Neural respiratory drive predicts long-term outcome following admission for exacerbation of COPD: a post hoc analysis

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ABSTRACT

Neural respiratory drive (NRD), as reflected by change in parasternal muscle electromyogram (EMGpara), predicts clinical deterioration and safe discharge in patients admitted to hospital with an acute exacerbation of COPD (AECOPD). The clinical utility of NRD to predict the long-term outcome of patients following hospital admission with an AECOPD is unknown. We undertook a post hoc analysis of a previously published prospective observational cohort study measuring NRD in 120 patients with AECOPD. Sixty-nine (57.5%) patients died during follow-up (median 3.6 years). Respiratory failure was the most common cause of death (n=29; 42%). In multivariate analysis, factors independently associated with an increased mortality included NRD (HR 2.14, 95% CI 1.29 to 3.54, p=0.003), age (HR 2.03, 95% CI 1.23 to 3.34, p=0.006), $PaCO_2$ at admission (HR 1.83, 95% CI 1.06 to 3.06, p=0.022) and long-term oxygen use (HR 2.98, 95% CI 1.47 to 6.03, p=0.002). NRD at hospital discharge could be measured in order to assess efficacy of interventions targeted to optimise COPD and reduce mortality following an AECOPD.

Original clinicaltrial.gov number: NCT01361451

INTRODUCTION

Following a severe acute exacerbation of COPD, patients are at high risk of readmission and death.[1 2] Neural respiratory drive (NRD) can be estimated using parasternal muscle electromyogram (EMGpara). EMGpara is a non-invasive physiological measurement which has demonstrated utility in determining the trajectory of recovery during hospital admission as well as predicting readmission following a hospital admission.[3] Indeed, Suh et *al* showed that NRD can predict early 14-day readmission in 120 unselected patients with acute exacerbations of COPD.[4] Although there are composite measures that predict long-term outcome based on disease severity in stable COPD,[5 6] there are few factors predicting the long-term outcome at the end of a severe exacerbation of COPD. The aim of the current study was to assess if NRD at hospital discharge following an admission due to an exacerbation of COPD could predict long-term mortality.

METHODS

The original study was registered as an observational cohort study (NCT01361451). The study was conducted between January 2011 and September 2013. Full details of the protocol are available in the cohort manuscript.[4] In brief, consecutive patients admitted to a UK urban teaching hospital with acute exacerbations of COPD were recruited and had daily measurements of NRD, using EMGpara, from admission until discharge.[4] In May 2017, we collected data from electronic medical records to assess the mortality status of all recruited patients. Cause of death was obtained from the medical cause of death certificate. EMG data are expressed as EMGpara (which corresponds to the measured EMGpara during tidal breathing), EMGpara%max (which corresponds to the ratio between EMGpara during tidal breathing and EMGpara during a maximal sniff manoeuvre) and NRD index (NRDI) (which corresponds to EMGpara%max*RR).

Data were assessed for normality using the Shapiro-Wilk test. Results are expressed as number and percentages, means and SD when normally distributed or medians and IQR when not normally distributed. Comparisons were performed using the t-test for normally distributed continuous variables and a Mann-Whitney U test for non-normally distributed continuous variables. Survival data were analysed using Kaplan-Meier method and log-rank test. Prognostic factors were identified using a multivariate Cox model. Prognostic factors with a p value <0.1 in univariate analyses were included in the multivariate Cox model. EMGpara%max was the only variable included in the model given its collinearity with NRDI. For the Cox model, all continuous variables were divided into two groups based on their median. For admission $PaCO_2$, the study population was divided into two groups: ≥6 or <6 kPa. Receiver-operator characteristic (ROC) analyses were used to assess performance of predictors of 5 years mortality. A predictive model was produced using logistic regression with variables from the Cox model. All tests were two-sided with the level of significance set at 0.05. Analyses were performed using GraphPad Prism V.6 for Mac OS X (GraphPad Software, La Jolla, California, USA) and IBM SPSS Statistics V.20.0 (IBM Corp, Armonk, New York, USA).

RESULTS

Of the 120 patients involved in the clinical trial, 69 (57.5%) had died by 1 May 2017, mean duration of follow-up was 3.4±1.8 years. Patients' clinical and physiological characteristics obtained during hospital admission are reported in table 1. During inpatient stay, eight (6%) received acute

Table 1 Population characteristics

	Patients alive at follow-up (n: 69) Mean±SD/median (IQR)	Patients dead at follow-up (n: 51) Mean±SD/median (IQR)	p value
Age (years)	66.3±10.0	72.5±8.9	<0.001
Male (%)	26 (51.0%)	32 (46.4%)	0.713
Body mass index (kg/m^2)	27.7 (23.3 to 33.6)	20.9 (18.2 to 27.7)	0.713
COPD history			
Current smoker (%)	23 (33.3%)	24 (41.1%)	0.136
Smoking history (pack-years)	40 (20 to 50)	40 (30 to 56)	0.213
Use of long-term oxygen therapy (%)	1 (2.0%)	12 (17.4%)	0.007
Exacerbation frequency (/12 months)	2 (0 to 4)	4 (1 to 6)	0.079
Hospital admission frequency (/12 months)	0 (0 to 1)	1 (0 to 2)	0.007
Comorbidities			
Ischaemic heart disease (%)	14 (27.5%)	20 (29.0%)	1
Cerebrovascular disease (%)	5 (9.8%)	8 (11.6%)	1
Hypertension (%)	25 (49.0%)	28 (40.6%)	0.457
Diabetes mellitus (%)	12 (17.4%)	8 (11.6%)	0.091
Admission			
MRC dyspnoea grade at admission	4 (3 to 5)	5 (4 to 5)	0.045
Respiratory rate at admission (/min)	25 (20 to 29)	26 (20 to 31)	0.670
DECAF score at admission	1 (0 to 1)	1 (0 to 2)	0.044
CAT at admission	30 (26 to 34)	27 (23 to 31)	0.022
Admission arterial blood gas			
pH	7.41 (7.37 to 7.45)	7.40 (7.35 to 7.42)	0.029
PaO_2 (kPa)	8.22 (7.46 to 8.91)	8.37 (7.42 to 9.84)	0.3756
$PaCO_2$ (kPa)	5.05 (4.61 to 5.91)	6.09 (4.96 to 7.24)	0.002
Bicarbonates (mmol/L)	24.4 (23.0 to 26.3)	26 (23/5 to 29.4)	0.023
At discharge			
CAT	24 (17 to 28)	24 (17 to 29)	0.507
Saint-Georges Respiratory Questionnaire	65.0 (59.5 to 75.4)	62.8 (56.8 to 72.2)	0.275
Hospital Anxiety and Depression Scale	15.5±7.5	15.7±7.7	0.775
FEV_1 (L)	0.85 (0.63 to 0.98)	0.62 (0.46 to 0.85)	<0.001
FVC (L)	1.62 (1.62 to 2.12)	1.40 (1.14 to 1.96)	0.067
Readmission or death within 28 days (%)	11 (26.6%)	18 (26.1%)	0.668
Baseline EMG			
EMG para (µV)	8.80 (6.46 to 14.7)	10.88 (7.43 to 17.55)	0.048
EMG para%max	15.1 (11.0 to 22.0)	16.5 (11.2 to 22.2)	0.446
Respiratory rate (/min)	21 (17 to 26)	21 (18 to 24)	0.885
NRDI (/min)	313 (221 to 438)	344 (228 to 456)	0.403
Discharge EMG			
EMGpara (µV)	8.17 (5.77 to 10.85)	11.33 (8.09 to 17.02)	<0.001
EMGpara%max	12.8 (9.1 to 17.4)	15.7 (11.8 to 22.6)	0.008
Respiratory rate (/min)	20 (18 to 23)	19 (17 to 22)	0.120
NRDI (/min)	228 (151 to 368)	319 (232 to 458)	0.004
EMG change from baseline to discharge			
ΔEMGpara (µV)	−0.74 (−5.06 to 0.36)	0.73 (-3.53 to 2.48)	0.016
ΔEMGpara%max	−1.96 (−7.61 to 0.79)	−0.95 (−4.44 to 3.24)	0.054
ΔRespiratory rate (/min)	−2 (−4 to 1)	−1 (−3 to 3)	0.043
ΔNRDI (/min)	−61(−173 to 8)	−9 (−112 to 73)	0.039

Δ, change in; CAT, COPD assessment tool; DECAF, dyspnea, eosinopenia, consolidation, acidemia, fibrillation; EMG, electromyography; MRC, medical research council; NRDI, neural respiratory drive index.

non-invasive ventilation. Medical cause of death was reported as respiratory failure for 29 (42.0%) patients, cardiac failure for five (7.2%), cancer for five (7.2%) and from other cause for two (2.9%). Cause of death could not be verified in 26 (37.7%) patients.

Regardless of the cause of death, an EMGpara%max at discharge ≥15% was associated with a worse prognosis with a median survival of 998 days versus 2002 days when compared with an EMGpara%max at discharge <15% (HR 1.89, 95% CI 1.19 to 3.08, p=0.009, log rank) (figure 1). Other prognostic factors

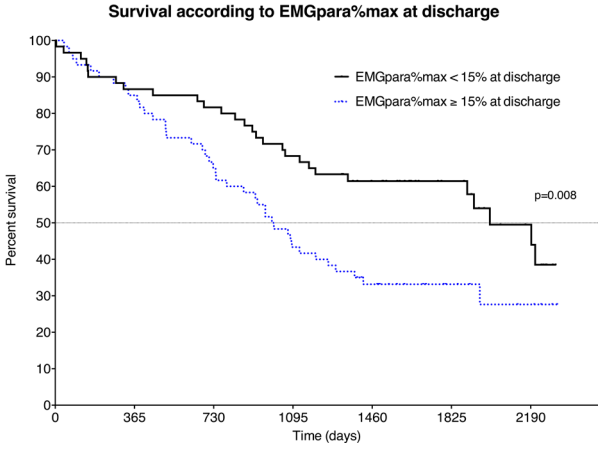

Figure 1 Survival according to EMGpara%max at discharge (continuous line: patients with EMGpara%max <15% at discharge, dot: patients with EMGpara%max ≥15% at discharge) (p=0.008, log rank). EMGpara, parasternal muscle electromyogram.

in the univariate analysis are reported in the online supplement etable 1. A post hoc analysis of respiratory-specific mortality indicated a stronger association with long-term outcomes with an EMGpara%max at discharge ≥15% being associated with a three-fold risk of respiratory-specific mortality when compared with an EMGpara%max <15% (HR 3.18, 95% CI 1.52 to 6.46, p=0.002, log rank, online supplement efigure 1).

In the multivariate analysis, factors associated with a poor prognosis were an EMGpara%max at discharge ≥15% (HR 2.14, 95% CI 1.29 to 3.54, p=0.003), an age ≥71 years (HR 2.03, 95% CI 1.23 to 3.34, p=0.006), a $PaCO_2$ at admission ≥6 kPa (HR 1.83, 95% CI 1.06 to 3.06, p=0.022) and previous long-term oxygen use (HR 2.98, 95% CI 1.47 to 6.03, p=0.002). In the multivariate analysis, FEV_1 at discharge and hospital admission frequency were not associated with long-term outcome (p=0.606 and 0.720, respectively).

ROC analysis for the prediction of 5 years mortality gave an area under the curve of 0.649, 0.626, 0.701 for EMGpara%max, age and admission $PaCO_2$, respectively (p=0.02, 0.006, <0.001, respectively). An individual risk score of all significant factors associated with poor prognosis was produced to predict 5-year mortality and provided an area under the curve of 0.747 (p<0.001) (online supplement etable 2 and online supplement efigure 2). The individual risk score performed better than the isolated predictors (EMGpara%max, p<0.001; age, p<0.020; admission $PaCO_2$, p=0.201). The regression model provided an individual risk score correctly classifying 74% of patients (online supplement etable 3).

DISCUSSION

This post hoc analysis has demonstrated that NRD, as reflected by EMGpara, is an independent predictor of long-term mortality in patients following an admission for an acute exacerbation of COPD. NRD, as reflected by EMGpara%max, at admission was similar between patients who died and those who remained alive at follow-up, as was early readmission within 28 days and 12-month mortality, indicating that the difference was likely not due to the severity of the index exacerbation. However, those who remained alive appear to have responded more favourably to treatment during the acute exacerbation with a reduction in EMGpara, EMGpara%max and NRDI indicating a favourable effect on the load–capacity–drive relationship of the respiratory system. Conversely, patients who died during follow-up demonstrated smaller changes in measures of NRD and therefore high levels at discharge, indicating either less reversible disease or more severe baseline COPD. This lack of improvement associated with a higher NRD at discharge highlights the severity of their respiratory disease more accurately than traditional markers such as FEV_1, the number of admissions for acute exacerbation of COPD or symptom-related questionnaires. The importance of an imbalance in the load–capacity–drive relationship of the respiratory system is highlighted by the fact that the principal cause of death was from respiratory failure rather than cardiovascular causes as is common in mild COPD.[7]

In our cohort, factors associated with poor survival were prescription of long-term oxygen therapy, age, admission $PaCO_2$ and EMGpara%max. Interestingly, the last two parameters can be treated with non-invasive ventilation providing a possible physiological rational for recently demonstrated benefits of this therapy.[8 9] Our findings are consistent with those of Esteban[10] and colleagues who demonstrated a link between 1-year survival and patient characteristics (age), clinical severity of COPD (presence of hypercapnia) and comorbidities in a large multicentre study. These findings demonstrate a potential role for NRD in the risk stratification of patients following a hospital admission secondary to an acute exacerbation of COPD. Future work will need to focus on strategies to reduce NRD to evaluate whether these can alter disease progression, risk of re-exacerbation and hospitalisation and long-term mortality.

CONCLUSION

In addition to the short-term value of using NRD to predict safe hospital discharge following a severe acute exacerbation of COPD, NRD at hospital discharge could be measured in order to assess efficacy of interventions targeted to optimise COPD and to reduce mortality following an acute exacerbation of COPD.

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