Brief Report

Prognostic Role of Cardiopulmonary Exercise Testing in Wild-Type Transthyretin Amyloid Cardiomyopathy Patients Treated With Tafamidis

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ABSTRACT

Background: The prognostic value of cardiopulmonary exercise testing (CPET) in patients with wild-type transthyretin cardiac amyloidosis treated with tafamidis is unknown.

Methods and Results: This retrospective study included patients with wtATTR who underwent baseline cardiopulmonary exercise testing and were treated with tafamidis from August 31, 2018, until March 31, 2020. Univariate logistic and multivariate cox-regression models were used to predict the occurrence of the primary outcome (composite of mortality, heart transplant, and palliative inotrope initiation). A total of 33 patients were included (median age 82 years, interquartile range [IQR] 79−84 years), 84% were Caucasians and 79% were males). Majority of patients had New York Heart Association functional class III disease at baseline (67%). The baseline median peak oxygen consumption (VO_2) and peak circulatory power (CP) were 11.35 mL/kg/min (IQR 8.5−14.2 mL/kg/min) and 1485.8 mm Hg/mL/min (IQR 988−2184 mm Hg/mL/min), respectively, the median ventilatory efficiency was 35.7 (IQR 31−41.2). After 1 year of follow-up, 11 patients experienced a primary end point. Upon multivariate analysis, the low peak VO_2 (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.23−0.79, $P = .007$], peak CP (HR 0.98, 95% CI 0.98−0.99, $P = .02$), peak oxygen pulse (HR 0.62, 95% CI 0.39−0.97, $P = .03$), and exercise duration of less than 5.5 minutes (HR 5.82, 95% CI 1.29−26.2, $P = .02$) were significantly associated with the primary outcome.

Conclusions: Tafamidis-treated patients with wtATTR who had baseline low peak VO_2, peak CP, peak O_2 pulse, and exercise duration of less than 5.5 minutes had worse outcomes. (*J Cardiac Fail 2021;27:1285−1289*)

Key Words: Wild-type transthyretin amyloid cardiomyopathy (wtATTR), tafamidis, cardiopulmonary exercise test (CPET), peak VO_2, exercise duration.

The wild-type transthyretin amyloid cardiomyopathy (wtATTR) is associated with significant morbidity and mortality with variable median survival of approximately 2−6 years.[1] Recently, tafamidis received approval from the US Food and Drug Administration for use in patients with ATTR cardiomyopathy after the ATTR-ACT randomized controlled trial showing improvement in quality of life and a mortality benefit.[2]

Cardiopulmonary exercise testing (CPET) is routinely used in the prognostication of patients with heart failure. The peak oxygen consumption (VO_2) and minute ventilation/carbon dioxide production (VE/VCO_2) slope have emerged as powerful and well-established prognostic indicators. Yunis et al[3] specifically looked at prognostic value of CPET in small cohort of patients with wtATTR and found worse survival in patients with an increased VE/

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VCO_2. However, there are no data regarding the usefulness of baseline CPET in patients with wtATTR before the initiation of tafamidis.

Methods

Patients

We conducted a retrospective study including patients treated with tafamidis with wtATTR amyloidosis adult (>18 years) between August 31, 2018, and March 31, 2020. Exclusion criteria were age less than 18 years, pregnancy, amyloid light chain amyloidosis, hereditary transthyretin amyloidosis, New York Heart Association (NYHA) functional class IV symptoms, and patients with wtATTR who did not receive tafamidis. The study was approved by the Institutional Review Board of the University of Kansas Medical Center. The study data were collected and managed using a REDCap electronic data capture tools hosted at our university.[4]

Cardiopulmonary Exercise Test

The CPET were performed within 1 month of tafamidis treatment. The peak exercise parameters included were systolic blood pressure, peak VO_2 (oxygen consumption), peak circulatory power (CP), peak end-tidal pressure carbon dioxide, and peak O_2 pulse (VO_2/HR). Other parameters included were respiratory exchange ratio, VE/VCO_2 slope, anerobic threshold, oxygen consumption at anerobic threshold, chronotropic incompetence, and exercise duration (minutes). All parameters were calculated as described in the American Heart Association's Clinician Guide to CPET.[5] The CP was defined as peak $VO_2\times$ Systolic blood pressure and is expressed in millimeters of mercury per milliliter per minute.

All patients underwent a baseline transthoracic echocardiogram, CPET, and Tc-PYP scan around initiation of the tafamidis treatment. The tafamidis was started within a median of 21 days (interquartile range [IQR] 0−31 days) of CPET. ATTR amyloidosis was diagnosed by cardiac uptake on ^{99m}Tc-PYP scan in the absence of monoclonal component or free light chains in the blood and urine. The exclusion of a mutant TTR allele by genomic DNA sequencing or mass spectrometry was done to diagnose wtATTR. The baseline cardiac biomarkers troponin-I and B-type natriuretic peptide were also obtained.

Follow-Up and Outcomes

All patients were followed for 1 year from the baseline CPET and the start of the tafamidis treatment. The primary composite outcome was a combination of mortality, heart transplant, or palliative inotrope initiation within 1 year of tafamidis initiation.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number of patients and percentages. The unpaired *t* test or Wilcoxon rank-sum test were used in continuous variables to compare patients with and without the primary composite outcome. Pearson's χ^2 was used in categorical variables between these subgroups.

A receiver operating characteristic curve analysis was performed to delineate the cutoff for exercise duration. An exercise duration of less than 5.5 minutes had area under the curve of 0.79 (sensitivity of 72.7% and specificity of 86.4%). Univariate logistic analyses were performed to identify the association between the key baseline variables and the primary composite outcome. Covariates with a *P* value of less than .2 (race and creatinine) were adjusted for in the multivariate model. Multivariate Cox regression was performed adjusting for race and creatinine level. A survival analysis was performed, and a Kaplan−Meier curve was generated to demonstrate the survival free of composite outcomes in patient with exercise duration of greater than 5.5 minutes and less than 5.5 minutes. The analyses were conducted using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 33 patients with wtATTR amyloid are included in the study. The median age was 82 years (IQR 79−84 years) and 79% patients were males, with majority of patients being Caucasians (84%). The majority of patients had NYHA functional class III (67%) heart failure symptoms at baseline. The median septal wall thickness is 1.58 cm (IQR 1.4−1.8 cm) and posterior wall thickness 1.5 cm (IQR 1.3−1.8 cm). A significantly greater proportion of patients with outcomes had NYHA functional class III symptoms (100% vs 50%, $P = .004$), higher median serum creatinine (1.65 vs 1.27, $P = .006$), and greater use of angiotensin-converting enzyme/angiotensin receptor blocker medications (18.2% vs 36.4%, $P = .02$) compared with patients without the primary outcome (Table 1).

The details of baseline CPET are provided in Table 1. The median peak VO_2 was 11.35 mL/kg/min (IQR 8.5−14.2 mL/kg/min) and the median peak CP was 1485.8 mm Hg/mL/min (IQR 988−2184 mm Hg/mL/min). The median VE/VCO_2 slope was 35.7 (IQR 31−41.2). Of 33 patients, 3 attempted but were unable to complete the CPET study owing to frailty. The median exercise duration was 6.35 minutes (IQR 4.8−7.8minutes). In comparing the patients who experienced a primary outcomes with those who did not, the median peak systolic blood pressure was 121 vs 153 mm Hg ($P = .02$), the median peak VO_2 was 7.6 vs 12.8 mL/kg/min ($P < .001$), the median peak CP was 884 vs 1928 mm Hg/mL/min ($P < .001$), the median peak VO_2/HR was 7 vs 9 mL/bpm ($P = .005$), and the median exercise duration was 4.4 minutes (IQR 3.6−4.7 minutes) vs 6.9 minutes (IQR 5.9−8.9 minutes, $P < .001$); all were significantly lower.

Univariate logistic regression analysis showed peak VO_2(odds ratio [OR] 0.27, 95% CI 0.10−0.73, $P = .010$),

Table 1. Baseline Characteristics in All Patients and According to Outcome

Characteristics	All ($N = 33$)	Primary outcome ($n = 11$)	No Primary Outcome ($n = 22$)	P Value
Demographics				
Median age, years (25%−75%)	82 (79−84)	82 (79−84)	82 (77−84)	.83
Male sex, *n* (%)	26 (78.79)	9 (81.82)	17 (77.27)	.763
Race, *n* (%)				.141
Caucasian	28 (84.85)	8 (72.73)	20 (90.91)	
African American	4 (12.12)	3 (27.27)	1 (4.55)	
Hispanic	1 (3.03)	0 (0.00)	1 (4.55)	
BMI, kg/m^2, mean ± SD	26.61 ± 4.15	27.29 ± 4.60	26.26 ± 3.97	.491
Afib, *n* (%)	28 (84.85)	10 (90.91)	18 (81.82)	.492
NYHA class III, *n* (%)	22 (66.67)	11 (100.00)	11 (50.00)	.004
Laboratory parameters				
Median BNP (25%−75%)	484 (244−992)	493 (345−992)	476.5 (344−751)	.68
Median Trop-I (25%−75%)	0.09 (0.04−0.18)	0.11 (0.06−0.21)	0.06 (0.03−0.095)	.15
Median serum creatinine (25%−75%)	1.36 (1.14−1.65)	1.65 (1.27−2.11)	1.27 (1.05−1.5)	.006
Median serum sodium (25%−75%)	138 (137−139)	139 (137−139)	138 (137−140)	.76
Medication				
ACE inhibitors or ARB, *n* (%)	10 (30.30)	2 (18.18)	8 (36.36)	.023
Beta-blockers, *n* (%)	20 (60.61)	6 (54.55)	14 (63.64)	.223
Aldactone, n (%)	22 (66.67)	8 (72.73)	14 (63.64)	.055
Statin, n (%)	22 (66.67)	9 (81.82)	13 (59.09)	.055
Tafamidis, *n* (%)	33 (100.00)	11 (100.00)	22 (100.00)	NA
Baseline echocardiography findings				
Median LVEF, % (25%−75%)	50 (40−55)	45 (40−55)	50 (40−60)	.34
Median septal wall thickness, cm (25%−75%)	1.58 (1.41−1.8)	1.6 (1.3−1.73)	1.55 (1.41−1.82)	.72
Median posterior wall thickness, cm (25%−75%)	1.5 (1.3−1.8)	1.46 (1.2−1.87)	1.52 (1.37−1.8)	.52
RV function, *n* (%)				.741
Moderate dysfunction	8 (24.24)	3 (27.27)	5 (22.73)	
Median LA volume index (mL/m^2) (25%−75%)	42.3 (32.2−48.6)	43.56 (28.46−48.92)	37.14 (33.29−48.13)	.86
Median PA systolic pressure, mm Hg (25%−75%)	37 (29−47)	40 (30−50)	37 (29−47)	.75
Baseline PYP scan				
H/CL, mean ± SD	1.69 ± 0.19	1.70 ± 0.17	1.68 ± 0.20	.825
Visual grading analysis, *n* (%)				.615
Grade 3	30 (90.91)	10 (90.91)	20 (90.91)	
CPET parameters				
Median Peak systolic BP, mm Hg (25%−75%)	144.5 (122−168)	153 (130−172)	121 (116−141)	.02
Median peak heart rate, beat/min (25%−75%)	109.5 (94−119)	1109.5 (90−121)	108.5 (107−115)	.06
Median peak VO_2, mL/kg/min (25%−75%)	11.35 (8.5−14.2)	12.8 (11−15)	7.6 (7−8.4)	<.001
Median peak circulatory power mm Hg/mL/min (25%−75%)	1485.8 (988−2184)	1927.6 (1246−2414)	883.5 (732.8−906.2)	<.001
Median peak respiratory exchange ratio (25%−75%)	1.16 (1.06−1.24)	1.16 (1.06−1.24)	1.15 (1.08−1.22)	.96
Median VE/VCO_2 slope (25%−75%)	35.7 (31−41.2)	35.6 (30.3−41.2)	36.2 (32.8−42.6)	.51
Median VO_2AT, mL/kg/min (25%−75%)	8 (6.3−9.0)	8 (6.0−9.6)	7.7 (7.1−8.1)	.75
Median Anaerobic threshold, % (25%−75%)	36.5 (32−52)	42 (29−53)	35 (34−36)	.52
Median $PETCO_2$, mm Hg (25%−75%)	31 (28−34)	31 (29−36)	29 (27.5−30)	.12
Median peak VO_2/HR, mL/bpm (25%−75%)	9 (8−10)	9 (8−12)	7 (5.0−8.5)	.005
Median exercise duration, min (25%−75%)	6.35 (4.8−7.8)	6.9 (5.9−8.9)	4.4 (3.6−4.7)	<.001
Chronotropic incompetence, *n* (%)	9 (30)	8 (36.4)	1 (12.5)	.21
Unable to tolerate CPET, *n* (%)	3 (9.09)	3 (27.27)	0 (0)	.01

ACE, angiotensin-converting enzyme; Afib, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; H/CL, heart/contralateral lung ratio; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PA, pulmonary artery; RV, right ventricle; SD, standard deviation; Trop-I, troponin I; BP, blood pressure; CPET, cardiopulmonary exercise test; peak VO_2, peak oxygen consumption; VE/VCO_2, ventilatory efficiency; VO_2AT, peak oxygen consumption at anerobic threshold; $PETCO_2$, peak end tidal Carbon dioxide; Peak VO_2/HR, peak oxygen pulse.

peak CP (OR 0.99, 95% CI 0.98−0.99, $P = .032$), and peak VO_2/HR (OR 0.46, 95% CI 0.24−0.87, $P = .018$) were significantly associated with the primary outcome. An exercise duration of less than 5.5 minutes was also significantly associated with the primary outcome (OR 7.1, 95% CI 1.4−36.1, $P = .02$). After adjustment of covariates using multivariate cox regression analysis, the peak VO_2(HR 0.43, 95% CI 0.23−0.79, $P = .007$), peak CP (HR 0.98, 95% CI 0.98−0.99, $P = .02$), peak VO_2/HR (HR 0.62, 95% CI 0.39−0.97, $P = .03$), and exercise duration of less than 5.5 minutes (HR 5.82, 95% CI 1.29−26.2; $P = .02$) independently predicted events during 1-year of follow-up (Table 2 and Fig. 1).

During the 1-year follow-up, 11 patients (33.3%) had composite primary outcome: 8 patients (24%) had all-cause mortality, 1 (3.03%) received a heart transplant, and 2 patients (6.06%) were started on palliative inotropes. The mean time to composite primary outcome was 213.6 ± 113 days and to all-cause mortality was 225.3 ± 108.4 days from tafamidis start date. In the total cohort, after 1 year of follow-up, 10 patients (30.3%) had HF hospitalizations. The majority of patients getting hospitalized were from the

Table 2. Univariate Logistic Regression and Multivariate Cox Regression Analysis for Key Cardiopulmonary Exercise Test Variables and Other Known Prognostic Variables in the Prediction of the Primary Outcome (All-Cause Death, Heart Transplant, and/or Inotrope Use)

Variables	Primary Outcome	
	OR (95% CI)	*P* Value
Univariate logistic regression		
Patient characteristics		
Age	0.99 (0.86−1.12)	.844
Sex	0.76 (0.12−4.70)	.764
Race (compared with Whites)		
African American	7.49 (0.67−83.26)	.101
Body mass index >30 kg/m^2	1.69 (0.30−9.36)	.549
Baseline echocardiographic findings		
Normal LVEF (compared with reduced LVEF [<50%])	0.69 (0.16−2.97)	.623
Severe septal wall thickness (cm)	1.44 (0.34−6.16)	.623
Severe posterior wall thickness (cm)	0.83 (0.18−3.68)	.801
Severe increased left atrial volume index (mL/kg/m^2)	1.22 (0.27−5.61)	.794
Laboratory parameters		
BNP	1.01 (0.99−1.03)	.43
Troponin	0.66 (0.14−3.08)	.59
Serum creatinine	27.2 (2.08−357.2)	.01
Serum sodium	0.96 (0.69−1.31)	.79
Baseline CPET parameters		
Peak systolic BP, mm Hg	0.96 (0.92−0.99)	.044
Peak Heart rate, beat/min	1.02 (0.98−1.07)	.365
Peak VO_2, mL/kg/min	0.27 (0.10−0.73)	.010
Peak circulatory power	0.99 (0.98−0.99)	.032
VE/VCO_2 slope	1.02 (0.93−1.12)	.624
VO_2AT (mL/kg/min)	0.89 (0.61−1.32)	.584
Anaerobic threshold (%)	0.96 (0.87−1.05)	.357
$PETCO_2$ (mm Hg)	0.89 (0.75−1.07)	.238
Peak VO_2/HR (mL/bpm)	0.46 (0.24−0.87)	.018
Chronotropic incompetence	0.25 (0.03−2.41)	.231
Exercise duration (>5.5 minutes compared with <5.5 minutes)	7.1 (1.4−36.1)	.02
Baseline PYP scan		
H/CL	1.59 (0.03−88.18)	.818
Multivariate Cox regression analysis*		
Baseline CPET parameters		
Peak systolic BP, mm Hg	0.97 (0.94−1.01)	.11
Peak heart rate, beat/min	1.03 (0.99−1.08)	.15
Peak VO_2, mL/kg/min	0.43 (0.23−0.79)	.007
Peak circulatory power	0.98 (0.98−0.99)	.02
VE/VCO_2 slope	1.02 (0.93−1.12)	.68
VO_2AT, mL/kg/min	1.02 (0.63−1.65)	.95
Anaerobic threshold, %	0.98 (0.89−1.09)	.68
$PETCO_2$, mm Hg	0.92 (0.74−1.15)	.46
Peak VO_2/HR, mL/bpm	0.62 (0.39−0.97)	.03
Chronotropic incompetence	0.32 (0.04−2.86)	.31
Exercise duration (>5.5 minutes compared with <5.5 minutes) hazard ratio	5.82 (1.29−26.2)	.02

BP, blood pressure; CI, confidence interval; OR, odds ratio; $PETCO_2$, peak end-tidal carbon dioxide; peak VO_2/HR, peak oxygen pulse. Other abbreviations as in Table 1.

*The HR and 95% CI are adjusted for race and creatinine.

primary outcome group (9 [81.8%] vs 1 [4.5%], $P < .001$) compared with those without a primary outcome.

Discussion

This novel study demonstrates the prognostic value of baseline CPET in patients with wtATTR who are treated with tafamidis. This study demonstrates that the pre-tafamidis baseline low peak VO_2, peak VO_2/HR, peak CP, and low exercise duration were significantly and independently associated with increased risk of early (<1 year) primary outcome (mortality, heart transplantation, or risk of inotrope initiation) in patients with wtATTR treated with tafamidis.

As seen in our study and others, a low peak VO_2 is an independent predictor of the worse outcomes in patients with wtATTR. The low peak VO_2 leading to a poor prognosis can be due to a decrease in stroke volume from restrictive physiology in these patients. A decrease in stroke volume over time in patients with ATTR amyloidosis had been associated with a worse prognosis.[6] Similarly, a low peak VO_2/HR, which can be thought of as surrogate for stroke volume, was also significantly associated with worse outcome in our study. Contrary to our study, a prior study in patients with wtATTR showed no significant association of peak VO_2 to mortality but VE/VCO_2 slope did.[3] The VE/VCO_2 slope was not significantly associated with the primary composite outcome in our study. wtATTR

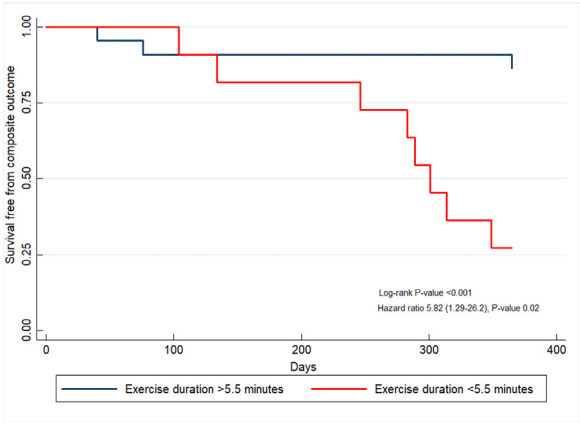

Fig. 1. Kaplan−Meier curve showing exercise duration comparison between patients who experienced a primary outcome (events) and patients who had no primary outcome (no events) group

phenotypically resembles HF with preserved ejection fraction. Similar to our study, in FIT-CPX study (a retrospective study of patients with HF with preserved ejection fraction), the VE/VCO_2 slope did not show a significant association with the composite outcome of heart transplantation and mortality, although peak VO_2 did.[7] This variability in prior studies compared with ours could be attributed to baseline differences in patient characteristics like age, sex, and severity of NYHA heart failure symptoms.

The peak CP was an independent predictor of composite outcome. The baseline median peak CP in our study was very low at 1485.8 mm Hg x mL/kg/min (IQR, 988−2184 mm Hg x mL/kg/min). This parameter demonstrates an insufficient cardiac response owing to restrictive physiology in patients with cardiac amyloid. This insufficient cardiac response is also reflected in an overall lower exercise duration. This finding of significant prognostic value of peak CP was also demonstrated in recent study on patients with cardiac amyloid.[8]

Our study has several limitations. As with other wtATTR studies, the sample size is small owing to the rarity of the disease. The study was conducted at a single quaternary center, which limits the generalizability of the study results to other geographic areas of the country. Also, because our hospital is a referral center, there is a possibility of referral bias. Furthermore, the results of our study should be taken as hypothesis generating and further studies are needed to confirm these findings.

Tafamidis is an expensive medication costing around $225,000 per annum, which can cause a substantial health burden. Currently, there are no data or societal guidelines on the selection of patients with wtATTR who would benefit from tafamidis. Our study shows that CPET, by providing predictors of early worse outcomes, can guide physicians in choosing patients for tafamidis treatment.

Declaration of Competing Interest

Dr Shah had briefly served as a consultant for Pfizer. No other co-authors have any disclosures.

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