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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

IS INSPIRATORY MUSCLE FUNCTION IMPAIRED IN PERSONS WITH CHRONIC NON-SPECIFIC LOW BACK PAIN?

Evelien Theunis
Stien Van Doninck
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Annick TIMMERMANS

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Research context

This master thesis is situated in the musculoskeletal rehabilitation domain. More specific, the target population is persons with chronic non-specific low back pain. This study is part of an ongoing doctoral study of our mentor Sim Klaps with the title ‘the Breathe Hitt trial’. So the results discussed here are preliminary. Measurements and research continue at REVAL in Diepenbeek. This study is a duo master's thesis, carried out by Evelien Theunis (E.T.) and Stien Van Doninck (S.V.D.) under the supervision of our mentor Sim Klaps and our promotor Annick Timmermans.

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1 Abstract

Background: Chronic non-specific low back pain (CNSLBP) has been associated with impaired postural control. The diaphragm, the primary inspiratory muscle, also plays an important role in postural control. An association between CNSLBP and impaired diaphragm functioning has been demonstrated in previous studies. The primary objective of this study is to evaluate the extent of impairment in diaphragm function (i.e. diaphragm strength and diaphragm fatigue) in persons with CNSLBP compared to age, sex and BMI-matched healthy controls (HC).

Methods: Nine persons with CNSLBP (31 yr, 6 male, 26.3 kg/m^2) and nine age-, gender- and BMI-matched healthy controls (30.2 yr, 6 male, 24 kg/m^2) were included in this cross-sectional comparative study. Diaphragm strength was measured using maximal inspiratory pressure (MIP). To induce inspiratory muscle fatigue, and thus diaphragm fatigue, a cardiopulmonary exercise test (CPET) was conducted. The difference in percentages in MIP before and after the CPET was used for measuring diaphragm fatigue immediately, 15 minutes and 30 minutes after CPET.

Results: No difference was found in baseline MIP between CNSLBP group and the control group (p=0.3161/ p=0.2981). There was no significant diaphragm fatigue present within both groups at T1, T2 and T3 after the CPET. For the CNSLBP group diaphragm fatigue was 3.32% (T1), 8.23% (T2) and 2.84% (T3). The HC group had a diaphragm fatigue of 2.85% (T1), 1.25% (T2) and 3.26% (T3). A significant difference in diaphragm fatigue between both groups was also not found (T1: p=0.9874; T2: p=0.5766; T3: p=0,9995).

Conclusion: Diaphragm strength and exercise-induced fatigue are not significantly different between persons with CNSLBP and healthy controls.

Keywords: CNSLBP, MIP, diaphragm strength, diaphragm fatigue

2 Introduction

Low back pain (LBP) is the number one cause of disability worldwide and the lifetime prevalence reaches up to 84% (Hartvigsen, Hancock et al. 2018) (Balague, Mannion et al. 2012). Pain becomes chronic in 20% of the LBP cases (Nielens, Van Zundert et al. 2006). Chronic LBP is defined as pain in the lower back (e.g. from the lower rib margins to the buttock creases) that persists for at least 12 weeks . In 85% of the cases, chronic LBP is not attributable to a recognizable, known specific pathology, and is therefore defined as chronic nonspecific LBP (CNSLBP). The point prevalence of CNSLBP is estimated at 23% and equally important, the point prevalence for persons who suffer from disability in activities of daily living caused by CNSLBP is approximately 11-12% (Airaksinen, Brox et al. 2006) (Andersson, Ejlertsson et al. 1993).

CNSLBP has been associated with impaired postural control, a term used to describe the way the central nervous system regulates sensory information from other systems in order to produce adequate motor output to maintain a controlled, upright posture (Saeid 2022). Previous studies showed that persons with CNSLBP exhibited altered postural control strategies such as rigid ankle strategy rather than a more multisegmental strategy compared to healthy controls (Ruhe, Fejer et al. 2011) (Brumagne, Diers et al. 2019). The primary trunk muscles involved in postural control are for example the rectus abdominis and the erector spinae. These trunk muscle groups are usually examined when studying postural control (Koch and Hansel 2019) (Ringheim, Austein et al. 2015). However, respiratory muscles like the diaphragm also have a prominent role in postural control (Airaksinen, Brox et al. 2006).

The diaphragm is a thin, dome-shaped muscle that separates the thoracic and abdominal cavity. The diaphragm is the primary inspiratory muscle and it is also involved in postural control in multiple manners (Kocjan, Adamek et al. 2017). Firstly, a direct mechanical effect is present via the attachments of the diaphragm crura (Hodges, Eriksson et al. 2005). The crura are two tendinous structures which are attached to the lumbar vertebra (Kocjan, Adamek et al. 2017). Secondly, the diaphragm also has the ability to modulate intra-abdominal pressure (iaP). These two mechanisms have been demonstrated to be contributing factors to stiffness of the trunk (Hodges, Eriksson et al. 2005). The dual role of the diaphragm has been confirmed in healthy persons, persons with chronic obstructive pulmonary disease and persons with CNSLBP (Kocjan, Adamek et al. 2017) (Hodges 1997) (Hodges 2000) (Janssens, Brumagne et al.

2010) (Mohan, Paungmali et al. 2018) (Vermeersch, Janssens et al. 2022) (Hamaoui, Do et al. 2001) (Beeckmans, Vermeersch et al. 2016) (Janssens, Brumagne et al. 2013). For example, when healthy persons performed postural tasks like rapid arm flexion while standing, studies have shown significant coactivation of the diaphragm with the abdominal and back muscles and an increase in iaP (Hodges 1997) (Hodges 2000). Additionally, Hodges et al. also found that diaphragm activity started prior to upper limb movement, this feedforward mechanism further strengthened the evidence that the diaphragm plays a role in postural control (Hodges and Gandevia 2000). Moreover, during different respiratory rate conditions (slow and fast breathing), persons with LBP showed an increase in COP displacement in comparison to healthy persons (Hamaoui, Do et al. 2001). Furthermore, it has been shown that when the diaphragm of healthy persons and persons with CNSLBP is loaded by inspiratory threshold loading and a postural task is performed, postural sway towards anterior posterior increases and the use of lumbar proprioception decreases. This finding also reinforces that persons with LBP show less optimal postural control strategies (Janssens, Brumagne et al. 2010).

An association between CNSLBP and impaired diaphragm functioning has been demonstrated in different studies (Mohan, Paungmali et al. 2018) (Vermeersch, Janssens et al. 2022) (Hamaoui, Do et al. 2001) (Hamaoui, Do et al. 2001) (Beeckmans, Vermeersch et al. 2016). Persons with CNSLBP show decreased diaphragm endurance, decreased diaphragm strength and increased diaphragm fatigability compared to healthy persons (Mohan, Paungmali et al. 2018) (Vermeersch, Janssens et al. 2022) (Hamaoui, Do et al. 2001). In addition, LBP has been associated with respiratory disorders like dyspnea, asthma and respiratory infections (Beeckmans, Vermeersch et al. 2016).

Different measurement techniques are available for quantification of the strength of the diaphragm. Invasive techniques such as esophageal and gastric balloons for recording transdiaphragmatic pressure (e.g gastric pressure minus esophageal pressure) are reliable and considered as the gold standard for the non-volatile assessment of diaphragm strength. However, invasive techniques are often complex, time-consuming, and uncomfortable for the patient (Spiesshoefer, Henke et al. 2019). Non-invasive techniques, such as measurements of mouth or nasal pressure are widely applied and accepted (Jalan 2015). An electronic pressure transducer can be used for measuring diaphragm muscle strength and norm values have been identified in different populations (Torres-Castro, Sepulveda-Caceres et al. 2019).

So the primary objective of this study is to evaluate the extent in which impaired diaphragm function (i.e. diaphragm strength and diaphragm fatigue) is present in persons with CNSLBP compared to healthy controls (HC). So, the first research hypothesis is: Diaphragm strength, measured as maximal inspiratory pressure, is reduced in persons with CNSLBP compared to HC. The second research hypothesis is: diaphragm fatigue, measured as maximal inspiratory pressure after CPET, is increased in persons with CNSLBP compared to HC.

3 Methods

3.1 Design

The proposed study is a cross-sectional comparative study that was carried out between 22/08/2022 and 14/04/2023. This study is part of a randomized controlled trial named *"The Breathe-(H)IT Trial: Multimodal high intensity training to improve diaphragm functioning in persons with chronic nonspecific low back pain".* Persons with CNSLBP and healthy controls performed measurements at one testing day at REVAL (Hasselt University, Diepenbeek, Belgium).

3.2 Recruitment and study population

3.2.1 Recruitment

Eight persons with CNSLBP and eight age-, sex-, and BMI-matched healthy controls were recruited through local distribution of flyers (e.g. in pharmacies, libraries, university facilities) in Limburg (BE), and adverts on social media. Interested persons received a patient information letter, and were invited for an (online) intake session by one of the researchers. During the intake session, the information letter was reviewed, study inclusion and exclusion criteria were evaluated, and a study-specific screening form concerning red flags for low back pain were filled out.

3.2.2 Eligibility criteria

3.2.2.1 Persons with CNSLBP

Dutch-speaking males and females (age 18-65 years) with chronic low back pain (i.e. pain localized below the costal margin and above the inferior gluteal folds, with or without referred leg pain for a period of at least twelve weeks), with a non-specific origin (i.e. pain of a nociceptive mechanical nature, not attributable to a recognizable, known, specific pathology, e.g. infection, tumor, osteoporosis, fracture, structural deformity, inflammatory disorder, radicular syndrome, or cauda equina syndrome) were eligible for study participation (Airaksinen, Brox et al. 2006). All patients were asked to provide proof of this medical diagnosis via a general practitioner or specialist referral letter.

Persons with CNSLBP were excluded when they had a pacemaker a chronic obstructive respiratory disorder ; comorbidities (e.g. musculoskeletal disorders apart from CNSLBP, neurological disorders or respiratory disorders) that can affect correct measurements of the MIP (30); negative advice from the general practitioner regarding sports medical screening; or were pregnant (Trigano, Blandeau et al. 2005) (Abd El Aziz, Elwahsh et al. 2017) (Moccellin and Driusso 2012, Casagrande, Gugala et al. 2015). The eligibility criteria are presented in Table 1.

Table 1. Eligibility criteria

Inclusion criteria	Rationale
18 to 65 years old	Study aimed at adult population
Non-specific low back pain for a period of at least 12 weeks	To measure the extent of reduced diaphragm function in this population
Dutch-speaking	Participants need to understand the instructions and questionnaires
Exclusion criteria	**Rationale**
Pacemaker	A pacemaker is sensitive for other electronic and magnetic fields
Chronic obstructive respiratory disorder	Respiratory system is impaired in this population
Negative advice regarding sport medical screening	A negative advice from the GP does not allow the performance of a maximal cardiopulmonary exercise test
Pregnancy	Limiting the number of factors that can influence the outcome (postural control)
Comorbidities (neurological disorders, respiratory disorders, or musculoskeletal disorders apart from CNSLBP that can affect the evaluation of the outcome)	Limiting the number of factors that can influence the outcome
History of spontaneous pneumothorax, severed eardrum, high end diastolic left ventricular pressure or heart failure patients with worsening of symptoms after inspiratory muscle training	Contraindications for a MIP measurement

3.2.2.2 Age-, sex- and BMI-matched healthy controls

Dutch-speaking males and females (age 18-65 years) without acute or chronic musculoskeletal complaints (i.e. Numeric Pain Rating Scale < 2/10 in the last 24 hours) were eligible for study participation. The exclusion criteria for the healthy controls are the same as those for the CNSLBP group.

3.3 Outcome measures

3.3.1 Demographic characteristics

The following information was collected for both groups: age, gender, body weight (measured, kg), and height (measured, cm). Another characteristic that was included for both groups was exercise capacity (l/min). These demographic characteristics were measured to ensure baseline characteristics were well balanced between both groups.

Exercise capacity

Cardiorespiratory exercise capacity was evaluated by using a continuous graded maximal cycle test (75 rpm) to volitional fatigue on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany). Maximal workload (Wmax), and time to exhaustion (TTE) were evaluated (Lluch Girbés E 2016). Participants started at a low workload that gradually increased after each completed minute (30W+15W/min). Maximal oxygen uptake (VO2max), expiratory volume (VE), respiratory exchange ratio (RER), and heart rate were determined through breath-by-breath gas exchange analysis (Cortex MetaMax 3B) and heartrate monitoring (Polar®, Finland). A minimum respiratory exchange ratio (RER) threshold of 1.10 was used to evaluate proper validity of the maximum effort (Thompson, Arena et al. 2013).

3.3.2 Baseline characteristics in CNSLBP group

For the CNSLBP group, baseline characteristics regarding their condition were checked. Different questionnaires were used to measure disability, pain, depression and anxiety.

Disability

The Modified Oswestry Disability Index (MODI) is a valid and reliable questionnaire for evaluating constraints experienced by persons in their daily activities due to chronic low back pain (Denteneer, Van Daele et al. 2018). It consists of ten items scored on a five-point scale. The total score is expressed in percentage and displays the degree of functional limitation. (0-20%: minimal disability; 20-40%: moderate disability; 41-60%: severe disability; 61-80%: cripple; 81-100%: bed-bound)

Pain

The Brief Pain Inventory (BPI) assesses the severity of pain, its impact on functioning, the location of pain, pain medications, and the amount of pain relief in the past 24 hours (Stanhope 2016). The body chart of this questionnaire was used to record the extent of pain, using the pain drawing method (Barbero, Moresi et al. 2015). The extent of pain might indicate the presence of widespread pain, which has been associated with altered nociceptive pain processing in chronic joint pain (Lluch Girbés E 2016). The BPI-Visual Analogue Scale was used for the baseline characteristics. The BPI-VAS is expressed on a scale of 10 and higher score means higher pain intensity.

Depression

The Beck Depression Inventory (BDI) is widely used as a self-reported questionnaire for assessing depression in persons with chronic pain (Geisser, Roth et al. 1997). It consists of 21 items scored on a four-point scale (0-3). Item scores are summed to obtain the total score with a maximal score of 63. A higher total score indicates more symptoms of depression. (Minimal depression: 0-13/63; mild depression: 14-19/63; moderate depression 20-28/63; severe depression: 29-63/63).

Anxiety

The State-Trait Anxiety Inventory (STAI) is a questionnaire for assessing state anxiety (i.e. anxiety about an event) and trait anxiety (i.e. anxiety as a personal characteristic) (Metzger 1976). It consists of 40 items scored on a four-point scale. Item scores are added to obtain the total score with a higher score indicating greater anxiety. The maximal score for both the STAI-state as the STAI-trait is 40 and they have both the same interpretation. (Low anxiety: 20-39/80; moderate anxiety: 40-59/80; high anxiety 60-80/80)

3.3.3 Primary outcome measures

3.3.3.1 Diaphragm strength

Maximal inspiratory pressure (MIP) is a reliable measure) to quantify inspiratory muscle strength. MIP will be measured at residual volume according to the method of Black and Hyatt (37) using an electronic pressure transducer (POWERbreathe International Ltd., type KH1, Warwickshire, UK) (Laveneziana, Albuquerque et al. 2019) (Black and Hyatt 1969). A minimum of five repetitions were performed, and tests were repeated until there was less than 5% difference between the best and second-best test. The highest pressure sustained over 1 second was defined as MIP (Rochester and Arora 1983).

3.3.3.2 Diaphragm fatigue

Diaphragm fatigue is defined as a reduction in the ability to produce inspiratory force following contractile activity (Kabitz, Walker et al. 2007). First, MIP was measured using an electronic pressure transducer (POWERbreathe International Ltd., type KH1, Warwickshire, UK). Then, the participant performed a maximal cardiopulmonary exercise test (CPET) on a bicycle ergometer. The MIP-measurement was repeated immediately, 15 minutes and 30 minutes after the CPET. The difference between the MIP-values before and after the CPET was used as a measure of diaphragm fatigue. Within the CNSLBP and HC group, differences were calculated and afterwards the difference between these groups was calculated.

3.4 Data analysis

The obtained data was analyzed by JMP Pro (16.1 SAS Inc, Cary, USA). Baseline characteristics of the participants were compared. Normality was checked with the Shapiro-Wilk test. The Brown-Forsythe test was used to check if the variances were equal. A rank-sum test and two-sample t-test were performed because conditions were met and the sample size of both groups were less than twenty. To perform a test on nominal data between 2 groups, a Fisher's exact test was conducted. This test was conducted because conditions were not met.

The statistical analysis for diaphragm strength was conducted with one-sided tests. The first null hypothesis stated that the diaphragm strength of the CNSLBP group was higher or equal in comparison to the control group. The alternative hypothesis stated that the diaphragm strength of the CNSLBP group was lower in comparison to the control group (H_{01}: $\mu_{DS\text{-}CNSLBP} \geq \mu_{DS\text{-}cotrol}$, H_{A1}: $\mu_{DS\text{-}CNSLBP} < \mu_{DS\text{-} control}$).

A rank-sum test and two-sample t-test were performed because conditions were met and the sample size of both groups were less than twenty. The tests were performed with a significance level of 0,05.

The tests for measuring diaphragm fatigue were also one-sided. The second null hypothesis stated that the diaphragm fatigue of the CNSLBP group was lower or equal in comparison to the control group. The alternative hypothesis stated that the diaphragm fatigue of the CNSLBP group was higher in comparison to the control group (H_{02}: $\mu_{DF\text{-}CNSLBP} \leq \mu_{DF\text{-}cotrol}$ H_{A2}: $\mu_{DF\text{-}CNSLBP} > \mu_{DF\text{-}control}$). A linear mixed model analysis was performed with diaphragm fatigue as a dependent variable. Mean percentages of the MIP values (MIP strength compared to MIP after CPET) were used for diaphragm fatigue. Group and time were used as fixed effects and these effects were also crossed and used as an interaction term. A Tukey honest significant difference (HSD) test was performed to correct for multiple comparisons in this study. It was used to examine the between and within group differences in diaphragm fatigue.

3.5 Sample size

An a priori sample size calculation was performed for the primary research question. The required sample size to detect a standardized effect size of 1 (10% difference divided by a standard deviation of 10%) with 80% power and a significance level of 0.05 is 14 persons per group. Assuming a 10% attrition rate, the adjusted sample size is 16 per group.

4 Results

4.1 Demographic characteristics

Demographic characteristics of the participants are displayed in Table 2. A total number of 18 persons participated in the study. There was no difference in age (p=0.4343/0.5000), gender (p=1.000) and BMI (p=0.1415/0.1861). Maximal exercise capacity (VO2max) was also taken into account and did not differ between the groups (p=0.0642/0.0910).

Table 2. Demographic characteristics of the participants

Variable	CNSLBP (n=9)	HC (n=9)	P-value (Student t-test/ Rank-sum test)
Age (yr)	31 +/- 10.7	30.2 +/- 8.7	0.4342/0.5000
Gender (m/f)	6/3	6/3	1.000 (Fisher 's Exact test)
BMI (kg/m^2)	26.3 +/- 5	24 +/- 3.4	0.1415/0.1861
VO2max (l/min)	36 +/- 6.5	42.7 +/- 10.6	0.0642/0.0910

Abbreviations: CNSLBP, chronic non specific lower back pain; HC, healthy controls; m, male; f, female; yr, year; BMI, body mass index; MIP, maximal inspiratory pressure; NC, not conducted because conditions were not met

Other characteristics of the CNSLBP group were also taken into account through questionnaires. These additional characteristics and their interpretation can be found in Table 3. Mean disability was 17.6% in the CNSLBP group which means the participants were minimally disabled. Mean pain of the group was 5.1 on the BPI-VAS with a maximum score of 10. Depression symptoms measured through the BDI were not present in most participants with a mean score of 12.2. On the other hand anxiety was generally present after measuring with the STAI-trait but not with the STAI-state. The mean scores were respectively 42.2 and 38.3 with a maximum score of 80.

Table 3. Baseline characteristics of the CNSLBP group obtained through questionnaires (n=9)

Questionnaire	Mean +/- SD	Interpretation	Number of participants
MODI	17.6 +/- 9.2	Minimal disability (0-20%)	5
		Moderate disability (20-40%)	4
		Severe disability (41-60%)	0
		Cripple (61-80%)	0
		Bed-bound (81-100%)	0
BPI-VAS	5.1 +/- 1.3	Max. score 10	
BDI	12.2 +/- 7.3	Minimal depression (0-13/63)	6
		Mild depression (14-19/63)	2
		Moderate depression (20-28/63)	0
		Severe depression (29-63/63)	0
STAI state	38.3 +/- 12.6	Low anxiety (20-39/80)	6
		Moderate anxiety (40-59/80)	2
		High anxiety (60-80/80)	1
STAI trait	42.4 +/- 14.5	Low anxiety (20-39/80)	5
		Moderate anxiety (40-59/80)	3
		High anxiety (60-80/80)	1

Abbreviations: CNSLBP, chronic non specific lower back pain; SD, standard deviation; MODI, Modified Oswestry Disability Index; BPI-VAS, Brief Pain Inventory-Visual Analogue Scale; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory

4.2 Diaphragm strength

No difference was found in MIP between CNSLBP group and the control group (student-t test: p=0.3161, rank-sum test: p=0.2981). The results of the baseline MIP measurement are presented in Figure 1. Mean MIP was 126.35 cmH2O for the HC group. In the CNSLBP group the mean MIP was 118.79 cmH2O. Thus, there is a difference of 7,56 cmH20 which accounts for 6,14 % difference between the two groups.

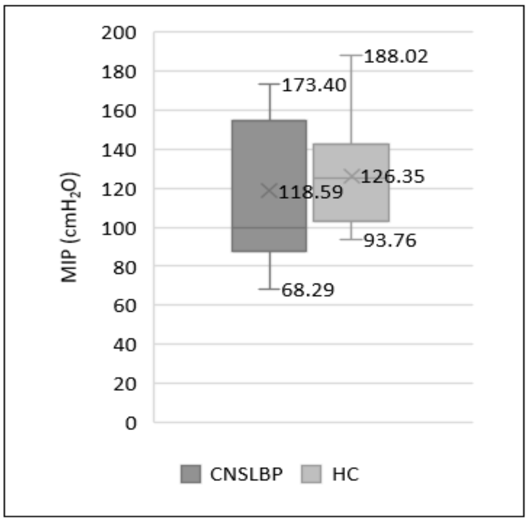

Figure 1. MIP strength between CNSLBP group and HC group

Abbreviations: MIP, maximal inspiratory pressure; CNSLBP, chronic non-specific lower back pain; HC, healthy controls

4.3 Diaphragm fatigue

Within and between group differences in diaphragm fatigue were measured. Mean difference in exercise-induced fatigue and p-values of the within and between group differences are displayed in Table 4. Higher scores meant higher exercise-induced fatigue, thus diaphragm fatigue.

Within-group differences

There was no significant diaphragm fatigue within the HC group at T1, T2 and T3 (T1: p=0.9996, T2: p=1.0000, T3: p=0.9981). In the CNSLBP group there was also no diaphragm fatigue measurable at T1, T2 and T3 (T1: p=0.9978, T2: p=0.7356, T3: p=0.9997). The highest score in diaphragm fatigue was at 15 minutes in the CNSLBP group with a difference of 8.23%. This was not statistically significant with a p-value of 0.7356. In conclusion, no diaphragm fatigue could be induced by the CPET in either the CNSLBP group or the HC group.

Between-group differences

A statistically significant difference between both groups was also not measured. (T1: p=1.0000, T2: p=0.8288, T3: p=1.0000). At 15 minutes with a difference of 6.98% there was also no statistically significant difference between the CNSLBP and HC group measurable with a p-value of 0.8288. MIP fatigue at T1, T2 and T3 after CPET in percentages between both groups are also displayed in Figure 2.

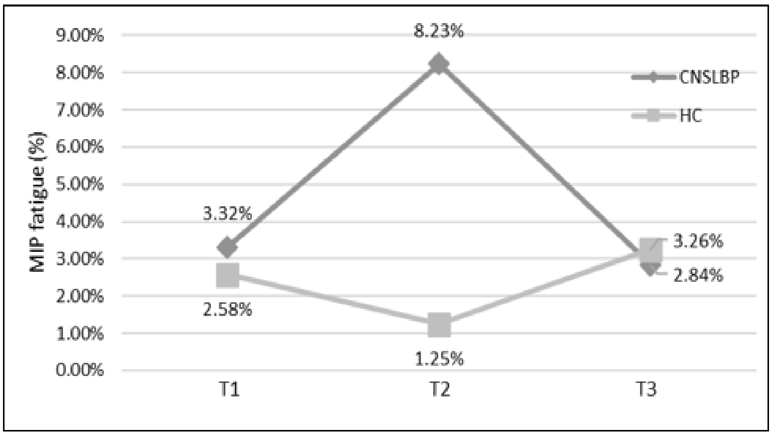

Figure 2. MIP fatigue between CNSLBP group and HC group at immediately, 15 and 30 minutes after CPET (T1, T2 and T3)

Abbreviations: MIP, maximal inspiratory pressure; CNSLBP, chronic non-specific lower back pain; HC, healthy controls; CPET, cardiopulmonary exercise testing

Table 4. Between and within group differences in MIP before CPET (T0) and MIP after CPET immediately (T1), 15 minutes (T2) and 30 minutes (T3)

	Within group differences (Tukey HSD test)				**Between group differences (Tukey HSD test)**
	HC		**LBP**		**HC vs LBP**
Time	Mean	P-value	Mean	P-value	P-value
T1	2.58%	0.9996	3.32%	0.9978	1.0000
T2	1.25%	1.0000	8.23%	0.7356	0.8388
T3	3.26%	0.9981	2.84%	0.9997	1.0000

Abbreviations: CNSLBP, chronic non specific lower back pain; HC, healthy controls; m, male; f, female; yr, year; BMI, body mass index; MIP, maximal inspiratory pressure; HSD, honestly significant difference

Gender differences

Furthermore, it was also investigated whether there was a difference in MIP fatigue between men and women. A gender difference was found in the CNSLBP group at T2 with a p-value of 0.0445 but not at T1 and T3 with a p-value of 0.0836 and 0.1549. In the HC group there was no significant difference between male and females with p-values of 0.2056, 0.5234 and 0.1807 for respectively T1, T2 and T3. The results are shown in Figure 3.

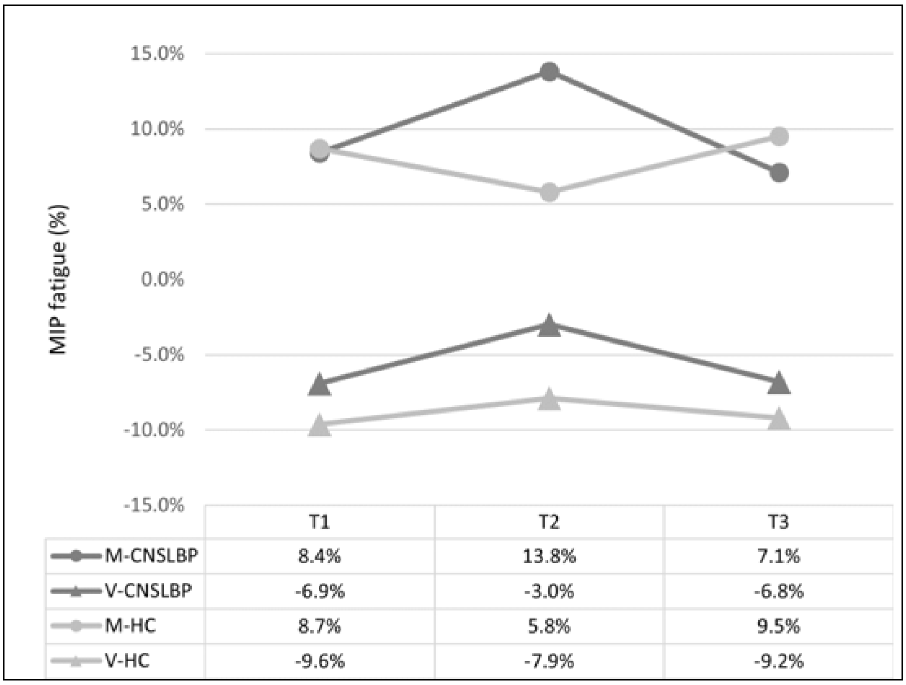

Figure 3. Gender differences in MIP fatigue between the CNSLBP group and HC group at immediately, 15 and 30 minutes after CPET (T1, T2 and T3)

Abbreviations: MIP, maximal inspiratory pressure; CNSLBP, chronic non-specific lower back pain; HC, healthy controls; CPET, cardiopulmonary exercise testing

5 Discussion

Overview

The results indicate that there is no significant difference in diaphragm strength or fatigue between the CNSLBP group and HC group. This does not support the hypothesis that diaphragm strength and fatigue would differ significantly in persons with CNSLBP compared to healthy controls. However, although diaphragm strength wasn't significantly different, the MIP strength in the HC group was approximately 6.4% higher than in the CNSLBP group. So, there is a shift towards a difference.

Other studies show that when specifically stressing the diaphragm, more fatigue occurs. Janssens et al (2013) investigated whether inspiratory muscle fatigue (IMF) occurred after different modes and conditions of inspiratory endurance in healthy individuals (Janssens, Brumagne et al. 2013). They included studies with five different forms of loading protocol were compared, namely (1) inspiratory resistive loading; (2) whole body exercise; (3) hyperpnea; (4) inspiratory resistive loading, whole body exercise or hyperpnea under changed oxygen or carbon dioxide fractions and (5) a combination of inspiratory resistive loading and whole body exercise. Besides, different measurement techniques were included like transdiaphragmatic pressure and maximum voluntary contractions. They found that independent of which modality, IMF emerged. But the most reliable methods for producing IMF were determined to be cycling at 85% of maximum and IRL at intensities between 60 and 80% of maximum.

Another study of Janssens et al. supports this finding (Janssens, Brumagne et al. 2013). In this similar study, it was investigated whether the people with LBP had more diaphragmatic fatigue than healthy controls after inspiratory muscle loading (IML). Ten people with LBP and ten healthy controls underwent IML whereby transdiaphragmatic twitch pressure was measured before the IML, but also 20 and 45 minutes afterwards. The results showed that diaphragmatic fatigue was present to a greater extent in people with LBP, with 80% of this group experiencing fatigue after 20 minutes and 70% after 45 minutes. For the healthy controls, this was 40% and 30%, respectively. This study supports our hypothesis that fatigue occurs more in people with LBP compared to healthy controls. What is the cause for these results not being visible in this study? In the study of Janssens et al, a different protocol was used to determine fatigue.

Instead of a CPET, an inspiratory muscle loading protocol was measured using a hand-held electronic loading equipment. Subjects were told to breathe against the inspiratory resistive load until the flow couldn't be sustained any longer. They were then requested to complete a breathing trial with a continuous preset inspiratory resistance of 70% of the maximum workload obtained throughout the incremental loading protocol. A possible explanation could be that more muscles are engaged during a CPET, allowing a limit to task failure to also occur peripherally. So, it could be that an inspirational limit was not yet present in some participants. With this method of IML, an attempt is made to engage only the inspiratory muscles.

Metaboreflex

It was also investigated whether inspiratory muscle fatigue occurred in both genders, looking at both the CNSLBP group and the healthy controls. In this study, a difference between men and women was established regarding muscle fatigue, in which women showed less fatigue. In the low back pain group, a significant difference was found at T2 (T1: p=0.0836; T2: p=0.0445; T3: p=0.1549). No significant difference between genders was found in the HC group (T1: p=0.2056; T2: p=0.5234; T3: p=0.1807). Nevertheless, women showed only negative values which indicates that they did not experience exercise induced fatigue. In contrast, men had positive values meaning a reduction between MIP before and after CPET. This could indicate that men did experience exercise induced fatigue. This could be explained by a variation in metaboreflex between men and women. The metaboreflex is a feedback mechanism from the muscles, in which the heart rate increases and the blood flow is redirected to the inspiratory muscles, resulting in reducing the blood flow to the extremities (Potter 2022) (Dubey, Tiwari et al. 2017). Multiple studies investigated gender differences concerning the metaboreflex. Welch et al examined this difference through an isocapnic inspiratory pressure-threshold loading (PTL, 60% maximal inspiratory mouth pressure). Nine men and nine women had to perform a single bout of constant load isocapnic PTL until task failure. They investigated the contractility of the diaphragm prior to and post the loading protocol by assessing the transdiaphragmatic twitch pressure. They found that the duration to task failure was significantly longer in women and the fatigue accumulated at a slower rate (Welch, Archiza et al. 2018). This indicates that the inspiratory muscles of women are better preserved against fatigue than those of men.

Furthermore, Smith et al also found that women have a weaker metaboreflex compared to men, meaning that men presented a higher blood pressure and a decreased limb blood flow than women (Welch, Archiza et al. 2018). Ten men and ten women completed inspiratory resistive breathing tasks and then different parameters were measured. So according to these findings, it supports our findings that inspiratory muscle fatigue occurred less in females. This could also explain why muscle fatigue did not occur within both the CNSLBP group and healthy control group. In these groups women were also included and thus the metaboreflex could be a contributing factor to explain the non-significant results within both groups regarding muscle fatigue.

Strengths and limitations

The study has some limitations. For example, the sample size may have been too small in comparison to the sample size calculation. As mentioned before, a total sample size of 32 was needed to obtain an adequate power. In this protocol, only 18 participants were included. A low sample size indicates insufficient power, this negatively impacts the probability that an acquired statistical effect approaches a real effect (Button, Ioannidis et al. 2013).

A strength of this study is that it took into account matching the baseline characteristics of individuals with LBP to healthy controls. More specifically, groups were matched according to age, gender and BMI.

And what about other modalities of sports being used? In this study, the decision was made to perform a CPET on a bicycle until task failure occurred. Could the implementation of another modality provide significant results? Brown et al. investigated whether IMF could also appear after swimming (Brown 2011). Ten experienced swimmers were included and had to perform three different swimming distances, namely 100-, 200- and 400 meters. Before and after these time trials, MIP was measured and the percentage of IMF was conducted. It was shown that IMF did not significantly occur after all-out swims. This can maybe be explained by the fact that swimmers have better trained inspiratory muscles because this sport demands it. Ohya et al. investigated whether IMF could occur after running. Eight trained women completed an 400 m and a 800 m track (Ohya, Yamanaka et al. 2016). MIP was assessed with a portable autospirometer before the warm-up and two minutes after the running tests.

The results showed that short duration running significantly induced IMF. This was the case for both the 400m and the 800m track with IMF values of respectively 10.0% and 15.1%. But a limitation of this study that has to be taken into account is that only women were selected to be part of this study. And as previously stated, women may be more resistant to fatigue than men.

But what about longer bouts of duration? Loke et al. investigated whether IMF could occur after endurance sports, namely marathon running (Loke 1982). Similarly, it could be asked whether the duration of exercise could be a contributing factor. Four men completed a marathon, diaphragm strength was measured by the maximal inspiratory and expiratory pressures. The findings of this study demonstrated that the maximal inspiratory and expiratory pressure levels of four runners post-marathon significantly decreased.

In conclusion it was shown that diaphragm fatigue was not present after a CPET in neither healthy persons or persons with CNSLBP. It was also shown in previous studies that with sports like swimming, diaphragm fatigue could also not be evoked. A common point of these studies was that the average duration of these exercises bouts were between ten and twenty minutes. These were certainly not long enough to elicit inspiratory muscle fatigue. In contrast a three hour long marathon was able to elicit diaphragm fatigue in healthy persons. A suggestion for further studies could be that a minimal duration of forty minutes for untrained persons could be adequate. When looking at the population in this study namely CNSLBP which are mostly untrained individuals, it is best to keep the modality cycling. Cycling is also proven to be an adequate sport to train untrained individual’s endurance.

Further investigations

Some specific recommendations are suggested for further investigations. First of all, the sample size should be on a larger scale so that accurate assumptions can be made with enough subjects. Furthermore, the duration until task exhaustion should possibly be extended as it seems that the diaphragm requires more time to be exhausted (T3 gives better results than T1). Because of the metaboreflex, it has been shown that women are better preserved against inspiratory muscle fatigue than men, therefore it can be thought that in one way or another, women need to become more inspiratory exhausted so that a difference between the sexes is not that clear anymore. This can be carried out by using different modalities for the sexes or by changing the duration of the task. This can be achieved by starting the exercise test at a lower percentage of maximum. In a similar study, it still ought to be important that the subjects of two groups are matched for age, BMI and gender (and possible other baseline characteristics e.g. sport level (VO2max)). In this study, the option to work with the MIP measurement was chosen. Even though this method is considered valid and reliable, other methods have been described, namely the so called phrenic nerve stimulation to measure transdiaphragmatic pressure. Using this approach, the diaphragm's unique contractile fatigue can be seen. The method decreases the involvement of the accessory muscles (Janssens, Brumagne et al. 2013). This can possibly lead to more significant results. And finally, a possible knowledge gap was mentioned earlier. In a subsequent study, one could work with dividing the CNLBP population into subgroups in order to get more of an idea of exactly what kind of patients are affected by this. Possible subgroups may involve classifying patients according to their score on the MODI scale.

6 Conclusion

First of all, diaphragm strength measured through the MIP was not significantly reduced in persons with CNSBLP compared to healthy controls. However, there was a trend towards a significantly reduced MIP of 6,4% in this population. Secondly, diaphragm fatigue was not statistically significant within both groups. Only at T2 a value of 8.23 % was measurable within the CNSLBP group, this value was also not significantly different from T0. A difference in diaphragm fatigue between the CNSLBP group and the HC group was also not statistically significant immediately, 15 and 30 minutes after the CPET. However, a significant difference was found between men and women for diaphragm fatigue, in which women showed less fatigue, partly explainable by the metaboreflex. More research is needed at a large-scale level to demonstrate an association.

7 References

Abd El Aziz, A. A., et al. (2017). "Diaphragmatic assessment in COPD patients by different modalities." Egyptian Journal of Chest Diseases and Tuberculosis **66**(2): 247-250.

Airaksinen, O., et al. (2006). "European guidelines for the management of chronic nonspecific low back pain." European spine journal **15**(Suppl 2): s192.

Andersson, H. I., et al. (1993). "Chronic pain in a geographically defined general population."

Balague, F., et al. (2012). "Non-specific low back pain." Lancet **379**(9814): 482-491.

Barbero, M., et al. (2015). "Test-retest reliability of pain extent and pain location using a novel method for pain drawing analysis." Eur J Pain **19**(8): 1129-1138.

Beeckmans, N., et al. (2016). "The presence of respiratory disorders in individuals with low back pain: A systematic review." Man Ther **26**: 77-86.

Black, L. and R. Hyatt (1969). "Maximal respiratory pressures normal values and relationship to age and sex. The American review of respiratory disease."

Brown, S., & Kilding, A. E. (2011). "Exercise-Induced Inspiratory Muscle Fatigue During Swimming The Effect of Race Distance."

Brumagne, S., et al. (2019). "Neuroplasticity of Sensorimotor Control in Low Back Pain." J Orthop Sports Phys Ther **49**(6): 402-414.

Button, K. S., et al. (2013). "Power failure: why small sample size undermines the reliability of neuroscience." Nat Rev Neurosci **14**(5): 365-376.

Casagrande, D., et al. (2015). "Low Back Pain and Pelvic Girdle Pain in Pregnancy." J Am Acad Orthop Surg **23**(9): 539-549.

Denteneer, L., et al. (2018). "The Modified Low Back Pain Disability Questionnaire: Reliability, Validity, and Responsiveness of a Dutch Language Version." Spine (Phila Pa 1976) **43**(5): E292-E298.

Dubey, P., et al. (2017). "Effect of Metaboreflex on Cardiovascular System in Subjects of Metabolic Syndrome." J Clin Diagn Res **11**(7): CC01-CC04.

Geisser, M., et al. (1997). "Assessing depression among persons with chronic pain using the Center for Epidemiological Studies-Depression Scale and the Beck Depression Inventory: a comparative analysis.".

Hamaoui, A., et al. (2001). "Does respiration perturb body balance more in chronic low back pain subjects than in healthy subjects Clinical biomechanics."

Hartvigsen, J., et al. (2018). "What low back pain is and why we need to pay attention." Lancet **391**(10137): 2356-2367.

Hodges, P. W., & Gandevia, S. C. (2000). "Changes in intra-abdominal pressure during postural and respiratory activation of the human diaphragm."

Hodges, P. W., Butler, J. E., McKenzie, D. K., & Gandevia, S. C. (1997). "Contraction of the human diaphragm during rapid postural adjustments.".

Hodges, P. W., et al. (2005). "Intra-abdominal pressure increases stiffness of the lumbar spine." J Biomech **38**(9): 1873-1880.

Hodges, P. W. and S. C. Gandevia (2000). "Activation of the human diaphragm during a repetitive postural task."

Jalan, N. S. (2015). "Intra-and inter-rater reliability of maximum inspiratory pressure measured using a portable capsule-sensing pressure gauge device in healthy adults."

Janssens, L., et al. (2013). "Proprioceptive changes impair balance control in individuals with chronic obstructive pulmonary disease." PLoS One **8**(3): e57949.

Janssens, L., et al. (2013). "Greater diaphragm fatigability in individuals with recurrent low back pain." Respir Physiol Neurobiol **188**(2): 119-123.

Janssens, L., et al. (2013). "The assessment of inspiratory muscle fatigue in healthy individuals: a systematic review." Respir Med **107**(3): 331-346.

Janssens, L., et al. (2010). "The effect of inspiratory muscles fatigue on postural control in people with and without recurrent low back pain."

Kabitz, H. J., et al. (2007). "New physiological insights into exercise-induced diaphragmatic fatigue." Respir Physiol Neurobiol **158**(1): 88-96.

Koch, C. and F. Hansel (2019). "Non-specific Low Back Pain and Postural Control During Quiet Standing-A Systematic Review." Front Psychol **10**: 586.

Kocjan, J., et al. (2017). "Network of breathing. Multifunctional role of the diaphragm: a review." Adv Respir Med **85**(4): 224-232.

Laveneziana, P., et al. (2019). "ERS statement on respiratory muscle testing at rest and during exercise." Eur Respir J **53**(6).

Lluch Girbés E, D. L., Barbero M, et al. (2016). "Expanded Distribution of Pain as a Sign of Central Sensitization in Individuals With Symptomatic Knee Osteoarthritis."

Loke, J., Mahler, D. A., & Virgulto, J. A. (1982). "Respiratory muscle fatigue after marathon running."

Metzger, R. (1976). "A reliability and validity study of the state-trait anxiety inventory."

Moccellin, A. S. and P. Driusso (2012). "Adjustments in static and dynamic postural control during pregnancy and their relationship with quality of life: A descriptive study." Fisioterapia **34**(5): 196-202.

Mohan, V., et al. (2018). "Respiratory characteristics of individuals with non-specific low back pain: A cross-sectional study." Nurs Health Sci **20**(2): 224-230.

Nielens, H., et al. (2006). "Chronic low back pain. Good Clinical practice (GCP)."

Ohya, T., et al. (2016). "The 400- and 800-m track running induces inspiratory muscle fatigue in trained female middle-distance runners." Journal of Strength and Conditioning Research.

Potter, V. (2022). "Respiratory Muscle-Induced Metaboreflex. POWERbreathe. ." from https://www.powerbreathe.com/respiratory-muscle-induced-metaboreflex/.

Ringheim, I., et al. (2015). "Postural strategy and trunk muscle activation during prolonged standing in chronic low back pain patients." Gait Posture **42**(4): 584-589.

Rochester, D. and N. Arora (1983). "Respiratory muscle failure."

Ruhe, A., et al. (2011). "Center of pressure excursion as a measure of balance performance in patients with non-specific low back pain compared to healthy controls: a systematic review of the literature." Eur Spine J **20**(3): 358-368.

Saeid, H. E. (2022). "Postural Control." from https://www.physio-pedia.com/Postural_Control.

Spiesshoefer, J., et al. (2019). "Noninvasive Prediction of Twitch Transdiaphragmatic Pressure: Insights from Spirometry, Diaphragm Ultrasound, and Phrenic Nerve Stimulation Studies." Respiration **98**(4): 301-311.

Stanhope, J. (2016). "Brief Pain Inventory review." Occup Med (Lond) **66**(6): 496-497.

Thompson, P., et al. (2013). "American College of Sports M. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition."

Torres-Castro, R., et al. (2019). "Agreement between clinical and non-clinical digital manometer for assessing maximal respiratory pressures in healthy subjects." PLoS One **14**(10): e0224357.

Trigano, A., et al. (2005). "Clinical study of interference with cardiac pacemakers by a magnetic field at power line frequencies." Journal of the American College of Cardiology **45**(6): 896-900.

Vermeersch, A., et al. (2022). "Preliminary study on the importance of the detection of respiratory problems in patients with low back pain."

Welch, J. F., et al. (2018). "Sex differences in diaphragmatic fatigue: the cardiovascular response to inspiratory resistance." J Physiol **596**(17): 4017-4032.