SFP SOCIÉTÉ FRANÇAISE DE PHYSIOTHÉRAPIE

# Feasibility of prescribed exercise programs in the rehabilitation of patients with cardiac amyloidosis

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**ABSTRACT**

**Objective**: We aimed to determine if prescribed exercise programs in rehabilitation of patients with cardiac amyloidosis was feasible and beneficial. **Methods**: This prospective monocentric pilot study was proposed to all adult patients, diagnosed with cardiac amyloidosis, and referred to the cardiac rehabilitation centre at the Henri Mondor University hospital (Créteil, France) between 2011 to 2015. All patients had clinical evaluations, laboratory tests, and echocardiographic examinations upon recruitment to the study. The cardiac exercise rehabilitation programme, in this study, comprised a baseline incremental system-limited exercise test followed by 20 endurance training sessions at a constant workload intensity. Cardiac exercise rehabilitation was deemed feasible if the patient completed the baseline test and $\geq 10$ sessions without an adverse event. Patients with a relative increase of $\geq 16\%$ in $VO_{2max}$ and/or maximal workload were considered to have benefited from cardiac exercise rehabilitation. **Results:** Overall, 27 cardiac amyloidosis patients were recruited. Cardiac exercise rehabilitation was feasible in 19 (70%) and not feasible in 8 (30%). Of the 19 patients whom cardiac exercise rehabilitation was feasible, cardiac exercise rehabilitation benefited 9 (47%). This benefit was significantly associated with lower N-type pro-brain natriuretic peptide levels, lower creatinineamia, and higher left ventricular ejection fraction at baseline. **Conclusion:** Cardiac exercise rehabilitation is feasible and beneficial in selected patients with cardiac amyloidosis.

**KEYWORDS:** AL amyloidosis, amyloidosis, ATTRv amyloidosis, ATTRwt amyloidosis, cardiac exercise rehabilitation.

## Introduction

There is evidence that cardiac exercise rehabilitation (CER) is safe and provides clinical benefits in patients with hypertrophic cardiomyopathy (HCM) [1, 2]. Recent diagnostic advances have allowed physicians to distinguish HCM from cardiac amyloidosis (CA) induced cardiomyopathy [3, 4, 5, 6, 7, 8, 9, 10]. Indeed, these cardiomyopathies share many signs and symptoms. However, despite the substantial therapeutic advances made for treating CA, the prognosis of CA patients is worse than that of HCM patients [11, 12]. In CA, data are required to demonstrate the benefit of CER and to identify patients most likely to benefit from CER. CA is a chronic disease characterized by the deposits of amyloid fibrils within the myocardium [13]. Besides amyloid fibril deposits in the heart, fibrils may also accumulate in other tissues and organs, including the kidneys, liver, soft tissues, and in peripheral motor and sensory nerves [14]. Amyloid infiltration of nerves leads to various disorders, including lumbar canal stenosis and sensory-motor neuropathies, that impair quality of life and exercise capacity. Patients with amyloidosis are classified according to the misfolded protein that forms the amyloid fibrils. The two most prominent types of systemic amyloidosis are light chain (AL) and transthyretin related (ATTR) amyloidosis. ATTR amyloidosis is further divided into hereditary ATTR (ATTRv) and wild-type ATTR (ATTRwt). The Secondary Prevention and Rehabilitation Section of European Association of Preventive Cardi-

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ology recently stated that cardiac rehabilitation, as secondary prevention, was the most cost-effective intervention in various cardiovascular disorders [15]. Cardiac rehabilitation did not only reduce cardiovascular mortality and morbidity but also increased patient quality of life. Cardiac rehabilitation comprises various interventions, including but not limited to dietary, psychosocial, and exercise interventions. Studies have shown that HCM patients benefits from CER [1, 2]. Wasserstrum et al. reported that exercise of moderate intensity was safe and was beneficial for most HCM patients [1]. Klempfer et al. reported that a supervised exercise program was safe and significantly improved symptoms, functional class (New York Heart Association classification), and functional capacity of HCM patients that remained symptomatic despite therapy [2]. To our knowledge, no study has yet assessed the benefits of CER in patients with CA. This paucity of data may partially be due to the poor prognosis of these patients. Exercise in CA patients may be hampered by neurological and renal symptoms, and by fatigue, known side effects of chemotherapy used to treat AL amyloidosis patients. A recent study showed the prognostic value of cardiopulmonary exercise testing, particularly VO2 max, combined with NT-proBNP levels in CA patients [16]. Exercise testing was also useful for assessing functional capacity, as well as circulatory and chronotropic responses in CA patients. We report the results of a pilot study examining the feasibility of CER in CA patients. The study aimed to assess the benefit derived from CER in CA patients.

## Figures and Tables

## Method

### Study design

This study was designed as a prospective monocentric pilot study. All consecutive patients diagnosed with cardiac amyloidosis between 2011 and 2015 and referred to the cardiac rehabilitation centre at the Henri Mondor University Hospital in Créteil, France, were requested to participate in the study. The study was conducted according to the declaration of Helsinki and French law. The study was approved by the French ethics committee, 'Comité de Protection des Personnes', at the Henri Mondor University Hospital.

### Study participants

Patients aged 18 years and older, with a confirmed diagnosed of cardiac amyloidosis according to current guidelines were eligible. Patients with light chain (AL) amyloidosis were diagnosed by a histological analysis of tissue biopsies with amyloid deposits stained for antibodies for kappa or lambda free immunoglobin light chains (FLC). While patients with ATTR were diagnosed with myocardial fixation on bisphosphonate scintigraphy, with or without a positive staining of biopsies using Congo Red and TTR antibodies. TTR genotyping was performed to distinguish between ATTRwt and ATTRv. All patients provided written consent prior to study participation.

### Data collected at baseline

Patients with suspected amyloidosis underwent a comprehensive clinical evaluation, as well as laboratory tests and echocardiographic examinations. The data concerning demographics (age and sex), clinical data (weight and height), amyloidosis (type of amyloidosis), medical history (presence or not of a pacemaker, atrial fibrillation, and/or ventricular arrythmia), and laboratory tests (haemoglobin, N-terminal pro-brain natriuretic peptide [NT-proBNP], and creatinine blood levels) were collected. Moreover, the data from the echocardiographic examination (left ventricular ejection fraction [LVEF], left ventricular hypertrophy [LVH], ratio of early transmitral blood-flow velocity over tissue Doppler early diastolic mitral-annulus velocity [E/e], and systolic pulmonary arterial pressure [PAP]) were collected.

### Cardiac exercise rehabilitation programme

The CER was supervised by a multidisciplinary team that included cardiologists, cardiovascular nurse specialists, physiotherapists, and exercise physiologists. The CER programme comprised a baseline incremental symptom-limited exercise test followed by 20 endurance training sessions at constant workload. A subgroup of patients performed cardiopulmonary exercise tests (CPET) before and after the training programme. When CPET was unavailable or not tolerated, conventional bicycle ergometers with simultaneous electrocardiographic recording were used. For the incremental exercise tests, the initial workload was 20 W, with an increase of 20 W every 2 minutes. For CPET, the increase was continuous (watt by watt), and for the conventional exercise test without CPET, the increase was stepwise. The training programme was group-based with a minimum of 3 sessions per week for outpatients and 5 sessions per week for inpatients. Each endurance training session consisted of 30 minutes of stationary cycling at a heart rate (HR) corresponding to the ventilatory threshold (VT) obtained during the baseline exercise test, according to standard cardiac rehabilitation recommendations [17]. When oxygen consumption was not measured, training HR was set at 60% 70% of the individual's HR reserve (maximal HR on incremental exercise test minus resting HR) [17]. In addition to the endurance training, all patients were systematically proposed supervised and guided resistance training 2-3 times per week. In patients with CPET, ventilation (VE), oxygen consumption ($VCO_2$) and carbon dioxide output ($VO_2$) were measured on a breath-by-breath basis via a computerised system (Medisoft, Belgium). In addition, maximal oxygen uptake (mL/kg/min), the first ventilatory threshold and ventilatory efficiency ($VCO_2$) were determined. Maximal oxygen uptake ($VO_{2max}$) was defined as the highest consecutive 30-second averaged value obtained during exercise test [18]. The first ventilatory threshold (measured by the Wasserman method) was defined as the point where ventilatory equivalent ratio for oxygen (VE/$VO_2$) starts to increase without concomitant increase in the ventilatory equivalent ratio for carbon dioxide (VE/$VCO_2$) [19]. During the programme, in all patients, intensity levels of exercise were systematically re-evaluated using the rating of perceived exertion (RPE) and were increased when RPE was <12 and decreased when RPE was >14 on the Borg's scale [20].

### Data collected during cardiac exercise rehabilitation

During CER, maximal and resting HR, and maximum workload observed were collected for all patients. Also, the chronotropic reserve was measured during the incremental exercise tests, but not during the exercise sessions at constant workload intensity. The chronotropic reserve is the capacity of the heart to increase its rate during exercise or other metabolic demands. In addition, in patients who underwent cardiopulmonary exercise testing, the $VO_{2max}$ and VE/$VCO_2$ ratio were collected. From the data, the percentage gain in maximal workload was calculated.

### Study objectives and outcomes

Our main objective was to assess the feasibility of CER in patients with CA. The programme was considered feasible if patients performed a valid baseline exercise test and completed $\geq 10$ of the scheduled training sessions without onset of an adverse event which limit the CER. Furthermore, we wanted to assess the functional benefit of CER in patients. A patient was considered to have benefited or responded to CER if there was a relative increase in VO2 max and/or maximal workload after CER of $\geq$ 16%. For patients, whose oxygen consumptions were not measured, a benefit or response was defined as an increase of $\geq 15\%$ in peak workload after CER.

### Statistical analysis

Categorical data are reported as numbers with percentages and compared using Chi2 tests. While continuous data are expressed as means with standard deviations and compared using two-tailed Student's t-tests. A p-value < 0.05 was considered statistically significant. Logistic regression was used to identify variables independently associated with the benefit from CER. Variables found to be significantly different ($p \leq 0.10$) in patients that benefited from CER compared to those without benefit. The following variables were included in the model: age, sex, and baseline levels of LVEF, serum creatinine, and log (NT-proBNP). Systolic pulmonary arterial pressure (PAP) was not included in the model since it was not measured in all patients. The cut-off limit for NT-proBNP was assessed using the Youden index [21, 22]. Statistical calculations were performed using the SPSS software package (SPSS Inc., Chicago IL, USA).

## Results

### Population characteristics

Between 2011 and 2015, 27 patients were prospectively recruited at Henri Mondor University Hospital in Créteil, France. Among the 27 patients with cardiac amyloidosis (CA) enrolled, 22 were male and the median age was 68 years, see Table 1. Sixteen (59%) had AL, 6 (22%) had ATTRv, and 5 (19%) had ATTRwt amyloidosis. Two-thirds of patients (18/27) had a cardiac pacemaker implanted. Median LVEF was 52% (IQR: 40-60), median LVH was 17 mm (IQR: 15-19), and the median ratio of early transmitral blood-flow velocity over tissue Doppler early diastolic mitral-annulus velocity (E/e) was 15 (IQR: 13-20). Concerning the baseline exercise capacities of the 27 patients: the median duration of the exercise test was 312 s (IQR: 165-474), the median resting HR was 80 bpm (IQR: 67-90), and the median maximum workload was 49 W (IQR: 30-78).

### Cardiac rehabilitation

CER proved to be feasible in 19 patients (70%, Table 1). In contrast, 8 patients (30%) were not able to perform at least half of the 20 scheduled training session - the CER failure cohort. Three patients, all with AL amyloidosis, could not perform the baseline incremental exercise testing: 1 patient due to pericardial effusion and 2 patients due to severe fatigue. The remaining 5 patients completed baseline CER assessments but failed to complete at least 10 training sessions, a patient with each of the following conditions: hip pain (coxalgia), knee pain (gonalgia), dysautonomia, neuropathic pain, and refractory asthenia. Overall, the demographic and baseline characteristics in the CER feasible and CER failure cohorts were similar. However, in the CER feasible cohort more patients had pacemakers, 16/19 (84%) versus 2/8 (25%), p = 0.0061, and baseline NT-proBNP levels were lower, 2239 ng/L (IQR: 860-9460) versus 8600 ng/L (IQR: 4749-18358), p = 0.043. In the CER feasible cohort, compared to the CER failure cohort the exercise test duration was significantly longer, 360 s (IQR: 245-508) versus 134 s (IQR: 110-252); p = 0.015, and the chronotropic reserve was significantly higher, 53% (IQR: 15%-72%) versus 7% (IQR: 5%-26%), p = 0.036. It is noteworthy that age and type of amyloidosis were not significantly associated with CER feasibility.

### Functional benefit

Of the 19 patients for whom CER was feasible, 9 patients (47%) had a functional benefit (Table 2). In these patients there were significant gains in maximal workload 34.7% (IQR: 19.6%-39.7%; p = 0.002). CPET were performed by 13 patients at baseline and by 15 patients at the end of CER. The presence or absence of meaningful functional benefit of CER was significantly associated with lower baseline NT-proBNP levels (872 ng/L [IQR: 493-1665] versus 7006 ng/L [IQR: 2600-18469]), lower serum creatinine (80.0 μmol/L [IQR: 73.5-123.5] versus 115.5 μmol/L [IQR: 97.3-263.3]), and higher LVEF (60% [IQR: 48%-62%] versus 39% [IQR: 32%-54%]), but not with the type of amyloidosis nor with LVH, see Table 2. It is noteworthy that none of the parameters measured during exercise, including VO2 max and chronotropic reserve, were significantly associated with the benefit of CER.

Identifying variables associated with a benefit from cardiac exercise rehabilitation Logistical regression, using age, sex, and baseline levels of LVEF, serum creatinine, and log (NT-proBNP), was used to identify variables independently associated with the functional benefit of CER. Of these variables, only log (NT-proBNP) was found to be associated with a benefit of CER: hazard ratio of 4.53; 214.2 (95% CI: 1.53-29993); p = 0.033. The Youden index identified a NT-proBNP level of <2700 ng/L as being associated with benefit from CER. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.93 (95% CI: 0.82-1.00), p < 0.001. Moreover, sensitivity was 89% and specificity was 80%: with a positive predictive value (PPV) of 80% and a negative predictive response (NPV) of 89%.

## Discussion

In our study, the first to our knowledge assessing CER feasibility in CA, CER proved to be feasible in 70% of the patients addressed to the cardiac rehabilitation centre. Compared to patients that could not complete the baseline assessment and at least half of the planned exercise sessions, significantly more patients for whom CER was feasible had pacemakers (84%) and baseline levels of NT-proBNP were significantly lower. Furthermore, the mean duration of the baseline exercise test was longer and the chronotropic reserve higher. Moreover, about half of them had a clinically meaningful functional benefit, with increased endurance and maximal workloads, when they completed the CER programme. In patients that benefited from CER, baseline levels of NT-proBNP and creatinineamia were lower, while LVEFs were significantly higher. In our analysis, a NT-proBNP cut-off of < 2700 ng/L proved useful to identify CA patients expected to benefit from CER. Our results reveal that patient selection is critical, both for CER feasibility and to identify patients most likely to benefit from CER.

Interestingly, our analysis did not identify the type of amyloidosis as significantly associated with CER feasibility. Of the 16 AL amyloidosis patients, CER was not feasible in 5 patients (31%): 3 failed to complete the baseline exercise test and 2 did not complete half of the scheduled exercise sessions. Among the 3 that failed to perform the baseline exercise test, 2 died within one month of enrolment. AL amyloidosis patients are often fragile with multiple organs infiltrated, about 80% of them have cardiac involvement, the severity of which determines survival [14, 23]. In AL patients with cardiac involvement, chemotherapy aims to rapidly eliminate amyloid precursors and to reduce amyloid deposits, thus improving cardiac function [14, 24]. However, chemotherapy with the associated side effects is difficult in these frail patients. The relative timing of CER with respect to chemotherapy needs to be evaluated for each AL patient, since performing CER while undergoing chemotherapy may be challenging. However, even though challenging, CER was feasible in 11 of the 16 AL patients. In AL patients where CER was feasible, cardiac involvement seems to be less severe as suggested by a significantly lower baseline mean NT-proBNP level in the CER feasible cohort, 2239 ng/L, compared to 8600 ng/L in the CER failure cohort. Our results suggest that CER is feasible in all types of CA, including selected AL amyloidosis patients with less severe cardiac involvement.

NT-proBNP may help select CA patients for whom CER is feasible and beneficial. In CA patients, NT-proBNP levels are often elevated due to hemodynamic burden [8]. NT-proBNP levels continue to increase with CA evolution and severity. Nicol et al. reported that NT-proBNP levels, and $VO_{2max}$, could predict death or heart failure-related hospitalisations in CA patients [16].

In addition to NT-proBNP levels, other selection criteria need to be assessed. The 6-minute walk test (6MWT) is clinically useful to assess cardiovascular fitness and could help select patients for CER [25]. Also, systematic screening for severe orthostatic disorders could identify patients with exercise intolerance and for whom CER will probably not be

**Table 1** Baseline patient characteristics according to feasibility of cardiac exercise rehabilitation.

| Variables | All | CER feasible cohort | CER failure cohort | p-value* |
|---|---|---|---|---|
| | n = 27 | n = 19 | n = 8 | |
| **Clinical characteristics:** | | | | |
| Age, years | 68 (61-78) | 66 (61-79) | 72 (58-78) | 0.94 |
| Male sex | 22 (81) | 15 (79) | 7 (88) | 1.00 |
| Body Mass Index, kg/m2 | 24.5 (21.8-27.6) | 24.5 (21.4-27.5) | 24.4 (22.1-29.5) | 0.89 |
| Type of amyloidosis | | | | 0.098 |
| AL | 16 (59) | 11 (58) | 5 (63) | |
| ATTRwt | 5 (19) | 2 (11) | 3 (38) | |
| ATTRv | 6 (22) | 6 (32) | 0 (0) | |
| Pacemaker | 18 (67) | 16 (84) | 2 (25) | **0.0061** |
| Atrial fibrillation | 12 (44) | 10 (53) | 2 (25) | 0.24 |
| Ventricular arrhythmia** | 10 (37) | 6 (32) | 4 (50) | 0.41 |
| **Laboratory**: | | | | |
| Haemoglobin, g/dL | 12.6 (11.2-13.6) | 12.2 (9.9-13.5) | 13.1 (11.8-14.3) | 0.243054 |
| 2239 | 8600 | **0.043** | | |
| NT-proBNP, ng/L | 3054 | 2239 | 8600 | **0.043** |
| | (1012-10794) | (860-9460) | (4749-18358) | |
| Serum creatinine, µmol/L | 113 (84-162) | 104 (80-141) | 147 (104-214) | 0.22 |
| **Echocardiography:** | | | | |
| LVEF, % | 52 (40-60) | 52 (38-60) | 53 (43-59) | 0.82 |
| LVH, mm | 17 (15-19) | 16 (14-20) | 18 (16-19) | 0.52 |
| E/e | 15 (13-20) | 16 (13-21) | 13 (9-20) | 0.52 |
| Systolic PAP, mmHg | 40 (30-44) | 39 (31-44) | 40 (24-43) | 0.41 |
| **Baseline exercise test:** | | | | |
| Duration, s | 312 (165-474) | 360 (245-508) | 134 (110-252) | **0.015** |
| Resting HR, bpm | 80 (67-90) | 79 (66-96) | 84 (71-89) | 0.89 |
| Maximum workload, W | 49 (30-78) | 60 (40-82) | 30 (25-45) | 0.063 |
| Chronotropic reserve, % | 29 (7.8-51) | 53 (15-72) | 7 (5-26) | **0.036** |

Continuous variables are expressed as median (IQR) and discrete variables as number (%). AL amyloidosis: light-chain amyloidosis; ATTRv amyloidosis: hereditary transthyretin related amyloidosis; ATTRwt amyloidosis: wild-type transthyretin related amyloidosis; bpm: beats per minute; CER: cardiac exercise rehabilitation; E/e: ratio of early transmitral blood-flow velocity over tissue Doppler early diastolic mitral-annulus velocity; HR: heart rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; NT-proBNP: N-type pro-brain natriuretic peptide; PAP: pulmonary arterial pressure; W: watt. *p-values <0.05 are in bold. **Ventricular arrythmia is defined as having $\geq 3$ consecutive beats at a rate >100 beats per min.

**Table 2** Patient characteristics according to functional benefit from cardiac exercise rehabilitation.

| Variables | Benefit<br>n = 9 | No benefit<br>n = 10 | p-value* |
|---|---|---|---|
| **Clinical characteristics:** | | | |
| Age, years | 64 (56-73) | 74 (65-85) | 0.95 |
| Male sex | 6 (67) | 9 (90) | **0.0001** |
| Body Mass Index, kg/m2 | 24.5 (20.6-28.1) | 25.2 (23.6-27.6) | 0.72 |
| Type of amyloidosis, AL vs ATTR | 5 (55.6) | 6 (60.0) | 0.61 |
| With pacemaker | 8 (88.9) | 8 (80.0) | 0.54 |
| With atrial fibrillation | 6 (66.7) | 4 (40.0) | 0.24 |
| **Biology characteristics** | | | |
| Haemoglobin, g/dL | 12.9 (9.4-13.6) | 12.0 (11.4-13.4) | 0.80 |
| NT-proBNP, ng/L | 872 (493-1665) | 7006 (2600-18469) | **0.001** |
| Serum creatinine, µmol/L | 80.0 (73.5-123.5) | 115.5 (97.3-263.3) | **0.035** |
| **Echocardiography-characteristics:** | | | |
| LVEF, % | 60 (48-62) | 39 (32-54) | **0.004** |
| LVH, mm | 15.0 (14.0-18.3) | 16.5 (15.0-19.0) | 0.84 |
| E/e | 13.5 (11.5-25.0) | 17.0 (14.0-20.5) | 0.32 |
| Systolic PAP, mmHg | 31.5 (29.3-36.8) | 43.5 (40.3-45.5) | 0.010 |
| **Baseline exercise test:** | | | |
| Duration, s | 360 (218-513) | 358 (224-511) | 0.99 |
| Resting HR, bpm | 81 (72-93) | 76 (63-97) | 0.60 |
| Maximal HR, bpm | 49 114 (97-146) | 113 (84-143) | 0.72 |
| % of maximal theoretical HR | 76 (65-87) | 81 (58-94) | 0.84 |
| Maximum workload, W | 70.0 (37.5-86.0) | 46.5 (37.5-76.3) | 0.40 |
| $VO_{2max}$, mL/kg/min | 11.7 (9.6-13.7) | 8.6 (6.6-16.7) | 0.37 |
| $VE/VCO_2$ | 40.0 (35.0-43.5) | 41.0 (36.0-75.0) | 0.53 |
| Chronotropic reserve, % | 46.7 (28.6-63.0) | 24.5 (8.1-70.0) | 0.40 |
| **Exercise training** | | | |
| Number of training sessions | 20.0 (18.5-39.5) | 18.0 (13.25-26.0) | 0.45 |
| Gain in maximal workload, % | 34.7 (19.6-39.7) | 0 (-8.9 to 12.0) | 0.002 |
| **Final exercise test** | | | |
| Duration, s | 496 (422-617) | 334(290-656) | 0.41 |
| Resting HR, bpm | 72 (64-81) | 77 (76-93) | 0.19 |
| Maximal HR, bpm | 117 (94-152) | 118 (104-131) | 0.96 |
| % of maximal theoretical HR | 69.5(64.3-98.5) | 83.0 (73.0-95.0) 0.61 | |
| $VO_{2max}$, mL/kg/min | 13.0 (11.7-15.7) | 7.9 (6.0-20.9) | 0.66 |
| $VE/VCO_2$ | 36.5 (32.8-42.0) | 39.0 (34.5-57.0) | 0.33 |
| Chronotropic reserve, % | 55.8 (45.2-83.9) | 53.3 (11.8-72.4) 0.54 | |

Continuous variables are expressed as median (IQR) and discrete variables as number (%). AL amyloidosis: light-chain amyloidosis; ATTR amyloidosis: transthyretin related amyloidosis; bpm: beats per minute; E/e: ratio of early transmitral blood-flow velocity over tissue Doppler early diastolic mitral-annulus velocity; HR: heart rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; NT-proBNP: N-type pro-brain natriuretic peptide; PAP: pulmonary arterial pressure; VO2 max: maximal volume of oxygen uptake; VCO2 max: maximum volume of carbon dioxide exhaled; VE: ventilation; VE/VCO2: ventilatory equivalent ratio for carbon dioxide; W: watt. *p-values <0.05 are in bold.

feasible [26].

In systemic amyloidosis, cardiac involvement depends on the subtype [27]. As mentioned above, about 80% of AL patients have cardiac involvement [14, 23]. In ATTRwt amyloidosis, the heart is almost always affected and about two-thirds have heart failure at diagnosis. In contrast, ATTRv amyloidosis patients have various phenotypes depending on the TTR mutation, with cardiac involvement in about 40% of the patients.

When amyloid fibrils infiltrate the heart, patients develop heart failure leading to reduced exercise capacity [16]. Nichol et al. observed that, $VO_{2max}$, circulatory power ($VO_{2max}$ multiplied by peak systolic blood pressure), and oxygen pulse ($VO_2$ divided by HR) were diminished in CA patients during exercise, due to low exercise inotropic reserve and restrictive heart filling patterns. It should be noted that he $VO_{2max}$ during exercise reflects not only the capacity of muscles to metabolise oxygen but also the subject's cardiac, vascular, and pulmonary capacities.

Furthermore, Nichols et al. observed that the VE/$VCO_2$ slope was increased in CA patients, reflecting the reduced cardiac output reserve during incremental exercise. This is possibly due to restrictive haemodynamics in CA patients with increased pressure in the left ventricle and in the pulmonary circulation during exercise. Haemodynamics of CA patients, at rest, using right heart catheterization have been assessed. Indeed, Russo et al. reported that haemodynamic profiles were similar in AL and ATTR patients: high resting right and left ventricular filling pressures with low cardiac outputs [28]. Clemmensen et al. reported that during exercise CA patients had severely reduced inotropic myocardial reserve and increased right and left ventricular filling pressures, measured by right heart catheterization [29]. Interestingly in CA patients, $VO_{2max}$ during incremental exercise was strongly related to the peak cardiac index (cardiac output indexed to body surface area). Overall, CA patients during exercise have a diminished cardiac output, with lower $VO_{2max}$, increased VE/$VCO_2$ slope, and a lower exercise capacity

Chronotropic incompetence (CI), the inability of the heart to respond to exercise, often occurs in patients with cardiovascular diseases. Chronotropic incompetence results in impaired exercise tolerance, reduced peak exercise capacity, diminished quality of life, and predicts all-cause mortality. Consequently, chronotropic incompetence in CA patients impacts clinical management, including the feasibility of CER. Indeed, a study assessed chronotropic incompetence during exercise in 40 HF patients equipped with wearable Holter-accelerometers, 50% of patients were chronotropic incompetent [30]. In chronotropic incompetent patients the 6MWT distance was significantly shorter and physical activity intensity, measured by the age-predicted maximal heart rate value, was significantly reduced. Similarly, Nicol et al. reported that 51% of CA patients assessed by CPET were chronotropic incompetent and that HR response during exercise correlated with $VO_{2max}$.

Interestingly, in our study a large proportion of CA patients for whom CER was feasible had rate responsive pacemakers, suggesting that modern pacemakers facilitate CER in CA patients. The significantly higher chronotropic reserve in patient that performed CER is probably at least partly due to the rate adaptive pacing of the pacemaker and not to the physiological HR response to exercise.

Amyloidosis is a complex disorder with various cardiac and extracardiac manifestations that makes healthcare management challenging. Despite the substantial therapeutic advances made in recent years, prognosis for amyloidosis and particularly CA patients remains poor. However, the improved diagnosis and treatment of chronotropic incompetence, conduction disorders, and arrhythmias has increased the feasibility of CER in CA patients. Moreover, in our study extracardiac amyloid involvement did not appear to limit CER. There is evidence that CER benefits patients with HCM, thus we can expect that CER will benefit selected CA patients: increasing quality of life and possibly survival.

CA patients undergoing CER can expect to increase their $VO_{2max}$ with possible survival benefits. Indeed, CA patients with lower $VO_{2max}$ ($\leq$13 mL/kg/min) had a significantly increased risk of heart failure hospitalizations and death [16].

### *Limitations*

Our study was designed as a pilot study to provide exploratory results assessing the feasibility and benefit of CER in CA patients and thus has several limitations. Our sample size was small and our results exploratory. Furthermore, we only examined the functional benefits after a 20-sessions training period. The long-term benefits of CER, including functional benefits, and the impact on quality of life, morbidity, and mortality beyond the CER programme will need to be assessed. Cardiopulmonary exercise testing was not available for all patients, thus limiting the statistical power of the results based on gas exchange measurements. Finally, the patients included in this study were on average younger than CA patients referred to our centre, therefore there is a potential selection bias.

## Conclusion

CER is feasible and beneficial in selected patients with CA. Further studies are required to assess the benefit, in terms of quality of life and other outcome, of CER in CA.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author, TD, upon reasonable request.

## References

[1] Yishay Wasserstrum, Iryna Barbarova, Dor Lotan, Rafael Kuperstein, Michael Shechter, Dov Freimark, Gad Segal, Robert Klempfner, and Michael Arad. Efficacy and safety of exercise rehabilitation in patients with hypertrophic cardiomyopathy. *Journal of Cardiology*, 74(5):466–472, 2019. doi: https://doi.org/10.1016/j.jjcc.2019.04.013.

[2] Robert Klempfner, Tamir Kamerman, Ehud Schwammenthal, Amira Nahshon, Ilan Hay, Ilan Goldenberg, Freimark Dov, and Michael Arad. Efficacy of exercise training in symptomatic patients with hypertrophic cardiomyopathy: results of a structured exercise training program in a cardiac rehabilitation center. *European Journal of Preventive Cardiology*, 22(1):13–19, 2015. doi: https://doi.org/10.1177/2047487313501277.

[3] Cesare de Gregorio, Giuseppe Dattilo, Matteo Casale, Anna Terrizzi, Rocco Donato, and Gianluca Di Bella. Left atrial morphology, size and function in patients with transthyretin cardiac amyloidosis and

primary hypertrophic cardiomyopathy–comparative strain imaging study–. *Circulation Journal*, 80(8):1830–1837, 2016. doi: https://doi.org/10.1253/circj.CJ-16-0364.

[4] Jing Wang, Amy Marzolf, Janet CL Zhang, Anjali Owens, and Yuchi Han. Cardiac amyloidosis masked as hypertrophic cardiomyopathy: a case report. *Cardiology Research*, 7(5):178, 2016. doi: doi:http://dx.doi.org/10.14740/cr496w.

[5] Henning Steen, Sorin Giusca, Moritz Montenbruck, Amit R Patel, Burkert Pieske, Andre Florian, Jennifer Erley, Sebastian Kelle, and Grigorios Korosoglou. Left and right ventricular strain using fast strain-encoded cardiovascular magnetic resonance for the diagnostic classification of patients with chronic non-ischemic heart failure due to dilated, hypertrophic cardiomyopathy or cardiac amyloidosis. *Journal of Cardiovascular Magnetic Resonance*, 23:1–17, 2021. doi: https://doi.org/10.1186/s12968-021-00711-w.

[6] Bo Da Nam, Sung Mok Kim, Hye Na Jung, Yiseul Kim, and Yeon Hyeon Choe. Comparison of quantitative imaging parameters using cardiovascular magnetic resonance between cardiac amyloidosis and hypertrophic cardiomyopathy: inversion time scout versus t1 mapping. *The International Journal of Cardiovascular Imaging*, 34: 1769–1777, 2018. doi: https://doi.org/10.1007/s10554-018-1385-2.

[7] Hye Na Jung, Sung Mok Kim, Jeong Hyun Lee, Yiseul Kim, Sang-Chol Lee, Eun-Seok Jeon, Hwan Seok Yong, and Yeon Hyeon Choe. Comparison of tissue tracking assessment by cardiovascular magnetic resonance for cardiac amyloidosis and hypertrophic cardiomyopathy. *Acta radiologica*, 61(7):885–893, 2020. doi: https://doi.org/10.1177/0284185119883714.

[8] Mathew S Maurer, Perry Elliott, Raymond Comenzo, Marc Semigran, and Claudio Rapezzi. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. *Circulation*, 135(14):1357–1377, 2017. doi: https://doi.org/10.1161/CIRCULATIONAHA.116.024438.

[9] Sévérine De Bruijn, Xavier Galloo, Gilles De Keulenaer, Edgard A Prihadi, Christiane Brands, and Mark Helbert. A special case of hypertrophic cardiomyopathy with a differential diagnosis of isolated cardiac amyloidosis or junctophilin type 2 associated cardiomyopathy. *Acta Clinica Belgica*, 76(2):136–143, 2021. doi: https://doi.org/10.1080/17843286.2019.1662572.

[10] Michael P Ayers, Adithya V Peruri, and Jamieson M Bourque. Transforming attr cardiac amyloidosis into a chronic disease: The enormous potential of quantitative spect to improve diagnosis, prognosis, and monitoring of disease progression, 2021.

[11] Pablo Garcia-Pavia, Claudio Rapezzi, Yehuda Adler, Michael Arad, Cristina Basso, Antonio Brucato, Ivana Burazor, Alida LP Caforio, Thibaud Damy, Urs Eriksson, et al. Diagnosis and treatment of cardiac amyloidosis. a position statement of the european society of cardiology w orking g roup on m yocardial and p ericardial d iseases. *European journal of heart failure*, 23(4):512–526, 2021. doi: https://doi.org/10.1002/ejhf.2140.

[12] Daniele Pasqualucci, Alessandra Fornaro, Gabriele Castelli, Alessandra Rossi, Anna Arretini, Chiara Chiriatti, Mattia Targetti, Francesca Girolami, Marco Corda, Pierpaolo Orrù, et al. Clinical spectrum, therapeutic options, and outcome of advanced heart failure in hypertrophic cardiomyopathy. *Circulation: Heart Failure*, 8(6):1014–1021, 2015. doi: https://doi.org/10.1161/CIRCHEARTFAILURE.114.001843.

[13] Giampaolo Merlini and Vittorio Bellotti. Molecular mechanisms of amyloidosis. *New England Journal of Medicine*, 349(6):583–596, 2003.

[14] Giampaolo Merlini. Al amyloidosis: from molecular mechanisms to targeted therapies. *Hematology 2014, the American Society of Hematology Education Program Book*, 2017(1):1–12, 2017. doi: https://doi.org/10.1182/asheducation-2017.1.1.

[15] Marco Ambrosetti, Ana Abreu, Ugo Corrà, Constantinos H Davos, Dominique Hansen, Ines Frederix, Marie C Iliou, Roberto FE Pedretti, Jean-Paul Schmid, Carlo Vigorito, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. a position paper from the secondary prevention and rehabilitation section of the european association of preventive cardiology. *European journal of preventive cardiology*, 28(5):460–495, 2021. doi: https://doi.org/10.1177/2047487320913379.

[16] Martin Nicol, Antoine Deney, Olivier Lairez, Giuseppe Vergaro, Michele Emdin, Alessandro Carecci, Jocelyn Inamo, Astrid Montfort, Remi Neviere, Thibaud Damy, et al. Prognostic value of cardiopulmonary exercise testing in cardiac amyloidosis. *European Journal of Heart Failure*, 23(2):231–239, 2021. doi: https://doi.org/10.1002/ejhf.2016.

[17] Antonio Pelliccia, Sanjay Sharma, Sabiha Gati, Maria Bäck, Mats Börjesson, Stefano Caselli, Jean-Philippe Collet, Domenico Corrado, Jonathan A Drezner, Martin Halle, et al. 2020 esc guidelines on sports cardiology and exercise in patients with cardiovascular disease: the task force on sports cardiology and exercise in patients with cardiovascular disease of the european society of cardiology (esc). *European heart journal*, 42(1):17–96, 2021. doi: https://doi.org/10.1093/eurheartj/ehaa835.

[18] Karlman Wasserman, James E Hansen, Darryl Y Sue, William W Stringer, and Brian J Whipp. *Principles of exercise testing and interpretation: including pathophysiology and clinical applications*, volume 37. LWW, 2005.

[19] Karlman Wasserman, Brian J Whipp, SN Koyl, and William L Beaver. Anaerobic threshold and respiratory gas exchange during exercise. *Journal of applied physiology*, 35(2):236–243, 1973. doi: https://doi.org/10.1152/jappl.1973.35.2.236.

[20] Bruno Pavy, Marie-Christine Iliou, Bénédicte Vergès-Patois, Richard Brion, Catherine Monpère, François Carré, Patrick Aeberhard, Claudie Argouach, Anne Borgne, Silla Consoli, et al. French society of cardiology guidelines for cardiac rehabilitation in adults. *Archives of cardiovascular diseases*, 105(5):309–328, 2012. doi: https://doi:10.1016/j.acvd.2012.01.010.

[21] Jingjing Yin, Fedelis Mutiso, and Lili Tian. Joint hypothesis testing of the area under the receiver operating characteristic curve and the youden index. *Pharmaceutical statistics*, 20(3):657–674, 2021. doi: https://doi.org/10.1002/pst.2099.

[22] Marcus D Ruopp, Neil J Perkins, Brian W Whitcomb, and Enrique F Schisterman. Youden index and optimal cut-point estimated from observations affected by a lower limit of detection. *Biometrical Journal: Journal of Mathematical Methods in Biosciences*, 50(3):419–430, 2008. doi: https://doi.org/10.1002/bimj.200710415.

[23] Brian Lilleness, Gheorghe Doros, Frederick L Ruberg, and Vaishali Sanchorawala. Establishment of brain natriuretic peptide-based criteria for evaluating cardiac response to treatment in light chain (al) amyloidosis. *British Journal of Haematology*, 188(3):424–427, 2020. doi: https://doi.org/10.1111/bjh.16198.

[24] Anita D'Souza, Ruta Brazauskas, Angela Dispenzieri, Julie Panepinto, and Kathryn E Flynn. Changes in patient-reported outcomes in light chain amyloidosis in the first year after diagnosis and relationship to nt-probnp change. *Blood cancer journal*, 11(2):29, 2021. doi: https://doi.org/10.1038/s41408-021-00412-8.

[25] Fang Liu, Alice YM Jones, Raymond CC Tsang, Yao Wang, Jing Zhou, Mingchao Zhou, and Yulong Wang. Noninvasive investigation of the cardiodynamic response to 6mwt in people after stroke using impedance cardiography. *Plos one*, 15(6):e0233000, 2020. doi: https://doi.org/10.1371/journal.pone.0233000.

[26] Michael Gutkin and Julian M Stewart. Orthostatic circulatory disorders: from nosology to nuts and bolts. *American journal of hypertension*, 29(9):1009–1019, 2016. doi: https://doi.org/10.1093/ajh/hpw023.

[27] E Muchtar, A Dispenzieri, H Magen, M Grogan, M Mauermann, ED McPhail, PJ Kurtin, N Leung, FK Buadi, D Dingli, et al. Systemic amyloidosis from a (aa) to t (attr): a review. *Journal of Internal Medicine*, 289(3):268–292, 2021. doi: https://doi.org/10.1111/joim.13169.

[28] Christopher Russo, Philip Green, and Mathew Maurer. The prognostic significance of central hemodynamics in patients with cardiac amyloidosis. *Amyloid*, 20(4):199–203, 2013. doi: https://doi.org/10.3109/13506129.2013.821406.

[29] Tor Skibsted Clemmensen, Henning Mølgaard, Jens Sörensen, Hans Eiskjaer, Niels Frost Andersen, Søren Mellemkjaer, Mads Jønsson Andersen, Lars Poulsen Tolbod, Hendrik J Harms, and Steen Hvitfeldt Poulsen. Inotropic myocardial reserve deficiency is the predominant feature of exercise haemodynamics in cardiac amyloidosis. *European Journal of Heart Failure*, 19(11):1457–1465, 2017. doi: https://doi.org/10.1002/ejhf.899.

[30] Hong Shen, Jianrong Zhao, Xiaohong Zhou, Jingbo Li, Qing Wan, Jing Huang, Hui Li, Liqun Wu, Shungang Yang, and Ping Wang. Impaired chronotropic response to physical activities in heart failure patients. *BMC cardiovascular disorders*, 17(1):1–8, 2017. doi: https://doi.org/10.1186/s12872-017-0571-9.