Early View

Research letter

Home parasternal electromyography tracks patient-reported and physiological measures of recovery from severe COPD exacerbation

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Home parasternal electromyography tracks patient-reported and physiological measures of recovery from severe COPD exacerbation

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“Take home” social media message:

Physiological phenotyping using daily home-based assessments reveals early improvement in load-capacity-drive imbalance following COPD exacerbation & feasibility of home parasternal electromyography measurement, which tracks symptoms, health status & spirometry.

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To the Editor:

Exacerbations of COPD remain a leading cause for emergency hospitalisation worldwide, and up to 28% of patients are readmitted within 30 days of discharge [1]. Recent analyses of over 2.3 million COPD hospitalisations highlight the dynamic and time-dependent nature of readmission risk, which peaks within the first 72 hours of discharge [2, 3]. Effective readmission prevention strategies remain elusive and recognition of re-exacerbations beyond daily symptom variability is challenging for both patients and clinicians. Promotion of transitional care services and 30-day readmission penalties implemented by policymakers worldwide have had limited impact [4]. Telemonitoring strategies incorporating symptom and vital observation monitoring (oxygen saturation (SpO₂), heart rate, respiratory frequency (fᵣ)) have consistently failed to demonstrate beneficial effects on hospitalisation risk [5]. Objective physiological monitoring has been explored using the forced oscillation technique, however this also failed to prolong time to first hospitalization [6].

Parasternal intercostal electromyography (EMG_{para}) is a non-invasive, effort-independent method of quantifying inspiratory muscle activity and may be used as a surrogate measure of neural respiratory drive (NRD). It has been used to evaluate load-capacity-drive imbalance of the respiratory muscle pump during COPD exacerbations, and inpatient measurements are sensitive to patient-reported and clinician-defined changes in clinical trajectory [7, 8]. In this study, we aimed to (1) conduct detailed physiological phenotyping of COPD exacerbation recovery using daily home-based measurements to elucidate mechanisms underpinning early readmission risk and (2) explore the feasibility of home EMG_{para} as a physiological biomarker of clinical trajectory to inform the design of effective transitional care strategies.

Methods

Consecutive patients admitted to a UK university hospital with a primary diagnosis of COPD exacerbation who were aged 40-80, did not require mechanical ventilation and had a body mass index under 35kg/m² were enrolled. This prospective observational cohort feasibility study received ethical approval (18/LO/0157) and was registered prospectively (NCT03443505).

Assessments were performed within 16 hours of hospitalisation, pre-discharge and daily at home for 30 days post-discharge. Home-based measurements were obtained during home visits conducted by
one member of the research team (RD). Symptoms were evaluated using the daily Exacerbations of Chronic Pulmonary Disease Tool (EXACT) [9] and modified Borg (mBorg) scale for breathlessness [10]. Physiological recovery was evaluated using daily measurement of heart rate, peripheral oxygen saturation (SpO2), respiratory rate (fR) and neural respiratory drive, quantified using EMGpara. EMGpara was measured with subjects in a seated position with the arms relaxed and supported to minimise tonic activity of adjacent chest wall musculature. Skin overlying the right and left second intercostal parasternal spaces and lateral aspect of the right clavicle was prepared using an abrasive gel (Nuprep gel, Weaver and Company, Colorado, US) and alcohol wipe (Clinell, GAMA healthcare, London, UK) prior to placement of wet gel electrodes (Ambu Blue Sensor Q, Ambu, St Ives, UK), which were connected to bipolar and ground electrodes. Signals were amplified with a gain of 1000, band-pass filtered at 10-2000 Hz and AC-coupled prior to acquisition and acquired using a 16-bit analogue-to-digital converter (Porti Physiological Amplifier, TMSi, Oldenzaal, Netherlands). A nasal cannula (Intersurgical, Berkshire, UK) positioned in subjects’ nares was connected to a differential pressure transducer (Pressure sensor, TMSi, Oldenzaal, Netherlands) to identify the respiratory cycle. Analogue-to-digital sampling was performed at 2 kHz and displayed on a laptop computer. At each home assessment, measurements were taken over 6 minutes of tidal breathing followed by sniff manoeuvres which were repeated until maximal volitional effort was achieved. For standardisation, home visits were conducted at the same time each day and EMGpara was measured before and after inhalation of patients’ short-acting bronchodilator. Traces were analysed offline by converting raw EMGpara signals to root mean squared (RMS) using a moving window of 50 milliseconds. RMS EMGpara peak values during tidal breathing were manually identified (mean EMGpara), normalised to the maximal volitional manoeuvre (EMGpara%max) and expressed as neural respiratory drive index (NRDI) (product of EMGpara%max and respiratory rate) [7, 8]. Standardised residuals (z-scores) were calculated using sex-specific normal values from healthy subjects [11]. Health-related quality of life (COPD Assessment Test (CAT) [12]) and handheld spirometry (FEV1, FVC, inspiratory capacity (IC) (EasyOne Diagnostic Spirometer, ndd Medical Technologies, Switzerland)) were measured weekly.

Data are presented as mean±SEM, median (IQR) and number (proportion; 95% confidence intervals). Data at successive timepoints were compared with repeated measures ANOVA, with post hoc comparisons using Bonferroni correction. Linear mixed model (LMM) regression (adjusted for
age, sex, body mass index (BMI) and annual exacerbation frequency) was used to analyse associations between $\text{EMG}_{\text{para}}$ indices and other measured patient-reported and physiological parameters. Area under the curve (AUC) and coefficient of variation (CV) were used to analyse changes and variability in symptoms and $\text{EMG}_{\text{para}}$. Analyses were performed using SPSS Statistics v26 (IBM Corp, NY, USA).

Results

Between February 2018 and June 2019, 427 patients hospitalised with AECOPD were screened for eligibility and 29 (6%) were invited to participate. The most common reasons for ineligibility were age $>$80 years (92; 22%), need for acute mechanical ventilation (85; 20%) and having a home environment deemed unsafe for lone researcher visits (57; 13%). Six patients (21%) declined to participate and 23 (79%) were recruited, of whom 4 were withdrawn due to ineligibility, 7 withdrew, and 12 completed the study. Those who declined or withdrew cited the burden of daily home visits as their reason. The admission characteristics of those completing the schedule of assessments include age $68\pm2.6$ years, 67% female, BMI $21.8\pm1.2$ kg/m$^2$, FEV$_1$ 23 (19-25)% predicted, 7 (58%) current smokers, $68\pm13$ pack-years, exacerbation frequency (number of exacerbations in the 12 months preceding admission) $3.6\pm0.5$, Charlson comorbidity index $4\pm1$ (ischaemic heart disease in 3 (25%;0-50), cerebrovascular disease in 2 (17%;8.3-33.3), hypertension in 3 (25%;0-50), type 2 diabetes mellitus in 1 (8.3%;0-25)), duration of hospitalisation $2(1.25-4.5)$ days. Regular COPD medications included as-required short-acting beta-2 agonist (SABA) (12, 100%), long-acting antimuscarinic (LAMA) (7, 58%; 41.7-75.0), combined inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) (9, 75%; 58.3-91.7), combination ICS LABA LAMA (1, 8%; 0-25.0), oral mucolytic (6, 50%; 25.0-75.0) and prophylactic macrolide antibiotic (2, 17%8.3-33.3). Patients received standardised acute medical therapy: nebulised bronchodilation (12, 100%), course of antibiotic and corticosteroid in 9 (75%; 58.3-91.7), corticosteroid alone in 3 (25%; 8.3-41.7) and outpatient follow-up.

232 of a possible 292 home visits (79%) were performed. There was 100% adherence to $\text{EMG}_{\text{para}}$ measurement, 457 traces were recorded, 100% were of analysable quality. Three patients (25%) were readmitted within 30 days, two (17%) within 48 hours. 12-month readmission rate and mortality were 75% and 42%, respectively. Patient-reported and physiological outcomes during 30-day follow-
up are reported in Figure 1. Improvements in EXACT score, FVC, IC and NRDI were observed between admission and week 1 post-discharge. 10 patients reached EXACT-defined recovery (sustained fall of ≥9 points from peak score), which corresponded to a 144±21%.min⁻¹ reduction in NRDI. In those not experiencing 30-day re-exacerbations, EXACT and CAT scores, SpO₂, hyperinflation (FVC and IC) and NRD indices (EMG_{para%max} and NRDI) improved between admission and day 30 post-discharge.

Adjusted univariate LMM analysis demonstrated that NRDI was associated with total EXACT score (estimate of fixed effect 3.91, 95%CI 2.79 to 5.03, p<0.001), the EXACT subdomains of breathlessness (estimate 2.40, 95%CI 1.76 to 3.05, p<0.001), cough and sputum (estimate 1.60, 95%CI 0.84 to 2.37, p<0.001) and chest symptoms (estimate 2.02, 95%CI 1.19 to 2.85, p<0.001), CAT (estimate 2.56, 95%CI 0.47 to 4.65, p=0.02), SpO₂ (estimate -11.58, 95%CI -16.92 to -6.23, p<0.001), heart rate (estimate 2.25, 95%CI 1.13 to 3.37, p<0.001), FEV₁ %predicted (estimate -1.87, 95%CI -3.62 to -0.12, p=0.04), FVC %predicted (estimate -1.36, 95%CI -2.29 to -0.44, p=0.01) and IC %predicted (estimate -1.26, 95%CI -2.29 to -0.23, p=0.02). Associations were present between the coefficient of variation for NRDI and total EXACT score (R²=0.39, p=0.03) and the breathlessness subdomain (R²=0.41, p=0.03). Associations between change and variability of NRDI and symptoms were strongest amongst the 5 patients experiencing 30-day re-exacerbations, in whom AUC for NRDI predicted AUC of total EXACT score (R²=0.94, p<0.01) and EXACT breathlessness (R²=0.94, p<0.01) and CV for NRDI predicted CV of total EXACT score (R²=0.98, p=0.001) and EXACT breathlessness (R²=0.94, p<0.01).

**Discussion**

This study provides detailed novel insights into the close relationship between neural respiratory drive and routinely measured patient-reported and physiological parameters during recovery from severe COPD exacerbations. These data also demonstrate that physiological recovery begins soon after hospital discharge, with improvements in hyperinflation (inspiratory capacity) and neural respiratory drive (EMG_{para}) reflecting early resolution of load-capacity-drive imbalance, with corresponding improvements in symptoms. Finally, home EMG_{para} measurement has been shown to be feasible to perform and tracks symptoms, health status, peripheral oxygenation, heart rate, spirometry and inspiratory capacity during exacerbation recovery.
By day 30 post-discharge, 3 of 12 patients were readmitted, 2 of whom were readmitted within 48 hours of discharge, consistent with international data [2, 3]. Physiological phenotyping revealed improvements in IC, EMG$_{para}$ and symptoms within seven days of discharge and stability of FEV$_1$:FVC and respiratory frequency. The demonstrated trajectory of improvement indicates that the early physiological recovery observed is a consequence of improved expiratory flow, resolution of hyperinflation and enhanced operating lung volumes, consistent with studies evaluating patients at later stages of exacerbation recovery [13, 14]. Reasons for 30-day readmissions are multifactorial, with risk factors including annual exacerbation frequency, comorbidities and hospital length of stay [15, 16]. We propose that reported reductions in readmission risk immediately post-discharge are partially attributable to physiological recovery, involving improved expiratory airflow and reduced neural respiratory drive, perceived by patients as improved breathlessness [2, 3].

These data also demonstrate that home EMG$_{para}$ measurements track spirometry, inspiratory capacity, quality of life and COPD symptoms following hospitalisation with an exacerbation of COPD, and the relationship appears enhanced in those experiencing 30-day re-exacerbation. Measurement of EMG$_{para}$ is feasible and well-tolerated at home, as demonstrated by high adherence to daily measurements and consistent capture of analysable signals. This simple, effort-independent and non-aerosol generating technique could be incorporated into existing community-based follow-up services to facilitate objective assessment of load-capacity-drive imbalance during exacerbation recovery and complement clinical evaluation and patient-reported outcomes. No home-based post-discharge patient-reported or physiological measure that predicts 30-day readmission has yet been identified [5, 6, 9, 17]. Future prospective validation is required to evaluate the clinical utility of EMG$_{para}$, either in isolation or in combination with conventional clinical measures, to predict re-exacerbation, facilitate early treatment and potentially avoid 30-day readmission. If found to be a sensitive physiological biomarker of re-exacerbation and readmission, translation of home EMG$_{para}$ from the research environment to clinical application may be facilitated through equipment simplification, integration of a validated scoring algorithm to circumvent the need for manual scoring, training of non-medical clinical staff, and identification of signal thresholds that trigger clinical alerts [18].

Generalisability of our data is limited by the small sample, comprised predominantly of patients with very severe COPD who were willing to accept daily home-based assessments. Physiological
evaluation of exacerbation recovery is notoriously challenging to conduct due to patient reluctance to attend repeated clinical assessments and perform forced respiratory manoeuvres during recovery [19]. Unlike previous studies, which have missing data and comparable sample sizes [13, 14], we mitigated loss to follow-up by using home-based assessments and achieved 100% adherence to EMG_{para} measurement.

Conclusions

In summary, daily home-based monitoring of COPD patients following hospitalisation with an exacerbation reveals improvements in symptoms, hyperinflation and neural respiratory drive within the first week of discharge, indicating early resolution of load-capacity-drive imbalance. These patients are at high risk of 30-day readmission, and the immediate post-discharge period represents a window of opportunity to identify and manage patients failing to recover. Home parasternal electromyography is a feasible surrogate measure of neural respiratory drive that tracks symptoms, quality of life, peripheral oxygenation, heart rate, spirometry and inspiratory capacity. It thus yields potential as an objective physiological biomarker of recovery and its utility in the transitional care setting is the focus of ongoing research.
Footnotes

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Ethics approval: This study was approved by the London-Westminster Research Ethics Committee (18/LO/0157) and registered as a prospective observational cohort study (NCT03443505).

References

Figure 1: Panel A depicts daily measurements of neural respiratory drive index (NRDI) (right y-axis) and Exacerbations of Chronic Pulmonary Disease Tool (EXACT) score, respiratory rate ($f_R$) and peripheral oxygen saturation ($SpO_2$) (left y-axis) at admission (A), discharge (D) and at home for 30-days post-discharge or until hospital readmission (1-30) for each patient. Dashed lines indicate the day of EXACT-defined recovery, if reached (9-point reduction from peak score sustained for 7 days [9]), dotted lines indicate a day of healthcare utilisation with light grey bars representing hospital readmission (subjects 1-3) and dark grey bars representing non-readmission re-exacerbation (subjects 4-5). Panel B illustrates the trajectory of patient-reported and physiological outcomes in non-readmitted patients (n=9). P-values refer to repeated measures analysis of variance, *p<0.05 compared to admission. Post hoc comparisons with Bonferroni correction were performed if a significant f ratio was obtained by one-way repeated measured ANOVA across all time points. †mBorg scores available for n=6; ‡1 patient was unable to perform pre-discharge spirometry due to breathlessness. Abbreviations: mBorg = Modified Borg Scale for breathlessness, CAT = COPD Assessment Test, HR = heart rate, FEV$_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, IC = inspiratory capacity, EMG$_{para\%max}$ = normalised mean parasternal electromyography, NRDI = neural respiratory drive index.