Telemedicine in Home NIV: Developing Health Informatics, Assessing Physiological Response, and Improving Patient Outcomes (THE HIPPO study)

A thesis presented by

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Summary

The landscape of digital technology innovations which can assist healthcare provision has expanded rapidly over the past decade. With the adoption of consumer and healthcare-based technologies including mobile device and network access, the use of tele-monitoring in the management of chronic medical conditions will be incorporated into routine clinical care within this generation. Remote patient monitoring has an established role in the management of patients with obstructive sleep apnoea syndrome who require positive airway pressure support. However, the use of two-way remote monitoring via a cloud-based platform to initiate and optimise home non-invasive ventilation (NIV) is novel. Rising obesity rates and new evidence supporting the use of home NIV in patients with severe chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure has resulted in increased referrals for breathing support assessment and treatment. Chronic hypercapnic respiratory failure develops as a consequence of imbalance in the respiratory load capacity drive relationship and is associated with high morbidity and mortality. Advanced physiological measurements such as parasternal electromyography (EMG) to quantify neural respiratory drive and forced oscillometry technique to quantify airway resistance and reactance are well established in research but evidence for their clinical application in disease monitoring in patients with sleep disordered breathing and chronic hypercapnic respiratory failure is lacking.

The anticipation is that big data from remote monitoring of home breathing support therapies and serial advanced physiological measurements will provide mechanistic insights of chronic respiratory failure, facilitate early optimisation of treatment, prompt early recognition of treatment failure and prioritise at risk patients to provide a personalised approach to the management of chronic respiratory disease. The aim of this thesis was to evaluate the adoption of two-way remote monitoring in patients with sleep disordered breathing and hypercapnic severe COPD and determine the feasibility of serial advanced physiological measurements in chronic respiratory disease.

Methods

A summary of the evolution of clinical pathways for two-way remote monitored breathing support and home ventilation in NHS Greater Glasgow and Clyde are detailed. A retrospective review of the clinical outcomes in observational cohorts of patients who were managed with two-way remote monitored home NIV for hypercapnic severe COPD and obesity related respiratory failure were evaluated. Clinical outcomes were compared to those of patients who survived a life-threatening exacerbation of COPD with persistent hypercapnic failure who were not referred for breathing support assessment (controls). Four physiological studies were performed. Firstly, the

optimisation of parasternal EMG signals using different skin preparation and electrodes was explored. Secondly, inter-observer variability of parasternal EMG analysis between two UK based respiratory physiology research centres was assessed. Thirdly, the simplification of neural respiratory drive index analysis by using EMG signals to estimate respiratory rate to determine the feasibility of future omission of additional sensors improving accessibility. The fourth study explored the feasibility of serial advanced physiological measurements alongside standard care in a wide range of respiratory diseases.

Results

Clinical pathways for remote management of breathing support patients are now routine clinical care within NHS Greater Glasgow and Clyde. It is feasible and safe to use remote monitored home ventilation in patients with hypercapnic severe COPD. Continued use of two-way remote monitored home NIV prolonged time to re-admission or death in patients with hypercapnic severe COPD when compared to the control cohort. Continued use of remote monitored home NIV in hypercapnic severe COPD resulted in a median reduction of 14 occupied bed days per annum. Continued use of remote NIV prolonged time to re-admission or death in patients with obesity related respiratory failure compared to those non-adherent or discontinued NIV. Two-way remote home NIV can facilitate safe day case initiation of home NIV in patients with stable hypercapnic respiratory failure. It is feasible to use long term cardiac electrodes for parasternal electromyography measurements. Acceptable reproducibility of parasternal EMG analysis between two UK research centres has been demonstrated. The derivation of respiratory rate from parasternal EMG signals is feasible. Serial advanced physiological measurements can be incorporated into standard care in a wide range of respiratory diseases. Serial oscillometry measurements in patients with obstructive sleep apnoea syndrome has provided novel insight into the role a small airways disease.

Conclusion

The work undertaken in this thesis enabled significant service improvement within NHS Greater Glasgow and Clyde. The utilisation of remote monitoring in disease management provides realistic service provision with tangible service and cost efficiencies, addressing increased service demands and justifying future cost-effective analysis. This work has been a catalyst for ongoing digital innovation projects incorporating EHRs, ambulatory physiological monitoring and home device data into a multi-media multi-disciplinary platform for high-risk COPD patients. Serial advanced physiology data has advocated ongoing studies in acute respiratory failure secondary to COVID-19 infection. Adoption of these new technologies into routine clinical care will address increasing service demands, improve patient outcomes, and provide physiological insights into chronic respiratory failure and COVID-19 related respiratory failure.

Contents

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Lists of publications

Some of the results within this thesis and subsequent work have been published, details are given below:

Full paper

McDowell GM, Sumowski M, Toellner H, Karok S, O'Dwyer C, Hornsby J, Lowe D, Carlin C. Two-way remote monitoring allows effective and realistic provision of home-NIV to COPD patients with persistent hypercapnia. *In submission BMJ Open Resp https://www.medrxiv.org/content/10.1101/2020.11.08.20227892v1*

Abstracts

McDowell GM, Dcruz R, Hart N, Murphy P, Carlin C. Inter-observer reproducibility assessment of parasternal electromyogram (EMGpara) analysis: a tale of two cities. European Respiratory Journal *October 2020,* 56 (suppl 64): 3086

McDowell GM, Dcruz R, Hart N, Murphy P, Carlin C. Simplifying the measurement of neural respiratory drive index: parasternal electromyogram to measure respiratory rate. European Respiratory Journal *October 2020,* 56 (suppl 64): 3085

Taylor A, Scott R, **McDowell GM**, McGinness P, Lowe D, Carlin C. RECEIVER trial: positive early experience and sustained patient engagement with a digital service model for COPD management. European Respiratory Journal *October 2020*, 56 (suppl 64): 1365

Sharma V, **McDowell GM**, Rodgers D, Routledge E, French T, Selfridge J, Taylor D, Colville D, Cameron A, Grose P, Van der Horst J, Cowan D, Cotton M. Retrospective analysis of CPAP using home NIV machines out with ICU for COVID-19. European Respiratory Journal *October 2020*, 56 (suppl 64): 3411

McDowell GM, Carlin C. Home remote-monitored auto-NIV in patients with chronic hypercapnic COPD: realistic provision, improved patient outcomes and future application. Scottish Thoracic Society *June 2019*, Methven prize winner

McDowell GM, Carlin C. Impulse oscillometry in obstructive sleep apnoea syndrome and its response to CPAP: feasibility and insights into pulmonary mechanics. Thorax *December 2019*, 74 (suppl 2): A162.2-A163

Toellner H, **McDowell GM**, Burns J, Sumowski M, Lowe D, Carlin C. Home remote-monitored auto-NIV: realistic provision and improved projected admission-free survival in patients with chronic hypercapnic COPD. Thorax *December 2018*, 73 (suppl 4): A197.3-A198

Sutherland F, **McDowell GM**, Beattie T, Hasting A, Carlin C, Beverland I. Home pollution monitoring in patients with sleep and respiratory disorders: feasibility and initial data. Thorax *December 2018*, 73 (suppl 4): A199

McDowell GM, Toellner H, Macfarlane D, Tourish R, Canavan C, Brown A, Ambler H, Carlin C. 2-way remote monitoring in adaptive mode allows effective and realistic provision of home Non-Invasive Ventilation (NIV) to patients with severe COPD. European Respiratory Journal *November 2018*, 52 (suppl 62):PA 1668

McDowell GM, Macfarlane D, Tourish R, Canavan C, Brown A, Ambler H, Carlin C. Early experience with 2-way remote monitoring for the initiation of volume-assured home non-invasive ventilation. Thorax *December 2017*, 72 (suppl 3): A150

R Tourish, **McDowell GM**, Macfarlane, Canavan C, Brown A, Ambler H, Carlin C. Feasibility and early benefits achieved by adopting telephone consultation and 2-way remote monitoring for initiation of CPAP therapy. Thorax *December 2017*, 72 (suppl 3): A198

McDowell GM, Carlin C. Use of Auto-titrating Protocols and 2-way remote monitoring of therapy to rationalise setup of nocturnal non-invasive ventilation. Scottish thoracic society *June 2017,* Methven prize winner

Carlin C, **McDowell GM**, Williams C, Brown A, Canavan C, Tourish R. Utility of an auto-titrating protocol for the setup of nocturnal non-invasive ventilation. Thorax *2016*; 71: A35

Carlin C, **McDowell GM**, Williams C, Brown A, Canavan C, Tourish R. Initial experience with volume assured pressure support mode NIV in tertiary breathing support service. Scottish Medical Journal, *2016*, 60, 4: NP9-NP23

Other peer reviewed publications

Carlin C, Taylor A, Van Loon I, **McDowell G**, Burns S, McGinness, Lowe D. Review article: Role for AI in respiratory diseases- COPD. Journal of hospital management and health policy. *In press*

McDowell GM. What's hot that the other lot got. Thorax *July 2018*, 73 (7) 696

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Finally, most importantly I dedicate this to all the patients who participated and continue to participate in our studies. I take with me the fond memories of a special patient, who despite the physical challenges of his condition, his enthusiasm for this project and advanced physiology was unparalleled. I thought of him often during the completion of this thesis. I hope I have done you proud.

Declaration

This thesis is entirely my own composition and the experimental work detailed within was undertaken by myself.

Signed…

Re-submitted with corrections on……16/02/2021…….

List of abbreviations

A	Cross section of the airway
AE-COPD	Acute exacerbation of chronic obstructive pulmonary disease
Ach	Acetylcholine
AHI	Apnoea hypopnoea index
ΔAHI	Change in AHI
AHP	Allied health professionals
AHRF	Acute hypercapnic respiratory failure
APAP	Auto-titrating positive airway pressure
AU	Arbitrary units
Audit-QIP	Audit- quality improvement project
AutoEPAP	Auto-titrating expiratory positive airway pressure
AVAPS	Average volume assured pressure support
AVAPS-AE	Average volume assured pressure support with auto-titrating expiratory positive airway pressure support
AWR	Airways resistance
Ax	Area of reactance
BMI	Body mass index
BP	Blood pressure
CBG	Capillary blood gas
CF	Cystic fibrosis
$cmsH_2O$	centimetres of water, measurement of pressure
CO	Carbon monoxide
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COPD-OSA	Chronic obstructive pulmonary disease- obstructive sleep apnoea overlap syndrome
CPAP	Continuous positive airway pressure therapy
CSF	Cerebral spinal fluid
CV	Coefficient variation

DA	Dopamine
DH	Dynamic hyperinflation
ECG	Electrocardiogram
EEG	Electroencephalogram
EELV	End expiratory lung volume
EFL	Expiratory flow limitation
EHR	Electronic health records
EMG	Electromyogram
EMGdi	Diaphragmatic electromyogram
EMGpara	Parasternal electromyogram
EMGpara%max	Normalised parasternal electromyogram
EMGpara-RR signal	Respiratory rate derived from RMS parasternal electromyography
ΔEMGpara	Change in parasternal electromyography
ΔEMGpara%max	Change in normalised parasternal electromyography
ΔmeanEMGpara	Change in mean parasternal electromyography
EOG	Electro-oculogram
EPAP	Expiratory positive airway pressure
mEPAP	Median expiratory positive airway pressure
95%EPAP	95^{th} centile expiratory positive airway pressure
ERV	Expiratory reserve Volume
ESS	Epworth sleepiness scale
FEF_{25-75}	Forced expiratory flow at 25% to 75% of vital capacity
FEV1	Forced expiratory volume in one second
FEV1/FEV6	Ratio of forced expiratory volume in 1 second to forced expiratory volume in 6 seconds
FEV1/FVC capacity	Ratio of forced expiratory volume in 1 second to forced vital
FFM	Full face mask
FOT	Forced oscillometry technique
FL	Flow limited

FRC	Functional residual capacity
Fres	Resonant frequency
GABA	Gamma amino-butyric acid
GA	Galanin
GGC	Greater Glasgow and Clyde
GGH	Gartnavel general hospital
GSBSRC	Glasgow sleep and breathing support research centre
HA	Histamine
HCO_3	Bicarbonate
HOT	Home oxygen therapy
HMV	Home mechanical ventilation
Hrs	Hours
HRQOL	Health related quality of life
iBR	Intelligent back up rate
IC	Intercostal
ICS	Intercostal space
ILD	Interstitial lung disease
IPAP	Inspiratory positive airway pressure
mIPAP	Mean inspiratory positive airway pressure
95%IPAP	95^{th} centile inspiratory positive airway pressure
IQR	Interquartile range
IRV	Inspiratory reserve volume
iVAPS	Intelligent volume assured pressure support
KCO	Transfer co-efficient
kPa	Kilo pascals
L	Litres
L/min	Litres/minute
LDT	Laterodorsal tegmentum
LSS	Limited polysomnography
mCAT	Modified COPD assessment tool

meanEMGpara	Mean parasternal electromyography measurement
meanEMGpara%max	Mean normalised parasternal electromyography measurement
meanNRDI	Mean neural respiratory drive index
ml	Millilitres
MIP	Mouth inspiratory pressure
MEP	Maximum expiratory pressure
MRC	Medical research council dyspnoea scale
MSc	Master of science degree
mV	Millivolts
NFL	Not flow limited
NHS	National health service
NIV	Non-invasive ventilation
NM	Nasal mask
NRD	Neural respiratory drive
NRDI	Neural respiratory drive index
ΔNRDI	Change in neural respiratory drive index
NREM	Non-rapid eye movement sleep stages
OBDs	Occupied bed days
ODI	Oxygen desaturation index
OHS	Obesity hypoventilation syndrome
ORRF	Obesity repeated respiratory failure
OSAS	Obstructive sleep apnoea syndrome
$P_{0.1}$	Pressure generate during the first 100ms of inspiration
PAP	Positive airway pressure
PCO_2	Partial pressure of carbon dioxide
PO_2	Partial pressure of oxygen
PEF	Peak expiratory flow
PEEP	Positive end expiratory pressure
P_{flex}	Inflexion point, pressure at which airway resistance is overcome
PLM	Periodic limb movement

Ppl	Pleural pressure
Pcrit	Critical pleural pressure
Paw	Airway pressure
Palv	Alveolar pressure
Pao	Airway opening pressure
Pel	Elastic recoil pressure
PS	ECOG performance status
PS	Pressure support
PSG	Polysomnography
PVA	Patient ventilator asynchrony
Q	Volumetric flow rate
QEUH	Queens Elizabeth University Hospital
R	Radius
RCT	Randomised control trial
REM	Rapid eye movement sleep stage
RIP	Respiratory impedance plethysmography
RMS	Root mean squared
Rrs	Resistance
RR	Respiratory rate
RV	Residual volume
R5	Total airways resistance
R20	Large airways resistance
R5-R20	Small airways resistance
SD	Standard deviation
SDB	Sleep disordered breathing
SHOOF	Scottish home oxygen order form
S_pO_2	Peripheral oxygen saturations
SNIP	Sniff nasal inspiratory pressure
ST	Spontaneous timed mode
TLC	Total lung capacity

TLCO	Transfer factor for the lung for carbon monoxide
TM	Telemedicine
TMN	Tuberomammillary nucleus
TOSCA	Transcutaneous peripheral oxygen saturations and carbon dioxide assessment
T_pCO_2	Transcutaneous partial pressure of carbon dioxide
T_pO_2	Transcutaneous partial pressures of oxygen
TST90	Total sleep time when oxygen saturations are less than 90% during polysomnography
VA	Lung volume in which carbon monoxide diffuses
Va	Alveolar ventilation
VAPS	Volume assured pressure support
VC	Vital capacity
Vc	Videoconference
VLPO	ventrolateral pre-optic area
vPAG	Ventral periaqueductal grey matter
V/Q mis-match	Ventilation/perfusion mismatch
Vt	Tidal volume
Xrs	Reactance
X5insp	Reactance at 5Hertz during inspiration
X5exp	Reactance at 5Hertz during expiration
Zrs	Respiratory impedence
5-HT	5-hydroxytryptamine
ΔXRS	In-breath difference in reactance at 5hertz
Δp	Pressure difference in the airways
μ	Dynamic viscosity

Chapter 1 Introduction

The primary function of the respiratory system is to maintain oxygen and carbon dioxide homeostasis through inhalation, gas exchange at the alveoli and exhalation. Ventilation is dependent on respiratory muscle capacity and neural respiratory drive (NRD) to overcome airways resistance, respiratory system compliance and the elastic load, otherwise known collectively as the respiratory load (Figure 1.1). An imbalance in these opposing forces can lead to alveolar hypoventilation and respiratory failure which often manifests in advanced pulmonary disease. Non-invasive ventilation (NIV) is used in acute and chronic hypercapnic respiratory failure to augment ventilation. Advances in telemedicine has enhanced the management of chronic health conditions. Two-way remote monitored home breathing support could facilitate early optimisation of home ventilation out with the hospital setting alleviating the increasing burden of obesity and chronic respiratory conditions present on health care.

This thesis will review the physiology of ventilation, physiology investigations, advanced physiology markers and the evolution of telemedicine. Evaluation of the implementation experience and outcomes of two-way remote monitored home NIV and Continuous positive airway pressure (CPAP) therapy as a novel treatment option for home ventilation and breathing support within Greater Glasgow and Clyde (GGC) will be reported. Subsequent clinical outcomes in patient cohorts provided with two-way remote monitored home NIV for persistent hypercapnic failure in severe chronic obstructive airways disease (COPD) and obesity related respiratory failure (ORRF) are examined. The feasibility of advanced physiological measurements will be reported as part of an observational cohort study of patients managed with two-way remote breathing support, “Exploratory Endpoints”.

1.1 Physiology of ventilation

The respiratory cycle consists of the inspiratory and expiratory phases to maintain adequate ventilation. The diaphragm, a thin, dome shaped muscle which fills the inferior thoracic aperture creating the floor of the thoracic cage and roof of the abdominal cavity, is integral to ventilation and is anchored along the costal cartilages, L1-L3 intervertebral discs and Xiphoid process. Motor innervation of the diaphragm originates from the cervical plexus, spinal roots C3-C5, which form the phrenic nerves. These run through the

posterior mediastinum to supply the right and left hemi-diaphragms. The diaphragm is activated during inspiration, flattening to cause a downwards movement. This increases intra-thoracic volume creating a sub-atmospheric intra-thoracic pressure gradient (transpulmonary pressure), effecting airflow into the lungs. (Figure 1.2) Simultaneously, activation of the external intercostal muscles (which pull the ribs in the anterior caudal direction) during inspiration increases intra-thoracic volume contributing to transpulmonary pressure. Damage to the phrenic nerve can manifest as hemi-diaphragm paralysis with paradoxical movement of the diaphragm during inspiration, impaired ventilation and subsequent dyspnoea.[1] As transpulmonary pressures equalise, inspiration ceases and the expiratory cycle begins where the elastic recoil of the lung and chest wall allow the thoracic cage and diaphragm to return to original positions. Activation of accessory muscles of expiration, in the abdominal wall and intercostal muscles are integral to maintain adequate ventilation during periods of increased respiratory load seen during exercise. Within the alveoli, surfactant produced by Type II epithelial cells within the alveolar wall reduces surface tension that opposes alveolar expansion. Depleted surfactant production results in alveolar collapse and impaired ventilation often seen in paediatric respiratory distress syndrome.

The non-linear relationship of pressure and volume during ventilation is demonstrated in figure 1.3 with the respiratory system compliance represented by the gradient of the slope at any given time. As maximal volumes are reached during inspiration, pressure changes slow down resulting in reduced compliance. (Figure 1.3) Obesity can result in reduced compliance due to the mass loading effect of increased adipose tissue within the chest wall and abdomen.[2][3]

Ventilation exchanges air to and from the alveoli, the thin-walled terminal sacs at the end of the airways surrounded by capillaries, to facilitate exchange of oxygen into the blood and carbon dioxide (CO_2) elimination into the alveoli during exhalation. Oxygenated blood travels from the lungs to the rest of the body where oxygen is taken up in the tissues during aerobic metabolism. Optimal gas exchange is governed by adequate ventilation, diffusion of gases and perfusion of the lungs. This physiological balance can be disrupted in disease, resulting in respiratory failure. For example, in COPD patients with emphysema

and hyperinflation, the ventilation perfusion relationship is impaired by limited diffusion capacity and inadequate ventilation. Heterogeneity of COPD can present with a variation of ventilation/perfusion (V/Q) mis-match patterns. An understanding of normal physiology and recognition of disease patterns can help personalise management of chronic disease. Tools to facilitate measurement and interrogation of physiological changes are vital to aid physiological phenotyping and optimisation of treatment in chronic respiratory disease.

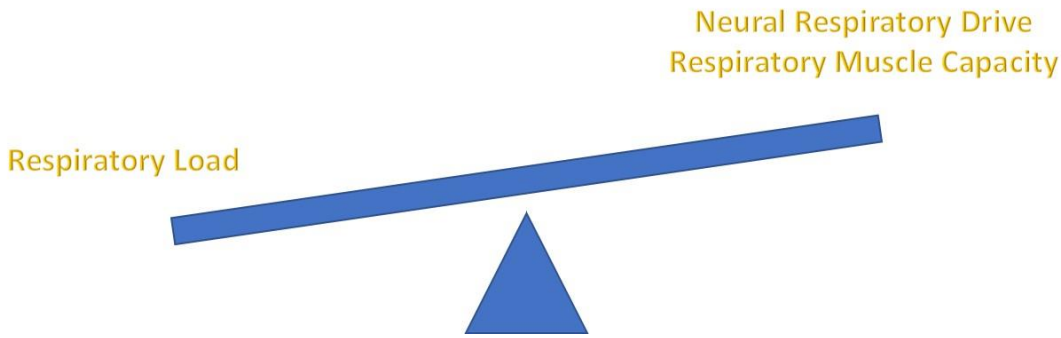


Figure 1-1 Ventilatory homeostasis

Illustration of the relationship of respiratory load with Neural Respiratory Drive and respiratory muscle capacity essential to maintain ventilatory homeostasis.

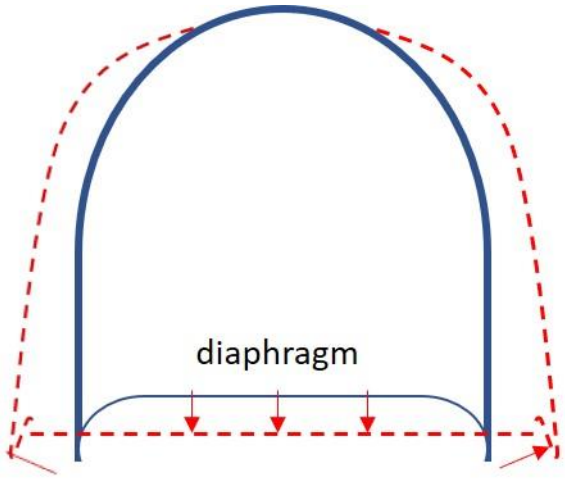


Figure 1-2 Respiratory mechanics

Illustration of thoracic wall and diaphragmatic movement during inspiration (-----), creating a transpulmonary pressure initiating the inspiratory cycle.

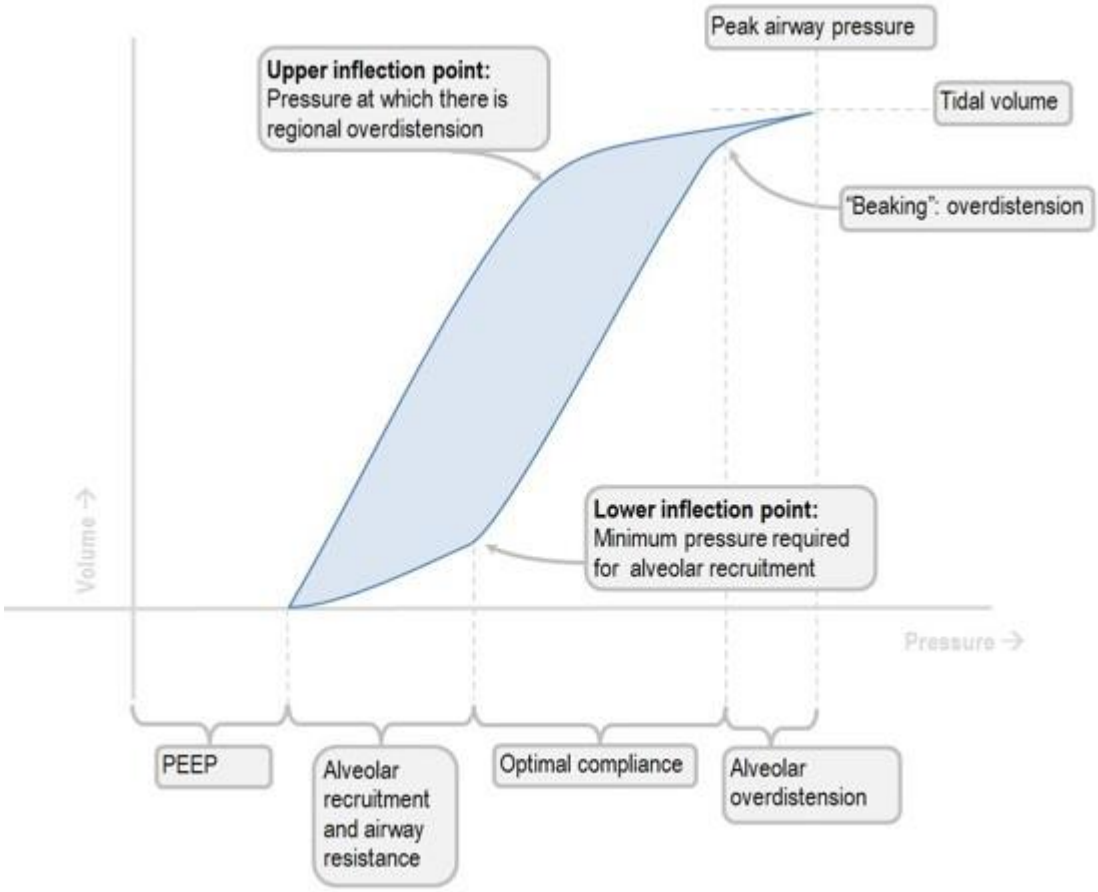


Figure 1-3 Pressure volume curve of a patient on volume control mode of ventilation

Illustration of the non-linear relationship between airways pressure (cms H_2O) and volume (Litres (L)) in a subject with no cardiorespiratory disease. Optimal compliance is demonstrated when pressure and volume have a linear relationship. Lower inflection point (P_{flex}) is the pressure at which airway resistance is overcome. Upper inflection point represents the elastic recoil of the chest wall and lung tissue.

1.2 Established methods for measuring lung function

Spirometry

Formal assessment of lung function can be quantified by spirometry or whole-body plethysmography. Spirometry quantifies lung function using forced expiratory manoeuvres. Forced Vital Capacity (FVC), the total volume exhaled following a maximal inspiration and forced exhalation, is measured in Litres (L).[4] Forced Expiratory Volume at one second (FEV1) is also measured during this manoeuvre and estimates airways resistance (AWR) in lung disease. The forced expiration to vital capacity ratio (FEV1/FVC) distinguishes normal, and obstructive airway disease as seen in Table 1.1. FEV1 is a bio-marker of disease progression and predictive of survival in neuro-muscular diseases but a less reliable predictor in disease progression in COPD patients.[5][6] In addition to measurement which can be compared with age-sex-ethnicity reference data, spirometry data can be presented graphically as flow-volume loops (Figure 1.4). Different disease states have typical effects on flow-volume loops, demonstrating the differential diagnostic value of spirometry in respiratory disease (Figure 1.4).[4]

During periods of increased load (exercise) the end expiratory lung volumes (EELV) decrease in normal subjects (Figure 1.5). In patients with COPD and obesity, resting tidal volumes shift to the left in comparison to normal subjects. In obesity and COPD, the EELV increases during periods of increased respiratory load, resulting in high volumes of ventilation, shifting to left, predisposing these subjects to dynamic hyperinflation and increase sensation of dyspnoea (Figure 1.5, leftward arrow).

Lung Volumes

Static lung volumes, including Total Lung Capacity (TLC), Residual Volume (RV) and Functional Residual Capacity (FRC), can be measured by whole body plethysmography or inert gas dilution techniques (figure 1.6). FRC marks the end of passive expiration and is reduced in morbid obesity as a consequence of decreased Expiratory Reserve Volume (ERV) whilst RV remains relatively preserved.[7], [8] Hyperinflation due to loss of lung elastic recoil secondary to emphysematous disease is measurable by increased RV, FRC or RV/TLC ratio.[9]

Diffusion Capacity

Diffusion capacity of the lung, measured by a single breath hold of dilute carbon monoxide (CO) estimates gas exchange and is represented by transfer factor for the lung for CO (TLCO), Lung volume in which CO diffuses (VA) and the transfer coefficient (KCO).

Compliance

Compliance is variable throughout the respiratory cycle and can be quantified as the gradient at any point in the pressure volume curve as seen in figure 1.3, with a reduction at maximal volumes. Dynamic compliance can be quantified using an oesophageal balloon catheter to measure pressure changes during the respiratory cycle. Due to invasive techniques and respiratory muscle load in disease, quantifying compliance is impractical out with research settings.

Airway Resistance and Reactance

AWR is inversely proportional to the radius of the airways, increasing in smaller airways due to reduced radial traction in airway calibre. Turbulent airflow during high pressure gradients, such as a forced expiratory manoeuvre, also increases AWR. Airway muscle tone is regulated by the sympathetic and parasympathetic nerves. Cholinergic parasympathetic activation causes bronchoconstriction and smooth muscle contraction. Muscarinic antagonist's reverse airway obstruction by blocking acetylcholine on muscarinic receptors in airways smooth muscle. Beta2-adrenergic agonists bind to Beta2 receptors on airway smooth muscles to open calcium-activated potassium channels hyperpolarising smooth muscle cells leading to smooth muscle relaxation, increased airway calibre and reducing AWR. Inhaled muscarinic antagonists and beta agonist therapy are used in obstructive airways disease.

Forced oscillometry technique (FOT) is a simple, non-invasive and effort independent test to quantify lung function including in-phase airways resistance and the out-of-phase

reactance. Forced oscillations of sound waves detect airway changes and together with pressure, flow transducers to determine respiratory impedance; the sum of resistance and reactance.[10] Reactance reflects capacitance (the elasticity of lung) and inertia properties of the lung. Resistance in both large and small airways can be derived from FOT and used as a bio-marker in small airways disease and obesity[10], [11] [12], [13] Further details of this technique and its application in disease monitoring are discussed in Chapters 2 & 5.

	Obstructive airways disease	Restrictive airways disease	Obesity
FEV1 (L)	Reduced	Normal/ Reduced	Normal/ Reduced
FVC (L)	Reduced	Reduced	Normal/ Reduced
FEV1/FVC	Reduced	Normal/ Increased	Normal/ Reduced
RV	Increased	Reduced	Normal/ Reduced
TLC	Increased	Reduced	Normal/ Reduced
RV/TLC	Increased	Normal/ Reduced	Normal/ Reduced
DLCO	Reduced	Reduced	Normal/ Reduced
KCO	Normal/ Reduced	Reduced	Normal/ Increased

Table 1-1 Spirometry patterns

Spirometry trends seen in obstructive airways disease, restrictive airways disease and obesity.

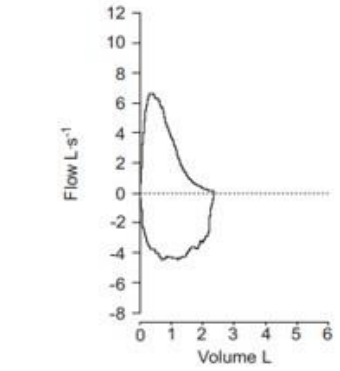


Figure 1.4.1 Flow–volume loop of a normal subject with end expiratory curvilinearity, which can be seen with ageing.

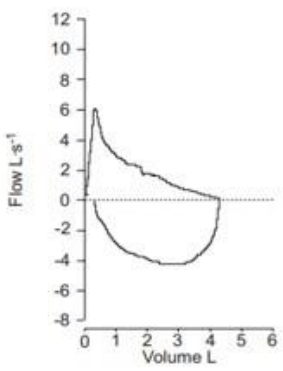


Figure 1.4.2 Moderate airflow limitation in a subject with asthma.

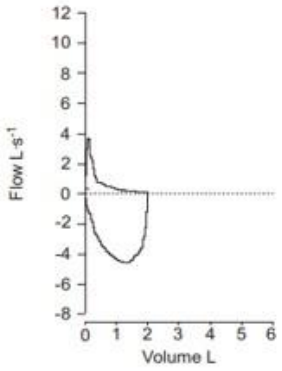


Figure 1.4.3 Severe airflow limitation in a subject with chronic obstructive pulmonary disease.

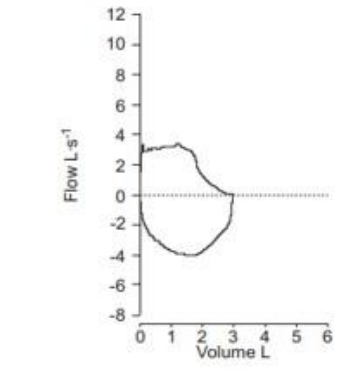


Figure 1.4.4 Variable intra-thoracic upper airway obstruction.

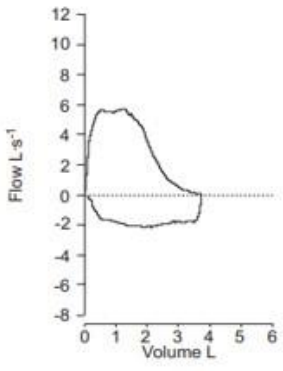


Figure 1.4.5 Variable extra-thoracic upper airway obstruction.

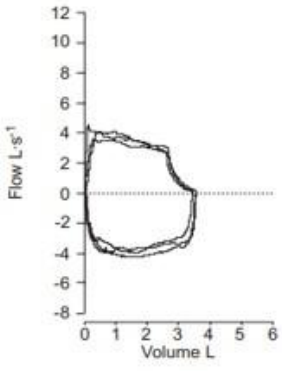


Figure 1.4.6 Fixed upper airway obstruction shown by three manoeuvres.

Figure 1-4 Flow Volume Loops

Illustration of flow volume loops from “Standardisation of spirometry” by Miller et al.[4] Flow-volume loop of normal physiology (Figure 1.4.1), moderate airflow limitation in asthma (Figure 1.4.2), severe airflow limitation in COPD (Figure 1.4.3), variable intra-thoracic upper airway obstruction (Figure 1.4.4), variable extra-thoracic upper airway obstruction (Figure 1.4.5) and fixed upper airway obstruction (Figure 1.4.6).

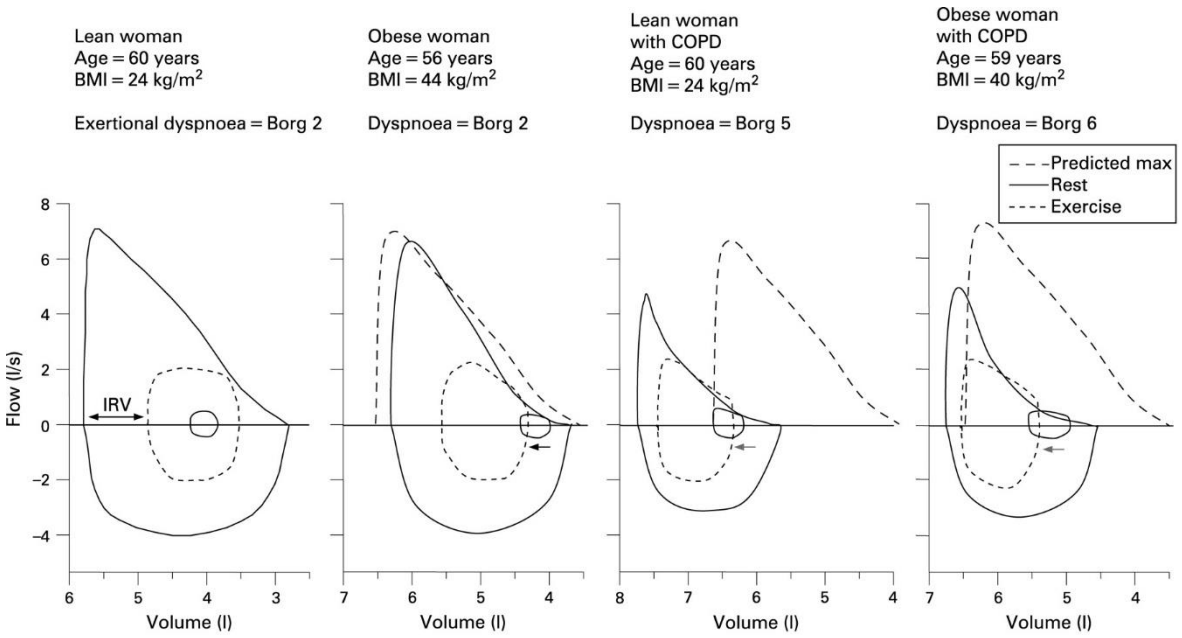


Figure 1-5 Flow volume loop in patients with obesity and COPD

Maximal and tidal flow volume loops in age-matched females with normal lung function, obesity, COPD, and obese COPD. Tidal volumes shift to the left in obesity and COPD. End expiratory lung volume decreases during exercise in the healthy female, the obese, COPD and obese COPD females demonstrate dynamic hyperinflation (leftward arrows). COPD demonstrates both flow and volume constraints, limiting peak ventilation during exercise.

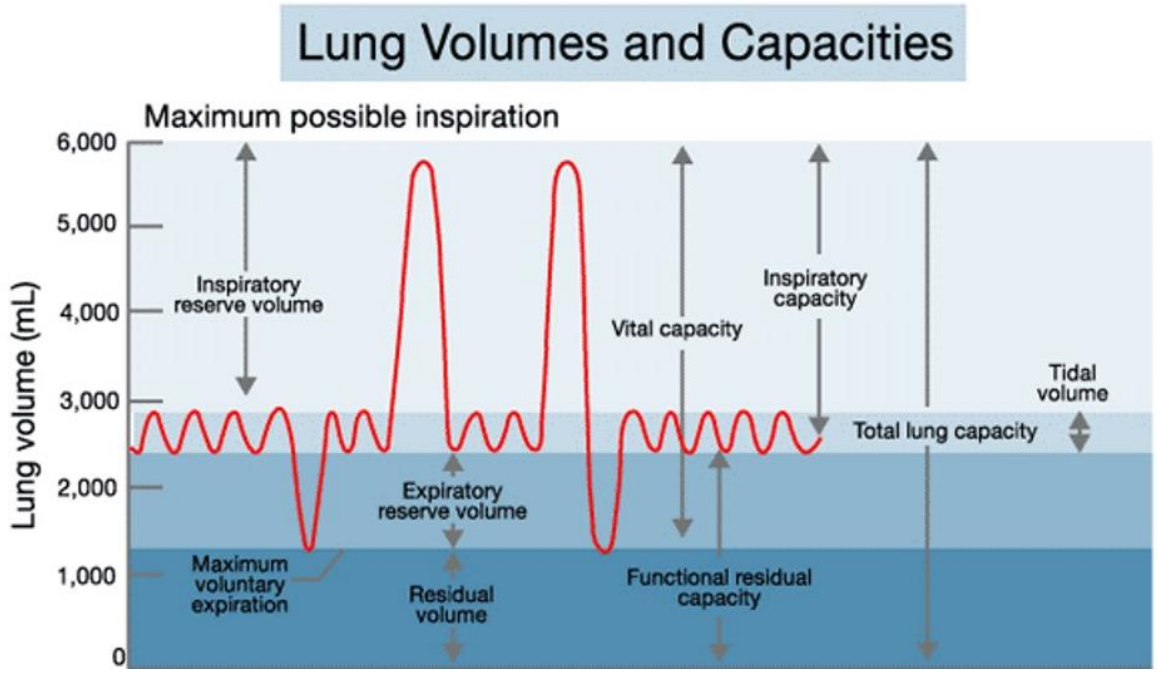


Figure 1-6 Lung volumes and capacities during the respiratory cycle

Illustration demonstrates total lung capacity measured in millilitres (mL) and volumes during tidal breathing (tidal volume). The forced vital capacity (vital capacity) is the sum of maximum inspiratory capacity (inspiratory capacity) and maximal voluntary expiration (Expiratory reserve volume). The inspiratory reserve volume represents the difference between the inspiratory capacity and tidal volumes. The functional residual capacity is the sum of expiratory reserve volume and residual volume.

1.3 Physiology in Sleep Medicine

Complex neurochemical pathways are integral to maintain the balance between states of wakefulness and sleep. Wakefulness is governed by the “ascending arousal system” containing neural pathways with serotonin, histamine, dopamine, acetylcholine, and noradrenaline neurotransmitters. Extracellular adenosine activates the ventrolateral pre-optic area (VLPO) suppressing the “ascending arousal system” and accumulates throughout wakefulness to induce sleep. (Figure 1.7) The central circadian clock in the suprachiasmatic nucleus further regulates the VLPO producing a complex balance between arousal neurochemicals, VLPO and the circadian cycle to maintain the sleep/wake cycle.[14], [15] Adenosine receptor antagonists, such as caffeine and theophylline inhibit the onset of sleep.[15] The orexin system, originating in the lateral hypothalamus, is another layer of control, promoting wakefulness and normal sleep architecture including influencing pathways responsible for rapid eye movement (REM) atonia. Damage to this system can result in excessive daytime somnolence, fragmented sleep and cataplexy seen in narcolepsy.[14]

Sleep is categorized as Rapid Eye Movement (REM) controlled by cholinergic neurons and Non-rapid Eye Movement (NREM) regulated by noradrenaline and serotonin pathways. Cholinergic activity increases in a cyclical manner during NREM stages to trigger REM sleep where almost complete muscle atonia with only the diaphragm maintaining ventilation pre-disposes patients with underlying respiratory disease to REM-related hypoventilation.

1.3.1 Investigations of Sleep Disordered Breathing (SDB)

Transcutaneous Pulse Oximetry and Carbon Dioxide Assessment (TOSCA)

Transcutaneous monitoring of capillary oxygen saturations and carbon dioxide levels can be measured using a sensor containing Oxygen (tpO_2) platinum cathode, a glass carbon dioxide ($tpCO_2$) sensor, heating element and reference electrode.[16] Summary of data acquired includes mean $tpCO_2$, maximum $tpCO_2$, mean tpO_2, minimum tpO_2 and oxygen desaturation index (ODI). This is used to screen for nocturnal hypoventilation and in the optimisation of NIV therapy. A TCM5 FLEX monitor (Radiometer Ltd, Copenhagen, Denmark) is used for transcutaneous monitoring in our service.

Limited Polysomnography

Limited channel polysomnography (LSS) measures 5 physiological variables overnight (nasal flow, pulse oxygen saturations, thoracic and abdominal respiratory impedance plethysmography (RIP) bands, body position and heart rate can be worn by the patient at home to identify and quantify the severity of sleep disordered breathing using apnoea/hypopnea index (AHI) and ODI. AHI >15events/hr is diagnostic of obstructive sleep apnoea (OSA) and correlated with daytime somnolence is diagnostic of obstructive sleep apnoea syndrome (OSAS). SOMNOmedics SOMNOscreen™ Plus (Randersacker, Germany) was used for limited polysomnography in this study.

Polysomnography

Polysomnography (PSG), the inpatient sleep laboratory investigation for sleep disordered breathing (SDB) incorporates 5 channel limited polysomnography with electroencephalogram (EEG), mandibular electromyogram (EMG), electro-oculogram (EOG), electrocardiogram (ECG), leg EMGs and a video recording (Figure 1.8). PSG facilitates sleep stage analysis via EEG analysis which is presented as a hypnogram. (Figure 1.9) Sleep staging combined with video and other analysis of the associated channels is used for the diagnosis of parasomnias, sleep movement disorders and contributes to the diagnosis of narcolepsy and other hypersomnia's. Polysomnography can be required for evaluation of selected patients with sleep disordered breathing, usually reserved for difficult cases, where there are medico-legal issues etc. SOMNOmedics SOMNOscreen™ Plus (Randersacker, Germany) equipment is used for inpatient polysomnography at our centre.

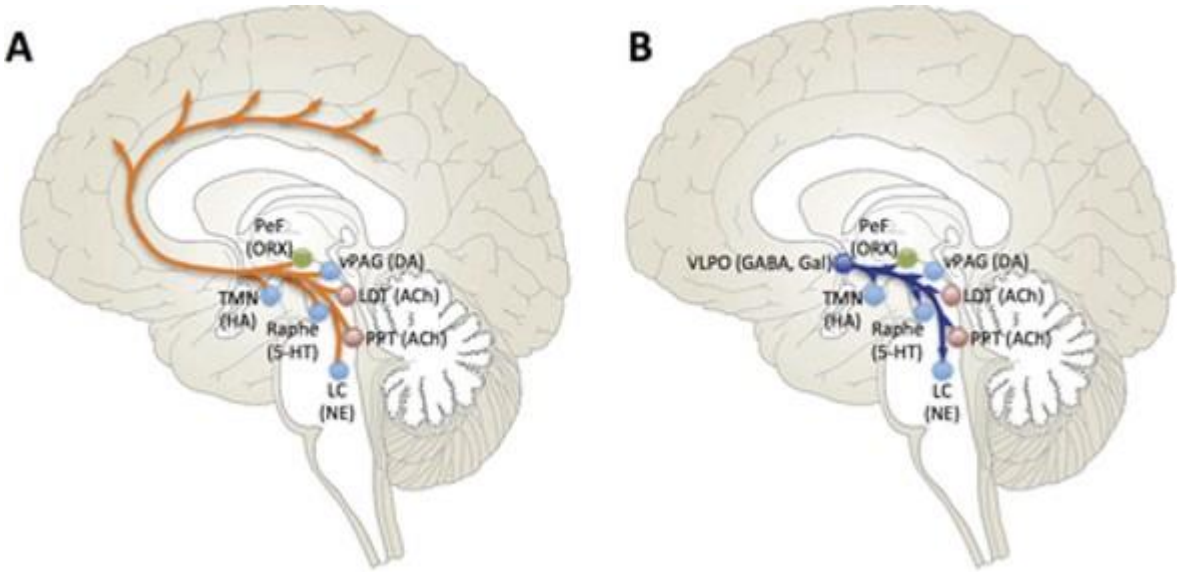


Figure 1-7 Neurochemical pathways of the sleep/ wake cycle

Illustration of neurochemical pathways in the brain that regulate sleep and wakefulness. A- The ascending arousal system with excitatory projections to the brain cortex. B- Hypothalamic pathways controlling the deactivation of the ascending arousal system. Both pathways include acetylcholine (Ach), dopamine (DA), histamine (HA), laterodorsal tegmentum (LDT), norepinephrine (NE), orexin (ORX), perifornical region (PeF), pedunculopontine tegmentum (PPT), tuberomammillary nucleus (TMN), ventral periaqueductal gray matter (vPAG), 5-hydroxytryptamine (5-HT). With the ventrolateral pre-optic area (VLPO) regulated by gamma amino-butyric acid (GABA) and galanin (Gal) in the hypothalamic pathways.

Figure 1-8 Polysomnography

Illustration of channels in a polysomnographic recording- including periodic limb movement (PLM, PLM1, PLM2), Snore monitoring (snore), flow analysis (flow), oxygen desaturation events (S_pO2 events), oxygen saturations trace (S_pO2), heart rate (Pulse), cardiac arousals (cardiac events), electrocardiogram (ECG), oro-nasal flow analysis (pressure flow), respiratory impedance plethysmography of thorax (Thorax) and abdomen (Abdomen).

Data presented illustrates obstructive sleep apnoea with regular obstructive breathing pauses (cessation of flow signal, variation in thoraco-abdominal movement) with associated desaturations and heart rate rises.

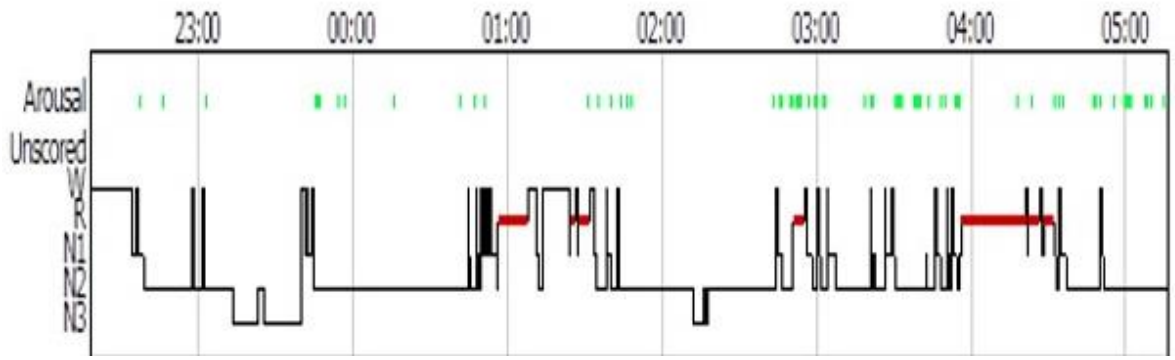


Figure 1-9 Hypnogram

Illustration of sleep stage analysis during polysomnography derived from electroencephalogram representing arousals, wakefulness (W), rapid eye movement sleep (R), non-rapid eye movement sleep stage 1,2 and 3 (N1, N2 and N3 respectively).

1.4 Respiratory muscle function

Impaired respiratory muscle capacity results in respiratory load-capacity imbalance and consequential alveolar hypoventilation. (Figure 1.1) Increased Neural Respiratory Drive (NRD), the neuronal activation to motor units from the respiratory centre, can maintain ventilation homeostasis and is associated with increased dyspnoea[17][18]. Diaphragmatic function is integral in the assessment of impaired respiratory muscle function and whilst chest radiography is a convenient screening tool to identify those at risk of diaphragmatic paralysis, it is not diagnostic.[19] Oesophageal balloon catheters, pressure transducers and phrenic nerve stimulation is well-established but an invasive uncomfortable method to quantify respiratory muscle capacity.[13], [20] Phrenic nerve activation by either electrical or the better tolerated magnetic stimulation can quantify hemi-diaphragmatic function.[21], [22] Positional Vital Capacity (VC) measurements provide a simple dynamic non-invasive assessment of the diaphragm. [1][23] Whilst sniff nasal inspiratory pressure (SNIP) and mouth inspiratory pressure (MIP) non-invasively quantifies global inspiratory muscle strength corresponding with airway and oesophageal pressures and although feasible in clinical practice, do not identify hemi-diaphragmatic weakness.[24][25] Maximum expiratory pressure (MEP) and peak expiratory flow (PEF) quantifies expiratory muscle strength and airway obstruction with cough PEF often used in neuromuscular disease monitoring to identify deteriorating respiratory function and airway clearance. [26]

Respiratory muscle weakness predisposes patients to nocturnal hypoventilation resulting in transient nocturnal hypercapnia and in severe cases persisting daytime hypercapnia. NIV can augment ventilation in these patients and may have benefit in those without daytime hypercapnia.[27]

1.5 Chemoreceptors in respiration

Ventilatory control incorporates a complex feedback loop integrating a sensory limb, central control, and effector limb (Figure 1.10). The sensory limbs consist of peripheral and central chemoreceptors which are located peripherally in the carotid/aortic bodies and centrally in the medulla oblongata of the brainstem.

Peripheral chemoreceptors detect changes in arterial pH, pCO_2 and pO_2 levels. In states of low pO_2 these receptors feedback to the medulla oblongata, pons, and cortical respiratory motor centres to increase respiratory rate, tidal volume, increase cardiac output and prioritise blood flow to the brain and kidneys. Central chemoreceptors detect changes in the pH of cerebral spinal fluid (CSF) , as a result of pCO_2 freely diffusing across the blood-brain barrier, where it dissociates to H^+ and HCO_3^-, lowering CSF pH, triggering the central chemoreceptors to stimulate the cortical respiratory motor centres and subsequent efferent limb of the feedback loop. In addition, mechanoreceptors in the chest wall feedback to the medulla where the central chemoreceptors respond to these signals and alter the ventilatory drive in the cortical respiratory motor centres stimulating the efferent limb/respiratory muscles to alter ventilatory patterns to normalise acid-base balance, pO_2 and pCO_2 levels.[28]

In states of persistent hypercapnia, the choroid plexus cells in the blood brain barrier facilitate bicarbonate ions to diffuse into the cerebral spinal fluid, altering the pH and resetting baseline pCO_2 levels. This is commonly seen in chronic hypercapnic failure secondary to severe COPD and obesity hypoventilation syndromes where normal compensatory mechanisms of increased ventilatory drive to increase alveolar ventilation are limited due to increased airway resistance, reduced compliance, increased respiratory load, respiratory muscle fatigue resulting in a blunted ventilatory response and higher baseline pCO_2 levels.

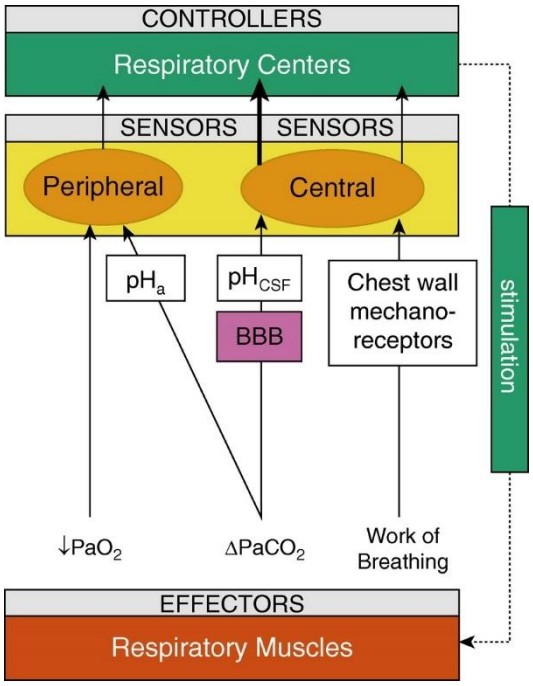


Figure 1-10 Ventilatory drive as a negative feedback loop

Control of ventilatory drive as a negative feedback loop. Peripheral chemoreceptors detect the change in pO_2 whilst both peripheral and central chemoreceptors detect changes in pH, pCO_2 and work of breathing via the mechano-receptors in the chest wall. Afferent feedback to the medulla and respiratory centres in the cortex result in efferent output to the effector muscles in the respiratory system to alter the ventilatory response to maintain acid-base balance, optimal pO_2 and pCO_2 levels.[28]

1.6 Neural Respiratory Drive

1.6.1 Neural respiratory drive: The evolution from invasive to non-invasive techniques

NRD represents the neuronal activation to motor units from the respiratory centre to overcome respiratory load to initiate the respiratory cycle. NRD is an established physiological marker in research to quantify the work of breathing.[29][17] An imbalance in the respiratory load capacity relationship results in alveolar hypoventilation and respiratory failure. (figure 1.1) Pressure generated during the first 100ms ($P_{0.1}$) of inspiration against an occluded airway, measured by a balloon catheter sited in the oesophagus, quantifies NRD but is dependent on flow generation, muscle integrity, muscle function and lung volume.[30], [31] In conditions such as Chronic Obstructive Pulmonary Disease (COPD) where dynamic hyperinflation (DH) and intrinsic positive end-expiratory pressure (PEEP) alters the length-tension properties of the diaphragm and increases inspiratory load required to overcome to initiate flow, $P_{0.1}$ is an unreliable

marker of NRD. Electromyogram (EMG) of the respiratory muscles, the diaphragm and intercostal muscles, is a feasible alternative to indirectly quantify NRD and demonstrates increased NRD in hyperinflation and COPD.[13], [32][29], [33]

Needle and surface EMGs first identified the role of the diaphragm in ventilation during tidal breathing and increased respiratory load.[20][34]–[39] Whilst preliminary animal studies demonstrated variable parasternal EMG activity in the rostro-caudal and mediolateral distribution during inspiration with similar distribution observed in human studies, identifying increasing inspiratory effort/EMG activity in the more caudal intercostal muscles with the greatest generated by the second intercostal muscle.[37], [38], [40][41]–[43] Normalising EMG by expressing NRD as a percentage of EMG signals during maximal manoeuvre such as maximum voluntary ventilation or maximal inspiration to total lung capacity, allows wider application as a biomarker in monitoring chronic disease, such as COPD and Cystic Fibrosis.[17]

Quantifying NRD using needle EMG limits contamination of adjacent muscle activity (cross-talk) and eradicates the need to normalise resting breath EMG to maximal manoeuvres to allow a wider application of NRD results.[41], [42] However, needle EMG represents single motor unit function, failing to quantify the total number of units recruited and therefore the global effect of the muscle on inspiration.[42] Multi-pair oesophageal electrode catheters inserted via the nasal passage with balloons in the oesophagus and the stomach, directly measures pressure changes during the respiratory cycle to quantify global activation of the diaphragm (EMGdi), independent of the muscle length and is an establish research tool to measure NRD in normal and chronic disease states but is invasive limiting its use in clinical practice.[18], [29], [44]–[46] Surface electrodes can represent global activation of the diaphragm during inspiration in both humans and dogs but cannot exclude cross-talk from adjacent intercostal or abdominal muscles activated during the respiratory cycle and during periods of increased respiratory load. [47]–[51] However, crosstalk during periods of quiet breathing or deep anaesthesia is negligible.[39], [48] Although not interchangeable with diaphragmatic EMG, parasternal EMG recordings via surface electrodes in the second intercostal space (EMGpara) is a

feasible non-invasive method of measuring respiratory load and NRD in research and clinical practice. [17][52], [53]

1.6.2 Neural respiratory drive in pulmonary disease

The altered length tension properties of the diaphragm in COPD patients reduces efficiency during inspiration, increases accessory muscle activation and increases NRD compared to healthy subjects correlating with disease severity.[54]–[58] NRD in COPD is increased compared to matched healthy subjects, and corresponds to disease severity and breathlessness.[29], [44], [57], [59], [60] In chronic respiratory disease, NRD rises during periods of increased respiratory load and can be negatively correlated with ventilation, otherwise referred to as neuro-ventilatory uncoupling and is evident when progressive dynamic hyperinflation (DH) during graded exercise impairs the pressure-generating capacity of the diaphragm.[57][29] During exercise progressive DH correlates with reduced pressure-generating capacity of the diaphragm and dyspnoea in COPD patients.[61] Long acting bronchodilators demonstrated improvement in lung function, reduction in dyspnoea and NRD in this cohort of patients.[61], [62] However, dyspnoea does not correlate with neuro-ventilatory uncoupling but represents the awareness of increased NRD secondary to altered respiratory load, providing insight into pathophysiology of dyspnoea in chronic disease.[63]

During states of increased respiratory load, parasternal intercostal muscle activation augments inspiratory effort in a rostro-caudal distribution. [37], [38], [41][64] Surface EMG of the second intercostal muscle demonstrates the greatest role in inspiration, is similar to diaphragmatic EMG and is a reliable reproducible method of quantifying NRD in COPD.[42], [43][53][65] NRD derived from parasternal EMG and NRD index (NRDI), the product of normalised EMG (EMGpara%max) and respiratory rate, can be used as a bio-marker of disease monitoring following exacerbations or periods of increased respiratory load in both COPD and asthmatic patients. [65], [66] Utilising EMGpara during acute exacerbations of COPD can predict safe discharge and readmission rates.[65], [67]

NRD correlates with lung function and acute exacerbations in Cystic Fibrosis(CF) and Interstitial Lung Disease (ILD).[17][68], [69][70] Higher NRD levels were observed in CF patients compared to healthy controls during exercise before they experienced increased dyspnoea, suggesting habituation of the sensation of breathlessness as a result of persistent high NRD levels in CF.[71] NRD is elevated in uncontrolled asthma compared to well controlled disease and matched healthy controls.[72]

1.6.3 Neural respiratory drive in obesity, obstructive sleep apnoea and breathing support

Increasing prevalence of obesity has led to an increase in morbidity and mortality.[73] As a result the prevalence of sleep disordered breathing (SDB) and chronic hypercapnic respiratory failure secondary to obesity has risen.[73] [74] NRD is elevated in patients with SDB and correlates with Body mass index (BMI). NRD further increases in the supine position representing increased PEEP in obese subjects.[75] Continuous Positive Airway Pressure (CPAP) therapy can offset PEEP with a subsequent reduction in NRD up to 30%.[75]–[77] Likewise, patients with chronic hypercapnic failure secondary to obesity demonstrate a decrease in NRD with adequate Non-invasive ventilation(NIV).[78] Quantification of this off-loading effect of NIV with NRD analysis predicts adherence in COPD-OSA overlap syndrome and potentially facilitate early optimisation of home ventilation and could predict treatment adherence.[79][80] However, challenges in domiciliary ventilation are increasing and evidence demonstrates patient ventilator asynchrony (PVA) in NIV for chronic hypercapnic failure can lead to decreased ventilator tolerance and de-ventilation dyspnoea.[81] Although parasternal EMG can detect PVAs during nocturnal NIV, the presence of PVAs does not impact nocturnal ventilation. [82][83]

NRD can be reliably measured by surface electrodes at the second intercostal space and provides an assessable technique to quantify NRD in chronic respiratory disease. NRD can stratify severity of disease, track fluctuations and predict clinical outcomes (successful discharge, optimised breathing support), facilitating a personalised approach to the management of chronic respiratory disease. Further evaluation of optimal techniques, feasibility of NRD as a biomarker of disease and its utility in clinical practice is indicated.

1.7 Telemedicine

Telemedicine(TM) is the delivery of health care and health information by incorporating information communication technologies in the exchange for health information to guide diagnosis, management and disease prevention when the patient and physician are in remote locations.[84][85] TM provides large datasets for evaluation, research and education for patients and healthcare professionals. Following the introduction of the internet, TM has developed from telephone-based consultations to the use of multimedia communications and wearable devices. [86] Modern digital infrastructure facilitates large data retrieval from wearable devices for research and analysis to deliver enhanced disease management and prevention of chronic disease.

1.7.1 Telemedicine in Obstructive Sleep Apnoea Syndrome (OSAS)

Obesity is a global health issue.[87], [88] With rising prevalence of both overweight and obesity comes further health implications, including diabetes[89], hypertension[90], cardiovascular disease[91], cerebrovascular disease[92], sleep disordered breathing[74] and all-cause mortality rates[93]. Obesity is a risk factor in obstructive sleep apnoea and the global obesity epidemic has resulted in increased prevalence of obstructive sleep apnoea syndrome (OSAS).[94], [95][74]

OSAS is characterised by repeated upper airway occlusion, arousals during periods of sleep with intermittent hypoxia and hypercapnia which produces increased sympathetic activity leading to oxidative stress and systemic inflammation.[96] Untreated OSAS has significant health implications including excessive daytime sleepiness[97], impaired concentration[98], road traffic accidents[99], hypertension[100], [101], diabetes[102], cerebrovascular events[103], cardiovascular events[104] and all-cause mortality[105]. Sleep disordered breathing(SDB), which includes OSAS and Obesity Hypoventilation Syndrome (OHS), is associated with increased health related contact, medication use and socioeconomic costs.[106] Continuous positive airway pressure (CPAP) is the standard treatment for OSAS, improving adverse health outcomes[107] and is cost-effective[108].

Adherence to treatment is integral in realising the long term benefits of CPAP in OSAS but studies have shown CPAP adherence to be low after the initial treatment phase[109], [110]. Telemedicine in SDB has potential to improve outcomes by providing patient support, early detection of treatment issues, reducing health professional's workload (if service re-orientation managed appropriately). Published work so far has shown the use of tele-monitoring, tele-communications and patient education can reduce the burden on health professionals whilst facilitating early detection of treatment issues[111]–[113]. However, uncertainty regarding the most important intervention which facilitates a greater treatment effect and implementation of an individualised approach within existing service remains a challenge[111], [114].

CPAP is an effective treatment for OSAS and can reduce adverse health outcomes if usage exceeds 4 hours of PAP a night[115]. Whilst patient perception of excessive sleepiness improves with the use of CPAP therapy exceeding 6 hours a night[116], compliance to CPAP therapy is poor with adherence levels as low as 46%[109]. Adherence ($\geq$70% days with CPAP usage $\geq$4hours; the level set for reimbursement in US health system) to CPAP therapy is seen as the major challenge in OSAS management and has been the focus of many telemedicine studies. However, adherence is population based and an imperfect surrogate endpoint for individual outcomes, as 3hours of continuous usage may reduce symptom burden in some patients whilst others may need more PAP usage. Factors influencing CPAP adherence, such as interface/device issues, intolerance of pressures, drying of the airways, claustrophobia and other psychological barriers, make this a difficult challenge to address[117]. Therefore, it is important to incorporate symptom burden, improvements in respiratory failure and other validated biomarkers when analysing PAP adherence. Telemedicine facilitates big data retrieval and individual data analysis to allow better understanding and provision of a personalised approach in the management of SDB.

Tele-monitoring (TM) of CPAP therapy has been shown to have a positive effect on patient outcomes with a positive trend in adherence and accuracy in the transmitted data in an early pilot study in 2007[118]. Tele-monitoring with identification of individuals with

therapy issues combined with telephone trouble-shooting has been shown to improve CPAP adherence.[119] Whilst patient access to web based telemonitoring improves CPAP adherence and encourages patients engagement, automated messaging (triggered by pre-set intervention points) with access to CPAP usage can also improve adherence and reduce time spent on patient education compared to standard therapy.[120][121][122] Although automated messaging with TM may improve patient outcomes, it is important to consider how this advice is delivered to ensure maximum patient benefit. Pengo et al evaluated the effect of positive framed messages compared to negative framed messages and usual care during the initiation of CPAP therapy and found an improvement in compliance with the positive message arm and 50% reduction in dropouts compared to other arms.[123]

Internet based resources for patient education have been shown to have a positive effect in adherence to CPAP[124]. Web based OSA education, telemonitoring with automated messaging demonstrated an improvement in treatment adherence in the combination of web-based education and TM with automated messaging arms compared to a single intervention or standard care. Whilst TM with automated messaging alone improved compliance, web-based education did not but demonstrated improved clinic attendance.[111]

Videoconference (VC) calls enable health professionals to educate and assess therapy issues such as mask fit and application which otherwise may have required a hospital visit. The use of VC in patient education during the initiation of CPAP therapy has been proven to be as effective as face-to-face training and may provide future service efficiencies[125]. Reassuringly, treatment adherence is equivalent in patients who are managed through videoconference calls in comparison to usual face-to-face consultations, supporting a scrutinised adoption of videoconferencing to determine its benefits on patient experience, travel and service efficiencies. [126]

Evidence of the cost-effectiveness of TM needed as many studies lack robust data and well-defined cost outcomes within their analysis. A systematic review of cost-

effectiveness of TM by De La Torre-Diez et al in 2015 highlighted the lack of robust randomised control trials in this area with many studies underpowered or low quality data[127]. However, more recent studies have demonstrated cost savings with TM justifying further exploration to optimise both patient and financial outcomes in future research[128]–[131].

Several studies have reviewed the impact of who delivers these interventions, comparing sleep physicians, primary care physicians and health care professionals[128], [129], [132], [133]. Although better outcomes were associated with sleep specialist involvement in CPAP management[132]–[134], more recent studies suggest that both primary care management of OSAS and health care professionals can deliver this service achieving similar patient outcomes[128], [129]. Task shifting the management of OSAS to primary care and health care professionals demonstrates not only service efficiencies but potential cost effectiveness and should not be ignored considering the burden on our specialist services.

[128]

1.7.2 Telemedicine in home NIV and its use in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition characterised by persistent and often progressive airflow obstruction that is not fully reversible and/or the destruction of the lung parenchyma[135]. Diagnosis is based on patient symptoms and spirometry. COPD is a smoking related disease but occupational exposures (harmful chemicals and dusts) contribute to this disease[136]. The prevalence of COPD increases with age and it is thought that approximately 3 million people in the UK have COPD with 2 million undiagnosed[136]. Exacerbations of COPD lead to impaired ventilatory function and gas exchange resulting in respiratory failure[137]. During exacerbations, a reduction in muscle function results in increased symptoms, increased healthcare usage and in severe cases results in hospital admissions. COPD exacerbations are the leading cause of hospitalisation in the UK, with 15.9% of all admissions[138] and have demonstrated a rise in health care cost of the general population[139]. COPD is the third most common cause of death in the USA[140] and is projected to be the fourth leading cause of death in the world by 2030[141]. COPD is characterised by progressive and irreversible airways disease. Airways obstruction and emphysema progress with

advancing age, resulting in a deterioration in obstruction of the large and small airways, small airways collapse, gas trapping, dynamic hyperinflation, and increased PEEP. The respiratory load in COPD rises and therefore NRD increases to maintain adequate ventilation compared to normal subjects, corresponding to disease severity and breathlessness.[29], [44], [59][57], [60]In severe disease, an increase in dead space, ventilation/perfusion mismatch and impaired transpulmonary pressures secondary to muscle shortening in dynamic hyperinflation contributes to hypercapnic failure. NIV can overcome intrinsic PEEP and augment ventilation.

Several studies reviewed the use of telemedicine in the management of COPD to optimise clinical and service outcomes with tele-monitoring of peripheral oxygen saturations (SpO_2) in COPD demonstrating no improvement in clinical outcomes compared to standard therapy[142]–[144]. In one study, telemonitoring of SpO_2 combined with heart rate monitoring, questionnaires, weekly weight and blood pressure measurements, did not improve patient outcomes but increased hospitalisation. [143] Although the incorporation of physiological parameters, symptom burden, telephone communication with patient education within tele-monitoring can improve clinical outcomes and healthcare usage, careful consideration of acceptable targets and interpretation must be established to ensure there is an overall benefit.[145][146] A multi-factorial approach to telemedicine in management of chronic disease, encouragement of patient engagement, patient education, appropriate service model and evidence based targets are required to deliver an individualised service beneficial to both the patients and health care resources.

The use of acute NIV in acute hypercapnic failure in an exacerbation of COPD has been well established with developing evidence of the use of domiciliary NIV in severe COPD. Recent studies have assessed the clinical benefits of home NIV in both stable COPD and following an acute exacerbation with a reduction in one year all-cause mortality seen in patients treated with high-intensity home NIV in severe stable COPD who had low emergency admission rates.[147] However, the RESCUE trial found no improvement in admission free survival in those treated with home NIV in severe COPD in patients with persistent hypercapnia 48 hours following acute NIV.[148] The failure to demonstrate a significant improvement in the time to re-admission or death and carbon dioxide reduction could be a result of the moderate pressure support delivered in this study compared to the Kohnlein et al. Nevertheless, this study highlighted the importance of

timing in the assessment for home NIV. Early initiation of home NIV following acute hypercapnic failure may not benefit all patients considering a cohort will return to a eucapnic state following an acute hypercapnic exacerbation of COPD.[148]

The UK HOT HMV study addressed the caveats recognised from previous studies to identify those who would gain maximal benefit from home NIV in severe COPD.[149] This study evaluated the impact of domiciliary NIV in addition to long term oxygen therapy in severe COPD with persisting chronic hypercapnic respiratory failure 2-4 weeks following an exacerbation requiring acute NIV. Time to hospital re-admission or death was prolonged in the home NIV and home oxygen arm in comparison to oxygen therapy alone. In addition, this study demonstrated a reduction in exacerbation frequency and control of ventilatory failure in the home NIV arm. Screening for persistent hypercapnic failure 2-4 weeks following an exacerbation minimises selection of patients who would otherwise have returned to an eucapnic state following a life-threatening exacerbation of COPD. However, only 6% of those screened were included in this study leading to patients who may otherwise have been considered for home NIV including the growing COPD-OSAS overlap cohort being excluded from analysis and therefore not fully representative of clinical practice. Likewise, patients unable to be stabilised for 2-4 weeks post hypercapnic exacerbation, who would likely be re-admitted would not have met the study requirements and should be considered a research priority to avoid repeated hospital admissions impacting on patient morbidity/mortality and has significant healthcare implications.[149]

As a result, tertiary referrals for home NIV has increased in light of the growing evidence supporting home NIV in hypercapnic severe COPD. [149][147][148], [150] Clinical assessment by a physician identifies those suitable for NIV therapy, assess patient engagement and cognitive ability to independently manage home NIV. Cognition can be significantly impaired in both stable COPD and to a greater degree following an acute exacerbation compared to controls[151]. Whilst low cognitive performance and independence was demonstrated in a range of respiratory diseases during inpatient NIV set-up and at 6-week review[152]. Early recognition of patients at risk of poor adherence to domiciliary NIV may facilitate a personalised approach to initiation and patient education to maximise benefits of home NIV[153].

Data analysis from tele-monitored NIV devices has been showed to be reliable and combined with SpO_2monitoring facilitates optimisation of NIV therapy and reduces nocturnal respiratory events. [154] Tele-monitoring data provides remote access of daily usage, indicating patients tolerance to NIV with low usage and signifying disease severity in those with increased use of home NIV.[155], [156] Early detection of excessive air leakage with tele-monitored NIV data can aid early optimisation of ventilation, improve sleep quality and adherence.[157], [158] Remote data from tele-monitored NIV devices provides accurate ventilation data to enable therapy optimisation with the potential to improve clinical and service outcomes in home NIV.[159]

Tele-monitoring of home ventilation provides a rich data set for future studies to create preventative models in chronic disease with predictors of exacerbations of chronic respiratory disease. Rising apnoea hypopnoea index (AHI) on NIV data analysis from tele-monitored devices correlates with exacerbated heart failure and fluid accumulation.[160] Whilst, a persistent rise in respiratory rate (RR) and percentage of respiratory cycles triggered by the patient was associated with increased risk of exacerbations in COPD, with higher RR shown up to 10 days preceding exacerbations. [161] [162] However, further studies are required to identify the best predictors in disease exacerbations from NIV data analysis.

Remote monitoring of PAP therapy provides the opportunity to explore the potential of day-case initiation of NIV in stable chronic hypercapnic patients. Patout et al demonstrated no difference in 3-month PCO2 and adherence rates in PSG home NIV set-up versus nurse-led oximetry-capnography monitoring set-up, suggesting a rationalised approach to NIV initiation is safe and effective[79]. Home NIV initiation with tele-monitoring in patients with stable chronic respiratory failure has been shown to be as effective as inpatient NIV initiation in terms of control of ventilation, quality of life and cost-effective[163].

The growing burden on the health service requires us to address the disease management both in acute exacerbations and chronic disease, utilise new technologies to identify physiological parameters which may be used as predictors of disease trajectory and potentially develop a personalised preventative disease management model. Specialist review is required to identify patients at a suitable timepoint following an exacerbation, assess physical and cognitive abilities to manage home NIV to ensure the appropriate

application of this new treatment in hypercapnic COPD patients. Telemedicine can enable the fusion of remote NIV/CPAP data, symptom burden, physiological parameters with improved communication technology to build a rich data set for analysis of predictors of disease and improve patient outcomes. Current studies are assessing the use of web-based platforms in remote monitoring of home NIV and other physiological parameters. At present, there are no multicentre studies utilising these methods to measure improvements in clinical outcomes.

1.8 Volume Assured Pressure Support modes of non-invasive ventilation

Volume assured pressure support (VAPS) titrates pressure support required to maintain a pre-set target tidal volume or target alveolar ventilation over several breaths during NIV. Average VAPS(AVAPS, Philips Respironics) mode targets tidal volume whilst intelligent VAPS (iVAPS, ResMed) adjusts both pressure support and respiratory rate to deliver target alveolar ventilation[164]. Target tidal volume and alveolar ventilation is calculated using height, arm span or ulnar length to estimated ideal body weight. Typical initial target tidal volume for non-invasive ventilation would range from 6mls/kg to 10mls/kg of ideal body weight (Figure 1.11). Auto-titration of expiratory pressures (AutoEPAP) is an additional function to offset variable expiratory flow limitation seen throughout sleep cycles and positions (Figure 1.12). AutoEPAP is estimated using oscillometry to assess changes in airways resistance and reactance (AVAPS AE) or by flow-time curve analysis (iVAPS autoEPAP).

AVAPS has been shown to be equivocal to fixed spontaneous-timed (ST) NIV in several studies of several disease cohorts[165][166][167]. Murphy et al, demonstrated control in nocturnal hypoventilation in COPD-OSA overlap with similar settings achieved overnight with auto-titrating NIV compared to standard fixed pressure support with polysomnography[168]. This study suggested improved treatment adherence and subjective sleep comfort with auto-titrating NIV[168]. Likewise, Storre et al demonstrated AVAPS and fixed NIV therapy was equivocal with improved perceived sleep efficiency with AVAPS therapy[169]. The use of AVAPS in acutely decompensated hypercapnic failure secondary to COPD exacerbations showed a greater improvement of ventilatory failure and conscious levels compared to ST mode NIV.[170] Similarly, the use of auto-titrating mode in patients with obesity hypoventilation has shown improved control of ventilatory failure compared to ST mode with similar improved subjective sleep quality.[171] Auto-titrating NIV can improve ventilation in chronic hypercapnic failure secondary to kyphoscoliosis and improve forced vital capacity with long term usage[172].

Utilising VAPS NIV in the initiation of home NIV has been shown to reduce the length of stay during hospital initiation whilst demonstrating equivocal control of ventilatory failure in stable hypercapnic severe COPD patients.[173]At our centre our evolved service model is based on the use of VAPS modes routinely. AVAPS-AE mode is typically used for acute NIV and initial titration during inpatient set up. Experience has shown reduction in occupied bed days for NIV initiation with this strategy.[174] Although the study numbers remain small, these demonstrated the safety of VAPS NIV in a wide range of diseases and its additional benefits compared to fixed ST NIV. Availability with two-way remote monitoring with the Lumis ResMed devices and reduced cost of these have made them the preferred device in NHS Scotland. iVAPS auto EPAP (Lumis, ResMed) is the default NIV mode for home use in this study.

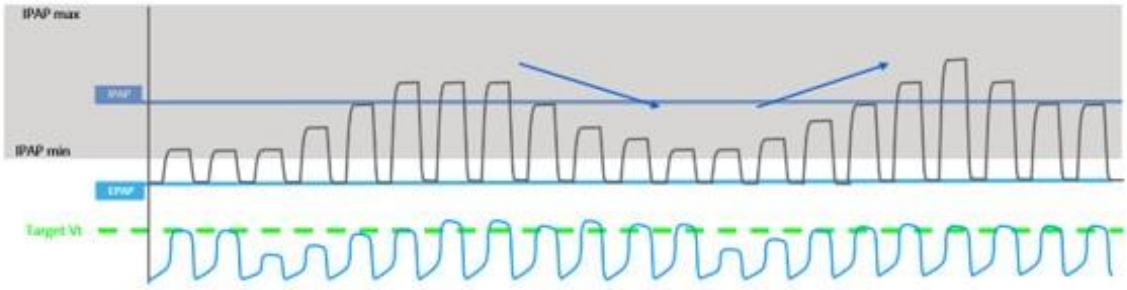


Figure 1-11 Average Volume Assured Pressure Support (AVAPS) non-invasive ventilation mode.

Illustration of AVAPS feature- automatic adjustments of pressure support according to patients needs to guarantee an average tidal volume (Target Vt), counterbalancing the changing workloads of ventilation due to body position, sleep stages and overall respiratory mechanics. Representing inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) requirements with maximum inspiratory positive airway pressure (IPAP max) and minimum inspiratory positive airway pressure (IPAP min) settings.

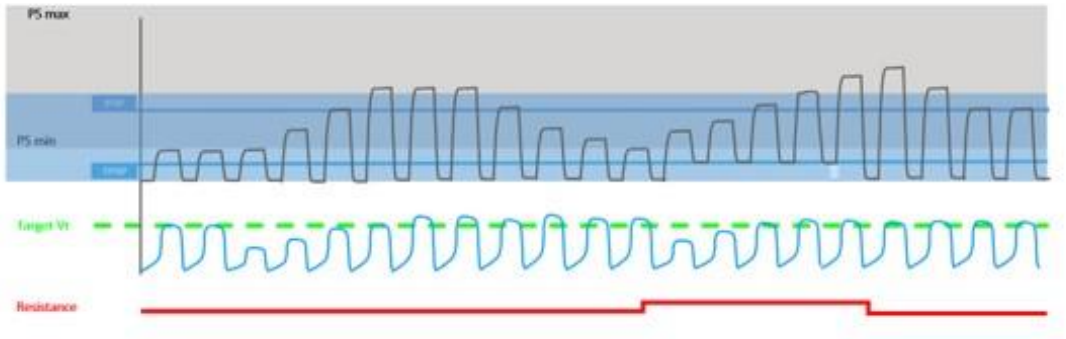


Figure 1-12 Average Volume Assured Pressure Support therapy with auto-titrating expiratory positive airway pressure (AVAPS-AE) non-invasive ventilation mode.

Algorithm responds to variations in inferred tidal volume and resistance (measured by oscillometry wave), adjusting therapy to maintain target tidal volume (Target Vt), airway patency, offset airway resistance (resistance) and expiratory flow limitation. Representing inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) requirements with minimum pressure support target (PS min) and maximum pressure support target (PS max).

1.9 Conclusion

The utilisation of advanced physiological measurements in combination with standard diagnostics provides valuable insights into the pulmonary mechanics of respiratory disease, facilitates physiological phenotyping, and have potential role as a biomarker in chronic respiratory disease to aid early identification of treatment success. Increased prevalence of obesity related respiratory failure and the strong evidence base for home non-invasive ventilation in hypercapnic severe COPD has led to increased pressures on tertiary breathing support services. Tele-monitoring of home NIV and CPAP facilitates prompt identification of therapy issues, early treatment optimisation, whilst providing a rich data set of ventilatory parameters and physiological response for further analysis, exploration into machine learning and development of predictive modelling. Fusion of advanced physiological measurements and tele-monitoring has the potential to provide physiological insights into chronic respiratory disease, respiratory failure, and its response to long term breathing support. Adaption of new technologies such as volume assured pressure support non-invasive ventilation, two-way remote tele-monitoring, and exploration of the feasibility of advanced physiological measurements of chronic respiratory disease will be discussed in this thesis.

Chapter 2 Materials and Methods

2.1 Two-way remote monitoring of home ventilation in the Glasgow Sleep and Breathing Support Research Centre

In Q2 of 2015, four hospitals within Glasgow, merged into one purpose built multi-million-pound hospital now known as the Queen Elizabeth University Hospital (QEUH), resulting in an exponential rise in in-patient breathing support assessment. The Glasgow Sleep and Breathing Support Research Centre (GSBSRC) was established in 2016 and based across two sites: the QEUH and Gartnavel General Hospital (GGH). Rising prevalence of obesity, obesity related respiratory failure (ORRF) and recent emerging evidence supporting home NIV in severe COPD with persistent hypercapnic failure has resulted in increased pressures on local services presenting many clinical and service challenges.

The legacy service model for initiation of home NIV incorporated in-patient multiple night NIV titration with transcutaneous monitoring with additional ancillary investigations if indicated. This was either during an elective admission or transfer to the tertiary centre in-patient beds at the QEUH. This model was unable to meet the heightened demands on the service from tertiary referrals, a reduction in bed availability due to the recent merge of local hospitals in to one site, unrepresentative sleep patterns and limited access to diagnostics.

GSBSRC adopted new technologies to aid in the development of new clinical pathways to improve diagnostics and service efficiencies. Utilising average volume assured pressure support with auto-EPAP(AVAPS-AE) mode NIV using a Respironics A40 device (Respironics, Philips, UK) for inpatient initiation, titration, benchmarking with transcutaneous monitoring and establishing on ST mode as destination therapy demonstrated significant service efficiencies in comparison to the previous in-patient model[174]. Procurement of NIV devices and future TM solutions are determined in NHS Scotland by the National Procurement Framework, where the evaluation of cost, device quality and vendor support are integrated, providing a ranked or open recommendation for device adoption within Scottish health boards, clinicians, and finance teams. Resmed ™ auto-titrating volume assured pressure support, CPAP and NIV generators are the number 1 preferred device supplier from the 2014 contract. Resmed ™ developed a range

of ventilators enabled with tele-monitoring via a data card and wireless connectivity for all Positive Airways Pressure (PAP) devices (Figure 2.1). This data is uploaded to Airview ™, a secure cloud-based patient management system, accessible to healthcare professionals to review patient data, analyse physiological parameters and adjust ventilator settings to facilitate early optimisation of treatment and improve patient outcomes (Figure 2.2 & Figure 2.3). NHS Scotland Sleep, Home Ventilation and Oxygen Procurement Framework 2018 determined there would be no extra cost for indefinite data provision from TM CPAP/NIV.

In addition to new device technology, the progressive introduction of electronic health records (EHR) throughout NHS Greater Glasgow and Clyde (NHS GG&C) has facilitated vetting of referrals and early investigations in those deemed to have a high probability of sleep disordered breathing (Figure 2.4). EHR portal is part of the Scottish Government initiative on e-Health, to allow immediate access to clinical notes, integrate patient journeys, to provide a safe and effective service whilst collating big data for audit and future population studies.

2.1.1 Initiation of Tele-monitored PAP therapy in GSBSRC

Home NIV was commenced in patients with persistent hypercapnic failure secondary to ORRF or severe COPD using Lumis 150 or Lumis 100 ventilators (Resmed, UK) (Figure 2.1). Both ventilators facilitate remote monitoring with the Lumis 150 providing adaptive mode average volume assured pressure support (iVAPs) in addition to Spontaneous Timed (ST) and lesser used NIV modes. Remote reviews of individual ventilatory requirements highlight therapy issues, enable remote therapy prescription changes to allow early optimisation of home NIV. (Figure 2.2 &2.3) Likewise, Obstructive Sleep Apnoea (OSA) patients with daytime somnolence were commenced on a similar device therapy via Airsense 10 Autoset (Figure 2.5) with remote monitoring and adaptive positive airways pressure support (APAP) or CPAP modes.

Assessment of suitability for inpatient or outpatient investigations was identified at breathing support clinic or via electronic vetting (Figure 2.4). Complex patients with

multiple medical conditions were investigated and initiated on PAP therapy on an in-patient basis. Inpatient PAP set up incorporates auto-titrating ventilators on initial night of PAP therapy to guide ventilator requirements necessary for domiciliary devices (Figure 2.6). Inpatient initiation allows daily clinical review of gas exchange, ventilation requirements and patient education to optimise therapy prior to discharge. All patients deemed suitable for remote monitoring were provided with written consent (Appendix 1) and the device activated prior to discharge with virtual clinic appointment one-week post-discharge.

Clinical pathways for remote review of patient data and telephone consultations have been developed and modified depending on type of PAP therapy and place of initiation (inpatient/outpatient). Virtual clinical review allows evaluation of investigations, clinical documentation, assessment of symptom burden and detailed TM data review of PAP therapy including compliance reports (Figs 2.2 & 2.3) to identify therapy issues to facilitate early optimisation. An outline of virtual clinic review structure is detailed in Figure 2.7.

2.1.2 Outpatient initiation of Tele-monitored PAP therapy

Day-case initiation of PAP therapy was considered in patients with stable COPD with persistent hypercapnia, obesity related respiratory failure or OSAS. Early remote data review (24-48hours) for patients who are frail or have multiple co-morbidities should be arranged. Formal virtual clinic review one-week following initiation facilitates detection of therapy issues to promote early optimisation. The out-patient pathway is detailed in Figure 2.8. Assessment of symptom burden, quality of sleep, device integration, therapy issues, remote prescription changes allow individualised follow up and optimisation of NIV. Six-week review is advised for patients who are frail, multiple comorbidities and severe hypercapnic failure. Whilst patients tolerating therapy with symptom control, patients from remote locations (Western Isles) and those with significant physical disability may be considered for three-month review.

Figure 2-1 Resmed Lumis 150™ bilevel positive airway pressure ventilator with humidification chamber that can be activated to allow two-way remote monitoring

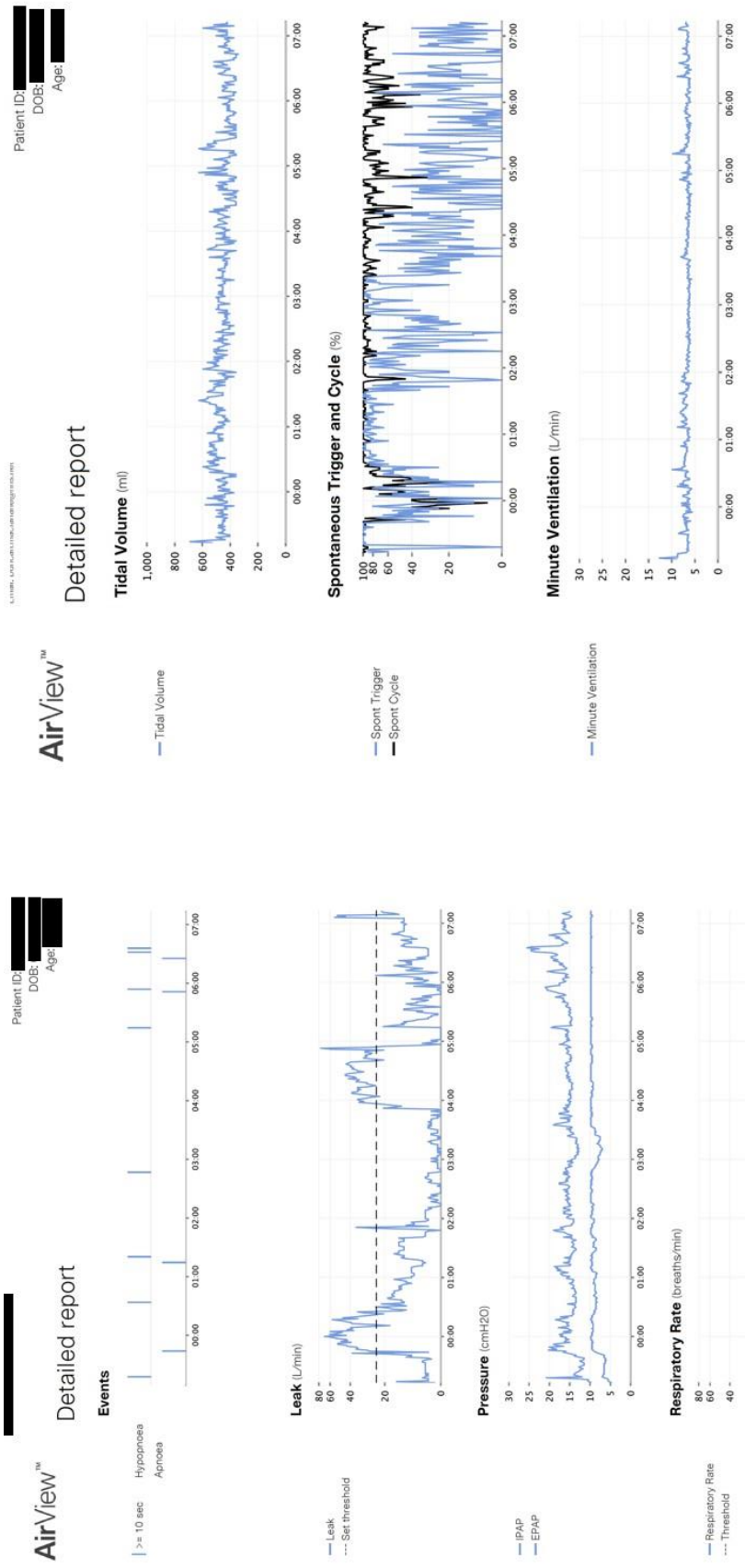
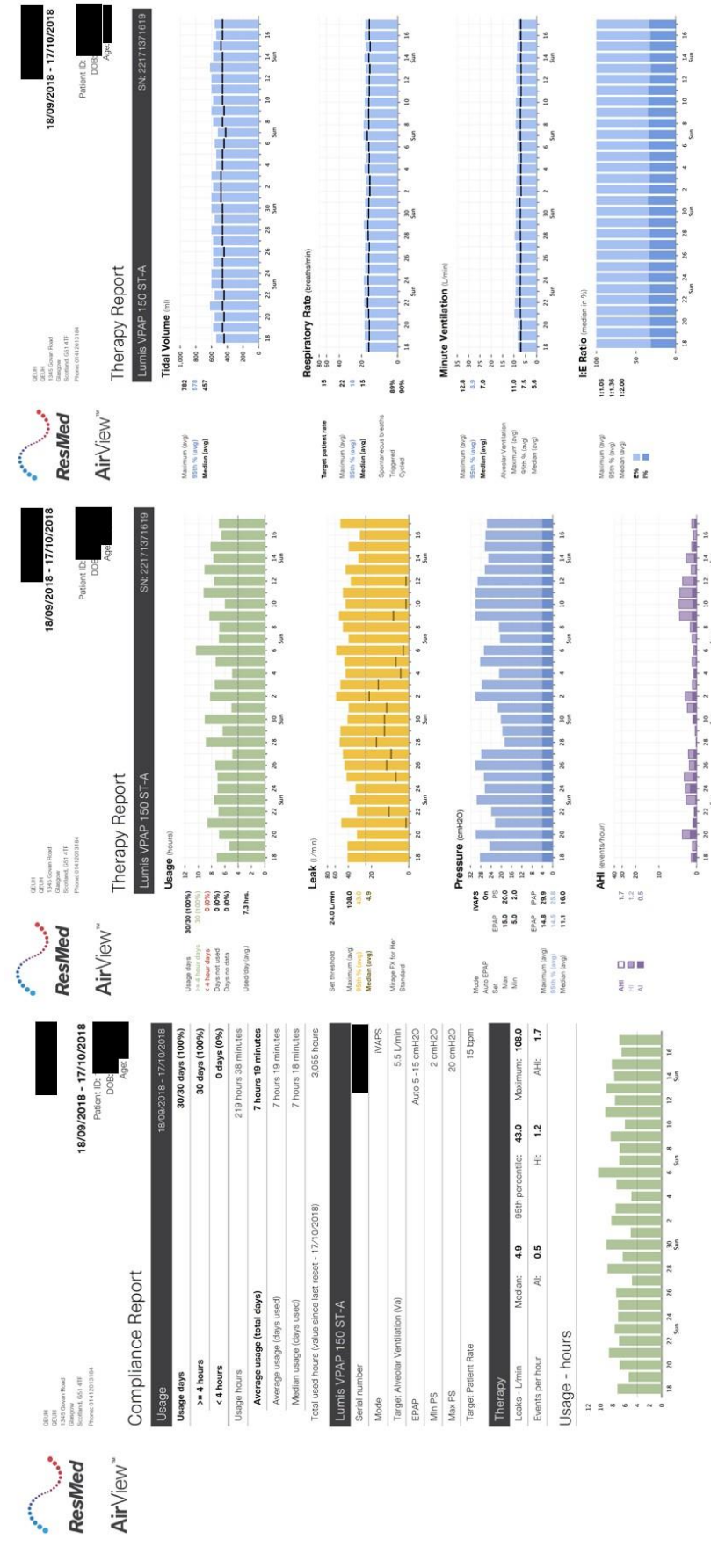


Figure 2.2: Ventilator data: Ventilatory data remotely downloaded Airview. This detailed report represents respiratory events (events), estimates the amount of leakage from the interface meausured in litres/min(L/min), inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) requirements measured in centimetres of water (cmH_2O), the patient respiratory rate (breathes/min), fixed respiratory rate threshold set by operator (Threshold), estimated tidal volumes measured in millilitres (ml), estimations of spontaneous trigger nd cycle (percentage (%)) and estimated minute ventilatilation measured in litres per minute (L/min).

Figure 2-2 Remote ventilator data downloaded from Airview



The compliance report quantifies therapy usage in number of days used and number of days achieved >4hours usage and < usage represented as days and percentage of days. Total number of hours of usage in a fixed time period (hrs), average dailuy usage (hrs), device details and settings, estimated leak represented by mean, 95th prcentile and maximum (L/min). Estimated events per hours representing apnoea index(AI), hypopnoea index (HI) and apnoea hypopnoea index (AHI). Therapy report shows a summary of ventilatory requirements on a dailuy basis- representing number of days achieve therapy > 4hours, number of days therapy <4hours, average dailuy usage (hrs), estimated leakage from interface (L/min) represented as maximum, 95TH percentile and median, postive ariway pressure requirements inlcuding IPAP and EPAP requirements expressed as maximum, 95TH percentile and median and the estimated apnoea hypopnoea index (events/hour) with inspiratory/expiratory ratio expressed as a percentage (%). Estimations of tdal volume (ml), minute ventilation (L/min) and alveolar ventilation (L/min) are expressed as maximum, 95TH percentile and median. Respiratpry rate is estimated and as expressed as maximum, 95TH percentile

Figure 2-3 Remote therapy reports: Therapy data remotely downloaded from Airview

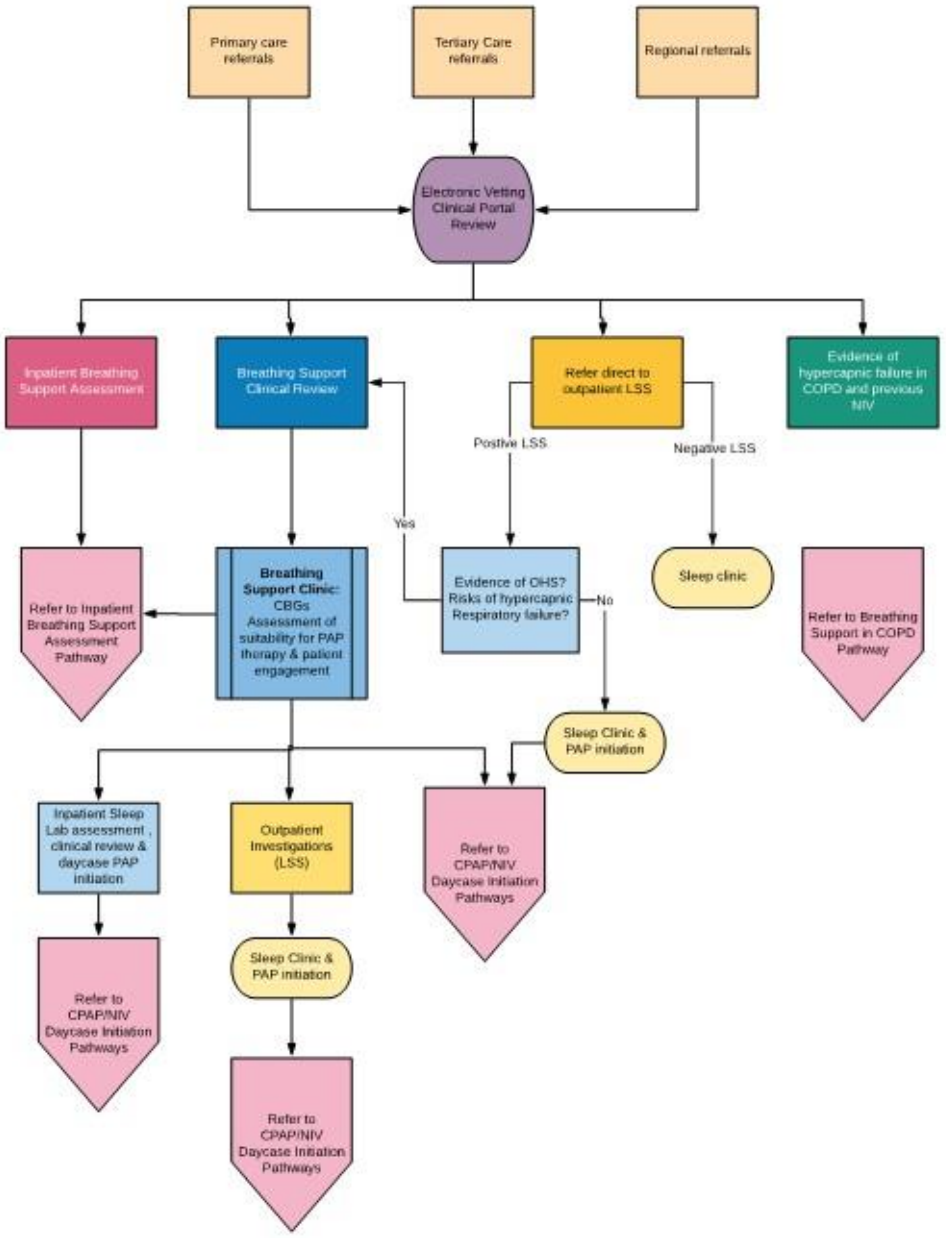


Figure 2-4 Electronic vetting for NHS Greater Glasgow and Clyde tertiary sleep service

Illustration of electronic vetting utilising electronic health records via clinical portal. Referral pathways include inpatient assessment, breathing support clinic review, referral directly for limited polysomnography (LSS) for high risk patients and hypercapnic severe COPD pathway. Patients with evidence of obesity hypoventilation on LSS are reviewed in breathing support clinic with capillary blood gas analysis (CBGs) prior to initiation of positive airway pressure (PAP) therapy- either continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV).

Figure 2-5 Auto-titrating positive airway pressure (PAP) device

The Airsense 10 Autoset device (ResMed, UK) delivers auto-tirating PAP therapy with the option to activate remote two-way monitoring.

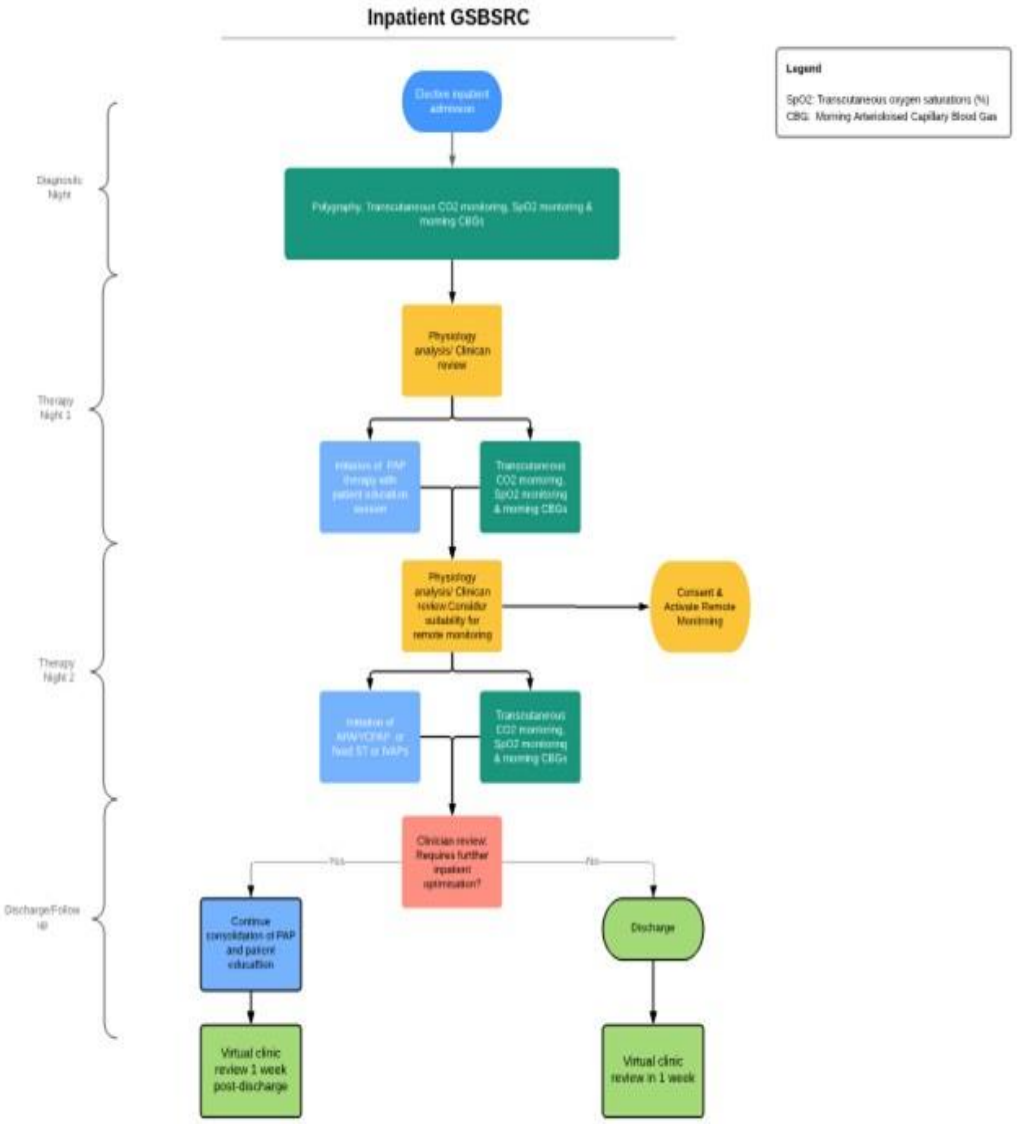


Figure 2-6 Inpatient pathway for breathing support assessment at Glasgow sleep and breathing support research centre.

The diagnostic evaluation includes polygraphy, transcutaneous monitoring of carbon dioxide (CO_2), oxygen saturations (SpO_2) and morning capillary blood gas analysis (CBGs). Therapy nights include the initiation of positive airway pressure therapy (PAP) or non-invasive ventilation(NIV), further monitoring if required. The second therapy night involves PAP or NIV titrations to auto-titrating PAP therapy (APAP), continuous positive airway pressure (CPAP), spontaneous-timed NIV (ST) or auto-titrating volume assured pressure support (iVAPS).

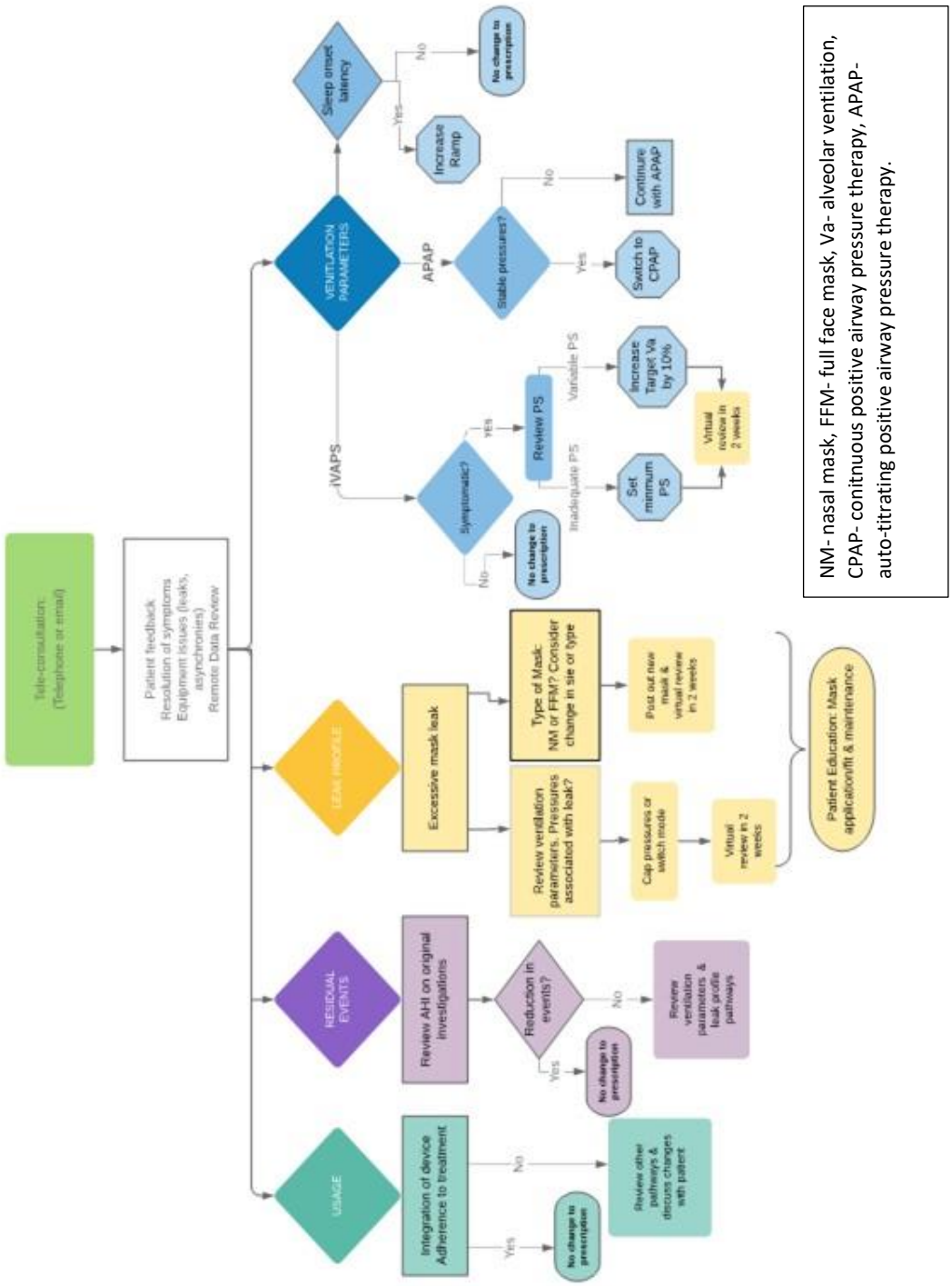


Figure 2-7 Remote data review, teleconsultation pathways and troubleshooting for Glasgow sleep and breathing support research centre

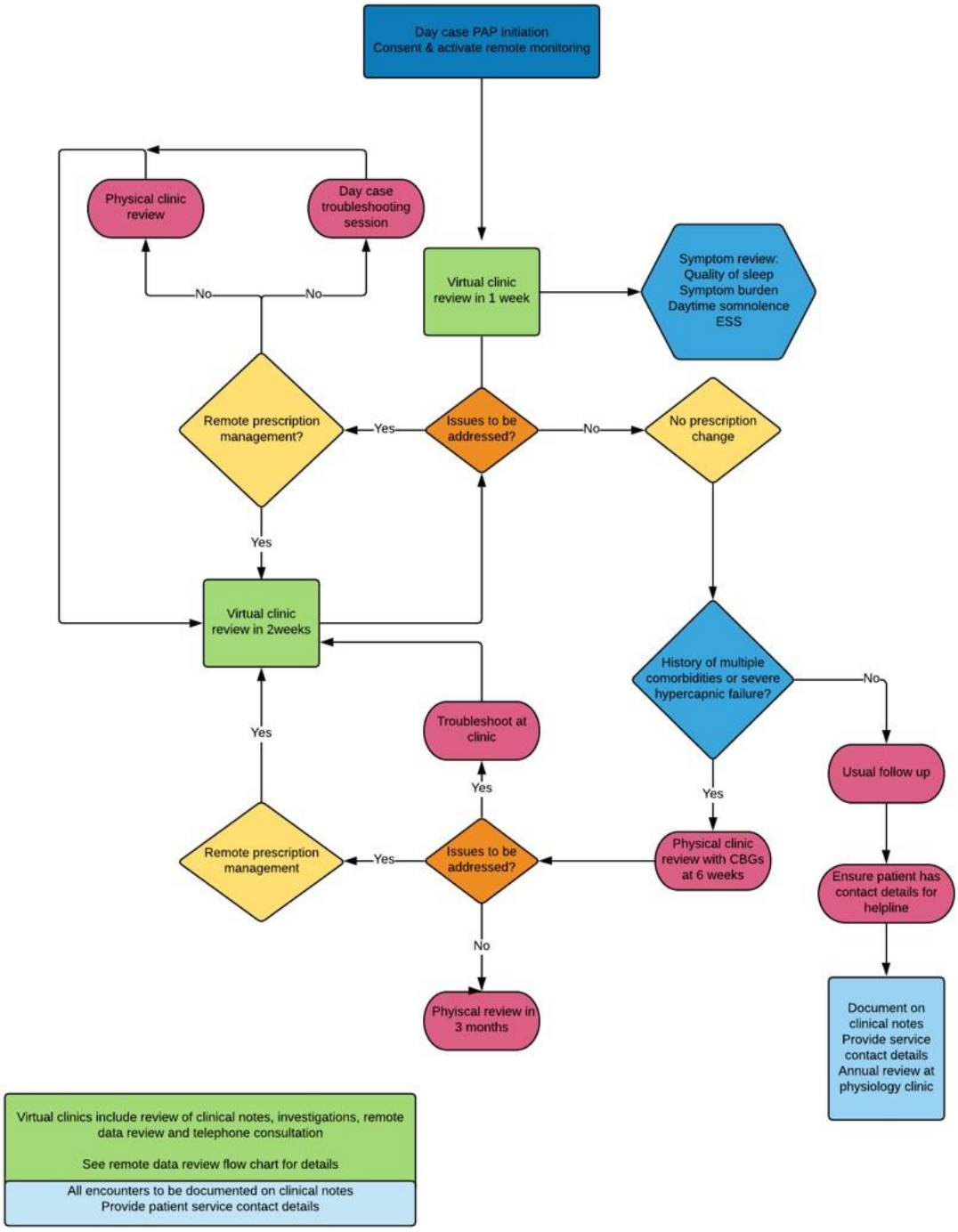


Figure 2-8 Day case positive airways pressure initiation pathway

Illustration of a typical pathway for day case initiation of PAP therapy in Glasgow sleep and breathing support research centre. CBGs- capillary blood gas analysis.

2.2 Clinical outcomes using remote monitored Non-invasive ventilation

Chapter 3 will focus on a retrospective review of an observational cohort of patients who were commenced on two-way remote monitored home NIV in severe COPD with persistent hypercapnic failure (cohort 1), patients who required acute NIV for hypercapnic failure secondary to an exacerbation of COPD but were not referred onward for long term breathing support (cohort 2- "control") within the GSBSRC service from March 2017 to January 2018. A further retrospective review of observational data from patients with ORRF (cohort 3) within the GSBSRC service was reviewed in NHS Greater Glasgow and Clyde between July 2016 and January 2018. GSBSRC COPD home NIV protocol is detailed in Figure 2.9. In this study we review the feasibility of two-way remote monitored home NIV in hypercapnic failure secondary to severe COPD and ORRF, the impact on clinical outcomes and service efficiencies.

2.3 Exploratory Endpoints

Chapter 5 focuses on exploratory advanced physiological endpoints incorporated within "The Exploratory Endpoints" study protocol (Appendix 2) allowing the inclusion of patients with any respiratory condition who can consent for exploratory physiological measurements to be taken alongside their standard respiratory care. Patients requiring two-way remote monitored PAP therapy or home NIV were also considered for recruitment and a typical pathway for the exploratory endpoints in this cohort is detailed in figure 2.10.

Patients who met the inclusion criteria seen in appendix 2 and physically able to participate in our physiology endpoints study alongside the standard care for respiratory conditions were given information detailing the study requirements (Appendix 3) and written consent was given (Appendix 4).

Baseline visit included basic anthropometrics, capillary blood gas in patients with evidence of chronic hypercapnic failure, parasternal electromyogram (EMGpara) measurements, forced oscillometry, heart rate variability, FEV1/FEV6, Blood pressure (BP) and Oxygen Saturations (SpO_2). All physiology methods will be discussed in detail below.

All patients completed Health Related Quality of Life Questionnaires (HRQOL) including the Epworth Sleepiness Scale (ESS), modified COPD Assessment Tool (mCAT), Medical research council dyspnoea score (MRC) and ECOG Performance Status (PS) (Appendix 5).

Study visits included baseline, 3months, 6 months and 12 months. All anthropometric and physiological measurements were repeated at each visit in addition to completion of symptom burden questionnaires. Virtual review of therapy for those managed with two-way remote monitored PAP therapy/NIV followed the patient pathways previously discussed in this Chapter.

2.3.1 Parasternal Electromyography

Neural Respiratory Drive can be quantified using surface electrodes positioned in the 2nd intercostal space, as discussed in Chapter 1. The simplification of this method is explored in Chapter 4 and appendices 6-8. Parasternal electromyography (EMGpara) is measured during tidal breathing at rest and normalised through maximal respiratory manoeuvres (EMGpara%max). Normalisation allows wider application within a study population. Neural Respiratory Drive Index (NRDI) is a product of normalised parasternal EMG (EMGpara%max) and respiratory rate (RR) which can be used as a physiological biomarker in disease monitoring and its clinical application is discussed in chapter 5.

Instrument Set up

Once the patient was in a semi-recumbent position in bed, electrode position was identified using bony landmarks to detect the 2nd intercostal space (Figure 2.11). Skin is cleaned and prepared, as discussed in detail in chapter 4, before electrodes were applied. Signals were sampled at 2kHz with band pass filters at 10Hz to 1000Hz by Dual Bio Amp (ADInstruments, Chalgrove, UK). Amplified signals were then passed to a digital converter (Powerlab, ADInstruments, Chalgrove, UK). Further analysis and digital filtering of signals was then done within Labchart software (ADInstruments, UK) on a personal computer. RR can be estimated from oro-nasal flow analysis or respiratory impedance plethysmography (RIP) bands. All study patients had respiratory rate estimated by RIP bands. In a small number of patients, oro-nasal flow was processed and analysed through a spirometer

module, Dual Bio Amp and Powerlab. PowerLab Input channel set up for signals are seen in Table 2.1.

All patients had at least 5 mins of resting tidal breathing prior to at least 10 sniff manoeuvres, measured as per ERS guidelines. EMGpara measurements were taken at baseline and where feasible at 3months and 6months alongside standard respiratory care including following the initiation of continuous positive airway pressure support or non-invasive ventilation depending on underlying diagnosis.

All results are presented as absolutes values, mean± standard deviation of EMGpara, EMGpara%max and NRDI at baseline, 3 months and 6months in each cohort.

2.3.2 Forced Oscillometry

The theory and application of forced oscillometry (FOT) has been discussed in Chapters 1 and 5. FOT is an established research tool in both paediatric and adult medicine, providing insights into pulmonary mechanics in normal and chronic respiratory disease.

Instrument set up

FOT was measured using a portable device (Tremoflo, Thorasys, Canada), facilitating study recruitment over split sites. Calibration of the device can only be completed when correlating software and Calibration Test Load is available and was completed before each study visit.

On the first study visit for each patient, a new folder identified by individual study number was created with patient demographics and smoking history. At each study visit a new mouthpiece with bacterial/viral filter is opened and placed on the handheld unit of the oscillometer. With the patient sitting in an upright position, a nose clip to seal nasal passages, face in an upward position of approximately 15° and hands supporting cheeks and mouth floor prior to the standard test initiation (Figure 2.12). Once a seal was created around the mouthpiece with the tongue underneath, the patient is asked to commence tidal breathing. When steady, quiet breathing had been observed for at least 3 cycles, the patient is informed, oscillometry measurements initiated and sampled for 20seconds on at least three occasions according to 2003 ERS guidelines[175]. In cases

where analysis of results demonstrated a Coefficient Variation (CV) greater than 15 if feasible, further measurements were taken.

The results are presented as the mean for each component calculated by FOT. FOT parameters calculated included: Total resistance (R5), Small airway resistance (R5-R20), Expiratory flow limitation represented by ΔXRS, Reactance (Ax) and tidal volumes.

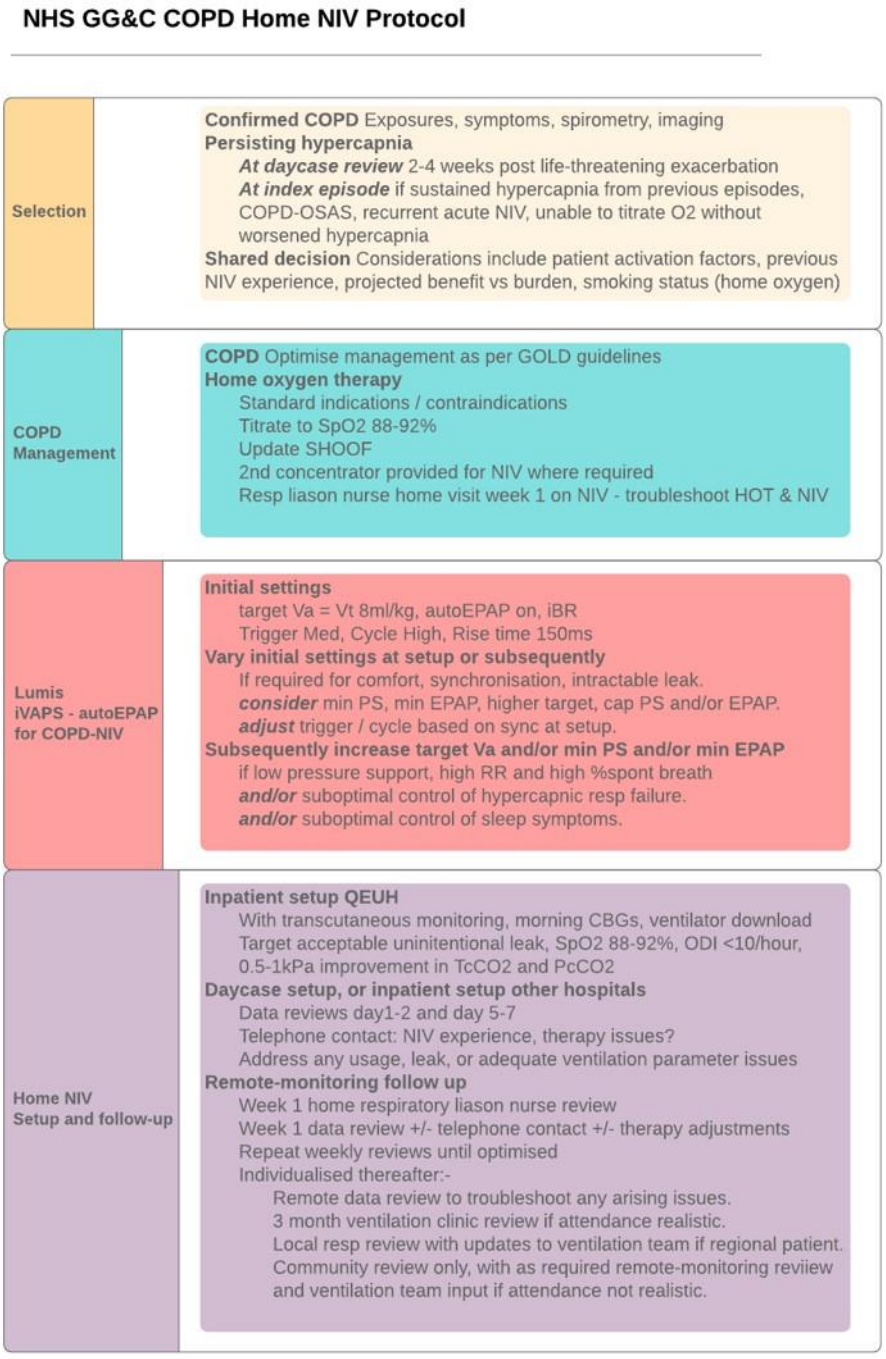
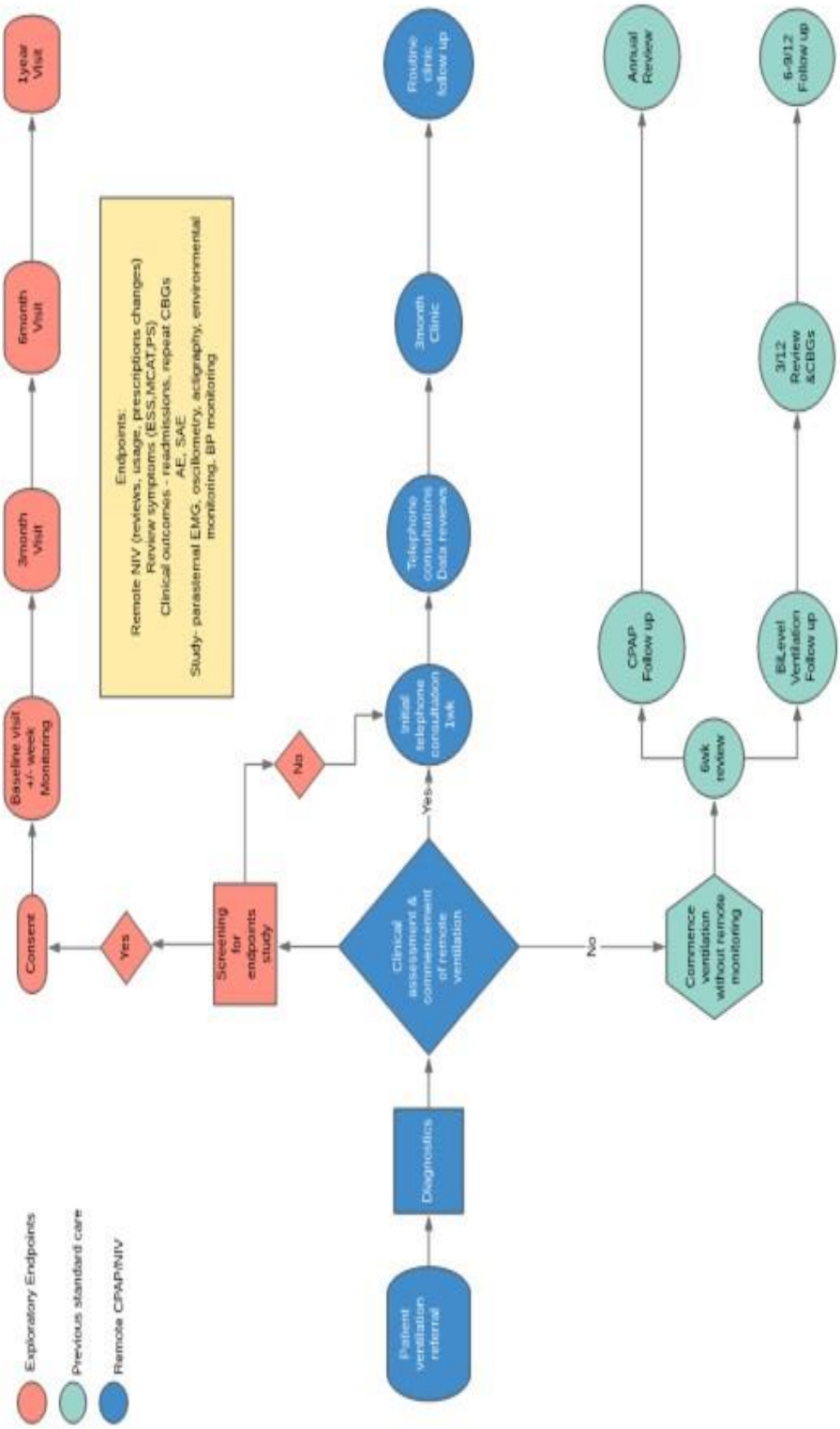


Figure 2-9 NHS Greater Glasgow and Clyde initiation of home non-invasive ventilation in patients with hypercapnic severe chronic obstructive pulmonary disease

SHOOF- Scottish home oxygen order form, Va- alveolar ventilation, autoEPAP- auto-titrating Expiratory positive airway pressure, iBR- intelligent back up rate, PS- pressure support, EPAP- expiratory positive airway pressure, %spont breath- percentage of spontaneous breaths, CBGs- capillary blood gas analysis, SPO_2- peripheral oxygen saturations (%), ODI- oxygen desaturation index, $TcCO_2$- Transcutaneous carbon dioxide (kilo pascals, kPa), $PcCO_2$- capillary carbon dioxide (kilo pascals, kPa).



All patients referred to the tertiary breathing support service are considered for two-way remote managed positive airway pressure (PAP) therapy or home non-invasive ventilation (NIV). Those deemed not suitable for remote monitoring follow the established pathway (green) for initiation and follow up. Typical follow up for remote monitored patients is demonstrated by the blue pathway. Typical follow up of patients recruited to the exploratory endpoints study is demonstrated on the orange pathway. NIV- non-invasive ventilation, CPAP- continuous positive airway pressure, ESS- Epworth sleepiness scale, mCAT- modified COPD assessment tool, PS- performance status, CBGs- capillary blood gas analysis, AE- adverse event, SAE- significant adverse event, EMG- electromyography, 3/12- 3 months, 6-9/12- 6-9 months.

Figure 2-10 Recruitment and patient pathway for exploratory endpoints study

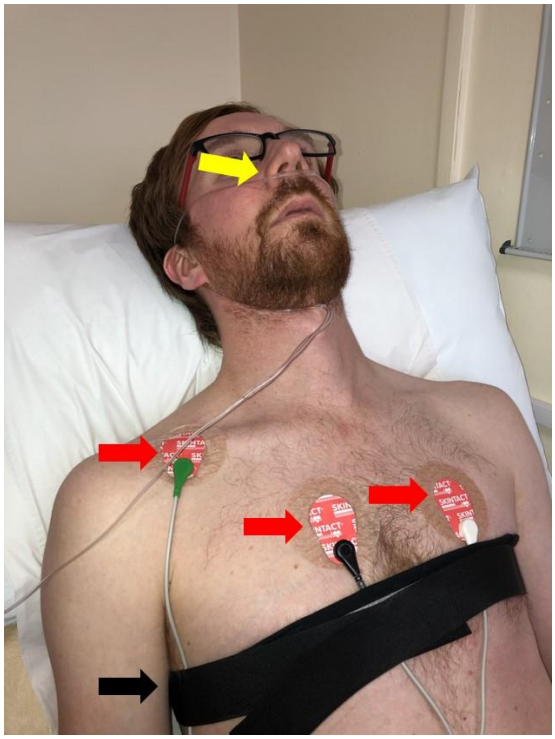


Figure 2-11 Parasternal electromyogram patient setup.

The study candidate is positioned at 45 degrees; bony landmarks are identified at the parasternal margins of the 2nd intercostal space and right clavicle as seen (Red arrows). Flow cannula is attached to the spirometer module and place on the patient for oro-nasal flow analysis (yellow arrow) and thoracic efforts are monitored by a respiratory impedance plethysmography band across the mid-point of the thorax (black arrow)

Channel	Signal
Channel 1	ECG
Channel 2	Filtered EMG
Channel 3	Thoracic RIP
Channel 4	Spirometry module

Table 2-1 Channel setup for parasternal electromyography analysis on the digital converter Power lab module (ADInstruments, Chalgrove, UK)

ECG- electrocardiography, EMG- electromyography, RIP- respiratory impedance plethysmography.

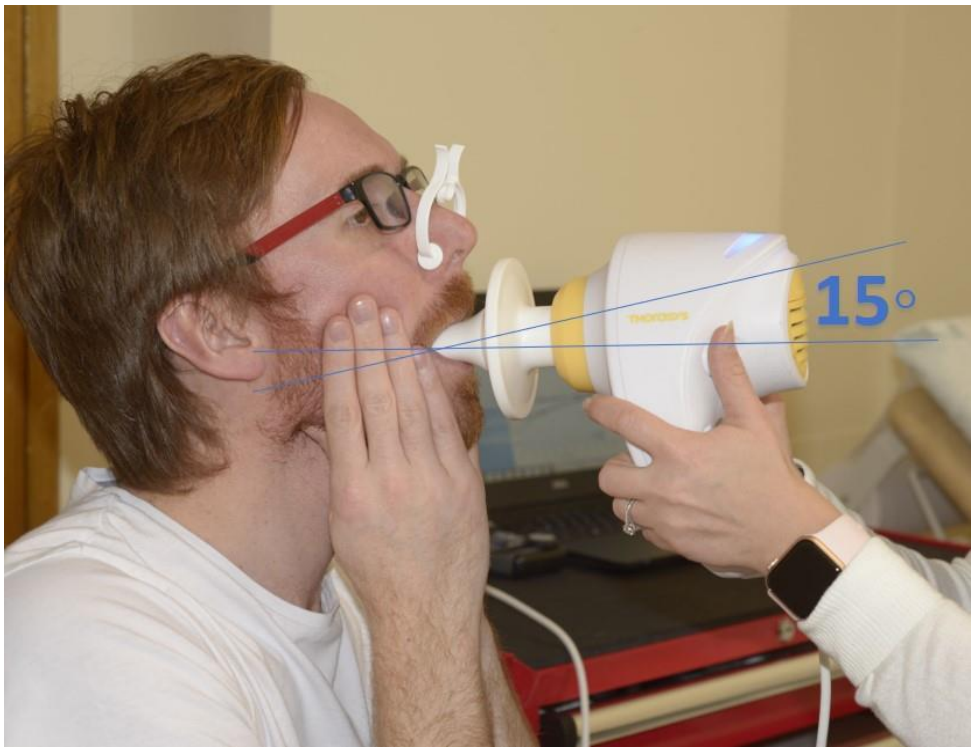


Figure 2-12 Forced oscillometry technique

Photograph demonstrating the standardised candidate setup for oscillometry measurements. At each study visit a new mouthpiece with bacterial/viral filter is opened and placed on the handheld unit of the oscillometer (blue arrow). With the patient sitting in an upright position, a nose clip to seal nasal passages (yellow arrow), face in an upward position of approximately 15° and hands supporting cheeks and mouth floor during tidal breathing prior to initiation of measurements.

Chapter 3 Clinical outcomes using remote monitored home non-invasive ventilation

3.1 Introduction

COPD is characterised by fixed airflow limitation which can follow a chronic progressive course. Severe airflow limitation in COPD predisposes to hypercapnic respiratory failure during acute exacerbations and persistent hypercapnic failure in stable severe disease. COPD is the second most common cause for emergency admissions in the UK which accounts for over 1 million bed days at a cost of over £800 million a year[176]. 34% of those admitted to hospital with an exacerbation of COPD are re-admitted within 90 days[177]. Exacerbations and hospital admissions are strongly associated with post-discharge mortality, the reduction of which are a COPD patient's priority[178][177][179]. Reducing exacerbations and subsequent hospital admissions should be a key priority to address the growing health and economic burden of COPD.

The risk of hospital re-admissions and future life-threatening events is high in patients who develop acute hypercapnic failure as a result of an exacerbation of COPD[180]. Acute NIV reduces hospital length of stay, need for intubation and mortality for patients with COPD exacerbation and decompensated hypercapnic respiratory failure[181]–[183].

Recurrent and persistent hypercapnic failure is associated with a decreased long term survival and higher admission frequency compared to severe COPD patients with transient hypercapnic failure following a life threatening exacerbation of COPD requiring acute NIV[184][185][186]. The application of home NIV in persistent hypercapnic failure in COPD has been an area of growing interest with high pressure NIV showing favourable outcomes in comparison to low pressure NIV[187][188]. Initial research in long term home NIV in hypercapnic COPD patients demonstrated no improvement in 1 year morbidity, mortality or hospitalisation in stable severe COPD[189] [190]. However, both studies included patients with severe COPD with infrequent exacerbations, low pressure support and did not confirm hypercarbia on arterial blood gases in one study prior to recruitment. McEvoy et al used low pressure support NIV in less severe COPD (FEV1 <50%) with mild hypercapnic failure (PCO_2 >6kPa) to demonstrate an improved survival but found a reduction in HRQOL outcomes and no reduction in hospitalisation[191]. A high-pressure support approach to domiciliary NIV focuses on improvement of gas

exchange to reduce the burden of hypercapnic severe COPD. However patient selection is important to ensure the correct delivery to confirm overall benefit as demonstrated in one study where recruitment too soon after a life-threatening exacerbation of COPD failed to identify those with less severe disease and transient hypercapnia who would not met the criteria for home NIV in usual practice[148]. Further high intensity home NIV studies have demonstrated improved HRQOL outcomes, control of hypoventilation and 1 year survival in severe COPD with more severe persistent hypercapnia (PCO_2 >6.6kPa)[147], [187]. The most recent landmark high intensity home NIV study, the UK HOT-HMV study demonstrated a significant improvement in time to re-admission following the initiation of home oxygen therapy and home NIV in patients with persistent hypercapnia 2-4 weeks following an acute exacerbation. [149] Additionally, the failure of formal clinical review by a respiratory physician following discharge after a life threatening hypercapnic exacerbation of COPD has been reported as high as 26% in the UK [192]. Patient selection with timely post-discharge assessment of persistent hypercapnic failure following an exacerbation is integral to delivering a safe and effective home NIV service in this heterogenous patient cohort and a future research priority.

Consideration of contributing co-morbidities such as co-existing obstructive sleep apnoea are important to determine PAP therapy delivery with a prevalence of COPD-OSA of 1-2%[193]. Several studies have shown an improvement in outcomes in COPD- OSA overlap patients with CPAP therapy but these were not randomised control trials nor included patients with hypercapnic failure on NIV[194], [195]. Screening for co-existing sleep disordered breathing would highlight the need for a multi-faceted approach in patient management, may provide improved PAP titration and outcomes but currently evidence for this is unclear therefore further RCTs are required. However utilising auto-titrating PAP therapy could address this without the need to screen all patients for COPD-OSA and should be a future research priority in a bid to rationalise the approach to initiation of home NIV in this patient cohort.

The severity of sleep disordered breathing is strongly associated with increasing obesity. Increased respiratory load of severe obesity can result in the imbalance of the respiratory load-capacity relationship (Figure 1.1) resulting in alveolar hypoventilation. The presence

of sleep disordered breathing and persistent daytime hypercapnia is diagnostic of obesity hypoventilation syndrome (OHS) otherwise referred to as obesity related respiratory failure (ORRF) in this thesis. Augmentation of ventilation with NIV in ORRF has been shown to improve morbidity and mortality[156], [196], [197]. Whilst, continuous positive airways pressure (CPAP) therapy offsets PEEP and has been shown to reduce the work of breathing in obesity[75]–[77]. PAP therapy in ORRF can be delivered by CPAP or NIV. Disease phenotyping may facilitate the use of appropriate PAP therapy and improve outcomes with recent studies demonstrating control of hypoventilation and symptoms with CPAP in ORRF with severe SDB (AHI >30 events/hr)[198][199]. In addition, Masa et al demonstrated a significant improvement in PCO_2 with NIV versus CPAP or lifestyle advice in ORRF with severe OSA, demonstrating an additional improvement in HRQOL outcomes, spirometry and 6-minute walk test results[199]. NIV can provide superior control of hypoventilation compared to CPAP and newer auto-titrating modes may also provide additional benefits such as improved sleep quality and control of ventilation [169]. As a result, NIV could be considered as first line therapy in ORRF with significant respiratory failure, recent acute decompensation or as second line following poor response to CPAP. However, there is a lack of larger non-inferiority RCT evidence demonstrating NIV as a superior treatment for ORRF and further studies powered to assess both clinical and physiological outcomes are required.

Telemedicine delivers health care and health information to patients in remote locations to aid diagnosis, optimise patient management, facilitate data retrieval for research evaluation and education using modern digital infrastructure and multimedia platforms[84]–[86]. Tele-monitoring of CPAP therapy in OSAS patients has been shown to have a positive effect on treatment adherence and patient engagement[118]–[120]. Incorporating telemonitoring and automated messaging in CPAP management can improve treatment adherence and reduce time spent on patient education with an importance on positive framed messaging to optimise patient outcomes[121]–[123]. The use of videoconference (Vc) calls can enable health professionals to educate and assess therapy issues within the home setting and has been shown to be as effective as face-to-face training with equivalent CPAP therapy adherence[125], [126]. Whilst the use of internet based patient education alone or in combination with telemonitoring and

automated messaging can improve treatment adherence to CPAP therapy[111][124]. These studies highlight that a multi-faceted approach to telemedicine in chronic disease is required to optimise patient outcomes and realise service efficiencies.

Whilst there is an established research base for telemonitoring in OSAS patients, telemonitoring in home NIV remains a research priority. Previous studies have demonstrated no improvement in clinical outcomes with telemonitoring of peripheral oxygen saturations (SpO_2) in COPD patients and can increase hospitalisation[142]–[144]. A multi-faceted approach incorporating physiological parameters, symptom burden, telephone communication with patient education within telemonitoring improves clinical outcomes and healthcare usage in COPD patients[145].

Patout et al demonstrated low cognitive performance and independence during inpatient NIV set-up and at 6-week review in a range of respiratory diseases[152]. Additionally, COPD can negatively impact patient cognition and to a greater degree following an acute exacerbation[151]. However early recognition of those at risk of poor adherence to NIV can facilitate personalised PAP initiation and education to maximise therapy benefits[200]. This cognitive impairment in patients requiring NIV invalidates any direct comparisons of clinical outcomes in telemonitored NIV with CPAP therapy in OSAS.

Telemonitoring of home NIV provides reliable ventilation data for clinician review, facilitates early optimisation of ventilation, improves treatment adherence and decreases healthcare utilisation[154][158][201][202]. Remote data retrieval facilitates the identification of poor tolerance, mask leakage resulting in suboptimal ventilation and NIV dependence signifying disease severity[155]–[158]. Remote data retrieval and analysis has been shown to predict disease exacerbation and could facilitate the development of preventative predictive personalised management of chronic disease[160]–[162]. Whilst safe remote NIV titration has been shown to be as effective in control of hypoventilation and HRQOL outcomes in telemonitored home NIV in hypercapnic severe COPD, negating the need for prolonged inpatient polysomnography driven NIV titration. Continued prospective analysis of telemonitored NIV data, symptoms burden, health care utilisation

and physiological parameters are required to build a rich data set for analysis of predictors of disease exacerbations and incorporation of such into multi-media-based platforms to develop a personalised predictive model of chronic disease management and realise service efficiencies.

This study reviews the feasibility and clinical outcomes of remote monitored home NIV in chronic respiratory failure patients following the adaption of this new technology and development of clinical pathways within NHS GG&C.

3.2 Hypothesis

Two-way remote monitoring of home non-invasive ventilation provides effective therapy and allows treatment provision to patients with persistent hypercapnic failure due to severe COPD and obesity-related respiratory failure.

3.3 Methods

3.3.1 Study design

A retrospective review of an observational cohort of patients with severe COPD with persistent hypercapnic failure who were commenced on two-way remote monitored home NIV (cohort 1), patients who required acute NIV for hypercapnic failure secondary to an exacerbation of COPD but were not referred onward for long term breathing support (cohort 2) within the GSBSRC service from February 2017 to January 2018. A further retrospective review of observational data from patients with ORRF (cohort 3) within the GSBSRC service was reviewed in NHS Greater Glasgow and Clyde between July 2016 and January 2018. All patients were vetted via electronic notes detailed in Figure 2.4 in Chapter 2.

3.3.2 Ethics

This study was sponsored by NHS Greater Glasgow & Clyde with research ethics approval proved by London Queen Square Research Ethics Committee (REC reference 16/LO/2090).

3.3.3 Severe COPD with persistent hypercapnic failure

We analysed the data of 69 COPD patients treated with acute NIV for decompensated hypercapnic respiratory failure within Queen Elizabeth University Hospital NHS GG+C. There are 2 separate cohorts (Figure 3.1).

Cohort 1: Intervention

Retrospective review of 42 patients commenced on 2-way remote monitored NIV following an admission with a life-threatening exacerbation of COPD and hypercapnic failure between 1st February 2017 and 31st January 2018. Indication for home NIV in severe COPD was persistent hypercapnic failure with PCO_2 levels >7kPa or >6.5kPa with re-current admissions with life-threatening exacerbations requiring acute NIV. Patients were initiated on home NIV after 2-4 weeks of stable disease following acute NIV. Patients were initiated on home NIV during index admissions when recurrent life-threatening admissions requiring acute NIV resulted in 2-4 weeks disease stability preceding home NIV initiation as an unrealistic target. Remote monitored NIV was delivered via a Lumis 150 ventilator (Resmed, UK) (Figure 2.1). Settings included fixed Spontaneous Timed mode (ST), or volume assured pressure support (iVAPS) with auto-titrating EPAP. This cohort can be further divided into total cohort of 42 patients and sub-group analysis including 28 patients who continued long term domiciliary NIV and 14 patients where NIV was discontinued for various clinical reasons. Data from hospital admissions, occupied bed days, respiratory nurse visits and mortality were included.

Cohort 2: Control Arm

A retrospective audit of 27 patients who required acute NIV for hypercapnic respiratory failure as a result of an exacerbation of COPD between March- November 2017 at the QEUH. This cohort has been treated as the control arm in the review as they required acute NIV for hypercapnic respiratory failure but were not referred on for breathing support assessment and initiation of domiciliary NIV. These patients had acute hypercapnic failure but may not have persistent hypercapnia.

3.3.4 Obesity related respiratory failure

Cohort 3: Obesity related respiratory failure (ORRF)

43 patients were initiated on home NIV during an inpatient admission with decompensated cardio-respiratory failure, elective inpatient admission or as a day-case initiation at GSBSRC. Indications for home NIV in ORRF were BMI> 35kg/m^2, persistent hypercapnia (PCO_2 >6kPa), evidence of sleep disordered breathing- where feasible full or limited polysomnography was performed. Inpatient initiation was considered where obesity related physical restrictions or place of residence precluded them from day-case initiation. All inpatients had continuous Transcutaneous Carbon Dioxide and Oxygen Assessment (TOSCA, TCM5, Radiometer, England) during the initiation night and on consolidation nights of home-NIV. Elective inpatient assessment is detailed in Figure 2.6 in Chapter 2. All inpatients were initiated on volume assured pressure support with auto titrating EPAP (iVAPS) on Lumis 150 devices (Lumis, Resmed, UK) (Figure 2.1). Day case initiation of home NIV was provided for patients with ORRF and stable hypercapnic failure as detailed in Chapter 2.

3.3.5 Data retrieval

All patients consented to their data being accessed and shared on Airview™ platform (Airview, RESMED, UK) by health professionals (Appendix 1). All patients were followed up via remote tele-consultation to optimise home NIV as detailed in Figure 2.5 in Chapter 2. Tele-consultation and remote access to ventilatory support data allowed individualised follow up including remote prescription change, interface changes, day case trouble shooting sessions or clinic reviews. Remote requirements data was collected from the Airview™ platform.

3.3.6 Outcome measures

Baseline data were recorded including gender, age, BMI, polysomnography (full or limited 5 channel) and lung function if available. Primary outcome in all cohorts was time to readmission or death, censored at date of admission, date of death or 28/7/2020. Secondary outcomes included time to re-admission, survival, number of hospital admissions, occupied bed days (OBDs), serial blood gas analysis, adherence to NIV therapy, remote NIV service requirements and allied health professional reviews. Target

adherence was ≥70% days with usage ≥4hours; the levels set for reimbursement in the US health system. Patients adherence to therapy are referred to as “users” and those failing to meet the target usage are known as “non-users” in these results. All data is presented as totals for cohort 1 and 2 with sub-group analysis for patients’ adherent and non-adherent to home NIV therapy in cohort 1. Data availability was limited in all cohorts with some historical data used (spirometry) in this retrospective review.

3.3.7 Statistical analysis

Baseline characteristics are presented as mean (standard deviation), median (interquartile range), absolute values or percentages where appropriate.

Primary outcomes and secondary outcomes are presented as Kaplan-Meier survival analysis and the Mantel-Cox log rank test for cohorts where appropriate.

Subgroup analysis compared those adherent with NIV therapy(“users”) and non-adherent patients (“non-users”) using Kaplan-Meier and Mantel-Cox tests. Normal distribution was tested using Shapiro-Wilk test. Wilcoxon signed-rank test was used for hospital admissions, OBDs, AHP input and control of hypoventilation. COPD data analysis was carried in IBM SPSS as part of a collaboration with the University of Glasgow and MSc Stratified Medicine project. Analysis was conducted using IBM SPSS Statistics V.24 (IBM, New York, USA) and Prism (GraphPad Software, San Diego, USA).

3.4 Results

3.4.1 Population demographics

Hypercapnic severe COPD

42 patient datasets representing patients commenced on two-way remote monitored home NIV and 27 patients were in the control cohort as shown in Table 3.1. Sex, BMI, and age are similar across both cohorts except for a higher rate of males and a lower rate of comorbidities (suspected or confirmed overlapping OSA, long term opiate therapy) in the NIV non-users' sub-group. The FEV1% predicted value was around 40% across both study groups, in line with a "severe" classification of COPD[183] considering spirometry data was historical rather than a contemporary result. There was a higher proportion of males to females in both cohort 1 and cohort 2. Mean age was 64.5 years with no age differences between the cohorts. BMI was higher in users of home NIV therapy compared to non-users. Comorbidities which could potentially contribute to hypercapnic respiratory failure were present in 14/42 (38%) of the home NIV cohort patients, including 10/14 patients with suspected or confirmed COPD-OSA overlap syndrome.

Obesity related respiratory failure

43 patient datasets representing ORRF initiated on two-way remote home NIV initiation with cohort demographics seen in Table 3.2. Mean age and sex was similar in this cohort and in sub-group analysis. Severe obesity was demonstrated with mean BMI of 49.9 kg/m^2. Sub-group analysis showed users of home NIV had a higher mean BMI, higher AHI, ODI and lower TST90 than non-users. Symptom burden measured by the Epworth Sleepiness Scale (ESS) was moderate and similar throughout sub-group analysis. Median CO_2 was 8.3 kPa and bicarbonate was 37mmol/L on initiation of home NIV in all ORRF patients. However, sub-group analysis of CO_2 and bicarbonate showed no difference in users versus non-users.

3.4.2 Primary outcome

Hypercapnic severe COPD

Time to re-admission or death was significantly prolonged in patients with persisting hypercapnic failure who commenced home NIV compared to the control cohort of COPD patients who had had an episode of acute hypercapnic respiratory failure but had not been referred for breathing support follow up ($p<0.01$) (Figure 3.2A). The median time to admission or death was 160 days (95% CI 69.4-250.6) in the home NIV cohort compared to 66 days (95% CI 21.9-84.7) in the control cohort. Subgroup analysis (Table 3.3) showed significant differences between the sub-cohort of home NIV users versus non-users (who discontinued home NIV) and the control cohort, both $p<0.001$ (Figure 3.2B). There was no significant difference between the control cohort and in non-users sub-group analysis($p=0.5$). Table 3.3 summarises time to admission or death, survival, and admission events in each group.

Obesity related respiratory failure

Time to re-admission or death analysis over the available follow-up period demonstrated a non-significant trend to poorer outcome in non-users in comparison to users of home NIV therapy (Figure 3.3) The median admission free survival could not be calculated as low event rates and good survival outcome resulted in data acquisition not passing the 50% probability of survival level.

3.4.3 Secondary Outcomes

3.4.3.1 Overall Survival

Hypercapnic severe COPD

Overall survival showed a non-significant trend to an improved survival in the home NIV cohort compared to the control cohort ($p=0.066$) (Figure 3.4Ai). Sub-group analysis demonstrated improved survival in NIV users versus non-users ($p=0.07$) (Figure 3.4Aii). Survival data did not pass 50% probability of survival level.

Obesity related respiratory failure

Sub-group analysis demonstrated a non-significant trend to improved survival in NIV users compared to the total study population and NIV non-users (Figure 3.5). Survival data did not pass 50% probability of survival level.

3.4.3.2 Time to hospital re-admission

Hypercapnic severe COPD

Time to hospital admission was significantly prolonged in the home NIV cohort compared to the control cohort ($p<0.05$) (Figure 3.4Bi). Sub-group analysis demonstrated a prolonged time to hospital admission in home NIV users compared to non-users and the control cohort (both $p <0.001$) (Figure 3.4ii). There was no significant difference between the control cohort and home NIV non-users ($p=0.38$). Median time to hospital admission for users was 390 days versus 49 days in non-users and 70 days in the control cohort. (Table 3.3)

Obesity related respiratory failure

Sub-group analysis demonstrated a non-significant trend to prolonged time to hospital admission in NIV users versus NIV non-users (Figure 3.6). Time to hospital admission data did not pass 50% probability level to calculate median values.

3.4.3.3 Healthcare usage

Hypercapnic severe COPD

Healthcare usage for 12months prior to and 12 months after the initiation of home NIV in hypercapnic severe COPD patients and sub-group analysis are presented in Table 3.4. Hospital admissions was significantly decreased in the 12 months following the initiation of home NIV in the analysis of cohort 1 (total) and in sub-group analysis of NIV users ($p<0.05$ both) (Figure 3.7A). The number of occupied bed days (OBDs) significantly decreased in the 12 months following home NIV initiation ($p<0.05$) (Figure 3.7B). Sub-group analysis demonstrated a non-significant reduction in OBDs in NIV users and NIV non-users, $p=0.05$ and $p=0.059$, respectively. Clinical review from a respiratory specialist

nurse or allied health professional (AHP) showed no significant change following NIV initiation (figure 3.7C).

Obesity related respiratory failure

Healthcare usage 12months prior to and 12months after the initiation of home NIV in patients with ORRF are presented in Table 3.5. The number of hospital admissions significantly decreased in the 12 months following the initiation of home NIV in the analysis of cohort 3 and in sub-group analysis of NIV users ($p< 0.05$ both) (Figure 3.8A). The number of occupied bed days significantly decreased following home NIV initiation and in sub-group analysis of NIV users ($p<0.05$ both) (Figure 3.8B).

3.4.3.4 Control of hypercapnic respiratory failure

Hypercapnic severe COPD

Follow up capillary blood gas measurements were only available in 13/42 patients. There was a significant reduction in PCO_2 and bicarbonate levels in home NIV users ($p<0.05$ both), with a modest non-significant reduction in home NIV non-users (Figure 3.9).

Obesity related respiratory failure

Follow up capillary bloods gas measurements were available in 31/43 patients. There was a significant reduction in PCO_2 and bicarbonate levels in home NIV users ($p<0.05$ both), with a non-significant reduction in home NIV non-users. (Figure 3.10)

3.4.3.5 Remote management of home Non-invasive ventilation

Hypercapnic severe COPD

All patients were initiated on average volume assured pressure support mode (iVAPS) with adaptive back up rate (iBR). 9 patients switched to spontaneous timed (ST) mode following data trends either on remote monitoring or during initiation. A low-pressure support requirement was demonstrated; median IPAP of 14 cmsH2O (95% CI 11-17.3 cmsH2O) and median EPAP of 4.9 cmsH2O (95% CI 4-8 cmsH2O) with lowest pressure support observed in non-users, as detailed in Table 3.6. Median back up rate was 18 breaths/min (95% CI 17-20 breaths/min). Requirements for remote management of

home NIV in this cohort are detailed in Table 3.7 and Figure 3.11. Following initiation of remote monitored home NIV a severe COPD patient would typically require 7 data reviews, 2 telephone consultations and 1 prescription change. A minority of patients required follow up day-case reviews or AHP input.

Obesity related respiratory failure

All patients were initiated on average volume assured pressure support mode (iVAPS) with adaptive back up rate (iBR). 4 patients switched to ST mode following data trends either on remote monitoring or during initiation. A low-pressure support requirement was demonstrated; median IPAP of 15.9 cmsH20 (95% CI 12.9- 18.6cmsH2O) and median EPAP of 9 cmsH20 (95% CI 6.3-10.4cmsH2O) with lowest pressure support requirements observed in non-users, as detailed in Table 3.8. Median back up rate was 18 breaths/min (95% CI 16-21 breaths/min). Requirements for remote management of home NIV in this cohort are detailed in Table 3.8 and Figure 3.12. Following the initiation of remote monitored home NIV a patient with ORRF would typically require 4 data reviews, 2 telephone consultations and 1 prescription change. A minority of patients required follow up as day-case reviews or with AHPs.

3.4.3.6 Inpatient versus day-case home NIV initiation

Hypercapnic severe COPD

27/42 patients were initiated on remote monitored home NIV during an inpatient admission following a life-threatening exacerbation of COPD. 2/42 patients were admitted electively for initiation due to travel restrictions preventing day case set-up. 6/42 patient were started on home NIV at a linked district general hospital utilising remote monitoring to avoid inpatient transfer to our tertiary inpatient service. Age and other demographics were similar between these sub-groups. (Table 3.9) There were no differences observed in adherence to home NIV, remote monitoring service requirements or outcomes observed in sub-groups analysis of day-case versus inpatient initiations (Table 3.9 & Figure 3.12). Similarly, sub-group analysis did not demonstrate significant differences in time to re-admission or death and overall survival (Figure 3.13). Small sample size is likely responsible for some non-significant data heterogeneities with the elective and regional inpatients home NIV patients.

Obesity related respiratory failure

24/43 patients were initiated on home NIV during their index admission, of which 5 patients were started on home NIV at a linked district general hospital and 4 patients during an elective admission. Age and other demographics were similar in sub-group analysis of this cohort. (Table 3.10) Adherence to home NIV was highest in those patients initiated on home NIV whilst as an inpatient either in the local or regional hospitals with a lower adherence to therapy observed in patients who had home NIV started as a day-case (56%). Whilst remote monitored service requirements were similar throughout the sub-groups. (Table 3.10) Sub-group analysis did not demonstrate significant differences in time to re-admission or death or overall survival. (Figure 3.14)

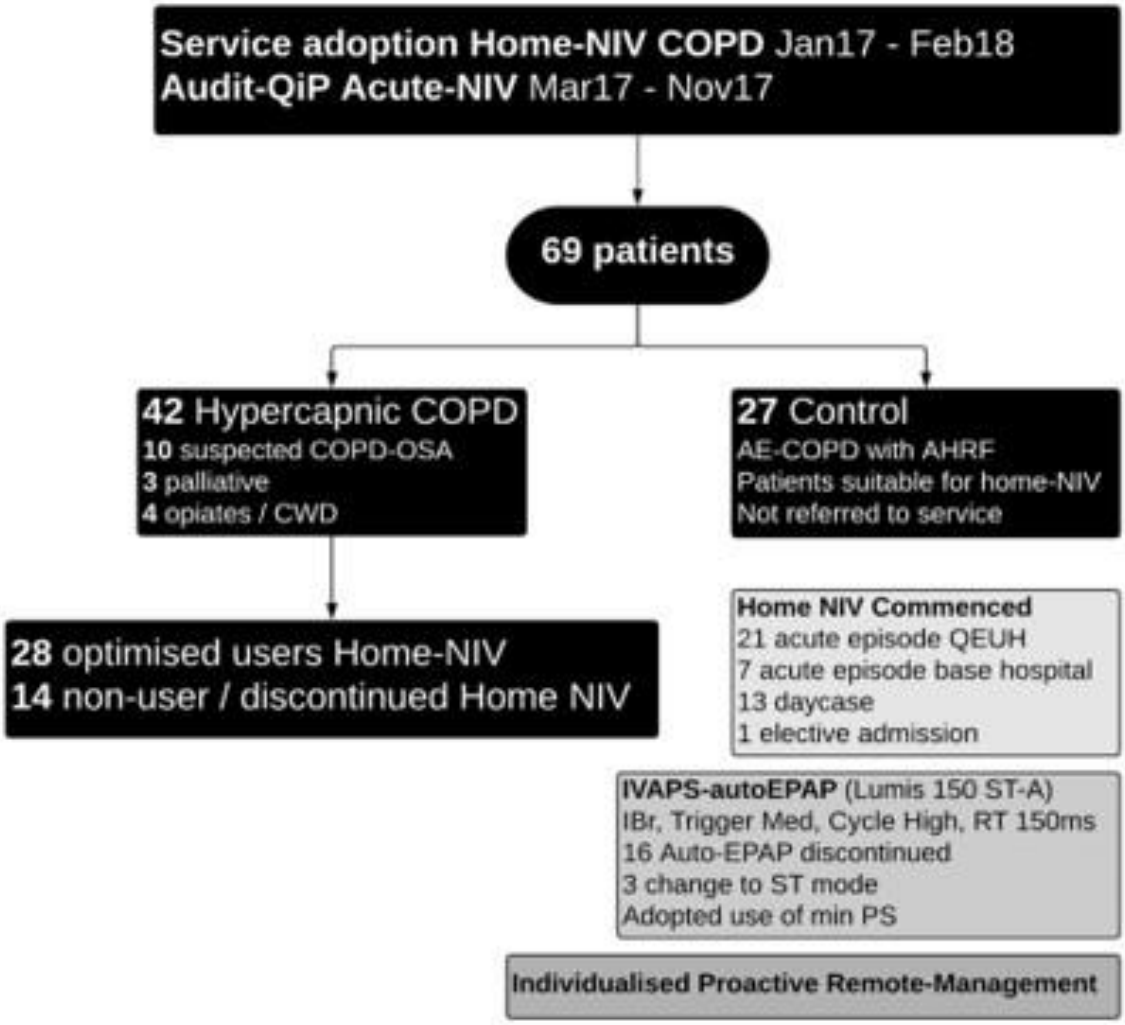


Figure 3-1 Service adoption of remote monitored home non-invasive ventilation (NIV) in NHS Greater Glasgow and Clyde and study summary of a retrospective review of patients with hypercapnic severe chronic obstructive pulmonary disease initiated on NIV

NIV- non-invasive ventilation, Audit-QIP- audit quality improvement project, COPD-OSA- chronic obstructive pulmonary disease- obstructive sleep apnoea overlap syndrome, AE-COPD- acute exacerbation of COPD, AHRF- acute hypercapnic respiratory failure, IVAPS-autoEPAP- auto-titrating volume assured pressure support with auto-titrating expiratory positive airway pressure, iBR- intelligent back up rate, ST- spontaneous timed, PS- pressure support.

	All patients		Home NIV						Control	
			Total		Users		Non-users			
		n		n		n		n		n
Gender	49M 20F	69	30M 12F	42	17M 11F	28	13M 1F	14	19M 8F	27
Mean age (SD)	64.55 (8.74)	69	63.31 (8.58)	42	62.54 (8.75)	28	64.86 (8.31)	14	66.48 (8.8)	27
Mean BMI (SD)	27.6 (9.09)	53	29.23 (10.71)	26	32.23 (10.63)	16	21.41 (9.42)	10	26.02 (7.06)	27
Mean FEV1% predicted (SD)	40.63 (16.63)	52	40.19 (15.45)	31	39.63 (16.28)	19	41.08 (14.7)	12	41.29 (18.61)	21
Comorbidity contributing to hypercapnian (%)			14 (38%)		11 (44%)		3 (21%)			

Table 3-1 Population demographics for patients admitted with a severe life-threatening exacerbation of COPD and hypercapnic failure.

This table represents those commenced on two-way remote monitored home NIV (home NIV) with sub-group analysis demonstrating adherence to treatment and those who were not referred for consideration of home NIV following acute NIV (control cohort). M-male, F-female, SD-standard deviation, BMI- body mass index, FEV1%- percentage predicted of forced expiratory volume in 1 second.

	Home NIV					
	Total		Users		Non-users	
		n		n		n
Gender	22 M 21F	43	16M 17F	33	6M 4F	10
Mean age (SD)	57 (13)	43	57 (13)	33	53.9(11.1)	10
Mean BMI (SD)	49.9 (11.5)	41	50 (11.5)	30	42.4(8.4)	9
Mean FEV1% predicted (SD)	64(21)	12	64(21)	10	80.5(6.4)	2
Mean FVC % predicted (SD)	68 (20)	12	68 (20)	10	80.5(5)	2
Mean FEV1/FVC % (SD)	87 (9)	12	87 (9)	10	96.5(14.8)	2
AHI	40 (31)	23	40 (31)	16	22.9(23.7)	7
ODI	40 (27)	23	40(27)	16	28.2(26)	7
Mean oxygen saturations % (SD)	85 (6)	21	85 (6)	15	84(5.6)	6
Mean TST90 % (SD)	63 (35)	21	63 (20)	13	74.7(34)	6
Mean ESS (SD)	15 (3)	9	15 (3)	5	14(4)	4
Median CO2 kPA (IQR)	8.4 (3)	37	7.6 (6.6- 10.3)	30	7.2(6.1-8.1)	8
Median HCO mmol/L (IQR)	37 (8)	37	36(29-41)	30	35(29-39)	8

Table 3-2 Population demographics for patients with Obesity related respiratory failure.

Patients treated with remote-monitored home NIV (home NIV) with sub-group analysis of those adherent to NIV (users) and those failing to meet targets as >4hours usage >70% of nights used (non-users). M-male, F-female, SD- standard deviation, IQR- interquartile range, BMI- body mass index, FEV1%- percentage predicted of forced expiratory volume in 1 second, FEV1/FVC- ratio of forced expiratory volume in 1 second to forced vital capacity, AHI- apnoea hypopnea index (events per hour), ODI- 4% oxygen desaturation index (events per hour), TST90-= percentage of total sleep time with oxygen saturations <90%, ESS- Epworth sleepiness scale, CO_2- carbon dioxide, HCO_3- bicarbonate.

	All patients	Home NIV			Control
		Total	**users**	**Non-users**	
Median study follow-up days (IQR)	323(260)	319 (213)	319 (229)	320 (323)	323 (382)
Median admission free survival, days (95% CI)	92 (25.71-158.32)	160(69.38-250.63)	390 (108.96-671.05)	47 (19.5-74.5)	66 (21.9-110.1)
Median time to hospital readmission, days (95% CI)	101 (0.69-201.32)	221 (47.77-394.23)	390	47 (18.95-75.02)	70 (55.31-84.69)
Admission events (%)	50 (72.5)	27 (64.3)	14 (50)	13 (92.9)	23 (85.2)
Hospital Re-admission Events (%)	42(67.7)	22 (59.5)	12 (46.2)	10 (90.0)	20 (80)
Mortality events (%)	20 (29)	9 (21.4)	4 (14.3)	5 (35.7)	11 (40.7)

Table 3-3 Primary and secondary outcomes in patients with hypercapnic severe chronic obstructive pulmonary disease who were commenced on two-way remote monitored home non-invasive ventilation (Home NIV) vs controls

Control- patients with hypercapnic severe chronic obstructive pulmonary disease who recently required acute NIV for a life-threatening exacerbation but were not referred on for consideration of home ventilation assessment.

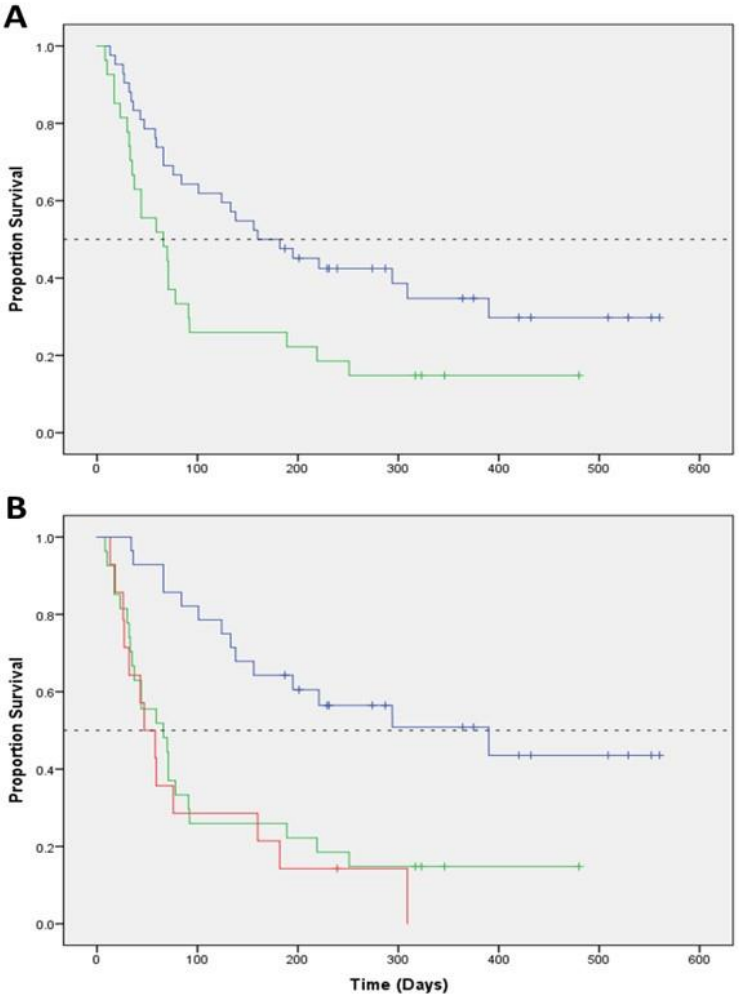


Figure 3-2 Kaplan-Meier analysis of time to re-admission or death in severe COPD patients initiated on home non-invasive ventilation (NIV)and vs control cohort

A- Time to re-admission or death in patients managed with remote monitored home NIV (blue) versus control cohort (green). B-Sub-group analysis of time to re-admission or death demonstrating those adherent to home NIV (users(blue)), those non-adherent or discontinued(non-users(red)) on home NIV compared to the control cohort (green). Control - hypercapnic severe COPD patients who survived recent life-threatening exacerbation but not referred on for home ventilation assessment.

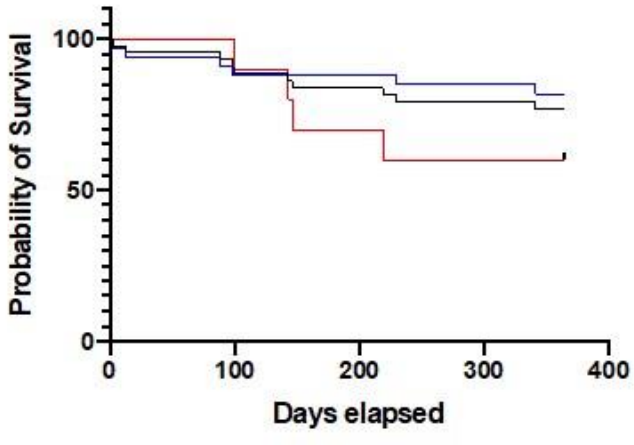


Figure 3-3 Kaplan-Meier analysis for time to re-admission or death in patients with obesity related respiratory failure initiated on home non-invasive ventilation:

Presented as total (black) and sub-group analysis time to admission or death in those adherent to home NIV (>70% nights used >4hours) (“users” (blue)) and patients failing to meet set adherence targets (‘non-users” (red)).

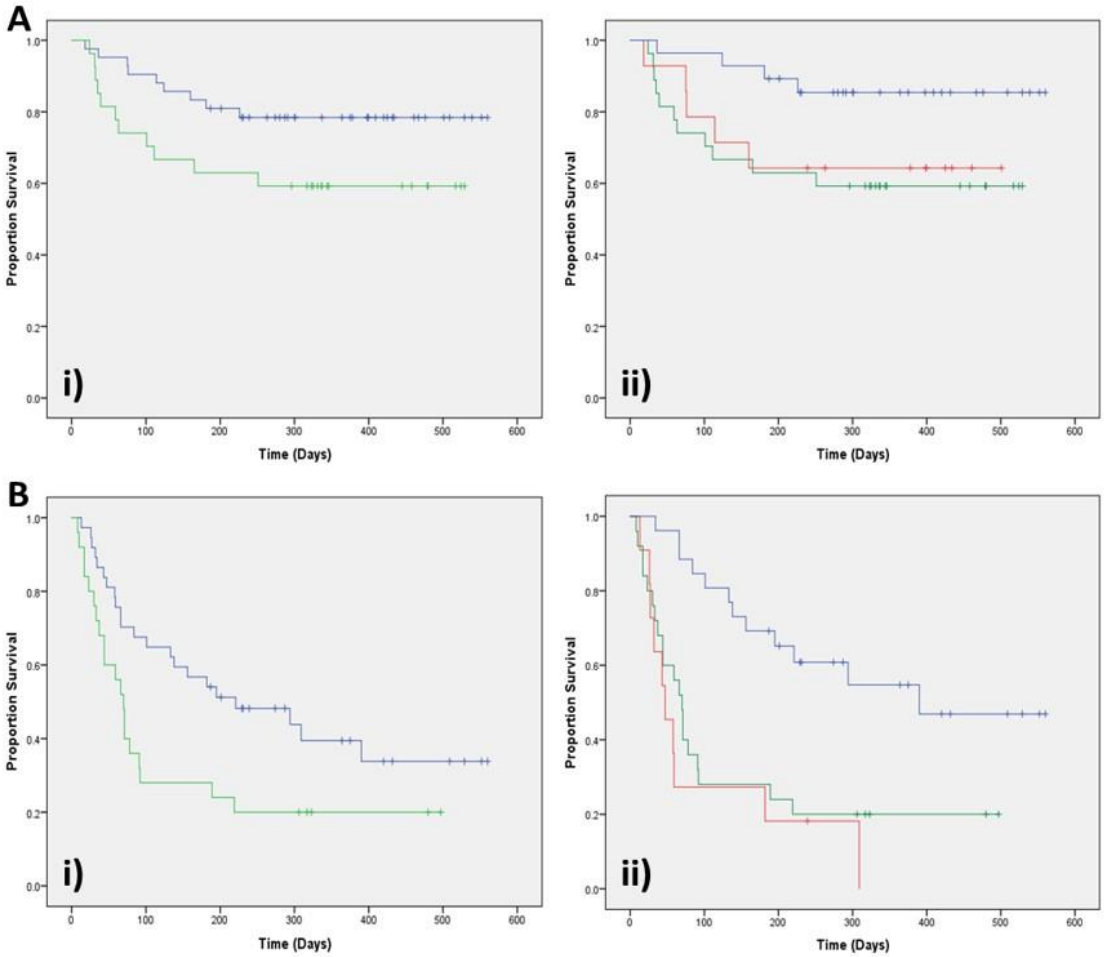


Figure 3-4 Kaplan-Meier analysis of overall survival and time to re-admission of patients with hypercapnic severe COPD initiated on remote monitored home non-invasive ventilation vs control cohort.

Ai- Kaplan-Meier analysis for overall survival in hypercapnic severe COPD patients initiated on remote monitored home non-invasive ventilation (NIV)(blue) and hypercapnic severe COPD who survived recent life-threatening exacerbation but not referred on for home ventilation assessment (control cohort) (green). **Aii**- Sub-group Kaplan-Meier analysis for overall survival in hypercapnic severe COPD patients in those adherent to home NIV (>70% nights used >4hours) ("users" (blue)), patients failing to meet set adherence targets ('non-users" (red)) and control cohort (green). **Bi**- Kaplan-Meier analysis of time to re-admission in hypercapnic severe COPD patients on remote monitored home NIV (blue) and control cohort(green). **Bii**- Sub-group Kaplan-Meier analysis of time to re-admission in those adherents to home NIV (users(blue)), those non-adherent or discontinued(non-users(red)) on home NIV compared to the control cohort (green).

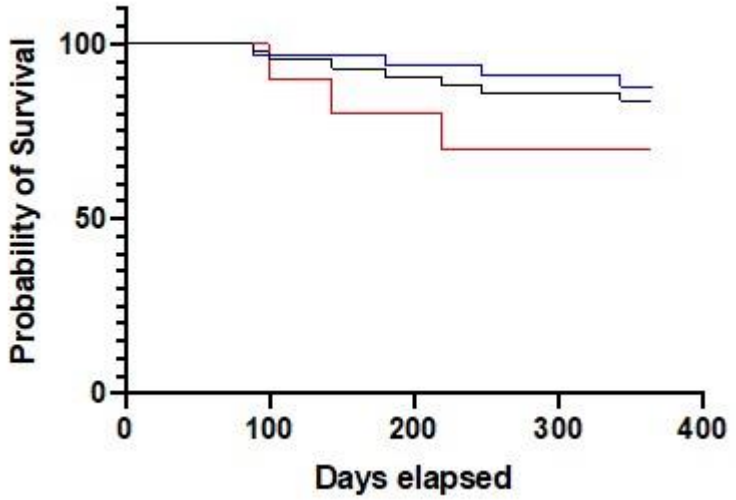


Figure 3-5 Kaplan-Meier analysis of overall survival in patients with obesity related respiratory failure initiated on home NIV

Presented as total cohort (black) and sub-group analysis of overall survival in those adherent to home NIV (>70% nights used >4hours) ("users" (blue)) and patients failing to meet set adherence targets ('non-users" (red)).

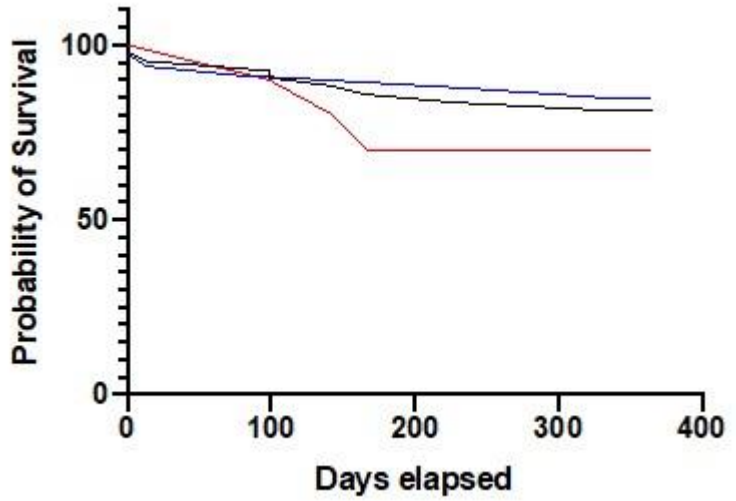


Figure 3-6 Kaplan-Meier analysis of time to re-admission in patients with obesity related respiratory failure initiated on home NIV

Presented as total cohort (black) and sub-group analysis of time to re-admission in those adherent to home NIV (>70% nights used >4hours) ("users" (blue)) and patients failing to meet set adherence targets ('non-users" (red)).

	Total		Users		Non-users	
	12 months pre NIV	12 months post-NIV	12 months pre NIV	12 months post-NIV	12 months pre NIV	12 months post-NIV
Hospital admissions (IQR)	1.5 (1-4)	1 (0-2)	1 (1-3)	0 (0-2)	3 (1-7)	2 (0-3.50)
Occupied bed days (IQR)	15 (3-32)	3 (0-21)	13.5 (6.75-26.75)	0 (0-16.25)	19 (1.5-4.2)	9 (0-21.5)
AHP reviews (IQR)	2 (1-4)	1 (0-3)	2 (0-5)	1 (0-3)	2 (1.75-4.25)	2 (0.3-3.75)

Table 3-4 Healthcare usage prior to and after the initiation of two-way remote monitored home non-invasive (NIV) in patients with hypercapnic severe COPD.

All data expressed as median and interquartile range (IQR). AHP- allied health professional.

	Total		Users		Non-users	
	12 months pre NIV	12 months post-NIV	12 months pre NIV	12 months post-NIV	12 months pre NIV	12 months post-NIV
Hospital admissions (IQR)	1 (0-1)	0(0)	1(1)	0(0)	0.5(0-2)	0(0)
Occupied bed days (IQR)	10(0-36)	0(0)	13(2-32)	0(0)	1.5(0-48)	0(0-0.5)

Table 3-5 Healthcare usage prior to and after the initiation of two-way remote monitored home NIV in patients with obesity related respiratory failure.

All data expressed as median and interquartile ranges (IQR)

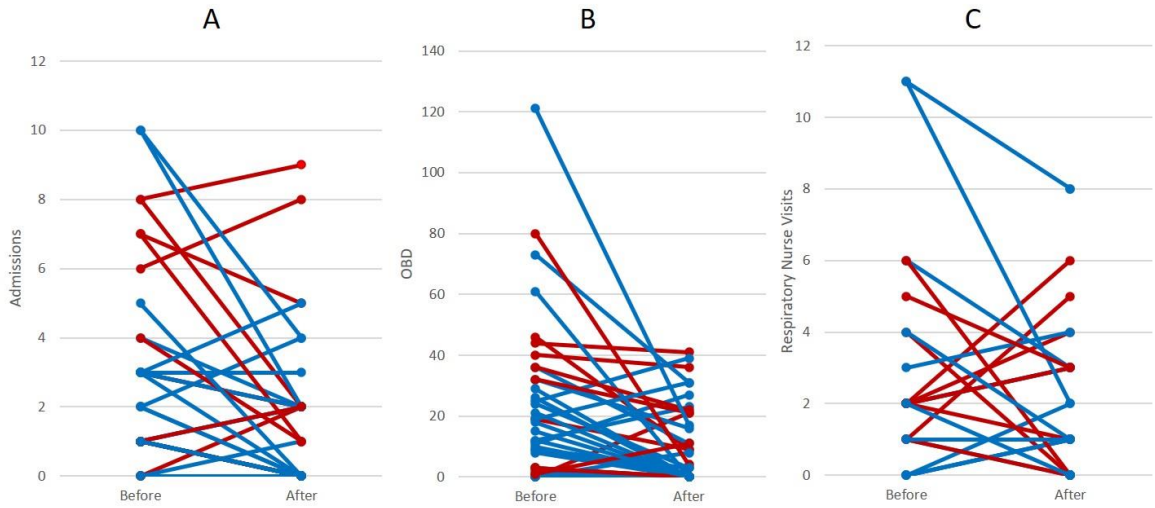


Figure 3-7 Healthcare usage prior to and after the initiation of remote monitored home non-invasive ventilation in patients with hypercapnic severe COPD.

Data presented as those adherent to therapy (>4hours use for >70% nights used) (blue) and those non-adherent to NIV (red). A-The individual number of hospital admissions per patient. B-Number of occupied bed days per patient (OBDs). C- Number of respiratory nurse home visits per patient.

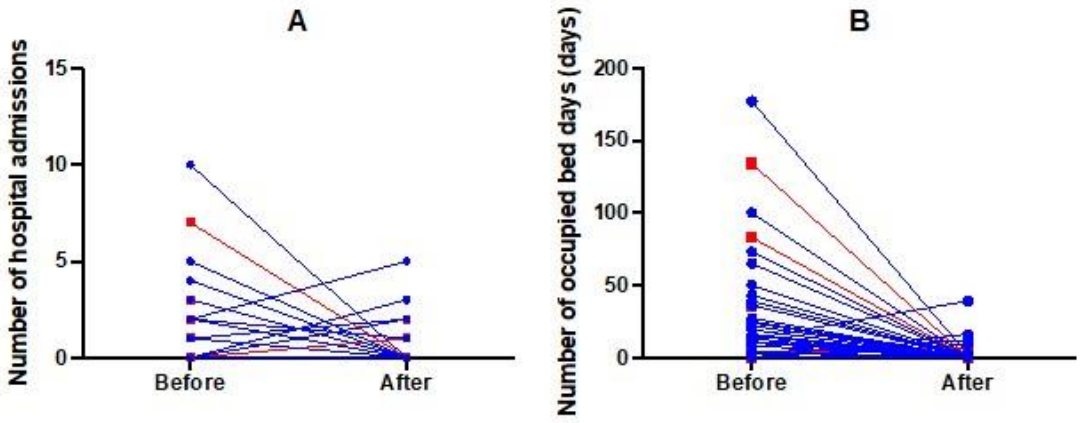


Figure 3-8 Healthcare usage prior to and after the initiation of remote monitored home non-invasive ventilation in patients with obesity related respiratory failure.

Data presented as those adherent to therapy (>4hours use for >70% nights used) (blue) and those non-adherent to NIV (red). A-The individual number of hospital admissions per patient. B-Number of occupied bed days per patient (OBDs).

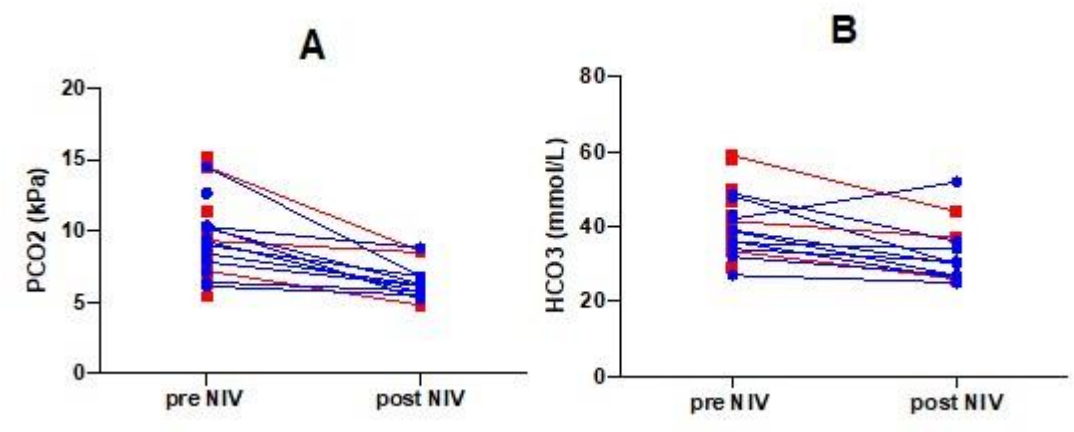


Figure 3-9 Serial blood gases measurements in patients with hypercapnic severe chronic obstructive pulmonary disease prior to and after initiation on remote monitored home non-invasive ventilation.

Data presented as those adherent to therapy (>4hours use for >70% nights used) (blue) and those non-adherent to NIV (red). A- Serial Carbon Dioxide (CO_2) measured in kilopascals (kPa). B- Serial bicarbonate (HCO_3) levels measured in millimoles per litre (mmol/L)

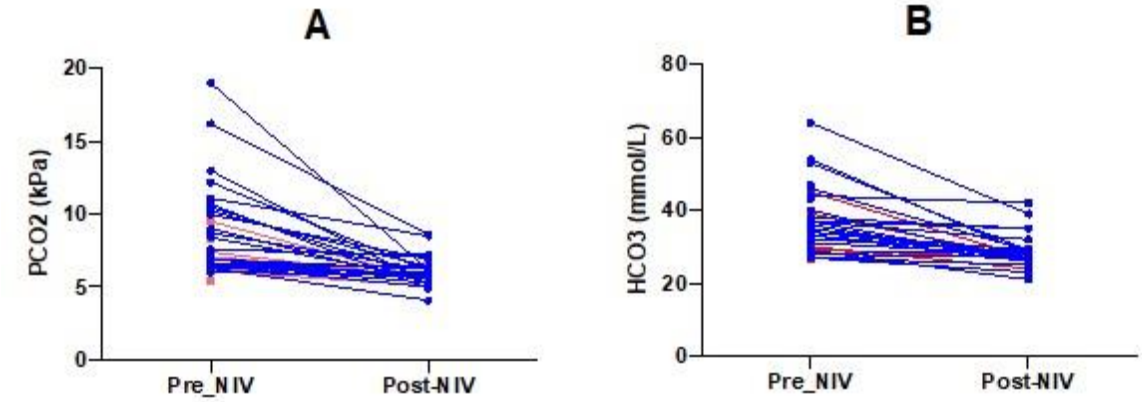


Figure 3-10 Serial blood gases measurements in patients with obesity related respiratory failure prior to and after initiation on remote monitored home non-invasive ventilation.

Data presented as those adherent to therapy (>4hours use for >70% nights used) (blue) and those non-adherent to NIV (red). A- Serial Carbon Dioxide (CO_2) measured in kilopascals (kPa). B- Serial bicarbonate (HCO_3) levels measured in millimoles per liter (mmol/L)

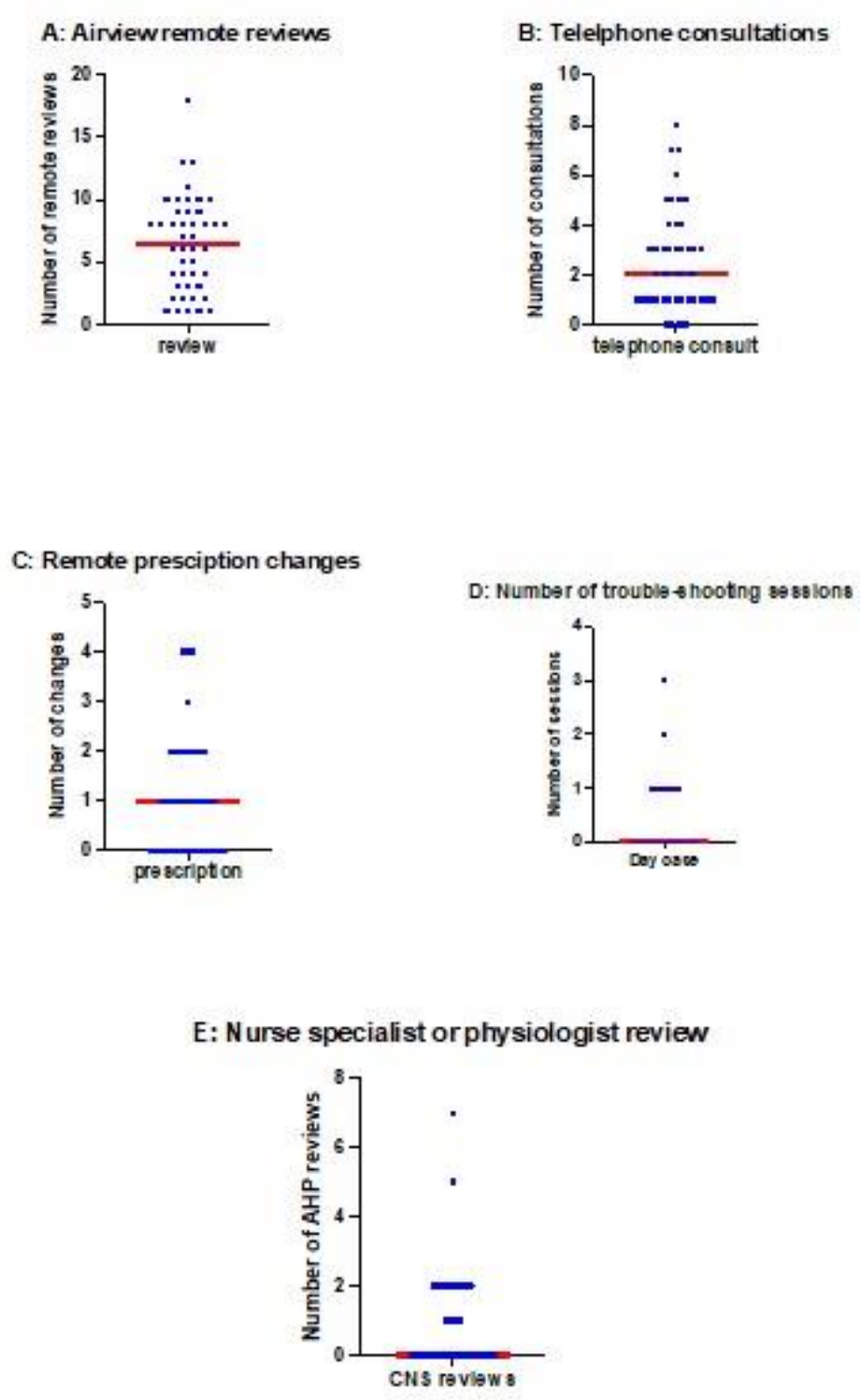


Figure 3-11 : Service requirements for remote management of home NIV in patients with hypercapnic severe COPD

A- Number of data reviews. B- Number of telephone consultations. C- Number of remote prescription changes. D- Number of day-case trouble shooting sessions. E- Number of nurse specialist or physiologist reviews. Median requirements highlighted (red line).

	Total	Users	Non-users
Median IPAP (IQR)	14 (11-17.3)	15.4(13.3-17.7)	11.2(7.9-15.3)
Median EPAP (IQR)	4.9 (4-8)	5.9(4-8.4)	4(4-5.8)
Median back up rate (IQR)	18 (17-20)	18(17-20)	18(17-20)
Median usage (hours) (IQR)	5.8 (2.5-7.3)	6.7(6-9.2)	2(0-3.2)

Table 3-6 Pressure support requirements with adaptive mode (iVAPS) ventilation in severe COPD with persistent hypercapnic failure.

Data presented as total group analysis and sub-group analysis patients in those adherent to home NIV (>70% nights used >4hours) ("users") and patients failing to meet set adherence targets ('non-users"). All pressures measured in centimetres of water ($cmsH_2O$) and back up rate measured in breaths/min. All presented as median and interquartile ranges (IQR). IPAP- inspiratory positive airway pressure, EPAP- expiratory positive airway pressure.

	COPD	ORRF
NIV data review (IQR)	7(3-9)	4 (3-4)
Telephone consultations (IQR)	2(1-4)	2(1-3)
Remote prescription changes (IQR)	1(0-2)	1(0-2)
Day case troubleshooting (IQR)	0(0-1)	0(0-1)
AHP reviews (IQR)	0(0-2)	0(0-1)

Table 3-7 Requirements for remote management of home non-invasive ventilation (NIV) in patients with hypercapnic severe COPD and obesity related respiratory failure

AHP- including allied health professionals such as specialist nurse or physiologist reviews. Expressed as median and interquartile ranges.

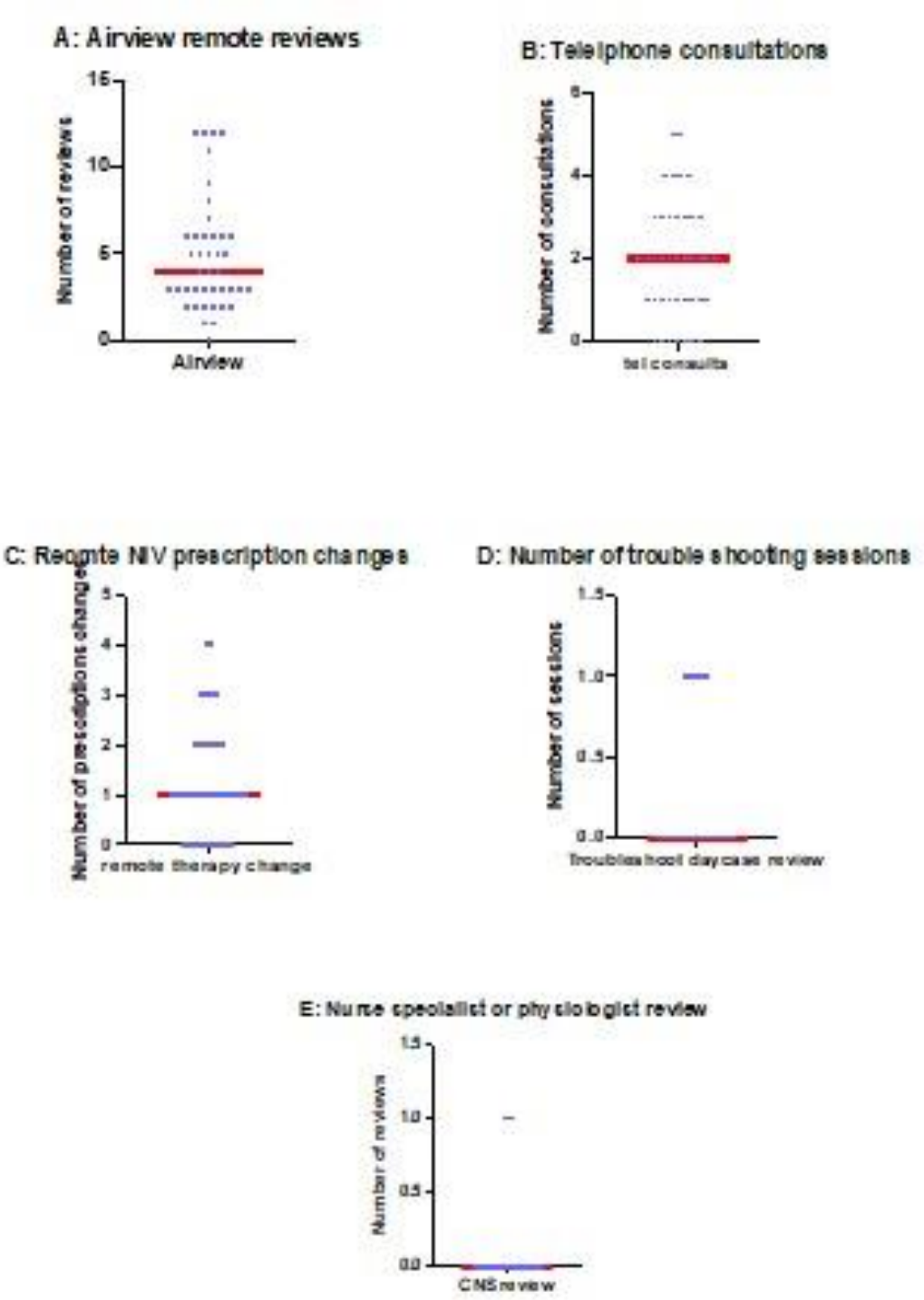


Figure 3-12 Service requirements for remote management of home non-invasive ventilation (NIV) for patients with obesity related respiratory failure

A- Number of data reviews. B- Number of telephone consultations. C- Number of remote prescription changes. D- Number of day case trouble shooting sessions. E- Number of nurse specialist or physiologist reviews. Median requirements highlighted (red line).

	Total	Users	Non-users
Median IPAP (IQR)	15.9(12.9-18.6)	16.7(13.3-19)	13(8.7-16.4)
Median EPAP (IQR)	9(6.3-10.4)	9.1(6.4-10.2)	8.5(6-11)
Median back up rate (IQR)	18(16-21)	18(16-22)	18(15-21)
Median usage (hours) (IQR)	5.7 (4.7-7)	5.9(5-7.2)	2.5(2-5)

Table 3-8 Pressure support requirements with adaptive mode (iVAPS) ventilation in patients with obesity related respiratory failure

Data presented as total group analysis and sub-group analysis of those adherent to home NIV (>70% nights used >4hours) ("users") and patients failing to meet set adherence targets ('non-users"). All pressures measured in centimetres of water ($cmsH_2O$) and back up rate measured in breaths/min. All presented as median and interquartile ranges (IQR). IPAP- inspiratory positive airway pressure, EPAP- expiratory positive airway pressure.

	Day-case	IP emergency	IP elective	Regional
Number of patients	12	21	2	6
Mean Age (SD)	62.9 (9.5)	62.4 (9.5)	62.5(3.5)	59.3(9.6)
Home NIV adherence (no. of patients)	5	9	0	3
Number of patients discontinued NIV	6	7	1	3
Median Airview reviews (IQR)	**6(3-8)**	**8(3-9)**	**7(6-7)**	**9(6-11)**
Telephone consultations	**4(2-5)**	**1(1-3)**	**4(1-6)**	**3(1-4)**
Prescription changes	**1(0-1)**	**1(0-2)**	**2(0-4)**	**1(1-1)**
Day case trouble shooting	**1(0-1)**	**0(0-2)**	**0(0)**	**0(0)**
AHP review	**0(0-1)**	**1(0-2)**	**1(0-2)**	**0(0-2)**
Median Time to re-admission or death (IQR) (days)	**131(31-365)**	**134(30-365)**	**96(34-158)**	**72(34-365)**
Median admission free days (IQR) (days)	**147(31-365)**	**85(27-365)**	**200(34-365)**	**52(30-74)**
Median survival (IQR) (days)	**365(330-365)**	**365(365)**	**262(158-365)**	**273(66-365)**

Table 3-9 Population demographics, remote requirements, and clinical outcomes of patients with hypercapnic severe COPD initiated on home non-invasive ventilation- inpatient versus outpatient initiation.

Treatment adherence (>70% of nights used for >4hours). NIV- non-invasive ventilation, IP-inpatient admission, AHP- allied health professionals, regional- regional hospital admission

	Day case	IP emergency	IP elective	Regional
Number	19	15	4	5
Mean Age (SD)	58(12)	56(14)	53(11)	54(12)
Home NIV adherence (no. of patients)	11	14	4	4
Number of patients discontinued NIV	3	1	0	1
Median Airview reviews (IQR)	**5(3-8)**	**3(2-5)**	**4(3-9)**	**5(3-6)**
Telephone consultations	**2(2-4)**	**2(0-3)**	**3(1-4)**	**1(1-2)**
Prescription changes	**1(1-2)**	**1(0-1)**	**2(1-3)**	**1(0-2)**
Day case trouble shooting	**0(0)**	**0(0)**	**0(0)**	**0(0)**
AHP review	**0(0)**	**0(0)**	**0(0)**	**0(0)**
Median Time to re-admission or death (IQR) (days)	**915 (166-1167)**	**965(672-1191)**	**1200(1130-1191)**	**1037(529-1140)**
Median admission free days (IQR) (days)	**952(166-1167)**	**965(672-1191)**	**1200(1130-1319)**	**1037(529-1140)**
Median survival (IQR) (days)	**1000(910-1174)**	**1138(902-1191)**	**1200(1130-1319)**	**1037(529-1140)**

Table 3-10 Population demographics, remote requirements, and clinical outcomes of patients with obesity related respiratory failure initiated on home non-invasive ventilation- inpatient versus outpatient initiation

Treatment adherence (>70% of nights used for >4hours). NIV- non-invasive ventilation, IP- inpatient admission, AHP- allied health professionals, regional- regional hospital admission

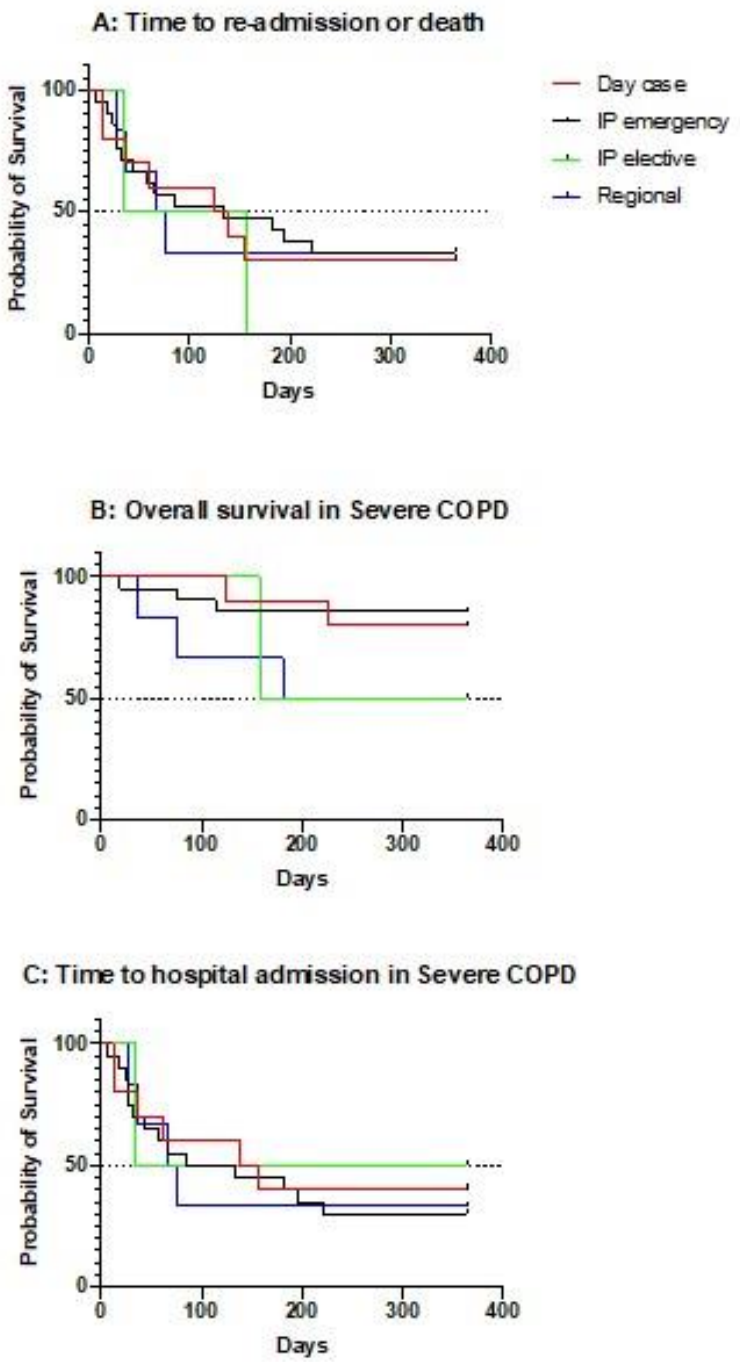


Figure 3-13 Kaplan-Meier analysis in severe COPD patients initiated on home non-invasive ventilation- inpatient versus outpatient initiation

A- Time to re-admission or death. B- Overall survival. C- Time to hospital admission. IP- inpatient admission, regional- regional hospital admission

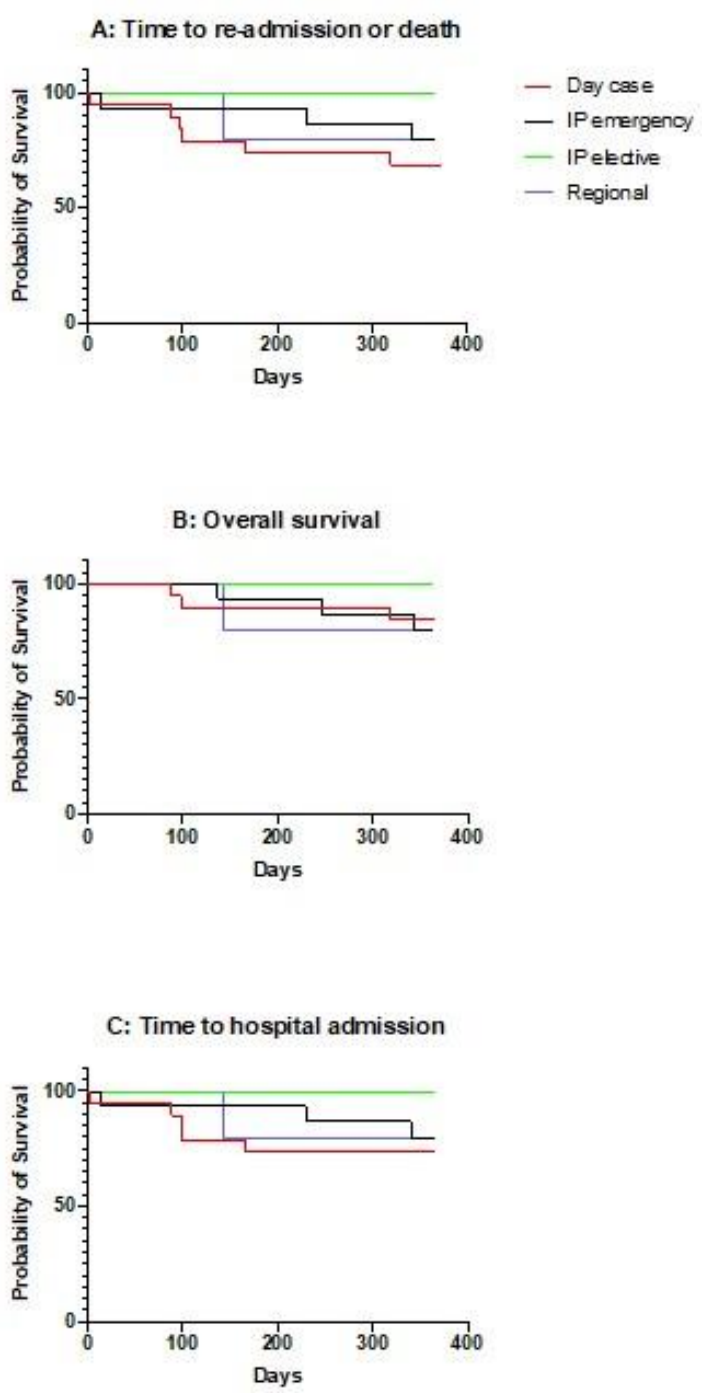


Figure 3-14 Kaplan-Meier analysis in patients with obesity related respiratory failure initiated on home non-invasive ventilation- inpatient versus outpatient initiation

A- Time to re-admission or death. B- Overall survival. C- Time to hospital admission. IP- inpatient admission, regional- regional hospital admission

3.5 Discussion

This study demonstrates the feasibility of delivering effective home NIV using two-way remote monitoring in patients with persistent hypercapnic failure due to severe COPD and obesity related respiratory failure.

3.5.1 Time to re-admission or death

This study demonstrates the realistic application and benefit of home NIV in patients with severe COPD and persisting hypercapnic failure supporting previous RCTs findings. Patients who continued home NIV showed significant improvement in time to re-admission or death during follow up, in comparison to a control cohort of patients who had life-threatening COPD exacerbations requiring acute NIV and had not been referred for breathing support assessment. There was no significant impact on outcomes to those poorly adherent or discontinued home NIV compared to the control cohort. These results are consistent with HOT-HMV trial by Murphy et al demonstrating the delay and reduction in hospital admissions in patients with COPD and persistent hypercapnic failure randomised to home oxygen therapy or home oxygen and home NIV[149]. Hypercapnic COPD patients in our cohort who continued home NIV with remote-monitoring had some differences from the patients in the HOT-HMV NIV treatment arm with less severe airflow obstruction and higher obesity rate. The similar outcomes however demonstrate ability to rapidly implement RCT evidence to real world experience and supports the realistic provision of remote monitored home NIV out-with a clinical trial setting.

Sub-group analysis of time to admission or death in the ORRF cohort demonstrated poorer outcomes in those patients who were non-adherent or discontinued home NIV, which is consistent with previous reports[196], [197], [203]. Data retrieval from remote monitoring of home NIV identifies low adherence and discontinuation of therapy facilitating early proactive interventions to optimise therapy. It is unclear if this would be acceptable to patients, deliverable or would improve overall outcomes. Qualitative studies exploring patient activation and patient views on proactive management of remote monitored NIV compliance data are logical. These could be followed up by co-design of deliverable interventions to tackle remote monitoring detected NIV compliance

issues, with observational or randomised trial to determine the service impact, patient outcomes, and cost-effectiveness of any intervention.

3.5.2 Control of hypercapnic respiratory failure

The secondary outcomes in this study support the use of remote monitored home NIV in hypercapnic severe COPD. Control of hypoventilation was confirmed by improved PCO_2 and serum bicarbonate measurements at follow up in NIV users (Figure 3.9). This improvement occurred despite the lower pressure support provision by home NIV in iVAPS auto-EPAP mode in comparison to previous high intensity home NIV studies[147], [148]. Comparable outcomes in this study provide reassurance about the safety and quality of this option, and of basing a service model around the utilisation of two-way remote monitored home NIV to provide early optimisation, improve service efficiencies and maintain patient outcomes.

Safety of remote monitored home NIV in ORRF was also confirmed with significant decreases in carbon dioxide and serum bicarbonate levels following initiation and remote optimisation (Figure 3.10). Similar low pressure support provision was observed in this cohort.

The back-up rate recorded in both cohorts was high in comparison to previous high intensity home NIV studies as a result of the auto titrating back up mode (iBR) integrated into IVAPS mode Resmed algorithm based on flow-time curve analysis, discussed in Chapter 1, section 1.8. Experience with iBR component of iVAPS mode in COPD is that higher target rate is required to achieve a proportion of mandatory breaths during the respiratory cycles with the treatment aim set a 50% spontaneous breaths and 50% triggered breathes. High trigger respiratory rates are not achieved with this mode. Utilising iVAPS mode we aimed to provide comfortable respiratory support to control hypoventilation rather than pre-set NIV pressure support and back up rate provision seen in “high intensity” home NIV studies.

3.5.3 Survival and Time to re-admission

Overall survival with home NIV in severe COPD and ORRF cohorts improved with adherence and continued use (Figures 3.4A & 3.5). Survival data in ORRF cohort was consistent with previous studies demonstrating poor outcomes in non-adherence and discontinuation of home NIV[196], [197], [203]. A similar trend was demonstrated in time to re-admission following home NIV initiation in severe COPD and ORRF (Figures 3.4B &3.6).

3.5.4 Cost-effectiveness

Further cost-effectiveness analysis of the HOT-HMV outcomes demonstrated a reduction in exacerbation-related costs and patient-reported costs in comparison to the control arm with the costs for the NIV device and physician visits having the greatest impact on cost per QALY[204]. The significant reduction in hospital admissions and occupied bed days, with a median reduction of 14 OBDs per patient per annum in those continued home NIV, without an increase in respiratory specialist nurse input in our study demonstrates potential cost savings and service efficiencies by utilising remote monitored home NIV in this service model. A similar decrease in health care usage was seen in the ORRF cohort with minimal requirement for day-case trouble-shooting sessions to optimise therapy. Individualised follow-up using remote monitored home NIV allows early optimisation, fewer physician reviews and reduces patient travel costs. There is no additional cost for NIV remote-monitoring data in NHS Scotland. Expansion of this service model which has lower device costs and requires fewer physician visits than the HOT-HMV service model would be anticipated to further enhance cost-effective care provision. Future assessments of cost effectiveness of remote monitored home NIV and the development of a proactive COPD service model are required.

3.5.5 In-patient versus outpatient initiation of home Non-invasive ventilation

Day-case initiation of home NIV has been shown to be non-inferior to inpatient NIV initiation and titration[205], [206]. Cost savings are evident with outpatient NIV initiation[205]. The utilisation of tele-monitoring in outpatient home NIV initiation has been shown to be safe with tangible cost effectiveness[163]. Whilst a recent randomised controlled trial has demonstrated that initiation of home NIV in COPD in an outpatient

setting utilising remote monitoring is non-inferior to inpatient NIV titration[207]. Control of hypoventilation confirmed its safety and whilst cost of outpatient initiation was associated with cost savings of >50% in comparison to inpatient set-up[207]. This study demonstrated similar outcomes from “gold standard” multi-night multi-sensor-based setup versus intensively monitored outpatient NIV setup. Our data provides similar outcomes supporting outpatient home NIV initiation with remotely monitored individualised follow up in severe COPD patients, with monitoring limited to capillary blood gases unless an inpatient stay was required. Conversely, clinical outcomes in the ORRF cohort were poorer in those initiated on home NIV as an outpatient. However, a recent multi-centred RCT has demonstrated outpatient home NIV initiation utilising volume assured pressure support modes in patients with obesity hypoventilation syndrome was non-inferior in control of hypoventilation and no difference in clinical effectiveness, cost or safety in comparison to inpatient NIV titration[208]. Full publication of this data is awaited and further cost analysis to be reviewed. This study was not powered to analyse this sub-group analysis and therefore these results are explorative but justify further studies to consolidate these findings in COPD patients, explore clinical outcomes in ORRF and allow further patient phenotyping to facilitate individualised patient pathways.

3.5.6 Remote monitoring

Remote monitoring of home NIV in various disease cohorts has been found to be non-inferior, acceptable for patients, improve therapy adherence and reduce healthcare usage with favourable cost efficiencies[201], [202], [209], [210]. Integrating telemonitoring of PAP therapy with two-way patient engagement devices to allow early optimisation can improve treatment adherence and reduction of mask leakage[211]. Monitoring and optimisation of home NIV is integral to continued home NIV usage. Maintaining adequate face to face reviews in patients with severe COPD can be challenging with physical inability to attend clinics, urgency of therapy changes and variable patient engagement with new therapies. Two-way remote monitored home NIV can provide an adjunct to routine clinical care, encourage patient engagement, allow early optimisation of home NIV, reduce travel costs and facilitate individualised follow up in severe COPD. Our study demonstrates the application and development of patient pathways utilising two-way remote monitored home NIV in severe COPD with persistent hypercapnic failure is an

effective and realistic solution to address the increasing pressures seen on home ventilation services. Benchmarking of outcomes with similar findings in recent published RCT data provides reassurance about the safety of remote monitored based approach to home NIV in this cohort of patients.

Recent studies have demonstrated significant cost savings with remote monitored PAP therapy in sleep disordered breathing[128]–[131]. Incorporating physiological parameters, symptoms burden, telephone consultation and patient education in tele-monitoring of COPD patients improves clinical outcomes and healthcare usage[145]. Remote monitoring of NIV data in COPD can allow early optimisation and early identification of patients at risk of exacerbations[160], [162], [201]. Large data sets available in remote monitored home ventilation justify further exploration into machine learned analysis utilising predictive algorithms to enable the development of an individualised predictive and proactive management model for patients requiring long term home ventilation.

3.5.7 Development of new patient pathways

Our study suggests that remote monitored home NIV can be safely initiated in patients with sustained hypercapnic respiratory failure during an acute episode as well as in stable disease. We utilised volume assured pressure support ventilation mode to achieve titration of home NIV without transcutaneous carbon dioxide monitoring. Control of hypercapnia and improvement in outcomes in-line with previous RCTs supports the safety of this approach. Routine transcutaneous monitoring in these cohorts can be challenging and often unrealistic considering physical implications of severe obesity and severe COPD and arranging hospital admission or providing an outreach home monitoring service. Local experience using volume assured pressure support has shown significant service efficiencies whilst allowing remote optimisation of NIV[174]. Utilising this mode, we targeted treatment for symptom benefit, remote monitored ventilation patterns and follow up capillary blood gas results rather than in-hospital titration of NIV setting in ST mode with continuous transcutaneous monitoring. Clinical user experience is positive and remote management did not require additional staffing nor additional day-case trouble-shooting sessions in severe COPD or ORRF cohorts. Continuous assessment and

development of these new patient pathways utilising remote monitored home NIV is required to ensure continued safety and quality of treatment is maintained.

3.6 Critique of methods

Sub-group analysis demonstrated that patients who discontinued on home NIV in hypercapnic severe COPD aligned closely with the control cohort outcomes, suggesting these patients were not negatively affected by a trial of home NIV. Further exploration and extrapolation of data in those who discontinued on home NIV is indicated to identify triggers for poor adherence to develop individualised patient pathways and proactive approach to home ventilation. However, we must recognise the possibility that despite optimisation efforts there may be a cohort of patients who will not continue this treatment modality.

This study has demonstrated the feasibility of delivering two-way remote monitored home NIV in severe COPD with persistent hypercapnic failure and ORRF. Clinical outcomes in both cohorts are encouraging but we must acknowledge this is a small retrospective study and all analyses are exploratory and control cohort was opportunistic rather than directly matched. Allocation of treatment was not randomised therefore confounding factors cannot be excluded when we interpret this data. The presence of the control cohort in this retrospective review highlights the need for improved educational resources for physicians and AHPs to ensure equitable access to home NIV for hypercapnic severe COPD. Incomplete demographic, comorbidity and compliance of other treatment modalities data means we are unable to confirm the control and COPD cohort were equally matched. RCTs of home NIV with survival as primary endpoint would be required to definitively resolve this but conduct of these would be unfeasible and given available evidence unethical. Efforts should focus on establishing large-scale observational data from registries and multi-site and tertiary collaboration.

Safety of remote monitored home NIV utilising iVAPS mode is demonstrated despite the lower than expected pressure support requirements and high back up rates determined by iBR in both cohorts and matches previous RCT results. The Resmed auto-titrating algorithm based on flow-time curve analysis could contribute to a shorter expiratory time

and therefore in flow limited patients may predispose to hyperinflation and NIV intolerance. Whilst, FOT based algorithm have demonstrated abolishment of EFL in COPD patients, resulting in low pressure support preventing hyperinflation and therefore may be better tolerated than an auto-titrating mode utilising flow-time curve analysis.[212] However, there is a lack of non-inferiority studies of ST versus auto-titrating modes, flow-time versus FOT based auto titrating modes or how settings should be altered to optimise NIV therapy and clinical outcomes in hypercapnic severe COPD patients (high intensity versus low intensity aiming for improved adherence rather than efficient correction of hypoventilation). Future clinical trial are required studies are required to determine the optimal mode for home NIV in this cohort of patients where continued use of home NIV demonstrates improved clinical outcomes and tangible services efficiencies .

3.7 Conclusions

This study confirms the benefits of two-way remote monitored home NIV for patients with persistent hypercapnic failure due to severe COPD and in obesity-related respiratory failure. Continued use of remote monitored home NIV in hypercapnic severe COPD patients was associated with improved time to re-admission or death in comparison to control cohort and to patients who discontinued home NIV. That noted time to re-admission or death improvements are in line with previous RCT data. It is feasible to utilise remote monitoring to initiate home NIV as an outpatient or to assist home NIV follow up after an acute admission episode. The reduction in health care usage with continued home NIV with no increase in service requirements highlights that remote monitored home NIV is an effective and realistic solution to address the growing demands in home ventilation.

Chapter 4 Simplifying the measurement of neural respiratory drive

4.1 Introduction

Ventilatory homeostasis is dependent on respiratory load, respiratory muscle capacity and neural respiratory drive (Chapter 1, Figure 1.1). Impairment of the respiratory muscle function can lead to respiratory capacity-load imbalance predisposing to alveolar hypoventilation and consequent respiratory failure. Neural respiratory drive (NRD), the neuronal activation to motor units from the respiratory centre, can maintain ventilation homeostasis during periods of impaired respiratory muscle function and is associated with dyspnoea at increased levels.[17], [18] NRD is a well-established advanced physiological marker in research and its evolution from an invasive research technique to an accessible non-invasive biomarker in respiratory disease monitoring was discussed in Chapter 1.

Parasternal electromyography (EMGpara) is a novel physiological measurement at the Glasgow Sleep and Breathing Support Research Centre (GSBSRC). Following collaborations with The Lane Fox Respiratory Physiology Research Centre (Guy's and St Thomas' NHS Foundation Trust, London) and a review of previously documented methodology of measuring NRD, local evaluation of parasternal EMG measurements to simplify the approach and optimise signal quality are explored in this chapter. Reliability of this new technique is evaluated through inter-observer variability analysis with the Lane Fox Respiratory Physiology Research Centre. Further exploration of the simplification of NRD measurements includes the utilisation of parasternal EMG signals to estimate the respiratory rate and directly compare with oro-nasal flow analysis and respiratory impedance plethysmography (RIP) band signals. Acceptable reliability of respiratory rate derived from parasternal EMG signal could allow the omission of oro-nasal flow cannula and RIP bands to reduce the equipment burden and simplify parasternal EMG setup for patients and technicians. Improving accessibility of parasternal EMG through simplification of the methodology would enable its uptake in further studies including ambulatory and home monitoring to facilitate physiological phenotyping, assess treatment response, provide mechanistic insights, and facilitate individualised management of chronic respiratory disease. Incorporation of a simplified approach to advanced physiological measurements into ambulatory wearable devices could provide invaluable data for machine learned analysis of predictors of disease trajectory with the potential to improve patient outcomes out with a research centre setting.

4.2 Hypothesis

Simplification of parasternal electromyography technique can reliably quantify neural respiratory drive.

4.3 Methods

4.3.1 Optimisation of skin preparation

In all scenarios the study candidate was in a semi-recumbent position in bed. Parasternal margins at the 2nd intercostal muscle and lateral right clavicle were palpated as discussed in Chapter 2 and appendix 6. In each scenario we evaluated different options for skin preparations and electrodes to optimise EMG signal.

Scenario 1: Skin preparation included skin prep gel (Nuprep, DO Weaver and Co, US). Electrocardiogram (ECG) electrodes (Covidien/Kendall MEDITRACE 100) were applied to the 2nd intercostal space using neuro-diagnostic electrode paste (Ten20, DO Weaver and co, US). EMG signals of tidal breathing were sampled using bio amp and PowerLab hardware. Samples were taken with limited polysomnography equipment (Somnotouch™ Resp Polygraphy, Germany) running simultaneously to explore if these resulted in any interference with EMG signal.

Scenario 2: Skin preparation included trace preparation tape (3M Red Dot Trace Prep, 3M, Canada), alcohol wipe and dried with standard gauze. Wet gel ECG electrodes (XLBLEU tab 'n' snap, Fannin Stroud, Dublin, Ireland) were positioned with the central gel pad in the 2nd intercostal space at the sternal margin and right clavicle. Signals were sampled during tidal breathing.

Scenario 3*:* Skin preparation included trace preparation tape (3M Red Dot Trace, 3M, Canada), alcohol wipe and dried with gauze. Cardiac Monitor ECG electrodes (Ambu Blue Sensor L Electrodes, Ambu, US) were positioned in the centre of 2nd intercostal space, at the sternal margin and at the right clavicle. Signals were sampled during tidal breathing.

Scenario 4: Skin preparation included trace preparation tape (3M Red Dot Trace, 3M, Canada), alcohol wipe and dried with gauze. Elite cardiac electrodes (Elite, Skintact, UK) were placed in 2nd intercostal space and right clavicle. Signals were sampled during tidal

breathing in a normal/control subject and in a patient with chronic obstructive pulmonary disease (COPD).

4.3.2 Reproducibility of parasternal electromyogram analysis between two UK based respiratory physiology research centres

Datasets were sampled from the Exploratory Endpoints study described in chapter 2 and further discussed in chapter 5. Ten patients were randomly selected from the Exploratory Endpoints study population using Excel software (Microsoft) "=Rand ()" function. The 10 randomly selected datasets represented a range of respiratory conditions (4 OSAS, 1 ORRF, 2 Severe COPD with hypercapnic failure, 1 Bronchiectasis with hypercapnic failure, 1 normal control and 1 patient with post-transplant hypoventilation).

These data were independently analysed in Labchart software (ADInstruments, Chalgrove, UK) by an investigator at each centre. Inter-observer reproducibility of EMGpara analysis was performed comparing results obtained by Glasgow Sleep and Breathing Support Research Centre (GSBSRC) and the Lane Fox Clinical Respiratory Physiology Research Centre (Guy's and St Thomas', London) investigators for EMGpara%max and its product Neural Respiratory Drive Index (NRDI).

4.3.3 Simplifying the measurement of neural respiratory drive index: can parasternal electromyogram signal be used to measure respiratory rate?

Parasternal EMG data was collected as described in Chapter 2 and appendix 6. 15 datasets from the Exploratory Endpoints study and 10 data sets from the Lane Fox Respiratory Research centre were analysed in Labchart software (ADInstruments, Chalgrove, UK). 15 patients had severe COPD, 1 COPD-OSA overlap, 5 OSAS, 4 normal controls. Low band pass sampling of the root mean squared signal of EMGpara (RMS EMGpara) was used to estimate the respiratory rate derived from EMG (EMGpara-RR). Reliability of EMGpara-RR was compared with respiratory rate derived from oro-nasal flow analysis in 25 datasets and respiratory impedance plethysmography (RIP) band signals in 15 datasets as detailed in appendix 8.

4.3.4 Data Analysis and statistics

Reproducibility of EMGpara%max and NRDI was determined using Pearson's correlation coefficient and Bland Altman analysis[213]. Normal distribution of data was confirmed by the Shapiro-Wilk test. Data analysis was performed by GraphPad, Prism software (GraphPad, San Diego, US). EMG data was presented as absolute values, mean, standard deviation and 95% limits of agreement. P value < 0.05 was considered statistically significant.

Bland Altman analysis evaluated agreement between NRDI derived from flow analysis, RIP bands and EMGpara-RR. Data analysis was performed by Graphpad, Prism Software (GraphPad, San Diego, US).

4.4 Results

4.4.1 Optimisation of skin preparation

Minor interference of the parasternal EMG signal was noted during activation of limited polysomnography equipment, as demonstrated in Figure 4.1. The parasternal EMG signal quality improved when trace preparation tape (3M Red Dot Trace Prep, 3M, Canada) was used in combination with an alcohol swab (Figure 4.2) compared to scenario 1 using Nuprep skin preparation gel and Ten20 electrode paste (Figure 4.1). EMG signal quality improved using cardiac monitor electrodes (Ambu Blue Sensor L Electrodes, Ambu, US) as described in scenario 3 (Figure 4.3). Optimal EMG signal was achieved using cardiac monitoring electrodes (Elite, Skintact, UK) to capture signals in a normal/control and a patient with COPD, as described in scenario 4 (Figure 4.4). Scenario 4 incorporated the same technique used for long duration ECG monitoring to optimise EMG signal and reduce interference.

4.4.2 Reproducibility of parasternal electromyogram analysis between two UK based respiratory physiology research centres

Observer A was investigator from GSBSRC. Observer B was investigator from Lane Fox Respiratory Unit. Considering raw data values, acceptable agreement was noted for EMGpara%max (table 4.1) and NRDI (table 4.2). Pearson correlation analyses demonstrate strong correlation between observer A and B for both EMGpara%max and NRDI (Figure 4.5). Bland Altmann analysis demonstrates acceptable agreement between observers A and B for EMGpara%max and NRDI (Figure 4.6). There are some outlying data points justified by the small sample size.

4.4.3 Simplifying the measurement of neural respiratory drive index: can parasternal electromyogram signal be used to measure respiratory rate?

Bland Altman analysis demonstrated good agreement for NRDI derived from EMGpara-RR and standard methodology using oro-flow signal analysis and RIP band analysis (Figure 4.7 A-C).

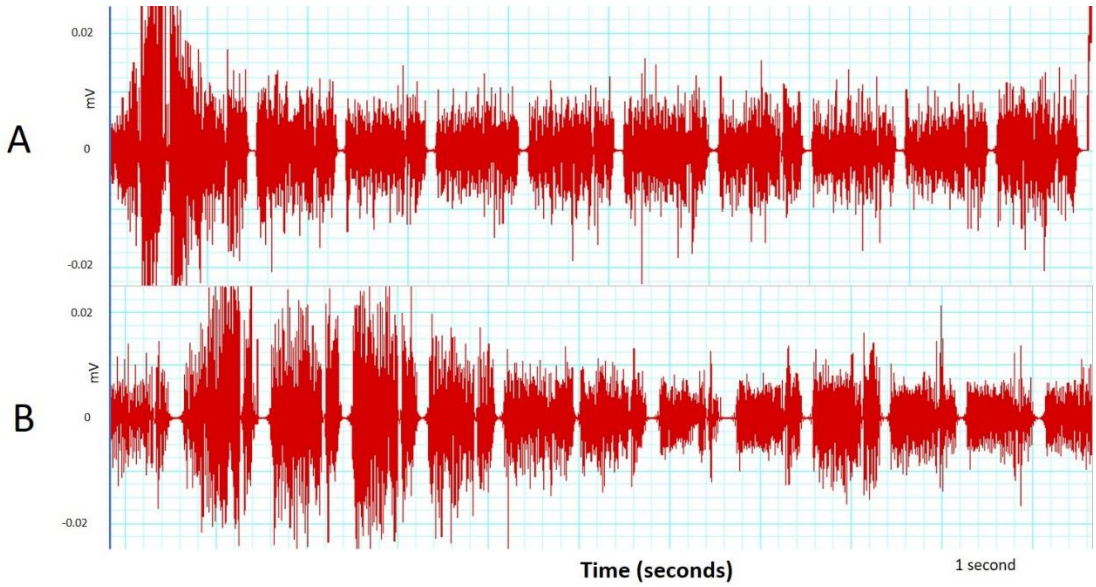


Figure 4-1 Parasternal EMGs, evaluating skin preparation and interference scenario 1

Raw electromyogram signal from the second intercostal parasternal muscles (measured in millivolts(mV)) using Nuprep skin preparation gel and MEDITRACE electrodes, demonstrating lack of interference from additional polysomnography monitoring equipment. A- Raw signal with somnotouch limited polysomnography active. B- Raw signal without somnotouch limited polysomnography.

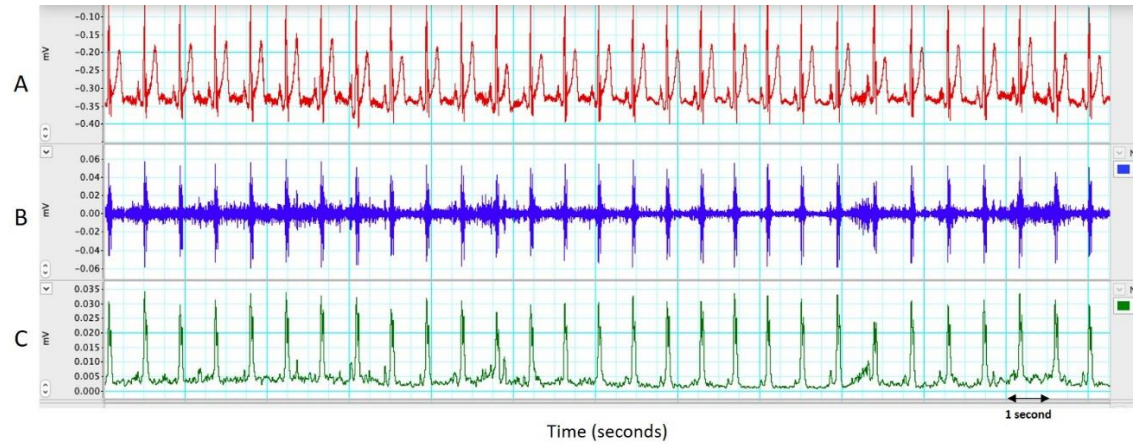


Figure 4-2 Parasternal EMG data, evaluating skin preparation scenario 2

Parasternal electromyogram from the second intercostal muscle using trace preparation tape, alcohol wipes and XBLEU electrodes. A- Electrocardiogram signal. B- Raw parasternal EMG signal. C- Root mean squared parasternal EMG signal. Channels A-C measured in millivolts(mV)

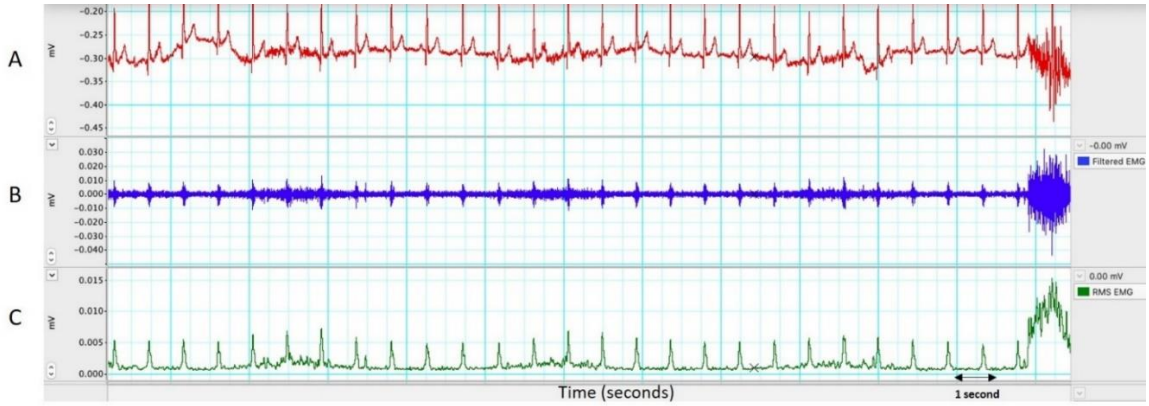
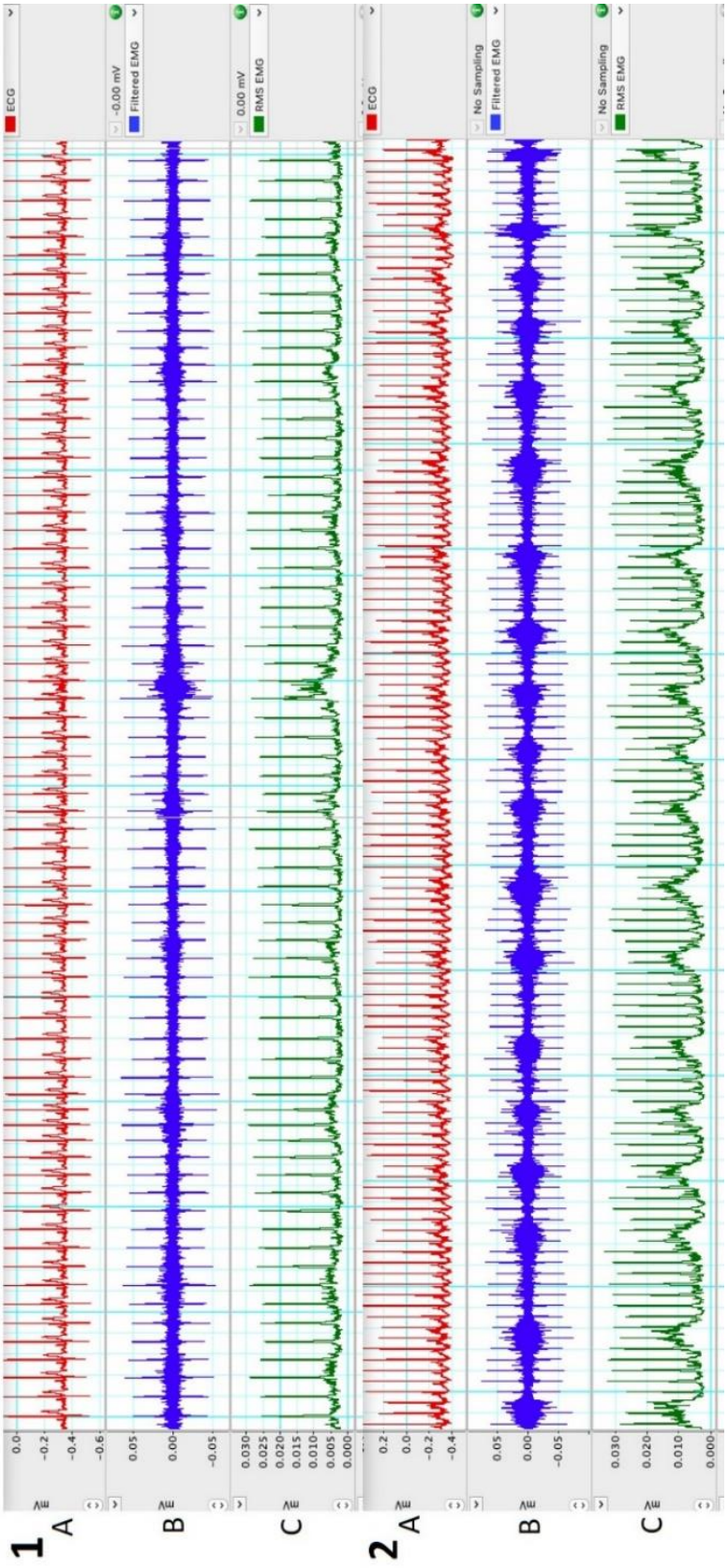


Figure 4-3 Parasternal EMG data, evaluating skin preparation scenario 3

Parasternal electromyogram of the second intercostal muscle using trace preparation tape, alcohol wipe and AMBU Blue Senor L electrodes. A- Electrocardiogram signal. B- Raw parasternal EMG signal. C- Root mean squared parasternal EMG signal. Channels A-C measured in millivolts(mV)



Parasternal electromyogram of the second intercostal muscle trace preparation tape, alcohol wipe and elite cardiac electrodes. A- Electrocardiogram signal. B- Raw parasternal EMG signal. C- Root mean squared parasternal EMG signal. Channels A-C measured in millivolts(mV). Panel 1- Patient with no cardiorespiratory disease. Panel 2- Patient with chronic obstructive pulmonary disease.

Figure 4-4 Parasternal EMG data, evaluating skin preparation scenario 3

EMGpara%max	Observer A	Observer B	A-B
1	14.826	13.209	1.617
2	24.088	23.592	0.495
3	15.901	14.147	1.755
4	15.296	14.896	0.399
5	12.061	12.756	-0.695
6	17.801	17.336	0.464
7	36.159	30.619	5.540
8	12.118	8.414	3.704
9	9.289	9.634	-0.335
10	6.806	5.687	1.118
Mean (SD)	16.4343 (8.4010)	15.0291(7.3871)	1.4062(1.9088)

Table 4-1 Normalised parasternal electromyogram results (EMGpara%max) for Glasgow Sleep and Breathing Support Research Centre (observer A) and the Lane Fox Respiratory Physiology Research Centre (observer B).

The mean difference in EMGpara%max is 1.406 ± 1.909 μV between Observer A and Observer B with limits of agreement of -2.338 and 5.148μV.

NRDI	Observer A	Observer B	A-B
1	122.29	112.887	9.403
2	370.467	413.410	-42.940
3	258.438	234.418	24.019
4	154	150.572	3.428
5	249.238	388.841	-139.60
6	371.077	358.711	12.366
7	650	545.794	104.206
8	90.625	80.386	10.239
9	125.6	127.108	-1.508
10	776.583	68.528	8.055
Mean (SD)	246.832(178.145)	248.065(166.995)	-1.234(60.717)

Table 4-2 Neural respiratory drive index (NRDI) results for Glasgow Sleep and Breathing Support Research Centre (observer A) and the Lane Fox Respiratory Physiology Research Centre (observer B).

The mean difference in NRDI is -1.233 ± 60.717 μV between Observer A and Observer B with limits of agreement of -120.2 and 117.8**.**

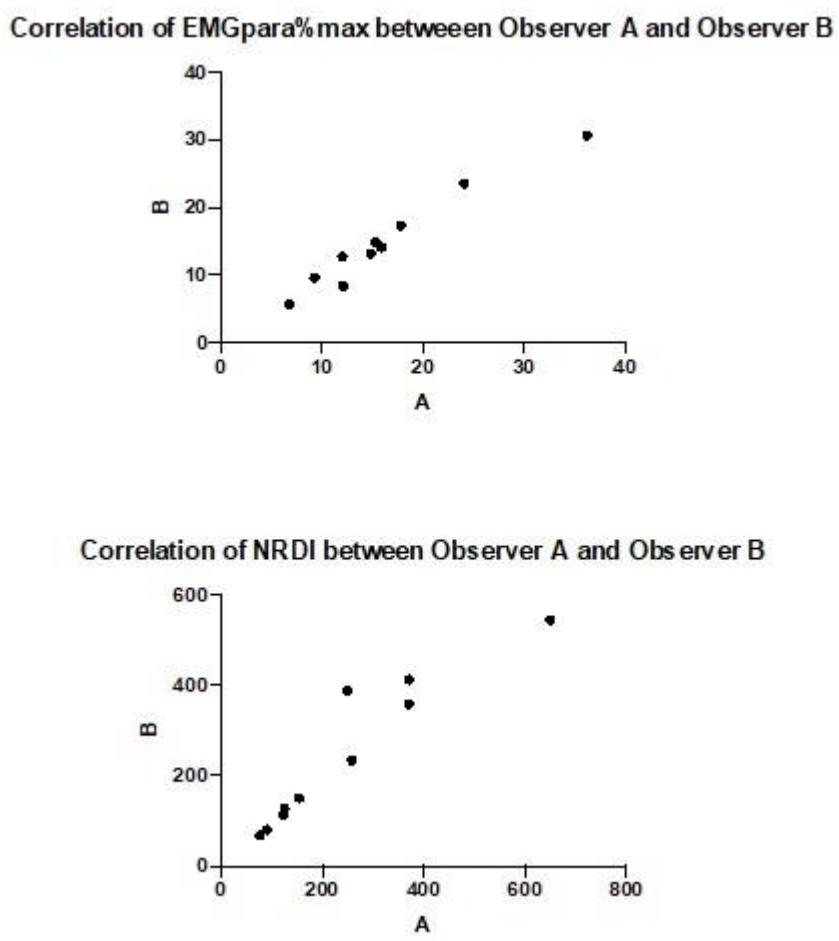


Figure 4-5 Pearson correlations show inter-observer agreement for the analysis of normalised parasternal electromyogram (EMGpara%max) and neural respiratory drive index (NRDI).

EMGpara%max correlation demonstrates r= 0.9789, 95%CI 0.9104 to 0.9952, p<0.0001. NRDI correlation demonstrates r=0.9401, 95%CI 0.7609 to 0.9861, p<0.0001. Observer A: Glasgow Sleep and Breathing Support Research Centre. Observer B: Lane Fox Respiratory Physiology Research Centre.

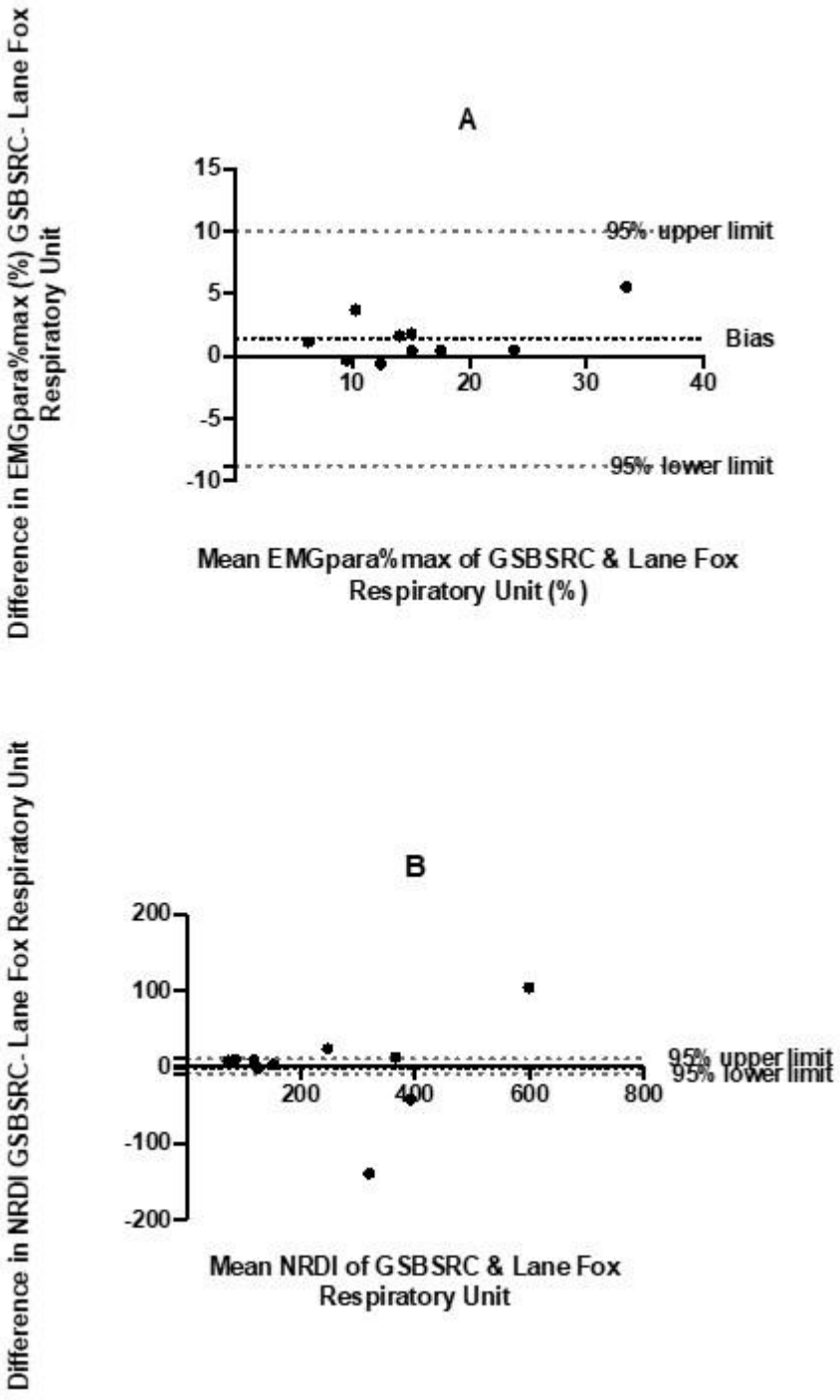


Figure 4-6 Bland-Altman plots show good inter-observer agreement for the analysis of normalised parasternal electromyogram (EMGpara%max) and neural respiratory drive index (NRDI).

A- Bland Altman analysis of normalised parasternal electromyogram (EMGpara%max). B- Bland Altman analysis of neural respiratory drive index (NRDI). Outlying data points for mean NRDI are judged acceptable given small sample size (n=10).

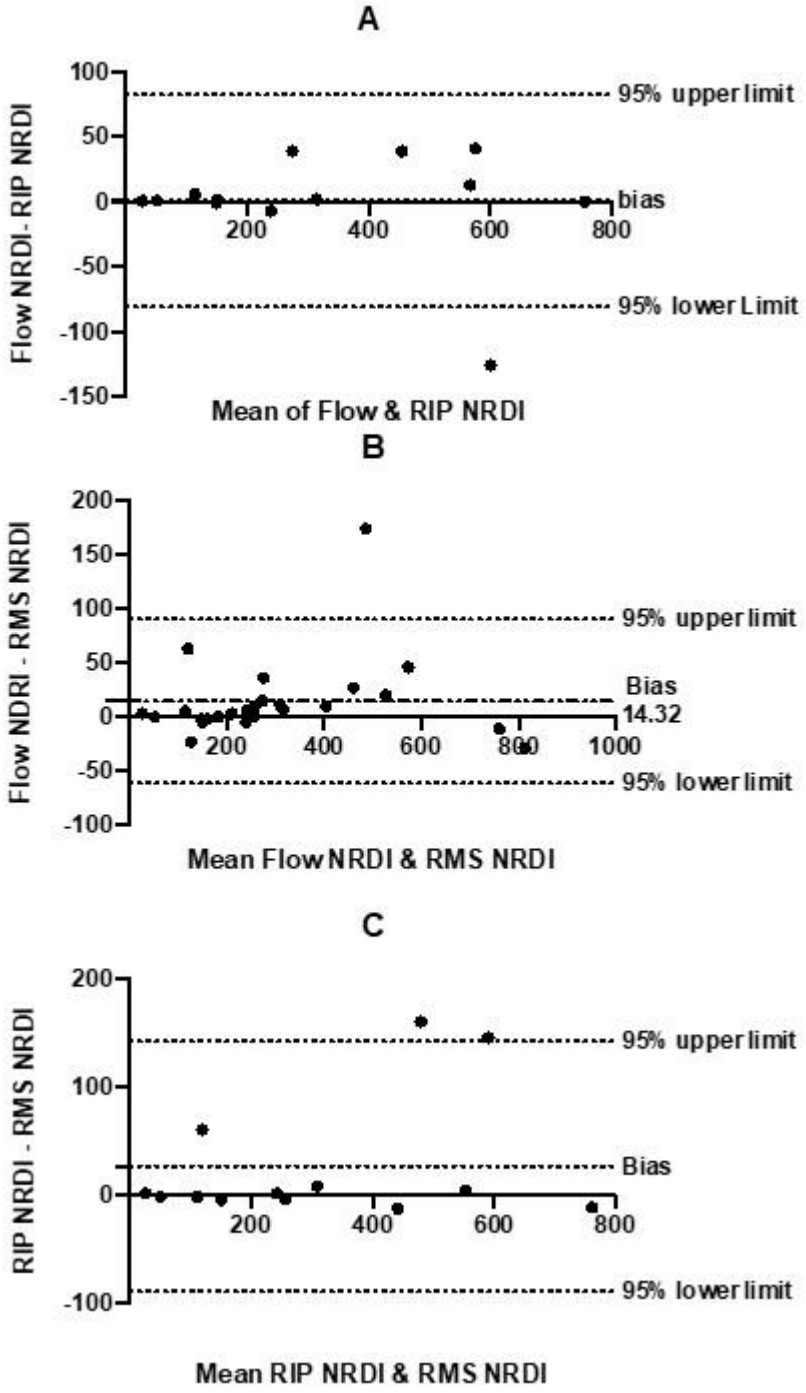


Figure 4-7 Bland-Altman plots show intra-technique agreement for the measurement of neural respiratory drive index (NRDI) derived from different respiratory rate (RR) sensors.

A- Bland-Altman analysis of neural respiratory drive index derived from oro-nasal flow analysis (Flow NRDI) and respiratory impedance plethysmography (RIP) band signals (RIP NRDI).

B- B- Bland Altman analysis of neural respiratory drive index derived from oro-nasal flow analysis (Flow NRDI) and respiratory rate derived from low band pass sampling of the parasternal electromyogram signal (RMS NRDI).

C- C- Bland Altman analysis of neural respiratory drive derived from RIP band analysis (RIP NRDI) and respiratory rate derived from low band pass sampling of the parasternal electromyogram signal (RMS NRDI).

4.5 Discussion

These data demonstrate the simplification of parasternal electromyography measurement is feasible and reliable to quantify NRD. We compared methods of skin preparation and different EMG electrodes. Simplified skin preparation method and long duration electrodes used for cardiac monitoring (Skintact) returned the highest quality EMG signals, with reduced interference from simultaneous device monitoring. These refinements resulted in a standardised practice which was simpler for the investigator, more acceptable for the subject and sustainable for long periods of continuous monitoring which can be required during complex interventions such as non-invasive ventilation titrations and potentially for ambulatory wearable EMG. This method was used in all study patients recruited for the Exploratory Endpoints study (Chapter 5).

This is the first published evidence of inter-observer variability of parasternal electromyogram data between two respiratory physiology research centres in the United Kingdom.[214] Our data demonstrated satisfactory inter-observer reproducibility of parasternal electromyography and its product neural respiratory drive index (NRDI) in a randomised group of patients with chronic respiratory disease. Previous inter-observer variability of EMGdi has been demonstrated in 5 COPD patients with an intraclass correlation(ICC) of 0.71.[29] Inter-observer variability of surface EMGdi in snoring children demonstrated ICC of 0.98[215]. This supports ongoing and future utilisation of parasternal EMG as an advanced physiological biomarkers and research endpoint as part of large multi-centred studies.

The estimation of respiratory rate derived from the root mean squared of parasternal EMG signals further simplifies NRD quantification and is reliable in comparison to the established practice of respiratory rate estimations from oro-nasal flow or respiratory impedance plethysmography (RIP) band signals.[216] These data suggest additional sensors, oro-flow nasal cannula and RIP bands, could be omitted during the measurement of parasternal EMG but further feasibility studies are necessary to consolidate our study findings. Rationalisation of NRD analysis would facilitate increased uptake of parasternal

EMG as a research endpoint, an advanced physiological biomarker in disease monitoring in clinical practice out with research centre and in ambulatory settings.

4.6 Critique of methods

4.6.1 Patient Selection for inter-observer variability analysis and simplification of neural respiratory drive analysis

Patients were recruited to the Exploratory Endpoints study, a prospective observational study. This study was not blinded and therefore underlying respiratory conditions were known to the assessor. However, all parasternal EMG analysis for the Exploratory Endpoints study was carried out by one assessor limiting variability.

During recruitment for the Exploratory Endpoints study, initial parasternal EMG hardware setup did not include the spirometer module due to lack of equipment and RIP bands were used for all study candidates recruited. The introduction of the spirometer module in the final months of recruitment allowed a limited number of datasets with a variety of respiratory diseases to be analysed (COPD, COPD-OSA overlap, OSAS and normal controls). Ongoing parasternal EMG studies at GSBSRC include RIP band and oro-nasal flow analysis. The 10 data sets from the Lane Fox Respiratory unit were from patients with severe COPD. Further studies with larger disease cohorts are justified to consolidate these study findings.

4.6.2 Surface parasternal electromyography measurements

As the data was used from two research centres, skin preparation and EMG set up may differ therefore absolute values for EMGpara from both sites may not be directly comparable. However, inter-observer variability demonstrates good reproducibility for parasternal EMG analysis and its product NRDI in both respiratory centres. All data analysed to derive the respiratory rate from parasternal EMG was carried out by one assessor, minimising variability of results. Further feasibility studies in multiple research centres could be considered to ensure skin preparation, EMG acquisition and analysis do not significantly impact NRD measurements and confirm the reliability of a simplified approach to NRD analysis.

As previously discussed in Chapter 1, there are some limitations with surface EMG data including crosstalk from accessory muscles and the effect of body habitus in signal quality. Needle electrode EMG method reduces interference but is invasive and not suitable for acutely unwell patients or for monitoring disease response to treatment. Analysis of parasternal EMG traces can be difficult in patients who have severe COPD with increased accessory muscle use during tidal breathing resulting in increased crosstalk of EMG signals. Subsequent use of RMS of parasternal EMG signal to derive the respiratory rate could be compromised. Likewise, low voltage signals seen in patients with severe obesity could limit respiratory rate derived from RMS of the parasternal EMG signal. These data justify future studies to consolidate that utilisation of parasternal EMG derived respiratory rate allows the omission of oro-nasal flow cannula and RIP band use to improve the accessibility of NRD measurements. Future work should include large sample sizes of patients with COPD and obesity to ensure validity of this simplified technique.

4.7 Conclusions

These data demonstrate the rationalised methodology for parasternal EMG measurement provides acceptable signal quality and simplification of NRD analysis using the RMS parasternal EMG signal to estimate the respiratory rate is reliable. The simplified skin preparation is less cumbersome, and the cardiac electrodes are compatible with longer periods of monitoring like those in ambulatory cardiac investigations. This simplified methodology will improve accessibility of parasternal EMG as all the equipment is readily available in cardiology units and on NHS Scotland procurement. Acceptable inter-observer variability between GSBSRC and the Lane Fox Respiratory Physiology Research centre endorses future multi-centre studies utilising EMGpara as a research endpoint and advanced physiological biomarker in chronic respiratory disease. The rationalisation of NRD analysis allowing the omission of oro-nasal flow and RIP band sensors could improve the accessibility of continuous parasternal EMG in the home and ambulatory settings. The combination of a simplified methodology and rationalised NRD analysis with omission of additional sensors could provide a less cumbersome and more accessible approach to the quantification of NRD. The development of ambulatory monitoring of NRD using these methods would increase the uptake of parasternal EMG as a research endpoint, provide physiological insights and facilitate disease monitoring. Improved accessibility of

parasternal EMG allows inclusion of patients susceptible to respiratory failure, who previously have been unable to participate in advanced physiological measurements due to the significant disease burden and physical debilitation of severe chronic respiratory disease to provide invaluable insights into pulmonary mechanics of severe respiratory disease and chronic respiratory failure.

Chapter 5 Exploratory Endpoints

5.1 Introduction:

The utilisation of advanced physiological measurements such as oscillometry (FOT) and neural respiratory drive (NRD) are well established in research and their clinical application as a bio-marker of respiratory disease has emerged providing valuable insights into pulmonary mechanics in chronic respiratory disease.[65], [217] This chapter will discuss the application and feasibility of measuring FOT and NRD in patients with sleep disordered breathing, hypercapnic severe COPD and COPD-OSA overlap syndrome.

During the expiratory phase of the respiratory cycle, maximum expiratory volumes are recorded in the first second of expiration. Applying the theory of Poiseuille's equation (Fig 5.1), where the amount of air expired in one second (FEV1) is directly proportional to the radius of the airways, diseases of the large airways classically present with a reduction in FEV1 compared to normal subjects. A reduction in the ratio of FEV1 to forced vital capacity (FVC) below 0.7 is referred to as airflow obstruction and is a common feature in chronic lung diseases. COPD is characterised by persistent respiratory symptoms, progressive airflow obstruction which is not fully reversible and associated with the inhalation of noxious particles or gas.[183][218] However, in normal ageing there can be a greater reduction in FEV1 compared to FVC resulting in ratios of 0.7 in the absence of obstructive airways disease therefore age-specific range should be considered in a new diagnosis of COPD.[219]

Negative pleural and alveolar pressures during inspiration correlate with inspiratory flow (Figure 5.2).[220] Expiration is protracted in obstructive airways disease due to airflow obstruction resulting in a reduction in flow below a critical point (Pcrit) required to maintain airway patency resulting in flow cessation, airways collapse and positive end-expiratory pressure within the airways(PEEP) referred to as the "waterfall concept" (Figure 5.3). This airflow limitation in expiration despite increasing pleural pressures is also known as expiratory flow limitation (EFL) and is present during maximal manoeuvres or during tidal breathing in severe obstructive airways disease.[221][222] Incomplete lung emptying at the end of expiration increases respiratory load on the inspiratory muscles to generate a pressure equivalent to PEEP, increasing work of breathing compared to normal subjects.[53] Increased End Expiratory Lung Volumes (EELV) secondary to incomplete lung emptying results in resting and dynamic lung hyperinflation. Hyperinflation reduces inspiratory muscle capacity, increasing the work of breathing, increased dyspnoea, reduced exercise capacity and can be predictive of mortality.[223][224][225][226] [227][228][229] Dynamic hyperinflation (DH) is seen during exercise in patients with airflow obstruction[230][231] and is aggravated during exacerbations of obstructive airways disease as a consequence of airway oedema, mucous congestion, increased airways resistance, exacerbated EFL and increased EELVs. The increased respiratory load and reduced lung capacity seen in DH

results in heightened NRD and/or increased respiratory rate, which can further exacerbates DH and dyspnoea.[137]

Recognition of EFL during tidal breathing identifies patients who are susceptible to aggravated hyperinflation, unstable alveolar ventilation, ventilation/perfusion (VQ) mismatching resulting in ventilatory failure and adverse clinical outcomes.[227], [229] However, quantification of EFL can be impractical with invasive oesphageal balloons or inconsistent with non-invasive flow-volume loop analysis which has high variablilty on an individual basis. Forced oscillometry technique (FOT), a non-invasive effort independent assessment of pulmonary mechanics can quantify in-breath EFL at rest and is equivalent to negative expiratory pressure assessments.[222] Dallaca demonstrated that breath by breath analysis using oscillometry can quantify EFL through the difference between inspiratory X5(X5insp) and expiratory X5(X5exp) otherwise known as ΔXRS (Figure 5.4).[232], [233][234]

5.1.1 Principles of forced oscillometry technique

FOT transmits pressure oscillations generated by a loud speaker into the lungs, with high to low frequency waves travelling to the alveoli to represent the large and small airways respectively. FOT quantifies pulmonary mechanics on a breath by breath basis through pressure flow analysis and is represented as respiratory impedence(Zrs), the sum of Resistance(Rrs) and Reactance(Xrs), which can be used as a generalised marker of airway resistance (Figure 5.5). Airway resistance can be further quantified into total airway resistence (R5), large (R20) and small (R5-R20) airways resistence with the latter contributing to approximately 20% of Rrs (Figure 5.6).[235] Reactance is the product of capacitance (a negative quantitiy representing the elastic properties of the lung) and inertance (Figure 5.5). Diseases of the smaller airways such as emphysema have a more negative reactance.[236] EFL is quantified by the difference between inspiratory reactance at 5Hz (X5insp) and expiratory reactance at 5Hz(X5exp) otherwise known as ΔXRS (Figure 5.4). Resonant frequency(Fres) is the frequency at which capacitance and inertance are equal to zero, with normal values at 7-12Hz and are increased in both obstructive and restrictive disease. Area of reactance (Ax) is the area under the reactance curve and reflects capacitance, the elastic properties of the lungs and correlates with R5-R20 (Figure 5.7).

5.1.2 Clinical application of oscillometry in respiratory disease

FOT can detect EFL present during tidal breathing in patients with COPD giving insight into pulmonary mechanics of severe airways disease and identifying those susceptible to dynamic hyperinflation.[237] Patients with COPD and tidal EFL demonstrated a greater improvement in airways resistence following beta agonist therapy compared to those without tidal EFL.[234] Serial FOT measurements in COPD patients with evidence of bronchodilator reversibility showed a larger fall in overall resistence and small airways resistence following beta agonist therapy compared to those with no reversibility, demonstrating the heterogeneity of pulmonary mechanics in COPD.[234] FOT has demonstrated a strong correlation between FEV1 and reactance in addition to reduced compliance in chronic respiratory disease and progressive airflow obstruction.[238] Additionally, the change in reactance in patients recovering from an exacerbation of COPD has been shown to correlate with improved symptom burden providing insights into the importance of small airways disease in the management of exacerbated COPD.[239] FOT facilitates physiological phenotyping of chronic respirtory disease such as COPD, leading to targeted treatments and potential disease monitoring.[6] [240]

FOT has been utilised in paediatric research in chronic respiratory diseases such as asthma and cystic fibrosis as it is effort independent and non-invasive. Small airways resistence has been shown to correlate with small airways disease (FEF_{25-75}) and airways inflammation measure by exhaled nitric oxide in asthma.[241] Small airways resistance and Ax was strongly associated with poorly controlled asthma with serial FOT measurements identifying patients requiring treatment optimisation to improve patient outcomes in difficult to control asthmatics.[242] In Cystic Fibrosis, FOT has shown an increased resistence and reduced reactance in symptomatic children and adults compared to normal subjects, with a correlation between FOT and standard pulmonary function investigations.[243], [244][245]

In obesity, compliance of the respiratory system is reduced whilst both expiratory reserve volume (ERV) and Functional Residual Capacity(FRC) are negatively correlated with BMI.[2][7] Decreased lung volumes and micro-atelectasis contributes to reduced compliance where tidal breathing occurs out-with the linear portion of the pressure-flow curve (Figure 5.3).[246] FOT has demonstrated increase airway resistance in obesity compared to normal subjects.[247], [248] In sleep disorder breathing, large and small airways resistance correlates with disease severity measured by AHI as does reactance at 5Hz (X5). [249][250][251] In the supine position, respiratory mechanics are altered due to abdominal contents splinting the diaphragm increasing airways resistance and EFL. As a result variable expiratory positive airway pressure (EPAP) requirements can be seen with postural changes in severe COPD.[252][253] FOT can identify dynamic EPAP requirements in severe COPD which would facilitate a personalised approach to

NIV titrations.[233] Whilst auto-tirating EPAP using FOT-based algorithm has been shown to abolish tidal EFL and reduce neural respiratory drive in hypercapnic severe COPD patients. [212]

FOT provides valuable insights into the pulmonary mechanics of chronic respiratory disease. The utilisation of FOT in physiological phenotyping, as a bio-marker of treatment success and in the management of respiratory failure could facilitate a personalised approach to the management of chronic respiratory disease, improving patient outcomes and service efficiency.

$$\Delta p = 8\mu LQ / \pi R^4 = 8\pi\mu LQ/A^2$$

Figure 5-1 Poiseuille Equation

Represents the relationship between volume of air expired and radius of the airways, explaining reduction in FEV1 in obstructive airways disease. Δp- the pressure difference in the airways, L- the length of airway, μ - the dynamic viscosity, Q- the volumetric flow rate, R- the radius of the airway, A- the cross section of the airway

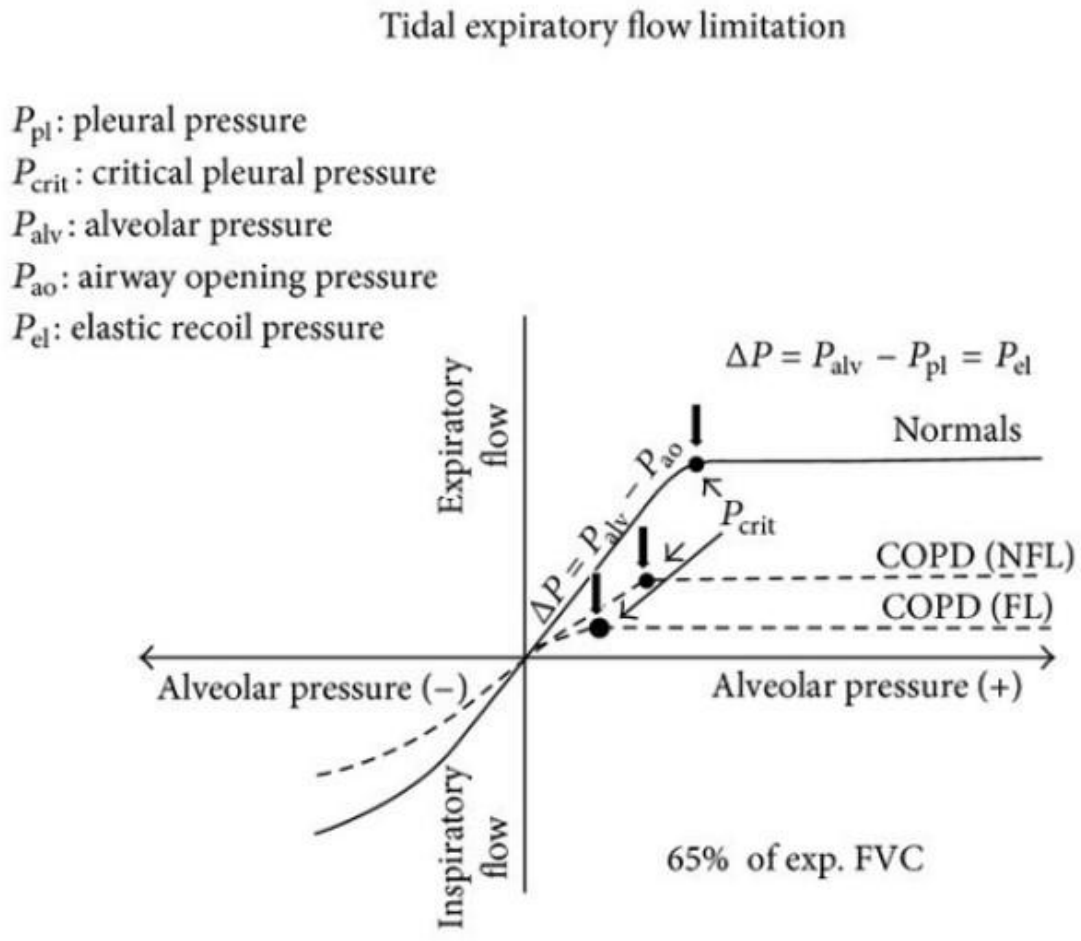


Figure 5-2 : Iso-volume flow pressure relationship of the respiratory cycle

Representation of change in expiratory flow following the critical pleural pressure point (Pcrit) in normal physiology, COPD patients without expiratory flow limitation (NFL) and COPD patients with tidal expiratory flow limitation (FL).[220]

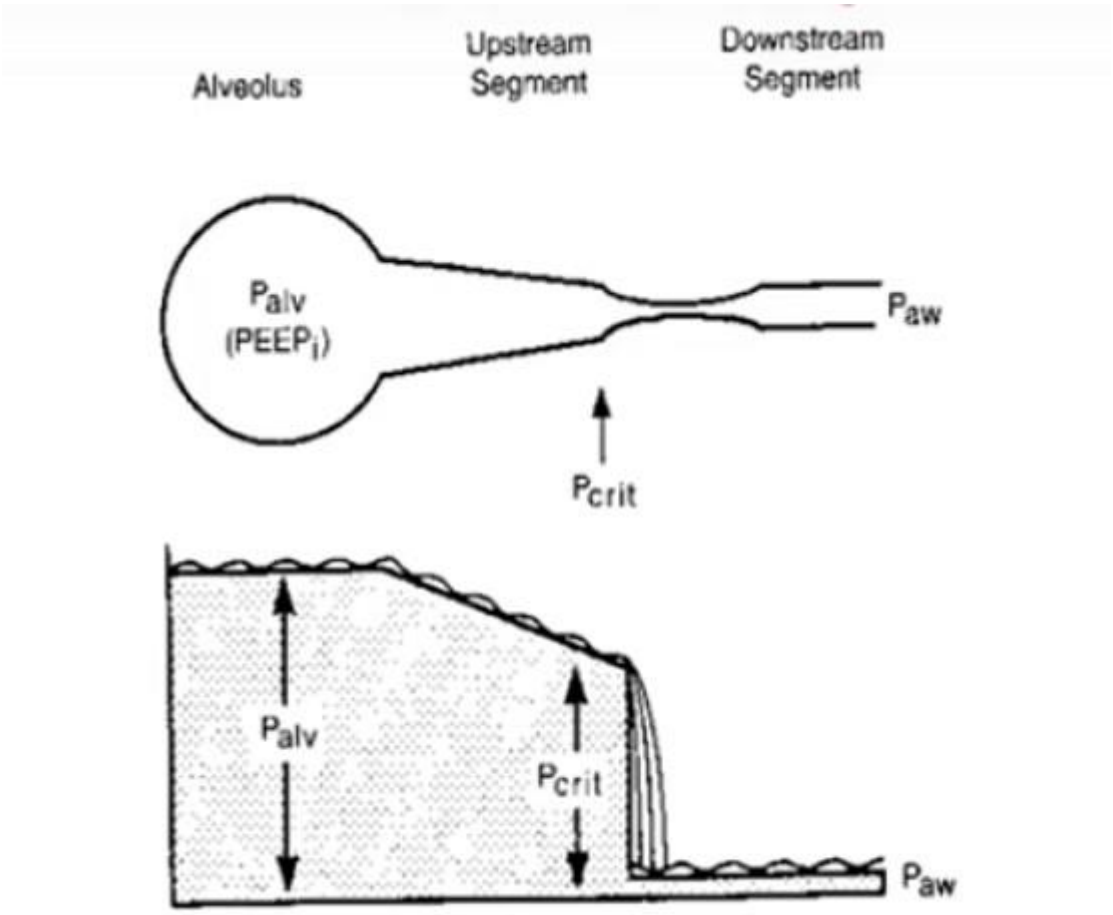


Figure 5-3 The waterfall concept- reduction of airflow below critical pressure point

Illustration showing the reduction in in air flow below the critical pressure point resutling in airways collapse and positive end-expiratory pressure. Palv- Alveolar pressure, Pcrit- critical pressure point, Paw- airway pressure.

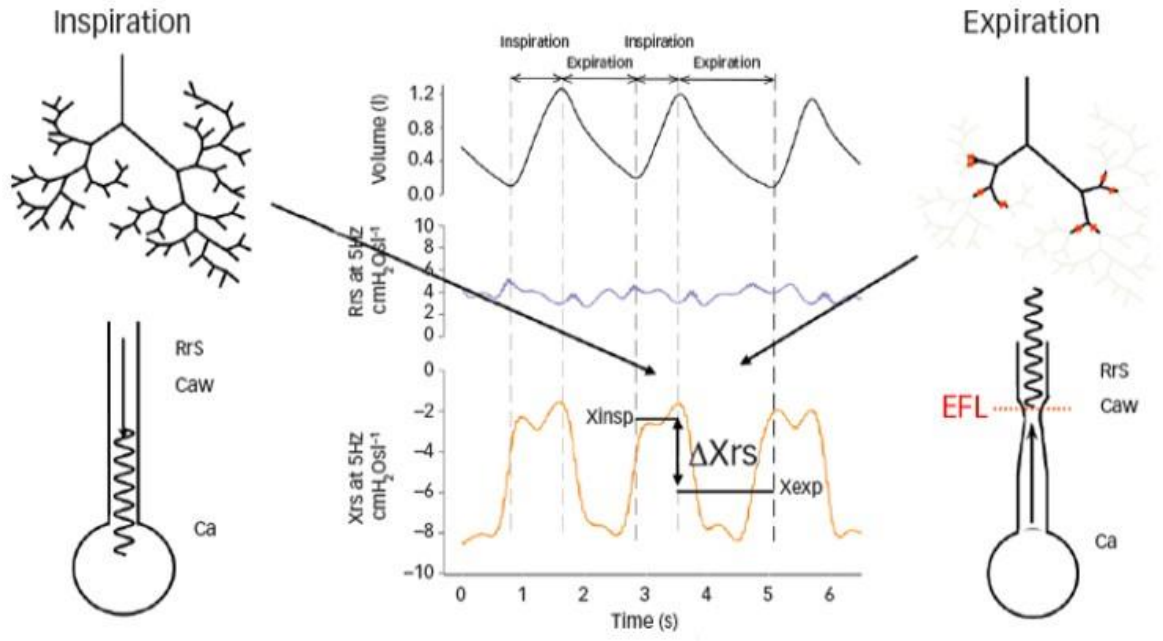
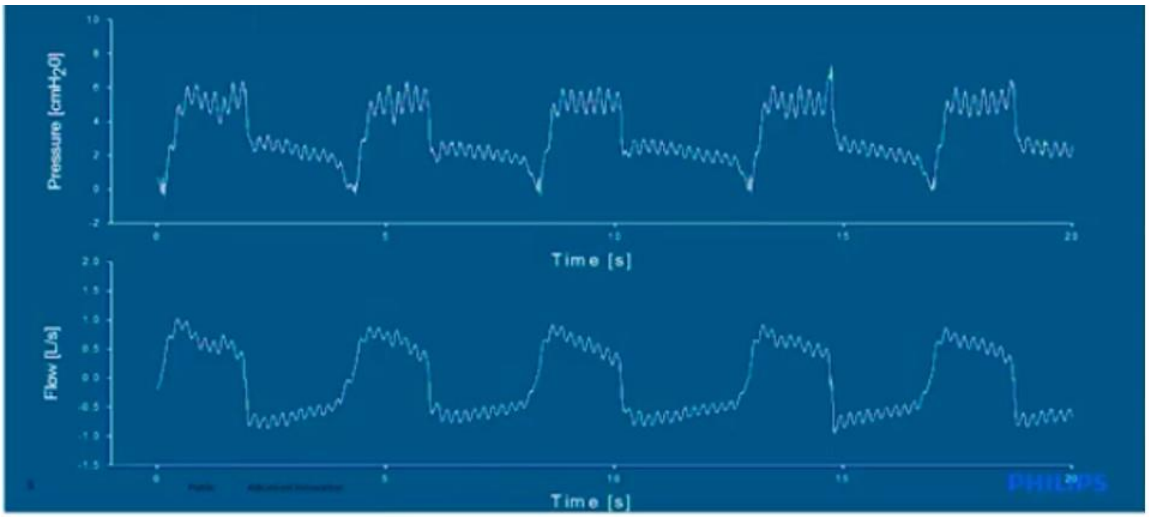


Figure 5-4 In breath analysis of reactance measured at 5Hz (ΔXRS)

Illustration of in-breath analysis to quantify expiratory flow limitation (EFL) through the difference between inspiratory X5(X5insp) and expiratory X5(X5exp) otherwise known as ΔXRS. Xrs- reactance (measured in cmH_20sl^{-1}), Rrs- resistance (measured in cmH_20sl^{-1}), Ca- alveolar pressure, Caw- airway pressure.



$$Zrs = Rrs + Xrs$$

Capacitance (-ive)

Inertive properties (+ive)

Figure 5-5 Forced oscillometry technique and principles of oscillometry

Illustration showing pressure (measured in cmsH_2O) and flow (measured in litres/second) variations during forced oscillometry measurments at tidal breathing. Equation demonstrating the sum of resistance (Rrs) + reactance (Xrs) equals respiratory impedence (Zrs). Reactance is the product of capitance and inertive properties of the lung.

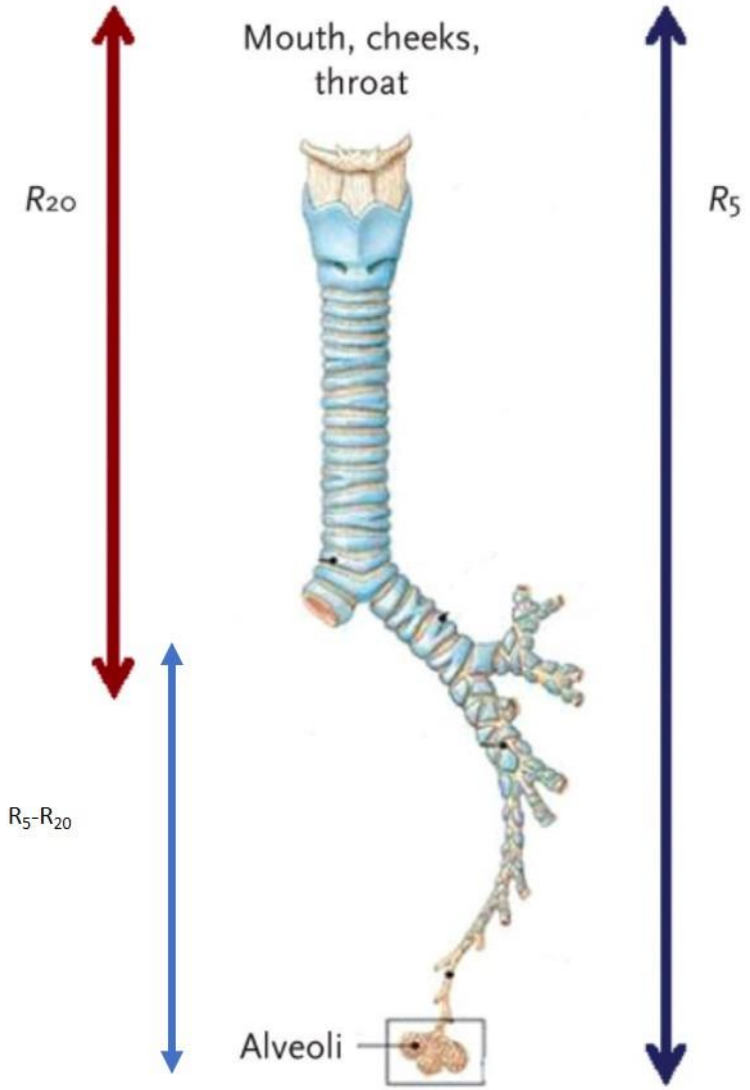


Figure 5-6 Airways resistance

Illustration representing Total airways resistance (R5), Large airways resistance (R20) and small ariways resistance (R5-R20) in the pulmonary tree.

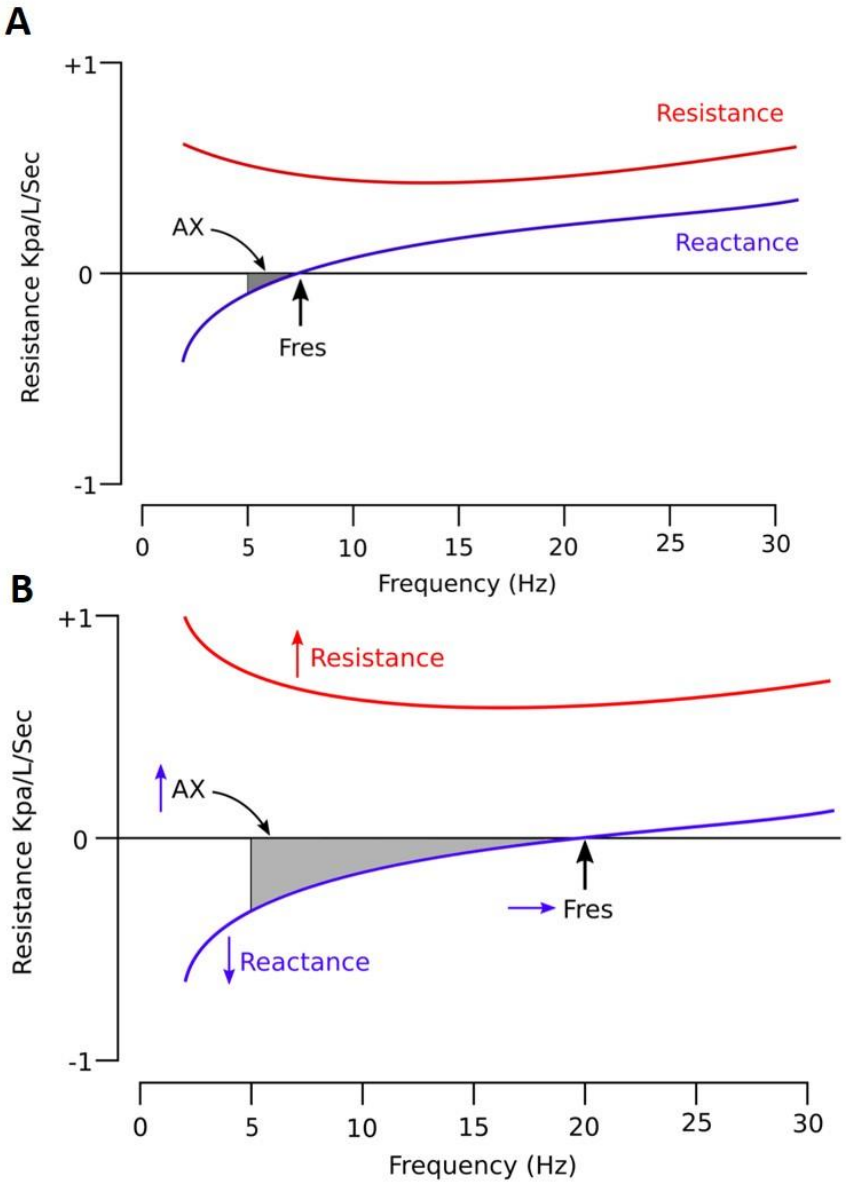


Figure 5-7 Forced oscillometry demonstrating area under the curve and resonant frequency in a normal subject (A) and in a patient with COPD (B)

5.1.3 Parasternal Electromyography

Surface parasternal electromyography measures the neuronal activation of motor units from the respiratory centre, otherwise known as neural respiratory drive (NRD). This advanced physiological biomarker quantifies the work of breathing providing insight into pulmonary mechanics and the respiratory load capacity relationship (Figure 1.1). The evolution of NRD techniques has been discussed in Chapter 1 & 4 with methods in Chapter 2 and appendices 6-8.

5.1.4 Neural respiratory drive in airways disease

Altered length tension properties of the diaphragm in COPD affect the position and efficiency during inspiration resulting in increased use of accessory muscle activation.[54]–[58] Resulting NRD in COPD is increased compared to matched healthy subjects, and corresponds to disease severity and dyspnoea.[29], [44], [59][57], [60] Progressive DH during graded exercise negatively impacts the pressure-generating capacity of the diaphragm which results in increased NRD and neuro-ventilatory uncoupling.[57] O'Donnell et al demonstrated a positive correlation between DH, increased dyspnoea and a reduction of the pressure-generating capacity of the diaphragm during graded exercise in COPD. Once minimal Inspiratory Reserve Volume (IRV) was reached the sensation of dyspnoea became intolerable and diaphragm efficiency was significantly impaired.[61] Long acting bronchodilators have demonstrated improvement in lung function, reduction in dyspnoea and NRD in this cohort of patients.[61], [62]

During states of increased respiratory load, the parasternal intercostal muscles are integral in accessory muscle activation to maintain ventilation and have a rostro-caudal distribution of EMG activity. [37], [38], [41][64] The second intercostal(IC) muscles demonstrated a similar activation as diaphragmatic EMG and contribute more to accessory inspiration than caudal IC muscles whose primary function is to maintain posture during tidal breathing.[42], [43] Quantifying NRD with parasternal EMG (EMGpara) of the second IC muscle is reliable and reproducible in COPD patients.[53][65] NRD increases in COPD during acute changes in respiratory load, such as histamine provocation or exacerbations and reduces following treatment.[65], [66] Neural Respiratory Drive Index (NRDI), a product of EMGpara%max and respiratory rate (RR), can be used as a biomarker of disease monitoring during exacerbations of COPD, with greater sensitivity and specificity than other physiological parameters.[65] Utilising EMGpara during acute exacerbations of COPD can predict safe discharge and readmissions rates, with reduced re-admission rates seen in those with a greater reduction in NRDI following treatment for an exacerbation.[65], [67]

NRD can be utilised to monitor a wide range of pulmonary diseases. Correlations between NRD, lung function and acute exacerbations have been demonstrated in Cystic Fibrosis(CF) and

Interstitial Lung Disease (ILD).[17][68], [69][70] Higher NRD levels were observed in CF patients compared to healthy controls during exercise, suggesting habituation of sensation of breathlessness with persistent high NRD levels in CF.[71] NRD is elevated in uncontrolled asthma compared to well controlled disease and matched healthy controls.[72]

5.1.5 Neural respiratory drive in obesity

Increasing prevalence of obesity has led to an increase in morbidity and mortality as a result of obesity related respiratory failure (ORRF).[73] The prevalence of Sleep Disordered Breathing (SDB) has risen as a result of the increased prevalence of obesity.[74]. A study of patients with SDB demonstrated a positive relationship between NRD and Body mass index (BMI), whilst highlighting an increase in NRD in the supine position, representing increased respiratory load, diaphragmatic splinting from abdominal mass effects and increased PEEP.[75] Continuous Positive Airway Pressure (CPAP) therapy can offset PEEP with subsequent reduction in NRD of up to 30%.[75]–[77] Patients with chronic hypercapnic respiratory failure secondary to obesity hypoventilation syndrome(OHS) demonstrate a decrease in NRD as a result of Non-invasive ventilation(NIV).[78] Quantification of this off-loading effect of NIV with NRD analysis can predict adherence in COPD-OSA overlap syndrome and potentially facilitate early optimisation in patients with chronic hypercapnic respiratory failure to improve patient outcomes.[79]

Another application of parasternal EMG monitoring is evaluating patient ventilator asynchrony (PVA) and potential utilising EMG signal to trigger NIV breaths, rather than relying on flow analysis. Previous studies showed no correlation between PVAs measured by parasternal EMG signals and control of ventilatory failure with nocturnal NIV.[82], [83] However, PVAs can lead to increased ventilator intolerance and de-ventilation dyspnoea and therefore further work is warranted to establish the role of NRD in the optimisation of domiciliary NIV.[81]

Parasternal EMG is accessible and provides insight into pulmonary mechanics of chronic respiratory disease. The evolution of NRD measurement and wider application supports its use as an advanced physiological biomarker of disease management. NRD has a potential role in disease optimisation and response to therapy during acute exacerbations to predict treatment success.

Advanced physiological measurements such as FOT and NRD in chronic respiratory disease can facilitate physiological phenotyping, targeted disease management, assess treatment response whilst providing invaluable insights into disease mechanics. This study will explore the feasibility of serial measurements of FOT and NRD alongside standard respiratory care in patients with a range of respiratory conditions out with a research centre or controlled research environment.

Demonstration of the feasibility would support implementation in future research in chronic respiratory disease.

5.2 Hypothesis

In this study we hypothesise that it is feasible and acceptable to monitor advanced physiological parameters such as FOT and neural respiratory drive in a wide range of patients with chronic respiratory disease. This study will give us insight into pulmonary mechanics of chronic respiratory disease, its response to standard therapy and long term two-way remote monitored PAP therapy or non-invasive ventilation.

5.3 Methods

5.3.1 Study design

This was a prospective observational study of the feasiblity of serial exploratory advanced physiology measurements in patients with a range of respiratory diseases and normal subjects. Exploratory Endpoints protocol and patient information sheets are detailed in Appendix 2 and 3. All exploratory research was undertaken alongside routine clinical care. (Figure 2.10)

Patients over the age of 16 years, able to provide informed consent, attending for routine clinical investigation and management with feasible timescales for repeat measurements were recruited. Main exclusion criteria was the inability to provide informed consent. We aimed to recruite approximately 75 patients with a range of chronic respiratory diseases as detailed in Appendix 2. Patients who met the inclusion criteria were provided with a patient information sheet (Appendix 3) and written consent was completed (Appendix 4).

105 patients were screened following tertiary referral for breathing support assessment or an acute decompensation resulting in hospital admission. 69 patients with a range of respiratory conditions were recruited. 12/69 patients were normal/controls where follow up visits were not arranged. 43/57 patients (excluding controls) attended study visit 1 and 26/57 patients attended at visit 2. 22 patients with hypercapnic severe COPD were screened with 10 patients recruited. In

this chapter we focus on the conditions who received similar respiratory management including patients managed with remote monitored PAP therapy for OSAS and home NIV for ORRF and hypercapnic severe COPD. Patients were separated into phenotypes OSAS, ORRF, hypercapnic severe COPD and COPD-OSA overlap. These diagnoses were determined by an experienced clinical team based on standard cardiorespiratory evaulation, clinical presentation, and current guidelines.

Baseline demographics and anthropometrics data were collected at the baseline visit. Symptom burden was assessed with Epworth sleepiness scale, MRC dyspnoea score, modified COPD assessment tool (mCAT) and performance status at each visit (Appendix 5). Spirometry was performed using a handheld device (Vitalograph copd-6 COPD Screening Device, Vitalograph, England) according to standardised ERS guidelines[4]. All patients suspected of sleep disordered breathing underwent laboratory-based polysomnography or home limited polysomnography to confirm sleep disordered breathing. Diagnosis of hypercapnic severe COPD was based on spirometry, clinical presentation and arterial blood gas analysis.

Forced oscillometry (FOT) was measured using a portable device (Tremflo, Thorasys, Canada) in the upright position as detailed in Chapter 2 (Figure 2.14). Measurements were taken during 3 cycles of steady tidal breathing. At least three measurements were taken according to ERS guidelines or more if the CV was greater than 15. Results are expressed in figures as the mean ± standard deviation.

Parasternal electromyography was measured as detailed in Chapter 2 and in Appendices 6&7. All data was collected with patient resting at 45degrees for at least 5 mins of tidal breathing followed by 10 sniff manoeuvres. Results are presented as absoluted values, mean ± standard deviation.

Anthropometric measurements, FOT, NRD, PAP/NIV usage, symptom burden and where feasible capillary or arterial blood gas data were collected at baseline, 3months, 6 months and 12 months following PAP/NIV initiation.

5.3.2 Ethics

This study was sponsored by NHS Greater Glasgow & Clyde with research ethics approval proved by London Queen Square Research Ethics Committee (REC reference 16/LO/2090)

5.3.3 Statistical analysis

Results are shown in Tables 5.1-5.17 with absolute values, mean ± Standard deviation(SD), percent predicted spirometry, PAP therapy represented as 95% and median pressures. Normal distribution of results was confirmed by Shapiro-Wilk test. Pearson correlation coefficients were calculated to evaluate lung function and other demographic data. Spearman's correlations were used in data found to be not normally distributed. Non-parametric Wilcoxon tests analysed changes in FOT and EMG data from baseline measurements. Relationships between mean EMGpara, EMGpara%max and NRDI and disease severity or symptoms were analysed using linear regression analysis. T tests were used were appropriate. P values <0.05 were considered statistically significant. All statistical analysis was carry out on Graphpad, Prism software.

5.4 Results

5.4.1 Obstructive Sleep Apnoea Syndrome

20 patients with OSAS were recruited between September 2017 and October 2018. Population demographics are shown in Table 5.1. The study populations mean age was 51.2 years (SD 13.3) and there was an equal proportion of male: female representation (10 males, 10 females). Mean BMI was 41 kg/m^2(SD 8.3 kg/m^2). Mean apnoea hypopnoea index (AHI) was 54 events/hour (SD 25 events/hour) and a mean oxygen desaturation index (ODI) of 47.9 events/hour (SD 18.2 events/hour). Mean oxygen saturations was 90.4% (SD 2.9%) and mean Total Sleep Time with oxygen saturations <90% (TST90) was 42.6% (SD 30.5%). Mean FEV1 was 82.4% (SD 23.7%) and FEV1/FVC was 83.9% (SD 6.7%)(Table 5.1). Daytime somnolence was quantified by the Epworth Sleepiness Score (ESS) with a mean of 14.5 (SD 3.9) for this population. Mean values of mCAT, MRC dyspnoea score and Performance status (PS) were 22.3 (SD 6.3), 2.4 (SD 1.1) and 1.8 (SD 0.6), respectively (Table 5.1).

All 20 patients used Auto-titrating positive airways pressure (APAP) and 50% reached target treatment adherence (≥70% days of CPAP usage ≥4hours; the level set for reimbursement in US health system). Mean 95th centile pressure requirements was 12.7 cmsH_2O (SD 1.8) and median pressure requirements was 9.7 cmsH_2O (SD 1.8). (Table 5.2) All patients were under remote PAP therapy review with average remote requirements of 4(SD 3)data reviews, 2(SD2) telephone consultations and no prescription changes or day case troubleshooting sessions. Mean follow up was 5.8 months. (Table 5.2)

Exploratory Endpoints

20 patients had FOT and EMGpara measurements taken at baseline. One patient failed to attend for further exploratory endpoints measurements. 19 patients had further measurements taken, 13 patients had FOT at 3 months and 11 patients at 6months. 14 patients had EMG para measured at 3 months and 11 patients at 6months. Baseline FOT and EMGpara are shown in Table 5.3 and appendix 9.

Oscillometry

A significant decrease in R5-R20 was observed in patient's adherent to PAP therapy at 3months (p<0.05)(Fig 5.8). Reactance measured by Ax and ΔXRS decreased with PAP adherence (p<0.05 for both) (Fig 5.9). A further decrease in $\Delta XRS$was demonstrated in those adherent to PAP therapy at 6months, p< 0.05 (Figure 5.9B). 50% of patietns demonstrated EFL on baseline COT (Table 5.3). Analysis of patients with expiratory flow limitation (ΔXRS> 0.28) demonstrated no significant correlation in between ΔXRS and BMI, FEV1, R5-R20, APAP pressures or symptom burden (measured by AHI, ODI, ESS, PS, mCAT or MRC). Total airways resistance (R5) decreased in patient's adherent to PAP therapy but did not reach statistical significance and increased in non-adherence (Appendix 9, Figure 9-1). Disease severity measured by AHI and ODI, demonstrated no correlation with BMI. There was no significant correlation with oscillometry results and disease severity or BMI. There were no significant correlations between FEV1 and FOT or PAP therapy requirements.

Parasternal Electromyography

A decreasing trend was shown in all three EMG parameters in those adherent to PAP therapy (Figure 5.10 &appendix 9). MeanEMGpara%max showed a decreasing trend at 3months (p=0.05)and 6 months (p= 0.09) in those adherent to PAP therapy (Figure 5.10B). NRDI and meanEMGpara showed a decreasing trend in those adherent to PAP therapy but did not reach statistical significance (Figure 5.10A&C). Disease severity measured by AHI and ODI demonstrates no statistical significant correlation with meanEMGpara, EMGpara%max or NRDI. Mean oxygen saturations and TST90 demonstrated no relationship with parasternal EMG data. There was no significant correlation with disease burden, measured by ESS, and meanEMGpara, EMGpara%max or NRDI.

Symptom burden

There was a significant decrease in ESS was observed at 3months and 6 months in all patients(p<0.05 for both). There was an overall decreasing trend from baseline values in PS, modified CAT score and MRC scores in both adherence and non-adherence of PAP therapy at 3 and 6 months but did not reach statistical significance. (Appendix 9)

	Sex (M/F)	Age	BMI	AHI	ODI	mean sats (%)	TST90 (%)	FEV1 (%)	FEV1/FVC (%)	ESS	mCAT	MRC	PS
1	M	52	33.6	42.6	43	86	97	95	83	15	18	1	2
2	F	45	34.4	24	62	89	59	35	73	21	28	2	2
3	M	59	41.2	54	55			83	84	9	14	1	2
4	M	54	35.5	30	30	94	2.3	96	90	10	24	1	1
5	M	66	34.3	29	28	93	72	82	80	15	19	2	2
6	F	54	31.4	50	52	89	49	101	81	13	11	1	1
7	F	48	37	60	59	92	31	89	90	13	18	1	1
8	F	37	55.8	82	80	92	27	102	84	18	29	2	2
9	F	45	45.3	29.2	21.8	94	8	99	100	15	21	3	2
10	M	81	35.8	71	60	88	94	60	75	11	15	3	2
11	M	39	60	79	50	87	31	60	93	18	31	4	2
12	M	70	54.7	46	70	90	52	71	79	8	33	4	2
13	F	53	48.7	118	31	83	87	89	86	21	28	3	2
14	M	52	33.9	29	28	93	6	92	80	14	17	2	1
15	M	37	45.7	66	73	91	36	97	78	12	20	3	2
16	F	48	38.8	24	29	92	8	78	90		30	3	2
17	M	39	41.2	74	73	92	57	112	85	20	18	2	2
18	F	25	42.2					100		17	22		1
19	M	50	33.4	66	36	91	35	89	86	11	22	3	1
20	M	70	37.9	54	29	91	15	17	77	14	28	4	3
Mean (SD)		51.2 (13.3)	41 (8.3)	54.1 (24.7)	47.9 (18.2)	90.4 (2.9)	42.6 (30.5)	82.4 (23.7)	83.9 (6.7)	14.5 (3.9)	22.3 (6.3)	2.4 (1.1)	1.8 (0.6)

Table 5-1 Population demographics for patients with obstructive sleep apnoea syndrome initiated on remote monitored positive airway pressure therapy

AHI- apnoea hypopnoea index (events/hour), ODI- oxygen desaturation index (events/hour), Mean sats%- mean peripheral oxygen saturations (%), TST90- percentage Total Sleep Time with oxygen saturations <90% during either limited or fully polysomnography, ESS- Epworth Sleepiness scale, mCAT -modified COPD assessment tool score, MRC- Medical research council dyspnoea score, PS- ECOG performance status.

	95%PAP ($cmsH_2O$)	Median PAP ($cmsH_2O$)	Adherence (Y/N)	Data reviews	Telephone consultations	Prescriptions changes	Day case visits	Follow up (months)
1	12.2	9.3	Y	10	7	0	0	12
2	15.2	12.5	Y	3	2	0	0	6
3	12.9	9.1	Y	5	2	1	0	6
4	16	13.6	Y	3	1	1	0	3
5	12.4	9.1	Y	4	2	0	1	3
6	11.5	8.9	Y	3	1	1	0	3
7	12.8	9.9	Y	3	1	0	0	6
8	11.8	9.5	Y	2	1	0	0	3
9			Y	6	3	0	0	3
10	12	9.4	Y	5	3	1	0	12
11	13.7	9.9	N	13	9	0	2	6
12			N	1	0	1	0	Lost to FU
13	15	10.4	N	1	0	0	0	Lost to FU
14	11	8	N	3	1	0	0	6
15	11	9.2	N	2	1	0	0	3
16	14.5	11.8	N	3	1	0	0	6
17	12.3	9.2	N	4	2	0	0	3
18	12.1	9.1	N	4	2	0	0	6
19			N					Lost to FU
20	8.9	5.3	N	7	4	0	0	12
Mean (SD)	12.7 (1.8)	9.7 (1.8)	10 Y/10N	4.3 (3.0)	(2.3) 2.3	0.3 (0.5)	0.2 (0.5)	5.8 (3.3)

Table 5-2 Breathing support requirements and requirements for remote management of auto-titrating positive airway pressures therapy (APAP mode) in patients with obstructive sleep apnoea syndrome

95% PAP- 95% centile PAP requirements. Adherence set as >4hours use for >70% nights used, the level set for reimbursement in US health system.

	R5	R5-R20	R20	Ax	ΔXRS	Vt (L)	Fres (hz)
1	5.18	1.03	4.15	25.88	0.19	1.31	29.9
2	6.46	0.14	6.32	1.69	0.65	0.32	8.8
3	5.05	1.15	3.9	21	0.32	1.2	23.15
4	8.26	2.17	6.09	17.64	1.22	0.92	21.48
5	7.25	2.93	4.32	48.71	0.99	0.77	31.83
6	5.22	0.34	4.88	6.67	-0.97	1.77	13.89
7	3.75	0.05	3.7	8.82	-0.35	0.8	15.5
8	5.04	0.93	4.11	15.94	-1.78	2.13	
9	6.19	1.26	4.93	17.5	-0.24	0.85	24.2
10	4.55	1.19	3.36	15.24	0.97	1.08	
11	6.15	2.33	3.82	32.06	2.59	0.92	24.22
12	4.24	1.59	2.65	24.38	0.79	1.11	22.81
13	6.44	1.13	5.31	26.94	0.67	0.99	23.51
14	4.22	1.01	3.21	18.8	0.36	1.32	25.93
15	3.17	0.57	2.6	2.69	-0.01	1.03	12.47
16	4.5	0.28	4.22	9.04	-0.38	0.97	16.73
17	6.39	2.73	3.66	24.68	0.21	1.11	22.7
18	4.8	0.89	3.91	11.93	-0.23	0.75	20.71
19	3.33	-0.73	4.06	6.76	1.33	0.89	12.41
20	22.65	0.48	22.17	12.26	0.04	0.69	
Mean (Standard deviation)	6.14 (4.10)	1.07 (0.93)	5.07 (4.14)	17.43 (11.18)	0.32 (0.92)	1.05 (0.39)	20.6 (6.38)

Table 5-3 Baseline oscillometry readings in patients with obstructive sleep apnoea syndrome initiated on remote monitored positive airway pressure therapy

R5- Large airways resistence, R20- Large airways resistence, R5-R20- small airways resistence, ΔXRS- in-breath change in reactance measured at 5Hz, Ax- reactance, Vt- tidl volume (litres), Fres- resonant frequency (Hertz). Highlighted ΔXRS identifies those with tidal expiratory flow limitation. All oscillometry measured in $cmsH_2OsL^{-1}$

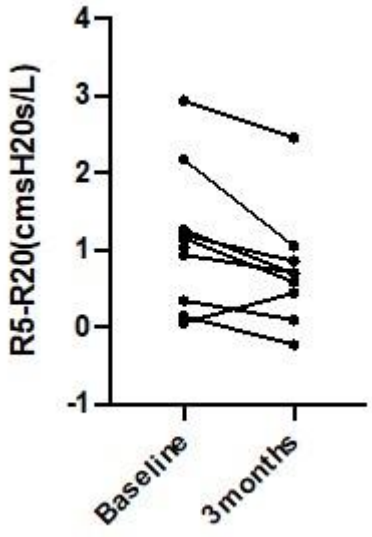


Figure 5-8 Change in small airways resistance in patients with obstructive sleep apnoea syndrome who were adherent to positive airway pressure therapy- baseline versus 3months

Adherence- >4hours use for >70% of the nights used. R5-R20 measured in $cmsH_2OsL^{-1}$

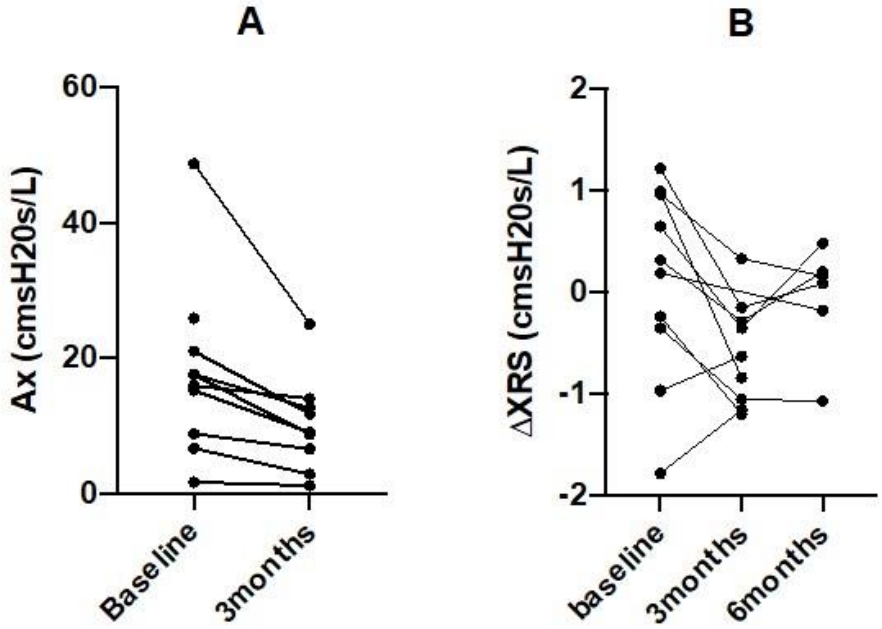


Figure 5-9 Change in reactance measurements in patients with obstructive sleep apnoea syndrome who were adherent to positive airway pressure therapy- baseline versus 3 months

A- Demonstration of reactance measured by area of reactance(Ax).

B- Demonstration of in-breath difference of reactance at 5Hz (ΔXR5)

Adherence- >4hours use for >70% of the nights used, All data measured in $cmsH_2OsL^{-1}$

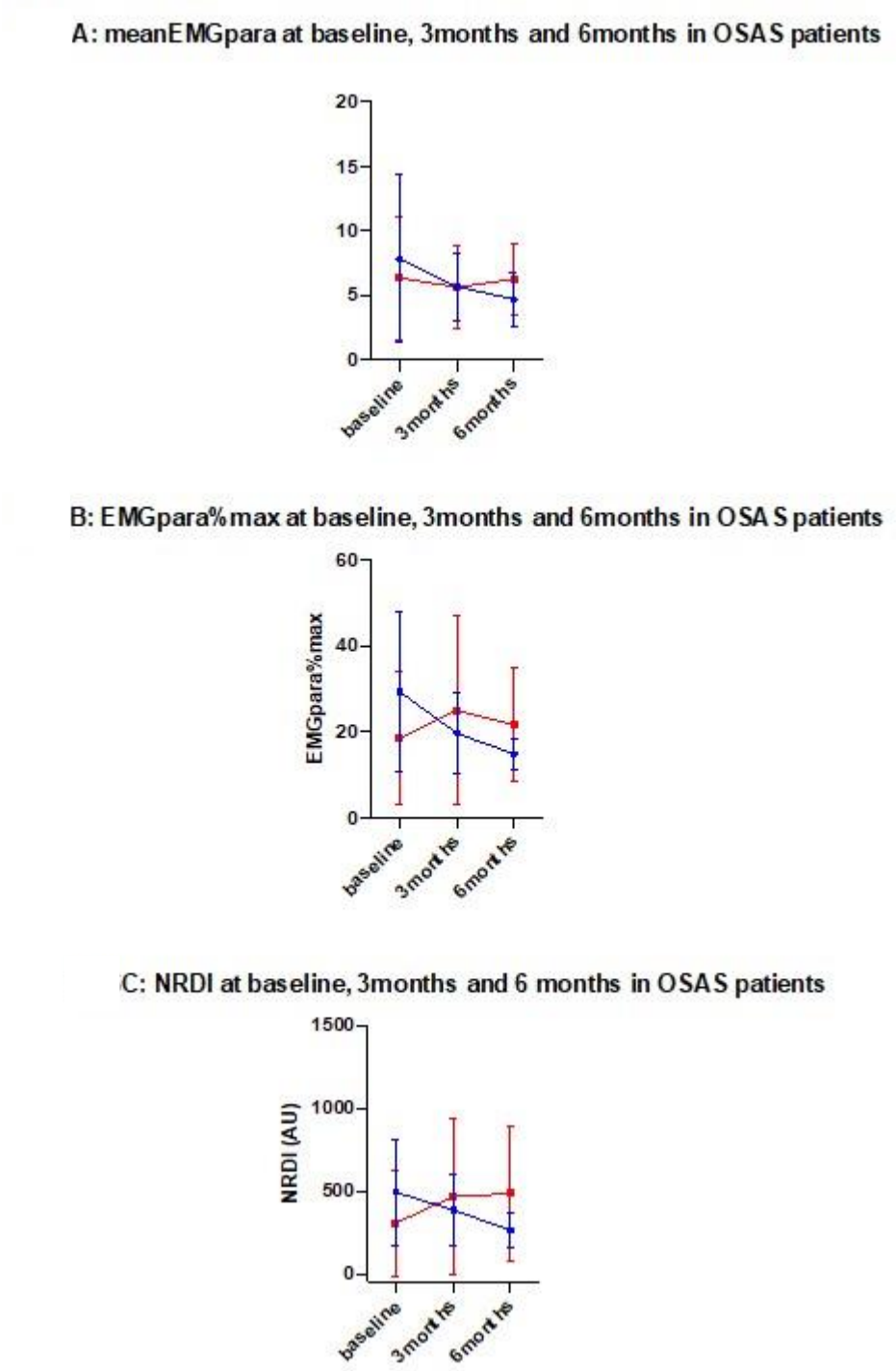


Figure 5-10 Mean changes in parasternal electromyography in patients with obstructive sleep apnoea syndrome treated with positive airway pressure (PAP) therapy

A- Average mean parasternal electrmyography (meanEMGpara) in those adherence (blue) and non-ahderence (red) to PAP therapy. B- Average normalised parasternal electrmyography (EMGpara%max) in those adherence (blue) and non-ahderence (red) to PAP therapy. C- Average neural respiratory drive index (NRDI) (measured in arbitary units (AU)) in those adherence (blue) and non-ahderence (red) to PAP therapy. (Adherence is considered >4hours use in >70% of nights used) Data plotted as mean and standard error of mean.

5.4.2 Obesity Related Respiratory Failure

4 patients with confirmed obesity related respiratory failure were recruited between September 2017 and August 2018. Population demographics are shown in Table 5.5. Two were males and two females with a mean age of 55.8 years (SD 10.7years). Mean BMI was 49.5 kg/m^2(SD 11.1 kg/m^2). Mean AHI was 61.3 events/hour (SD 17.1 events/hour) and ODI was 64.1 events/hours (SD 17.7 events/hour). Mean oxygen saturations were 81.8% (SD 8.9%) and mean TST90 was 61.3% (SD 31.3%). Mean FEV1 and FEV1/FVC was 42.8% (SD 12.8%) and 79.3% (SD 15.9%), respectively(Table 5.5). Daytime somnolence quantified by ESS showed a mean of 17.8 (SD 3.5). Mean mCAT, MRC dyspnoea score and performance status(PS) was 23(SD 2.8), 4(SD 0.8) and 2.5(SD 0.6) respectively(Table 5.4).

All subjects were treated with auto-titrating NIV (iVAPS) and auto-titrating expiratory positive airways pressure (AutoEPAP). 50% achieved target treatment adherence (≥70% days of PAP usage ≥4hours; the level set for reimbursement in US health system) (Table 5.6). Mean 95% IPAP values were 21.6cmH20 (SD 5.6cmH20) with a mean median IPAP of 14.8cmH20 (SD 2.6cmH20). 95% EPAP and median EPAP values were 10.9 cmsH_2O (SD 4.1 cmsH_2O) and 9.6 cmsH_2O (SD 3.8 cmsH_2O) respectively(Table 5.6). Control of hypoventilation is demonstrated with decreasing serial carbon dioxide and bicarbonate levels (Appendix 9, Figure 9-4). All patients were under remote PAP therapy review with average remote requirements of 6 data reviews (SD 2.8), 3(SD0.6) telephone consultations, 1 (SD1.3) prescriptions changes and no day-case troubleshooting sessions. Mean follow up was 8.3 months. (Table 5.5)

Exploratory Endpoints

All patients had FOT and EMGpara measurements taken at baseline visits. 3 had further measurements at 3months, 3 at 6months and 2 at 12 months. Baseline FOT and EMGpara are shown in Appendix 9 (Tables 9.2 & 9.3).

Oscillometry

FEV1 and FOT had a positive correlations with 95%EPAP and median EPAP values shown in Figure 5.11 and Table 5.6. $\Delta XRS$and Ax demonstrated a strong correlation with median IPAP, r= 0.955 p<0.05 and r= 0.94 p=0.05, respectively (Figure 5.11 A & B). Median EPAP requirements showed a strong correlation with R5 and AX, r=0.99 p<0.05 and r= 0.99 p<0.05, respectively (Figure 5.11C&D). FEV1 demonstrated a strong correlation with median EPAP requirements, r= 0.93 p=

0.23 (Figure 5.11E). Symptom burden measured by ESS and MRC did not demonstrate a relationship with baseline FOT data.

There was a non-significant decreasing trend in Total airways resistance(R5) in all subjects at 3months(p=0.25) and 6months (p=0.25). In most subjects large (R20) and small airways resistance(R5-R20) decreased with NIV but did not reach statistical significance. Reactance measured by ΔXRS and Ax demonstrated a non-significant decreasing trend in all subjects (Appendix 9)

AHI showed a non-significant positive correlation with BMI, r=0.89 p=0.31 (Figure 5.16B). There was a strong correlation with AHI and R5-R20, r=0.88 p=0.32.(Figure 5.16C). ODI demonstrated a negative correlation with ΔXRS, r=-0.62 p0.38(Figure 5.16D). BMI demonstrates a strong correlation with R5-R20, r=0.87 p=0.13(Figure 5.16E). A strong positive correlation was seen in BMI versus R5(r=0.8 p=0.33), R20(r=0.8 p=0.33) and Ax(r=0.8 p=0.33) seen in Figures 5.16 F-H). BMI and FEV1 showed a positive correlation, r=0.76 p=0.24 (Figure 5.16I). FEV1 demonstrated a non-significant positive correlation with R5(r= 0.69 p=0.31) and R5-20 (r=0.71 p=0.29) (Appendix 9).

Parasternal Electromyography

There were no significant trends in meanEMGpara, EMGpara%max or NRDI observed at 3months, 6months and 12 months. There was no significant correlation between change in AHI (ΔAHI) and change in NRDI ($\Delta NRDI$), change in meanEMGpara ($\Delta meanEMGpara$) or change in EMGpara%max ($\Delta EMGpara\%max$). Diesease severity measured by AHI and ODI demonstrated no significant correlations with meanEMGpara, EMGpara%max of NRDI. There was no relationship demonstrated between mean oxygen saturations or TST90 with parasternal EMG data. Symptom burden measured by ESS did not show a relationsip with meanEMGpara, EMGpara%max or NRDI.

Symptom burden

There no significant change in symptom burden, measured by ESS, mCAT, MRC dyspnoea score or performance status, in adherence and non-adherence to NIV at 3, 6 or 12months.

	Sex (m/f)	Age (yrs)	BMI	AHI	ODI	mean Sats (%)	TST90(%)	ESS	FEV1 (%)	FEV1/ FVC (%)	ESS	M CAT	MRC	PS
1	F	62	61.7	66.6	60	90	28	22	45	84	22		4	3
2	F	42	56	74.8	84.2	78	90	19	60	85	19	25	4	2
3	M	66	38.6	42	42	88	66	16	32	56	16	21	3	2
4	M	53	41.7		70	71			34	92	14		5	3
Mean (SD)		55.8 (10.7)	49.5 (11.1)	61.1 (17.1)	64 (17.8)	81.8 (8.9)	61.3 (31.3)	17.5 (2.1)	42.78 (12.8)	79.3 (15.9)	17.8 (3.5)	23 (2.8)	4 (0.8)	2.5 (0.6)

Table 5-4 Population demographics in patients with obesity related respiratory failure managed with remote monitored home non-invasive ventilation

AHI- apnoea hypopnoea index (events/hr), ODI- oxygen desaturation index (events/hour), mean sats- mean peripheral oxygen saturations (%), TST90- percentage Total Sleep Time with oxygen saturations <90 during limited or fully polysomnography, ESS- Epworth Sleepiness Scale (ESS), mCAT- modified COPD assessment tool score, MRC- Medical Research Council dyspnoea scale, PS- ECOG Performance Scale

	95% IPAP ($cmsH_2O$)	mIPAP ($cmsH_2O$)	95% EPAP ($cmsH_2O$)	mEPAP ($cmsH_2O$)	Adherence (Y/N)	Data reviews	Telephone consultations	Prescription changes	Day case visits	Follow up (months)
1	28.7	18.5	14.9	13.9	Y	10	3	3	0	12
2	15.9	13.3			Y	4	3	1	0	12
3	18.8	14.8	11.1	8.3	N	4	2	0	0	6
4	23	12.6	6.7	6.6	N	6	2	1	0	3
Mean (SD)	21.6 (5.56)	14.8 (2.63)	10.9 (4.10)	9.6 (3.82)		6 (2.83)	2.5 (0.58)	1.25 (1.26)	0	8.25 (4.5)

Table 5-5 Breathing support requirements and remote monitoring requirements in patients with obesity related respiratory failure requiring home non-invasive ventilation

All patients were managed on auto-titrating volumes assured pressure support. 95%IPAP- 95th centile inspiratory positive airways pressures, mIPAP- median inspiratory positive airways pressures, 95EPAP- 95th centile expiratory positive airways pressures, mEPAP- median expiratory positive airways pressures. Adherence- ≥70% days of PAP usage ≥4hours; the level set for reimbursement in US health system.

	mIPAP	95% EPAP	mEPAP
R5	r=0.74 p=0.26	r=0.93 p=0.242	r=0.99 p<0.05
R20	r=0.75 p=0.253	r=0.88 p=0.316	r=0.99 p=0.099
R5-R20	r=0.68 p=0.319	r=0.99 p=0.078	r=0.98 p=0.14
ΔXRS	r= 0.96 p<0.05	r=0.99 p=0.087	r=0.89 p=0.304
Ax	r= 0.95 p=0.05	r=0.96 p=0.186	r=0.99 p<0.05

Table 5-6 Correlations between baseline oscillometry and positive airway pressure requirements in patients with obesity related respiratory failure requiring home non-invasive ventilation

Statistical signifcant findings are highlighted in red (p<0.05). R5- Large airways resistence, R20- Large airways resistence, R5-R20- small airways resistence, ΔXRS- in-breath change in reactance measured at 5Hz, Ax- reactance, mIPAP- median inspiraotry positive airway pressure requirements, 95%EPAP- 95th centile expiratory positive ariway pressure requirements, mEPAP- median expiratory positive airway pressure requirements.

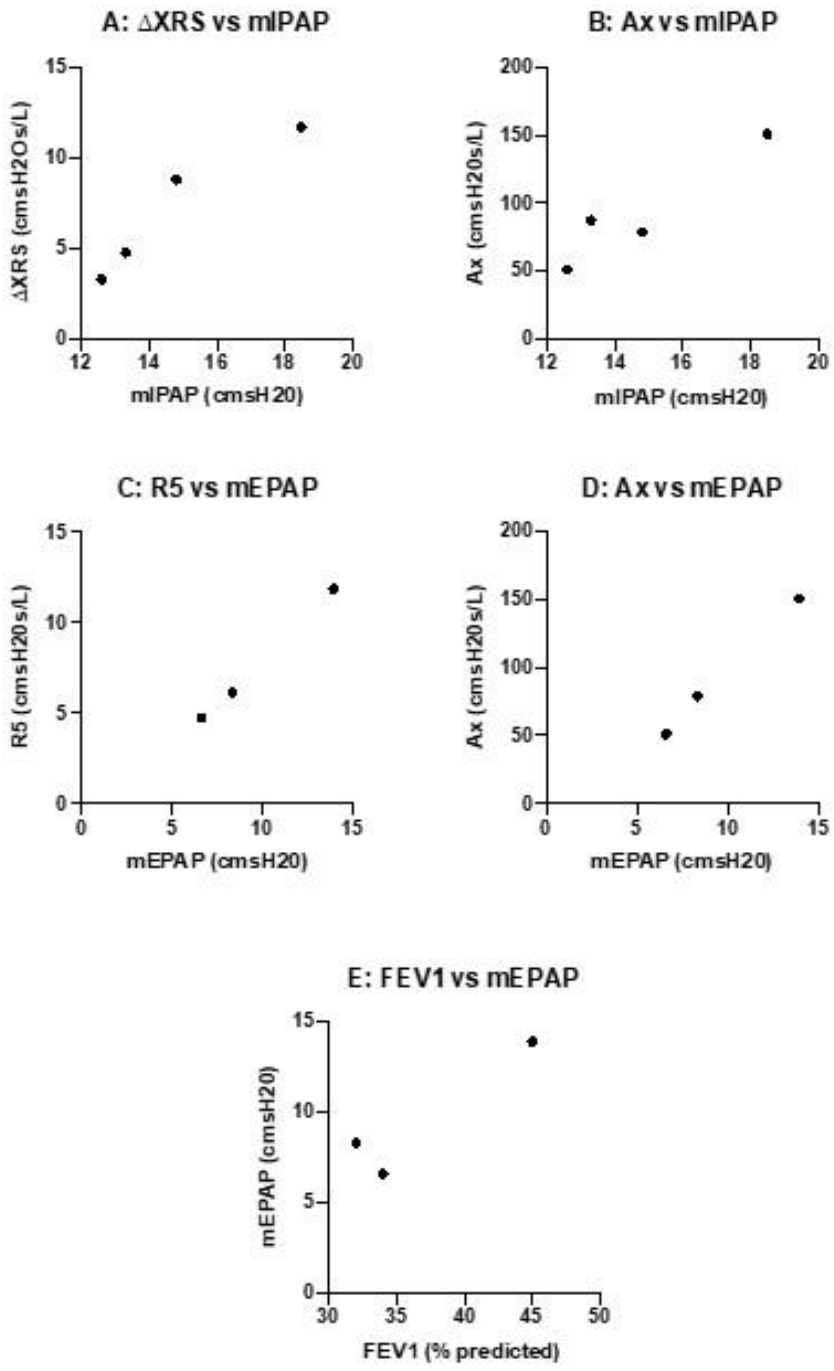


Figure 5-11 Correlations between baseline oscillometry and positive airway pressure requirements in patients with obesity related respiratory failure requiring non-invasive ventilation

A- Correlation in the change in in-breath reactance at 5Hz (ΔXRS) and median inspirtory positive airways pressure requirements (mIPAP). B- Correlation in baseline reactacnce (Ax) and and median inspirtory positive airways pressure requirements (mIPAP). C- Correlation of large airways resistence (R5) and median expirtory positive airways pressure requirements (mEPAP). D- Correlation in reactance (Ax) and median expirtory positive airways pressure requirements (mEPAP). E- Correlation between forced expiratory volume in 1 second (FEV1) and and median expirtory positive airways pressure requirements (mEPAP). All oscillometry measured in cmsH$_2$Os/L. All PAP requirements measured in cmsH$_2$O.

5.4.3 Severe COPD with persistent hypercapnic failure

10 patients with confirmed COPD with persistent hypercapnic respiratory failure were recruited between September 2017 and August 2018. Population demongraphics are shown in Table 5.10. There were 7 females and 3 males with a mean age of 59.6 years (SD 7.3years). Mean FEV1 was 26.3% (SD 5.1%) and FEV1/FVC of 52.9% (SD 11.49%). Mean arterial carbon dioxide (PCO_2) was 7.9 kPa (SD 1.1kPa) and mean bicarbonate of 34.1 mmol/L (SD 3.2mmol/L). Baseline symptom burden showed no intrusive daytime somnolence with a mean ESS of 6.6 (SD 4) but severe respiratory symptoms with a mean mCAT score of 29.8 (SD 5.2) with functional limitations represented by mean MRC score of 4.7 (SD 0.5) and mean performance status of 3. (Table 5.7)

All patients were managed with auto-titrating NIV(iVAPS) and auto-titrating expiratory positive airways pressure (AutoEPAP). 2 patients achieved target treatment adherence (≥70% days of CPAP usage ≥4hours; the level set for reimbursement in US health system)(Table 5.8). Mean 95% IPAP values were 19 $cmsH_2O$ (SD 6.3 $cmsH_2O$) with a mean median IPAP of 14 $cmsH_2O$ (SD 4.6 $cmsH_2O$). 95% EPAP and median EPAP values were 9.4 $cmsH_2O$ (SD 3.3 $cmsH_2O$) and 7.4 $cmsH_2O$ (SD 2.3 $cmsH_2O$) respectively. All patients were managed with 2-way remote monitored NIV, mean remote review of data was 6 and 3 telephone consultations with 1 prescription change (Table 5.8). No patients required day case NIV trouble shooting session and the majority of patients were followed up for 6 months (mean 6.3 months). Serial measurements of ventilation represented by carbon dioxide and bicarbonate demonstrated a non-significant decrease in bicarbonate in the majority of users and a decrease in CO_2 in users of NIV (Appendix 9).

Exploratory Endpoints

All patients had FOT and EMGpara measurements taken at baseline visits. 3 had further measurements at 3months and 6 at 6months. Baseline FOT and EMGpara are shown in Table 5.9 and appendix 9.

Oscillometry

Change in ΔXRS showed a strong relationship with change in MRC dyspnoea scale at 3months (r= 88, p= 0.32). Symptom burden measured by mCAT and MRC did not demonstrate a relationship with ΔXRS in those who had EFL at baseline. In majority of patients total airway resistance(R5) and large (R20) decreased with NIV but did not reach statistical significance. Reactance measured by ΔXRS and Ax demonstrated a no significant trend in all subjects. (Appendix 9). There were no correlations demonstrated between BMI with FOT or PAP therapy requirements. No correlation was demonstrated between severity of disease measured by FEV1 with FOT or PAP therapy.

Parasternal Electromyography

There were no significant trends in meanEMGpara, EMGpara%max or NRDI observed at 3months and 6months (Appendix 9). There was no significant correlation between change in AHI (ΔAHI) and change in NRDI ($\Delta NRDI$), change in meanEMGpara ($\Delta meanEMGpara$) or change in EMGpara%max ($\Delta EMGpara\%max$). Disease severity measured by FEV1 demonstrated no significant correlations with meanEMGpara, EMGpara%max of NRDI. There was no correlation with symptom burden measured by ESS, mCAT or MRC with parasternal EMG data. Severity of respiratory failure measured by CO_2 and bicarbonate did not demonstrate a significant relationship with parasternal EMG data.

Symptom Burden

There was no significant change in symptom burden, measured by ESS, mCAT, MRC dyspnoea score or performance status, in adherence and non-adherence to NIV at 3 or 6months.

	Sex (m/f)	Age (yrs)	BMI (kg/m²)	FEV1 (%)	FEV1/FVC (%)	PCO2 (kPa)	HCO_3 (mmol/L)	PO2 (kPa)	ESS	mCAT	MRC	PS
1	F	60	30.4	30	69	6.59	34	11.5	6	26	5	3
2	F	67	31.6	20	54	8.8	36	7.2	8	20	4	3
3	**F**	**57**	**16**	23	**52**	**8.2**	**35**		**6**	37	**5**	**3**
4	M	59	25.7	18	35	6.5	34	10	3	31	4	3
5	M	59	26.2	28	39	6.7	32	7.1	5	34	5	3
6	F	69	28.4	27	60	9.8	36	6.7	11	28	5	3
7	F	60	22.7	29	69	8.4	39	7.8	1	34	5	3
8	F	54	32.8	26	44	7.2	32	8.4	9	29	5	3
9	F	67	26.4	26	57	8.8	36	7.2	3	25	5	3
10	M	44	25	36	50	8.1	27	6.5	14	34	4	3
Mean (SD)	7F 3M	59.6 (7.3)	26.5 (4.9)	26.3 (5.1)	52.9 (11.5)	7.9 (1.1)	34.1 (3.3)	8.0 (1.7)	6.6 (4)	29.8 (5.2)	4.7 (0.5)	3 (0)

Table 5-7 Population demographics in patients with hypercapnic severe chronic obstructive pulmonary disease who require home non-invasive ventilation

M- male, F- female, BMI- body mass index (kg/m^2), FEV1- forced expiratory volume in 1 second (percentage predicted), FEV1/FVS- ratio of forced expiratory volume in one second to forved vital capacity (%), PO_2- arterial oxygen (kilo pascals (kPa), ESS- Epworth Sleepiness Scale, mCAT- modified COPD assessment tool, MRC- Medical research council dyspnoea scale, PS- ECOG performance status. Degree of hypercapnic failure is represented by baseline carbon dioxide (PCO2, measured in kilo pascals (kPa)) and bicarbonate levels (HCO_3 measured in millimoles/litre (mmol/L)).

	95%IPAP ($cmsH_2O$)	mIPAP ($cmsH_2O$)	95%EPAP ($cmsH_2O$)	mEPAP ($cmsH_2O$)	Data reviews	Telephone consultations	Prescriptions changes	Day case visits	Follow up (months)
1	22.9	13.2	4.9	4.9	4	2	0	0	8
2	29.1	23.9	14.3	11.4	6	3	0	0	6
3	12.1	10.6	7.1	6.7	8	6	2	0	6
4	8	7.2	5.3	5.1	3	3	0	0	d/c
5	18.9	11.8	10.6	6.8	2	0	0	0	6
6	23.9	16.5	11.7	9.3	10	4	1	0	6
7	17.3	13.8	8.9	5.4	7	2	1	0	6
8	19.3	13.3	12.7	10	6	2	1	0	6
9	19.7	15.9	9	6.7	4	4	1	0	6
10									
Mean (SD)	19 (6.3)	14 (4.6)	9.4 (3.3)	7.4 (2.3)	5.6 (2.6)	2.9 (1.7)	0.7 (0.7)	0	6.3 (0.7)

Table 5-8 Breathing support requirements in patients with hypercapnic severe chronic obstructive pulmonary disease managed with remote monitored home non-invasive ventilation

All were managed with auto-titrating volumes assured pressure support (iVAPS). 95%IPAP- 95th centile inspiratory positive airways pressure requirements, mIPAP- median inspiratory positive airway pressure requirements, 95%EPAP- 95th centile expiratory positive airways pressure requirements, mEPAP-median expiratory positive airways pressure requirements. D/C- discontinued. All pressures measured in cms H_2O.

	R5	R5-R20	R20	Ax	ΔXRS	Vt (L)
1	4.96	1.47	3.49	26.37	-0.45	0.65
2	5.8	2.72	3.6	83.27	3.36	0.52
3	6.54	2.66	3.88	63.2	-0.21	0.61
4	4.87	2.18	2.69	88.12	4.58	1.05
5	4.83	1.82	3.01	58.44	2.63	0.8
6	11.4	4.96	6.44	141.62	5.51	0.47
7	4.91	1.99	2.92	64.42	3.99	0.82
8	8.87	3.36	5.51	130.8	11.29	0.7
9	8.6	-1.19	9.79	67.29	3.3	0.42
10	6.5	2.43	4.07	37.81	3.28	0.91
Mean (SD)	6.73 (2.22)	2.24 (1.55)	4.54 (2.19)	76.13 (36.69)	3.73 (3.26)	0.7 (0.2)

Table 5-9 Baseline oscillometry measurements in patients with hypercapnic severe chronic obstructive pulmonary disease requiring home non-invasive ventilation

R5- Large airways resistence, R20- Large airways resistence, R5-R20- small airways resistence, ΔXRS- in-breath change in reactance measured at 5Hz, Ax- reactance, Vt- tidal volumes (litres). Highlighted ΔXRS identifies tidal expiratory flow limitation. All oscillometry measured in $cmsH_2OsL^{-1}$

5.4.4 Chronic obstructive pulmonary disease- obstructive sleep apnoea overlap syndrome

8 patients with COPD-OSA overlap were recruited between September 2017 and August 2018. Population demographics are shown in Table 5.10. There were 4 females and 4 males with a mean age of 60.6years (SD 8.7years) and mean BMI of 40.4 kg/m^2(SD 8.3 kg/m^2). Mean FEV1 was 48.4% (SD 22.5%) and FEV1/FVC of 65% (SD 14%). Mean arterial carbon dioxide (CO_2) was 7.6 kPa (SD 1.3kPa) and mean bicarbonate of 33.6 mmol/L (SD 4.5mmol/L). Mean AHI and ODI were 34.8 events/hr (SD 17.2 events/hr) and 38.9 events/hours(SD 27.7 events/hr), respectively. Mean oxygen saturations was 87.7% (SD 6.3%) and mean TST90 was 66.5% (SD 44.9%). Baseline symptom burden showed a mild intrusive daytime somnolence with a mean ESS of 12.3 but severe respiratory symptoms with a mean mCAT score of 27 and functional limitations represented by mean MRC score of 3.4 and mean performance status of 2.4. (Table 5.10)

8 patients were managed with auto-titrating NIV(iVAPS) and auto-titrating expiratory positive airways pressure (AutoEPAP) and one with APAP. 2 patients achieved target treatment adherence (≥70% days of CPAP usage ≥4hours; the level set for reimbursement in US health system)(Table 5.11). Mean 95% IPAP values were 14.1 cmsH_2O (SD 4.3 cmsH_2O with a mean median IPAP of 10.7 cmsH_2O (SD 4.3 cmsH_2O). 95% EPAP and median EPAP values were 7.7 cmsH_2O (SD 1.8 cmsH_2O) and 6.3 cmsH_2O (SD 1.3 cmsH_2O) respectively. (Table 5.11) All patients were managed with 2-way remote monitored NIV, mean remote review of data was 5 and 4 telephone consultations with 1 prescription change (Table 5.11). 2 patients required day case NIV trouble shooting sessions.

Exploratory Endpoints

All patients had FOT and EMGpara measurements taken at baseline visits. 2 had further measurements at 3months and 6months. Baseline FOT and EMGpara are shown in Table 5.12 and Appendix 9.

Oscillometry

Disease severity measured by ODI demonstrated a significant relationship with 95%IPAP requirements, r= 0.91, p<0.05. AHI demonstrated a strong but non-significant relationship with 95%IPAP requirements, r= 0.84 p=0.08. Disease severity demonstrated a strong relationship with all PAP requirements but did not correlate with baseline FOT data. BMI or FEV1 did not correlate with baseline FOT or PAP requirements.(Appendix 9) Airway resistance decreased in 1 patient who was adherent to PAP therapy. Reactance measured by ΔXRS and Ax demonstrated a non

significant decreasing trend in 2/3 patients. Symptom burden measured by ESS, MRC and mCAT scores did not show a relationship in patients with tidal EFL at baseline.

Parasternal Electromyography

Symptom burden measured by ESS demonstrated a strong relationship with baseline NRDI, R^2= 0.85 $p<0.05$ (Figure 5.12). There were no significant trends in meanEMGpara, EMGpara%max or NRDI observed at 3months and 6months. Disease severity measured by AHI and ODI demonstrated no significant correlations with baseline EMG data. There was no correlation with ESS and meanEMGpara or EMGpara%max. Hypoxic burden measured by mean saturations and TST90 did not demonstrate a relationship with parasternal EMG data. FEV1 did not showed signifcant relationship with baseline EMG parameters. Severity of respiratory failure measured by PCO2 and HCO3 did not demonstrate a significant relationship with parasternal EMG data. No significant relationships between symptom burden measure by mCAT score or MRC dyspnoea scale and baseline parasternal EMG data were demonstrated.

Symptom Burden

There no significant change in symptom burden, measured by ESS, mCAT, MRC dyspnoea score or performance status, in adherence and non-adherence to PAP therapy at 3 or 6 months.

	Sex (m/f)	Age (yrs)	BMI (kg/ m^2)	FEV1 (%)	FEV1/ FVC (%)	PCO_2 (kPa)	HCO_3 (mmol/L)	AHI (e/hr)	ODI (e/hr)	mean Sats (%)	TST 90 (%)	ESS	MCAT	MRC	PS
1	F	64	44.8	78	78	7.8	33	20.7	19.8	82	92	5	23	5	3
2	M	60	36	37	51	8.2	31	31	45	86	92	11	24	2	2
3	M	77	30			6.7	33	47.4	75.7	86	98	10		5	3
4	M	49	37.6	19	45	6.7	29	17	5	98	2	5	28	2	2
5	F	54	42.6	45	76	10.2	42.9	62.5	64.7	82	99	19	30	4	2
6	F	57	32	80	78			29.9	23	92	16	17	19	1	1
7	F	57	56	41	56	7	31.5							4	3
8	M	67	43.8	39	71	6.9	35					19	38	4	3
Mean (SD)	5F 4M	60.6 (8.7)	40.4 (8.3)	48.4 (22.5)	65 (14)	7.6 (1.3)	33.6 (4.5)	34.8 (17.2)	38.9 (27.7)	87 (6.3)	66.5 (44.9)	12.3 (6.1)	27 (6.6)	3.4 (1.5)	2.4 (0.7)

Table 5-104 Population demographics of patients with chronic obstructive pulmonary disease-obstructive sleep apnoea overlap syndrome requiring home non-invasive ventilation

AHI- apnoea hypopnoea index (events/hr), ODI- oxygen desaturation index (events/hr), mean sats- mean peripheral oxygen saturations (%), TST90- percentage Total Sleep Time with oxygen saturations <90 during limited or fully polysomnography, ESS- Epworth Sleepiness Scale, mCAT-modified COPD assessment tool score, MRC- Medical Research Council dyspnoea scale, PS- ECOG Perfomrance Scale. Degree of hypercapnic failure is represented by baseline carbon dioxide (PCO2) measured in kilo pascals (kPa) and bicarbonate levels (HCO_3) measured in millimoles/Litre (mmol/L).

	Mode	95%IPAP ($cmsH_2O$)	mIPAP ($cmsH_2O$)	95%EPAP ($cmsH_2O$)	mEPAP ($cmsH_2O$)	Data reviews	Telephone consultations	Prescription changes	Day case visits	Follow up (months)
1	iVAPS	14.2	12.3	7.7	6.1	3	2	1	0	6
2	iVAPS	13.1	7.6	7.2	6.6	3	0	0	0	
3	iVAPS	20.9	17.8	9.3	7.2	3	2	1	1	3
4	iVAPS	9	6.1	4.9	4.1	4	4	0	0	2
5	iVAPS									
6	APAP	10.7	8.3			10	8	2	1	6
7	iVAPS									
8	iVAPS	16.8	11.9	9.3	7.3	7	5	2	0	12
Mean (SD)		14.1 (4.3)	10.7 (4.3)	7.7 (1.8)	6.3 (1.3)	5 (2.9)	3.5 (2.8)	1 (0.9)	0.3 (0.5)	5.8 (3.9)

Table 5-51 Breathing support requirements in patients with chronic obstructive pulmonary disease- obstructive sleep apnoea overlap syndrome requiring remote monitored home non-invasive ventilation

8 patients were managed with auto-titrating volumes assured pressure support (iVAPS) and 1 with auto-titrating positive airways pressure support (APAP). 95%IPAP- 95^{th} centile inspiratory positive airways pressure requirements, mIPAP- median inspiratory positive airways pressure requirements IPAP, 95%EPAP- 95^{th} centile expiratory positive airways pressure requirements, mEPAP- median expiratory positive airways pressure requirements. All pressure support measured in $cmsH_2O$.

	R5	R5-R20	R20	Ax	ΔXRS	Vt(L)
1	6.75	1.19	5.56	94.12	7.76	0.56
2	5.08	2.52	2.56	32.37	1.01	0.91
3						
4	6.19	2.76	3.43	101.81	10.67	1
5	5.4	1.33	4.07	49.38	4.86	0.9
6	6.7	2.59	4.11	27.76	4.86	0.9
7						
8	6.86	3.09	3.77	56.57	2.91	0.76
Mean (SD)	6.16 (0.76)	2.25 (0.79)	3.92 (0.99)	60.34 (31.11)	5.35 (3.45)	0.84 (0.16)

Table 5-12 Baseline oscillometry measurements in patients with chronic obstructive pulmonary disease- obstructive sleep apnoea (COPD-OSA) overlap syndrome requiring remote monitored home non-invasive ventilation

R5- Large airways resistence, R20- Large airways resistence, R5-R20- small airways resistence, ΔXRS- in-breath change in reactance measured at 5Hz, Ax- reactance, Vt- tidal volumes (litres(L)). Highlighted ΔXRS identifies tidal expiratory flow limitation. All oscillometry measured in cmsH_2Os/L.

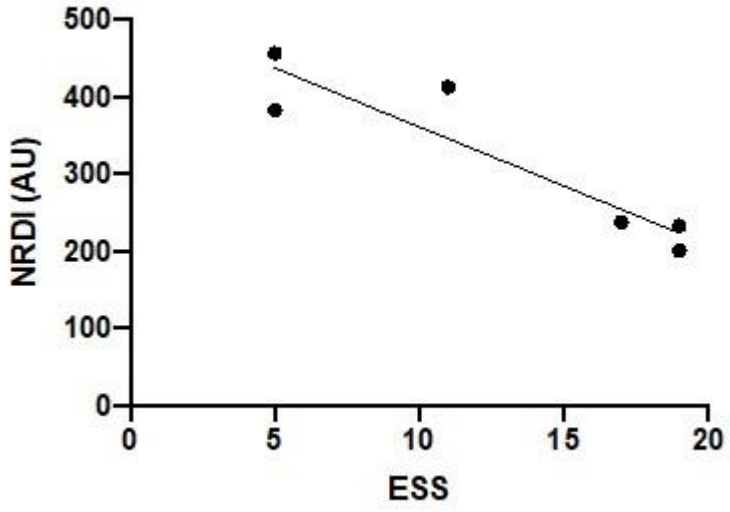


Figure 5-12 Linear regression analysis of baseline Epworth sleepiness scale and neural respiratory drive index in patients with chronic obstructive pulmonary disease-obstructive sleep apnoea overlap syndrome requiring home non-invasive ventilation

5.5 Discussion

This study demonstrates the feasibility of serial advanced physiological measurements in patients managed with remote monitored PAP/NIV therapy for sleep disordered breathing, COPD-OSA overlap and severe COPD with persistent hypercapnic failure.

5.5.1 Obstructive Sleep Apnoea Syndrome

This small population represents a typical cohort of patients with severe sleep disordered breathing with mean AHI of 60 events/hr and mean ODI of 44.8 events/hr with a moderate symptom burden, mean ESS of 14/24. There was expected attrition of patient follow up with 55% attending the 6month study visit. This is not unexpected, as symptom resolution with PAP therapy results in poor attendance for clinical follow up. There were no significant correlations with disease severity (measured by AHI or ODI) and FOT results in our OSAS cohort, contradicting previous studies demonstrating correlation between airways resistance and reactance with disease severity suggesting both upper airway resistance and elastic recoil may contribute to the mechanics of OSAS.[250][251] However, 50% of patients demonstrated EFL on baseline FOT measurements demonstrating the effect of extra-thoracic restriction secondary to severe obesity resulting in low tidal volumes and predisposign the small airways to collapse and EFL.

In this cohort we demonstrated novel physiological insights into pulmonary mechanics in OSAS with significant reductions at 3months in small airways resistance(R5-R20), in-breath X5 (ΔXRS) and reactance(Ax) in patients adeherent to PAP therapy. Total airways resistance demonstrated a reducing trend with adherence to PAP therapy and an increase in non-adherence at 3 months. The decreasing trend in all parasternal EMG parameters in those adherent to PAP therapy is consistent with previous studies showing increased NRD, respiratory muscle unloading with PAP therapy and subsequent reductions in NRD parameters.[254][77], [255] These data suggest long term PAP therapy may alter pulmonary mechanics of the large and small airways in patients with OSAS, justifying further prospective studies to define the potential role for serial oscillometry alongside symptom burden in this cohort to provide further insights into disease mechanics and personalised approach to disease management.

5.5.2 Obesity related respiratory failure

This small cohort of patients demonstrated severe ORRF with a mean BMI of 49.5 kg/m^2, AHI of 61 events/hour and ODI of 64 events/hour and moderate to high symptom burden (mean ESS 17.7/24). There was expected attrition of patient follow up with 50% attending the 12month study visit and is not unexpected in this cohort of sleep disorder breathing as previously

discussed. Median IPAP requirements significantly correlate with XRS and Ax which is consistent with increased extra-thoracic restriction secondary to severe obesity, low tidal volumes, predisposing the small ariways to collapse and EFL. In combination with reduced compliance IPAP requirements would demonstrate a positive correlation. Severe obesity increased both the large airway resistence and higher EPAP pressures are not unexpected in this cohort as demonstrated in Table 5.6.

Strong correlations between BMI and small airways resistance is consistent with previous evidence demonstrating increased airway resistance and small airways resistance correlates with decreasing FRC and ERV in obesity.[256] Patients with obesity are susceptible to restrictive pulmonary defects, reduced airways calibre, reduced elastic recoil, decreasing pulmonary compliance and lung volumes, resulting in micro-atelectasis and heterogenicity of ventilation.[7], [257][258][256]

Control of hypoventilation was achieved with moderate pressure support requirements. Parasternal EMG data did not exhibit any significant trends following NIV initiation which contradicts previous studies demonstrating significant reductions in NRD with CPAP and NIV in ORRF patients.[76], [77], [259][78]

We have demonstrated it is feasible to measure FOT and parasternal EMG in this cohort, although our small number of patients has limited the identification of significant changes in serial measurements. Untreated ORRF has a higher risk of developing pulmonary hypertension and increased mortality.[73], [260], [261] Idenification and treatment of ORRF with PAP therapy reduces morbidity and mortality.[196], [262][263] Serial advance physiology measurements could provide further insights into the mechanics of ORRF and its response to home NIV justifying further studies with a focus on treatment response, symptom burden and early optimisation of NIV.

5.5.3 Chronic obstructive airways disease

This small cohort of patients with severe COPD and persistent hypercapnia represents similar cohort studied in the UK HOT HMV trial with a mean FEV1 of 26% and mean PCO2 of 7.91kPa.[264][148] Low daytime somnolence scoring suggests no evidence of underlying sleep disordered breathing, despite the lack of baseline polysomnography on this cohort. However, the high symptom burden (mean mCAT score of 29.8, MRC score of 4.7 and performance status of 3) demonstrates a cohort of patients with significant physical limitation due to severe COPD. More than 50% of hypercapnic severe COPD patients screened did not participate in the study which

may reflect the burden of disease resulting in physical limitations and corresponds to symptoms burden recorded in this cohort.

All patients received NIV in auto-titrating mode delivering an unexpected low pressure support requirement to improve hypercapnia. This contrasts with previous studies demonstrating improvement in time to re-admission or death in those treated with NIV for severe COPD with hypercapnic failure using high-intensity spontaneous-timed (ST) modes.[148], [264] Minimal remote prescription management was required during the 6 month period of follow up (3 telephone consultation & 1 prescription change). Adherence to NIV was potentially suboptimal in this cohort, and future studies to address any issues elicited by remote monitoring to improve treatment adherence are justified.

This is the first observational study to demonstrate serial FOT measurements following the initiation of home NIV in hypercapnic severe COPD patients. Although 8 out of 10 patients had tidal EFL, this did not correlate with their baseline symptom burden. However, change in ΔXRS at 3months demonstrated a strong relationship with change in symptom burden measured by MRC dyspnoea scale, which is consistent with previous evidence showing a changes in FOT predicted symptoms measured by the St George Respiratory Questionnaire (SGRQ) score.[239] . Large and small airways resistance decreased following the initiation of home NIV in this cohort. There were no correlations between baseline FOT measurements and NIV requirements in this cohort, contradicting previous findings by Dellaca et al demonstrated a correlation between change in EFL in the upright and supine positions in COPD patients with changes in PEEP requirements.[253] However, we did not review serial FOT measurements following postural changes.

Serial NRD measurements did not demonstrate significant change following the initiation of home NIV therapy which could be explained by the small sample size and poor treatment adherence. However, normalised baseline parasternal EMG (EMGpara%max) measurements in this cohort were similar to those shown in previous diaphragmatic EMGs in COPD.[29] There was no correlation with NRD parameters and symptom burden or disease severity, contradicting previous studies demonstrating increased NRD in COPD, corresponding to disease severity and dyspnoea. [29], [44], [57], [59]

These data support the feasibility of serial FOT and NRD measurement in hypercapnic severe COPD patients managed with home NIV. NRD has been used as a physiological biomarker in disease monitoring in exacerbations of COPD and in quantification of NRD offloading in COPD-OSA overlap patients treated with NIV.[65], [67], [79] Small sample numbers and low adherence rates may have impacted the significance of these exploratory outcomes but justifies future studies

utilising advanced physiology as bio-markers in disease management and potential role in optimisation of home NIV in this cohort of patients.

5.5.4 Chronic obstructive pulmonary disease- Obstructive Sleep Apnoea overlap syndrome

This small cohort represents patients with moderate COPD (mean FEV1 48%) and moderate sleep disordered breathing (mean AHI 35 events/hr and ODI 39events/hr) and established hypercapnic failure (mean PCO2 7.64kPa). There was a high symptom burden with mean mCAT score of 27 but mild daytime somnolence (mean ESS 12.3). All patients were established on auto-titrating volume assured pressure support with auto-titrating EPAP mode which like the COPD cohort delivered unanticipated low pressure support in comparison to previous studies.[79][194] We were unable to demonstrate whether hypoventilation in this cohort was controlled with low pressure support due to lack of data and high attrition rates. Baseline anthropometrics and disease severity did not correlate with FOT or NRD data.

NRDI demonstrated a strong negative relationship with symptoms of daytime somnolence measured by ESS, suggesting that obstructive airways disease is more influential on the respiratory load capacity relationship than the co-existing sleep disordered breathing. NRD reductions did not correlate with treatment adherence as previously demonstrated in patients with COPD-OSA.[80] However, there was a strong correlation with disease severity of co-existing sleep disordered breathing (AHI and ODI) and PAP requirements, justifying further larger studies incorporating advanced physiological measurements to expand our knowledge of pulmonary mechanics in COPD-OSA overlap syndrome, facilitate physiological phenotyping of COPD-OSA and treatment optimisation of home NIV.

5.6 Critique of the methods

Patient selection

Patient recruitment for exploratory endpoints study has been discussed in detail in Chapter 2. As this was a prospective observational study, patients were not randomised and therefore subject to selection bias. The aim of this study was to demonstrate feasibility of serial advanced physiological measurements throughout the patient's treatment journey with remote monitored PAP therapy, as a result patient selection may have skewed these results somewhat and larger studies are required to consolidate feasibility.

Population phenotyping

Patients groups were determined by an experienced clinical team, standard cardiorespiratory evaluations and clinical guidelines. Baseline physiology demonstrated obstructive spirometry in 1 patient with ORRF (Table 5.4) and a higher than expected BMI (BMI>30) in 3/10 hypercapnic severe COPD patients (Table 5.7). Likewise 50% of COPD-OSA cohort had normal spirometry suggesting a possiblity of incorrect phenotyping. However, all baseline spirometry readings were taken with a handheld device after inhaled therapy rather than formal pulmonary function laboratory spirometry and therefore may not be fully representatiave of co-exisiting airways disease. Additionally, polysomnography was not available for all patients, therefore only patients with high clinical suspicion of SDB had sleep studies. Formal baseline lung function and polysomnography in all patients would facilitate correct phenotyping and potentially allow further analysis of subsequent exploartory physiology measurements to provide further insights into respiratory mechanics and physiology respnose to PAP and home NIV therapy.

Study population size and statistical analysis

As our aim was to assess feasibility of serial FOT and EMG measurements, the study was not powered to evaluate changes in these physiological parameters. Small study population size and disease heterogeneity may have limited the statistical significance of both oscillometry and parasternal EMG measurements. Therefore, interpretations of descriptive data and correlations with disease severity, anthropometrics and exploratory physiology is limited but supports future larger observational studies in chronic respiratory disease and SDB.

Lung function

The primary aim of our study was to assess the feasibility of advanced physiological measurements in patients with chronic respiratory disease requiring remote monitored PAP therapy and therefore full lung function including body plethysmography was not recorded in all patients. These detailed tests are valuable to assess full lung function and identify those with co-morbid airflow obstruction and SDB. However, simple handheld spirometry was measured at every study visit to identify those with obstructive airways disease. Future insights into pulmonary mechanics and the advanced physiological markers should incorporate full lung function.

Physiological measurements

All advanced physiological measurements were carried out by one investigator and therefore limiting any variation in techniques discussed in Chapter 2 and Appendices 6 and 7.

5.7 Conclusions

These data support the feasibility of serial advanced physiology measurements can be incorporated alongside standard respiratory care in a range of respiratory conditions out with a research centre setting. It is feasible for serial advanced physiology measurements to be recorded in patients managed with remote monitored PAP/NIV therapy. Symptom burden and physical limitation of disease seen in the hypercapnic severe COPD patients may limit recruitment in future studies requiring study centre visits but this feasiblity data justifies future emphasis on ambulatory advanced physiology measurements in those restricted by disease burden. However, we have demonstrated novel insights into the role of small airways disease in OSAS patients using serial FOT measurements. Small sample size limited exploratory advanced physiology analysis and justifies further studies incorporating FOT and NRD to facilitate physiological phenotyping, targeted disease management, early assessment of treatment response and optimisation, provide insights into pulmonary mechanics, assess the potential use as an advance physiological biomarker with a further focus on ambulatory methods to allow inclusion of those patients debilitated by the significant disease burden of severe respiratory diseases.

Chapter 6 Discussion

The aim of this thesis was to explore the use of advanced physiological measurements in chronic respiratory disease, evaluate the adoption of new technologies in home ventilation and determine the feasibility of serial advanced physiological measurements alongside standard care in chronic respiratory disease out with the research centre setting. Data from advanced physiology will support current knowledge and provide novel mechanistic insights into respiratory disease and chronic respiratory failure.

The data presented in this thesis demonstrates:

- Significant service development required to integrate two-way remote monitored breathing support and home ventilation within a tertiary service
- The realistic provision of two-way remote monitored home NIV in patients with hypercapnic severe chronic obstructive pulmonary disease and obesity related respiratory failure
- Acceptable reproducibility of parasternal electromyogram analysis between two UK based research centres
- Simplification of parasternal electromyogram measurements are reliable improving accessibility and advocates future adoption into clinical practice
- It is feasible for exploratory endpoints such as forced oscillometry and parasternal EMG to be incorporated into standard clinical care in chronic respiratory disease

6.1: Adoption of new technologies in Glasgow Sleep and Breathing Support Service

Inpatient sleep and breathing support referrals significantly rose following the merge of four hospitals in Glasgow to form the Queen Elizabeth University Hospital (QEUH) in 2015. Failure of the legacy service model to meet the heightened service demands justified the exploration of new technologies to improve service efficiencies and patient outcomes. The Glasgow Sleep and breathing support research centre was established in early 2016 to address these increase needs through the adoption of new technologies and established a research base for future studies and service development. Utilisation of average volume assured pressure support with autoEPAP (AVAPS-AE) to benchmark inpatient domiciliary NIV titration demonstrated a reduction in occupied bed days in

comparison to legacy services. Incorporation of auto-titrating PAP and NIV devices enabled with two-way remote monitoring allowed the development of remote managed patient pathways with prompt identification of therapy issues, early remote optimisation of breathing support/ventilation and facilitated day case initiation of home NIV therapy in patients with stable hypercapnic respiratory failure providing noteworthy service efficiencies. The integration of clinical notes, investigations, and patient journeys into electronic health records (EHR) throughout Greater Glasgow and Clyde facilitated virtual vetting and timely investigations in those deemed high risk of sleep disordered breathing. Collation of data from EHRs and two-way remote monitoring of breathing support/home ventilation provides big data for further population studies to define high risk groups requiring enhanced personalised patient management pathways to ensure patient safety, improve clinical outcomes and measurable service efficiencies.

6.2: Adaption of home non-invasive ventilation utilising two-way remote NIV- realistic provision and clinical outcomes

The data presented in this thesis demonstrates it is feasible to deliver effective home NIV using two-way remote monitoring in patients with persistent hypercapnic failure secondary to severe COPD and obesity related respiratory failure. Successful development of patient pathways for remote monitored home NIV allows prompt recognition of therapy issues and early remote optimisation of ventilation in the home setting. Whilst the reductions in carbon dioxide and bicarbonate in both cohorts confirms the safety of two-way remote monitored home NIV.

Prolongation of time to re-admission or death in hypercapnic severe COPD patients who continued using remote monitored home NIV validates previous study findings and demonstrates the realistic application of home NIV out with the research setting. Similar results are seen with continued use of remote monitored home NIV in patients with ORRF and are consistent with previous research findings. Notably, continued use of two-way remote NIV in patients with hypercapnic severe COPD resulted in a median reduction of 14 occupied bed days without shifting service demands to the community respiratory team, demonstrating tangible potential cost savings. Two-way remote monitored NIV facilitates day case initiation of home NIV in stable hypercapnic respiratory failure,

introducing significant potential cost savings and service efficiencies. Our data demonstrates the safety of day case initiation supporting previous study findings suggesting non-inferiority compared to inpatient multi-night multi-sensor titration and justifies future studies of cost-effectiveness of this service model.

These data justify future studies in both severe COPD and ORRF cohorts to confirm patient safety, assess cost-effectiveness of two-way remote monitored service models and present clinical outcomes. Two-way remote NIV/PAP service pathways are incorporated into routine clinical practice in the West of Scotland with approximately 1300 patients on remote monitored PAP therapy and 350 patients newly managed with remote monitored NIV since 2016. Further acquisition of remote NIV data will improve understanding, reveal novel physiological insights, and build a foundation of data for future population studies, for analysis and predictive modelling to facilitate personalised patient care in chronic respiratory disease. As a result, NHS GGC have been awarded over £1.7 million in funding (from Innovate UK, ResMed investigator-initiated research programme and the Scottish Government) for future studies in digital innovation incorporating physiology monitoring and remote monitored home ventilation in patients with COPD. The details of the RECEIVER study are discussed in section 6.5 of this chapter. Outcomes from this will include qualitative user experience and ongoing service development with interoperability evaluation as post-doctoral research in GSBSRC.

6.3: Accessibility of parasternal electromyogram measurements

The data presented in chapter 4: Simplifying the measurement of neural respiratory drive confirms it is feasible to use similar equipment utilised for longer term cardiac investigations for parasternal electromyography and maintain high quality signals. The utilisation of long-term cardiac electrodes in our exploratory endpoints study and inter-observer variability analysis supports the simplification of parasternal EMG technique. Acceptable reproducibility of parasternal EMG analysis between two UK sites supports future multi-centre studies of neural respiratory drive as a research endpoint and advanced physiological biomarker in chronic respiratory disease. The estimation of respiratory rate derived from RMS of parasternal EMG signal introduces potential further

rationalisation of parasternal EMG measurements. The hypothetical omission of oro-nasal flow analysis and RIP band signals would improve accessibility of NRD measurements as a research endpoint, advanced physiological biomarker, enable future ambulatory and home monitoring in those debilitated by severe chronic respiratory disease. This data justifies future studies utilising this simplified methodology to consolidate our findings and allow wider application in the ambulatory setting.

6.4: Advanced physiological markers in chronic respiratory disease

The data presented as part of the Exploratory Endpoints study within this thesis supports the feasibility of incorporating serial advanced physiological measurements alongside standard clinical care for patients with a wide range of chronic respiratory conditions. It is feasible to monitor FOT and NRD in patients managed with two-way remote monitored breathing support and home ventilation. A significant reduction in small airways resistance, in-breath X5 (ΔXRS) and reactance was seen in patients with OSAS adherent to PAP therapy at 3months and baseline FOT measurements demonstrated tidal expiratory flow limitation in 50% of this cohort. This novel insight into pulmonary mechanics suggest heterogeneity of large and small airway disease in OSAS, a disease previously characterised by recurrent upper airway obstruction in obesity.

Airways resistance reduced following the initiation of PAP therapy or home NIV in all disease cohorts providing mechanistic insights into the effect of long-term breathing support in chronic respiratory disease. Likewise, NRD decreased following auto-titrating PAP initiation in OSAS patients which is consistent with previously demonstrated respiratory muscle “unloading” seen with PAP therapy.

80% of patients with hypercapnic severe COPD demonstrated tidal EFL which is representative of the significant disease burden seen in a cohort susceptible to aggravated hyperinflation, unstable alveolar ventilation, V/Q mismatching predisposing to chronic respiratory failure requiring home NIV. This cohort demonstrated a strong correlation between the change in ΔXRS and change in symptoms measured by MRC dyspnoea scale 3 months following NIV initiation, suggesting small airways disease may be more influential on respiratory symptoms in COPD than previously assumed. However,

serial physiology measurements were more challenging in this COPD cohort compared to those with sleep disordered breathing, due to physical limitations and symptom burden of disease. Future emphasis on ambulatory or home monitoring of advanced physiology is justified in this cohort to facilitate further disease phenotyping, target disease management, and provide mechanistic insights into chronic respiratory disease and respiratory failure.

6.5: Future work

6.5.1: RECEIVER: Digital Service Model for Chronic Obstructive Pulmonary Disease

(Clinical trials.gov identifier: NCT04240353)

The work in this thesis and the development of a clinical service model has facilitated a prospective observational study evaluating the implementation of digital innovations to enable routine care. Sponsored by NHS Greater Glasgow and Clyde in collaboration with the University of Glasgow and digital technology company, StormID™, GSBSRC is currently recruiting to an observational study of establishing a resource for high-risk COPD patients containing symptom diaries, continuous physiology monitoring via Fitbit™ and home NIV device, supporting self-management, record service requirements and enabling communications with the clinical teams via a cloud-based dashboard and mobile device. The incorporation of multi-media telemedicine with improved patient education will encourage patient engagement, endorse self-management, establish trusted communication, and develop a platform to collate wearable and device data with EHRs. Patient acceptability of new technologies in chronic disease management, service development and patient outcomes will be evaluated in post-doctoral research at GSBSRC. The acquisition of large data will facilitate future machine learned analysis for predictive modelling in this high-risk group of patients.

6.5.2: COVID-19 Advanced Respiratory Physiology (CARP) Study

The work presented in this thesis demonstrating the feasibility of serial advanced physiology measurements alongside standard respiratory care has resulted in £123,000 funding (Chief Science Office (RARC-19)) for a prospective observational study to determine the feasibility of in-hospital wearable respiratory sensors for serial advanced physiology monitoring in patients admitted to hospital with COVID-19 related respiratory failure. 51 patients have been recruited in the first 3 months to December 2020. The study will determine the feasibility of parasternal EMG, electrical impedance tomography and continuous wrist actigraphy on patients admitted with COVID-19 related respiratory failure. Further feasibility of extended wearable devices following hospital discharge after COVID-19 respiratory failure will be determined. Exploratory correlations of wearable and serial advanced physiology measurements with clinical events, changes in respiratory status, following interventions and post-discharge recovery to determine the disease behaviours and provide physiological insights to inform future work in disease monitoring and predictive modelling into severe COVID-19 respiratory failure.

6.5.3: Advanced physiology in severe emphysematous COPD patients

This thesis has demonstrated the feasibility of serial monitoring of advanced physiology in patients with chronic respiratory diseases justifying future studies focusing on specific patient cohorts such as severe emphysematous COPD patients who would be considered for lung volume reduction interventions. A large prospective observational study would be required in this cohort of patients where advance physiology measurements (FOT and NRD) at initial assessment for lung volume reduction and subsequent serial measurements following interventions, such as endobronchial valve insertion, would directly quantify expiratory flow limitation in conjunction with standard pulmonary function tests. This would provide mechanistic insights on the respiratory muscle load capacity relationship following surgical interventions. A prospective observational study of this kind would determine the feasibility of advanced physiology in this cohort of patients, establish their use as a biomarker and explore correlations with clinical outcomes. Utilising FOT as a non-invasive effort independent measurement of EFL to identify those eligible for lung volume reduction would be more acceptable in comparison

to strenuous pulmonary function testing in this cohort with increased symptom burden secondary to severe chronic respiratory disease.

6.5.4: Advanced physiology in the optimisation of breathing support and ventilation

The data presented in this thesis supports ongoing development of NRD as a research endpoint and clinical biomarker of chronic respiratory disease. Serial NRD analysis has demonstrated an "offloading" effect on the respiratory muscle capacity with a fall in NRD following the initiation of PAP therapy. Likewise, devices utilising FOT based auto titrating EPAP targeted to abolish expiratory flow limitation have demonstrated reduction in NRD in patients with hypercapnic severe COPD. In addition, continuous parasternal EMG measurements during NIV has been shown to identify patient ventilator asynchrony which correlates with ventilator intolerance and de-ventilation dyspnoea. This justifies future studies incorporating serial FOT and NRD analysis in patients with chronic respiratory failure to facilitate NIV titration and explore auto titrating NIV targets to optimise home ventilation. Furthermore, the potential continuous parasternal EMG monitoring in the ambulatory setting to allow remote assessment of work of breathing would facilitate early optimisation of home ventilation, could improve patient tolerance, and provide mechanistic insights into ventilatory control in chronic hypercapnic respiratory failure.

6.5.5 Clinical respiratory failure team in NHS Greater Glasgow and Clyde

This thesis builds a foundation for future development of a tertiary specialist respiratory failure team within NHS Greater Glasgow and Clyde. Current recruitment for the RECEIVER study has demonstrated a focus on facilitating remote early therapy optimisation with a multidisciplinary approach incorporating physicians, physiologists, respiratory specialist nurses, pharmacists, physiotherapists, and data sharing on EHRs for wider access for other practitioners. Multi-disciplinary face to face clinics with availability from the above specialists, clinical physiology, capillary blood analysis and medical physics would facilitate a one-stop assessment for those requiring physical review and device servicing.

The increasing inpatient burden of acute respiratory failure and its management during the COVID-19 pandemic has highlighted the importance of a multi-disciplinary approach in a specialist acute respiratory failure department to safely manage patients with unstable acute respiratory failure by physicians who have an established interest in non-invasive and invasive ventilation. The establishment of a respiratory support unit would develop patient care pathways for the management of acute respiratory failure, improve patient outcomes, enable patient-physician education of evolving breathing support therapies and champion new technologies whilst facilitating ongoing research in advanced physiology and breathing support in acute and chronic respiratory failure.

6.6 Conclusions

In conclusion, the data presented in this thesis is considered exploratory but has enabled the establishment of a remote breathing support service within NHS Greater Glasgow and Clyde, which has been an invaluable tool for the management of home ventilation and breathing support during the global COVID-19 pandemic and the practical challenges it has created. This data has been the catalyst for ongoing digital innovation in clinical practice with the formation of a multidisciplinary multimedia interactive platform for prompt recognition of condition instability, early optimisation of patient care, encourage patient engagement and potential development of a proactive predictive model for the management of chronic respiratory failure. Our exploratory work has advocated ongoing studies incorporating advanced physiology in chronic respiratory failure and COVID-19 related respiratory failure. This data demonstrates the tangible benefit of telemedicine at a time where unprecedented demands on our service have called for adoption of new technologies to facilitate standard respiratory care. I hope this data encourages the wider respiratory community to explore the incorporation of new technologies including wearable ambulatory monitoring, the utilisation of advanced physiology as disease biomarkers and provide physiological insights into both chronic respiratory disease and COVID-19 related respiratory failure.

Chapter 7 References

[1] A. S. Patel, C. O'Donnell, M. J. Parker, and D. H. Roberts, "Diaphragm Paralysis Definitively Diagnosed by Ultrasonography and Postural Dependence of Dynamic Lung Volumes after Seven Decades of Dysfunction," *Lung*, vol. 185, no. 1, pp. 15–20, Feb. 2007.

[2] A. Naimark and R. M. CHERNIACK, "Compliance of the respiratory system and its components in health and obesity," *J. Appl. Physiol.*, vol. 15, no. 3, pp. 377–382, May 1960.

[3] K. Parameswaran, D. C. Todd, and M. Soth, "Altered respiratory physiology in obesity.," *Can. Respir. J.*, vol. 13, no. 4, pp. 203–210, May 2006.

[4] M. R. Miller *et al.*, "Standardisation of spirometry," *European Respiratory Journal*. 2005.

[5] F. Baumann *et al.*, "Use of respiratory function tests to predict survival in amyotrophic lateral sclerosis.," *Amyotroph. Lateral Scler.*, vol. 11, no. 1–2, pp. 194–202, Jan. 2010.

[6] C. Crim *et al.*, "Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results," *Respir. Med.*, vol. 105, no. 7, pp. 1069–1078, Jul. 2011.

[7] W. Ladosky, M. A. M. Botelho, and J. P. Albuquerque, "Chest mechanics in morbidly obese non-hypoventilated patients," *Respir. Med.*, 2001.

[8] R. L. Jones and M.-M. U. Nzekwu, "The effects of body mass index on lung volumes.," *Chest*, vol. 130, no. 3, pp. 827–833, Sep. 2006.

[9] G. T. Ferguson, "Why does the lung hyperinflate?," in *Proceedings of the American Thoracic Society*, 2006.

[10] S. Bickel, J. Popler, B. Lesnick, and N. Eid, "Impulse Oscillometry," *Chest*, vol. 146, no. 3, pp. 841–847, Sep. 2014.

[11] S. Levra *et al.*, "Impact of environmental exposure on respiratory tract in school children," *Eur. Respir. J.*, vol. 50, no. suppl 61, p. PA4147, Sep. 2017.

[12] J. C. H. Yap, R. A. Watson, S. Gilbey, and N. B. Pride, "Effects of posture on respiratory mechanics in obesity," *J. Appl. Physiol.*, 1995.

[13] “ATS/ERS Statement on Respiratory Muscle Testing,” *Am. J. Respir. Crit. Care Med.*, vol. 166, no. 4, pp. 518–624, Aug. 2002.

[14] D. W. Carley and S. S. Farabi, “Physiology of Sleep.,” *Diabetes Spectr.*, vol. 29, no. 1, pp. 5–9, Feb. 2016.

[15] C. B. Saper, G. Cano, and T. E. Scammell, “Homeostatic, circadian, and emotional regulation of sleep.,” *J. Comp. Neurol.*, vol. 493, no. 1, pp. 92–98, Dec. 2005.

[16] I. B. Infant and 2008, “Transcutaneous monitoring–understanding the principles,” *infantjournal.co.uk* .

[17] C. C. Reilly *et al.*, “Neural respiratory drive, pulmonary mechanics and breathlessness in patients with cystic fibrosis.,” *Thorax*, vol. 66, no. 3, pp. 240–246, Mar. 2011.

[18] C. J. Jolley, Y. M. Luo, J. Steier, G. F. Rafferty, M. I. Polkey, and J. Moxham, “Neural respiratory drive and breathlessness in COPD.,” *Eur. Respir. J.*, vol. 45, no. 2, pp. 355–364, Feb. 2015.

[19] A. Chetta, A. K. Rehman, J. Moxham, D. H. Carr, and M. I. Polkey, “Chest radiography cannot predict diaphragm function,” *Respir. Med.*, 2005.

[20] S. Field, S. Sanci, and A. Grassino, “Respiratory muscle oxygen consumption estimated by the diaphragm pressure-time index.,” *J. Appl. Physiol.*, vol. 57, no. 1, pp. 44–51, Jul. 1984.

[21] G. H. Mills, D. Kyroussis, C. H. Hamnegard, M. I. Polkey, M. Green, and J. Moxham, “Bilateral magnetic stimulation of the phrenic nerves from an anterolateral approach.,” *Am. J. Respir. Crit. Care Med.*, vol. 154, no. 4, pp. 1099–1105, Dec. 2012.

[22] Y. M. Luo *et al.*, “Diaphragm electromyogram measured with unilateral magnetic stimulation,” *Eur. Respir. J.*, vol. 13, no. 2, pp. 385–390, Feb. 1999.

[23] T. Weinstock, D. Roberts, S. Loring, and C. O’Donnell, “Postural Dependence of Vital Capacity in Assessment of Diaphragm Dysfunction.,” 2009.

[24] N. Koulouris, L. G. Vianna, D. A. Mulvey, M. Green, and J. Moxham, “Maximal Relaxation Rates of Esophageal, Nose, and Mouth Pressures during a Sniff Reflect

Inspiratory Muscle Fatigue," *Am. Rev. Respir. Dis.*, vol. 139, no. 5, pp. 1213–1217, Dec. 2012.

[25] J. M. Miller, J. Moxham, and M. Green, "The Maximal Sniff in the Assessment of Diaphragm Function in Man," *Clin. Sci.*, vol. 69, no. 1, pp. 91–96, Jul. 1985.

[26] P. Tzani *et al.*, "The value of cough peak flow in the assessment of cough efficacy in neuromuscular patients. A cross sectional study.," *Eur. J. Phys. Rehabil. Med.*, vol. 50, no. 4, pp. 427–432, Aug. 2014.

[27] S. Ward, M. Chatwin, S. Heather, and A. K. Simonds, "Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia," *Thorax*, vol. 60, no. 12, pp. 1019–1024, Dec. 2005.

[28] C. W. Lanks, D. Y. Sue, and H. B. Rossiter, "A pickwickian problem: How is breathing controlled?," in *Annals of the American Thoracic Society*, 2019.

[29] C. J. Jolley *et al.*, "Neural respiratory drive in healthy subjects and in COPD.," *Eur. Respir. J.*, vol. 33, no. 2, pp. 289–297, Feb. 2009.

[30] W. A. Whitelaw, J. P. Derenne, and J. Milic-Emili, "Occlusion pressure as a measure of respiratory center output in conscious man.," *Respir. Physiol.*, vol. 23, no. 2, pp. 181–199, Mar. 1975.

[31] W. A. Whitelaw and J. P. Derenne, "Airway occlusion pressure.," *J. Appl. Physiol.*, vol. 74, no. 4, pp. 1475–1483, Apr. 1993.

[32] M. I. Polkey, D. Kyroussis, C. H. Hamnegard, G. H. Mills, M. Green, and J. Moxham, "Diaphragm strength in chronic obstructive pulmonary disease.," *Am. J. Respir. Crit. Care Med.*, vol. 154, no. 5, pp. 1310–1317, Dec. 2012.

[33] A. De Troyer, J. B. Leeper, D. K. McKenzie, and S. C. Gandevia, "Neural drive to the diaphragm in patients with severe COPD.," *Am. J. Respir. Crit. Care Med.*, vol. 155, no. 4, pp. 1335–1340, Apr. 1997.

[34] A. De Troyer, "Inspiratory elevation of the ribs in the dog: primary role of the parasternals.," *J. Appl. Physiol.*, vol. 70, no. 4, pp. 1447–1455, Apr. 1991.

[35] A. De Troyer and D. Leduc, "Effect of diaphragmatic contraction on the action of

the canine parasternal intercostals.," *J. Appl. Physiol.*, vol. 101, no. 1, pp. 169–175, Jul. 2006.

[36] A. D. De Troyer, "The canine phrenic-to-intercostal reflex.," *J. Physiol.*, vol. 508 (Pt 3, no. Pt 3, pp. 919–927, May 1998.

[37] A. De Troyer and A. Legrand, "Inhomogeneous activation of the parasternal intercostals during breathing.," *J. Appl. Physiol.*, vol. 79, no. 1, pp. 55–62, Jul. 1995.

[38] A. Legrand, A. Brancatisano, M. Decramer, and A. De Troyer, "Rostrocaudal gradient of electrical activation in the parasternal intercostal muscles of the dog.," *J. Physiol.*, vol. 495 (Pt 1, no. Pt 1, pp. 247–254, Aug. 1996.

[39] A. De Troyer, "The electro-mechanical response of canine inspiratory intercostal muscles to increased resistance: the caudal rib-cage.," *J. Physiol.*, vol. 451, pp. 463–476, Jan. 1992.

[40] A. Legrand and A. De Troyer, "Spatial distribution of external and internal intercostal activity in dogs.," *J. Physiol.*, vol. 518, no. Pt 1, pp. 291–300, Jul. 1999.

[41] A. De Troyer, R. B. Gorman, and S. C. Gandevia, "Distribution of inspiratory drive to the external intercostal muscles in humans.," *J. Physiol.*, vol. 546, no. Pt 3, pp. 943–954, Feb. 2003.

[42] S. C. Gandevia, A. L. Hudson, R. B. Gorman, J. E. Butler, and A. De Troyer, "Spatial distribution of inspiratory drive to the parasternal intercostal muscles in humans.," *J. Physiol.*, vol. 573, no. Pt 1, pp. 263–275, May 2006.

[43] T. A. Wilson, A. Legrand, P.-A. Gevenois, and A. De Troyer, "Respiratory effects of the external and internal intercostal muscles in humans," *J. Physiol.*, vol. 530, no. 2, pp. 319–330, Aug. 2004.

[44] C. Sinderby, J. Beck, J. Spahija, J. Weinberg, and A. Grassino, "Voluntary activation of the human diaphragm in health and disease.," *J. Appl. Physiol.*, vol. 85, no. 6, pp. 2146–2158, Dec. 1998.

[45] Y. M. Luo and J. Moxham, "Measurement of neural respiratory drive in patients with COPD," *Respir. Physiol. Neurobiol.*, vol. 146, no. 2–3, pp. 165–174, Apr. 2005.

[46] J. Beck, C. Sinderby, L. Lindström, and A. Grassino, "Effects of lung volume on

diaphragm EMG signal strength during voluntary contractions.," *J. Appl. Physiol.*, vol. 85, no. 3, pp. 1123–1134, Sep. 1998.

[47] A. B. Sprikkelman, L. A. van Eykern, M. S. Lourens, H. S. Heymans, and W. M. van Aalderen, "Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children.," *J. Appl. Physiol.*, vol. 84, no. 3, pp. 897–901, Mar. 1998.

[48] C. Sinderby, S. Friberg, N. Comtois, and A. Grassino, "Chest wall muscle cross talk in canine costal diaphragm electromyogram.," *J. Appl. Physiol.*, vol. 81, no. 5, pp. 2312–2327, Nov. 1996.

[49] M.-Y. Chien, Y.-T. Wu, and Y.-J. Chang, "Assessment of Diaphragm and External Intercostals Fatigue from Surface EMG using Cervical Magnetic Stimulation.," *Sensors (Basel).*, vol. 8, no. 4, pp. 2174–2187, Mar. 2008.

[50] Y. M. Luo, M. I. Polkey, R. a Lyall, and J. Moxham, "Effect of brachial plexus co-activation on phrenic nerve conduction time.," *Thorax*, vol. 54, no. 9, pp. 765–770, Sep. 1999.

[51] F. Bellemare and A. Grassino, "Effect of pressure and timing of contraction on human diaphragm fatigue.," *J. Appl. Physiol.*, vol. 53, no. 5, pp. 1190–1195, Nov. 1982.

[52] E. J. Maarsingh, L. A. van Eykern, A. B. Sprikkelman, M. O. Hoekstra, and W. M. van Aalderen, "Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility.," *J. Appl. Physiol.*, vol. 88, no. 6, pp. 1955–1961, Jun. 2000.

[53] M. L. Duiverman, L. A. van Eykern, P. W. Vennik, G. H. Koëter, E. J. W. Maarsingh, and P. J. Wijkstra, "Reproducibility and responsiveness of a noninvasive EMG technique of the respiratory muscles in COPD patients and in healthy subjects.," *J. Appl. Physiol.*, vol. 96, no. 5, pp. 1723–1729, May 2004.

[54] D. Kyroussis, M. I. Polkey, C. H. Hamnegard, G. H. Mills, M. Green, and J. Moxham, "Respiratory muscle activity in patients with COPD walking to exhaustion with and without pressure support.," *Eur. Respir. J.*, vol. 15, no. 4, pp. 649–655, Apr. 2000.

[55] J. T. Sharp, N. B. Goldberg, W. S. Druz, H. C. Fishman, and J. Danon,

"Thoracoabdominal motion in chronic obstructive pulmonary disease.," *Am. Rev. Respir. Dis.*, vol. 115, no. 1, pp. 47–56, Jan. 1977.

[56] W. D. C. Man *et al.*, "Effect of salmeterol on respiratory muscle activity during exercise in poorly reversible COPD.," *Thorax*, vol. 59, no. 6, pp. 471–476, Jun. 2004.

[57] C. SINDERBY *et al.*, "Diaphragm Activation during Exercise in Chronic Obstructive Pulmonary Disease," *Am. J. Respir. Crit. Care Med.*, vol. 163, no. 7, pp. 1637–1641, Dec. 2012.

[58] S. C. Gandevia, J. B. Leeper, D. K. McKenzie, and A. De Troyer, "Discharge frequencies of parasternal intercostal and scalene motor units during breathing in normal and COPD subjects.," *Am. J. Respir. Crit. Care Med.*, vol. 153, no. 2, pp. 622–628, Feb. 1996.

[59] C. Jolley, Y.-M. Luo, J. Steier, G. Rafferty, M. Polkey, and J. Moxham, "Neural respiratory drive and breathlessness during incremental cycle and treadmill exercise in chronic obstructive pulmonary disease," *Lancet*, vol. 383, p. S63, Feb. 2014.

[60] C. J. Jolley and J. Moxham, "A physiological model of patient-reported breathlessness during daily activities in COPD.," *Eur. Respir. Rev.*, vol. 18, no. 112, pp. 66–79, Jun. 2009.

[61] D. E. O'Donnell, A. L. Hamilton, and K. A. Webb, "Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD.," *J. Appl. Physiol.*, vol. 101, no. 4, pp. 1025–1035, Oct. 2006.

[62] D. E. O'Donnell *et al.*, "Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD.," *Eur. Respir. J.*, vol. 23, no. 6, pp. 832–840, Jun. 2004.

[63] C. T. Mendonca, M. R. Schaeffer, P. Riley, and D. Jensen, "Physiological mechanisms of dyspnea during exercise with external thoracic restriction: role of increased neural respiratory drive.," *J. Appl. Physiol.*, vol. 116, no. 5, pp. 570–581, Mar. 2014.

[64] A. De Troyer, A. Legrand, P. A. Gevenois, and T. A. Wilson, "Mechanical advantage of the human parasternal intercostal and triangularis sterni muscles.," *J. Physiol.*, vol. 513 (Pt 3, no. Pt 3, pp. 915–925, Dec. 1998.

[65] P. B. Murphy *et al.*, “Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD.,” *Thorax*, vol. 66, no. 7, pp. 602–608, Jul. 2011.

[66] E. J. W. Maarsingh, L. A. van Eykern, R. J. de Haan, R. W. Griffioen, M. O. Hoekstra, and W. M. C. van Aalderen, “Airflow limitation in asthmatic children assessed with a non-invasive EMG technique.,” *Respir. Physiol. Neurobiol.*, vol. 133, no. 1–2, pp. 89–97, Oct. 2002.

[67] E.-S. Suh *et al.*, “Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD.,” *Thorax*, vol. 70, no. 12, pp. 1123–1130, Dec. 2015.

[68] C. C. Reilly, C. J. Jolley, C. Elston, J. Moxham, and G. F. Rafferty, “Measurement of parasternal intercostal electromyogram during an infective exacerbation in patients with cystic fibrosis.,” *Eur. Respir. J.*, vol. 40, no. 4, pp. 977–981, Oct. 2012.

[69] L. Smith *et al.*, “S55 Neural Respiratory Drive Using Parasternal Electromyography In Clinically Stable Cystic Fibrosis Patients: A Physiological Marker Of Lung Disease Severity And Exercise Capacity,” *Thorax*, vol. 69, no. Suppl 2, pp. A30–A31, Nov. 2014.

[70] A. Kaaba *et al.*, “S54 Neural Respiratory Drive Measured Using Parasternal Intercostal Muscle Electromyography In Patients With Interstitial Lung Disease,” *Thorax*, vol. 69, no. Suppl 2, pp. A30–A30, Nov. 2014.

[71] C. C. Reilly, C. J. Jolley, C. Elston, J. Moxham, and G. F. Rafferty, “Blunted perception of neural respiratory drive and breathlessness in patients with cystic fibrosis.,” *ERJ open Res.*, vol. 2, no. 1, pp. 57–2015, Jan. 2016.

[72] J. Steier, C. J. Jolley, M. I. Polkey, and J. Moxham, “Nocturnal asthma monitoring by chest wall electromyography,” *Thorax*, vol. 66, no. 7, pp. 609–614, Jul. 2011.

[73] S. Nowbar *et al.*, “Obesity-Associated hypoventilation in hospitalized patients: Prevalence, effects, and outcome,” *Am. J. Med.*, 2004.

[74] P. E. Peppard, T. Young, J. H. Barnet, M. Palta, E. W. Hagen, and K. M. Hla, “Increased Prevalence of Sleep-Disordered Breathing in Adults,” *Am. J. Epidemiol.*, vol. 177, no. 9, pp. 1006–1014, Apr. 2013.

[75] J. Steier, C. J. Jolley, J. Seymour, M. Roughton, M. I. Polkey, and J. Moxham, “Neural respiratory drive in obesity.,” *Thorax*, vol. 64, no. 8, pp. 719–725, Aug. 2009.

[76] S. Xiao *et al.*, “Continuous Positive Airway Pressure and Breathlessness in Obese Patients with Obstructive Sleep Apnea: A Pilot Study.,” *Sleep*, vol. 39, no. 6, pp. 1201–1210, Jun. 2016.

[77] Y. M. Luo *et al.*, “Neural drive during continuous positive airway pressure (CPAP) and pressure relief CPAP,” *Sleep Med.*, vol. 10, no. 7, pp. 731–738, Aug. 2009.

[78] A. Onofri *et al.*, “Neural respiratory drive and cardiac function in patients with obesity hypoventilation syndrome following initiation of non-invasive ventilation,” *J. Thorac. Dis.*, vol. 10, no. S1, pp. S135–S143, Jan. 2018.

[79] M. Patout, G. Arbane, A. Cuvelier, J.-F. Muir, N. Hart, and P. B. Murphy, “Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial,” *Thorax*, vol. 74, no. 1, pp. 83–86, Dec. 2018.

[80] M. Patout, G. Arbane, J.-F. Muir, A. Cuvelier, N. Hart, and P. B. Murphy, “Non-invasive ventilation (NIV) setup for COPD-OSA overlap syndrome: Is polysomnography (PSG) useful?,” 2016.

[81] D. Adler *et al.*, “Polysomnography in stable COPD under non-invasive ventilation to reduce patient-ventilator asynchrony and morning breathlessness.,” *Sleep Breath.*, vol. 16, no. 4, pp. 1081–1090, Dec. 2012.

[82] F. Fanfulla, A. E. Taurino, N. D. Lupo, R. Trentin, C. D’Ambrosio, and S. Nava, “Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic non-invasive mechanical ventilation,” *Respir. Med.*, vol. 101, no. 8, pp. 1702–1707, Aug. 2007.

[83] M. Ramsay *et al.*, “Parasternal electromyography to determine the relationship between patient-ventilator asynchrony and nocturnal gas exchange during home mechanical ventilation set-up.,” *Thorax*, vol. 70, no. 10, pp. 946–952, Oct. 2015.

[84] R. L. Bashshur, T. G. Reardon, and G. W. Shannon, “Telemedicine: A New Health Care Delivery System,” *Annu. Rev. Public Health*, 2000.

[85] S. Ryu, “Telemedicine: Opportunities and Developments in Member States: Report on the Second Global Survey on eHealth 2009 (Global Observatory for eHealth Series, Volume 2),” *Healthc. Inform. Res.*, vol. 18, no. 2, pp. 153–155, Jun. 2012.

[86] E. M. Strehle and N. Shabde, “One hundred years of telemedicine: does this new technology have a place in paediatrics?,” *Arch. Dis. Child.*, vol. 91, no. 12, pp. 956–959, Dec. 2006.

[87] M. Ng *et al.*, “Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013,” *Lancet*, 2014.

[88] C. Keating, K. Backholer, and A. Peeters, “Prevalence of overweight and obesity in children and adults,” *Lancet*, vol. 384, no. 9960, pp. 2107–2108, Dec. 2014.

[89] S. Wild, G. Roglic, A. Green, R. Sicree, and H. King, “Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030,” *Diabetes Care*, 2004.

[90] J. M. do Carmo *et al.*, “Obesity-Induced Hypertension: Brain Signaling Pathways.,” *Curr. Hypertens. Rep.*, vol. 18, no. 7, p. 58, Jul. 2016.

[91] B. G. Nordestgaard *et al.*, “The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach.,” *PLoS Med.*, vol. 9, no. 5, p. e1001212, Jan. 2012.

[92] T. Kurth *et al.*, “Body mass index and the risk of stroke in men.,” *Arch. Intern. Med.*, vol. 162, no. 22, pp. 2557–2562, Dec. 2002.

[93] K. M. Flegal, B. I. Graubard, D. F. Williamson, and M. H. Gail, “Cause-specific excess deaths associated with underweight, overweight, and obesity.,” *JAMA*, vol. 298, no. 17, pp. 2028–2037, Nov. 2007.

[94] J. F. Garvey, M. F. Pengo, P. Drakatos, and B. D. Kent, “Epidemiological aspects of obstructive sleep apnea.,” *J. Thorac. Dis.*, vol. 7, no. 5, pp. 920–929, May 2015.

[95] S. Bailly *et al.*, “Obstructive Sleep Apnea: A Cluster Analysis at Time of Diagnosis.,” *PLoS One*, vol. 11, no. 6, p. e0157318, Jan. 2016.

[96] P. Lévy *et al.*, “Obstructive sleep apnoea syndrome,” *Nat. Rev. Dis. Prim.*, vol. 1, p. 15015, Jun. 2015.

[97] D. J. Gottlieb *et al.*, “Relation of Sleepiness to Respiratory Disturbance Index,” *Am. J. Respir. Crit. Care Med.*, vol. 159, no. 2, pp. 502–507, Dec. 2012.

[98] H. C. Kim, T. Young, C. G. Matthews, S. M. Weber, A. R. Woodward, and M. Palta, “Sleep-disordered breathing and neuropsychological deficits. A population-based study.,” *Am. J. Respir. Crit. Care Med.*, vol. 156, no. 6, pp. 1813–1819, Dec. 1997.

[99] S. Tregear, J. Reston, K. S. J. of clinical sleep, and 2009, “Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis,” *jcsm.aasm.org* .

[100] P. E. Peppard, “Is obstructive sleep apnea a risk factor for hypertension?--differences between the Wisconsin Sleep Cohort and the Sleep Heart Health Study.,” *J. Clin. Sleep Med.*, vol. 5, no. 5, pp. 404–405, Oct. 2009.

[101] P. E. Peppard, T. Young, M. Palta, and J. Skatrud, “Prospective study of the association between sleep-disordered breathing and hypertension.,” *N. Engl. J. Med.*, vol. 342, no. 19, pp. 1378–1384, May 2000.

[102] H. G. Preethi Rajan, “Obstructive sleep apnea as a risk factor for type 2 diabetes mellitus,” *Nat. Sci. Sleep*, vol. 7, pp. 113–125, Jan. 2015.

[103] F. Baratta *et al.*, “Severity of OSAS, CPAP and cardiovascular events: A follow-up study,” *Eur. J. Clin. Invest.*, 2018.

[104] Y. K. Loke, J. W. L. Brown, C. S. Kwok, A. Niruban, and P. K. Myint, “Association of Obstructive Sleep Apnea With Risk of Serious Cardiovascular Events,” *Circ. Cardiovasc. Qual. Outcomes*, vol. 5, no. 5, pp. 720–728, Sep. 2012.

[105] T. Kendzerska, A. S. Gershon, G. Hawker, R. S. Leung, and G. Tomlinson, “Obstructive Sleep Apnea and Risk of Cardiovascular Events and All-Cause Mortality: A Decade-Long Historical Cohort Study,” *PLoS Med.*, vol. 11, no. 2, p. e1001599, Feb. 2014.

[106] P. Jennum and J. Kjellberg, “Health, social and economical consequences of sleep-disordered breathing: a controlled national study,” *Thorax*, vol. 66, no. 7, pp. 560–566, Jul. 2011.

[107] J. F. Guest, M. Panca, E. Sladkevicius, S. Taheri, and J. Stradling, “Clinical Outcomes

and Cost-effectiveness of Continuous Positive Airway Pressure to Manage Obstructive Sleep Apnea in Patients With Type 2 Diabetes in the U.K.," *Diabetes Care*, vol. 37, no. 5, pp. 1263–1271, May 2014.

[108] J. F. Guest, M. T. Helter, A. Morga, and J. R. Stradling, "Cost-effectiveness of using continuous positive airways pressure in treating severe obstructive sleep apnoea/hypopnoea syndrome in the UK," vol. 17, Jan. 2008.

[109] N. B. Kribbs *et al.*, "Objective Measurement of Patterns of Nasal CPAP Use by Patients with Obstructive Sleep Apnea," *Am. Rev. Respir. Dis.*, vol. 147, no. 4, pp. 887–895, Dec. 2012.

[110] C. L. Rosen *et al.*, "A Multisite Randomized Trial of Portable Sleep Studies and Positive Airway Pressure Autotitration Versus Laboratory-Based Polysomnography for the Diagnosis and Treatment of Obstructive Sleep Apnea: The HomePAP Study," *Sleep*, vol. 35, no. 6, pp. 757–767, Jun. 2012.

[111] D. Hwang *et al.*, "Effect of Telemedicine Education and Telemonitoring on Continuous Positive Airway Pressure Adherence. The Tele-OSA Randomized Trial," *Am. J. Respir. Crit. Care Med.*, vol. 197, no. 1, pp. 117–126, Dec. 2017.

[112] D. Hwang, "Monitoring Progress and Adherence with Positive Airway Pressure Therapy for Obstructive Sleep Apnea: The Roles of Telemedicine and Mobile Health Applications," *Sleep Med. Clin.*, vol. 11, no. 2, pp. 161–171, Jun. 2016.

[113] D. Leger, M. Elbaz, B. Piednoir, A. Carron, and J. Texereau, "Evaluation of the add-on NOWAPI® medical device for remote monitoring of compliance to Continuous Positive Airway Pressure and treatment efficacy in obstructive sleep apnea.," *Biomed. Eng. Online*, vol. 15, no. 1, p. 26, Feb. 2016.

[114] J. L. Pépin, R. Tamisier, D. Hwang, S. Mereddy, and S. Parthasarathy, "Does remote monitoring change OSA management and CPAP adherence?," *Respirology*, vol. 22, no. 8, pp. 1508–1517, Oct. 2017.

[115] D. J. Bratton, T. Gaisl, A. M. Wons, and M. Kohler, "CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis.," *JAMA*, vol. 314, no. 21, pp. 2280–2293, Dec. 2015.

[116] M. Gasa *et al.*, “Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure.,” *J. Sleep Res.*, vol. 22, no. 4, pp. 389–397, Aug. 2013.

[117] A. M. Sawyer, N. S. Gooneratne, C. L. Marcus, D. Ofer, K. C. Richards, and T. E. Weaver, “A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions.,” *Sleep Med. Rev.*, vol. 15, no. 6, pp. 343–356, Dec. 2011.

[118] C. J. Stepnowsky, J. J. Palau, M. R. Marler, and A. L. Gifford, “Pilot randomized trial of the effect of wireless telemonitoring on compliance and treatment efficacy in obstructive sleep apnea.,” *J. Med. Internet Res.*, vol. 9, no. 2, p. e14, May 2007.

[119] N. Fox *et al.*, “The Impact of a Telemedicine Monitoring System on Positive Airway Pressure Adherence in Patients with Obstructive Sleep Apnea: A Randomized Controlled Trial,” *Sleep*, vol. 35, no. 4, pp. 477–481, Apr. 2012.

[120] S. T. Kuna *et al.*, “Web-Based Access to Positive Airway Pressure Usage with or without an Initial Financial Incentive Improves Treatment Use in Patients with Obstructive Sleep Apnea.,” *Sleep*, vol. 38, no. 8, pp. 1229–1236, Aug. 2015.

[121] D. Munafo, W. Hevener, M. Crocker, L. Willes, S. Sridasome, and M. Muhsin, “A telehealth program for CPAP adherence reduces labor and yields similar adherence and efficacy when compared to standard of care.,” *Sleep Breath.*, vol. 20, no. 2, pp. 777–785, May 2016.

[122] D. Sparrow, M. Aloia, D. A. Demolles, and D. J. Gottlieb, “A telemedicine intervention to improve adherence to continuous positive airway pressure: a randomised controlled trial.,” *Thorax*, vol. 65, no. 12, pp. 1061–1066, Dec. 2010.

[123] M. F. Pengo *et al.*, “The effect of positive and negative message framing on short term continuous positive airway pressure compliance in patients with obstructive sleep apnea,” *J. Thorac. Dis.*, vol. 10, no. S1, pp. S160–S169, Jan. 2018.

[124] C. Stepnowsky, C. Edwards, T. Zamora, R. Barker, and Z. Agha, “Patient Perspective on Use of an Interactive Website for Sleep Apnea,” *Int. J. Telemed. Appl.*, vol. 2013, no. 24, pp. 1–10, Mar. 2013.

[125] V. Isetta *et al.*, “Telemedicine-based approach for obstructive sleep apnea management: building evidence.,” *Interact. J. Med. Res.*, vol. 3, no. 1, p. e6, Feb.

2014.

[126] R. Parikh, M. N. TouVelle, H. Wang, and S. N. Zallek, “Sleep Telemedicine: Patient Satisfaction and Treatment Adherence,” *home.liebertpub.com*, vol. 17, no. 8, pp. 609–614, Sep. 2011.

[127] I. de la Torre-Díez, M. López-Coronado, C. Vaca, J. S. Aguado, and C. de Castro, “Cost-utility and cost-effectiveness studies of telemedicine, electronic, and mobile health systems in the literature: a systematic review.,” *Telemed. J. E. Health.*, vol. 21, no. 2, pp. 81–85, Feb. 2015.

[128] N. Tarraubella *et al.*, “Management of obstructive sleep apnoea in a primary care vs sleep unit setting: a randomised controlled trial.,” *Thorax*, vol. 73, no. 12, pp. 1152–1160, Dec. 2018.

[129] C. L. Chai-Coetzer *et al.*, “Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: a randomized trial.,” *JAMA*, vol. 309, no. 10, pp. 997–1004, Mar. 2013.

[130] V. Isetta *et al.*, “A Bayesian cost-effectiveness analysis of a telemedicine-based strategy for the management of sleep apnoea: a multicentre randomised controlled trial.,” *Thorax*, vol. 70, no. 11, pp. 1054–1061, Nov. 2015.

[131] C. Turino *et al.*, “Management of continuous positive airway pressure treatment compliance using telemonitoring in obstructive sleep apnoea.,” *Eur. Respir. J.*, vol. 49, no. 2, p. 1601128, Feb. 2017.

[132] S. Parthasarathy, P. L. Haynes, R. Budhiraja, M. P. Habib, and S. F. Quan, “A national survey of the effect of sleep medicine specialists and American Academy of Sleep Medicine Accreditation on management of obstructive sleep apnea.,” *J. Clin. Sleep Med.*, vol. 2, no. 2, pp. 133–142, Apr. 2006.

[133] S. Parthasarathy, S. Subramanian, and S. F. Quan, “A multicenter prospective comparative effectiveness study of the effect of physician certification and center accreditation on patient-centered outcomes in obstructive sleep apnea.,” *J. Clin. Sleep Med.*, vol. 10, no. 3, pp. 243–249, Mar. 2014.

[134] S. Pamidi, K. L. Knutson, F. Ghods, and B. Mokhlesi, “The impact of sleep consultation prior to a diagnostic polysomnogram on continuous positive airway

pressure adherence.," *Chest*, vol. 141, no. 1, pp. 51–57, Jan. 2012.

[135] J. L. I. Alonso and C. M. Paredes, "Chronic obstructive pulmonary disease (COPD)," *Med.*, 2018.

[136] D. Wang *et al.*, "Chronic obstructive pulmonary disease in over 16s: diagnosis and management | introduction | Guidance and guidelines | NICE," *Thorax*, 2008.

[137] D. E. O'Donnell and C. M. Parker, "COPD exacerbations · 3: Pathophysiology," *Thorax*. 2006.

[138] J. A. Wedzicha and T. A. Seemungal, "COPD exacerbations: defining their cause and prevention," *Lancet*. 2007.

[139] A. Khakban *et al.*, "Ten-Year Trends in Direct Costs of COPD," *Chest*, vol. 148, no. 3, pp. 640–646, Sep. 2015.

[140] A. J. Guarascio, S. M. Ray, C. K. Finch, and T. H. Self, "The clinical and economic burden of chronic obstructive pulmonary disease in the USA," *Clin. Outcomes Res. CEOR*, vol. 5, pp. 235–245, Jan. 2013.

[141] C. D. Mathers and D. Loncar, "Projections of global mortality and burden of disease from 2002 to 2030," *PLoS Med.*, 2006.

[142] H. Pinnock *et al.*, "Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial.," *BMJ*, vol. 347, no. oct17 3, pp. f6070–f6070, Oct. 2013.

[143] M. Chatwin *et al.*, "Randomised crossover trial of telemonitoring in chronic respiratory patients (TeleCRAFT trial).," *Thorax*, vol. 71, no. 4, pp. 305–311, Apr. 2016.

[144] J. P.-C. Chau *et al.*, "A feasibility study to investigate the acceptability and potential effectiveness of a telecare service for older people with chronic obstructive pulmonary disease," *Int. J. Med. Inform.*, vol. 81, no. 10, pp. 674–682, Oct. 2012.

[145] C. Esteban *et al.*, "Outcomes of a telemonitoring-based program (telEPOC) in frequently hospitalized COPD patients.," *Int. J. Chron. Obstruct. Pulmon. Dis.*, vol. 11, no. 1, pp. 2919–2930, Jan. 2016.

[146] T. W. Ho *et al.*, “Effectiveness of Telemonitoring in Patients with Chronic Obstructive Pulmonary Disease in Taiwan-A Randomized Controlled Trial,” *Sci. Rep.*, 2016.

[147] T. Köhnlein *et al.*, “Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial,” *Lancet Respir. Med.*, vol. 2, no. 9, pp. 698–705, Sep. 2014.

[148] F. M. Struik *et al.*, “Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study,” *Thorax*, vol. 69, no. 9, pp. 826–834, Aug. 2014.

[149] P. B. Murphy *et al.*, “Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation,” *JAMA*, vol. 317, no. 21, pp. 2173–2177, Jun. 2017.

[150] J. M. Tuggey, P. K. Plant, and M. W. Elliott, “Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis.,” *Thorax*, vol. 58, no. 10, pp. 867–871, Oct. 2003.

[151] A. F. Crisan *et al.*, “Montreal cognitive assessment in COPD,” *Eur. Respir. J.*, vol. 44, no. Suppl 58, p. P4753, Sep. 2014.

[152] M. Patout *et al.*, “Home non-invasive ventilation (NIV) : Patients cognitive performance and skills at setup,” *Eur. Respir. J.*, vol. 48, no. suppl 60, p. PA2162, Sep. 2016.

[153] M. Patout *et al.*, “Home non-invasive ventilation (NIV): Identification of patients at risk of non-adherence at setup,” *Eur. Respir. J.*, vol. 48, no. suppl 60, p. OA3532, Sep. 2016.

[154] C. Rabec *et al.*, “Evaluating noninvasive ventilation using a monitoring system coupled to a ventilator: a bench-to-bedside study.,” *Eur. Respir. J.*, vol. 34, no. 4, pp. 902–913, Oct. 2009.

[155] P. Pasquina, J.-P. Janssens, O. Contal, and D. Adler, “Software for Home Ventilators and Leak Compensation: Key Technical and Practical Applications BT - Noninvasive

Mechanical Ventilation," in *Noninvasive Mechanical Ventilation*, no. Chapter 8, Cham: Springer International Publishing, 2016, pp. 81–88.

[156] J.-C. Borel *et al.*, "Long-term adherence with non-invasive ventilation improves prognosis in obese COPD patients," *Respirology*, vol. 19, no. 6, pp. 857–865, Aug. 2014.

[157] T. J. Meyer *et al.*, "Air Leaking Through the Mouth During Nocturnal Nasal Ventilation: Effect on Sleep Quality," *Sleep*, vol. 20, no. 7, pp. 561–569, Jul. 1997.

[158] S. K. Mansell *et al.*, "Using domiciliary non-invasive ventilator data downloads to inform clinical decision-making to optimise ventilation delivery and patient compliance," *BMJ open Respir. Res.*, vol. 5, no. 1, p. e000238, Mar. 2018.

[159] A. Pinto, J. P. Almeida, S. Pinto, J. Pereira, A. G. Oliveira, and M. de Carvalho, "Home telemonitoring of non-invasive ventilation decreases healthcare utilisation in a prospective controlled trial of patients with amyotrophic lateral sclerosis," *J. Neurol. Neurosurg. Psychiatry*, vol. 81, no. 11, pp. 1238–1242, Nov. 2010.

[160] A. Palot, D. Jaffuel, M. Gouitaa, C. Tummino, D. Charpin, and P. Chanez, "A place for Apnea Hypopnea Index telemonitoring in preventing heart failure exacerbation?," *Sleep Med.*, vol. 29, pp. 18–19, Jan. 2017.

[161] J. C. Borel *et al.*, "Parameters recorded by software of non-invasive ventilators predict COPD exacerbation: a proof-of-concept study," *Thorax*, vol. 70, no. 3, pp. 284–285, Feb. 2015.

[162] S. Blouet, J. Sutter, E. Fresnel, A. Kerfourn, A. Cuvelier, and M. Patout, "Prediction of severe acute exacerbation using changes in breathing pattern of COPD patients on home noninvasive ventilation," *Int. J. Chron. Obstruct. Pulmon. Dis.*, vol. Volume 13, pp. 2577–2586, Jan. 2018.

[163] A. Hazenberg, H. A. M. Kerstjens, S. C. L. Prins, K. M. Vermeulen, and P. J. Wijkstra, "Initiation of home mechanical ventilation at home: A randomised controlled trial of efficacy, feasibility and costs," *Respir. Med.*, vol. 108, no. 9, pp. 1387–1395, Sep. 2014.

[164] K. G. Johnson and D. C. Johnson, "Treatment of sleep-disordered breathing with positive airway pressure devices: Technology update," *Medical Devices: Evidence*

and Research. 2015.

[165] C. Ambrogio, X. Lowman, M. Kuo, J. Malo, A. R. Prasad, and S. Parthasarathy, “Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency,” *Intensive Care Med.*, 2009.

[166] P. B. Murphy *et al.*, “Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: A randomised controlled trial,” *Thorax*, 2012.

[167] E. Crisafulli, G. Manni, M. Kidonias, L. Trianni, and E. M. Clini, “Subjective sleep quality during average volume assured pressure support (AVAPS) ventilation in patients with hypercapnic COPD: A physiological pilot study,” *Lung*, 2009.

[168] P. B. Murphy *et al.*, “Safety and efficacy of auto-titrating noninvasive ventilation in COPD and obstructive sleep apnoea overlap syndrome.,” *Eur. Respir. J.*, vol. 46, no. 2, pp. 548–551, Aug. 2015.

[169] J. H. Storre *et al.*, “Average volume-assured pressure support in obesity hypoventilation: A randomized crossover trial,” *Chest*, 2006.

[170] K. Harold *et al.*, “Noninvasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease and hypercapnic encephalopathy,” *BMC Pulm. Med.*, 2013.

[171] M. Patout *et al.*, “AVAPS-AE vs. ST mode: A randomised controlled trial in patients with obesity hypoventilation syndrome,” 2018.

[172] P. Piesiak, A. Brzecka, M. Kosacka, and R. Jankowska, “Efficacy of noninvasive volume targeted ventilation in patients with chronic respiratory failure due to kyphoscoliosis,” *Adv. Exp. Med. Biol.*, 2015.

[173] N. S. Oscroft, R. Chadwick, M. G. Davies, T. G. Quinnell, and I. E. Smith, “Volume assured versus pressure preset non-invasive ventilation for compensated ventilatory failure in COPD,” *Respir. Med.*, 2014.

[174] C. Carlin, G. McDowell, C. Williams, A. Brown, C. Canavan, and R. Tourish, “S59 Utility of an auto-titrating protocol for the setup of nocturnal non-invasive ventilation,” *Thorax*, vol. 71, no. Suppl 3, pp. A35–A35, Dec. 2016.

[175] E. Oostveen *et al.*, “The forced oscillation technique in clinical practice: methodology, recommendations and future developments.,” *Eur. Respir. J.*, vol. 22, no. 6, pp. 1026–1041, Dec. 2003.

[176] NHS Medical Directorate, “COPD Commissioning Toolkit: A Resource for Commissioners,” *COPD Comm. Toolkit*, 2012.

[177] C. M. Roberts, D. Lowe, C. E. Bucknall, I. Ryland, Y. Kelly, and M. G. Pearson, “Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease,” *Thorax*, 2002.

[178] S. Hartl *et al.*, “Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit,” *Eur. Respir. J.*, 2016.

[179] Y. Zhang *et al.*, “A systematic review of how patients value COPD outcomes,” *Eur. Respir. J.*, 2018.

[180] C. M. Chu, V. L. Chan, A. W. N. Lin, I. W. Y. Wong, W. S. Leung, and C. K. W. Lai, “Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure,” *Thorax*, 2004.

[181] Y. Kondo, J. Kumasawa, A. Kawaguchi, R. Seo, E. Nango, and S. Hashimoto, “Effects of non-invasive ventilation in patients with acute respiratory failure excluding post-extubation respiratory failure, cardiogenic pulmonary edema and exacerbation of COPD: a systematic review and meta-analysis,” *J. Anesth.*, 2017.

[182] C. R. Osadnik, V. S. Tee, K. V Carson-Chahhoud, J. Picot, J. A. Wedzicha, and B. J. Smith, “Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease.,” *Cochrane database Syst. Rev.*, vol. 7, no. 8860, p. CD004104, Jul. 2017.

[183] C. F. Vogelmeier *et al.*, “Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report,” *American Journal of Respiratory and Critical Care Medicine*. 2017.

[184] A. S. Fazekas *et al.*, “Long-term outcomes after acute hypercapnic COPD exacerbation: First-ever episode of non-invasive ventilation,” *Wien. Klin. Wochenschr.*, 2018.

[185] J. J. Soler-Cataluña, M. Á. Martínez-García, P. Román Sánchez, E. Salcedo, M. Navarro, and R. Ochando, “Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease,” *Thorax*, 2005.

[186] A. F. Connors *et al.*, “Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments),” *Am. J. Respir. Crit. Care Med.*, 1996.

[187] M. Dreher, J. H. Storre, C. Schmoor, and W. Windisch, “High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial,” *Thorax*, vol. 65, no. 4, pp. 303–308, Apr. 2010.

[188] W. Windisch, M. Haenel, J. H. STorre, and M. Dreher, “High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD,” *Int. J. Med. Sci.*, 2009.

[189] C. Casanova *et al.*, “Long-term Controlled Trial of Nocturnal Nasal Positive Pressure Ventilation in Patients With Severe COPD,” *Chest*, vol. 118, no. 6, pp. 1582–1590, Dec. 2000.

[190] E. Clini *et al.*, “The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients,” *Eur. Respir. J.*, vol. 20, no. 3, pp. 529–538, Sep. 2002.

[191] R. D. McEvoy *et al.*, “Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial,” *Thorax*, vol. 64, no. 7, pp. 561–566, Jun. 2009.

[192] M. Juniper, G. Ellis, N. C. E. Smith, K. L. Protopapa, and M. Mason, “Inspiring change: A review of the quality of care provided to patients receiving acute non-invasive ventilation,” *Natl. Confid. Enq. into Patient Outcome Death*, 2017.

[193] W. T. McNicholas, “Chronic obstructive pulmonary disease and obstructive sleep apnoea-the overlap syndrome.,” *J. Thorac. Dis.*, 2016.

[194] J. M. Marin, J. B. Soriano, S. J. Carrizo, A. Boldova, and B. R. Celli, “Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: The overlap syndrome,” *Am. J. Respir. Crit. Care Med.*, 2010.

[195] P. Jaoude, T. Kufel, and A. A. El-Solh, “Survival benefit of CPAP favors hypercapnic patients with the overlap syndrome,” *Lung*, 2014.

[196] L. A. P. De Llano *et al.*, “Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome,” *Chest*, 2005.

[197] P. Priou *et al.*, “Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome,” *Chest*, 2010.

[198] A. J. Piper, D. Wang, B. J. Yee, D. J. Barnes, and R. R. Grunstein, “Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation,” *Thorax*, 2008.

[199] J. F. Masa *et al.*, “Efficacy of different treatment alternatives for obesity hypoventilation syndrome: Pickwick study,” *Am. J. Respir. Crit. Care Med.*, 2015.

[200] M. Patout *et al.*, “Home non-invasive ventilation (NIV): Identification of patients at risk of non-adherence at setup,” in *ERS International Congress 2016 abstracts*, 2016, vol. 48, no. suppl 60, p. OA3532.

[201] A. Pinto, J. P. Almeida, S. Pinto, J. Pereira, A. G. Oliveira, and M. De Carvalho, “Home telemonitoring of non-invasive ventilation decreases healthcare utilisation in a prospective controlled trial of patients with amyotrophic lateral sclerosis,” *J. Neurol. Neurosurg. Psychiatry*, 2010.

[202] J. Moreira *et al.*, “Compliance with home non-invasive mechanical ventilation in patients with chronic respiratory failure: Telemonitoring versus usual care surveillance - a randomized pilot study,” *Eur. Respir. J.*, 2014.

[203] J. C. Borel *et al.*, “Noninvasive ventilation in mild obesity hypoventilation syndrome: A randomized controlled trial,” *Chest*, 2012.

[204] T. GOSS *et al.*, “COST-EFFECTIVENESS OF HOME OXYGEN THERAPY-HOME MECHANICAL VENTILATION (HOT-HMV) FOR TREATMENT OF COPD WITH CHRONIC HYPERCAPNIC RESPIRATORY FAILURE FOLLOWING AN ACUTE EXACERBATION OF COPD IN THE US,” *Chest*, 2018.

[205] M. Pallero *et al.*, “Ambulatory adaptation to noninvasive ventilation in restrictive

pulmonary disease: A randomized trial with cost assessment," *Respir. Med.*, vol. 108, no. 7, pp. 1014–1022, Jul. 2014.

[206] M. Chatwin, A. H. Nickol, M. J. Morrell, M. I. Polkey, and A. K. Simonds, "Randomised trial of inpatient versus outpatient initiation of home mechanical ventilation in patients with nocturnal hypoventilation," *Respir. Med.*, 2008.

[207] M. L. Duiverman *et al.*, "Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: A randomised controlled trial," *Thorax*, 2020.

[208] P. B. Murphy *et al.*, "Late Breaking Abstract - Cost-effectiveness of outpatient (OP) vs. inpatient (IP) setup of home non-invasive ventilation (NIV) in obesity hypoventilation syndrome (OHS): A Randomised Clinical Trial," 2019.

[209] J. Young, N. Ashforth, K. Price, A. Wilson, and A. Nickol, "Remote monitoring of home non-invasive ventilation: a feasibility study," *Eur. Respir. J.*, vol. 52, no. suppl 62, p. PA1669, Sep. 2018.

[210] S. McLean, U. Nurmatov, J. L. Liu, C. Pagliari, J. Car, and A. Sheikh, "Telehealthcare for chronic obstructive pulmonary disease," *Cochrane Database Syst. Rev.*, 2011.

[211] H. Woehrle *et al.*, "Effect of a patient engagement tool on positive airway pressure adherence: analysis of a German healthcare provider database," *Sleep Med.*, 2018.

[212] E. S. Suh *et al.*, "Autotitrating external positive end-expiratory airway pressure to abolish expiratory flow limitation during tidal breathing in patients with severe COPD: a physiological study," *Eur. Respir. J.*, 2020.

[213] J. Martin Bland and D. G. Altman, "STATISTICAL METHODS FOR ASSESSING AGREEMENT BETWEEN TWO METHODS OF CLINICAL MEASUREMENT," *Lancet*, 1986.

[214] G. McDowell, R. Dcruz, N. Hart, P. Murphy, and C. Carlin, "Inter-observer reproducibility assessment of parasternal electromyogram(EMGpara) analysis: a tale of two cities," 2020.

[215] S. Y. chu Chuang, A. Teng, J. E. Butler, S. C. Gandevia, H. Selvadurai, and A. Jaffe, "Validation of a quantitative method to measure neural respiratory drive in

children during sleep," *Respir. Physiol. Neurobiol.*, 2017.

[216] G. McDowell, R. Dcruz, N. Hart, P. Murphy, and C. Carlin, "Simplifying the measurement of neural respiratory drive index: parasternal electromyogram to measure respiratory rate," 2020.

[217] I. Milesi, R. Porta, L. Barbano, S. Cacciatore, M. Vitacca, and R. L. Dellacà, "Automatic tailoring of the lowest PEEP to abolish tidal expiratory flow limitation in seated and supine COPD patients," *Respir. Med.*, 2019.

[218] GOLD Report, "Global initiative for chronic obstructive lung disease 2020 Report," *Glob. Initiat. Chronic Obstr. Lung Dis.*, 2020.

[219] J. A. Hardie, A. S. Buist, W. M. Vollmer, I. Ellingsen, P. S. Bakke, and O. Mørkve, "Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers," *Eur. Respir. J.*, 2002.

[220] C. Tantucci, "Expiratory flow limitation definition, mechanisms, methods, and significance," *Pulmonary Medicine*. 2013.

[221] R. E. HYATT, "The interrelationships of pressure, flow, and volume during various respiratory maneuvers in normal and emphysematous subjects.," *Am. Rev. Respir. Dis.*, 1961.

[222] R. L. Dellacà *et al.*, "Expiratory flow limitation detected by forced oscillation and negative expiratory pressure," *Eur. Respir. J.*, 2007.

[223] N. G. Koulouris, I. Dimopoulou, P. Valta, R. Finkelstein, M. G. Cosio, and J. Milic-Emili, "Detection of expiratory flow limitation during exercise in COPD patients," *J. Appl. Physiol.*, 1997.

[224] D. K. McKenzie, J. E. Butler, and S. C. Gandevia, "Respiratory muscle function and activation in chronic obstructive pulmonary disease," *Journal of Applied Physiology*. 2009.

[225] A. De Troyer and T. A. Wilson, "Effect of acute inflation on the mechanics of the inspiratory muscles," *Journal of Applied Physiology*. 2009.

[226] A. De Troyer, "Effect of hyperinflation on the diaphragm," *European Respiratory Journal*. 1997.

[227] C. Casanova *et al.*, “Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease,” *Am. J. Respir. Crit. Care Med.*, 2005.

[228] D. E. O’Donnell, P. Laveneziana, K. Webb, and J. A. Neder, “Chronic obstructive pulmonary disease: Clinical integrative physiology,” *Clinics in Chest Medicine*. 2014.

[229] A. L. P. Albuquerque *et al.*, “Inspiratory fraction and exercise impairment in COPD patients GOLD stages II-III,” *Eur. Respir. J.*, 2006.

[230] P. G. Ferreira *et al.*, “Dynamic hyperinflation and exercise limitations in obese asthmatic women,” *J. Appl. Physiol.*, 2017.

[231] L. Zhao, L. Peng, B. Wu, X. Bu, and C. Wang, “Effects of dynamic hyperinflation on exercise capacity and quality of life in stable COPD patients,” *Clin. Respir. J.*, 2016.

[232] R. L. Dellacà *et al.*, “Detection of expiratory flow limitation in COPD using the forced oscillation technique,” *Eur. Respir. J.*, 2004.

[233] R. L. Dellacà, M. Rotger, A. Aliverti, D. Navajas, A. Pedotti, and R. Farré, “Noninvasive detection of expiratory flow limitation in COPD patients during nasal CPAP,” *Eur. Respir. J.*, 2006.

[234] R. L. Dellacà, P. P. Pompilio, P. P. Walker, N. Duffy, A. Pedotti, and P. M. A. Calverley, “Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD.,” *Eur. Respir. J.*, vol. 33, no. 6, pp. 1329–1337, Jun. 2009.

[235] J. C. Hogg, J. Williams, J. B. Richardson, P. T. Macklem, and W. M. Thurlbeck, “Age as a Factor in the Distribution of Lower-Airway Conductance and in the Pathologic Anatomy of Obstructive Lung Disease,” *N. Engl. J. Med.*, 1970.

[236] H. N. Tse, C. Z. Steven Tseng, K. Y. Wong, K. S. Yee, and L. Y. Ng, “Accuracy of forced oscillation technique to assess lung function in geriatric COPD population,” *Int. J. COPD*, 2016.

[237] C. Crim *et al.*, “Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results,” *Respir. Med.*, vol. 105, no. 7, pp. 1069–1078, Jul. 2011.

[238] U. Kolsum *et al.*, “Impulse oscillometry in COPD: Identification of measurements

related to airway obstruction, airway conductance and lung volumes," *Respir. Med.*, vol. 103, no. 1, pp. 136–143, Jan. 2009.

[239] M. K. Johnson, M. Birch, R. Carter, J. Kinsella, and R. D. Stevenson, "Measurement of physiological recovery from exacerbation of chronic obstructive pulmonary disease using within-breath forced oscillometry.," *Thorax*, vol. 62, no. 4, pp. 299–306, Apr. 2007.

[240] M. K. Johnson, M. Birch, R. Carter, J. Kinsella, and R. D. Stevenson, "Measurement of physiological recovery from exacerbation of chronic obstructive pulmonary disease using within-breath forced oscillometry," *Thorax*, vol. 62, no. 4, pp. 299–306, Apr. 2007.

[241] P. A. Williamson, K. Clearie, D. Menzies, S. Vaidyanathan, and B. J. Lipworth, "Assessment of Small-Airways Disease Using Alveolar Nitric Oxide and Impulse Oscillometry in Asthma and COPD," *Lung*, vol. 189, no. 2, pp. 121–129, Dec. 2010.

[242] Y. Shi, A. S. Aledia, A. V Tatavoosian, S. Vijayalakshmi, S. P. Galant, and S. C. George, "Relating small airways to asthma control by using impulse oscillometry in children," *J. Allergy Clin. Immunol.*, vol. 129, no. 3, pp. 671–678, Mar. 2012.

[243] G. L. Hall *et al.*, "Respiratory function in healthy young children using forced oscillations," *Thorax*, 2007.

[244] C. L. Gangell, F. Horak, H. J. Patterson, P. D. Sly, S. M. Stick, and G. L. Hall, "Respiratory impedance in children with cystic fibrosis using forced oscillations in clinic," *Eur. Respir. J.*, 2007.

[245] A. N. Lima, A. C. D. Faria, A. J. Lopes, J. M. Jansen, and P. L. Melo, "Forced oscillations and respiratory system modeling in adults with cystic fibrosis," *Biomed. Eng. Online*, 2015.

[246] P. Pelosi, M. Croci, I. Ravagnan, P. Vicardi, and L. Gattinoni, "Total Respiratory System, Lung, and Chest Wall Mechanics in Sedated-Paralyzed Postoperative Morbidly Obese Patients," *Chest*, 1996.

[247] F. Zerah, A. Harf, L. Perlemuter, H. Lorino, A. M. Lorino, and G. Atlan, "Effects of obesity on respiratory resistance," *Chest*, 1993.

[248] I. Rubinstein, N. Zamel, L. DuBarry, and V. Hoffstein, “Airflow limitation in morbidly obese, nonsmoking men,” *Ann. Intern. Med.*, 1990.

[249] H. Liu, W. Ni, J. Zhao, S. Xiong, Y. Xu, and Z. Zhang, “The diagnosis value and its implication of impulse oscillometry in obstructive sleep apnea syndrome patients.,” *J. Tongji Med. Univ.*, vol. 20, no. 4, pp. 280–282, Jan. 2000.

[250] L. Huiguo, N. Wang, Z. Jianping, X. Shengdao, X. Yongjian, and Z. Zhenxiang, “The diagnosis value and its implication of impulse oscillometry in obstructive sleep apnea syndrome patients,” *J. Tongji Med. Univ.*, vol. 20, no. 4, pp. 280–282, Dec. 2000.

[251] A. Abdeyrim *et al.*, “What can impulse oscillometry and pulmonary function testing tell us about obstructive sleep apnea: a case-control observational study?,” *Sleep Breath.*, vol. 20, no. 1, pp. 61–68, May 2015.

[252] R. S. Dattani, C. B. Swerner, J. R. Stradling, and A. R. Manuel, “Exploratory study into the effect of abdominal mass loading on airways resistance and ventilatory failure.,” *BMJ open Respir. Res.*, vol. 3, no. 1, p. e000138, Jan. 2016.

[253] “Automatic tailoring of positive end-expiratory pressure (PEEP) by forced oscillation technique (FOT) during non-invasive ventilation: Effects of posture and exertion in COPD,” *Eur. Respir. J.*, 2012.

[254] Y. M. Luo *et al.*, “Neural respiratory drive during apnoeic events in obstructive sleep apnoea,” *Eur. Respir. J.*, 2008.

[255] S. Xiao *et al.*, “Neural respiratory drive (NRD) during continuous positive airway pressure (CPAP) titration in awake obese subjects with obstructive sleep apnoea (OSA),” in *Annual Congress 2015*, 2015, vol. 46, no. suppl 59, p. OA295.

[256] R. Pellegrino *et al.*, “Ventilation heterogeneity in obesity,” *J. Appl. Physiol.*, 2014.

[257] S. W. LITTLETON, “Impact of obesity on respiratory function,” *Respirology*, vol. 17, no. 1, pp. 43–49, Dec. 2011.

[258] S. W. LITTLETON and A. Tulaimat, “The effects of obesity on lung volumes and oxygenation,” *Respir. Med.*, vol. 124, pp. 15–20, Mar. 2017.

[259] Y. M. Luo *et al.*, “Neural drive during continuous positive airway pressure (CPAP)

and pressure relief CPAP," *Sleep Med.*, 2009.

[260] C. A. Kauppert *et al.*, "Pulmonary hypertension in obesity-hypoventilation syndrome," *Respir. Med.*, 2013.

[261] G. Berg, K. Delaive, J. Manfreda, R. Walld, and M. H. Kryger, "The use of health-care resources in obesity-hypoventilation syndrome," *Chest*, 2001.

[262] F. Heinemann, S. Budweiser, J. Dobroschke, and M. Pfeifer, "Non-invasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome," *Respir. Med.*, vol. 101, no. 6, pp. 1229–1235, Jun. 2007.

[263] J. L. Pépin, J. C. Borel, and J. P. Janssens, "Obesity hypoventilation syndrome: An underdiagnosed and undertreated condition," *American Journal of Respiratory and Critical Care Medicine*. 2012.

[264] P. B. Murphy *et al.*, "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.," *JAMA*, vol. 317, no. 21, pp. 2177–2186, Jun. 2017.

Chapter 8 Appendices

Appendix 1: Consent form for data sharing on the Airview™ platform

ResMed
Changing lives with every breath

Consent to "AirView"

With the online application "AirView", your homecare provider, physician, hospital, sleep lab or other service provider ("**Service Provider**") is able to monitor your sleep diagnosis and/or therapy from a distance.

For this purpose, data collected by ResMed devices used to diagnose or treat patients with sleep-disordered breathing ("**Device**" or "**Devices**") – such as the length of time the Device and the mask are used, leakage figures, pressure values or the apnoe-hypopnoea index – are transmitted to AirView in encrypted form. The Device is identified by means of the serial number; no personal data such as your name or address are sent. Afterwards, the data which have been transmitted can only be attributed to you personally by your own Service Provider(s), who can then use the information for your treatment.

In AirView, the data is transferred in encrypted form either via a mobile communications network or online by your Service Provider.

AirView is operated for ResMed SAS (Parc Technologique de Lyon, 292 Allée Jacques Monod, 69791 Saint Priest Cedex, France) by a provider specialised in handling health data (currently: Informatique de Securité SAS, at 2 Avenue des Puits, 71300 Montceau-les-Mines, France), who ensures compliance with the very strict criteria laid down for hosting health data.

By giving consent, you agree to your data being transmitted, processed and used in AirView. If however, you want to revoke this consent, you can do so at any time without stating the reasons. To do that, simply contact your Hospital/Service Provider in writing.

I consent to my data being transmitted, processed and used in AirView in the manner described above.

I have received a copy of this declaration of consent.

_____
Patient's signature

_____
Telephone number

_____
Date

_____
Email address

AFFIX PATIENT LABEL

_____
Device S/N & DN

Review Method

Remote Review ❒

Physical Review ❒

Appendix 2: Exploratory Endpoints Study Protocol

NHS Greater Glasgow and Clyde

Feasibility and Serial Change in Exploratory Endpoints (Parasternal EMG, Oscillometry, Actigraphy, Home BP, Electrical Impedance Tomography and Environmental Monitoring) in Patients with Respiratory Disorders

Exploratory Endpoints in Respiratory Disorders

Running title:	Exploratory Endpoints in Respiratory Disorders
Protocol Version:	v2
Date:	30th March 2017
REC Reference Number:	
ISRCTN/Clinical trial.gov:	
Sponsor's Protocol Number:	GN17RM179
Sponsor:	NHS Greater Glasgow & Clyde
Funder:	Endowment

Amendment number	Date	Protocol version

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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NHS Greater Glasgow and Clyde

STUDY SYNOPSIS

Title of Study:	Feasibility and Serial Change in Exploratory Endpoints (Parasternal EMG, Oscillometry, Actigraphy, Home BP and Environmental Monitoring) in Patients with Respiratory Disorders
Study Centre:	NHS Greater Glasgow & Clyde: Queen Elizabeth University Hospital & Gartnavel General Hospital
Duration of Study:	24 months
Primary Objective:	To determine whether acquisition of a set of exploratory clinical monitoring endpoints is feasible and acceptable in patients with a range of respiratory disorders
Secondary Objective:	Acquire preliminary dataset to establish normal and condition specific typical ranges for neural respiratory drive, airways resistance/reactance, daytime activity, sleep profiles, heart rate variability, home blood pressure and air pollution exposure in cohort of patients with normal respiratory status, and with a selection of key respiratory diagnoses Determine correlations/variations between change in patient's respiratory status (evaluated by established standard clinical parameters) during follow up and after therapeutic interventions, for neural respiratory drive, airways resistance/reactance, daytime activity, sleep profiles, heart rate variability, home blood pressure and air pollution exposure
Primary Endpoint:	Feasibility of this study protocol in research or clinical practice
Secondary Endpoints:	Feasibility, reproducibility and performance of individual exploratory monitoring tools - parasternal EMG, oscillometry, electrical impedance tomography (EIT), wristwatch and chest actigraphy, home diary blood pressure recording, home & personal air pollution monitoring - in patients with a range of respiratory disorders. Change in exploratory physiology data vs change in respiratory status relevant to underlying individual respiratory condition (ie recovery from exacerbation; improvement in dyspnoea/QoL scores; improvement in respiratory failure; improvement in monitoring chest x-ray, blood gas, spirometry or other routine investigations). Exploratory physiology data derived from study investigations:- • Neural respiratory drive (parasternal EMG performed by standard technique) • Airway resistance and reactance (oscillometry performed by standard technique) • Lung volumes (measured by electrical impedance tomography) • 7 day daytime activity and sleep profile (wrist watch and chest actigraphy) • 7 day heart rate and home blood pressure variability (chest actigraphy and diary of home BP) • 7 day home and personal air pollution monitoring (nitrogen dioxide passive diffusion tubes, $PM_{2.5}$ and

	black carbon micro-PEM monitor and/or black carbon personal sampling pump filter based measurement)
Methodology:	Observational cohort study
Sample Size:	5-10 patients for each specific condition; approximately 75 patient total anticipated
Screening:	Inpatients, daycase and outpatients with respiratory disorders particularly those with exacerbation or proposed for significant therapeutic intervention. Patients identified by collaborating clinicians and nurse specialists.
Registration/ Randomisation:	Cohort study, no randomisation. Research undertaken alongside routine clinical care. Opportunistically recruit patients whose condition and planned clinical attendances will provide opportunity to undertake proposed investigations, and plausibly recognise changes in the exploratory physiology measurements. 5-10 patients each with:- • Non-respiratory sleep disorders attending for polysomnography and then sleep clinic follow up (normal controls for cardio-respiratory physiology and air pollution measurements) • Obstructive sleep apnoea syndrome • Nocturnal hypoventilation disorders • Pleural effusion • Cystic fibrosis • Pulmonary hypertension with right heart failure • Acute exacerbation of airways disease (asthma, COPD, non-CF bronchiectasis) • Interstitial lung disease • Respiratory failure requiring nasal hi-flo oxygen • Respiratory failure requiring acute non-invasive ventilation
Main Inclusion Criteria:	• Informed consent • Attending for routine clinical care and undergoing clinical management with change/improvement in underlying condition anticipated, within feasible timescales for repeat measurements of parasternal EMG, oscillometry and actigraphy • Age >16 years
Main Exclusion Criteria:	• Inability to comprehend informed consent
Statistical Analysis:	Descriptive qualitative analysis will be undertaken for the feasibility evaluations. Correlation and variation analyses will be performed for respiratory status (by standard clinical parameters), Δ secondary endpoint monitoring results and changes in measured air pollution.

Title

Feasability and Serial Change in Exploratory Endpoints (Parasternal EMG, Oscillometry, Actigraphy, Electrical Impedance Tomography, Home BP and Environmental Monitoring) in Patients with Respiratory Disorders

Short Title

Exploratory Endpoints in Respiratory Disorders

Introduction

Background and rationale

Monitoring of respiratory disorders with current investigation tools is challenging. Co-morbidities and patient capacity confound the performance and results of standard pulmonary function and exercise tests, and these standard tests are often insensitive to changes even with therapies/interventions of obvious benefit. It is plausible that new non-invasive investigation tools - surface intercostal parasternal electromyogram (EMG), portable airways oscillometry, wearable activity/heart rate variability monitors - will offer considerable benefits. These clinical investigation and monitoring tools potentially provide novel insights into relevant aspects of clinical physiology in human disease which have previously not been explored, due to technical challenges now overcome by modern equipment. Evaluation of these exploratory physiology measurements will likely provide novel insights into disease pathophysiology and treatment effects[1,2,3]. For many patients and investigators these investigation techniques are easier to perform and less burdensome than conventional respiratory investigations and therefore more applicable and reproducible for a wider range of patients (many of whom cannot currently struggle to perform standard pulmonary function and exercise tests). The measurements obtained from these newer techniques may be more sensitive to change with therapies, and by conducting these as a baseline and follow up investigation panel we may be better able to resolve questions about individual disease status vs confounding comorbidity. If these points were confirmed, these new investigation techniques may help rationalise respiratory condition treatment and other management decisions in routine clinical practice, and help establish clinical trial endpoints to better scrutinise respiratory clinical research.

There are notable reports about the utility of the individual investigation techniques - parasternal EMG, airways oscillometry, wristwatch/chest actigraphy and electrical impedance tomography - selected for this project: correlations in change in these with outcomes and management decisions have been described in multiple small previous studies[4-8]. Based on these early reports, various investigator-led and commercial clinical trial protocols are now proposing these measurements as secondary endpoints. In this study we propose to evaluate for the first time performing this panel of investigations simultaneously, in patients

with targeted selection of respiratory conditions at baseline and during follow up (from an exacerbation and/or after treatment or other clinical intervention). We will also perform these measurements in a recruited group of patients with non-respiratory sleep disorders (who have no respiratory comorbidity) to establish normal ranges in our population, and refine investigation performance practicalities. The purposes of this proposed study are to establish investigator competence with these investigations in research practice, determine the feasibility of performing this research investigation set simultaneously in the respiratory patient group, and obtain initial correlation/variance pilot data with the measurements derived from these investigations, for future endpoint validation studies, which would include benchmarking changes in these with 'hard' clinical endpoints.

Air pollution exposure is recognised as a major public health priority and variations in pollution exposure may account for variability in cardiorespiratory physiology in healthy individuals and variations in clinical status in patients with respiratory disorders[9,10]. Variations in air pollution could potentially account for changes in neural drive, airway resistance/reactivity, sleep integrity, heart rate and blood pressure variability[8,11]. Variability in air pollution could therefore confound correlation of these novel physiology measurements with respiratory disease status. Clinical significance of this is uncertain and accordingly we propose in this study to undertake home/personal air pollution monitoring, simultaneous with the other investigations, in a selected subgroup of patients. Principle aim is to determine the feasibility of this air pollution monitoring, but the results will also provide initial data to help evaluate interplay between changes in respiratory disease status, changes in physiological measurements and air pollution exposure. The acquired data will also help advance understanding of burden and importance of pollution exposure within our service catchment area, and provide hypothesis generating data about associations between variations in the exploratory clinical physiology measurements under investigation and variations in air pollution.

The investigations and monitoring proposed are non-invasive investigations with minimal patient burden. Based on accumulated knowledge of these monitoring investigations individually, performing these as an investigation panel would seem to have considerable potential to help our understanding, monitoring and treatment validation across a range of respiratory conditions. This proposed study is designed to help us judge the feasibility of this investigation panel, and obtain pilot data (specific to our local patient population) in subgroups of respiratory conditions.

Parasternal intercostal electromyogram (EMG)

This is performed with 2 small monitoring pads (identical to those for a simple ECG cardiac tracing) placed on the chest at either side of the upper sternum. Sleep study equipment with ECG, saturation finger probe, nasal flow cannulae and thorax/abdomen effort bands will be simultaneously worn to provide reference data on respiratory rate, heart rate, respiratory effort and airflow. After confirming acquisition of an adequate EMG trace the patient is monitored for a short period performing resting breathing, followed by a sniff maximal

inspiration manoeuvre, and other standard respiratory physiology breathing manoeuvers (inspiratory capacity, vital capacity, inspiratory and expiratory mouth pressures). In patients who are able measurements are repeated in supine and upright sitting position. In selected patients undergoing overnight sleep studies a continuous overnight EMG recording would be obtained. Depending on the underlying patient diagnosis, parasternal EMG will be repeated with varying frequency prior to and following treatment interventions and over time course of recovery from the acute illness. Measurement of parasternal EMG typically takes 10-15 minutes, for the majority of patients this would be undertaken on 2 or 3 occasions (before and after treatment intervention) but for selected patients recovering from an acute illness in-hospital this may be repeated (up to daily) across a 10-14 day admission.

Results from parasternal intercostal EMG correlate with those from diaphragm EMG. Neural respiratory drive (determined from the ratio of sniff:resting EMG amplitude) obtained by surface parasternal intercostal EMG provides an integration of the load-compliance of the respiratory system, and clinical utility (diagnostic differentiation, monitoring deterioration and improvement, clinical management decisions) of these measurements has been shown in small studies.

Airways oscillometry

This is performed similar to standard lung function measurements (nose clips, patient seals lips on mouthpiece) but with the advantage that patients need only undertake a short period of measured resting breathing, rather than repeated forced inspiratory and expiratory breathing manoeuvres. The equipment applies different frequency waveforms and results with these describe resistance/reactance/airways obstruction at different levels (central, large and small airways). Reproducibility and utility of oscillometry in various areas of clinical practice has been reported, but routine clinical use with newly available portable equipment has not been established.

Depending on the underlying patient diagnosis, airways oscillometry will be repeated with varying frequency prior to and following treatment interventions and over time course of recovery from the acute illness. Measurement of airways oscillometry typically takes 10-15 minutes, for the majority of patients this would be undertaken on 2 or 3 occasions (before and after treatment intervention) but for selected patients recovering from an acute illness in-hospital this may be repeated (up to daily) across a 10-14 day admission. Patient's who are able would also undertake handheld spirometry (standard breathing test) alongside the airways oscillometry manouvers, to provide reference measurements.

Electrical impedance tomography (EIT)

This technique measures lung volumes and changes in regional ventilation (eg in response to therapy) with a 16 electrode belt. Changes in electrical current transmission determines the air content of lungs across the reference points of the electrodes which are sited on the belt around the circumference of the chest wall. Acquiring EIT measurements simply involves study subject wearing the monitoring belt around their chest for the period of measurement. There is no discomfort or specific additional manoeuvres required and this

measurement. There is no discomfort or specific additional manoeuvres required and this test will be conducted simultaneously with the parasternal EMG. EIT will be performed at baseline and following an intervention in the range of patient's conditions, but restricted availability to the monitoring equipment may mean that it is only performed in a subset of patients.

Actigraphy and home blood pressure monitoring

7 days of home actigraphy and morning/evening home blood pressure recordings will be undertaken in a subset of patients (those having outpatient treatment of non-respiratory sleep disorders, obstructive sleep apnoea or nocturnal hypoventilation) prior to and following treatment intervention. Patients will wear wrist and chest strap actigraphy with heart rate variability monitoring, and be provided with home monitor and diary to undertake twice daily blood pressure measurements.

A variety of wristwatch and similar movement +/- heart rate monitoring tools have been widely adopted by the general population, promoted for fitness and lifestyle tracking. There are conflicting reports about the clinical utility of these, but with their simple application and widespread availability, further research scrutiny is appropriate. Chest based actigraphy (actiheart device) provides additional information with accurate heart rate, heart rate variability and derived energy expenditure measurements. Changes in these may reflect respiratory disease progress or treatment impact, and may account for variability in blood pressure measurements. Interaction between respiratory disorders, respiratory therapies and blood pressure control are notable, and this dataset will provide information on the feasibility and utility of pursuing this further in our patient population, with this research methodology. We will also obtain pilot data determining the utility of wristwatch actigraphy alone, vs higher fidelity chest actigraphy with heart rate variability data.

Air pollution monitoring

We have developed an easy to operate, small and lightweight 7-day air pollution monitoring pack, which will be provided to patients to deploy in their home. The air pollution monitoring pack meets standard infection control criteria. Air pollution monitoring will be undertaken as a sub-study only in those patients undergoing management at home with pre-post clinic/daycase follow up (eg those commencing treatment for obstructive sleep apnoea or nocturnal hypoventilation). Patients' exposure to indoor and outdoor traffic-related air pollutants will be estimated from 7-day average measurements of nitrogen dioxide, fine particles ($PM_{2.5}$), and black carbon. Simultaneous 7-day outdoor air pollution levels in the patient's home locus will be monitored with diffusion tubes placed by the research team on lamppost nearby. All environmental monitoring equipment is CE marked (and being used for its intended purpose) with exception of micro-PEM monitor: this is research equipment developed in collaboration between Strathclyde University and Research Triangle Institue, US – see collaboration letter attached for further details. Electrical safety of all of the equipment for this study will be re-confirmed by NHS GGC medical physics team.

Prior experience of intervention

There is considerable experience with endpoint evaluation and performance of complex investigational clinical physiology testing within the NHS GGC clinical research group. Early experience with performance and interpretation of oscillometry and actiheart measurements has been established. Investigator team visit to an experienced collaboration site (Dr P Murphy, Lane Fox Unit, St Thomas' Hospital London) to obtain further experience with intercostal EMG acquisition and interpretation is arranged, with ongoing support confirmed. Collaborations with Professor S Padmanabhan University of Glasgow BHF GCRC and Dr I Beverland University of Strathclyde Civil and Environmental Engineering are in place for evaluation of results of cardiovascular and air pollution monitoring findings.

Study hypothesis

This set of non-invasive clinical monitoring tools offers prospects for providing a rich dataset of exploratory physiology data in patients with respiratory disorders, but more immediately these investigation modalities are individually proposed for adoption as clinical trial endpoints. We believe it will be feasible to perform this collection of investigations in patients with the range of respiratory conditions - including those with a range of acuities - that we currently focus research expertise on, but this requires objective confirmation.

Aim, Primary and Secondary Objectives and Outcome Measures

Observational cohort study to determine feasibility and acceptability of simultaneously acquiring non-invasive exploratory clinical physiology investigations (parasternal EMG, portable oscillometry, actigraphy and serial home blood pressure measurement) and air pollution monitoring in patients with a selection of respiratory disorders in which changes in these investigations are likely to provide clinical insights and have utility for clinical management.

Primary Endpoint

- Number of patients in whom proposed investigation set is completed vs number screened and vs number enrolled in study with incomplete investigation set

Secondary endpoints

- Feasibility, reproducibility and performance of individual exploratory monitoring tools - parasternal EMG, oscillometry, electrical impedance tomography, wristwatch and chest actigraphy, home diary blood pressure recording, home & personal air pollution monitoring - in patients with a range of respiratory disorders.

- Change in exploratory physiology data vs change in respiratory status relevant to underlying individual respiratory condition (ie recovery from exacerbation; improvement in dyspnoea/QoL scores; improvement in respiratory failure; improvement in monitoring

chest x-ray, blood gas, spirometry or other routine investigations). Exploratory physiology data derived from study investigations:-

- Neural respiratory drive (parasternal EMG performed by standard technique)
- Airway resistance and reactance (oscillometry performed by standard technique)
- Lung volumes (as determined by electrical impedance tomography)
- 7 day daytime activity and sleep profile (wrist watch and chest actigraphy)
- 7 day heart rate and home blood pressure variability (chest actigraphy and diary of home BP)
- 7 day home and personal air pollution monitoring (nitrogen dioxide passive diffusion tubes, PM2.5 and black carbon micro-PEM monitor and/or black carbon personal sampling pump filter based measurement)

Study Design

This study observational cohort study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006).

Study Population

Patients with the target range of conditions will be identified from clinic, day ward, acute admissions and inpatient wards at Gartnavel General and Queen Elizabeth University Hospitals.

We aim to recruit 5-10 patients (each) with the range of respiratory conditions in which serial changes in neural drive, oscillometry, EIT and actigraphy are of most interest. Patients proposed for recruitment are those with:-

- Non-respiratory sleep disorders attending for polysomnography and then sleep clinic follow up: normal controls for cardio-respiratory physiology measurements
- Obstructive sleep apnoea syndrome
- Nocturnal hypoventilation disorders
- Pleural effusion
- Cystic fibrosis
- Pulmonary hypertension with right heart failure
- Acute exacerbation of airways disease (asthma, COPD, non-CF bronchiectasis)
- Interstitial lung disease
- Respiratory failure requiring nasal hi-flo oxygen
- Respiratory failure requiring acute non-invasive ventilation

Inclusion criteria

- Written informed consent
- ≥18 years of age
- Attending for routine clinical care and undergoing clinical management with change/improvement in underlying condition anticipated, within feasible timescales for

repeat measurements of parasternal EMG, oscillometry and actigraphy +/- home BP and air pollution monitoring

Exclusion criteria

- Inability to comprehend informed consent

Identification of participants and consent

We will recruit patients in whom a change in their condition across a time period suitable for repeat measurements of parasternal EMG, oscillometry, EIT -and actigraphy pre, during and post treatment intervention is achievable, and for which changes in these might be expected. For example, patients who have a stable pleural effusion under routine monitoring would not be enrolled, whereas a patient with a pleural effusion attending for daycase pleural drainage and clinical follow up and chest x-ray 1 week later would be offered recruitment.

The research team for this project are part of the patient's direct care team. Patients for screening will be identified and approached for informed consent by the investigators. Given the low risk and minimal burden of the research investigations, patients who agree to participate after discussions and reading patient information sheet will undergo consent and initial physiological measurements at this first visit. Up to 2 hours for patient consideration of information and discussion with the research team or independent parties would be available. Requiring a longer delay before informed consent would be impractical and would require burden of additional/unscheduled study visit for patient, rather than opportunistically performing study procedures alongside routine clinical care.

Written informed consent will then be obtained by participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Standard participant letter to GP would be issued.

Study duration

Patients will be involved in the study for 1-12 weeks depending on the nature and acuity of their underlying respiratory condition. For example, patients with acute respiratory failure or exacerbation of cystic fibrosis may be in the study for 1-2 weeks and have repeated EMG, oscillometry and EIT measurements. Repetitions of measurements may be on the same day (after a treatment intervention eg commencement of nasal hi-flo therapy) or day-day (eg following treatment progress and exacerbation recovery). Patients with sleep, obstructive sleep apnoea or nocturnal hypoventilation will undergo initial EMG, oscillometry, EIT and 7

day actigraphy and home blood pressure measurements at diagnostic attendance, and then at routine follow up after a period of home nocturnal CPAP or NIV treatment, typically 8-12 weeks later.

Withdrawal of subjects

Patients who withdraw consent for the study would have no further study procedures performed, but would be recorded as not wishing to proceed and this would be included in the primary endpoint analysis. Patients who have a deterioration of their underlying condition or develop intercurrent illness during the study would not have repeat physiological measurements undertaken if these were judged unfeasible (eg planned routine clinical attendance by patient now not possible) or inappropriate by the investigator team. These patients would be included in the primary endpoint analysis.

Assessment of Safety

Patient questionnaires on feasibility / acceptability of this research protocol will be scrutinised for safety comments (eg skin reaction to monitoring equipment) and these would be reported to the sponsor.

Statistics and Data Analysis

Source documents will be the hospital medical records, radiographs, investigation reports and correspondence on NHS GGC clinical portal. CRF entries will be source documents for recordings of exploratory physiology and timing outcomes. Additional source documents will comprise the questionnaires and visual scales.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number, not by name.

All written data will be held in a locked, fire-proof cabinet in the Department of Respiratory Medicine at Gartnavel General or Queen Elizabeth University Hospitals. All electronic data will be held in NHS Greater Glasgow and Clyde. Data will be in network drive / safestick (NHS GGC approved secure) accessible only to investigators. Data management will conform to the NHS GGC and NSS data protection policies.

Data analysis for the primary endpoint will be comparison of number of patients in whom investigation set was completed vs those incomplete. Acceptability and patient written feedback will be described descriptively. For the patient numbers initially proposed,

analyses of the with correlation of physiology and air pollution measurements with routine clinical/investigation parameters and comparison (correlation/variation analyses) of changes in these at follow up will be exploratory and hypothesis/pilot data generating: the aim is to determine feasibility and priorities for future research study. If initial scrutiny suggests correlation or significant changes in the physiology monitoring, normal distribution, Student's t-test (with Bonferonni corretion) and analysis of variance will be undertaken where appropriate.

Supplementary air pollution correlation/variance data analysis will be undertaken by Dr I Beverland and collaborating colleagues at Dept of Civil and Environmental Engineering, University of Strathclyde. Personal/patient identifiable data will not be transferred or accessible to non-clinical collaborators.

STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when recruitment target has been reached and final patient has completed follow up routine care/study visit.

Protocol Amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor. The CI will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office(s).

Ethical Consideration

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996], Edinburgh [2000], Seoul [2008] and Fortaleza [2013]).

Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this clinical trial. Patients will only be allowed to enter the study once they have provided written informed consent. The CI will be responsible for updating the Ethics committee of any new information related to the study.

Finance and Indemnity

This study is sponsored by NHS Greater Glasgow & Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

Investigator salary time is covered by NRS/NHS GGC career research fellowship (Dr Carlin) and breathing support research fellowship (Dr McDowell). Research equipment for the physiology measurements is in place in NHS GGC clinical research facility. Minor consumable cost for intercostal EMG and oscillometry measurements will be met from West Glasgow Sleep research endowment fund. Air pollution monitoring equipment and analysis costs are met by University of Strathclyde

NHS employed researchers will be covered for negligent harm through the NHS CNORIS indemnity scheme. University employee will be indemnified by the University of Glasgow's Clinical Trials insurance policy.

Publications

Study results will be presented at local, national and international respiratory research meetings and submitted for peer review publications.

Appendix 3: Patient information sheet for Exploratory Endpoint study

Respiratory Department
Gartnavel General Hospital
1053 Great Western Road
Glasgow G12 0YN

Exploratory Endpoints in Respiratory Disorders

Information Sheet

We would like to invite you to take part in a research study. Before you decide whether to participate you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research team consists of Dr Chris Carlin, Consultant Respiratory Physician, Prof Sandosh Padmanabhan from BHF Glasgow Cardiovascular Research Centre at the University of Glasgow, and Dr Grace McDowell, Clinical Fellow in Sleep and Breathing Support Medicine. This study will contribute to further post-graduate qualification for Dr McDowell. We will also be working with Dr Iain Beverland, University of Strathclyde and Fiona Sutherland, PHD student.

What is the purpose of the study?

Respiratory diseases area quite common medical problem. The standard medical tests (Pulmonary Function breathing tests and exercise tests) that we use can often be too strenuous for patients with breathing problems. These standard tests also don't acquire all the clinical information that we would like to have. As a result, it can sometimes be difficult to monitor respiratory conditions and improvements with treatment.

There are some new tests now available which might be useful in monitoring respiratory conditions. The tests are less invasive, easier to perform and therefore more reliable and easier to repeat. Early research with the new tests has given us promising results. We want to

determine if using these new non-invasive tests over the course of your treatment, will give us helpful information about your respiratory diagnosis/diagnoses, and help us monitor your condition and your response to treatment. This will allow us to determine how useful these new tests are.

We are not sure if these new tests will be more sensitive to changes/improvements in your respiratory condition than standard tests. If these novel non-invasive tests are however found to be more sensitive to change, we could potentially simplify investigations and better judge treatments of respiratory conditions in the future.

Air pollution is a major concern to respiratory and general health. We know that air pollution can cause and aggravate respiratory conditions, but we require more information in the West of Scotland to understand more accurately how it affects respiratory conditions and treatment responses. We will ask a proportion of patients in this study to take some air pollution monitoring equipment home with them, to combine that with the results of our other new tests.

We hope to recruit at least 75 patients with a wide range of respiratory conditions, identified from our inpatient or outpatient clinics at the Queen Elizabeth Universiety Hospsital and Gartnavel General Hospital.

Why have I been invited?

You have been selected as you are currently under the care of the respiratory department and will be commencing new treatments to improve your respiratory condition. We would like to use these new tests at the beginning (prior to starting treatment) and then at intervals throughout your treatment to measure your body's response to treatment.

Do I have to take part?

Participation is voluntary. We will describe the study to you and go through this information sheet. You will be asked to sign a consent form to participate. You will be free to withdraw from

this study at any point, without giving a reason. This study will not interfere with the standard of care you receive now or in future treatments. If you do wish to withdraw consent, please contact us as below. If you withdraw your consent to proceed, you will not have any further study procedures performed but your details would be recorded as not wishing to proceed and including in the end of study analysis.

What does taking part involve?

Once you have agreed to participate in this study, we can take the initial measurements straight away.

Participation in the study will involve:-

- Measurement of electrical signals from the breathing muscles (intercostal EMG). This involves wearing some monitoring leads on the skin at the front of your chest (similar as those for an ECG test). We would take recordings with you breathing at rest and doing some simple breathing manoeuvres and changing position. This test will take approximately 10-15 mins and the majority of patients will have this done 2-3 occasions (before and after commencing treatment). Some patients who are recovering from anacute illness as an inpatient will have these measurements done throughout their admission.
- Simple breathing tests (oscillometry and FEV1-6). These involve a short period of breathing and blowing into a lightweight tube: similar but less intensive that standard lung function breathing tests. This test will take 10-15mins and the majority of patients will have this down 2-3 times, depending on when you were attending or how long you were staying in hospital.
- Wearing a chest strap and/or wristwatch heart rate and activity monitor (similar to a "fitbit") for that you will wear continuously for 7 days
- Taking twice daily measurements of your blood pressure at home for 14 days, using a small cuff and machine that we provide, and you would record the results in a diary which we will provide for you on joining the study.

- Taking a lightweight air pollution monitoring pack home and keeping this in your home for 7 days

We will also note how feasible it was to perform the study tests alongside your routine care, and ask you to give us some simple feedback about you involved these tests were for you.
Depending on your condition and your treatment plan we may only undertake the EMG and breathing tests. If you have the equipment to wear and take home, we will either arrange to get it back at your next appointment or arrange postal return or collection of the equipment.

During the study you would also have all of the usual clinical monitoring for your condition and treatment which you are having. As a result we will have access to your medical records. We will note the results of these for the study, to compare with the study test results. Your standard care will not be compromised by participating in this study, and the study won't require any additional hospital attendances.

What happens to the information?

Your identity and personal information will be completely confidential. Personal details are only available to the research team and NHS Greater Glasgow and Clyde, who may look at the data to make sure the study is being conducted correctly. All data will remain confidential and will be stored on electronic records on NHS GG&C server. We will let your GP know that you are taking part in the study.

Once we have completed this study, we will anonymise all results when using the data for research purposes. A selection of anonymised data will be sent to Strathclyde University for analysis. Data sharing in the field of research has become increasingly important in the development and application of new technologies and treatments. We aim to share the anonymised data with our peers not only through peer reviewed scientific journals but also in the application of applied research in other health boards.

If you would like to know your personal results from the study or the overall findings of our study please contact Dr McDowell or Dr Carlin. (See contact details below)

What are the possible benefits of taking part?

Contributing to this study will provide us with valuable information on these new non-invasive tests and potentially rationalise investigations and monitoring of respiratory conditions in the future. Your participation will also improve our knowledge of the effects of air pollution on respiratory disease.

Occasionally the study tests might identify a health problem that you had without knowing it (eg high blood pressure). If that were to happen, we would advise on any additional tests or treatment needed, and let your GP know about the findings.

What are the possible disadvantages and risks taking part?

There are no perceived disadvantages by participating in this study. The recordings of these new non-invasive tests would be taken alongside standard treatment for your respiratory condition.

Who has reviewed the study?

This study has been reviewed by the NHS National Research Ethics Service.

Who do I contact if I encounter any problems or have any further questions?

Dr Grace McDowell can be contacted via email or telephone for any questions about the study. Please see contact details below.

If you have questions or concerns about this project that you'd wish to discuss with an independent clinician, please contact Dr Gordon MacGregor, Consultant Respiratory Physician Queen Elizabeth University Hospital, telephone: 0141 451 6092. The usual NHS complaints procedure is available to you.

Contacts:

Chief Investigator

Dr Chris Carlin

Consultant Physician

Dept of Respiratory Medicine

Queen Elizabeth University Hospital

1345 Govan Road

Glasgow G51 4TF

Tel - 0141 451 6088

Email –christopher.carlin@ggc.scot.nhs.uk

Co-investigator

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Clinical Research Fellow

Dept of Respiratory Medicine

Queen Elizabeth University Hospital

1345 Govan Road

Glasgow G51 4TF

Tel - 0141 451 6088

Email – gmcdowell@nhs.net

Thank-you for reading this information sheet

Appendix 4: Consent form for the Exploratory Endpoints study

Respiratory Department
Gartnavel General Hospital
1053 Great Western Road
Glasgow G12 0YN

CONSENT FORM

Study Title: Exploratory Endpoints in Respiratory Disorders.

IRAS ID: **Participant's ID:**

	Please initial in boxes below
I confirm I have read and understand the information sheet dated 13th June 2017 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily.	
I understand that participation is voluntary, and I am free to withdraw at any time without my medical care being affected.	
I understand by participating in this study I have agreed to the correct use of the ambulatory equipment supplied for the 7-day monitoring and will ensure its safe return at the end of this period.	
I understand by participating in this study, the research team will have access to my medical records.	
I understand by participating in this study I will be required to repeat several of the tests at fixed intervals throughout my treatment.	
I understand that any information recorded in this study will remain confidential and that it may be looked at by representatives of the study Sponsor, NHS GG&C, for audit purposes. Data used for research purposes and publications will be anonymised.	
I understand the data collected may be used in a research thesis published in scientific literatures and presented at scientific conferences.	
I agree to participate in the above study	

Please sign and print below to confirm consent:

Participant
Name: Signature: Date:

Investigator/Co-investigator
Name: Signature: Date:

Appendix 5: Exploratory Endpoints patient questionnaires

Study Title: Exploratory Endpoints in Respiratory Disorders.

IRAS ID: 226158 **Participants ID:**

QUESTIONNAIRES

EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations? Please try to work out how likely you would be affected, even if you haven't done some of these.

0 = would never doze

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

SITUATION	**CHANCE OF DOZING (0-3)**
Sitting and reading	
Watching TV	
Sitting still in a public place (e.g a theatre, a cinema, or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when the circumstances allow	
Sitting talking to someone	
Sitting quietly after lunch without having drunk alcohol	
In a car or bus while stopped for a few minutes in traffic	
TOTAL	

University of Glasgow

NHS Greater Glasgow and Clyde

Study Title: Exploratory Endpoints in Respiratory Disorders.

IRAS ID: **Participants ID:**

QUESTIONNAIRES

MODIFIED COPD ASSESSMENT TEST (CAT)

The COPD assessment tool is used to assess the management of lung conditions. We have modified this questionnaire so it is applicable to all our patients, with or without COPD.

For each item below, please score your symptoms from one to 5 by circling the appropriate number. 1 being the least symptomatic to 5 being the most problematic symptoms.

SYMPTOMS		SYMPTOMS	SCORE
I never cough	1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	1 2 3 4 5	My chest is completely full of phlegm (mucus)	
When I walk up a hill or flight of stairs I am not breathless	1 2 3 4 5	When I walk up a hill or flight of stairs I am very breathless	
My chest does not feel tight at all	1 2 3 4 5	My chest feels very tight	
I am not limited doing any activities	1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	1 2 3 4 5	I am not confident leaving my home because of my lung condition	
I sleep soundly	1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	1 2 3 4 5	I have no energy at all	
TOTAL SCORE:			

Study Title: Exploratory Endpoints in Respiratory Disorders.

IRAS ID: **Participants ID:**

QUESTIONNAIRES

MODIFIED BRITISH MEDICAL RESEARCH COUNCIL DYSPNOEA SCALE (MRC)

This assessment tool is used regularly in all our patients to give us information on how breathless you are. Please answer the question below:

Do you suffer from breathlessness? **Yes** **No**

If yes please highlight by circling the grade of breathlessness you feel you suffer from.

DEGREE OF BREATHLESSNESS RELATED TO ACTIVITIES	GRADE
Not troubled by breathlessness except on strenuous exercise	1
Short of breath when hurrying on the level or walking up a slight hill	2
Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace	3
Stops for breath after walking about 100 yards or after a few minutes on level ground	4
Too breathless to leave the house, or breathless when undressing	5

ECOG PERFOMANCE STATUS

This assessment tool is used regularly to highlight how symptomatic our patients are and how this affects everyday living. Please circle how you feel your condition has affected your daily life. Please only select one option.

ECOG PERFORMANCE STATUS	GRADE
Fully active, able to carry on all pre-condition performance without restriction	1
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work	2
Capable of only limited self-care; confined to bed or chair for more than 50% of waking hours	3
Completely disabled; cannot carry on any self-care; totally confined to bed or chair	4

Study Title: Exploratory Endpoints in Respiratory Disorders. and Clyde

IRAS ID: **Participants ID:**

STUDY QUESTIONNAIRE

Below are several statements/questions which we would like you to complete. This feedback gives us information on how you found being a participant in the study and how we can improved our practice for the future.
Please circle the appropriate response to each question/statement:

INFORMED CONSENT:

1. I was given enough time to read and ask questions about the study prior to consenting:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

2. The information leaflets and consent forms were clear and easy to understand:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

3. The research team answered any questions I had about the study/consent:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

4. I understood what the trial involved at time of consent:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

PARTICIPATION:

5. I was informed what was going to happen throughout the course of the study:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

6. I was treated with respect throughout the study:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

and Clyde

Study Title: Exploratory Endpoints in Respiratory Disorders.

IRAS ID: **Participants ID:**

7. My medical needs were meet throughout the participation in this study:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

8. All equipment given to me for home monitoring was straight forward to use and clear instructions provided on the information sheets.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

9. It was easy to contact the appropriate member of the research team if required:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

OVERALL IMPRESSIONS:

10. I feel that participation in this study was not intrusive to my medical care:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

11. I would participate in future studies:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

12. Overall, my experience participating in this study was positive:

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Comments:

Do you have any comments or remarks you would like to address to us about this study?

Study Title: Exploratory Endpoints in Respiratory Disorders

IRAS ID: **Participants ID:**

AIR POLLUTION QUESTIONNAIRE

Please circle the appropriate answer. We welcome any comments you may have.

QUESTIONS		
1. Did transporting the air pollution monitoring equipment from and to the hospital cause any difficulties?	YES	NO
Comments:		
2. Was the equipment noisy and disturb your daily life?	YES	NO
Comments:		
3. Was the information sheet, concerning air monitoring, clear enough or would you have liked more details?	YES	NO
Comments:		
4. Is there a gas cooker in your home?	YES	NO
Comments:		
5. Are there any smokers in your home?	YES	NO
How many?		

6. Do you have any comments or remarks you would like to address to us about the practicality of our study?

Appendix 6: Parasternal electromyography method

Neural Respiratory Drive is measured via parasternal EMG electrode signals sampled with band pass filters via the Dual Bio Amp (ADInstruments, Chalgrove, UK) Amplified signals are passed to a digital converter (Powerlab, ADInstruments, Chalgrove, UK). Filtering and analysis are done within Labchart software (ADInstruments, UK) on a personal computer. Airflow is measure via a spirometry model signals are amplified and passed to the digital converter before analysis in Labchart software. (figure 8.1)

Method:

1. Set up ADInstruments with a personalised computer (PC) with Labchart software for data collection and analysis
2. Set up PowerLab input channels as detailed below:

Channel	Signal
Channel 1	ECG
Channel 2	Filtered EMG
Channel 3	Thoracic RIP
Channel 4	Spirometry module

3. Turn on PC and ADInstruments, ensuring spirometry module is resting separate to the Bio Amp and Powerlab modules to avoid overheating. Allow at least 5 minutes for the spirometry module to warm up, when ready the light will turn green.
4. Position patient at 45degrees and ensure they are comfortable in this position for prolonged period.
5. Preparation of the skin prior to electrode application- palpate the 2nd intercostal space (ICS) and locate position approximately 3cms from central sternum. Shave area (if required) exfoliate with trace preparation tape (3M Red Dot Trace, 3M, Canada), clean with alcohol wipe and apply electrodes (Elite, Skintact, UK). Ensure the centre of the electrode is in the middle of intercostal space.
6. Repeat skin preparation and electrode placement for lateral right clavicle position electrode.
7. Attached electrode leads as detailed below and in Figure 8.2.
   Green (ground)- Right lateral clavicle

Black (positive)- Right 2nd ICS

White (negative)- Left 2nd ICS

8. Place Thoracic RIP band across the mid chest. Avoid direct contact with parasternal electrodes. (figure 8.2)
9. Attached nasal flow cannula to spirometry module and position on the patient.
10. Ask the patient to relax and record normal tidal breathing via Lab chart software.
11. Once 5 minutes of tidal breathing is recorded inform the patient of transition to maximal manoeuvres recordings. Mark the end of 5 minutes of tidal breathing on Lab chart.
12. Mark Labchart recording with “Measurement commencing” and ask the patient to close their mouth and continue breathing via the nasal passages.
13. Prepare patient with count down of 3 breathes prior to a maximal sniff manoeuvre. Mark on Lab chart software at the time of “Sniff”.
14. Repeat this process at least 10 times with a minimal of 30seconds of rest between each manoeuvre as per ERS guidelines.
15. Once recording completed, stop Labchart. At this point if indicated patients can be moved to supine or upright positions and the above method repeated.
16. Remove nasal cannula, RIP bands and electrodes.
17. Save Labchart file under study number.

Figure 8.1: Parasternal electromyography set up: Parasternal electromyography measured with ADInstruments for EMG measurements.

A- Dual Bio Amp, B- PowerLab digital converter, C- Spirometry module.

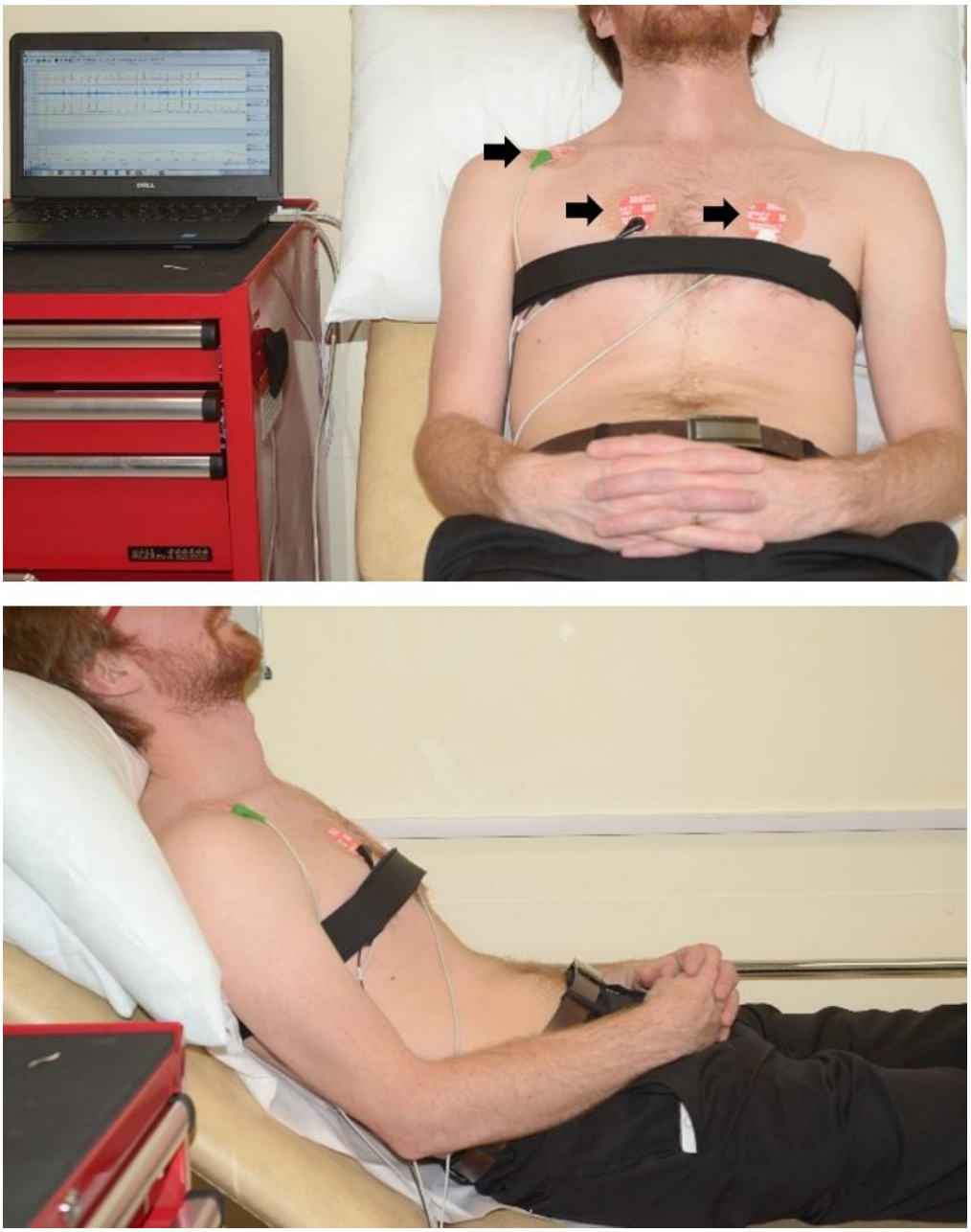

Figure 8.2: Patient position for parasternal electromyogram recording: Patient positioned at 45 degrees with parasternal electrodes placed in the 2nd intercostal space and right clavicle (black arrows). Respiratory impedance plethysmography (RIP) band is wrapped around the patient's thorax.

Appendix 7: Parasternal electromyography analysis

1. Open file on Labchart software
2. Right click on heading of columns in data pad sheet to set up:

   Column 1: Time at maximum (Statistics, Time of maximum value, Source: Channel EMG RMS)

   Column 2: Maximum value (Statistics, Max Value, Source EMG RMS)

   Column 3: Average Cyclic Rate (Cyclic measurements, Av. Cyclic rate, Source: Can be Channel Airflow or RIP bands)

   Column 4: Comments (Comments, Full comments, Source: Any channel)

3. Review tidal breathing and select time where there is one minute of continuous resting breaths with minimal artifacts (usually the last minute of tidal breathing).
4. Review the peaks in RMS EMG. Only select RMS EMG out with the ECG signal. See Figure 8.3
5. Select peak RMS EMG of tidal breaths and save to data pad by selecting “cmd” + ”D“keys (“ctl” +”D”). Repeat for each breath in the one minute of tidal breathing.
6. Repeat steps 4 and 5 for the 10 sniff measurements. (Ensure RMS EMG is out with the ECG signal)
7. Save the Labchart file. Copy and paste the data pad to excel or mac equivalent.
8. Calculate the mean EMGpara during tidal breathing.
9. Select the maximum RMS EMG value during manoeuvres (Sniffs) which must be within 10% of other RMS EMG values for sniffs.
10. Calculate $EMG_{para\%max}$ for each value selected during tidal breathing:

    $$EMG_{para\%max} = (RMS\ EMG_{tidal} / RMS\ EMG_{maxsniff}) \times 100$$

11. Calculate Neural Respiratory Drive Index (NRDI) for each value selected during tidal breathing:

    $$NRDI = EMG_{para\%max} \times Average\ cyclic\ rate$$

12. Calculate mean $EMG_{para\%max}$ values and mean NRDI values.
13. Record meanEMG_{para}, mean $EMG_{para\%max}$ and meanNRDI for each study candidate.
14. Repeat analysis (Steps1-13) for all subsequent readings following interventions/treatments.

15. Calculate absolute and percentage change in meanEMG_{para}, mean $EMG_{para\%max}$ and meanNRDI for each study candidate following intervention.

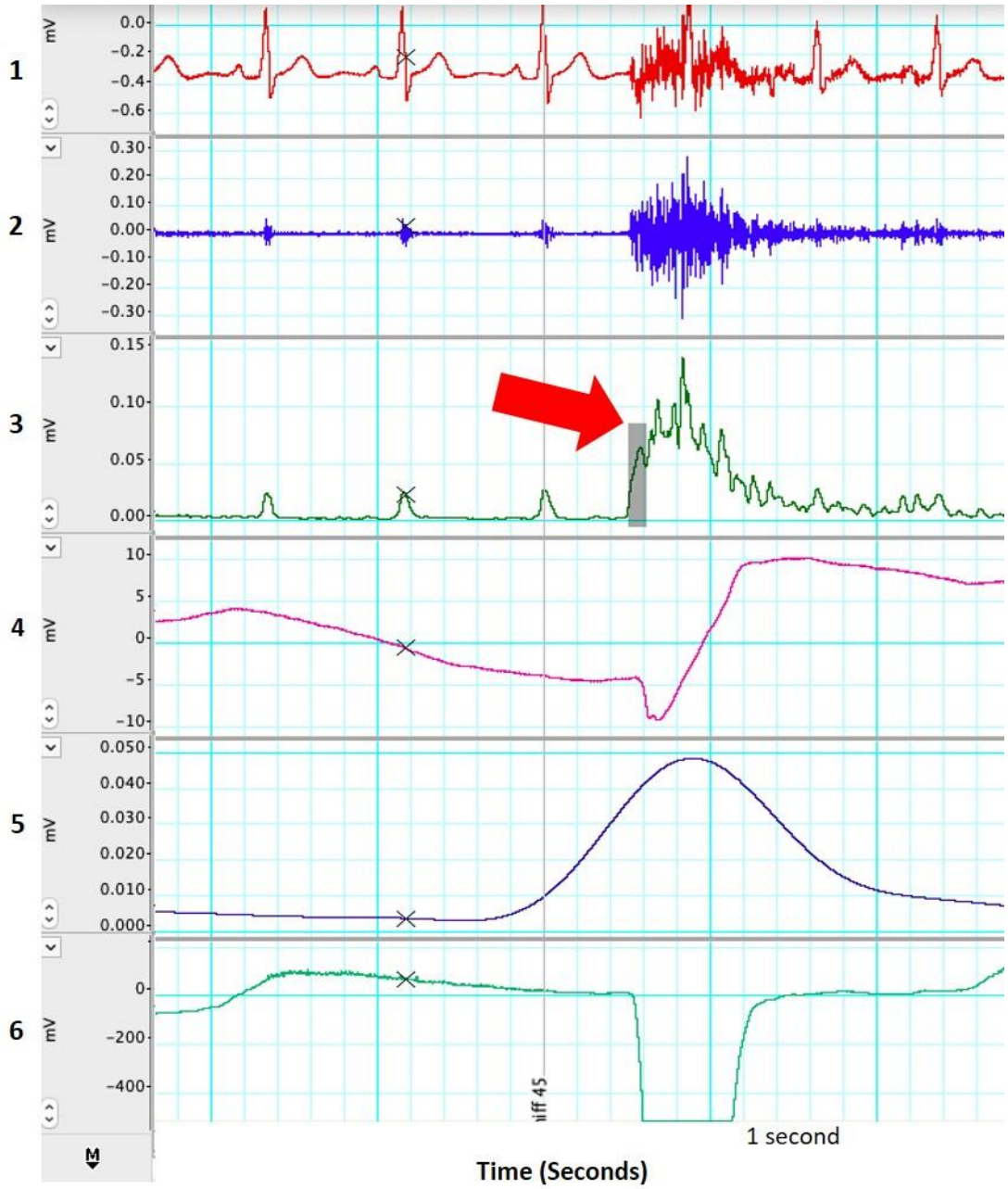

Figure 8.3: **Parasternal electromyogram (EMG) data selection for analysis with the maximum peak of the root mean squared EMG signal (red arrow).**

Channel 1- Electrocardiogram signals, Channel 2- Filtered EMG signals, Channel 3- Root mean squared of EMG, Channel 4- Oro-nasal flow analysis, Channel 5- Respiratory rate derived from the root mean squared EMG signals (RMS RR), Channel 6- Respiratory impedance plethysmography band signals

Appendix 8: Simplification of parasternal electromyography: deriving estimated respiratory rate from the root mean squared parasternal electromyogram signals.

1. Parasternal EMG measurements should be collected as described in Appendix 6.
2. To use RMS signal to estimate RR, select digital filter on a spare channel, the source should be RMS channel and filter set to “low pass” with a cut off 0.5Hz to filter ECG spikes. (fig 8.5)
3. Name Channel RMS RR, respiratory rate derived from root mean squared EMG signal. (Fig 8.4)
4. Right click on columns in data pad to set up:
   Column 1: Time at maximum (Statistics, Time of maximum value, Source: Channel EMG RMS)
   Column 2: Maximum value (Statistics, Max Value, Source EMG RMS)
   Column 3: Average Cyclic Rate (Cyclic measurements, Av. Cyclic rate, Source: Can be Channel Airflow or RIP bands)
   Column 4: Average Cyclic Rate (Cyclic measurements, Av. Cyclic rate, Source RMS EMGpara-RR)
   Column 5: Comments (Comments, Full comments, Source: Any channel)
5. Proceed with analysis detailed in steps 3-15 in Appendix 7
6. Calculate meanNRDI derived from RMS EMGpara-RR.

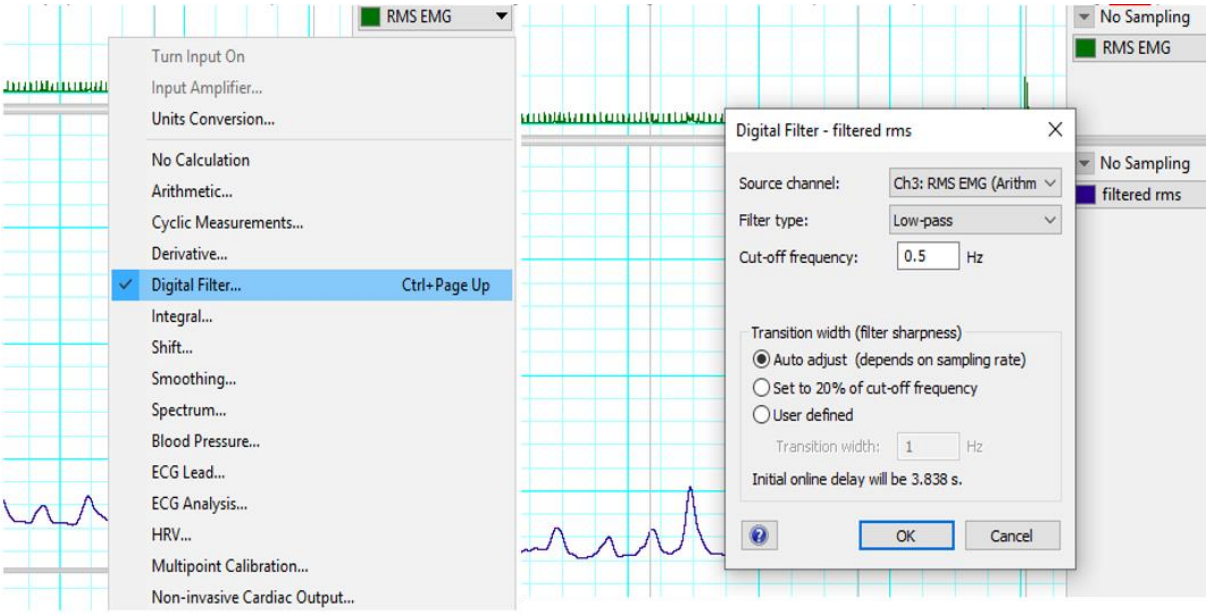

Figure 8.4: Digital filer selection in data pad for derived respiratory rate from root mean squared parasternal electromyogram signal.

Appendix 9: Exploratory Endpoints advance physiology results.

1			
2	7.54545	47.1591	1019
3	14.5636	51.1004	813
4	4.94167	16.8658	213
5	7.9	24.921	648
6	3.36364	14.6884	294
7	2.675	10.3682	197
8	5.67273	17.9516	192
9	4.52667	36.5054	807
10	23.65	62.0091	608
11	13.3933	56.512	1135
12	7.79444	22.2063	227
13	4.06	16.371	316
14	3.42308	6.42233	73
15	15.136	19.039	266
16	4.333	17.4731	255
17	1.34	2.9005	51
18	3.33636	16.9358	238
19	5.91667	12.9358	149
20	4.475	9.0771	212
Mean (Standard deviation)	7.09 (5.52)	23.68 (17.33)	393.05 (323.38)

Table 9.1 Parasternal electromyography measurements at baseline visit in patients with obstructive sleep apnoea syndrome initiated on remote monitored positive airway pressure therapy

meanEMGpara- mean parasternal electromyography (microvolts), meanEMGpara%max- mean normalised parasternal Electromyography (microvolts), NRDI- Neural Respiratory Drive Index (arbitrary units)

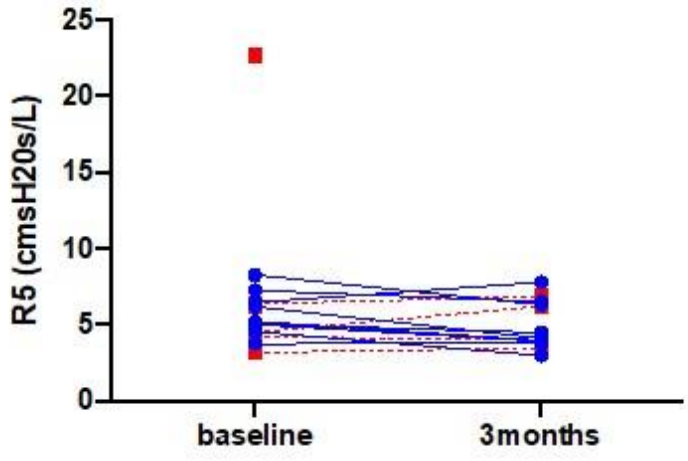

Figure 9-1 Total airways resistance in patients with obstructive sleep apnoea syndrome

Presentation of change in total airways resistence after 3 months of positive airway pressure therapy. Total airway resistane decreased in patient adherent to PAP therapy (blue)(>4hours use for >70% of nights) compared to those non—adherent (red).

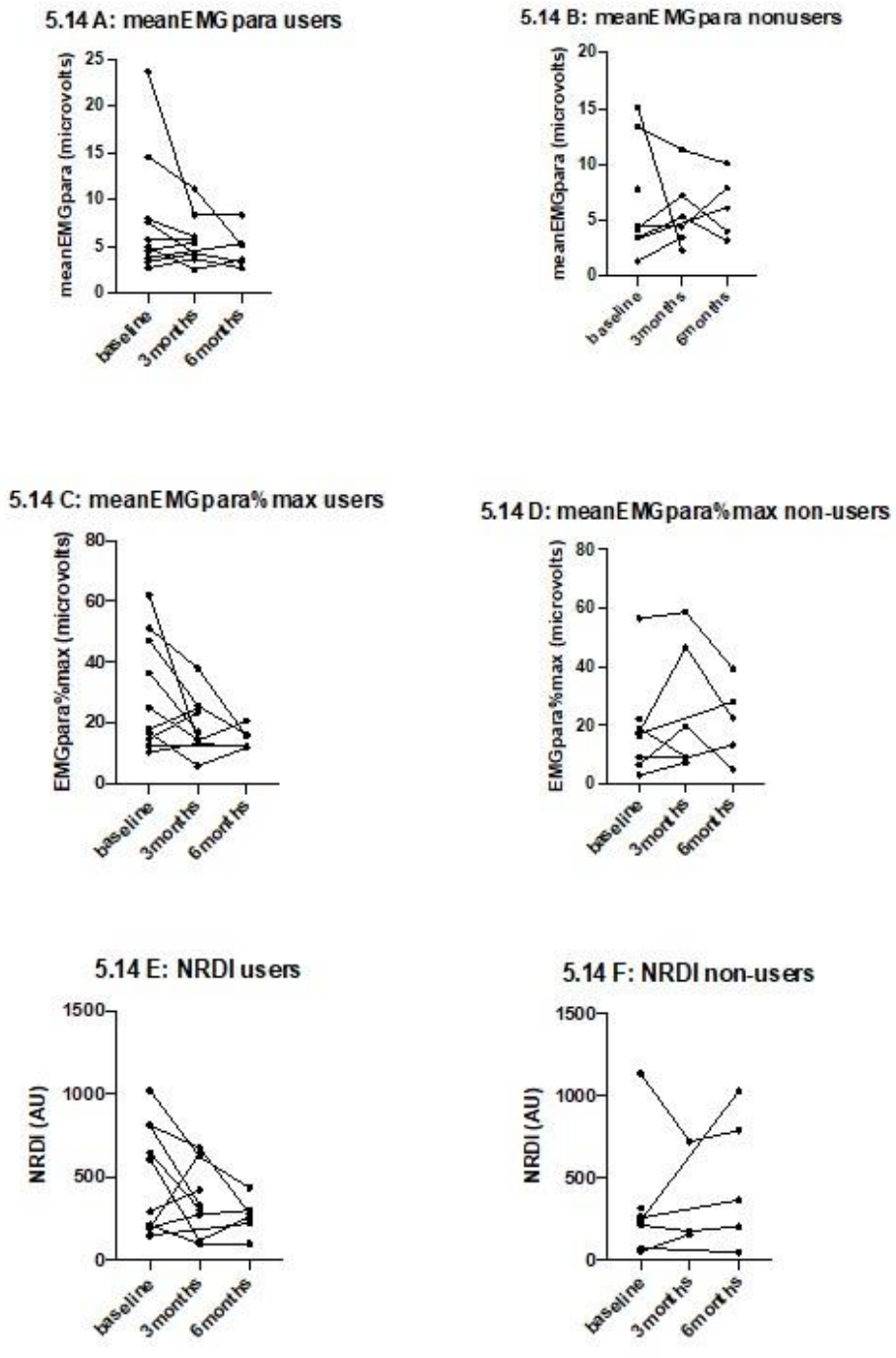

Figure 9-2 Parasternal electromyography in patient with obstructive sleep apnoea syndrome treated with positive airway pressure (PAP) therapy

A- mean parasternal electromyography (meanEMGpara) in patients adherent to PAP therapy at 3 and 6 months. B- mean parasternal electromyography (meanEMGpara) in patients not adherent to PAP therapy at 3 and 6 months. C- Normalised parasternal electrmoygraphy (EMGpara%max) in patients adherent to PAP therapy at 3 and 6 months. D- Normalised parasternal electrmoygraphy (EMGpara%max) in patients not adherent to PAP therapy at 3 and 6 months. E- Neural respiratory drive index (NRDI) (measured in arbitary units (AU)) in patients adherent to PAP therapy at 3 and 6 months. F- Neural respiratory drive index (NRDI) (measured in arbitary units (AU)) in patients not adherent to PAP therapy at 3 and 6 months. All parasternal electrmyography measured in microvolts. (Adherence is considered >4hours use in >70% of nights used)

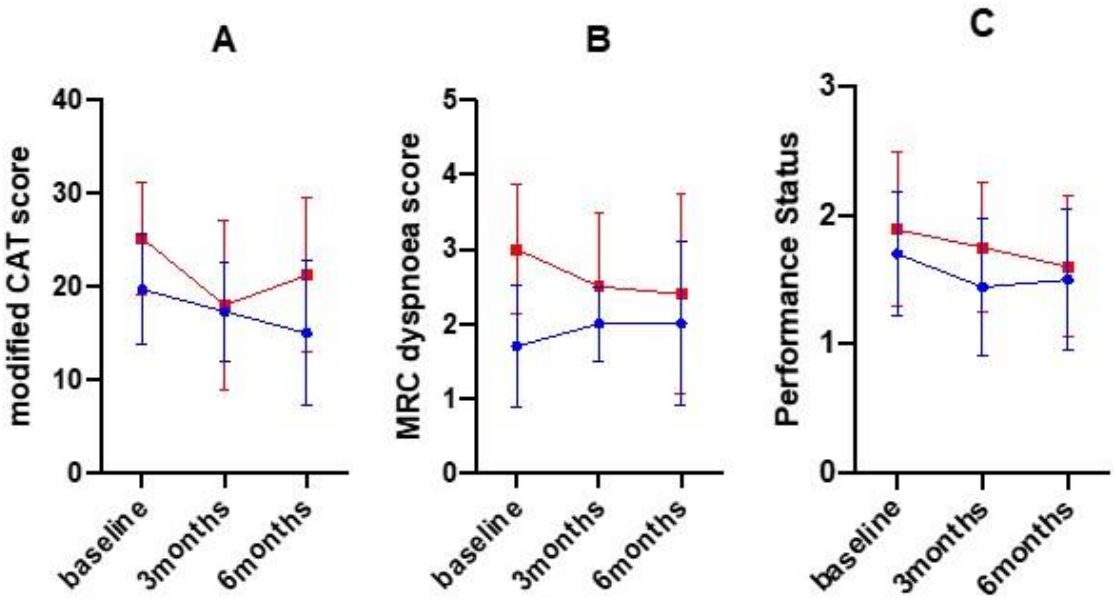

Figure 9-3 Change in symptom burden in patients with obstructive sleep apnoea syndrome treated with positive airway pressure (PAP) therapy

A- modified chronic obstructive pulmonary disease assessment tool (mCAT) score, B- Medical research council dyspnoea scale (MRC), C- Performance status (PS) at baseline, 3months and 6months in adherence (blue) and non-adherence (red) to PAP therapy. (Adherence is considered >4hours use in >70% of nights used). Plotted as mena and standard error.

	R5	R5-R20	R20	Ax	ΔXRS	Vt (L)
1	11.85	3.96	7.89	150.81	11.69	0.7
2	9.66	3.6	6.06	87.22	4.76	0.83
3	6.12	2.58	3.54	78.76	8.81	0.77
4	4.72	1.54	3.18	50.87	3.3	0.82
Mean (SD)	8.09 (3.26)	2.92 (1.09)	5.17 (2.22)	91.92 (42.22)	7.14 (3.83)	0.78 (0.06)

Table 9.2 Baseline oscillometry readings in patients with obesity related respiratory failure requiring home non-invasive ventilation.

R5- Large airways resistence, R20- Large airways resistence, R5-R20- small airways resistence, ΔXRS- in-breath change in reactance measured at 5Hz, Ax- reactance. Highlighted $\Delta\mathrm{XRS}$ identifies tidal expiratory flow limitation. All oscillometry measured in $cmsH_2OsL^{-1}$

	Mean EMGpara	Mean EMGpara%max	NRDI
1	3.7444	42.5585	438
2	4.675	16.3373	321
3	8.6	15.7509	334
4	6.9882	15.7392	328
Mean Standard deviation	6.00 (2.20)	22.6 (13.31)	355.25 (55.42)

Table 9-3 Baseline parasternal electromyography measurements in patients with obesity related respiratory failure who were initiated on remote monitored non-invasive ventilation

meanEMGpara- mean parasternal electromyography (microvolts), meanEMGpara%max- mean normalised parasternal electromyography (microvolts), NRDI-Neural Respiratory Drive Index (arbitrary units (AU))

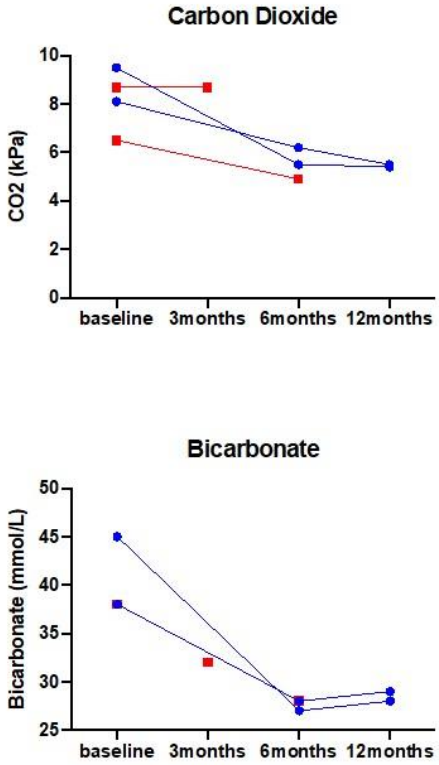

Figure 9-4 Control of hypoventilation in patients with obesity related respiratory failure treated with non-invasive ventilation

Illustration of blood gas patients who were adherent (blue) and non-adherent (red) to home non-invasive . Serial carbon dioxide (CO_2) (measured in kilo pascals (kPa)) and bicarbonate (measured in millimoles per litre (mmol/L) at baseline, 3months, 6months and 12 months after the initiation of non-invasive ventilation. (Adherence- >4hours use for >70% of nights used)

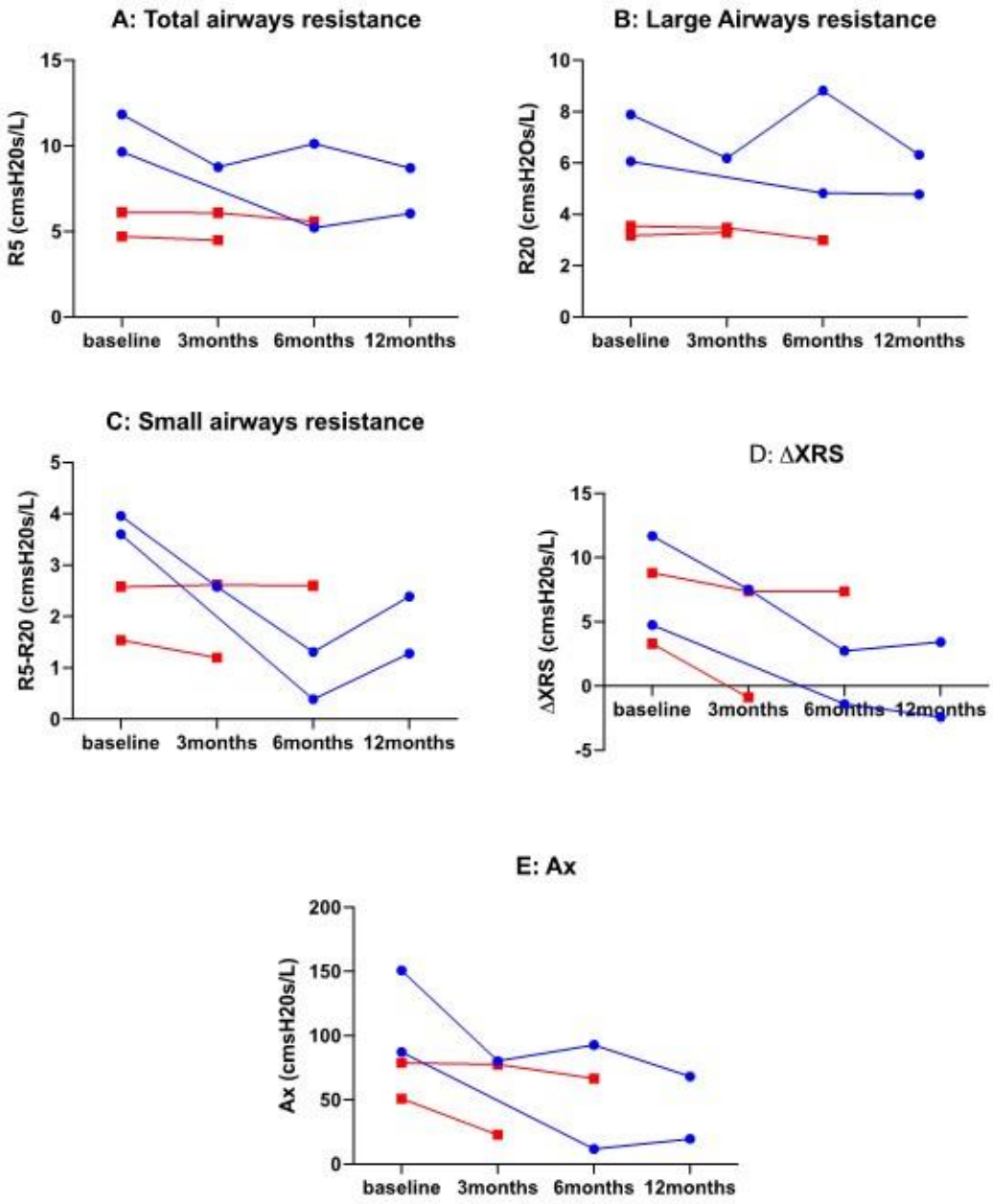

Figure 9-5 Serial measurements of airways resistance and reactance in patient with obesity related respiratory failure treated with non-invasive ventilation

Illustration of changes in oscillometry in patients with ORRF who were adherent (blue) and non-adherent (red) at baseline to 12 months following initiation. A- total airways resistence (R5), B- Large airways resistence (R20), C- small airways resisitence (R5-R20), D In-breath change in reactance at 5Hz (ΔXRS), E- reactacne (Ax). All oscillometry measured in cmsH_2Os/L). (Adherence- >4hours use for >70% of nights used)

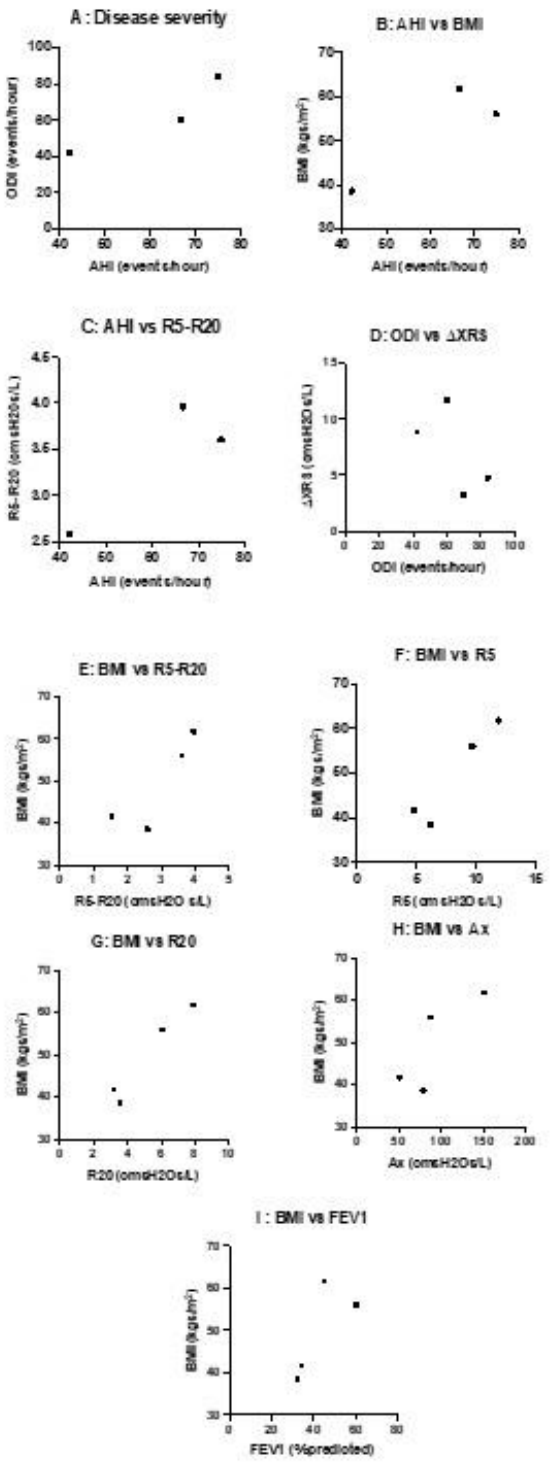

Figure 9-6 Correlations between severity of sleep disordered breathing, body mass index (BMI (kg/m2)), forced expiratory volume in 1 second (FEV1) and baseline oscillometry in patients with obesity related respiratory failure requiring non-invasive ventilation

AHI- apnoea hypopnoea index(events/hour), ODI- oxygen desaturation index (events/hour), R5- total airways resistence (cmsH$_2$Os/L), R20- large airways resistence (cmsH$_2$Os/L), R5-R20- small airways resistence (cmsH$_2$Os/L), ΔXRS- in-breath change in reactance measured at 5Hz (cmsH$_2$Os/L), Ax- reactance (cmsH$_2$Os/L).

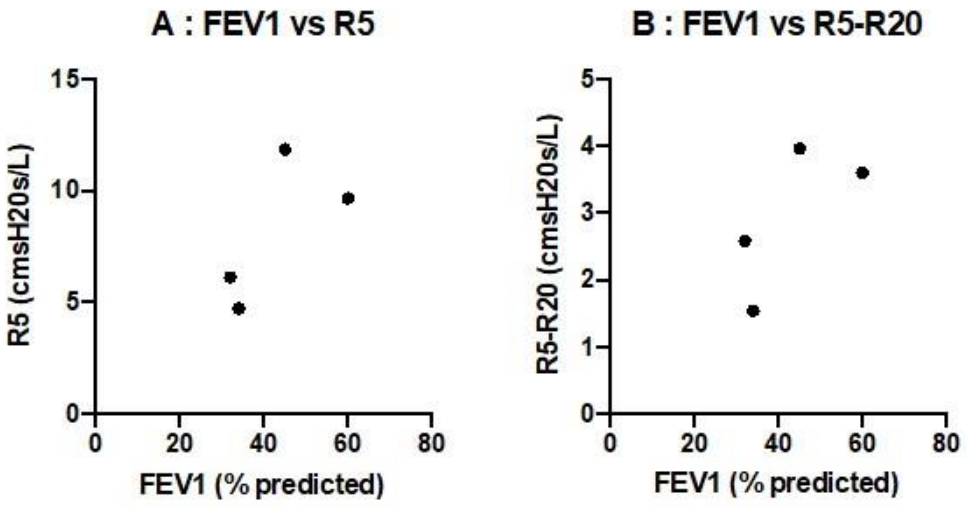

Figure 9-7 Correlations between forced expiratory volume in 1 second (FEV1 (percentage predicted)) and baseline oscillometry in patients with obesity related respiratory failure requiring non-invasive ventilation

A- Correlation between FEV1 and large airways resistence (measured in cmsH_2Os/L). B- Correlation between FEV1 and small airways resistence (R5-R20 (measured in cmsH_2Os/L)).

	meanEMGpara	meanEMGpara%max	NRDI (AU)
1	11.04	38.6014	560
2	4.93	12.5445	285
3	9.86471	23.7238	522
4	13.3929	16.9642	288
5	14.225	17.6708	382
6	11.981	29.0808	521
7	12.3333	22.8395	394
8	6.35	10.1763	119
9	17.3444	49.5554	973
10	16.1133	22.1033	424
Mean (SD)	11.76 (3.93)	24.32 (12.06)	446.8 (227.84)

Table 9-4 Baseline measurements parasternal electromyography in patients with hypercapnic severe chronic obstructive pulmonary disease who require home non-invasive ventilation

meanEMGpara- mean parasternal electromyography(microvolts) , meanEMGpara%max- mean normalised parasternal electromyography (microvolts), NRDI- Neural Respiratory Drive Index (Arbitrary units (AU))

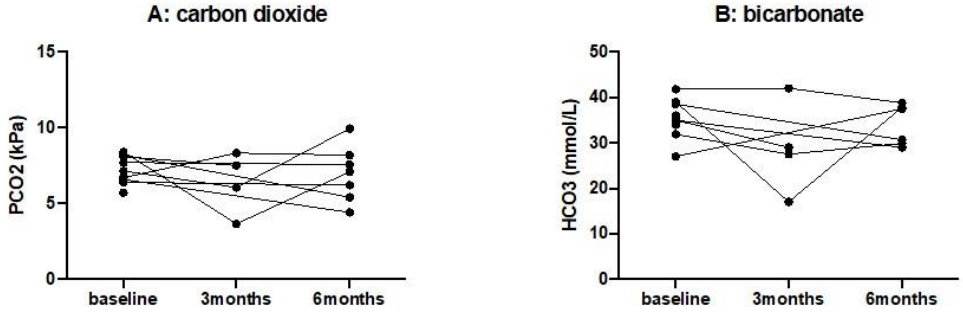

Figure 9-10 Serial blood gas analysis in patients with hypercapnic severe COPD following the initiation of home non-invasive ventilation at baseline, 3 months, and 6 months.

A: Serial Carbon Dioxide (CO_2) measured in kilo pascals (kPa). B- Serial serum bicarbonate levels (HCO_3) mesured in millimoles/litre (mmol/L)

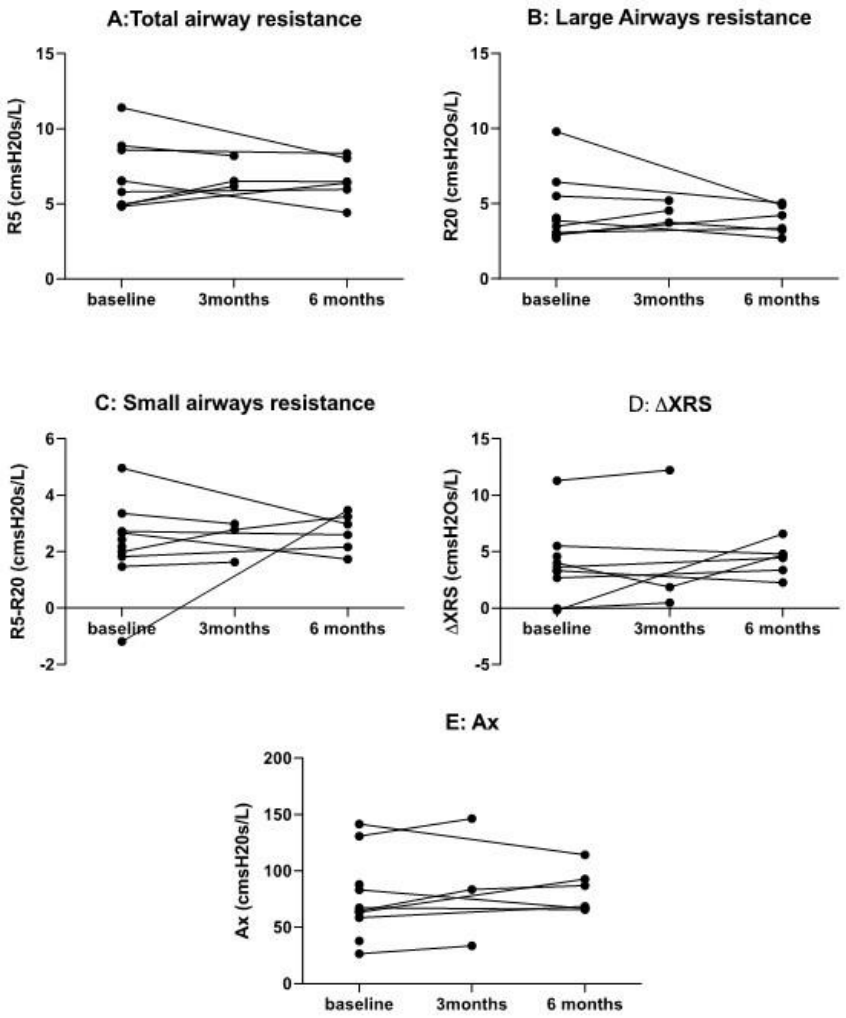

Figure 9-11 : Serial measurements of airways resistance and reactance in patients with hypercapnic severe chronic obstructive pulmonary disease treated with non-invasive ventilation at baseline to 6 months

A- total airways resistence (R5), B- Large airways resistence (R20), C- small airways resisitence (R5-R20), D In-breath change in reactance at 5Hz (ΔXRS), E- reactance (Ax). All oscillometry measured in cmsH_2Os/L.

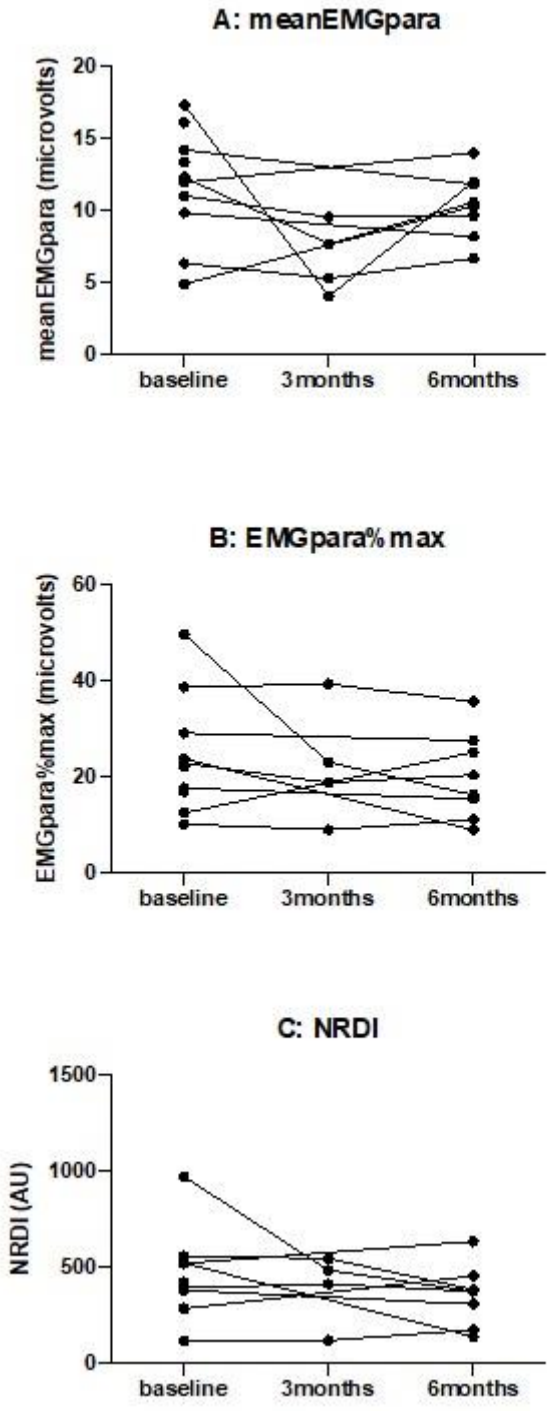

Figure 9-12 Serial measurements of parasternal electromyography (EMG) in patients with hypercapnic severe chronic obstructive pulmonary disease requiring home non-invasive ventilation

A- Changes in mean parasternal electromyography (meanEMGpara) following the initiation of NIV at 3 & 6 months. B- Changes in normalised parasternal electromyography (EMGpara%max) following the initiation of NIV at 3 & 6 months. C- Changes in neural respiratory drive index (NRDI) following the initiation of NIV at 3 & 6 months. EMG measured in mirovolts. NRDI measured in arbitrary units.

	meanEMGpara	meanEMGpara%max	NRDI
1	5.5357	17.8126	383
2	14.2187	19.7905	413
3			
4	12.4167	25.2371	457
5	4.5375	12.9642	233
6	3.65	15.6652	238
7	4.63	33.7956	663
8	4.8923	17.9864	201
Mean (SD)	7.13 (4.3)	20.46 (6.99)	369.71 (163.4)

Table 8-1 Baseline parasternal electromyography measurements in patients with chronic obstructive pulmonary disease- obstructive sleep apnoea overlap syndrome requiring remote monitored home non-invasive ventilation

meanEMGpara- Mean parasternal electromyography (microvolts), MeanEMGpara%max- mean normalised parasternal electromyography (microvolts), NRDI- Neural Respiratory Drive Index (Arbitrary units)

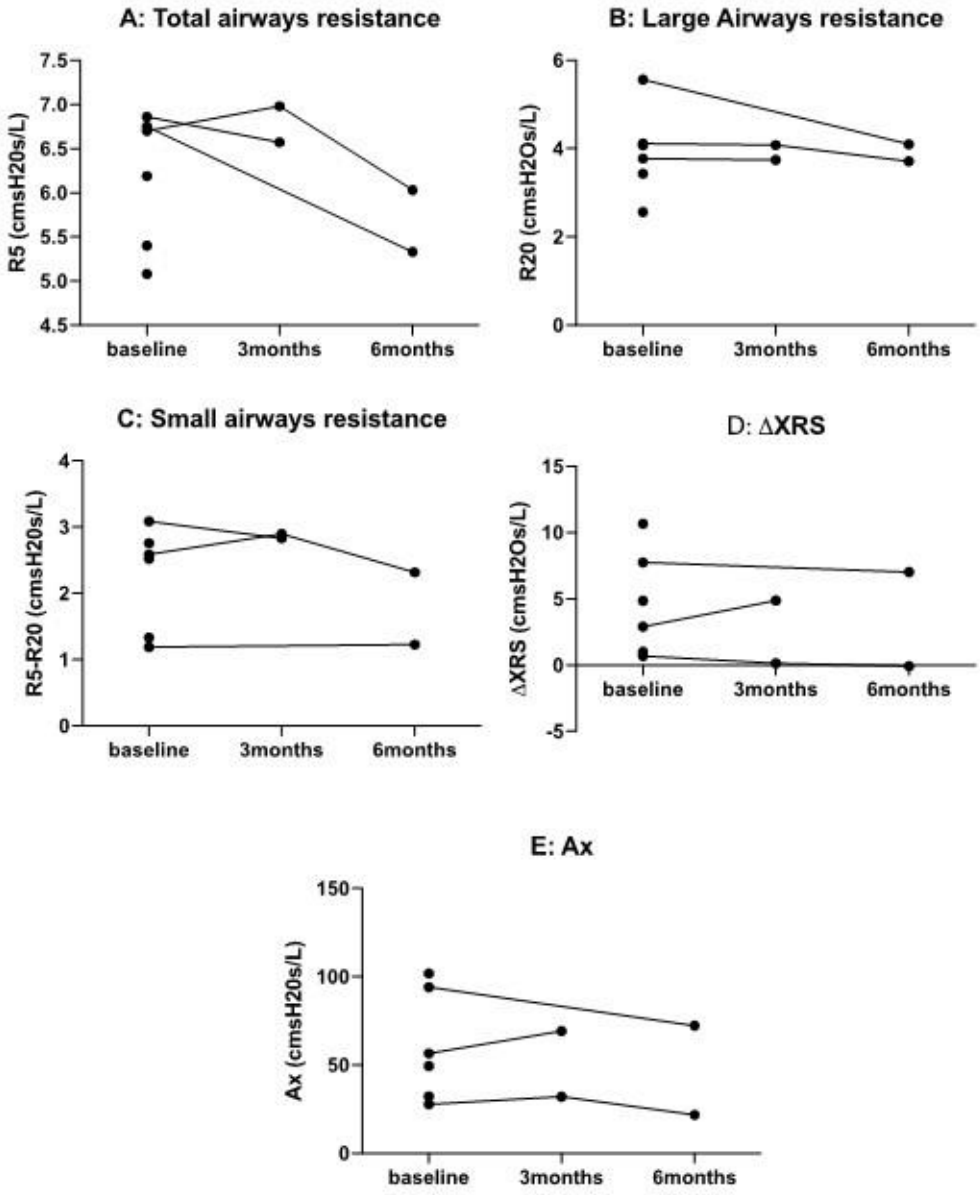

Figure 9-13 Serial measurements of airways resistance and reactance in patient with chronic obstructive pulmonary disease- obstructive sleep apnoea overlap syndrome treated with non-invasive ventilation at baseline to 6 months following initiation

A- total airways resistence (R5), B- Large airways resistence (R20), C- small airways resisitence (R5-R20), D In-breath change in reactance at 5Hz (ΔXRS), E- reactance (Ax). All oscillometry measured in cmsH_2Os/L.

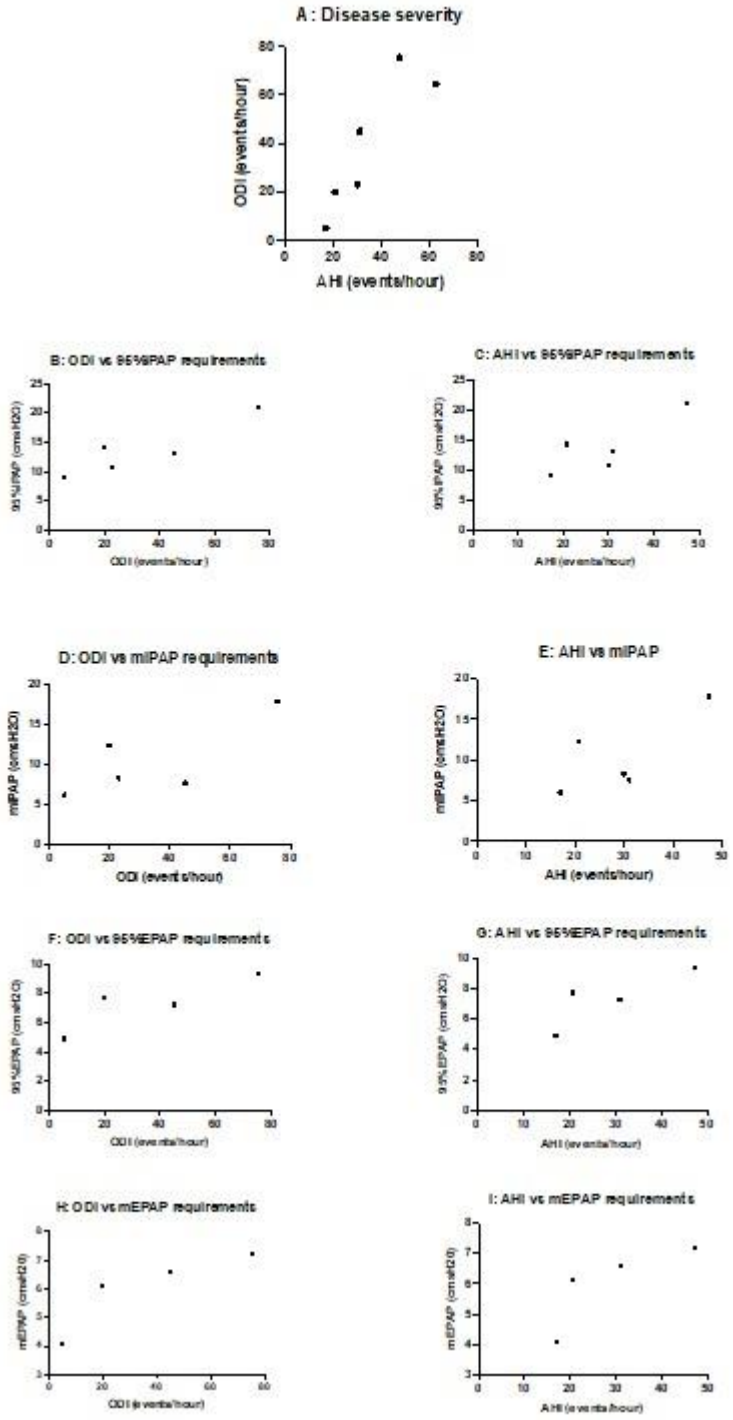

Figure 9-14 Correlations between disease severity, positive airway pressure requirements in patients with chronic obstructive pulmonary disease- obstructive sleep apnoea overlap who were treated with home non-invasive ventilation

A- Oxygen desaturation index (ODI) (events/hour) vs apnoea hypopnoea index (AHI) (events/hr), B- ODI (events/hr) vs 95% inspiraotry positive airway pressure requirements (95%IPAP(cmsH20)), C- AHI (events/hour) vs 95%IPAP (cmsH20), D- ODI (events/hr) vs median inspiratory positive airway pressure requirements (mIPAP(cmsH20), E- AHI (events/hr) vs mIPAP (cmsH20), F- ODI (events/hr) vs 95% expiratory positive airway pressure requirements (95% EPAP (cmsH20)), G- AHI (events/hr) vs 95% EPAP (cmsH20), H- ODI (events/hour) vs median inspiratory positive