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High and low level pressure support during walking in people with severe kyphoscoliosis

Short title: NIV during walking in severe kyphoscoliosis

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ABSTRACT

To determine whether the level of pressure support (PS) provided during exercise influences endurance time in people with severe kyphoscoliosis, a double-blind randomised crossover study was performed. We hypothesised that high level PS would be required to enhance endurance time in this population with high impedance to inflation.

Thirteen participants with severe kyphoscoliosis performed four endurance treadmill tests in random order: unassisted; with sham PS; low level PS of 10 cmH_2O (PS 10) and high level PS of 20 cmH_2O (PS 20). Participants and assessors were blinded to the level of PS delivered during exercise. Endurance time was greater with PS 20 (median 217 seconds; interquartile range (IQR) 168-424) compared with unassisted exercise (139 seconds, IQR 111-189), sham PS (103 seconds, IQR 88-155) and PS 10 (159 seconds, IQR 131-206). In addition, isotime respiratory rate was decreased by 8 breaths/minute (95% CI -11 to -5) and isotime oxygen saturation increased by 4% (95% CI 1 to 7) with PS 20 compared with unassisted exercise.

People with severe kyphoscoliosis require high level PS during walking to improve exercise performance. Investigation of high level PS as an adjunct to exercise training or to assist in the performance of daily activities is warranted.

KEYWORDS: chronic respiratory failure, exercise; hypercapnia, neuromuscular and chest wall disorders, non-invasive ventilation

Individuals with severe kyphoscoliosis commonly have a ventilatory limitation to exercise [1] and report severe exertional dyspnoea [2]. Unfortunately there are limited strategies available that improve exercise capacity in this population. Supplemental oxygen (O_2) during walking was shown to improve dyspnoea and oxygen saturation (SpO_2) in moderate to severe kyphoscoliosis although exercise capacity did not increase [3]. In contrast, nocturnal non-invasive ventilatory (NIV) support was associated with improvements in exercise performance in the absence of exercise training in people with chronic hypercapnic respiratory failure (HRF) secondary to severe kyphoscoliosis [4, 5]. However activity levels [6] and exercise capacity [7] remained well below normal, placing these individuals at risk of further deconditioning which may impact the performance of daily activities.

The effect of NIV during exercise in severe kyphoscoliosis is unclear. Pressure support (PS) of 10-14 cmH_2O during treadmill walking reduced distance walked compared to unassisted exercise [8], whereas PS of 19 cmH_2O during constant work rate cycling increased endurance time compared to unassisted exercise [2]. Whether the level of PS provided during exercise has an effect on the efficacy of PS during exercise is unknown. The aim of the present study was to determine the effect of high level, low level and sham PS during treadmill walking on endurance time compared to walking unassisted in patients with severe kyphoscoliosis already established on domiciliary NIV. We hypothesised that high level PS would be required to increase exercise endurance time due to the high impedance to chest wall inflation commonly observed in this population. If high level PS during treadmill walking can improve exercise performance, it may have a role during exercise training or in assisting people with severe kyphoscoliosis to perform everyday activities.

METHOD

Participants

Individuals aged 18 years or older with severe kyphoscoliosis were recruited from our home ventilation programme. Kyphoscoliosis was defined as "severe" if chronic HRF was present as a result of chest wall restriction. Exclusion criteria included: medically unstable over the past month requiring hospitalisation; resting arterial pH <7.35; temperature > 38ºC; resting systolic blood pressure < 90 or >160 mmHg, diastolic blood pressure < 60 or >100 mmHg; myocardial infarct or unstable angina during the previous month; resting pulse rate >120 beats/minute; orthopaedic or neurological disorders that were likely to limit walking ability.

Study design and protocol

A randomised, double blind, crossover study with repeated measures was conducted. Four endurance treadmill exercise tests were performed in random order: unassisted; sham PS (continuous positive airway pressure (CPAP) 4 cmH_2O); PS 10; and PS 20. The randomisation scheme was generated using the website http://www.Randomization.com and test order was concealed in a sealed opaque envelope until written informed consent was obtained. For the three tests with PS both participants and the assessors were blinded to the level of PS provided. Participants were told that bilevel machine settings would be different for each test with PS and that the best way to set the machine, or whether the machine was better than unassisted exercise, was unknown. The level of PS was set on the bilevel machine by one investigator and the settings were concealed. The investigator did not interact with participants or assessors during the tests. Participants received standardised encouragement each minute during the test.

Prior to each treadmill test, participants rested for five minutes while breathing under the conditions of the next test intervention. In addition, participants rested for at least 30 minutes between treadmill tests and until SpO_2, heart rate (HR), dyspnoea, perceived exertion (leg fatigue) and blood pressure (BP) had returned to baseline. The study protocol and measures are displayed in Figure 1. Endurance time, the

reason for exercise cessation and the primary symptom that limited exercise were recorded. If SpO_2 was <89% at rest, supplemental O_2 was added to achieve a SpO_2 of 90-93%, and was not adjusted further during exercise. Ethical approval was obtained from the Human Ethics Committee of Sydney South West Area Health Service and The University of Sydney. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12608000155392).

Endurance Treadmill Test

The treadmill test was an externally paced, constant work rate, endurance test. Walking speed was set at 80% of the average walking speed achieved during a two minute walk test (2MWT) [9] that was performed at least one hour prior to the treadmill tests. Participants were familiarised to the walking speed for approximately 20 seconds, at least 30 minutes before the first treadmill test. The speed remained consistent across the four tests. The treadmill test ceased if the participant felt too breathless or fatigued to continue, or if SpO_2 fell below 75%.

Measures

Participant Characteristics

Anthropometric data was recorded and a daytime resting arterial blood sample was analysed (Radiometer ABL700, Radiometer Medical, Copenhagen, Denmark). Pulmonary function tests were performed: spirometry; static lung volumes; maximum voluntary ventilation (MVV) measured over 12 seconds (Sensormedics, 6200 Autobox, Sensormedics Corporation, Yorba Linda, CA, USA); maximum inspiratory and expiratory mouth occlusion pressures from residual volume and total lung capacity respectively (Morgan Medical Limited, Gilingham, UK). All measured values were compared to reference values [10-13]. Arm span was used to calculate percent predicted values [14].

Exercise

Oxygen saturation and HR were measured via a finger probe (Radical, Masimo, Irvine CA, USA). Measurements of pH, partial pressure of carbon dioxide (PCO_2) and lactate (La) were obtained from arterialised venous blood samples. See online depository for further details. Blood pressure was measured manually. Rate of perceived exertion (RPE), which reflected leg muscle exertion, and dyspnoea were measured on a 0-10 category-ratio scale [15].

Expiratory flow was measured via a mesh screen pneumotachograph (3830B Hans Rudolph, Shawnee, Kansas, USA) placed between the oronasal mask and the expiratory port within the bilevel circuit. Data were collected at a sampling frequency of 100Hz. During unassisted exercise, flow was also measured using the oronasal mask and pneumotachograph in order to keep dead space (195mL) consistent between the interventions. If participants could not tolerate the oronasal mask during unassisted exercise, ventilation was measured via a mouthpiece system (dead space 100mL). Respiratory rate (RR) was measured during the final 20 seconds of the baseline period, isotime exercise and the end of exercise.

Pressure support

Pressure support was delivered via an oronasal mask (Ultra-Mirage Full Face Mask™, ResMed, Sydney, Australia) using a pressure preset bilevel machine (VPAPIII STA™, ResMed, Sydney, Australia) set in the spontaneous mode. The expiratory port on the mask was sealed and the mask elbow removed to allow attachment of a mesh screen pneumotachograph. An expiratory port (Ultra-Mirage Nasal Mask™ elbow, ResMed, Sydney, Australia) was placed after the pneumotachograph. During sham PS, the device was set at CPAP 4 cmH_2O. For PS 10 and PS 20, expiratory positive airway pressure was set at 4 cmH_2O, and PS was set at 10 cmH_2O or 20 cmH_2O above this

respectively. The inspiratory trigger threshold was set to "high" (2.5 L/min), rise time to 100 ms, $IPAP_{max}$ 1.3 s and $IPAP_{min}$ 0.1 s. The maximum inspiratory flow rate capacity was >220 L/min.

Data analysis and statistics

An estimate of the required sample size was calculated using data from the first five participants. To detect a 60 second (equivalent to 50%) change in endurance time with PS, using a SD estimate of 49 seconds, power of 0.8, and α of 0.05, a sample of 13 participants was required. SPSS Version 14.0 statistical software was used for data analysis. Descriptive data for continuous variables are presented as mean ± SD or median (interquartile range). Linear mixed model analyses were performed to determine firstly, if there was a difference between the four interventions (unassisted exercise, sham PS, PS 10 or PS 20) with respect to treadmill walking endurance time, and secondly, to determine if there was a difference between the four conditions at different time points (rest, isotime, end exercise, and change from rest to end exercise) with respect to physiological and subjective variables. Isotime was defined as the duration of the shortest treadmill test. The effect of test order on primary and secondary outcome measures was also assessed. A significance level of $\alpha<0.05$ was used. If a significant difference was detected between the four interventions for a specific variable, pairwise comparisons were performed along with a sharper Bonferroni correction [16] of p values.

RESULTS

Participants

Thirteen participants (7 females) with severe kyphoscoliosis were recruited. Static lung volumes and MVV could not be measured in one participant due to intolerable dyspnoea while breathing on the mouthpiece. Therefore data are reported for 12 participants. Participant characteristics are described in Table 1.

Table 1 Participant characteristics

		Value	Percent predicted
	Age (yrs)	59 (55 - 62)	
	Height (m)	1.46 ± 0.10	
	Arm span (m)	1.66 ± 0.15	
	BMI ($kg.m^{-2}$)	25.3 ± 5.2	
Resting ABG	pH	7.40 (7.36 - 7.42)	
	$PaCO_2$ (mmHg)	48.6 (46.0 - 56.1)	
	PaO_2 (mmHg)	67.5 (60.0 - 79.0)	
	HCO_3^- (mmol/L)	30.0 ± 2.3	
	SaO_2 (%)	93.4 ± 2.9	
	Supp O_2 (L/min)	0 (0 – 0.5)	
Pulmonary function	FEV_1 (L)	0.51 (0.48 - 0.62)	20 ± 6
	FVC (L)	0.72 ± 0.31	22 ± 7
	FEV_1/FVC (%)	83 (74 - 88)	
	$PI_{max1.0}$ (cmH_2O)	-34.8 ± 15.5	45 ± 19
	$PE_{max1.0}$ (cmH_2O)	87.7 ± 45.0	78 ± 33
	MVV (L/min)	23.7 ± 6.1	23 ± 5
	TLC (L)	1.916 ± 1.030	35 ± 15
	FRC (L)	1.379 ± 0.810	46 ± 23
	IC (L)	0.537 ± 0.256	22 ± 9
	RV (L)	1.131 ± 0.708	57 ± 31
Domiciliary NIV	Time on NIV (years)	11.9 ± 4.7	
	Compliance (hours/night)	8.9 ± 2.6	
	Pressure/volume preset devices	11/2	
	IPAP (cmH_2O) (n=11)	17.0 ± 2.4	
	EPAP (cmH_2O) (n=11)	6.0 ± 1.1	
	PS (cmH_2O) (n=11)	11.0 ± 2.9	
	V_T (L) (n=2)	0.650 ± 0.212	
	Nocturnal supp O_2 (L/min) (n = 2)	3.0 (2.0 - 4.0)	

Data are presented as mean ± SD or median (interquartile range). BMI: body mass index; ABG: arterial blood gas; $PaCO_2$: arterial carbon dioxide tension; PaO_2: arterial oxygen tension; HCO_3^-: arterial bicarbonate ion concentration; SaO_2%: oxygen saturation; FiO_2: fraction of inspired oxygen; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $PI_{max1.0}$: maximal inspiratory mouth occlusion pressure over one second; $PE_{max1.0}$: maximal expiratory mouth occlusion pressure over one second; MVV: maximum voluntary ventilation; TLC: total lung capacity; FRC: functional residual capacity; IC: inspiratory capacity; RV: residual volume; NIV: non-invasive ventilation; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure; PS: pressure support (difference between IPAP and EPAP); V_T: tidal volume; Supp O_2: supplemental oxygen

Endurance treadmill test

Endurance Time

Mean treadmill walking speed was 2.9 ± 0.6 km/h (median intensity 80% (IQR 75 – 80) of 2MWT average walking speed). Individual and group endurance time data for each of the four interventions are displayed in Figure 2. Endurance time data were not normally distributed and were transformed using log(x) prior to analysis. There was a difference in endurance time between walking unassisted, with sham PS, PS 10 and PS 20 (p=0.02). Pairwise comparisons revealed that PS 20 (median 217 seconds; interquartile range (IQR) 168-424) significantly increased endurance time compared to

walking unassisted (139 seconds, IQR 111-189), with sham PS (103 seconds, IQR 88-155) and PS 10 (159 seconds, IQR 131-206) after a sharper Bonferroni adjustment [16] for multiple comparisons. Endurance time was also greater with PS 10 compared with sham PS (See online depository, Table 4). There was no effect of test order on endurance time.

Physiological and Subjective Responses to Pressure Support during Exercise

Ventilation data were lost for one participant therefore V_E, V_T and RR are reported for 12 participants. Three participants used 1L/min of supplemental O_2 during the treadmill tests as room air SpO_2 was <89% at rest. During unassisted exercise, four participants breathed via an oronasal mask and eight via a mouthpiece. While breathing unassisted at rest prior to each endurance treadmill test, there were no differences between interventions with respect to SpO_2, cardiovascular variables, dyspnoea, RPE, La or arterialised venous pH and PCO_2 (see online depository). There was no effect of test order on any of the physiological or subjective outcome measures.

At isotime exercise, there was a difference between interventions with respect to SpO_2 ($p<0.001$), dyspnoea ($p=0.006$), RPE ($p=0.013$), RR ($p<0.001$) and V_T ($p=0.018$). Pairwise comparisons of the four interventions are shown in Table 2 and Figure 3. A moderate inverse correlation was found between the change in endurance time and the change in isotime dyspnoea with PS 20 during walking compared with unassisted exercise (Spearman's rho -0.651, $p = 0.016$, Figure 4). At end exercise, there was a difference between interventions with respect to DBP ($p=0.02$), MAP ($p=0.007$), La ($p=0.002$), RR ($p<0.001$), V_T ($p=0.003$) and V_E ($p=0.015$). Pairwise comparisons of the four interventions are reported in Table 3. The mean ratio of peak minute ventilation during unassisted exercise to maximum voluntary ventilation (V_E/MVV) was 95 ± 49%. The primary symptom at end exercise for each intervention is reported in Figure 5. See online depository for further data.

Table 2 Pairwise comparisons of unassisted exercise, exercise with sham pressure support, pressure support 10 cmH_2O and pressure support 20 cmH_2O for physiological and subjective variables at isotime

	Comparison	Mean (SD) vs Mean (SD)	Mean difference (95% CI)	p value	Adjusted p value
SpO_2 (%)	PS 20 vs UnA	88.2 (4.5) vs 84.2 (6.5)	4 (1 to 7)	0.007	0.021
	PS 20 vs PS 10	88.2 (4.5) vs 87.2 (5.2)	1 (-2 to 4)	0.45	NS
	PS 10 vs UnA	87.2 (5.2) vs 84.2 (6.5)	3 (0 to 6)	0.041	NS
	PS 20 vs Sham	88.2 (4.5) vs 81.8 (6.6)	6 (4 to 9)	<0.001	<0.001
	PS 10 vs Sham	87.2 (5.2) vs 81.8 (6.6)	5 (3 to 8)	0.001	0.002
	Sham vs UnA	81.8 (6.6) vs 84.2 (6.5)	-2 (-5 to 0)	0.112	NS
Dyspnoea (Borg)	PS 20 vs UnA	2.0 (2.2) vs 3.7 (2.7)	-1.7 (-3.0 to -0.3)	0.018	NS
	PS 20 vs PS 10	2.0 (2.2) vs 2.7 (1.8)	-0.7 (-2.0 to 0.6)	0.31	NS
	PS 10 vs UnA	2.7 (1.8) vs 3.7 (2.7)	-1.0 (-2.3 to 0.4)	0.160	NS
	PS 20 vs Sham	2.0 (2.2) vs 4.4 (2.6)	-2.4 (-3.7 to -1.1)	0.001	0.001
	PS 10 vs Sham	2.7 (1.8) vs 4.4 (2.6)	-1.7 (-3.0 to -0.4)	0.016	0.032
	Sham vs UnA	4.4 (2.6) vs 3.7 (2.7)	0.7 (-0.6 to 2.0)	0.28	NS
RPE (Borg)	PS 20 vs UnA	2.8 (2.1) vs 4.5 (2.8)	-1.8 (-3.1 to -0.5)	0.012	0.012
	PS 20 vs PS 10	2.8 (2.1) vs 2.9 (2.2)	-0.2 (-1.5 to 1.2)	0.82	NS
	PS 10 vs UnA	2.9 (2.2) vs 4.5 (2.8)	-1.6 (-2.9 to -0.3)	0.012	0.024
	PS 20 vs Sham	2.8 (2.1) vs 4.5 (2.4)	-1.7 (-3.0 to -0.4)	0.014	0.042
	PS 10 vs Sham	2.9 (2.2) vs 4.5 (2.4)	-1.6 (-2.9 to -0.3)	0.025	NS
	Sham vs UnA	4.5 (2.4) vs 4.5 (2.8)	0 (-1.4 to 1.3)	0.96	NS
RR (breaths/min)	PS 20 vs UnA	33.9 (7.9) vs 41.7 (9.2)	-7.9 (-11.0 to -4.8)	<0.001	<0.001
	PS 20 vs PS 10	33.9 (7.9) vs 38.3 (9.4)	-4.4 (-7.4 to -1.4)	0.008	0.024
	PS 10 vs UnA	38.3 (9.4) vs 41.7 (9.2)	-3.5 (-6.5 to -0.4)	0.032	NS
	PS 20 vs Sham	33.9 (7.9) vs 40.0 (10.3)	-6.1 (-9.2 to -3.1)	<0.001	<0.001
	PS 10 vs Sham	38.3 (9.4) vs 40.0 (10.3)	-1.8 (-4.7 to 1.2)	0.253	NS
	Sham vs UnA	40.0 (10.3) vs 41.7 (9.2)	-1.7 (-4.8 to 1.3)	0.272	NS
V_T (mL)	PS 20 vs UnA	0.539 (0.173) vs 0.462 (0.136)	0.076 (-0.003 to 0.155)	0.058	NS
	PS 20 vs PS 10	0.539 (0.173) vs 0.483 (0.143)	0.055 (-0.021 to 0.132)	0.151	NS
	PS 10 vs UnA	0.483 (0.143) vs 0.462 (0.136)	0.021 (-0.003 to 0.155)	0.588	NS
	PS 20 vs Sham	0.539 (0.173) vs 0.412 (0.120)	0.127 (0.050 to 0.203)	0.002	0.002
	PS 10 vs Sham	0.483 (0.143) vs 0.412 (0.120)	0.072 (-0.003 to 0.146)	0.059	NS
	Sham vs UnA	0.412 (0.120) vs 0.462 (0.136)	-0.051 (-0.128 to 0.025)	0.183	NS

SpO_2: oxygen saturation (%); Dyspnoea (Borg); RPE: rate of perceived exertion (Borg); RR: respiratory rate; V_T: tidal volume (L); PS 20: pressure support 20 cmH_2O; UnA: unassisted exercise; PS 10: pressure support 10 cmH_2O; Sham: sham pressure support; Adjusted p: p value adjusted using a sharper Bonferroni correction [16]; NS: not significant

Table 3 Pairwise comparisons of unassisted exercise, exercise with sham pressure support, pressure support 10 cmH_2O and pressure support 20 cmH_2O for physiological variables at end exercise

	Comparison	Mean (SD) vs Mean (SD)	Mean difference (95% CI)	p value	Adjusted p value
DBP (mmHg)	PS 20 vs UnA	93.3 (10.5) vs 90.4 (10.6)	2.9 (-1.2 to 7.1)	0.17	NS
	PS 20 vs PS 10	93.3 (10.5) vs 89.5 (10.2)	3.8 (-0.2 to 7.9)	0.063	NS
	PS 10 vs UnA	89.5 (10.2) vs 90.4 (10.6)	-1.0 (-5.1 to 3.2)	0.64	NS
	PS 20 vs Sham	93.3 (10.5) vs 84.8 (12.5)	8.5 (4.5 to 12.6)	<0.001	<0.001
	PS 10 vs Sham	89.5 (10.2) vs 84.8 (12.5)	4.7 (0.6 to 8.8)	0.025	NS
	Sham vs UnA	84.8 (12.5) vs 90.4 (10.6)	-5.7 (-9.8 to -1.5)	0.009	0.018
MAP (mmHg)	PS 20 vs UnA	112.3 (11.9) vs 112.6 (12.6)	-0.3 (-5.1 to 4.4)	0.88	NS
	PS 20 vs PS 10	112.3 (11.9) vs 109.7 (12.3)	2.6 (-2.1 to 7.2)	0.27	NS
	PS 10 vs UnA	109.7 (12.3) vs 112.6 (12.6)	-2.9 (-7.7 to 1.9)	0.22	NS
	PS 20 vs Sham	112.3 (11.9) vs 104.9 (13.8)	7.4 (2.8 to 12.0)	0.003	0.006
	PS 10 vs Sham	109.7 (12.3) vs 104.9 (13.8)	4.8 (0.2 to 9.5)	0.042	NS
	Sham vs UnA	104.9 (13.8) vs 112.6 (12.6)	-7.7 (-12.5 to -3.0)	0.002	0.002
La (mmol/L)	PS 20 vs UnA	2.02 (0.93) vs 1.65 (0.80)	0.37 (0.27 to 0.71)	0.035	NS
	PS 20 vs PS 10	2.02 (0.93) vs 1.66 (0.49)	0.35 (0.01 to 0.70)	0.043	NS
	PS 10 vs UnA	1.66 (0.49) vs 1.65 (0.80)	0.02 (-0.33 to 0.36)	0.93	NS
	PS 20 vs Sham	2.02 (0.93) vs 1.29 (0.41)	0.72 (0.38 to 1.07)	<0.001	<0.001
	PS 10 vs Sham	1.66 (0.49) vs 1.29 (0.41)	0.37 (0.03 to 0.71)	0.035	NS
	Sham vs UnA	1.29 (0.41) vs 1.65 (0.80)	-0.35 (-0.70 to -0.01)	0.043	NS
RR (breaths/min)	PS 20 vs UnA	40.0 (8.6) vs 47.0 (10.4)	-7.0 (-9.7 to -4.2)	<0.001	<0.001
	PS 20 vs PS 10	40.0 (8.6) vs 41.7 (10.5)	-1.7 (-4.3 to 1.0)	0.21	NS
	PS 10 vs UnA	41.7 (10.5) vs 47.0 (10.4)	-5.3 (-8.1 to -2.6)	<0.001	<0.001
	PS 20 vs Sham	40.0 (8.6) vs 40.5 (9.5)	-0.5 (-3.2 to 2.2)	0.70	NS
	PS 10 vs Sham	41.7 (10.5) vs 40.5 (9.5)	1.2 (-1.5 to 3.8)	0.38	NS
	Sham vs UnA	40.5 (9.5) vs 47.0 (10.4)	-6.5 (-9.2 to -3.7)	<0.001	<0.001
V_T (mL)	PS 20 vs UnA	0.569 (0.174) vs 0.471 (0.132)	0.097 (0.019 to 0.177)	0.016	0.032
	PS 20 vs PS 10	0.569 (0.174) vs 0.505 (0.159)	0.064 (-0.012 to 0.141)	0.098	NS
	PS 10 vs UnA	0.505 (0.159) vs 0.471 (0.132)	0.034 (-0.045 to 0.113)	0.39	NS
	PS 20 vs Sham	0.569 (0.174) vs 0.419 (0.131)	0.150 (0.073 to 0.227)	<0.001	<0.001
	PS 10 vs Sham	0.505 (0.159) vs 0.419 (0.131)	0.086 (0.009 to 0.162)	0.029	NS
	Sham vs UnA	0.419 (0.131) vs 0.471 (0.132)	-0.052 (-0.131 to 0.027)	0.19	NS
VE (L/min)	PS 20 vs UnA	21.325 (5.293) vs 19.543 (6.332)	1.782 (-1.735 to 5.298)	0.31	NS
	PS 20 vs PS 10	21.325 (5.293) vs 19.023 (4.061)	2.302 (-1.127 to 5.730)	0.18	NS
	PS 10 vs UnA	19.023 (4.061) vs 19.543 (6.332)	-0.520 (-4.037 to 2.997)	0.77	NS
	PS 20 vs Sham	21.325 (5.293) vs 15.588 (2.722)	5.738 (2.309 to 9.166)	0.002	0.002
	PS 10 vs Sham	19.023 (4.061) vs 15.588 (2.722)	3.436 (0.007 to 6.865)	0.05	NS
	Sham vs UnA	15.588 (2.722) vs 19.543 (6.332)	-3.956 (-7.472 to -0.439)	0.029	NS

DBP: diastolic blood pressure (mmHg); MAP: mean arterial pressure (mmHg); La: lactate (mmol/L); RR: respiratory rate; V_T: tidal volume (L); V_E: minute ventilation (L); PS 20: pressure support 20 cmH_2O; UnA: unassisted exercise; PS 10: pressure support 10 cmH_2O; Sham: sham pressure support; Adjusted p: p value adjusted using a sharper Bonferroni correction [16]; NS: not significant

DISCUSSION

To our knowledge, this study is the first double blind, randomised, crossover study to examine the effects of different levels of PS during exercise in severe kyphoscoliosis. The main finding was that high level PS (20 cmH_2O) during treadmill walking significantly increased exercise endurance time compared to walking unassisted, with sham PS or low level PS (10 cmH_2O). Endurance time was also

increased with PS 10 compared to sham PS. In addition, PS 20 during walking improved isotime SpO_2, reduced RR and leg muscle fatigue, and decreased dyspnoea compared to walking unassisted.

Effect of high and low level pressure support during exercise on endurance time

Our finding that high level PS (20 cmH_2O) during treadmill walking improved endurance time is consistent with other studies that have found that similar or higher levels of PS (19-37 cmH_2O) during cycling exercise increased endurance time compared to unassisted exercise in individuals with chronic respiratory failure, primarily due to kyphoscoliosis [2], or pulmonary tuberculosis sequalae [17]. In the present study, treadmill exercise was performed rather than cycling exercise as treadmill walking closely resembles a functional daily activity. However, walking is more likely to be limited by breathlessness [18], and a greater degree of O_2 desaturation tends to occur in comparison to cycling exercise [19]. Therefore our finding that high level PS improves treadmill walking endurance time may be important when considering the specificity of training for a functional task such as walking.

Our finding that low level PS (10 cmH_2O) did not increase exercise endurance time compared with unassisted exercise is consistent with the study of Highcock *et al* [8] who also found that low level PS during treadmill walking did not improve distance walked compared to unassisted exercise in eight people with severe scoliosis. As chest wall compliance is greatly reduced in severe kyphoscoliosis [20], high inflationary pressures may be required to achieve an adequate tidal volume and to unload the respiratory muscles. Respiratory muscle unloading appears crucial for NIV to be of benefit during exercise in people with chronic obstructive pulmonary disease (COPD) [21] and therefore, relatively low levels of PS during exercise may not unload the respiratory muscles sufficiently to assist exercise performance in individuals with severe kyphoscoliosis. In contrast to the studies cited above, the advantage of the present study was that we examined the effect of both high and low level PS during

exercise in the same subjects. Furthermore, both participants and assessors were blinded to the level of PS provided during exercise thereby reducing the risk of bias.

While the combination of NIV and O_2 during exercise has previously been shown to improve endurance time above that of NIV or O_2 alone during exercise in patients with severe chest wall restriction secondary to post tuberculosis sequelae [17], no consistent effect on endurance time was observed in the three subjects who used supplemental O_2 in the present study. For example, the change in endurance time with PS 20 plus O_2 compared to unassisted exercise with O_2 ranged between -37% and 90% for these individuals, which spanned the results from the whole group (Figure 4). However, a larger sample size would be required to draw definitive conclusions about the effect of PS plus O_2 during exercise in people with severe kyphoscoliosis.

Potential mechanisms of benefit of high level pressure support during exercise

The mechanisms by which PS 20 increased exercise endurance time may relate to the improvement in pattern of breathing and oxygenation, and the reduction in dyspnoea and leg muscle fatigue that were demonstrated. One striking effect of PS 20 during exercise was the marked reduction in respiratory rate at isotime compared to sham PS, PS 10 and unassisted exercise. Despite exercising for longer with PS 20 compared with unassisted exercise, the reduction in respiratory rate of almost eight breaths per minute was also maintained at end exercise. Surprisingly, only a small increase in V_T was observed with PS 20 compared to unassisted exercise, such that overall V_E did not significantly change. Nonetheless, by adopting a more efficient pattern of breathing, dead space ventilation would be reduced and gas exchange improved [22].

People with severe kyphoscoliosis and chronic respiratory failure also develop a combined respiratory and metabolic acidosis during exercise [22], which could impair respiratory muscle function [23, 24].

We found that end exercise pH and PCO_2 were no worse with PS 20 compared to the other three conditions despite having exercised for longer with PS 20. This suggests that PS 20 delayed the development of exercise induced hypercapnia compared to unassisted exercise, consistent with the findings of Vila *et al* [22]. At end exercise, blood La was significantly higher with PS 20 compared with sham PS, and tended to be greater than with unassisted exercise or PS 10. This is likely to reflect of the longer endurance time associated with PS 20 compared to the other interventions.

Isotime SpO_2 was higher with PS 20, and to a lesser extent with PS 10, compared to unassisted exercise and sham PS. Consequently, increased O_2 delivery to the peripheral muscles may have contributed to the improved performance with PS 20. It was surprising that isotime SpO_2 was higher with PS 20 compared with unassisted exercise given the marked fall in RR, small rise in V_T, and small fall in V_E that was observed with PS 20. However, even though V_E was higher during unassisted exercise, dead space ventilation was also likely to be higher due to the faster RR and therefore alveolar ventilation may not have increased as might have been expected. Also, no consistent pattern was observed between individual changes in V_E and isotime SpO_2, suggesting that factors other than an increase in V_E contributed to the improvement in isotime SpO_2 with PS 20 in some individuals. A major improvement in ventilation-perfusion matching is an unlikely explanation, although the short term effect of PS on ventilation-perfusion matching has not been assessed in severe kyphoscoliosis. It is possible that PS 20 unloaded the respiratory muscles and reduced the O_2 cost of breathing (VO_2resp) compared with unassisted exercise resulting in a higher SpO_2 at isotime. The VO_2resp can represent a substantial proportion of total oxygen consumption in patients with cardiorespiratory disease [25]. In severe COPD, NIV has been shown to unload the respiratory muscles during exercise [21, 26]. Whether the same effect occurs in severe kyphoscoliosis remains to be demonstrated. Finally, despite endurance time being greater with PS 20, there was no difference in end exercise SpO_2 between

conditions, indicating that participants performed more exercise with PS 20 before reaching the same level of O_2 desaturation.

Although detailed assessment of the effect of PS during exercise on the cardiovascular system was beyond the scope of the present study, one potential side effect of high level PS is a reduction in venous return which may also decrease cardiac output. We found no change in HR at isotime exercise between conditions, and end exercise MAP was not reduced with PS 20 compared with sham PS, PS 10 or unassisted exercise suggesting no observable detrimental cardiovascular effects of high level of PS occurred. However, a previous study showed that people with thoracic scoliosis develop exercise induced pulmonary hypertension (PHT) inversely proportional to VC, FRC and TLC [27]. Subjects in the present study had significantly reduced static lung volumes and may have been at risk of developing severe exercise induced PHT. In COPD, PHT limits stroke volume during exercise [28] and has a detrimental effect on exercise capacity [29]. While long term nocturnal NIV was found to reduce PHT in people with severe restrictive thoracic disorders [30], presumably through the reversal of hypoxaemia and hypercapnia, the acute effect of high level PS on the development of exercise induced PHT and the resultant effect on stroke volume and exercise tolerance is unknown in patients with severe kyphoscoliosis but may warrant investigation.

Subjective responses to PS during exercise largely reflected the physiological responses to PS during exercise. By reducing unpleasant symptoms such as breathlessness and leg muscle fatigue, PS 20 enabled participants to tolerate exercise for longer. Isotime dyspnoea was reduced by both PS 20 and PS 10 compared to sham PS. Pressure support 20 cmH_2O also reduced isotime dyspnoea by a mean of almost two points on the Borg scale compared to unassisted exercise. The reduction in isotime dyspnoea appeared to be an important mechanism influencing the exercise response during PS 20, with those subjects with a greater reduction in dyspnoea tending to have a greater increase in endurance time

with PS 20 (Figure 5). Knowledge of this relationship may assist clinicians to titrate optimal, individualised high levels of PS during walking in people with severe kyphoscoliosis in order to maximise the response to PS during exercise. Almost half of the participants during PS 20 stopped exercise due to leg muscle fatigue rather than breathlessness (Figure 5). This suggests that the reduction in breathlessness allowed a greater amount of work to be performed by the locomotor muscles, to the point of leg muscle fatigue in some cases, which may be important during exercise training. Likewise, isotime RPE was reduced by a mean of almost two points on the Borg scale with PS 20 and PS 10 compared to unassisted exercise and sham PS, with a slightly greater effect observed with PS 20. This lower perception of respiratory and locomotor effort during exercise most likely allowed participants to tolerate exercise for longer.

Limitations

The authors acknowledge the difficulty of blinding participants and assessors to the different levels of PS used in the present study. Every attempt was made to achieve blinding, including the randomisation of test order and concealment of ventilator settings from assessors and participants. None of the participants had used CPAP prior to the present study, and participants were not aware of the PS levels being tested or the study hypothesis. In addition, the instructions and encouragement given to participants was standardised to reduce potential bias.

Clinical Implications

The findings of this study provide evidence that the efficacy of PS during exercise in severe kyphoscoliosis depends on the level of PS provided. Identification of ventilator settings that provide the greatest improvement in exercise performance is important if PS is to be used as an adjunct to exercise training, or to assist in the performance of daily activities. Whether even higher levels of PS could result in greater improvements in exercise performance is unknown. However, the delivery of

very high levels of PS may be limited by mask leak, patient discomfort and the possible cardiovascular consequences of larger positive intra-thoracic pressure. Patient selection may also affect the response to PS during exercise. The current study demonstrated the efficacy of high level PS in severe chest wall restriction, a finding supported by Borel *et al* [2, 31] who showed that subjects with severe chest wall restriction had a greater response to high level PS during exercise compared to those with moderate restriction. In addition, ventilator capacity [8] and choice of interface may impact on an individual's response to NIV-assisted exercise.

Conclusion

High level pressure support (20 cmH_2O) during treadmill walking in people with severe kyphoscoliosis increases endurance time, improves pattern of breathing and oxygenation, and reduces the perception of leg muscle fatigue and dyspnoea compared to unassisted exercise. Low level PS (10 cmH_2O) did not increase endurance time compared to unassisted exercise, indicating that the level of PS provided during exercise influences the efficacy of the intervention. Investigation of the role of high level PS during exercise training or during daily activities in subjects with severe chest wall restriction who demonstrate an acute improvement in exercise performance with PS is warranted.

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Figure 1

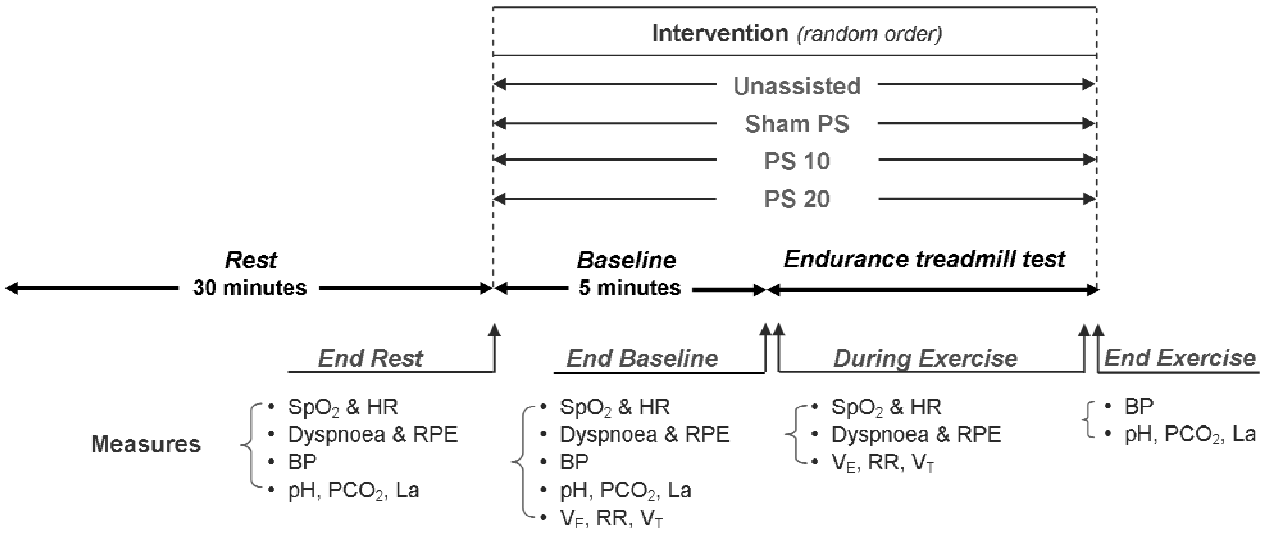

Figure 2

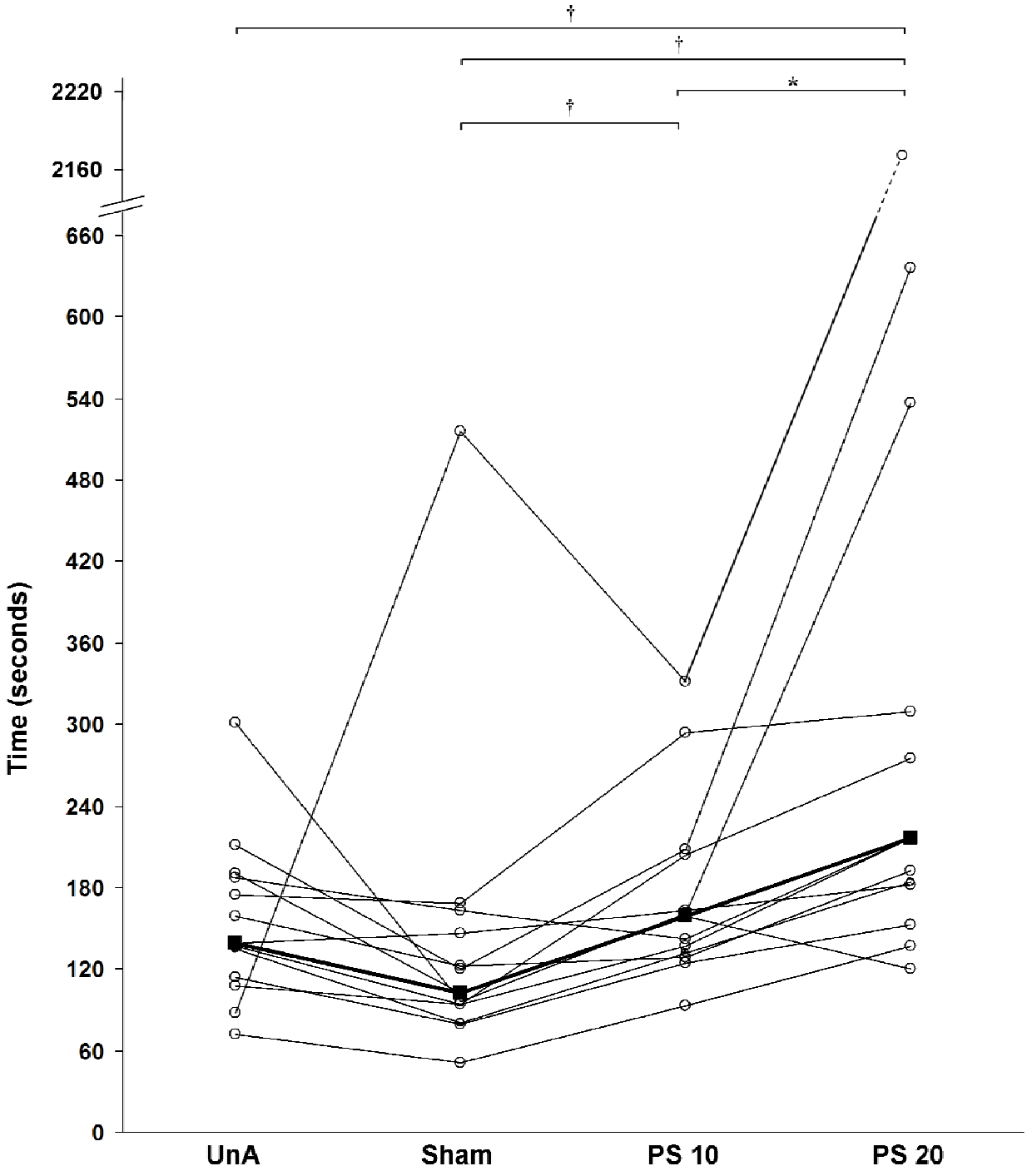
†
†
*
†
2220
2160
660
600
540
480
420
360
300
240
180
120
60
0
Time (seconds)
UnA
Sham
PS 10
PS 20

Figure 3

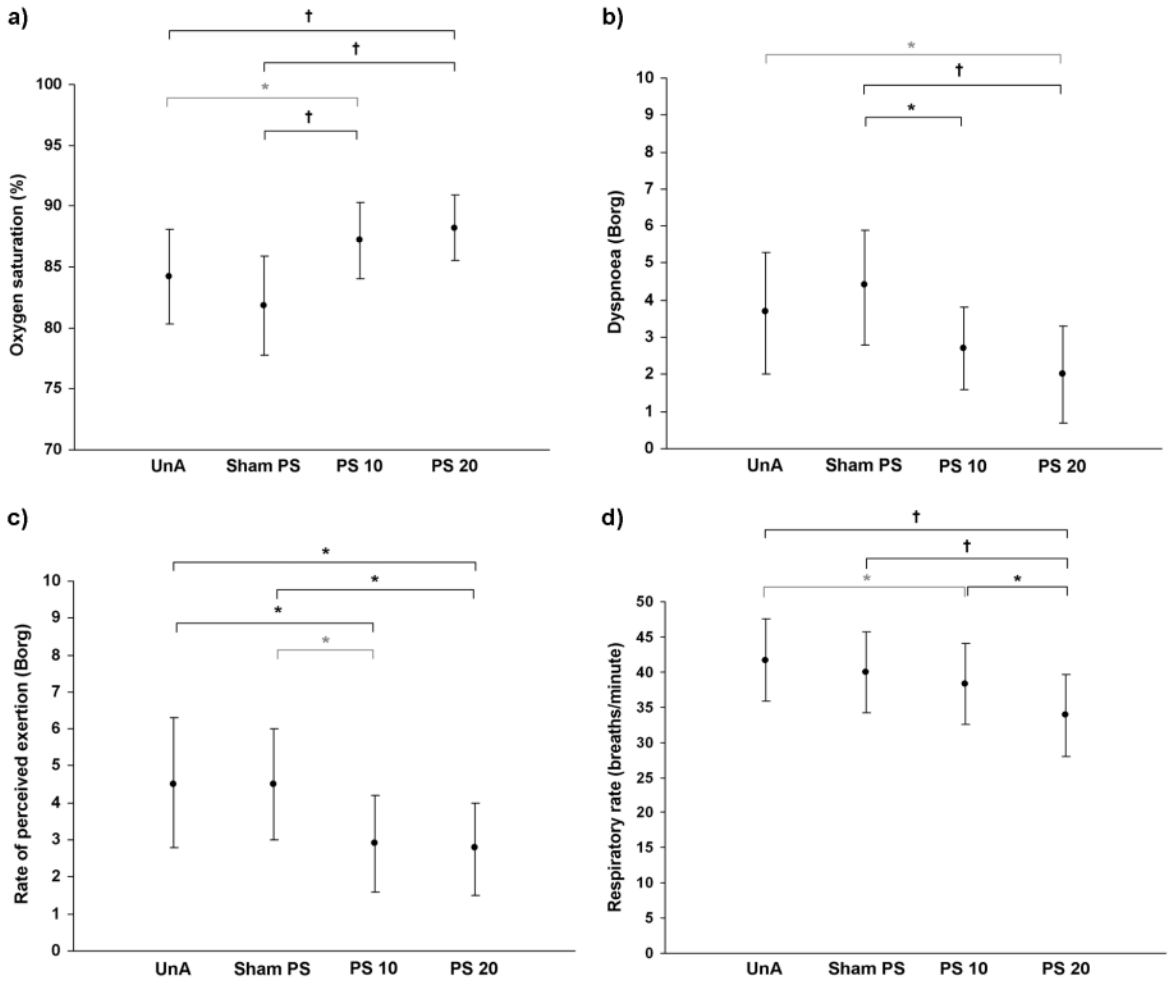
a)
Oxygen saturation (%)
100
95
90
85
80
75
70
UnA
Sham PS
PS 10
PS 20
b)
Dyspnoea (Borg)
10
9
8
7
6
5
4
3
2
1
0
UnA
Sham PS
PS 10
PS 20
c)
Rate of perceived exertion (Borg)
10
9
8
7
6
5
4
3
2
1
0
UnA
Sham PS
PS 10
PS 20
d)
Respiratory rate (breaths/minute)
50
45
40
35
30
25
20
15
10
5
0
UnA
Sham PS
PS 10
PS 20

Figure 4

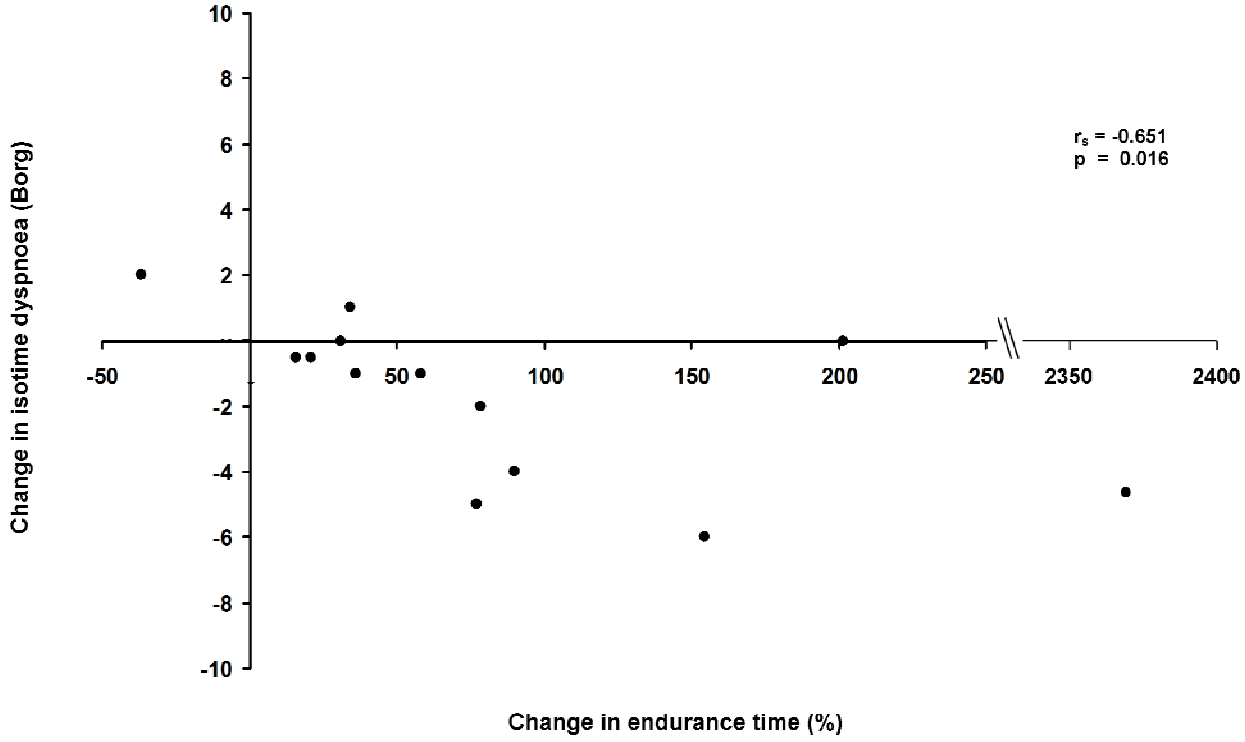

Figure 5