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Pick your threshold: a comparison among different methods of anaerobic threshold evaluation in heart failure prognostic assessment.

Elisabetta Salvioni, PhD, Massimo Mapelli, MD, Alice Bonomi, PhD, Damiano Magrì, MD, Massimo Piepoli, MD, Maria Frigerio, MD, Stefania Paolillo, MD, Ugo Corrà, MD, Rosa Raimondo, MD, Rocco Lagioia, MD, Roberto Badagliacca, MD, Pasquale Perrone Filardi, MD, Michele Senni, MD, Michele Correale, MD, Mariantonietta Cicoira, MD, Enrico Perna, MD, Marco Metra, MD, Marco Guazzi, MD, Giuseppe Limongelli, MD, Gianfranco Sinagra, MD, Gianfranco Parati, MD, Gaia Cattadori, MD, Francesco Bandera, MD, Maurizio Bussotti, MD, Federica Re, MD, Carlo Vignati, MD, Carlo Lombardi, MD, Angela B. Scardovi, MD, Susanna Sciomer, MD, Andrea Passantino, MD, Michele Emdin, MD, Claudio Passino, MD, Caterina Santolamazza, MD, Davide Girola, MD, Denise Zaffalon, MD, Fabiana De Martino, MD, Piergiuseppe Agostoni, MD, PhD, on behalf of MECKI score research group (see appendix)

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Pick your threshold: a comparison among different methods of anaerobic threshold evaluation in heart failure prognostic assessment.

Elisabetta Salvioni[1], PhD, Massimo Mapelli[1,2], MD, Alice Bonomi[1], PhD, Damiano Magrì[3], MD, Massimo Piepoli[4], MD, Maria Frigerio[5], MD, Stefania Paolillo[6], MD, Ugo Corrà[7], MD, Rosa Raimondo[8], MD, Rocco Lagioia[9], MD, Roberto Badagliacca[10], MD, Pasquale Perrone Filardi[11], MD, Michele Senni[12], MD, Michele Correale[13], MD, Mariantonietta Cicoira[14], MD, Enrico Perna[5], MD, Marco Metra[15], MD, Marco Guazzi[16], MD, Giuseppe Limongelli[17], MD, Gianfranco Sinagra[18], MD, Gianfranco Parati[19,20], MD, Gaia Cattadori[21], MD, Francesco Bandera[22,23], MD, Maurizio Bussotti[24], MD, Federica Re[25], MD, Carlo Vignati[1], MD, Carlo Lombardi[15], MD, Angela B. Scardovi[26], MD, Susanna Sciomer[10], MD, Andrea Passantino[27], MD, Michele Emdin[28,29], MD, Claudio Passino[28], MD, Caterina Santolamazza[5], MD, Davide Girola[30], MD, Denise Zaffalon[18], MD, Fabiana De Martino[1], MD, Piergiuseppe Agostoni[1,2], MD, PhD, on behalf of MECKI score research group (see appendix)

1. Centro Cardiologico Monzino, IRCCs, Milan, Italy;
2. Department of clinical sciences and community health, Cardiovascular section, University of Milan, Milan, Italy;
3. Department of Clinical and Molecular Medicine, Azienda Ospedaliera Sant'Andrea, "Sapienza" Università degli Studi di Roma, Roma, Italy
4. UOC Cardiologia, G da Saliceto Hospital, Piacenza, Italy
5. Dipartimento Cardiologico "A. De Gasperis", Ospedale Cà Granda- A.O. Niguarda, Milano, Italy
6. IRCCS SDN Istituto di Ricerca, Napoli, Italy
7. Cardiology Department, Istituti Clinici Scientifici Maugeri, IRCCS, Veruno Institute, Veruno, Italy
8. Divisione di Cardiologia Riabilitativa, Istituti Clinici Scientifici Maugeri, Tradate, Italy. Varese, Italy
9. UOC Cardiologia di Riabilitativa, Mater Dei Hospital, Bari, Italy
10. Dipartimento di Scienze Cliniche, Internistiche, Anestesiologiche e Cardiovascolari, "Sapienza", Rome University, Rome, Italy
11. Department of Advanced Biomedical Sciences, Federico II University of Naples and Mediterranea CardioCentro, Naples, Italy
12. Department of Cardiology, Heart Failure and Heart Transplant Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
13. Department of cardiology, University of Foggia, Foggia, Italy
14. Section of Cardiology, Department of Medicine, University of Verona, Italy
15. Cardiology, Department of Medical and Surgical Specialities, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy
16. Ospedale San Paolo, Università degli studi di Milano, Italy
17. Cardiologia SUN, Ospedale Monaldi (Azienda dei Colli), Seconda Università di Napoli, Napoli
18. Cardiovascular Department, "Azienda Sanitaria Universitaria Giuliano-Isontina", Trieste, Italy
19. Istituto Auxologico Italiano, Milan, Italy

20. Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
21. Unità Operativa Cardiologia Riabilitativa, IRCCS Multimedica, Milano, Italy
22. Department of Biomedical Sciences for Health, University of Milano, Milan, Italy.
23. Cardiology University Department, IRCCS Policlinico San Donato, Milan, Italy
24. Cardiac Rehabilitation Unit, Istituti Clinici Scientifici Maugeri, Scientific Institute of Milan, Milan, Italy
25. Cardiology Division, Cardiac Arrhythmia Center and Cardiomyopathies Unit, San Camillo-Forlanini Hospital, Roma, Italy
26. Cardiology Division, Santo Spirito Hospital, Roma, Italy
27. Division of Cardiology, Istituti Clinici Scientifici Maugeri, Institute of Bari, Bari, Italy
28. Institute of Life Science, Scuola Superiore Sant'Anna, Pisa, Italy
29. Fondazione Gabriele Monasterio, CNR-Regione Toscana, Pisa, Italy
30. Clinica Hildebrand Centro di riabilitazione Brissago, Switzerland

Short title: Computation of anaerobic threshold in HF prognosis

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Corresponding author:
Prof. Piergiuseppe Agostoni, MD, PhD,
Centro Cardiologico Monzino, IRCCS
Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan
Via Parea, 4, 20138 Milan, Italy
Phone 0039 02 58002772
E-mail piergiuseppe.agostoni@unimi.it; piergiuseppe.agostoni@ccfm.it

Abstract

Background

In clinical practice, anaerobic threshold (AT), is used to guide training and rehabilitation programs, to define risk of major thoracic or abdominal surgery, and to assess prognosis in heart failure (HF). VO_2AT has been reported as absolute value (VO_2ATabs), as percentage of predicted peak VO_2 (VO_2AT%peak_pred) or as percentage of observed peak VO_2 value (VO_2AT%peak_obs). A direct comparison of the prognostic power among these different ways to report AT is missing.

Research Question

What is the prognostic power of these different ways to report AT?

Study Design and Methods

Observational cohort study. We screened data of 7746 HF patients with history of reduced ejection fraction (<40%), recruited between 1998 and 2020 and enrolled in the MECKI register. All patients underwent a maximal cardiopulmonary exercise test (CPET), executed using a ramp protocol on an electronically braked cycle ergometer.

Results

In this study we considered 6157HF patients with identified AT. Follow up was 4.2 years (1.9-5.0). Both VO_2ATabs (823(305 mL/min)) and VO_2AT%peak_pred (39.6(13.9%)) but not VO_2AT%peak_obs (69.2(17.7%)) well stratified the population as regards prognosis (composite endpoint: cardiovascular death, urgent heart transplant or left ventricular assist device). Comparing AUC values, VO_2ATabs (0.680) and VO_2AT%peak_pred (0.688) performed similarly, while VO_2AT%peak_obs (0.538) was significantly weaker (P<0.001). Moreover, VO_2AT%peak_pred AUC value was the only performing as well as AUC based on peakVO_2 (0.710), with even a higher AUC (0.637 vs. 0.618 respectively) in the group with severe HF (peakVO_2<12mL/min/kg). Finally, the combination of VO_2AT%peak_pred with Peak VO_2 and VE/VCO_2 shows the highest prognostic power.

Interpretation

In HF, VO_2AT%peak_pred is the best way to report VO_2 at AT in relation to prognosis, with a prognostic power comparable to that of peak VO_2 and, remarkably, in severe HF patients.

Keywords: Anaerobic threshold; cardiopulmonary exercise test; prognosis; heart failure

Abbreviation list

anaerobic threshold as absolute value: VO_2ATabs

anaerobic threshold as percentage of the observed maximum: $VO_2AT\%peak\_obs$

anaerobic threshold as percentage of the predicted maximum VO_2: $VO_2AT\%peak\_pred$

anaerobic threshold: AT

Area under the curve: AUC

carbon dioxide production: VCO_2

cardiopulmonary exercise test: CPET

end-tidal pressure of CO_2: $PetCO_2$

end-tidal pressure of O_2: $PetO_2$

heart failure: HF

left ventricular assist device: LVAD

oxygen uptake: VO_2

receiver-operating characteristic: ROC

respiratory exchange ratio: RER

urgent heart transplant: HT

ventilation: VE

Since its discovery 50 years ago [1-4] , the anaerobic threshold (AT) has fascinated scientists regarding the physiological origin, meaning and the utility of its identification in prognostic assessment[5,6], alongside peak oxygen uptake (peak VO_2) and ventilation vs. CO_2 relationship (VE/VCO_2 slope), the two mainly prognosis-related variables of cardiopulmonary exercise test (CPET).

Even on its denomination there is some controversy. As a matter of facts, AT has also named gas exchange threshold, or ventilatory threshold [1]. Indeed, the term anaerobic is still used, but mainly for historical reasons, since the concept that AT is associated to hypoxia is not supported by evidence albeit it is clear that AT is associated with sustained elevation of lactate [4]. At AT hyperventilation occurs in response to extra amount of CO_2 production due to the greater prevalence of lactate acidosis as an additional source of energy. AT correct identification by respiratory gas exchange test is challenging, and several methods have been proposed [7,8], whose results are not always consistent and in agreement [9,10].

AT relevance in the physiology of exercise is unquestionable: its value is indicative of the subject's training, exercise intensity [11], metabolic efficiency status and specifically muscle efficiency [12] and muscle O_2 extraction [13]. Moreover, AT has been used to guide training and rehabilitation programs or to define when it is safe to undergo major thoracic or abdominal surgery [4,14,15]. Not only that, in patients with heart failure (HF) undergoing a maximal CPET, the failure to identify AT indicates a very poor prognosis [5,6,16]. In addition, VO_2 values measured at AT (VO_2ATabs) stratify the prognosis of these patients[5,17].

Given the significant inter-subject variability of CPET parameters to increase their clinical power in identifying the severity of exercise limitation, they are expressed not only in absolute value, but also as a percentage of their predicted value [18,19]. In the case of AT, on top of the absolute value, it can be reported as the percentage of the predicted maximum VO_2 (VO_2AT%peak_pred) [8,20,21] or as a percentage of the peak VO_2 achieved by the subject during exercise (VO_2AT%peak_obs) [11-13]. The latter is quite commonly reported, although this can introduce errors because maximal VO_2 declines more than VO_2AT with age[22]. Moreover, VO_2AT expressed as % of observed peak may be misleading, when used for prognostication, in the case of patients' not maximal effort.

Studies of comparison of the prognostic value of AT when expressed as absolute value (VO_2AT abs) vs. as VO_2AT%peak_pred or vs. as VO_2AT%peak_obs are lacking. In this work, we compared these three variables in a large multicentric population with HF with reduced ejection fraction aiming to evaluate which of them is better to use for prognostication considering both the entire HF population or specific HF phenotypes as atrial fibrillation (AF) patients or patients with different HF severity.

Methods

The study population included patients with HF with history of reduced ejection fraction, recruited in the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI score project) [18]. Specifically, inclusion criteria were previous or present HF symptoms (NYHA functional class I-IV, stage B and C of ACC/AHA classification) and previous documentation of left ventricular ejection fraction (LVEF)<40%, unchanged HF medications for at least three months, ability to perform a CPET, and no major cardiovascular treatment or intervention scheduled. Exclusion criteria were: history of pulmonary embolism, moderate-to-severe aortic and mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina and significant ECG alterations, or presence of any clinical comorbidity interfering with exercise performance.

All patients underwent a CPET, performed using a ramp protocol on an electronically braked cycle ergometer. Specifically, the CPET protocol was tailored to the patient's functional status so that the patient reached peak exercise in in eight to twelve minutes[23], but tests were stopped only as patients reported to have reached their maximal effort, regardless of the respiratory exchange ratio (RER) value. A familiarization test was recommended. In all tests, ventilation and respiratory gases were collected breath by breath and analyzed following a standard technique[24]. PeakVO_2 was calculated as the 20-second average of the highest recorded VO_2, while VE/VCO_2 slope was calculated as the slope of the linear relationship between ventilation (VE) and carbon dioxide production (VCO_2) from one minute after the beginning of loaded exercise to the end of the isocapnic buffering period. AT was identified using a V-slope analysis of VO_2 and VCO_2, and it was confirmed by specific trends of VE vs. VO_2 (VE/VO_2) and CO_2 (VE/VCO_2), and of end-tidal pressure of O_2 ($PetO_2$) and CO_2 ($PetCO_2$) [3,25]. Indeed, at AT VE/VO_2 but not VE/VCO_2 increases while $PetO_2$ increases, being $PetCO_2$ still flat. Each center was responsible for tests analysis and each test had to be evaluated by two CPET experts and a third expert should be consulted in case of disagreement. VO_2AT%peak_pred was calculated according to Hansen et al[26]. AT was reported as VO_2ATabs, as a percentage of peak VO_2 predicted (VO_2AT%peak_pred) and as a percentage of measured peak VO_2 (VO_2AT%peak_obs) (figure 1).

Follow-up and data management

Patient follow-up and data management procedures were performed as previously described [18]. In brief, follow-up was carried out according to the local HF program, and it ended with the last clinical evaluation or with patients' death, urgent heart transplant (HT) defined as UNOS status 1 [27], or left ventricular assist device (LVAD) implantation. If a patient died outside the hospital where they were followed up, medical records of the event and the reported cause of death were considered. For prognosis evaluation the end point was the composite of cardiovascular death, urgent HT, or LVAD implantation. The study was approved by the local ethics committee (CCM04_21 PA).

Statistical analysis

Continuous variables are presented as mean(standard deviation. For continuous variables the differences between the two groups of AT or patients with AF vs. sinus rhythm were calculated with *t*-test for independent samples or χ^2 test for categorical data. Missing data were not computed being <2% for all analyzed variables.

Event-free survival (absence of the composite of cardiovascular death, urgent HT, or LVAD implantation), stratified for the 3 tertiles of the selected variables, was estimated by Kaplan-Meier curves. Comparisons between Kaplan Meier curves were made by LongRank test, with Tukey Kramer adjustment used for multiple comparisons.

The ability of these variables to predict of the composite of cardiovascular death, urgent HT, or LVAD implantation, was quantified by the area under the receiver-operating characteristic (ROC) curve (AUC) as well as by Harrell’s concordance statistic. Comparisons were performed as recommended by DeLong et al.[28]

The AUC comparisons were performed both on the entire population and on subgroups according to peakVO_2 tertiles or presence/absence of AF.

All tests were 2-tailed, and $P<0.05$ was required for statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, US).

Results

The study population included 7746 HF patients enrolled in the MECKI score registry [18] at the end of 2020, who underwent a CPET between 1998 and 2020 (age 61.6(12.6) years, 82% males) with a median follow up of 4.2 years (1.9-5.0). 1681 cardiovascular events – 1441 cardiovascular death, 202 HT and 38 LVAD- were observed with an average 42 events/1000 patients/year.

We excluded from the analysis 1589 patients in whom AT could not be detected at CPET (figure 2). These patients had more severe HF as shown by exercise performance (Peak VO_2 914(383) mL/min vs. 1208(428, *P*<0.001; Peak VO_2 12.15(4.23) mL/min/kg vs. 15.49(4.79)mL/min/kg (*P*<0.001), VE/VCO_2 slope 36.6(9.3) vs. 32.3(7.2), *P*<0.001, AT non detectable and detectable, respectively) and worse prognosis as shown by the event rate observed (62 events/1000patients/years vs. 38, *P*=0.01) .

Accordingly, the remaining 6157 subjects who performed a CPET with an identified AT (61.6(12.6) years, 84% males, 4.2 years (1.9-7.5) follow up, 1212 cardiovascular events -1043 cardiovascular deaths 144 transplant 25 LVAD-) represent the population of this study. Table 1 shows the main characteristics of these patients and ongoing therapy at the time of CPET. Of note, therapy was set by the referring physician and considered optimized according to guidelines available when patients were recruited. Table 2 shows the main CPET results of HF subjects with an identified AT. Among these patients, 1409 patients reported a maximal effort albeit they did not reach the RER criterion for a maximal test (RER>1.05). In comparison with patients who reached this criterion (RER ≥1.05), those who did not were similar regarding parameters of HF severity and were included in the present analysis. In the studied HF population (N= 6157) average AT values were: VO_2AT abs 823(305) mL/min, VO_2AT abs 10.55(3.50) mL/min/kg, VO_2AT%peak_pred 39.6(13.9) %(and VO_2AT%peak_obs(69.2(17.7) %. Figure 3 shows the Kaplan Meier curves for the study end point (combination of cardiovascular death, urgent transplant or LVAD implantation) according to analyzed AT values. In the case of VO_2AT%peak_obs (figure 3, middle panel), the stratification of the risk is less accurate as the two lower tertiles overlap (*P*= 0.927) while all the other curves are significantly different

(P<0.001). Also, survival results were comparable if patients with RER<1.05 were excluded. Finally, results were not influenced by patients age and gender.

Comparing the three ways to evaluate AT with respect to events at two years of follow up, we found in the overall population similar AUC values between VO_2ATabs and VO_2AT%peak_pred, while the VO_2AT%peak_obs one was significantly lower (P<0.001), (figure 4). Moreover, VO_2AT%peak_pred AUC value was the only performing as well as AUC based on peakVO_2, while the performance of both VO_2ATabs and VO_2AT%peak_obs were significantly worse (supplemental table 1). Harrell's concordance statistic provided very similar results and are reported in the supplemental material as supplemental table 2.

In addition, taking as reference the VE/VCO_2 slope AUC, both VO_2AT%peak_pred and VO_2ATabs, either as mL/min or mL/min/kg, have a similar prognostic accuracy, while VO_2AT%peak_obs AUC is significantly lower (supplemental table 1). Finally, combining AUC of PeakVO_2 and VE/VCO_2 with each of the three VO_2AT variables, only with VO_2AT%peak_pred the curve is significantly improved, p=0.012 (supplemental figure 1).

We also grouped the population according to the severity of the functional limitation as identified by CPET [29]: group 1 with peak VO_2<12 (n=1452), group 2, with peakVO_2 12-16 (n=2254), and group 3 with peak VO_2>16 mL/kg/min (n=2436). The AUC comparisons among each group are reported in figure 5. Regardless of the HF severity group VO_2AT%peak_obs AUC was weaker as prognosis predictor. Of note, in the group of most severe patients (group 1) the VO_2AT%peak_pred AUC value was the highest.

Finally, the study population presented 940 out of 6157 patients (15.3%) with AF. Patients with AF had a lower peakVO_2 than patients in sinus rhythm but higher VO_2AT%peak_obs values, indicating a postponed AT (Table 3). The AUC comparisons of patients in sinus rhythm were similar to those of the general population. Specifically, VO_2AT%peak_pred AUC (0.6848) was the only one performing as well as peak VO_2 AUC (0.7051), while VO_2ATabs and VO_2%peak_obs performed significantly worse (0.6766, P<0.001 and 0.5399, P<0.0001 respectively). Differently, in AF population the AUC of both VO_2AT%peak_pred (0.6926) and VO_2ATabs (0.6830) were both statistically comparable (P=ns) to that of peak VO_2 (0.6992), while

VO_2%peak_obs AUC confirms to be less accurate also in this subgroup (0.4944, $P<0.001$). Again, no differences were observed when considering absolute values as mL/min or as mL/min/kg.

Discussion

The present study investigated a large population of patients with history of reduced ejection fraction and compared three different ways of reporting VO_2at AT (VO_2ATabs, VO_2AT%peak_pred, and VO_2AT%peak_obs) in order to identify the most accurate method of expressing AT in relation to HF prognosis. Our results show that the capacity to stratify the population is similar for VO_2ATabs and VO_2AT%peak_pred and, in both cases, better than VO_2AT%peak_obs. Furthermore, VO_2AT%peak_pred is the only parameter to have an AUC as good as that of peak VO_2. Finally, the advantage of using VO_2AT%peak_pred instead of other methods for presenting AT appears to be particularly relevant when estimating prognosis in patients with reduced exercise performance in whom peak VO_2 may be more difficult to be reached due to severe exercise impairment and for this reason its clinical reliability is questionable. It must be recognized, however, that no difference between VO_2ATabs and VO_2AT%peak_pred on AUC values was observed and that from a practical point of view, AUC values of 0.680 and 0.688 sound rather comparable. Indeed, VO_2AT%peak_pred seems to 'win on points' VO_2ATabs, at least when considering an patients with moderate HF, in sinus rhythm and who performed a maximal or near maximal effort.

We present data from a large population of HF patients with history of reduced ejection fraction followed in 26 Italian HF centers. Follow-up was prolonged, with a relevant number of events observed. AT was not identified in 20% of cases, a number in line with previous publications [30]. In previous analysis of the MECKI score dataset, we identified that the absence of an identified AT was associated with a very poor prognosis [6,16]. This was confirmed in the present study in larger HF population [6,16]. The AT was identified in the remaining 6157 cases. The present study extends the investigation about the value of AT as a prognostic marker in the MECKI score population and it analyzes which of the three more common methods to report

AT has the greatest prognostic power. Interestingly, VO_2AT%peak_pred showed the highest performance, comparable to that of peak VO_2 and VE/VCO_2 slope, both of which have recognized pivotal role in HF prognosis. Not only that, its combination with Peak VO_2 and VE/VCO_2 significantly improves the prognostic power.

In the present analysis a non-negligible group of patients (n= 1409) had a peak exercise RER <1.05. Albeit exercise was symptom limited and self-interrupted by patients we have no proof that maximal effort was really reached. Previous findings and studies on CPET parameters, as we did for the present analysis, suggested to consider also these patients when evaluating HF prognosis and exercise performance [31]. Of note, excluding the cases with a peak RER < 1.05 did not change our findings.

Conceptually, AT is important in all HF patients, but its prognostic role is particularly relevant when the reliability of peak VO_2 value is questionable. In fact, sometimes peak VO_2 can be influenced by the patient's willingness or can be altered by arrhythmias, ischemia or severe hypertension, that occur more frequently when the subject reaches the maximum effort. In these cases, it may be appropriate to use a sub-maximal VO_2 value[17]. In clinical practice, in case of submaximal effort, VE/VCO_2 slope is usually preferred to peak VO_2, as also suggested in the heart transplantation guidelines [32]. On the basis of the present study we suggest that AT data and specifically VO_2 AT%peak_pred can also be utilized as a sub-maximal parameter for assessing prognosis, while other VO_2 values at AT seem less efficacious. Accordingly, our findings reinforce the original and historic data by Janicki and Weber who reported VO_2 at peak and AT in parallel [33]. The findings of this study are most relevant in severe HF since patients with advanced disease a true maximal performance may not be reached for several reasons and, consequently, peak VO_2 may be in a few cases unreliable. Of note in severe HF a maximal effort may be considered by patients and medical personal as risky. Moreover, patients with severe HF are the ones who most need a precise risk assessment that should be used also for LVAD/HT indication. Interestingly, dividing subjects according to their functional impairment (i.e. peak VO_2), we obtained the highest VO_2 AT%peak_pred AUC in the most severe cases.

HF patients with permanent AF represent a special population since they have a lower performance (lower peak VO_2) and a VO_2AT that seems to be, on the average, 10% higher than that in sinus rhythm patients. AF patients shows a peculiar behavior of heart rate and cardiac output at the beginning of exercise, with the increased heart rate response likely due to an increased sympathetic drive triggered to maintain cardiac output [16,34,35]. Indeed, as shown by Magrì et al. the prognostic meaning of AT in patients with HF and AF is different compared to patients in sinus rhythm [16]. In the present study we confirmed these peculiar characteristics and we found that the prognostic power of VO_2AT%peak_pred is maintained also in this specific HF population, although the reliability of VO_2AT%peak_pred is similar to that of VO_2AT abs, and both are similar to that of peak VO_2 values (i.e. AUC of these three variables are not statistically different).

The results of the present study open the need for further studies evaluating the efficiency of VO_2AT%peak_pred in multiparametric patient evaluation. In fact, it has now been demonstrated that multiparametric prognostic scores are superior to any single parameter for estimating the risk in HFrEF. Currently, in these patients, the most effective score is the MECKI score[36-38], which uses CPET parameters, combined with blood chemistry (hemoglobin, sodium, and glomerular filtration rate estimated from creatinine) and echocardiographic (LVEF) parameters[18]. It might therefore be desirable to use AT value instead of peak VO_2 when the patient has not reached maximal effort or it is not clear whether a true maximal effort has been obtained, albeit this hypothesis needs to be evaluated in a dedicated analysis.

The study has a few limitations which need to be acknowledged. First of all, the retrospective nature of the present analysis. Second, the V-slope analysis was used to identify AT and the possible presence of a dual AT not considered [9]. Third, it is unknown whether treatment or training influence the onset of AT and how this can affect HF prognosis.

Interpretation

This study demonstrates that VO_2AT%peak_pred is the best way to express VO_2 at AT in relation to prognosis, with a prognostic power comparable to that of peak VO_2 and VE/VCO_2 slope especially in more severe patients.

Take home pullout:

Study Question

Any differences in prognostic power of VO_2 at anaerobic threshold (AT) expressed as absolute value (VO_2ATabs), as percentage of predicted peak VO_2 (VO_2AT%peak_pred) or as percentage of observed peak VO_2 value (VO_2AT%peak_obs)?

Results

Comparing AUC values, VO_2AT%peak_obs was significantly weaker, while VO_2AT%peak_pred was the only performing as well as peakVO_2, with even a higher AUC in the group with severe HF peakVO_2<12mL/min/kg).

Interpretation

In HF, VO_2AT%peak_pred is the best way to report VO_2 at AT in relation to prognosis and its combination with Peak VO_2 and VE/VCO_2 has the highest prognostic power.

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Figure Legend

Figure 1:

Graphical representation of the 3 possible ways to report anaerobic threshold (AT): absolute value (VO_2AT abs, red line); percentage of predicted peak VO_2 (VO_2AT%peak_pred, yellow line); percentage of observed peak VO_2 (VO_2AT%peak_obs, orange line). Green columns represent the portion of VO_2 below the AT, expressed as percentage of VO_2ATobs (left) or of VO_2ATabs (right), while the orange areas show the difference of those percentage to their reference value.

VO_2AT %peak_obs = VO_2ATabs / peak VO_2x 100
VO_2AT%peak_pred = VO_2ATabs / predicted peak VO_2 x 100

Figure 2

Scheme representing population selection.

Figure 3

Survival according to the study end point (combination of cardiovascular death, urgent transplant or LVAD implantation) in the heart failure population. The three panels show the stratification of the patients divided in tertiles based on the three analyzed anaerobic threshold variables: VO_2AT%peak_predicted (upper panel), VO_2AT%peak_obs (middle panel), VO_2ATabs (lower panel, results were similar when VO_2AT_abs was expressed in mL/min and in mL/min/kg). Tertiles for VO_2AT%peak_pred were : ≤33 ; >33-≤43.8; >43.8. were Tertiles for VO2%peak_obs: ≤62.6 ; >62.6-≤75.2; >75.2 and tertiles for VO2ATabs were: ≤664 ; >664-≤908.5; >908.5.

Figure 4

Receiving operating curves and area under the curve (AUC) values according to VO_2AT%peak_predicted, VO_2AT%peak_obs, and VO_2AT_abs (results were similar when VO_2AT_abs was expressed in mL/min and in mL/min/kg).

Figure 5

Area under the curve values of the three variables under study (VO_2AT%peak_predicted, VO_2AT%peak_observed, and VO_2AT absolute value) in relation to peak VO_2 obtained by dividing the population into three groups according to severity. Specifically, group 1: peak VO_2<12 mL/min/kg, group 2: peak VO_2 12-16 mL/min/kg, peak VO_2>16 mL/min/kg. Results were similar when VO_2AT_abs was expressed in mL/min and in mL/min/kg.

*= p<0.005 vs. Peak VO_2

Figure 1 supplemental

Comparison of AUCs obtained combining the two main variables of cardiopulmonary exercise test (Peak VO_2 and VE/VCO_2 slope) with the variables under study (VO_2AT%peak_predicted, VO_2AT%peak_observed, and VO_2AT absolute value).

Table 1 Main characteristics of the heart failure population with identified anaerobic threshold (N=6157)

Variable	**Mean**	***(SD)***
Age (years)	61.6	(12.6)
Body mass index (kg/m²)	26.7	(4.4)
LVEF (%)	33.0	(10.3)
EDV (ml)	183	(75)
ESV (ml)	126	(64)
Hb (g/dl)	13.5	(1.9)
MDRD (ml/min/1.73m²)	72.6	(24.0)
Na^+	139.5	(3.19)
Variabile	**n**	**%**
Sex (males, %)	5181	75%
NYHA 1 (n, %)	1080	18%
NYHA 2 (n, %)	3485	57%
NYHA 3 (n, %)	1496	24%
NYHA 4 (n, %)	75	1%
Idiopathic etiology (n, %)	2280	41%
Ischemic etiology (n, %)	2623	47%
Valvular etiology (n, %)	232	4%
Therapy		
ACE inhibitors (n, %)	4420	72%
AT1 inhibitors (n, %)	1150	19%
Beta-blockers (n, %)	5384	88%
Diuretics (n, %)	4792	78%
Statins (n, %)	2853	47%
Mineralcorticoid antagonists (n, %)	3142	52%
Antiplatelets (n, %)	3252	53%
Anticoagulants (n, %)	1721	28%
Amiodarone (n, %)	1416	23%

LVEF: left ventricular ejection fraction: EDV: end-diastolic volume; ESV: end-systolic volume; Hb: hemoglobin; MDRD: Glomerular filtration rate by modification of diet in renal disease; NYHA: New York Heart Association class; ACE: Angiotensin converting enzyme; AT1: Angiotensin II Type 1 Receptor; Hb: hemoglobin.

Table 2: Cardiopulmonary exercise test results of the patients with identified anaerobic threshold (N=6157)

Variabile	***Mean***	***SD***
Peak VO_2 (ml/min)	1150	(435)
Peak VO_2 (ml/min/kg)	14.8	(4.9)
Peak VO_2 % pred	56.1	(17.5)
VE/VCO_2 Slope	33.2	(7.9)
VO_2/WR slope	9.7	(2.2)
Workload (Watt)	52.3	(24.6)
Peak RER	1.12	(0.16)
VO_2 ATabs (ml/min)	823	(305)
VO_2 ATabs (ml/min/kg)	10.6	(3.5)
VO_2 AT%peak_obs	69.2	(17.7)
VO_2 AT %peak_pred	39.6	(13.9)

Peak VO_2: oxygen uptake at peak exercise; VE/VCO_2 slope: minute ventilation/carbon dioxide production relationship slope; WR: work; RER: respiratory exchange ratio; VO_2ATabs= oxygen uptake at anaerobic threshold absolute value; VO_2AT%peak_obs: = oxygen uptake at anaerobic threshold as % of observed peak; VO_2AT %peak_pred: = oxygen uptake at anaerobic threshold as % of predicted peakVO_2.

Table 3 Differences between patients with and without atrial fibrillation.

	Sinus rhythm (n=5211)		***Atrial fibrillation (n=940)***		***P***
PeakVO_2	1229	(436)	1100	(363)	<0.0001
VO_2 ATabs	830	(311)	779	(266)	<0.0001
VO_2 AT %peak_obs	69	(14)	73	(31)	<0.0001

Peak VO_2: oxygen uptake at peak exercise; VO_2ATabs= oxygen uptake at anaerobic threshold absolute value; VO_2 AT%peak_obs: = oxygen uptake at anaerobic threshold as % of observed peak;

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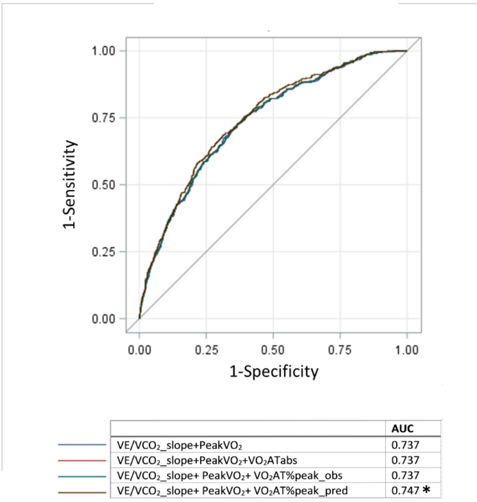
Appendix

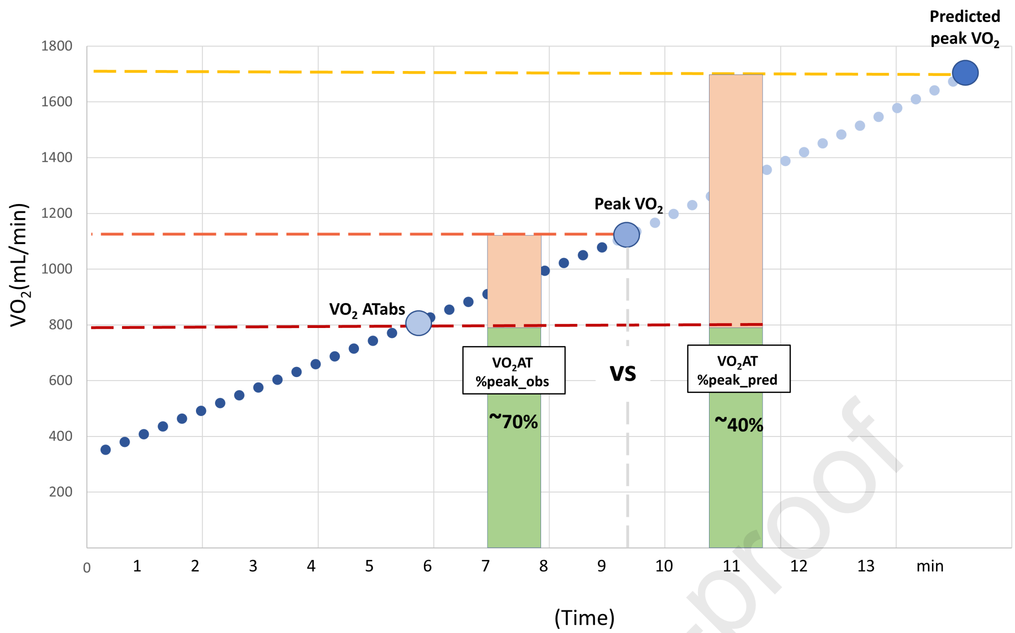
Other participants to the MECKI score group to be acknowledged:

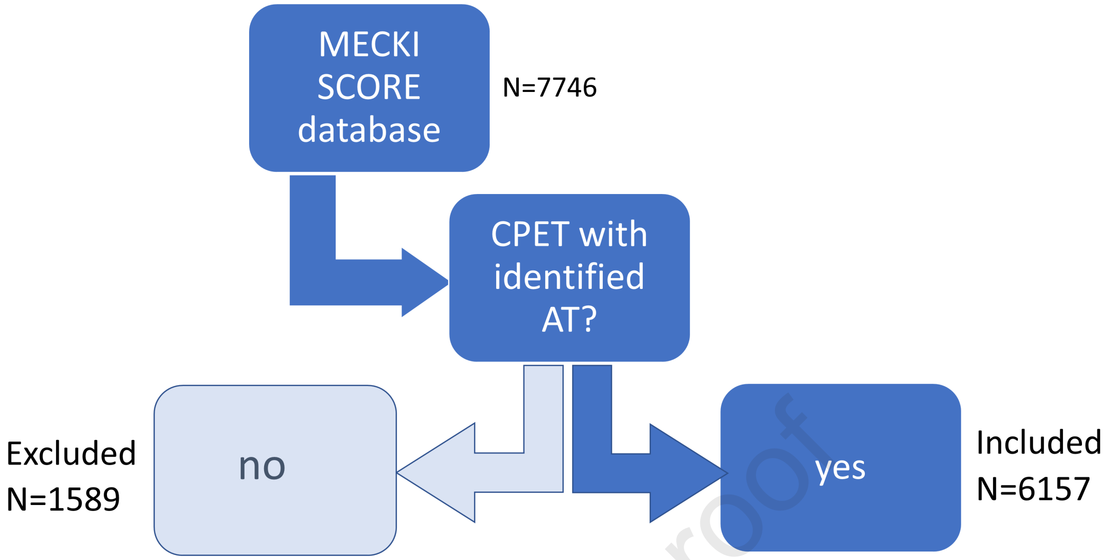
- Centro Cardiologico Monzino, IRCCs, Milan, Italy
  Stefania Farina, Beatrice Pezzuto, Anna Apostolo, Pietro Palermo, Mauro Contini, Paola Gugliandolo, Irene Mattavelli, Michele Della Rocca
- Department of Clinical and Molecular Medicine, Azienda Ospedaliera Sant'Andrea, "Sapienza" Università degli Studi di Roma, Roma, Italy
  Giovanna Gallo
- Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, "Sapienza", Rome University, Rome, Italy:
  Federica Moscucci
- Department of Cardiology, Heart Failure and Heart Transplant Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy:
  Anita Iorio
- UOC Cardiologia, G da Saliceto Hospital, Piacenza, Italy
  Geza Halasz, Bruno Capelli, Simone Binno
- Cardiologia SUN, Ospedale Monaldi (Azienda dei Colli), Seconda Università di Napoli, Napoli
  Giuseppe Pacileo, Fabio Valente, Rossella Vastarella
- Cardiovascular Department, Ospedali Riuniti and University of Trieste, Trieste, Italy:
  Denise Zaffalon, Cosimo Carriere, Marco Masè, Marco Cittar, Andrea Di Lenarda
- Istituto Auxologico Italiano, Milan, Italy:
  Sergio Caravita, Elena Viganò
- Cardiac Rehabilitation Unit, Istituti Clinici Scientifici Maugeri, Scientific Institute of Milan, Milan, Italy:
  Giovanni Marchese

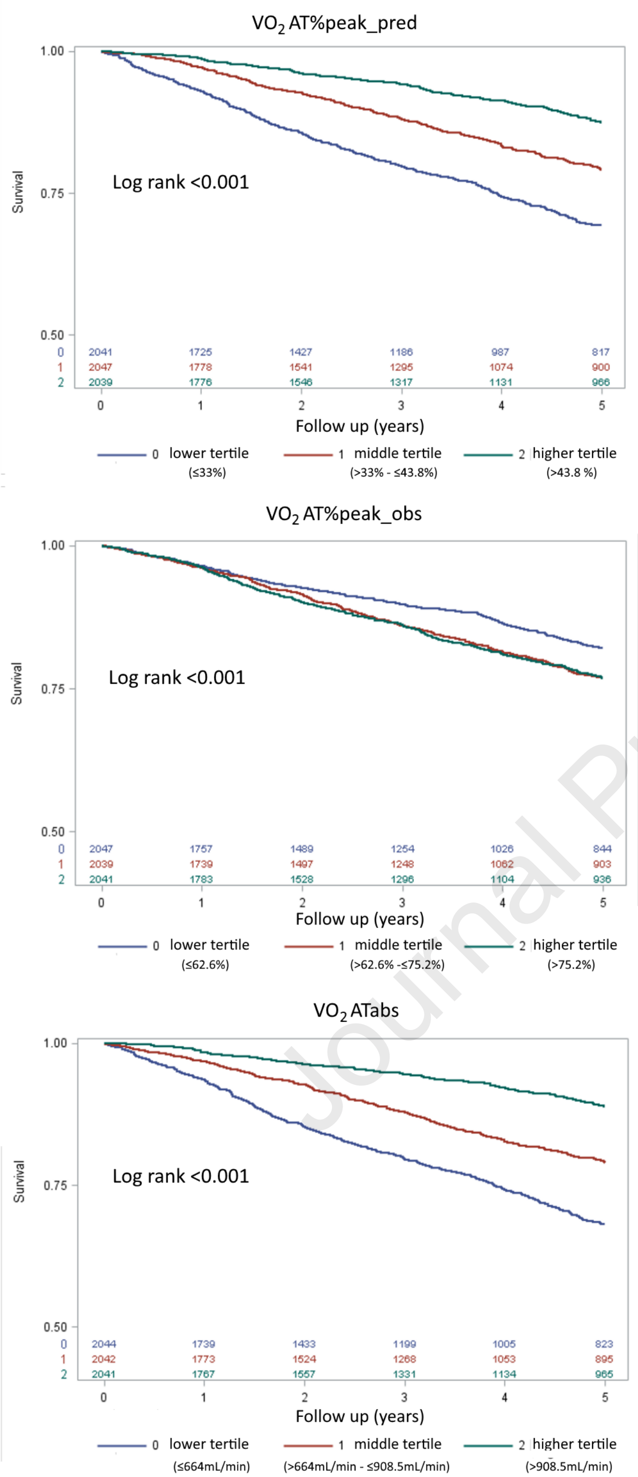
- Cardiology Division, Santo Spirito Hospital, Roma, Italy:
  Roberto Ricci, Luca Arcari
- Division of Cardiology, Istituti Clinici Scientifici Maugeri, Institute of Cassano Murge, Bari, Italy:
  Domenico Scrutinio
- U.O. Cardiologia, S. Chiara Hospital, Trento, Italy:
  Elisa Battaia, Michele Moretti
- Ospedali Riuniti, Ancona, Italy:
  Maria Vittoria Matassini; Matilda Shkoza
- UOSD di Cardiologia/UTIC dell'IRCCS Neurolesi di Messina
  Roland Herberg
- Federico II hospital, Napoli, Italy:
  Antonio Cittadini, Andrea Salzano, Alberto Marra
- ISMETT, Palermo, Italy
  Eluisa Lafranca
- Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli Hospital, Palermo, Italy:
  Giuseppe Vitale



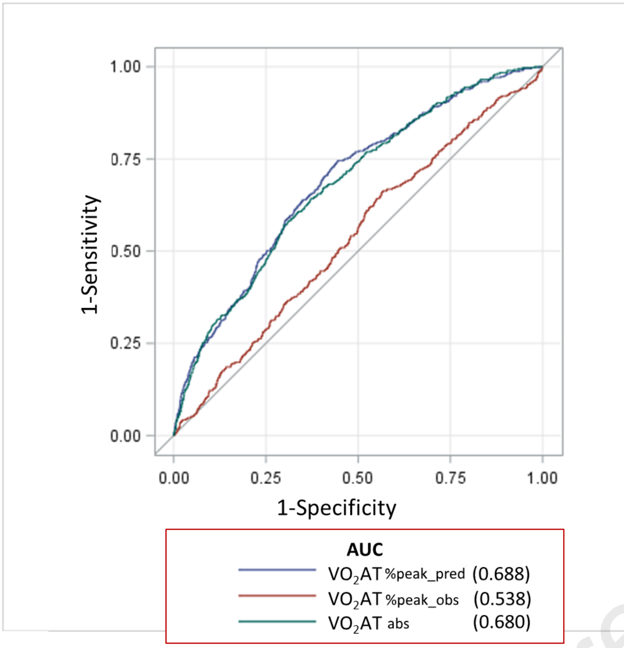
* p= 0.012 vs VE/VCO_2_slope+PeakVO_2


Predicted
peak VO2
1800
1600
1400
1200
1000
800
600
400
200
VO2(mL/min)
Peak VO2
VO2 ATabs
VO2AT
%peak_obs
VS
VO2AT
%peak_pred
~70%
~40%
0
1
2
3
4
5
6
7
8
9
10
11
12
13
min
(Time)

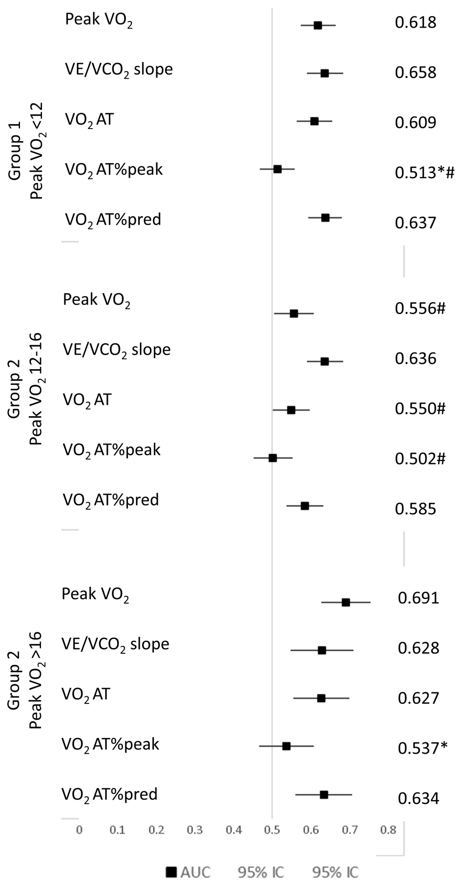

MECKI SCORE database
N=7746
CPET with identified AT?
Excluded N=1589
no
yes
Included N=6157



VO2 AT%peak_pred
Log rank <0.001
Survival
1.00
0.75
0.50
0 2041 1725 1427 1186 987 817
1 2047 1778 1541 1295 1074 900
2 2039 1776 1546 1317 1131 966
0 1 2 3 4 5
Follow up (years)
0 lower tertile (≤33%)
1 middle tertile (>33% - ≤43.8%)
2 higher tertile (>43.8 %)
VO2 AT%peak_obs
Log rank <0.001
Survival
1.00
0.75
0.50
0 2047 1757 1489 1254 1026 844
1 2039 1739 1497 1248 1062 903
2 2041 1783 1528 1296 1104 936
0 1 2 3 4 5
Follow up (years)
0 lower tertile (≤62.6%)
1 middle tertile (>62.6% -≤75.2%)
2 higher tertile (>75.2%)
VO2 ATabs
Log rank <0.001
Survival
1.00
0.75
0.50
0 2044 1739 1433 1199 1005 823
1 2042 1773 1524 1268 1053 895
2 2041 1767 1557 1331 1134 965
0 1 2 3 4 5
Follow up (years)
0 lower tertile (≤664mL/min)
1 middle tertile (>664mL/min - ≤908.5mL/min)
2 higher tertile (>908.5mL/min)



	p
VO_2AT%peak_pred – Vo_2_ATabs	0.446
VO_2AT%peak_obs – Vo_2_ATabs	<0.001
VO_2AT%peak_pred – VO_2AT%_obs	<0.001



* p<0.05 vs Peak VO_2 # p<0.05 vs VE/VCO_2 slope

Supplemental table 1: comparison between AUC at 2 years taking as reference peakVO_2 or VE/VCO_2

		Ref. VE/VCO_2 slope (AUC 0.705) (n = 6032)	*Ref. peak VO_2 (AUC 0.710) (n = 6032)*
	AUC	*P*	*P*
VO_2 ATabs (ml/min)	0.680 (0.653-0.708)	0.1489	0.0014
VO_2 ATabs (ml/min/kg)	0.671 (0.642-0.698)	0.0637	0.0085
VO_2 AT % obs	0.538 (0.509-0.568)	<0.0001	<0.0001
VO_2 AT %peak_pred	0.688 (0.661-0.715)	0.3868	0.1635

Peak VO_2: oxygen uptake at peak exercise; VE/VCO_2 slope: minute ventilation/carbon dioxide production relationship slope; VO_2ATabs= oxygen uptake at anaerobic threshold absolute value; VO_2 AT%peak_obs: = oxygen uptake at anaerobic threshold as % of observed peak; VO_2AT%peak_pred: = oxygen uptake at anaerobic threshold as % of predicted peakVO_2.

Supplemental table 2: Harrell's concordance statistic

	AUC	**Harrell's Concordance Statistic**
VO_2 ATabs (ml/min)	0.680	0.650
VO_2 AT % obs	0.538	0.538
VO_2 AT %peak_pred	0.688	0.642

VO_2ATabs= oxygen uptake at anaerobic threshold absolute value; VO_2 AT%peak_obs: = oxygen uptake at anaerobic threshold as % of observed peak; VO_2AT%peak_pred: = oxygen uptake at anaerobic threshold as % of predicted peakVO_2.