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ORIGINAL ARTICLE

Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD

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ABSTRACT

Rationale Hospitalised patients with acute exacerbation of COPD may deteriorate despite treatment, with early readmission being common.

Objectives To investigate whether neural respiratory drive, measured using second intercostal space parasternal muscle electromyography (EMG_{para}), would identify worsening dyspnoea and physician-defined inpatient clinical deterioration, and predict early readmission.

Methods Patients admitted to a single-site university hospital with exacerbation of COPD were enrolled. Spirometry, inspiratory capacity (IC), EMG_{para}, routine physiological parameters, modified early warning score (MEWS), modified Borg scale for dyspnoea and physician-defined episodes of deterioration were recorded daily until discharge. Readmissions at 14 and 28 days post discharge were recorded.

Measurements and main results 120 patients were recruited (age 70±9 years, forced expiratory volume in 1 s (FEV_1) of 30.5±11.2%). Worsening dyspnoea, defined as at least one-point increase in Borg scale, was associated with increases in $EMG_{para\%max}$ and MEWS, whereas an increase in $EMG_{para\%max}$ alone was associated with physician-defined inpatient clinical deterioration. Admission-to-discharge change (Δ) in the normalised value of EMG_{para} ($\Delta EMG_{para\%max}$) was inversely correlated with ΔFEV_1 ($r=-0.38$, $p<0.001$) and ΔIC ($r=-0.44$, $p<0.001$). $\Delta EMG_{para\%max}$ predicted 14-day readmission (OR 1.13, 95% 1.03 to 1.23) in the whole cohort and 28-day readmission in patients under 85 years (OR 1.09, 95% CI 1.01 to 1.18). Age (OR 1.08, 95% CI 1.03 to 1.14) and 12-month admission frequency (OR 1.29, 1.01 to 1.66), also predicted 28-day readmission in the whole cohort.

Conclusions Measurement of neural respiratory drive by EMG_{para} represents a novel physiological biomarker that may be helpful in detecting inpatient clinical deterioration and identifying the risk of early readmission among patients with exacerbations of COPD.

Trial registration NCT01361451.

Key messages

What is the key question?

- Can non-invasive measurement of neural respiratory drive identify clinical deterioration and the risk of early readmission in patients admitted with exacerbation of COPD?

What is the bottom line?

- Neural respiratory drive, measured by second intercostal space parasternal muscle electromyography, is a physiological biomarker of worsening breathlessness and physician-defined clinical deterioration in COPD exacerbations, and may predict early readmission.

Why read on?

- The results of a large physiological observational cohort study are presented, validating a novel physiological biomarker that represents the balance between the load and the capacity of the respiratory muscle pump during exacerbations of COPD.

INTRODUCTION

Acute exacerbations of COPD (AECOPD) are common, accounting for 12.5% of emergency admissions in the UK[1] with an in-hospital mortality of up to 10%.[2] Eighteen percent of patients with AECOPD present to the emergency department with acute hypercapnic respiratory failure[3] and a further 5% will develop late respiratory acidosis. Twenty percent of hospitalised patients with AECOPD are readmitted within 28 days,[4 5] and financial penalties are now in operation for acute care hospitals in the UK and USA for readmissions within 30 days.[6 7] It is a health economic priority to identify COPD treatment failure promptly and reduce readmissions, and biomarkers that can achieve this will therefore be of significant clinical value.

Previous studies have reported the patient characteristics that predict readmission among hospitalised patients with COPD,[2 8–11] but these are limited by their dependence on non-modifiable parameters, rather than on the trajectory of response to treatment. In addition, early-warning scores,[12] often used to track inpatient clinical deterioration and trigger escalation of care, vary in their ability to predict outcomes such as critical care admission and hospital mortality,[13] limiting the usefulness of these approaches.

More advanced physiological measurements of elastic and threshold respiratory load are difficult

during an acute exacerbation as invasive monitoring of pleural pressure is poorly tolerated. In addition, the measurement of ventilation in flow-limited patients characterised by neuroventilatory uncoupling, as a result of severe hyperinflation, has significant caveats and therefore the non-invasive measurement of neural respiratory drive (NRD), which is a direct reflection of the imbalance between respiratory muscle load and capacity, would be a preferred option. Indeed, NRD as an advanced physiological biomarker, provides a direct measure of the balance between respiratory muscle load and capacity,[14] and has gained increasing attention in the acute setting.[15]

Recently, surface electromyography (EMG) of the second intercostal space parasternal muscles (EMG_{para}) has been used as a non-invasive alternative to the invasive oesophageal measurement[16] of NRD in patients with COPD, asthma and cystic fibrosis.[15 17 18] Murphy *et al*[15] previously showed, in a pilot feasibility study of this technique, that the change in NRD during hospital admission was a biomarker of physician-defined clinical deterioration, and furthermore, change in NRD from admission to discharge identified patients with COPD who were readmitted within 14 days. However, this previous study was in a small group of selected patients with COPD, with the majority of patients having only a single pair of NRD measurements made during their hospital admission.

We therefore hypothesised that, in a large, prospective observational cohort study of patients hospitalised with exacerbation of COPD, changes in daily measurements of NRD between hospital admission and discharge would predict readmission within 14 and 28 days. We further hypothesised that change in NRD would objectively identify worsening dyspnoea and physician-defined clinical deterioration.

METHODS

Patients

The study was approved by the London-Bentham Research Ethics Committee and participants provided written informed consent. The authors registered the study as an observational cohort study (NCT01361451). Patients with a physician diagnosis of acute exacerbation of COPD, defined according to clinical features and basic investigations,[1] were enrolled within 12 h of admission to a UK teaching hospital. The requirement for admission was determined by the attending physician. Patients were excluded if they had another cause for their acute admission (eg, acute heart failure, PE), cognitive impairment, active cancer or significant psychosocial factors.

Admission data

Demographic and anthropometric data were collected. FEV_1, FVC and inspiratory capacity (IC)[19] were measured using a pneumotachometer (3830, Hans-Rudolph, Shawnee, USA) or a handheld spirometer (Micro, Carefusion, Basingstoke, UK) according to international standards.[20] Symptoms were assessed using the Medical Research Council (MRC) Dyspnoea scale,[21] the modified Borg scale for dyspnoea[22] and the COPD Assessment Test (CAT).[23] Standard physiological observations (respiratory rate, heart rate, oxygen saturation, body temperature and blood pressure) were collected; an aggregate score derived from these was recorded as the modified early warning score (MEWS), according to local protocol.

EMG_{para} measurement

EMG_{para} was measured with patients in a semi-recumbent or seated position, as previously described.[15] After skin preparation, two surface electrodes (Blue Sensor Q, Ambu, St Ives, UK) were placed in the second intercostal spaces, immediately lateral to the sternum. The skin was marked to allow placement of electrodes in an identical position throughout the study. Nasal cannulae connected to a differential pressure transducer (Technical services, Lane Fox Respiratory Unit, London, UK) identified inspiration and expiration phases (figure 1). EMG_{para} signals were amplified and sampled at 2 kHz (Dual Bioamp and Powerlab, AD Instruments, Chalgrove, UK). Signals were analysed using Labchart software (AD Instruments) on a personal computer. The peak root mean square EMG_{para} activity for each inspiration was averaged over 1 min of tidal breathing and normalised to a value of EMG_{para} obtained during a maximal inspiratory sniff manoeuvre, obtained before each measurement.[15] Two measures of NRD were derived, including (1) $EMG_{para\%max}$, the mean peak inspiratory tidal EMG_{para} normalised to the maximal manoeuvre; and (2) NRDI (Neural Respiratory Drive Index), the product of $EMG_{para\%max}$ and respiratory rate.[15]

Study protocol

EMG_{para}, modified Borg scale, FEV_1, FVC and IC were measured at least daily, between admission and medical fitness for

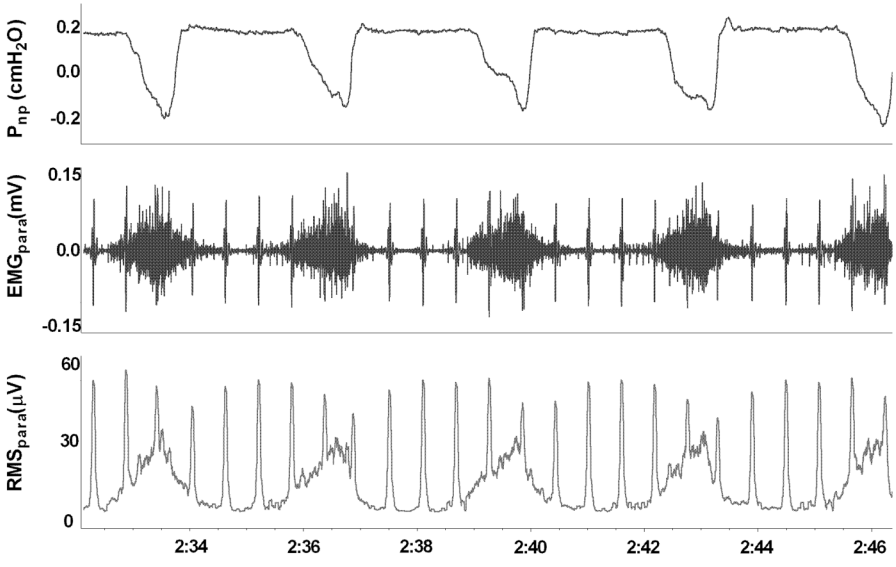

Figure 1 Representative trace of nasal pressure and second intercostal space parasternal electromyogram during tidal breathing in a patient with COPD during an exacerbation. P_{np}, nasal pressure; EMG_{para}, parasternal electromyogram; RMS_{para}, root mean square of EMG_{para}.

discharge, and at least 2 h after the last bronchodilator dose. Medical fitness for discharge was determined by the senior attending physician, which was either senior resident or consultant. Supplemental oxygen was provided as instructed by the attending physicians. Patients were settled at rest for 7 min before EMG_{para} traces were acquired for analysis. Patients requiring non-invasive ventilation (NIV) had measurements taken after 10 min off NIV. The attending physicians, who were blinded to EMG_{para} data, were asked to provide an opinion regarding clinical improvement or deterioration between successive assessments. EMG_{para} data were analysed after patients' discharge from hospital. Data for readmissions and deaths were obtained from patients and their relatives, and from medical records. Admission-to-discharge changes in $EMG_{para\%max}$ and NRDI were expressed as $\Delta EMG_{para\%max}$ and ΔNRDI, respectively. Changes in $EMG_{para\%max}$ and NRDI between consecutive inpatient measurements were denoted $\Delta EMG_{para\%max,cons}$ and $\Delta NRDI_{cons}$, respectively.

Primary endpoint and power calculation

Although this was an observational cohort study, an a priori primary endpoint of 28-day readmission was taken as this was considered to have major clinical relevance to the current financial penalty systems for readmission in the UK and USA. Secondary endpoints were 14-day readmission and clinical deterioration, defined by (1) at least one-point increase in Borg scale[24] between consecutive recordings, or (2) attending physician opinion. A sample size of 120 was determined from published pilot data[15] with a presumed 28-day readmission rate of 20% to detect a difference in NRDI of 203/min between readmitted and non-readmitted patients with a power of 80%.

Statistical analysis

Paired data were analysed using t or Wilcoxon signed-rank tests. Readmitted and non-readmitted groups were compared using independent t or Mann–Witney U tests. Death after discharge without early readmission was analysed together with readmissions. Logistic regression and receiver-operator characteristic (ROC) analyses were used to identify, and test the utility of, predictors of readmission. Kaplan–Meier plots and log rank tests were used to analyse time to readmission. Generalised linear mixed model (GLMM) analyses were used to assess the association between $\Delta EMG_{para\%max,cons}$ and episodes of worsening dyspnoea or with physician-defined deterioration. For the purposes of this study, death was analysed with the readmission data.

RESULTS

Admission, clinical course and readmission data

A total of 131 patients were enrolled between January 2011 and September 2013 (see online supplementary figure E1), and 120 patients completed the study between admission and discharge (table 1). Twenty (16.7%) patients were unable to perform FEV_1 and FVC manoeuvres at admission, while 27 (22.5%) patients could not perform admission IC manoeuvres. Three (2.5%) patients declined arterial blood gas sampling. Eight (6.7%) patients required NIV or high-dependency care following admission to hospital. There were no patients who received high-flow humidified oxygen therapy. A further three (2.5%) patients deteriorated more than 12 h after admission and required NIV. Median length of hospital stay was 3 (IQR 2–6) days. Median interval from the date of medical fitness for discharge to the date of discharge was 0 (IQR 0–1) days. One patient died 3 days after discharge from hospital.

Table 1 Baseline characteristics at admission to hospital

Anthropometrics, smoking and previous exacerbations	
Age (years)	70 (9)
Male (%)	58 (48.3)
BMI (kg/m^2)	25.3 (7.2)
Current smokers (%)	47 (39.2)
Smoking history (pack years)	40 (25–50)
Exacerbation frequency (/12 months)	3 (1–5)
Hospital admission frequency (/12 months)	1 (0–2)
Current exacerbation history	
Duration of symptoms (days)	4 (2–7)
Systemic steroids prior to admission (%)	26 (21.7)
Antibiotics prior to admission (%)	30 (25.0)
Comorbidities	
Ischaemic heart disease (%)	34 (28.3)
Cerebrovascular disease (%)	13 (10.8)
Hypertension (%)	53 (44.2)
Diabetes mellitus (%)	20 (16.7)
Disease severity	
GOLD stage 2 (%)*	4 (4)
GOLD stage 3 (%)*	36 (36)
GOLD stage 4 (%)*	60 (60)
MRC dyspnoea grade	4 (4–5)
Admission investigations	
Arterial blood gases†	
pH	7.39 (0.06)
p_aCO_2 (kPa)	5.82 (1.39)
p_aO_2 (kPa)	8.83 (2.98)
Bicarbonate (mEq/L)	25.7 (3.8)
Base excess (mmol/L)	0.63 (3.1)
Lactate (mmol/L)	1.7 (1.5)
Routine laboratory tests	
C-reactive protein (mmol/L)	65 (100)
Creatinine (μmol/L)	72 (45)
Fibrinogen (mmol/L)‡	4.6 (1.5)
Leucocytes (×10^3/μL)	11.9 (4.8)
Neutrophils (×10^3/μL)	8.4 (5.0)
Eosinophils (×10^3/μL)	0.3 (0.7)
Haemoglobin (g/dL)	13.8 (1.7)
Platelets (×10^9/L)	259 (87)
Radiographic consolidation	25 (20.8)
Length of hospital stay (days)	3 (2–6)
Deaths within 28 days (%)	1 (0.8)
Readmission within 28 days (%)	26 (21.7)
Deaths within 14 days (%)	1 (0.8)
Readmission within 14 days (%)	15 (12.5)

Mean (SD), Median (IQR) or N (%).
*N=100.
†N=117.
‡N=68.
BMI, body mass index; GOLD, Global initiative for chronic Obstructive Lung Disease; MRC, Medical Research Council; P_aCO_2, arterial partial pressure of carbon dioxide; P_aO_2, arterial partial pressure of oxygen.

Fourteen-day and 28-day readmission rates were 12.5% and 21.7%, respectively. The single death was analysed with the readmission data.

Early warning scores, symptom scores and physiological data

MEWS, modified Borg scale and CAT scores all improved from admission to discharge (table 2). FEV_1, FVC and IC increased over this period, with a concomitant fall in $EMG_{para\%max}$ and NRDI (table 2).

Table 2 Physiological measurements at admission and discharge

	Admission	Discharge	p Value
Spirometry			
FEV_1 (L)*	0.69 (0.28)	0.75 (0.31)	<0.001
FVC (L)*	1.51 (0.56)	1.63 (0.54)	0.02
FEV_1%predicted (%)*	30.5 (11.2)	33.7 (12.2)	<0.001
FEV_1/FVC ratio (%)*	47.4 (12.8)	48.9 (13.2)	0.184
Inspiratory capacity (L)†	1.39 (0.58)	1.56 (0.63)	<0.001
Symptom scores			
Modified Borg scale	3 (2–5)	2 (1–3)	<0.001
COPD assessment test	29 (24–32.75)	24 (17–29)	<0.001
Routine observations			
S_pO_2 (%)	92.6 (3.5)	93.4 (2.8)	0.024
Temperature (°C)	36.5 (0.6)	36.3 (0.5)	0.023
Heart rate (/min)	97.2 (15.8)	84.8 (12.9)	<0.001
Respiratory rate (/min)	23.1 (4.3)	20.4 (2.4)	0.024
MEWS	3 (2–5)	2 (1–3)	<0.001
Parasternal EMG parameters			
Sniff (maximum) EMG (μV)	74.8 (37.3)	76.5 (39.1)	0.35
$EMG_{para\%max}$ (%)	17.4 (8.2)	15.8 (7.3)	0.017
NRDI (/min)	372 (205)	329 (196)	0.018

Values are expressed as mean (SD) or median (IQR).
*N=100.
†N=93.
EMG, electromyography; MEWS, medical early warning score; NRDI, Neural Respiratory Drive Index; S_pO_2, transcutaneous oxygen saturation.

Relationship between NRD, physiological parameters and dyspnoea

Admission-to-discharge change (Δ) in $EMG_{para\%max}$ was inversely correlated with ΔFEV_1 (r=−0.38, p<0.001), ΔFVC (r=−0.31, p=0.003) and ΔIC (r=−0.44, p<0.001) (figure 2). However, there was no correlation between $\Delta EMG_{para\%max}$ and Δmodified Borg scale, ΔCAT score or ΔMEWS. Increases in FEV_1 and IC were independently associated with reductions in $EMG_{para\%max}$ on multiple linear regression analysis (ΔFEV_1 standardised coefficient β=−0.36, p=0.001; ΔIC β=−0.26, p=0.019). $\Delta EMG_{para\%max}$ was weakly correlated with age (r=+0.24, p=0.009). ΔNRDI was weakly inversely correlated with ΔFEV_1 (r=−0.30, p=0.004), ΔFVC (r=−0.29, p=0.007) and ΔIC (r=−0.40, p<0.001), as well as with body mass index (r=−0.27, p=0.005). There were no correlations between ΔNRDI and ΔBorg scale or ΔMEWS.

Predictors of readmission within 28 days

Twenty-seven (22.5%) patients were readmitted or died within 28 days of hospital discharge. Independent sample analysis showed significant differences in age, MRC grade, admission haemoglobin levels, hospital admission frequency in the previous 12 months (admission frequency), $\Delta EMG_{para\%max}$ and ΔNRDI between readmitted and non-readmitted groups at 28 days (table 3). There were no significant differences in the values of $EMG_{para\%max}$ and NRDI at discharge between the two groups. With the exception of the MRC grade, univariate analysis demonstrated that all of these parameters predicted readmission at 28 days (table 4). However, in multivariable stepwise logistic regression analysis, only age and admission frequency predicted 28-day readmission (adjusted OR 1.08, 95% CI 1.03 to 1.14, p=0.004, and adjusted OR 1.29, 95% CI 1.01 to 1.66; p=0.043, respectively). Change in $EMG_{para\%max}$ between admission and discharge did not predict 28-day readmission in the whole cohort. The rate of radiographic consolidation was not significantly different between the two groups (11.1% for the readmitted vs 23.7% for the non-readmitted group; p=0.16).

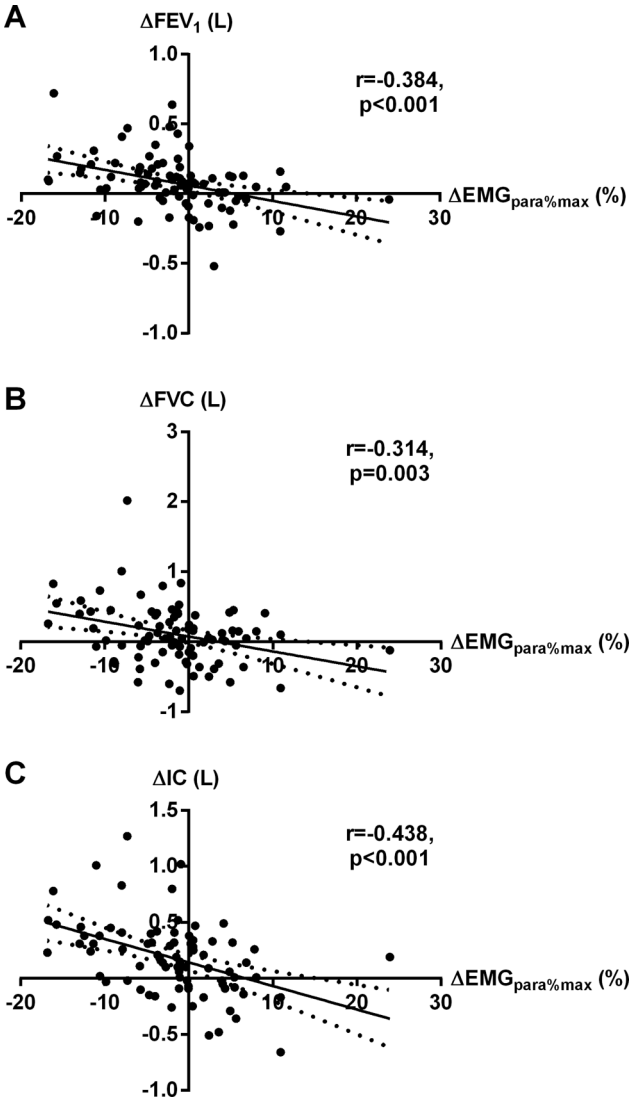

Figure 2 Relationship between admission-to-discharge change in $EMG_{para\%max}$, and changes in (A) FEV_1, (B) FVC and (C) IC. $EMG_{para\%max}$, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; IC, inspiratory capacity.

In accordance with the correlation, albeit weak, between $\Delta EMG_{para\%max}$ and age, a post hoc, exploratory analysis was performed among patients below an arbitrary age cut-off of 85 years (n=112). There were 23 (20.5%) readmissions within 28 days among these patients. Under these circumstances, older age (adjusted OR 1.10, 95% CI 1.02 to 1.16; p=0.017) and increasing $EMG_{para\%max}$ between admission and discharge (adjusted OR 1.09, 95% CI 1.01 to 1.18, p=0.023) were predictive of 28-day readmission. ROC analysis for the prediction of 28-day readmission in patients under 85 years produced an area under the ROC curve (AUC) of 0.70 for age and 0.66 for $\Delta EMG_{para\%max}$.

Predictors of readmission within 14 days

Sixteen (13.3%) patients were readmitted or died within 14 days of discharge. There were differences in MRC grade and

Table 3 Differences between readmitted and non-readmitted patients within 28 days

	28-day readmission N=27	Non-readmitted at 28 days N=93	p Value
Age (years)	75 (9)	68 (9)	0.001
MRC dyspnoea grade	5 (4–5)	4 (3–5)	0.013
Admission frequency (/12 months)	1 (1–3)	0 (0–2)	0.006
Admission haemoglobin (g/dL)	13.1 (1.8)	14.0 (1.7)	0.017
$\Delta EMG_{para\%max}$ (%)	+1.5 (8.4)	−2.4 (7.2)	0.018
ΔNRDI (/min)	+28 (217)	−64 (189)	0.032
ΔModified Borg scale	−2 (−2.5 to −2)	−1 (−3 to −1)	0.58
ΔCAT	−7 (−12 to 0)	−5 (−9 to 0)	0.30
ΔRespiratory rate (/min)	−3.2 (5.3)	−2.6 (4.0)	0.50

Values are expressed as mean (SD) or median (IQR).
CAT, COPD Assessment Test; $EMG_{para\%max}$, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; MRC, Medical Research Council; NRDI, Neural Respiratory Drive Index.

$\Delta EMG_{para\%max}$ between the readmitted and non-readmitted groups (table 5), but MRC grade did not predict 14-day readmission in the univariate logistic regression model (table 6). Only admission-to-discharge increases in $EMG_{para\%max}$ (adjusted OR 1.12, 95% CI 1.03 to 1.21, p=0.005) predicted 14-day readmission on multivariable stepwise logistic regression analysis. ROC analysis for the prediction of 14-day readmission gave an AUC of 0.70 for $\Delta EMG_{para\%max}$. By contrast, AUC for ΔFEV_1 and ΔIC were 0.57 and 0.56, respectively (figure 3). The failure of $\Delta EMG_{para\%max}$ to fall by more than 3.1% between admission and discharge had a sensitivity of 93.8% and a specificity of 41.3% to detect 14-day readmission, with a positive predictive value (PPV) of 19.7% and a negative predictive value (NPV) of 97.7%. Again, there was a non-significant difference in the rate of radiographic consolidation between the groups (6.25% for the readmitted vs 23.1% for the non-readmitted group, p=0.123). Kaplan–Meier analysis showed that patients whose $EMG_{para\%max}$ failed to fall by less than 3.1% between admission and discharge had a shorter time to readmission than those whose $EMG_{para\%max}$ fell by more than 3.1% (log rank test p=0.03) (figure 4).

When ΔNRDI was used instead of $\Delta EMG_{para\%max}$ in the regression model as a measure of NRD, it also predicted 14-day readmission or death (ΔNRDI: OR 1.003, 95% CI 1.001 to 1.006, p=0.01). ROC analysis for the prediction of 14-day readmission gave an AUC of 0.70 for NRDI.

Table 4 Univariate logistic regression analysis for predictors of 28-day readmission

	OR	p Value	95% CI
Age	1.09	0.002	1.03 to 1.15
Hospital admission frequency	1.35	0.013	1.07 to 1.71
Haemoglobin	0.73	0.020	0.56 to 0.95
$\Delta EMG_{para\%max}$	1.08	0.022	1.01 to 1.15
ΔNRDI	1.002	0.036	1.000 to 1.005
ΔModified Borg scale	1.07	0.49	0.88 to 1.29
ΔCAT	0.98	0.82	0.93 to 1.03
ΔRespiratory rate	0.97	0.50	0.88 to 1.07

CAT, COPD Assessment Test; $EMG_{para\%max}$, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; NRDI, neural respiratory drive index.

Table 5 Differences between readmitted and non-survivors and non-readmitted survivors within 14 days

	14-day readmission or death N=16	Non-readmitted at 14 days N=104	p Value
MRC dyspnoea grade	5 (4–5)	4 (4–5)	0.039
$\Delta EMG_{para\%max}$ (%)	+3.6 (8.3)	−2.3 (7.2)	0.003
ΔNRDI (/min)	+71 (221)	−61 (190)	0.012
ΔModified Borg scale	−0.25 (−2 to 1)	−1 (−3 to 0)	0.12
ΔCAT	−8.5 (−11 to −2)	−5 (−9 to 1)	0.16
ΔRespiratory rate (/min)	−2.6 (3.5)	−2.8 (4.4)	0.87

Values are expressed as mean (SD) or median (IQR).
CAT, COPD Assessment Test; $EMG_{para\%max}$, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; MRC, Medical Research Council; NRDI, Neural Respiratory Drive Index.

Detection of in-hospital clinical deterioration

A total of 475 pairs of consecutive EMG_{para} data were acquired from the 122 patients who provided at least one pair of analysable data; although 120 patients completed investigations between hospital admission and discharge, two further patients gave at least one pair of analysable data before withdrawal from the study. Patients had a median of three pairs of measurements (range 1–23) between admission and discharge. There were 116 episodes of worsening dyspnoea, defined as at least one-point increase in Borg scale. On univariate GLMM analysis, an increase in MEWS ($\Delta MEWS_{cons}$) and in $EMG_{para\%max}$ ($\Delta EMG_{para\%max,cons}$) between consecutive recordings was associated with symptomatic deterioration (table 7). Multivariable GLMM analysis showed that $\Delta MEWS_{cons}$ (adjusted OR 1.36, 95% CI 1.01 to 1.84, p=0.04) and $\Delta EMG_{para\%max,cons}$ (adjusted OR 1.07, 95% CI 1.01 to 1.14, p=0.027) were independently associated with worsening of dyspnoea. Multivariable GLMM analysis showed that $\Delta EMG_{para\%max,cons}$ (coefficient 0.05, 95% CI 0.01 to 0.09, p=0.024) and ΔIC_{cons} (coefficient −1.11, 95% CI −2.19 to −0.03, p=0.044) were independently associated with changes in Borg scale of any magnitude between consecutive recordings.

There were 35 episodes of physician-defined deterioration. Only an increase in $EMG_{para\%max}$ between consecutive measurements was associated with physician-defined deterioration ($\Delta EMG_{para\%max,cons}$ OR 1.030, 95% CI 1.003 to 1.055, p=0.03).

Table 6 Univariate logistic regression analysis for predictors of 14-day readmission

	OR	p Value	95% CI
MRC dyspnoea grade	1.86	0.09	0.92 to 3.76
$\Delta EMG_{para\%max}$	1.12	0.005	1.03 to 1.21
ΔNRDI	1.003	0.014	1.001 to 1.006
ΔModified Borg scale	1.23	0.10	0.96 to 1.57
ΔCAT	0.99	0.67	0.92 to 1.05
ΔRespiratory rate (/min)	1.01	0.87	0.89 to 1.15

Values are expressed as mean (SD) or median (IQR).
CAT, COPD Assessment Test; $EMG_{para\%max}$, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; MRC, Medical Research Council; NRDI, Neural Respiratory Drive Index.

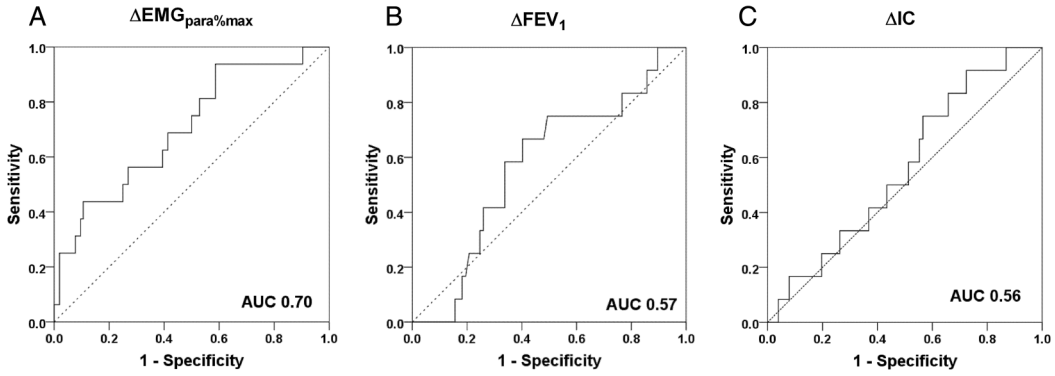

Figure 3 Receiver-operator curves for prediction of 14-day readmission for (A) $\Delta EMG_{para\%max}$, (B) ΔFEV_1, and (C) ΔIC. $EMG_{para\%max}$, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; IC, inspiratory capacity; ROC, receiver-operator curve; AUC, area under the receiver-operator curve.

DISCUSSION

In this single-centre validation study of an advanced physiological biomarker performed in an unselected cohort of acutely unwell patients with COPD, the failure of NRD to fall between admission and discharge predicted readmission within 14 days of discharge. Furthermore, this failure was predictive of readmission within 28 days in those patients under 85 years of age, but not in the cohort as a whole. In addition to the utility of this test to predict clinical outcome following hospital discharge, an increase in NRD between consecutive daily measurements detected episodes of worsening dyspnoea and physician-defined in-hospital clinical deterioration. The physiological rationale of employing NRD was strongly supported by the relationship with change in respiratory muscle physiological load between admission and discharge.

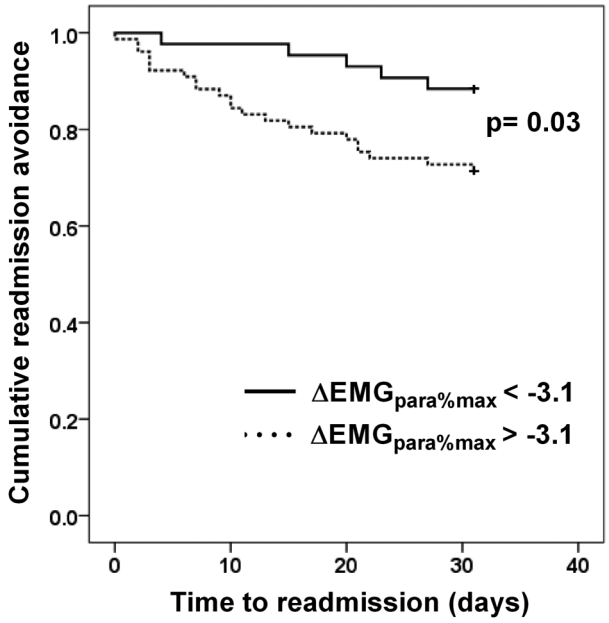

Figure 4 Time-to-readmission Kaplan–Meier plots for patients whose $EMG_{para\%max}$ fell by more than 3.1% between admission and discharge (solid line), and those whose $EMG_{para\%max}$ fell by less than 3.1% (dotted line). $EMG_{para\%max}$, 1 min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre.

Critique of the method

Every attempt was made to enrol consecutive eligible patients with a screening to recruitment ratio of 3.4:1 achieved, which is acceptable for such an observational detailed physiological study. Few of the patients enrolled into this study required non-invasive or invasive ventilation at admission, which adds to the generalisability of this study and indeed the current cohort was wholly representative of UK patients admitted to the acute medical wards.[2] Patients presenting in acute hypercapnic respiratory failure were frequently unable to provide written informed consent, and the study did not have ethical approval for proxy assent and retrospective patient consent.

In line with our previous work,[15] up to one-fifth of patients were unable to perform forced respiratory manoeuvres at admission, which supports the clinical rationale for non-invasive measurements, such as EMG_{para}, being performed during resting tidal breathing. This could be accommodated into the routine monitoring of acutely unwell patients with COPD as a measure of the respiratory load–capacity balance. The acquisition of respiratory EMG needs to be performed in a standardised manner as variations in electrode position and skin preparation can have a small influence on the magnitude of the signals; however, we have previously published data demonstrating the reproducibility of EMG_{para}.[15 18] Although there was variability in the value of the maximal EMG obtained during the sniff procedure between admission and discharge (see online supplementary figure E2), there was no overall increase during the course of the hospital stay and therefore it is unlikely that the reduction in $EMG_{para\%max}$ between admission and discharge was driven by a fall in the maximal EMG_{para}.

Table 7 Generalised linear mixed modelling analysis for factors associated with clinical deterioration in symptoms as defined by ≥1 point increase in Borg scale

	Adjusted OR	p Value	95% CI
$\Delta MEWS_{cons}$	1.157	0.048	1.001 to 1.338
$\Delta EMG_{para\%max,cons}$ (%)	1.05	0.001	1.02 to 1.08

$\Delta EMG_{para\%max,cons}$, change in $EMG_{para\%max}$ between consecutive inpatient measurements; $EMG_{para\%max}$, 1- min mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre; $\Delta MEWS_{cons}$, change in modified early warning score between consecutive measurements.

Clinical applicability of the findings

Readmission within 14 days

Although the cut-off level for $\Delta EMG_{para\%max}$ of −3.1% has a low PPV for 14-day readmission, the high NPV indicates that NRD has clinical utility as a risk-stratification tool for patients with COPD being discharged from hospital. Patients whose $EMG_{para\%max}$ falls by more than 3.1% during hospital admission are at very low risk of 14-day readmission and indeed these patients have greater time to readmission. The selected cut-off value is similar in magnitude to the fall in $EMG_{para\%max}$ observed amongst non-readmitted patients in the pilot study of Murphy *et al*,[15] indicating the reproducibility of this technique. Pharmacological and technological therapies could be used in future studies to target a reduction in EMG_{para}, with the aim of optimising pulmonary mechanics, which could potentially reduce readmission rates. The cut-off value of −3.1% requires further prospective validation to become a useful clinical tool.

Readmission within 28 days

The admission-to-discharge change in NRD failed to predict 28-day readmission across all age groups. This is perhaps unsurprising as several previous studies have shown that age[25 26] and admission frequency[8 27] are strongly predictive of readmission. In elderly patients, functional impairment and the burden of chronic disease[28] play a major role in influencing readmission and, in the current study, it appears to be more influential than the failure to enhance the respiratory muscle load–capacity balance. The current data support the concept that the inpatient trajectory of NRD was a key factor influencing 14-day readmission in all age groups and 28-day readmission in those patients less than 85 years of age. Early readmission, under these circumstances, indicates a failure of the inpatient treatment to modify the airways obstruction and lung hyperinflation, and thereby to ameliorate the respiratory muscle load–capacity balance. Future studies should focus on strategies to modify the load–capacity balance and reduce NRD with the aim of promoting safe discharge. The authors acknowledge the limitations of the post-hoc application of an age cut-off of 85 years and wholly appreciate that this is an exploratory analysis and prospective validation will be required to assess 28-day readmission. However, this does not detract from the potential clinical implications of this approach and this analysis ensures that the appropriate target patient group are recruited into any future trials.

Clinical deterioration during admission

We have shown that increases in EMG_{para} predicted worsening of dyspnoea during hospital admission. NRD has the potential to be used to deliver enhanced monitoring for patients who are either unable to communicate their clinical condition effectively or those who fail to recognise the severity of their symptoms, which is a priority in healthcare systems where clinical resources, in terms of nursing and other clinical personnel, are increasingly being rationed. Although Murphy *et al*[15] found that EMG_{para} distinguished between physician-defined improvement and deterioration, this was only in a small number of episodes. We have reproduced these findings in a much larger unselected cohort. Importantly, $\Delta EMG_{para\%max}$ was the only parameter that correlated with physician-defined deterioration, supporting NRD as a physiological biomarker for the early identification of treatment failure.

Physiological validity of NRD in the acute setting

In this cohort of acutely unwell patients with COPD, we observed a correlation between $\Delta EMG_{para\%max}$ and ΔFEV_1, supporting the hypothesis that EMG_{para} reflects the resistive load imposed on the respiratory system during an acute exacerbation. Furthermore, there was a direct relationship between $\Delta EMG_{para\%max}$ and ΔIC, indicating that changes in the elastic and threshold loads imposed by hyperinflation can be detected by EMG_{para}. It appears therefore, that EMG_{para} reflects the changes in pulmonary mechanics that accompany an exacerbation of COPD. While the reduction in NRD with decreasing hyperinflation may be due, in part, to the increase in respiratory muscle length, rather than due to a reduction in NRD,[29] animal studies of parasternal intercostal muscle activation at high lung volume have shown that parasternal muscle EMG tends to remain stable despite acute lung hyperinflation.

CONCLUSION

During recovery from an acute exacerbation of COPD requiring hospital admission, change in NRD from admission to discharge predicted 14-day readmission in all age groups and 28-day hospital readmission in patients under 85 years old. In addition, change in NRD between successive inpatient measurements was able to detect worsening dyspnoea and physician-defined clinical deterioration. Second intercostal space parasternal EMG is a novel advanced physiological monitoring tool that may be clinically useful in identifying treatment failure during hospital admission and for predicting safe discharge, which is a priority for all acute healthcare organisations.

Contributors Study concept and design: E-SS, PBM, MIP, NSH, GR, JM, NH. Acquisition, analysis or interpretation of data: E-SS, SM, MR, RH, MK, KO, KH, AD and NH. Drafting of the manuscript: E-SS, SM, PBM, NH. Critical revision of the manuscript for important intellectual content: RH, MR, MK, AD, MIP, KO, KH, NSH, GR, JM and NH. Statistical analysis: E-SS, SM, AD. Obtained funding: NH. Administrative, technical or material support: SM, RH, MR, KH, KO, GR. Study supervision: NH, JM.

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Competing interests E-SS was in receipt of an unrestricted educational grant from Philips Research to develop physiological monitoring techniques in patients with COPD. MIP reports personal fees from Philips during the conduct of the study. PBM reports travel fees to conferences, lecture fees and hospitality from Philips Respironics, and hospitality from Resmed. JM has a patent US20130310699 A1 pending to Guy's and St Thomas' NHS Foundation Trust and King's College London. NH reports salary contributions made to Guy's and St Thomas' NHS Foundation Trust from Philips Respironics during the conduct of the study; salary contribution made to Guy's and St Thomas' NHS Foundation Trust, consultancy, lecture fees and unrestricted grants from Philips Respironics outside the submitted work; consultancy, lecture fees and unrestricted grants from Fisher Paykel outside the submitted work; consultancy, lecture fees and unrestricted grants from Resmed outside the submitted work; consultancy, lecture fees and unrestricted grants from B&D Electromedical outside the submitted work; and lecture fees from Linde outside the submitted work; NH has a patent US20130310699 A1 pending to Guy's and St Thomas' NHS Foundation Trust and King's College London.

Ethics approval London-Bentham Research Ethics Committee.

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Online data supplement

METHODS

Sniff manoeuvre

The sniff manoeuvre was selected in preference to the maximal inspiratory pressure or inspiratory capacity manoeuvres, as it is manageable for patients to perform when they are acutely unwell with coryzal symptoms accompanying an acute exacerbation [1 2]. Patients were requested to perform "a short, sharp sniff in, as hard as you can" on at least three occasions, until two values were obtained within 10% of each other.

RESULTS

Recruitment and data collection

Enrolment data for this detailed physiological observational cohort study are shown in Figure E1. 597 EMG_{para} measurements were made in 122 patients over 521 inpatient days, yielding 475 pairs of consecutive data. For the analysis of inpatient clinical deterioration, 88% of consecutive measurements were made at an interval of 1 day or less; 8% were made at an interval of 2 days and 4% were made at an interval of 4 days or more. All 120 patients included in the admission-to-discharge analysis for readmission risk had EMG_{para} measurements on the day of admission and the day of fitness for discharge.

Prediction of respiratory admissions and acute healthcare utilisation within 14 and 28 days

Respiratory admissions

There were 14 (11.7%) respiratory admissions within 14 days and 25 (20.8%) respiratory admissions within 28 days of hospital discharge. As with all-cause readmissions, higher positive values of $\Delta EMG_{para\%max}$ were associated with increased risk of 14-day respiratory readmission (OR 1.13 95% CI 1.04 to 1.23). In patients under 85, increased admission frequency (OR 1.48, 95% CI 1.11 to 1.98) and higher $\Delta EMG_{para\%max}$ (OR 1.10, 95% CI 1.01 to 1.20) were associated with increased risk of 28-day respiratory readmission.

Acute healthcare utilisation

There were 18 (15%) episodes of acute healthcare utilisation within 14 days and 29 (24.2%) episodes of acute healthcare utilisation within 28 days of hospital discharge. These included hospital admissions and attendances to the emergency department that did not require admission. A greater change in $EMG_{para\%max}$ was associated with an increased risk of 14-day acute healthcare utilisation (OR 1.11, 95% CI 1.03 to 1.20). In patients under 85, increased age (OR 1.08, 95% CI 1.009 to 1.146), increased admission frequency (OR 1.38, 95% CI 1.03 to 1.84) and greater values of $\Delta EMG_{para\%max}$ (OR 1.09, 95% CI 1.002 to 1.175) were associated with 28-day acute healthcare utilisation.

Dynamic hyperinflation and neural respiratory drive

A correlation was noted between admission-to-discharge changes in IC and changes in $EMG_{para\%max}$ (Figure 2C). Patients whose IC increased between admission and discharge demonstrated a fall in NRD ($\Delta EMG_{para\%max}$ -3.2±7.2%), whilst those whose IC decreased

demonstrated an increase in NRD ($\Delta EMG_{para\%max}$ +1.1±5.4%). This difference between the two groups was significant (p=0.005). However, there were no differences in readmission rate at either 14 or 28 days between patients whose IC increased and decreased during hospital admission.

Patients without radiographic consolidation

20.8% of patients had radiographic consolidation on chest X-Ray at admission. There were no differences between readmitted and non-readmitted groups, either at 14 or 28 days, in terms of the proportion of patients with radiographic consolidation. When patients with radiographic consolidation were excluded, 28-day readmission was associated with age alone (OR 1.082, p=0.004) in the whole cohort, and age (OR 1.074, p=0.049) and ΔEMGpara%max (OR 1.112, p=0.019) in patients under the age of 85 years. 14-day readmission was associated with $\Delta EMG_{para\%max}$ alone (OR 1.124, p=0.006).

DISCUSSION

Critique of the method

Frequency of data acquisition

The study protocol stipulated that daily EMG measurements were undertaken at a similar time each day, but this was, on occasions, impossible due to either the patient or research team being unavailable, or patient refusal. However, the majority of measurements were obtained on consecutive days in these acutely unwell patients. Despite the large number of patients included, this study was conducted in a single centre university hospital with an established and extensive experience of respiratory muscle measurements.

Changes in sniff EMG between admission and discharge

The value of parasternal EMG during tidal breathing was normalised against the maximum parasternal EMG value obtained during a maximal sniff manoeuvre. Although, as expected, there was variation in the maximum values within the cohort between admission and discharge (*Fig. E2*), the research team gave significant attention to the technical set up and application of the EMG_{para} measurement. In particular, the skin was marked so that the electrode position was the same on each day of EMG_{para} measurement and therefore we do not consider technical acquisition of the signal to be a contributing factor. Indeed, we consider that $EMG_{para\%max}$ using daily measurements of maximum sniff EMG_{para} to be an appropriate method. However, we acknowledge that the variation in sniff EMG would, in part, be as a consequence of variations in effort as the clinical condition and ability of the patient to perform this volitional test changes. Having said that, we observed that there was no difference between the sniff EMG_{para} between the readmitted and non-readmitted groups. Furthermore, when the EMG values were normalised to the maximum value of parasternal EMG obtained at the time of discharge (i.e. when the patients were at their most stable; $EMG_{para\%max@discharge}$), the ability of EMG_{para} to predict clinical outcomes was preserved. An increase in $EMG_{para\%max@discharge}$ (adjusted OR 1.09, 95% CI 1.01 to 1.19) between admission and discharge was associated with increased risk of 28-day readmission in patients under 85 (n=112). In the whole cohort, a rise in $EMG_{para\%max@discharge}$ was associated with increased risk of 14-day readmission (OR 1.10, 95% CI 1.02 to 1.20). Increases in $EMG_{para\%max@discharge}$ also predicted 14-day respiratory readmissions (OR 1.12, 95% CI 1.02 to 1.22) and 14-day acute healthcare utilisation (OR 1.10, 95% CI 1.02 to 1.19).

When the tidal breathing EMG_{para} values at discharge were expressed as a ratio of the values at admission ($EMG_{para,discharge}/EMG_{para,admission}$), the ability of EMG_{para} to predict 14-day respiratory readmissions was still preserved ($\Delta EMG_{para,discharge}/EMG_{para,admission}$: OR 3.69, 95% CI 1.02 to 13.36). Even without normalising against a maximal value of EMG, the change in raw EMG_{para} values from admission to discharge was able to predict the clinically important outcome of respiratory readmission; however, this parameter was unable to predict 14- or 28-day all-cause readmission, which is currently of major importance for UK and US acute healthcare organisations.

Clinical applicability of the findings

Relationship between dyspnoea and NRD

Previous studies in patients with chronic respiratory disease during exercise have shown a close relationship between levels of dyspnoea and NRD [1 3 4]. In the current study, although EMG_{para} was able to detect worsening breathlessness between consecutive measurements, there was no correlation between admission-to-discharge change in perceived breathlessness and change in $EMG_{para\%max}$. This observation highlights the limitation of the laboratory model of breathlessness and the acute condition. Specifically, the incremental increase in dyspnoea in stable patients undergoing a standardised exercise test differs from the variation in dyspnoea in acutely unwell patients over the treatment course of an exacerbation. In addition, the course of a hospital admission is over days, whereas patients undergoing a short, clearly defined exercise test have a clear perception of their breathlessness, which can be referenced to their resting state at each point of the exercise protocol.

Fig. E1 Flow diagram for screening and enrolment of COPD patients

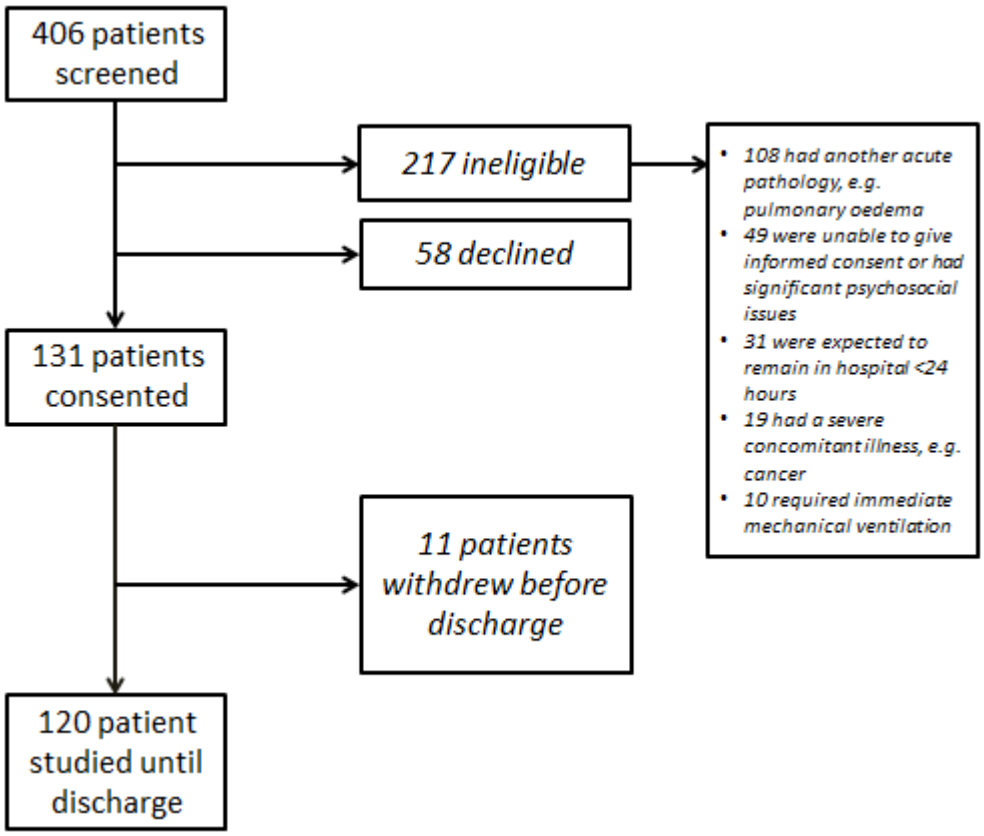
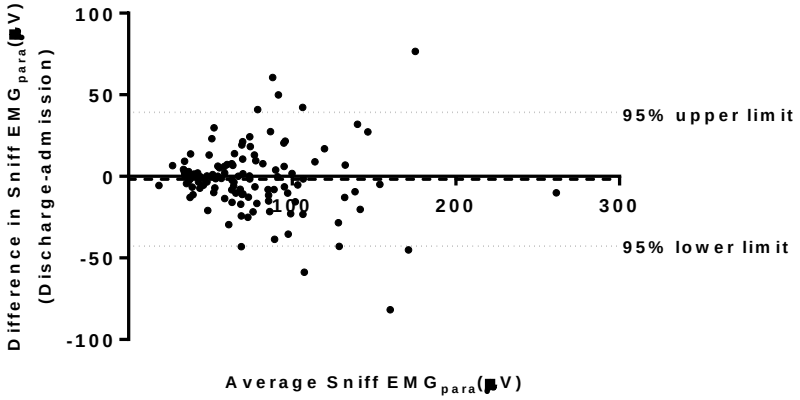


Figure E2. Bland-Altman plot showing variation in sniff EMG measurements between hospital admission and discharge



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