Prognostic Value of Indeterminable Anaerobic Threshold in Heart Failure

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Background—In patients with heart failure (HF), during maximal cardiopulmonary exercise test, anaerobic threshold (AT) is not always identified. We evaluated whether this finding has a prognostic meaning.

Methods and Results—We recruited and prospectively followed up, in 14 dedicated HF units, 3058 patients with systolic (left ventricular ejection fraction <40%) HF in stable clinical conditions, New York Heart Association class I to III, who underwent clinical, laboratory, echocardiographic, and cardiopulmonary exercise test 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 in reduced peak oxygen uptake and higher metabolic exercise and cardiac and kidney index score value, a powerful prognostic composite HF index (P<0.001). At multivariable analysis, the following variables were significantly associated with primary study end point: peak oxygen uptake (% pred; P<0.001; hazard ratio [HR]=0.977; confidence interval [CI]=0.97–0.98), ventilatory efficiency slope (P=0.01; HR=1.02; CI=1.01–1.03), hemoglobin (P<0.05; HR=0.931; CI=0.87–1.00), left ventricular ejection fraction (P<0.001; HR=0.948; CI=0.94–0.96), renal function (modification of diet in renal disease; 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 nonidentification (P<0.05; HR=1.41; CI=1.06–1.89). Nonidentification of AT remained associated to prognosis also when compared with metabolic exercise and cardiac and kidney index score (P<0.01; HR=1.459; CI=1.09–1.10). Similar results were obtained for the secondary study end point.

Received April 2, 2013; accepted July 15, 2013.

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*A list of all MECKI Score Research Group is given in the Appendix.

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Circ Heart Fail **is available at http://circheartfailure.ahajournals.org** **DOI: 10.1161/CIRCHEARTFAILURE.113.000471**

Conclusions—The inability to identify AT most often occurs in patients with severe HF, and it has an independent prognostic role in HF. **(*Circ Heart Fail*. 2013;6:977-987.)**

Key Words: exercise ■ follow-up studies ■ 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.[1,2] 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 O_2 flow between capillaries and mitochondria, the type of muscular fibers, and their metabolic capability must be relatively homogeneous.[3] This is not always the case in patients with heart failure (HF) who have an uneven distribution of blood flow to muscles and an uneven use of O_2, so that, for example, an important percentage of subjects with HF increase their capillary P_{O_2} toward the end of exercise.[4–7] Inhomogeneity of blood flow distribution, of O_2 flow resistance, and of O_2 use 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.[8]

Clinical Perspective on p 987

From a clinical point of view, the value of oxygen uptake (V_{O_2}) at AT is used for grading the severity of HF or the effects of therapy, or to assess cardiovascular risk in case of surgery,[9–18] and it has been proposed as an alternative to peak V_{O_2}, being it independent of patients' motivation, exercise protocol, and exercise duration.[19] However, even in the presence of anaerobic metabolism, AT is not identified in a large number of patients with HF.[8,20–22] 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 used a multicenter HF database, generated and continuously updated by the metabolic exercise and cardiac and kidney index (MECKI) score research group.[23]

Methods

Population

The study cohort consists of a population of patients with systolic HF recruited and prospectively followed up 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.[23] In brief, we evaluated patients with present or previous history of HF who had been in New York Heart Association functional class I to III, stable clinical conditions, and medication since ≥3 months before enrollment. Patients with comorbidities 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.[23] In brief, we recorded anthropometric parameters, HF pathogenesis, 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.[24] Left ventricular volumes and ejection fraction (LVEF) were calculated by echocardiography.[25]

Cardiopulmonary Exercise Tests

CPET were performed using an electronically braked cycle-ergometer or a treadmill. For comparison with cycle-ergometer, treadmill peak V_{O_2} data were reduced by 10%.[26] The exercise protocol was set to achieve peak exercise in 10 minutes.[19] 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 2 CPET experts. AT was measured by V-slope analysis of V_{O_2} and V_{CO_2}, and it was confirmed by ventilatory equivalents and end-tidal pressures of CO_2 and O_2.[1,27] If AT was not detected or a significant disagreement on its value was reported by ≥2 experts, AT was considered as not identified. Exercise-induced periodic breathing was defined as a cyclic fluctuation of ventilation.[28] Ventilatory efficiency (V_E/V_{CO_2}) slope was calculated as the linear relation slope between VE and V_{CO_2} 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 V_{O_2} and MECKI score, a recently reported HF prognostic score that combines CPET, echocardiographic and laboratory parameters, namely peak V_{O_2} (%pred), V_E/V_{CO_2} slope, LVEF, Na^+, MDRD, and Hb.[23] As previously done by Wasserman et al,[29] 3 peak V_{O_2}–based groups were defined: peak V_{O_2} < 12 mL/min per kilogram, between 12 and 16 and >16. As for MECKI score, patients were divided into tertiles. Finally, we grouped patients with identified AT according to their VO_2AT, and we compared them with patients without identified AT.

Patients' Follow-Up

Patients' follow-up was performed 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 noncardiovascular 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.[23] 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

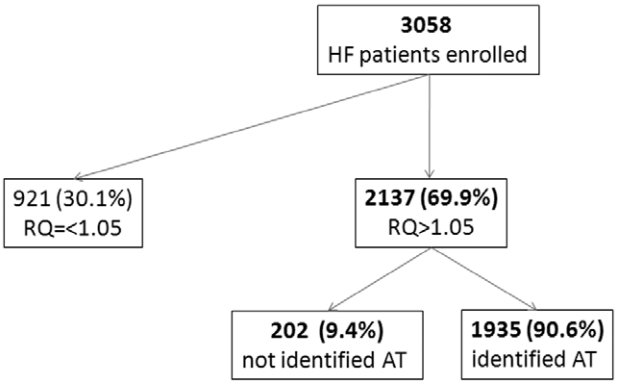

Figure 1. Scheme of patient selection for study evaluation. AT indicates anaerobic threshold; HF, heart failure; and RQ, respiratory quotient.

experts (M.P. and D.M.) not involved in the recruitment of patients. 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 the subjects gave informed consent.

Statistical Analysis

Continuous variables were presented as means±SDs, and categorical variables were presented as frequencies and percentages. Anova or unpaired *t* test were used as appropriate for comparison between groups, and χ^2 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 Vo_2 and between identifiable/unidentifiable AT and MECKI score, adjusting the former for age, LVEF, MDRD, Na^+, Hb, VE/Vco_2, 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 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 2 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, sex, Vo_2 peak (% of predicted), VE/Vco_2 slope, LVEF in the regression model. Second, 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. The number of missing data for Hb was 289, and ≈120 for 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 Vo_2 and MECKI score. A $P<0.05$ value considered as statistically significant. Statistical analysis was performed using SAS 9.2 (SAS Institute, Inc, Cary, NC) or IBM SPSS 20.0 (SPSS-PC+ Inc, Chicago, IL).

Results

We obtained data from 3058 patients with HF who met the study inclusion/exclusion criteria. A total of 921 cases were excluded from further analysis because their peak RQ was ≤1.05 (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, 78% 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 antialdosteronic 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% of patients had a cardiac resynchronization therapy. Peak Vo_2 was <12 mL/min per kilogram 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.

Table 1. Differences According to Anaerobic Threshold Identification in the Total Population

	Total Population (N=2137)	Identified AT (n=1935)	Unidentified AT (n=202)	*P*
Age, y	60±12	60±12	63±12	<0.001
Sex (m/f)	1801/336	1649/286	152/50	<0.001
VE/Vco_2 slope	33.0±7.6	32.5±7.2	38.3±9.7	<0.001
Vo_2 (% of predicted)	53.6±15.5	54.5±15.3	45.0±14.3	<0.001
Hb, g/dL	13.5±1.5	13.5±1.5	13.2±1.6	0.006
LVEF, %	31.0±9.0	31.3±9.0	29.3±9.4	0.001
MDRD, mL/min	68.9±21.6	69.3±21.7	35.0±21.7	0.012
Na^+, mmol/L	139.4±3.1	139.4±3.2	139.7±3.2	0.298
PB, n (%)	399 (18.6)	314 (16.0)	85 (42)	<0.001
MECKI score*	0.103 (0.03–0.14)	0.059 (0.03–0.13)	0.13 (0.05–0.23)	<0.001
Exercise duration, min	8.12±2.87	8.31±2.84	6.23±2.51	<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 χ^2 when appropriate. AT indicates anaerobic threshold; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; MECKI, metabolic exercise and cardiac and kidney indexes; Na^+, sodium; PB, periodic breathing during exercise; VE/Vco_2, ventilatory efficiency; and Vo_2, oxygen uptake.

*Identifies the probability of cardiovascular death or urgent cardiac transplant within 2 y.[23]

Patients with peak Vo_2 <12 mL/min per kilogram or in the highest MECKI tertile (≥0.104) had a more severe HF, were older, mainly male, with higher VE/Vco_2 slope, lower Hb concentration, and lower LVEF and renal function (Tables 2 and 3). AT was not identified in 202 cases (9.45%), belonging in 110 (18%), 67 (8%), and 25 (3%) cases to group <12, 12 to 16, and >16 mL/min per kilogram, respectively (P<0.001) and 33 (17%), 50 (26%), and 112 (57%) cases to the first, second, and third tertiles of MECKI score, respectively (P<0.001). Moreover, peak Vo_2, or MECKI score, and impossibility to detect AT resulted significantly associated with univariable and multivariable logistic regression model (P<0.001), adjusting the latter for age, LVEF, MDRD, Na^+, Hb, VE/Vco_2 and periodic breathing (peak Vo_2), or for age and periodic breathing (MECKI score).

Characteristics of patients with HF according to the presence or absence of AT identification are reported in Table 1. Patients with HF in whom AT was reached, but not detected, were older and more often female, had most often periodic breathing, higher VE/Vco_2 and MECKI score, and lower peak Vo_2, Hb, LVEF, and kidney function. In each peak Vo_2–based group, the presence of an identified/unidentified AT was associated with significant differences in measured parameters: VE/Vco_2 slope, peak Vo_2, presence of periodic breathing, and MECKI score in peak Vo_2 <12 mL/min per kilogram patients, VE/Vco_2 slope, sex, presence of periodic breathing in peak Vo_2 between 12 and 16 mL/min per kilogram patients; presence of periodic breathing in peak Vo_2 >16 mL/min per kilogram patients (Tables 2 and 3), 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 (Tables 2 and 3).

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 Vo_2 (<12 mL/min per kilogram) patients or in patients with the highest tertile of the MECKI score (≥0.104; Figure 3). Conversely, in patients with less severe exercise impairment, as those with peak Vo_2 between 12 and 16 mL/min per kilogram or with peak Vo_2 >16 mL/min per kilogram, 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 because of the lower incidence of AT nonidentification and to the lower amount of events in these patients (Figure 3). However, when formally tested, the interaction between AT identification and peak Vo_2 or MECKI groups was not significant. Patients with HF with identified AT (n=1935) were grouped in tertiles according to Vo_2 value at AT: AT ≤8.5 mL/min per kilogram (n=644), between 8.5 and 11.0 (n=640), and ≥11.0 (n=650), and those with lower Vo_2 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 4). Peak Vo_2 (%), VE/Vco_2 slope, Hb, Na+, MDRD, LVEF, and the

Table 2. Differences According to Anaerobic Threshold Identification in the 3 Peak Vo_2–Based Groups

	Vo_2 <12 mL/min per kilogram				Vo_2≥12≤16 mL/min per kilogram				Vo_2>16 mL/min per kilogram				
	All (618)	AT 1 (508)	AT0 (110)	P	All (798)	AT 1 (731)	AT0 (67)	P	All (721)	AT 1 (696)	AT0 (25)	P	ANOVA
Age, y	65±10	65±10	65±11	0.871	62±11	62±11	62±12	0.762	55±13	55±13	57±11	0.378	<0.001
Sex (m)	471 (76.2%)	389 (76.5%)	82 (74.5%)	0.650	673 (84.3%)	626 (85.6%)	47 (70.14%)	0.002	657 (91.12%)	634 (91.09%)	23 (92%)	1.000	<0.001
VE/Vco_2 slope	37.7±8.8	36.8±8.3	41.9±10.1	<0.001	32.6±6.4	32.4±6.3	35.0±7.9	0.002	29.5±5.3	29.4±5.3	31.4±6.1	0.068	<0.001
Vo_2 (% pred)	39.9±10.9	40.7±11.0	36.7±10.0	<0.001	52.6±10.4	52.7±10.4	51.8±10.6	0.496	66.5±12.9	66.6±12.9	63.5±11.9	0.246	<0.001
Hb, g/dL	13.0±1.6	13.0±1.5	13.0±1.8	0.971	13.4±1.6	13.5±1.6	13.3±1.4	0.370	13.9±1.4	13.9±1.4	13.7±1.4	0.408	<0.001
LVEF, %	28.9±9.0	29.2±8.9	27.7±9.1	0.109	31.1±9.0	31.1±9.0	30.5±9.6	0.583	32.9±8.7	33.0±8.7	31.9±9.1	0.557	<0.001
MDRD, mL/min	61.7±21.5	61.8±21.7	61.7±21.1	0.977	68.4±20.5	68.5±20.7	67.5±19.2	0.720	75.9±20.6	76.0±20.7	74.7±19.6	0.768	<0.001
Na^+, mmol/L	139.3±3.4	139.3±3.4	139.4±3.5	0.687	139.4±3.2	139.4±3.3	140.4±2.9	0.020	139.6±2.8	139.7±2.8	139.2±2.2	0.479	0.121
PB (yes)	163 (26.4%)	115 (22.63%)	48 (43.64%)	<0.001	159 (19.92%)	131 (17.92%)	28 (41.79%)	<0.001	77 (10.67%)	68 (9.77%)	9 (36%)	<0.001	<0.001
MECKI score	0.14 (0.07–0.27)	0.13 (0.07–0.25)	0.19 (0.11–0.31)	<0.001	0.07 (0.035–0.12)	0.06 (0.03–0.12)	0.07 (0.04–0.14)	0.118	0.03 (0.016–0.055)	0.03 (0.016–0.054)	0.033 (0.019–0.09)	0.239	<0.0001

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 χ^2 when appropriate. AT 0 indicates unidentified anaerobic threshold; AT 1, identified anaerobic threshold; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; MECKI, metabolic exercise and cardiac and kidney indexes; Na^+, sodium; PB, periodic breathing; VE/Vco_2, ventilatory efficiency; and Vo_2, oxygen uptake.

Table 3. Differences According to Anaerobic Threshold Identification in the 3 Peak MECKI Score Tertiles

	MECKI Score ≥0.104				MECKI Score ≥0.038<0.104				MECKI Score <0.038				
	All (690)	AT 1 (578)	AT0 (112)	*P*	All (690)	AT 1 (640)	AT0 (50)	*P*	All (689)	AT 1 (656)	AT0 (33)	*P*	ANOVA
Age, y	62±11	62±11	63±11	0.313	61±12	61±12	63±13	0.307	58±13	58±12	62±10	0.107	<0.001
Sex (m)	606 (87.82%)	516 (89.27%)	90 (80.35%)	0.008	567 (82.17%)	533 (83.28%)	34 (68%)	0.007	571 (82.87%)	548 (83.53%)	23 (69.69%)	0.04	<0.01
VE/Vco_2 slope	38.9±8.2	38.2±7.7	42.7±9.8	<0.001	31.7±5.3	31.6±5.3	33.5±5.3	0.014	28.3±4.4	28.2±4.4	30.4±5.6	<0.01	<0.001
Vo_2 (%pred)	41.2±10.4	41.8±10.4	37.9±10.1	<0.001	53.9±11.1	54.2±11.0	50.2±11.0	0.496	65.9±13.6	66.1±13.7	63.0±11.2	0.185	<0.001
Hb, g/dL	13.0±1.6	13.0±1.6	13.0±1.8	0.975	13.5±1.5	13.5±1.5	13.5±1.4	0.828	14.0±1.4	14.0±1.4	13.4±1.4	0.032	<0.001
LVEF, %	23.9±6.9	23.8±6.9	24.5±6.8	0.309	30.6±6.7	30.5±6.5	31.7±8.6	0.232	38.7±6.7	38.6±6.8	40.7±5.9	0.077	<0.001
MDRD, mL/min	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	<0.001
Na^+, mmol/L	138.6±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	<0.001
PB (yes)	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 v(42.42%)	<0.001	<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 χ^2 when appropriate. AT 0 indicates unidentified anaerobic threshold; AT 1, identified anaerobic threshold; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; MECKI, metabolic exercise and cardiac and kidney indexes; Na^+, sodium; PB, periodic breathing; VE/Vco_2, ventilatory efficiency; and Vo_2, oxygen uptake.

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

impossibility of identifying AT were independently related to prognosis, regardless of the study end point considered (Table 5). 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 Vo_2 [%], VE/Vco_2 slope, Hb, Na^+, MDRD, LVEF; Table 5). We also performed a Vo_2 stratified Cox regression according to the 3 above-reported peak Vo_2 classes, comparing patients with HF with unidentified versus 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 Vo_2 <12 mL/min per kilogram, 12 to 16 mL/min per kilogram, and >16 mL/min per kilogram, 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 patients with HF who reached anaerobic metabolism as defined by a peak exercise RQ >1.05 during an incremental exercise, AT was not identified by standard

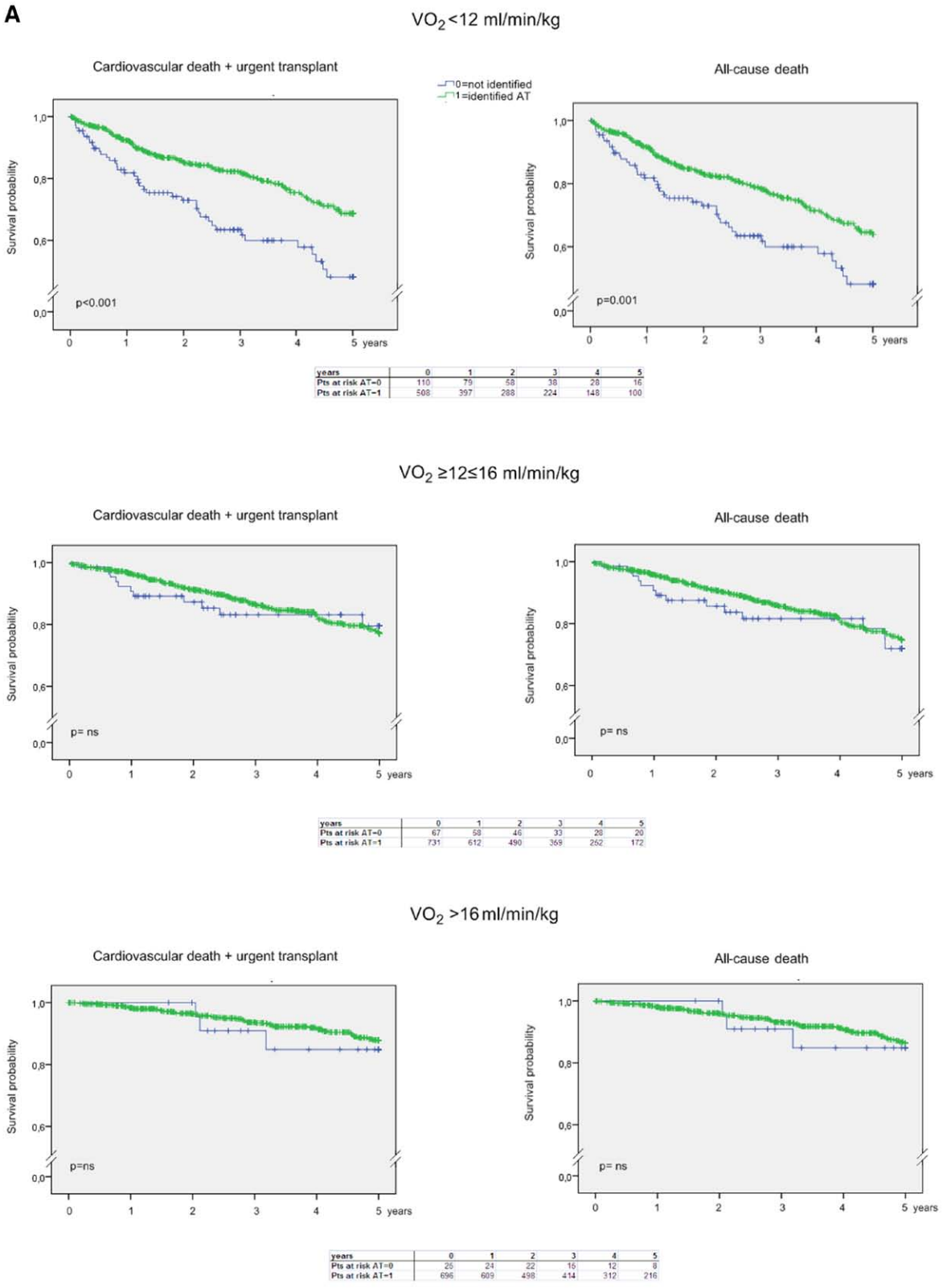

Figure 3. Survival rate of patients with most severe heart failure, according to oxygen uptake (Vo_2; **A**).

methods in 10% of cases. This percentage was significantly higher in most patients with severe HF. 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.[9] Indeed, in the absence of significant clinical

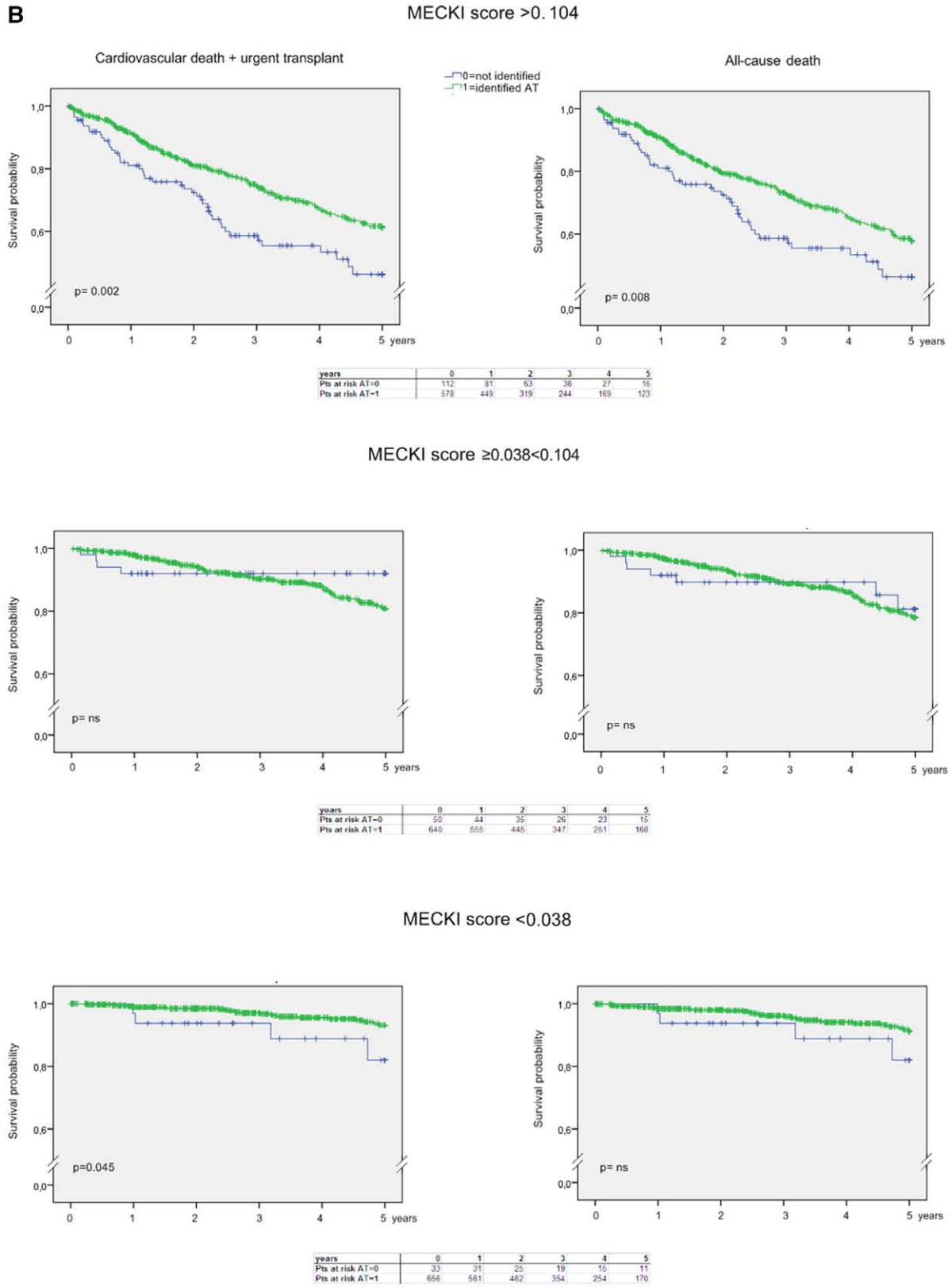

Figure 3 (Continued). or metabolic exercise and cardiac and kidney index (MECKI) score (**B**). Kaplan–Meier curves, according to anaerobic threshold identification for the primary end point (death+urgent cardiac transplant, **left**) and for the secondary end point (all-cause death, **right**), stratify only in patients with lower peak V_{O_2} or higher MECKI score. Green line=identified AT group; Blue line=not identified AT group.

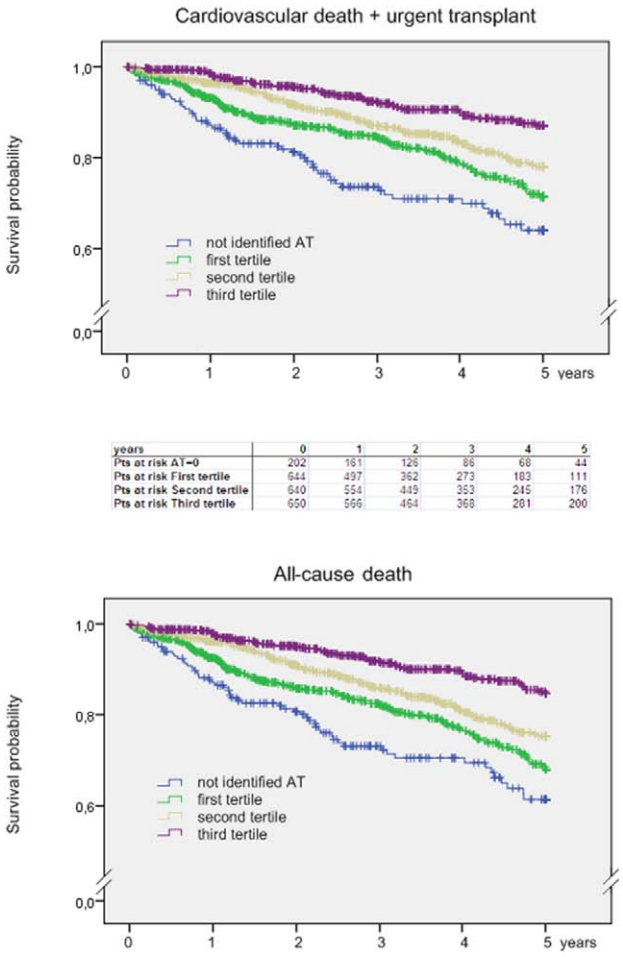

Figure 4. Total population survival rate: Kaplan–Meier curves stratified according to oxygen uptake (Vo_2)/mL per kilogram at anaerobic threshold (AT) or lack of identification, for the primary end point (death+urgent cardiac transplant, **top**) and for the secondary end point (all-cause death, **bottom**). First tertile (green line): Vo_2 at AT ≤8.5 mL/min per kilogram; second tertile (yellow line): Vo_2 at AT >8.5 and < 11 mL/min per kilogram; third tertile (purple line): Vo_2 at AT >11 mL/min per kilogram. Blue line indicates not identified AT group.

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.[30]

Several prognostic studies in HF have considered CPET data as relevant,[13,14,18,23,31,32] including Vo_2 at AT.[9–17,31] 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 used to produce ATP regardless of AT identification.[3,9] In a previous study, we showed that the impossibility of identifying AT was associated to CPET parameters suggestive of poor exercise performance.[8] However, the presence of a true maximal effort was not mandatory in that study, so that an indeterminable AT was associated, at in least in some cases, with a poor effort by the patients and a submaximal exercise.[8] Conversely, 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 patients with HF who performed a maximal or nearly maximal effort and reached anaerobic metabolism was inversely related to peak Vo_2, and to HF prognosis as assessed by the MECKI score. The majority of patients with unidentified AT had peak Vo_2 <12 mL/min per kilogram and a MECKI score ≥0.104. Accordingly, these patients belong to a high-risk category of HF patients, as suggested by peak Vo_2 and MECKI score as well as by several other parameters (Tables 2 and 3).[23]

The finding that the impossibility of identifying AT in patients with HF 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 Vo_2 at AT (≤8.5 mL/min per kilogram). Our finding extends to patients with HF who likely reached anaerobic metabolism unlike that in the previous observations by Katz et al[22] and Opasich et al,[32] who showed that peak Vo_2 maintains its prognostic role even in patients with severe HF in whom AT was not detected. Indeed, conversely from Katz et al[22] and Opasich et al,[32] 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 Vo_2. 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 nonidentification 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 because of 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 Vo_2, at AT was lower in short tests (5 minutes) than in longer tests (10 and 15 minutes), but AT was identified or not identified independently of test duration.[19] Also psychogenic hyperventilation may make AT identification difficult. However, in case of hyperventilation, CO_2 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 intramuscle and intermuscle distribution of blood flow during exercise, an uneven O_2 flow resistance between capillary bed and mitochondria, and the presence of muscular fibers with uneven O_2 extraction/utilization capability are the most likely.[4–7] 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

Table 4. Heart Failure Prognosis (Univariable Analysis)

	Cardiovascular Death+Transplant				All-Cause Death			
Parameters	Hazard Ratio	95% Hazard Ratio Confidence Limits		*P*	Hazard Ratio	95% Hazard Ratio Confidence Limits		*P*
Age, y	1.01	1.002	1.019	0.0212	1.01	1.002	1.019	0.0123
Sex	1.113	0.835	1.484	0.4659	1.167	0.886	1.535	0.2714
LVEF, %	0.933	0.922	0.945	<0.001	0.941	0.931	0.952	<0.001
MDRD, mL/min	0.983	0.978	0.989	<0.001	0.986	0.981	0.99	<0.001
Na^+, mmol/L	0.959	0.929	0.99	0.009	0.963	0.935	0.992	0.014
Hb, mg/dL	0.857	0.801	0.917	<0.001	0.843	0.791	0.898	<0.001
VE/V_{CO_2} slope	1.057	1.046	1.068	<0.001	1.055	1.045	1.066	<0.001
V_{O_2} (% of predicted)	0.958	0.95	0.965	<0.001	0.959	0.952	0.966	<0.001
PB	1.314	1.033	1.67	0.0259	1.311	1.046	1.644	0.0189
MECKI score*	1.56	1.505	1.68	<0.001	1.558	1.477	1.643	<0.001
AT nonidentification	1.949	1.479	2.567	<0.0001	1.894	1.455	2.466	<0.0001

AT indicates anaerobic threshold; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; MECKI, metabolic exercise and cardiac and kidney indexes; Na^+, sodium; PB, periodic breathing; VE/V_{CO_2}, ventilatory efficiency; and V_{O_2}, oxygen uptake.

*Hazard ratio expressed for each 0.1 U of MECKI score increase.

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.[14,28] 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,[33] 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. First, we admit that, by applying ≤1.05 as peak exercise RQ cutoff value, we likely excluded some patients with HF who had done a true maximal test. Second, because the follow-up was quite long, treatment strategies were required to be upgraded in many patients, including implantable cardioverter-defibrillator implantation and cardiac resynchronization therapy implementation, which might have, per se, influenced the prognosis. Third, several parameters known to be related to HF prognosis

Table 5. Heart Failure Prognosis (Multivariable Analysis) With and Without MECKI Score

	Cardiovascular Death+Transplant				All-Cause Death			
Parameters	Hazard Ratio	95% Hazard Ratio Confidence Limits		*P*	Hazard Ratio	95% Hazard Ratio Confidence Limits		*P*
With single variables								
Age, y	1.002	0.99	1.012	0.7224	1.004	0.99	1.014	0.4657
V_{O_2} (% of predicted)	0.977	0.97	0.986	<0.001	0.977	0.97	0.986	<0.001
VE/V_{CO_2} slope	1.02	1.01	1.033	<0.01	1.019	1.01	1.032	<0.01
Hb, mg/dL	0.931	0.87	1.00	0.0498	0.909	0.85	0.973	<0.01
Na^+, mmol/L	0.967	0.94	0.998	0.0358	0.968	0.94	0.998	0.0338
MDRD, mL/min	0.99	0.98	0.995	<0.001	0.992	0.99	0.998	<0.01
LVEF, %	0.948	0.94	0.961	<0.001	0.955	0.94	0.967	<0.001
PB	1.032	0.8	1.325	0.8056	1.044	0.83	1.322	0.7194
AT nonidentification	1.414	1.06	1.893	0.0202	1.39	1.05	1.838	0.0207
With MECKI score								
Age, y	1.004	0.99	1.013	0.4452	1.005	0.99	1.014	0.2747
PB	1.059	0.825	1.359	0.6531	1.069	0.845	1.353	0.5778
MECKI score*	1.568	1.482	1.659	<0.001	1.535	1.453	1.622	<0.001
AT nonidentification	1.459	1.096	1.943	<0.01	1.446	1.099	1.901	<0.01

AT indicates anaerobic threshold; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; Na^+, sodium; PB, periodic breathing; VE/V_{CO_2}, ventilatory efficiency; and V_{O_2}, oxygen uptake.

*Hazard ratio expressed for each 0.1 U of MECKI score increase.

were not considered, such as intraventricular delay and BNP (brain natriuretic peptide) or NT-proBNP (N-terminal-proBNP) value. Fourth, 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 on 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 attributable to the strong physiological meaning of an unidentifiable AT. Therefore, the V_{O_2} 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, patients with HF with an unidentifiable AT should be considered at high risk.[9–18]

Appendix 1

Other members of the MECKI score research group are the following: 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 Confalonieri, S. Maugeri Foundation, Veruno: Pantaleo Giannuzzi, Ospedali Civili, Brescia: Livio Dei Cas, Federico II Hospital: Prof. Pasquale Perrone Filardi, Paola Gargiulo.

Appendix 2

Recruitment of patients: A total of 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.

Disclosures

None.

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CLINICAL PERSPECTIVE

We observed for the first time that the absence of an identified anaerobic threshold has an independent prognostic role in heart failure, considering several parameters related to heart failure prognosis at multivariable analysis either as isolated parameters or as combined in the metabolic exercise, cardiac and kidney index score (MECKI score). This is attributable to the strong physiological meaning of an unidentifiable anaerobic threshold. Indeed, several physiological mechanisms may explain why anaerobic threshold is not identifiable: an uneven intramuscle and intermuscle distribution of blood flow during exercise, an uneven O_2 flow resistance between capillary bed and mitochondria, and the presence of muscular fibers with uneven O_2 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. For a clinical point of view, the present study is useful because it enables an understanding of information previously considered noninformative as relevant prognostic information, which we need to consider when evaluating a cardiopulmonary exercise test in patients with heart failure.

Circulation
Heart Failure

Prognostic Value of Indeterminable Anaerobic Threshold in Heart Failure

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on behalf of the MECKI Score Research Group*

Circ Heart Fail. 2013;6:977-987; originally published online July 23, 2013;
doi: 10.1161/CIRCHEARTFAILURE.113.000471
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297