Original research

Prevalence and functional impact of chronotropic incompetence in amyloid cardiomyopathy: a multicentre analysis

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ABSTRACT

Background Little evidence is available about heart rate (HR) response to exercise as well as its relationship with functional capacity in amyloid cardiomyopathy. Then, in a multicentre cohort of patients with amyloid cardiomyopathy, we investigated the prevalence of chronotropic incompetence (CI) and its relationships with cardiopulmonary exercise testing (CPET) variables.

Methods Data from 172 outpatients with amyloid cardiomyopathy who performed a maximal CPET and who had no significant rhythm disorders were analysed.

Results The prevalence of CI differed depending on the age-predicted peak HR (pHR%) cut-off value adopted, ranging from 16% to 59%. pHR% correlated non-linearly with peak oxygen uptake (pVO_2), either as expressed as a percentage of the maximum predicted or as mL/kg/min ($p<0.001$). Although to a lesser extent, pHR% correlated inversely with ventilatory efficiency ($p<0.001$). A pHR%≤75% resulted in the most accurate cut-off value in identifying a moderate-to-severe exercise impairment (sensitivity 72%; specificity 73%; area under the curve 77.2%).

Conclusions CI is prevalent in patients with amyloid cardiomyopathy in sinus rhythm, its percentage varying according to the pHR% cut-off value. A blunted exercise-induced HR response correlated with a poor exercise capacity even in this setting of patients, a pHR%≤75% cut-off value being possibly useful in centres without CPET availability to identify a significant exercise impairment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiopulmonary exercise testing (CPET) represents an emerging noninvasive tool in managing patients with in amyloid cardiomyopathy. Indeed, within the CPET-derived variables, both peak oxygen uptake (pVO2) and ventilation to carbon dioxide production relationship (VE/VCO2) slope have been shown as independent prognostic parameters after adjusting for known predictors. Conversely, little evidence is available about the prevalence of chronotropic incompetence (CI) and its relationship with exercise capacity in this specific setting.

WHAT THIS STUDY ADDS

⇒ A great portion of patients with in amyloid cardiomyopathy suffers from CI, although the effective prevalence of this feature varies greatly according to the different cut-off of the age-predicted peak HR (pHR%) values adopted. CI presence strongly correlated with a poor exercise capacity, pHR% showing a significant relationship with the main CPET-derived parameters. Furthermore, the present provides data regarding the accuracy of a few pHR% cut-off values in identifying those patients with a moderate-to-severe exercise impairment as arbitrarily defined by a pVO2≤60% of the maximum predicted, the 75% threshold resulting as the most accurate.

INTRODUCTION

Amyloidosis represents a multi-faceted pathological condition with markedly different morphologic, functional and clinical spectra, all due to a misfolded proteins' deposition within diverse tissues.[1] Specifically, cardiac involvement in amyloidosis leads to peculiar forms of heart failure (HF) with preserved ejection fraction primarily characterised by increased left ventricular filling pressures and, with disease worsening, by reduced cardiac output and ejection fraction.[2–4] Accordingly, as in all the HF settings,[5] also in amyloid cardiomyopathy, the pivotal symptom is represented by a progressive impairment of functional capacity.[6] Consequently, even in these patients, growing evidence strongly supports cardiopulmonary exercise testing (CPET) as the best noninvasive approach to obtain a comprehensive functional assessment.[7] Furthermore, within the CPET-derived variables, both peak oxygen uptake (pVO_2) and ventilation to carbon dioxide production relationship (VE/VCO_2) slope

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our data might be helpful in daily clinical practice, especially considering that the CPET is not always available in all centerscentres whereas the HR-derived variables are easily obtainable from a simple exercise test. Specifically, besides supplying a snapshot of CI prevalence and its functional impact in amyloid cardiomyopathy, due to its high negative predictive value, a 75% cutoffcut-off value for pHR% might identify those patients who are less likely to need a more exhaustive functional evaluation, such as CPET.

have been shown as independent prognostic parameters after adjusting for known predictors.[7–10] As regards pVO_2, it is dependent on cardiac output (stroke volume (SV) * heart rate (HR)), O_2 arterial content and O_2 extraction by the peripheral tissues.[11] Of note, in a restrictive cardiomyopathy as in the case of amyloid cardiomyopathy, HR should play a great role in maintaining the cardiac output during exercise. However, differently from other HF settings,[12–14] there is little evidence regarding the prevalence of chronotropic incompetence (CI) as well as its relationship with exercise capacity in patients with cardiac amyloidosis. Exploring this aspect might be of pathophysiological and clinical interest since that, besides the diastolic and systolic impairment, also autonomic dysfunction, and disruptions of the heart conduction system impact functional capacity by worsening the HR response to exercise.[15] Furthermore, despite the growing popularity and diffusion of CPET, there are still several centres where CPET cannot be executed and where an easy-to-obtain variable, such as peak HR during a maximal exercise test, might be helpful in the functional status definition.

Therefore, in a large cohort of stable consecutive outpatients diagnosed with amyloid cardiomyopathy, this multicentre study investigated first the prevalence of CI, estimated by using a few different cut-offs of the age-predicted peak HR (pHR%). Thereafter, possible relationships between exercise-induced HR and the main CPET-derived variables have been explored, with a special focus on the pHR% versus pVO_2 relationship and pHR% accuracy in identifying a moderate-to-severe exercise impairment.

METHODS

Study sample

We analysed data of 231 consecutive stable outpatients from three expert centres (Centro Cardiologico Monzino, Milan, Italy; Sant'Anna Scuola Universitaria Superiore Pisa, Italy; Medical University of Vienna, Austria) diagnosed between 2019 and 2023 with wild-type transthyretin amyloidosis (ATTR), hereditary or variants of ATTR, light chain amyloidosis (AL) or combined forms of ATTR and AL cardiomyopathy, in accordance with the current guidelines.[1 16]

Primary inclusion criteria were stable clinical conditions with unchanged medications for at least 3 months, availability of a maximal symptom-limited CPET performed on a cycle ergometer, absence of comorbidities or non-cardiac amyloid-related organ involvement which directly interfere with exercise performance such as moderate-to-severe anaemia (haemoglobin levels <100 g/L), severe obstructive/restrictive lung disease, significant peripheral vascular disease, exercise-induced angina and/or ST changes as well as moderate-to-severe polyneuropathy disabilities. Furthermore, to avoid confounders regarding the HR kinetics,[17] patients with atrial fibrillation (AF), those with second or higher degree atrioventricular block as well as with a pacemaker-dependent rhythm were excluded.

Noteworthy, all patients enrolled were still naïve to disease-specific therapy (ie, tafamidis). Indeed, in our centres, consistent with their clinical condition, all the referred patients with suspected amyloid cardiomyopathy received a baseline comprehensive clinical and instrumental evaluation, including a functional one by means of a maximal CPET, to confirm the diagnosis and starting a possible disease-specific therapy.

Cardiopulmonary exercise testing

A maximal, symptom-limited CPET was performed on an electronically braked cycle ergometer (Centro Cardiologico Monzino, IRCCS: Bike Lode B.V. Groningen, The Netherlands; Sant'Anna Scuola Universitaria Superiore: eBIKE GE Healthcare Chicago, USA; Medical University of Vienna: eBIKE GE Healthcare Chicago, USA) connected to a metabolic chart (Centro Cardiologico Monzino: Quark PFT Cosmed, Roma, Italy; Sant'Anna Scuola Universitaria Superiore Pisa: Dual Monitor Vyntus CPX Vyaire Medical GmbH, Hoechberg, Germany; Medical University of Vienna: Dual Monitor Vyntus CPX Vyaire Medical GmbH, Hoechberg, Germany). A personalised ramp exercise protocol was chosen, aiming at a test duration of 10±2 min. The exercise was preceded following a standard technique, specifically by a 2-minute resting phase with breath-by-breath gas exchange monitoring followed by a 3-minute unloaded warm-up. CPET was self-terminated by the patient when referring to maximal effort and as confirmed by a peak respiratory exchange ratio (RER) ≥1.05. A breath-by-breath analysis of O_2, carbon dioxide (CO_2) and ventilation (VE) was performed, and peak values were computed as the highest observed measurements (20 s average). The predicted pVO_2 was determined by using the sex, age and weight-adjusted Hansen/Wasserman equations. The anaerobic threshold (AT) was identified through a V-slope analysis of VO_2 and CO_2 production (VCO_2) and was confirmed through the specific behaviour of the ventilatory equivalents of O_2 (VE/VO_2) and CO_2 (VE/VCO_2), as well as through the end-tidal pressure of O_2 and CO_2. The relation between VE and VCO_2 (ie, the ventilatory efficiency) was analysed as the slope (VE/VCO_2 slope) of the linear relationship between VE and VCO_2 from 1 min after the beginning of the loaded exercise to the end of the isocapnic buffering period.[18]

A 12-lead ECG, blood pressure and HR were recorded. Specifically, pHR was collected during CPETs, whereas rest HR was measured after at least 2 min of rest in a seated position on the cycle ergometer. Peak HR was also analysed as a percentage of the maximum predicted value according to the standard formula (pHR% = (pHR / 220 – age) × 100) so that a possible clinical impact was explored using both its continuous values and according to different cut-off values with 5% of the predicted values incremental steps.[12–14] The peak HR reserve (pHRR) was also obtained according to the following formula: pHRR%, chronotropic index = {(pHR – resting HR)/[(220 – age) – resting HR]} × 100.

Statistical analysis

Unless otherwise indicated, all data are expressed as mean±SD. Data with skewed distribution are given as median and IQR difference (75th percentile–25th percentile). Categorical variables were compared with a difference between the proportion test; a two-sample t-test was used to compare the general characteristics and other continuous linear data between the study groups; the Wilcoxon test was used to compare non-normally

distributed variables. We supplied a description of the main data characteristics, pooling the data but, due to the clear multilevel structure, that is, patients are clustered into three centres, we performed a random effects regression, with centre-specific Gaussian-distributed intercepts. We also investigated for potential non-linear relationships between the main CPET parameters (pVO_2 and VE/VCO_2 slope) and pHR%, using a polynomial specification of the linear predictor. Furthermore, we also considered possible interactions between exercise data and β-blocker therapy. Accordingly, we define the following three models: Model 1: pVO_2, % of predicted = $\beta_0 + \beta_1$ (pHR, % of predicted) + β_2 (pHR, % of predicted)^2 + β_3 Betablocker + Centre; Model 2: pVO_2, mL/kg/min = $\beta_0 + \beta_1$ (pHR, % of predicted) + β_2 (pHR, % of predicted)^2 + β_3 Betablocker + Centre; Model 3: VE/VCO_2 slope = $\beta_0 + \beta_1$ (pHR, % of predicted) + β_2 (pHR, % of predicted)^2 + β_3 Betablocker + Centre where Centre$\sim N(0,\sigma)$. Conditional R^2 was also computed taking both the fixed and random effects into account.

Finally, receiver-operating curves (ROC) were also estimated to display the capacity of pHR% to discriminate between patients with a moderate-to-severe exercise impairment arbitrarily defined as a pVO_2 lower than 60% of the maximum predicted. According to this approach, we reported the thresholds corresponding to the best sum of sensitivity and specificity. Furthermore, we also tested the accuracy of a few possible alternative pHR% cut-off values, usually adopted in clinical settings.

Statistical analysis was performed using R (R Development Core Team, 2009) packages. All tests were two-sided. A p value lower than or equal to 0.05 was considered statistically significant.

RESULTS

General characteristics of the study population

Starting from the initial pool of 231 outpatients with amyloid cardiomyopathy, a total of 172 patients (74%) met the inclusion/exclusion criteria (151 ATTR of whom 8 with hereditary ATTR, 16 AL and 5 mixed AL and ATTR forms) and were therefore considered for the present analysis. Indeed, data from 59 patients were ruled out due to one or more of the previously mentioned exclusion criteria, AF being the most prevalent hindering condition with 51 (22%) patients affected. Within the study population, due to the usual centres' strategy (see Methods), the time frame between the baseline CPET assessment and the definite diagnosis of amyloid cardiomyopathy was quite short for most of them (less than 3 months average).

Table 1 reports in detail the main clinical and exercise test data collected at the study run-in in the overall sample. The study population consisted mostly of elderly male patients (mean age 73 years) with a moderate exercise limitation (pVO_2 averagely 70% of the maximum predicted). There was a substantial percentage of patients in whom the AT was not identified (nearly 10% of the total sample).

With respect to therapy, we reported only the β-blocker datum which is the only agent used in the present study population possibly interfering with HR kinetics. The indications for β-blockers' therapy, present in 66 patients, were related to the presence of one or more of the following clinical conditions: arterial hypertension (34 cases, 51%), history of paroxysmal AF (17 cases, 26%), ischaemic heart disease (5 cases, 7%) and palpitations (18 cases, 27%). This treatment, at the CPET evaluation, was present in slightly more than a third of the study sample with a relatively low dosage, the latter being converted to equivalent doses of bisoprolol to avoid confounding (ie, the daily dosage in patients taking carvedilol was divided by 5, the dose of metoprolol was divided by 20 while the nebivolol dose was left unchanged).[12–14 19] Table 2 shows a comparison within the study cohort grouped according to the β-blocker therapy presence. The two subgroups were well matched with respect to the main anthropometric, clinical and submaximal exercise data, whereas the subgroup of patients on β-blockers showed lower pHR and pVO_2 values, expressed either in absolute or as a percentage of the maximum predicted.

Table 1 Main clinical variables of the overall study sample (n=172 patients)

General data	
Age, years	73±9
Male, n %	155 (90)
Body Mass Index, kg/m^2	26.3±3.8
NT-proBNP, pg/mL	1728(2377)
LVEF, %	53±8
β-Blockers, n (%)	66 (38)
β-Blockers dosage*, mg	3.3±1.8
Exercise testing variables	
Rest HR, bpm	71±14
Rest SBP, mm Hg	128±18
HR at AT, bpm	91±19
VO_2 at AT, mL/kg/min	11.8±3.8
WL at AT, W	37±19
pHR, bpm	120±24
pHR%, % of predicted	82±17
ΔHR, bpm	49±20
pHHR%, % of predicted	67±32
pVO_2, mL/kg/min	15.4±4.2
pVO_2, % of predicted	71±19
O_2 pulse peak, mL/beat	10.8±3.1
Peak WL, W	82±32
Peak SBP, mm Hg	166±26
VE/VCO_2 slope	36.7±7.8
RER	1.12±0.06

Data are expressed as mean±SD, as absolute number of patients (% on the total sample) or as median (75th–25th percentile).
*Bisoprolol dose equivalent (see the Methods section for details).
AT, anaerobic threshold; HR, heart rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pHR, peak HR; pHRR, peak HR reserve (chronotropic index); pVO_2, peak oxygen consumption; RER, respiratory exchange ratio; SBP, systolic blood pressure; VE/VCO_2, ventilatory equivalents of carbon dioxide; WL, workload; ΔHR, (pHR – resting HR).

CI prevalence and association with functional capacity

The overall prevalence of CI was remarkable, but it differed significantly depending on the pHR% cut-off value adopted, ranging from 59% with a pHR% cut-off value ≤85% to 16% with a pHR% cut-off value ≤65% (figure 1). Table 3 details the main clinical and CPET-derived variables in the overall study sample when categorised according to different pHR% cut-off values ranging from 85% to 65%, with the exercise impairment degree raising with the reduction of the pHR% cut-off values adopted.

The random-effects regression analysis reported in table 4 shows a significant positive relationship, although non-linear, between pHR% and pVO_2, either in terms of absolute values corrected for body weight (mL/kg/min) or expressed as a percentage of the maximum predicted (%) (figure 2, upper panels). Similarly,

Table 2 Main clinical variables of the overall study sample according to the β-blocker therapy

General data	β-Blocker group 66)	No β-blocker group 106)	P values
Age, years	73±9	74±9	Ns
Male, n %	59 (89)	90 (85)	Ns
Body Mass Index, kg/m^2	27±4	26±3.7	Ns
NT-proBNP, pg/mL	1894 (2432)	1463 (2283)	Ns
LVEF, %	51±10	53±9	Ns
β-Blockers dosage**, mg	3.3±1.8	–	
Exercise testing variables			
Rest HR, bpm	70±14	72±14	Ns
Rest SBP, mm Hg	127±19	128±18	Ns
HR at AT, bpm	91±19	91±19	Ns
VO_2 at AT, mL/kg/min	9.2±2.7	9.8±3.2	Ns
WL at AT, W	38±17	37±20	Ns
pHR, bpm	114±22	123±25	0.010
pHR%, % of predicted	78±15	84±17	0.007
ΔHR, bpm	44±19	52±21	0.009
pHHR%, % of predicted	59±28	73±34	0.007
pVO_2, mL/kg/min	14.4±3.8	16.1±4.4	0.010
pVO_2, % of predicted	67±19	74±18	0.012
O_2 pulse peak, mL/beat	10.9±3.3	10.8±3.0	Ns
Peak WL, W	78±26	84±35	Ns
Peak SBP, mm Hg	163±27	168±28	Ns
VE/VCO_2 slope	37.1±8.7	36.4±7.2	Ns
RER	1.11±0.05	1.12±0.07	Ns

*Bisoprolol dose equivalent (see the Methods section for details).
AT, anaerobic threshold; HR, heart rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pHR, peak HR; pHRR, peak HR reserve (chronotropic index); pVO_2, peak oxygen consumption; RER, respiratory exchange ratio; SBP, systolic blood pressure; VE/VCO_2, ventilatory equivalents of carbon dioxide; WL, workload; ΔHR, (pHR – resting HR).

the pVO_2 values worsened with the reduction of the pHR% value according to different cut-offs (figure 2, lower panels). Also, although to a lesser extent, a similar behaviour has been observed between pHR% and ventilatory efficiency (table 4 and figure 3). No significant influence of β-blockers' therapy on the abovementioned relationships was found (table 4). Furthermore, due to the multilevel data structure (properly accounted for as discussed in the Statistical analysis section), a certain amount of heterogeneity across centres was estimated (random effect SD (σ) for model 1=0.002, for model 2=0.559, for model 3=2.094) and, accordingly, accounted by within the linear mixed models.

Eventually, focusing on the discrimination power of pHR% in detecting those patients with a moderate-to-severe exercise limitation, the ROC analysis showed that the best threshold was a pHR%≤75.6% (sensitivity 72%; specificity 73%; positive predictive value (ppv) 50%; negative predictive value (npv) 87%; area under the curve 77.2%) (figure 4). For clinical purposes, the following pHR% cut-off values were also tested: pHR%≤65% (sensitivity 34%; specificity 94%; ppv 67%; npv 79%); pHR%≤70% (sensitivity 53%; specificity 85%; ppv 56%; npv 83%), pHR%≤75% (sensitivity 70%; specificity 73%; ppv 49%; npv 86%), pHR%≤80% (sensitivity 77%; specificity 58%; ppv 41%; npv 87%) and pHR%≤85% (sensitivity 87%; specificity 50%; ppv 40%; npv 91%).

DISCUSSION

The present multicentre analysis, on a relatively large cohort of stable consecutive outpatients with amyloid cardiomyopathy, showed that a great portion of patients suffered from a blunted exercise-induced HR response, although the effective prevalence of CI varies greatly according to the different pHR% cut-off values adopted. Overall, the CI presence strongly correlated with a poor functional status, pHR% showing a significant relationship with the main CPET-derived parameters. Lastly, our data suggest a pHR%≤75% as the most accurate CI cut-off value in identifying those patients with a moderate-to-severe exercise impairment (ie, pVO_2≤60%), this finding being useful in those centres where CPET cannot be executed.

CI has been proposed as a significant player, recently even shown to be in almost half of all patients,[20] in determining the exercise impairment in amyloid cardiomyopathy[10] as well as, more in general, in HF with preserved ejection fraction.[21 22] The presence of cardiac amyloid infiltration leads to diastolic dysfunction because of chamber dilatation and neurohumoral activation with a progressive inability to augment the stroke volume in a physiological manner.[23] Moreover, due to morphological remodelling and de-differentiation of cardiomyocytes, physiological electrical conduction is impaired, which provides the conditions for the potential development of AF and/or other conduction disturbances, mainly in the most advanced disease stage.[24] Given those factors, it is reasonable that the HR response to exercise remains crucial in determining the final pVO_2 value.

However, in amyloid cardiomyopathy both the autonomic dysfunction and the disruptions of the heart conduction system might exert a detrimental effect on chronotropism, thus wasting the above-mentioned compensative mechanism.[6 15] Additionally, a mechanism potentially influencing chronotropism may be related to the exaggerated metaboreflex sensitivity in patients with ATTR, which leads to a reduced stroke volume and cardiac output. The combination of inadequate HR response and increased metaboreflex sensitivity may create a cycle where exercise becomes increasingly difficult and leads to early fatigue.[25] Eventually, the occurrence of AF and/or of atrioventricular or intraventricular conduction defects leading to pacemaker implantation alter definitively the physiological HR response to exercise.[17] However, although recent studies highlighted CI as a prevalent clinical feature and a detrimental factor in amyloid cardiomyopathy, a focused analysis on this topic is still lacking. Indeed, a most recent elegant paper by Pate and colleagues[10] conducted on a remarkable cohort of patients with ATTR, besides supporting the CPET-derived variables (ie, pVO_2 and ventilatory efficiency) as powerful predictors of prognosis, found a pHR% reduction in all the study sample which was independent of the cardiac infiltration degree evaluated at cardiac MRI. Furthermore, the same paper also attempted a CI analysis by means of the chronotropic index, the latter being strongly impaired in the overall cohort (average values lower than 60%) but not independently related to prognosis at multivariate analysis. However, it should be noted that the abovementioned study included more than half of patients with AF (40%) and paced-guided rhythm (11%) with obvious consequences in terms of HR-derived data interpretation. Furthermore, they analysed CI based on the pHRR%, which depends more on the delta HR (ie, pHR – resting HR) than on the pHR%, as the pHR is crucial in determining cardiac output at the end of exercise mainly in

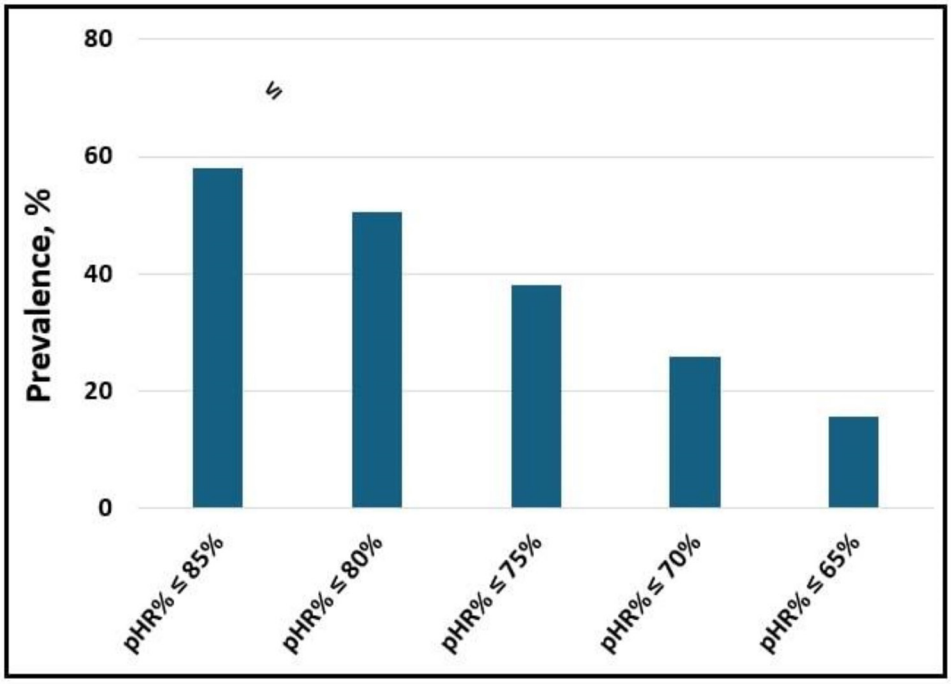

Figure 1 CI prevalence according to different pHR% cut-off values. Data about CI prevalence according to different cut-off values in the cohort of patients with amyloid cardiomyopathy in sinus rhythm (n=172). CI, chronotropic incompetence; pHR%, peak HR expressed as a percentage of the maximum predicted.

the context of amyloid cardiomyopathy. Conversely, the present research paper, conducted within a cohort of patients all on sinus rhythm, provides originally a snapshot view of the CI prevalence according to different cut-off values of pHR%, the latter being ultimately the most common parameter to define the HR behaviour during a maximal exercise.[13]

As in many other HF settings,[12–14 26] the estimated prevalence of CI varied greatly according to the pHR% cut-off value

Table 3 Main clinical variables of the overall study sample categorised according to different pHR% cut-off values

General data	pHR≤85% 103 (60%)	pHR≤80% 90 (52%)	pHR≤75% 68 (39%)	pHR≤70% 46 (27%)	pHR≤65% 28 (16%)
Age, years	72±9	72±9	71±10	70±11	71±11
Male, n %	89 (86)	77 (86)	58 (85)	38 (83)	22 (79)
Body Mass Index, kg/m^2	26.5±4.1	26.6±4.1	26.9±4.4	27.0±4.7	26.9±4.4
NT-proBNP, pg/mL	1962 (3294)	1969 (3420)	1982 (3418)	2310 (3451)	3373 (5316)
LVEF, %	52±9	52±10	52±9	52±10	52±9
β-Blockers, n (%)	48 (47)	41 (46)	35 (51)	22 (48)	13 (46)
β-Blockers dosage*, mg	3.4±1.6	3.4±1.7	3.5±1.6	3.7±1.6	3.7±1.6
Exercise testing variables					
Rest HR, bpm	66±11	64±10	65±10	62±9	59±6
Rest SBP, mm Hg	126±18	126±19	125±19	125±19	121±16
VO_2 at AT, mL/kg/min	9.2±2.8	9.3±2.8	9.1±2.7	9.0±2.9	8.5±2.5
WL at AT, W	38±19	37±19	36±15	36±16	37±14
ΔHR, bpm	38±14	36±13	33±11	31±11	28±11
pHRR%, % of predicted	51±14	47±13	40±11	35±10	30±11
pVO_2, mL/kg/min	14.4±3.9	14.3±4.0	13.4±3.6	13.1±3.5	12.0±3.3
pVO_2, % of predicted	65±17	64±16	60±15	58±15	55±17
O_2 pulse peak, mL/beat	11.0±3.1	11.2±3.1	11.2±3.2	11.3±3.4	11.1±3.6
Peak WL, W	74±30	73±30	67±27	65±27	57±24
Peak SBP, mm Hg	163±29	162±28	162±29	160±29	157±28
VE/VCO_2 slope	37.7±8.4	38.0±8.0	38.4±8.2	39.3±9.1	40.7±10.7
RER	1.12±0.07	1.11±0.06	1.13±0.07	1.10±0.04	1.13±0.05

*Bisoprolol dose equivalent (see the Methods section for details).
AT, anaerobic threshold; HR, heart rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pHR, peak HR; pHRR, peak HR reserve (chronotropic index); pVO_2, peak oxygen consumption; RER, respiratory exchange ratio; SBP, systolic blood pressure; VE/VCO_2, ventilatory equivalents of carbon dioxide; WL, workload; ΔHR, (pHR – resting HR).

Table 4 Relationship between main CPET parameters and pHR% (linear mixed effects models)

	Model 1 pVO_2, % of predicted	Model 2 pVO_2, mL/kg/min	Model 3 VE/VCO_2 slope
Intercept (β_0)	−63.652	−12.232	88.700
SE	24.325	5.760	10.956
P value	0.009	0.034	< 0.001
pHR, % of predicted (β_1)	2.848	0.604	−1.157
SE	0.577	0.137	0.259
P value	< 0.001	< 0.001	< 0. 001
pHR, % of predicted squared (β_2)	−0.014	−0.003	0.006
SE	0.003	0.001	0.001
P value	< 0.001	< 0.001	< 0.001
β-Blockers' therapy	−3.745	−1.127	0.256
SE	2.515	0.595	1.122
P value	0.138	0.060	0.820
Conditional R^2	0.284	0.244	0.236

See the Statistical Analysis section for further explanations.
CPET, cardiopulmonary exercise testing; pHR, peak HR; pVO_2, peak oxygen consumption; VE/VCO_2, ventilatory equivalents of carbon dioxide.

adopted, ranging from 16% up to 59% of the study population. Most importantly, the present study findings support a significant relation between pHR% and pVO_2. Noteworthy, the coefficients were higher than those we previously reported in a study conducted in patients with HF with mildly reduced ejection fraction.[14] This finding reinforces the HR role in determining the pVO_2 in a restrictive HF phenotype. In such a context, differently from the HF with reduced LVEF setting,[12 19] a potentially detrimental role of negative chronotropic drugs might be reasonable and, supporting the hypothesis, compared with a well-matched subgroup off therapy, we found a worse exercise-induced HR response and lower pVO_2 values in the subgroup on β-blocker.

Eventually, although we are fully convinced that pVO_2 remains pivotal in the functional status and prognostic evaluation of amyloid cardiomyopathy,[7–10] our data might be reassuring in daily clinical practice, especially considering that the CPET is not always available in all centres whereas the HR-derived variables are easily obtainable from a simple exercise test. Accordingly, in such cases, although chronotropic variables should be considered as continuous from a pathophysiological viewpoint, the present provides data regarding the accuracy of a few pHR% cut-off values in identifying those patients with a moderate-to-severe exercise impairment as arbitrarily defined by a $pVO_2 \leq 60\%$ of the maximum predicted, the 75% threshold resulting as the most accurate. However, although highly desirable in clinical practice, mainly considering its high negative predictive value, the proposed cut-off value seems to exert its best clinical utility as a screening tool to identify those patients with a preserved exercise capacity who are less likely to need a precise functional evaluation, such as CPET.

LIMITATIONS

The retrospective nature of the present analysis together with the not homogeneous study sample in terms of amyloid cardiomyopathy aetiology both represent significant limitations that need to be acknowledged. However, besides the fact that nearly the 90% of patients evaluated had a ATTR aetiology, it is highly reasonable a detrimental role of CI due to the restrictive nature of the amyloid cardiomyopathy per se and, as previously highlighted, the pHR% reduction is prevalent regardless of the cardiac amyloid burden.[10]

Our analysis involved only patients still naïve to disease-specific therapy (ie, tafamidis), thus we cannot speculate about a possible restoration of the HR kinetics with respect this specific medical treatment.[27] Similarly, due to the study design, we might

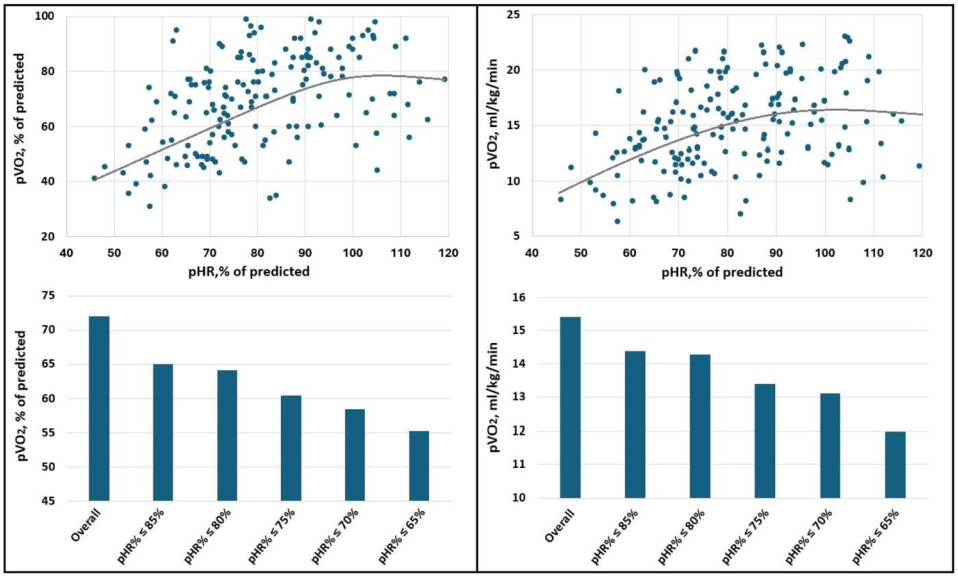

Figure 2 Relationships between exercise-induced HR response and pVO_2. *Upper panels:* Relationship between pHR% and pVO_2 expressed as percentage of a maximum predicted VO_2 (left) and pVO_2 absolute values corrected for a kg of body weight (mL/kg/min) (right). The trend lines represent the fitted polynomial trend obtained from the mixed effects model (see the Statistical section and table 4 for details). *Lower panels:* Average pVO_2 values (left: pVO_2 expressed as a percentage of maximum predicted VO_2; pVO_2 absolute values corrected for a kg of body weight) in CI groups categorised according to pHR% different cut-off values. CI, chronotropic incompetence; pHR%, peak HR expressed as a percentage of the maximum predicted; pVO_2, peak oxygen uptake.

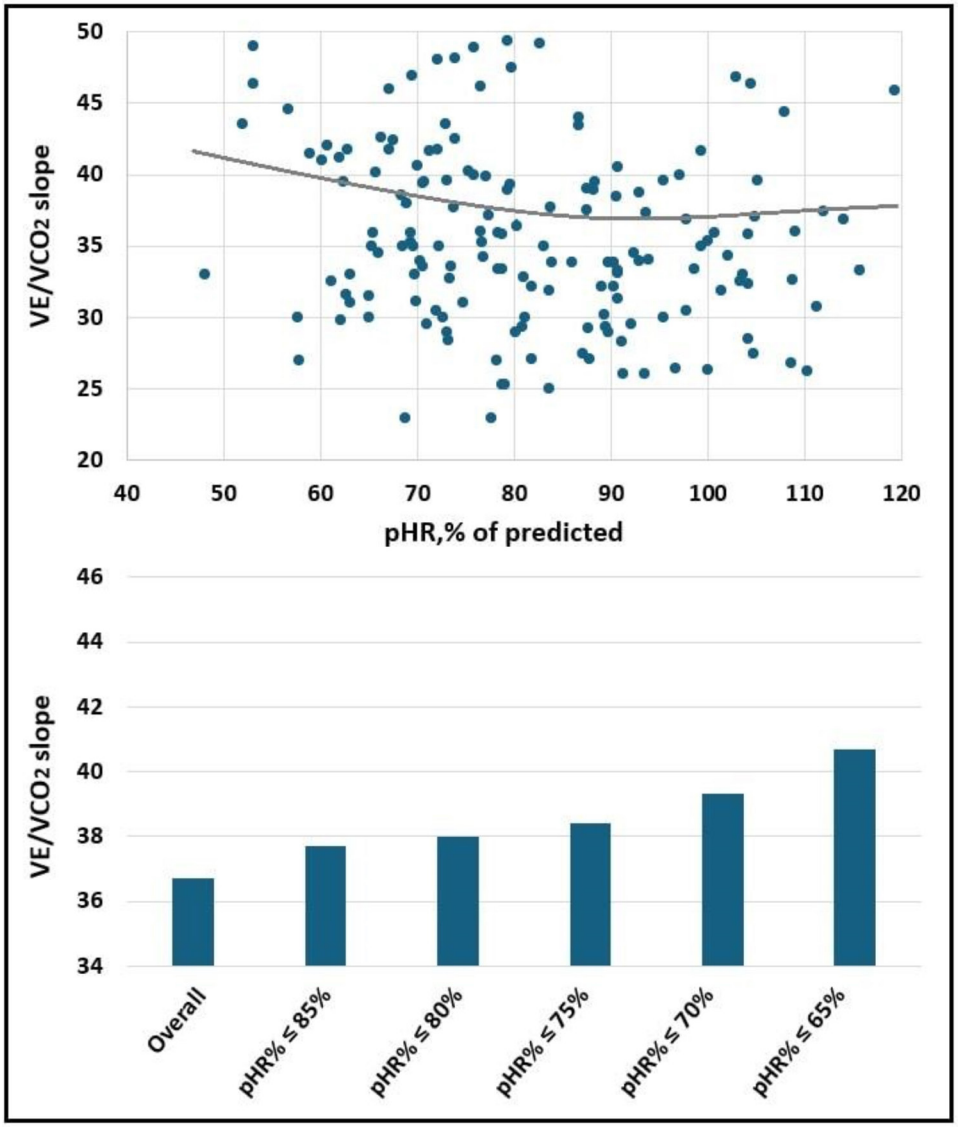

Figure 3 Relationships between exercise-induced HR response and ventilatory efficiency. *Upper panels:* Relationship between pHR% and ventilatory efficiency. The trend lines represent the fitted polynomial trend obtained from the mixed effects model (see Statistical section and table 4 for details). *Lower panels:* Average VE/VCO_2 slope values in CI groups categorised according to pHR% different cut-off values. CI, chronotropic incompetence; HR, heart rate; pHR%, peak HR expressed as percentage of the maximum predicted; VE/VCO_2 slope, relationship between ventilation versus carbon dioxide production.

only speculate about a possible negative impact of β-blocker therapy on exercise capacity in this setting of patients due to their prevalent restrictive phenotype. Furthermore, we excluded those patients with AF which represents a common comorbidity in amyloid cardiomyopathy.[10 28] However, due to the well-known differences in HR kinetics during exercise as well as in pharmacological strategies,[17 29] we considered the choice to evaluate only patients in sinus rhythm a strength rather than a real limitation of the present paper. Notably, as per our previous research papers,[12–14] we adopted a unique formula for pHR% not accounting for the gender difference, the main underlying reasons being: (a) the historical pHR% formula by Fox does not account for gender type; (b) pHR% formulas accounting for gender exist but they are not routinely used in clinical practice; (c) our sample includes a really small percentage of female (around 10%). Similarly, we avoided complicating the present CI analysis by using 'dedicated' formulas to estimate maximal pHR in patients taking β-blockers, mainly because: (a) they are not routinely used in daily clinical practice;(b) they have not been validated for the disease setting explored in this study; (c) β-blocker therapy was present in only one-third of the study sample and, furthermore, at low dosages.

Another possible limitation, proper due to the actual aim of the study, is that we did not examine the prognostic impact of CI, thus precluding any discussion regarding the use of HR-derived variable in identifying those patients at high risk of cardiovascular death or HF hospitalisation on top of the main CPET-derived parameter. Similarly, cannot speculate about the clinical and prognostic meaning of the nearly 10% of not-identified AT, this clinical feature is known to be an additive negative prognostic marker in HF with reduced ejection fraction.[30] Last, from a technical viewpoint, although performed and evaluated by physicians highly trained, the CPET-derived variables analysis was not centralised but performed independently by each recruiting centre and adopting different CPET equipment both in terms of bikes and metabolic charts.

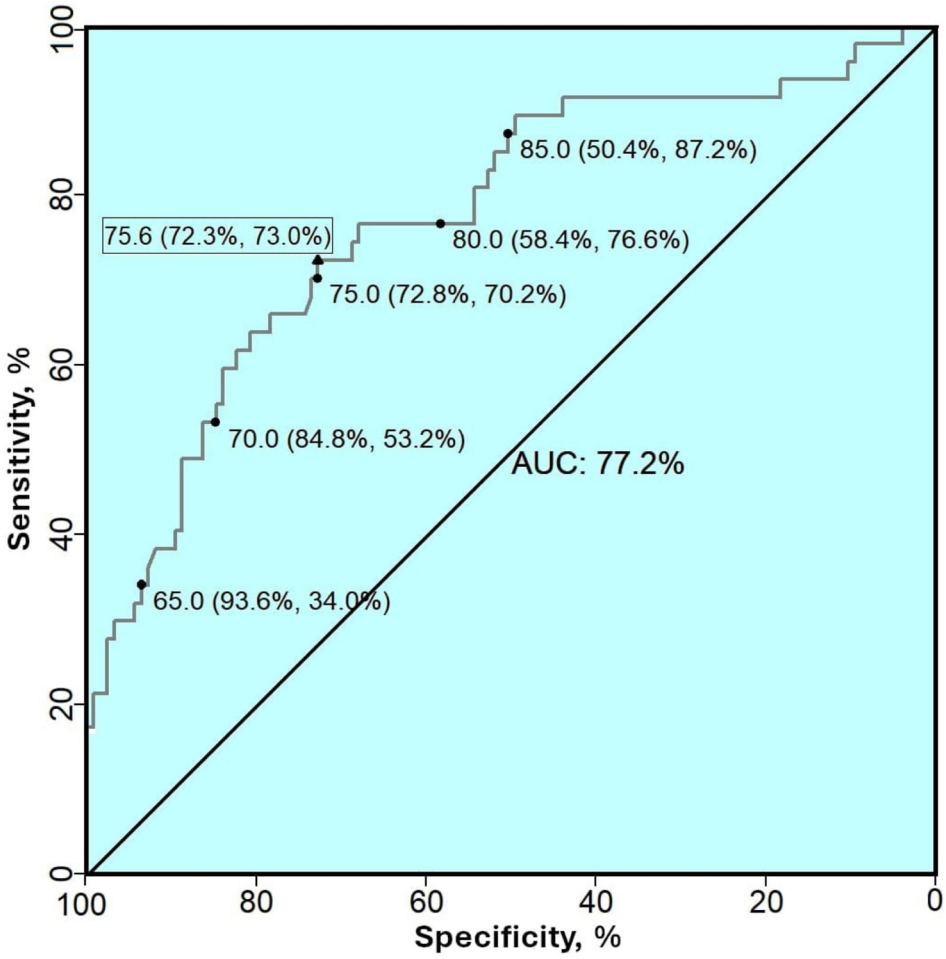

Figure 4 Result from the receiving (ROC) operator curve analysis. ROC analysis showing the pHR% threshold with the best accuracy (triangle) in identifying those patients with a moderate-to-severe exercise impairment ($pVO_2 \leq 60\%$ of the maximum predicted) as well as the other pHR% cut-off tested (circles). AUC, area under the curve; pHR%: peak HR expressed as a percentage of the maximum predicted.

CONCLUSIONS

Data collected from a multicentre cohort of patients with amyloid cardiomyopathy in sinus rhythm shows a high prevalence of CI, with percentages varying based on the selected pHR% cut-off value. Moreover, it confirms a significant relationship between a blunted heart rate response to exercise and poor exercise capacity, as indicated by pVO_2 values. A pHR%≤75% appears to be the most accurate cut-off for identifying moderate-to-severe exercise impairment, making it potentially useful in centres without access to CPET. Whether CI could serve as a reliable outcome predictor in amyloid cardiomyopathy, as it does in other HF contexts, needs to be investigated in larger prospective studies.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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