



# Neural respiratory drive in healthy subjects and in COPD

C.J. Jolley\*, Y.-M. Luo<sup>#</sup>, J. Steier\*, C. Reilly\*, J. Seymour\*, A. Lunt\*, K. Ward\*, G.F. Rafferty\*, M.I. Polkey<sup>†</sup> and J. Moxham\*

**ABSTRACT:** The aim of the present study was to use the diaphragm electromyogram (EMG<sub>di</sub>) to compare levels of neural respiratory drive (NRD) in a cohort of healthy subjects and chronic obstructive pulmonary disease (COPD) patients, and to investigate the relationship between NRD and pulmonary function in COPD.

EMG<sub>di</sub> was recorded at rest and normalised to peak EMG<sub>di</sub> recorded during maximum inspiratory manoeuvres (EMG<sub>di</sub> % max) in 100 healthy subjects and 30 patients with COPD, using a multipair oesophageal electrode. EMG<sub>di</sub> was normalised to the amplitude of the diaphragm compound muscle action potential (CMAP<sub>di,MS</sub>) in 64 healthy subjects.

The mean  $\pm$  SD EMG<sub>di</sub> % max was  $9.0 \pm 3.4\%$  in healthy subjects and  $27.9 \pm 9.9\%$  in COPD patients, and correlated with percentage predicted forced expiratory volume in one second, vital capacity and inspiratory capacity in patients. EMG<sub>di</sub> % max was higher in healthy subjects aged 51–80 yrs than in those aged 18–50 yrs ( $11.4 \pm 3.4$  versus  $8.2 \pm 2.9\%$ , respectively). Observations in the healthy group were similar when peak EMG<sub>di</sub> or CMAP<sub>di,MS</sub> were used to normalise EMG<sub>di</sub>.

Levels of neural respiratory drive were higher in chronic obstructive pulmonary disease patients than healthy subjects, and related to disease severity. Diaphragm compound muscle action potential could be used to normalise diaphragm electromyogram if volitional inspiratory manoeuvres could not be performed, allowing translation of the technique to critically ill and ventilated patients.

**KEYWORDS:** Chronic obstructive pulmonary disease, electromyography, respiratory diaphragm

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 severity is categorised in terms of forced expiratory volume in one second (FEV<sub>1</sub>) in management guidelines [1], correlations between FEV<sub>1</sub> and breathlessness [2] or quality of life are modest [3], and reported relationships between FEV<sub>1</sub> 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 humans, 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<sub>di</sub>), 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

## AFFILIATIONS

\*King's College London School of Medicine, King's College Hospital, <sup>†</sup>Royal Brompton Hospital, London, UK, <sup>#</sup>Guangzhou Institute of Respiratory Diseases, Guangzhou Medical College, State Key Laboratory of Respiratory Disease, Guangzhou, China.

## CORRESPONDENCE

C.J. Jolley  
Dept of Asthma  
Allergy and Respiratory Science  
King's College London School of Medicine  
King's College Hospital  
Bessemer Road  
London SE5 9PJ  
UK  
Fax: 44 2032993589  
E-mail: caroline.jolley@kcl.ac.uk

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## STATEMENT OF INTEREST

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developed and used to measure NRD [11–14]. Using these electrodes, SINDERBY *et al.* [7] have shown that the amplitude of EMG<sub>di</sub> is higher in patients with significant respiratory disease than in healthy subjects, when normalised to each subject's volitional maximum (EMG<sub>di</sub> % max). However, the number of subjects in the study was small (five healthy males, five COPD patients and five post-polio infection), and it was not designed to explore the use of EMG<sub>di</sub> % max as a marker of disease severity.

The main aims of the present study were to use the EMG<sub>di</sub> to measure NRD in a large cohort of healthy subjects for comparison with levels of NRD in COPD patients, and to investigate the relationship between NRD and pulmonary function in COPD. It was hypothesised that resting EMG<sub>di</sub> % max would be significantly higher in COPD patients than in healthy subjects, and that resting EMG<sub>di</sub> % 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<sub>di,MS</sub>) and the peak root mean square of spontaneous EMG<sub>di</sub> activity (RMS-EMG<sub>di,peak</sub>) recorded during maximal volitional inspiratory manoeuvres. If so, normalising EMG<sub>di</sub> to CMAP<sub>di,MS</sub> 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<sub>di</sub> nonvolitionally in this way could be particularly valuable in the critical care population, particularly in the assessment of the need for ventilatory support, where EMG<sub>di</sub> % 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 neurally adjusted ventilatory assist (NAVA) technology currently in development [15].

## METHODS

### Subjects

In total, 100 healthy subjects (mean ± SD age 40.3 ± 17.4 yrs (range 18–79 yrs); 56% male; ethnicity: 54% Chinese, 36% white European, 10% other) and 30 COPD patients (age 66.6 ± 7.82 (52–88) yrs; 76.0% male; ethnicity: 63% white European, 37% Chinese; FEV<sub>1</sub> 34.8 ± 13.9% predicted) were studied. The subjects' age, height, weight and body mass index (BMI) were documented. Spirometry (FEV<sub>1</sub> and 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 (King's College Hospital, London, UK) procedures.

### Instrumentation and signal processing

EMG<sub>di</sub> 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 supplementary material.

### EMG<sub>di</sub> 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<sub>di</sub> during resting breathing, subjects sat quietly in a relaxed posture for ≥5 min, until ≥2 min of stable, consistent EMG<sub>di</sub> signals had been recorded. Airflow was measured through a mouthpiece connected in series to a pneumotachograph. EMG<sub>di</sub> 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 15 s ("sprint MVV"). Manoeuvres 1–3 were repeated at least three 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<sub>di</sub>

The raw signal was converted to root mean square (RMS; Powerlab Chart v5.4 software, ADInstruments, Chalgrove, UK), using a time constant of 50 ms and a moving window. The maximum RMS-EMG<sub>di</sub> value during 100-ms subdivisions of each breath was then determined, manually selecting EMG<sub>di</sub> signals falling between QRS complexes of the ECG artefact. The mean maximum RMS-EMG<sub>di</sub> per breath over two representative 30-s subdivisions of the whole recording was then calculated.

### Calculation of EMG<sub>di</sub> % max

EMG<sub>di</sub> signals recorded during each of the maximum inspiratory manoeuvres were converted to RMS. The largest RMS-EMG<sub>di</sub> value calculated by analysis of these recordings was labelled "RMS-EMG<sub>di,peak</sub>". EMG<sub>di</sub> % max for each subject was then calculated as the mean maximum RMS-EMG<sub>di</sub> per breath as a percentage of RMS-EMG<sub>di,peak</sub>.

### Assessment of intra- and interobserver reproducibility of EMG<sub>di</sub> % max

In total, 10 healthy subjects were studied on two occasions >24 h apart, at the same time of day. The intraobserver reproducibility of EMG<sub>di</sub> % max measurements was assessed by comparing the results of a single investigator's (C.J. Jolley) analysis of measurements made on two separate days. The interobserver reproducibility of EMG<sub>di</sub> % max measurements was assessed by comparing the results of two investigators' (C.J. Jolley and C. Reilly) analysis of a single set of measurements in five of these subjects.

### Bilateral anterolateral magnetic phrenic nerve stimulation

Bilateral anterolateral magnetic phrenic nerve stimulation (BAMPS) was performed using two double circular 43-mm coils (P/N 9784-00; Magstim Co., Whitland, UK) placed anterolaterally over the left and right phrenic nerves, as previously described [17]. The coils were powered by a Magstim 200 stimulator (Magstim Co.). 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 CMAP<sub>di,MS</sub> was measured as the peak–trough amplitude, as previously described [18]. The interoccasion coefficient of variation (CV) in the previous study was 8.6% [18].

### Statistical analysis

Ranges of EMG<sub>di</sub> % max were 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. Values of p were considered to be significant at <0.05 level. Relationships between EMG<sub>di</sub> and anthropometric or lung function variables were investigated by regression analysis. Intra- and interobserver reproducibility was assessed by calculating the CV 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.

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<sub>di</sub> values during the different manoeuvres are given in the online supplementary material.

#### Healthy subjects

The mean ± SD EMG<sub>di</sub> % max of the healthy group was 9.0 ± 3.4%. The EMG<sub>di</sub> % max was 9.2 ± 3.4% for males and 8.8 ± 3.3% for females (p=0.53).

Correlations between EMG<sub>di</sub> % max and age, height, weight and BMI are shown in table 2. EMG<sub>di</sub> % max was slightly higher in healthy subjects aged 51–80 yrs (26% of the total healthy subjects, 13 male) than in those aged 18–50 yrs (74% of the total, 43 male; 11.4 ± 3.40 versus 8.16 ± 2.92%, respectively; p=0.001), although the overall linear correlation between EMG<sub>di</sub> % max and age was weak (r=0.34, p<0.001; see online supplementary material). There was no significant difference in RMS-EMG<sub>di,peak</sub> between the older and younger cohorts (226.4 ± 71.7 versus 250.3 ± 67.4 μV, respectively). There were weak but significant negative correlations between EMG<sub>di</sub> % max and absolute FEV<sub>1</sub> (r= -0.34, p=0.001), and between EMG<sub>di</sub> % max and absolute VC (r= -0.21, p=0.04).

**TABLE 1** Demographic and anthropometric data for all healthy subjects and chronic obstructive pulmonary disease (COPD) patients

	Healthy	COPD	p-value
Subjects n	100	30	
Age yrs	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 <sup>-2</sup>	23.0 ± 3.26	23.0 ± 4.39	0.95
Male %	56.0	73.3	0.14
FEV <sub>1</sub> % pred	104.5 ± 14.3	34.8 ± 13.9	
VC % pred	106.4 ± 13.4	83.0 ± 18.6	

Data are presented as mean ± SD, unless otherwise stated. BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in one second; % pred: % predicted; VC: vital capacity.

These data gave 95% confidence intervals of EMG<sub>di</sub> % max of 7.5–8.8% in normal subjects aged 18–50 yrs, and 10.1–12.8% in subjects aged >50 yrs.

Sniff nasal inspiratory pressure (SNIP) was higher in the subjects aged 18–50 yrs than in those aged 51–80 yrs (91.4 ± 22.3 versus 80.5 ± 16.3 cmH<sub>2</sub>O, respectively; p=0.04), but the relationship between EMG<sub>di</sub> % max and SNIP values was weak (r=0.19, p=0.06; n=98). The difference between maximal inspiratory pressure (P<sub>I,max</sub>) in those aged 18–50 yrs and those aged 51–80 yrs approached statistical significance (80.6 ± 32.6 versus 69.5 ± 20.7 cmH<sub>2</sub>O, respectively; p=0.09). There was no significant relationship between EMG<sub>di</sub> % max and P<sub>I,max</sub> (r=0.10, p=0.31).

Correlations between EMG<sub>di</sub> % max and age, height, weight and BMI were similar in the white European and Chinese subgroups. Data comparing EMG<sub>di</sub> % max values in white European and Chinese ethnic groups are provided in the online supplementary material.

#### CMAP<sub>di,MS</sub>

CMAP<sub>di,MS</sub> was assessed in 64 subjects. Supramaximality was judged to have been achieved when the mean CMAP<sub>di,MS</sub> amplitude at 100% MSO was less than 5% greater than the highest mean CMAP<sub>di,MS</sub> amplitude achieved at the lower stimulator outputs. Using these criteria, supramaximality was achieved in 92.8% of the subjects. The CMAP<sub>di,MS</sub> amplitude achieved at 100% MSO values was recorded if supramaximality was not achieved.

Representative traces recorded during BAMPS are shown in the online supplementary material. The mean ± SD CMAP<sub>di,MS</sub> amplitude was 2.4 ± 0.7 mV. The 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<sub>di,MS</sub> amplitude and RMS-EMG<sub>di</sub>

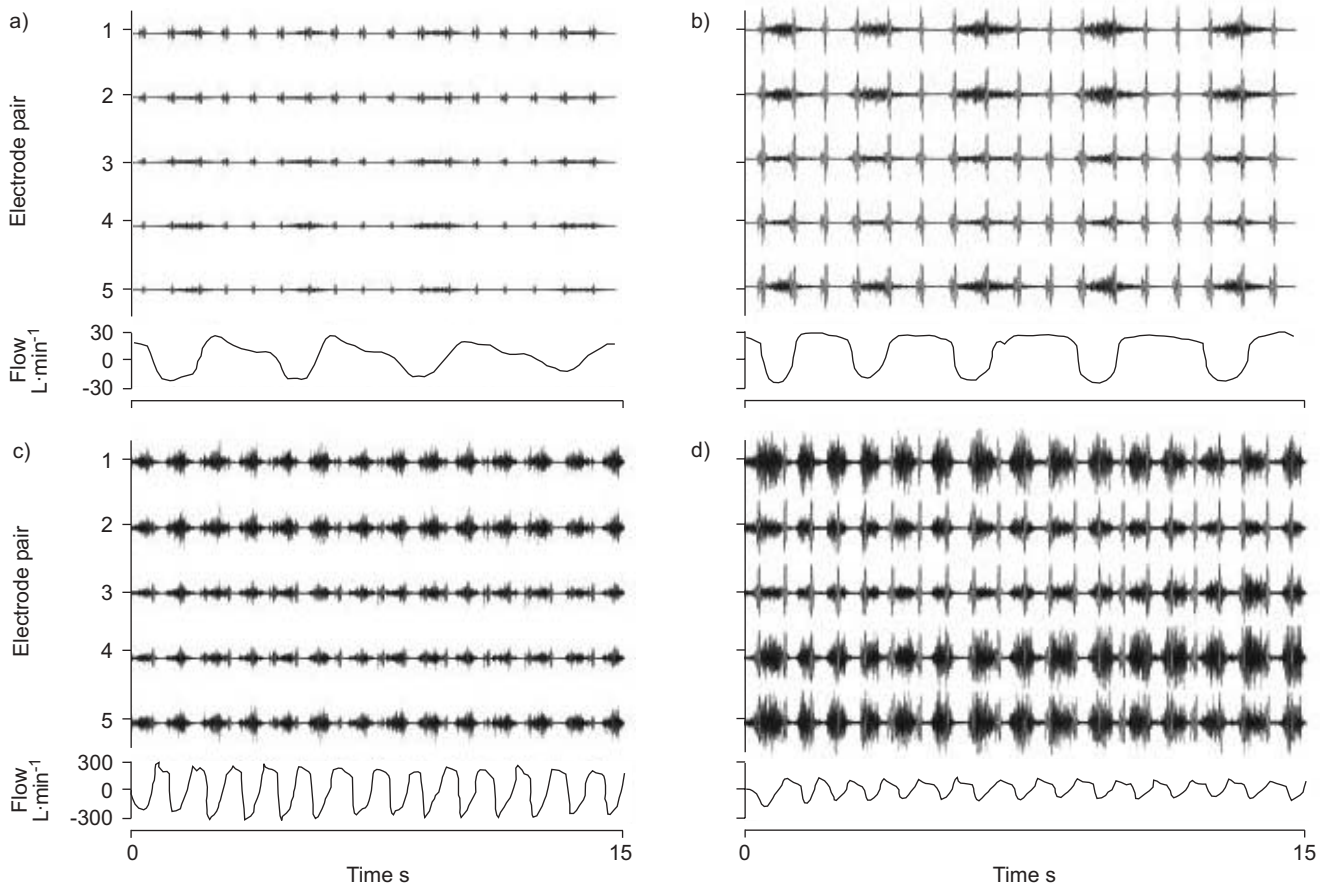
Linear regression analysis revealed a positive correlation between each subject's RMS-EMG<sub>di,peak</sub> and CMAP<sub>di,MS</sub> amplitude (r=0.59, p<0.001; fig. 2). The mean ± SD RMS-EMG<sub>di</sub> per breath (in μV) expressed as a percentage of CMAP<sub>di,MS</sub> amplitude (RMS-EMG<sub>di</sub>/CMAP<sub>di,MS</sub>) was 0.9 ± 0.4%. The relationships between RMS-EMG<sub>di</sub>/CMAP<sub>di,MS</sub> and age, height, weight and BMI were similar to those with EMG<sub>di</sub> % max (table 2).

#### COPD patients

EMG<sub>di</sub> % max in the COPD patients was 27.9 ± 9.9%. This was significantly higher than EMG<sub>di</sub> % max recorded in the 26 healthy controls matched for age, height, weight and BMI (11.4 ± 3.4%; p<0.001; table 3 and fig. 3). COPD patients generated a smaller tidal volume (V<sub>T</sub>) as a percentage of the predicted VC (VC<sub>pred</sub>) per unit EMG<sub>di</sub> % max ((V<sub>T</sub> % VC<sub>pred</sub>)/(EMG<sub>di</sub> % max)) than the healthy controls (0.8 ± 0.4 versus 1.4 ± 0.6 arbitrary units, respectively; table 3 and fig. 3).

All patients completed FEV<sub>1</sub> and VC measurements, and IC was measured in 20 patients. Significant correlations, best described by curve regression functions, were observed between EMG<sub>di</sub> % max and FEV<sub>1</sub> % pred, VC % pred and IC % pred, and between (V<sub>T</sub> % VC<sub>pred</sub>)/(EMG<sub>di</sub> % max) and FEV<sub>1</sub> % pred, VC % pred





**FIGURE 1.** Representative traces at rest (a and b) and during maximum voluntary ventilation (c and d) in a healthy subject (a and c) and in a severe chronic obstructive pulmonary disease patient (b and d). Diaphragm electromyogram traces recorded from electrode pairs 1 to 5 (distal to proximal) are shown. The scale of each electrode pair is +500 to -500  $\mu\text{V}$ . Flow is calibrated with inspiration as negative values.

and IC % pred (table 4, fig. 4 and additional figures in the online supplementary material).

**Peak RMS-EMG<sub>di</sub> values during different maximal inspiratory manoeuvres**

Data are presented as median (interquartile range (IQR)), as the sprint MVV data were non-normally distributed. The data are also presented in tables S2 and S3 and in figure S3, in the online supplementary material.

The TLC and  $P_{I,max}$  manoeuvres yielded peak values most frequently in the healthy group (31% each), and the TLC

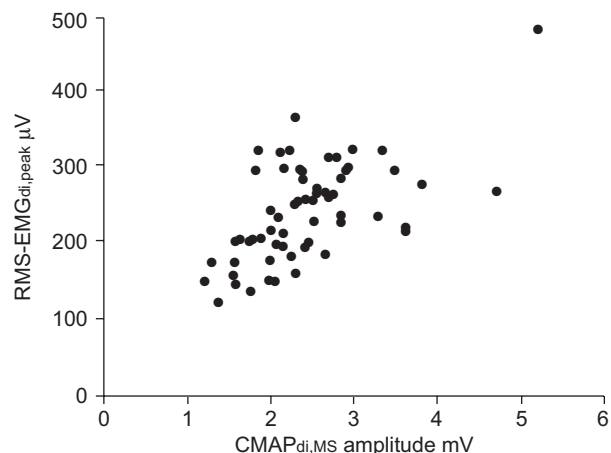
manoeuvre yielded the highest RMS-EMG<sub>di</sub> values on average in that group (median (IQR) 208.2 (98.7)  $\mu\text{V}$ ). The sniff manoeuvre yielded peak values most frequently in the COPD group (33%) and yielded the highest RMS-EMG<sub>di</sub> values on average in that group (170.6 (76.5)  $\mu\text{V}$ ). The MVV manoeuvre yielded the lowest values in both groups (healthy 158.7 (78.4)  $\mu\text{V}$ , COPD 150.2 (97.2)  $\mu\text{V}$ ) despite yielding the highest value in 26% of the COPD group.

There were no significant differences between RMS-EMG<sub>di</sub> values when the manoeuvres were compared for the COPD group (using the Wilcoxon signed-rank test to compare values

**TABLE 2** Correlations between EMG<sub>di</sub> % max and RMS-EMG<sub>di</sub>/CMAP<sub>di,MS</sub>, and height, weight, BMI and age in healthy subjects

	Height		Weight		BMI		Age	
	r-value	p-value	r-value	p-value	r-value	p-value	r-value	p-value
<b>EMG<sub>di</sub> % max</b>	0.002	0.62	0.09	0.39	0.12	0.24	0.34	<0.001
<b>RMS-EMG<sub>di</sub>/CMAP<sub>di,MS</sub></b>	-0.05	0.69	0.08	0.53	0.14	0.29	0.28	0.02

EMG<sub>di</sub>: diaphragm electromyogram; % max: % maximum; RMS: root mean square; CMAP<sub>di,MS</sub>: amplitude of the diaphragm compound muscle action potential following bilateral anterolateral magnetic stimulation; BMI: body mass index.



**FIGURE 2.** Relationship between amplitude of the diaphragm compound muscle action potential following bilateral anterolateral magnetic stimulation ( $CMAP_{di,MS}$ ) and peak root mean square of spontaneous diaphragm electromyogram activity ( $RMS-EMG_{di,peak}$ ). Linear regression analysis revealed a positive correlation between each subject's  $RMS-EMG_{di,peak}$  and  $CMAP_{di,MS}$  amplitude ( $r=0.59$ ,  $p<0.001$ ).

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 10 subjects, was 0.94 [19]. The mean  $\pm$  SD CV was  $0.09 \pm 0.05$ .

##### Interobserver reproducibility

The mean  $\pm$  SD CV of  $EMG_{di}$  % max between measurements made in five subjects on the same day, comparing the results of analysis by two investigators, was  $0.10 \pm 0.08$ . The intraclass correlation coefficient was 0.71. Tables and Bland–Altman plots of these data are presented in the online supplementary material.

## DISCUSSION

The present study is the first to define normal ranges of NRD as  $EMG_{di}$  % max in a large population of healthy adults; the largest previous study included 15 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 the current cohort of healthy subjects was  $9.0 \pm 3.4\%$  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  $8.4 \pm 2.5\%$  and  $43.4 \pm 22.1\%$  in five healthy and five severe COPD patients, respectively, using similar methods. The lower average  $EMG_{di}$  % max found in the present COPD patients is

**TABLE 3** Demographic, anthropometric, lung function and  $EMG_{di}$  % max data for COPD patients and healthy subjects matched for age, height, weight and BMI

	Healthy	COPD	p-value
Subjects n	26	30	
Age yrs	$64.8 \pm 7.4$	$66.6 \pm 7.8$	0.41
Height m	$1.66 \pm 0.1$	$1.66 \pm 0.08$	0.79
Weight kg	$69.0 \pm 13.0$	$63.9 \pm 13.9$	0.15
BMI $kg \cdot m^{-2}$	$24.9 \pm 3.3$	$23.0 \pm 4.4$	0.06
Male %	50.0	73.3	0.10
FEV <sub>1</sub> % pred	$110.8 \pm 16.9$	$34.8 \pm 13.9$	<0.001
VC % pred	$113.3 \pm 15.3$	$83.0 \pm 18.6$	<0.001
Vt mL	$499.3 \pm 167.4$	$608.3 \pm 199.4$	0.03
Vt % VC <sub>pred</sub>	$14.5 \pm 4.0$	$18.7 \pm 5.6$	0.002
Tidal RMS- $EMG_{di}$ per breath $\mu V$	$24.8 \pm 9.4$	$53.2 \pm 29.0$	<0.001
RMS- $EMG_{di,peak}$ $\mu V$	$226.4 \pm 71.7$	$188.9 \pm 68.8$	0.052
$EMG_{di}$ % max	$11.4 \pm 3.4$	$27.9 \pm 9.9$	<0.001
(Vt % VC <sub>pred</sub> )/( $EMG_{di}$ % max) AU	$1.4 \pm 0.6$	$0.8 \pm 0.4$	<0.001

Data are presented as mean  $\pm$  SD, unless otherwise stated.  $EMG_{di}$ : diaphragm electromyogram; % max: % maximum; COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in one second; % pred: % predicted; VC: vital capacity; Vt: tidal volume; % VC<sub>pred</sub>: percentage of predicted VC; RMS: root mean square; RMS- $EMG_{di,peak}$ : peak RMS of spontaneous  $EMG_{di}$  activity; AU: arbitrary units.

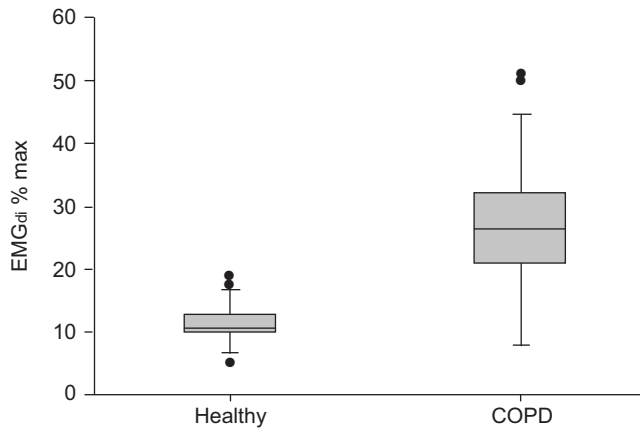
likely to reflect the range of disease severity. By showing that there is a correlation between  $EMG_{di}$  % max and the degree of airflow obstruction and hyperinflation, and that this is a reproducible measure, the present study builds on earlier observations and demonstrates the potential value of  $EMG_{di}$  % 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.

#### 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 the older (51–80 yrs of age) cohort compared with that of subjects aged <50 yrs is likely to reflect the known “normal” changes in ventilatory mechanics occurring with increased age. Declines in FEV<sub>1</sub> [20], VC [21], respiratory muscle strength [22] and 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<sub>1</sub>



**FIGURE 3.** Box-and-whisker plots comparing diaphragm electromyogram as a percentage of maximum ( $EMG_{di} \% \max$ ) in 30 chronic obstructive pulmonary disease (COPD) patients with 26 healthy subjects matched for age, height, weight and body mass index. Comparisons are made using the independent samples t-test. The box length is the interquartile range. ●: outliers, *i.e.* cases with values between 1.5 and 3 interquartile ranges from the upper or lower edge of the box.

and VC are consistent with this. The current observation that the correlation of SNIP and  $P_{I,\max}$  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.

### COPD

The results of the present 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 with 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 nondiaphragmatic muscles [25] is increased in COPD. However, DE TROYER *et al.* [24] and GANDEVIA *et al.* [25] 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. First, the diaphragm must generate more pressure to achieve a given  $V_T$ , compared with healthy subjects. Increased airways resistance in COPD results in significant expiratory airflow limitation at rest, leading to gas trapping, which increases intrathoracic 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.* [26] demonstrated a linear negative correlation of twitch transdiaphragmatic pressure with increasing lung volume of  $3.5 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}$ . The ability of the diaphragm to generate

**TABLE 4** Correlations between  $EMG_{di} \% \max$  and  $(V_T \% VC_{\text{pred}})/(EMG_{di} \% \max)$  and % predicted FEV<sub>1</sub>, VC and IC

	FEV <sub>1</sub> % pred		VC % pred		IC % pred	
	r <sup>2</sup>	p-value	r <sup>2</sup>	p-value	r <sup>2</sup>	p-value
<b>EMG<sub>di</sub> % max</b>	0.40	<0.001	0.61	<0.001	0.28	0.02
<b>(V<sub>T</sub> % VC<sub>pred</sub>)/ (EMG<sub>di</sub> % max)</b>	0.25	0.005	0.48	<0.001	0.36	0.006

EMG<sub>di</sub>: diaphragm electromyogram; % max: % maximum; V<sub>T</sub>: tidal volume; VC: vital capacity; % VC<sub>pred</sub>: percentage of predicted VC; FEV<sub>1</sub>: forced expiratory volume in one second; IC: inspiratory capacity; % pred: % predicted.

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 ventilation/perfusion ( $V'/Q'$ ) mismatch [27].

Although RMS- $EMG_{di,\text{peak}}$  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  $23.5 \pm 8.2\%$ , still significantly higher than  $EMG_{di} \% \max$  in the healthy group ( $p < 0.001$ ).

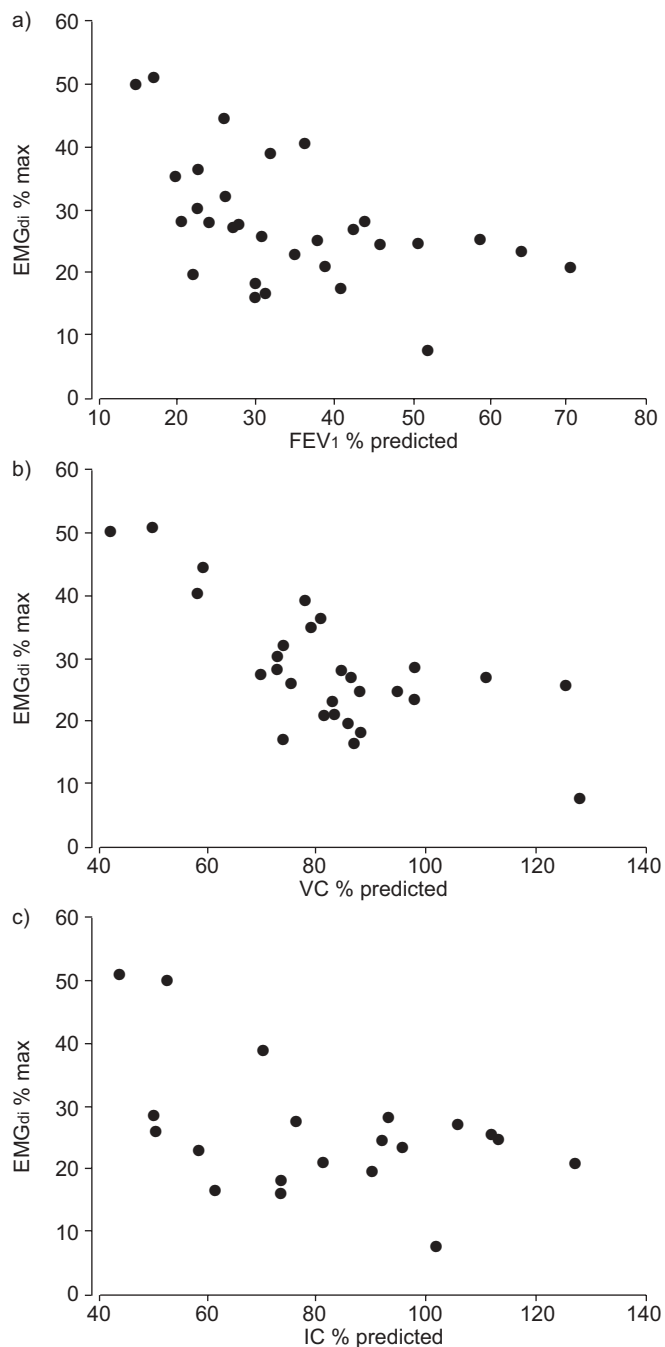
### Significance of raised $EMG_{di} \% \max$ and reduced $(V_T \% VC_{\text{pred}})/(EMG_{di} \% \max)$ in COPD

The current finding that  $EMG_{di} \% \max$  is raised, and is negatively correlated with FEV<sub>1</sub>, VC and the degree of hyperinflation at rest (described in terms of IC % pred) 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 hypoxaemia, hypercapnia and  $V'/Q'$  mismatch, than were carried out in the present study.

$(V_T \% VC_{\text{pred}})/(EMG_{di} \% \max)$  was lower in COPD patients than healthy subjects, reflecting neuromechanical uncoupling in COPD, and this correlated with disease severity. Neuro-mechanical 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 100 ms ( $P_{0.1}$ ), or the amplitude of tidal oesophageal pressure swings, which will underestimate levels of NRD in COPD patients with the most neuromechanical dissociation.

### Bilateral CMAP<sub>di,MS</sub> values

To the best of the current authors' knowledge, there have been no previous studies that have compared CMAP<sub>di,MS</sub> and RMS- $EMG_{di,\text{peak}}$  in healthy subjects. Normal ranges of bilateral



**FIGURE 4.** Scatter plots showing correlations between diaphragm electromyogram as a percentage of maximum ( $EMG_{di} \% \max$ ) and percentage predicted a) forced expiratory volume in one second ( $FEV_1$ ), b) vital capacity (VC) and c) inspiratory capacity (IC), using curve estimation models. Regression coefficients ( $r^2$  values) and  $p$ -values were as follows: a)  $r^2=0.40$ ,  $p<0.001$ ; b)  $r^2=0.61$ ,  $p<0.001$ ; c)  $r^2=0.28$ ,  $p=0.02$ .

$CMAP_{di}$  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. The present findings of a mean  $\pm$  SD  $CMAP_{di,MS}$  amplitude of  $2.4 \pm 0.7$  mV and a PNCT of  $6.9 \pm 0.7$  ms are consistent, following extrapolation from bi- to unilateral measurements, with a unilateral  $CMAP_{di,MS}$

amplitude and PNCT of  $1.45 \pm 0.35$  and  $6.9 \pm 0.9$  ms (right) and  $1.68 \pm 0.47$  and  $7.6 \pm 0.7$  ms (left), as previously recorded in a similar manner [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 nonvolitional  $EMG_{di}$  in healthy subjects suggests that the nonvolitional 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  $P_{0.1}$ , 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

The current study 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 herein discussed. 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 mentioned in the foregoing discussion, could in addition be measured nonvolitionally 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 the current authors' 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, the present study has demonstrated, in a large cohort of healthy subjects and patients with chronic obstructive



pulmonary disease, that levels of neural respiratory drive, measured as diaphragm electromyogram as a percentage of maximum, are higher in patients with chronic obstructive pulmonary disease than in healthy subjects, and highest in patients with the most severe airflow obstruction and hyperinflation. Diaphragm electromyogram as a percentage of maximum therefore provides a composite measure of ventilatory load and capacity, and could provide a method of assessing chronic obstructive pulmonary disease severity. Normal ranges of diaphragm electromyogram as a percentage of maximum have also been established, which may be used for comparative data in future studies in patients with chronic obstructive pulmonary disease, or indeed any other cardiorespiratory disease, to further understanding of the pathophysiology of ventilatory failure. The current findings also demonstrate that nonvolitional activation of the diaphragm is of potential use in the assessment of diaphragm electromyogram as a percentage of maximum in patients who are unable to perform maximal volitional inspiratory manoeuvres.

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