ORIGINAL ARTICLE

Parasternal electromyography to determine the relationship between patient-ventilator asynchrony and nocturnal gas exchange during home mechanical ventilation set-up

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ABSTRACT

Introduction Patient-ventilator asynchrony (PVA) can adversely affect the successful initiation of non-invasive home mechanical ventilation (HMV). The aim of this observational study was to quantify the prevalence of PVA during initiation of HMV and to determine the relationship between PVA and nocturnal gas exchange.
Method Type and frequency of PVA were measured by surface parasternal intercostal muscle electromyography, thoracoabdominal plethysmography and mask pressure during initiation of HMV. Severe PVA was defined, as previously, as asynchrony affecting ≥10% of breaths.
Results 28 patients (18 male) were enrolled aged 61±15 years and with a body mass index of 35±9 kg/m^2. Underlying diagnoses were neuromuscular disease with or without chest wall disease (n=6), obesity related chronic respiratory failure (n=12) and COPD (n=10). PVA was observed in all patients with 79% of patients demonstrating severe PVA. Triggering asynchrony was most frequent, observed in 24% (IQR: 11–36%) of breaths, with ineffective efforts accounting for 16% (IQR: 4–24%). PVA types were similar between disease groups, with the exception of auto-triggering, which was higher in patients with COPD (12% (IQR: 6–26%)). There was no correlation observed between PVA and time spent with oxygen saturations ≤90%, mean oxygen saturations or transcutaneous carbon dioxide levels during overnight ventilation.
Conclusions Severe PVA was identified in the majority of patients, irrespective of pathophysiological disease state. This was not associated with ineffective ventilation as evidenced by gas exchange.

Key messages

What is the key question?
▶ To quantify the prevalence of patient-ventilator asynchrony (PVA) during home non-invasive ventilation set-up and to determine the relationship between PVA and nocturnal gas exchange?

What is the bottom line?
▶ PVA, measured using parasternal electromyography, is a very frequent event and, in contrast to current opinion, this study has shown that PVA was not associated with an adverse impact on nocturnal gas exchange.

Why read on?
▶ This physiological study of overnight set-up of non-invasive ventilation in patients with chronic respiratory failure using surface parasternal electromyography provides a comprehensive assessment of the type and frequency of PVA encountered when initiating home non-invasive ventilation.

INTRODUCTION

A European survey performed in 2005 reported that almost 22 000 patients with chronic respiratory failure were receiving home mechanical ventilation (HMV) with either non-invasive or invasive ventilation.[1] Despite the clinical benefits, a significant proportion of patients are unable to adhere to their HMV prescription.[2] Certain factors affecting adherence to HMV are difficult to modify, such as mask claustrophobia, but the clinical set-up of non-invasive ventilation (NIV) is operator-dependent and indeed could be enhanced if patient-ventilator synchrony were achieved.

Patient-ventilator asynchrony (PVA) describes the poor interaction between the patient and the ventilator and is the consequence of the respiratory muscle activity of the patient being opposed to the action of the ventilator. These are, in general, grouped as triggering and cycling PVA. PVA adversely effects respiratory muscle unloading during mechanical ventilation,[3 4] which is reported from previous studies to negatively impact on the nocturnal gas exchange and sleep quality.[5–8] Furthermore, asynchronous breaths have previously been observed to have unfavourable clinical consequences including dyspnoea perception,[9–13] patient discomfort and intolerance[14 15] and reduced adherence to NIV.[16] Previous studies have reported that PVA can have an adverse clinical impact if greater than 10% of the breaths are asynchronous,[14 17 18] albeit a minimal clinically important difference

with non-invasive ventilator support has yet to be reported. Furthermore, there are limited data on the type and prevalence of asynchronous events during NIV.

More recently, the surface parasternal electromyogram (sEMGpara) has been used for the non-invasive measurement of neural respiratory drive in acute and stable settings, including overnight measurements during sleep in patients with chronic respiratory disease.[11–13 19] As PVA describes the coordination between the respiratory effort of the patient and the mechanical breaths delivered by the ventilator, a real-time measurement of the relationship between neural respiratory drive during inspiration and the timing of ventilator pressurisation is required. We hypothesised, using this novel comparative technique, that we could quantify the type and prevalence of PVA in patients with chronic respiratory failure secondary to restrictive and obstructive lung disease during overnight HMV set-up and, in addition, investigated the relationship between PVA and nocturnal gas exchange.

METHODS
Patients
Patients were referred to a tertiary centre for management of chronic respiratory failure between September 2010 and December 2012. All participants provided written informed consent at enrolment.

Definition of PVA
Following a comprehensive review of the literature (see online supplementary material for search terms) and discussions with international HMV experts, a group consensus was reached in defining the types of PVA. We divided PVA into triggering and cycling asynchronies and used these as reference for this study.[14 17 20 21] The triggering asynchronies included ineffective efforts, auto-triggering, double triggering and multiple triggering and the cycling asynchronies included premature expiratory cycling, delayed expiratory cycling and autocycling. The definitions of the specific types of triggering and cycling PVA, with worked examples, are described in detail in the online supplementary appendix E1 and figure E1–E8.

NIV set-up and measurements
All patients were admitted for nocturnal set-up and titration of NIV (NIPPY3+ ventilator; B&D Electromedical, Stratford-upon-Avon, UK) according to standard clinical protocols depending upon their underlying pathophysiological condition (see online supplementary appendix E2a–E2c) in a pressure support mode with a fixed backup rate set at two breaths below the resting breathing rate, as previously reported.[22] Measurement of sEMGpara was employed as a physiological biomarker to mark the onset and level of neural respiratory drive.[11–13] The second intercostal space was identified using bony landmarks and skin was prepared with EMG contact gel (Nuprep, DO Weaver and Co, Colorado, USA). Wet gel electrodes (Neuroline 720, Ambu, Ballerup, Denmark) were placed adjacent to the sternal edge in the second intercostal spaces. The sEMGpara signal was amplified, processed, filtered and analysed in standard conditions according to the methods previously described[12] (see online supplementary material for details). sEMGpara recordings were performed with the patient lying in bed in their preferred sleeping position and acquired throughout the whole night. Respiratory inductance plethysmography (Respitrace, Sensormedics, Miami Beach, Florida) was concurrently used to measure chest wall excursion and abdominal wall excursion to assist the analyser to gait against postural sEMGpara movement artefacts. Patients underwent overnight

measurements of mask pressure using a standard pressure transducer with a range between $+200$ cm H_2O and -200 cm H_2O (GM Instruments, Kilwinning, UK). Transcutaneous oximetry (SpO_2) and capnometry ($TcCO_2$) were calibrated to arterial carbon dioxide levels and measured using a TOSCA 500 monitor (Radiometer Medical, Copenhagen, Denmark). All data were analysed using LabChart V7.3.7 (AD Instruments, Chalgrove, UK) (figure 1).

Type and frequency of PVA
Manual recording analysis was performed in 10 min epochs throughout the whole night of NIV use, with the final 2 min of each epoch analysed for type and frequency of PVA according to the a priori definitions (see online supplementary appendix E1 and figures E1–E8). The 1st hour of recording and movement artefacts were discarded with the nearest artefact-free 2 min epoch analysed instead. The proportion of PVA was calculated as the number of asynchronous breaths divided by the total number of breaths (requested and delivered) multiplied by 100, as described by Thille et al.[17]

Ventilator set-up
Every ventilator-delivered breath in the 10 min epochs was analysed as a triggered pressure support delivered breath, an inappropriate auto-triggered delivered breath or an appropriate pressure control delivered 'backup' breath (identified by rate and set inspiratory time). All ventilators were set in pressure support (S/T) mode with a backup rate set 2 below the resting respiratory rate. Comparative analysis of the PVA frequency when patients received ≥70% breaths from either pressure supported (patient triggered) or pressure controlled (ventilator delivered) ventilation was performed.

Inter-rater reliability of PVA
Two assessors (authors MR and SM) were blinded and independently scored 10 randomly selected 1 h sections of recorded data from 10 patients. Asynchronous events were manually assessed according to the a priori definitions (see online supplementary appendix E1 and figures E1–E8).

Statistical analysis
Patient demographic data and the type of ventilator-delivered breaths are expressed as mean±SD, and a one-way analysis of variance and pairwise tests with a Bonferroni correction were used to compare patient groups. Data that was not normally distributed are reported as median values with IQRs. Comparative analysis of the differences in the ventilator set-up parameters and frequency of the types of PVA between the patient groups were made using the Kruskal-Wallis test. Comparative analysis between the number of pressure support breaths and pressure control breaths delivered by the ventilator were assessed using a Mann-Whitney U test. Simple rank regressions were performed to assess the strength of the relationship with PVA and nocturnal gas exchange. Statistical analyses were conducted using SPSS (V.19, IBM Corporation, USA) and GraphPad (Prism 6, GraphPad software, USA). A p value <0.05 was taken to represent statistical significance. Further details of the statistical analyses performed are placed in the online supplementary material.

RESULTS
Type and frequency of PVA
Patient demographics
All 28 patients (18 male) approached were recruited at an age of 61±15 years, a body mass index (BMI) of 35±9 kg/m², an
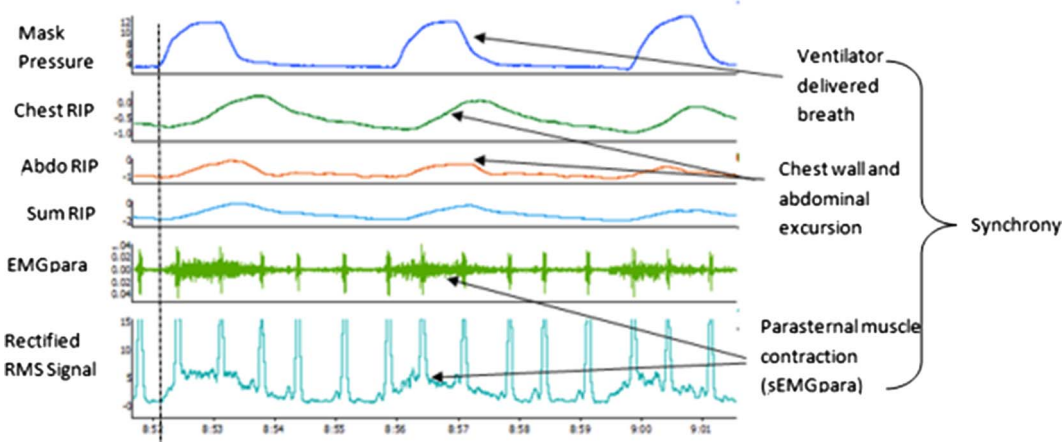
Figure 1 An example of satisfactory patient ventilator synchrony. Chest RIP, chest wall respiratory inductance plethysmography; Abdo RIP, abdominal respiratory inductance plethysmography; Sum RIP, combined chest and abdominal inductance plethysmography; EMGpara, parasternal intercostal electromyography; RMS, rectified root mean square of parasternal electromyography signal.

FEV_1 of 1.1 ± 0.5 L and an FVC of 1.6 ± 0.7 L. Six patients had neuromuscular disease with or without chest wall disease (NMD-CWD), 12 had obesity related respiratory failure (ORRF; BMI ≥ 30 kg/m^2 with a daytime $pCO_2 \geq 6$ kPa in the absence of any other cause) and 10 had COPD. Baseline demographic data are presented in table 1.

There were no differences in the age of the patients between patient groups and all patients had a BMI in the 'overweight' or 'obese' range. Four of the 10 patients with COPD had concurrent upper airways obstruction defined by a baseline oxygen desaturation index below 4% above 10 events per hour reflecting increasing trends of obesity in the UK. Patients with COPD were also more hypoxic and hypercapnic than the patients with NMD-CWD at baseline (arterial oxygen level 7.6 ± 1.4 kPa vs 9.2 ± 0.6 kPa; $p < 0.04$ and arterial carbon dioxide level 7.9 ± 1.0 kPa vs 6.6 ± 1.0 kPa; $p < 0.03$, respectively).

Ventilator set-up
There was no difference between the number of pressure supported and pressure controlled breaths delivered overnight across the whole group ($44 \pm 26\%$ vs $41 \pm 31\%$; $p=0.7$). Individual disease groups exhibited different interactions with the ventilator in terms of triggering the ventilator (table 2). Furthermore, as expected, those patients from the cohort that received over 70% pressure support breaths (n=6) had a higher

percentage of asynchronous breaths overnight than those patients that received over 70% pressure control breaths (n=5) (30% (27–38%) vs 9% (1–10%), respectively; $p < 0.01$). Patients that received more than 70% pressure support breaths demonstrated higher levels of ineffective efforts than those with more than 70% of pressure control delivered breaths (15% (10–20%) vs 1% (0–2%); $p < 0.01$).

Further details of the ventilator settings used between patient groups is available in the online supplementary material results section.

Patient-ventilator asynchrony
A total of 27 637 breaths were analysed from the 2 min epochs of overnight data recorded. Combined triggering and cycling PVA had an overall prevalence of $28 \pm 19\%$ across all patients studied. Indeed, 79% of patients were observed to have an asynchrony index greater than 10% of breaths (range 11–63%). Ineffective efforts were the most common PVA observed in 89.3% of patients and accounted for $15 \pm 11\%$ of breaths. Other PVA including auto-triggering, delayed expiratory cycling and premature cycling were observed in 85.7%, 67.9% and 85.7% of patients but with only 3% (0–9%), 1% (0–5%) and 1% (0–2%) of the total breaths affected, respectively. Double triggering, multiple triggering and autocycling were less frequent affecting 53.6%, 35.7% and 46.4% of patients,

Table 1 Comparison of baseline patient demographics by disease group

Demographics	COPD (n=10)	NMD-CWD (n=6)	ORRF (n=12)	p Value
Age (years)	66 ± 10	58 ± 22	59 ± 16	0.54
BMI (kg/m^2)	30.0 ± 5.2	27.2 ± 5.3	43.0 ± 4.8	<0.0001*
FEV_1 (% predicted)	31.1 ± 11.3	32.7 ± 11.3	52.5 ± 20.2	<0.01*
FVC (% predicted)	52.4 ± 9.7	30.5 ± 10.7	55.6 ± 19.0	<0.01*
FEV_1/FVC (% ratio)	45.8 ± 11.0	85.4 ± 3.6	81.2 ± 8.5	<0.001*
PaO_2 (kPa)	7.6 ± 1.4	9.2 ± 0.6	8.3 ± 1.0	<0.03*
$PaCO_2$ (kPa)	7.9 ± 1.0	6.6 ± 1.0	7.1 ± 0.9	<0.04*
HCO_3^- (mmols/l)	33.5 ± 3.2	30.8 ± 3.8	31.5 ± 3.8	0.28

*A one-way analysis of variance was used to compare the demographics between disease groups, p value <0.05 was taken to represent statistical significance.
BMI, body mass index; HCO_3^-, serum bicarbonate level; NMD-CWD, neuromuscular disease with or without chest wall disease; ORRF, obesity related respiratory failure; $PaCO_2$, arterial carbon dioxide level; PaO_2, arterial oxygen level.

Table 2 Comparison of non-invasive ventilator set-up by disease group

Ventilator parameters	COPD	NMD-CWD	ORRF	p Value
IPAP (cmH$_2$O)	18 (18–25)	15 (14–21)	20 (18–28)	0.1
EPAP (cmH$_2$O)	4 (3–7)	3 (3–4)	9 (8–12)	<0.001*
Backup rate (breaths/min)	14 (11–14)	14 (14–14)	14 (13–16)	0.3
% Pressure support breaths	60±25	34±24	36±56	0.06
% Pressure control breaths	25±30	47±24	51±31	0.09
% Ineffective efforts	15±11	19±13	13±10	0.4
% Total patient ventilator asynchrony	43±29	29±19	24±17	0.3

*A Kruskal-Wallis test was used to compare the ventilator parameters between disease groups, p value <0.05 was taken to represent statistical significance.
All results expressed as median and IQR.
Pressure support breaths and pressure control breaths represent the ventilator delivered breaths, ineffective efforts represent the patient demanded breaths that were not met, combined they represent all breaths (requested and delivered).
EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NMD-CWD, neuromuscular disease with or without chest wall disease; ORRF, obesity related respiratory failure.

respectively, and these accounted for 0% (0–1%), 0% (0–0)% and 0% (0–0%) of breaths, respectively.

Comparison of PVA by disease category

Across all groups, triggering asynchronies were greater than cycling asynchronies with 24% (11–36%) of total breaths demonstrating triggering asynchronies and 5% (1–8%) of total breaths demonstrating cycling asynchronies in all patients (p<0.0001). PVA, including triggering asynchronies (table 3) and cycling asynchronies (table 4), was observed in all patient groups ranging from 33% (19–78%) of total breaths in patients with COPD, 31% (10–45%) of breaths in patients with NMD-CWD and 29% (9–38%) of breaths in patients with ORRF (p=0.3).

The most frequent asynchrony was ineffective effort, albeit there was no difference across the disease groups (p=0.4). The only difference observed between patients with COPD, NMD-CWD and ORRF was in auto-triggering, affecting 12% (6–36%), 6% (1–8%) and 2% (0–6%) of breaths, respectively (p=0.04).

Overnight gas exchange

Overnight gas exchange was assessed using nocturnal oximetry and capnography, which has been shown to accurately monitor and track changes in nocturnal gas exchange in patients receiving NIV.[23] Patients demonstrated nocturnal hypoventilation with a mean SpO$_2$ of 91±7% and TcCO$_2$ of 7.8±1.3 kPa during the first night of NIV set-up without the use of supplemental oxygen. Of the overnight total analysis time 35±33% was spent with oxygen saturations below 90% (TBI90) in a subset of 16 patients. Patients with ORRF were more hypoxic overnight than patients with NMD-CWD (SpO$_2$ of 88±8% vs 96±4%; p=0.02). There were no associations observed between total

overnight PVA events and nocturnal SpO$_2$ (r^2=0.08; p=0.16) and TcCO$_2$ (r^2<0.001; p=0.94). Furthermore, there was no relationship observed between nocturnal SpO$_2$ and TcCO$_2$ and the percentage of ineffective efforts (r^2=0.04; p=0.32 and r^2=−0.04; p=0.32, respectively). Finally, there was no association observed between the TBI90 and the percentage of asynchronous breaths or ineffective efforts (r^2=−0.02; p=0.12 and r^2=−0.08; p=0.36, respectively) in the subset of patients examined.

Inter-rater reliability of assessment of PVA

Ten patients (four COPD, four ORRF and two NMD-CWD) were included in this substudy. A total of 4603 breaths were analysed by two independent scorers with PVA reported in 812 (35%) and 891 (39%) breaths, respectively. The intraclass correlation coefficient between the scorers was 0.84 (0.74–0.90). The predominant asynchrony reported was ineffective efforts, for which there was the closest interobserver agreement with an intraclass correlation coefficient of 0.94 (0.79–0.99). The agreement for triggering and cycling PVA are shown in tables 5 and 6. The lowest agreement was observed in the autocycling asynchrony (0.22; −0.54–0.74), albeit this had a very low frequency and was observed in <1% of the total breaths analysed.

DISCUSSION

This is the first study to report a comprehensive overnight assessment of PVA during first night initiation of non-invasive ventilation. Previous studies have either been daytime or overnight studies in patients established on HMV and these studies lacked description of all types and frequencies of PVA.[6–8 14 17 24] Neural respiratory drive, as measured from surface electromyogram of the second intercostal parasternal muscles, combined with

Table 3 Triggering asynchrony during overnight NIV setup

% of breaths	COPD	NMD-CWD	ORRF	p Value
% Ineffective efforts	15 (6–23)	24 (5–27)	14 (2–21)	0.4
% Auto-triggering	12 (6–36)	2 (0–6)	6 (1–8)	0.04*
% Multiple triggering	0 (0–0)	0 (0–0)	0 (0–0)	0.1
% Double triggering	0 (0–1)	0 (0–3)	0 (0–1)	0.6
% Total triggering asynchrony	26 (13–66)	27 (7–39)	21 (9–31)	0.3

A Kruskal-Wallis test was used to compare patient-ventilator asynchrony between disease groups, p value <0.05 was taken to represent statistical significance.
NMD-CWD, neuromuscular disease with or without chest wall disease; ORRF, obesity related respiratory failure.

Table 4 Cycling asynchrony during overnight NIV setup

% of breaths	COPD	NMD-CWD	ORRF	p Value
% Premature expiratory cycling	1 (0–4)	1 (0–4)	1 (0–2)	0.9
% Delayed expiratory cycling	2 (0–7)	2 (0–5)	0 (0–3)	0.5
% Auto-cycling	1 (0–4)	0 (0–0)	0 (0–0)	0.2
% Total cycling asynchrony	7 (4–10)	4 (3–6)	3 (1–7)	0.2

A Kruskal-Wallis test was used to compare patient-ventilator asynchrony between disease groups, p value <0.05 was taken to represent statistical significance.
NMD-CWD, neuromuscular disease with or without chest wall disease; ORRF, obesity related respiratory failure.

Table 5 Agreement of triggering asynchrony between two independent scorers

Type of asynchrony	Scorer 1 n (% breaths)	Scorer 2 n (% breaths)	ICC (95% CI)	Bland-Altman analysis bias (95% limits of agreement)
Ineffective efforts	484 (21%)	466 (21%)	0.94 (0.79 to 0.99)	1.8 (−30.1 to 33.7)
Auto-triggering	164 (7%)	231 (10%)	0.77 (0.19 to 0.94)	−6.7 (−25.4 to 12.0)
Double triggering	22 (<1%)	11 (<1%)	0.67 (0.11 to 0.91)	1.1 (−1.9 to 4.1)
Multiple triggering	4 (<1%)	4 (<1%)	1.00	0.0 (0.0 to 0.0)

ICC, intraclass correlation coefficient.

measurements of thoracoabdominal motion and mask pressure has been shown to be accurate and reliable in assessing trigger and cycling PVA during NIV. Importantly, we have detailed the high prevalence of PVA during initiation of HMV in patients with stable chronic respiratory failure and shown that up to a third of the breaths were asynchronous during the initiation of HMV, irrespective of the underlying disease pathology. Triggering asynchrony rather than cycling asynchrony was shown to be the most frequent PVA. Of major relevance to the clinician, there was no relationship between PVA and overnight gas exchange, which implies that the adequate delivery of ventilation during HMV set-up, based on the frequency and level of airway pressurisation, is of greater importance to optimise adequacy of gas exchange, rather than optimising PVA.

Critique of the method
We acknowledge that sEMGpara has recognised limitations, including postural artefacts and potential contamination of the signal from other chest wall muscles.[25] Needle electrodes could have been used to directly isolate parasternal muscle activity, but this is unsuitable for overnight monitoring in the clinical setting and may risk pneumothorax.[26] Alternatively, an oesophageal electrode may be used to monitor the diaphragm electromyogram, but again this is poorly tolerated in stable patients and the use of such an invasive technique in clinical practice for overnight studies is wholly challenging.

Although patients in this study were directly observed to be sleeping overnight by the research team, this was not confirmed through full montage polysomnography (PSG) and the authors acknowledge this. However, PSG is not routinely used in clinical practice for HMV initiation in the UK, and indeed recent European guidance has recommended using PSG only when simple tools to optimise NIV set-up have failed.[27]

For practical reasons, and based on our previous daytime laboratory studies,[28] mask leak was not assessed in this overnight study as the burden of the pneumotach in the experimental mask-ventilator circuit actually contributed to greater air leak and consequently this would have increased PVA. Indeed, air leak induced PVA would have been a major confounder during the overnight studies.[7 14]

Physiological observations
Prevalence of PVA
By using a non-invasive approach to monitor physiological variables over the whole night, we have demonstrated that the prevalence of PVA, irrespective of the underlying disease pathology, was substantially greater than that previously reported.[6–8 14 17 24] Up to a third of all breaths, during NIV set-up, were asynchronous. PVA was demonstrated in all patients studied, compared with previous studies which have reported a PVA prevalence of 0–77% of patients.[5 24] These current data reflect the enhanced details of this advanced monitoring technique.

Triggering asynchrony
An ineffective effort was the most frequent type of PVA observed during the initiation of HMV. Similar to recent work by Carlucci et al,[16] there was no difference in the prevalence of this asynchrony between the patient groups. Interestingly, auto-triggered breaths affected most patients, but the frequency of these events was very low. Furthermore, auto-triggering was most commonly observed in patients with COPD and this is likely to be a consequence of mask leak, as previously reported.[24] In addition, patients with COPD have an increased airway secretion load and this has previously been demonstrated to contribute to auto-triggering of the ventilator.[29] Despite the observation that double triggering and multiple triggering were demonstrated in up to 50% of patients, the frequency of this PVA in the current study was very low and therefore unlikely to have clinical relevance during the initiation of HMV. Furthermore, cycling asynchrony was observed to be infrequent.

Asynchrony and overnight gas exchange
Despite higher levels of asynchrony observed in our cohort, there was no demonstrable effect on overnight gas exchange. This is in contrast to previous data suggesting that ineffective efforts are associated with overnight oxygen desaturation.[6] This may, in part, be explained by the ventilator backup rate in the current study, supported by the proportion of pressure controlled breaths delivered, which was up to 46%, depending on the patient group. The study by Fanfulla et al[6] was performed

Table 6 Agreement of cycling asynchrony between two scorers

Type of asynchrony	Scorer 1 n (% breaths)	Scorer 2 n (% breaths)	ICC (95% CI)	Bland-Altman analysis bias (95% limits of agreement)
Premature cycling	88 (4%)	124 (5%)	0.73 (0.26 to 0.92)	−3.6 (−18.7 to 11.5)
Extended cycling	45 (2%)	50 (2%)	0.76 (0.31 to 0.93)	−0.5 (−8.6 to 7.6)
Auto-cycling cycling	5 (<1%)	5 (<1%)	0.22 (−0.54 to 0.74)	0.0 (−2.3 to 2.3)

A total of 4603 breaths were analysed with patient ventilator asynchrony reported in 812 and 891 breaths by scorer 1 and scorer 2, respectively.
ICC, intraclass correlation coefficient.

in patients already established on HMV and the study used low level pressure support and, rather unusually for patients with NMD, there was no back-up rate applied. This would not be the current clinical approach, based on the current evidence, which supports the use of a mandatory backup rate in patients with NMD,[30] patients with ORRF[22][31] and patients with COPD.[32] The current data have demonstrated that optimal set-up of the inspiratory positive airway pressure, the expiratory positive airway pressure and the backup rate is more important, in terms of control of gas exchange, than PVA.

Clinical implications
Previous work has shown that clinician scoring of PVA through non-invasive measurements of ventilator flow and pressure waveform fail to report up to two-thirds of events.[33] Other studies using automated algorithms to detect asynchrony have improved frequency detection but have been limited in detailing the type of PVA.[34][35] However, the current study has demonstrated adequate levels of agreement between two independent observers comprehensively reporting triggering and cycling asynchrony. This non-invasive technique is potentially suitable to assist the clinician in optimising the ventilator settings during NIV set-up with real-time visual feedback of the impact of the ventilator changes at the bedside. For example, this novel approach can determine the physiological cause of the double triggered breath, where other methods would fail. This event can occur due to the first ventilator-delivered breath prematurely cycling out and the second ventilator-delivered breath appropriately triggered by the ongoing inspiratory effort of the patient, evidenced by increasing amplitude of the neural respiratory drive (figure 2A). Alternatively, this event can reflect

inappropriate auto-triggering of the second breath such that there is no increase in the neural respiratory drive observed (figure 2B). The addition of sEMGpara, as a marker of neural inspiratory drive, assists the scorer in distinguishing between the two phenomena and enables appropriate adjustment of the ventilator.

Previous work has suggested that PVA, in particular ineffective efforts, has an adverse effect of overnight gas exchange.[6] However, the data from the current study have shown that during NIV set-up PVA has limited impact on gas exchange, in terms of SpO_2, TBI90 and $TcCO_2$ levels. Even high levels of asynchrony, irrespective of the type, had limited effect on overnight gas exchange, suggesting that adequate ventilation, based on inspiratory and expiratory positive airway pressures and backup rate, will enhance gas exchange irrespective of patient-ventilator synchronisation. Furthermore, the current study indicates that optimising the ventilator settings so that the patient receives a greater proportion of pressure controlled breaths than pressure supported breaths may confer a benefit in reducing levels of PVA and, in particular, ineffective efforts. This is supported by previous data published by our own group on morbidly obese patients[22] and it may explain, in part, the benefits of a high intensity non-invasive positive pressure ventilation in stable COPD.[32] Controlled data detailing the effect of PVA on patient-centred outcomes, such as sleep quality, daytime symptoms and health related quality of life, will be reported in the future (http://www.clinicaltrials.gov NCT01371149).

CONCLUSION
Physiological measurements combining neural respiratory drive, thoracoabdominal movement and mask pressure monitoring
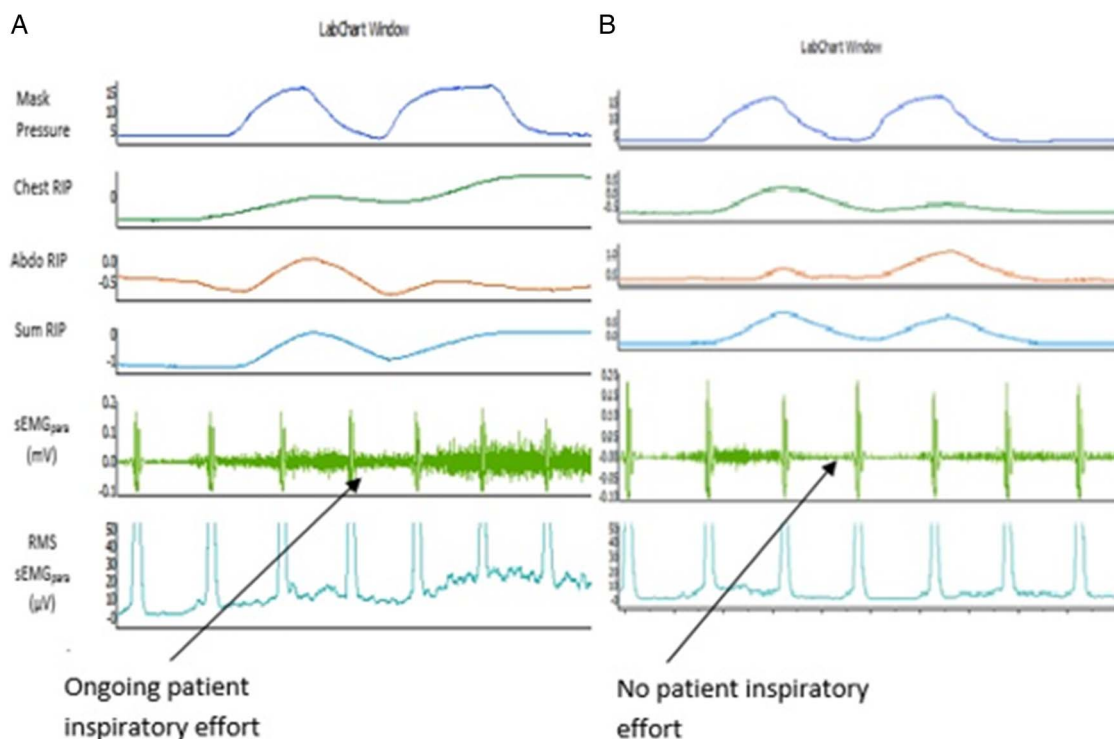

Figure 2 'Double triggering' was confirmed with the addition of second intercostal space electromyography to the mask pressure measurement and respiratory inductance plethysmography. (A) shows a prematurely cycled breath with ongoing patient inspiratory effort to trigger a second ventilator-delivered breath and (B) shows a patient-triggered breath followed by a nonpatient-triggered breath, which by definition is an 'auto-triggered' breath. Chest RIP, chest wall respiratory inductance plethysmography; Abdo RIP, abdominal respiratory inductance plethysmography; Sum RIP, combined chest and abdominal inductance plethysmography; EMGpara, parasternal intercostal electromyography; RMS, rectified root mean square of parasternal electromyography signal.

have been shown as a reliable technique to non-invasively score the type and frequency of PVA observed during initiation of NIV in patients with chronic respiratory failure. Using this technique, we have demonstrated high levels of asynchrony, irrespective of the underlying aetiology of chronic respiratory failure, with triggering asynchrony reported as the most frequent type of asynchrony observed. Of major clinical relevance, there was no correlation between the type and frequency of asynchrony and overnight gas exchange during inpatient NIV set-up.

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ON LINE SUPPLEMENT

METHODS

Details of literature review performed (Appendix 1)

A literature review was conducted using PubMed database. Search terms included patient ventilator asynchrony, patient ventilator dysynchrony, patient ventilator interaction, non-invasive ventilation, invasive ventilation, ineffective triggering, ineffective efforts, automatic triggering, ventilator cycling asynchrony, premature expiratory cycling, delayed expiratory cycling, multiple triggering, neural respiratory drive and neural adjust ventilatory assist.

Surface parasternal electromyogram (sEMGpara) signal processing

sEMGpara signals were processed using a high differential amplifier with band pass filters set at 10Hz and 2000Hz (Bio Amps, AD Instruments, Oxford, UK). An additional adaptive mains filter and AC coupling were used. Amplified signals were passed to an analogue to digital convertor (Powerlab, ADInstruments, Chalgrove, UK) and analysed on a personal computer. Further digital filtering occurred at 20Hz after data acquisition (LabChart v7.1, ADInstruments, Chalgrove, UK). sEMGpara signals were analysed using the root mean squared (RMS) of the raw sEMGpara signal with a 40ms moving window analogous to the algorithm previously described [1].

Statistical analyses

Patient demographic data and the type of ventilator delivered breaths are expressed as mean ± standard deviation and a one-way analysis of variance with a Bonferroni correction was used to compare patient groups. All other data were not normally distributed and reported as median (inter-quartile range). Differences in the frequency of the types of PVA

and ventilator set up parameters between the patient groups were made using the Kruskal – Wallis test. Comparative analysis between the number of pressure support breaths and pressure control breaths delivered by the ventilator were assessed using a Mann-Whitney t-test. Simple regression on ranks were performed to assess the relationship with PVA and nocturnal gas exchange. To assess inter-rater reliability of identifying PVA, intraclass correlation coefficient (ICC) was analysed. This was based on 2-way random effects model with absolute agreement to measure reliability. The agreement between each pair of observations was also assessed using Bland and Altman plots [2].

RESULTS

Ventilator settings

There was a trend for a difference in the mode of ventilation in the different disease groups with COPD patients receiving 60±25% of the delivered breaths in a pressure support mode, whereas ORRF and NMD-CWD patients received just 36±56% and 34±24% of the delivered breaths in the pressure support mode, respectively (p = 0.06). Although inspiratory positive airway pressure (IPAP) levels across the groups were similar (p = 0.12), as expected, obese patients received higher expiratory positive airway pressure (EPAP) levels to control for upper airway obstruction (p = 0.0004). There was no difference observed in the set back up rate between the patient groups (p = 0.29).

Relationship between PVA and nocturnal gas exchange

There was no association observed between total patient-ventilator asynchronous events and mean transcutaneous carbon dioxide (r^2 <0.001; p = 0.94), mean oxygen saturations (r^2 =

0.08; p = 0.16) and time spent overnight with oxygen saturations below 90% (r^2 = -0.02; p = 0.12) (*Fig. A*).

Figure A: Relationship between total patient-ventilator asynchrony events and nocturnal gas exchange
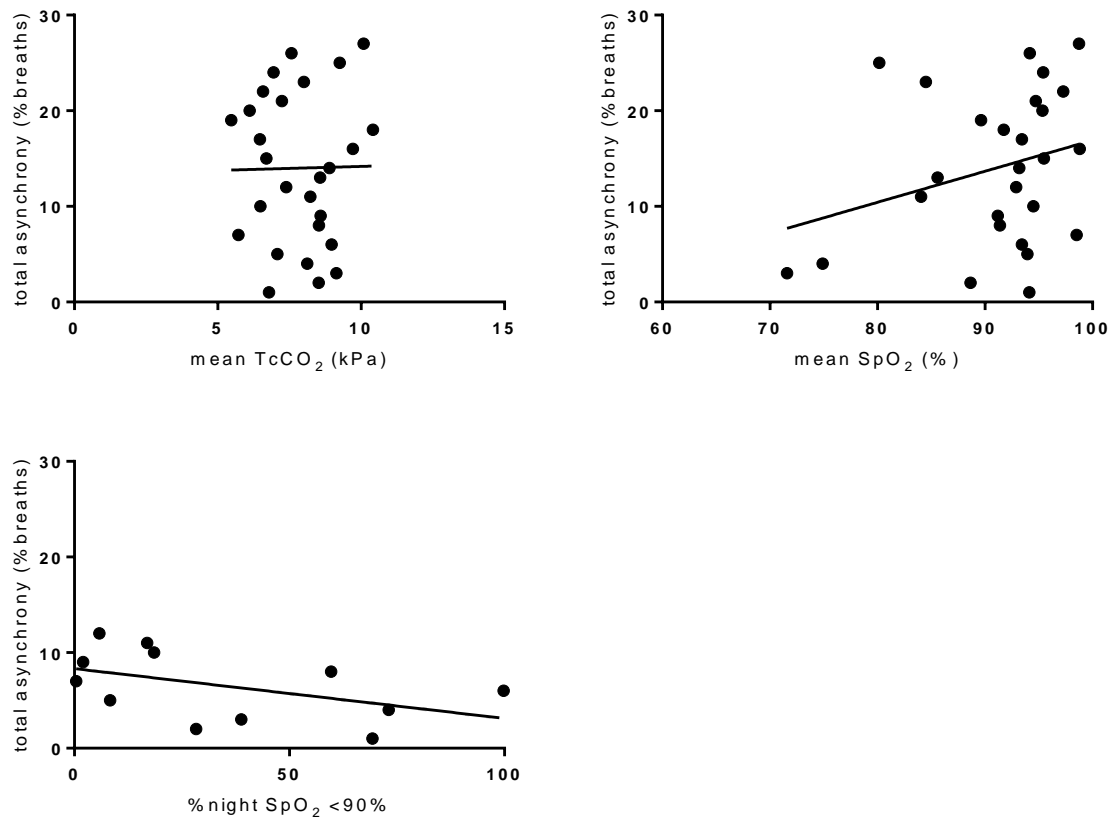
Furthermore, there was no correlation observed between total ineffective efforts and mean transcutaneous carbon dioxide (r^2 = -0.04; p = 0.31), mean oxygen saturations (r^2 = 0.04; p = 0.32) and time spent overnight with oxygen saturations below 90% (r^2 = -0.08; p = 0.36) (Fig. B).

Figure B: Relationship between ineffective efforts and nocturnal gas exchange
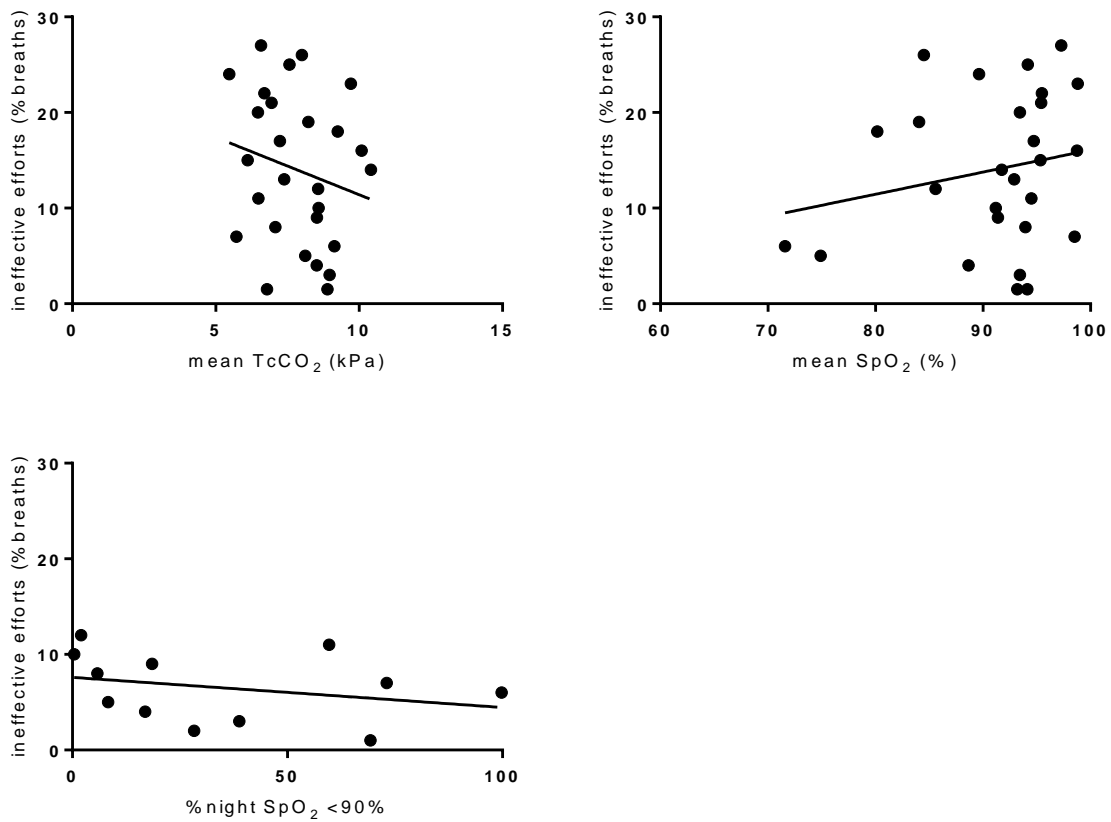
DISCUSSION

Rationale to support the use of second intercostal space parasternal surface EMG (sEMG$_{para}$)

The sEMG$_{para}$ are obligatory inspiratory muscles recruited in concert with the diaphragm with a strong correlation between the sEMGpara and diaphragm electrical activity shown both in hypercapnic stimulation and inspiratory threshold loading tests [3-5]. These data support the use of sEMG$_{para}$ as a non-invasive alternative. This physiological signal is further enhanced, as a clinical tool, by satisfactory skin preparation and placement of the electrodes

which optimising the quality and quantity of the signal measured. In previous studies, we have comprehensively demonstrated that adequate signals can be obtained in a variety of clinical conditions, in both the acute and stable state, using $sEMG_{para}$ [1, 6-8]. The stability and responsiveness of the signal combined with an in depth assessment and visual inspection of the respiratory inductance plethysmography (RIP), mask pressure signal and the sEMGpara, confirmed the phasic inspiratory $sEMG_{para}$ signal and any periods contaminated with movement and other non-respiratory artefacts were removed. Of the 168 hours reviewed in this study, in 165 hours (98.2%) a representative 2-minute sample could be analysed every 10 minutes. For 3 hours the signal was lost due to profuse sweating and loss of electrode contact or drop out associated with overnight toileting. This affected 2 of the 28 patients studied. Every patient in the study had greater than 50% of the night with analysable data, indicating that this is a suitable physiological monitoring tool.

This study was performed in a specialist unit with researchers and clinicians that are expert in respiratory physiological measurement and NIV set up. Despite this caveat, the authors consider that this simple technique of combining $sEMG_{para}$ with thoraco-abdominal movement and measurements of mask pressure is a novel clinical monitoring approach for HMV set up. Indeed, with the intended progression from a labour-intensive manual approach to an automated system of signal processing and analysis, the clinical applicability would be an important translational physiological advance. Automated downloads could be reported to the clinician, in a similar manner to the overnight respiratory and polysomnographic studies used in routine clinical practice, with the reports extended to detailing PVA and overnight gas exchange. This could not only support inpatient initiation of

NIV, but also outpatient and home set up of HMV, which have increasing popularity driven by patient preference and financial gains, but this will need to be proven.

Critique of the Method

All patients were studied using a NIPPY3+ ventilator (B&D Electromedical, Stratford-upon-Avon, United Kingdom). This reflects our own clinical practice, but importantly this allowed a standardisation of the equipment to ensure that we could have a robust comparative analysis of patient-ventilator asynchrony across the different patient groups, in particular, in terms of the ventilator triggering, airway pressurisation and cycling performance. The authors acknowledge that the levels of patient-ventilator asynchrony may be related to the performance characteristics of this ventilator and discrepancies between other studies may reflect the use of different domiciliary ventilators.

Patients adhered to the NIV for variable amounts of time overnight, as would be expected on the first night of use. To account for this difference, we used the asynchrony index described by Thille and colleagues [9] and reported the patient-ventilator asynchrony as a percentage of total breaths analysed. However, the high prevalence of PVA in this study may be related to disturbances during the first night of NIV use resulting in a 'first night' effect and may not represent PVA levels following adaption to NIV in the home. This will be investigated as part of an ongoing randomised controlled trial, which is due to report later this year (www.clinical trials.gov NCT 01371149).

The authors were initially concerned that $sEMG_{para}$ would lack the sensitivity to measure neural respiratory drive in the neuromuscular patients. However, contrary to our original concerns, we observed that $sEMG_{para}$ signal could be easily identifiable and a stable signal

obtained due to the lack of interruption by movement artefact. Importantly, we also demonstrated that ineffective efforts that were related to intercostal parasternal muscle activity but without corresponding chest wall excursion would be missed using standard measurement techniques, but were easily identifiable using the combination of $sEMG_{para}$, thoraco-abdominal motion and mask pressure. Again, this extends the utility of using the novel approach.

Cycling Asynchrony

Cycling asynchrony was observed to be much less frequent than triggering asynchrony in all patient groups. Although premature and extended expiratory cycling affected the majority of patients, these accounted for only a few of the ventilator supported breaths. Unlike previous reports, which have observed an increased prevalence in extended expiratory cycling in COPD patients, we found no difference in either premature or extended cycling between the patient groups [10]. Auto-cycling affected half of the patients, but again, this accounted for a small fraction of the total ventilated breaths highlighting that cycling asynchrony is probable not a clinical relevant problem during NIV initiation, albeit we have not measured sleep quality with full montage polysomnography.

Comprehensive assessment of patient-ventilator asynchrony

Assessing the prevalence of patient-ventilator asynchrony in detail is challenging. This complex physiological measurement is influenced by a numbers of factors including the length and timing of the observation time, the detection method used, the experience of the scorer and the reporting method employed [11, 12]. Short observation periods will fail to capture all the asynchronous events due to the often intermittent nature of the

phenomenon, whereas variance in asynchrony levels between wakefulness and sleep limit the value of daytime studies [13]. Indeed, the majority of the current literature reports the measurement of patient-ventilator asynchrony during less than thirty minutes of ventilator support (12, 13, 18-22).

The method of reporting asynchrony also influences the prevalence of event reporting with the more advanced physiological methods reporting greater detail. The physiological 'gold standard' to measure patient-ventilator asynchrony involves the measurement of the oesophageal pressure, inspiratory and expiratory flow and diaphragm electromyogram. However, these invasive measurements are poorly tolerated in non-sedated patients and therefore this has limited the widespread use in routine clinical practice. Conversely, using much simpler non-invasive markers of mask pressure and inspiratory and expiratory flow and comparing with the ventilator flow and pressure waveforms reduces the ability to determine the type and frequency of the asynchrony. However, the current data has validated the combination of $sEMG_{para}$ with the measurements of thoraco-abdominal movement and mask pressure. This non-invasive technique was well tolerated and it is a useful method to assess asychrony at the bedside in patients receiving NIV. Importantly, the reliability of using this technique and the agreement in the scoring of the type and frequency of asynchrony between the two independent scorers was more than adequate for ineffective efforts, by far the most prevalent PVA. Although autocycling was difficult to confirm between the two scorers, these events accounted for only 0.1% of the total breaths and thus their clinical relevance is extremely low. In the future, we should consider that the number of asynchronous breaths is normalised to the length of the observation period during sleep and wakefulness to determine the prevalence of patient-ventilator synchrony.

APPENDIX E1: Definitions of patient ventilator asynchronies during non-invasive ventilation

TRIGGERING ASYNCHRONY

Ineffective Effort

An ineffective effort is an asynchronous event where the patient exhibits inspiratory effort demanding a breath without a corresponding breath being delivered by the ventilator.

Visual inspection definition is that there is sEMGpara activity (neural respiratory drive) and associated thoraco-abdominal respiratory inductance plethysmography (RIP) band movement but without a corresponding increase in mask pressure (*Figure E1*).

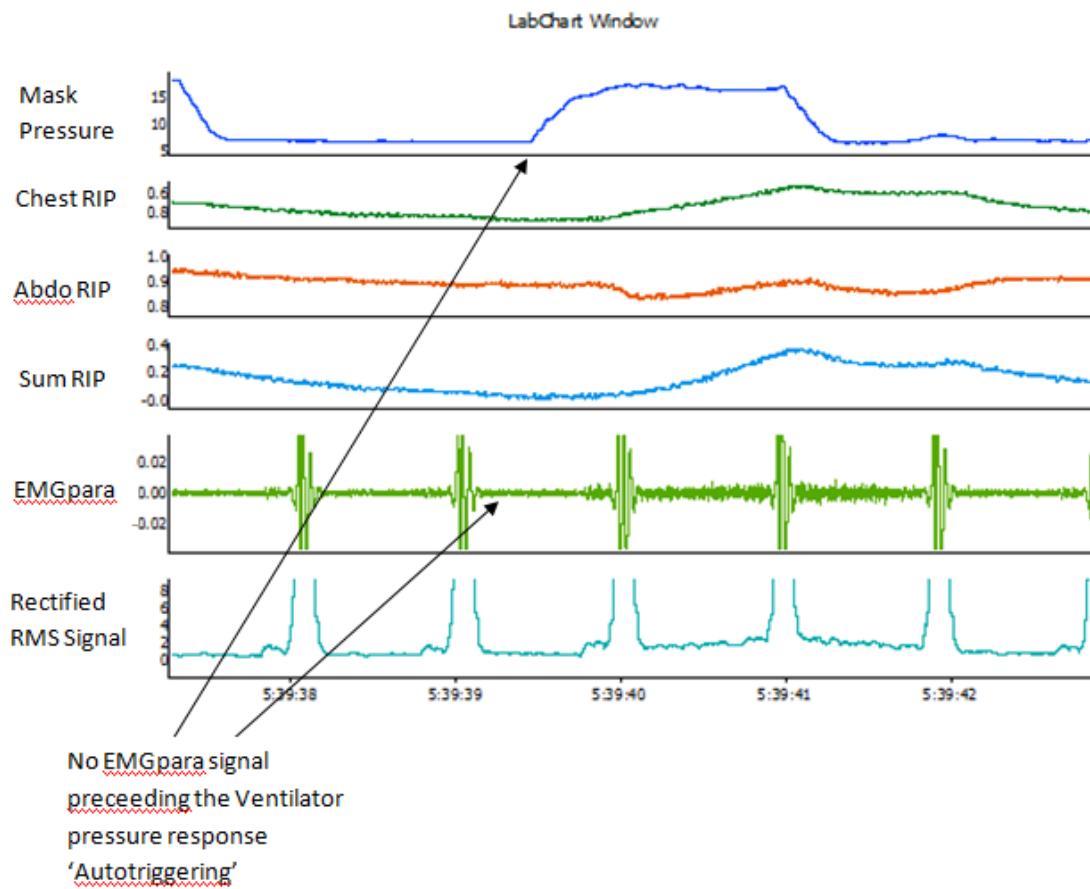**Figure E1: A representative trace of an *ineffective effort***
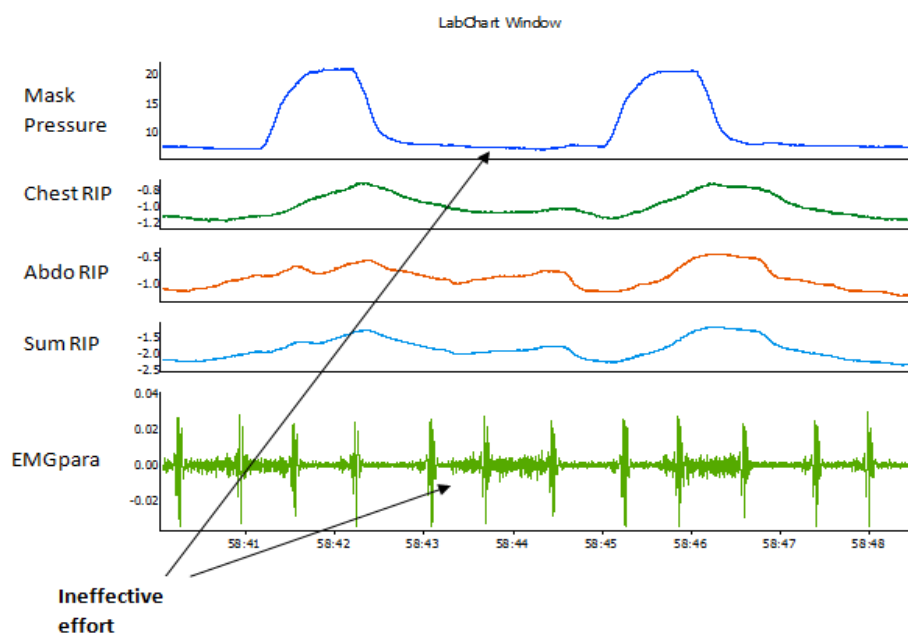
Abbreviations: Chest RIP = chest respiratory inductance plethysmography, Abdo RIP= abdominal respiratory inductance plethysmography and EMGpara = parasternal intercostals electromyography

Auto-triggering

Auto-triggering represents an inappropriate ventilator delivered breath that is not triggered by the patient. This can occur as either a pressure supported ventilator delivered breath or a pressure controlled ventilator delivered breath. This can be challenging to identify in commonly used modes of non-invasive ventilation e.g. spontaneous-timed mode

With a pressure supported ventilator delivered breath, the asynchrony occurs without a preceding sEMGpara signal and with delayed chest and abdominal movement after the onset of pressure delivered by the ventilator. To confirm this, the inspiratory time will be different to set back-up inspiratory time (*Figure E2*).

Figure E2: A representative trace of an *auto-triggered pressure support delivered breath*

LabChart Window

Mask Pressure
Chest RIP
Abdo RIP
Sum RIP
EMGpara
Rectified RMS Signal

No EMGpara signal preceeding the Ventilator pressure response 'Autotriggering'

In contrast, to be an auto-triggered pressure controlled delivered breath, the breath must have the set inspiratory time and be delivered at an inappropriate time when compared to the set back-up rate. For example, at a back-up rate of 6, a pressure controlled ventilator delivered breath would be expected every 10 seconds. If a breath was delivered at the pre-set inspiratory time, 4 seconds after the previous breath without any patient inspiratory effort this would be an auto-triggered pressure controlled ventilator delivered breath.

Figure E3: A representative trace of an *auto-triggered pressure controlled ventilator delivered breath*
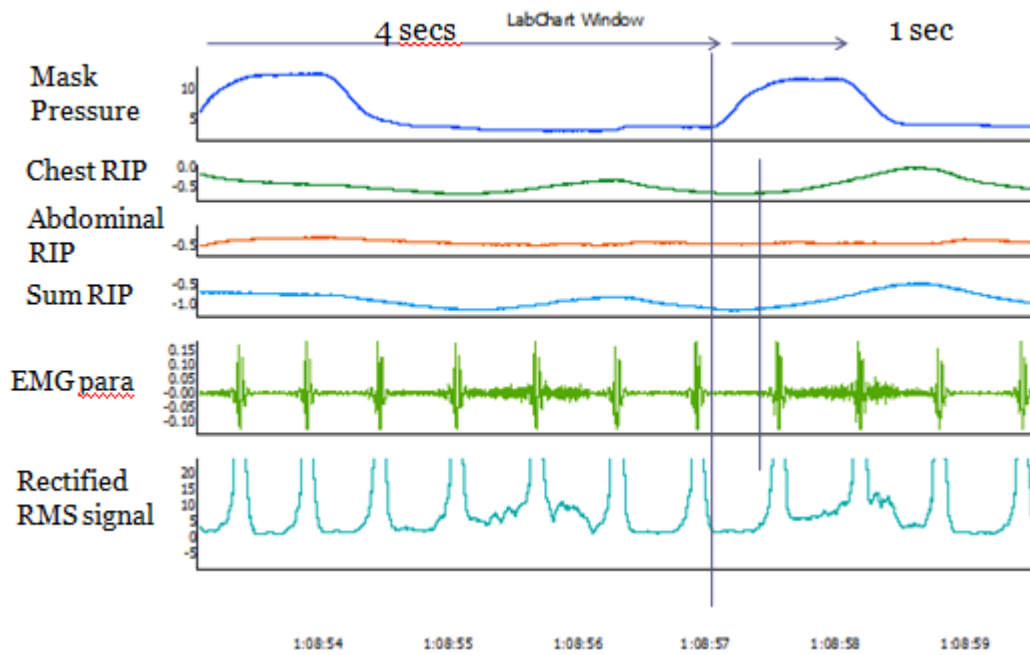
Double triggering

Double triggering is an asynchronous event in which a patient demands a single breath but two breaths are delivered by the ventilator. We defined double triggering as two breathing cycles of the ventilator delivered separated by a short expiratory time (defined as up to 1 second). The first cycle must be patient triggered, the second cycle is not. (Figure E4).

Figure E4: A representative trace of *'double triggering'*

A single patient inspiratory effort, two breaths delivered by the ventilator (<1 sec between the breaths)
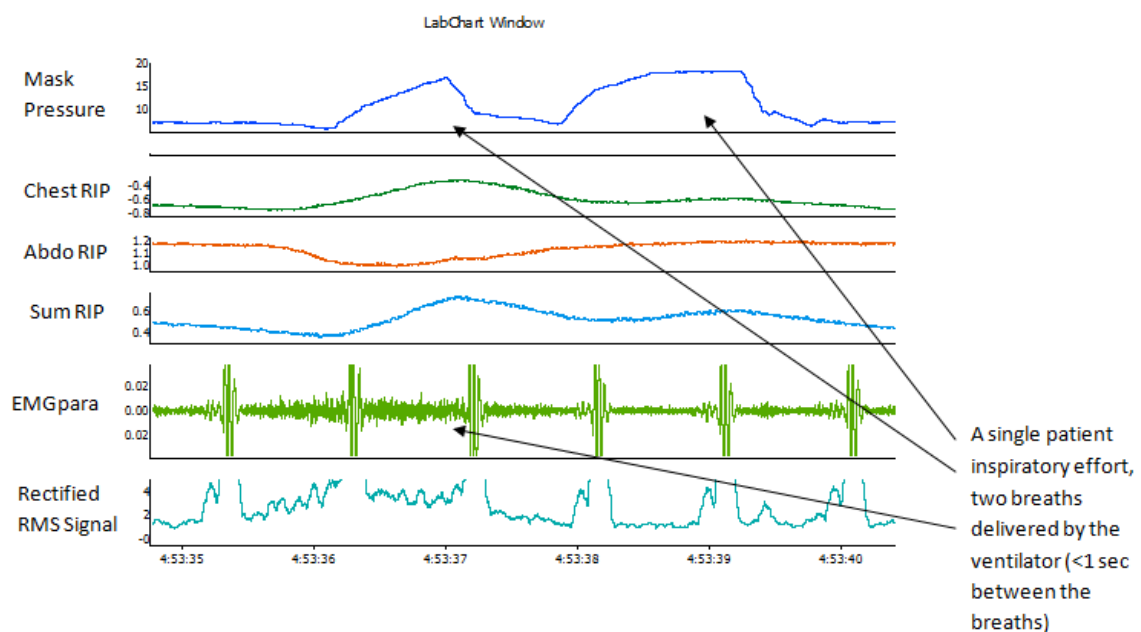
Multiple triggering

Multiple triggering is an asynchronous event in which a patient makes a single continuous demand for a breath that triggers multiple ventilator delivered breaths. This requires sEMGpara activity, representing neural respiratory drive, to be continuously present throughout all the delivered breaths. A single continuous thoraco-abdominal motion is observed (Figure E5).

Figure E5: A representative trace of *multiple triggering'*

Multiple ventilator delivered breaths with persistent patient effort (sEMGpara activity) and a single chest movement (chest RIP)
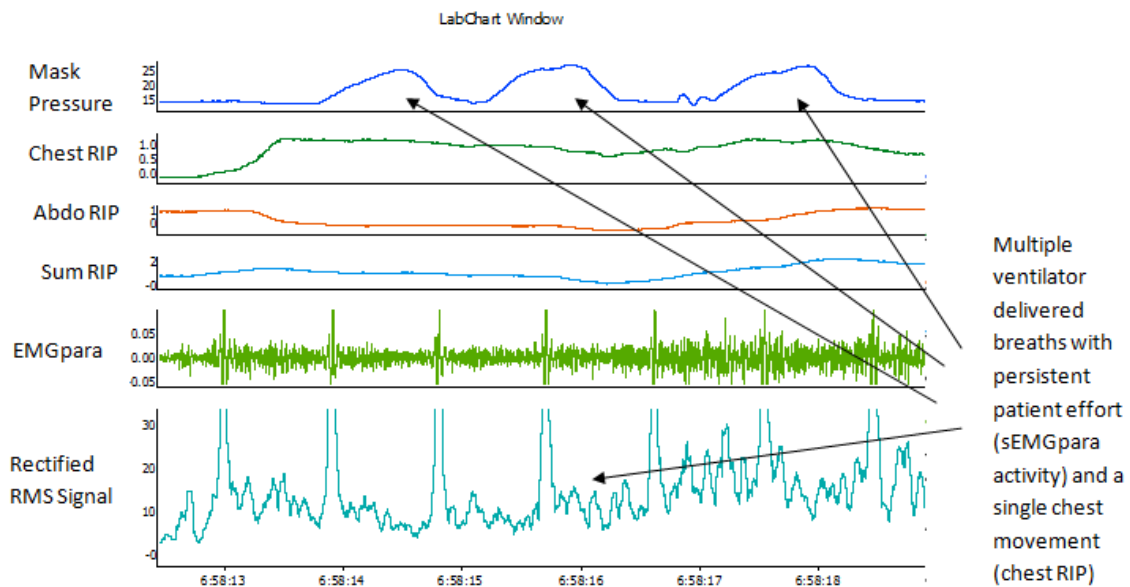
CYCLING ASYNCHRONY

Premature expiratory cycling asynchrony

With premature expiratory cycling, neural inspiratory drive of the patient (evidence by sEMGpara activity) continues as the ventilator cycles into expiration. (Figure E6). To score and report this, we have defined it as occurring when the following rules are present:

1) The ventilator cycles to expiration which is defined as a reduction in the pressure signal towards the baseline whilst sEMGpara activity continues

2) Thoraco-abdominal band movement continues outwards (indicative of inspiration) as the ventilator cycles into expiration

Figure E6: A representative trace of *premature expiratory cycling*
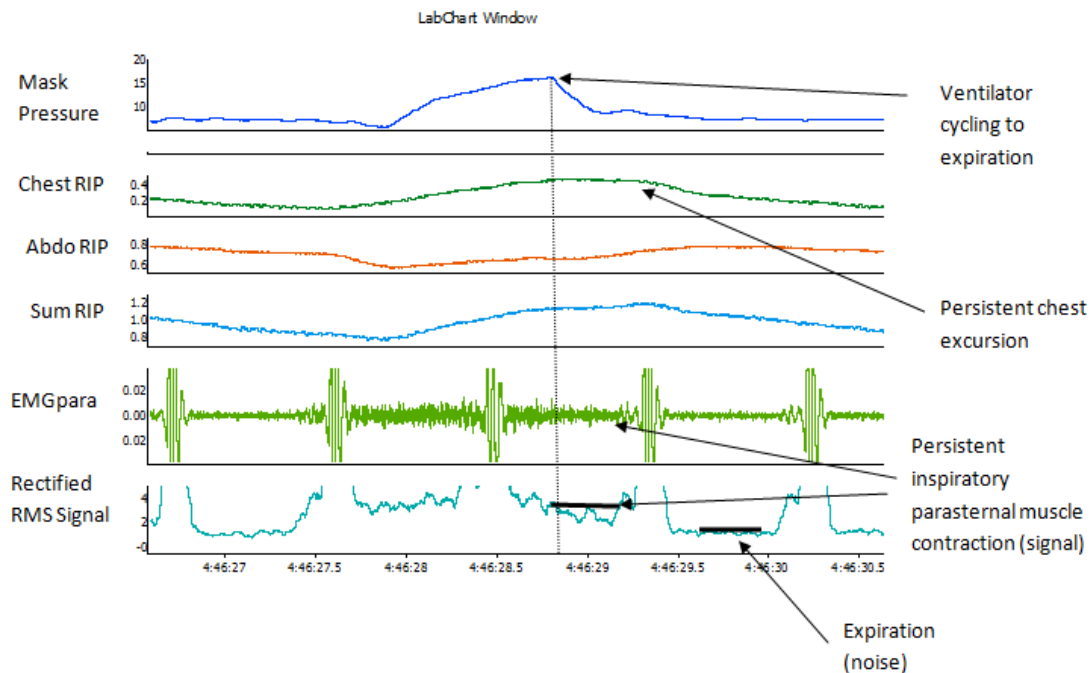
Extended expiratory cycling asynchrony

Extended expiratory cycling is a mismatch in which the neural respiratory drive of the patient ceases but the ventilator continues to deliver a breath (Figure E7). We have defined with the following rules:

1) sEMGpara activity ceases 20ms prior to the expiratory phase

2) An increase in the pressure wave is observed as the patient attempts to expire

3) Abdominal EMG signal is visible indicating expiratory muscle activity

#1 will always be present. #2 and #3 can be absent, but both of these will facilitates identification.

Figure E7: A representative trace of *delayed expiratory cycling*
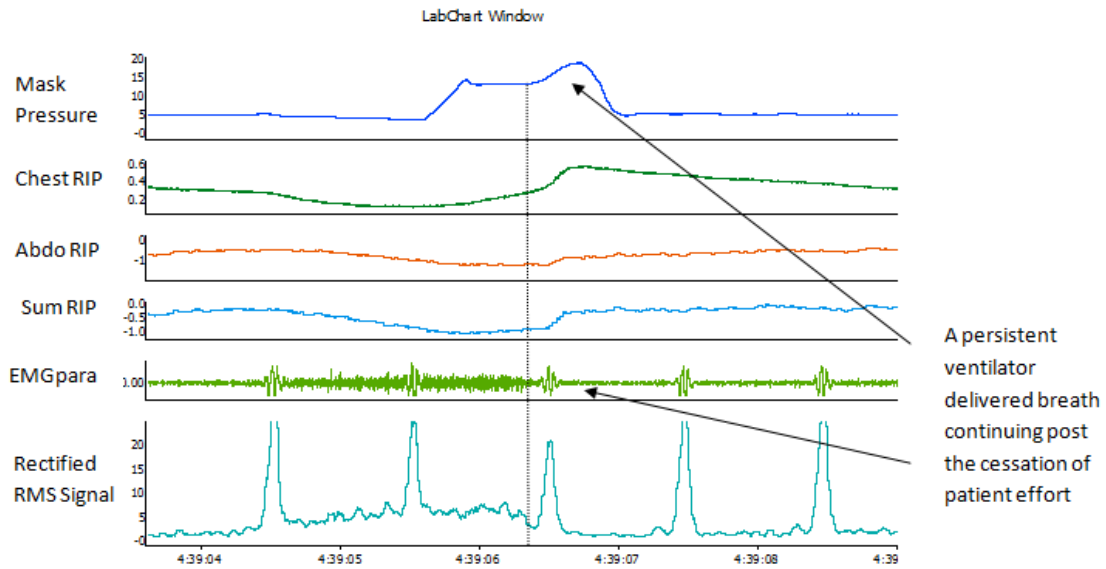
Autocycling

Autocycling is defined as multiple episodes of ventilator delivered breaths being delivered in rapid succession but distinct in nature. Two or more ventilator breaths must be delivered each separated by a short expiratory time of less than 1 second. These are not triggered by the patient but occasionally sEMGpara activity is observed as the patient attempts to co-ordinate with the ventilator (Figure E8).

Figure E8: A representative trace of 'autocycling'
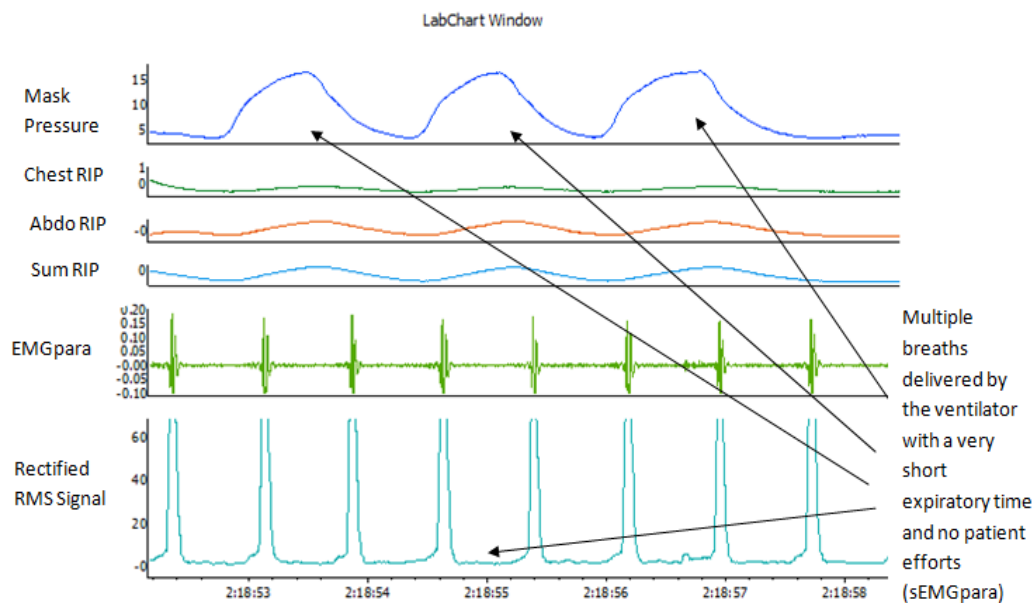
APPENDIX E2a: Protocolised set-up of home mechanical ventilation for patients with chronic obstructive pulmonary disease (COPD) used at the Lane Fox Respiratory Unit, St. Thomas' Hospital, London UK

Lane Fox Unit Ventilator Set-up
Updated 2013

COPD
Includes COPD/OSA Overlap

APPENDIX E2b: Protocolised set-up of home mechanical ventilation for patients with obesity related respiratory failure (ORRF) used at the Lane Fox Respiratory Unit, St. Thomas' Hospital, London UK
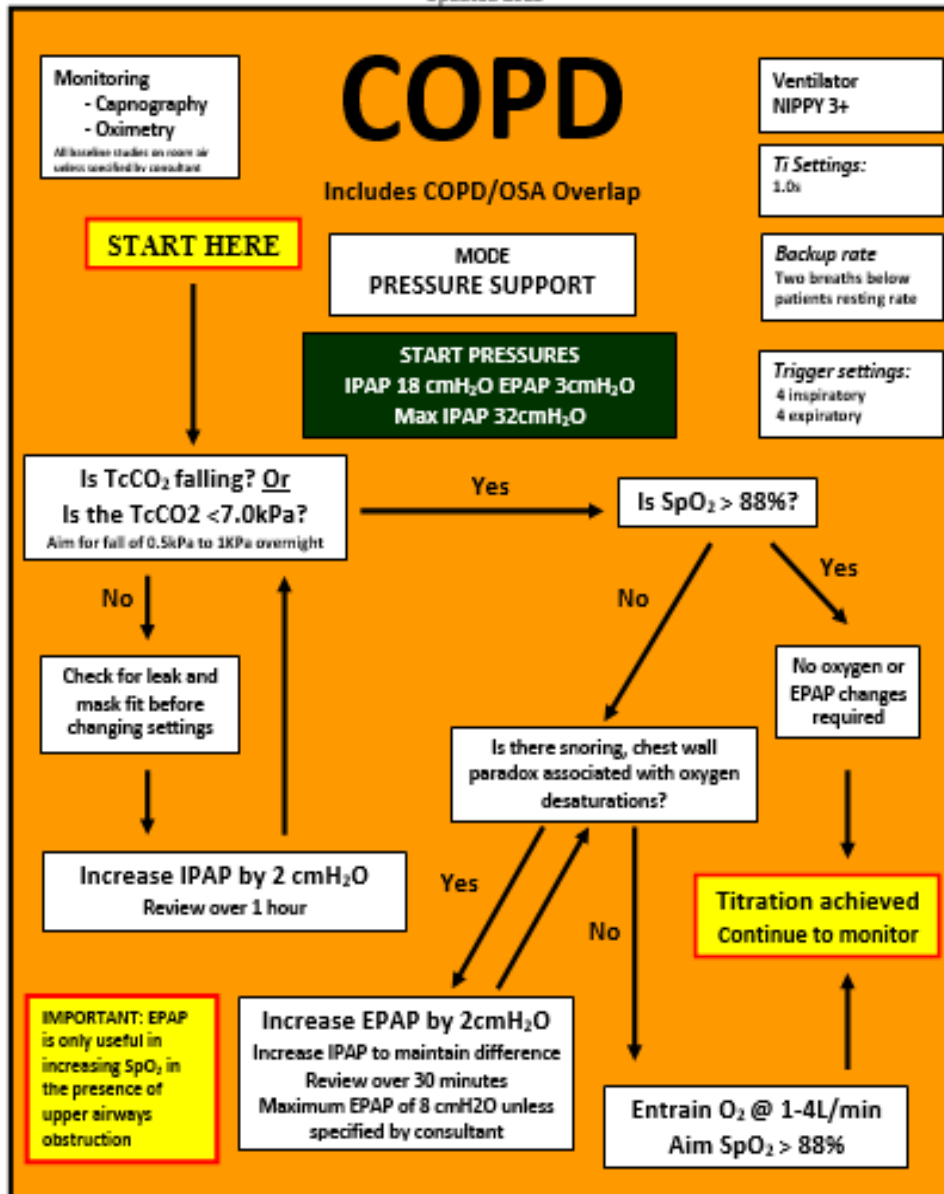

Lane Fox Unit Ventilator Set-up
Updated 2013

OBESITY RELATED RESPIRATORY FAILURE
OSA
OSA-OHS
Lone OHS

TOSCA Monitoring
- Capnography
- Oximetry

All baseline studies on room air unless specified by consultant

START HERE

Ventilator NIPPY 3+

Ti Settings: 1.2s

Backup rate
Two breaths below patients resting rate

Trigger settings:
4 inspiratory
4 expiratory

MODE
PRESSURE SUPPORT

STARTING PRESSURES
OSA-OHS - IPAP 18cmH2O EPAP 8cmH2O
Lone OHS - IPAP 18cmH2O EPAP 4cmH2O
Max Settings IPAP 32 cmH2O EPAP 14 cmH2O

Is there persistent snoring, chest wall paradox with oxygen desaturations?

No →

Is $TcCO_2$ falling? Or Is the $TcCO2$ <7.0kPa?

Aim for fall of 0.5kPa to 1kPa overnight

Yes

Check for leak and mask fit before changing settings

No

Check for leak and mask fit before changing settings

Is SpO_2 > 88%?

Increase EPAP by 2cmH$_2$O
Review over 30 minutes
Do not increase EPAP above 14 cmH2O unless specified by the consultant

Yes

No

Increase IPAP by 2cmH$_2$O
Review over 1 hour

IMPORTANT:
(1) If the patient has a PaCO$_2$ less than 6kPa on room air (i.e. failed CPAP) then there is no indication for an IPAP > 20 cmH$_2$O
(2) If the patient has significant oxygen desaturations during CPAP trial convert to NIV

Entrain O$_2$ @ 1-4L/min
Aim SpO$_2$ > 88%

Titration achieved
Continue to monitor

APPENDIX E2c: Protocolised set-up of home mechanical ventilation for patients with neuromuscular and chest wall disease (NMD-CWD) used at the Lane Fox Respiratory Unit, St. Thomas' Hospital, London, UK

Lane Fox Unit Ventilator Set-up
Updated 2013

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