Prognostic Value of Indeterminable Anaerobic Threshold in Heart Failure

Agostoni et al: Indeterminable Anaerobic Threshold in HF Prognosis

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DOI: 10.1161/CIRCHEARTFAILURE.113.000471

Journal Subject Codes: 26; 110
Abstract

**Background**—In heart failure (HF) patients, during maximal CardioPulmonary-Exercise test (CPET), anaerobic threshold (AT) is not always identified. We evaluated whether this finding has a prognostic meaning.

**Methods and Results**—We recruited and prospectively followed – in 14 dedicated HF units – 3058 systolic (LVEF <40%) HF patients in stable clinical conditions, NYHA class I-III, who underwent clinical, laboratory, echocardiographic and CPET investigations at study enrollment. We excluded 921 patients who did not perform a maximal exercise, based on lack of achievement of anaerobic metabolism (peak Respiratory Quotient ≤1.05). Primary study end point was a composite of cardiovascular death and urgent cardiac transplant, and secondary end point was all-cause death. Median follow up was 3.01(1.39-4.98) years. AT was identified in 1935 out of 2137 patients (90.54%). At multivariable logistic analysis, failure in detecting AT resulted significantly associated with reduced peak Oxygen uptake (VO₂) and higher MECKI score value, a powerful prognostic composite HF index (p<0.001).

At multivariable analysis, the following variables were significantly associated to primary study end point: peak VO₂ (% pred, p<0.001, HR=0.977, CI=0.97-0.98), VE/VCO₂ slope (p=0.01, HR=1.02, CI=1.01-1.03), hemoglobin (p<0.05, HR=0.931, CI=0.87-1.00), LVEF (p<0.001, HR=0.948, CI=0.94-0.96), renal function (MDRD, p<0.001, HR=0.990, CI=0.98-0.99), sodium (p<0.05, HR=0.967, CI=0.94-0.99), and AT non-identification (p<0.05, HR=1.41, CI=1.06-1.89). Non-identification of AT remained associated to prognosis also when compared to MECKI score (p<0.01, HR=1.459, CI=1.09-1.10). Similar results were obtained for the secondary study end point.

**Conclusions**—The inability to identify AT most often occurs in patients with severe HF, and it has an independent prognostic role in HF.

**Key Words:** exercise; follow-up study; heart failure; oxygen; prognosis
The anaerobic threshold (AT) concept is based on the principle that energy production shifts from an aerobic metabolism to a metabolism that combines both anaerobic and aerobic patterns during a progressively increasing workload exercise. According to the concept of “threshold”, the shift of metabolic pathway during incremental exercise must be more or less simultaneous among active muscular fibers. Therefore, the distribution of blood flow during exercise to and into muscles, the resistance to O₂ flow between capillaries and mitochondria, the type of muscular fibers and their metabolic capability must be relatively homogeneous. This is not always the case in heart failure patients (HF) who have an uneven distribution of blood flow to muscles and an uneven O₂ utilization, so that, for example, an important percentage of HF subjects increase their capillary pO₂ toward the end of exercise.

Inhomogeneity of blood flow distribution, of O₂ flow resistance and of O₂ utilization should widen the time frame where anaerobiosis starts to develop among the muscular fibers, in few cases making the threshold indefinable. If this hypothesis is correct, then AT should be more frequently undetectable in patients with a more severe disease.

From a clinical point of view, the value of VO₂ at AT is used for grading the severity of HF or the effects of therapy, or to assess cardiovascular risk in case of surgery, and it has been proposed as an alternative to peak VO₂, being it independent of patients’ motivation, exercise protocol and exercise duration. However, even in the presence of anaerobic metabolism, AT is not identified in a large number of HF patients. It is unknown whether the finding of a reached but indeterminable AT has a clinical meaning.

The present study was therefore undertaken to assess the clinical and prognostic significance of AT detection in patients with systolic HF. To find it out, we utilized a multicenter HF database, generated and continuously updated by the MECKI score research group.
Methods

Population. The study cohort consists of a population of systolic HF patients recruited and prospectively followed in 14 Italian HF centers (appendix 2). At enrollment, patients were evaluated, and clinical history, laboratory, ECG, echocardiographic and cardiopulmonary exercise test (CPET) data were collected. Study inclusion/exclusion criteria and patients’ follow up were previously described. In brief, we evaluated patients with present or previous history of HF who had been in NYHA functional class I-III, stable clinical conditions and medication since at least 3 months before enrollment. Patients with co-morbidities affecting exercise capacity or with exercise-induced angina or significant ECG alterations were excluded. Only patients who performed what they considered as a maximal effort were included in the original database. In the present analysis, however, to be sure that anaerobic metabolism was reached during exercise, we only evaluated patients who achieved a peak exercise Respiratory Quotient (RQ) > 1.05.

Clinical laboratory and echocardiographic evaluations were recorded as previously described. In brief, we recorded anthropometric parameters, HF etiology, hemoglobin (Hb), serum sodium (Na⁺), potassium (K⁺) and creatinine. We calculated glomerular filtration rate by means of the Modification of Diet in Renal Disease (MDRD) formula. Left ventricular volumes and ejection fraction (LVEF) were calculated by echocardiography

Cardiopulmonary exercise tests (CPET). CPET were performed using an electronically braked cycle-ergometer or a treadmill. For comparison with cycle-ergometer, treadmill peak VO₂ data were reduced by 10%. The exercise protocol was set to achieve peak exercise in 10 minutes. In the absence of clinical events, CPET was self-interrupted by the patients when they stated that they had reached a maximal effort. Expiratory gases and ventilation data were recorded and analyzed breath by breath by two CPET experts. Anaerobic threshold was measured by V-slope analysis of VO₂ and VCO₂, and it was confirmed by ventilatory...
equivalents and end-tidal pressures of CO₂ and O₂. If AT was not detected or a significant
disagreement on its value was reported by at least 2 experts, AT was considered as not
identified. Exercise-induced periodic breathing was defined as a cyclic fluctuation of
ventilation. VE/VCO₂ slope was calculated as the linear relation slope between VE and
VCO₂ from 1 minute after the beginning of loaded exercise up to the isocapnic buffering
period.

**Patient grouping.** Data were analyzed considering the entire population and after grouping
patients according to peak VO₂ and MECKI score (Metabolic Exercise and Cardiac and
Kidney Indexes), a recently reported HF prognostic score that combines CPET,
echocardiographic and laboratory parameters – namely peak VO₂ (%pred), VE/VCO₂ slope,
LVEF, Na⁺, MDRD, and Hb. As previously done by Wasserman et al., 3 peak VO₂-based
groups were defined: peak VO₂ < 12 ml/min/kg, between 12 and 16 and >16. As for MECKI
score, patients were divided in tertiles. Finally, we grouped patients with identified AT
according to their VO₂AT and we compared them with patients without identified AT.

**Patients’ follow up.** Patients’ follow up was carried out according to the local HF program in
a theoretically endless fashion. Follow up ended with the last clinical evaluation in the center
where the patient had been recruited or with the patient’s death. If the patient did not show
up at the scheduled follow-up visit, they or their family were called on the phone and their
visit was rescheduled at their desire. If the patient died outside the hospital where he was
followed up, we obtained medical records of the event and the cause of death. Patients who
died from non cardiovascular reasons were considered censored at the time of the event. The
primary end point of the study was a composite of cardiovascular death, including stroke, and
urgent cardiac transplant, and the secondary end point was all-cause death.

**Data Management and analysis.** Details of data management were previously reported,
including a data quality control management. In brief, a quality control was set up at
Centro Cardiologico Monzino, where P.A. was the director of the center and responsible for data collection, while individual investigators were responsible for their own records. All investigators were experts on CPET and HF. Data collection was computerized. Quality data control included the control center staff as well as external experts (M.P. and D.M.) not involved in patients’ recruitment. All computerized data were stored on a secure network that limited access to authorized individuals.

The study was approved by an institutional review committee and that the subjects gave informed consent.

**Statistical analysis**

Continuous variables were presented as means ± standard deviations and categorical variables as frequencies and percentages. ANOVA or unpaired t-test were used as appropriate for comparison between groups, and Chi square test was used for comparing categorical variables. Skewed distributed variables were reported as median and interquartile range and compared by the Wilcoxon signed-rank test.

We used multivariable logistic regression model for evaluating, at baseline, the association between identifiable/unidentifiable AT and VO2 and between identifiable/unidentifiable AT and MECKI score, adjusting the former for age, FE, MDRD, Na+, Hb, VE/VCO2 and periodic breathing, and the latter for age and periodic breathing.

Potential predictors of mortality were identified by univariable Cox regression analysis. A multivariable Cox proportional hazard model was used for assessing the independent prognostic value of AT adjusted for the variables significant at the univariable analysis.

When MECKI score was considered in multivariable analysis, parameters generating this score were excluded. Hazard ratios (HR) and 95% confidence intervals were calculated.

Kaplan Meier survival curves were implemented for AT, and survival curves were compared...
using log-rank test. A regression-based imputation analysis was used for missing data on Hb, Na⁺ and MDRD. Although there is a small difference between the percentages of missing data in the two groups of unidentified/identified AT, there is no relationship between AT and missing data, because of some reasons. First of all, we included AT together with age, gender, VO₂ peak (% of predicted), VE/VCO₂ slope, LVEF in the regression model. Secondly, a Sensitivity Analysis was performed to assess a model without the imputation approach, and the hazard ratio did not change, thus we can assume missing data as Missing at Random (MAR). The number of missing data for Hb was 289, and about 120 each variable for Na⁺ and MDRD. No data were missing for the other variables. Cox regression was also performed after grouping patients according to peak VO₂ and MECKI score. A p < 0.05 value considered as statistically significant.

Statistical analysis was performed using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina) or IBM SPSS 20.0 (SPSS-PC+ Inc, Chicago, Illinois).

Results

We obtained data from 3058 HF patients who met the study inclusion/exclusion criteria. 921 cases were excluded from further analysis because their Peak RQ was ≤ 1.05 in (Figure 1). The remaining 2137 patients performed CPET on a cycle-ergometer (2085 cases) or on a treadmill (52 cases). Mean follow up was 3.4 years (range 1 day to 14 years). We observed 562 total deaths, 482 cardiovascular deaths and 87 urgent cardiac transplants. At study enrollment, seventy-eight percent of patients were treated with angiotensin I converting enzyme inhibitors, 13% with angiotensin II receptor blockers, 80% with β-blockers, 79% with diuretics, 48% with anti-aldosteronic drugs, 47% with antiplatelets drugs, 31% with oral anticoagulants, 26% with digitalis, and 25% with amiodarone. Moreover, 18% of patients had implantable cardioverter-defibrillator, and 8% had a cardiac resynchronization therapy. Peak
VO₂ was < 12 ml/min/kg in 618 cases, between 12 and 16 in 798 cases, and >16 in 721 cases. Some of the most often recognized prognostic HF parameters of the entire population are reported in Table 1.

Patients with peak VO₂ < 12 ml/min/kg or in the highest MECKI tertile (≥ 0.104) had a more severe HF, were older, mainly male, with higher VE/VCO₂ slope, lower Hb concentration and lower LV and renal function (Table 2). Anaerobic threshold was not identified in 202 cases (9.45%), belonging in 110 (18%), 67 (8%), and 25 (3%) cases to group <12, 12-16, and >16 ml/min/Kg, respectively (p < 0.001) and 33 (17%), 50 (26%), and 112 (57%) cases to the 1st, 2nd, and 3rd tertiles of MECKI score, respectively (p < 0.001). Moreover, peak VO₂, or MECKI score, and impossibility to detect AT resulted significantly associated at univariable and multivariable logistic regression model (p < 0.001), adjusting the latter for age, FE, MDRD, Na⁺, Hb, VE/VCO₂ and periodic breathing (peak VO₂), or for age and periodic breathing (MECKI score).

Characteristics of HF patients according to the presence or absence of AT identification are reported in Table 1. Heart failure patients in whom AT was reached but not detected were older and more often female, had most often periodic breathing, higher VE/VCO₂ and MECKI score and lower peak VO₂, Hb, LVEF, and kidney function. In each peak VO₂-based group, the presence of an identified/unidentified AT was associated with significant differences in measured parameters: VE/VCO₂ slope, peak VO₂, presence of periodic breathing and MECKI score in peak VO₂ < 12ml/min/kg patients, VE/VCO₂ slope, gender, presence of periodic breathing in peak VO₂ between 12 and 16 ml/min/kg patients; presence of periodic breathing in peak VO₂ > 16 ml/min/kg patients (Table 2), all suggestive of a more severe disease in those with unidentified AT. Similarly, when grouping patients according to MECKI score tertiles, unidentified AT was associated to MECKI values suggestive of poorer prognosis (Table 2).
The impossibility of identifying AT was associated to a significantly worse prognosis at Kaplan Meier evaluation in the entire population (Figure 2) and, when grouping patients, only in the group with lower peak VO₂ (< 12ml/min/kg) patients or in patients with the highest tertile of the MECKI score (≥0.104) (Figure 3). Differently, in patients with less severe exercise impairment – as those with peak VO₂ between 12 and 16 ml/min/kg or with peak VO₂ >16 ml/min/kg – or in patients with less severe HF, as those with middle or lowest MECKI score tertiles, the impossibility of identifying AT was only associated with a not significant trend toward a worse prognosis at Kaplan Meier evaluation, likely due to the lower incidence of AT not-identification and to the lower amount of events in these patients (Figure 3). However, when formally tested, the interaction between AT identification and peak VO₂ or MECKI groups was not significant. Heart failure patients with identified AT (n = 1935) were grouped in tertiles according to VO₂ value at AT: AT ≤ 8.5 ml/min Kg (n = 644), between 8.5 and 11.0 (n = 640), and ≥ 11.0 (n = 650), and those with lower VO₂ values had a worse prognosis. However, the patients with unidentified AT had the worst survival considering both end points of the study (Figure 4). Multivariable analysis was performed considering the variables that were linked to prognosis at univariable analysis (Table 3). Peak VO₂ (%), VE/VCO₂ slope, Hb, Na⁺, MDRD, LVEF, and the impossibility of identifying AT were independently related to prognosis, regardless of the study end point considered (Table 4). Notably, the impossibility of identifying AT maintained a significant prognostic role. A similar result was obtained including the MECKI score value in the multivariable analysis, instead of using the single variables by which the score is derived (Peak VO₂ (%), VE/VCO₂ slope, Hb, Na⁺, MDRD, LVEF) (Table 4). We also performed a VO₂ stratified Cox regression according to the 3 above-reported peak VO₂ classes, comparing HF patients with unidentified vs. identified AT. Hazard Ratios were 1.77 (1.24-2.53), 1.15 (0.67-1.96), and 1.10 (0.35-348) for peak VO₂ < 12ml/min/kg, 12-16 ml/min/kg, and >16
ml/min/kg, respectively. After adjusting for MECKI score Hazard Ratios were 1.57 (1.09-2.27), 1.17 (0.69-2.00), and 0.85 (0.26-2.72), respectively.

Discussion

This study shows that, in HF patients who reached anaerobic metabolism as defined by a peak exercise RQ > 1.05 during an incremental exercise, AT was not identified by standard methods in 10% of cases. This percentage was significantly higher in most severe HF patients. The impossibility of identifying AT was associated to a worse prognosis. Notably, this impossibility maintained its negative prognostic role in HF even at a multivariable analysis, which included several HF prognostic parameters.

Defining an effort as maximal for a given individual is a matter of debate. Indeed, in the absence of significant clinical events, CPET is self-interrupted by patients when they feel that they have reached a maximal effort, regardless of the encouragement to continue by the supervising medical staff. In HF, a RQ ratio > 1.05 is considered as an indication of a significant effort by the patient.

Several prognostic studies in HF have considered CPET data as relevant, including VO₂ at AT. In the present study, we confirmed this finding. However, although anaerobic metabolism had been reached, AT was not identified in ~10% of cases, making it difficult to allocate these patients in a specific HF or surgical risk category. Indeed, the evidence of RQ > 1.05 at peak exercise of a ramp protocol exercise test implies that the anaerobic metabolism has been utilized to produce ATP regardless of AT identification. In a previous study, we showed that the impossibility of identifying AT was associated to CPET parameters suggestive of poor exercise performance. However, the presence of a true maximal effort was not mandatory in that study, so that an indeterminable AT was associated, at least in some cases, with a poor effort by the patients and a submaximal exercise.
Differently, in the present study, we excluded ~30% of patients from the analysis because RQ was ≤ 1.05, although they reported a maximal effort. An indeterminable AT in HF patients who performed a maximal or nearly maximal effort and reached anaerobic metabolism was inversely related to peak VO2, and to HF prognosis as assessed by the MECKI score. The majority of patients with unidentified AT had peak VO2 <12ml/min/kg and a MECKI score ≥0.104. Accordingly, these patients belong to a high-risk category of HF patients, as suggested by peak VO2 and MECKI score as well as by several other parameters (Table 2). The finding that the impossibility of identifying AT in HF patients who reached anaerobic metabolism during exercise has a prognostic role is a novel observation. Most importantly, patients with an unidentified AT had a poor prognosis, worse than patients with low VO2 at AT (≤8.5 ml/min/kg). Our finding extends to HF patients who likely reached anaerobic metabolism the previous observations by Katz et al22 and Opasich et al32, who showed that peak VO2 maintains its prognostic role even in severe HF patients in whom AT was not detected. Indeed, differently from Katz et al22 and Opasich et al32, we have excluded subjects who, for a variety of reasons, did not perform a metabolic maximal or nearly maximal effort, and we showed a prognostic role of an unidentified AT independent of several prognostic variables including peak VO2. Notably, the lack of AT identification has a demonstrated negative prognostic capacity only in patients with most severe HF. Indeed, the number of cases of AT non-identification and of events observed in our population with less severe HF (Figure 3) was relatively small and insufficient for interaction analysis. Some technical aspects may be the reason for an undetectable AT, including a test too short to collect enough data points and a relevant hyperventilation at the beginning of exercise. The former may be due to the selection of a too demanding ramp protocol. Indeed, although the average exercise duration in patients with undetectable AT was shorter (6.23±2.51 minutes), it was long enough to allow the collection of an adequate amount of data points for AT detection. We
previously showed that workload, but not VO₂, at AT was lower in short tests (5 minutes) than in longer tests (10 and 15 minutes), but AT was identified or not indentified independently of test duration. Also psychogenic hyperventilation may make AT identification difficult. However, in case of hyperventilation, CO₂ storages are significantly reduced, so that RQ declines during exercise and an RQ > 1.05 is rarely observed at peak exercise. Several physiological mechanisms may also explain why AT is not identifiable: an uneven intra and inter-muscle distribution of blood flow during exercise, an uneven O₂ flow resistance between capillary bed and mitochondria, and the presence of muscular fibers with uneven O₂ extraction/utilization capability are the most likely. In sum, the time frame during which anaerobiosis develops in the different muscle fibers in a ramp protocol exercise becomes wide, so that a “threshold” shared by the majority of muscle fibers does not exist. It is therefore conceivable that the identification of AT most often lacks in patients with severe HF, who most frequently have the above-described physiological impairments.

In the present study, we showed that an unidentified AT was related to several parameters suggestive of a worse prognosis, including the presence of exercise-induced periodic breathing. Indeed, periodic breathing may per se make AT identification difficult, particularly when it lasts throughout the exercise. This is the case in a minority of patients with exercise-induced periodic breathing, but this information was unfortunately not available for the present data set of patients. Moreover, in 58% of cases with an unidentified AT, exercise-induced periodic breathing was not observed.

Few study limitations should be acknowledged. Firstly, we admit that, by applying ≤1.05 as peak exercise RQ cut-off value, we likely excluded some HF patients who had done a true maximal test. Secondly, because the follow up was quite long, treatment strategies required to be upgraded in many patients, including ICD implantation and CRT implementation, which might have per se influenced the prognosis. Thirdly, several parameters known to be related
to HF prognosis were not considered, such as intraventricular delay and BNP or NT-proBNP value. Fourthly, we have not measured blood lactates during exercise, so that we did not evaluate whether the presence of an undetectable AT was associated to a lower or higher amount of exercise-induced lactic acid production. Finally, we have no information as regards reproducibility of undetection of AT.

In conclusion, we observed for the first time that the absence of an identified AT has an independent prognostic role in HF, considering several parameters related to HF prognosis at multivariable analysis either as isolated parameters or as combined in the MECKI score. This is due to the strong physiological meaning of an unidentifiable AT. Therefore, the VO₂ value at AT is clinically relevant in HF if anaerobic metabolism is reached, but also the finding of the impossibility of identifying AT should be carefully considered. Consequently, HF patients with an unidentifiable AT should be considered at high risk.

Appendix 1. Other members of the MECKI score research group are: Centro Cardiologico Monzino, IRCCS, Milano: Erica Bertella, Stefania Farina, Cardiologia Riabilitativa, Istituto Auxologico Italiano: Gabriella Malfatto, Cardiologia SUN, Ospedale Monaldi Napoli: Giuseppe Pacileo, Teo Roselli, Andrea Buono, Raffaele Calabrò, "S. Maugeri" Foundation, IRCCS, Cassano Murge: Andrea Passantino, Daniela Santoro, Saba Campanale, Domenica Caputo, "S. Maugeri" Foundation, Tradate: Donatella Bertipaglia, Ospedali Riuniti and University of Trieste: Emanuela Berton, Fondazione G. Monasterio: Luigi E Pastormerlo, S. Maugeri Foundation, Tradate: Raffaella Vaninetti, Ospedali Riuniti, Trieste: Marco

Disclosures
None.
Appendix 2. Patients’ recruitment: 924 patients were recruited and followed at Centro Cardiologico Monzino, Milan, 332 at S. Maugeri Foundation, Cassano Murge, 216 at Fondazione G. Monasterio, Pisa, 121 at S. Maugeri Foundation, Tradate, 41 at Lancisi Hospital, Ancona, 77 at Monaldi Hospital, Naples, 260 at S. Spirito Hospital, Rome, 22 at S. Luca Hospital, Milan, 59 at S. Paolo Hospital, Milan, 219 at Ospedali Civili, Brescia, 171 at Ospedali Riuniti, Trieste, 356 at S. Maugeri Foundation, Veruno, 64 at S. Camillo Hospital, Rome, and 196 at Ospedale Civile Maggiore, Verona.

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Table 1. Differences according to anaerobic threshold identification in the total population

<table>
<thead>
<tr>
<th></th>
<th>total population</th>
<th>Identified AT</th>
<th>Unidentified AT</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n=2137 )</td>
<td>( n=1935 )</td>
<td>( n=202 )</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>60 ± 12</td>
<td>60 ± 12</td>
<td>63 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gender (m/f)</strong></td>
<td>1801/336</td>
<td>1649/286</td>
<td>152/50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>VE/VCO_{2}slope</strong></td>
<td>33.0 ± 7.6</td>
<td>32.5 ± 7.2</td>
<td>38.3 ± 9.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>VO_{2} (% of predicted)</strong></td>
<td>53.6 ± 15.5</td>
<td>54.5 ± 15.3</td>
<td>45.0 ± 14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hb (g/dl)</strong></td>
<td>13.5 ± 1.5</td>
<td>13.5 ± 1.5</td>
<td>13.2 ± 1.6</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>31.0 ± 9.0</td>
<td>31.3 ± 9.0</td>
<td>29.3 ± 9.4</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>MDRD (ml/min)</strong></td>
<td>68.9 ± 21.6</td>
<td>69.3 ± 21.7</td>
<td>52.0 ± 21.7</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Na^{+} (mmol/l)</strong></td>
<td>139.4 ± 3.4</td>
<td>139.4 ± 3.2</td>
<td>139.7 ± 3.2</td>
<td>0.298</td>
</tr>
<tr>
<td><strong>PB (n, %)</strong></td>
<td>399 (18.6%)</td>
<td>314 (16.0%)</td>
<td>85 (42%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MECKI score</strong></td>
<td>0.103 (0.03-0.14)</td>
<td>0.059 (0.03-0.13)</td>
<td>0.13 (0.05-0.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Exercise duration (min)</strong></td>
<td>8.12 ± 2.87</td>
<td>8.31 ± 2.84</td>
<td>6.23 ± 2.51</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Identifies the probability of cardiovascular death or urgent cardiac transplant within 2 years (see Reference 23).

Data are mean±SD and median (interquartile ranges) for continuous variables or number (%) of subjects for categorical variables. \( p \) values were calculated by Student t-test or Wilcoxon Rank-Sum Test or by Chi-square when appropriate.

AT = anaerobic threshold, VE/VCO_{2}=Ventilatory efficiency, VO_{2}= Oxygen uptake, Hb= hemoglobin, LVEF= left ventricular ejection fraction, MDRD= Modification of Diet in Renal Disease, Na^{+}= Sodium, PB= Periodic breathing during exercise, MECKI= Metabolic exercise and cardiac and kidney indexes.
### Table 2. Differences according to anaerobic threshold identification in the three peak VO2 based groups and MECKI score tertiles

<table>
<thead>
<tr>
<th></th>
<th>VO2&lt;12 ml/min/kg</th>
<th>VO2≥12≤16 ml/min/kg</th>
<th>VO2&gt;16 ml/min/kg</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AT 1 (508)</td>
<td>AT O (110) p</td>
<td>AT 1 (731)</td>
<td>AT O (67) p</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>65±10</td>
<td>65±10</td>
<td>65±11</td>
<td>0.871</td>
</tr>
<tr>
<td><strong>Gender (m)</strong></td>
<td>471 (76.2%)</td>
<td>389(76.5%)</td>
<td>82(74.5%)</td>
<td>0.650</td>
</tr>
<tr>
<td><strong>VE/VO2slope</strong></td>
<td>37.7±8.8</td>
<td>36.8±8.3</td>
<td>41.9±10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PO2 (%) pred</strong></td>
<td>39.9±10.9</td>
<td>40.7±11.0</td>
<td>36.7±10.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hb (g/dl)</strong></td>
<td>13.0±1.6</td>
<td>13.0±1.5</td>
<td>13.0±1.8</td>
<td>0.971</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>28.9±9.0</td>
<td>29.2±8.9</td>
<td>27.7±9.1</td>
<td>0.109</td>
</tr>
<tr>
<td><strong>MDRD(ml/min)</strong></td>
<td>61.7±21.5</td>
<td>61.8±21.7</td>
<td>61.7±21.1</td>
<td>0.977</td>
</tr>
<tr>
<td><strong>Na+ (mmol/l)</strong></td>
<td>139.3±3.4</td>
<td>139.3±3.4</td>
<td>139.4±3.5</td>
<td>0.687</td>
</tr>
<tr>
<td><strong>PB (yes)</strong></td>
<td>163(26.4%)</td>
<td>115(22.63%)</td>
<td>48(33.64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MECKI score</strong></td>
<td>0.14(0.07-0.27)</td>
<td>0.13(0.07-0.25)</td>
<td>0.19(0.11-0.31)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

|                | AT 1 (578)       | AT O (112) p        | AT 1 (640)       | AT O (50) p | AT 1 (689) | AT O (33) p |       |
| **MECKI score**|                  |                      |                  |            |            |            | ANOVA |
| ≥0.104         | 62±11            | 62±11               | 63±11            | 0.313   | 61±12      | 61±12      | 62±13     | 0.307   | 58±13      | 58±13      | 62±10     | 0.107  | <0.001    |
| ≥0.038<0.104   | 567(82.17%)      | 533(83.28%)         | 34(68%)          | 0.007   | 517(82.87%)| 548(83.53%)| 23(69.69%)| 0.04    | 28.3±4.4   | 28.2±4.4   | 30.4±6.8  | <0.01   | <0.001    |
| <0.038         | 31.7±5.3         | 31.6±5.3            | 33.5±5.3         | 0.014   | 30.8±5.7  | 30.5±5.6  | 31.7±5.6  | 0.232   | 38.7±6.7  | 38.6±6.8  | 40.7±5.9  | 0.077   |
| ≥0.104         | 58.8±20.1        | 58.7±20.2           | 59.5±20.6        | 0.704   | 69.4±19.6 | 69.3±19.7 | 71.0±16.7 | 0.598   | 78.7±20.6 | 78.8±20.7 | 78.0±20.9 | 0.854   |
| ≥0.038<0.104   | 138.8±3.5        | 138.4±3.5           | 139.3±3.4        | 0.015   | 139.8±3.0 | 139.7±3.0 | 140.8±3.4 | 0.020   | 140.1±2.8 | 140.1±2.8 | 139.8±2.4 | 0.655   |
| <0.038         | 177(25.65%)      | 126(21.79%)         | 51(45.53%)       | <0.001  | 121(17.53%)| 103(16.09%)| 18(36%)   | <0.001  | 95(13.78%)| 81(12.34%)| 14(42.42%)| <0.001 |

Data are mean±SD and median (interquartile ranges) for continuous variables or number (%) of subjects for categorical variables. P values were calculated by Student t-test or Wilcoxon Rank-Sum Test or by Chi-square when appropriate.

AT 1 = identified anaerobic threshold, AT 0 = unidentified anaerobic threshold. VE/VO2=Ventilatory efficiency, VO2= Oxygen uptake, Hb= hemoglobin, LVEF= left ventricular ejection fraction, MDRD= Modification of Diet in Renal Disease, Na+ = Sodium, MECKI= Metabolic exercise and cardiac and kidney indexes.
Table 3. Heart failure prognosis (Univariable analysis)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cardiovascular death+ transplant</th>
<th>All cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% Hazard Ratio Confidence Limits</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.01</td>
<td>1.002 - 1.019</td>
</tr>
<tr>
<td>Gender</td>
<td>1.113</td>
<td>0.835 - 1.484</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.933</td>
<td>0.922 - 0.945</td>
</tr>
<tr>
<td>MDRD (ml/min)</td>
<td>0.983</td>
<td>0.978 - 0.989</td>
</tr>
<tr>
<td>Na⁺ (mmol/l)</td>
<td>0.959</td>
<td>0.929 - 0.99</td>
</tr>
<tr>
<td>Hb (mg/dl)</td>
<td>0.857</td>
<td>0.801 - 0.917</td>
</tr>
<tr>
<td>VE/VCO₂slope</td>
<td>1.057</td>
<td>1.046 - 1.068</td>
</tr>
<tr>
<td>VO₂ (% of predicted)</td>
<td>0.958</td>
<td>0.95 - 0.965</td>
</tr>
<tr>
<td>PB</td>
<td>1.314</td>
<td>1.033 - 1.67</td>
</tr>
<tr>
<td>MECKI score*</td>
<td>1.56</td>
<td>1.505 - 1.68</td>
</tr>
<tr>
<td>AT non- identification</td>
<td>1.949</td>
<td>1.479 - 2.567</td>
</tr>
</tbody>
</table>

VE/VCO₂= Ventilatory efficiency, VO₂= Oxygen uptake, Hb= hemoglobin, LVEF= left ventricular ejection fraction, MDRD= Modification of Diet in Renal Disease, Na⁺= Sodium, PB= Periodic breathing, AT= Anaerobic threshold, MECKI= Metabolic exercise and cardiac and kidney indexes.

*Hazard ratio expressed for each 0.1 unit of MECKI score increase
Table 4. Heart failure prognosis (Multivariable analysis) without and with MECKI score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cardiovascular death+ transplant</th>
<th></th>
<th></th>
<th>All cause death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% Hazard Ratio</td>
<td>p</td>
<td>Hazard Ratio</td>
<td>95% Hazard Ratio</td>
</tr>
<tr>
<td></td>
<td>Confidence</td>
<td>Limits</td>
<td></td>
<td>Confidence</td>
<td>Limits</td>
</tr>
<tr>
<td>With single variables:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.002</td>
<td>0.99</td>
<td>1.012</td>
<td>0.7224</td>
<td>1.004</td>
</tr>
<tr>
<td>VO₂ (% of predicted)</td>
<td>0.977</td>
<td>0.97</td>
<td>0.986</td>
<td>&lt;0.001</td>
<td>0.977</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>1.02</td>
<td>1.01</td>
<td>1.033</td>
<td>&lt;0.01</td>
<td>1.019</td>
</tr>
<tr>
<td>Hb (mg/dl)</td>
<td>0.931</td>
<td>0.87</td>
<td>1.00</td>
<td>0.0498</td>
<td>0.909</td>
</tr>
<tr>
<td>Na⁺ (mmol/l)</td>
<td>0.967</td>
<td>0.94</td>
<td>0.998</td>
<td>0.0358</td>
<td>0.968</td>
</tr>
<tr>
<td>MDRD (ml/min)</td>
<td>0.99</td>
<td>0.98</td>
<td>0.995</td>
<td>&lt;0.001</td>
<td>0.992</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.948</td>
<td>0.94</td>
<td>0.961</td>
<td>&lt;0.001</td>
<td>0.955</td>
</tr>
<tr>
<td>PB</td>
<td>1.032</td>
<td>0.8</td>
<td>1.325</td>
<td>0.8056</td>
<td>1.044</td>
</tr>
<tr>
<td>AT non-identification</td>
<td>1.414</td>
<td>1.06</td>
<td>1.893</td>
<td>0.0202</td>
<td>1.39</td>
</tr>
<tr>
<td>With MECKI score:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.004</td>
<td>0.99</td>
<td>1.013</td>
<td>0.4452</td>
<td>1.005</td>
</tr>
<tr>
<td>PB</td>
<td>1.059</td>
<td>0.825</td>
<td>1.359</td>
<td>0.6531</td>
<td>1.069</td>
</tr>
<tr>
<td>MECKI score*</td>
<td>1.568</td>
<td>1.482</td>
<td>1.659</td>
<td>&lt;0.001</td>
<td>1.535</td>
</tr>
<tr>
<td>AT non-identification</td>
<td>1.459</td>
<td>1.096</td>
<td>1.941</td>
<td>&lt;0.001</td>
<td>1.446</td>
</tr>
</tbody>
</table>

VE/VCO₂=Ventilatory efficiency, VO₂= Oxygen uptake, Hb= hemoglobin, LVEF= left ventricular ejection fraction, MDRD= Modification of Diet in Renal Disease, Na⁺= Sodium, PB= Periodic breathing, AT= Anaerobic threshold

*Hazard ratio expressed for each 0.1 unit of MECKI score increase
Figure Legends

Figure 1. Scheme of patient selection for study evaluation.

Figure 2. Total population survival rate (n=2137): Kaplan-Meier curves stratified according to anaerobic threshold identification for the primary end point (death + urgent cardiac transplant, upper panel) and for the secondary end point (all-cause death, lower panel). Green line=identified AT group; Blue line=not identified AT group.

Figure 3. Survival rate of most severe HF patients, according to VO₂ (panel A) or MECKI score (panel B). Kaplan-Meier curves, according to anaerobic threshold identification for the primary end point (death + urgent cardiac transplant, left panels) and for the secondary end point (all-cause death, right panels), stratify only in patients with lower peak VO₂ or higher MECKI score. Green line=identified AT group; Blue line=not identified AT group.

Figure 4. Total population survival rate: Kaplan-Meier curves stratified according to VO₂/ml/Kg at anaerobic threshold (AT) or lack of identification, for the primary end point (death + urgent cardiac transplant, upper panel) and for the secondary end point (all-cause death, lower panel). First tertile (green line): VO₂ at AT <=8.5 ml/min/Kg; Second tertile (yellow line): VO₂ at AT >8.5 and < 11 ml/min/Kg; Third tertile (purple line): VO₂ at AT >11 ml/min/Kg. Blue line=not identified AT group.
3058
HF patients enrolled

921 (30.1%)
RQ=<1.05

2137 (69.9%)
RQ>1.05

202 (9.4%)
not identified AT

1935 (90.6%)
identified AT
Cardiovascular death + urgent transplant

Survival probability

0 1 2 3 4 5 years

1 = identified AT
0 = not identified AT

Pts at risk AT=0: 292 181 126 98 68 44
Pts at risk AT=1: 1935 1769 1763 1760 1756 1753

All-cause death

Survival probability

0 1 2 3 4 5 years

1 = identified AT
0 = not identified AT
Prognostic Value of Indeterminable Anaerobic Threshold in Heart Failure
Piergiuseppe Agostoni, Ugo Corrà, Gaia Cattadori, Fabrizio Veglia, Elisa Battaia, Rocco La Gioia, Angela B. Scardovi, Michele Emdin, Marco Metra, Gianfranco Sinagra, Giuseppe Limongelli, Rosa Raimondo, Federica Re, Marco Guazzi, Romualdo Belardinelli, Gianfranco Parati, Damiano Magrì, Cesare Fiorentini, Mariantonietta Cicoira, Elisabetta Salvioni, Marta Giovannardi, Alessandro Mezzani, Domenico Scrutinio, Andrea Di Lenarda, Valentina Mantegazza, Roberto Ricci, Anna Apostolo, AnnaMaria Iorio, Stefania Paolillo, Pietro Palermo, Mauro Contini, Corrado Vassanelli, Claudio Passino and Massimo F. Piepoli

Circ Heart Fail. published online July 23, 2013;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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