6.01)	<0.0001	0.0003

* comparison of all continuous variables vs. peak VO_2-lean and of all categorical variables vs. peak VO_2-lean <24.9 mL/min/kg. Abbreviations as in Table 1.

while MVO_2-weight did not have any prognostic power (p=0.14). Similarly, MVO_2-lean <24.9 mL/ min/kg was shown to be a more significant prognosis survival marker in mild CHF (p=0.002, RR:7.34, 95% CI: 2.56 – 21.05) in comparison to MVO_2-weight values <14 mL/min/kg (p=0.01, RR: 5.48, 95% CI: 1.47 – 20.42) as well as MVO_2-weight values <15.5 mL/min/kg (p=0.04, RR: 3.16, 95% CI: 1.06 – 9.48).

In the multivariate analysis (Table 3), only MVO_2-lean was shown to be an independent prognostic marker when compared to age and LVEF and the χ^2 test value increased when the statistical model included MVO_2-lean. In the multivariate model, which included the NYHA staging and age, MVO_2-weight again lost its predictive value while MVO_2-lean remained an independent prognostic marker of survival.

With the use of the Cox proportional hazard model with two variables in which we included cardiac cachexia, both MVO_2-lean as well as MVO_2-weight were shown to be independent prognostic markers of survival, with MVO_2-lean having the greater χ^2 value. In two-variable models in which the VE/VCO_2 curve was included, MVO_2-lean was shown to be an independent prognostic marker while only a statistically non-significant trend to MVO_2-weight was detected.

Receiver Operating Characteristics curves (ROC)

Table 4 presents the area under the ROC curves of the cardiopulmonary exercise variables. This area was greater for MVO_2-lean in relation to MVO_2-weight (p=0.02), while no statistically significant difference was seen between the VE/VCO_2 curve and LVEF. The optimal value for MVO_2-lean (24.9 mL/min/kg) presented 64.6% sensitivity (95% CI: 53.3 - 74.9) and 81.1% specificity (95% CI: 68.0 - 90.5) in the prediction of survival (area under the ROC curve 0.732±0.043, 95% CI: 0.649 - 0.804). The area under the curve for MVO_2-lean was larger than that for MVO_2-weight at 12, 15, 18, 21, 24, 27 and 30 months (p<0.05 for all comparisons) (Figure 1).

The Kaplan-Meier survival curves were designed by subdividing the patients into four groups according to the optimal MVO_2-lean values and the VE/VCO_2 curve, as these were calculated from the ROC curves (Figure 2).

Discussion

In this study we tried to show that the adjustment of peak oxygen consumption to the total muscle mass permits us to have a more reliable prognostic marker for the patients with CHF. In 135 ambulatory male patients with CHF, MVO_2-lean was shown to be a stronger prognostic marker of survival than MVO_2-weight. Especially, in milder forms of CHF, MVO_2-weight had no predictive value for survival, whereas MVO_2-lean maintained its predictive value.

Table 3. Cox proportional hazard (multivariate analyses).

Paired analysis 1	p	Relative Risk (95% CI)	χ^2
Multivariate analysis 1			
Peak VO_2–weight (mL/min/kg)	NS	–	26.8
Age (years)	0.005	1.05 (1.01-1.08)	
LVEF (%)	0.001	0.96 (0.94-0.98)	
Multivariate analysis 2			
Peak VO_2–M (mL/min/kg)	0.02	0.95 (0.91-0.99)	29.7
Age (years)	0.01	1.04 (1.01-1.07)	
LVEF (%)	0.004	0.97 (0.94-0.99)	
Multivariate analysis 3			
Peak VO_2–weight (mL/min/kg)	NS	–	21.9
NYHA class	0.06	1.52 (0.99-2.34)	
Age (years)	0.009	1.04 (1.01-1.06)	
Multivariate analysis 4			
Peak VO_2–lean (mL/min/kg)	0.02	0.94 (0.90-0.99)	25.8
NYHA class	NS	–	
Age (years)	0.02	1.03 (1.01-1.06)	
Multivariate analysis 5			
Peak VO_2–weight (mL/min/kg)	0.002	0.93 (0.90-0.98)	29.8
Cardiac cachexia	0.001	2.58 (1.46-4.56)	
Multivariate analysis 6			
Peak VO_2–lean (mL/min/kg)	0.008	0.92 (0.87-0.98)	24.6
Cardiac cachexia	0.0001	2.96 (1.70-5.18)	
Multivariate analysis 7			
Peak VO_2–weight (mL/min/kg)	0.06	0.95 (0.89-1.00)	22.4
VE/VCO_2 slope	0.0009	1.03 (1.01-1.05)	
Multivariate analysis 8			
Peak VO_2–lean (mL/min/kg)	0.005	0.94 (0.90-0.99)	26.5
VE/VCO_2 slope	0.007	1.03 (1.01-1.04)	

Abbreviations as in Table 1.

Predictive markers of survival in CHF

Since the first report regarding the use of cardiopulmonary exercise in the evaluation of patients with CHF[10], many researchers have shown the strong prognostic relation between oxygen consumption at maximal exercise and the survival of these patients[3,11,12]. Especially, Mancini et al[3] showed that when MVO_2-weight value is higher than 14 mL/min/kg then prognosis is good and does not improve after heart trans-

Table 4. Area Under Receiver Operating Characteristic Curve, sensitivity and specificity for exercise and clinical variables for mortality.

	AUC±SE	p value*	Best cut-off value	Sensitivity	Specificity
VO_2–lean (mL/min/kg)	0.732±0.043	–	24.9	64.6	81.1
VO_2–weight (mL/min/kg)	0.686±0.045	0.02	15.5	70.7	64.2
VE/VCO_2 slope	0.683±0,048	0.33	37.8	74.4	62.3
LVEF (%)	0.689±0.047	0.65	23	79.5	55.8
Age (years)	0.592±0.051	0.02	57.3	46.3	81.1
BMI (kg/m^2)	0.620±0.048	0.06	21.9	86.6	35.8

* all variables vs. peak VO_2-lean (mL/min/kg). AUC: area under the curve; SE: standard error. Other abbreviations as in Table 1.

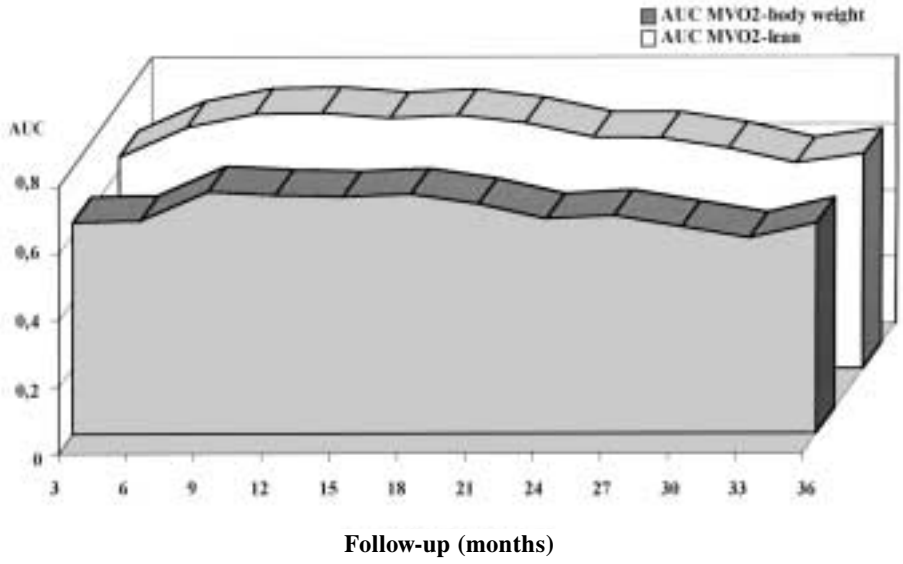

Figure 1. ROC areas under the curve of peak VO_2-lean and peak VO_2-weight of 135 male CHF patients. The difference between the two variables is statistically significant at 12 (p=0.01), 15 (p=0.04), 18(p=0.04), 21 (p=0.01), 24 (p=0.009), 27 (p=0.04) and 30 months (p=0.03).

plantation. MVO_2-weight has the same predictive value in patients older than 70 years[13]. In this study, the MVO_2-weight value was shown to be statistically significantly higher in patients with the better survival and was a strong prognostic factor of survival.

Despite its high predictive value, the use of MVO_2-weight has important limitations especially in women and obese patients[14], as well as in patients with MVO_2-weight >18 mL/min/kg[15]. As oxygen consumption is influenced by sex, body weight and age[16], it has been proposed to be expressed as the ratio of the maximal predicted[17]. This permits the partial correction of the differences observed between men and women in various age groups.

Peripheral variables that influence exercise tolerance in CHF

The understanding of the mechanisms which lead to decreased oxygen consumption in cardiopulmonary exercise testing in patients with CHF may improve its predictive value. Skeletal muscles play an impor-

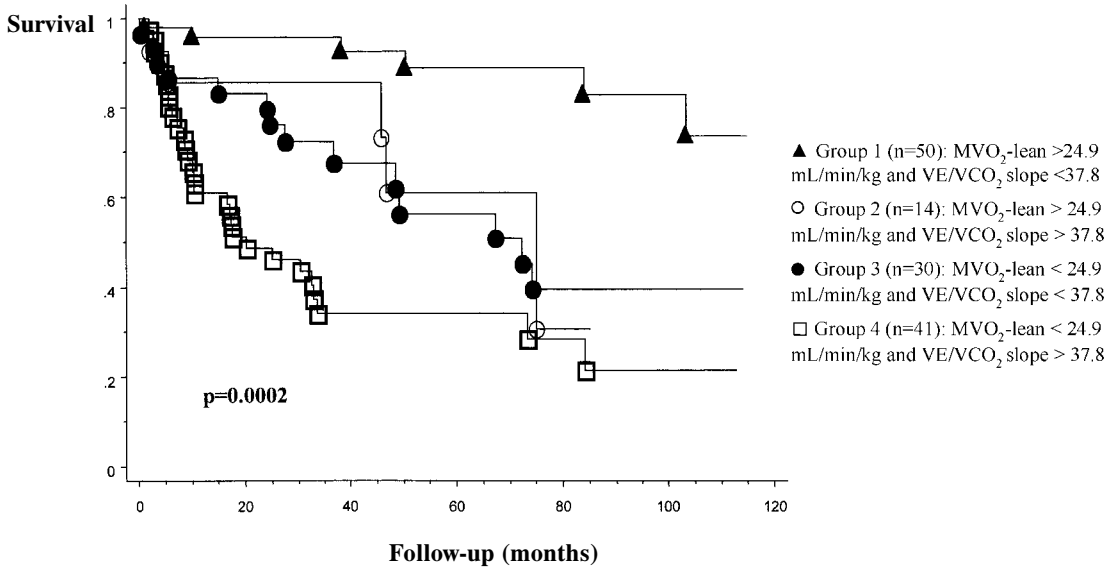

Figure 2. Kaplan Meier survival curves of four groups of patients with CHF divided according to best cut-off values of peak VO_2-lean and VE/VCO_2 slope derived from ROC curves.

tant role in CHF physiopathology. They exhibit functional[18], metabolic[19,20] and morphological changes[21], which are prognostic markers of decreased exercise tolerance[22]. It has also been proposed that many of the symptoms present in this syndrome could possibly be attributed to hemodynamic changes in the periphery, which leads to the formation of the "muscle hypothesis in CHF"[23]. Thus, at a metabolic/biochemical level, there is a disorder of the oxidative phosphorylation, which results in a decrease in the ATP production in skeletal muscle and an increase of the toxic intracellular NO levels, as well as in a decrease of the oxidative enzymes, the mitochondrial and type I muscle fibers density in relation to type II muscle fibers[19,20,22,24,25]. The muscular atrophy which is noticed in these patients is the result of skeletal muscle cell apoptosis and it has been shown that apoptosis is related to the decrease of MVO_2[26]. Muscle mass changes may also explain the differences in exercise tolerance seen between men and women. This finding is not strange at all if we consider the important role played by the total skeletal muscle mass in exercise tolerance[4].

Lean-adjusted MVO_2 is an improvement of an older prognostic marker

The relation between peak oxygen consumption and skeletal muscle mass in CHF has been known for many years[22]. However, MVO_2 is, as a rule, adjusted as regards to body weight, in which metabolically inactive tissues as fatty tissue and bone are included. Body weight fluctuations may influence the interpretation of the cardiopulmonary testing results, especially in women and obese patients who have larger amounts of fatty tissue. Conventional MVO_2-weight underestimates true exercise tolerance and, as shown in this study, true prognosis. Considering the clinical usefulness of MVO_2, a more rational approach would be to adjust the absolute MVO_2 value (in mL/min) to the muscular tissue mass and not to the total body weight.

In the population we analyzed, this adjustment improved the predictive value of MVO_2 in survival analysis and increased the area under the ROC curve at 12, 15, 18, 21, 24, 27 and 30 months of follow-up. Especially interesting is the fact that in milder forms of CHF (NYHA functional status I and II), MVO_2-weight lost its predictive value whereas MVO_2-lean maintained it to a statistically significant degree. In a recent study in clinically stabilized patients with CHF, Osman et al used the technique of skin fold thickness evaluation for the MVO_2 adjustment to fatty tissue[27], and showed that this adjustment may slightly improve MVO_2 prognostic value. On the other hand, no immediate comparison between the two variables was performed, the number of events was low (14 deaths and 15 transplantations) and the study population had strangely low mortality (6% after 18.9±11.3 months' follow-up). In our study, body composition was calculated by DEXA, which is a most widely accepted relatively inexpensive and with minimal exposure to radiation method. This method was evaluated years ago[28] and has proven to be superior to skin fold thickness in various clinical assessments and especially in the obese patients[29,30.31]. We also proved that the optimal value for MVO_2-lean as regards survival prognosis is 24.9 mL/min/kg. This variable both as continuous as well qualitative is a stronger prognostic factor of survival than MVO_2-weight.

The implementation of such a marker in clinical practice may help in the improved evaluation of disease severity, especially in patient groups in whom the prognostic value of MVO_2 is questionable. This marker may also prove to be useful, after its appropriate evaluation in patient selection for heart transplantation. As transplant donations are limited, only a very small percentage of these patients may ultimately benefit from this kind of treatment[32]. Thus, there is an imperative need to limit heart transplantations to those patients who are likely to benefit the most through this procedure[3,33].

Study limitations

The presence of heart cachexia, which is a strong prognostic marker may improve the predictive value of MVO_2-lean[7]. For this reason we included cachexia in the multivariate analysis and despite this, MVO_2-lean maintained its predictive value. Also, the relatively low patient number and the even smaller number of endpoints did not allow the study of this marker in patient subgroups as the obese, the patients with ischemic heart disease and the patients with dilated cardiomyopathy. Lastly, the absence of women from this study did not allow the study of the marker in this important patient subgroup. We believe that the behavior of the novel prognostic marker in these patient subgroups presents a significant question which may be answered in future studies.

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