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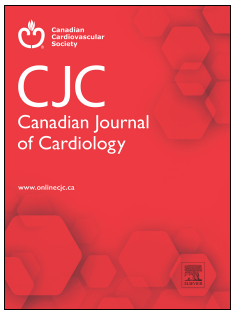

Serial changes in CPET parameters in untreated patients with transthyretin cardiac amyloidosis

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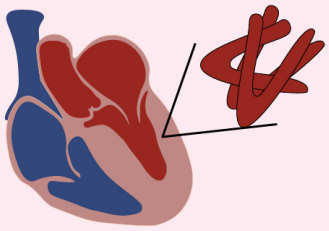
55 patients with transthyretin cardiomyopathy (ATTR) underwent 2 serial cardiopulmonary exercise testing (CPET) with a time interval of 14 (13-16) months

Median age was 80 (76-83) years, 91% were men

78% wild type ATTR 22% hereditary ATTR

76% NYHA class II/III

61% NAC stage I



Over time CPET parameters significantly worsened over time while echocardiography parameters remained unchanged

	T1	T2	Adjusted coefficient 95% CI	p value
Peak VO2 max, ml/kg/min	15 (12-18)	13 (12-16)	-1.29 (-1.85 - -0.74)	<0.01
%ppVO2, %	71 (60-83)	66 (57-68)	-4.5 (-6.9 - -2.02)	<0.01
VE/VCO2 slope	31 (26-34)	38 (32-43)	8.6 (6-11)	<0.01
Anaerobic Threshold, ml/kg/min	9.1 (7.1-11.2)	10 (8.1-11)	0.77 (0.1-1.44)	0.02
Exercise time (seconds)	449 (335-535)	388 (324-476)	-39 (-59 - -19)	<0.01
METs	4.7 (4-5.5)	4.4 (3.6-5.3)	-0.47 (-0.69 - -0.2)	<0.01
Peak heart rate (bpm)	117 (101-132)	120 (103-136)	1.76 (-4.1 – 7.7)	0.56
Peak systolic pressure (mmHg)	155 (135-165)	140 (120-155)	-10.8 (-16.2 - -5.4)	<0.01
WATTs	80 (60-100)	70 (50-100)	-10.3 (-13 - -6.9)	<0.01

Medians and interquartile range of CPET variables and adjusted mean differences from linear regressions (adjustment for age, use of beta blockers, time interval between exams, baseline value).%ppVO2: percentage of predicted peak VO2. 95% CI: 95% confidence interval. T1: first CPET. T2: second CPET.

CPET parameters may be used as an early marker of disease progression and may guide disease-specfic treatment strategy

Serial changes in CPET parameters in untreated patients with transthyretin cardiac amyloidosis

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Abstract

Background: Transthyretin amyloid cardiomyopathy (ATTR-CM) is associated with a progressive reduction of functional capacity. The progression of cardiopulmonary exercise testing (CPET) parameters over time is still unknown.

Methods: In this study 55 patients with ATTR-CM underwent two serial cardiological evaluation and CPET in a National Referral Center for cardiac amyloidosis (Careggi University hospital, Florence).

Results: Forty-three patients (78%) had wild type ATTR. Median age was 80 (76-83) years, 50 patients (91%) were men. At baseline median peak oxygen consumption (pVO2) was 15 (12-18) ml/kg/min, percentage of predicted pVO2 (%ppVO2) was 71 (60-83) % and VE/VCO2 slope was 31 (26-34). After a median follow-up of 14 (13-16) months, pVO2, %ppVO2 and VE/VCO2 slope were significantly worsened (-1.29ml/kg/min, CI -1.85 to -0.74, $p<0.01$, -4.5% CI -6.9 to -2.02, $p<0.01$, 8.6 CI 6 to 11, $p<0.01$, respectively). Furthermore, exercise time (-39 seconds, CI -59 to -19, $p<0.01$), exercise tolerance (-0.47 METs, CI -0.69 to -0.2, $p<0.01$) and peak systolic pressure (-10.8 mmHg, CI -16.2 to -5.4, $p<0.01$) were significantly reduced. The worsening in CPET variables did not correspond to a significant change in echocardiographic parameters.

Conclusions: Cardiorespiratory response to exercise significantly worsened over a short period of time in patients with ATTR-CM. Serial CPET may be useful to identify early disease progression.

Abbreviations: ATTR-CM: Transthyretin amyloid cardiomyopathy, ATTRwt: wild-type transthyretin amyloid cardiomyopathy, ATTRv: hereditary transthyretin amyloid cardiomyopathy, CA: cardiac amyloidosis, CI: confidence interval, CPET: Cardiopulmonary Exercise testing, NAC: national amyloid center stage, PASP: pulmonary arterial systolic pressure, pVO2: Peak oxygen consumption, %ppVO2: percentage of predicted peak VO2, SBP: systolic blood pressure, VCO_2: carbon dioxide production, VE/VCO_2 slope: minute ventilation/carbon dioxide production.

Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare disease characterized by cardiac accumulation of amyloid fibrils whose precursors may be senescent or genetically mutated transthyretin. The fibrils may infiltrate every cardiac structure from the myocardium to the valves and the conduction system, leading to the development of a pseudo-hypertrophic phenotype, valvulopathies, conduction disturbances and eventually heart failure.

Cardiopulmonary exercise testing (CPET) proved to be safe and effective for evaluating functional capacity and prognostic stratification in ATTR-CM.[1–3] However, the cardiorespiratory response to exercise assessed by repeated CPET evaluations has never been addressed. In this study, for the first time, the progressive changes of CPET parameters in patients with ATTR-CM have been evaluated.

Methods

This study prospectively enrolled all patients with ATTR-CM consecutively evaluated at the Tuscan Regional Amyloidosis centre of Careggi University Hospital (Florence, Italy) from February 2018 to March 2019. The study was approved by the Institutional Ethics Committee (protocol number 11171). Clinical evaluation, echocardiography and CPET were performed. The diagnosis of ATTR-CM was established through the identification of TTR amyloid deposits on endomyocardial biopsy or by cardiac uptake grade 2 or 3 on 99Tc-HMDP scintigraphy and suggestive findings on echocardiogram or cardiac magnetic resonance in the absence of monoclonal protein[4]. Genetic testing for TTR pathogenic/likely pathogenic variants was performed in all patients.

Clinical data included the following: 1) clinical examination 2) electrocardiography, 3) echocardiography, (4) CPET.

Patients were clinically stable at the time of CPET and no variation in diuretic dose nor hospital admission for HF in the previous 60 days were registered.

The CPET was performed on a bicycle ergometer (Formula ESAOTE® Biomedica, Italy) with concomitant respiratory gas analysis. One-minute warm-up exercise was followed by an incremental workload protocol. The workload protocols (10 watts/1 min or 25 watts/2 min) were tailored to the individual patient's characteristics (age, sex, height, weight, NYHA class). Blood pressure was measured every 1 or 2 minutes and oxygen saturation was monitored throughout the test. The airflow analyser (CPX Medical Graphics system®, Breeze software, Medical Graphics Corporation Minnesota USA) allowed for breath-by-breath analysis with continuous measurements of minute ventilation (VE), tidal volume, respiratory rate, oxygen uptake (VO_2), and carbon dioxide production (VCO_2), that were averaged from five consecutive breaths. O_2, CO_2 analysers and flow mass sensors were calibrated before each test. Aerobic capacity was expressed as maximal VO_2 consumption (peak VO_2, ml/kg/min), and identified as the mean O_2 uptake measured over the last 30 seconds of exercise. Percentage of predicted normal value for peak VO_2 (%ppVO2) was reported using Wasserman's equation.[5] Peak respiratory exchange ratio (RER) was the highest recorded value averaged over a 15- or 20- second sampling interval during the last 60 seconds of exercise; a peak value ≥1.1 represented a maximal test. [6,7] Anaerobic threshold (AT) was the point at which CO_2 production increased excessively in relation to O_2 consumption and RER exceeded 1.0. [7] Ventilation efficiency (VE/VCO_2 slope) was evaluated from the slope of VE versus VCO_2 over the linear portion of the curve [6,8]

An abnormal blood pressure response to exercise was defined as follows[9]:

1) flat systolic blood pressure (SBP) response: a systolic blood pressure rise of less than 20 mmHg from baseline during exercise.
2) exercise-induced hypotension: any decrease in systolic blood pressure below baseline occurring during the exercise or recovery phase in the absence of an initial rise, or

alternatively, a sustained (>1 min in duration) decrease of ≥ 20 mmHg during exercise after an initial rise.

Chronotropic incompetence was considered present when the difference between maximal exercise heart rate and heart rate 1 minute into recovery was <12 bpm. [6,7] CPET was performed on optimal medical therapy without discontinuation of the habitual drug regimen.

Statistical analysis

Continuous variables were reported as median [inter-quartile range], categorical variables were described as frequency (percentage). A linear mixed regression model was used for continuous variables while categorical variables were analysed through mixed-effects binomial logistic model. The models included patient ID as random effects and were adjusted for age, use of beta blockers, time interval between CPET studies and baseline value. Statistical significance was defined as an $\alpha < 0.05$. All analyses were performed using STATA 17 (StataCorp. 2021).

Results

The original study population included *75* patients with ATTR-CM, of these 55 underwent a second CPET after a median time interval of 14 (13-16) months (Table 1). In the original cohort 6 patients died, 6 could not perform the second CPET due to worsening heart failure, 1 had a stroke, 1 had sarcopenia, 1 had cognitive impairment, 5 refused to perform the second test. None of the patients was on disease modifying therapy. Median age at first CPET was 80 (76-83) years and 50 patients (91%) were men (Table 1). Twelve (22%) patients had hereditary ATTR-CM (ATTRv), with the most frequent mutation being Ile68Leu (n=8, 66%). Patients were mostly in NYHA class II; at baseline, the median ejection fraction was 57% (52-62) and the majority of patients showed moderate-to-severe diastolic dysfunction (Table 2 and Table 3). The echocardiographic parameters from the first to the second evaluation were unaltered, except for pulmonary arterial systolic pressure which was significantly reduced (-4.3 CI -6.5 to 2.12, p<0.01). At baseline median pVO2 was 15 (12-

18) ml/kg/min, %ppVO2 was 71 (68-83) % and exercise time was 449 (335-535) seconds (Table 4). Median VE/VCO2 slope was 31 (26-34). At the second CPET compared to the first, pVO2 and %ppVO2 were significantly reduced (-1.29, CI -1.85 to -0.74, p<0.01, -4.5 CI -6.9 to -2.02, p<0.01, respectively), while VE/VCO2 slope was significantly increased (8.6 CI 6 to 11, p<0.01). Total exercise time, maximal workload achieved in metabolic equivalents (METs) and WATTs were reduced, as well as peak systolic blood pressure (SBP) (Table 4). The adjusted Odds ratio for developing an abnormal pressure response to exercise was significantly increased (Table 5).

Furthermore, we evaluated the change in CPET parameters in patients with National Amyloid Center stage (NAC) I (n= 34, 61%) compared to patients in NAC stage II/III; however no significant differences emerged (Supplementary tables S1 and S2).

Discussion

In this study, for the first time, the evolution of CPET parameters in patients with ATTR-CM in natural history has been addressed. After a median follow-up of 14 (13-16) months, aerobic capacity (pVO2 peak and %ppVO2), ventilatory efficiency, and exercise tolerance were significantly worsened despite unaltered systolic and diastolic function evaluated by echocardiography.

Ventilatory efficiency expressed by the ratio of minute ventilation to carbon dioxide production (VE/VCO2 slope) showed the greatest worsening. The rise in VE/VCO2 slope appears greater in ATTR-CA patients compared to patients with isolated chronic heart failure. While the mean change in VE/VCO2 slope was 8.6 (6-11) in our sample, in a cohort of 62 patients with chronic heart failure the mean change per year was approximately 2. [10]In the same study, time changes in pVO2 per year were predictors of outcome independently of changes of VE/VC2O2 slope and left ventricular ejection fraction. [10]

The increase in VE/VCO2 slope in these patients may be the result of multiple concomitant causes such as: (1) autonomic dysfunction leading to inappropriate hyperventilation, (2) restrictive lung

disease, (3) respiratory muscular weakness and (4) increased ventilation/perfusion heterogeneity due to right ventricular dysfunction during exercise. Autonomic neuropathy with exaggerated sympathoexcitation associated with blunted parasympathetic tone may enhance the ventilatory response to chemoreceptors leading to hyperventilation.[11] Autonomic dysfunction is frequently observed in hereditary and, to a lesser extent, in patients with ATTRwt.[12] In fact, a greater sympathetic hyperactivity has been shown in patients with ATTRwt compared to matched patients with non-amyloidotic heart failure[13]. Furthermore, pulmonary restriction is a common finding in CA [14], and may be related to amyloid deposition within the lungs[15]. The restrictive respiratory pathophysiology may hinder the increase in tidal volume (TV) during exercise leading to shallow and fast breathing patterns [14]. Respiratory muscle weakness may also contribute to impaired increment in TV [16]. Moreover, an increase in VE/VCO2 slope in patients with chronic heart failure may be due to an abnormal pulmonary perfusion. Invasive measures during exercise in patients with CA have shown a reduced pulmonary arterial compliance with elevated right heart filling pressures that may affect an afterload-dependent right ventricle, reducing lung perfusion [17]. Therefore, ventilation increases during exercise, but cardiac output may not rise proportionally, worsening the heterogeneity of pulmonary ventilation to perfusion and increasing the dead space fraction (dead space/tidal volume).

Aerobic capacity (expressed by VO2peak and %ppVO2) showed a slight but significant reduction. In fact, a 2 mL/kg/min change may represent a remarkable worsening for patients with a baseline peak VO2 of 15 mL/kg/min accounting for a reduction of around 13%. This reduction appears noteworthy in contrast to the decline in pVO2 seen in both healthy subjects and patients with heart failure. Indeed, pVO2 tends to decline with aging, and in a cohort free of clinical heart disease from the Baltimore Longitudinal Study of Aging, the mean predicted longitudinal 10-year rate of change in pVO2 for 70-year-old men was -7.8ml/kg/min corresponding to a 2.4% decline per year.[18]

In the HF-ACTION clinical trial 1620 patients with chronic heart failure with reduced ejection fraction underwent two CPET evaluations in 3 months. In this cohort the median pVO2 was 15.0 (11.9 – 18.0) mL/kg/min and for each 6% decrease in pVO2 there was a 5% greater risk for the primary outcome and all-cause hospitalizations over a mean follow-up time of 30 months.[19]

In a further study, 231 patients with chronic heart failure and reduced ejection fraction, underwent two CPETs separated by a mean interval of almost a year (mean interval of 258± 42 days). Patients with a pVO2 decline of more than 6%, over a 3 years follow-up, had a significantly higher total mortality rate of 51% compared to 21% in patients with stable pVO2 and 14% in case of a pVO2 increase.[20]

In an expanding landscape of treatment options for patients with ATTR-CA, the progression of CPET parameters could be used as an objective measure of response to therapy and may help clinicians in the decision to maintain or modify their approach.

pVO2 decline may be due to several causes. Patients with ATTR have shown a profound myocardial contractile reserve deficiency that causes an inadequate stroke volume improvement relative to VO2 increase [16,17]. The myocardial contractile reserve may be blunted because of an inefficient myocardial oxidative metabolism resulting in an elevated myocardial oxygen consumption but reduced stroke work [21]. The excessive oxygen consumption in turn could be a compensatory mechanism to ensure adequate cardiac output despite perfusion abnormalities and amyloid-related mitochondrial uncoupling [21].

Furthermore, from a structural point of view, the small left ventricular cavity and the increased myocardial stiffness impede the physiological increase in stroke volume during exercise.[22] Therefore the exercise-induced cardiac output rise is achieved through increases in heart rate, hence the poor tolerability of beta blocker therapy in this population.[16]

Patients with early and advanced ATTR-CA evaluated by NAC stage seem to show similar progression of CPET parameters, however the small sample size may have limited our capacity to capture possible differences.

We found a reduction in pulmonary artery systolic pressure (PASP) over time in our cohort; however, we think that this phenomenon does not affect the exercise capacity evaluated through use of CPET. The explanation for its reduction may be twofold. First, there is a trend towards reduction in right ventricular function evaluated by TAPSE (TAPSE T1 18 (15-21) mm; TAPSE T2 18 (14-20) mm, adjusted coefficient CI 95% -1.03 (-2.15 – 0.03), p value =0.05). A reduced right ventricular function may lead to reduced right ventricular stroke volume and underestimation of tricuspid regurgitation velocity and PASP.[23] Furthermore, with the progression of the disease, patients with ATTR-CA need increasing doses of diuretics [24] that could lead to PASP reduction.

In conclusion, in a cohort of patient with ATTR-CA in natural history, CPET is able to detect a decline in cardiorespiratory response to exercise. The cardiorespiratory function worsening is not associated with variations in echocardiographic parameters, thus repeated CPET may be used to recognize early disease progression and functional impairment. Although our study focused on patients with ATTR in natural history, CPET could be a useful tool to determine non-response or disease progression despite a disease modifying treatment.

The greatest limitation of this study is the limited sample size that represent a single-centre experience. Furthermore, the findings are confined to patients who were able to perform two CPETs and, therefore there is a selection bias against patients with more aggressive disease progression.

Conclusion

Cardiorespiratory response to exercise in patients with ATTR-CM significantly declines over a short median time interval of 14 months following the natural course of the disease. Serial CPET may identify early disease progression, even in absence of echocardiography changes.

Further studies are needed to understand if repeated CPET may detect disease progression with use of disease-modifying therapy and if it may help to identify non-responders in a future era of different targeted therapies.

The authors confirm that a patient consent form has been obtained for this article.

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Variables		All patients (N=55)
Age, years		80 (76-83)
Men, n (%)		50 (91)
ATTR type, n (%)	ATTRv ATTRwt	12 (22%) 43 (78%)
Diabetes, n (%)		8 (14)
Hypertension, n (%)		37 (67)
Systolic blood pressure, mmHg		120 (110-140)
Perugini Score	1 2 3	2 (4) 18 (33) 35 (64)
NYHA, n (%)	I II III	13 (23%) 37 (67%) 5 (9%)
NT-proBNP pg/mL		2633 (1230-4270)
TnI (ng/L)		0.06 (0.04-0.08)

Creatinine (mg/dL)	1.06 (0.97-1.26)
eGFR MDRD, mL/min	71 (59-78)
NAC stage I NAC stage II NAC stage III	34 (61) 17(31) 4 (7)

Table 1 Baseline characteristics.

ATTR-CM: Transthyretin amyloid cardiomyopathy, ATTRwt: wild-type transthyretin amyloid cardiomyopathy, ATTRv: hereditary ATTR-CM, NYHA New York heart association, GFR glomerular filtration rate.

	T1	T2	Adjusted coefficient 95% CI	p value

IVS thickness (mm)	17.5 (15.5-20)	18 (16-20)	0.4 (-0.1 – 0.91)	0.12
PW thickness (mm)	16 (14-18.5)	17 (15-19)	0.02 (-0.5-0.57)	0.94
LA volume (ml)	95 (75-110)	96 (77-110)	-0.6 (-7.9 - 6.6)	0.85
LV EF (%)	57 (52-62)	56 (49-60)	-1.72 (-3 – 0.24)	0.08
TAPSE	18 (15-21)	18 (14-20)	-1.03 (-2.15 – 0.03)	0.05
PASP	**40 (33-48)**	**34 (29-40)**	**-4.3 (-6.5 - -2.12)**	**<0.01**
LVEDV	97 (80-110)	95 (76-112)	-5.1 (-11 – 0.86)	0.09
SV	52 (40-63)	48 (40-61)	-3.6 (-7 - 0.3)	0.07

Table 2. Medians and interquartile range of echocardiography variables and adjusted mean differences from linear regressions (adjustment for age, time interval between exams, baseline value). 95% CI: 95% confidence interval. LVEDV left ventricle end diastolic volume, IVS interventricular septum, PW left ventricle posterior wall, LA left atrium, LV EF: left ventricular ejection fraction, TAPSE tricuspid annular plane systolic excursion, SV stroke volume, PAPs pulmonary artery pressure. T1: first exam. T2: second exam.

	T1	T2	Adj Odds ratio 95% CI	p value
Diastolic dysfunction II/III	42 (76%)	46 (84%)	2.87 (0.7 – 11.5)	0.14

Table 3. Adjusted odds radio for developing diastolic dysfunction (adjustment for age, time interval between exams, and baseline value). T1: first exam. T2: second exam.

	T1	T2	Adjusted coefficient 95% CI	p value
Peak VO2 max, ml/kg/min	**15 (12-18)**	**13 (12-16)**	**-1.29 (-1.85 - -0.74)**	**<0.01**
%ppVO2, %	**71 (60-83)**	**66 (57-68)**	**-4.5 (-6.9 - -2.02)**	**<0.01**
VE/VCO2 slope	**31 (26-34)**	**38 (32-43)**	**8.6 (6-11)**	**<0.01**
Anaerobic Threshold, ml/kg/min	**9.1 (7.1-11.2)**	**10 (8.1-11)**	**0.77 (0.1-1.44)**	**0.02**
Exercise time (seconds)	**449 (335-535)**	**388 (324-476)**	**-39 (-59 - -19)**	**<0.01**
METs	**4.7 (4-5.5)**	**4.4 (3.6-5.3)**	**-0.47 (-0.69 - -0.2)**	**<0.01**
Peak heart rate (bpm)	**117 (101-132)**	**120 (103-136)**	**1.76 (-4.1 – 7.7)**	**0.56**
Peak systolic pressure (mmHg)	**155 (135-165)**	**140 (120-155)**	**-10.8 (-16.2 - -5.4)**	**<0.01**
WATTs	**80 (60-100)**	**70 (50-100)**	**-10.3 (-13 - -6.9)**	**<0.01**

Table 4. Medians and interquartile range of CPET variables and adjusted mean differences from linear regressions (adjustment for age, use of beta blockers, time interval between exams, baseline value).%ppVO2: percentage of predicted peak VO2. 95% CI: 95% confidence interval. T1: first CPET. T2: second CPET.

	T0	T1	Adj Odds ratio 95% CI	p value
Chronotropic incompetence, n (%)	33 (60)	33 (60)	0.88 (0.36-2.37)	0.88
Abnormal pressure response to exercise, n(%)	**17 (31)**	**27 (49)**	**7.14 (1.82-28.5)**	**0.005**
Beta blockers, n (%)	34 (62)	22 (40)	0.29 (0.11-0.81)	0.01
Sinus rhythm, n (%)	32 (58)	29 (52)	2.7 (0.5-15)	0.24

Table 5. Adjusted Odds ratio (age, CPET interval, beta blocker use (except for the variable beta blocker itself and baseline value). CI: 95% confidence interval. T1: first CPET. T2: second CPET.

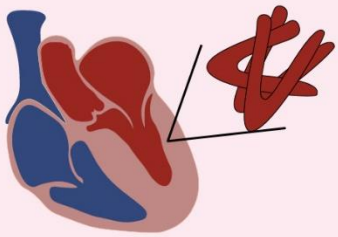
55 patients with transthyretin cardiomyopathy (ATTR) underwent 2 serial cardiopulmonary exercise testing (CPET) with a time interval of 14 (13-16) months

Median age was 80 (76-83) years, 91% were men

78% wild type ATTR 22% hereditary ATTR

76% NYHA class II/III

61% NAC stage I



Over time CPET parameters significantly worsened over time while echocardiography parameters remained unchanged

	T1	T2	Adjusted coefficient 95% CI	p value
Peak VO2 max, ml/kg/min	15 (12-18)	13 (12-16)	-1.29 (-1.85 - -0.74)	<0.01
%ppVO2, %	71 (60-83)	66 (57-68)	-4.5 (-6.9 - -2.02)	<0.01
VE/VCO2 slope	31 (26-34)	38 (32-43)	8.6 (6-11)	<0.01
Anaerobic Threshold, ml/kg/min	9.1 (7.1-11.2)	10 (8.1-11)	0.77 (0.1-1.44)	0.02
Exercise time (seconds)	449 (335-535)	388 (324-476)	-39 (-59 - -19)	<0.01
METs	4.7 (4-5.5)	4.4 (3.6-5.3)	-0.47 (-0.69 - -0.2)	<0.01
Peak heart rate (bpm)	117 (101-132)	120 (103-136)	1.76 (-4.1 – 7.7)	0.56
Peak systolic pressure (mmHg)	155 (135-165)	140 (120-155)	-10.8 (-16.2 - -5.4)	<0.01
WATTs	80 (60-100)	70 (50-100)	-10.3 (-13 - -6.9)	<0.01

Medians and interquartile range of CPET variables and adjusted mean differences from linear regressions (adjustment for age, use of beta blockers, time interval between exams, baseline value).%ppVO2: percentage of predicted peak VO2. 95% CI: 95% confidence interval. T1: first CPET. T2: second CPET.

CPET parameters may be used as an early marker of disease progression and may guide disease-specfic treatment strategy

Graphical abstract.