27th Hellenic Thoracic Society

ADMISSION PREVENTION IN COPD

Using Translational Physiological Science to Design Future Clinical Trials

Nicholas Hart
Professor of Respiratory & Critical Care Medicine
Clinical Director of Lane Fox Respiratory Service
St Thomas' Hospital
Director of Research Delivery
Guys & St Thomas' NHS Foundation Trust
London UK

Joint Editor-in-Chief
THORAX

nicholas.hart@gstt.nhs.uk
@NickHartThorax

Conflict of Interest Disclosure

Real or perceived direct or indirect conflicts of interest that relate to this presentation:

Affiliation	Nature of conflict
Tobacco-industry and tobacco corporate affiliate related conflict of interest	**Not applicable**
Grants/Research Support (to my institution)	**Philips** **Resmed** **Fisher-Paykel** **B&D Electromedical**
Honoraria or consultation fees	**Astra Zeneca** **GSK** **Philips** **Resmed** **Fisher-Paykel** **B&D Electromedical**
Participation in a company sponsored bureau	**Philips** **Resmed**
Stock shareholder	**Not applicable**
Spouse/partner	**Not applicable**
Other support or other potential conflict of interest	**Nil**

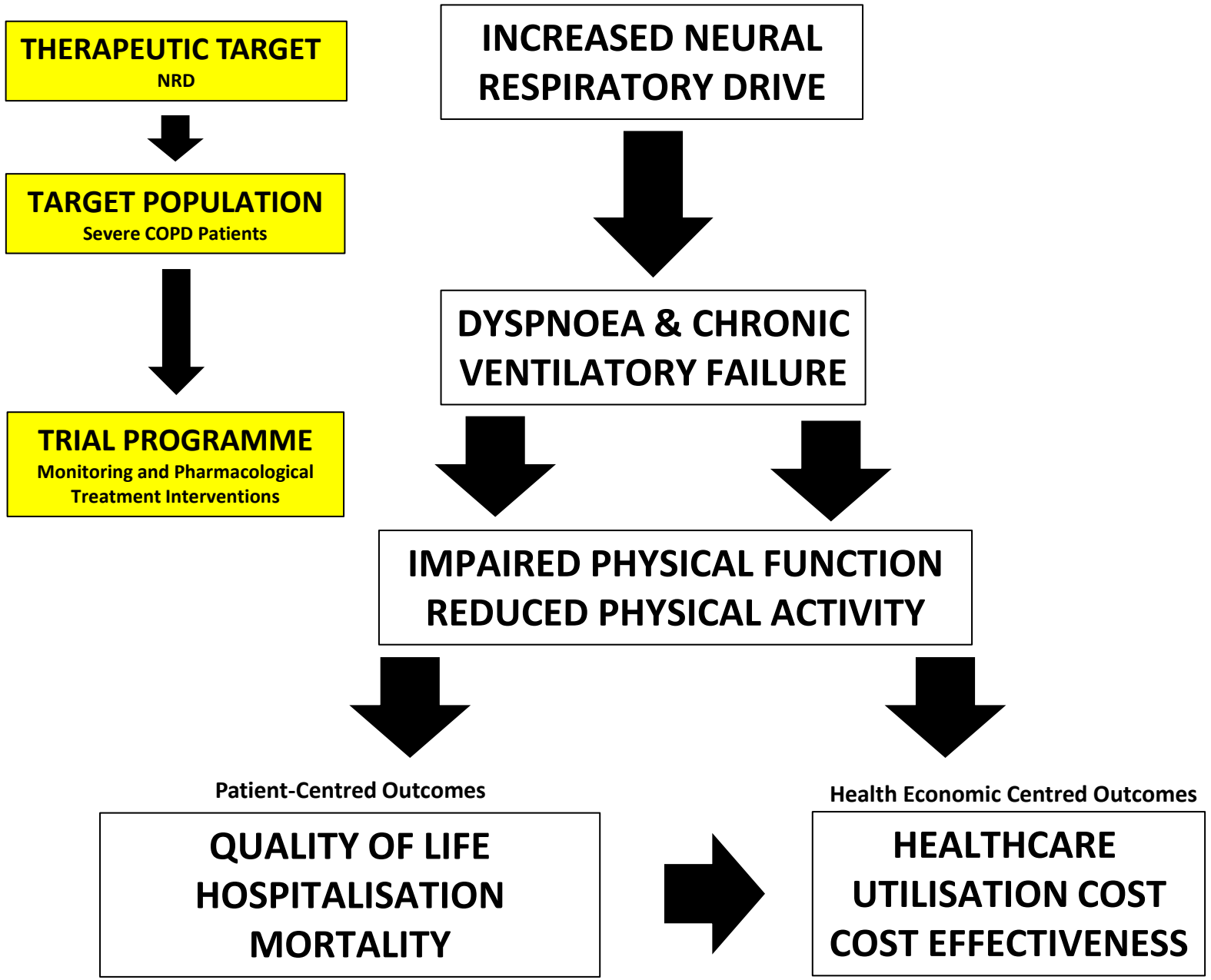
LANE FOX CLINICAL RESPIRATORY PHYSIOLOGY CENTRE

MUSCLE STRUCTURE & MUSCLE FUNCTION

FUNCTIONAL OUTCOME

CLINICAL OUTCOME

SAFE DISCHARGE & ADMISSION PRVENTION STRATEGY



LANE FOX CLINICAL RESPIRATORY PHYSIOLOGY RESEARCH CENTRE

LANE FOX CLINICAL RESPIRATORY PHYSIOLOGY GROUP

- Prof Joerg Steier
- Dr Bronwen Connolly
- Dr Patrick Murphy***
- Dr Phil Marino
- Dr Eui-Sik Suh*
- Dr Swapna Mandal
- Dr Michelle Ramsay**
- Dr Maxine Patout
- Miss Gill Arbane

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- Prof John Moxham
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- Dr Caroline Jolley
- Dr Abdel Douri

ROYAL BROMPTON HOSPITAL

- Prof Michael Polkey
- Dr Nicholas Hopkinson
- Dr William Man

PEER-REVIEWED AWARDS

European Respiratory Society GSK Award 2014*; European Respiratory Society British Lung Foundation Award 2014**; European Respiratory Society Intensive Care Assembly Non-Invasive Ventilation Group 2013**, American Thoracic Society Critical Care Assembly 2011 ***, European Respiratory Society Intensive Care Assembly Non-Invasive Ventilation Group 2010*

Biomarkers to Predict Outcome

NEJM 2012

'In recent decades, biomarkers have become essential in diagnosing disease and assessing response to therapy. The increasing quantitative rigor and efficiency of these tests have led to the possibility of 'personalized medicine'. Despite such progress, the way in which a physician uses biomarkers recapitulates an enduring practice of medicine: measure the patient, think about the result and make a decision'

Aaron S. Kesselheim, M.D., J.D., M.P.H., and Jason Karlawish, M.D.

BIOMARKER

- Indicator of either
  - –a normal or pathogenic processes
  - –a response to therapeutic interventions
- Objectively measured and evaluated
- Generally a substance or molecule

National Institute of Health

Sputum

- Similar cellular composition to BAL
  - Presence of sputum eosinophilia predicts response to corticosteroids and a larger response to bronchodilators
- Inflammatory mediators
  - IL-8, IL-6 and TNFα increased in severe COPD
  - Sputum IL-8 increases with decreasing FEV_1

BAL

- Samples cells from lungs periphery
- Cellular composition
  - >80% alveolar macrophages, plus neutrophils and T-cells
  - Some patients have increased eosinophils
- Inflammatory mediators
  - Elevated eosinophil cationic protein, myeloperoxidase, IL-8
  - Mast cell activation with raised tryptase and histamine levels
  - Increase in elastase and decrease in anti-elastase activity in COPD

Serum biomarkers

- **TNFα, IL-8, CRP, leptin, endothelin-1, fibrinogen, IL-6 and leukotriene E4** all increased in exacerbations of COPD compared to stable disease
- **hsCRP** – most effective biomarker in distinguishing AECOPD from stable state, but magnitude of CRP does not reflect severity of exacerbation
- **Procalcitonin** levels not significantly increased in AECOPD due to bacterial infection, but PCT-guided treatment reduces antibiotic use
- High initial **fibrinogen** levels predict moderate-to-severe exacerbations

Exhaled gases

- FENO
  - Increased in AECOPD
  - Associated with presence of eosinophils
  - Predicts steroid responsiveness
  - Tends not to be elevated in the stable state
- CO levels and exhaled volatile hydrocarbons not found to be useful biomarkers
- Exhaled breath condensates
  - Highly variable levels of inflammatory mediators

Bronchial biopsies

- In stable COPD
  - Increased **macrophages** and **activated T-lymphocytes (CD8+)** expressing
    - IFNγ, CXCL10, IL-9
    - Type-1 response-associated chemokines, e.g. CXCR3
  - Prominent neutrophilia
- During exacerbations
  - **Eosinophil and neutrophil** recruitment
  - Increased expression of chemoattractants, e.g. CCL5 and CXCL5
- Disease progression
  - **Increased NF-κB expression** with disease severity

Sputum

- Similar cellular
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disease severity

What is an Advanced Physiological Biomarker?

ADVANCED PHYSIOLOGICAL BIOMARKER

- Indicator of either
  - –a normal or pathogenic processes
  - –a response to therapeutic interventions
- Objectively measured and evaluated
- ~~Generally a substance or molecule~~

National Institute of Health

ADVANCED PHYSIOLOGICAL BIOMARKER

- Diagnostic marker
- Marker of disease severity
- Marker of disease progression
- Marker of treatment effect

ADVANCED PHYSIOLOGICAL BIOMARKER

- Diagnostic marker
- Marker of disease severity
- Marker of disease progression
- Marker of treatment ~~effect~~ failure

ACUTE MYOTRACE PROGRAMME:

Developing Advanced Respiratory Physiological Biomarkers to Risk Stratify AECOPD Patients to Enhance Safe Discharge and Prevent Admission

MYOTRACE PROGRAMME:
Advanced Respiratory Physiological Monitoring

- **Breathlessness is a subjective condition reported by the patient (SYMPTOM)**
- **Dyspnoea is an objective condition reported by the clinician (SIGN)**

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Advanced Respiratory Physiological Monitoring

- **Breathlessness is a subjective condition reported by the patient (SYMPTOM)**
- **Dyspnoea is an objective condition reported by the clinician (SIGN)**

How do we integrate these subjective and objective measurements?

How do we translate these measurements into clinical practice?

Financial Cost of Acute Exacerbations of COPD

- US data has shown that AECOPD account for
  - 1.5 million ED attendances
  - 726,000 hospitalisations
  - 119,000 deaths
- Direct costs have been estimated at $29.5 billion with indirect costs of $20.4 billion
- UK data has shown that AECOPD has 20% hospital readmission rate within 28 days and up to a third of patients readmitted within 3 months
- UK & US incentivised performance by the introduction of financial penalties for patients who are readmitted to acute hospitals within 28 days

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Human Cost of Acute Exacerbations of COPD

- **An acute exacerbation of COPD has detrimental effects on lung function, HRQL and exercise capacity**
- **Patients with >3 exacerbations per year have a 5-year survival rate of only 30%**
- **Exacerbation-free patients have a 5-year survival rate of 80%**

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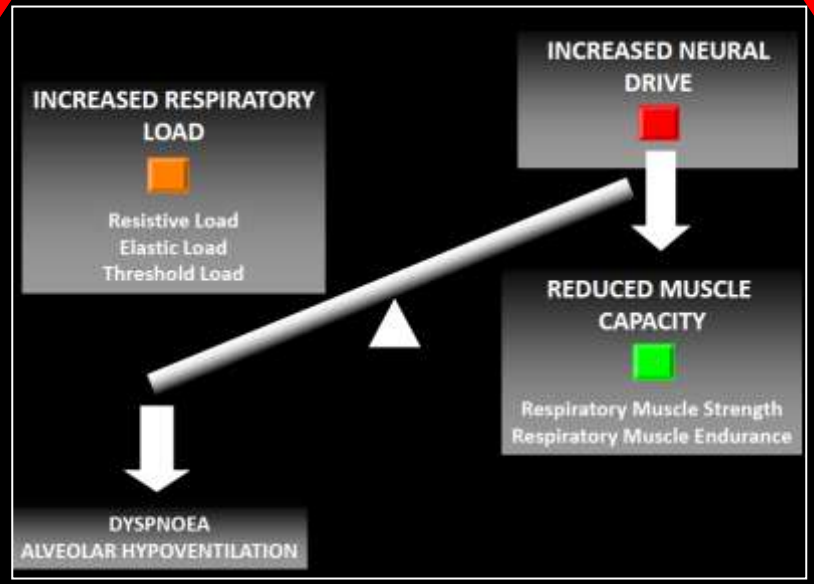
Treatment Success

High Airflow Obstruction
Increase Resistive Load
Dynamic Lung Hyperinflation
Increase Threshold Load
Diaphragm Mechanically Disadvantage
Reduce Capacity

Neural Respiratory Drive Increases

AECOPD



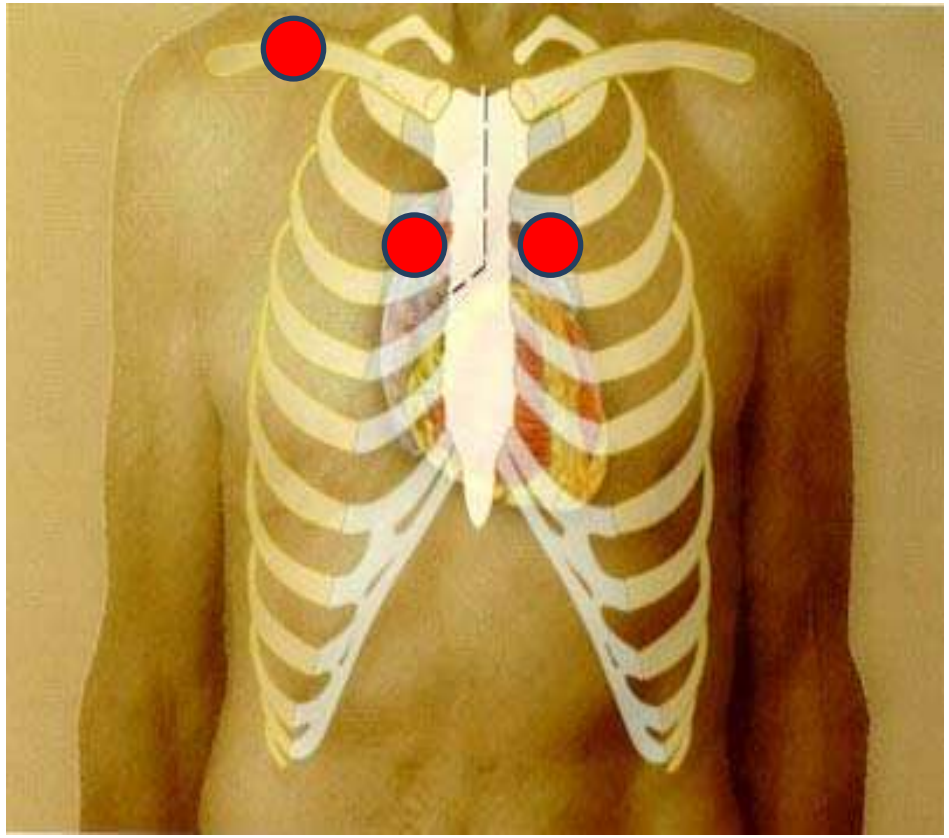
Neural Respiratory Drive Decreases

Fall in Airflow Obstruction
Reduce Resistive Load
Dynamic Lung Deflation
Reduce Threshold Load
Diaphragm Mechanically Advantage
Increase Capacity

AECOPD represent an acute shift in the load-capacity-drive relationship

Myotrace - A Non-Invasive Technique

- 2nd Intercostal Parasternal muscles
  - Obligate muscles of inspiration
  - Amenable to surface EMG



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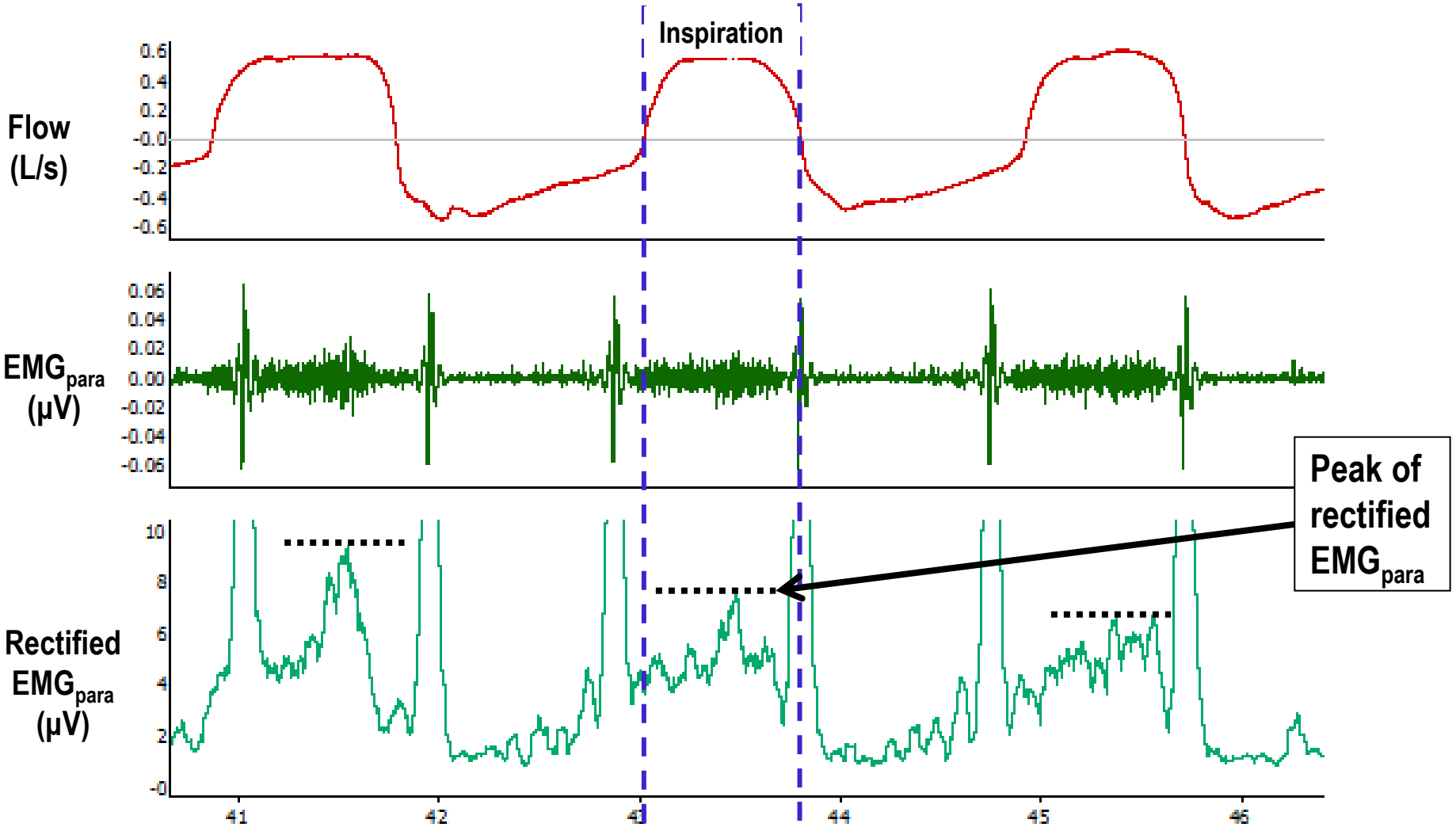
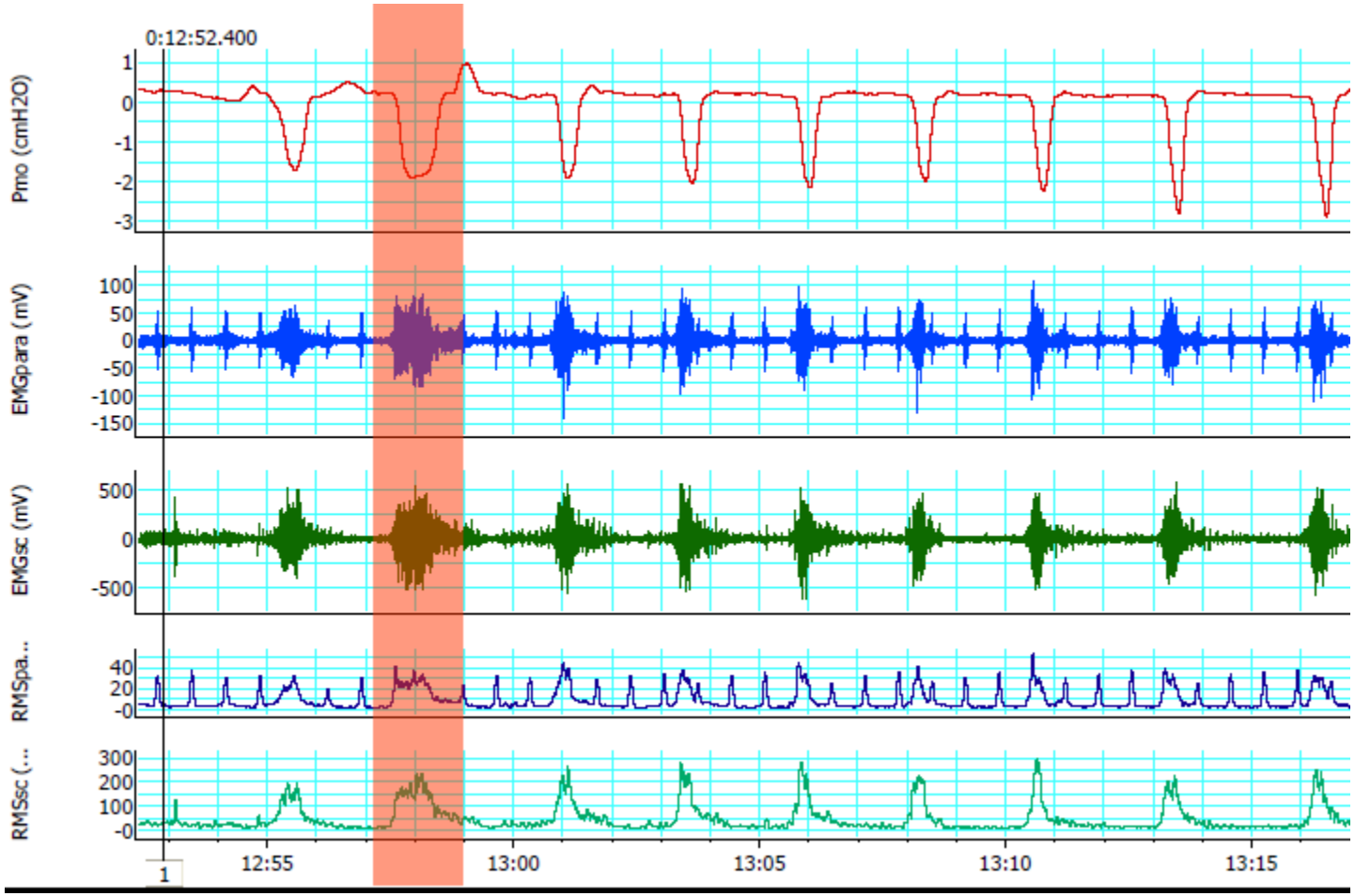
Parasternal EMG (EMG_{para})



Sniff Manoeuvre



EMGpara%max.RR = NRDI

Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD

Thorax 2011;**66**:602–608. doi:10.1136/thx.2010.151332

Patrick B Murphy,[1] Atul Kumar,[2] Charles Reilly,[1] Caroline Jolley,[1] Stephan Walterspacher,[2] Fiammetta Fedele,[3] Nicholas S Hopkinson,[4] William D-C Man,[4] Michael I Polkey,[4] John Moxham,[1] Nicholas Hart[5]

Table 3 Difference between admission and discharge of measured physiological variables in 30 patients either readmitted (n=9) or not readmitted (n=21) within 14 days of hospital discharge

	ΔMEWS*	ΔFEV$_1$†	Previous admissions*	ΔEMG$_{para\%max}$	ΔNRDI
Readmitted	0 (−1–2)	0.09±0.15	4 (0–14)	1.98±4.36	76±134
Not readmitted	0 (−3–2)	0.08±0.10	3 (0–10)	−4.05±10.30	−127±305
Mean difference (95% CI)		0.1 (0.14 to 0.11)		6.03 (11.5 to 0.54)	203 (39 to 366)
p Value	0.5	0.8	0.1	0.03	0.02

MYOTRACE 1 - Pilot study
Murphy *et al* Thorax 2011

- **Limitations**
  - **Small selected cohort**
  - **Readmission endpoint was not *a priori***
  - **Subjective assessment of clinical change**
  - **Small number of data pairs for comparison (37 pairs among 30 patients)**

MYOTRACE 2 Hypothesis

Neural respiratory drive predicts early readmission following hospitalisation for acute exacerbation of COPD

OPEN ACCESS

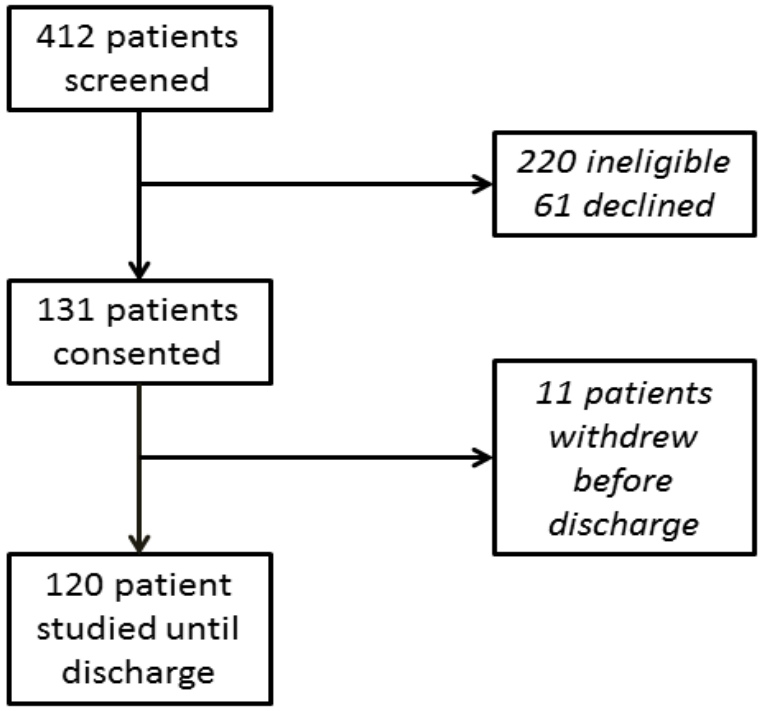
ORIGINAL ARTICLE

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

Eui-Sik Suh,[1,2] Swapna Mandal,[1,2] Rachel Harding,[1] Michelle Ramsay,[1,2] Meera Kamalanathan,[1] Katherine Henderson,[3] Kevin O'Kane,[4] Abdel Douiri,[5] Nicholas S Hopkinson,[6] Michael I Polkey,[6] Gerrard Rafferty,[2] Patrick B Murphy,[1,2] John Moxham,[2] Nicholas Hart[1,2]

Thorax. 2015 Dec;70(12):1123-30

- **120 patients completed admission-to-discharge EMG studies, daily IC, spirometry**
- **>600 individual studies in 122 patients**



Results

Age (years)	70 (9)
Male (%)	58 (48·3)
BMI (kg/m^2)	25·3 (7·2)
Current smokers (%)	47 (39·2)
Exacerbation frequency (/12 months)	3 (1-5)
Hospital admission frequency (/12 months)	1 (0-2)
Duration of symptoms (days)	4 (2-7)
Systemic steroids prior to admission (%)	26 (21·7)
Antibiotics prior to admission (%)	30 (25·0)

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Results

GOLD stage 2 (%)*	4 (4)
GOLD stage 3 (%)*	36 (36)
GOLD stage 4 (%)*	60 (60)
MRC dyspnoea grade	4 (4-5)
Length of hospital stay (days)	3 (2-6)
Deaths within 28 days (%)	1 (0·8)
Readmission at 28 days (%)	26 (21·7)
Deaths within 14 days (%)	1 (0·8)
Readmission at 14 days (%)	15 (12·5)

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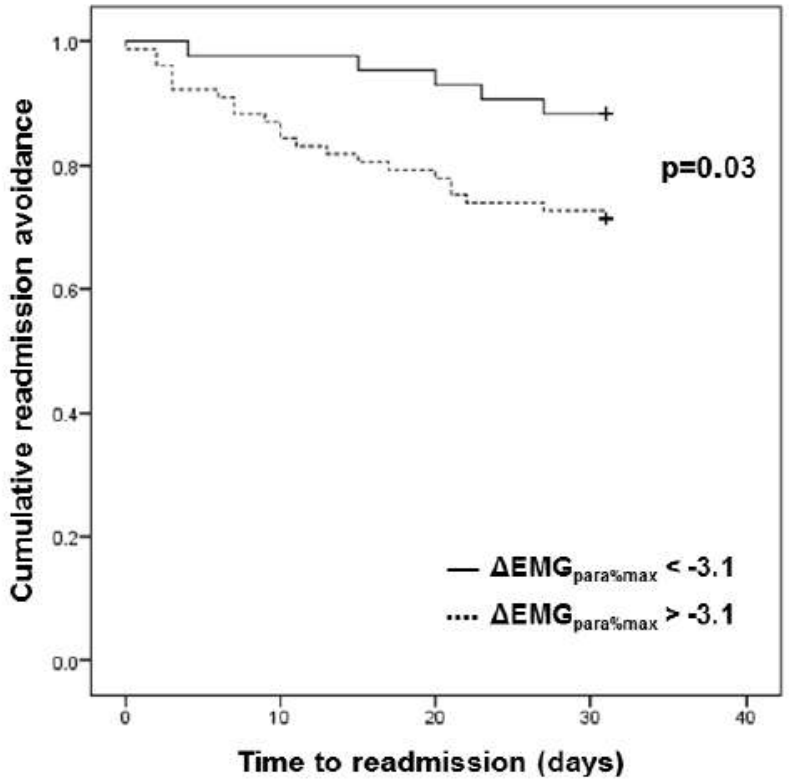
MYOTRACE II
Readmission Prediction

Readmission Prediction → **28 Day Readmission** $\Delta EMG_{para\%max}$ (Under 85 years)

Whole group

$\Delta EMG_{para\%max}$: OR 1·127, 95% CI 1·034 to 1·228, p=0·007

PREDICTING SAFE DISCHARGE: 14-Day Readmission



ΔEMG$_{para\%max}$
OR 1·127, 95% CI 1·034 to 1·228, p=0·007

'The failure of ΔEMG$_{para\%max}$ 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 or death. The positive predictive value (PPV) was 19·7% with a negative predictive value (NPV) of 97·7%'

Time-to-readmission Kaplan-Meier plots for patients whose EMGpara%max fell by more than 3.1% between admission and discharge (solid line), and those whose EMGpara%max fell by less than 3.1% (dotted line).

Abbreviations: EMG$_{para\%max}$ = 1-minute mean magnitude of rectified inspiratory parasternal EMG activity normalised to a maximal manoeuvre

Suh et al Thorax 2015

Under Review
Thorax R1

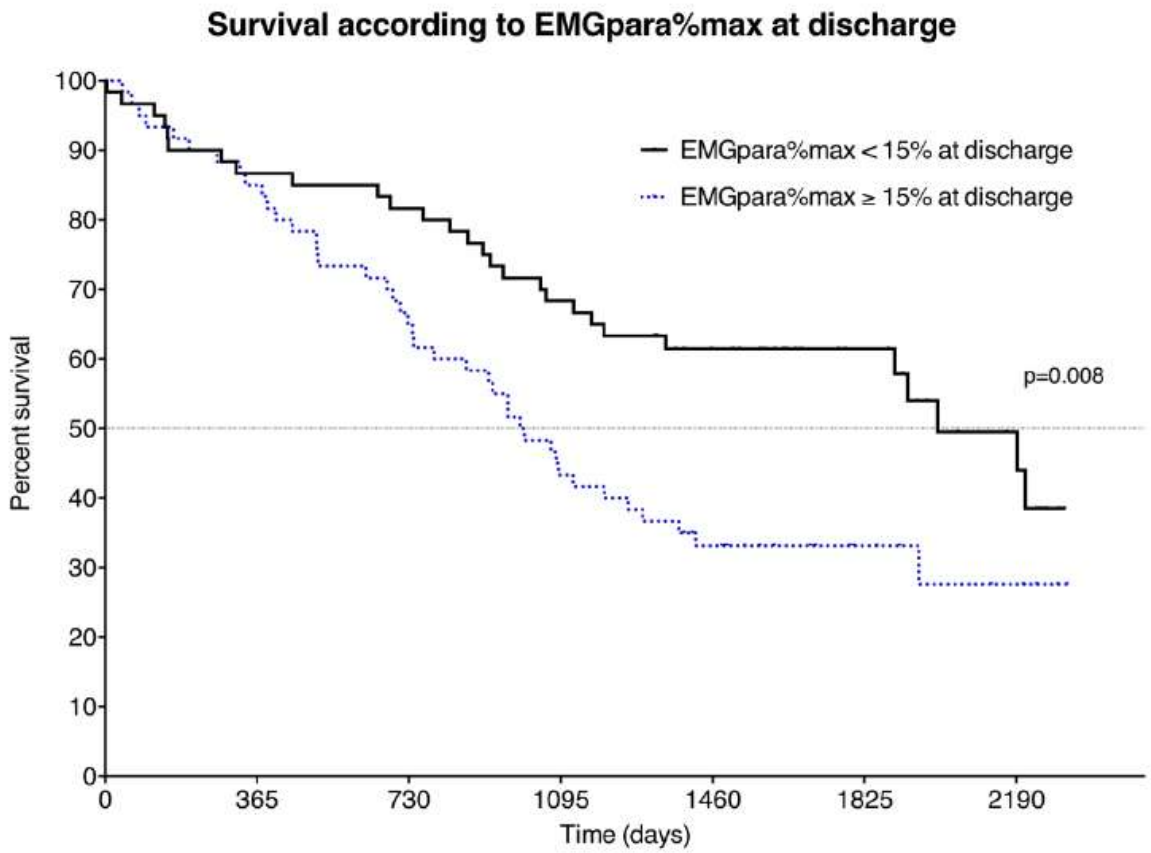
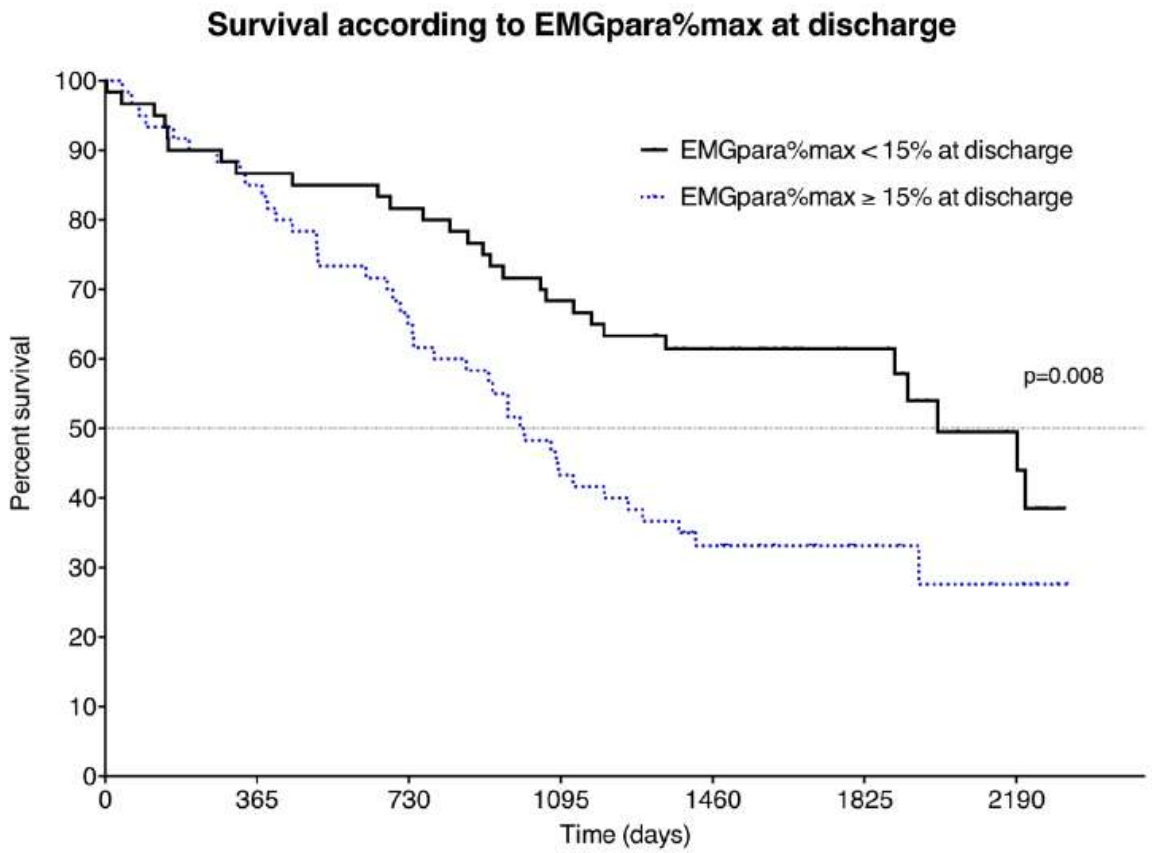


Figure 1: Survival according to EMGpara%max at discharge (continuous line: patients with EMGpara%max < 15% at discharge, dot: patients with EMGpara%max ≥ 15% at discharge) (p:0.008, log-rank)

Under Review
Thorax R1



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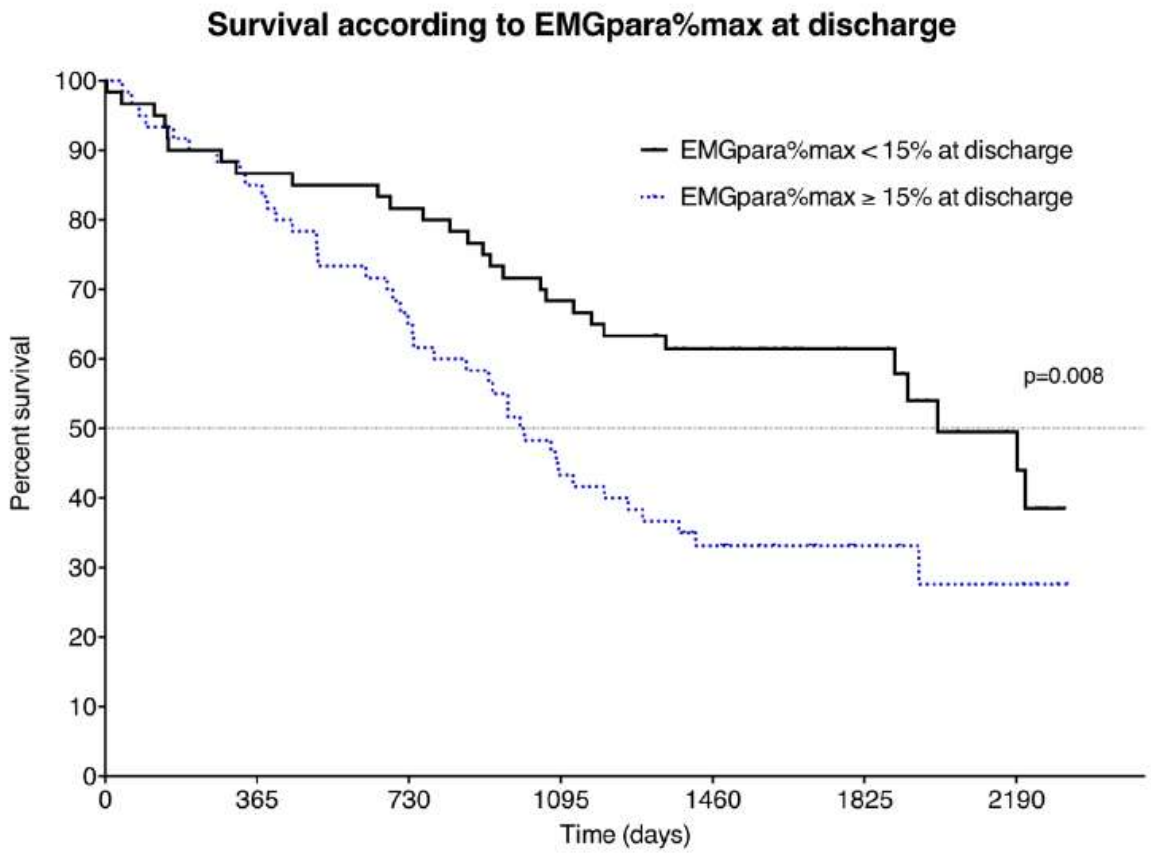
Increase Mortality

- NRD (HR 2.14 95% CI 1.29 – 3.54; p =0.003)
- Age (HR 2.03 95% CI 1.23 – 3.34; p =0.006)
- PaCO2 at admission (HR 1.83 95% CI 1.06 – 3.06; p =0.02)
- LTOT use (HR 2.98 95% CI 1.47 – 6.03; p =0.002)

Under Review
Thorax R1



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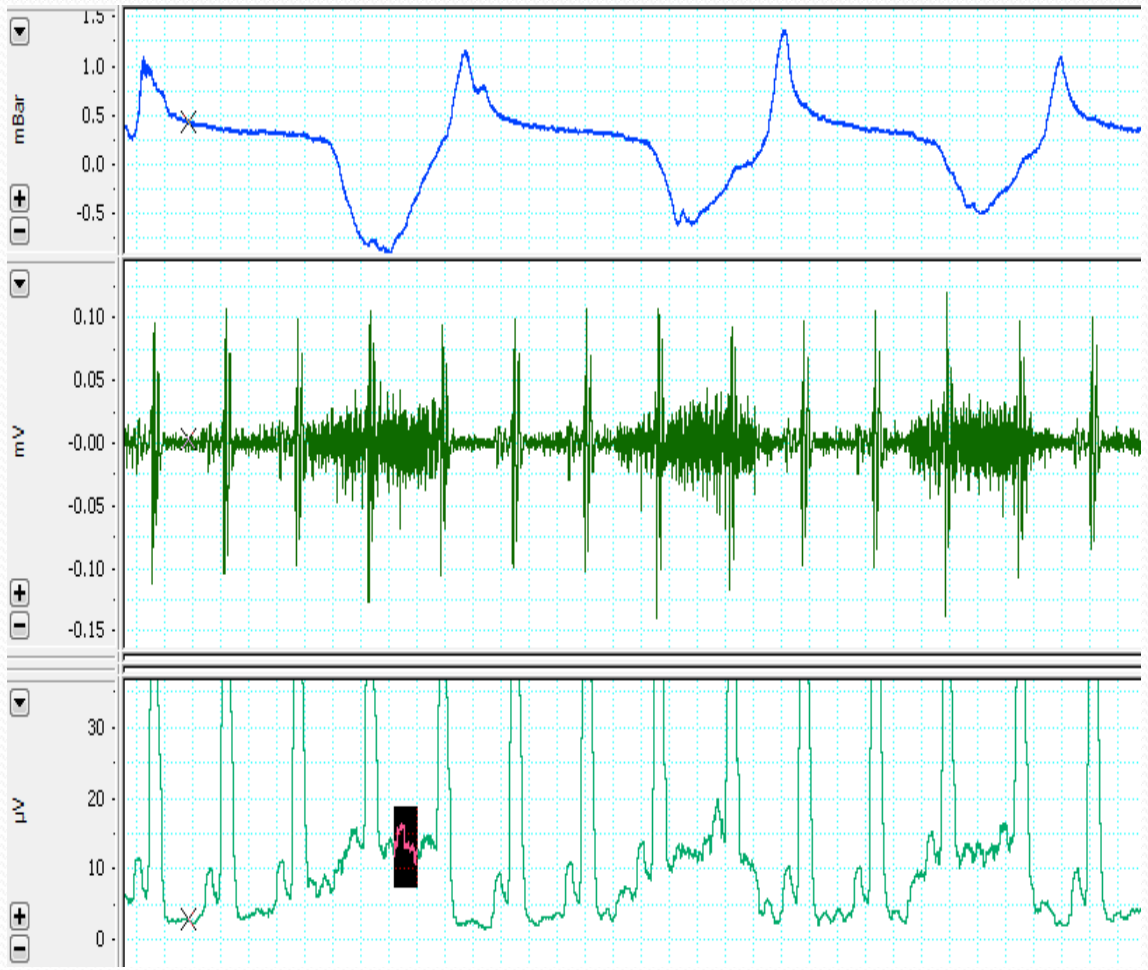
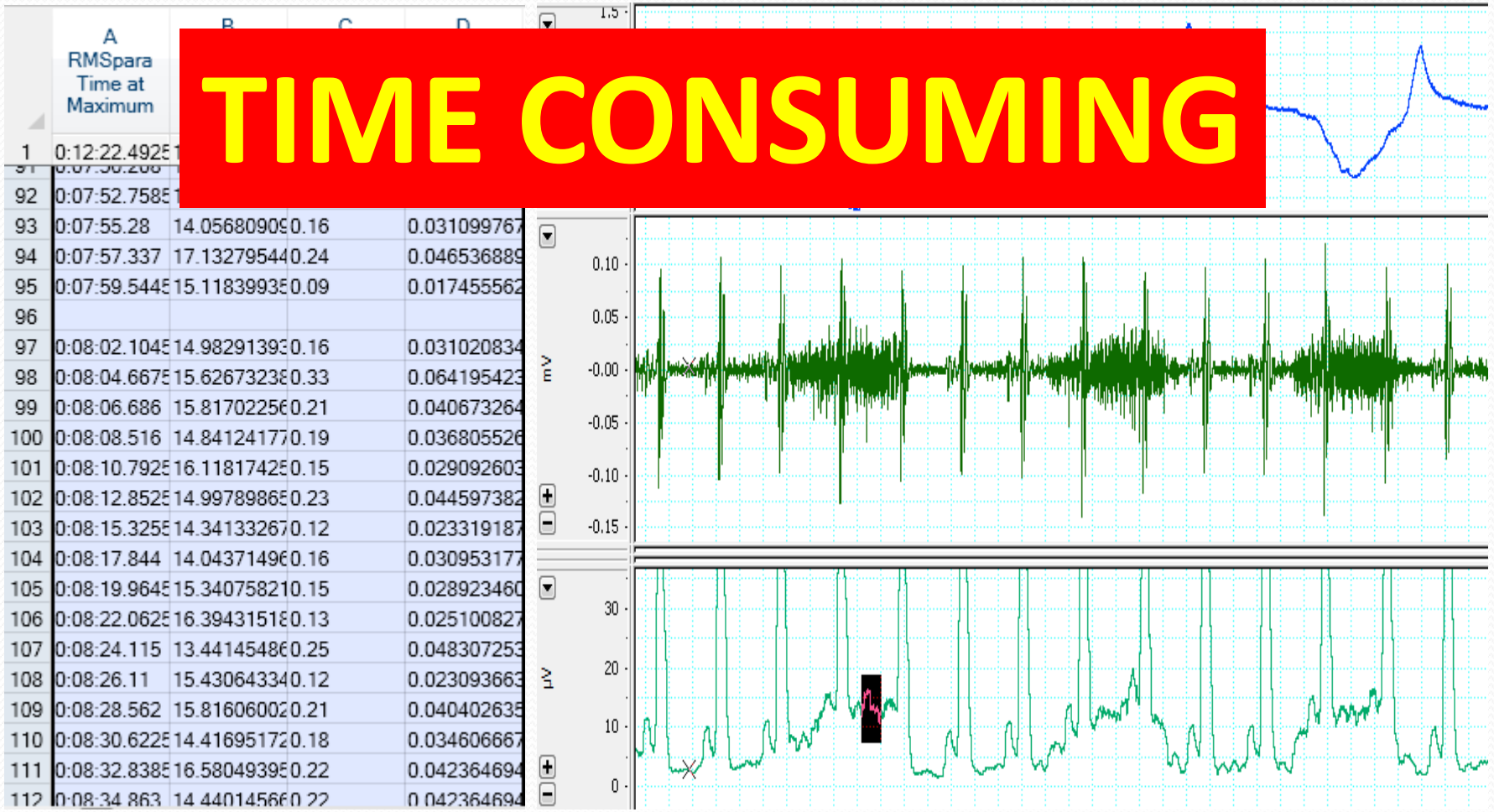
MYOTRACE III
Development of the Automated Algorithm

	A RMSpara Time at Maximum	B RMSpara Maximum Value µV	C Selection Duration s	D volume Maximum - Minimum L
1	0:12:22.4925	16.50594995	0.17	0.031111044
92	0:07:52.7585	15.56949586	0.16	0.031223806
93	0:07:55.28	14.05680909	0.16	0.031099767
94	0:07:57.337	17.13279544	0.24	0.046536889
95	0:07:59.5445	15.11839935	0.09	0.017455562
96				
97	0:08:02.1045	14.98291393	0.16	0.031020834
98	0:08:04.6675	15.62673238	0.33	0.064195423
99	0:08:06.686	15.81702256	0.21	0.040673264
100	0:08:08.516	14.84124177	0.19	0.036805526
101	0:08:10.7925	16.11817425	0.15	0.029092603
102	0:08:12.8525	14.99789865	0.23	0.044597382
103	0:08:15.3255	14.34133267	0.12	0.023319187
104	0:08:17.844	14.04371496	0.16	0.030953177
105	0:08:19.9645	15.34075821	0.15	0.028923460
106	0:08:22.0625	16.39431518	0.13	0.025100827
107	0:08:24.115	13.44145486	0.25	0.048307253
108	0:08:26.11	15.43064334	0.12	0.023093663
109	0:08:28.562	15.81606002	0.21	0.040402635
110	0:08:30.6225	14.41695172	0.18	0.034606667
111	0:08:32.8385	16.58049395	0.22	0.042364694
112	0:08:34.863	14.44014566	0.22	0.042364694



MYOTRACE III
Development of the Automated Algorithm

TIME CONSUMING



	A RMSpara Time at Maximum	B	C	D
1	0:12:22.4925			
92	0:07:52.7585			
93	0:07:55.28	14.05680909	0.16	0.03109976
94	0:07:57.337	17.13279544	0.24	0.04653688
95	0:07:59.5445	15.11839935	0.09	0.01745556
96				
97	0:08:02.1045	14.98291393	0.16	0.03102083
98	0:08:04.6675	15.62673238	0.33	0.06419542
99	0:08:06.686	15.81702256	0.21	0.04067326
100	0:08:08.516	14.84124177	0.19	0.03680552
101	0:08:10.7925	16.11817425	0.15	0.02909260
102	0:08:12.8525	14.99789865	0.23	0.04459738
103	0:08:15.3255	14.34133267	0.12	0.02331918
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106	0:08:22.0625	16.39431518	0.13	0.02510082
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109	0:08:28.562	15.81606002	0.21	0.04040263
110	0:08:30.6225	14.41695172	0.18	0.03460666
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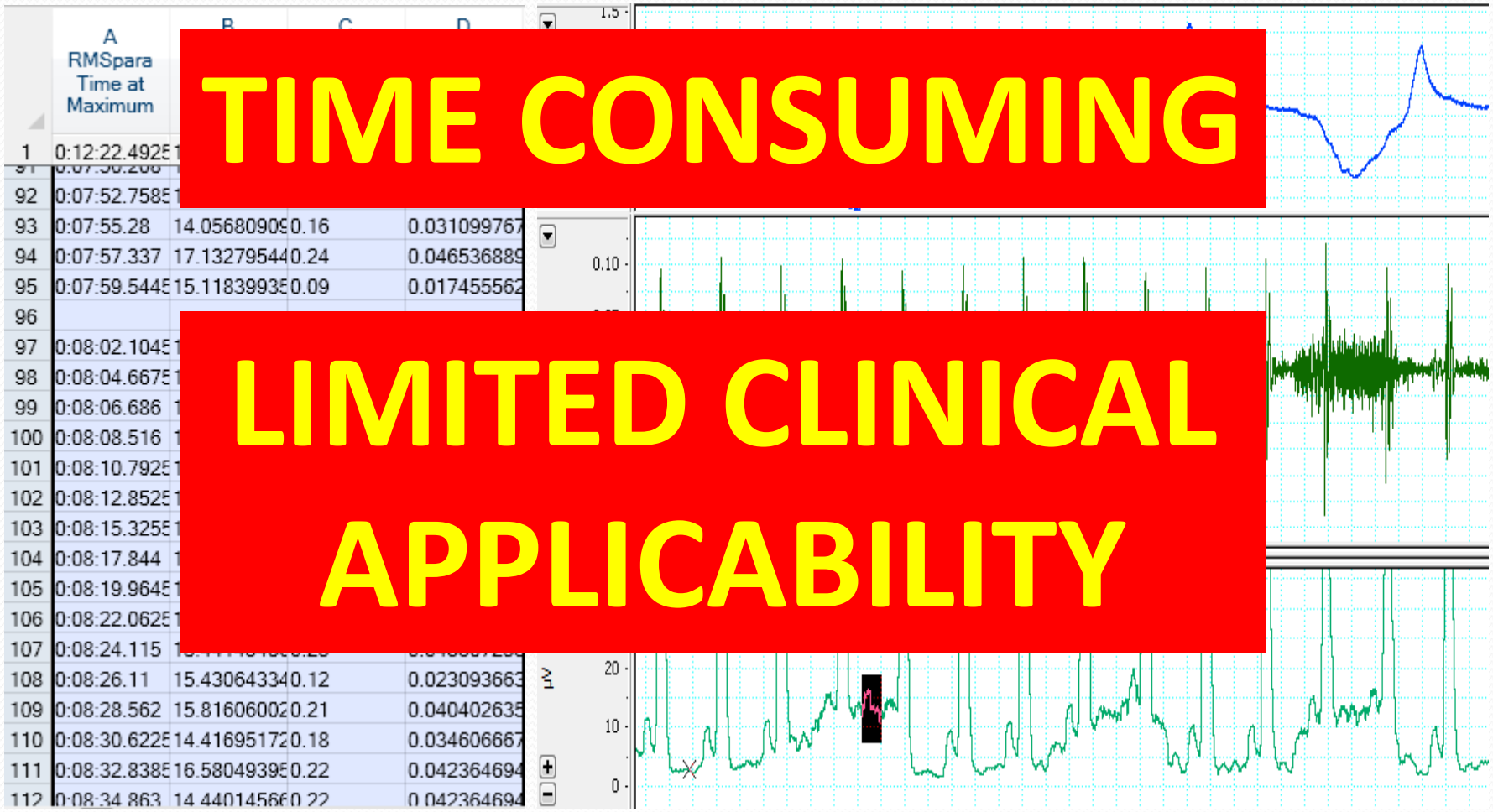
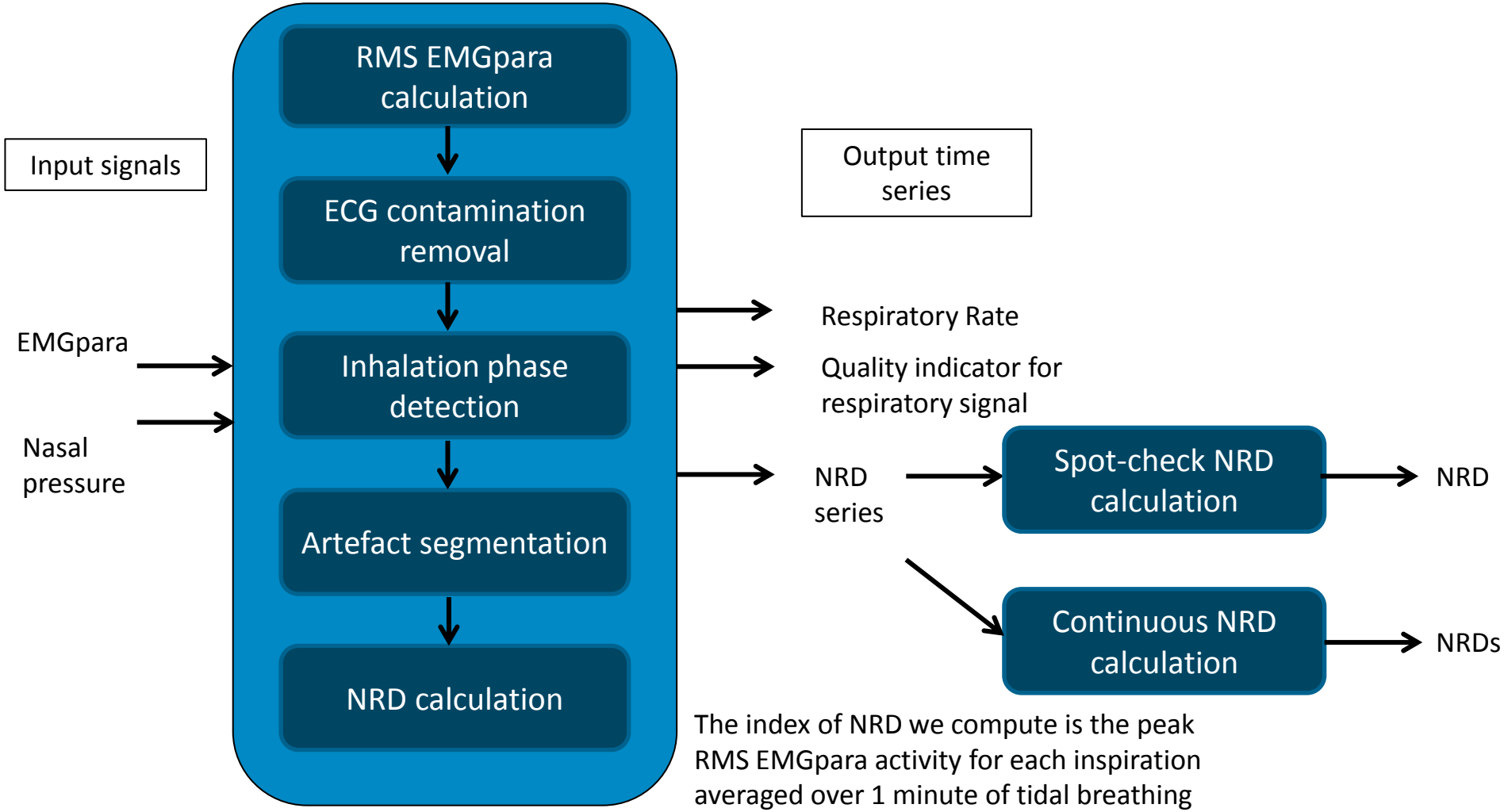
MYOTRACE III
Development of the Automated Algorithm



TIME CONSUMING

LIMITED CLINICAL APPLICABILITY

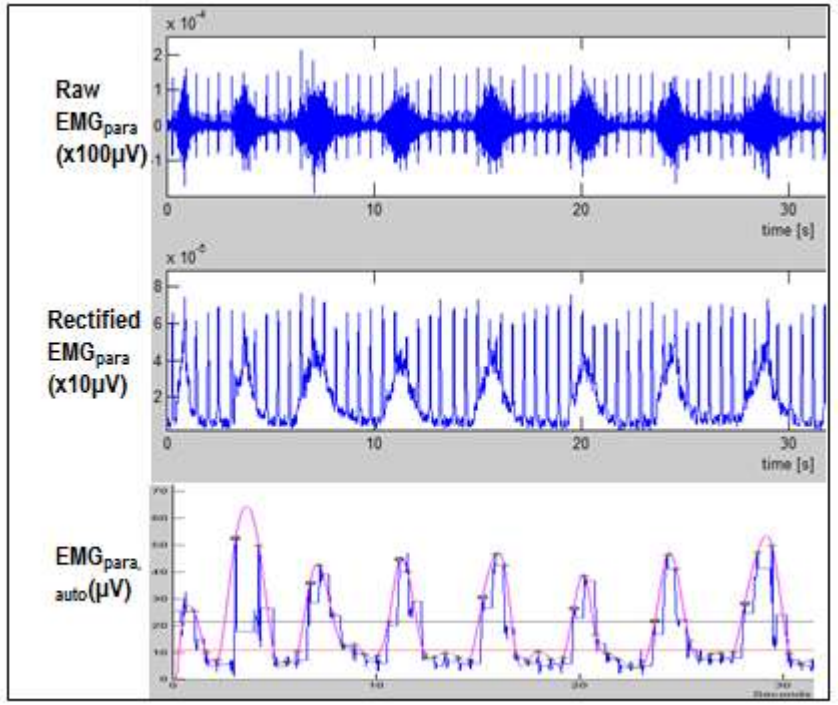
Signal processing algorithm



The index of NRD we compute is the peak RMS EMGpara activity for each inspiration averaged over 1 minute of tidal breathing

MYOTRACE III
Development of the Automated Algorithm

- In collaboration with Philips Research
- Automated algorithm
  - Remove ECG
  - Artefact detection



WHAT HAVE WE LEARNT?

- Advanced respiratory physiological biomarker to risk stratify AECOPD patients to enhance safe discharge
- Neural respiratory drive is a clinical useful, biomarker that can predict safe discharge in patients following an admission with AECOPD
- Reduction in neural respiratory drive could be used as a therapeutic target
- Translational physiological science is required to design future clinical trials

WHAT HAVE WE LEARNT?

- **TARGET POPULATION**
  - AECOPD patients who do not have a fall in neural respiratory drive of 3.1% between admission and discharge are the high risk group
- **INTERVENTION**
  - New molecules and targeted drug delivery directed to reduce neural respiratory drive to prevent readmission to hospital
- **CORE OUTCOME MEASURES**
  - Mechanistic e.g. Neural respiratory drive
  - Patient-Centred e.g. quality of life, functional capacity, physical activity
  - Healthcare utilisation e.g. cost utility, cost effectiveness

PROMOTING SAFE DISCHARGE & PREVENTING READMISSION IN SEVERE COPD PATIENTS

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PROMOTING SAFE DISCHARGE & PREVENTING READMISSION IN SEVERE COPD PATIENTS

- TARGET POPULATION

THERAPEUTIC TARGET
e.g. NRD

risk group

- **INTERVENTION**
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PROMOTING SAFE DISCHARGE & PREVENTING READMISSION IN SEVERE COPD PATIENTS

- TARGET POPULATION

THERAPEUTIC TARGET
e.g. NRD

risk group

TARGET POPULATION
e.g. severe COPD Patients

neural respiratory drive to prevent readmission to hospital

- **CORE OUTCOME MEASURES**
  - Mechanistic e.g. Neural respiratory drive
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PROMOTING SAFE DISCHARGE & PREVENTING READMISSION IN SEVERE COPD PATIENTS

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THERAPEUTIC TARGET
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TARGET POPULATION
e.g. severe COPD Patients

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THERAPEUTIC INTERVENTION
e.g. pharmacological & non-pharmacological

- Patient-Centred e.g. quality of life, functional capacity, physical activity
- Healthcare utilisation e.g. cost utility, cost effectiveness

PROMOTING SAFE DISCHARGE & PREVENTING READMISSION IN SEVERE COPD PATIENTS

- TARGET POPULATION

THERAPEUTIC TARGET

e.g. NRD

risk group

TARGET POPULATION

e.g. severe COPD Patients

neural respiratory drive to prevent readmission to hospital

THERAPEUTIC INTERVENTION

e.g. pharmacological & non-pharmacological

- Patient-Centred e.g. quality of life, functional capacity

CORE OUTCOME SET

e.g. admission free survival, cost effectiveness

PROMOTING SAFE DISCHARGE & PREVENTING READMISSION IN SEVERE COPD PATIENTS

- TARGET POPULATION

THERAPEUTIC TARGET

e.g. NRD

COST & CLINICAL EFFECTIVENESS

- Patient-Centred e.g. quality of life, functional capacity

CORE OUTCOME SET

e.g. admission free survival, cost effectiveness

CONCLUSION

- Make the measurements
- Interpret the data
- Use the measurements to design the future clinical trials
  - TARGET POPULATION
  - INTERVENTION
  - CORE OUTCOME

Unstable Post AECOPD Patients

Does home NIV improve outcome in hypercapnic COPD patients post exacerbation?

Ⓟ Ⓘ Ⓒ Ⓞ

JAMA | Original Investigation

Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation

A Randomized Clinical Trial

June 6, 2017, Vol 317, No. 21, Pages 2149-2248

Patrick B. Murphy, PhD; Sunita Rehal, MSc; Gill Arbane, BSc (Hons); Stephen Bourke, PhD; Peter M. A. Calverley, PhD; Angela M. Crook, PhD; Lee Dowson, MD; Nicholas Duffy, MD; G. John Gibson, MD; Philip D. Hughes, MD; John R. Hurst, PhD; Keir E. Lewis, MD; Rahul Mukherjee, MD; Annabel Nickol, PhD; Nicholas Oscroft, MD; Maxime Patout, MD; Justin Pepperell, MD; Ian Smith, MD; John R. Stradling, PhD; Jadwiga A. Wedzicha, PhD; Michael I. Polkey, PhD; Mark W. Elliott, MD; Nicholas Hart, PhD

American Thoracic Society 2017
JAMA & NEJM Session: Discussions on the Edge
Dr Jeff Drazen and Dr George O'Connor
22nd May 2017


Original Investigation

Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial

Editorial

Home Noninvasive Ventilation to Reduce Readmissions for Chronic Obstructive Pulmonary Disease

High Attention Score compared to outputs of the same age (99th percentile)
High Attention Score compared to outputs of the same age and source (97th percentile)
Top 5% of all research outputs scored by Altmetric

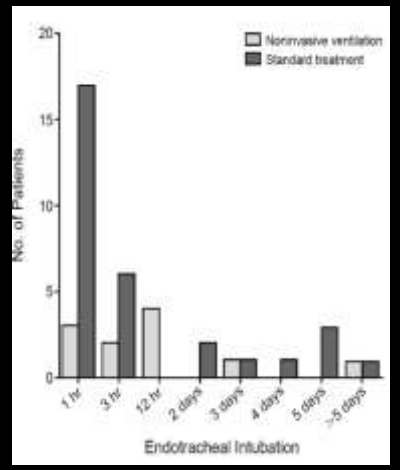
49 Citations WOS

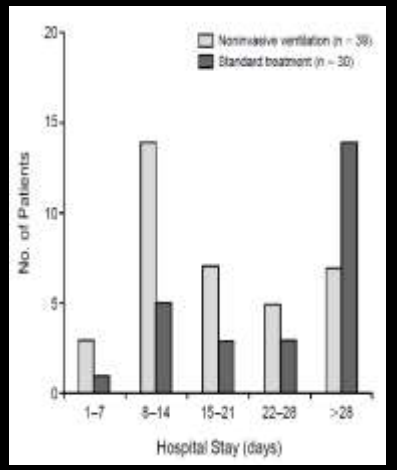
41,965 manuscript views

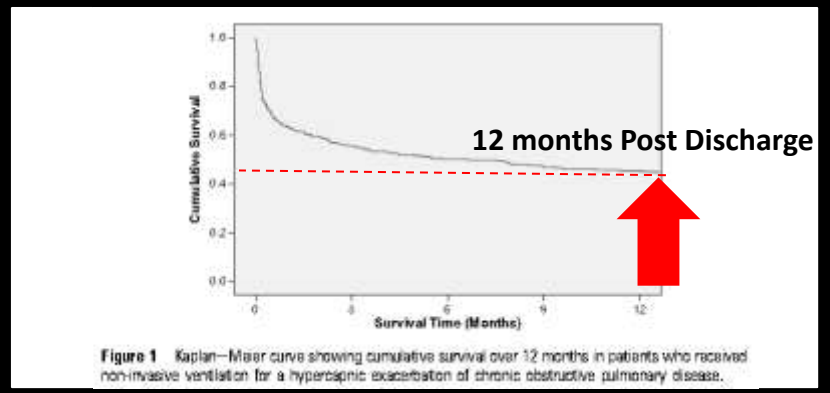
BEST CLINICAL PRACTICE:

NIV in acute hypercapnic respiratory failure is best practice

- **Acute NIV Clinical Evidence**
  - **Reduced mortality (NNT 8)**
  - **Reduced intubation rate (NNT 5)**
  - **Reduced hospital stay**
  - **>45% mortality at 12m**
- **Post AECOPD**
  - **Persistent hypercapnia associated with poor outcome**
  - **Transient hypercapnia associated with similar outcome to eucapnia**







Brochard et al 1995; Kramer et al 1995; Martin et al 2000; Bott et al 1993; Plant et al, 2000; Lightowler et al 2003; Murray et al 2011: Connors et al 1996; Costello et al 1997

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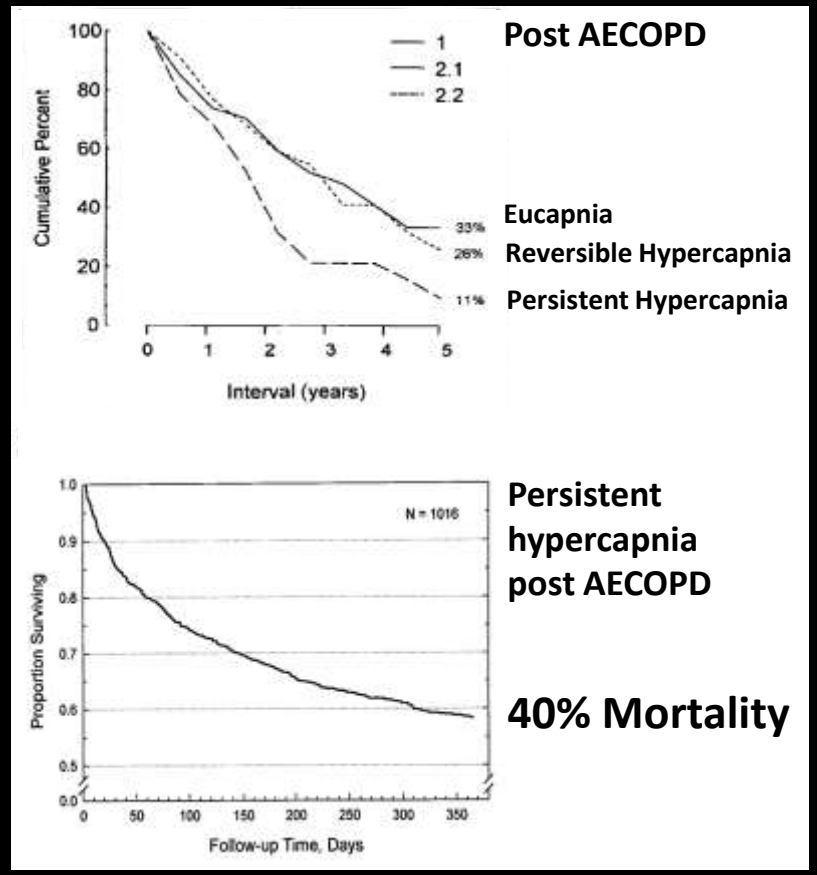

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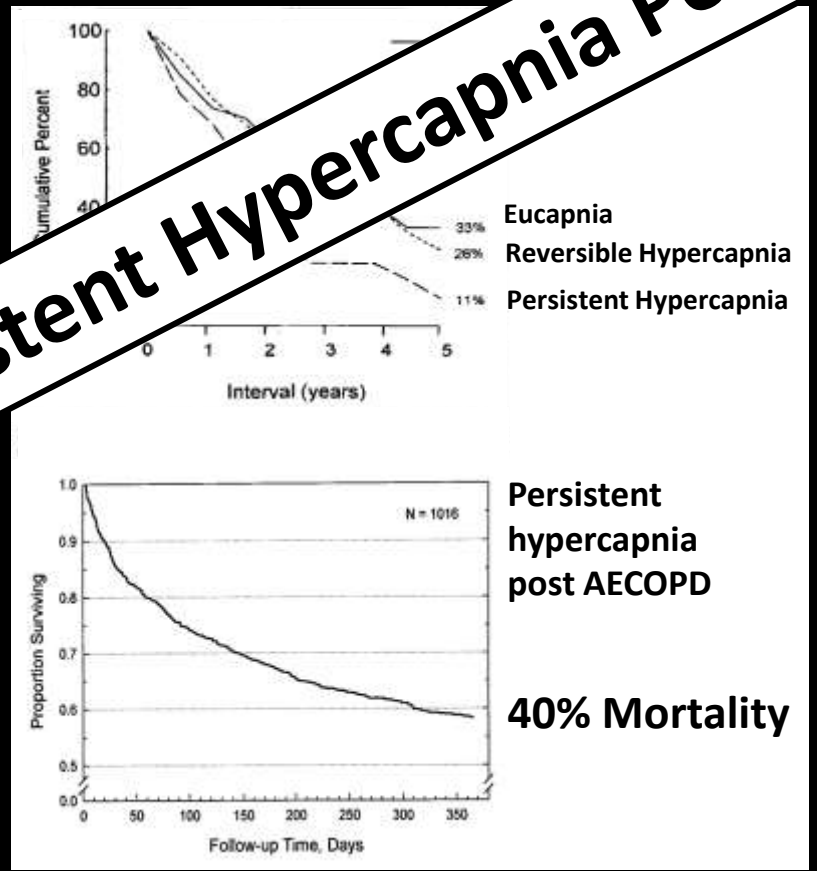

Persistent hypercapnia post AECOPD

40% Mortality

Readmission & Death with Persistent Hypercapnia Post Acute NIV

Brochard et al 1995; Kramer et al 1995; Martin et al 2000; Bott et al 1993; Plant et al, 2000; Lightowler et al 2003; Murray et al 2011: Connors et al 1996; Costello et al 1997

HYPOTHESIS

NIV titrated to treat nocturnal hypoventilation and improve admission free survival following an acute life threatening exacerbation of COPD in patients with persisting hypercapnia

Trial Design

JAMA | Original Investigation

Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation

Murphy et al 2017

P **PaCO2>52mmHg 2-4 weeks post acute hypercapnic exacerbation of COPD requiring acute NIV**

HOT HMV Changing the outcome in COPD

	HOT HMV (N=57)	HOT (N=59)	Total (N=116)
Age (years)	66.4 (10.2)	67.1 (9.0)	66.7 (9.6)
Median BMI (kg/m^2)	21.5 (18.8 to 24.5)	22.2 (17.9 to 26.9)	21.6 (18.2 to 26.1)
Prior use of LTOT (n (%))	40 (70%)	40 (68%)	80
≥3 COPD related admissions in last year	30 (53%)	31 (53%)	61
Gender (female) (n (%))	29 (51%)	32 (54%)	61
Median smoking pack year history	42.0 (30.5 to 60.0)	45.0 (31.0 to 55.0)	44.0 (31.0 to 60.0)
FEV_1	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
FEV_1 (%)	24.0 (8.6)	22.9 (8.6)	23.4 (8.6)
FVC	1.8 (0.8)	1.5 (0.6)	1.7 (0.7)
FVC (%)	57.4 (19.7)	49.3 (20.4)	53.2 (20.4)
FEV_1/FVC	0.3 (0.1)	0.4 (0.1)	0.4 (0.1)
PaO_2 on room air (kPa)	6.4 (1.2)	6.4 (1.1)	6.4 (1.1)
$PaCO_2$ on room air (kPa)	7.9 (0.9)	7.9 (0.9)	7.9 (0.9)
pH 7.30-7.35 n (%)	5 (9%)	2 (3%)	7 (6%)
Median SGRQ summary	74.7 (63.7 to 81.7)	71.0 (62.6 to 78.6)	73.8 (63.3 to 80.3)
SRI summary	45.8 (15.0)	46.9 (15.6)	46.4 (15.2)
Median MRC dyspnoea score	5.0 (4.0 to 5.0)	5.0 (4.0 to 5.0)	5.0 (4.0 to 5.0)

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- **Severe COPD**
- **Following a life threatening exacerbation of COPD requiring acute NIV**
- **Chronic hypercapnic respiratory failure ($PaCO_2$ > 52mmHg) 2-4 weeks post AECOPD**
- **Without other significant cause of sleep disordered breathing / respiratory failure**
- **Intervention administered in the recovery phase**

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n=59

HOT HMV Changing the outcome in COPD

Visit	Number of patients included in analyses		Mean (95% CI)		Treatment effect within each group (mean difference from baseline (95%CI))		Treatment effect (Mean between group difference from baseline (95% CI))	P-value	Treatment effect (Mean between group difference from baseline (95% CI))	P-value
	Home Oxygen Therapy and Home NIV	Home Oxygen therapy	Home NIV & home oxygen therapy (mmHg)	Home oxygen therapy (mmHg)	Home NIV & home oxygen therapy (mmHg)	Home oxygen therapy (mmHg)	Adjusted for baseline effect[a] (95% CI)		Adjusted effect[b] (95% CI)	
Mean $tcCO_2$										
Baseline[c] (pre-treatment)	57	59	65 (62 to 67)	65 (63 to 67)						
Day 1 (on treatment)	45	46	56 (53 to 59)	65 (62 to 67)	-8.9 (-11.7 to -6.2)	0.8 (-0.5 to 0.7)	-8.9 (-11.4 to -6.5)	<.001	-9.1 (-11.6 to -6.6)	<.001
6 months	24	16	53 (48 to 58)	56 (50 to 62)	-14.3 (-19.7 to -8.9)	-8.6 (-15.2 to -1.9)	-2.0 (-8.8 to 4.7)	.56	-4.7 (-11.6 to 2.3)	.18
12 months	24	19	50 (44 to 55)	61 (56 to 66)	-16.6 (-21.5 to -11.6)	-4.4 (-10.1 to 1.4)	-10.8 (-16.8 to -4.9)	<.001	-10.7 (-16.4 to -5.1)	<.001

12 months: 11mmHg difference between HOT-HMV and HOT treatment (17% reduction)

JAMA | Original Investigation

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C → **Standard COPD Treatment & HOT n=57**

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O **Primary Outcome:**
Time to readmission or death

I

Standard COPD Treatment & home NIV & HOT
n=59

Standard COPD Treatment & HOT
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HOT HMV Changing the outcome in COPD

JAMA | Original Investigation

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Time to readmission or death

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n=59

4.3 months (IQR 1.3-13.8)

Adjusted hazard ratio of 0.49 (95% CI, 0.31-0.77; *p* = 0.002)

C → **Standard COPD Treatment & HOT**
n=57

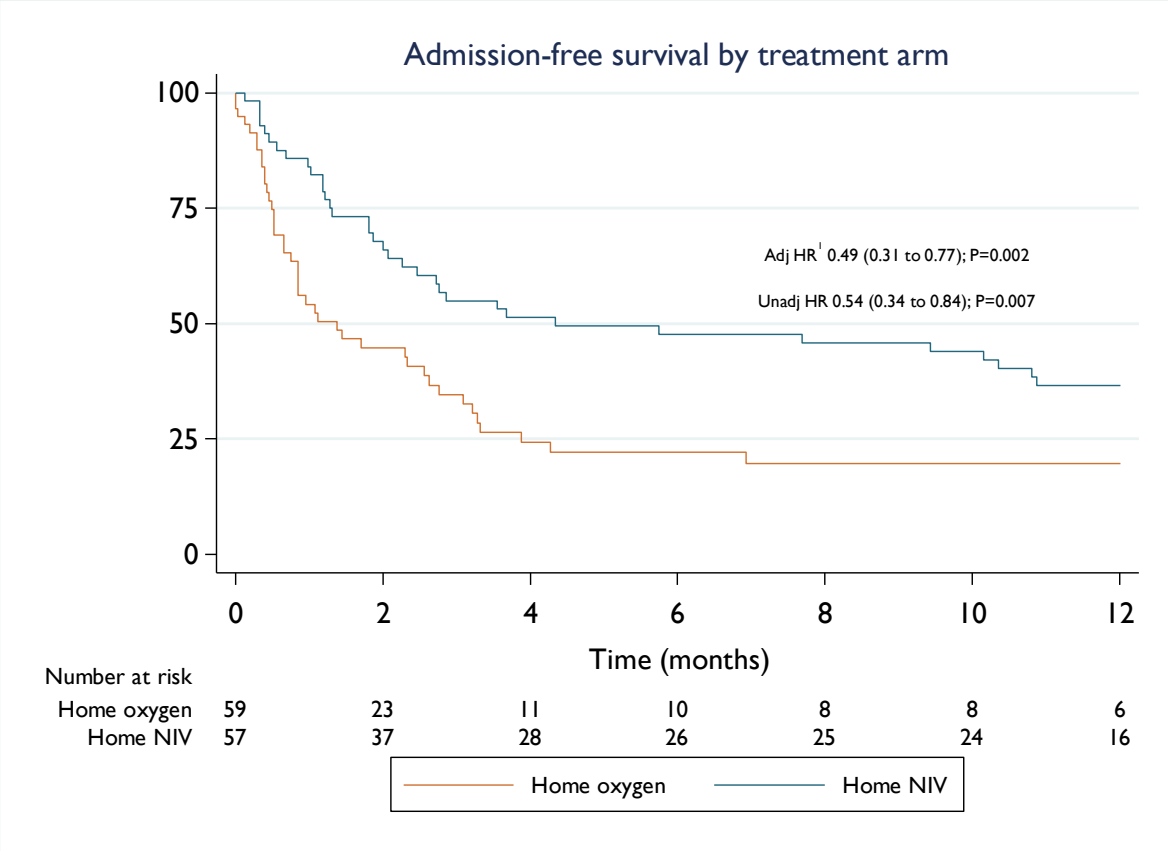
1.4 months (IQR 0.5-3.9)

HOT HMV Changing the outcome in COPD

PRIMARY OUTCOME

HOT-HMV increased time to readmission or death by 90 days

HOT-HMV reduced the likelihood of readmission or death by over 50%



	HOT HMV N=57	HOT N=59
Number admitted	33 (58%)	38 (64%)
Number of deaths	5 (9%)	4 (7%)
Total number meeting primary endpoint	38 (67%)	42 (71%)
Median admission free survival time (m)	4.3	1.4
Unadjusted HR (95% CI)	0.54 (0.34 to 0.84); P=0.007	
Adjusted HR (95% CI)	0.49 (0.31 to 0.77); P=0.002	
Number needed to treat	6	

12-month risk of readmission or death
HOT-HMV Group 63.4%
HOT Group 80.4%
Absolute risk reduction of 17.0% (95%CI, 0.1%-34.0%)

Adjusted for Age, BMI, Current LTOT use, Frequency of COPD admission

HOT HMV Changing the outcome in COPD

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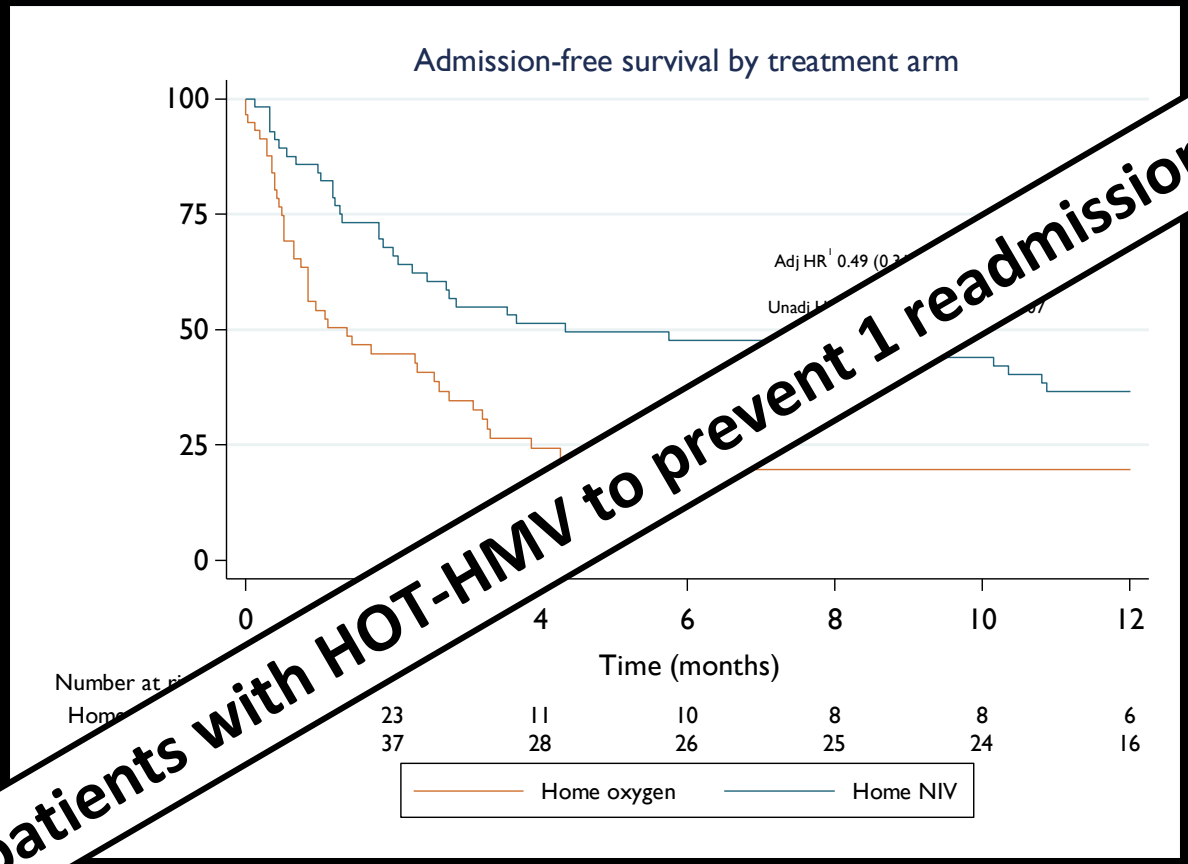

Need to Treat 6 patients with HOT-HMV to prevent 1 readmission or death within 1 year

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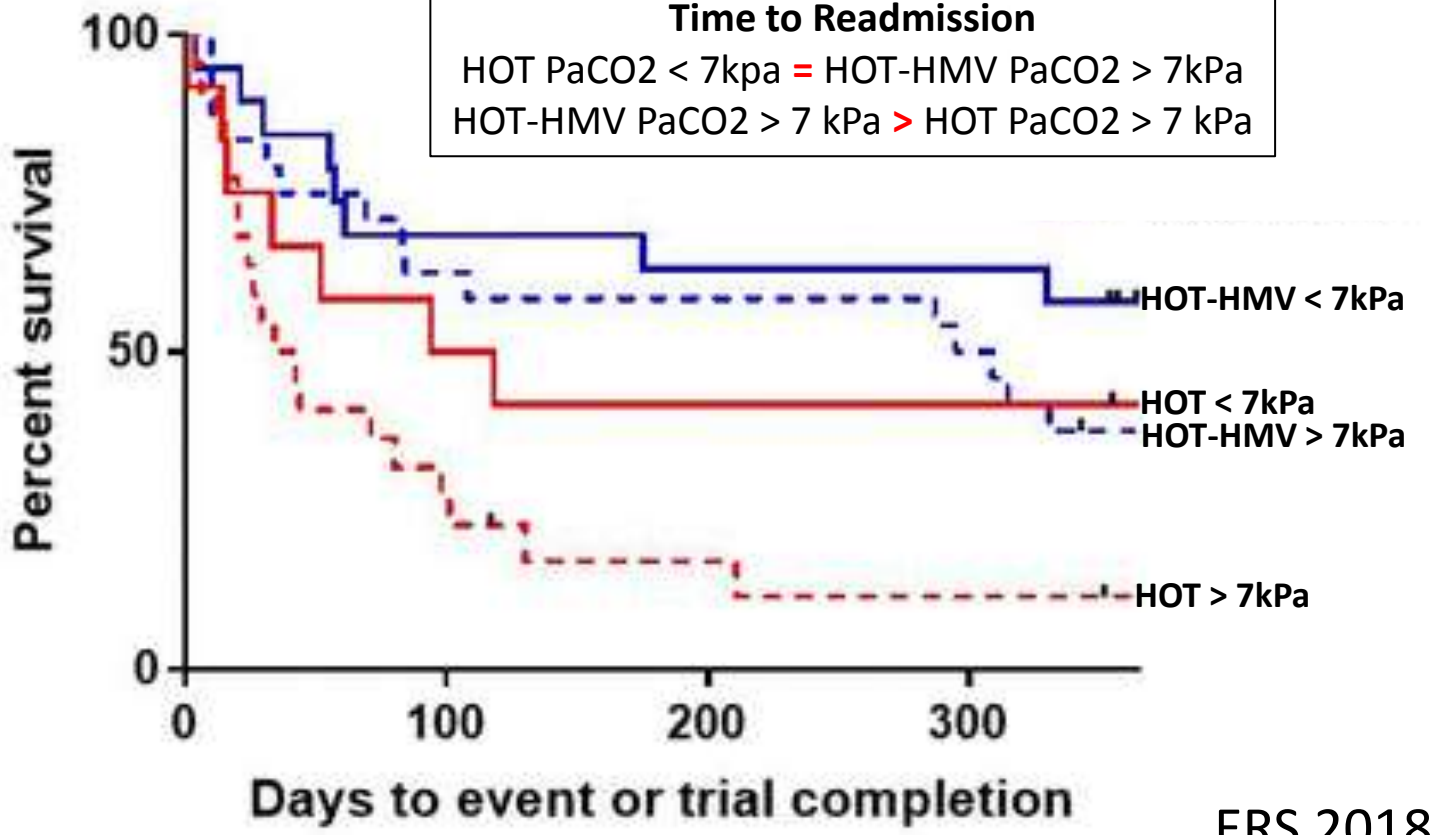
Admission-free survival of patients randomised to HOT or HOT-HMV divided by persistent hypercapnia at 6 weeks

Time to Readmission
HOT PaCO2 < 7kpa = HOT-HMV PaCO2 > 7kPa
HOT-HMV PaCO2 > 7 kPa > HOT PaCO2 > 7 kPa



ERS 2018

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Time to readmission:
Persistent hypercapnia treated with HOT-HMV vs. persistent hypercapnia treated with HOT 302d v 38d, HR 0.44, 95%CI 0.22 to 0.88, p=0.008

Is HOT-HMV treatment cost effective?

Manuscript Under Review

HOT HMV Changing the outcome in COPD

Patient-Level Medical Resource Utilization

- Equipment (oxygen concentrators and home NIV devices, including maintenance and support)
- Physician contacts and hospital admissions due to exacerbations
- Patient reported medications
- Additional primary and secondary care contacts
- Costs calculated at the patient level by multiplying observed MRU by standard unit costs (£2017) from a National Health Service

OUTCOME

- Quality adjusted life years (QALYs) estimated based on EuroQOL-5D data

12-month Costs by Treatment

	Intervention Group (n=57)	Control Group (n=59)	Difference
Total device costs	£6,679	£2,684	£3,995
NIV device	£4,814	£1,412	£3,402
Diagnostic tests	£467	£467	£0
Titration	£531	£156	£375
Oxygen supply	£868	£649	£218
Total exacerbation costs	£4,679	£5,821	-£1,141
Admission	£4,624	£5,791	-£1,167
Physician treatment	£51	£28	£23
Self treatment	£4	£1	£2
Total patient reported costs	£6,044	£8,381	-£2,337
Increased steroid inhaler usage	£1	£5	-£5
Increased reliever inhaler usage	£43	£67	-£24
Steroid tablets	£10	£8	£2
Antibiotics treatment	£43	£25	£18
Additional primary/secondary care visits	£5,947	£8,275	-£2,328
Total costs	£17,403	£16,885	£518
Total QALYs	0.3600	0.3100	0.0500

HOT HMV Changing the outcome in COPD

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ADVERSE: Device Costs

FAVOURABLE: Exacerbation Costs

FAVOURABLE: Patient Reported Costs

HGT HMV Changing the outcome in COPD

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ADVERSE: Total Costs £518

FAVOURABLE: QALYs (0.05)

FAVOURABLE: Cost per QALY £10,360

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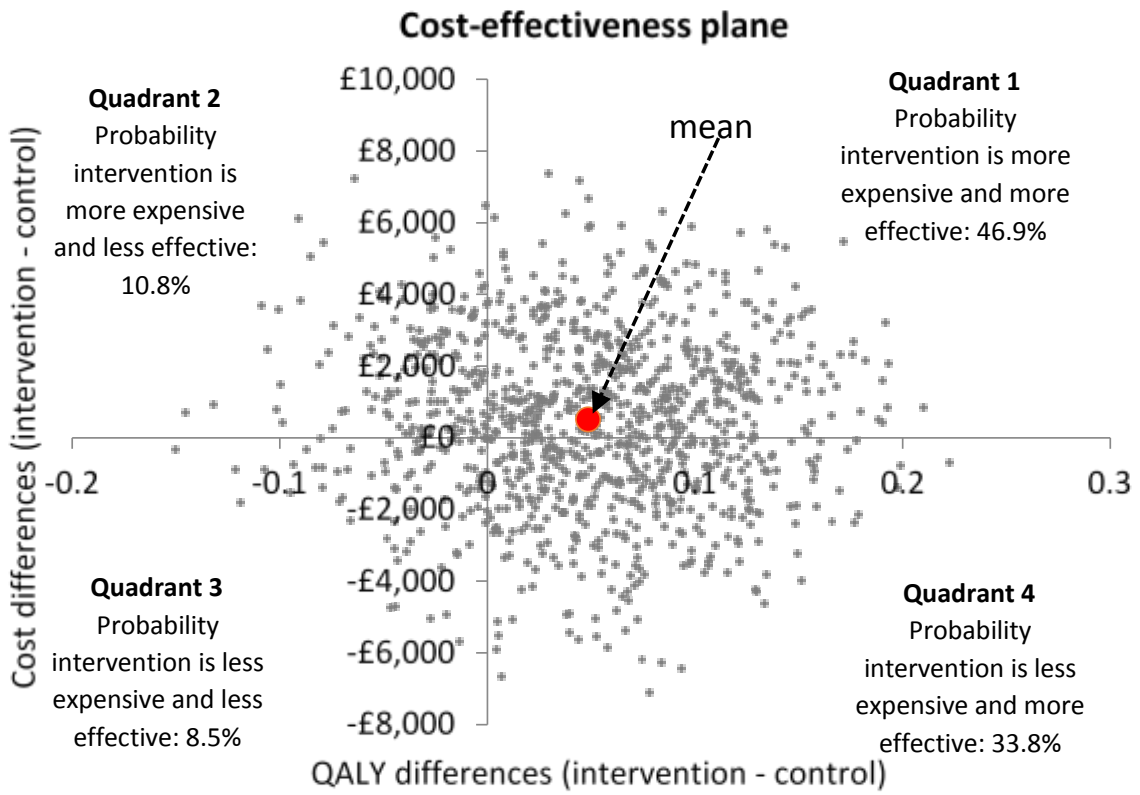
HOT-HMV IS A COST EFFECTIVE TREATMENT

RSE: Total Costs £518

FAVOURABLE: QALYs (0.05)

FAVOURABLE: Cost per QALY £10,360

Figure 1a Cost-effectiveness plane for home non-invasive ventilation with home oxygen therapy vs. home oxygen therapy alone (UK intention to treat analysis)



Cost Effectiveness Planes

Less Effective | More Effective

More Expensive

Less Expensive

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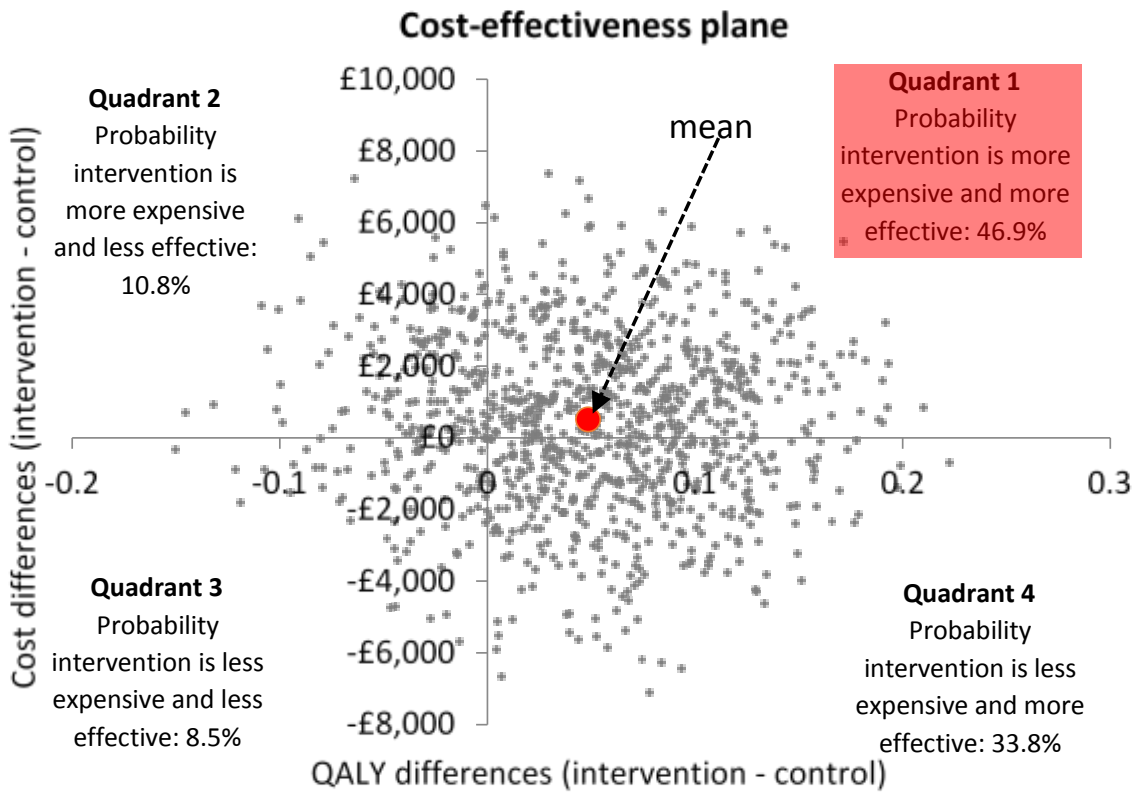

Cost Effectiveness Planes

Less Effective | More Effective

More Expensive

Less Expensive

US 12-month Costs by Treatment

	Intervention Group (n=57)	Control Group (n=59)	Δ
Total device costs	**$4,298**	**$1,582**	**$2,715**
NIV device	$2,867	$673	$2,194
Diagnostic tests	$172	$172	$0.00
Titration	$463	$136	$327
Oxygen supply	$795	$602	$194
Total exacerbation costs	**$8,598**	**$10,683**	**-$2,086**
Admission	$8,495	$10,638	-$2,144
Physician treatment	$36	$19	$16
Self treatment	$67	$26	$42
Total patient reported costs	**$11,563**	**$16,121**	**-$4,558**
Increased steroid inhaler usage	$56	$438	$947
Increased reliever inhaler usage	$88	$137	$208
Steroid tablets	$558	$465	$692
Antibiotics treatment	$56	$47	$77
Additional primary/secondary care visits	$10,805	$15,033	$18,389
Total costs	**$24,458**	**$28,386**	**-$3,928**
Total QALYs	**0.49**	**0.41**	**0.08**

HCT HMV Changing the outcome in COPD

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Incremental Cost Effectiveness Ratio (ICER)/ Cost per QALY gained of $-50,856

HCT HMV Changing the outcome in COPD

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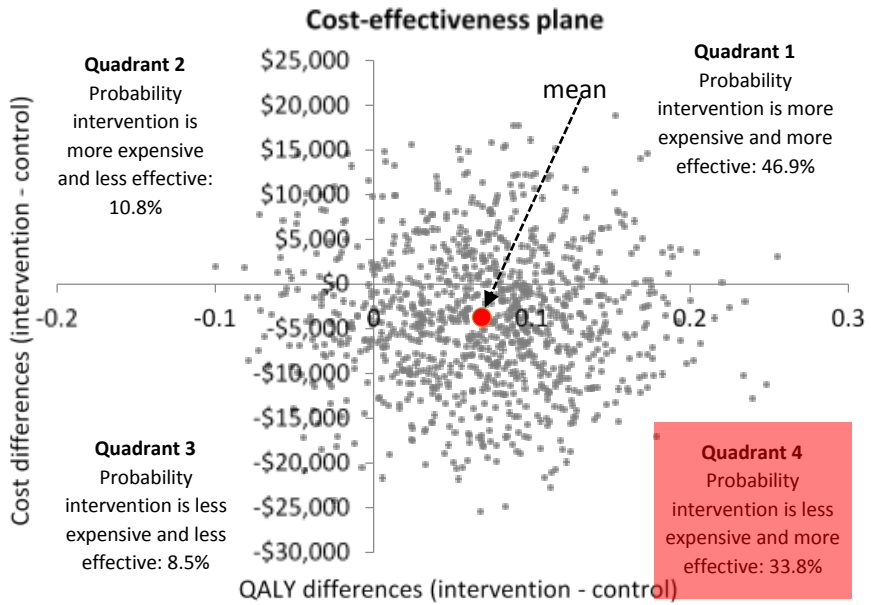
Antibiotics treatmen	$56	$47	$77
Additional primary/secondary care visits	$10,805	$15,033	$18,389
Total costs	**$32,024**	**$30,162**	**$1,861**
Total QALYs	**0.4874**	**0.4101**	**0.0772**

Figure 3b Cost-effectiveness plane for home non-invasive ventilation with home oxygen therapy vs. home oxygen therapy alone (US intention to treat analysis)



Abbreviation: QALY=quality adjusted life year

Does home NIV improve outcome in hypercapnic COPD patients post exacerbation?

Does home NIV improve outcome in hypercapnic COPD patients post exacerbation?

- HOT-HMV data supports the initiation of NIV in COPD patients who remain persistently hypercapnic 2-4 weeks after cessation of acute NIV
- If the $PaCO_2$ is > 52 mmHg and the PaO_2 < 55 mmHg at 2-4 weeks after cessation of acute NIV this should prompt the clinician to consider initiating HMV in addition to HOT
- HOT-HMV is a cost-effective treatment in the UK and more effective and less costly compared to oxygen therapy alone in the US

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GOLD COPD

Table 3.10. Oxygen therapy and ventilatory support in stable COPD

Oxygen therapy

- The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia **(Evidence A)**.
- In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance **(Evidence A)**.
- Resting oxygenation at sea level does not exclude the development of severe hypoxemia when traveling by air **(Evidence C)**.

Ventilatory support

- NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($PaCO_2 \geq 52$ mmHg) **(Evidence B)**.

NICE COPD

Non-invasive ventilation

1.2.70 Refer people who are adequately treated but have chronic hypercapnic respiratory failure and have needed assisted ventilation (whether invasive or non-invasive) during an exacerbation, or who are hypercapnic or acidotic on long-term oxygen therapy, to a specialist centre for consideration of long-term non-invasive ventilation. [2004]

CONCLUSION

- **Detailed PICO evaluation ensures the right patient receives right treatment at the right time in the right environment**
- **HOT-HMV treatment has been shown to be clinically effective to improve outcome and cost effective in COPD patients with persistent hypercapnia post life-threatening exacerbation**
- **GOLD 2018 and NICE 2018 has systematically and comprehensively graded providing support for the use of HOT-HMV post life-threatening acute exacerbation of COPD**

COPD Post Acute NIV pathway

Guy's and St Thomas' NHS
NHS Foundation Trust

Acute exacerbation of COPD[1] requiring NIV (pH<7.35, PaCO2>6kPa)

↓

Patient able to tolerate NIV with clinical improvement (pH>7.35)

↓

Suspected chronic hypercapnia[2] with no evidence of obesity or OSA[3]

1. Diagnosis of COPD
   a. Established diagnosis of COPD (FEV1/FVC <0.7) **OR**
   b. Suspected clinical diagnosis of COPD (>10 pack year history, progressive dyspnoea, cough, sputum, recurrent LRTI)
2. Features of chronic persistent hypercapnia
   a. Admission cBE >2 / $cHCO_3$ >28 mmol/L
   b. $PaCO_2$ > 7kPa 2 weeks post resolution of respiratory acidosis

Google 'Lane Fox Unit'/SPECIALITIES TAB

Clinical stability off NIV → **e-Referral for HOT review within 2-4 weeks**

Unable to wean from or clinical instability off NIV → **For consideration of NIV setup pre-discharge**

CONCLUSION

- Admission prevention in COPD is a priority for patients, clinicians and healthcare
- Measuring neural respiratory drive may be useful to risk stratify COPD in terms of promoting safe discharge and reducing readmission
- If the $PaCO_2$ is > 52 mmHg and the PaO_2 < 55 mmHg at 2-4 weeks after cessation of acute NIV this should prompt the clinician to consider initiating HMV in addition to HOT
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RIGHT PATIENT ✓
RIGHT TIME ✓
RIGHT TREATMENT ✓
RIGHT ENVIRONMENT ✓

With thanks to…

The patients

Lane Fox Clinical Respiratory Physiology Research Centre

Principal Investigators **Dr Bronwen Connolly, Dr Patrick Murphy, Dr Joerg Steier, Dr Eui-Sik Suh, Dr Michelle Ramsay, Dr Maxine Patout, Dr Phil Marino, Professor Louise Rose & Professor Nicholas Hart**

Clinical Research Fellows **Dr Rebecca D'Cruz, Dr Neeraj Shah**

Clinical Trials Co-ordinator **Miss Gill Arbane**

London Respiratory Muscle Group

Professor Michael Polkey, Dr Bronwen Connolly, Professor Nicholas Hart, Dr Nicholas Hopkinson, Dr William Mann, Dr Vicky McBean, Dr Patrick Murphy, Dr Joerg Steier and Professor John Moxham

Centre for Human and Applied Physiological Science

Professor Steve Harridge, Dr Caroline Jolley, Dr Gerrard Rafferty

British Lung Foundation

CanHELP Charity

Glaxo SmithKline

Guy's & St Thomas' Charitable Foundation

European Intensive Care Society

European Respiratory Society

Fisher-Paykel (unrestricted grant)

Medical Research Council

National Institute of Health Research

NHS Innovations London

Peel Medical Charity

Philips-Respironics (unrestricted grants)

Philips (unrestricted grants)

Resmed Charitable Foundation

Resmed (unrestricted grants)

e-mail: nicholas.hart@gstt.nhs.uk

Lane Fox Respiratory Service *Specialists in Complex Home Ventilation, Weaning & Rehabilitation* *Est. 1989*