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ORIGINAL ARTICLE
Exercise Physiology

Prognostic Value of Submaximal Cardiopulmonary Exercise Testing in Patients With Cardiac Amyloidosis

Robin Willixhofer, MD; Nikita Ermolaev, MD; Christina Kronberger, MD; Mahshid Eslami, MSc; Johannes Vilsmeier, MSc; René Rettl, MD, PhD; Christian Nitsche, MD, PhD; Andreas Kammerlander, MD, PhD; Jutta Bergler-Klein, MD; Johannes Kastner, MD; David Niederseer, MD, PhD, BSc; Roza Badr Eslam, MD

Background: This study assessed the prognostic value of submaximal cardiopulmonary exercise testing (CPET) in cardiac amyloidosis and explored CPET as an alternative to the 6-min walk test (6MWT).

Methods and Results: In this single-center prospective observational study, 160 patients with cardiac amyloidosis (87% male; mean age 78±7 years) were evaluated. A total of 145 performed maximum symptom limited CPET. The $\dot{V}E/\dot{V}CO_2$ slope was 39±8, submaximal power output (SPO) was 24.75±11.50 W, and $\dot{V}O_2$ at anaerobic threshold (AT) was 8.13±2.29 mL/min/kg. During follow up, 34 (21.25%) patients died, and another 34 (21.25%) experienced heart failure (HF)-related hospitalization, with 15 (9.38%) patients experiencing both events. Univariate analysis showed that $\dot{V}E/\dot{V}CO_2$ slope (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.86–0.93; P<0.001) and SPO (HR 0.91; 95% CI 0.87–0.96; P<0.001) were predictors of mortality. In multivariate analysis, $\dot{V}E/\dot{V}CO_2$ slope remained a significant predictor (HR 0.92; 95% CI 0.88–0.97; P<0.001) for both all-cause mortality and HF-related hospitalization independently. A SPO cut-off of <28 W predicted a worse outcome for both measures independently. Moderate correlations for $\dot{V}E/\dot{V}CO_2$ slope (−0.56 [CI −0.67, −0.42]) and SPO (0.55 [CI 0.42, 0.67]) with 6MWT distance have been found.

Conclusions: These findings highlight CPET parameters, particularly $\dot{V}E/\dot{V}CO_2$ slope and SPO with a cut-off <28 W, as predictors of survival and HF-related hospitalization in cardiac amyloidosis.

Key Words: Cardiac amyloidosis; Cardiomyopathy; Cardiopulmonary exercise testing

Cardiac amyloidosis (CA) is an infiltrative storage disease that is a characterized by the deposition of misfolded proteins within the extracellular space of the myocardium leading to a restrictive cardiomyopathy (CM).[1] There are different types of CA with transthyretin amyloidosis (ATTR) with both wild-type (ATTRwt) and variant (ATTRv) forms, as well as light chain amyloidosis (AL), being the most prevalent forms of the disease.[2] Patients diseased with either form are known to have a bad prognosis of 3.6 years for untreated ATTRwt, 2.6 years for ATTRv and <6 months for untreated AL.[3–6] The prognostication in those patients is often done via clinical staging tools that incorporate a multitude of cardiac biomarkers or parameters related to functional capacity.[4,5,7–9]

Being a restrictive CM, a disease hallmark is exertional dyspnea that worsens over the course of the disease, which may be caused due to the progressive stiffening and diastolic dysfunction of both ventricles leading to reduced cardiac output and a worsened ventilatory efficiency, potentially related to pulmonary hypertension in this collective.[10,11]

Ventilatory efficiency is best described as the relationship between minute ventilation ($\dot{V}E$) in liters per minute, being defined as breathing frequency multiplied by tidal volume and the elimination of carbon dioxide ($\dot{V}CO_2$) from the system.[12] Both variables are tightly regulated and have a multitude of proposed mechanisms of dysfunction that are yet not fully understood in this patient collective. As this is a relationship between measurable variables, a multitude of information can be gathered by close examination of

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Department of Internal Medicine II, Clinical Division of Cardiology (R.W., N.E., C.K., M.E., R.R., C.N., A.K., J.B.-K., J.K., R.B.E.), Institute for Medical Statistics (J.V.), Medical University of Vienna, Vienna, Austria; Hochgebirgsklinik Davos (D.N.), Christine Kühne Center for Allergy Research and Education (CK-CARE) (D.N.), Medicine Campus Davos, Davos; and Department of Cardiology, Center of Translational and Experimental Cardiology (CTEC), University Heart Center Zurich, University Hospital Zurich, University of Zurich, Zurich (D.N.), Switzerland

The first two authors contributed equally to this work (R.W., N.E.).

Mailing address: Roza Badr Eslam, MD, University Clinic of Internal Medicine II, Clinical Division of Cardiology, Währinger Gürtel 18-20, 1090 Vienna, Austria. email: roza.badreslam@meduniwien.ac.at

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patients using the gold-standardized assessment of exertional dyspnea via cardiopulmonary exercise testing (CPET). CPET can evaluate the degree of cardiopulmonary dysfunction, with defining predisposing limitations of either the heart, lungs or metabolic pathways. This differentiation of limitations allows the disease mechanisms influencing functional capacity to be highlighted.[12–14]

As a well-established prognostic CPET parameter, the $\dot{V}E/\dot{V}CO_2$ slope is related to 2 gradients within the same exercise test, the anaerobic threshold (AT) and the respiratory compensation point (RCP), depicting the full course of ventilatory efficiency. However, several authors describe the measurement of the $\dot{V}E/\dot{V}CO_2$ slope via different pathways ranging from the evaluation of the slope until the AT up to the evaluation of the full slope, with all methods allowing valuable information about patient's ventilatory efficiency, although there is still no consensus regarding the correct measurement, as different methods of measurement lead to slightly different results.[15]

Besides the $\dot{V}E/\dot{V}CO_2$ slope, oxygen uptake ($\dot{V}O_2$) at peak exercise has been shown to be prognostic in patients with CA. However, because values of $\dot{V}E/\dot{V}CO_2$ slope might be measured differently and peak values for $\dot{V}O_2$ are only applicable in symptom-limited maximum exertion and/or objective cut-offs for individual peak performance, these variables might be of limited significance in patients not fulfilling maximum test criteria. Therefore, there is a need to evaluate the prognostic capacity of CPET parameters during submaximal exercise testing, which has previously been shown to be of significance in patients with heart failure (HF).[16–20]

Therefore, we aimed to test whether submaximal CPET-derived parameters enable prognostication in patients with CA. Additionally, as a secondary objective, we wanted to test whether submaximal CPET can be used interchangeably with the 6-min walk test (6MWT) in this patient collective in order to have a wider array of options if patients are not capable of performing a 6MWT, and cycling exercise might be easier than walking fast paced.

Methods

In this single-center prospective observational study, we evaluated 160 patients who presented to the CA outpatient clinic at the Clinical Division of Cardiology at the Medical University of Vienna.

Ethical Considerations

This study was conducted in the frame of a single-center clinical registry (EK 1918/2019), and was approved by the local ethics committee at the Medical University of Vienna. The study protocol and procedures complied with the principles outlined in the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines. Prior to study enrollment, all patients gave written informed consent and were informed that they could withdraw consent at any time during the study duration.

Study Design

Patients included in this study needed to be aged ≥18 years and have a fixed diagnosis of CA (either ATTR, AL or mixed phenotypes), depicted using standardized diagnostic algorithms. Diagnosis of CA was done non-invasively in 145 patients via positive bone scintigraphy or cardiac magnetic resonance imaging, and invasively in 15 patients using endomyocardial biopsy. Patients needed to be willing to perform a symptom-limited maximum exercise test and follow study related instructions.

Patients underwent structured anamnesis, blood testing and functional capacity assessment via the 6MWT followed by CPET, with ample rest time in between tests. Patients were treated with best medical therapy (BMT) but naïve to disease-specific therapy (DST). The 6MWT was conducted in close proximity to the outpatient clinic to reduce pretest exertion. The tests were done according to proposed test procedures.[21]

At CPET, patient demographics (age, weight, height, relative and absolute contraindications for the test procedure) were recorded, followed by proper fitting of the patient to a cycle ergometer (Ergometer E-Bike REF 2017911-007). The tests were performed using incremental work rate protocols with step protocols characterized by gradual work rate increase each minute of exercise with an aimed duration of 10 min. The step protocols were fitted to the individual patients via assessment of subjective daily physical activity and the results of the 6MWT. All tests were performed as standard.[22]

Ventilation parameters and gas exchange variables were recorded breath by breath using a face mask (Dual-Monitor Vyntus CPX SN 42600071, Carl Reiner, Austria). Vital parameters, including electrocardiogram and heart rate, were monitored continuously, with blood pressure measured every 2 min (using GE CAM USB CardioSoft 12-channel-PC-ECG). Measurements were taken for up to 2 min at rest, during exercise, and up to 3 min during recovery. Gas exchange values were reported as averages of the first 30 s and last 30 s of each minute. The AT was determined through V-slope analysis of $\dot{V}O_2$ and $\dot{V}CO_2$, as well as trends in $\dot{V}E$ vs. $\dot{V}O_2$ and CO_2, and end-tidal pressures of O_2 and CO_2. Evaluated point of measurement CPET variables ($\dot{V}O_2$, O_2 pulse) and submaximal power output as wattage at the AT were analyzed at the AT to evaluate submaximal effort. The $\dot{V}E/\dot{V}CO_2$ slope was calculated using a regression line with best fit to the relationship between $\dot{V}E$ and $\dot{V}CO_2$ from steady state exercise until the AT.[15]

Outcome Assessment

Study procedures were followed by long-term assessment of all-cause mortality and HF-related hospitalization via regular patient interaction in the outpatient clinic, as well as regular review of digital patient records within our clinical administrative system by manual review of clinical documents.

Statistical Analysis

All analyses were conducted using R (version 4.4.0). Metric variables are summarized using the number of valid (i.e., non-missing) observations, mean, median, standard deviation, first and third quartiles and interquartile range, as well as minimum and maximum. Categorical variables are summarized using the number of valid observations, as well as counts and percentages of categories.

For the primary objective, we fitted univariate proportional hazards model for each of the following covariates: O_2 pulse at AT, $\dot{V}E/\dot{V}ECO_2$ slope, $\dot{V}O_2$/kg at AT, SPO and 6MWT. In addition to these univariate models, we also fitted a multivariate proportional hazards model that included the CPET covariates simultaneously. We used Akaike's information criterion (AIC) and the concordance

Table 1. Baseline Demographic and Clinical Characteristics of Patients With CA (n=160)

Characteristic	Patients with CA
Sex, male	139 (87)
Age at study entry (years)	78±7
Body mass index (kg/m^2)	26±4
Systolic blood pressure at rest (mmHg)	132 [120–140]
Diastolic blood pressure at rest (mmHg)	80 [70–88]
Non-sinus rhythm	72 (45)
6-min walk distance (m)	396±119
Borg rating of perceived exertion (scale)	4±2
NYHA functional class (class)	2 [2–2]
Class I	34 (21)
Class II	76 (48)
Class III	33 (21)
NYHA class unknown	17 (11)
Leg edema	36 (23)
Stable angina pectoris	8 (5)
NT-proBNP (ng/L)	2,548 [1,347–4,580]
HsTnT (ng/L)*	64±63
Diagnosis of CA	
ATTRwt	128 (80)
ATTRv	10 (6)
ATTR without genotyping*	15 (9)
ATTR combined with AL	7 (4)
Comorbidities	
Chronic obstructive pulmonary disease	18 (11)
Coronary artery disease	58 (36)
Peripheral artery disease	4 (3)
History of myocardial infarction	14 (9)
History of stroke	10 (6)
History of carcinoma	33 (21)
Type 2 diabetes	27 (17)
Hyperlipidaemia	93 (58)
Spinal canal stenosis	10 (6)
Carpal tunnel syndrome	66 (41)
Polyneuropathy	69 (43)
ATTR-CM specific parameters at baseline	
Perugini grading scale (grading)	3 [2–3]
Unknown grading	2 (1)
0	0 (0)
1	0 (0)
2	39 (24)
3	88 (55)
Cardiac magnetic resonance imaging	16 (10)
Endomyocardial biopsy	15 (9)
Transthoracic echocardiography parameters at baseline	
LV diameter (mm)	42 [38–48]
Right ventricular diameter (mm)	34 [30–38]
Left atrial diameter (mm)	62 [57–66]
Right atrial diameter (mm)	60 [55–66]
Left atrial volume (mL)	90 [66–117]
Right atrial volume (mL)	66 [50–94]
LV end diastolic volume (mL)	75 [61–91]
LV ejection fraction (%)	51 [44–60]
LV global longitudinal strain (%)*	−12 [−16, −10]
Presence of apical sparing	74 (46)
Intraventricular septum diameter (mm)	19 [16–23]
Systolic pulmonary pressure (mmHg)*	48 [37–57]
Aortic valve stenosis	18 (11)
Medical/device therapy potentially influencing CPET evaluations at baseline	
Antiplatelet	32 (20)
Anticoagulation	95 (59)
Lipid drugs	85 (53)
Loop diuretics	88 (55)
Mineralocorticoid receptor antagonist	74 (46)
Antihypertensive	123 (77)
β-blocker	82 (51)
ACE inhibitor	33 (21)
AT2 blocker	47 (29)
Calcium channel blocker	20 (13)
Nitrates	1 (1)
Diabetic medication	30 (19)
Thereof SGLT2 inhibition	20 (13)
Antiarrhythmic drug	16 (10)
Intracardiac device, yes	23 (14)

*<50% of patient data available. Continuous variables are presented as median [IQR], or mean±SD, while categorical variables are shown as n (%). ACE, angiotensin-converting enzyme; AL, amyloidosis; AT2, angiotensin II; ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CA, cardiac amyloidosis; CM, cardiomyopathy; CPET, cardiopulmonary exercise testing; HsTnT, highly sensitive troponin T; LV, left ventricular; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2.

(**Table 1** continued the next column.)

index (C-Index) to compare the models. For the secondary objectives, we fitted both univariate linear models, with performance on the 6MWT as the response variable and each CPET measurement as a covariate, as well as a multivariate model that included all CPET variables simultaneously. The (adjusted) R^2 values from these models were used to evaluate the predictive ability of CPET measurements for 6MWT performance. In addition, cut-offs for dichotomizing $\dot{V}E/\dot{V}CO_2$ slope and SPO were determined by maximizing the C-Index over a grid of values covering the respective ranges of these covariates using the CatPredi package (Irantzu Barrio and Maria Xose Rodriguez-Alvarez 2022).

Results

We evaluated 160 patients, of whom 128 (80%) were diseased with ATTRwt, 10 (6%) with ATTRv, 15 (9%) ATTR patients did not consent to genotyping, and 7 (4%) patients had a mixed phenotype of ATTR and AL-CM. Patients were predominately male (87%), had a mean age of 78 (±7) years, N-terminal B-type natriuretic peptide levels of 2,548 (1,347–4,580) ng/L, a 6MWT distance of 396 (±119) m and a Borg rating of perceived exertion

(BORG) of 4 (±2) at the time of study entry. Patients presented predominantly with New York Heart Association (NYHA) functional classification II (48%), alongside leg edema (23%) and stable angina pectoris (5%) symptoms.

Comorbidities were prevalent among patients, with 36% having coronary artery disease, 21% with a history of carcinoma, 11% with a chronic obstructive pulmonary disease, and 17% had type 2 diabetes. CA-specific comorbidities included polyneuropathy (43%), carpal tunnel syndrome (41%), and spinal canal stenosis (6%).

Further patient characteristics, including best medical treatment and echocardiography results, are shown in **Table 1**.

CPET

Of the 160 patients enrolled in the study who underwent basic assessment, 145 were able to perform symptom-limited maximum CPET.

Following determination of the AT in the 145 examinations, submaximal CPET parameters at the AT showed a SPO of 24.75 (±11.50) W, $\dot{V}O_2$ of 8.13 (±2.29) mL/min/kg, an O_2 pulse of 7.29 (±2.41) mL/beat and a $\dot{V}E/\dot{V}CO_2$ slope of 39 (±8). The respiratory exchange quotient (RQ) was 0.82 (±0.08), indicating submaximal exercise. More results of submaximal CPET, including rest values, are shown in **Table 2**.

Table 2. CPET Parameters at Rest and AT in Patients With CA (n=145)

CPET parameter (n=145)	Mean ± SD
Work capacity at AT (W)	24.75±11.50
Resting heart rate (beats/min)	74±14
Resting RQ (value)	0.82±0.07
RQ at AT (value)	0.82±0.08
Resting $\dot{V}O_2$ (mL/min)	380±142
$\dot{V}O_2$ at AT (mL/min)	620±188
$\dot{V}O_2$/kg at AT (mL/min/kg)	8.13±2.29
Resting $\dot{V}CO_2$ (mL/min)	313±123
$\dot{V}CO_2$ at AT (mL/min)	504±147
Resting $\dot{V}E$ (L/min)	15±5
$\dot{V}E$ at AT (L/min)	22±6
Resting O_2 pulse (mL O_2/beat)	5.08±1.82
O_2 pulse at AT (mL O_2/beat)	7.29±2.41
Resting $PetCO_2$ (mmHg)	27.54±3.12
$PetCO_2$ at AT (mmHg)	29.48±3.84
$\dot{V}E/\dot{V}CO_2$ slope (value)	39±8

Continuous variables are presented as mean ± SD. AT, anaerobic threshold; $PetCO_2$, end-tidal carbon dioxide partial pressure; RQ, respiratory exchange quotient; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}O_2$, oxygen consumption; $\dot{V}E$, minute ventilation; $\dot{V}E/\dot{V}CO_2$ slope, ratio between minute ventilation and carbon dioxide production. Other abbreviations as in Table 1.

Predictors of Survival

During the follow-up period, 34 (21.25%) patients died and 34 (21.25%) had a HF-related hospitalization. Of all patients with events, 15 (9.38%) experienced both outcomes.

The results of univariate and multivariate Cox proportional hazards models evaluating the association between CPET parameters and all-cause mortality are summarized in **Table 3**. Each CPET variable (O_2 pulse at AT, $\dot{V}E/\dot{V}CO_2$ slope, $\dot{V}O_2$/kg at AT, and SPO) and the distance covered during the 6MWT were significant predictors of survival in the univariate analysis. Of note, the estimates for the $\dot{V}E/\dot{V}CO_2$ slope were recorded such that the hazard ratio estimate corresponds to the effect of a decrease in the $\dot{V}E/\dot{V}CO_2$ slope, showcasing an inverted relationship between survival and the parameter. Furthermore, in the multivariate model, which included all CPET variables simultaneously, $\dot{V}E/\dot{V}CO_2$ slope remained a statistically highly significant predictor of all-cause mortality while SPO remained at least borderline significant.

The Kaplan-Meier survival curves with statistically significant log-rank tests for subgroups (as shown in **Figures 1** and **2**) of the walked distance during the 6MWT with a cut-off at 350 m and a $\dot{V}E/\dot{V}CO_2$ slope cut-off at 40 confirmed the significant associations between these variables and survival, with both being particularly strong predictors (P<0.001). Additionally, these variables were also strong predictors of HF-related hospitalization, as indicated by the univariate analysis. A lower $\dot{V}E/\dot{V}CO_2$ slope and a greater 6MWT distance were associated with reduced hospitalization risk (P<0.001 and P=0.009, respectively), as shown in **Table 4**. Multivariate analysis further demonstrated that the $\dot{V}E/\dot{V}CO_2$ slope remained a significant predictor, even after adjusting for other CPET variables (P=0.02).

On top of that, the Kaplan-Meier survival curve stratified by dichotomized SPO (**Figure 3**), with a cut-off <28 W (determined based on the ability to maximize the C-Index) showed significant associations with survival outcomes (log-rank test P<0.001), although not statistically significant in multivariate analysis (P=0.054). The cut-off remained non-significant for time to HF-related hospitalization in multivariate analysis, but had a significant log-rank test (P=0.012).

Submaximal CPET Parameters Predicting the 6MWT Distance

Each evaluated submaximal CPET parameter was significantly associated with the distance covered in the 6MWT when considered independently (P<0.001 for all). In the multivariate model, which included all CPET variables, SPO and $\dot{V}E/\dot{V}CO_2$ slope were the strongest predictors of the 6MWT distance, with statistically significant coefficients (P=0.001 and P<0.001, respectively). This model (all measured CPET variables) explained 42% of the variance in 6MWT distance (R^2=0.42) as seen in **Table 5**. The scatterplots provided in the **Supplementary Figure** illustrate the relationships between each evaluated CPET parameter and the 6MWT distance, with superimposed least-squares regression lines revealing weak to moderate correlations, as reflected in the Pearson correlation coefficients, with $\dot{V}E/\dot{V}CO_2$ slope and SPO being moderately associated with coefficients of −0.56 (CI −0.67, −0.42) and 0.55 (CI 0.42, 0.67) respectively. Importantly, the negative correlation observed between $\dot{V}E/\dot{V}CO_2$ slope and the 6MWT distance suggests that an increase in $\dot{V}E/\dot{V}CO_2$ slope, which indicates poorer ventilatory efficiency, is associated with a decrease in the patient's submaximal exercise capacity as measured using the 6MWT.

Discussion

The present study reinforces the importance of CPET parameters in prognostication and assessment of submax-

Table 3. Univariate and Multivariate Cox Proportional Hazards Models for Submaximal Exercise Testing Parameters in Patients With Cardiac Amyloidosis: Predicting All-Cause Mortality

Covariate	HR (95% CI)	SE	z	P value	AIC	C-Index (95% CI)
Univariate						
6MWT (m)						
Unstandardized	0.99 (0.99, 1)	0.00	−3.73	<0.001	189.41	0.7 (0.59, 0.82)
Standardized	0.45 (0.29, 0.68)	0.22				
O_2 pulse at AT (mL O_2/beat)						
Unstandardized	0.77 (0.65, 0.92)	0.09	−2.99	0.003	261.38	0.7 (0.62, 0.78)
Standardized	0.54 (0.36, 0.81)	0.21				
$\dot{V}E/\dot{V}CO_2$ slope						
Unstandardized	0.89 (0.86, 0,93)	0.02	−5.07	<0.001	249.33	0.75 (0.66, 0.83)
Standardized	0.38 (0.27, 0.56)	0.19				
$\dot{V}O_2$/kg at AT						
Unstandardized	0.68 (0.54, 0.85)	0.11	−3.37	<0.001	258.82	0.71 (0.61, 0.79)
Standardized	0.41 (0.25, 0.69)	0.26				
SPO						
Unstandardized	0.91 (0.87, 0.96)	0.02	−3.81	<0.001	253.69	0.76 (0.68, 0.82)
Standardized	0.35 (0.2, 0.6)	0.28				
Multivariate						
O_2 pulse at AT (mL O_2/beat)						
Unstandardized	0.95 (0.76, 1.18)	0.11	−0.49	0.622	243.65	0.8 (0.74, 0.88)
Standardized	0.88 (0.52, 1.48)	0.27				
$\dot{V}E/\dot{V}CO_2$ slope						
Unstandardized	0.92 (0.88, 0.97)	0.02	−3.44	<0.001		
Standardized	0.5 (0.34, 0.74)	0.20				
$\dot{V}O_2$/kg at AT						
Unstandardized	0.92 (0.69, 1.23)	0.15	−0.55	0.579		
Standardized	0.83 (0.43, 1.6)	0.33				
SPO						
Unstandardized	0.95 (0.89, 1)	0.03	−1.93	0.054		
Standardized	0.53 (0.28, 1.01)	0.33				

Hazard ratios (HR) with 95% confidence intervals (CI), standard errors (SE), z-statistics, P values, Akaike information criterion (AIC), and concordance index (C-Index) are provided for each parameter, including the 6-min walk test (6MWT), oxygen pulse at anaerobic threshold (O_2 pulse at AT), minute ventilation to carbon dioxide output ratio ($\dot{V}E/\dot{V}CO_2$ slope), oxygen consumption per kilogram at anaerobic threshold ($\dot{V}O_2$/kg at AT), and submaximal power output (SPO).

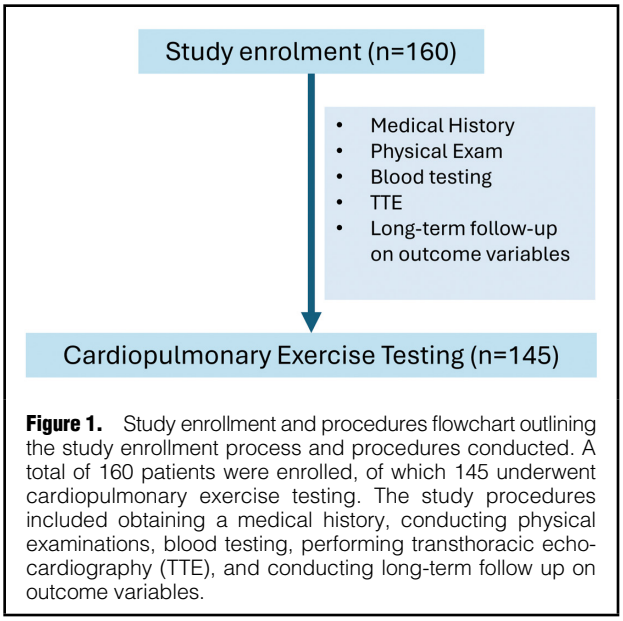

Figure 1. Study enrollment and procedures flowchart outlining the study enrollment process and procedures conducted. A total of 160 patients were enrolled, of which 145 underwent cardiopulmonary exercise testing. The study procedures included obtaining a medical history, conducting physical examinations, blood testing, performing transthoracic echocardiography (TTE), and conducting long-term follow up on outcome variables.

imal exercise capacity in patients with CA. Our findings demonstrate that the $\dot{V}E/\dot{V}CO_2$ slope, along with SPO, might play a crucial role in predicting outcomes in patients with CA. Furthermore, the association between submaximal CPET parameters and the 6MWT might allow evaluation of the submaximal functional capacity in more detail utilizing CPET.

$\dot{V}E/\dot{V}CO_2$ Slope

The $\dot{V}E/\dot{V}CO_2$ slope, which reflects ventilatory efficiency, demonstrated the strongest association with survival and time to HF-related hospitalization, where a lower slope was associated with improved outcomes. The prognostic value of the $\dot{V}E/\dot{V}CO_2$ slope has been described previously,[18,19] but only for the combined endpoints of both HF-related hospitalization and all-cause mortality; in our cohort, it is the first time it has been shown predictive for HF-related hospitalizations alone.

Our Kaplan-Meier survival curves evaluated the prognostic significance of the $\dot{V}E/\dot{V}CO_2$ slope and 6MWT distance for previously suggested subgroups stratified by these parameters.[18,23] Patients with a $\dot{V}E/\dot{V}CO_2$ slope >40 or a

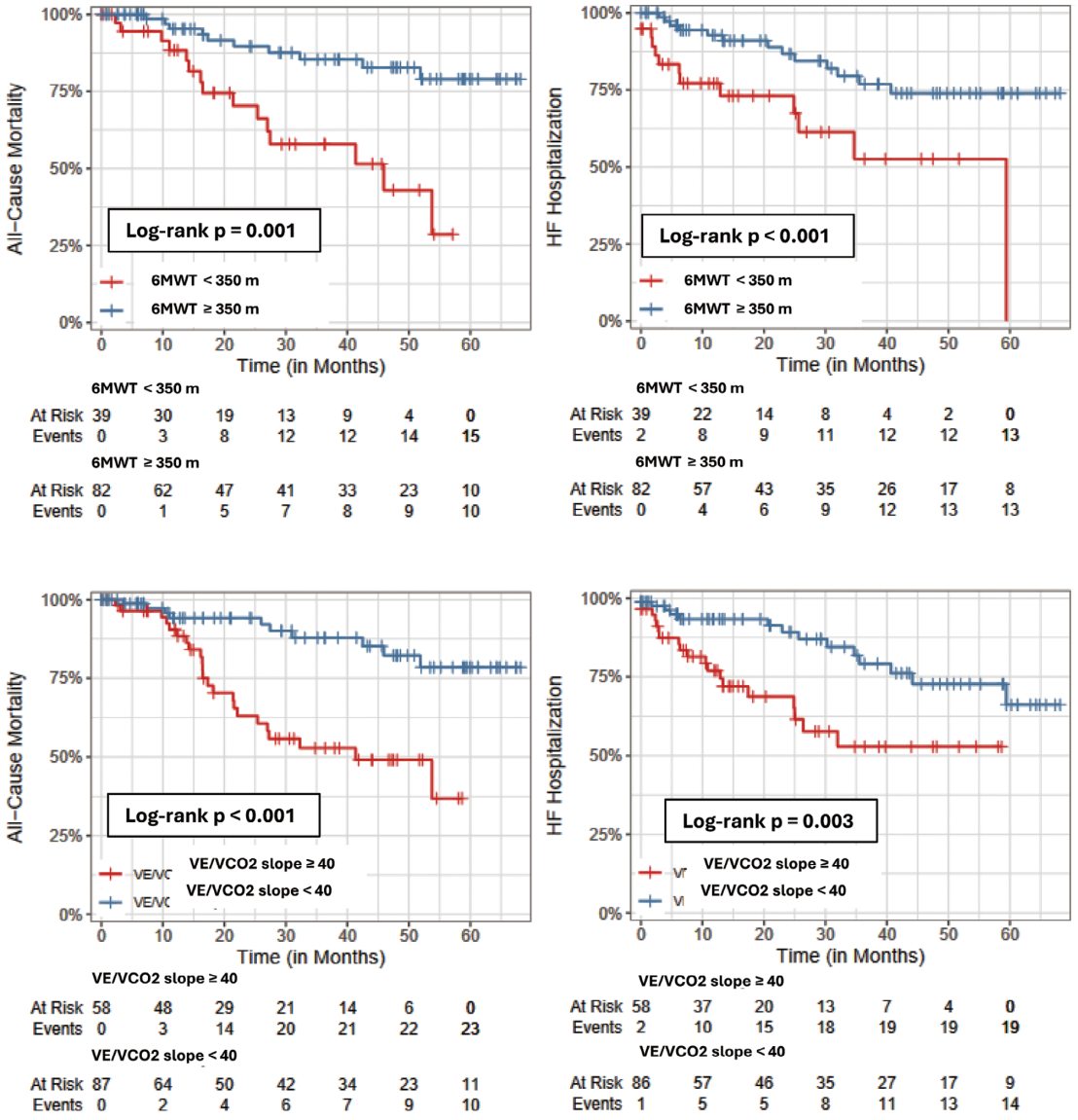

Figure 2. Kaplan-Meier analysis of all-cause mortality and heart failure (HF)-related hospitalization stratified by ventilatory efficiency slope ($\dot{V}E/\dot{V}CO_2$ slope) and 6-min walk test (6MWT) distance. Patients with a $\dot{V}E/\dot{V}CO_2$ slope ≥40 or a 6MWT distance <350 m exhibited significantly worse outcomes. The log-rank P values indicate the statistical significance of these differences.

6MWT distance <350 m exhibited significantly poorer survival outcomes and shorter time to HF-related hospitalization in our cohort, repeatedly highlighting the potential of these cut-offs to stratify risk in clinical settings in patients with CA.

Although the prognostic capability and cut-offs for the $\dot{V}E/\dot{V}CO_2$ slope have been proposed for patients with CA, conflicting evidence highlights the need to revisit the prognostic capacity of this parameter.[24] Our findings strengthen the prognostic capability of the $\dot{V}E/\dot{V}CO_2$ slope in that patient collective, further highlighting that the disease-specific exercise limitation is indeed of prognostic significance.[25]

In fact, patients with CA exhibit distinct exercise limitations compared with those with non-CA HF, including higher ventilatory inefficiency (elevated $\dot{V}E/\dot{V}CO_2$ slope) and an earlier AT. These differences might be driven by severe diastolic dysfunction and reduced cardiac output caused by amyloid infiltration, further characterized by impaired right ventricular-pulmonary artery coupling.[25–27]

Moreover, the $\dot{V}E/\dot{V}CO_2$ slope might be of relevance for treatment decision pathways, rendering it as a potential key parameter in the optimization of fluid management. It has been shown that a $\dot{V}E/\dot{V}CO_2$ slope increase is related to volume overload,[28,29] which is common in patients with CA. Therefore, it might be necessary to monitor the $\dot{V}E/\dot{V}CO_2$ slope in patient follow ups to identify subclinical volume overload and the beginning of pleural or pericardial effusion.[30]

Table 4. Univariate and Multivariate Cox Proportional Hazards Models for Submaximal Exercise Testing Parameters in Patients With Cardiac Amyloidosis: Predicting Heart Failure-Related Hospitalization

Covariate	HR (95% CI)	SE	z	P value	AIC	C-Index (95% CI)
Univariate						
6MWT (m)						
Unstandardized	1 (0.99, 1)	0.00	−2.61	0.009	251.23	0.65 (0.53, 0.76)
Standardized	0.62 (0.43, 0.89)	0.18				
O_2 pulse at AT (mL O_2/beat)						
Unstandardized	0.85 (0.72, 1)	0.08	−2.00	0.045	264.90	0.64 (0.51, 0.74)
Standardized	0.68 (0.46, 0.99)	0.20				
$\dot{V}E/\dot{V}CO_2$ slope						
Unstandardized	0.92 (0.89, 0,96)	0.02	−3.71	<0.001	275.50	0.69 (0.59, 0.79)
Standardized	0.52 (0.36, 0.73)	0.18				
$\dot{V}O_2$/kg at AT						
Unstandardized	0.7 (0.56, 0.88)	0.11	−3.15	0.002	267.13	0.71 (0.58, 0.8)
Standardized	0.45 (0.27, 0.74)	0.26				
SPO						
Unstandardized	0.96 (0.92, 0.99)	0.02	−2.27	0.023	272.46	0.67 (0.56, 0.76)
Standardized	0.61 (0.4, 0.93)	0.22				
Multivariate						
O_2 pulse at AT (mL O_2/beat)						
Unstandardized	1.02 (0.83, 1.25)	0.10	0.16	0.874	258.25	0.75 (0.66, 0.84)
Standardized	1.04 (0.64, 1.7)	0.25				
$\dot{V}E/\dot{V}CO_2$ slope						
Unstandardized	0.95 (0.9, 0.99)	0.02	−2.33	0.02		
Standardized	0.62 (0.42, 0.93)	0.20				
$\dot{V}O_2$/kg at AT						
Unstandardized	0.78 (0.58, 1.04)	0.15	−1.70	0.089		
Standardized	0.56 (0.29, 1.09)	0.34				
SPO						
Unstandardized	1 (0.95, 1.05)	0.03	−0.08	0.937		
Standardized	0.98 (0.55, 1.73)	0.29				

HR with 95% CI, SE, z-statistics, P values, AIC, and C-Index are provided for each parameter, including the 6MWT, O_2 pulse at AT, minute ventilation to carbon dioxide output ratio ($\dot{V}E/\dot{V}CO_2$ slope), $\dot{V}O_2$/kg at AT, and SPO. Abbreviations as in Table 3.

Submaximal Power Output

SPO was not definitely associated with survival, but needs consideration as it was almost borderline significant in our cohort. To effectively show an association between survival and SPO, a ramp protocol for submaximal CPET may strengthen our findings in future studies, as this would eliminate the stepwise appearance of results, as seen in the **Supplementary Figure**. In our cohort, more than half of the patients were treated with β-blockers at study enrollment. Recently, it has been shown that β-blockers were associated with a higher AT but unchanged 6MWT in patients with HF with preserved ejection fraction.[31] Indeed, CA is known to be primarily associated with preserved ejection fraction, which was also true in our collective.[32] Therefore, β-blockers might have caused a gap in between results of the 6MWT and submaximal CPET; however, our cohort showed an earlier AT and lower 6MWT, meaning that the tendency of parameters moved in conjunction with each other.

However, SPO did have a feasible cut-off for prognosis, with levels below the cut-off (i.e., <28 W) indicating a worse prognosis, as seen with the significant log-rank test in **Figure 3** for both all-cause mortality and HF-related hospitalization. This in turn might be useful in patients with CA unable to perform maximum symptom-limited CPET, as submaximal exercise testing has only been described in patients with HF.[16]

The fact that $\dot{V}O_2$/kg at AT is predictive for survival in patients with HF could not be shown in our cohort of patients with CA indicates a potential difference in exercise response, highlighting the need to identify different CPET markers for disease progression in patients with CA.

Submaximal CPET and the 6MWT

Regarding submaximal exercise capacity, the study revealed that CPET parameters, particularly the $\dot{V}E/\dot{V}CO_2$ slope and SPO, might be predictors of the 6MWT distance. The multivariate model explained 42% of the variance in 6MWT performance, indicating that ventilatory efficiency and submaximal workload capacity are determinants of functional exercise capacity in CA patients. The observed negative correlation between the $\dot{V}E/\dot{V}CO_2$ slope and 6MWT distance further emphasizes the inverse relationship between ventilatory inefficiency and reduced exercise capacity, which might have significant implications for patient management as exercise induced pulmonary hypertension is common in CA patients, highlighting the need to further tackle the pathophysiological mechanisms of

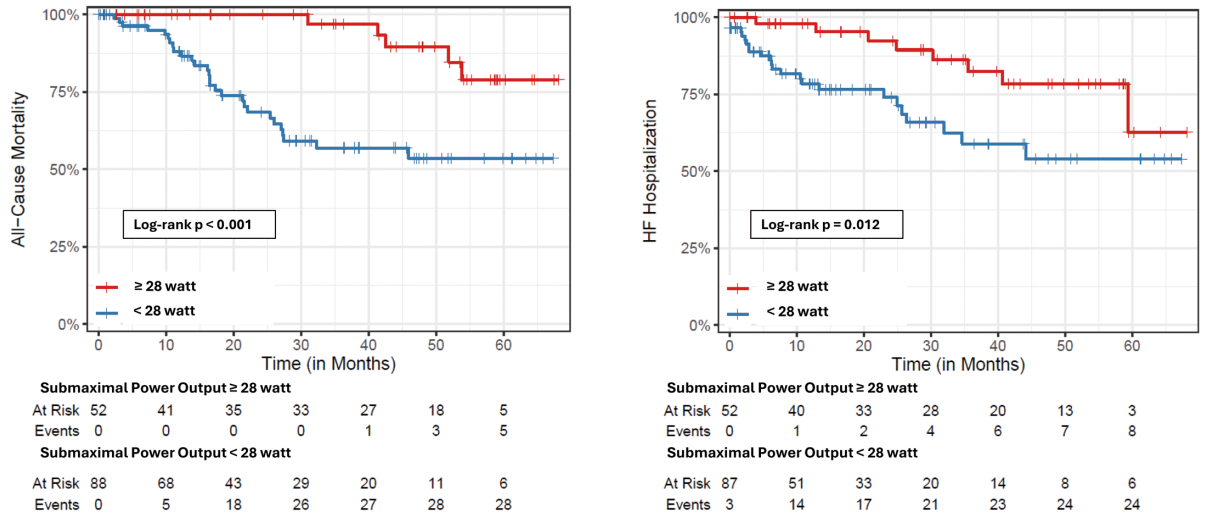

Figure 3. Kaplan-Meier analysis of all-cause mortality and heart failure (HF)-related hospitalization stratified by submaximal power output (SPO) during cardiopulmonary exercise testing (CPET). Patients with SPO ≥28 W showed significantly better outcomes compared with those with SPO <28 W. The statistical significance of these findings is indicated by the log-rank P values.

Table 5. Linear Regression Models Predicting Distance Covered During the 6MWT

Model	Covariable	Estimate (95% CI)	SE	t	DF	P value	R^2 (95% CI)
$\dot{V}O_2$/kg at AT only	(Intercept)	226.13 (152.68, 299.59)	37.09	6.10	116	<0.001	0.17 (0.07, 0.29)
	$\dot{V}O_2$/kg AT	21.41 (12.83, 29.98)	4.33	4.95	116	<0.001	
SPO (W)	(Intercept)	260.04 (216.74, 303.33)	21.86	11.90	115	<0.001	0.31 (0.17, 0.45)
	SPO	5.53 (3.99, 7.07)	0.78	7.12	115	<0.001	
O_2 pulse at AT (mL O_2/beat) only	(Intercept)	280.33 (214.98, 345.69)	32.99	8.50	113	<0.001	0.12 (0.03, 0.25)
	O_2 pulse at AT	16.59 (8.17, 25)	4.25	3.91	113	<0.001	
$\dot{V}E/\dot{V}CO_2$ slope only	(Intercept)	721.71 (633.5, 809.92)	44.55	16.20	119	<0.001	
	$\dot{V}E/\dot{V}CO_2$ slope	−8.32 (−10.56, −6.08)	1.13	−7.34	119	<0.001	
All CPET variables	(Intercept)	502.98 (369.36, 636.6)	67.42	7.46	109	<0.001	0.42 (0.3, 0.57)
	O_2 pulse at AT	2.65 (−6.08, 11.38)	4.41	0.60	109	0.549	
	$\dot{V}E/\dot{V}CO_2$ slope	−5.66 (−8.03, −3.28)	1.20	−4.72	109	<0.001	
	$\dot{V}O_2$/kg AT	0.9 (−10.31, 12.11)	5.65	0.16	109	0.874	
	SPO	3.5 (1.45, 5.56)	1.04	3.38	109	0.001	

Results of linear regression models predicting the distance covered during the 6MWT based on various submaximal CPET parameters. Estimates, 95% CI, SE, t-statistics, degrees of freedom (DF), P values, and coefficients of determination (R^2) are shown for each model. R^2, coefficient of determination; $\dot{V}E/\dot{V}CO_2$ slope, ratio of minute ventilation to carbon dioxide output. Other abbreviations as in Tables 1–3.

functional capacity limitation in this collective.[11]

The 6MWT has previously been used to assess submaximal exercise capacity and monitor disease course in patients with CA and remains a relatively convenient exam.[23,33] However, CPET is a rather inconvenient examination in CA, that needs consideration to be a fixed part of the prognostic work-up as evidence for the prognostic capacity of this method is accumulating.[9] Furthermore, the ability of CPET to monitor the disease course and be a prescription tool for cardiac rehabilitation highlights the

potential benefits for personalized medicine in patients with CA.[19,20,34]

Therefore, the present study addressed the challenge of optimizing functional testing in patients with CA, especially those unable to perform a 6MWT or symptom-limited maximum CPET. Indeed, the 6MWT is often required to prescribe disease-specific therapy, but many patients face limitations due to some degree of polyneuropathy (43% in our collective), which might lead to gait dysfunction.[2] Therefore, walking tests might be more burdensome than cycling tests. Our findings aim to reduce the double burden of performing both a CPET and a 6MWT by demonstrating that CPET, even if submaximal, can serve as a valuable alternative and offer clinical insights.

These findings suggest that detailed cardiopulmonary assessment through evaluating maximum CPET at a defined submaximal benchmark (i.e., AT) provides valuable prognostic information in patients with CA. The now newly described submaximal CPET prognostic parameter of SPO with a cut-off at 28 and the confirmation of the $\dot{V}E/\dot{V}CO_2$ slope as a predictive marker in the submaximal CPET setting could enhance risk stratification and guide treatment decisions to optimize patient care.

Study Limitations

Although submaximal CPET is valuable, this study denotes a few limitations. First, not all patients enrolled in the study were physically able to undergo CPET or had undergone CPET without a proper test duration, hindering the proper identification of the AT in those tests. Second, the exercise tests in this study were incremental ramp tests, with short steps, which might not reflect the actual standard for maximum exercise testing anymore; however, it must be noted that even though no ramp test was used, the aim of our study was the evaluation of submaximal results and not peak values.

Conclusions

The present study underscores the pivotal role of submaximal CPET in the comprehensive evaluation of patients with CA. The identification of $\dot{V}E/\dot{V}CO_2$ slope and SPO as key predictors of survival, HF-related hospitalizations and exercise capacity highlights their potential use in guiding clinical decision-making and underscores the need for further research to refine prognostic models based on these parameters.

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IRB Information

The single-center clinical registry (EK 1918/2019) was approved by the local ethics committee at the Medical University of Vienna, Austria.

Disclosures

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Data Availability

The data supporting the findings of this study are available from the corresponding author on reasonable request.

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Supplementary Files

Please find supplementary file(s);
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