The effect of learning on ventilatory responses to inspiratory threshold loading in COPD

Gavin A. Sturdy\textsuperscript{a,b}, David R. Hillman\textsuperscript{a}, Daniel J. Green\textsuperscript{b}, Sue C. Jenkins\textsuperscript{c,d}, Nola M. Cecins\textsuperscript{c,d}, Peter R. Eastwood\textsuperscript{a,b,*}

\textsuperscript{a}Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia
\textsuperscript{b}Department of Human Movement and Exercise Science, University of Western Australia, Nedlands WA 6009, Australia
\textsuperscript{c}Department of Physiotherapy, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia
\textsuperscript{d}School of Physiotherapy, Curtin University of Technology, Bentley, WA 6102, Australia

Received 29 December 2002; accepted 14 July 2003

Summary

Background: Progressive threshold loading (PTL) is a common test of respiratory muscle endurance. Healthy naive subjects improve endurance with successive exposures to PTL by altering their breathing responses, thus necessitating a familiarization period before reproducible measures can be obtained. This study sought to determine whether a similar "learning effect" is evident in patients with COPD, and what the mechanism of any such effect may be.

Methods: Ten subjects with COPD (FEV\textsubscript{1} 34±13% predicted) underwent PTL on four occasions (424 h apart). During PTL measurements were obtained of breathing pattern and maximum threshold pressure (P\textsubscript{thmax}) achieved. Maximum inspiratory pressure (P\textsubscript{Imax}) was measured on each occasion.

Results: Over the four tests P\textsubscript{Imax} improved by 21\pm16\% (P<0.05) and P\textsubscript{thmax} by 32\pm21\% (P<0.05) with a plateau in these measures achieved by test three. P\textsubscript{thmax}/P\textsubscript{Imax} was unchanged, being 61\pm11\% at test one and 67\pm12\% at test four. In contrast to healthy subjects, PTL was not associated with increased expiratory time or decreased end-expiratory lung volume.

Conclusions: In contrast to P\textsubscript{Imax} and P\textsubscript{thmax}, which changed with successive tests, a single measure of the ratio P\textsubscript{thmax}/P\textsubscript{Imax} may present a useful guide to the endurance capacity of the respiratory muscles in patients with COPD.

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KEYWORDS

Inspiratory muscles; Respiratory muscle strength; Respiratory muscle endurance

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have impaired respiratory muscle function, which contributes significantly to their overall disease burden. Usually function is defined in terms of muscle strength and endurance. Measurement of respiratory muscle strength is a well-established technique\textsuperscript{1} and normative values are available. However this is not the case for measurement of respiratory muscle endurance with many different methods (application of external resistive, elastic and threshold loads) and protocols (constant versus incremental) currently in use. One method gaining popularity is based on work by Martyn et al.,\textsuperscript{2} where an inspiratory threshold load...
is progressively increased until the subject is unable to continue, the point of “task failure”. The load achieved at task failure has been used to define the endurance capacity of the inspiratory muscles.

We have previously shown in healthy naïve subjects that there is a systematic increase in endurance over the first few exposures to progressive threshold loading, following which highly reproducible measurements are obtained. The mechanism of this increase appeared to be a change in breathing pattern which served to minimize the sensation of respiratory load and increase recovery time for the inspiratory muscles between efforts Recognition of such a “learning effect” is important, as the potential for improvement in respiratory muscle strength or endurance with training or treatment could be overstated if its existence was unrecognized.

It is unclear, however, whether such a learning period is also required when measuring respiratory muscle endurance with progressive threshold loading in patients with COPD, or what the mechanism of any such increase may be. The literature is conflicting regarding the reproducibility of such tests in this patient group with some studies reporting a learning effect and others finding no such effect. Recently, we utilized progressive threshold loading in subjects with moderate-to-severe COPD to evaluate the effects of a program of respiratory muscle training and noted an increase in performance during a familiarization period where subjects repeated the task on multiple days. In this paper we present an analysis of the mechanisms underlying these changes in performance in this patient group.

**Methods**

**Subjects**

Ten out-patients with COPD (8 male) who were scheduled to commence a pulmonary rehabilitation program participated in this study. All were naïve to the threshold loading task. Subjects were required to be less than 75 years old, have moderate-to-severe airflow obstruction (FEV1 <65% predicted), minimal airway reversibility, be on stable drug therapy and have no significant coexisting disease which could affect their ability to perform the tests of respiratory muscle function. Eight subjects were ex-smokers, one was a non-smoker and one was a current smoker. Anthropometric measurements and lung function data of the subjects are shown in Table 1. The study was approved by the Human Research Ethics Committee of Sir Charles Gairdner Hospital and written informed consent was obtained prior to participation.

**Table 1** Subject characteristics (n = 10)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64 ± 7</td>
<td>49–74</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 ± 6</td>
<td>161–183</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77 ± 12</td>
<td>62–100</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 ± 4.2</td>
<td>20–33</td>
</tr>
<tr>
<td>TLC, l</td>
<td>7.4 ± 1.6</td>
<td>4.9–9.3</td>
</tr>
<tr>
<td>% predicted</td>
<td>119 ± 24</td>
<td>93–147</td>
</tr>
<tr>
<td>FVC, l</td>
<td>3 ± 1</td>
<td>1.8–4.7</td>
</tr>
<tr>
<td>% predicted</td>
<td>80 ± 25</td>
<td>45–126</td>
</tr>
<tr>
<td>RV, l</td>
<td>4.2 ± 1.5</td>
<td>2.4–6.1</td>
</tr>
<tr>
<td>% predicted</td>
<td>187 ± 68</td>
<td>90–281</td>
</tr>
<tr>
<td>FEV1₁, l</td>
<td>0.93 ± 0.31</td>
<td>0.53–1.36</td>
</tr>
<tr>
<td>% predicted</td>
<td>34 ± 12</td>
<td>19–51</td>
</tr>
<tr>
<td>DLCO, mm/min/mmHg</td>
<td>12.3 ± 4.6</td>
<td>5.6–20.3</td>
</tr>
<tr>
<td>% predicted</td>
<td>55 ± 20</td>
<td>24–85</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. BMI, body mass index; TLC, total lung capacity; FVC, forced vital capacity; RV, residual volume; FEV1₁, forced expiratory volume in one second; DLCO, carbon monoxide diffusing capacity.

**Study design**

Over a 2-week period resting pulmonary function was measured and four separate tests (each >24 h apart) of respiratory muscle strength and endurance were performed. Subjects were instructed to take their usual medications as scheduled on each day of testing to control for any potential drug effects on respiratory muscle function. All measures of respiratory muscle function were performed by the same researcher at the same time of day.

**Measurements**

**Resting pulmonary function.** Measurements were obtained of total lung capacity (body plethysmograph, Collins Inc, Braintree, Ma), forced vital capacity, residual volume (RV), residual volume; FEV₁, forced expiratory volume in one second; DLCO, carbon monoxide diffusing capacity.

**Respiratory muscle strength.** Respiratory muscle strength was assessed before and immediately after (approximately 60s) each test of respiratory muscle endurance (see below) by measurement of
the peak pressure developed during maximal inspiratory efforts ($P_{\text{Imax}}$) at functional residual capacity (FRC) against an occluded mouthpiece. Measurements were performed while subjects breathed on a flanged mouthpiece attached to the same device as used to assess respiratory muscle endurance (below). A constant FRC was ensured for all efforts by continuous monitoring of end-expiratory lung volume via a summed Respitrace signal (see below). On each occasion measurements were repeated until three peak pressures were obtained within 5% of each other. The highest of these was recorded as $P_{\text{Imax}}$.

Respiratory muscle endurance. Respiratory muscle endurance was assessed using progressive inspiratory threshold loading. Subjects breathed through a pneumotachograph connected in series to a modified inspiratory threshold valve, which required the development of a negative threshold pressure ($P_{\text{th}}$) before inspiratory airflow was achieved. Seat and mouthpiece height were determined on the first testing occasion and maintained constant for all subsequent tests. No instructions were given to the subject regarding the breathing pattern to adopt during tests. Each minute, $P_{\text{th}}$ was increased by adding weights to the valve until the subject was no longer able to sustain the task despite strong encouragement (task failure). The magnitude of each load increment was identical for all pre- and post-training tests, being equivalent to approximately 10% of the $P_{\text{Imax}}$ measured on the first testing occasion.

During each test breath-by-breath measurements were obtained of $P_{\text{th}}$ (Microswitich, Honeywell, Freeport, IL), inspiratory flow and tidal volume ($V_t$, Fleisch pneumotachograph and differential pressure transducer, Validyne, Northbridge, CA). Arterial $O_2$ saturation ($\text{SaO}_2$, finger probe, pulse oximeter; Ohmeda 3700, Boulder, CO) and transcutaneous $PCO_2$, ($P_{tc}CO_2$, TCM3, Radiometer, Copenhagen) were monitored throughout the test. Measurements of $P_{tc}CO_2$ were calibrated to a resting arterial sample obtained prior to the final study. Inspiratory time ($T_i$) and expiratory time ($T_e$) were derived from the pressure signal. Rib cage and abdominal motion were continuously monitored by respiratory inductance pneumography (Respitrace, Ardsley, NY) with the transducers at the level of the nipples and umbilicus respectively. These signals were calibrated by an isovolume manoeuvre and electronically summed to provide a measure of volume displacement. Changes in end-expiratory lung volume during the test were determined by referencing the summed Respitrace signal to measurements at FRC and RV obtained before and after loaded breathing. End-expiratory lung volume was expressed as a percentage of expiratory reserve volume (RV = 0%, FRC = 100%). We have previously validated this method of measuring end-expiratory lung volume in healthy subjects against measurements obtained using body plethysmography. All data were recorded on a 12-channel direct writing polygraph (Graphtec Corp. Yokohama, Japan).

During the final 10 s of each minute the sensation of dyspnea and perception of effort were estimated using a 10-point Borg scale. On entry to the study, subjects were instructed in the use of the scales. Prior to beginning each test, they were reminded of the difference between "respiratory discomfort" (perception of dyspnea) and "effort required to take a breath" (perception of effort). At the end of each minute cards showing a Borg scale for "breathlessness" and "effort" were held in front of the subject who was asked to point to the number and/or descriptor that best corresponded to their sensations at the time.

Statistical analyses

In each test inspiratory load was expressed as a percentage of the $P_{\text{Imax}}$ achieved on that testing occasion ($\%P_{\text{Imax}}$). Maximum $P_{\text{th}}$ ($P_{\text{Imax}}$) was defined as the inspiratory pressure developed at the highest load sustained for >30 s. While inspiratory load was increased by approximately 10% of $P_{\text{Imax}}$ for each subject, the number of data points obtained during a test varied between subjects according to the number of increments achieved. Therefore, to facilitate comparisons between subjects, data obtained during a test were averaged into bins corresponding to increments in $P_{\text{Imax}}$ of between 12.5% and 25%.

One-way repeated measures ANOVA was used to compare test-to-test changes in measures of respiratory muscle function. Two-way ANOVA with repeated measures was used to evaluate differences in $P_{\text{Imax}}$ before and after each of the loaded breathing tests, and to examine the between-test and between-load differences for each respiratory variable. Post hoc analyses were performed using a Tukey correction. For the purpose of clarity, error bars describing data points in Figs. 2 and 3 are shown as the mean ± SEM; otherwise all data are reported as mean ± SD; $P < 0.05$ was considered significant.

Results

There was no significant difference between $P_{\text{Imax}}$ measured before and immediately after any of the
four progressive threshold loading tests (Table 2); accordingly the highest pre- or post-testing value was used to represent the daily $P_{\text{Imax}}$. The end-expiratory lung volume at which the maximal inspiratory efforts were initiated was closely monitored, and was found to be similar on each testing occasion (expiratory reserve volume = 45 ± 10% of vital capacity).

$P_{\text{Imax}}$ increased by 21 ± 16% ($P < 0.05$) over the four testing days, while $P_{\text{thmax}}$ increased by 33 ± 21% ($P < 0.05$) (Table 2 and Fig. 1A). All of the improvement occurred over the first three exposures, as $P_{\text{Imax}}$ and $P_{\text{thmax}}$ were not significantly different between tests three and four (64 ± 21 and 66 ± 19 cmH$_2$O, 44 ± 18 and 45 ± 19 cmH$_2$O, respectively). The time taken to complete each test of progressive threshold loading increased from 6.4 ± 1.6 min at test one to 8.3 ± 1.9 min at test four ($P < 0.05$). The ratio $P_{\text{thmax}}/P_{\text{Imax}}$ was not significantly different between tests, being 61 ± 11% at test one and 67 ± 12% at test four (Fig. 1B).

Systematic changes in breathing pattern were observed both with increasing inspiratory load and from test one to test four (Figs. 2 and 3). Within each test minute ventilation ($V_e$) increased up to

### Table 2 Test-to-test changes in maximum inspiratory pressure ($P_{\text{Imax}}$) and maximum threshold pressure ($P_{\text{thmax}}$)

| Subject | Test 1 | | | Test 2 | | | Test 3 | | | Test 4 |
|---------|-------|---|---|-------|---|---|-------|---|---|-------|---|---|-------|---|---|-------|---|---|
|         | $P_{\text{Imax}}$ | $P_{\text{thmax}}$ | $P_{\text{Imax}}$ | $P_{\text{thmax}}$ | $P_{\text{Imax}}$ | $P_{\text{thmax}}$ | $P_{\text{Imax}}$ | $P_{\text{thmax}}$ |
|         | pre  | post | pre  | post | pre  | post | pre  | post |
| 1       | 66   | 56   | 42   | 61   | 66   | 35   | 64   | 66   | 42   | 74   | 74   | 50   |
| 2       | 66   | 56   | 41   | 59   | 52   | 42   | 67   | 51   | 47   | 65   | 71   | 47   |
| 3       | 39   | 49   | 20   | 67   | 59   | 37   | 66   | 60   | 41   | 66   | 72   | 32   |
| 4       | 33   | 55   | 36   | 39   | 41   | 31   | 63   | 60   | 45   | 60   | 49   | 45   |
| 5       | 49   | 52   | 36   | 55   | 59   | 39   | 59   | 57   | 39   | 65   | 59   | 44   |
| 6       | 61   | 64   | 49   | 69   | 68   | 47   | 87   | 99   | 81   | 91   | 86   | 79   |
| 7       | 97   | 89   | 71   | 98   | 97   | 73   | 96   | 93   | 64   | 91   | 93   | 72   |
| 8       | 21   | 27   | 13   | 23   | 26   | 19   | 30   | 33   | 19   | 33   | 35   | 18   |
| 9       | 47   | 46   | 26   | 59   | 45   | 40   | 57   | 50   | 40   | 53   | 55   | 41   |
| 10      | 33   | 25   | 20   | 36   | 37   | 20   | 38   | 33   | 21   | 40   | 33   | 25   |
| Mean    | 51   | 52   | 35   | 57   | 55   | 38   | 63   | 60   | 44   | 64   | 63   | 45   |
| SD      | 22   | 18   | 17   | 21   | 20   | 15   | 20   | 22   | 18   | 19   | 20   | 19   |

All values are expressed in cmH$_2$O. Measurements of $P_{\text{Imax}}$ were obtained before (pre) and immediately after (post) each test of progressive threshold loading.

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**Figure 1** Change in respiratory muscle strength (maximal inspiratory pressure, $P_{\text{Imax}}$), endurance (maximum threshold pressure, $P_{\text{thmax}}$) and the ratio $P_{\text{thmax}}/P_{\text{Imax}}$ from four successive testing occasions (each ≥ 24 h apart). $n = 10$, error bars ± SD, *$P < 0.05$ compared to test one.
50% $P_{thmax}$ before gradually declining back to baseline levels with further increases in inspiratory load. Breathing frequency (fR) progressively increased with increasing inspiratory load, being primarily responsible for the initial increase in $V_e$. At higher loads the rise in fR was not of sufficient magnitude to offset a fall in $V_t$ and $V_e$ fell as a consequence. Both $T_i$ and $T_e$ fell with increasing inspiratory load, accounting for the increase in fR. $T_e$ decreased out of proportion to $T_i$, so that duty cycle ($T_i/T_{tot}$) systematically increased with increasing inspiratory load. With the decrease in $T_i$ mean inspiratory flow ($V_t/T_i$) increased at lower loads but then decreased in parallel with the fall in $V_t$ at higher loads. Up to an inspiratory load of 50% $P_{thmax}$ there was a marginal increase in $SaO_2$ and fall in $P_{tc}CO_2$. Beyond this workload $SaO_2$ progressively decreased and $P_{tc}CO_2$ increased. Subjects tended to increase end-expiratory lung volume with increasing load. Perception of effort and breathlessness increased with increasing load.

From test to test, at equivalent loads $V_e$ was unchanged and changes in fR remained similar. However within-breath timing changed: $T_i$ significantly decreased ($P<0.05$), $T_e$ tended to increase, hence $T_i/T_{tot}$ decreased ($P<0.05$). $V_t/T_i$ increased with successive tests ($P<0.01$), as a consequence of the fall in $T_i$ and a tendency for $V_t$ to increase. The tendency to increase end-expiratory lung volume was less during test four than the preceding tests. There were no consistent differences in the pattern of change of $SaO_2$, $P_{tc}CO_2$ or the sensations of breathlessness or effort with successive tests.

**Discussion**

This study has shown that in subjects with moderate-to-severe COPD there is a systematic increase in $P_{thmax}$ over the first few exposures to progressive threshold loading with reproducible
measurements being obtained by test three. The increase in $P_{\text{thmax}}$ was associated with an increase in $P_{\text{Imax}}$, such that the ratio $P_{\text{thmax}}/P_{\text{Imax}}$ was unchanged from test to test. Compensatory changes in breathing pattern in response to increased inspiratory loads were observed both within and between tests. Changes in inspiratory time, flow and ventilation were similar in direction but smaller in magnitude than those we have previously reported in healthy subjects. However the presence of airflow obstruction appears to preclude the capacity to increase $T_e$ and decrease end-expiratory lung volume with increasing load which are important compensatory strategies employed by healthy subjects.

Controversy exists as to whether a familiarization period is required when testing respiratory muscle strength and endurance in patients with COPD, and, if required, how long this familiarization period should be. The data in the present study indicates that at least two familiarization tests are required before reproducible measurements of $P_{\text{Imax}}$ and $P_{\text{thmax}}$ can be obtained. While such a finding is in agreement with others who have noted increases in $P_{\text{Imax}}$ and $P_{\text{thmax}}$ with successive tests in similar patients groups, it is in conflict with other reports which have shown no effect of repeated studies on either $P_{\text{Imax}}$ or $P_{\text{thmax}}$. None of these studies have undertaken a detailed analysis of the mechanisms underlying any observed test-to-test changes in performance.

The reasons for these disparate findings are unclear as most have studied patients of similar age and severity of airflow limitation, and have used similar measurement techniques. In the case of $P_{\text{Imax}}$, we chose to have subjects perform maximal inspiratory efforts at FRC rather than RV, which was used in most previous

**Figure 3** Effect of progressively increasing inspiratory threshold load (expressed as % $P_{\text{thmax}}$) on mean inspiratory flow ($V_t/T_i$), end-expiratory lung volume (EELV), expiratory reserve volume (ERV), where 100% ERV = functional residual capacity (FRC), arterial oxygen saturation ($\text{SaO}_2$), transcutaneous CO$_2$ tension ($P_{\text{tcCO}_2}$) and sensation of breathlessness (dyspnea) and effort. Mean data from four successive testing occasions (each $\geqslant 24$ h apart), $n = 10$, error bars $\pm$ SEM. #, test number.
studies. We found that subjects with moderate-to-severe expiratory airflow limitation had difficulty performing multiple measurements of $P_{\text{Imax}}$ at RV as it requires substantial time and effort for the subject to exhale to RV, as well as to recover between attempts. Furthermore, while reflecting the maximal strength generating capacity of the respiratory muscles, our findings suggest that measurement of $P_{\text{Imax}}$ at RV is an inappropriate reference value in patients with moderate-to-severe COPD, as they do not breathe below FRC during progressive threshold loading (see below).

Because of the rapidity of the observed changes, it is unlikely that the improvement in $P_{\text{Imax}}$ with successive tests was a consequence of training-induced increases in inherent muscle contractility. Changes which characterize neuromuscular adaptation with strength training, such as more synchronous motoneuron firing or an increased rate or number of motor units firing, appear to require a more intense training regimen over a longer period of time, being weeks rather than days.16-18 A more likely mechanism is improved co-ordination of those respiratory muscles contributing to the pressure generated and/or to sensory conditioning as a consequence of the repeated exposures to the same task.15,19

Like $P_{\text{Imax}}$, $P_{\text{thmax}}$ systematically improved with repeated tests, reaching a plateau by test three. Systematic changes in breathing pattern were observed during each test (Figs. 2 and 3). $V_t$, $V_e$ and $f_R$ initially increased and then decreased, and $f_R$ progressively increased by virtue of a decrease in both $T_i$ and $T_e$. The decrease in $T_e$, seen in patients with COPD contrasts markedly with a progressive increase in $T_e$ observed in healthy subjects,3,4 an effective strategy by which end-expiratory lung volume is reduced and force generating capacity of the loaded inspiratory muscles optimized. The presence of expiratory airflow limitation in patients with COPD prevents this compensatory strategy from being adopted. This finding indicates that $P_{\text{Imax}}$ should be measured at FRC, reflecting the lung volume at which these patients can generate maximal pressure both at rest and during loaded breathing. It is likely therefore, that the majority of previous studies which have referenced $P_{\text{thmax}}$ to $P_{\text{Imax}}$ developed at RV3-8 will have underestimated the proportion of load-generating capacity achieved by their COPD patients at task failure.

A further consequence of failure to decrease end-expiratory lung volume is that the capacity to increase $V_t$ is constrained, as increases during loading are normally achieved by an increase in end-expiratory lung volume and a decrease in end-expiratory lung volume.3,4 As a result, increases in $V_t$ necessitate a disproportionate increase in $f_R$. In healthy individuals, for any given load successive tests are accompanied by a decrease in $T_i$ and increase in $V_e$ so that $V_t/T_i$ increases.3,4 A increasing $V_t/T_i$ is a particularly effective strategy for dealing with threshold loads where, once the threshold pressure is achieved, flow is independent of pressure. Patients with COPD also decreased $T_i$ and increased $V_t$; however, the magnitude of these changes was substantially less than in healthy individuals as a result of constraints in their capacity to increase $V_t$. This constraint in breathing pattern may be responsible for the observation that sensation of effort and breathlessness, which appear related to both load and timing3,20 were submaximal at task failure.21-23

While $P_{\text{Imax}}$ and $P_{\text{thmax}}$ increased with successive tests, the ratio $P_{\text{thmax}}/P_{\text{Imax}}$ was unchanged. The proportional increases in $P_{\text{Imax}}$ and $P_{\text{thmax}}$ over the learning period suggests a common mechanism for their change. This appears likely to be related to improved respiratory muscle coordination (see above) rather than a change in the inherent endurance capacity of muscles which may be better reflected in the ratio $P_{\text{thmax}}/P_{\text{Imax}}$. While this ratio remains constant, it also remains low (67% of $P_{\text{Imax}}$) relative to that achieved in normal healthy subjects where, following familiarization, $P_{\text{thmax}}$ exceeds 78% of their $P_{\text{Imax}}$.3,4 This persistent low ratio implies deconditioning and impaired endurance of the respiratory muscles in these patients.7,24,25 The potential utility of this ratio as a measure of endurance capacity is supported by the observation that it can increase significantly in patients with COPD following a program of high-intensity respiratory muscle training.9

In summary, our finding of a systematic increase in $P_{\text{Imax}}$ and $P_{\text{thmax}}$ over successive tests emphasizes the need for a familiarization period when testing respiratory muscle function in patients with COPD. Not accounting for these learning effects would result in an underestimation of $P_{\text{Imax}}$ and $P_{\text{thmax}}$ by 21% and 33%, respectively. It was notable, however, that the ratio $P_{\text{thmax}}/P_{\text{Imax}}$ was unchanged from test to test, implying that a single measurement of this ratio could provide a useful guide to the endurance capacity of the respiratory muscles in patients with COPD. Expiratory airflow limitation limits the capacity of these patients to modify breathing pattern and end-expiratory lung volume during progressive threshold loading, thus, $P_{\text{Imax}}$ should be measured at resting FRC, as it best reflects available inspiratory pressure generating capacity when under load.
Acknowledgements

This work was funded in part by National Health and Medical Research Council (Australia) Grant 212016.

References