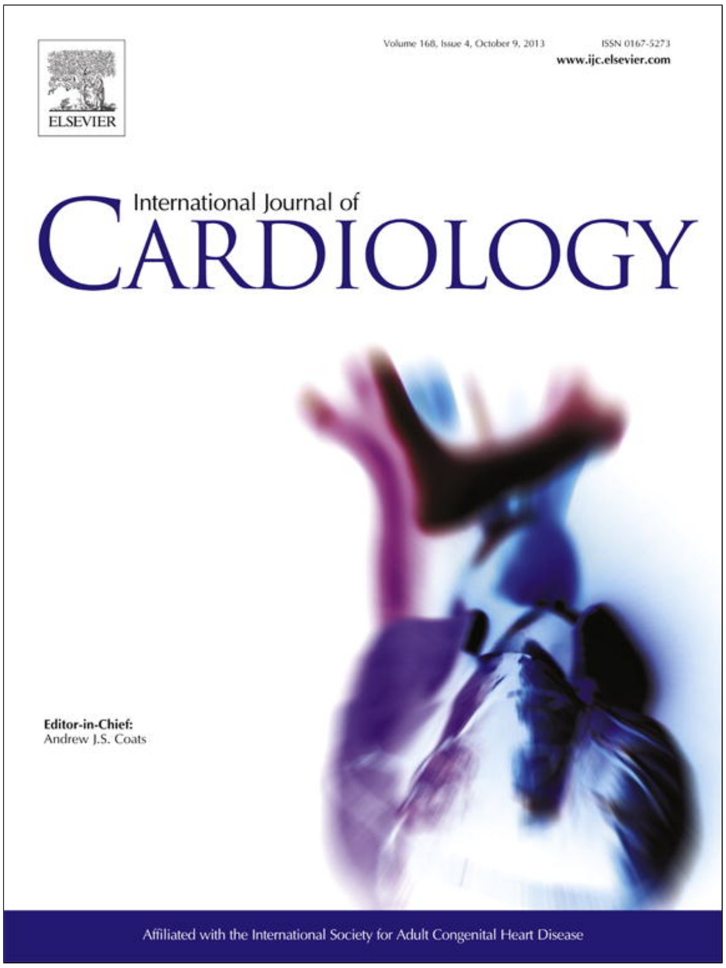
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Greater prognostic value of peak VO_2 after exercise training program completion in heart failure patients

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Background: Exercise capacity, best reflected by peak exercise oxygen consumption (peak VO_2), is a powerful prognostic factor in patients with chronic heart failure (CHF). However, the optimal time to assess exercise capacity for prognosis remains unclear and whether an exercise training program (ETP) to improve exercise capacity alters the prognostic value of cardiopulmonary exercise (CPX) testing variables in CHF is unknown.
Methods and results: CHF patients who underwent an ETP in two cardiac rehabilitation centers between 2004 and 2009 were prospectively included, and CPX testing was performed before and after ETP completion. We included 285 consecutive patients who underwent an ETP (19.4 ± 8.7 training sessions in 4 to 10 weeks), including segmental gymnastics and cycling sessions. During follow-up (12 months), 14 patients died, 6 underwent cardiac transplantation and 15 were hospitalized for acute heart failure. Univariate analysis and receiver operating characteristic (ROC) curve analysis showed that CPX variables, especially peak oxygen consumption and circulatory power (product of peak VO_2 × peak systolic blood pressure) before and after ETP completion predicted prognosis. However, CPX data obtained after ETP completion had the best prognostic value (area under the ROC curve = 0.79 ± 0.03 for peak VO_2 after ETP completion vs 0.64 ± 0.04 before ETP completion, $p < 0.0001$). The results did not change even when considering only deaths.
Conclusion: In patients with stable CHF who can exercise, the prognostic value of CPX data seems greater after versus before completion of a hospital-based ETP. Therefore, CPX capacity for prognostic purposes should at best be assessed after cardiac rehabilitation.

1. Introduction

Exercise capacity, usually best reflected by peak exercise oxygen consumption (peak VO_2), has been consistently shown to be one of the most powerful independent prognostic factors in patients with chronic heart failure (CHF) [1,2]. Although guidelines recommend performing cardiopulmonary exercise (CPX) testing in patients in "stable condition" [3], the definition of "stable condition" may reflect very different functional and fitness status.

In patients with coronary artery disease (CAD), the prognostic value of exercise testing is better after versus before completion of an exercise training program (ETP) [4]. Surprisingly, this question has never been assessed among CHF patients, although prognostication including CPX evaluation is crucial, leading to major therapeutic decisions: After ETP completion, peak VO_2 improvement can be so important that it may change therapeutic options, leading for example to reconsider a heart transplantation indication. Thus, timing of functional assessment by CPX could be of major importance and whether changes in cardiopulmonary performance with rehabilitation alter the prognostic evaluation is unknown. Indeed, does a peak VO_2 of 12 $ml \cdot kg^{-1} \cdot min^{-1}$ have the same prognostic value for a patient a few weeks after a long hospitalization or for a patient who performs regular exercise training?

Our hypothesis is that prognostic assessment of CHF patients by CPX is of more value when performed once peripheral deconditioning has been most corrected after ETP completion. Thus, we aimed to compare the prognostic value of CPX results obtained before and after an ETP in stable CHF patients with left ventricular (LV) systolic dysfunction.

2. Methods

All CHF patients with LV systolic dysfunction (left ventricular ejection fraction [LVEF] <45%) who were able to undergo an ETP in a cardiac rehabilitation center (Les Grands Prés or Lariboisière hospitals) between January 2004 and November 2009 were prospectively

Abbreviations: CHF, chronic heart failure; ETP, exercise training program; BNP 1 and 2, brain natriuretic protein level at admission and after ETP; LVEF, left ventricular ejection fraction; Peak VO_2 1 and 2, peak oxygen consumption at admission and after ETP; %PP VO_2 1 and 2, % predicted peak oxygen consumption at admission and after ETP; CP 1 and 2, circulatory power at admission and after ETP; VE/VCO_2 slopes 1 and 2, VE/VCO_2 slope at admission and after ETP completion; VT, ventilatory threshold.

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included in the study. The medical regimens of all enrolled patients were optimized, and all patients were clinically stable. We excluded patients with non-cardiovascular causes of exercise limitation, primary valve disease, congenital heart disease, hypertrophic or restrictive cardiomyopathy, active myocarditis, acute coronary syndrome or acute heart failure decompensation within the previous month or for whom coronary revascularization or cardiac surgery was planned.

Each patient gave their informed consent before performing the first exercise test. The study was approved by the internal review board (Grands Prés Ethics Committee, number 2/77).

Patients at inclusion underwent Doppler echocardiography and measurement of plasma levels of hemoglobin, creatinine and B-type natriuretic peptide (BNP) and CPX parameters (performed before the first training session). The CPX test was repeated just after the completion of the ETP.

2.1. Doppler echocardiography

M-mode, 2-D images, and flow and tissue Doppler recordings were obtained for all patients with use of a Doppler transthoracic echocardiograph (GE Vivid 5 or 7, Horten, Norway). 2-D imaging was performed as usual in parasternal long- and short-axis views and apical 4- and 2-chamber views.

LV end-diastolic diameter was measured in the TM mode from the longitudinal long- or short-axis view. Doppler recordings were obtained in the apical 4-chamber view. The sample volume was positioned at the tips of the mitral leaflets to measure the transmitral pulsed Doppler velocity: E and A were the peak values reached in early diastole and after atrial contraction, respectively. The sample volume was positioned at the lateral mitral annulus (apical 4-chamber view) to measure tissue Doppler velocity Ea corresponding to early diastolic displacement and the mitral E/Ea ratio was calculated. LV systolic and diastolic volumes and LVEF were derived from biplane apical (2- and 4-chamber) views with a modified Simpson's rule algorithm [5]. Systolic pulmonary artery pressure was calculated from tricuspid or pulmonary insufficiency according to Bernoulli's law.

2.2. Cardiopulmonary exercise test

Exercise was performed on a bicycle with 10 W/min workload increments up to exhaustion (with a peak respiratory exchange ratio always >1.0) [6]. Respiratory gas analysis involved use of a CPX-D Medical Graphics system (St Paul, MN) or an Oxycon Pro Jaeger (San Diego, CA, USA). VO_2, CO_2 production (VCO_2) and ventilation (VE) were measured on a breath-by-breath basis. The percent predicted peak VO_2 (%PP VO_2) was calculated as peak VO_2 divided by maximal predicted peak VO_2 according to the values reported by Wasserman et al. [7]. The ventilatory threshold (VT) was measured by classical methods: the V-slope, the method using the ventilatory equivalents for O_2 and CO_2 and the one using the end-tidal pressures in O_2 and CO_2 [8,9]. If agreement between results from these methods was poor, the ventilatory equivalent method was favored. The VE/VCO_2 slope [10,11], which has been shown in recent years to have high prognostic value, was calculated by automatic linear regression fitting with the breath-by-breath values obtained during the entire exercise test from initiation to peak [12]. The peak circulatory power (CP) was defined as peak VO_2 × peak systolic blood pressure (SBP) and was expressed in ml/min/kg·mm Hg.

Exercise tests were performed the day before and the day after ETP completion by the same person and on the same machine.

2.3. Exercise training

Patients underwent 3 to 5 training sessions per week for 4 to 10 weeks in a cardiac rehabilitation center. Outpatients underwent the rehabilitation in a day-care hospital. Thus, they underwent 3 training sessions per week for 8 to 10 weeks. The other patients were hospitalized in the cardiac rehabilitation center (inpatients) and underwent more sessions (4 to 5 training sessions per week) for 4 weeks. The ETP program was an individualized program. The protocol stated that training on bicycle was to be performed at an intensity level (assessed by heart rate) corresponding to the ventilatory threshold determined at the initial CPX evaluation. After 5 min of warm-up, patients had to exercise for 20 min. The sessions were then followed by a 5-min cool-down period. Patients who achieved their assigned intensity level were allowed to progressively increase their work rate. Segmental training sessions with low weightlifting were systematically added to improve muscle strength [2]. For patients with more severe disease or who were cachectic, endurance training was started only after some days of resistance training. Blood pressure and heart rate were measured at rest, in the middle of the cycle ergometer session and 5 min after the end of each session, during the recovery time. Patients who underwent fewer than 8 sessions were excluded from the study.

2.4. Outcomes

Outcomes were assessed directly by contacting the patient, the family, or the patient's practitioner. With a 12-month follow-up starting after the first training session, the primary end-point was combined death + heart transplantation + hospitalization for acute heart failure, and the secondary one was death.

2.5. Statistical analysis

Normally distributed continuous data are presented as mean ± SD. Non-normally distributed continuous variables are presented as mean ± SD and as median and 25th–75th percentiles (plasma BNP level and number of exercise training sessions). Data were compared by Student *t* test or Mann–Whitney *U* test for non-normally distributed variables. Univariate analysis involved clinical, echocardiographic and especially ergometric variables obtained at baseline and after ETP completion as well as change in CPX data before and after ETP completion. Multivariate analysis consisted of Cox models, including the main clinical, echocardiographic and ergometric parameters after exclusion of collinear factors.

Receiver operating characteristic (ROC) curves (obtained by use of Medcalc v11.4.4.0) were constructed by plotting true-positive rates (sensitivity) against false-positive rates (1−specificity) to compare discriminatory accuracy for survival and event-free survival for peak VO_2, CP and VE/VCO_2 slope obtained before and after ETP completion. The ROC curves were compared with use of the z statistic [13].

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

3.1. Baseline characteristics of patients

We included 285 consecutive patients. The mean age was 55 ± 11 years, 79% were male, and 93% were in sinus rhythm. The etiology of the heart failure was ischemic in 49% of the cases; the mean LVEF was 29 ± 8%. Most of the patients received diuretics, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) and beta-blockers. Patient characteristics are summarized in Table 1.

3.2. Exercise training sessions

Patients underwent 19.4 ± 8.7 training sessions. No serious cardiac event occurred during the training program. The exercise capacity of trained patients improved significantly as indicated by increases in VT by + 13.3% (+1.6 ± 0.2 $ml \cdot kg^{-1} \cdot min^{-1}$, $p < 0.0001$) and in peak VO_2 by 14.2% (+2.4 ± 0.3 $ml \cdot kg^{-1} \cdot min^{-1}$, $p < 0.0001$). In the same way, O_2 pulse significantly increased after ETP completion (from 0.137 ± 0.045 to 0.156 ± 0.039 ml $O_2 \cdot kg^{-1} \cdot beat^{-1}$, $p < 0.0001$). Patients were able to achieve maximal or near-maximal exercise tests at both time points, as reflected by respiratory exchange ratio > 1.10 (1.10 ± 0.04 at test 1 vs 1.13 ± 0.03 at test 2, p = 0.3). Peak VO_2 improvement did not differ between inpatients and outpatients (2.7 ± 5.7 vs 1.9 ± 2.3 $ml \cdot kg^{-1} \cdot mn^{-1}$, p = 0.16).

Details of the evolution of CPX variables are summarized in Table 2.

3.3. Outcome

Within a 12-month follow-up, 35 patients had a cardiac event: 14 died, 6 underwent cardiac transplantation and 15 others were hospitalized for acute heart failure. Six patients were lost to follow-up. All deaths were related to a cardiac event.

Patients with a cardiac event were more often male, diabetic, in atrial fibrillation, had an ischemic etiology of the heart failure, and had low LVEF and high filling pressures (as attested by E/Ea) and BNP and creatinine plasma levels. They also had significantly lower exercise capacity, before and after rehabilitation, and had undergone slightly fewer training sessions than patients without a cardiac event (Tables 1 and 2).

As expected, cardiac event were more often in the inpatient group (n = 99) than in the outpatient group (n = 186), given that higher risk patients are usually managed as inpatients while less severe ones are usually managed as outpatients.

Table 1
Patient characteristics.

	All patients n = 285	No cardiac event n = 250	Cardiac event n = 35
Baseline characteristics			
Male, n (%)	225 (79)	195 (78)	30 (86)*
Age (y)	55 ± 11	54.7 ± 11.1	58.7 ± 14.7
Inpatients, n (%)	99 (35)	80 (32)	19 (55)†
Outpatients, n (%)	186 (65)	170 (68)	16 (46)
Ischemic etiology, n (%)	139 (49)	115 (46)	24 (66) *
Diabetes, n (%)	40 (14)	30 (12)	10 (33) *
Sinus rhythm, n (%)	265 (93)	237 (95)	28 (78) *
Implantable cardiac defibrillator	20 (7)	17 (7)	3 (11)
Cardiac resynchronization therapy	27 (9)	21 (9)	6 (17)
LVEF (%)	29 ± 8	30 ± 8	26 ± 6*
Systolic PAP (mm Hg)	37 ± 10	36 ± 9	41 ± 13*
Plasma BNP level (pg/ml)	593 ± 608	565 ± 605	732 ± 591
	361 (177–803)	316 (172–774)	669 (308–1155)*
Creatinine level (μM/l)	109 ± 35	106 ± 33	125 ± 46*
Hemoglobin level (g/dl)	13.0 ± 1.8	13.1 ± 1.8	12.8 ± 1.8
Treatment			
Loop diuretics, n (%)	231 (81)	200 (80)	31 (92)
ACE-I or ARB, n (%)	279 (98)	245 (98)	34 (95)
Beta-blockers, n (%)	268 (94)	237 (95)	31 (89)
Bisoprolol, n [dose (mg)]	199 (3.7 ± 2.0)	177 (3.7 ± 2.3)	22 (3.8 ± 3.0)
Carvedilol, n [dose (mg)]	54 (19 ± 15)	40 (18.9 ± 15.3)	11 (19.3 ± 15.6)
Spironolactone, n (%)	162 (57)	140 (56)	22 (62)
Statins, n (%)	116 (41)	100 (40)	16 (50)

Data are number (%) or mean ± SD for normally distributed continuous variables and median (25th–75th) for non-normally distributed variables (plasma BNP level).
LVEF: left ventricular ejection fraction, PAP: pulmonary arterial pressure, BNP: brain natriuretic protein, ACE-I: angiotensin converting enzyme inhibitors, ARB: angiotensin II receptor blocker.
* $p < 0.05$ comparing cardiac event vs. no cardiac event.
† $p < 0.05$ comparing inpatients vs outpatients.

3.4. Analysis of event-free survival

The CPX variables obtained before and after ETP completion (maximum SBP, maximum workload, VT, peak VO_2, $\%PPVO_2$, CP, and VE/VCO_2 slope) were significant predictors of outcome, as were changes in peak workload, peak VO_2, $\%PPVO_2$, peak CP and VT. Chi-square data strongly suggested that CPX data obtained after ETP completion had greater prognostic value (Table 3). The results remained unchanged even when considering only deaths (data not shown).

Univariate analysis revealed that the usual clinical data (New York Heart Association [NYHA] functional class, sinus rhythm, ischemic etiology, presence of diabetes), echocardiographic variables (LVEF, systolic pulmonary artery pressure, E/Ea ratio), and biological variables (baseline creatinine and plasma BNP levels) were significantly predictive of outcome: we did not show these data because the aim of this study was to compare the prognostic value of CPX data obtained before and after ETP completion and not to analyze the predictive factors for peak VO_2 improvement or for outcome.

Although the determination of the independent predictors of outcome was beyond the scope of this study, we performed a multivariate analysis (after exclusion of colinear factors) including main clinical, echocardiographic, VE/VCO2 slope at admission and change in peak VO_2 after ETP completion: only BNP level and E/Ea ratio at admission, and change in peak VO_2 after ETP completion were significant predictors of outcome (Table 4).

Finally, ROC curve analysis of VT, peak VO_2, $\%PPVO_2$, and peak CP confirmed the greater prognostic value of CPX variables obtained after ETP completion than those obtained at admission (Table 5 and Fig. 1). The results remained unchanged even when considering only deaths (Table 6, Fig. 2).

Table 2
Cardiopulmonary exercise (CPX) variables obtained before and after completion of an exercise training program (ETP).

CPX variables	All patients n = 285	No cardiac event n = 250	Cardiac event n = 35
Before ETP			
Workload 1 (watts)	83 ± 27	85 ± 28	69 ± 16*
Max HR 1	118 ± 23	120 ± 23	108 ± 22*
VT 1 ($ml \cdot kg^{-1} \cdot min^{-1}$)	12.0 ± 3.3	12.2 ± 33	10.9 ± 2.6*
Peak VO_2 1 ($ml \cdot kg^{-1} \cdot min^{-1}$)	16.2 ± 5.7	16.6 ± 5.8	13.7 ± 3.6*
$\%PPVO_2$ 1 (%)	56 ± 16	57 ± 16	48 ± 12*
CP 1 ($ml \cdot kg^{-1} \cdot min^{-1} \cdot mm$ Hg)	2166 ± 1024	2243 ± 1065	1685 ± 564*
VE/VCO_2 slope 1	37 ± 9	36 ± 9	42 ± 9*
After ETP completion			
Workload 2 (watts)	100 ± 35	103 ± 34	73 ± 22*
Max HR 2	120 ± 23	120 ± 23	109 ± 21*
VT 2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	13.6 ± 3.9	13.9 ± 3.9	11.6 ± 3.0*
Peak VO_2 2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	18.5 ± 5.6	19.1 ± 5.4	14.0 ± 3.5*
$\%PPVO_2$ 2 (%)	65 ± 20	67 ± 20	48 ± 13*
CP 2 ($ml \cdot kg^{-1} \cdot min^{-1} \cdot mm$ Hg)	2538 ± 1007	2665 ± 998	1673 ± 613*
VE/VCO_2 slope 2	35 ± 8	34 ± 7	40 ± 7*
Number of training sessions	19.4 ± 8.7	19.8 ± 8.7	17.2 ± 8.2
	20 (12–30)	20 (12–30)	14 (11–20)*

Data are number (%) or mean ± SD for normally distributed continuous variables and median (25th–75th) for non-normally distributed variables (number of training sessions).
Workloads 1 and 2: maximal workload obtained at admission and after ETP.
Max HR 1 and 2: maximal heart rate obtained at admission and after ETP.
VT 1 and 2: ventilatory threshold at admission and after ETP.
Peak VO_2 1 and 2: peak oxygen consumption at admission and after ETP.
$\%PPVO_2$ 1 and 2: % predicted peak oxygen consumption at admission and after ETP.
CP 1 and 2: circulatory power at admission and after ETP.
* $p < 0.05$ comparing cardiac event vs. no cardiac event.

4. Discussion

This study shows, for the first time, that CPX data obtained after cardiac rehabilitation in CHF patients have a stronger prognostic value for such patients than that obtained before the exercise program.

Exercise capacity has long been considered one of the most powerful prognostic factors in CHF patients, whatever the variable considered. It may have profound influence on CHF management and outcome, because, for example, the indication of medical strategies such as cardiac transplantation may be guided by objective assessment of exercise capacity, given the relative unreliability of the functional evaluation by

Table 3
Univariate analysis of CPX variables that predicted cardiac events in patients who underwent an ETP.

	Chi-square statistic	95% confidence interval	p value
Max SBP 1	5.7	0.98 (0.96–0.99)	0.002
Workload 1	8.6	0.97 (0.96–0.99)	0.002
VT 1	4.9	0.88 (0.79–0.99)	0.04
Peak VO_2 1	10.2	0.86 (0.78–0.95)	0.001
%PPVO_2 1	11.5	0.95 (0.92–0.95)	0.0007
VE/VCO_2 slope 1	9.3	1.04 (1.01–1.07)	0.002
CP 1	12	0.99 (0.99–1.00)	0.0007
Max SBP 2	25	0.97 (0.97–0.98)	<0.0001
Workload 2	22	0.97 (0.95–0.98)	<0.0001
VT2	10	0.82 (0.74–0.93)	0.001
Peak VO_2 2	28	0.78 (0.72–0.85)	<0.0001
%PPVO_2	40	0.94 (0.93–0.95)	<0.0001
VE/VCO_2 slope 2	12	1.06 (1.03–1.11)	0.0002
CP 2	35	0.99 (0.99–1.00)	<0.0001
Δ SBP	8	0.98 (0.96–0.99)	0.004
Δ workload	20	0.96 (0.95–0.99)	<0.0001
Δ VT	4.3	0.87 (0.77–0.98)	0.03
Δ peak VO_2	7	0.96 (0.93–0.99)	0.009
Δ %PP VO_2	6	0.96 (0.94–0.98)	0.01
Δ VE/VCO_2 slope 2	0.1	0.99 (0.93–1.05)	0.8
Δ CP	7.5	1.00 (1.00–1.00)	0.005
Number of training sessions	3.8	0.94 (0.89–1.01)	0.06

Max SBP 1 and 2: maximal systolic blood pressure at admission and after ETP.
VT 1 and 2: ventilatory threshold at admission and after ETP.
Peak $VO_2$1 and 2: peak oxygen consumption at admission and after ETP.
%PPVO_2 1 and 2: % predicted peak oxygen consumption at admission and after ETP.
CP 1 and 2: circulatory power at admission and after ETP.
VE/VCO_2 slopes 1 and 2: VE/VCO_2 slope at admission and after ETP completion.
Δ: change in exercise variables between admission and after ETP.

Table 5
Comparison of receiver operating characteristic (ROC) curves of cardiopulmonary exercise variables obtained before and after ETP considering death, heart transplantation and hospitalization for acute decompensated heart failure with 1-year follow-up.

	AUC	SE	95% CI	p value
%PPVO_2 2	0.790	0.0392	0.737–0.836	
%PP VO_2 1	0.662	0.0473	0.603–0.717	<0.0001
Peak VO_2 2	0.788	0.0386	0.735–0.834	
Peak VO_2 1	0.641	0.0473	0.582–0.697	<0.0001
CP 2	0.827	0.0380	0.774–0.872	
CP1	0.674	0.0485	0.612–0.732	<0.0001
VE/VCO_2 slope 2	0.704	0.0499	0.642–0.762	
VE/VCO_2 slope 1	0.709	0.0472	0.647–0.766	NS

AUC: area under the ROC curve, SE: standard error, 95% CI: 95% confidence interval.
Peak VO_2 1 and 2: peak oxygen consumption at admission and after ETP.
%PPVO_2 1 and 2: % predicted peak oxygen consumption at admission and after ETP.
CP 1 and 2: circulatory power at admission and after ETP.
VE/VCO_2 slopes 1 and 2: VE/VCO_2 at admission and after ETP completion.
NS: nonsignificant.

only the NYHA classification [14]. However, exercise capacity reflects the cardiopulmonary reserve only at a given time and may differ by patients' heart failure history.

The prognostic value of exercise capacity changing with time has been assessed in CHF: some studies have shown that increased peak VO_2 during a long follow-up is associated with improved outcome [15–18]. This observation can have some important implications: Stevenson et al. [15] assessed the prognostic value of improved exercise capacity with medical treatment. They followed severe CHF patients with peak $VO_2 < 14$ ml·kg^{-1}·min^{-1} who were referred for heart transplantation. Prognosis was good for patients with increased peak $VO_2 > 2$ ml·kg^{-1}·min^{-1} and peak $VO_2 > 12$ ml·kg^{-1}·min^{-1} on a second test performed 3 to 12 months later, and they could be safely withdrawn from a heart transplantation list. However, in this study, patients did not undergo formal rehabilitation or training; moreover, the study was undertaken before the era of modern and effective treatments such as beta-blockers, cardiac resynchronization therapy and implantable cardiac defibrillators. Furthermore, the two exercise test evaluations were separated by a long and non-uniform period of time (4 months to 3 years) and the time-related changes in exercise tolerance could be related to many factors such as medical treatment adaptations, spontaneous disease evolution, and exercise activity. Finally, the prognostic value of CPX data obtained before and after rehabilitation was not specifically assessed.

The prognostic value of exercise capacity improvement after ETP has been assessed in CAD patients. Vanhees et al. showed that the prognostic value of peak VO_2 was higher after than before rehabilitation, even after adjustment for age and other significant covariates. Every 1% increase in exercise capacity was associated with a 2% reduction in cardiovascular mortality [4]. However, this study did not include patients with significant LV dysfunction or heart failure; moreover, peripheral deconditioning, which may be markedly improved by training, is expected to be more important in CHF than in CAD [19]. Exercise training allows for the correction, in part, of most of the peripheral abnormalities [20,21] and tends to decrease neurohormonal stimulation [22] without deleterious effect on left ventricular remodeling [23]. Therefore, our study is the first to specifically assess the prognostic value of peak VO_2 changes after a formal, time-calibrated ETP in patients with CHF.

In daily life, the exercise capacity of CHF patients is assessed in very different conditions. Some patients undergo CPX evaluation a few weeks after hospitalization or after a long period of physical inactivity, and others undergo the same evaluation after performing a regular physical training program. For instance, a peak VO_2 of 11 or 12 ml·kg^{-1}·min^{-1} probably does not have the same meaning

Table 4
Multivariate analysis of CPX variables that predicted cardiac events in patients who underwent an ETP.

CPX variables	Chi-square statistic	p value
Age	3.6	0.06
Sinus rhythm	0.05	0.8
Plasma BNP level at admission	4.0	0.04
LVEF	0.3	0.6
Δ peak VO_2	15	<0.0001
VE/VCO2 slope at admission	1.8	0.18
E/Ea ratio at admission	1	0.01

LVEF: left ventricular ejection fraction.
Δ: change in peak VO_2 between admission and after ETP.

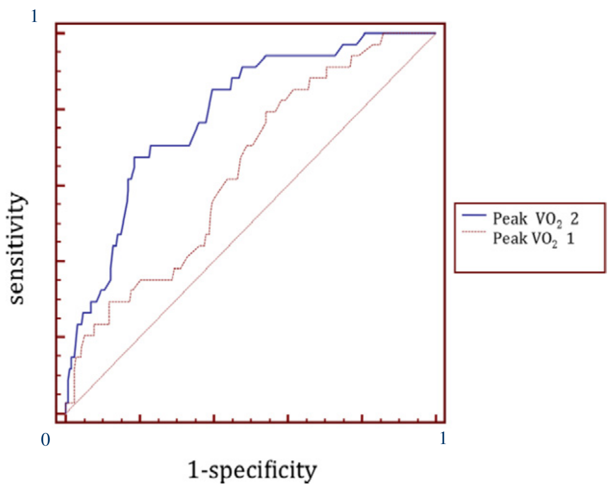

Fig. 1. Comparison of receiver operating characteristic (ROC) curves of the prognostic value of peak VO_2 obtained after (peak VO_2 2) versus before (peak VO_2 1) completion of an exercise training program (ETP) considering death, heart transplantation and hospitalization for acute heart failure, with 1-year follow-up.

Table 6
Comparison of ROC curves of cardiopulmonary exercise variables before and after ETP considering death with 1-year follow-up.

	AUC	SE	95% CI	p value
%PPVO$_2$ 2	0.810	0.0656	0.758–0.854	
%PPVO$_2$ 1	0.748	0.0643	0.693–0.798	0.03
Peak VO$_2$ 2	0.800	0.0719	0.749–0.845	
Peak VO$_2$ 1	0.732	0.0835	0.676–0.783	0.02
CP 2	0.817	0.0731	0.763–0.863	
CP 1	0.721	0.0872	0.661–0.776	0.04
VE/VCO$_2$ slope 2	0.706	0.0903	0.643–0.763	
VE/VCO$_2$ slope 1	0.698	0.0853	0.635–0.755	0.8

AUC: area under the ROC curve, SE: standard error, 95% CI: 95% confidence interval.
Peak VO$_2$ 1 and 2: peak oxygen consumption at admission and after ETP.
%PPVO$_2$ 1 and 2: % predicted peak oxygen consumption at admission and after ETP.
CP 1 and 2: circulatory power at admission and after ETP.
VE/VCO$_2$ slopes 1 and 2: VE/VCO$_2$ slope at admission and after ETP completion.

whether the patient is markedly deconditioned or not. The risk of neglecting this information is to propose aggressive intervention (cardiac transplantation, for example, based on a baseline peak VO$_2$ of 11 ml·kg^{-1}·min^{-1} that may increase to 14 ml·kg^{-1}·min^{-1} after rehabilitation, with a clearly better expected outcome).

We previously showed that in CHF patients, the lack of improvement in exercise capacity after a short supervised ETP has a strong prognostic value for cardiac events, independently of LVEF, NYHA status and BNP level [24]. Multivariate analysis confirmed the independent prognostic value of peak VO$_2$ changes after ETP completion.

Of note, for all variables (except VE/VCO$_2$ slope as we assessed it), the change in CPX values with a training program has significant prognostic value that, however, seems to remain lower than that after the final CPX test. Furthermore, while the prognostic values of peak VO$_2$ and VE/VCO$_2$ slope seem to be similar at baseline, our results indicate a better prognostic value for peak VO$_2$ than VE/VCO$_2$ slope after ETP completion. This is perhaps because ETP is associated with an important variation of peak VO$_2$ versus a minor modification of VE/VCO$_2$ slope. Finally, peak VO$_2$ improvement cannot be interpreted as a simply better exercise-test cooperation: peak VO$_2$ is a reproducible measurement in CHF, even in the absence of a preliminary test to familiarize the patient with the equipment [25]; furthermore, patients performed maximal exercise tests before and after ETP completion, as reflected by the absence of a significant difference between the 2 respiratory exchange ratios, with both values greater than 1.1.

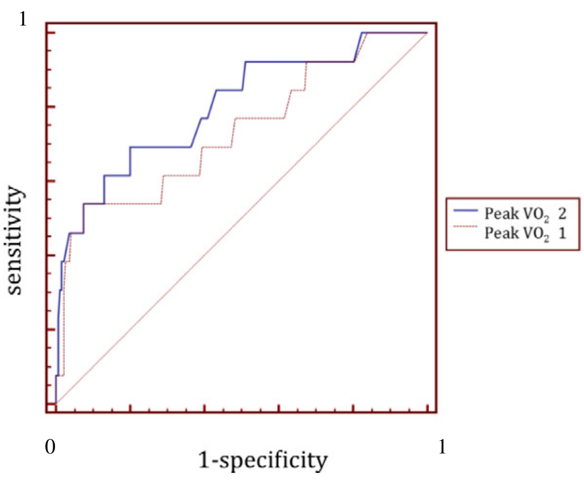

Fig. 2. Comparison of ROC curves of the prognostic value of peak VO$_2$ obtained after (peak VO$_2$ 2) versus before (peak VO$_2$ 1) ETP completion considering death with 1-year follow-up.

Given the important prognostic implications of exercise capacity for CHF patients and for treatment, all CHF patients should be provided an ETP, when possible, to better decide the therapeutic choices.

Our results can be explained by two main reasons:First, baseline exercise capacity assessment does not take into account the relative roles of limited cardiac or peripheral reserves during exercise: some patients may be deconditioned, others not. After training, most of the peripheral abnormalities, which play a major part in peak VO$_2$ value, should be ameliorated, if not corrected, and the peak exercise capacity should mainly reflect the cardiac response. We speculate that outcome is determined more by the cardiac than peripheral reserve during maximal exercise and may explain why the second assessment of exercise capacity, less affected by deconditioning, has more prognostic value.

Second, as shown previously [24], the lack of improvement in exercise capacity with ETP probably delineates patients with poor outcome.

5. Limitations

We included only CHF patients who were able to perform ETP. The average age of the patients was lower than that observed in most heart-failure drug trials [26,27] or surveys but is consistent with that in heart-failure exercise trials [28–30]. This study included a relative small number of patients in terms of the wide period of inclusion because, since we wanted to include only patients with stable disease, we excluded a large number of patients addressed in our rehabilitation centers less than one month after the last cardiovascular acute event.

In some patients, treatments were optimized during the ETP. So exercise capacity evolution may have been due in part to medical treatment change and not just the exercise training effect. However, in all heart-failure trials, medical treatment evolution is adapted relative to the patient's state at the practitioner's discretion.

6. Conclusions

In patients with stable CHF, the prognostic value of CPX data seems greater after than before completion of a hospital-based, moderate-intensity ETP. Therefore, in patients who can be trained, CPX assessment for prognostic purposes should be done after a rehabilitation program.

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