Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation

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ABSTRACT To determine whether patients with chronic airflow limitation have a specific alteration in skeletal muscle performance, the strength and endurance of inspiratory and limb muscles were compared in 11 patients with chronic airflow limitation and 11 control subjects during maximal voluntary contractions. Peak inspiratory pressure at observed functional residual capacity (FRC) was significantly less in the patients than in the control subjects (mean 72 (SD 25) v 93 (21) cm H2O), though only two patients had low maximal pressures across a wide volume range. Maximal voluntary torque of the elbow flexor muscles was also reduced in the patients but the difference was not significant (60 (17) v 72 (18) Nm). During the endurance sequence of 18 maximal voluntary contractions (10 s duration, 5 s rest interval) the decline in peak and average force was less for the inspiratory muscles than for the elbow flexors in both groups. Inspiratory muscle endurance was slightly greater in the patients with chronic airflow limitation than in the control subjects, whereas limb muscle endurance was slightly impaired in the patients. In three patients with chronic airflow limitation, two of whom had low maximal inspiratory pressures at FRC, the ability to drive the diaphragm voluntarily was examined by stimulating the phrenic nerves during maximal inspiratory efforts. Each patient was capable of full activation of the diaphragm during the maximal inspiratory efforts. These results suggest that the relative preservation of inspiratory muscle performance in patients with chronic airflow limitation may be an adaptive response to respiratory “loading.”

Introduction

In patients with chronic airflow limitation the inspiratory muscles are required to overcome increased airway resistance and increased inspiratory elastance as functional residual capacity (FRC) increases. In addition to increasing the elastic load to breathing, this overinflation places the inspiratory muscles at a suboptimal length for generation of muscle tension and reduces the mechanical efficiency of the diaphragm and rib cage.12 The inspiratory muscles, especially the diaphragm, may therefore be susceptible to fatigue as a result of increased loading and diminished “capacity” to produce inspiratory force.13 An alternative view is that with chronic loading the respiratory muscles of patients with chronic airflow limitation may behave like other skeletal muscles and undergo an adaptive response to the functional overload.5-7

The inspiratory muscles of healthy subjects have been shown to be highly resistant to the development of fatigue induced by repeated maximal static contractions compared with the expiratory muscles and the muscles acting to flex or extend the elbow joint.8 In asthmatic subjects who had frequent episodes of bronchoconstriction the endurance of inspiratory and expiratory muscles was greater than that of control subjects, but the performance of the elbow flexors was similar for the two groups.9

In the present study repeated maximal static contractions were used to compare the strength and endurance of inspiratory muscles in patients with chronic airflow limitation with those of control subjects. The performance of a limb muscle was also tested because the illness or drug treatment may have
resulted in a global change of skeletal muscle function. Phrenic nerve stimulation was used to assess the degree of voluntary activation of the phrenic motoneurone pool in some of the patients with chronic airflow limitation. Preliminary results have been presented in brief form.

Methods

The strength and endurance of the inspiratory muscles and the flexors of the elbow were studied in 11 patients with chronic airflow limitation and 11 control subjects. All subjects were male. The procedures were approved by the institutional ethics committee and informed consent was obtained.

Subjects

Patients with chronic airflow limitation were included in the study if they had (1) moderate or severe airflow obstruction (FEV₁ < 60% of the predicted value) or (2) substantial hyperinflation (FRC > 75% predicted TLC), or both (see table for their lung function values). None had taken part in a respiratory muscle training programme. No control subject had a history of asthma, other lung disease, or neuromuscular disorders and all had normal spirometric variables and absolute lung volumes. The two groups were well matched for age (50 (SD 15) years for chronic airflow limitation, 48 (18) years for control), height (1·70 (0·07), 1·78 (0·09), m), and weight (70 (8), 75 (8) kg).

The subjects with chronic airflow limitation were studied when well, usually just before or shortly after discharge from hospital after treatment for an acute exacerbation. None had evidence of right ventricular failure. All subjects completed a questionnaire (see below), performed spirometric tests, underwent measurements of thoracic gas volume and maximal inspiratory pressures at different lung volumes, and, finally, performed tests of muscle strength and endurance.

Questionnaire

The amount of general activity of subjects during the preceding two months was graded by a five-tier scale that ranged from "sedentary" (score = 0) to "endurance training for sporting events" (score = 4). Tobacco consumption was quantified and subjects with intercurrent illnesses were detected.

Eight subjects with chronic airflow limitation were smokers or ex-smokers with a mean (SD) average consumption of 23 (16) cigarettes a day or 37 (25) packet years (range 19–92 packet years); six control subjects were smokers or ex-smokers (9 (8) cigarettes per day, 10 (8) packet years). Five patients with chronic airflow limitation (including the three non-smokers) gave a history of severe, poorly controlled asthma with a mean duration of 12 (range 2–30) years. All patients complained of exertional dyspnoea, nine had a cough, and eight produced sputum for more than three months a year. All patients had been maintained on long term treatment with beta agonist aerosols or nebuliser solution and oral theophylline. Eight had been having prednisolone (dose ranging from 7·5 to 30 mg daily or alternate days) for more than two months before testing. At the time of the study all but one were taking a higher dose of corticosteroids that they had started while in hospital. Eight patients were also regular users of inhaled beclomethasone dipropionate (200–1000 μg/day). Questions about intake of standard foods over the previous two months suggested that all subjects had an adequate diet.

Pulmonary Function Tests

Vital capacity was measured with a water sealed spirometer. FEV₁, forced vital capacity (FVC), and FEV₁/FVC% were measured from the best of three maximal expiratory flow-volume manoeuvres. Functional residual capacity and total lung capacity (TLC) were measured by Boyle’s law (panting frequency 1 Hz) with a pressure compensated, integrated flow body plethysmograph. The system was calibrated with a 4 litre syringe. Pressure was measured with a differential pressure transducer (Statham PM 131 TC) calibrated with a water manometer. Predicted values were calculated with standard regressions for white men on the basis of age, height, and weight. ¹ FRC was significantly increased in the patients (table), compatible with the degree of airflow obstruction, but the increase in TLC was not significant (see ref 12). The relation between maximal static inspiratory pressure and absolute lung volume was also determined with the subject seated in the body plethysmograph, and provided with visual feedback of airway pressure.

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**Pulmonary Function Tests**

| Pulmonary function (mean (SD) % predicted unless stated otherwise) in control subjects and patients with chronic airflow limitation (CAL) |
|---|---|---|
| Control | CAL | p |
| FEV₁ | 103 (10) | 50 (14) | † |
| FVC | 109 (8) | 83 (8) | < 0·001 |
| FEV₁/FVC% | 76 (6) | 50 (13) | < 0·001 |
| FRC | 109 (20) | 138 (32) | † |
| TLC | 105 (9) | 109 (20) | NS |
| Activity score† | 1-4 (0·7) | 0-6 (0·9) | < 0·01 |

*Absolute ratio expressed as a percentage.
†Activity scale (0–4; see under "Methods") to assess the level of physical activity.
| Significance levels for differences in FEV₁ and FRC are not reported because abnormality of either variable was a criterion for inclusion in the study. |
| FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; FRC—functional residual capacity; TLC—total lung capacity. |
Subjects were coached to avoid glottic closure or "cheek artefact," which was detected as a pressure swing accompanied by an appropriately small change in plethysmographic volume. A 30 minute rest period separated these measurements from the endurance tests.

**MEASUREMENT OF STRENGTH AND ENDURANCE**

For each muscle group subjects performed a series of 18 maximal static contractions lasting 10 seconds separated by rest intervals of five seconds (duty cycle 67%). Rest periods of about 30 minutes separated tests of the two muscle groups and the order of testing varied between subjects.

Maximal inspiratory efforts were made at measured FRC against a closed airway with the subject seated in the body plethysmograph. Subjects initially performed several brief (1–2 s) maximal inspiratory efforts with visual feedback of airway pressure until reproducible values were obtained. To allow for any drift of the volume signal because of temperature changes during the endurance test, inspiratory capacity was initially determined during several maximal inflations from a stable end expiratory level. Before every static effort subjects inhaled to TLC and then exhaled the appropriate volume before the shutter was closed and the maximal inspiratory contraction begun. Throughout every contraction subjects were continually and loudly exhorted, in a standard way, to maintain a maximal effort by an operator who could not see the force being generated.

For the first three seconds of each contraction absolute lung volume, airway pressure, and time were stored by a microprocessor at a sampling rate of 100 Hz. Subsequently values were sampled at 100 Hz and averaged for periods of 100 ms, and the averaged values were stored. The average pressure sustained throughout the contraction was calculated on line and stored with the initial peak pressure and the initial absolute lung volume.

As there was some variation in the absolute lung volumes at which individual contractions were started (usually within 400 ml) the maximal static pressure-volume relationship for each subject was used to correct the pressure measurements. A curve of best fit was drawn by hand through the points. Graphical methods were used to derive scaling factors for the expected change in maximal inspiratory pressure for 100 ml changes in absolute lung volume above and below the mean initial volume for the series of 18 contractions. The appropriate scaling factor was then applied if necessary to the values for peak and average pressure for each contraction. The magnitude of this scaling factor clearly depended on the position of FRC in relation to the curve of static pressure and lung volume (see, for example, fig 1). For most subjects the difference in maximal inspiratory pressure for a change in lung volume of 100 ml above or below FRC is less than 5 cm H\textsubscript{2}O.

An identical protocol was followed for maximal contractions of the elbow flexors, performed with the subject seated comfortably at a table and the dominant arm fixed to a vertical isometric myograph. The forearm was placed supine and the elbow flexed at 90 degrees with the upper arm held horizontal by fixation of the shoulder. Torque (which is directly proportional to force) was measured continuously. Data from limb contractions were analysed by measuring the initial peak force and the average force maintained throughout each contraction.

The strength of both muscle groups (maximal inspiratory pressure and torque of the elbow flexors) was taken as the largest pressure (or torque) achieved in the first three contractions of the endurance test. This peak always occurred within the first two to three seconds of a contraction and was within 5% of the maximal value achieved in the preliminary trials. For both limb and inspiratory muscles indices of endurance were calculated as the ratio between the peak (or average) force in the better of the last two contractions and the peak (or average) value in the best of the first three contractions. These indices are considered measures of endurance and are expressed as percentages.

During the inspiratory endurance test oxygen was released into the breathing circuit at 6 l/min for all subjects. During inspiratory resistive loading in healthy subjects a reduction in the concentration of inspired oxygen appears to decrease endurance time, whereas breathing 100% oxygen increases endurance time. In contrast, Gandevia et al found that supplemental oxygen made no difference in healthy subjects to the endurance profile in a series of maximal static inspiratory efforts. Patients with severe pulmonary disease, however, had difficulty in maintaining the maximal inspiratory pressure for the required 10 seconds without supplemental oxygen.

**ASSESSMENT OF DIAPHRAGMATIC ACTIVATION**

Additional experiments were performed on three patients with chronic airflow limitation, two of whom were selected because their maximal inspiratory pressures were below the normal range (see under "Results"). Oesophageal, gastric, and transdiaphragmatic pressures were recorded with a multilumen gastro-oesophageal catheter, which also enabled diaphragmatic electromyographic activity (EMG) to be measured via Ag-AgCl ring electrodes 1 and 6 cm proximal to a stabilising balloon at the gastro-oesophageal junction. All EMG signals were amplified (× 1000–5000) and filtered (band width 3.2–1.6 KHz). The phrenic nerve was stimulated at or below the level
of the cricoid cartilage (bilaterally in one patient and unilaterally in two) with adjustable probe electrodes mounted on movable stages attached to a firm neck brace. The anode was fixed to the manubrium. Rectangular pulses (100–200 μs duration, up to 400 v) were delivered while the electrode position was adjusted so that supramaximal stimuli (as judged by the diaphragmatic compound muscle action potential) were delivered to the phrenic nerve with minimal spread to the brachial plexus. Stimuli delivered during strong contractions were 1:3–2 times the stimulus intensity required to produce a maximal muscle action potential at rest at FRC.

Subjects performed brief maximal inspiratory efforts against a closed airway, similar to those they had performed during the endurance test. Several trials were undertaken without interpolated stimuli and the size of the maximal inspiratory pressure was compared with that obtained during the endurance test. Then at least five maximal attempts were made with interpolation of supramaximal unilateral or bilateral phrenic nerve stimulation. Evoked pressure changes were measured after each attempt from oscilloscope records at high gain. Data were also recorded on FM tape for subsequent analysis. The resolution of the technique was 0·5 cm H₂O with the use of a voltage clamp circuit. Failure to detect an evoked response suggests that at least 95% of the stimulated muscle was fully activated by the voluntary effort.

STATISTICS

Unless stated otherwise, results are reported as means with standard deviations in parentheses. Differences in strength and the indices of endurance (defined above) between groups of subjects were assessed by unpaired two tailed t tests. Differences between the relative performance of the two muscle groups were tested with paired t tests. Results were accepted as statistically significant if p < 0·05. The influence of chronic airflow limitation on muscle performance was also tested for both muscle groups by analysis of variance and covariance with the MANOVA programme from SPSSx (Statistical Package for Social Sciences). To control for variation in strength between subjects, values were normalised to the largest of the first three contractions. The natural logarithm of the normalised value was used to satisfy the linear model of the statistical programme.

UNITS

All respiratory pressures are given in absolute cm H₂O. These values are converted to kPa by multiplying them by 0·098.

Results

MAXIMAL INSPIRATORY PRESSURE-VOLUME RELATIONSHIP

Individual results for the relation between maximal inspiratory pressure and absolute lung volume are plotted in relation to each subject's observed TLC in figure 1. Two patients had values for maximal inspiratory pressure (MIP) below the observed control range at all lung volumes but only one had values outside the accepted normal range. The latter

Fig 1 Individual results for the relation between maximal inspiratory pressure and absolute lung volume in patients with chronic airflow limitation, plotted relative to each patient's observed total lung capacity (TLC). The shaded area represents the observed range for control subjects.
Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with CAL

patient had severe chronic airflow limitation and emphysema and had been having long term maintenance prednisolone. This subject also had the lowest value for elbow flexor strength (fig 2). Three patients with values for maximal inspiratory pressure at the extremes of the observed range (two low, one high) subsequently underwent electrophysiological studies of voluntary activation of the diaphragm (see below).

**STRENGTH AND ENDURANCE**

The mean (SD) maximal inspiratory pressure (MIP), taken as the peak of the best of the first three contractions in the endurance test, was 72 (25) cm H2O at FRC for subjects with chronic airflow limitation, significantly less than that for control subjects (93 (21) cm H2O; p < 0.05, see also figure 2). Maximal elbow flexor torque (60 (17) Nm) in patients with chronic airflow limitation was less than that for control subjects (72 (18) Nm), though the difference was not statistically significant. The maximal inspiratory pressure at FRC showed a significant positive correlation with maximal elbow flexor torque (fig 2).

Data from a typical sequence of contractions are shown in figure 3. During the series of 18 contractions with a duty cycle of 67% (see under "Methods") the peak and average pressures produced by the inspiratory muscles declined, but in all subjects studied there was a greater relative decline in the peak and average force produced by the elbow flexors (p < 0.001; figs 4 and 5). The results for control subjects are similar to those obtained in previous studies that used an identical protocol.9 13

For the elbow flexors peak and average force were consistently better maintained by the control subjects (fig 4) but the difference at the end of the test was small (control 60% (9%) of the initial value, chronic airflow limitation 57% (12%)). By contrast, inspiratory muscle performance was better in the patients than in the control subjects (fig 5). The difference in relative decline of pressure was small but consistent (chronic airflow limitation 93% (14%) of the initial value, control 88% (15%)). Analyses of variance with data for peak and average force from the 18 contractions showed significantly better performance of the inspiratory muscles of the patients with chronic airflow limitation than of the control subjects (p < 0.01 for both peak and average sustained pressure). In the

**Fig 2 Individual results for maximal inspiratory pressure at functional residual capacity for patients with chronic airflow limitation (open circles) and control subjects (closed circles) plotted against each subject’s maximal torque exerted by the elbow flexors.**

**Fig 3 Records from a typical study in a control subject. Repeated maximal static contractions of the inspiratory muscles (upper panel) at functional residual capacity and of the elbow flexors (lower panel). The contractions lasted 10 seconds with rest intervals of five seconds (that is, a duty cycle of 67%). Peak pressure or torque was achieved in the first two seconds of any contraction. After 18 contractions the decline in peak and average sustained force was less for the inspiratory muscles than for the elbow flexors. Each vertical calibration bar indicates the range from zero to the specified pressure or torque.**
Fig 4  Maximal performance of the elbow flexors tested with 18 maximal static contractions of 10 seconds' duration separated by rest intervals of five seconds in 11 subjects with chronic airflow limitation (open circles) and 11 control subjects (closed circles). Each data point represents the mean and SEM for the peak force (left panel) and the average force sustained for 10 seconds (right panel) in the better of each two consecutive contractions, expressed as a percentage of that attained in the best of the first three contractions. The first two contractions are depicted separately. There was a trend for elbow flexor torque to be slightly better maintained by the control subjects.

Fig 5  Maximal performance of the inspiratory muscles tested with 18 maximal inspiratory contractions of 10 seconds' duration separated by rest intervals of five seconds in 11 subjects with chronic airflow limitation (open circles) and 11 control subjects (closed circles). Each data point represents the mean and SEM for the peak pressure (left panel) and average pressure sustained for 10 seconds (right panel) in the better of each two consecutive contractions, expressed as a percentage of that attained in the best of the first three contractions. There was a clear trend for inspiratory pressure to be better maintained by the subjects with chronic airflow limitation.
Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with CAL

![Diagram](image)

Fig 6   Endurance of the inspiratory muscles (above) and of the elbow flexors (below) for patients with chronic airflow limitation (open circles) and controls (closed circles) plotted in relation to each subject’s FEV₁ (% predicted). There was a significant positive correlation for elbow flexor endurance and FEV₁ (% predicted) in the patients with chronic airflow limitation (p < 0.01).

Discussion

In the patients with chronic airflow limitation maximal static inspiratory pressure at FRC was 23% lower than that of the control subjects (p < 0.05) and there was a smaller reduction in maximal static torque of the elbow flexors (17%) that was not statistically significant. There were small differences between the subject groups in the relative endurance of the two muscle groups, with inspiratory pressure slightly better maintained by the patients with chronic airflow limitation, and elbow torque by the control subjects. The substantial difference in endurance between the two muscle groups in both the patients and the control subjects has been documented and discussed previously.8–13,25,26

The enhanced endurance was attributed, in part, to relative preservation of intramuscular perfusion of the diaphragm or intercostal muscles, or both, during loaded inspiratory efforts.13,26

The use of repeated maximal static contractions to compare endurance properties of different muscles may be invalid if the muscles are not activated maximally during voluntary contractions. In healthy
Subjects' maximal activation of the relevant motoneurone pool has been documented for several limb muscles, including the elbow flexors and diaphragm. If the subjects with chronic airflow limitation were not able to activate the diaphragm maximally during the endurance test, it would not be surprising that endurance appeared to be enhanced. Supramaximal stimulation of the phrenic nerve or nerves, however, showed that complete voluntary activation of the phrenic motoneurone pool had been achieved in these three patients (who included two with the lowest values for maximal inspiratory pressure). When the sensitivity of this test was investigated recently, the results suggested that failure to activate 2% of the stimulated muscle mass voluntarily can be detected during twitch interpolation.

**Performance of Limb Muscles in Chronic Airflow Limitation**

Several factors may have contributed to the reduction in limb muscle performance in the patients. As expected, the general level of activity of the patients was significantly less than that of the control group. Secondly, metabolic factors may have contributed to the poor performance. Slight changes in enzyme activities have been found in the muscles of patients with chronic airflow limitation. Thirdly, cardiovascular output or oxygen delivery to the muscles (or both) may have been decreased in the patients. Fourthly, although the mean weight for subjects in the two groups was similar (see under "Methods"), there may have been an alteration in body habitus or usage of upper body musculature, or both, in the patients.
Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with CAL

with chronic airflow limitation. Six patients had been taking long term oral prednisolone, which may have contributed to a reduction in proximal muscle strength. Malnutrition and decreased muscularity (including that of the diaphragm) have been reported in some studies of patients with advanced chronic airflow limitation. We found that limb muscle endurance in patients with chronic airflow limitation was correlated positively with airway function, as estimated by measurement of FEV₁ (and FEV₁/FVC). This interesting finding does not, however, distinguish between the possible mechanisms.

INSPIRATORY MUSCLE ENDURANCE IN CHRONIC AIRFLOW LIMITATION

Estimates of respiratory muscle strength in patients with pulmonary disease have yielded conflicting results, largely because maximal static respiratory pressures are also influenced by changes in lung volume and chest shape. Byrd and Hyatt claimed that the strength of respiratory muscles was increased in patients with chronic obstructive lung disease when the values were related to predicted rather than the observed absolute lung volume. Braun and Rochester allowed for differences between patients and control subjects in the passive recoil pressure of the respiratory system and concluded that maximal inspiratory pressure was reduced in the patient group. They claimed that the reduction stemmed primarily from the mechanical disadvantage of the inspiratory muscles and that inspiratory muscle force was further compromised by generalised muscle weakness in severe chronic obstructive pulmonary disease. Other studies have also reported decreased inspiratory pressures for patients with severe chronic obstructive lung disease. The latter results would be consistent with recent findings of reductions in muscle fibre size in the diaphragm but not intercostal muscles of patients with emphysema. By contrast, studies of non-obese asthmatic subjects have shown normal or increased values for maximal inspiratory pressure, despite the presence of hyperinflation.

In the present study the overall reduction in maximal inspiratory pressure at FRC in the patients was similar in relative terms to that observed for elbow flexors. FRC, however, was significantly increased in the subjects with chronic airflow limitation. Only one patient had values that were well below the control range when maximal inspiratory pressure was plotted as a function of observed TLC. If the reduction in strength of the elbow flexors reflected a global alteration in skeletal muscle force, the present results suggest that the inspiratory muscles of the patients may have been spared.

Despite claims that the respiratory muscles of patients with obstructive pulmonary disease are unduly prone to fatigue, there have been few direct studies of respiratory muscle endurance in such patients. Evidence from this and a previous study does not support the idea that inspiratory muscles are especially susceptible to fatigue in patients with obstructive disorders. McKenzie and Gandevia found in asthmatic subjects with frequent episodes of wheeze that the strength of the inspiratory and expiratory muscles was normal and the endurance of both muscle groups was enhanced. The current study provides the first evidence that not only is there no specific impairment of inspiratory muscle endurance in subjects with chronic airflow limitation but there may be slight enhancement. This contrasts with the slight impairment in endurance of the elbow flexors of patients with chronic airflow limitation.

The relative sparing of inspiratory muscle performance in subjects with chronic airflow limitation could reflect the relative increase in FRC and consequent shortening of inspiratory muscles. When limb muscles contract at a short muscle length there is a decrease in maximal force (the length-tension effect) and an enhancement of endurance at least as great as that documented here for the inspiratory muscles of patients with chronic airflow limitation. McKenzie and Gandevia have shown, however, that the endurance of the inspiratory muscles of normal subjects is slightly less during repeated contractions at a high lung volume (that is, with shortened inspiratory muscles) than during contractions at FRC. This apparently paradoxical result for the inspiratory muscles was attributed to variations in intramuscular perfusion between the two muscles and the influence of pleural pressure on diaphragmatic blood flow (see McKenzie and Gandevia for full discussion). Given that some impairment of inspiratory muscle endurance might have been expected in the patients owing to hyperinflation, the small enhancement documented in the present study is especially notable. Taken with the evidence for a global impairment of skeletal muscle performance, the present results suggest that the inspiratory muscles of the patients may have been trained for endurance by the loads imposed by the pulmonary disorder.

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