ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Research letter

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

Rebecca Francesca D'Cruz, Eui-Sik Suh, Georgios Kaltsakas, Amy Dewar, Neeraj Mukesh Shah, Rita Priori, Abdel Douiri, Louise Rose, Nicholas Hart, Patrick Brian Murphy

Please cite this article as: D'Cruz RF, Suh E-S, Kaltsakas G, *et al*. Home parasternal electromyography tracks patient-reported and physiological measures of recovery from severe COPD exacerbation. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00709-2020).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

©The authors 2021. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

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

Rebecca Francesca D'Cruz[1,2], Eui-Sik Suh[1,3], Georgios Kaltsakas[1,2], Amy Dewar[4], Neeraj Mukesh Shah[1,2], Rita Priori[5], Abdel Douiri[6], Louise Rose[1,7], Nicholas Hart[1,2], Patrick Brian Murphy[1,2]

1. Lane Fox Clinical Respiratory Physiology Research Unit, Guy's and St Thomas' NHS Foundation Trust, United Kingdom
2. Centre for Human and Applied Physiological Sciences, King's College London, United Kingdom
3. Faculty of Life Sciences and Medicine, King's College London, United Kingdom
4. Department of Respiratory Medicine, Guy's and St Thomas' NHS Foundation Trust, United Kingdom
5. Philips Research, Eindhoven, The Netherlands
6. School of Population Health and Environmental Sciences, King's College London, United Kingdom
7. Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, King's College London, United Kingdom

Corresponding author: Dr Patrick Murphy, Lane Fox Clinical Respiratory Physiology Research Unit, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, SE1 7EH. Email: patrick.murphy@gstt.nhs.uk

"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.

ORCID iD:

Rebecca Francesca D'Cruz 0000-0001-5245-9911
Eui-Sik Suh 0000-0002-4883-0084
Georgios Kaltsakas 0000-0002-6852-1553
Amy Dewar 0000-0001-7960-0866
Neeraj Mukesh Shah 0000-0002-7679-0825
Rita Priori 0000-0001-8050-7108)
Abdel Douiri 0000-0002-4354-4433
Louise Rose 0000-0003-1700-3972
Nicholas Hart 0000-0002-6863-585X
Patrick Brian Murphy 0000-0002-1500-611X

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 (SpO_2), heart rate, respiratory frequency (f_R)) 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/m^2 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 (SpO_2), respiratory rate (f_R) and neural respiratory drive, quantified using EMG_{para}. EMG_{para} 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 EMG_{para} was measured before and after inhalation of patients' short-acting bronchodilator. Traces were analysed offline by converting raw EMG_{para} signals to root mean squared (RMS) using a moving window of 50 milliseconds. RMS EMG_{para} peak values during tidal breathing were manually identified (mean EMG_{para}), normalised to the maximal volitional manoeuvre ($EMG_{para\%max}$) and expressed as neural respiratory drive index (NRDI) (product of $EMG_{para\%max}$ 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 (FEV_1, 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 EMG_{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 EMG_{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±2.6 years, 67% female, BMI 21.8±1.2 kg/m^2, FEV_1 23 (19-25)% predicted, 7 (58%) current smokers, 68±13 pack-years, exacerbation frequency (number of exacerbations in the 12 months preceding admission) 3.6±0.5, Charlson comorbidity index 4±1 (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 anti-muscarinic (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 EMG_{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, SpO_2, 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), SpO_2 (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) , FEV_1 %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 (R^2=0.39, p=0.03) and the breathlessness subdomain (R^2=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 (R^2=0.94, p<0.01) and EXACT breathlessness (R^2=0.94, p<0.01) and CV for NRDI predicted CV of total EXACT score (R^2=0.98, p=0.001) and EXACT breathlessness (R^2=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

Acknowledgements: We wish to thank the Integrated Respiratory Team at Guy's and St Thomas' Hospital NHS Foundation Trust for their assistance in identifying hospitalised COPD patients.

Author contributions: NH and PBM designed the study, RFD acquired and analysed the data and prepared the first draft of the manuscript. ADo provided statistical support. All authors contributed to revising the manuscript for important intellectual content and approving the final version of the manuscript. NH, PBM and RFD take responsibility for the accuracy and integrity of the data.

Support statement: RFD was funded by the National Institute for Health Research to conduct this study (NIHR-INF-0415, DRF-2018-11-ST2-037). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

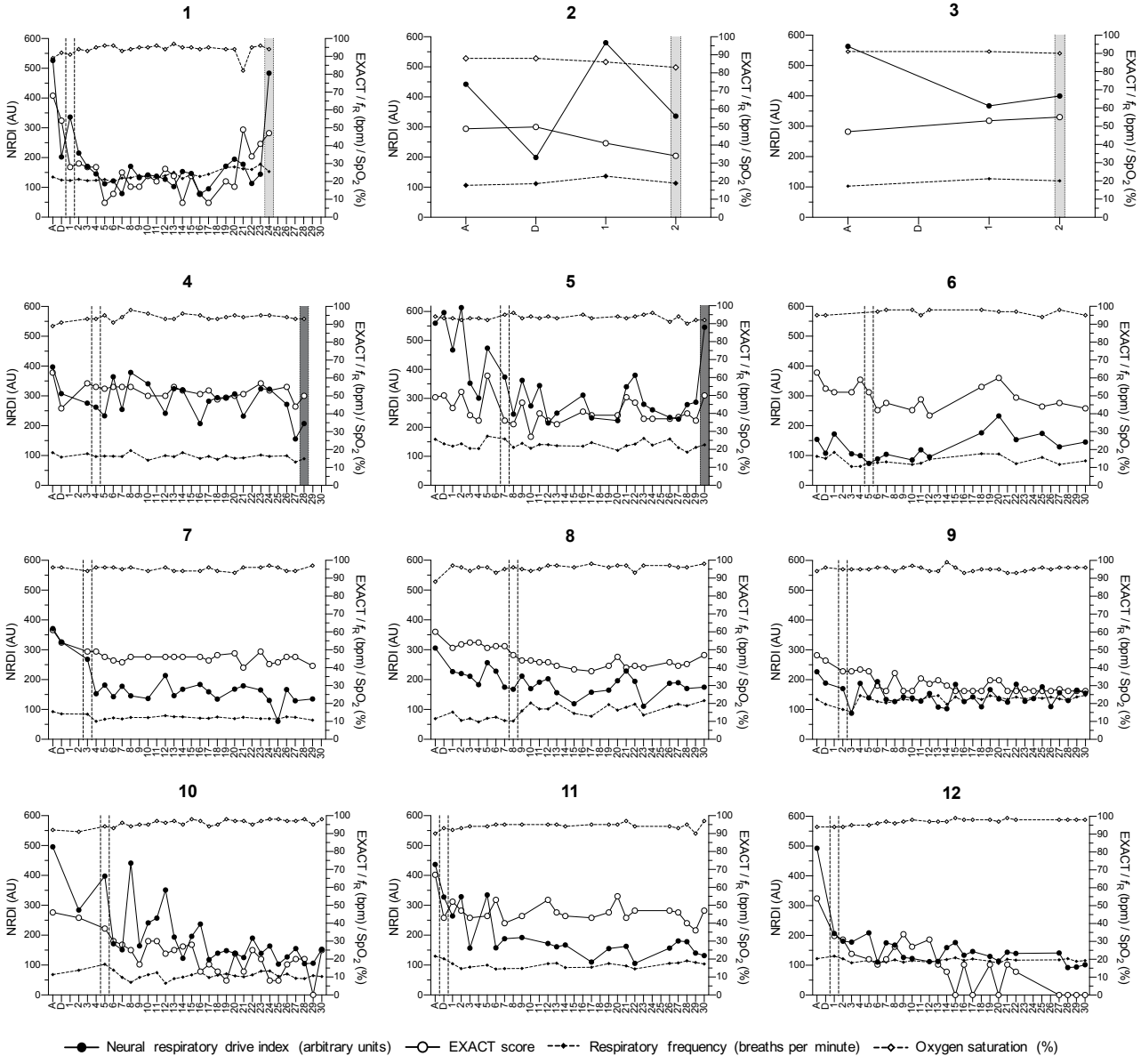
Ethics approval: This study was approved by the London-Westminster Research Ethics Committee (18/LO/0157) and registered as a prospective observational cohort study (NCT03443505).

References

1. Sjoding MW, Cooke CR, (2014) Readmission penalties for chronic obstructive pulmonary disease will further stress hospitals caring for vulnerable patient populations. Am J Respir Crit Care Med 190: 1072-1074
2. Lindenauer PK, Dharmarajan K, Qin L, Lin Z, Gershon AS, Krumholz HM, (2018) Risk Trajectories of Readmission and Death in the First Year after Hospitalization for Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 197: 1009-1017
3. Jacobs DM, Noyes K, Zhao J, Gibson W, Murphy TF, Sethi S, Ochs-Balcom HM, (2018) Early Hospital Readmissions after an Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the Nationwide Readmissions Database. Ann Am Thorac Soc 15: 837-845
4. Myers LC, Faridi MK, Hasegawa K, Hanania NA, Camargo CA, Jr., (2020) The Hospital Readmissions Reduction Program and Readmissions for Chronic Obstructive Pulmonary Disease, 2006-2015. Ann Am Thorac Soc 17: 450-456
5. Al Rajeh AM, Hurst JR, (2016) Monitoring of Physiological Parameters to Predict Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review. J Clin Med 5
6. Walker PP, Pompilio PP, Zanaboni P, Bergmo TS, Prikk K, Malinovschi A, Montserrat JM, Middlemass J, Sonc S, Munaro G, Marusic D, Sepper R, Rosso R, Siriwardena AN, Janson C, Farre R, Calverley PMA, Dellaca RL, (2018) Telemonitoring in Chronic Obstructive Pulmonary Disease (CHROMED). A Randomized Clinical Trial. Am J Respir Crit Care Med 198: 620-628
7. Murphy PB, Kumar A, Reilly C, Jolley C, Walterspacher S, Fedele F, Hopkinson NS, Man WD, Polkey MI, Moxham J, Hart N, (2011) Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. Thorax 66: 602-608
8. Suh ES, Mandal S, Harding R, Ramsay M, Kamalanathan M, Henderson K, O'Kane K, Douiri A, Hopkinson NS, Polkey MI, Rafferty G, Murphy PB, Moxham J, Hart N, (2015) Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD. Thorax 70: 1123-1130
9. Leidy NK, Wilcox TK, Jones PW, Roberts L, Powers JH, Sethi S, Group E-PS, (2011) Standardizing measurement of chronic obstructive pulmonary disease exacerbations. Reliability and validity of a patient-reported diary. Am J Respir Crit Care Med 183: 323-329
10. Borg GA, (1982) Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14: 377-381
11. MacBean V, Hughes C, Nicol G, Reilly CC, Rafferty GF, (2016) Measurement of neural respiratory drive via parasternal intercostal electromyography in healthy adult subjects. Physiol Meas 37: 2050-2063
12. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N, (2009) Development and first validation of the COPD Assessment Test. Eur Respir J 34: 648-654
13. Stevenson NJ, Walker PP, Costello RW, Calverley PM, (2005) Lung mechanics and dyspnea during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 172: 1510-1516
14. Parker CM, Voduc N, Aaron SD, Webb KA, O'Donnell DE, (2005) Physiological changes during symptom recovery from moderate exacerbations of COPD. Eur Respir J 26: 420-428
15. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W, Calverley P, Rennard S, Wouters EF, Wedzicha JA, Evaluation of CLtIPSEI, (2010) Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 363: 1128-1138
16. Alqahtani JS, Njoku CM, Bereznicki B, Wimmer BC, Peterson GM, Kinsman L, Aldabayan YS, Alrajeh AM, Aldhahir AM, Mandal S, Hurst JR, (2020) Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis. Eur Respir Rev 29
17. Sloots JM, Barton CA, Buckman J, Bassett KL, van der Palen J, Frith PA, Effing TW, (2017) The predictive value of an adjusted COPD assessment test score on the risk of respiratory-related hospitalizations in severe COPD patients. Chron Respir Dis 14: 72-84
18. Devot S, Derkx R, Van der Laar J, Suh E-S, Hart N, (2014) An automated algorithm to calculate neural respiratory drive (NRD) from the parasternal electromyogram (EMG) in patients with an acute exacerbation of COPD (AECOPD). European Respiratory Journal 44: P2149
19. Calverley P, (2006) Exercise and dyspnoea in COPD. European Respiratory Review 15: 72-79

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.

(A)



(B)

	Admission	Discharge	Days 1-7	Days 8-14	Days 15-21	Days 22-30	p-value
Number of assessments	9	6	51	49	46	58	
Patient-reported							
EXACT score	57±2.6	48±2.2	43±1.5*	37±1.5*	34±2.4*	34±2.0*	**<0.001**
mBorg score†	6±1.7	4±1.0	2±0.4	2±0.3	2±0.3	1±0.3	0.16
Weekly CAT score	32±2.1	31±2.2	23±3.2	21±3.2*	19±1.7*	20±3.2*	**0.001**
Physiological							
HR (beats/min)	94±3.6	90±1.4	87±1.9	83±1.7	82±1.7	84±1.7	0.07
SpO_2 (%)	92±0.9	94±0.8	95±0.2	96±0.2	96±0.3	95±0.3	**0.01**
f_R (breaths/min)	18±1.6	18±1.4	16±0.6	17±0.7	17±0.7	17±0.6	0.23
FEV_1 (L)‡	0.63±0.10	0.62±0.17	0.78±0.15	0.86±0.16	0.86±0.16	0.88±0.16	0.11
FEV_1 %predicted (%)‡	25±4	24±7	34±7	38±9	38±9	39±9	0.11
FVC (L)‡	1.70±0.21	1.50±0.29	2.14±0.21*	2.39±0.24*	2.28±0.22	2.41±0.23*	**0.001**
FVC %predicted (%)‡	54±5	45±8	72±9	81±11	78±11	82±10	**0.01**
FEV_1:FVC (%)‡	0.38±0.04	0.41±0.05	0.37±0.06	0.37±0.06	0.38±0.06	0.36±0.06	0.83
IC (L)‡	1.24±0.14	1.43±0.19	1.63±0.15*	1.77±0.17*	1.72±0.16*	1.81±0.19*	**0.001**
IC %predicted (%)	49±5	50±4	66±7*	73±9*	70±7*	73±8*	**0.001**
$EMG_{para\%max}$ (%)	21.9±3.4	16.9±3.0	14.6±0.9	12.4±0.8	11.5±0.6*	10.7±0.6	**<0.01**
$EMG_{para\%max}$ *z*-score	5.29±1.25	4.88±1.87	3.12±0.51	2.05±0.30*	1.71±0.30*	1.67±0.27*	**0.001**
NRDI (%.min^{-1})	382±44	309±68	232±17*	197±12*	182±9*	177±11*	**<0.001**
NRDI *z*-score	5.95±1.63	5.84±2.50	3.08±0.60*	1.99±0.33*	1.58±0.29*	1.81±0.36*	**<0.01**