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RESEARCH ARTICLE | *Case Studies in Physiology*

Exercise-induced diaphragm fatigue in a Paralympic champion rower with spinal cord injury

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Tiller NB, Aggar TR, West CR, Romer LM. Exercise-induced diaphragm fatigue in a Paralympic champion rower with spinal cord injury. *J Appl Physiol* 124: 805–811, 2018. First published November 30, 2017; doi:10.1152/jappphysiol.00870.2017.—The aim of this case report was to determine whether maximal upper body exercise was sufficient to induce diaphragm fatigue in a Paralympic champion adaptive rower with low-lesion spinal cord injury (SCI). An elite arms-only oarsman (age: 28 yr; stature: 1.89 m; and mass: 90.4 kg) with motor-complete SCI (T₁₂) performed a 1,000-m time trial on an adapted rowing ergometer. Exercise measurements comprised pulmonary ventilation and gas exchange, diaphragm EMG-derived indexes of neural respiratory drive, and intrathoracic pressure-derived indexes of respiratory mechanics. Diaphragm fatigue was assessed by measuring pre- to postexercise changes in the twitch transdiaphragmatic pressure ($P_{di,tw}$) response to anterolateral magnetic stimulation of the phrenic nerves. The time trial (248 ± 25 W, 3.9 min) elicited a peak O₂ uptake of 3.46 l/min and a peak pulmonary ventilation of 150 l/min (57% MVV). Breath-to-stroke ratio was 1:1 during the initial 400 m and 2:1 thereafter. The ratio of inspiratory transdiaphragmatic pressure to diaphragm EMG (neuromuscular efficiency) fell from rest to 600 m (16.0 vs. 3.0). Potentiated $P_{di,tw}$ was substantially reduced (–33%) at 15–20 min postexercise, with only partial recovery (–12%) at 30–35 min. This is the first report of exercise-induced diaphragm fatigue in SCI. The decrease in diaphragm neuromuscular efficiency during exercise suggests that the fatigue was partly due to factors independent of ventilation (e.g., posture and locomotion).

NEW & NOTEWORTHY This case report provides the first objective evidence of exercise-induced diaphragm fatigue in spinal cord injury (SCI) and, for that matter, in any population undertaking upper body exercise. Our data support the notion that high levels of exercise hyperpnea and factors other than ventilation (e.g., posture and locomotion) are responsible for the fatigue noted after upper body exercise. The findings extend our understanding of the limits of physiological function in SCI.

Paralympics; respiratory mechanics; rowing; upper body exercise; wheelchair sport

INTRODUCTION

High-intensity, whole body exercise is sufficient to induce contractile fatigue of the diaphragm in healthy, able-bodied

subjects. This exercise-induced diaphragm fatigue has been documented following cycle ergometry and treadmill running, as demonstrated by 15–30% pre- to postexercise reductions in the twitch transdiaphragmatic pressure ($P_{di,tw}$) response to bilateral phrenic nerve stimulation (6, 18). More recently, we reported nonsignificant reductions in $P_{di,tw}$ following high-intensity arm ergometry in healthy, able-bodied subjects (36) and in athletes with high-lesion (cervical) spinal cord injury (SCI) (35). Since the severity of diaphragm fatigue after whole body exercise is critically dependent on diaphragmatic workload (5), it is likely that upper body exercise imposed insufficient stress on the diaphragm to induce contractile fatigue, and was likely a function of the subjects' low aerobic fitness and/or small active muscle (35, 36).

Individuals with cervical SCI often exhibit chronic respiratory dysfunction owing to weakness of the respiratory muscles, reduced compliance of the lung and chest wall, and increased abdominal compliance (8). The impact of SCI on respiratory function is usually less severe in those with lower lesions (28, 31). Moreover, paraplegics with low-lesion SCI exhibit greater control of the upper limbs and trunk as well as supraspinal control over the major portion of the sympathetic chain, manifesting in greater cardiac capacity and oxygen uptake relative to high-lesion paraplegics or tetraplegics (11). It is not currently known whether a greater cardiorespiratory capacity predisposes individuals with low-lesion SCI to exercise-induced diaphragm fatigue. Rowing is considered to be one of the most physiologically demanding sports, with ventilatory requirements that are substantial relative to arm cranking (37). Exercise-induced diaphragm fatigue is most likely to occur in response to maximal rowing because the diaphragm must contract to expand the ribcage during inspiration while also opposing mechanical forces transmitted through the thorax (24, 32). An important, yet undetermined, component of diaphragm fatigue relates to the measured inspiratory muscle “work,” which comprises both the exercise hyperpnea and the additional mechanical demands imposed by upper body locomotor mechanics.

Accordingly, the aim of this study was to use phrenic nerve stimulation to assess diaphragm fatigability in response to a simulated 1,000-m arms-only rowing time trial performed by an elite Paralympic oarsman. This case study presented a unique opportunity to investigate the limits of physiological function in low-lesion SCI; therefore, a further aim was to

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Table 1. Pulmonary function

	Absolute	%Predicted
FEV ₁ , liter	5.49	114
VC, liter	7.57	130
FEV ₁ /VC, %	72.5	88
TLC, liter	10.1	126
RV, liter	2.71	145
FRC, liter	4.68	130
IC, liter	5.44	124
PEF, l/s	13.1	124
MVV ₁₂ , l/min	262	141
P _{I,max} , cmH ₂ O	217	192
P _{E,max} , cmH ₂ O	252	163
Raw _{eff} , kPa/s	0.23	77
sRaw _{eff} , kPa·s ⁻¹ ·l ⁻¹	1.19	101
D _{L,CO} , mmol·min ⁻¹ ·kPa ⁻¹	17.2	131

FEV₁, forced expiratory volume in one second; VC, vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; PEF, peak expiratory flow; MVV₁₂, maximum voluntary ventilation in 12 s; P_{I,max}, maximum static inspiratory pressure; P_{E,max}, maximum static expiratory pressure; Raw_{eff}, effective airway resistance; sRaw_{eff}, specific effective airway resistance; D_{L,CO}, diffusion capacity for carbon monoxide. Predicted values for pulmonary volumes, capacities, and flows are from Quanjer et al. (27); MVV from Grimby and Söderholm (14); and maximum static respiratory pressures from Wilson et al. (39).

quantify the physiological demands of adaptive rowing, with emphasis on the respiratory neuromechanical responses.

CASE PRESENTATION

Participant

The participant was a Paralympic, World, and European champion oarsman with traumatic motor-complete SCI (T₁₂, ASIA Impairment Scale grade A) who competed for Great Britain in the “arms and shoulders” single sculls classification (1 × AS). At the time of study, the participant was the reigning Paralympic champion and in a maintenance phase of aerobic training. The participant’s characteristics were as follows: age: 28 yr; stature: 1.89 m; body mass: 90.4 kg; time postinjury: 6.5 yr. Before testing, the participant abstained from strenuous exercise for 48 h, caffeine and alcohol for 12 h, and food for 3 h, and was not taking any drugs known to influence the exercise response. The study was approved by the institutional research ethics committee, and the participant provided written informed consent.

Experimental Overview

The participant visited the laboratory on two occasions separated by 48 h. The first visit comprised pulmonary function testing and a thorough familiarization with the nerve stimulation protocol. At the second visit, the participant completed a simulated 1,000-m arms-only time trial on an adapted rowing ergometer, with assessment of cardiorespiratory, metabolic and respiratory neuromechanical responses. Exercise-induced diaphragm fatigue was assessed via magnetic stimulation of the phrenic nerves.

Resting Pulmonary Function

Pulmonary volumes, capacities, flows, and resistance were assessed using whole body plethysmography, and diffusion capacity via CO-rebreathe (Masterscreen Body; CareFusion,

Hampshire, UK). Maximum inspiratory pressure at residual volume (P_{I,max}) and maximum expiratory pressure at total lung capacity (P_{E,max}) were measured using a handheld device (MicroRPM; CareFusion). All procedures were conducted in accordance with recommended standards (13, 22, 25, 38).

Time trial

After a self-selected warm-up, the participant completed a simulated 1,000-m rowing time trial on an adapted rowing ergometer (Concept 2C, Nottingham, UK) fitted with a custom nonmovable seat and with the flywheel resistance (drag factor) adjusted to 140. The participant wore regulation strapping at chest level to secure the upper body to the seat. Stroke force and length were assessed using a bespoke transducer and potentiometer affixed to the ergometer handle. Pulmonary ventilation and gas exchange were assessed continuously using an online system (Oxycon Pro; CareFusion) and averaged over the last 30 s of each 200-m split. A 20- μ l capillary blood sample was collected from the earlobe immediately after exercise and every 2 min thereafter for the determination of peak blood lactate concentration [BLa] (Biosen C-Line Sport; EKF Diagnostics, Barleben, Germany). Locomotor-respiratory coupling was calculated as the ratio of complete or partial respiratory cycles within a given stroke (7).

Diaphragm function. Neuromuscular activation of the diaphragm (EMG_{di}) was assessed using a bespoke multipair esophageal electrode catheter (Gaeltec Devices; Dunvegan, Isle of Sky, UK) that was inserted pernasally and positioned using standard procedures (21). Inspiratory tidal EMG_{di} was normalized against the highest root mean square (RMS) recorded during a maximal Müller maneuver. Esophageal pressure (P_{es}) and gastric pressure (P_{ga}) were measured using two independent pressure transducers that were attached to the

Table 2. Mechanical and cardiorespiratory responses to a 1,000-m arms-only rowing time trial

	Rest	200 m	400 m	600 m	800 m	1,000 m
Split time, s	—	44.2	47.3	47.5	47.4	47.2
Power output, W	—	293	239	234	235	240
Mean handle drive force, N	—	458	451	433	414	361
Maximum handle drive force, N	—	933	865	825	771	726
Drive handle travel, m	—	0.84	0.85	0.88	0.89	0.89
Stroke rate, stroke/min	—	45	37	37	38	44
$\dot{V}O_2$, l/min	0.39	2.61	3.13	3.31	3.23	3.30
$\dot{V}O_2$, ml·kg ⁻¹ ·min ⁻¹	4.3	28.9	34.6	36.6	35.7	36.5
$\dot{V}CO_2$, l/min	0.33	2.31	3.53	3.91	3.76	3.79
RER	0.84	0.88	1.13	1.18	1.15	1.16
$\dot{V}E$, l/min	10.4	71.7	102.9	139.6	144.0	142.3
V _T , liter	0.81	1.63	2.84	1.93	1.91	1.99
f _R , breaths/min	13	44	37	71	68	64
T _I , s	2.49	0.64	0.77	0.37	0.36	0.40
T _E , s	2.43	0.71	0.86	0.45	0.41	0.45
T _{TOT} , s	4.92	1.35	1.63	0.82	0.77	0.85
T _I /T _{TOT}	0.51	0.47	0.47	0.45	0.47	0.47
V _T /T _I , l/s	0.33	2.56	3.69	5.18	5.29	5.03
V _T /T _E , l/s	0.33	2.30	3.30	4.30	4.66	4.42
$\dot{V}E/\dot{V}O_2$	26.4	27.5	32.9	42.2	44.6	43.1
$\dot{V}E/\dot{V}CO_2$	31.3	31.0	29.2	35.7	38.3	37.6

Values during exercise are mean data for the final 30 s of each 200-m split. $\dot{V}O_2$, O₂ uptake; $\dot{V}CO_2$, CO₂ output; RER, respiratory exchange ratio; $\dot{V}E$, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; T_I, inspiratory time; T_E, expiratory time; T_{TOT}, total respiratory time.

catheter proximally and distally to the electrodes (33). Transdiaphragmatic pressure (P_{di}) was obtained by online subtraction of P_{es} from P_{ga} . Tidal inspiratory P_{di} (ΔP_{di}) was calculated as the change in P_{di} between points of zero flow. To quantify the extent to which the diaphragm was recruited for nonrespiratory tasks, diaphragm neuromuscular efficiency was calculated as the ratio of ΔP_{di} (cmH₂O) to EMG_{di} (%RMS_{max}) (1).

Phrenic nerve stimulation. Two magnetic stimulators (Magstim 200; The Magstim Company, Whitland, Wales), each connected to a 25-mm figure-of-eight coil, were used to stimulate the phrenic nerves for the determination of twitch trans-

diaphragmatic pressure ($P_{di,tw}$) at baseline and at 15–20 and 30–35 min after exercise. The procedure was identical to that used in our previous study of athletes with cervical SCI (35). A preexercise incremental stimulation protocol was performed to determine whether depolarization of the phrenic nerves was maximal. All subsequent stimulations were discharged at 100% stimulator power when the participant was relaxed at functional residual capacity with the glottis closed. Membrane excitability was determined by measuring the peak-to-peak amplitude and duration of magnetically evoked M-waves. We have previously discussed the potential sources of error associated with nerve stimulation protocols (35, 36).

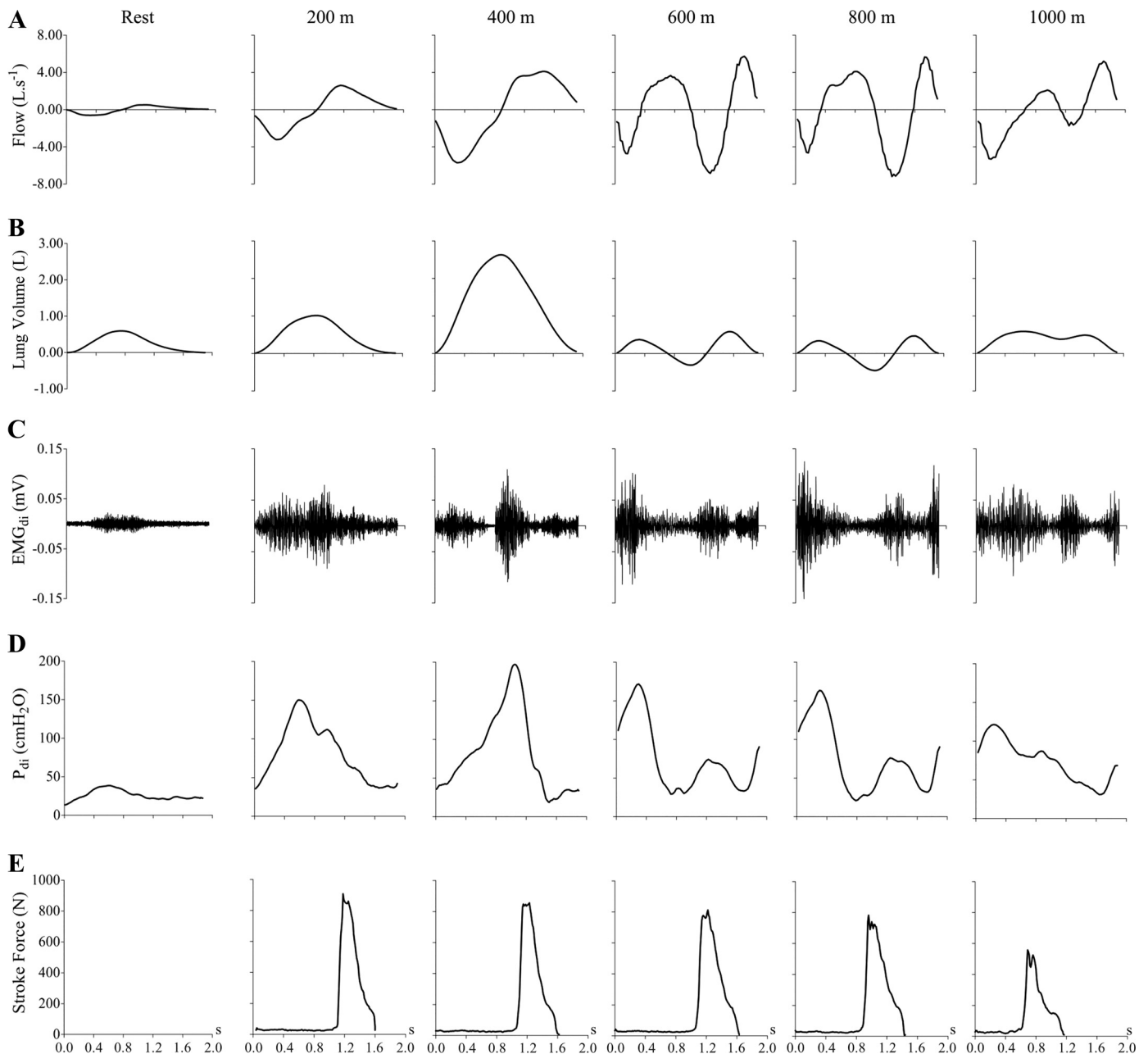


Fig. 1. Ensemble averaged data for respiratory neuromuscular function at rest and during simulated 1,000-m arms-only rowing time trial. Inspiration is illustrated by negative flow. Breath-to-stroke ratio was 1:1 for the initial 400 m and 2:1 thereafter. Data are expressed “per breath” at rest, and “per stroke” during exercise whereby a given locomotor cycle was anchored such that the end of the power stroke (start of recovery phase) delineated the start and end-points of each cycle. A: flow. B: lung volume. C: diaphragm EMG (EMG_{di}). D: transdiaphragmatic pressure (P_{di}). E: stroke force.

Data Processing

Handle force and displacement, in addition to respiratory pressure and airflow signals, were passed through an amplifier (1902; Cambridge Electronic Design, Cambridge, UK) and digitised at a sampling frequency of 150 Hz using an analog-to-digital converter (micro 1401 mkII; Cambridge Electronic Design). EMG signals were sampled at 4 kHz, high-pass filtered at 100 Hz, and notch filtered at 50 Hz (20). ECG artifact was removed from the EMG waveforms using a custom script procedure (3).

RESULTS

Pulmonary Function

Baseline pulmonary function generally exceeded predicted values for healthy, able-bodied individuals (Table 1), with no evidence of any preexisting respiratory disorder.

Time Trial

Cardiorespiratory responses to the simulated 1,000-m time trial are shown in Table 2. The time trial was completed in 3.89 min at a power output of 248 ± 25 W (mean \pm SD). Power output peaked during the initial 200 m and then stabilized for the remainder of the trial, maintained by small increases in

stroke rate and length. Oxygen uptake (\dot{V}_{O_2}) and minute ventilation (\dot{V}_E) increased sharply over the initial 200–400 m and increased at a more gradual rate thereafter, reaching peak values of 3.46 l/min ($38.3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and 150 l/min [57% of measured maximum voluntary ventilation (MVV_{12})], respectively. Minute ventilation over the initial 400 m was achieved primarily via increases in tidal volume (V_T), with respiratory frequency (f_R) entrained with stroke rate at a breath-to-stroke ratio of 1:1, switching to 2:1 after 400 m (Fig. 1). The change in respiratory pattern was accompanied by reductions in breath timing (T_I , T_E , and T_{TOT}) and increases in ventilatory drive (V_T/T_I , V_T/T_E). Blood lactate concentration was 0.7 mmol/l at baseline, peaking at 15.8 mmol/l at 8 min postexercise. Inspiratory transdiaphragmatic pressure swings decreased after 200 m whereas EMG_{di} tended to increase, resulting in a fall in $\Delta P_{di}/EMG_{di}$ (i.e., a reduction in diaphragm neuromuscular efficiency) (Fig. 2). Immediately following the cessation of exercise, absolute ventilation during five respiratory cycles increased substantially (13.6 to 18.7 liters), primarily the result of an increased tidal volume (2.7 to 3.1 liters), whereas transdiaphragmatic pressure swings and diaphragm EMG decreased (ΔP_{di} , 133 to 53 cmH_2O ; EMG_{di} , 91 to 58% RMS_{max}) (Fig. 3).

Diaphragm fatigue. Potentiated $P_{di,tw}$ was substantially reduced below baseline at 15–20 min after exercise (41 vs. 61 cmH_2O), with only partial recovery at 30–35 min (50 cmH_2O).

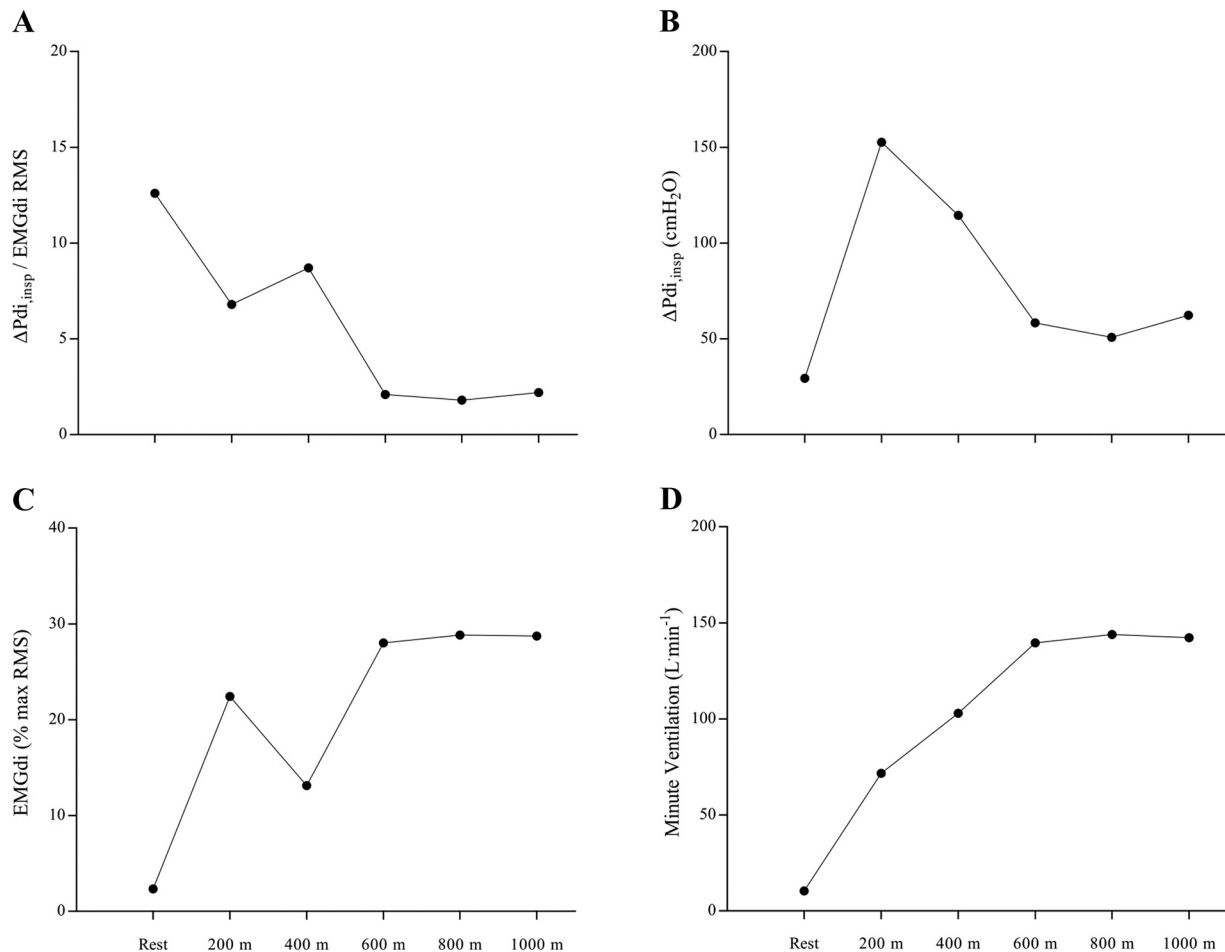


Fig. 2. Ratio of inspiratory transdiaphragmatic pressure (ΔP_{di}) to diaphragm EMG (EMG_{di}) (A), ΔP_{di} (B), EMG_{di} (C), and minute ventilation (\dot{V}_E) (D) during a simulated 1,000-m arms-only rowing time trial.

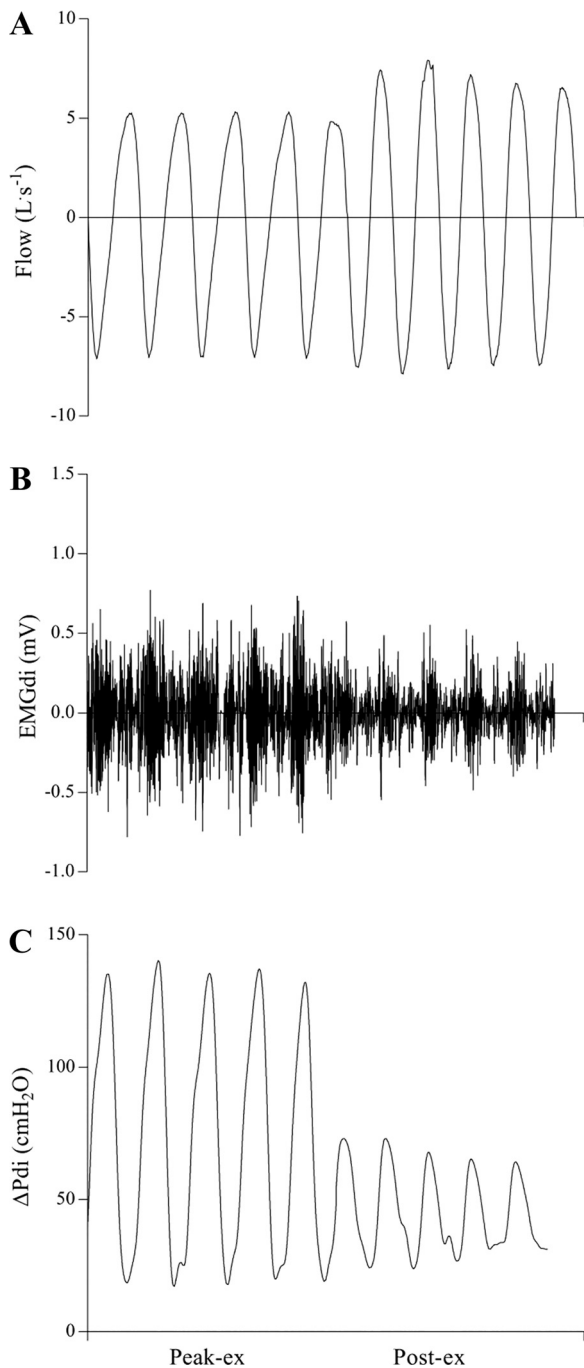


Fig. 3. Respiratory neuromechanical responses during 5 breaths at peak exercise and 5 breaths immediately after the abrupt cessation of exercise. A: flow. B: diaphragm EMG (EMG_{di}). C: transdiaphragmatic pressure (ΔP_{di}).

Moreover, maximum inspiratory P_{di} and maximum inspiratory P_{es} were markedly reduced at 15–20 min after exercise ($P_{di,max}$, 200 vs. 233 cmH_2O ; $P_{es,max}$, 157 vs. 183 cmH_2O). Nerve stimulation during the preexercise incremental stimulation protocol was not deemed to be supramaximal, as indicated by a small increase in $P_{di,tw}$ (40 to 45 cmH_2O) when stimulator intensity was increased from 95–100%. Evoked diaphragm M-waves were similar at baseline, 15–20 min, and 30–35 min after exercise (amplitude 8.5, 8.4 vs. 8.2 mV; duration 1.5, 1.4 vs. 1.3 ms).

DISCUSSION

This study provides the first objective evidence of exercise-induced diaphragm fatigue following upper body exercise. In a Paralympic champion oarsman with low-lesion SCI, we noted a substantial (33%) reduction in evoked transdiaphragmatic pressure at 15–20 min after a simulated 1,000-m time trial, with only partial recovery by 30–35 min. The ratio of inspiratory transdiaphragmatic pressure to diaphragm EMG (diaphragm neuromuscular efficiency) fell substantially during the early phase of exercise. Furthermore, tidal transdiaphragmatic pressure fell immediately on exercise cessation despite maintained pulmonary ventilation. These data suggest that diaphragm fatigue was partly due to work derived from nonrespiratory loading.

Muscle fatigue is defined as a condition in which there is a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load, and which is reversible with rest (26). Moreover, respiratory muscle fatigue is considered present if there is a ≥ 10 –15% reduction in $P_{di,tw}$ relative to baseline (15), i.e., a change that is two- to threefold the typical variation in resting $P_{di,tw}$. Based on these criteria, we are confident that the fatigue observed was physiologically meaningful. The magnitude of the postexercise reduction in $P_{di,tw}$ was similar to that noted for able-bodied subjects following high-intensity lower limb cycle ergometry and treadmill running (6, 18).

When interpreting our findings, there are several technical considerations that warrant discussion. Using identical stimulation procedures, we have previously obtained a within-day, between-occasion coefficient of variation for potentiated $P_{di,tw}$ of $\sim 3\%$ in athletes with cervical SCI (35), and we are confident that a similar level of reliability was achieved presently. It is important to note, however, that some recovery of diaphragm function likely occurred during the delay between end exercise and the postexercise evaluation of neuromuscular function. The delay was necessary to enable lung volumes (and hence muscle length) to return to baseline, but the severity of fatigue was likely underestimated as a consequence (9). A second factor that may have contributed to an underestimation of diaphragm fatigue is that supramaximal stimulation of the phrenic nerves was not achieved. Supramaximal stimulation can be difficult to achieve in subjects with short, thick necks (23), and it is plausible that supramaximal stimulation is less frequently achieved in subjects with a large body mass due to larger respiratory muscles. Importantly, there were no substantial changes in diaphragm muscle M-wave characteristics (amplitude and duration) when baseline stimulations were compared with those delivered at 15–20 and 30–35 min after exercise. This strongly suggests that the reductions in evoked pressure were attributable to contractile fatigue rather than transmission failure or derecruitment of muscle fibers.

The present observation of exercise-induced diaphragm fatigue in a highly trained athlete with low-lesion (thoracic) SCI extends our understanding of how SCI impacts on cardiorespiratory function. In the current study, ventilatory demands were substantial (peak ventilation of 150 l/min; 57% MVV). These findings, along with those of previous studies in which we failed to observe diaphragm fatigue during upper body exercise at lower ventilations (35, 36), support the notion that high ventilation might be a prerequisite for exercise-induced diaphragm fatigue. How-

ever, since upper body tasks place additional mechanical loads on the thoracic complex for stiffening the spine (16, 17) and maintaining torso stabilization (10), it is possible that the fatigue observed presently was not attributable exclusively to the exercise hyperpnea. In an effort to quantify the diaphragmatic contribution to postural stability during maximal arms-only rowing, we compared the data from five respiratory cycles immediately before the cessation of the time trial (peak exercise) to five respiratory cycles performed immediately after the abrupt cessation of exercise when ventilation was still high (2). When the high thoracic loads of exercise were relinquished, there was an abrupt increase in tidal volume (2.7 to 3.1 liters), suggesting that arm exercise imposes a degree of constraint on the ribcage. Despite an increase in ventilation immediately postexercise (13.6 to 18.7 liters), there was a substantial and instantaneous decrease in inspiratory transdiaphragmatic pressure and diaphragm EMG (see Fig. 3). Furthermore, during exercise, the ratio between inspiratory transdiaphragmatic pressure and diaphragm EMG (i.e., diaphragm neuromuscular efficiency) tended to decrease as the time trial progressed (see Fig. 2). Thus it appears that a large portion of diaphragm activity during the time trial was a result of postural and/or locomotor tasks.

The participant exhibited a breath-to-stroke ratio of 1:1 during the initial 400 m, after which he assumed a ratio of 2:1 with a concomitant reduction in tidal volume (2.8 to 1.9 liters; see Fig. 1). Able-bodied rowers entrain ventilation at integer multiples of stroke rate (1:1, 2:1, or 3:1), with a 2:1 entrainment pattern most common during a 2,000-m time trial (30), and this appears congruent with our observations for arms-only rowing. The sharp and dramatic increase in respiratory frequency at 400 m is in accordance with previous studies noting that ventilation during upper body exercise is achieved primarily via increases in respiratory frequency (34). During lower body exercise, tidal volume tends to plateau at 50–60% of vital capacity (4), and yet, our participant exhibited an increase in respiratory frequency at 400 m when tidal volume was only 38% of vital capacity. It is likely that the twofold increase in respiratory frequency resulted from a necessity to coordinate respiratory rhythm with the frequency of the power stroke, and these data reinforce the notion that, during rowing, ventilation is subordinate to locomotor drive (30).

The present findings have potential implications for individuals with SCI. Exercise-induced diaphragm fatigue may limit endurance performance via reflex effects of breathing on vascular function (12). A fatigue-induced metaboreflex would be expected to cause sympathoexcitation and vasoconstriction of exercising limb vasculature, thereby reducing limb blood flow and accelerating locomotor muscle fatigue. This, in turn, may limit endurance performance via alterations in effort perceptions and central motor output to the upper limbs. A further consideration is that a reduction in neuromuscular efficiency of the diaphragm during exercise (i.e., increased ratio of ΔP_{di} -to-EMG_{di}) may impact negatively on exertional breathlessness and endurance performance. In healthy, able-bodied subjects, neuromuscular uncoupling of the diaphragm during exercise is unlikely to contribute to exertional breathlessness (1). In clinical populations with diaphragm weakness/dysfunction, however, neuromuscular uncoupling of the diaphragm has been mechanistically linked to exertional breathlessness (19). This may be pertinent for individuals with cervical or high-thoracic

SCI, who often exhibit chronic symptoms resulting from pulmonary dysfunction (8). Finally, in addition to lung volume restriction, many individuals with tetraplegia exhibit airway obstruction resulting from overriding cholinergic airway tone (29), which exacerbates sensations of breathlessness. The present findings, therefore, provide a physiological rationale for the further exploration of dyspnea and neuromuscular uncoupling in SCI.

In conclusion, this case report provides the first objective evidence of exercise-induced diaphragm fatigue in SCI. In combination with other recent findings (35, 36), our data support the notion that the work incurred by the diaphragm during high-intensity upper body exercise is a principal determinant of exercise-induced diaphragm fatigue. Moreover, the decrease in diaphragm neuromuscular efficiency noted during upper body exercise suggests that factors other than ventilation (e.g., posture and locomotion) must also contribute to the fatigue. These findings extend our understanding of the limits of physiological function in SCI and may have important implications for individuals who exercise using the upper limbs.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

N.B.T., C.R.W., and L.M.R. conceived and designed research; N.B.T., T.R.A., and L.M.R. performed experiments; N.B.T. analyzed data; N.B.T., T.R.A., and L.M.R. interpreted results of experiments; N.B.T. prepared figures; N.B.T. drafted manuscript; N.B.T., C.R.W., and L.M.R. edited and revised manuscript; N.B.T., T.R.A., C.R.W., and L.M.R. approved final version of manuscript.

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