Cardiopulmonary exercise test predicts sustained ventricular arrhythmias in chronic heart failure

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Abstract

Background The cardiopulmonary exercise test (CPX) is an affordable tool for risk prediction in patients with chronic heart failure (CHF). We aimed to determine the role of CPX parameters in predicting the risk of incidence of sustained ventricular arrhythmias (SVA) in CHF.

Methods Sixty-one consecutive patients with CHF enrolled in the Daunia Heart Failure Registry underwent CPX and were followed for 327 ± 247 days. Clinical follow-up was performed every month and anticipated in case of re-hospitalisation for cardiac disease. Incidence of SVA was evaluated by direct clinical examination (ECG, ambulatory ECG).

Results Patients with episodes of SVA (N 14) showed lower values of pVO_2 and $PetCO_2$, and higher values of VE/VCO_2 , VE/VCO_2 slope, and $VE\%$. After correction for age, gender, diabetes, ischaemic heart disease and left ventricular ejection fraction, peak VO_2 (hazard ratio (HR) 0.68, 95 % confidence interval (CI) 0.51–0.91, $p < 0.05$), $VE\%$ (HR 1.38, 95 % CI 1.04–1.84, $p < 0.05$), VE/VCO_2 (HR 1.38, 95 % CI 1.04–1.82, $p < 0.05$), VE/VCO_2 slope (HR 1.77, 95 % CI 1.31–2.39, $p < 0.01$), $PetCO_2$ (HR 0.66, 95 % CI 0.50–0.88, $p < 0.01$) were found as predictors of SVA. At Kaplan-Meier analysis, lower event-free rates were found in subjects with peak VO_2 values below median (log rank $p < 0.05$), values of VE/VCO_2 above mean ($p < 0.05$), higher VE/VCO_2 slope tertiles ($p < 0.05$), and values of $PetCO_2$ below median ($p < 0.05$).

Conclusions CPX provides prognostic independent information for risk of SVA in subjects with CHF.

Keywords Chronic heart failure · Cardio-pulmonary exercise test · Ventricular arrhythmias

Introduction

The cardiopulmonary exercise test (CPX) is an established tool for clinical management of patients with chronic heart failure (CHF). Consensus statements on CHF have supported this method and its applications for quantifying functional capability, establishing the severity of CHF, evaluating therapy, prescribing exercise, and, most notably, stratifying risk [1–3]. CPX parameters were used as predictors of cardiac-related mortality and hospitalisation [4, 5].

Although sudden death based on malignant ventricular arrhythmias (VA) is responsible for a significant number of fatalities in subjects with CHF, the ability of CPX to identify patients at risk for sudden arrhythmic death is not well known. We therefore aimed to assess the value of CPX in predicting the incidence of sustained VA (SVA) (sustained ventricular tachycardia and ventricular fibrillation) in patients with CHF.

Methods

Sixty-one consecutive patients with CHF and left ventricular (LV) systolic dysfunction from the Daunia Heart Failure Registry [6] were enrolled in the study and evaluated with CPX.

All patients were required to be clinically stable for at least 1 month; patients were excluded if they had unstable angina, prior myocardial infarction within the last 3 months, severe valvular disease, severe obstructive or restrictive lung disease (FEV_1 and FVC < 60 % of predicted value), symptomatic

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peripheral vascular disease, or orthopaedic problems that limited exercise performance. Further exclusion criteria were evidence, both as history or actual signs or symptoms, of neurological diseases such as stroke, dementia, or any kind of cerebrovascular disease.

Medical history, heart rate, systolic blood pressure, body mass index, New York Heart Association (NYHA) class, and medications were recorded.

All patients underwent conventional 2D echocardiography and then CPX in order to evaluate exercise capacity (ramp and constant workload) in an ambulatory setting and under resting conditions and were then followed up for a mean of 327 ± 247 days. Clinical follow-up was performed every month; it was anticipated in case of re-hospitalisation for cardiac disease. Incidence of SVA (either sustained ventricular tachycardia, defined as a regular wide-complex tachycardia (≥ 120 ms), lasting >30 s or leading to a haemodynamic compromise, at a rate of >120 beats/min, or ventricular fibrillation) was evaluated in all patients by direct clinical examination (ECG or ambulatory ECG). An episode at home, with possible signs and symptoms of SVA, was only sufficient to define an event if documented by ECG.

All patients gave informed consent. The study was approved by the local ethics committee and was conducted according to the ethical standards for experiments in human subjects established by the Declaration of Helsinki.

Echocardiography

Conventional echocardiography was used to assess LV dimensions and LV ejection fraction (LVEF). Transthoracic echocardiography was performed with the use of iE33 (Philips Medical Systems, Andover, MA, USA). All echocardiographic studies were performed and interpreted by experienced physicians. LV dimensions and LVEF were calculated as recommendations in the joint ASE/ESC guidelines [7]. LVEF was calculated according to Simpson's rule. Pulsed Doppler mitral inflow velocities were obtained by placing a 1–2 mm sample volume between the tips of the mitral leaflets in the apical four-chamber view. The Doppler beam was aligned parallel to the direction of flow.

Cardiopulmonary exercise testing

Incremental CPX was performed on a cyclo-ergometer (Ergometrics Lode Medical Technology-Corival, Groningen, the Netherlands) using a ramp protocol that was personalised with the objective of each patient reaching maximum exercise within 8 to 10 min. After 60 s of unloaded pedalling at 60 rpm, work was continuously increased at a rate of 4 to 10 W/min starting at 0 W. In all cases, breath-by-breath expiratory gases and ventilation analysis were performed (Vmax Spectra 29S, Sensor

Medics, Yorba Linda, CA). Anaerobic threshold (AT) was measured with the V-slope analysis from the plot of VCO_2 vs. VO_2 on equal scales. The AT value was confirmed by ventilatory equivalents and end-tidal pressures of CO_2 and O_2 . If no agreement was obtained, the AT was considered not identified. The VO_2 /work rate relationship was evaluated throughout the entire exercise. The VE/VCO_2 slope was calculated as the slope of the linear relationship between VE and VCO_2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. Peak exercise ventilation as % of a predicted value (VE%) was also reported. ECG and heart rate were assessed continuously.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation, categorical variables were presented as percentages. Mean values were compared with Student's *t*-test for variables with a normal distribution or with the Mann–Whitney non-parametric *U* test for variables with a non-normal distribution. Percentages were compared with the χ^2 test. A logistic regression analysis was performed to identify predictors of SVA.

Univariate results were corrected in a multivariate analysis for age, gender, diabetes, ischaemic aetiology and LVEF. A second multivariate pooled analysis was performed including all significant predictors of SVA, age, gender, diabetes, ischaemic aetiology and LVEF for a direct comparison of univariate predictors.

Survival rates were assessed with log-rank test and reported on Kaplan–Meier plots. A $p < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics of patients are given in Table 1. During follow-up period, 14 patients (23 %) showed episodes of SVA (13 SV tachycardias, 1 ventricular fibrillation); significant differences with controls were detectable with regards to LVEF (24.7 ± 6.9 % vs 30.4 ± 6.2 %, $p < 0.01$), and LV end-systolic diameter (65.6 ± 13.0 mm vs 56.1 ± 8.2 mm, $p < 0.01$) (Table 1). Patients with episodes of SVA were characterised by lower values of peak VO_2 (11.10 ± 1.69 vs 13.20 ± 3.56 ml/Kg/min, $p < 0.05$) and PetCO_2 (32.2 ± 3.7 vs 36.0 ± 4.2 mmHg, $p < 0.01$) and higher values of VE/VCO_2 (37.7 ± 4.6 vs 34.4 ± 4.6 , $p < 0.05$), VE/VCO_2 slope (35.2 ± 8.4 vs 29.7 ± 4.1 , $p < 0.01$) and VE% (55.3 ± 26.6 vs 43.7 ± 12.4 , $p < 0.05$) (Table 1).

At logistic regression analysis, peak VO_2 (hazard ratio (HR) 0.68 95 % confidence interval (CI) 0.51–0.91, $p < 0.05$), VE% (HR 1.38 95 %-CI 1.04–1.84, $p < 0.05$), VE/VCO_2 (HR 1.38 95 %-CI 1.04–1.82, $p < 0.05$), VE/VCO_2 slope (HR 1.77,

Table 1 Patient characteristics

	All patients (N 61)		Ventricular arrhythmias (N 14)		Controls (N 47)		
	Mean	SD	Mean	SD	Mean	SD	P
Age	58	10	57	8	58	11	n.s.
Male	93 %		100 %		91 %		n.s.
CHD	43 %		43 %		43 %		n.s.
Hypertension	51 %		64 %		47 %		n.s.
COPD	42 %		64 %		35 %		n.s.
Diabetes	27 %		36 %		24 %		n.s.
CKD	21 %		14 %		24 %		n.s.
Creatinine	1.3	0.5	1.3	0.5	1.3	0.6	n.s.
BMI kg/m ²	30.2	4.2	32.6	2.7	29.5	4.3	<0.05
NYHA III	58 %		86 %		49 %		<0.05
LVEF	29.1	6.7	24.7	6.9	30.4	6.2	<0.01
LVEDD	67.4	10.7	76.9	14.1	64.6	7.6	<0.001
LVESD	58.1	10.1	65.6	13.0	56.1	8.3	<0.05
LAD	49.0	8.0	53.6	6.1	47.6	8.0	<0.05
ICD	41 %		79 %		30 %		<0.01
CRT	10 %		14 %		9 %		n.s.
Ventricular arrhythmias	23 %						
Statins	70 %		64 %		72 %		n.s.
ACE-i	65 %		64 %		65 %		n.s.
ARB	25 %		36 %		22 %		n.s.
BB	95 %		93 %		96 %		n.s.
BNP	292.6	539.0	649.4	906.2	130.4	121.5	n.s.
%VO ₂ max	51.9	16.0	54.0	15.1	51.3	16.3	n.s.
VO ₂ peak ml/kg/m	12.7	3.3	11.1	1.7	13.2	3.6	<0.05
AT L/min	0.8	0.3	0.8	0.2	0.8	0.3	n.s.
%AT	36.1	10.8	36.0	10.4	36.1	11.1	n.s.
VO ₂ /WR slope	10.8	1.7	11.2	1.6	10.7	1.8	n.s.
VO ₂ Work	12.5	12.5	11.2	1.6	12.9	14.2	n.s.
O ₂ pulse	9.7	2.7	10.5	2.1	9.5	2.9	n.s.
O ₂ pulse %	70.3	20.1	71.5	21.7	69.9	19.8	n.s.
HR max	111.3	22.7	103.9	24.0	113.6	22.0	n.s.
% HR max	69.5	13.7	64.6	15.0	71.0	13.2	n.s.
SP max	125.7	30.3	118.5	30.0	128.2	30.4	n.s.
DP max	82.2	15.4	80.0	18.7	83.0	14.3	n.s.
RER	1.1	0.1	1.0	0.1	1.1	0.1	n.s.
RER >1.05	0.5	0.5	0.4	0.5	0.6	0.5	n.s.
VE max	42.3	11.7	45.6	9.8	41.3	12.2	n.s.
% VE max	46.5	17.3	55.3	26.6	43.7	12.4	<0.05
Respiratory reserve (%)	53.8	16.7	52.8	10.5	54.0	18.1	n.s.
RR (B/min)	29.0	6.4	29.1	7.2	28.9	6.2	n.s.
VE/VO ₂	33.1	4.4	35.1	4.1	32.4	4.4	n.s.
VE/VCO ₂	35.2	4.6	37.7	4.6	34.4	4.3	<0.05
VE/VCO ₂ slope	31.1	6.0	35.3	8.4	29.7	4.1	<0.01
VE/VCO ₂ @AT	34.6	4.8	37.0	6.5	34.2	4.5	n.s.
PetCO ₂ @AT	36.9	4.0	34.8	5.9	37.3	3.6	n.s.
PetCO ₂	35.1	4.4	32.2	3.7	36.0	4.3	<0.01
PetO ₂	110.1	6.2	112.6	3.7	109.3	6.6	n.s.

Table 1 (continued)

	All patients (N 61)		Ventricular arrhythmias (N 14)		Controls (N 47)		P
	Mean	SD	Mean	SD	Mean	SD	
VD/VT rest	0.9	4.9	2.8	9.5	0.3	0.1	n.s.
VD/VT max	0.9	4.9	2.9	10.1	0.2	0.2	n.s.
SpO ₂ rest	97.7	2.2	97.9	3.4	97.6	1.7	n.s.
SpO ₂ max	97.3	2.2	97.1	3.1	97.4	1.8	n.s.
Watts	64.0	22.8	54.2	16.2	66.9	23.8	n.s.

ARB angiotensin receptor blocker, *BB* beta blocker, *BMI* body mass index, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *CRT* cardiac resynchronisation therapy, *LAD* left anterior descending artery, *LVEDD* left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter

95 %-CI 1.31–2.39, $p < 0.01$), and PetCO₂ (HR 0.66, 95 %-CI 0.50–0.88, $p < 0.01$) were predictors of incidence of SVA during follow-up, even after correction for age, gender, diabetes, ischaemic heart disease, and LVEF (Fig. 1).

In a pooled multivariable analysis model including peak VO₂, VE%, VE/VCO₂, VE/VCO₂ slope, PetCO₂, age, gender, diabetes, ischaemic heart disease, and LVEF; peak VO₂ and VE% were the only CPX-related independent predictors of SVA ($p < 0.01$ and $p < 0.05$ respectively).

Lower event-free rates at survival analysis were found in subjects with peak VO₂ values below median (log rank $p < 0.05$), values of VE/VCO₂ above mean (long rank $p < 0.05$), higher VE/VCO₂ slope tertiles (log rank $p < 0.05$), and values of PetCO₂ below median (log rank $p < 0.05$) (Fig. 2).

Comparing subjects with LVEF < 30 %, those with peak VO₂ < 12 mg/kg/min and those with both conditions, the combined use of echocardiographic and CPX parameters identified patients with higher rates of incidence of sudden

Fig. 1 Predictors of incidence of sustained ventricular arrhythmias at univariate logistic regression

Fig. 2 Event-free Kaplan-Meier survival curves for peak VO_2 , $\text{VE}\%$, VE/VCO_2 , VE/VCO_2 slope, PetCO_2

cardiac arrest during follow-up (Fig. 3, log rank $p < 0.01$) with a significantly higher predictive power (Fig. 4, 39 %, 36 %, 60 % respectively, $p < 0.05$).

Discussion

As shown in our study, CPX evaluation may stratify the risk of SVA in CHF. CPX is a clinical tool essential for follow-

up and risk stratification of patients with CHF. Maximal oxygen uptake (peak VO_2) achieved during CPX has been the most commonly used parameter in deciding on medical management and interventions, including transplantation [8]. The available consensus guidelines have focused on the application of specific cut-points for peak VO_2 in stratifying patients with CHF into low- and high-risk categories [9, 10]. A growing body of studies over the last decade has demonstrated that the minute ventilation/carbon dioxide

Fig. 3 Higher incidence of sustained ventricular arrhythmias in subjects with both left ventricular ejection fraction <30 % and VO₂ peak <12 mg/kg/min (log rank $p < 0.01$)

production (VE/VCO₂ slope), index of ventilatory inefficiency, more powerfully predicts mortality, hospitalisation, or both, than peak VO₂ in CHF patients [11]. Other expressions of ventilatory inefficiency associated with poor outcomes in CHF include the end-tidal carbon dioxide pressure (PetCO₂) at rest and during exercise [12].

In patients with CHF, the risk of sudden cardiac death increases with deteriorating LV function. Recommendations for the use of implantable cardioverter defibrillators (ICDs) for primary prevention of sudden cardiac death have been based upon the LVEF. Current guidelines recommend an ICD for heart failure (HF) patients with LVEF ≤ 35 % and NYHA functional class II or III; however, because the majority of HF patients who qualify for ICD implantation based on these criteria will not have an event requiring ICD therapy over several years of follow-up, additional methods of risk stratification for sudden death are clearly needed. To improve the identification of patients at risk for sudden

Fig. 4 Higher accuracy in predicting the incidence of sustained ventricular arrhythmias in subjects with both left ventricular ejection fraction <30 % and VO₂ peak <12 mg/kg/min ($p < 0.05$)

death, several criteria other than LVEF have been proposed and studied. Markers of autonomic tone, including heart rate turbulence and QT dynamicity, have shown some ability to predict total mortality but not arrhythmic events [13].

Although CPX has become an established tool in the management of patients with CHF and peak VO₂, VE/VCO₂ slope, PetCO₂ are used as predictors of cardiac-related mortality and hospitalisation, CPX parameters as predictors of SVA in patients with CHF have been rarely reported. We found that several CPX parameters may identify subjects with CHF and left ventricular systolic dysfunction at risk for SVA. These findings are even more evaluable considering the fact that most patients enrolled were on optimal medical treatment.

In a previous work, Arena et al. showed lower peak VO₂ and higher VE/VCO₂ slope in HF patients with arrhythmic death than controls. However, in this study, exercise oscillatory breathing was the strongest predictor of sudden cardiac death and a possible marker for prioritisation of antiarrhythmic strategies [14]. We have not documented differences in exercise oscillatory breathing between SVA and controls, probably because of the small size of the population.

Recently, Cale et al. evaluated the value of CPX parameters in predicting shocks and other arrhythmic events in HF patients with ICD, and identified a high-risk group for arrhythmias; during a minimum follow-up of 180 days, sustained VT was recorded in 38 % of patients. CPX showed that the group with appropriate shock had lower peak VO₂, AT and chronotropic reserve. Univariate analysis identified peak VO₂, AT, VE/VCO₂ slope, resting heart rate, heart rate decrease during the first minute of recovery, and systolic blood pressure during exercise as predictive of the composite endpoint (shock/ventricular fibrillation/sustained VT). Multivariate analysis identified resting heart rate and peak VO₂ as independent predictors, with HR 1.04 (95 % CI 1.00–1.09) and HR 0.88 (95 % CI 0.78–0.98) respectively [15].

Excess ventilation during exercise with accompanying dyspnoea is characteristic of CHF, and these patients often exhibit increased VE/VCO₂ compared with controls. The mechanism of excess ventilation in CHF patients during exercise is not completely understood. It may be related to enhanced output of chemoreceptors or peripheral muscle ergo receptors, increased dead space-tidal volume ratio due to increased contribution of high ventilation-perfusion lung regions or rapid shallow breathing, caused by earlier onset of lactic acidosis, or likely resulting from a combination of these causes [16].

Furthermore, Giannoni et al. showed that increased chemosensitivity to hypoxia and hypercapnia, particularly when combined, is associated with neurohormonal impairment,

worse ventilatory efficiency, Cheyne-Stokes respiration and a higher incidence of arrhythmias [17]; probably all these factors might play a central pathophysiological role in patients with HF and trigger Vas [18].

Corrà et al [8]. demonstrated that VE/VCO₂ slope was the strongest independent predictor of outcome in patients with intermediate peak VO₂ (between 10 and 18 mL/kg/min), and the best cutoff value was 35. Our data show that patients with CHF and episodes of SVA have higher values of VE/VCO₂ and VE/VCO₂ slope, even after multivariate analysis.

The decreased end-tidal PCO₂ during exercise, which is caused by high ventilation/perfusion ratio mismatching, reflects both reduced cardiac output response to exercise and increased exercise ventilation due to enlarged physiological dead space in advanced CHF [19].

Myers et al. demonstrated that reduced PetCO₂ reflects impairments in the functional, ventilatory, and cardiac performance response to exercise in patients with HF [12]. Arena showed, by univariate Cox regression analysis, that several expressions of peak VO₂, VE/VCO₂ relationship, and PetCO₂ were significant predictors of hospitalisation [20]. However, multivariate Cox regression analysis revealed that the VE/VCO₂ slope significantly predicted hospitalisation, but peak VO₂ and PetCO₂ did not provide additional predictive value. Also in our study, patients with episodes of SVA showed lower values of PetCO₂.

The main novelty of this study lies in the demonstration that CPX assessment may provide an additional prognostic stratification in prediction of SVA, beside well-established clinical tools such as LVEF. We showed that patients with impaired echocardiographic as well as CPX values may have a poorer prognosis and an incremental risk of future SVA.

The mechanisms by which a poor performance at CPX may lead to future SVA are not completely known. Subjects with increased exercise capacity, however, have less severe arrhythmia after controlled exercise training [21]. Peak VO₂ are related to left ventricular filling pressures [22] and ventricular stretch is well recognised as a trigger for VAs. According to some studies, impaired longitudinal and circumferential strains are associated with lower functional capacity and abnormal findings at ambulatory ECG monitoring [23]; peak oxygen consumption correlated with ventricular strain. Moreover, catecholamine levels are increased in subjects with a poorer performance at CPX [24]. There is a clear relationship between exercise intolerance and levels of neurohormonal factors and pro-inflammatory cytokines in patients with stable CHF [25]. Noradrenaline and brain natriuretic peptide levels were shown to rise in parallel with the degree of exercise intolerance. Therefore, there is evidence that a link exists between results at CPX and rhythm disturbances.

Limitations

The main limitation of the study is the small number of patients enrolled and low sensibility of ECG and ambulatory ECG in detecting incidence of SVA; these preliminary results need to be confirmed in larger cohorts of patients with more sensitive tools for the detection of SVA. The small number of arrhythmic events partially limits the significance of multivariable analysis. Further studies should evaluate the prognostic role of CPX in the prediction of SVA in subjects with LVEF >35 %.

Conclusion

CPX may independently predict incidence of SVA in subjects with CHF and LV systolic dysfunction.

Conflict of interest The authors have no conflict of interest to disclose.

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