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Title: Neural Respiratory Drive in Healthy Subjects and in Chronic Obstructive Pulmonary Disease

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Running title: Neural Respiratory Drive in Health and COPD

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Abstract

Background: We aimed to use the diaphragm electromyogram (EMG_{di}) to compare levels of neural respiratory drive (NRD) in a cohort of healthy subjects and COPD patients, and to investigate the relationship between NRD and pulmonary function in COPD.

Methods: EMG_{di} was recorded at rest and normalised to peak EMG_{di} recorded during maximum inspiratory manoeuvres (EMG_{di}%max) in 100 healthy subjects and 30 patients with COPD, using a multipair oesophageal electrode. EMG_{di} was normalised to the amplitude of the diaphragm compound muscle action potential ($CMAP_{di}MS$) in 64 healthy subjects.

***Results*:** EMG_{di}%max was 9.0 (3.4)% in healthy subjects and 27.9 (9.9)% in COPD ($p<0.001$), and correlated with %predicted FEV_1 ($r^2 = 0.40$, $p<0.001$), VC ($r^2 = 0.61$, $p<0.001$), and inspiratory capacity ($r^2 = 0.28$, $p=0.02$) in patients. EMG_{di}%max was higher in healthy 51-80 year olds than 18-50 year olds (11.4 (3.4) vs 8.2 (2.9) %, $p<0.001$). Observations in the healthy group were similar when peak EMG_{di} or $CMAP_{di}MS$ were used to normalise EMG_{di}.

Conclusions: Levels of NRD were higher in COPD than healthy subjects, and related to disease severity. $CMAP_{di}MS$ could be used to normalise EMG_{di} if volitional inspiratory manoeuvres cannot be performed, allowing translation of the technique to critically-ill and ventilated patients.

Keywords: Chronic Obstructive Pulmonary Disease, Respiratory Diaphragm, Electromyography

Introduction

Objective markers of disease severity that reflect the physiological load on the respiratory system in chronic obstructive pulmonary disease (COPD) are currently lacking. Although COPD disease severity is categorised in terms of FEV_1 in management guidelines [1], correlations between FEV_1 and breathlessness [2] or quality of life are modest [3], and reported relationships between FEV_1 and prognosis are inconsistent [4-6]. Two small studies confirm that neural respiratory drive (NRD) is increased in COPD [7] and relates to symptoms [8], but the use of measurements of NRD to assess disease severity in COPD has not been fully investigated, in part because there are no data to define ranges of NRD within the healthy population.

In COPD, mechanical abnormalities including airflow obstruction, static and dynamic hyperinflation and intrinsic positive end expiratory pressure increase the load on the respiratory muscles. The translation of inspiratory muscle contraction into negative intrathoracic pressure, and of pressure changes to ventilation, is impaired as a consequence of muscle shortening, increased velocity of contraction, alteration in geometry and reduced compliance of the respiratory system. This results in high NRD in COPD, and disproportionate increases whenever airways obstruction worsens (and hyperinflation increases) or ventilatory requirements increase. The neural output of the brainstem respiratory centre cannot easily be measured directly in man, but NRD can be assessed indirectly by quantifying the electromyogram (EMG) of the respiratory muscles, which provides a method of assessing the level and pattern of their activation [9]. The EMG of the diaphragm (EMG_{di}), the major inspiratory muscle during resting tidal breathing in healthy individuals, can be recorded specifically using oesophageal electrodes positioned at the diaphragm crus [10]. Multipair oesophageal electrode catheters have been developed and used by other groups [11, 12], and ourselves [13, 14], to measure NRD. Using these electrodes, Sinderby et al have shown that the amplitude of EMG_{di} is higher in patients with significant respiratory disease than in healthy subjects, when normalised to each subject's volitional `maximum ("EMG_{di}%max") [7]. However, the number of subjects in this study was small (five healthy men, five COPD patients, and five post polio infection), and it was not designed to explore the use of EMG_{di}%max as a marker of disease severity.

The main aims of this study were to use the diaphragm electromyogram (EMG_{di}) to measure NRD in a large cohort of healthy subjects for comparison with levels of NRD in COPD, and to investigate the relationship between NRD and pulmonary function in COPD. We hypothesised that resting EMG_{di}%max would be significantly higher in COPD than healthy subjects, and that resting EMG_{di}%max would be highest in COPD patients with the most severe disease. A further aim was to test the hypothesis that there is a positive correlation between the amplitude of the diaphragm compound muscle action potential recorded following bilateral anterolateral magnetic stimulation ($CMAP_{di}MS$) and the peak root mean square of spontaneous EMG_{di} activity (RMS $EMG_{di}peak$) recorded during maximal volitional inspiratory manoeuvres. If so, normalising EMG_{di} to $CMAP_{di}MS$ could avoid the difficulties associated with the use of volitional tests of maximum diaphragm activation for normalisation in clinical situations where it is impossible to perform the necessary inspiratory manoeuvres. Assessing the load on the respiratory system by quantifying EMG_{di} non-volitionally in this way could be particularly valuable in the critical care population, particularly in the assessment of the need for ventilatory support, where EMG_{di}%max values could provide an index of ventilatory reserve. Indeed, calibration of the level of ventilatory support in response to levels of neural respiratory drive is the basis of novel neural-assist ventilator technology (NAVA) currently in development [15].

Methods

Subjects

100 healthy subjects (mean (SD) age 40.3 (17.4), range 18-79 years, 56% male, ethnicity: 54% Chinese, 36% white European, 10% other) and 30 COPD patients (age 66.6 (7.82) years, range 52-88 years, 76.0% male, ethnicity: 63% white European, 37% Chinese, FEV_1 34.8 (13.9) % predicted) were studied. The subjects' age, height, weight and body mass index (BMI) were documented. Spirometry (FEV_1, slow vital capacity (VC)), and inspiratory capacity (IC) were also measured in COPD patients. Informed consent was taken and the study was performed in accordance with Local Research Ethics Committee procedures.

Instrumentation and signal processing

EMG_{di} recordings were made from the crural diaphragm using multipair oesophageal electrode catheters, as previously described [13]). Further details of the electrode design, positioning and signal processing are given in the online depository.

EMG_{di} recordings at rest and during maximal inspiratory manoeuvres

Recordings were made sitting upright in a chair, with a nose clip in place for all measurements except sniff nasal pressure. To record EMG_{di} during resting breathing, subjects sat quietly in a relaxed posture for at least 5 minutes, until at least 2 minutes of stable, consistent, EMG_{di} signals had been recorded. Airflow was measured through a mouthpiece connected in series to a pneumotachograph. EMG_{di} was then recorded during four inspiratory manoeuvres: 1) maximal inspiration to total lung capacity (TLC); 2) maximal static inspiratory effort at functional residual capacity (FRC) against a closed valve [16]; 3) maximal sniff from FRC; and 4) maximum voluntary ventilation for 15s ("sprint MVV"). Manoeuvres 1 – 3 were repeated at least 3 times, until the investigator was satisfied that a truly maximum effort had been performed. The sprint MVV was performed once only.

Calculation of resting EMG_{di}

The raw signal was converted to root mean square (RMS) (Powerlab Chart v5.4 software, ADInstruments), using a time constant of 50 ms and a moving window. The maximum RMS EMG_{di} value during 100ms subdivisions of each breath was then determined, manually selecting EMG_{di} signals falling between QRS complexes of the

ECG artefact. The mean maximum RMS EMG_{di} per breath over two representative 30-second subdivisions of the whole recording was then calculated.

Calculation of EMG_{di}%max

EMG_{di} signals recorded during each of the maximum inspiratory manoeuvres were converted to RMS as above. The largest RMS EMG_{di} value calculated by analysis of these recordings was labelled "RMS EMG_{di}peak". EMG_{di}%max for each subject was then calculated as the mean maximum RMS EMG_{di} per breath as a percentage of RMS EMG_{di}peak.

Assessment of intra- and inter-observer reproducibility of EMG_{di}%max

10 healthy subjects were studied on two occasions more than 24 hours apart, at the same time of day. The intra-observer reproducibility of EMG_{di}%max measurements was assessed by comparing the results of a single investigator's (CJ) analysis of measurements made on two separate days. The inter-observer reproducibility of EMG_{di}%max measurements was assessed by comparing the results of two investigators' (CJ and CR) analysis of a single set of measurements in five of these subjects.

Bilateral anterolateral magnetic phrenic nerve stimulation (BAMPS)

BAMPS was performed using two double circular 43-mm coils (P/N 9784-00) placed anterolaterally over the left and right phrenic nerves, as previously described [17]. The coils were powered by a Magstim 200 stimulator (Magstim Co.,Whitland, Dyfed, UK). During the study subjects were seated upright in a chair with a nose clip in place. Stimulation was performed at end-expiration with the abdomen unbound. BAMPS was performed at 80%, 85%, 90%, 95% and 100% maximum stimulator output (MSO) to determine supramaximality. The amplitude of the diaphragm compound muscle action potential ($CMAP_{di}$MS) was measured as the peak-trough amplitude as previously described [18]. The inter-occasion coefficient of variation (CV) in this previous study was 8.6% [18].

Statistical analysis

Statistical analysis was carried out using SPSS software v 11.0 for Mac (SPSS Inc, Chicago, Illinois) and GraphPad Prism 5 v5.0 for Windows (GraphPad software Inc).

Ranges are expressed as 95% confidence intervals of the mean. Comparisons between healthy and COPD subjects were made using independent sample t-tests except comparisons of sex distributions, which were made using Fisher's exact test. P-values were considered to be significant at <0.05 level. Relationships between EMG_{di} and anthropometric or lung function variables were investigated by regression analysis. Intra- and inter-observer reproducibility was assessed by calculating the coefficient of variation and by Bland-Altman analysis [19].

Results

Data are presented as mean (SD). Anthropometric and lung function data for both healthy subjects and COPD patients are summarised in table 1.

Table 1

	Healthy	**COPD**	**p**
n	100	30	
Age (years)	40.0 (17.4)	66.6 (7.82)	<0.001
Height (m)	1.65 (0.08)	1.67 (0.08)	0.29
Weight (kg)	62.9 (12.1)	63.9 (13.9)	0.75
BMI (kg/m^2)	23.0 (3.26)	23.0 (4.39)	0.95
%male	56.0	73.3	0.14
FEV_1%pred	104.5 (14.3)	34.8 (13.9)	
VC%pred	106.4 (13.4)	83.0 (18.6)	

Representative traces at rest and during maximum voluntary ventilation in a healthy subject and a COPD patient are shown in figure 1. Comparisons of peak RMS EMG_{di} values during the different manoeuvres are given in the online depository.

(Figure 1)

Healthy subjects

The mean EMG_{di}%max of the healthy group was 9.0 (3.4)%. The EMG_{di}%max was 9.2 (3.4) for males, and 8.8 (3.3) for females (p=0.53).

Correlations between EMG_{di}%max and age, height, weight and BMI are shown in table 2. EMG_{di}%max was slightly higher in 51-80 year olds (26% of the total, 13/26

male) than 18-50 year-olds (74% of the total, 43/74 male): 8.16 (2.92) vs 11.4 (3.40) (p=0.001), although the overall linear correlation between EMG_{di}%max and age was weak (r = 0.34, p<0.001) (figure in online depository). There was no significant difference in RMS EMG_{di}peak between the older and younger cohorts (226.4 (71.7) vs 250.3 (67.4) μV). There were weak but significant negative correlations between EMG_{di}%max and absolute FEV_1 (r = -0.34 p= 0.001); and between EMG_{di}%max and absolute VC: r = -0.21 p= 0.04.

Sniff nasal inspiratory pressure (SNIP) was higher in the 18-50 year-olds (91.4 (22.3 cmH_2O) than the 51-80 year olds (80.5 (16.3) cmH_2O, p=0.04), but the relationship between EMG_{di}%max and SNIP values was weak (r=0.19, p=0.06 (n=98)). The difference between PI_{max} in 18-50 year-olds (80.6 (32.6) cmH_2O) and 51-80 year olds (69.5 (20.7) cmH_2O) approached statistical significance (p=0.09). There was no significant relationship between EMG_{di}%max and PI_{max} (r=0.10, p=0.31).

Correlations between EMG_{di}%max and age, height, weight and BMI were similar in the white European and Chinese subgroups (see online depository).

These data give normal ranges (using 95% confidence intervals) of EMG_{di}%max of 7.5 to 8.8% in subjects aged 18-50 years, and 10.1 to 12.8% in subjects aged more than 50 years old.

Data comparing EMG_{di}%max values in White European and Chinese ethnic groups are provided in the online depository.

$CMAP_{di}MS$

$CMAP_{di}MS$ was assessed in 64 subjects. Supramaximality was judged to have been achieved when the mean $CMAP_{di}MS$ amplitude at 100% maximum stimulator output (MSO) was less than 5% greater than the highest mean $CMAP_{di}MS$ amplitude achieved at the lower stimulator outputs. Using these criteria, supramaximality was achieved in 92.8% of the subjects. The $CMAP_{di}MS$ amplitude achieved at 100% MSO values was recorded if supramaximality was not achieved.

Representative traces recorded during BAMPS are shown in the online depository. The mean $CMAP_{di}MS$ amplitude was 2.4 (0.7) mV. The mean phrenic nerve conduction time (PNCT), defined as the time from the stimulation artefact to the onset of the CMAP, was 6.9 (0.7) ms.

Relationships between $CMAP_{di}MS$ amplitude and RMS EMG_{di}

Linear regression analysis revealed a positive correlation between each subject's RMS EMG_{di}peak and $CMAP_{di}MS$ amplitude ($r=0.59$, $p<0.001$) (figure 2). Mean RMS EMG_{di} per breath (μV) expressed as a percentage of $CMAP_{di}MS$ amplitude (RMS EMG_{di} / $CMAP_{di}MS$) was 0.9 (0.4)%. The relationships between RMS EMG_{di} / $CMAP_{di}MS$ and age, height, weight and BMI were similar to those with EMG_{di}%max (table 2)

Table 2

	Height		**Weight**		**BMI**		**Age**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**
EMG_{di}%max	0.002	0.62	0.09	0.39	0.12	0.24	0.34	<0.001
RMS EMG_{di} / $CMAP_{di}MS$	-0.05	0.69	0.08	0.53	0.14	0.29	0.28	0.02

(Figure 2)

COPD patients

EMG_{di}%max in the COPD patients was 27.9 (9.9)%. This was significantly higher than EMG_{di}%max recorded in 26 healthy controls matched for age, height, weight and BMI (11.4 (3.4), $p<0.001$) (table 3 and figure 3). COPD patients generated a smaller tidal volume%predicted VC per unit EMG_{di}%max (V_T%VC_{pred}/EMG_{di}%max) than the healthy controls: 0.8 (0.4) vs 1.4 (0.6) a.u (table 3, figure 3).

Table 3

	Healthy	COPD	p
n	26	30	
Age (years)	64.8 (7.4)	66.6 (7.8)	0.41
Height (m)	1.66 (0.1)	1.66 (0.08)	0.79
Weight (kg)	69.0 (13.0)	63.9 (13.9)	0.15
BMI (kg/m^2)	24.9 (3.3)	23.0 (4.4)	0.06
%male	50.0	73.3	0.10
FEV_1%pred	110.8 (16.9)	34.8 (13.9)	<0.001
VC%pred	113.3 (15.3)	83.0 (18.6)	<0.001
V_T (ml)	499.3 (167.4)	608.3 (199.4)	0.03
V_T %VC_{pred}	14.5 (4.0)	18.7 (5.6)	0.002
Tidal RMS EMG_{di} per breath (µV)	24.8 (9.4)	53.2 (29.0)	<0.001
RMS EMG_{di}peak (µV)	226.4 (71.7)	188.9 (68.8)	0.052
EMG_{di}%max	11.4 (3.4)	27.9 (9.9)	<0.001
V_T %VC_{pred}/EMG_{di}%max (a.u.)	1.4 (0.6)	0.8 (0.4)	<0.001

(Figure 3)

All patients completed FEV_1 and VC measurements, and IC was measured in 20. Significant correlations, best described by curve regression functions, were observed between EMG_{di}%max and FEV_1% predicted, VC% predicted and IC% predicted, and between tidal volume (V_T)%VC_{pred} per EMG_{di}%max and FEV_1% predicted, VC%

predicted and IC% predicted (table 4, figure 4 and additional figures in the online depository).

Table 4

	FEV_1%predicted		**VC%predicted**		**IC%predicted**	
	r^2	**p**	**r^2**	**p**	**r^2**	**p**
EMG_{di}%max	0.40	<0.001	0.61	<0.001	0.28	0.02
V_T%VC_{pred}/ EMG_{di}%max	0.25	0.005	0.48	<0.001	0.36	0.006

(Figures 4 a-c)

Peak RMS EMG_{di} values during different maximal inspiratory manoeuvres
Here the data are presented as median (IQR), as the sprint maximum voluntary ventilation (MVV) data were non-normally distributed. (The data are also presented in table S2 and S3, and in figures S3a)-b), in the online depository).

The total lung capacity (TLC) and maximum mouth inspiratory pressure (PI_{max}) manoeuvres yielded peak values most frequently in the healthy group (31% each), and the TLC manoeuvre yielding the highest RMS EMG_{di} values on average in that group (median (interquartile range) 208.2 (98.7) μV). The sniff manoeuvre yielded peak values most frequently in the COPD group (33%) and yielded the highest RMS EMG_{di} values on average in that group (170.6 (76.5)) μV). The MVV manoeuvre yielded the lowest values in both groups (healthy 158.7 (78.4) μV, COPD 150.2 (97.2) μV) despite yielding the highest value in 26% of the COPD group.

There were no significant differences between RMS EMG_{di} values when the manoeuvres were compared for the COPD group (using the Wilcoxon signed-rank test to compare values within the same subject). In the healthy group, significant differences were observed between all manoeuvres except sniff and PI_{max} (p=0.62).

Intrasubject and interobserver reproducibility of EMG_{di}%max in healthy subjects

Intrasubject reproducibility

The coefficient of repeatability between EMG_{di}%max measurements made and analysed by the same investigator on two separate days, in ten subjects, was 0.94 [19]. The mean (SD) coefficient of variation (CV) was 0.09 (0.05).

Interobserver reproducibility

The mean coefficient of variation (CV) of EMG_{di}%max between measurements made in five subjects on the same day, comparing the results of analysis by two investigators, was 0.10 (0.08). The intraclass correlation coefficient was 0.71.

(Tables and Bland Altman plots of these data are presented in the online depository).

Discussion

This is the first study to define normal ranges of NRD as EMG_{di}%max in a large population of healthy adults; the largest previous study included fifteen participants [7]. In healthy subjects, levels of EMG_{di}%max increased slightly with age, but there were no significant correlations between EMG_{di}%max and sex, height, weight or BMI in this largely non-obese population.

EMG_{di}%max was found to be significantly higher in the COPD group than in matched healthy subjects. The average EMG_{di}%max in our cohort of healthy subjects was 9.0 (3.4) % overall, which is of the same order as levels of EMG_{di}%max described previously in a smaller study by Sinderby et al. [7], who demonstrated resting values of 8.4+/-2.5% and 43.4+/-22.1% in five healthy and five severe COPD patients respectively, using similar methods. The lower average EMG_{di}%max found in our COPD patients is likely to reflect the range of disease severity. By showing that there is a correlation between EMG_{di}%max and the degree of airflow obstruction and hyperinflation, and that this is a reproducible measure, the present study builds on earlier observations and demonstrates the potential value of EMG_{di}%max as an objective marker of disease severity in COPD.

Determinants of EMG_{di}%max

In general, levels of NRD increase when the load on the respiratory muscles increases relative to their capacity, i.e. if the load increases, the capacity of the muscles decreases, or a combination of these two changes. Levels of EMG_{di}%max can therefore be explained in terms of ventilatory mechanics, and the pathophysiological changes in ventilatory mechanics that occur with disease.

1. Healthy subjects

An average EMG_{di}%max of 9.0% in normal subjects, in whom it can be assumed that there is no neuromechanical dissociation, is consistent with the high levels of ventilatory reserve that are known to exist in healthy individuals. The slightly increased EMG_{di}%max observed in our older (51-80 year-old) cohort when compared to that of subjects aged less than 50 years old is likely to reflect the known "normal" changes in ventilatory mechanics occurring with increased age. Declines in FEV_1 [20] and VC [21], respiratory muscle strength [22] and reduced chest wall compliance [23]

observed during healthy ageing all increase the load:capacity ratio of the respiratory muscle pump, reducing ventilatory reserve, and would explain the tendency to higher levels of EMG_{di}%max in the older age group. The findings of significant negative correlations between EMG_{di}%max and absolute FEV_1 and VC are consistent with this. Our observation that the correlation of SNIP and PImax with EMG_{di}%max is weak suggests that altered lung and chest wall mechanics are more important contributors to increased drive than reduced diaphragm contractility in the healthy older cohort.

2. COPD

The results of the study confirm the hypotheses that EMG_{di}%max would be higher in COPD patients than healthy subjects, and that the levels of EMG_{di}%max would be highest in patients with the most severe disease. High levels of EMG_{di}%max indicate that there is a relative increase in the RMS of EMG_{di} in COPD compared to healthy subjects i.e. recruitment of larger numbers of diaphragm motor units and/or an increase in diaphragm motor unit firing rate in COPD. It is, in fact, well known that the firing frequency of motor neurons supplying both the diaphragm [24] and non-diaphragmatic muscles [25] is increased in COPD. However, Gandevia and De Troyer used needle electrodes, which is clearly not feasible in general clinical practice.

The increase in the RMS of EMG_{di} in COPD is likely to be the result of three main factors. Firstly, the diaphragm must generate more pressure to achieve a given tidal volume when compared to healthy subjects. Increased airways resistance in COPD results in significant expiratory airflow limitation at rest, leading to gas trapping, which increases intra-thoracic end expiratory pressure. A positive end expiratory pressure imposes a threshold load that must be overcome before inspiratory airflow can be generated. A reduction in chest wall compliance, as hyperinflation progresses, also contributes to the mechanical load associated with inspiration in severe disease. Hyperinflation is also due to a loss of elastic recoil in emphysema. Secondly, the maximum pressure generating capacity of the diaphragm is reduced. Polkey et al demonstrated a linear negative correlation of twitch transdiaphragmatic pressure with increasing lung volume of 3.5 cm H_2O/l [26]. The ability of the diaphragm to generate transdiaphragmatic and oesophageal pressure is therefore reduced in COPD and these changes are exaggerated with acute-on-chronic hyperinflation. Thirdly, patients with

COPD need to generate increased absolute levels of ventilation to overcome VQ mismatch [27].

Although RMS EMG_{di}peak in COPD patients was 83% lower than in healthy subjects, a lower denominator is unlikely to explain the higher EMG_{di}%max in COPD, as correcting for this gives an average EMG_{di}%max in COPD of 23.5 (8.2) %, still significantly higher than EMG_{di}%max in the healthy group ($p<0.001$).

Significance of raised EMGdi%max and reduced V_T%VC_{pred}/EMG_{di}%max in COPD

Our finding that EMG_{di}%max is raised, and is negatively correlated with FEV_1, VC, and the degree of hyperinflation at rest (described in terms of IC% predicted) in COPD, reinforces the contention that, by providing a composite measure of ventilatory load and capacity, EMG_{di}%max could provide an alternative method of assessing COPD disease severity. This could be the focus of future studies in larger numbers of COPD patients, including a more detailed investigation of the relationship between EMG_{di}%max and other physiological measures, including hypoxemia, hypercapnia and ventilation-perfusion mismatch, than were carried out in the present study.

V_T%VC_{pred} generated per unit EMG_{di}%max (V_T/ EMG_{di}%max) is lower in COPD than healthy subjects, reflecting neuromechanical uncoupling in COPD, and we have shown that this correlates with disease severity. Neuromechanical dissociation has previously been demonstrated during exercise in COPD using EMG_{di} measurements[28], but the relationship with disease severity has not previously been documented. This observation also emphasises the value of EMG_{di}%max over other commonly used indirect measures of ventilatory drive, such as mouth occlusion pressure at 100ms ($P_{0.1}$), or the amplitude of tidal oesophageal pressure swings, which will underestimate levels of NRD in COPD patients with the most neuromechanical dissociation.

Bilateral $CMAP_{di}$MS values

To the best of our knowledge there have been no previous studies that have compared $CMAP_{di}$MS and RMS EMG_{di}peak in healthy subjects. Normal ranges of bilateral $CMAP_{di}$ amplitudes and PNCT recorded using an oesophageal electrode catheter

following BAMPS have also not previously been reported, principally because each phrenic nerve is usually assessed separately. Our findings of a $CMAP_{di}MS$ amplitude of 2.4 (0.7) mV, and a PNCT of 6.9 (0.7) ms are consistent, following extrapolation from bi- to unilateral measurements, with a mean (SD) unilateral $CMAP_{di}MS$ amplitude and PNCT of 1.45 (0.35) and 6.9 (0.9) ms (right) and 1.68 (0.47) and 7.6 (0.7) ms (left) recorded in a similar manner by our group previously [18].

Potential use of $CMAP_{di}MS$ amplitude to normalise EMG_{di} values

The finding that there are relationships between the amplitude of the volitional and non-volitional EMG_{di} in healthy subjects suggests that the non-volitional signal ($CMAP_{di}MS$ amplitude) may be used in place of the volitional RMS $EMG_{di}peak$ when normalising resting EMG_{di} to maximum. This could be of particular importance during the assessment of patients on intensive care units (ICUs), who are unable to generate maximal volitional inspiratory efforts. Potential applications include prediction of weaning failure in patients with respiratory muscle load:capacity imbalance sufficient to impact critically on ventilatory reserve. Levels of EMG_{di}%max above the normal range would indicate that NRD had increased in response to an increase in ventilatory load with respect to the capacity of the respiratory muscles. Conversely, reductions in NRD, measured by assessing airway occlusion pressure ($P_{0.1}$) have been shown to be predictive of extubation failure on paediatric ICU [29]. $P_{0.1}$ would, however, underestimate NRD in patients with disordered ventilatory mechanics, such as in COPD where neuromechanical dissociation progresses exponentially as airflow obstruction and hyperinflation worsen [28]. This approach would also allow the level of EMG_{di} activity at which neural-assist ventilators such as NAVA [15] are triggered to be defined as EMG_{di}%max, hence defining this threshold in terms of ventilatory reserve. Since ventilatory failure is the outcome of a critically low ventilatory reserve, this could prove to be a more appropriate approach than increasing NAVA support in response to changes from baseline EMG_{di} activity.

Potential clinical applications of EMG_{di} measurements to quantify NRD

This technique could be usefully applied to measure disease severity, progression, and responses to treatment, in any disorder characterised by increased ventilatory load (e.g. airflow obstruction in asthma and COPD, reduced lung compliance in pulmonary

fibrosis, or cardiac failure), reduced ventilatory capacity (in neuromuscular disease), or where there is a combination of both factors, such as in COPD, as discussed in this paper. The value of the method over other objective physiological measurements of disease severity, such as spirometry, or measurement of lung volumes, is that recording EMG_{di} gives a breath-by- breath measure of the load on the respiratory system, and can be used to provide measurements continuously during sleep without waking the patient [30], during exercise [28], and, as discussed above, could in addition be measured non-volitionally in ventilated patients. The main factor limiting the translation of the technique to clinical practice is the acceptability of the oesophageal catheters to patients. However, in our experience of the use of these and similar catheters to assess intrathoracic pressure in clinical practice, the catheters are acceptable in >95% of patients, and are usually well tolerated.

In conclusion, we have demonstrated, in a large cohort of healthy subjects and patients with COPD, that levels of NRD, measured as EMG_{di}%max, are higher in patients with COPD than healthy subjects, and that EMG_{di}%max is highest in patients with the most severe airflow obstruction and hyperinflation. EMG_{di}%max therefore provides a composite measure of ventilatory load and capacity, and could provide a method of assessing COPD disease severity. We have also established normal ranges of EMG_{di}%max, which may be used for comparative data in future studies in patients with COPD, or indeed any other cardiorespiratory disease, to further our understanding of the pathophysiology of ventilatory failure. Our findings also demonstrate that non-volitional activation of the diaphragm is of potential use in the assessment of EMG_{di}%max in patients who are unable to perform maximal volitional inspiratory manoeuvres.

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Competing interests

The authors have no competing interests to disclose

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Table legends

Table 1

Demographic and anthropometric data for all healthy subjects and COPD patients. BMI = body mass index. FEV_1%pred = FEV_1 % predicted value, VC%pred = VC % predicted value.

Table 2

Correlations between EMG_{di}%max, and RMS EMG_{di} / $CMAP_{di}MS$, and height, weight, BMI and age in healthy subjects. RMS = root mean square. $CMAP_{di}MS$ = amplitude of the diaphragm compound action potential following bilateral anterolateral magnetic stimulation. BMI = body mass index.

Table 3

Demographic, anthropometric, lung function, and EMG_{di}%max data for COPD patients and healthy subjects matched for age, height, weight and BMI. RMS = root mean square. V_T = tidal volume. VC_{pred} = predicted vital capacity. $V_T\%VC_{pred}/EMG_{di}\%max$ = tidal volume % predicted vital capacity per unit EMG_{di}%max.

Table 4

Correlations between EMG_{di}%max, and $V_T\%VC_{pred}/EMG_{di}\%max$, and %predicted FEV_1, VC and IC. $V_T\%VC_{pred}/EMG_{di}\%max$ = tidal volume % predicted vital capacity per unit EMG_{di}%max.

Figure legends

Figure 1:

Representative traces at rest and during maximum voluntary ventilation in a healthy subject and in severe COPD. EMG_{di} traces recorded from electrode pairs 1 to 5 (distal to proximal) are shown. Scale of each electrode pair = +500 to -500 μV. Flow is calibrated with inspiration as negative values. MVV = maximum voluntary ventilation.

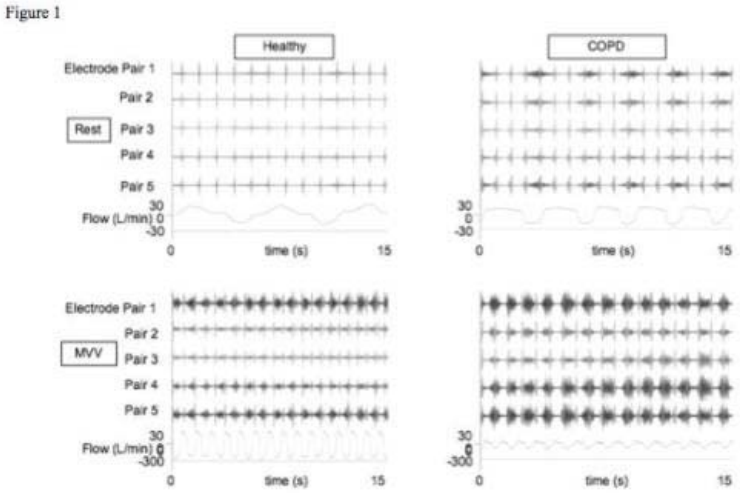


Figure 2

Relationship between $CMAP_{di}MS$ amplitude and RMS $EMG_{di}peak$. Linear regression analysis revealed a positive correlation between each subject's RMS $EMG_{di}peak$ and $CMAP_{di}MS$ amplitude ($r=0.59$, $p<0.001$)

Figure 2

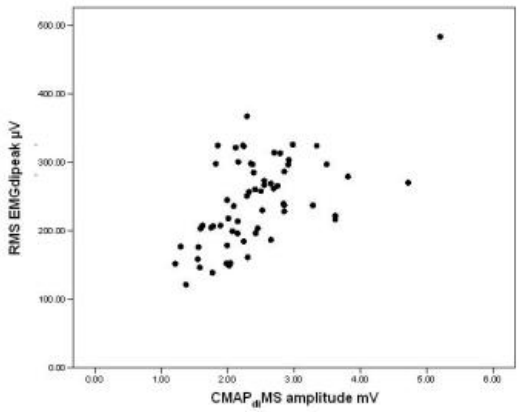
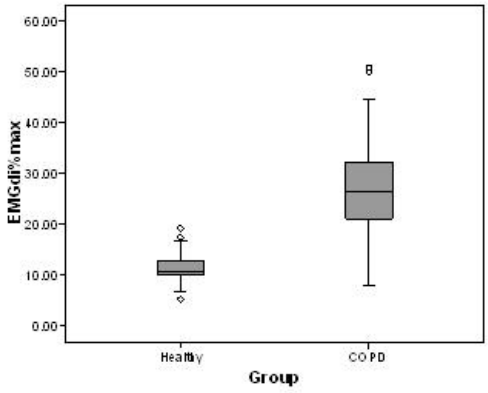


Figure 3

Box and whisker plot comparing EMG_{di}%max in 30 COPD patients with 26 healthy subjects matched for age, height, weight and BMI. Comparisons are made using the independent samples t-test. (o Identifies outliers i.e. cases with values between 1.5 and 3 interquartile ranges from the upper or lower edge of the box. The box length is the interquartile range).

Figure 3

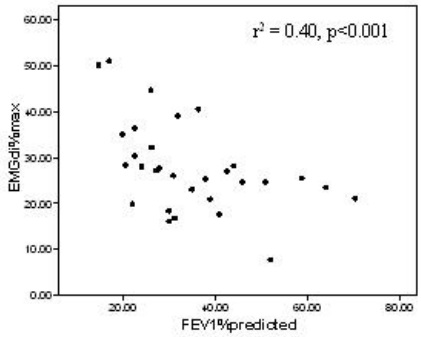


Figures 4(a) to (c)

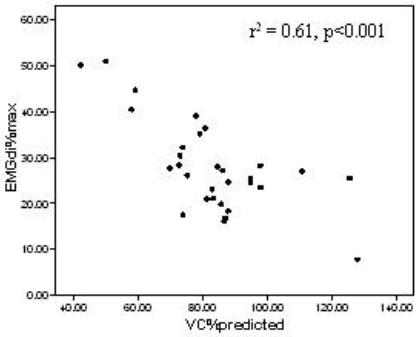
Scatter plots showing correlations between EMG_{di}%max and (a) FEV_1%predicted, (b) VC%predicted and (c) IC %predicted using curve estimation models. Regression coefficients are shown as r^2 values. p= p-value.

Figures 4a)-c)

4a)



4b)



4c)