Central Sensitization and Physical Functioning in patients with Chronic Low Back Pain

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Maximal Cardiopulmonary Exercise Test in patients with chronic low back pain: Feasibility, Tolerance and relation with Central Sensitization An observational study

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ABSTRACT

Purpose. To analyze the feasibility of and pain-related tolerance to a maximal cardiopulmonary exercise test (CPET), and the relationship between the aerobic capacity and central sensitization (CS) in patients with chronic low back pain (CLBP).

Methods. An observational study, combining a cross-sectional and a prospective 24-hour follow-up was performed. Participants underwent a maximal CPET on a cycle ergometer and were assessed with three measures of CS (CS Inventory, quantitative sensory testing and heart rate variability). Before the CPET, immediately afterwards and 24 hours after, the Pain Response Questionnaire (PRQ) was filled out. The CPET was considered feasible when >80% performed maximally, and tolerable when <20% reported relevant pain increase, body reactions and additional pain medication use in the PRQ. Multiple regression analyses were applied to assess the relationship between the aerobic capacity (VO_2max) and CS measures, corrected for confounders.

Results. 74 patients with CLBP participated of which 30 were male, mean age was 40.4 years (SD: 12.4) and median VO_2max was 23.9 ml/kg/min (IQR: 18.2–29.4). CPET was completed by 92%. No serious adverse events occurred. A relevant pain increase was reported in the upper legs by 40% immediately after CPET and by 28% 24 hours afterwards, 27% reported body reactions after 24 hours, and 22% increased pain medication use 24 hours after CPET. Very weak and not significant relations ($r_{partial}$=-0.21 to 0.05; p>0.10) were observed between aerobic capacity and CS measures.

Conclusions. A maximal CPET is feasible in patients with CLBP. Most, but not all, tolerated it well. CS was not related to aerobic capacity.

INTRODUCTION

Chronic low back pain (CLBP) is a serious health issue, as expressed in being the main cause of years lived with disability [1], substantial negative economic consequences (direct and indirect costs) [2], and moderate treatment outcomes [3]. CLBP is characterized by its considerable impact on individuals' daily functioning, quality of life, and physical functions and body structures [4,5]. Although there is still a knowledge gap concerning the relationship between physical functioning and CLBP [6,7], it can be assumed that a subgroup of patients with CLBP are less physically active and, consequently, deconditioned.

Research into deconditioning of patients with CLBP has primarily been performed with submaximal testing [8–11]. A submaximal testing seems to be reliable [11]; however, it lacks accuracy because of the indirect way to estimate a maximal aerobic capacity [12], even when the submaximal testing is lean body mass based [13]. Consequently, submaximal testing procedures can lead to substantial under- or overestimation of results [14,15]. Heart rate (HR) guided exercise tests and its estimations of aerobic capacity cannot be used when patients use HR controlling medication; for instance, beta-blockers. Even though maximal exercise testing is considered the gold standard to assess maximal aerobic capacity [16], the use of a maximal cardiopulmonary exercise test (CPET) is only little explored [11,17,18]. A possible explanation is that the performance of a CPET, due to being a straining activity, can be limited by pain [19] and might not be tolerated by patients with CLBP. Systematically gathered data on pain reports of patients undergoing maximal CPET are lacking, leaving room for beliefs among clinicians and researchers that this procedure may be unsafe, unfeasible and intolerable for patients with CLBP. Moreover, while exercise therapy is recommended for the treatment of CLBP [20],the interventions and their outcomes are inconsistent; challenging the implementation of exercise interventions [21].When safe, feasible and tolerated well, maximum CPET could be applied to assess the aerobic capacity of patients with CLBP and provide valid information for the decision-making in the design and administration of treatment programs.

Central sensitization (CS) reflects the increased responsiveness to noxious and non-noxious stimuli. CS is characterized by enhanced sensitivity, including hyperalgesia, allodynia, extended receptor area, temporal summation, after sensations and decreased ability to inhibit descending pain pathways [22]. Hypothetically, CS and physical functioning, as objectified by (maximal) aerobic capacity, could be related in patients with CLBP. For example, higher levels of CS are related to an elevated pain sensation [23], and because some studies have reported lower levels of aerobic capacity in patients with CLBP compared

to healthy participants [8,17], lower levels of aerobic capacity can be expected at higher levels of CS. However, this relationship has not been up to now investigated.

Therefore, this study aimed to enhance the knowledge and understanding on the assessment of physical functioning –expressed as aerobic capacity– and its association with CS in patients with CLBP, as a basis for possible new angles for treatment and recommendations. The objectives of the study were:

1. To analyze the feasibility of and pain-related tolerance to a maximal CPET.
2. To analyze the relationship between CS and aerobic capacity.

It was hypothesized that CPET is feasible for patients with CLBP although with some pain responses as a result of the straining activity; and that higher levels of CS are related to lower levels of aerobic capacity in patients with CLBP.

MATERIALS AND METHODS

An observational study, combining a cross-sectional design and a prospective 24-hour follow-up, took place in a center for rehabilitation of a university medical center in the Netherlands, from September 2017 to June 2019. The study is part of a comprehensive project of which the protocol is described in detail elsewhere [24]. Medical ethical approval was obtained from the corresponding medical ethical committee (METc2016/702). The procedures comply the ethical standards of the Declaration of Helsinki of 1975, revised in 2013 [25]. The STROBE [26] reporting guideline was applied.

Participants

Consecutive adult patients (age 18 to 65) with primary CLBP (ICD-11 code: MG30.02) [27] admitted to treatment in an outpatient pain rehabilitation center, were eligible for the study. Patients with CLBP who based on their file have specific conditions which can better account for the pain (neuralgia or radicular leg pain), a major disorder or co-morbidity that could interfere with the study measures (e.g. affecting their physical and/or mental functioning), a specific contraindication to CPET, taking medication that could influence HR variability (HRV) measures (i.e. beta- blockers), were pregnant or not competent to follow instructions, were excluded. All participating patients signed an informed consent.

Procedures and measures

At baseline of an interdisciplinary pain rehabilitation program, the maximal aerobic capacity of patients was assessed with a CPET per regular institutional procedures. Concurrently to the test, the feasibility and pain-related tolerance measures were applied. In addition, CS and secondary measures (personal and clinical information) were collected also at baseline.

Main measures

Patients underwent a CPET to obtain the peak oxygen uptake per kilogram in ml/min/kg (VO_2max per kg), representing patient's aerobic capacity standardized for the body mass. A maximal exercise test, such as CPET, provides a direct, reliable and reproducible measurement of VO_2max in normal subjects and patients [28]. The test was performed on a cycle ergometer (Ergoselect 200, Ergoline, Bitz, Germany) following a defined ramp protocol. The assessment was performed by an experienced exercise physiologist and a specialized physician or nurse, who were not blinded to the purposes of the study but to concurrent CS measures. The assessors decided the starting workload and ramp (5 to 25 watt/minute) depending on patient's fitness level. The test started with a 3-minute unloaded warm-up at a constant speed of 60-70 rotations per minute. Afterwards, the workload was increased at a constant rate (ramp) while the cadence was maintained, until the maximal performance was achieved: a temporary loss of strength and energy (=exhaustion), a plateau in the peak oxygen uptake (VO_2max), a ≥1.10 respiratory exchange ratio (RER)[1], and/or a HR ≥85% of the predicted maximal HR [28]. Along with VO_2max per kg, the oxygen uptake at anaerobic threshold in l/min, RER, percentage of predicted maximal HR, workload in watts and energy expenditure in metabolic equivalent of tasks (METs) were recorded. At the end of the test patient-reported and assessor-observed exertions measured with Borg's rating of perceived exertion (RPE, 6–20) scale were collected. Borg's RPE scale is a reliable and valid instrument to measure work intensity because it is highly correlated with HR (r=0.74) and blood lactate (r=0.83) [29].

The Pain Response Questionnaire (PRQ) [30] was used to assess the occurrence of unfavorable pain responses after the CPET in patients with CLBP. PRQ part 1 measures the pain intensity in an 11-point numeric rating scale (NRS, 0–10) of four predefined body locations (shoulders, upper back, low back and upper legs). The NRS is a valid and reliable measure of pain intensity [31].

1. The respiratory exchange ratio (RER) can reflect the metabolic rate. Its value is the ratio of carbon dioxide production (VCO_2) to the oxygen consumption (VO_2)[28].

PRQ part 2 assesses whether straining activities were performed besides the CPET, the presence of not previously felt body reactions, and the additional use of pain medication due to the CPET. Patients were asked to fill in the questionnaire on three occasions: before performing the CPET, immediately afterwards and 24 hours later.

The CS Inventory part A (CSI-A) was used to assess the presence of the most common CS-related symptoms, such as pain all over the body, stress worsening symptoms, or being easily tired with physical activity. It is a 25-item questionnaire in which each symptom is assessed on a 5-point Likert scale (from 0 – Never to 4 – Always). A higher total sum score (0–100) means more frequent CS-related symptoms. The Dutch version of the CSI has excellent internal consistency (Cronbach α=0.91) and test-retest reliability (ICC=0.91 and 0.88) in controls and patients with chronic musculoskeletal pain [32].

The root mean square of successive differences (RMSSD) is a measure of the parasympathetic activity of the autonomic nervous system (ANS) and relatively independent of the individual's breathing frequency. In patients with chronic pain, the parasympathetic activity tends to be decreased and the sympathetic activity tends to be increased, which can contribute to underlying mechanisms of CS [33]. The RMSSD was obtained through a HRV assessment, a non-invasive reliable and valid standardized test which determines the function of the ANS [34]. The assessment was performed by physical therapists trained by the HeartMath Institute. During the HRV patients are instructed to sit and breathe normally for five minutes. An ear pulse sensor is connected to a computer where time-domain variables in milliseconds (RMSSD, mean time interval between two consecutive R-waves (R-R interval) and standard deviation of normal-to-normal interval (SDNN)) and a frequency-domain variable in ms^2/Hz (high frequency (HF)) were collected and recorded with emWave PC software (emWave®, HeartMath Inc., Boulder Creek, California) [35]. Before the entry into the database, the recordings were corrected for potential artifacts.

The quantitative sensory testing (QST) is a battery of standardized physical tests designed to describe and assess the somatosensory function. The procedure included five bedside examination tests executed according to the German research network on neuropathic pain (DFNS) guidelines and one test executed in accordance to the Nijmegen-Aalborg screening QST (NASQ) guidelines [36,37]. The QST protocol involved the assessment of: sharp cutaneous pain sensation (mechanical pain threshold—MPT), blunt pressure pain sensation (pressure pain threshold—PPT), allodynia (dynamic mechanical allodynia—DMA), touch sensation (mechanical detection threshold—MDT), temporal summation (wind-up ratio—WUR) and descending pain modulation (conditioned pain modulation—

CPM). The QST battery was performed by a trained researcher not blinded to the purposes of the study, but blinded to the concurrently collected data. The completion of the QST battery took about one hour. A detailed description of the QST tests is presented in Appendix 1.

Secondary measures

The following personal information was reported by patients in a self-constructed form: age, sex, height, weight, body mass index, pain duration (years since pain onset), pain medication, educational level, work status and physical work demands per dictionary of occupational titles [38].

Furthermore, clinical information was collected with the following questionnaires: pain intensity (Visual Analogue Scale—VAS-pain, 0–10) [31], disability (Pain Disability Index—PDI, 0–70) [39], physical functioning (Rand36 Physical Functioning subscale—Rand36-PF, 0–100) [40], catastrophizing (Pain Catastrophizing Scale—PCS, 0–52) [41], injustice (Injustice Experience Questionnaire—IEQ, 0–48) [42], and psychological traits (Brief Symptom Inventory Global Severity Index T-score—BSI-SGIT, 0–100) [43]. All these questionnaires have shown acceptable psychometric qualities [31,44–48] and have been elucidated elsewhere [24].

Statistical analysis

The sample size, set at 77 participants, is an estimation, of an exploratory nature, and its calculation has been described in the protocol [24]. Before statistical analyses, main measures' variables were computed:

- A dichotomous variable was created, which grouped in one category patients whose peak HR was ≥85% of the predicted maximal HR and/or RER was ≥1.10 from the CPET report, and in another category those who did not.
- The difference in pain intensity rating of the PRQ between before the CPET and immediately afterwards, and between before and 24 hours later was calculated per body location. Based on this calculation, for each body location patients were categorized into one of two groups per minimal important change (MIC) [49]: patients with a relevant pain increase (difference was of at least 2 points), and those who did not reach a relevant pain increase (difference was less than 2 points).
- DMA of the QST, was categorized into: no DMA, DMA pain score 0–1, and DMA pain score 1–100 [50].

Subsequently, data distribution and missing values were inspected. Normal distribution was a Z-score between -1.96 and +1.96 for skewness and kurtosis. If a main variable had a minimum of 10% of missing data, participants with missing data were compared to participants without missing data on age, sex, aerobic capacity (VO_2max per kg), maximal performance (≥85% predicted maximal HR and/or ≥1.10 RER), pain intensity (VAS) and disability (PDI). If the difference between the two groups was not statistically significant, analyses were performed pairwise. But if the two groups differed significantly from each other, an appropriate solution such as multiple imputation was applied [51].

To analyze the feasibility of and pain-related tolerance to CPET, descriptive statistics were run. Operational criteria to interpret feasibility and tolerance were developed (Table 1).

Table 1. Hypotheses of feasibility of and pain-related tolerance after a maximal CPET.

	Supported when:	**Definition**
Feasibility	≥80% maximal performance	Maximal performance during CPET, either: - Peak HR: ≥85% predicted maximal HR - RER: ≥1.10
Pain-related tolerance	≤20% relevant pain increase	Relevant pain increase: MIC (≥2 absolute points) pain increase in NRS, PRQ part 1
	≤20% body reactions	PRQ part 2
	≤20% pain medication use	PRQ part 2

Abbreviations: CPET, Cardiopulmonary exercise test; HR, Heart rate, MIC, minimal important change; NRS, Numeric rating scale; PRQ, Pain response questionnaire; RER, Respiratory exchange ratio.

To analyze the relationship between CS and aerobic capacity, partial correlation and multiple regression analyses were executed. In Spearman's rho partial correlation analyses, main measures and secondary measures were entered, and corrected for age and sex. In multiple regression analyses, VO_2max per kg was the dependent variable, CSI-A, RMSSD and the test with the highest correlation coefficient of the QST battery were the independent variables, and age and sex were the confounders. Other secondary measures, such as patient characteristics and additional measures collected from QST and HRV were selected depending on their correlation coefficient, r≥0.1. These entered to the multiple regression model in a stepwise forward method and were retained if their attrition was significant ($p<0.05$).

The significance of the analyses was set at p<0.01 for partial correlation and sensitivity analyses of missing data to correct for type I error, and at p<0.05 for multiple regression analyses. All analyses were executed with SPSS (SPSS Statistics version 23, IBM Corp., USA).

RESULTS

A total of 77 patients enrolled in the study. One patient dropped out before the CPET took place and two patients were excluded: one due to having a major disorder that interfered with the measures (exclusion criterion) and the other due to undergoing a not intended submaximal test. A final sample of 74 patients with CLBP participated. Of the participating patients 40.5% were men with a mean age of 41.9 years (SD: 11.8) and 59.5% were women whose mean age was 39.4 years (SD: 12.9). The mean VO_2max were 2.4 l/min (SD: 0.7) and 1.8 l/min (SD: 0.3) for men and women respectively. Demographic and clinical characteristics are presented in Table 2.

Table 2. Description of participating patients (n=74).

	n	mean ± SD / %
Demographic characteristics		
Age (years)	74	40.4 ± 12.4
Sex	74	
Men	30	40.5%
Women	44	59.5%
Body mass index (kg/m²) [a]	74	27.0 (24.1 – 30.6)
Pain duration (years) [a]	74	2.1 (1.3 – 4.2)
Use of medication	72	
Use pain medication	53	73.6%
No use of pain medication	19	24.6%
Educational level	70	
Primary	2	2.9%
Secondary	40	57.1%
Bachelor or higher	28	40.0%
Physical Work Demands (DOT)	74	
Sedentary	18	24.3%
Light	32	43.2%
Medium	20	27.0%
Heavy	4	5.4%

Table 2. *[Continued]*

	n	mean ± SD / %
Working status	74	
Working	27	36.5%
Reduced/Adapted work	17	23.0%
Sick-leave	9	12.2%
Disability pension	7	9.5%
Not working	10	13.5%
Other	4	5.4%
Clinical characteristics		
Pain intensity (VAS Pain, 0–10)	73	4.7 ± 2.2
Disability (PDI, 0–70)	72	36.7 ± 11.9
Physical functioning (Rand36-PF, 0–100)	73	51.5 ± 19.5
Catastrophyzing (PCS, 0–52)	65	18.9 ± 10.2
Injustice (IEQ, 0–48) [a]	70	16.0 (9.8 – 23.0)
Distress (BSI-GSIT, 0–100) [a]	65	38.1 (33.0 – 45.5)
Aerobic capacity (CPET)		
Maximal oxygen uptake per kilogram (VO_2max per kg, ml/kg/min) [a]	74	23.9 (18.2 – 29.4)
Maximal performance	68	91.9%
Submaximal performance	6	8.1%
Oxygen uptake at anaerobic threshold (l/min) [a]	74	1.2 (1.0 – 1.4)
Workload (watts) [a]	74	162.0 (134.8 – 192.5)
Energy expenditure (MET) [a]	74	6.8 (5.2 – 8.4)
Patient's reported exertion (RPE, 6–20)	74	16.1 ± 2.3
Assessor's observed exertion (RPE, 6–20)	68	17.2 ± 2.0
Central sensitization (CS)		
CSI		
CS-related symptoms (CSI-A, 0–100) [a]	70	40.5 (31.0 – 50.0)
QST		
Sharp cutaneous pain sensitivity (MPT, mN) [a]	70	73.3 (31.7 –190.7)
Blunt pressure pain sensitivity (PPT, N) [a]	70	53.9 (41.7 – 72.6)
Allodynia (DMA)	69	0.0%
Touch sensation (MDT, mN) [a]	70	3.3 (1.6 – 8.2)
Temporal summation (WUR) [a]	59	2.4 (1.8 – 3.2)
Descending pain modulation (CPM, %) [a]	69	6.9 (-4.5 – 23.2)

Table 2. *[Continued]*

	n	mean ± SD / %	
HRV			
Parasympathetic/vagal tone (RMSSD, ms) [a]	69	41.4	(31.5 – 54.6)
Parasympathetic/vagal tone (HF, ms^2/Hz) [a]	69	102.3	(63.0 – 196.0)
Mean inter-beat time interval (R-R interval, ms) [a]	69	816.7	(746.8 – 917.6)
Standard deviation of R-R intervals (SDNN, ms) [a]	69	56.9	(41.7 – 72.8)

[a], variables not normally distributed, median and interquartile range [IQR 25–75] is given. Abbreviations: BSI, Brief Symptom Inventory; CPET, Cardiopulmonary exercise test; CPM, Conditioned pain modulation; CSI, Central sensitization inventory; DMA, Dynamic mechanical allodynia; DOT, Dictionary of occupational titles; GSIT, Global severity index T-score; HF, High frequency; HRV, Heart rate variability; IEQ, Injustice experience questionnaire; MDT, Mechanical detection threshold; MET, Metabolic equivalent of tasks; MPT, Mechanical pain threshold; PCS, Pain catastrophizing scale; PDI, Pain disability index; PF, Physical functioning; PPT, Pressure pain threshold; QST, Quantitative sensory testing; RMSSD, Root mean square of successive differences; RPE, Rating of perceived exertion; SDNN, Standard deviation of normal-to-normal range VAS, Visual analogue scale; WUR, Wind-up ratio.

More than 10% of data were missing on the variables temporal summation (WUR) and PRQ part 1 for shoulders, upper back and upper legs. The reason for WUR was methodological, only the locations where the standardized pinprick of 256 mN was suprathreshold were calculated (see Appendix 1); for PRQ part 1 questionnaire, participants did not rate the pain intensity for shoulders, upper back and upper legs. No significant differences were found between patients with and without missing data ($p>0.094$). No further data handling was deemed necessary.

Regarding the feasibility of CPET, 91.9% of the participants performed maximally (Table 2). Consequently, CPET can be assessed as feasible for patients with CLBP (see Table 1). Differences in pain intensity at different body locations were observed immediately and 24 hours after CPET assessment (Table 3). The percentage of patients experiencing an increase in pain in the shoulders (5.4% / 10.2%), upper back (12.5% / 12.7%) and low back (11.1% / 8.6%) immediately and 24 hours after CPET respectively was below 20%. Pain in the upper legs increased in more than 20% of the patients immediately and 24 hours after the CPET (39.6% / 27.8% respectively). Furthermore, 16.2% and 26.8% reported bod y reactions immediately and 24 hours after the CPET. 22.2% mentioned an increase in pain medication use 24 hours after the CPET (Appendix 2). Overall, results exceeded in part the criteria for tolerance (Table 1). No serious adverse events occurred.

Table 3. Description of pain response to CPET per the body locations (n=74).

	Before CPET		Immediately after CPET			24 hours after CPET		
	n	mean±SD	n	mean±SD	Participants with MIC pain increase	n	mean±SD	Participants with MIC pain increase
Shoulders	63	2.4 ± 2.7	56	2.2 ± 2.6	5.4%	59	2.2 ± 2.7	10.2%
Upper back	59	2.0 ± 2.4	57	2.1 ± 2.4	12.5%	60	2.1 ± 2.4	12.7%
Low back	73	5.5 ± 2.2	73	5.2 ± 2.6	11.1%	71	5.4 ± 2.4	8.6%
Upper legs	57	2.6 ± 3.0	60	4.1 ± 3.0	39.6%	63	3.4 ± 2.9	27.8%

Abbreviations: CPET, Cardiopulmonary exercise test; IQR, Interquartile range 25-75; MIC, minimal important change.

Partial correlation analyses showed weak and not significant associations between aerobic capacity and CSI-A, QST tests or RMSSD (r=-0.184 to 0.175; p>0.132). For the multiple regression models, MDT was chosen as representative for QST to enter along with CSI-A and RMSSD (Table 4). The final multiple regression model explained 68.1% of the total adjusted variance (p<0.001) and included data of 66 patients and a total of seven variables. CSI-A, MDT and RMSSD maintained weak and not significant correlations ($r_{partial}$=-0.213 to 0.051; p>0.099) when the rest of the confounding variables age, sex, workload and mean inter-beat time interval (R-R interval) were accounted for (Table 5).

Table 4. Results of Spearman partial correlation analyses of the association of maximal aerobic capacity (VO_2max per kg) with CS measures, main secondary measures, and corrected for age and sex.

		Aerobic capacity
Aerobic capacity	Maximal performance (yes/no)	-0.34**
	Oxygen uptake at anaerobic threshold	0.47***
	Workload	0.73***
	Patient's reported exertion (RPE)	-0.00
	Assessor's observed exertion (RPE)	0.12
Central sensitization	CSI	
	CS-related symptoms (CSI-A)	-0.03
	QST	
	Sharp cutaneous pain sensitivity (MPT)	-0.03
	Blunt pressure pain sensitivity (PPT)	-0.02
	Touch sensation (MDT)	-0.18
	Temporal summation (WUR)	-0.01
	Descending pain modulation (CPM)	0.07
	HRV	
	Parasympathetic/vagal tone (RMSSD)	0.17
	Parasympathetic/vagal tone (HF)	0.16
	Mean inter-beat time interval (R-R interval)	0.38**
	Standard deviation of R-R intervals (SDNN)	0.28*
Participants' characteristics	Pain medication	-0.09
	Pain intensity (VAS pain)	-0.25*
	Disability (PDI)	-0.31*
	Physical functioning (Rand36-PF)	0.35**
	Catastrophyzing (PCS)	-0.06
	Injustice (IEQ)	-0.09
	Distress (BSI-GSIT)	0.04

Significance level: *, p<0.05; **, p<0.01; ***, p<0.001. Abbreviations: BSI, Brief Symptom Inventory; CPM, Conditioned pain modulation; CSI, Central sensitization inventory; GSIT, Global severity index T-score; HF, High frequency; HRV, Heart rate variability; IEQ, Injustice experience questionnaire; MDT, Mechanical detection threshold; MPT, Mechanical pain threshold; PCS, Pain catastrophizing scale; PDI, Pain disability index; PF, Physical functioning; PPT, Pressure pain threshold; QST, Quantitative sensory testing; RMSSD, Root mean square of successive differences; RPE, Rating of perceived exertion; SDNN, Standard deviation of normal-to-normal range; VAS, Visual analogue scale; WUR, Wind-up ratio.

Table 5. Multiple regression model of maximal aerobic capacity (VO_2max per kg) with CS (CSI, MDT and RMSSD), corrected for age, sex and relevant confounders.

		B	[95 % CI]	p	Beta	$r_{partial}$
(Constant)		3.22	[-8.52 , 14.96]	0.585		
Central sensitization	CS-related symptoms (CSI-A)	0.02	[-0.07 , 0.11]	0.716	0.03	0.05
	Touch sensitivity (MDT)	-0.14	[-0.30 , 0.03]	0.099	-0.13	-0.21
	Parasympathetic/vagal tone (RMSSD)	0.01	[-0.05 , 0.07]	0.695	0.03	0.05
Confounders	Age	-0.17	[-0.28 , -0.06]	0.003	-0.27	-0.38
	Sex	-0.39	[-3.06 , 2.27]	0.769	0.03	0.04
	Workload	0.09	[0.06 , 0.12]	<0.001	0.61	0.64
	Mean inter-beat time interval (R-R interval)	0.02	[0.00 , 0.03]	0.007	0.22	0.34

Abbreviations: CSI, Central sensitization inventory; MDT, Mechanical detection threshold; RMSSD, Root mean square of successive differences.

DISCUSSION

Results show that maximal CPET is feasible; most patients were able to perform the test maximally. Following the CPET, more than 20% of the patients reported a relevant pain increase in the legs (but not in other regions), not previously felt body reactions, and additional pain medication use. Aerobic capacity was not related to any of the CS measures assessed. The aerobic capacity of patients with CLBP has been little explored with a maximal CPET [11,17,18]. Pain could have limited patients' performance [19], which may also have led to beliefs against assessing their maximal aerobic capacity. In contrast, the findings of this study seem to strengthen the possible implementation of a maximal exercise test in patients with CLBP. CPET, considered the gold standard for the assessment of the aerobic capacity [16], can be useful at baseline of the rehabilitation for the evaluation of patients' aerobic capacity and for an optimal design of exercise interventions to promote the functioning of patients with CLBP. As a result, the CPET may assist clinicians in the decision-making of the design and administration of more personalized and effective programs. An unforeseen additional result of this study that may benefit patients was the non-standardized observation that many patients were positively surprised that they could tolerate the required maximal physical intensity.

Our feasibility results are in agreement with earlier research [17,18], indicating that a maximal CPET provides valid results in the majority of patients with CLBP. The maximal performance threshold definition from earlier research [17,18] was stricter than the one used in the present study (≥90% of the predicted maximal HR or ≥1.13 RER). Post-hoc analyses using those thresholds reveal that 85.1% of patients with CLBP were able to perform maximally. Such outcome reinforces the feasibility of CPET and its adequacy to provide valid assessment of the aerobic capacity of patients with CLBP.

The decision to apply a CPET in patients with CLBP also depends on the way such test is tolerated in relation to pain. There were some pain responses to CPET performance; nevertheless, these can be considered normal to the straining activity. First, an increase in pain was reported in the legs, but not in other body regions. This outcome seems compatible with the major effort made by the upper leg muscles to perform a CPET on a bicycle ergometer, and the consequent upper leg soreness. In the able bodied population the temporal raise in pain in the upper legs after performing a CPET on a bicycle ergometer, for instance as muscle soreness, is well-known and considered normal [52–54]. In previous studies, where other types of straining activities were performed by patients with CLBP and able-bodied participants, similar pattern of pain increase and decrease were observed [30]; suggesting indirect evidence for

the interpretation that the observed symptom pattern following CPET, should be considered a normal response to unfamiliar physical activity. Second, some general body reactions were reported after the CPET; but this occurrence too is similarly recorded in able-bodied after CPET [52,53]. Third, an increase in pain medication use was reported 24 hours after the CPET. Although, reasons for additional medication use were not recorded, its use could have been due to the muscle soreness in the legs. The results on pain-related tolerance to a CPET are inconclusive. However, on the one hand, most patients were able to perform (near) maximally with no serious adverse effects occurring, most patient's pain-related tolerance was good, and their response to the test is to a large extent similar to that of able-bodied [55]. On the other hand, a maximal test is the gold standard, more accurate [12], reliable and valid [16] than a submaximal test. Overseeing and weighing all benefits and harms of a maximal CPET, we regard application of maximal CPET in patients with CLBP justifiable.

The literature on the relation between aerobic capacity and CS is limited, hindering the comparability of the results of our study. Our results match those of a very similar study, in which patients with CLBP underwent a maximal aerobic capacity test and no association with CSI-A was reported [56]. Furthermore, this same study showed associations with pain intensity and disability whose significance did not remain after the correction for age and sex, which also resembles our results. The associations of aerobic capacity with QST and/or parasympathetic/vagal tone (RMSSD in our study) have no comparability. MDT has not been related to aerobic capacity before. And studies on aerobic capacity and vagal modulation indicate a positive association at rest in healthy participants [57]. However, no studies have been found which studied this relationship in patients with chronic pain.

Previous research on aerobic capacity in patients with CLBP found no relation between pain intensity and pain-related factors, such as avoidance, disability or catastrophizing [9,56,58]. If CS is present, patients may experience greater pain and more affected pain-related factors including ANS and psychosocial factors. Because aerobic capacity has been unrelated to those factors which are enhanced in CS, a lack of association between aerobic capacity and CS may be plausible. As opposed to this, an association between CS and heightened pain response to a straining activity as the CPET could be expected in a subgroup with exercise induced hyperalgesia [59]. Testing such hypothesis may be subject of future studies.

Strengths of the study include the enhancement of insights on the application of maximal exercise testing in patients with CLBP. It shows, amongst others, that CPET can be applicable and provides information on the usability of it.

Furthermore, this study adds to the knowledge of CS in patients with CLBP. It applies and combines state of the art CS measurement tools for a more complete description of the phenomenon.

The generalizability of the outcomes may be limited due to selection bias. Patients with a specific contraindication to CPET or taking medication that may influence HRV measures (i.e. beta-blockers) were not included. Most routinely used exercise tests are directed by HR, which cannot be used with beta-blockers. This would be an additional reason to perform a breathing gas analysis system such as the one used in our study. Unfortunately, due to concurrent HRV measures, this was not tested. Also, participation was voluntary and patients were informed that they would perform a CPET additional to their regular baseline assessment for treatment [24] before signing the informed consent. The participants in our study reported slightly better clinical characteristics than patients attending pain rehabilitation treatment in the Netherlands [60], though differences were not relevant [49]. Another limitation is that pain response measures are limited to 24 hours; as a result, we cannot substantiate or refute our hypothesis that after a CPET elevated PRQ values will return to the pretest levels. Additionally, thresholds for the feasibility of and pain-related tolerance to CPET were rather strict and arbitrary. Duque et al. [18] revealed a lower percentage (69%) of patients with CLBP being able to complete a CPET, but their criteria were stricter. Consequently, the threshold in our study was set higher, at 80%. Respecting the pain-related tolerance to CPET, in lack of previous studies on which to base on the threshold, it was arbitrarily decided on clinical experience. Finally, during the assessment of MDT and MPT of the QST protocol, floor and ceiling effects were noticed; the influence of these effects on the results is nevertheless inconsequential.

Further research in pain-related tolerance of patients with CLBP to a maximal CPET with larger samples, for a longer period of time (more measurement time-points), and compared to matched able-bodied, should be able to provide better insights on the pain tolerance progression. Furthermore, because in patients with CS pain experience is enhanced, future research should also consider the potential implication of CS on pain-related tolerance. Eventually, the recommendations and management of patients with CLBP will be improved.

A maximal CPET is feasible in patients with CLBP. Most, but not all, tolerated it well in relation to pain. CS is not related to aerobic capacity. More research is needed to understand the pain response to a maximal CPET on a period longer than 24 hours, whether a similar experience can be expected in able-bodied, and whether CS involved in it.

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APPENDIX

Appendix 1. Description of the QST assessment [24].

Five bedside examination tests (MPT, PPT, DMA, MDT and WUR) were executed according to the German research network on neuropathic pain (DFNS) guidelines [36]. First, the five tests were performed in a training location and, afterwards, anew in six body locations including the most painful location. The assessment ended with the CPM executed in accordance to the Nijmegen-Aalborg screening QST (NASQ) guidelines [37].

- *MPT*. Measures sharp cutaneous pain sensitivity by assessing the ability to perceive sharp, pricking, or stinging stimuli on the skin with a set of weighted pinprick stimulators (the PinPrick Stimulator Set, MRC Systems, Germany). The procedure is performed with a method of limits starting with the lowest intensity and progressively increasing until a change from touch to a sharp, pricking, or stinging feeling is perceived by the patient. The first suprathreshold stimulus is recorded in millinewtons. The test-retest (r=0.80) and inter-observer reliability (r=0.80) of MPT is good [61].
- *PPT*. Measures blunt pressure pain sensitivity on muscles. The tip (1 cm^2) of an electronic pressure algometer (Force Ten FDX, Wagner Instruments, USA) is placed on the skin and progressively the pressure is increased until patients report a change from pressure to painful, defined as burning, drilling or aching sensation. The intensity when pressure became painful in recorded in newtons. The test-retest (r=0.88) and inter-observer reliability (r=0.84) of the PPT is good [61].
- *DMA*. Measures whether allodynia is present. A soft brush (SENSElab, Brush-05, Somedic, Hörby, Sweden) is swiped on the skin. Whether the swipe is felt or not and, if felt, the pain intensity with a numeric rating scale (NRS, 0–100) is recorded. The test-retest (r=0.87) and inter-observer reliability (r=0.79) of the DMA is good [61].
- *MDT*. Measures pain sensitivity by assessing the ability to detect light touch on the skin with the von Frey filaments (OptiHair2-Set, Marstock Nervtest, Germany). Similar to MPT, the procedure for MDT is a modified method of limits starting with the filament of 16 mN of intensity and progressively decreasing if the stimulus is felt until no touch sensation is perceived by the patient. If the starting filament is not felt the reverse procedure with increasing intensity filaments is applied until the threshold is found. The intensity of the first subthreshold stimulus is recorded in millinewtons. The test-retest (r=0.90) and inter-observer reliability (r=0.89) of the MDT is good [61].

- *WUR*. Measures the temporal summation to repeated noxious stimuli. A suprathreshold weighted pinprick of 256 mN (the PinPrick Stimulator Set, MRC Systems, Germany) is applied once and again on a train of 10 repetitions in a 1-second interval. To ensure the assessment with a suprathreshold stimulus of 256 mN, the WUR is performed in the locations with an MPT below or equal to 256 mN. The pain intensity of the single stimulus and of the train is assessed with the NRS (0 to 100) and introduced to calculate the ratio as follows: WUR=(NRS-10/NRS-1). The test–retest (r=0.67) and inter-observer reliability (r=0.56) for the WUR is poor [61].
- *CPM*. Measures the descending pain modulation of the nervous system by using a paradigm that includes the combination of a test stimulus before and after a thermal conditioning stimulus. The test stimulus (PPT, see above) is applied in the non-dominant side quadriceps. The conditioning stimulus is applied in the dominant hand, which is immersed on a bucket with ice and cold water for as long as possible, up to a maximum of 3 minutes. The PPTs recorded before and after the thermal conditioning stimulus are introduced to calculate the CPM percentage: CPM=[(PPTpost–PPTpre)/PPTpre]∗100. The combination of PPT and cold conditioning stimuli is one of the most reliable methods to assess CPM and the test-retest reliability is modest (ICC=0.49 and coefficient of variation=63.6%) [62].

The mean of the body locations for each of the five bedside examination tests is calculated, with the exception of the training location and if at least four out of the six locations have data.

Appendix 2. Patient-reported straining activities +/- 24 hours the CPET took place, body reactions after CPET, and pain handling 24 hours after CPET are presented.

	Before test (n=70)	Immediately after CPET (n=74)	24hr after CPET (n=72)
	n (%)	n (%)	n (%)
Heavy or unusual physical activities in the last 24 hours	11 (15.7%)	na	13 (18.3%)
New body reactions following CPET	na	12 (16.2%)	19 (26.8%)
Use of additional pain medication following CPET	na	na	16 (22.2%)

Abbreviations: CPET, Cardiopulmonary exercise test; na, not applicable.