[Original Research]

CHEST

Anaerobic Threshold and Respiratory Compensation Point Identification During Cardiopulmonary Exercise Tests in Chronic Heart Failure

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Q7 **BACKGROUND:** We evaluated the prognostic significance of the simple presence or absence of identifiable anaerobic threshold (AT) and respiratory compensation point (RCP) at cardiopulmonary exercise tests (CPETs) performed with a maximal incremental exercise protocol.

METHODS: In the present multicenter study, we retrospectively analyzed data in 1,995 patients with heart failure with reduced ejection fraction (HFrEF). All underwent clinical and laboratory evaluation, echocardiography, and maximal CPET at baseline. The analysis was performed according to absence of identified AT and RCP (group 1: n = 292; 15%), presence of AT but absence of identified RCP (group 2: n = 920; 46%), and presence of both AT and RCP (group 3: n = 783; 39%). The study end point was the composite of cardiovascular mortality, urgent heart transplant, and left ventricular assist device implantation.

RESULTS: Median follow-up was 2.97 years (interquartile range, 1.50-5.35 years). Eighty-seven (30%), 169 (18%), and 111 (14%) events were observed in groups 1, 2, and 3, respectively ($P = .025$). Compared with results in group 3 (patients with the best survival), the likelihood of reaching the study end point increased 2.7 times when neither AT nor RCP were identified (hazard ratio, 2.74) and 1.4 times when only AT was identified (hazard ratio, 1.39). Moreover, adding the presence or absence of identified AT and RCP improved the prognostic power of peak oxygen uptake because a significant reclassification was obtained
Q8 Q9 (3.57%; 95% CI, 1.9%-5.2%; $P < .001$).

CONCLUSIONS: AT and RCP identification has a potential role in the prognostic stratification of HFrEF.

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KEY WORDS: anaerobic threshold; exercise; heart failure; prognosis; respiratory compensation
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ABBREVIATIONS: AT = anaerobic threshold; BNP = brain natriuretic peptide; CPET = cardiopulmonary exercise test; CV = cardiovascular; HF = heart failure; HFrEF = HF with reduced ejection fraction; HT = heart transplant; LVAD = left ventricular assist device; MECKI = Metabolic Exercise Cardiac Kidney Indexes; NYHA = New York Heart Association; PB = periodic breathing; RCP = respiratory compensation point; RER = respiratory exchange ratio; VCO_2 = CO_2 production; VE = ventilation; VO_2 = oxygen uptake
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A progressively increasing workload exercise test is the most used protocol for assessing exercise performance in cardiopulmonary exercise tests (CPETs).[1] In such a protocol, ventilation (VE) increases with three distinguishable phases: the first up to the anaerobic threshold (AT); the second between the AT and the respiratory compensation point (RCP), known as the isocapnic buffering period; and the third from the RCP to the end of exercise.[2,3] The three phases may be linked to different VE domains—specifically, oxygen uptake (VO_2), CO_2 production (VCO_2), and unbuffered acidosis (ie, pH reduction, for the first, second, and third phases, respectively).[3]

In patients with heart failure (HF), these three phases are identified, provided that a maximal effort is performed, with a few exceptions, such as extreme HF severity and breathing pattern abnormalities such as exercise-induced periodic breathing (PB).[4,5] The VO_2 at AT has been suggested to have a prognostic value and to be a marker of HF severity.[6,7] Notably, even the absence of an identifiable AT, despite the achievement of exercise-induced anaerobiosis, has a strong prognostic power.[4]

Only few reports evaluated the prognostic power of RCP identification and of VO_2 value at RCP in patients with HF, although RCP VO_2 is related to the buffering capability of H^+ produced by exercise-induced acidosis and, consequently, its value may carry important physiologic and prognostic information.[8,9] However, the precise definitions of VO_2 at AT or RCP have been questioned, and even skilled readers from highly experienced laboratories may provide different values.[10,11] Conversely, the presence or absence of AT and RCP, independent of their precise value, is rarely questionable and much less reader dependent. We hypothesized that the presence of identified AT and RCP, independent of VO_2 value at AT and RCP, is associated with better survival than is the case in which only RCP or neither AT and RCP is identified. Accordingly, we retrospectively analyzed survival in patients with HF with reduced ejection fraction (HFrEF) who claimed that they had performed a maximal effort, grouping patients according to (1) absence of identified AT or RCP, (2) presence of identified AT and absence of RCP, and (3) presence of identified AT and RCP.

Materials and Methods

We retrospectively analyzed data from a cohort of 1,995 patients with a history of HFrEF, enrolled and prospectively followed up in four highly experienced HF units. Inclusion criteria were history of HF, New York Heart Association (NYHA) functional classes I through IV, stages B and C of American College of Cardiology/American Heart Association classification and documented reduced ejection fraction (< 45%), unchanged HF medications for at least 3 months, ability to perform a CPET, and no major cardiovascular (CV) interventions 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.[12] At enrollment, clinical history and therapy information were recorded, and then physical examination, laboratory analyses, ECG, transthoracic echocardiography, and CPET were performed, as previously described. Kidney function (estimated glomerular filtration rate) was assessed by means of the Modification of Diet in Renal Disease formula.[13] All patients were in the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score database.[12]

CPET

All patients performed what they considered a maximal, symptom-limited effort. CPETs were performed on a cycle ergometer by using a personalized ramp exercise protocol aimed at achieving peak exercise in approximately 10 minutes.[14] All patients performed at least one familiarization CPET. In all tests, VE and respiratory gases were collected breath by breath and analyzed according to a standard technique.[15] AT, RCP, and peak exercise data are 20-second averages. 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 oxygen and end-tidal pressure of CO_2.[3,16] The RCP was identified when the VE/VCO_2 relationship increased, and it was confirmed by a simultaneous reduction of end-tidal pressure of CO_2.[17] Peak exercise was the highest VO_2 value observed. Oxygen pulse was calculated as VO_2/heart rate. Respiratory gas exchange ratio was calculated as VCO_2/VO_2. The VO_2/work relationship was calculated throughout the exercise test, whereas the VE vs VCO_2 slope was calculated from the beginning of exercise up to RCP. Exercise-induced PB was identified as a cyclic fluctuation of VE present at rest and during exercise, with amplitude swings > 30% of the mean VE, > 15% for at least 60% of the exercise.[18] All tests were reevaluated for the present analysis by two of six CPET experts (C. C., P. A., M. P., U. C., M. M., C. V.), and a third expert was consulted in case of disagreement.

Data Analysis and Study End Points

The data analysis was performed grouping patients according to the absence of an identified AT or RCP (group 1), presence of identified

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TABLE 1] Population Characteristics: Demographic, Laboratory, and Treatment Data

Characteristic	Entire Population (N = 1,995)	No. Missing	Neither AT nor RCP Identified (Group 1: n = 292; 15%)	No. Missing	AT Identified, RCP Not Identified (Group 2: n = 920; 46%)	No. Missing	Both AT and RCP Identified (Group 3: n = 783; 39%)	No. Missing	*P* Value
Age, y	62 ± 11[a]	16	64 ± 11[a]	5	62 ± 11[a]	0	61 ± 11[a]	11	.002
Follow-up, d	1,085 (547-1,952)[b]	0	843 (404-1,581)[b]	0	1,097 (604-1,930)[b]	0	1,149 (553-2,049)[b]	0	< .001
Male	1,669 (84)[c]	0	226 (77)[c]	0	761 (83)[c]	0	682 (87)[c]	0	< .001
BMI, kg/m^2	27 ± 4[a]	6	26 ± 5[a]	2	27 ± 4[a]	0	27 ± 4[a]	4	.026
SBP, mm Hg	118 ± 17[a]	329	113 ± 16[a]	89	118 ± 17[a]	176	120 ± 18[a]	64	< .001
DBP, mm Hg	74 ± 9[a]	327	73 ± 9[a]	89	74 ± 9[a]	175	75 ± 10[a]	63	.027
HR, beats/min	70 ± 12[a]	328	73 ± 14[a]	90	70 ± 12[a]	175	69 ± 11[a]	63	< .001
NYHA class	2.09 ± 0.7[a]	0	2.33 ± 0.66[a]	0	2.10 ± 0.68[a]	0	1.97 ± 0.61[a]	0	< .001
Hemoglobin, g/dL	13.7 ± 1.6[a]	130	13.4 ± 1.7[a]	33	13.6 ± 1.6[a]	63	13.8 ± 1.5[a]	34	< .001
Creatinine, mg/dL	1.20 ± 0.44[a]	79	1.26 ± 0.49[a]	14	1.21 ± 0.46[a]	39	1.16 ± 0.39[a]	26	.003
MDRD formula, eGFR mL/min/1.73 m^2	70 ± 23[a]	95	66 ± 26[a]	19	70 ± 23[a]	39	72 ± 22[a]	37	.002
BNP, pg/mL	307 (128-824)[b]	1,074	770 (265-1,748)[b]	177	380 (157-828)[b]	505	205 (91-586)[b]	392	< .001
Uric acid, mg/dL	6.6 ± 1.9[a]	504	6.8 ± 2[a]	100	6.5 ± 1.9[a]	229	6.6 ± 1.8[a]	175	.19
Lymphocytes, %	27 ± 8[a]	409	27 ± 9[a]	81	27 ± 9[a]	190	27 ± 9[a]	138	.386
Atrial fibrillation	324 (16)[c]	3	67 (23)[c]	2	153 (16)[c]	1	104 (13)[c]	0	< .001
LBBB	369 (23)[c]	404	33 (17)[c]	103	159 (23)[c]	221	177 (25)[c]	80	.077
QRS complex, ms	123 ± 3[a]	419	134 ± 39[a]	106	124 ± 35[a]	230	119 ± 35[a]	83	< .001
ICD	684 (34)[c]	6	113 (39)[c]	3	293 (32)[c]	2	278 (36)[c]	1	.055
CRT	179 (9)[c]	67	29 (11)[c]	20	73 (8)[c]	35	77 (10)[c]	12	.33
LVEF, %	31.8 ± 9[a]	58	28.4 ± 9.6[a]	9	31.8 ± 9.1[a]	22	33 ± 9.3[a]	27	< .001
ACE inhibitors	1,548 (78)[c]	8	229 (79)[c]	2	733 (80)[c]	3	586 (75)[c]	3	.053
ARBs	317 (16)[c]	8	46 (16)[c]	2	132 (14)[c]	3	139 (18)[c]	3	.16
β-blockers	1,657 (83)[c]	8	230 (80)[c]	2	750 (82)[c]	3	677 (87)[c]	3	.003
Loop diuretics	1,612 (81)[c]	9	269 (91)[c]	2	757 (83)[c]	4	591 (76)[c]	3	< .001
Statins	866 (44)[c]	12	107 (37)[c]	3	386 (42)[c]	6	373 (48)[c]	3	.0033
Mineralocorticoid inhibitors	1,049 (53)[c]	8	178 (61)[c]	2	489 (53)[c]	3	382 (49)[c]	3	.0013

(Continued)

TABLE 1] (Continued)

Characteristic	Entire Population (N = 1,995)	No. Missing	Neither AT nor RCP Identified (Group 1: n = 292; 15%)	No. Missing	AT Identified, RCP Not Identified (Group 2: n = 920; 46%)	No. Missing	Both AT and RCP Identified (Group 3: n = 783; 39%)	No. Missing	*P* Value
Amiodarone	577 (29)[c]	9	71 (24)[c]	2	269 (29)[c]	3	237 (30)[c]	4	.16
Digoxin	301 (15)[c]	8	80 (28)[c]	2	143 (16)[c]	3	78 (10)[c]	3	< .001
Antiplatelets	1,151 (58)[c]	8	172 (59)[c]	2	540 (59)[c]	3	439 (56)[c]	3	.49
Oral anticoagulant therapy	630 (32)[c]	8	113 (39)[c]	2	293 (32)[c]	3	224 (29)[c]	3	.0058
Allopurinol	637 (32)[c]	12	113 (39)[c]	3	317 (35)[c]	3	207 (27)[c]	3	< .001

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AT = anaerobic threshold; BNP = brain natriuretic peptide; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HR = heart rate; ICD = implantable cardioverter/defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; NYHA = New York Heart Association; RCP = respiratory compensation point; SBP = systolic blood pressure.
[a]Mean ± SD.
[b]Mean (range).
[c]No. (%).

AT but absence of identified RCP (group 2), and presence of both identified AT and RCP (group 3). In the unlikely event at sea level of AT and RCP overlapping (ΔVO_2 < 10 mL/min), we considered both as reached.[19]

Data analysis was performed in two steps. In the first step, HF severity and prognosis in the three groups were assessed. The former was assessed by comparing several parameters associated with HF severity such as NYHA class, peak exercise VO_2, VE/VCO_2 slope, exercise-induced PB, natriuretic peptide type B, estimated glomerular filtration rate, and left ventricular ejection fraction. The latter was assessed by using Kaplan-Meier survival analysis including the log-rank test for overall survival outcomes, using as study end point the composite of CV mortality and urgent heart transplant (HT) defined as the United Network for Organ Sharing state for HT[20] or left ventricular assist device (LVAD) implantation. Finally, hazard ratio was assessed to identify the increase of risk from group 3 (both AT and RCP identified) to group 2 (only AT identified) and group 1 (neither AT nor RCP identified). In the second step, we analyzed whether the identification or nonidentification of AT and RCP improved the prognostic power of peak VO_2, VE/VCO_2 slope, MECKI score, NYHA class, and exercise-induced PB. To do so, we used integrated discrimination index analysis.

Follow-up and Data Management

Patient follow-up and data management procedures were performed as previously described.[12] 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 HT, or LVAD implantation. If a patient died outside the hospital where he or she was followed up, medical records of the event and the reported cause of death were considered. The study was approved by the local ethics committee, and all patients signed an informed consent form at the time of enrollment (CE n. R116/14-CCM127).

Statistical Analysis

Continuous variables are presented as mean ± SD, and they were compared using analysis of variance. Nonnormally distributed variables are reported as median and interquartile range and compared with the Kruskal-Wallis test. Categorical data were compared using the χ^2 test or the Fisher exact test, as appropriate. Event-free survival (absence of the composite of CV death, urgent HT, or LVAD implantation), stratified for the three study groups, was estimated by using Kaplan-Meier curves. Cox regression was used to estimate crude hazard ratios. We used the integrated discrimination index to estimate the additional prognostic value of the presence or absence of identified AT and RCP when added to peak VO_2 (mL/min/kg), VE/VCO_2 slope, MECKI score, NYHA class, or exercise-induced PB, all well-known predictors of survival in HF. For continuous variables, the number of patients reclassified in a new risk category was calculated by using net reclassification improvement. Reclassification allowed reallocation of patients in the appropriate risk category. Reclassification tables were constructed by using the tertiles of the event risk. Reclassification statistics were assessed by using the macros published by Cook and Ridker.[21] All tests were two-tailed, and P < .05 was required for statistical significance. All analyses were performed using software (SAS version 9.4; SAS Institute).

Results

In total, 1,995 patients were analyzed: 292 (15%) were in group 1, 920 (46%) were in group 2, and the remaining 783 (39%) were in group 3. AT and RCP overlapped in

TABLE 2] Cardiopulmonary Exercise Test Data

Parameter	Entire Population (N = 1,995)	No. Missing	Neither AT nor RCP Identified (Group 1: n = 292; 15%)	No. Missing	AT Identified, RCP Not Identified (Group 2: n = 920; 46%)	No. Missing	Both AT and RCP Identified (Group 3: n = 783; 39%)	No. Missing	*P* Value
VO_2 peak, mL/min	1,201 ± 423[a]	0	908 ± 340[a]	0	1,199 ± 422[a]	0	1,310 ± 400[a]	0	< .001
VO_2 peak, mL/kg/min	15.4 ± 4.6[a]	0	12.4 ± 3.8[a]	0	15.5 ± 4.6[a]	0	16.5 ± 4.5[a]	0	< .001
VO_2 peak, % predicted	58 ± 16[a]	0	47 ± 15[a]	0	58 ± 16[a]	0	61 ± 16[a]	0	< .001
HR peak, beats/min	120 ± 24[a]	6	113 ± 25[a]	2	120 ± 23[a]	4	123 ± 24[a]	0	< .001
HR peak, %predicted	77 ± 15[a]	22	73 ± 16[a]	7	77 ± 14[a]	4	78 ± 15[a]	11	< .001
Workload peak, W	82 ± 35[a]	43	59 ± 27[a]	10	82 ± 35[a]	6	92 ± 33[a]	27	< .001
Workload peak, % predicted	55 ± 21[a]	53	45 ± 23[a]	12	56 ±21[a]	9	59 ± 19[a]	32	< .001
Peak oxygen pulse, mL/beats/min	10.2 ± 3.4[a]	6	8.4 ± 3.2[a]	2	10.2 ± 3.3[a]	4	10.9 ± 3.2[a]	0	< .001
VO_2/work slope	10.3 ± 1.9[a]	643	10 ± 2.4[a]	172	10.2 ± 2[a]	297	10.4 ± 1.7[a]	174	.1036
VE/VCO_2 slope	32 ± 7[a]	30	37 ± 11[a]	8	31 ± 6[a]	14	31 ± 6[a]	8	< .001
RR peak, n	32 ± 7[a]	464	31 ± 7[a]	87	31 ± 7[a]	250	32 ± 6[a]	127	.25
VE peak, L/min	50 ± 15[a]	35	41 ± 13[a]	5	48 ± 14[a]	12	55 ± 15[a]	18	< .001
VT peak, L/min	1.60 ± 0.5[a]	476	1.27 ± 0.42[a]	89	1.53 ± 0.47[a]	254	1.78 ± 0.5[a]	133	< .001
RER peak, n	1.12 ± 0.08[a]	10	1.08 ± 0.11[a]	3	1.11 ± 0.09[a]	3	1.14 ± 0.09[a]	4	< .001
Periodic breathing	92 (4.6)[b]	2	37 (12.7)[b]	2	32 (3.5)[b]	0	23 (2.9)[b]	0	< .001

RER = respiratory exchange ratio; RR = respiratory rate; VCO_2 = CO_2 production; VE = ventilation; VO_2 = oxygen uptake; VT = tidal volume. See Table 1 legend for expansion of other abbreviations.
[a]Mean ± SD.
[b]No. (%).

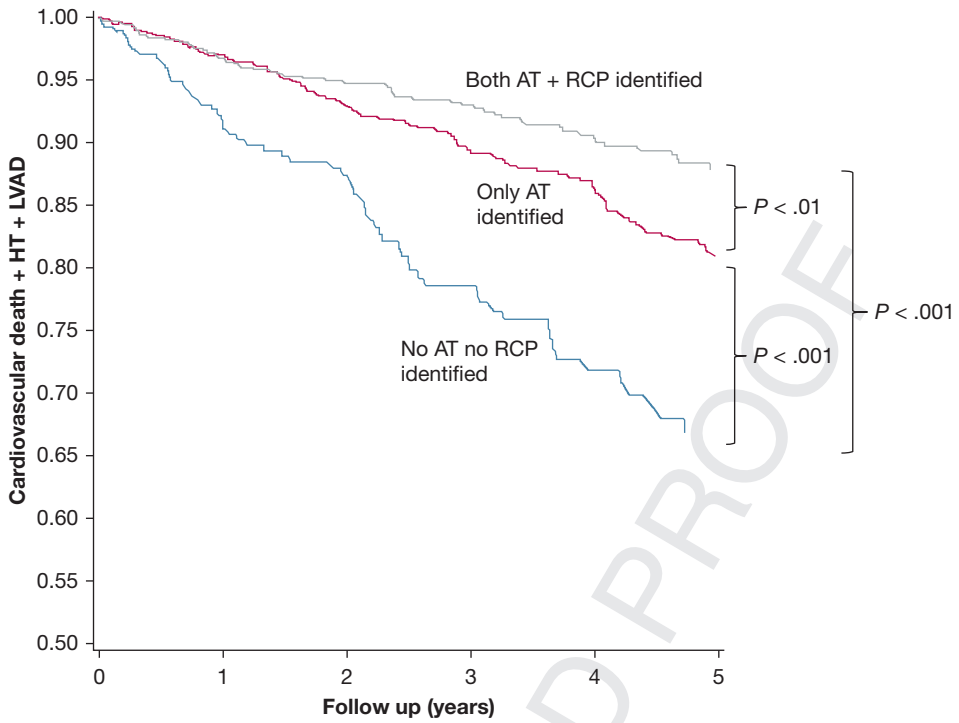

Figure 1 – *Five-year survival assessed according to the composite of cardiovascular death, urgent HT, and LVAD in group 1 (neither AT nor RCP identified), group 2 (AT identified but RCP not identified), and group 3 (both AT and RCP identified), respectively. AT = anaerobic threshold; HT = heart transplant; LVAD = left ventricular assist device; RCP = respiratory compensation point.* Q41 Q21

three cases. Anthropometric, clinical, laboratory, and CPET data for the entire study population and for the three groups are reported in Tables 1 and 2. As expected, patients in group 1 achieved a lower peak respiratory exchange ratio (RER). From group 3 to group 1, patients were progressively older and had more severe HF, as documented by NYHA class, peak exercise VO_2, peak workload, peak oxygen pulse, VO_2/work and VE/VCO_2 relationships, brain natriuretic peptide (BNP), Modification of Diet in Renal Disease, left ventricular ejection fraction, and QRS duration. Patients were treated with up-to-date HF medical therapy, without significant differences between the three groups, except for diuretics and mineralocorticoid receptor blockers, which increased from group 3 to group 1, and statins and β-blockers were lower in group 1.

The median follow-up was 2.97 years (25th-75th interquartile range, 1.50-5.35 years) in the total population and 2.31 (1.11-4.33), 3.00 (1.65-5.00), and 3.15 (1.52-5.00), in groups 1, 2, and 3, respectively ($P = .0014$). We observed 87 (30%), 169 (18%), and 111 (14%) events in groups 1, 2, and 3, respectively ($P = .025$). After a 5-year follow-up, survival rate assessed as CV death, urgent HT, or LVAD implantation significantly improved from group 1 to group 3 (Fig 1, Table 3). Compared with results in group 3 (patients who had the best survival), the likelihood of reaching the study end point increased 2.7 times when neither AT nor RCP were identified (hazard ratio, 2.74) and 1.4 times when only AT was identified (hazard ratio, 1.39). Q15

Moreover, adding the presence or absence of identified AT and RCP to these variables allowed us to obtain the following integrated discrimination index items: peak VO_2/kg, 0.0058 (CI, 0.0012-0.0105; $P < .001$); VE/VCO_2 slope, 0.0096 (CI, 0.0039-0.0153; $P < .001$); MECKI score, 0.0015 (CI, −0.001 to 0.0039; $P = .122$); NYHA class, 0.0148 (CI, −0.0153 to 0.0067; $P < .001$); and PB, 0.0157 (CI, 0.0082-0.232; $P = .001$). These results allowed a proper reclassification of several subjects (Table 4). Q16

Discussion

The major finding of the present study is that the absence of an identified AT or RCP, regardless of absolute values of VO_2 or work rate, pinpointed patients with HFrEF with a worse prognosis compared with that in patients in whom AT and RCP were identified. An intermediate prognosis was observed in patients with HFrEF with an identified AT but no RCP. We showed

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TABLE 3] Outcomes

Outcome	Entire Population (N = 1,995)	No. Missing	Neither AT nor RCP Identified (Group 1: n = 292; 15%)	No. Missing	AT Identified, RCP Not Identified (Group 2: n = 920; 46%)	No. Missing	Both AT and RCP Identified (Group 3: n = 783; 39%)	No. Missing	*P* Value
Deaths (all causes), HT, LVAD	367 (18)[a]	0	87 (30)[a]	0	169 (18)[a]	0	111 (14)[a]	0	< .001
Cardiovascular deaths, HT, LVAD	278 (14)[a]	0	71 (24)[a]	0	127 (14)[a]	0	80 (10)[a]	0	< .001

HT = heart transplant; LVAD = left ventricular assist device. See Table 1 legend for expansion of other abbreviations.
[a]No. (%).

that the presence or absence of identified AT and RCP has a potential prognostic role, simplifying the analysis of CPET and avoiding the need for a detailed assessment of AT and RCP and of the VO_2 value at AT and RCP. Moreover, the analysis of AT and RCP identification improves the prognostic power of peak VO_2, confirming the strong physiologic meaning of AT and RCP (Table 4).

A CPET is considered representative of a maximal effort when an RER > 1.05 has been reached.[22] However, in patients with severe HF, this RER value may not be reached, and the peak exercise RER value has a limited prognostic function in patients who state that they made a maximal effort.[23] Accordingly, in patients with HF, the definition of a real maximal effort from a metabolic point of view can be imprecise, and it bears some degree of uncertainty. To avoid this limitation in the present analysis, we excluded tests stopped for any reason by the medical surveillance personnel, and we only considered CPETs self-interrupted by the patients because they believed they had reached a maximal effort, regardless of the RER value observed at peak exercise.

AT is the exercise level above which an anaerobic metabolism is added to the aerobic. A few models have been proposed to identify AT, with some differences in reported AT values, which may be relevant in some cases.[24] AT may be not identified if lactate increase is not reached because of insufficient effort or in many cases in which erratic breathing or PB is recorded or with inhomogeneity of muscle fiber function, perfusion, or capillary mitochondrial oxygen flow resistance.[4,25-27] Starting from the pioneering work of Weber and Janicki,[28] several reports showed that VO_2 at AT bears a relevant prognostic power in HF and helps to grade HF severity. In a previous study, we reported that a nonidentified but reached AT was associated with a worse prognosis than was an identified AT, regardless of the AT VO_2 value.[4] In the present study, as in previous reports,[4,29] patients in group 1 (nonidentifiable AT and RCP) are a minority of the cases (15%), but they had worse exercise performance, overall greater HF severity, and poorer long-term survival than did patients in group 2 (identifiable AT but nonidentifiable RCP) and group 3 (both AT and RCP identifiable).

Patients with HF with identified AT but no RCP are a sizable percentage of cases (46%). These patients had better exercise performance and lower HF severity if compared with those in group 1 but worse if compared with those in group 3, for whom RCP was detectable.

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TABLE 4] Reclassification of Risk by Adding AT and RCP Evaluation to Peak VO_2 or to VE/VCO_2, With Respect to Only Peak VO_2 or VE/VCO_2 at 5-Year Follow-up

	5-Year Risk Categories Plus AT and RCP Identification			Percentage Reclassified Into New Risk Category	
5-Year Risk Category	1	2	3	Lower	Higher
VO_2[a]					
1					
No. (%)	556 (89.82)	63 (10.18)	0 (0)	…	10
Observed risk	0.092	0.189	…	…	…
No. of events	47	10	0	…	…
2					
No. (%)	95 (14.73)	502 (77.83)	48 (7.44)	15	7
Observed risk	0.080	0.178	0.263	…	…
No. of events	7	76	10	…	…
3					
No. (%)	0 (0)	92 (14.91)	525 (85.09)	15	…
Observed risk	…	0.296	0.353	…	…
No. of events	0	21	137	…	…
VE/VCO_2[b]					
1					
No. (%)	277 (68.40)	128 (31.60)	0 (0)	…	32
Observed risk	0.049	0.123	…	…	…
No. of events	13	14	0	…	…
2					
No. (%)	259 (22.29)	765 (65.83)	138 (11.88)	22	12
Observed risk	0.097	0.190	0.340	…	…
No. of events	23	122	35	…	…
3					
No. (%)	0 (0)	106 (28.27)	269 (71.73)	28	…
Observed risk	…	0.359	0.365	…	…
No. of events	0	28	72	…	…

See Table 1 and 2 legends for expansion of abbreviations.
[a]Risk tertiles for VO_2: 1, ≤ 0.11; 2, 0.11-0.2; 3, ≥ 0.2.
[b]Risk tertiles for VE/VCO_2: 1, ≤ 0.13; 2, 0.13-0.17; 3, ≥ 0.2.

There are two major physiologic reasons at the basis of this finding. First, the identification of RCP implies, in all cases but three, the presence of an isocapnic buffering period, which indicates the presence of CO_2 storage in the body, an unlikely event in patients with severe HF who have CO_2 loss due to hyperventilation.[3,19] Second, exercise performance above AT is strictly dependent on cardiac output increase, which is limited in patients with more severe HF.[30]

According to the present study results, obtained in a sizable population of patients with HF followed for a prolonged period, we observed that the presence or absence of AT and RCP has strong prognostic power in patients with HFrEF. Notably, the presence or absence of AT and RCP greatly simplifies the interpretation of CPET without the need for a precise definition of AT and RCP, which is often uncertain. Prospectively, our findings could help an automatic computerized CPET reading.

Peak VO_2 has a recognized prognostic power in patients with HF.[1] However, several reports showed that the prognostic power of peak VO_2 is improved when peak VO_2 is considered in combination with other CPET-derived parameters or when peak VO_2 is combined in prognostic scores.[7,12,31,32] In the present study, we showed that the prognostic power of peak VO_2 can be improved simply by adding the evaluation of the presence or absence of AT and RCP. The same happens

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when the evaluation of the presence or absence of AT and RCP is added to other frequently used HF prognostic tools such as VE/VCO_2 slope, MECKI score, NYHA class, or exercise-induced PB (Table 4). In this regard, adding the presence or absence of AT and RCP to the MECKI score did not demonstrate an improved prognostic capacity, but only a tendency, which likely is due to the strong prognostic power of the multiparametric MECKI score.

A few study limitations must be acknowledged. First, this is a retrospective study performed in four HF and CPET expert centers. The use of highly experienced laboratories increases the homogeneity of the medical personnel's behavior, and it allows a more standardized procedure. Consequently, the extrapolation of these results to less experienced and active laboratories may be questionable. AT and RCP may not be identified in the case of hyperventilation because of ambient noise or a short stabilization time before effort. Similarly, an inappropriate choice of exercise work-rate increase may lead to a too short or too long exercise evaluation. Regardless, the simple definition of presence or absence of AT and RCP is likely less dependent on technical errors than are VO_2 values. However, we have not evaluated whether analysis of this study's CPETs by nonexperienced readers provides results similar to those we observed. Furthermore, the method we proposed for assessing HF severity on the basis of the presence or absence of AT and RCP must be assessed further in a larger population and in less experienced or active laboratories.

Q17 Second, the follow-up was long, but the analysis was performed by evaluating a static picture of the population at study enrollment without taking into account the possible changes in treatments during follow-up, carrying a possible prognostic association. Third, the results of this study are applicable only to patients with HFrEF because preserved systolic function was not addressed. Similarly, it is unknown whether the same results apply to patients with other diseases, such as pulmonary hypertension, obstructive and restrictive lung diseases, or interstitial lung diseases, that influence exercise performance.

Fourth, the repeatability of AT and RCP identification Q18 was not assessed. Fifth, a few data were missing (Tables 1, 2, 3), albeit with a similar distribution among groups. The BNP data have a relevant number of missing cases. At the beginning of the MECKI score program, BNP was not routinely collected in several centers. Consequently, BNP data must be considered with caution. Sixth, we did not perform any application of our findings to a computerized CPET-reading system. Accordingly, its feasibility is unknown and needs to be assessed. Finally, the prognostic power of the presence or absence of AT and RCP was limited to a few, mainly CPET-derived parameters and scores, but several, including other prognostic multiparametric scores, were not tested. However, the absolute prognostic power analysis of AT and RCP presence or absence was outside the scope of the present work but needs to be evaluated in further studies.

Conclusions

In conclusion, the identification of AT and RCP per se and regardless of VO_2 at AT and RCP has prognostic power in patients with HFrEF, underlining its strong physiologic meaning.

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