Neural Respiratory Drive in Patients with COPD during Exercise Tests

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Key Words
Chronic obstructive pulmonary disease • Diaphragm • Neural respiratory drive • Respiratory muscle function

Abstract
Background: It is unknown whether neural drive is comparable in constant rate and incremental exercise tests. Few data have previously been available to address this question because of the lack of reliable methods to assess neural respiratory drive in patients with chronic obstructive pulmonary disease (COPD). Objectives: The aims of this study are to determine whether neural respiratory drive during constant rate exercise differs from that during incremental exercise and to determine whether neural respiratory drive was maximal at the end of exhaustive exercise tests. Methods: We studied sixteen patients with moderate-severe COPD (mean ± SD FEV1, 29 ± 10%). Both diaphragmatic electromyogram (EMG) and transdiaphragmatic pressure were recorded with a combined multipair electrode balloon catheter during incremental and constant (80% of maximal oxygen consumption derived from a prior incremental exercise test) treadmill exercise. Minute ventilation and oxygen uptake were also measured. Results: Root mean square (RMS) of the diaphragmatic EMG increased gradually without a plateau during incremental exercise, whereas the RMS increased initially and reached a plateau during constant work rate exercise. The RMS of the diaphragmatic EMG at the end of exercise was similar for both incremental and constant work rate exercise (176 ± 42 μV vs. 184 ± 39 μV); these values were 70 and 73% of maximal values recorded over the study. Conclusions: The pattern of increase in neural respiratory drive during incremental exercise is different to that observed during constant work rate exercise, but both exercise protocols are terminated when the patients achieve a similar but submaximal drive.

Introduction

In patients with chronic obstructive pulmonary disease (COPD), it has previously been shown that transdiaphragmatic pressure (Pdi) increases initially and reaches a plateau during constant work rate cycle ergometry or treadmill exercise, and that diaphragm fatigue does not develop [1–3]. It is, however, difficult to extrapolate the findings of these studies to levels of neural respiratory drive during exercise in COPD because of the lack of reliable methods to measure neural respiratory drive in this patient population. Occlusion pressure (P0.1), tidal volume and Pdi [3, 4] have limitations as measures of neural respiratory drive in COPD because disordered ventilatory mechanics, the development of intrinsic positive end
Different research groups patients with COPD reached a plateau during constant treadmill exercise in phragmatic EMG and ventilation increased initially and contrast, we and others have shown that both the dia-

rathoracic respiratory drive in normal subjects is a more reliable method that has been recently used to assess neu-


Neural respiratory drive has been studied by record-

ing the diaphragmatic EMG during exhaustive incre-

mental bicycle exercise in COPD [10], and has been found to increase progressively throughout the exercise test. In contrast, we and others have shown that both the dia-

phragmatic EMG and ventilation increased initially and reached a plateau during constant treadmill exercise in patients with COPD [9, 12]. Inconsistent results from dif-

ferent research groups [9, 10] may be because of different exercise protocols. We therefore hypothesized that neural respiratory drive during constant rate exercise may differ from that during incremental exercise. We also deter-

mine whether neural respiratory drive was maximal at the end of exhaustive exercise tests.

Methods

Sixteen clinically stable patients with moderately severe COPD were studied. All patients were free of clinically significant coex-

istent disease that might affect neural respiratory drive, and had not had an exacerbation of COPD within the preceding month. Patients with orthopedic or cardiovascular contraindications to exercise were excluded. Usual medications including broncho-

dilators were allowed. Our local ethics committee approved the study, and all subjects gave their informed consent. Anthropo-

metric data are shown in Table 1.

The diaphragmatic EMG was recorded from a multipair esophageal electrode catheter without (6 subjects) and with gas-

tric and esophageal balloons (10 subjects). The size, material and configuration of electrode were the same for both catheters except that the combined esophageal-gastric balloon electrode catheter had, additionally, two balloons mounted on it. The diameter of the catheter was 2.8 mm. The most proximal coil (coil 0) was con-

nected to the ground and was 2 cm away from coil 1. Coils 1–9 were designed for recording and were 1 cm in length with a gap of 1 mm between adjacent coils. Five consecutive recording pairs were formed with an interelectrode distance of 3.4 mm within a pair. Two balloons, 7 cm in length and 6 mm in diameter, were mounted on the catheter 1 cm proximal to coil 0 and 2 cm distal to coil 9, and the distance between the two balloons was 15.8 cm. The proximal balloon was used for measurement of esophageal pressure and the distal balloon for gastric pressure. The diameter of the inner lumen of the two tubes for pressure measurement was 1.0 mm. The combined electrode-balloon catheter system was passed pernally. Electrode 5 was positioned close to the dia-

phragm based on the amplitude of signals, with a large EMG sig-

nal from pairs 1 and 5 (fig. 1) and the smallest EMG signal from pair 3. The EMG signals were band-pass filtered between 20 and 1,000 Hz and amplified (bio-amplifier Model RA-8, Yinghui, Guangzhou, China).

Esophageal Pressure and Gastric Pressure

When electrode coil 5 was located close to the diaphragm, the two balloons were positioned at the mid-esophagus and stomach, respectively. Satisfactory placement of the balloons was further confirmed by a sniff maneuver and pushing the abdomen. When the catheter was satisfactorily placed, the balloon-electrode cath-

ter was securely fixed at the nose. The esophageal balloon filled with 0.8 ml air and the gastric balloon filled with 1.0 ml air. Both esophageal pressure (Pes) and gastric pressure (Pga) were mea-

sured with a pressure transducer and a bio-amplifier with a band pass filter of DC to 30 Hz.

Study Protocol

Each subject visited the laboratory twice. The purpose of the first visit was to allow subjects to practice the inspiratory maneu-

vers described below, and to determine maximal oxygen con-

sumption during exhaustive incremental treadmill exercise. Lung function tests were also performed on the first visit. The second visit took place within a week of the first visit, and on this occa-

sion, an esophageal catheter was placed as described above.

In order to normalize the diaphragmatic EMG to a maximum signal, the diaphragmatic EMG was recorded during the follow-

ing maneuvers: maximum sniff efforts from functional residual capacity (FRC), maximal isovolumetric contraction at FRC, and maximal inspiration from FRC to total lung capacity (TLC). Each maneuver was repeated until three reproducible values were ob-

tained, and there was a 1-min period of rest between maneuvers. After maximal EMG and pressure were measured, subjects were asked to perform both incremental and constant treadmill exer-

cise protocols with a gap of 1 h between the two protocols. The protocol performed first was chosen at random. The incremental treadmill exercise protocol consisted of 3 min standing still, fol-

lowed by an increase in the workload every 3 min by increasing the speed by 0.5 km/h and the slope by 2% until intolerable dys-

pnoea or exhaustion occurred. The constant work rate protocol was performed at 80% of maximal oxygen consumption achieved.

<table>
<thead>
<tr>
<th>Table 1. Anthrometric and lung function data</th>
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<tbody>
<tr>
<td>Age, years</td>
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<td>Gender, male</td>
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<td>Height, cm</td>
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<td>Weight, kg</td>
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<td>BMI</td>
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<td>FEV1, % predicted</td>
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<td>FVC, l</td>
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<td>FEV1/FVC, %</td>
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<tr>
<td>FEV1/FVC, % predicted</td>
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<td>PaCO2, mm Hg</td>
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<td>PaCO2, mm Hg</td>
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</table>

2 Respiration Luo/Li/Jolley/Wu/Steier/Moxham/Zhong
in the incremental exercise test until intolerable dyspnoea or exhaustion developed. Maximal inspiratory maneuvers were performed every minute during exercise to obtain maximal EMG during exercise.

Respiratory pressures and the diaphragmatic EMG were recorded continuously using the Powerlab recording system (ADInstruments, Castle Hill, N.S.W., Australia) during both incremental and constant rate exercise. SaO₂ was measured by pulse oximetry (Capnocheck Plus 9004-001, BCI, Waukesha, Wisc., USA). Metabolic data were recorded with an automated exercise testing system (AD Instruments). Symptoms of breathlessness and leg fatigue were scored with the Borg scale at rest and at the end of each exercise.

Data Analysis and Presentation
The diaphragmatic EMG reported was that from the electrode pair with the largest EMG amplitude for each breath. The largest value from different maneuvers including inspiratory capacity during exercise was taken as the maximal EMG and was used to standardize data during exercise. Data are presented as mean ± SD. t tests and one way analysis of variance were used to determine differences. Significance was accepted at p < 0.05.

Results
The mean maximal root mean square (RMS) of the diaphragmatic EMG (RMS EMGdi) at rest was 196 ± 53 μV. The maximal value at rest was usually (11 of 16 patients) obtained from maximal inspiration to TLC from FRC (TLC maneuver). There were four subjects whose maximal EMG at rest was from sniff maneuver and only one subject whose maximal RMS was from maximal isometric contraction at FRC. Maximal Pdi was usually recorded from a sniff maneuver, and the Pdi from the sniff maneuver (84.1 ± 14.4 cm H₂O) was significantly larger than that from maximal isometric contraction at FRC (77.6 ± 27.9 cm H₂O; p < 0.05). The maximal RMS EMGdi recorded at any point during the study, including maximal inspiratory capacity maneuvers during exercise, was 250 ± 57 μV.

The diaphragmatic EMG could be reliably recorded during both incremental and constant exercise. The pair which recorded the maximal EMG at rest was usually the same as that which recorded the maximal EMG at the end of exercise (fig. 2). All patients stopped exercise because of extreme breathlessness or both breathlessness and leg fatigue during both incremental and constant treadmill exercise, except one (COPD 6) who reported that leg fatigue was the main cause of termination of incremental exercise.

Incremental Exercise
RMS EMGdi increased gradually without a plateau during incremental exercise. RMS EMGdi at the end of
exercise was significantly greater than that at rest (176 ± 42 µV vs. 44 ± 15 µV, p < 0.001) and represented 70% of maximal RMS EMGdi measured during the study (EMGdi%max = 70%; fig. 3). Minute ventilation (VE), oxygen uptake (VO2) and Pdi were also significantly increased during exercise (fig. 4). VE, VO2 and Pdi at the end of exercise were 32.3 ± 9.6 l/min, 20.0 ± 7.0 ml·kg⁻¹·min⁻¹ and 19.7 ± 10.5 cm H2O, and were significantly larger than those at the beginning of the test (10.8 ± 2.6 l/min, 4.6 ± 1.2 ml·kg⁻¹·min⁻¹ and 8.0 ± 1.9 cm H2O, respectively). Pdi at the end of exercise became significantly smaller rather than larger than Pes because Pga swings gradually became negative during inspiration. Borg breathlessness scores (7.0 ± 2.7) were not significantly higher than leg fatigue scores (5.7 ± 3.8) at the end of incremental exercise (p > 0.05).

**Constant Work Rate Exercise**

RMS EMGdi at the end of exercise (184 ± 39 µV) was significantly larger than that at rest (43 ± 17 µV) and represented about 73% of maximal RMS EMGdi. VE, VO2
and Pdi were 31.3 ± 8.8 l/min, 19.2 ± 7.1 ml·kg⁻¹·min⁻¹ and 17.8 ± 8.3 cm H₂O at the end of exercise and were significantly larger than those at the beginning of exercise (10.7 ± 2.5 l/min, 4.6 ± 1.2 ml·kg⁻¹·min⁻¹ and 7.8 ± 2.6 cm H₂O, respectively). RMS EMGdi, Pes, Pdi and VE increased initially and reached a plateau during the constant work rate exercise tests (fig. 3, 4).

Comparison of Neural Drive, Pdi and Ventilatory Responses during Constant Work Rate and Incremental Exercise
RMS EMGdi, Pes, VE and VO₂ reached a plateau during constant exercise, as shown in figures 3 and 4, whereas they did not achieve a plateau during incremental exercise. Pdi reached a plateau during both incremental and constant work rate exercise tests. The RMS EMGdi, Pdi, VE, VO₂, dyspnoea Borg scores and leg fatigue scores were similar at the end of incremental and constant work rate exercise (table 2). Pga during expiration was 1.2 ± 4.0 cm H₂O and 1.7 ± 4.5 cm H₂O at the beginning of exercise and increased gradually over the exercise period (fig. 2, 5). Pga at expiration at the end of exercise was similar for both tests (32.3 ± 19.1 vs. 31.5 ± 19.2 cm H₂O, p > 0.05; table 2).

Discussion
This study demonstrates that the diaphragmatic EMG increases progressively over the incremental treadmill exercise test, without a plateau, but the diaphragmatic EMG increases initially and reaches a plateau during con-
stant work rate treadmill exercise. Although there was a difference in the pattern of increase of the diaphragmatic EMG during the two exercise protocols, the RMS EMG at the end of incremental exercise is similar to that at the end of constant work rate exercise, indicating that both exercise protocols can generate equal but submaximal neural drive.

Critique of the Method

To assess neural respiratory drive during exercise, accurate recording of the diaphragmatic EMG is critical [8, 13]. Our electrode catheter had a very small gap between the electrodes allowing accurate tracking of the movement of the diaphragm during exercise where dynamic hyperinflation is expected to occur [4, 14]. We standardized the diaphragmatic EMG during exercise by the maximal EMG obtained over the study including maximal inspiration maneuvers during rest and exercise. Our experience is that maximal diaphragm activity can be recorded from a maximal maneuver at rest for normal trained subjects. It can be difficult for patients with COPD to perform truly maximal inspirations. Even though highly reproducible measurements were obtained in the present study, it is possible that values could still be submaximal in some patients [15].

Significance of the Findings

The results of this study indicate that either a constant work rate exercise or incremental exercise protocol may be used to study the maximum level of diaphragmatic EMG activity during exercise, providing that the patients exercise to exhaustion, and are primarily limited by breathlessness. The pattern of Pes and Pdi increases were different for the incremental and constant work rate exercise tests. For example, Pes increased in a curvilinear fashion without a plateau during the incremental exercise test, whereas it increased more rapidly initially and then reached a plateau during the constant work rate exercise protocol. The rate of increase in Pdi during the constant work rate exercise test was initially also more rapid than during the incremental exercise test, but a similar plateau was reached (constant work rate) or approached (incremental test) in both tests. Theoretically, the Pdi plateau could be due to respiratory muscle fatigue which could limit further increases in Pdi. However, low frequency diaphragm fatigue does not occur with exhaustive exercise in COPD [2, 16]. Plateauing of Pdi during exercise is sometimes attributed to dynamic hyperinflation [10, 16, 17] through the known length-tension relationship of the diaphragm. If dynamic hyperinflation is an important factor contributing to the reduction of Pdi, as suggested by Sinderby et al. [10], Pes would also be affected because dynamic hyperinflation causes a disproportionate reduction in Pes compared with Pdi [18]. However, increases of Pes during exercise were larger than those of Pdi in our

Table 2. Neural drive, breathlessness scores and ventilatory response at the end of incremental and constant exercise

<table>
<thead>
<tr>
<th></th>
<th>Incremental</th>
<th>Constant</th>
<th>p value</th>
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<tbody>
<tr>
<td>RMS, μV</td>
<td>176 ± 42</td>
<td>184 ± 39</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pdi, cm H2O</td>
<td>19.7 ± 10.5</td>
<td>17.8 ± 8.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pes, cm H2O</td>
<td>45.4 ± 19.9</td>
<td>41.3 ± 21.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pga (expiration), cm H2O</td>
<td>32.5 ± 19.1</td>
<td>31.5 ± 19.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VO2, ml·kg⁻¹·min⁻¹</td>
<td>20.0 ± 7.0</td>
<td>19.2 ± 7.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>32.3 ± 9.6</td>
<td>31.3 ± 8.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Respiratory rate, b/min</td>
<td>31 ± 6</td>
<td>30 ± 6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>135 ± 22</td>
<td>134 ± 23</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Dyspnea, Borg</td>
<td>7.0 ± 2.7</td>
<td>7.7 ± 2.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Leg fatigue, Borg</td>
<td>5.7 ± 3.8</td>
<td>6.4 ± 3.9</td>
<td>&gt;0.05</td>
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</table>

Fig. 5. Gastric pressure during expiration (Pga-exp). Pga-exp increased during both exercise tests. Pga-exp at the end of exercise was 26 and 18 times larger than at the beginning of exercise for incremental and constant exercise tests, respectively.
study. Abdominal muscle recruitment, serving as a form of inspiratory assist [3], may also lead to reductions in the Pdi as it is derived as Pga – Pes. In the present study, we found that Pga during expiration increased 26- and 18-fold over the incremental and constant exercise, respectively. Failure to increase Pdi during exercise was largely due to contraction of abdominal muscle during expiration, with subsequent relaxation during inspiration (fig. 2), which caused negative rather than positive swings of Pga during inspiration. These observations suggest that inspiratory muscle recruitment, especially abdominal muscle activity during expiration, may have been the more important factor limiting increases in Pdi in the present study. Indeed, Ninane et al. [19] demonstrated that the transversus abdominis was usually active during expiration and relaxed during inspiration in patients with COPD even at rest, indicating a reduced Pdi at least partially because of abdominal muscle activity during expiration causing Pga to become negative during the relaxation associated with inspiration.

The similarity of neural drive at the end of constant work rate and incremental exercise mirrors findings in a previous study which showed that oxygen uptake at the end of constant work rate exercise at high load was similar to that at the end of incremental exercise [20]. Although both incremental and constant work rate exercise are frequently used in clinical practice, constant work rate exercise is generally considered to be more useful when assessing the effect of treatment in patients with COPD [21]. The fact that neural respiratory drive increases more steeply at the beginning of exercise and that subjects are exposed to high neural respiratory drive for longer periods during the constant work rate compared with the incremental exercise test, as shown in figure 3, may help to explain why a previous study showed that constant work rate exercise was more sensitive in detecting the effect of oxitropium bromide on exercise performance [21].

This is the first study to directly compare neural respiratory drive during incremental and constant work rate treadmill exercise, and to demonstrate a similar, submaximal neural respiratory drive at the end of both protocols in patients with COPD. The observation that patients stop at the same submaximal level of neural respiratory drive is interesting. If, as has been suggested, breathlessness is related to the sense of inspiratory muscle effort [22], one explanation for our observation is that patients stop exercising at the degree of breathlessness at which their symptoms become unpleasant, which is at a submaximal level of neural respiratory drive. Alternatively, submaximal neural respiratory drive could be due to central inhibition, which has been used to explain the observation that diaphragm fatigue is not associated with exhaustive exercise in patients with COPD [2]. The fact that there was a plateau of the diaphragmatic EMG during constant exercise may support the hypothesis. Indeed, neural inhibition is a common physiological phenomena under an increased respiratory load in both animals and humans. Bellemare and Bigland-Ritchie [23] reported that a reduced diaphragm force induced by increased inspiratory load was mainly because of central inhibition. An animal study has also shown that neural respiratory drive is always submaximal even under high load [24]. Furthermore, Sassoon et al. have shown that application of an inspiratory load in rabbits led to respiratory failure and inhibition of the neural drive rather than diaphragm fatigue [25]. Although Sinderby et al. [10] claimed that inhibition of neural respiratory drive did not exist in patients with COPD, their conclusion was based on data derived from incremental exercise which terminated when the diaphragmatic EMG just reached the level of plateau for constant exercise. Because exercise was able to be sustained after neural drive first reached a plateau, we believed that factors other than the level of neural respiratory drive determine the point at which patients stop exercise.

In conclusion, exhaustive constant work rate and incremental exercise protocols can generate similar but submaximal levels of neural respiratory drive in COPD. Patients may not reach maximum levels of neural respiratory drive because they stop exercising when breathlessness becomes unpleasant, at submaximal levels of drive. The diaphragmatic EMG is a more reliable measure of neural respiratory drive than Pdi in both constant work rate and incremental treadmill exercise protocols because of interference by abdominal muscle activity.

Acknowledgments

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