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ORIGINAL ARTICLE

Exercise limitations in amyloid cardiomyopathy assessed by cardiopulmonary exercise testing—A multicentre study

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Abstract

Aims Amyloid cardiomyopathy is caused by the deposition of light chain (AL) or transthyretin amyloid (ATTR) fibrils, that leads to a restrictive cardiomyopathy, often resulting in heart failure (HF) with preserved or reduced ejection fraction. This study aimed to determine whether cardiac output reduction or ventilation inefficiency plays a predominant role in limiting exercise in patients with amyloid cardiomyopathy.

Methods We conducted a multicentre prospective study in patients with AL or ATTR cardiomyopathy who underwent cardiopulmonary exercise testing across four centres. Patients were compared with a propensity-score matched HF cohort based on age, gender, left ventricular ejection fraction (LVEF), and peak oxygen consumption (VO_2).

Results Data from 267 amyloid patients aged 77 (72, 81) years, 86% male, with a median N-terminal pro B-type natriuretic peptide (NT-proBNP) of 2187 (1140, 4383) ng/L, exercise parameters of peak VO_2 of 14.1 (11.6;16.9) mL/min/kg, a minute ventilation to carbon dioxide production (VE/VCO_2) slope of 37.4 (32.5, 42.6) and a LVEF of 50% (44%, 59%) were analysed. We identified 251 amyloid cardiomyopathy–HF matches. Amyloid patients had a signifnicantly higher VE/VCO_2 slope [37.4, inter quartile range (IQR): 32.7, 43.1 vs. 32.1, IQR: 28.7, 37.0, $P < 0.0001$], NT-proBNP (2249, IQR: 1187, 4420 vs. 718, IQR: 405, 2161 ng/L, $P < 0.001$), peak heart rate (121 ± 28 vs. 115 ± 27 beats/min, $P = 0.007$) and peak ventilation (51, IQR: 42, 62 vs. 43, IQR: 33, 53 L/min, $P < 0.0001$) with earlier anaerobic threshold (VO_2 at AT: 8.9, IQR: 6.8, 10.8 vs. 10.8, IQR: 8.9, 12.7 mL/min/kg, $P < 0.0001$) compared with HF. Between amyloid patients, AL patients ($n = 27$) were younger (63, IQR: 58, 70 vs. 78, IQR: 72, 81 years, $P < 0.0001$), had lower VE/VCO_2 slope (35.0, IQR: 30.0, 38.7 vs. 38.0, IQR: 32.8, 43.1, $P = 0.019$), higher end-tidal carbon dioxide partial pressure both at AT (35.1 ± 4.8 vs. 31.4 ± 4.7 mmHg, $P < 0.001$) and peak exercise (32, IQR: 28, 35 vs. 30, IQR: 26, 33 mmHg, $P = 0.039$) as compared with ATTR ($n = 233$).

Conclusions A higher VE/VCO_2 slope and an earlier AT, determining functional capacity impairment, was assessed in patients with amyloid cardiomyopathy compared with the matched HF cohort. Additionally, patients with ATTR might display more severe exercise limitations as compared with AL.

Keywords functional capacity; heart failure; restrictive cardiomyopathy; transthyretin amyloidosis; light chain amyloidosis

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Introduction

Amyloidosis describes a pathological condition that is characterized by the deposition of misfolded proteins, resulting in a variety of distinct symptoms that range in severity. These protein deposits can occur in any organ across different tissues, with cardiac forms, including light chain amyloidosis (AL), wild-type transthyretin amyloidosis (ATTR) and hereditary variants of ATTR leading to restrictive cardiomyopathy and heart failure (HF).[1–4]

The increased ventricular filling pressures, due to myocardial stiffness, impair the heart's ability to relax and fill during exercise, resulting in HF with preserved ejection fraction.[5,6] However, as amyloid cardiomyopathy progresses, systolic dysfunction may develop, ultimately leading to HF with reduced ejection fraction.[7,8]

The cardinal symptom of amyloid cardiomyopathy is progressive shortness of breath, which leads to a reduced functional capacity. In addition to diastolic and systolic dysfunction, functional capacity may also be limited by autonomic dysfunctions that affect heart rate and blood pressure responses during exercise, as well as disruptions in the heart's electrical conduction system, resulting in arrhythmias and chronotropic incompetence.[9]

For the assessment of functional capacity, symptom-limited maximal cardiopulmonary exercise testing (CPET) is considered the gold standard for HF patients, regardless of left ventricular ejection fraction (LVEF).[10,11] Similarly, for prognosis, several studies indicate that CPET derived parameters are valuable for both HF and amyloid cardiomyopathy. Among the various parameters described, peak oxygen consumption (VO_2) and the relationship between minute ventilation (VE) and carbon dioxide production (VCO_2) as the VE/VCO_2 slope, have received the most significant attention.[12]

Therefore, our objective was to evaluate exercise limitations in patients with amyloid cardiomyopathy compared with those with chronic HF, and to determine whether cardiac output (CO) reduction or ventilation inefficiency plays a predominant role during exercise in amyloid patients. We hypothesize that patients with amyloid cardiomyopathy exhibit distinct exercise limitations compared with patients with chronic HF.

Moreover, as an explorative analysis, we aimed to test whether any differences exist in functional capacity between patients with AL and ATTR cardiomyopathy.

Methods

Study design and setting

In this prospective multicentre observational study, we compared patients with chronic HF, derived from the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) dataset[13,14] with a population of amyloid cardiomyopathy patients matched for age, gender, LVEF and peak VO_2.

Patients were included by four expert centres (*Centro Cardiologico Monzino*, Milan, Italy; *Sant' Anna Scuola Universitaria Superiore*, Pisa, Italy; *Ospedale S. Andrea*, *Università La Sapienza*, Roma; and the Medical University of Vienna, Austria). Patients of all centres were collected consecutively and gave written, informed consent for local registries at the corresponding hospitals. All clinical registries were approved by their local ethics committee (Ethics committee identification number: Milan, CCM 1979; Pisa, 22711; Rome, CE 6962/2022; Vienna, 1918/2019) and were conducted conforming with the Declaration of Helsinki.

We included patients aged ≥18 years, diagnosed with either ATTR, AL or combined forms of ATTR and AL cardiomyopathy, which have been diagnosed in accordance with proposed diagnostic strategies.[15] Patients with non-cardiac amyloid-related organ involvement, limiting exercise performance, such as higher grades of polyneuropathy (polyneuropathy disability score > IIIb) were excluded. Patients were treated with best medical treatment and all ATTR patients were naïve to disease specific therapy (e.g., tafamidis). Further, patients with AL or combined forms of ATTR and AL were mostly naïve to disease-specific therapy; however, patients that had a history of chemotherapy for AL were non-responders at the time of CPET as defined by a change of the difference in free light chains of less than 50% in between treatment cycles.[15] We also evaluated HF patients derived from the MECKI score database,[13] with a known HF aetiology other than amyloidosis, to allow for matched assessment between amyloid cardiomyopathy and HF cases. Among the MECKI score inclusion criteria[13] were capability to perform a CPET, stable clinical condition, optimized medical treatment and a history of reduced LVEF HF.

Exercise capacity

All patients conducted a baseline CPET with gas exchange analysis after successful initiation of best medical treatment and stable HF symptoms > 1 month. CPET was performed on a cycle ergometer (*Centro Cardiologico Monzino*, IRCCS: Bike Lode B.V. Groningen, the Netherlands; *Sant' Anna Scuola Universitaria Superiore*: GE eBIKE GE Healthcare Chicago, USA; *Ospedale S. Andrea*, *Università La Sapienza*: Bike Lode B.V. Groningen, the Netherlands; Medical University of Vienna: eBIKE GE Healthcare Chicago, United States of America) with a personalized ramp protocol and an aimed test duration of 10 ± 2 min.[16] Patients were motivated to perform a maximum effort. However, CPET were self-ended by the patients when they felt they had reached a maximal effort and were unable to exercise further. Of note, average peak exercise respiratory exchange ratio was 1.1 ± 0.12

confirming that a maximal effort was reached at least in the great majority of cases.[17] Parameters for gas exchange and ventilation were collected breath-by-breath using a face masks (*Centro Cardiologico Monzino*: Quark PFT Cosmed, Roma, Italy; *Sant' Anna Scuola Universitaria Superiore Pisa*: Dual Monitor Vyntus CPX Vyaire Medical GmbH, Hoechberg, Germany; *Ospedale S. Andrea*, *Università La Sapienza*: Quark PFT Cosmed, Roma, Italy; Medical University of Vienna: Dual Monitor Vyntus CPX Vyaire Medical GmbH, Hoechberg, Germany). CPET were performed, reported and analysed as standard across all centres.[17] Parameters included physical performance in Watts, VO_2, VE/VCO_2 slope and oxygen pulse (VO_2/heart rate). Values at peak exercise were defined as the highest 30 s average in the last minute of maximum exercise. Predicted peak VO_2 and VE/VCO_2 slope were calculated according to Hansen et al.[18] and Salvioni et al.[19] The anaerobic threshold was determined using the V-slope method with a confirmation via plots for ventilatory equivalents and end-tidal partial pressures of O_2 and CO_2.[17,20] Vital parameters (heart rate, blood pressure and electrocardiography) and CPET variables were assessed for at least 1 min at rest, during the exercise protocol and up to 3 min at recovery.

Statistical analysis

All data were uniformly collected in one database, being analysed via one method at *Centro Cardiolgico Monzino*, IRCCS. Continuous variables were expressed as means ± standard deviation or median and [interquartile range] as appropriate while discrete variables as absolute numbers and percentages. Unpaired *t*-test or Kruskal–Wallis test was employed to assess differences between groups for continuous variables, while χ^2 test or Fisher's exact test was performed for analyses involving categorical variables. In order to identify two homogeneous groups, a 1 to 1 propensity score matching was applied, between amyloid patients and the MECKI dataset, using a set of variables selected through an epidemiological approach, namely, age, gender, LVEF and peak VO_2 (mL/min/kg).

Standardized mean difference (SMD) was estimated to evaluate the balance of baseline variables in matched groups. An SMD lower than 0.10 was considered an index of good balance.

Correlation with VE/VCO_2 slope and peak VO_2% predicted were assessed by Spearman's coefficient only in the cohort diagnosed with amyloidosis. For each of the indicated outcomes, significantly correlated variables were identified and a set of variables with a variance inflation factor of less than 2 was created to reduce the effect of multicollinearity. The identified variables were involved in a multiple linear regression model with stepwise selection in order to identify predictors of VE/VCO_2 slope and peak VO_2% predicted. All right-skewed variables were log-transformed before the multiple linear regression.

Statistical analysis was performed using SAS statistical package v. 9.4 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided. A *P* value lower than or equal to 0.05 was considered as statistically significant. Boxplots were illustrated using ggplot2 package of RStudio v. 4.3.1 (RStudio, Boston, MA, USA).

Results

We studied 267 patients with amyloid cardiomyopathy of whom 27 had AL, 233 ATTR and 6 had both AL and ATTR. In one case, the amyloid type was unspecified at the time of this study. On average, amyloid cardiomyopathy patients had a moderate to severe HF as shown by natriuretic peptides [N-terminal pro B-type natriuretic peptide (NT-proBNP) = 2187 (1140, 4383) and brain natriuretic peptide = 438 (275, 686)] and exercise parameters [peak VO_2 (mL/min/kg) = 14.1 (11.6;16.9), peak VO_2 in percentage of predicted = 60 (49, 71) and VE/VCO_2 slope = 37.4 (32.5, 42.6)]. Additional characteristics of the amyloid patient cohort including echocardiography and staging are reported in *Table* 1.

Exercise limitations in amyloid cardiomyopathy versus chronic HF

A total of 7876 HF cases were available in the MECKI score database at the time of the present analysis, with a complete data set for matching purposes. MECKI score database included patients with history of reduced LVEF. Specifically, at MECKI score run-in evaluation, 6278 patients had persistent reduced LVEF, and 1598 had improved LVEF $\geq$ 40%. In amyloid patients, LVEF was $\geq$40% in 221 and $<$40% in 36 cases and not available in 10 cases. The median year of enrolment for the matched MECKI cohort was 2010 [interquartile range (IQR): 2007, 2013] and 2019 (IQR: 2008, 2023) for the amyloidosis cohort.

We were able to identify 251 propensity score matched pairs after one-to-one matching. Gender, LVEF and peak VO_2 (*Figure* S1) were well balanced (SMD $<$ 0.1 as reported in *Table* 2), while age had a small imbalance between HF and amyloid cases (SMD = 0.14). Compared with matched HF patients, amyloid cases had a much higher VE/VCO_2 slope, both as absolute value and as a percentage of predicted, higher natriuretic peptides, peak heart rate and peak VE (*Table* 2 and *Figure* 1) with an earlier anaerobic threshold in amyloid patients (lower workload and VO_2).

Considering the entire amyloid population (*n* = 267), the variables that had a variance inflation factor $<$ 2 and were significantly correlated with peak VO_2 (% of predicted) were

Table 1 Main clinical, instrumental and CPET-derived data in the entire cardiac amyloidosis sample.

Anthropometric, cardiac ultrasound and laboratory data (n = 267)	
Males (n, %)	229 (86)
Age (years)	77 (72;81)
BMI (kg/m^2)	26 (24;28)
LVEF (%)	50 (44;59)
Left ventricular diameter (mm)	45 (40;49)
Right ventricular diameter (mm)	31 (27;35)
Left atrial diameter (mm)	53 (46;63)
Right atrial diameter (mm)[a]	60 (56;66)
Left atrial volume (mL)	81 (68;101)
Right atrial volume (mL)[a]	66 (48;93)
Left ventricular end-diastolic volume (mL)	88 (70;117)
Left ventricular global longitudinal strain (%)[a]	−13 (−15;-11)
Intraventricular septum diameter (mm)	18 (16;21)
E to A ratio[a]	2 (1;3)
E to E′ ratio[a]	15 (12;20)
TR velocity (m/s)	27 (23;30)
Systolic pulmonary pressure (mmHg)	40 (33;48)
TAPSE	17 (14;20)
BNP (pg/mL)	438 (275;686)
Nt-ProBNP (ng/L)	2,187 (1,140;4,383)
eGFR (mL/min/1.73 m^2)	78 (65;84)
Type of cardiac amyloidosis (n = 267)	
AL (n, %)	27 (10.11)
ATTR (n, %)	233 (87.73)
ATTRwt (n, %)	229 (98.28)
ATTRv (n, %)	4 (1.72)
Mixed phenotype (n, %)	6 (2.25)
Unknown (n, %)	1 (0.37)
Staging (n = 187)	
UK staging system[21] (ATTRwt,v)	
Stage I (n, %)	115 (61.50)
Stage II (n, %)	64 (34.22)
Stage III (n, %)	8 (4.28)
CPET data (n = 267)	
Peak heart rate (bpm)	121 ± 28
Peak heart rate (% of max pred.)	84 ± 20
Peak VO_2 (mL/min/kg)	14.1 (11.6;16.9)
Peak VO_2 (% of predicted)	60.0 (49.1;70.9)
Peak O_2 pulse (mL/beat)	9.9 (7.9;11.9)
Peak ventilation (L/min)	50 (42;62)
Peak load (Watt)	74 (55;94)
Peak $PETCO_2$ (mmHg)	30 (26;32)
Peak RER	1.1 ± 0.12
VE/VCO_2 slope	37.4 (32.5;42.6)
VE/VCO_2 slope (% of predicted)	137 (118;156)
VO_2 at AT (mL/min/kg)	8.9 (6.8;10.8)
O_2 pulse at AT (mL/min/kg)	7.8 (6.1;9.9)
Ventilation at AT (L/min)	24 (20;30)
Load at AT (Watt)	30 (20;45)
$PETCO_2$ at AT (mmHg)	31.7 ± 4.8

Note: Continuous variables are shown in median with interquartile range in brackets, mean ± standard deviation or in frequencies (with percentages in brackets).
Abbreviations: AL, light chain amyloidosis; AT, anaerobic threshold; ATTR, transthyretin amyloidosis; ATTRv, hereditary form of transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BMI, body mass index; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise test; E to A ratio, ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole; E to E′, ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; $PETCO_2$, end-tidal carbon dioxide partial pressure; RER, respiratory exchange ratio; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VCO_2, carbon dioxide production; VE, ventilation; VO_2, oxygen uptake.
[a]Less than 50% of patient data available.

age, LVEF, VE/VCO_2 slope (log), body mass index, peak heart rate (log), VO_2 at the anaerobic threshold mL/min (log), peak workload (Watt) and NT-proBNP (log). Conversely, the correlating variables for VE/VCO_2 slope (log) were age, LVEF, body mass index, peak heart rate (log), NT-proBNP (log), peak VO_2 (% of predicted) and peak end-tidal carbon dioxide partial pressure ($PETCO_2$) (mmHg). The multiple linear regression analysis showed that age, peak heart rate, VO_2 at anaerobic threshold, peak workload and body mass index were positively associated with peak VO_2 (% of predicted) while VE/VCO_2 slope (log) and NT-proBNP (log) were negatively associated. Peak heart rate (log), peak VO_2 (% of predicted) and peak $PETCO_2$ (mmHg) were the predictors for VE/VCO_2 slope (log) (*Table* 3). If absolute, peak VO_2 (mL/min/kg) or VE/VCO_2 slope (% of predicted) were considered as the same variables as reported above, which remained associated with the peak VO_2 value or VE/VCO_2 slope in percentage of predicted, respectively.

Exercise limitations in ATTR versus AL cardiomyopathy

Comparing AL patients (n = 27) with ATTR cases (n = 233), AL patients were younger with no significant differences in LVEF and peak VO_2 (*Figure* S2). However, AL patients showed a lower absolute VE/VCO_2 slope and higher $PETCO_2$ both at anaerobic threshold and peak exercise (*Table* 4, *Figure* 2). The anaerobic threshold was identified in 81% and 90% of cases in AL and ATTR cases, respectively. Of note, when VE/VCO_2 was analysed as a percentage of predicted, we could only observe a non-significant trend towards a lower value in AL versus ATTR patients.

Discussion

The present study shows that exercise in patients with amyloid cardiomyopathy is characterized by a reduced VO_2 and an increased VE/VCO_2 slope, with the latter being the leading exercise abnormality, as shown by the comparison with HF patients matched by age, gender, LVEF and peak VO_2.

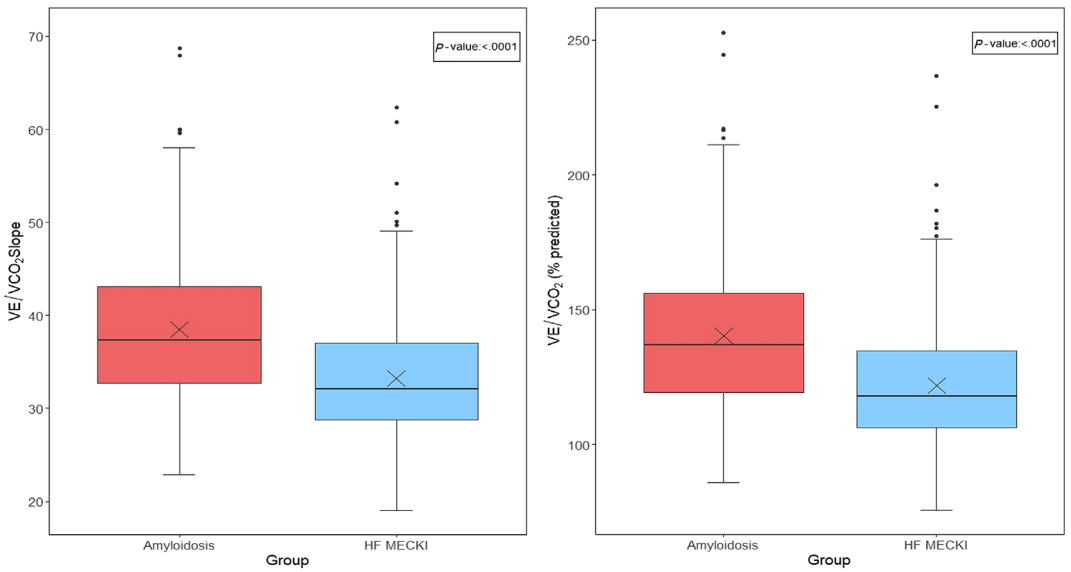
The cardiac amyloid population we studied is probably the largest in which CPET is reported. It is similar to that previously reported in a few studies[10,22–24] and included patients with different amyloid forms. Peak VO_2 and VE/VCO_2 slope were on the average abnormal. Moreover, multiple regression analysis showed that peak VO_2 and VE/VCO_2 slope were associated with each other as well as with a few parameters confirming that functional capacity abnormalities are due to several mechanisms, where CPET allows a holistic evaluation (*Table* 3).

Table 2 Anthropometric, laboratory and CPET data of cardiac amyloidosis patients with the matched heart failure population.

Anthropometric, cardiac ultrasound and laboratory data	MECKI (n = 251)	Amyloidosis (n = 251)	P value	SMD
Males (n, %)	219 (87.3)	223 (88.8)	0.5821	0.05
Age (years)	75 (67, 81)	77 (71, 81)	0.1153	0.14
Height (cm)	170 ± 8	172 ± 8	0.0001	0.35
Weight (kg)	75.3 ± 11.5	77.9 ± 12.9	0.0181	0.21
BMI (kg/m^2)	26 (24, 28)	26 (24, 28)	0.7364	0.03
LVEF (%)	50 (41, 59)	50 (44, 58)	0.7221	0.03
BNP (pg/mL)	159 (79, 341)	441 (267, 731)	<0.0001	1.13
Nt-ProBNP (ng/L)	718 (405, 2161)	2249 (1187, 4420)	0.0001	0.91
CPET data				
Peak heart rate (bpm)	115 ± 27	121 ± 28	0.0073	0.24
Peak heart rate (% of max predicted)	79 ± 19	84 ± 20	0.0047	0.26
Peak VO_2 (ml/min/kg)	13.6 (11.4, 16.8)	14.2 (11.6, 16.9)	0.5890	0.05
Peak VO_2 (% of predicted)	57.8 (46.9, 66.0)	59.9 (49.1, 71.1)	0.1222	0.14
Peak O_2 pulse (mL/beat)	9.6 (7.7, 11.8)	9.9 (7.9, 12.0)	0.1606	0.13
Peak ventilation (L/min)	43 (33, 53)	51 (42, 62)	<0.0001	0.57
Peak load (Watt)	71 (53, 97)	74 (55, 93)	0.8122	0.02
Peak RER	1.08 ± 0.11	1.1 ± 0.12	0.0525	0.18
VE/VCO_2 slope	32.1 (28.7, 37.0)	37.4 (32.7, 43.1)	<0.0001	0.72
VE/VCO_2 slope (% of predicted)	118 (106, 135)	137 (119, 156)	<0.0001	0.72
VO_2 at AT (mL/min/kg)	10.8 (8.9, 12.7)	8.9 (6.8, 10.8)	<0.0001	0.68
O_2 pulse at AT (mL/min/kg)	8.34 (7.04, 10.41)	7.75 (6.00, 9.80)	0.0072	0.30
Load at AT (Watt)	50 (34, 66)	30 (20, 45)	<0.0001	0.89

Note: Continuous variables are shown in median with interquartile range in brackets, mean ± standard deviation or in frequencies (with percentages in brackets). SMD for skewed variables was estimated using variables ranks.
Abbreviations: AT, anaerobic threshold; BMI, body mass index; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise test; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; $PETCO_2$, end-tidal carbon dioxide partial pressure; RER, respiratory exchange ratio; SMD, standardized mean difference. VCO_2, carbon dioxide production; VE, ventilation; VO_2, oxygen uptake.

Figure 1 Differences in ventilation efficiency between cardiac amyloidosis and heart failure. Differences in the minute ventilation to carbon dioxide production (VE/VCO_2) slope via boxplots in cardiac amyloidosis patients compared with individually 1:1 matched heart failure patients of the MECKI score pool. Abbreviations: HF-MECKI, heart failure cohort of the MECKI score registry; P value, measure of statistical significance; VE/VCO_2, minute ventilation to carbon dioxide production.



Exercise limitations in ATTR versus AL cardiomyopathy

The cohort of amyloid patients predominantly had ATTR cardiomyopathy, but also 27 patients with AL derived cardiomyopathy were identified. To the best of our knowledge, the present is the first report in which AL patients were evaluated by CPET and compared with ATTR cases.[25] AL cases were younger, consistent with previous studies[5,26] and demonstrated similar peak exercise performance both in terms of

Table 3 Multivariable analysis in cardiac amyloidosis patients.

Multivariable for peak VO_2 (% predicted)	Beta	*P*-value	95% CL	
VE/VCO_2 slope[a]	−12.873	.003	−21.301	−4.444
Age	0.276	.0035	0.092	0.461
BMI (kg/m^2)	0.524	.0173	0.094	0.954
NT-ProBNP (ng/L)[a]	−2.526	.0039	−4.232	−0.819
Peak heart rate[a]	9.776	.009	2.471	17.080
VO_2 at anaerobic threshold (mL/min)[a]	8.169	.0008	3.459	12.879
Peak workload (Watt)	0.205	<.0001	0.142	0.268
Multivariable for VE/VCO_2 slope				
Peak heart rate (bpm)	−0.11793	.0059	−0.202	−0.0343
Peak VO_2 (% of predicted)	−0.00244	.0003	−0.004	−0.0011
Peak $PETCO_2$ (mmHg)	−0.02902	<.0001	−0.033	−0.0250

Note: Variables with a variance inflation factor of less than 2 were involved in a multiple linear regression model with stepwise selection in order to identify predictors of VE/VCO_2 slope and peak VO_2. All right-skewed variables were log-transformed before the multiple linear regression.
Abbreviations: BMI, body mass index; NT-proBNP, N-terminal pro B-type natriuretic peptide; $PETCO_2$, end-tidal carbon dioxide partial pressure; VCO_2, carbon dioxide production; VO_2, oxygen consumption.
[a]Expressed as logarithm.

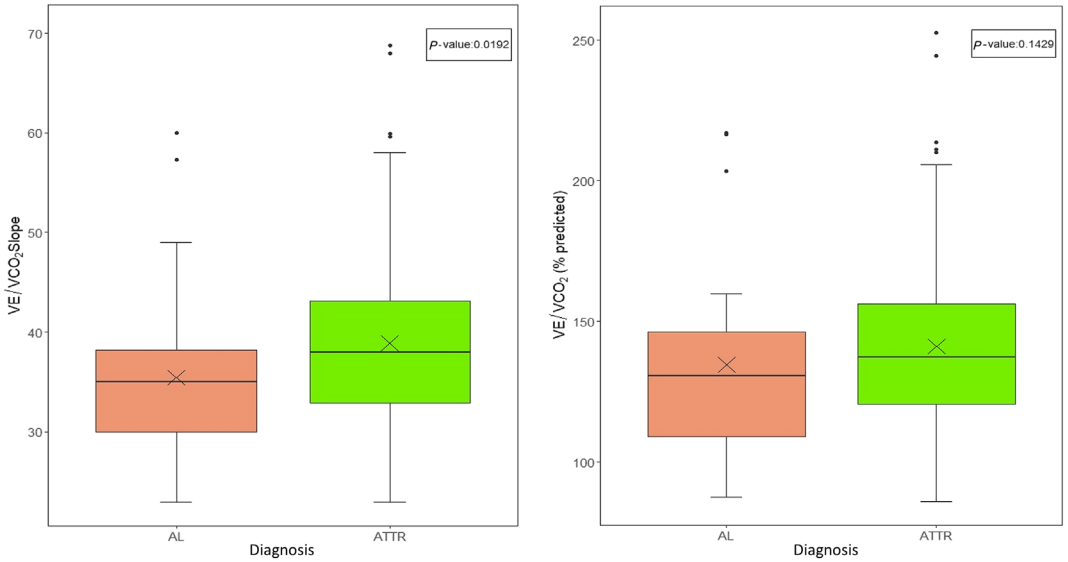
Table 4 Comparison between AL and ATTR patients.

Anthropometric, cardiac ultrasound and laboratory data	AL (n = 27)	ATTR (n = 233)	*P*-value
Males (n, %)	20 (74)	198 (85)	.0141
Age (years)	63 (58;70)	78 (72;81)	<.0001
Height (cm)	171 ± 10	172 ± 8	.2995
Weight (kg)	73.5 ± 13.5	78.5 ± 12.8	.0626
BMI (kg/m2)	24 (22;28)	26 (24;28)	.1106
LVEF (%)	50 (50;60)	50 (43;58)	.0546
BNP (pg/mL)	400 (239;686)	446 (344;776)	.3831
Nt-ProBNP (ng/L)	2,142 (1,514;6,885)	2,297 (1,136;4,083)	.2279
CPET data			
Peak heart rate (bpm)	115 (102;123)	118 (101;137)	.3024
Peak heart rate (% of max pred.)	73 (65;81)	83 (72;96)	.0018
Peak VO_2 (mL/min/kg)	14.7 (12.6;19.8)	14.2 (11.6;16.8)	.2588
Peak VO_2 (% of predicted)	56.4 ± 15.5	60.6 ± 15.3	.1834
Peak O_2 pulse (mL/beat)	10 (8.2;11.0)	9.9 (7.9;12.1)	.3472
Peak ventilation (L/min)	47 (37;65)	51 (43;63)	.3504
Peak load (Watt)	75 (62;98)	74 (55;93)	.3947
Peak $PETCO_2$ (mmHg)	32 (28;35)	30 (26;33)	.0368
Peak RER	1.11 (1.07;1.22)	1.1 (1.04;1.16)	.3046
VE/VCO_2 slope	35.0 (30.0;38.7)	38.0 (32.8;43.1)	.0192
VE/VCO_2 slope (% of predicted)	131 (107;148)	137 (120;156)	.1429
VO_2 at AT (mL/min/kg)	10.0 (8.4;13.5)	8.9 (6.8;10.7)	.0220
O_2 pulse at AT (mL/min/kg)	8.38 ± 2.55	8.02 ± 2.61	.5348
Ventilation at AT (L/min)	26.8 (21.6;33.0)	24.0 (20.0;30.0)	.1913
Load at AT (Watt)	46 (35;60)	30 (20;44)	.0002
VCO_2 at AT (mL/min)	722 (603;897)	593.4 (432;791)	.0177
$PETCO_2$ at AT (mmHg)	35.1 ± 4.8	31.4 ± 4.7	.0005

Note: Continuous variables are shown in median with interquartile range in brackets, mean (±) or in frequencies (with percentages in brackets).
Abbreviations: AL, light-chain amyloidosis; AT, anaerobic threshold; ATTR, transthyretin amyloidosis; BMI, body mass index; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise test; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; $PETCO_2$, end-tidal carbon dioxide partial pressure; RER, respiratory exchange ratio; VCO_2, carbon dioxide production; VE, ventilation; VO_2, oxygen consumption.

VO_2 and workload achieved. Additionally, the severity of HF, as assessed by NT-proBNP levels, was comparable. However, the anaerobic threshold was postponed in AL cases compared with ATTR cases, with a higher VO_2, workload and $PETCO_2$. This implies a higher CO at least in the early phases of exercise in AL patients. Indeed, the higher CO in patients with AL-CA was likely attributable to a more efficient adaptation of stroke volume rather than heart rate during exercise. This is evidenced by the significantly lower percentage of predicted peak heart rate in AL-CA as compared with ATTR-CA.

Figure 2 Differences in ventilation efficiency between AL and ATTR patients. Differences in the minute ventilation to carbon dioxide production (VE/VCO_2) slope via boxplots between AL and ATTR patients. Abbreviations: AL, light-chain amyloidosis; ATTR, transthyretin; *P* value, measure of statistical significance; VE/VCO_2, minute ventilation to carbon dioxide production.



These differences might be also attributed to the distinct pathophysiological characteristics of both types of CA. AL involves multiple organs to a greater extent than ATTR, which is predominantly affecting the heart.[27,28] Additionally, age as an influencing factor on CPET variables in HF may also explain the findings of better CO in AL patients.[29–31] Moreover, due to the different nature of AL and ATTR, it is likely that the AL CA diagnosis was obtained earlier in the history of the diseases as compared with ATTR. Finally, the ventilation inefficiency was higher in ATTR patients with higher VE/VCO_2 slopes and lower $PETCO_2$ both at anaerobic threshold and peak exercise. The higher VE/VCO_2 slope is at least partially attributable to age and gender differences, as the age- and gender-normalized VE/VCO_2 slope shows only a trend towards higher values in ATTR cases.

Additionally, differences in disease progression have to be taken into account. Besides amyloid fibril deposition, AL patients often present with cardiac dysfunction not only due to HF but also due to myocarditis-like features such as ventricular arrhythmias.[32] Initiation of disease specific therapy in AL patients can lead to a degree of haematological regression, resulting in milder disease characterized by prevalent HF and lack of acute inflammation.[32] As the time of CPET in relation to AL-specific therapy may vary, the haematological regression may explain the findings mentioned above.

Overall, these data suggest that, in our cohort, AL patients compared with ATTR patients exhibit a trend towards having less advanced disease and/or have had shorter time to adapt to the amyloid deposition.

Exercise limitations in amyloid cardiomyopathy versus HF cases

The MECKI score database was used to identify patients with characteristics that allowed a proper with amyloid cases. The MECKI score data are probably the largest HF population set with several variables including CPET.[13]

In chronic HF among CPET parameters both peak VO_2 and VE/VCO_2 slope have a strong and independent role in defining both functional capacity and prognosis. Albeit the genesis of abnormal peak VO_2 and VE/VCO_2 slope are multifactorial, the general consensus is, that the former is mainly related to low CO and abnormal O_2 delivery and utilization by the working muscles while the latter is related to increased dead space, ventilation mismatch and abnormal ventilatory drive, combined leading to inefficiency of ventilation. Of note, several more are the possible original causes of exercise induced ventilation inefficiency including acute volume overload.[33] In patients with amyloid cardiomyopathy, a volume overload and a tendency towards a pleural or pericardial effusion is common.[34] Indeed, in healthy subjects and in HF patients, rapid saline infusion is associated with a VE/VCO_2 slope increase.[35,36]

The peculiar finding of CPET in amyloid patients is ventilation inefficiency, as suggested by a high VE/VCO_2 slope and a low $PETCO_2$ value. The increase in VE/VCO_2 slope may be due to several mechanisms, including a rapid increase in pulmonary artery wedge pressure and ventilation/perfusion mismatch. The former is associated with increased ventricular stiffness of the amyloid heart, often referred to as the ‘stone

heart of the antiques' while the latter can result from a blunted CO increase during exercise, pulmonary hypertension or a damaged alveolar capillary membrane.[37] All these events are possible in cardiac amyloidosis and likely contribute to the very high VE/VCO_2 slope observed in these patients.

Matching patients based on peak VO_2, the early anaerobic threshold in amyloid patients compared with those with HF may reveal fundamental disease mechanisms that affect exercise performance. The anaerobic threshold, a measure of sustainable O_2 uptake, may be influenced not only by the fixed stroke volume but also by the chronotropic incompetence, often seen in amyloid patients.[38,39] Additionally, microvascular dysfunction, which reduces oxygen delivery, might also influence the anaerobic threshold and may be as pronounced or even more severe in amyloid patients compared with those with HF.[40]

To strengthen these findings, further studies are needed to evaluate other mechanisms behind ventilation inefficiency (e.g., mechanisms of impaired reflexes such as chemoreflex, baroreflex or ergoreflex). Albeit the present study was not designed to analyse clinical implications, our findings suggest that the treatment of cardiac amyloidosis may be guided by changes in the VE/VCO_2 slope. This implies that high diuretic doses or pulmonary hypertension specific drugs might play a role. Finally, we showed that CPET is versatile and can be used to enhance understanding, prognosis and management of patients with cardiac amyloidosis.

In the present study, we demonstrated not only the presence of a marked ventilation inefficiency, evidenced by an elevated VE/VCO_2 slope and low $PETCO_2$, but also showed the pivotal role of VE/VCO_2 slope abnormalities in determining functional capacity impairment in amyloid cardiomyopathy. Indeed, even after matching for LVEF and peak VO_2 amyloid cases have a much higher VE/VCO_2 slope.

Limitations

The present study has a few limitations that should be acknowledged. First, although all CPET examinations were conducted and evaluated by recognized CPET experts, the evaluations were not centralized and were performed independently by each recruiting centre. Second, we did not measure CO during exercise, which is known to enhance CPET interpretation. Third, as a multicentre study, the data collection regarding medications, comorbidities and variations in disease severity was not uniform. Lastly, we did not assess previous physical activity (e.g., sports participation) through the patients' lifetimes, therefore associations between those factors and CPET results were not evaluated. The information about lifetime sport or physical activity in cardiac amyloidosis would increase our understanding of relationships with those factors and physical performance in advanced disease stages.

Conclusions

In conclusion, we showed that CPET is feasible in amyloid cardiomyopathy regardless of the amyloid type and that, in amyloid patients, ventilation inefficiency is the major determinant of exercise limitation.

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Conflict of interest

Robin Willixhofer: travel expenses by Pfizer Corporation Austria GmbH, Vienna, Austria; Contini Mauro has nothing to disclose. Michele Emdin has nothing to disclose. Damiano Magrì has nothing to disclose. Alice Bonomi has nothing to disclose. Elisabetta Salvioni has nothing to disclose. Celeste Fabrizio has nothing to disclose. Alberico Del Torto has nothing to disclose. Claudio Passino has nothing to disclose. Chiara Arzilli has nothing to disclose. Emiliano Fiori has nothing to disclose. Nicolò Capra has nothing to disclose. Beatrice Musumeci has nothing to disclose. Giuseppe Vergaro has nothing to disclose. Vincenzo Castiglione has nothing to disclose. Giacomo Tini has nothing to disclose. Andrea Baggiano has nothing to disclose. Iacopo Fabiani has nothing to disclose. Susanna Sciomer has nothing to disclose. Piergiuseppe Agostoni received support for travel expenses and honoraria for lecturing from Novartis, BNS, Bayer, Schiller, Vyare, BNS. Roza Badr-Eslam: received research grants by OrphaCare GmbH, Vienna, Austria, and AstraZeneca Österreich GmbH, Vienna, Austria, speaker fees from Merck Sharp & Dohme Ges.m.b.H., Vienna, Austria, AOP Orphan Pharmaceuticals GmbH, Vienna, Austria and OrphaCare GmbH, Vienna, Austria. Christina Kronberger: travel expenses by OrphaCare GmbH, Vienna, Austria. Andreas Kammerlander has nothing to disclose. Rene Rettl: Speaker fees and congress support from Akcea Therapeutics Germany GmbH, Munich, Germany, Alnylam Germany GmbH, Munich, Germany, and speaker fees and research grants from Pfizer Corporation Austria GmbH. Christophe D. J. Capelle has nothing to disclose.

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Permission note

All material is original to this submission and has not been previously published.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Differences in peak VO_2 between cardiac amyloidosis and heart failure. Differences in peak oxygen consumption via boxplots in cardiac amyloidosis patients compared to individually 1:1 matched heart failure cohort of the MECKI score pool. Abbreviations: HF-MECKI = heart failure cohort of the MECKI score registry; *P*-value = measure of statistical significance; VO_2 = oxygen consumption.

Figure S2: Differences in peak VO_2 between AL and ATTR patients. Differences in peak oxygen consumption via boxplots between AL and ATTR patients. Abbreviations: AL = light-chain amyloidosis; ATTR = transthyretin; *P*-value = measure of statistical significance; VO_2 = oxygen consumption.

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