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 $\pm$ 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

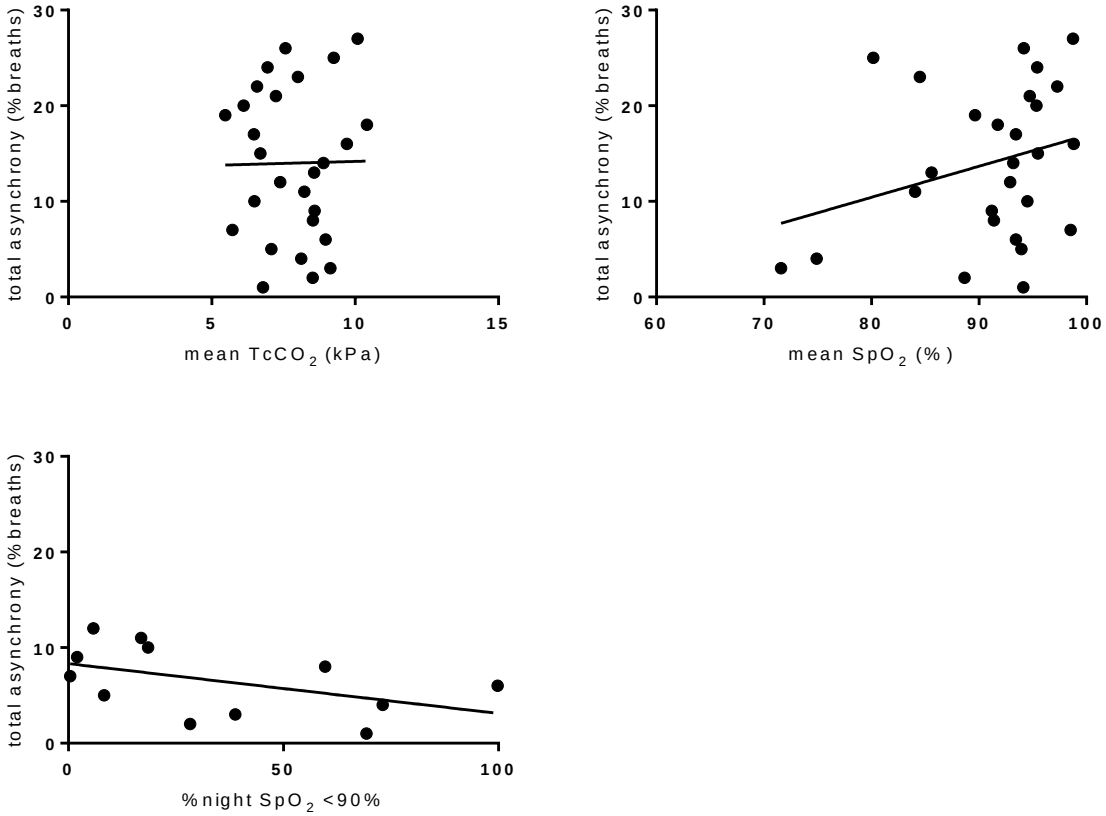
There was a trend for a difference in the mode of ventilation in the different disease groups with COPD patients receiving 60±25% of the delivered breaths in a pressure support mode, whereas ORRF and NMD-CWD patients received just 36±56% and 34±24% of the delivered breaths in the pressure support mode, 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 ($r^2 =$

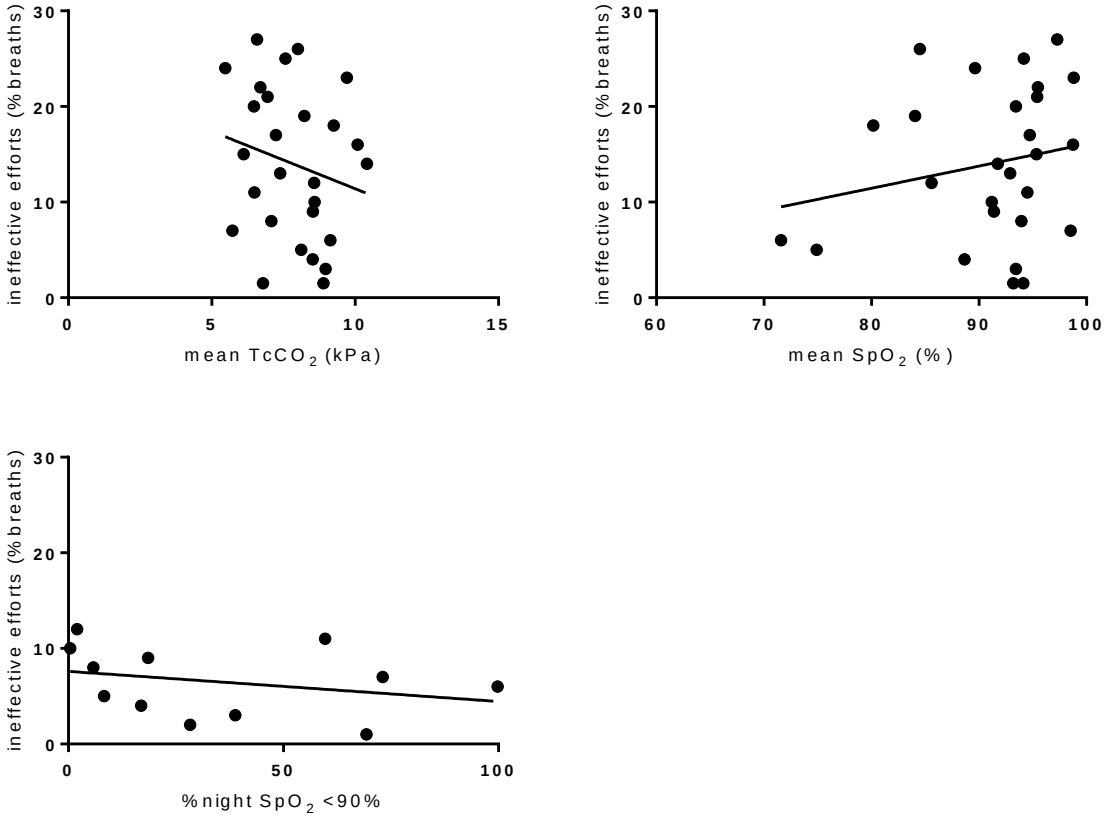
0.08; p = 0.16) and time spent overnight with oxygen saturations below 90% (r^2 = -0.02; p = 0.12) (*Fig. A*).

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

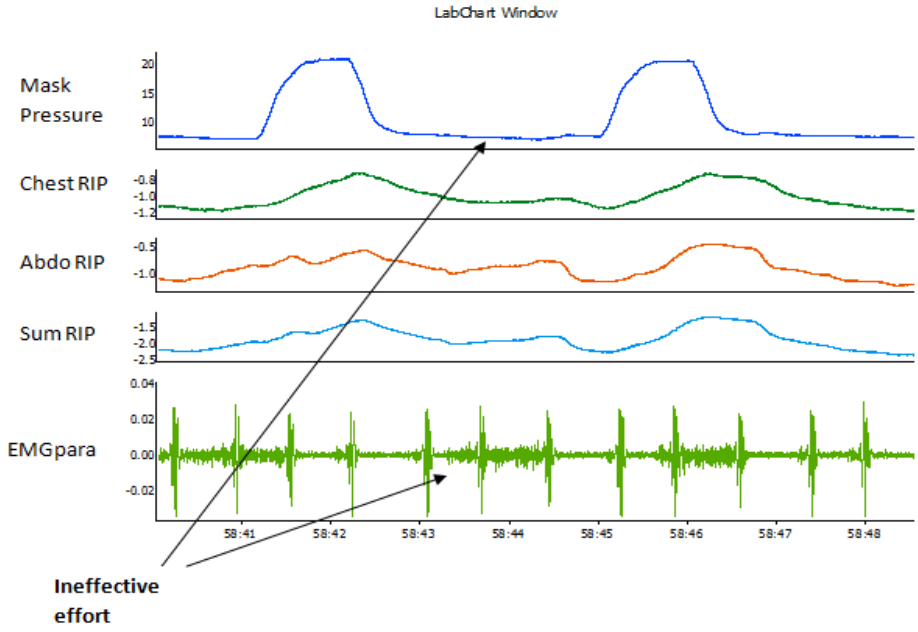
TRIGGERING ASYNCHRONY

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*



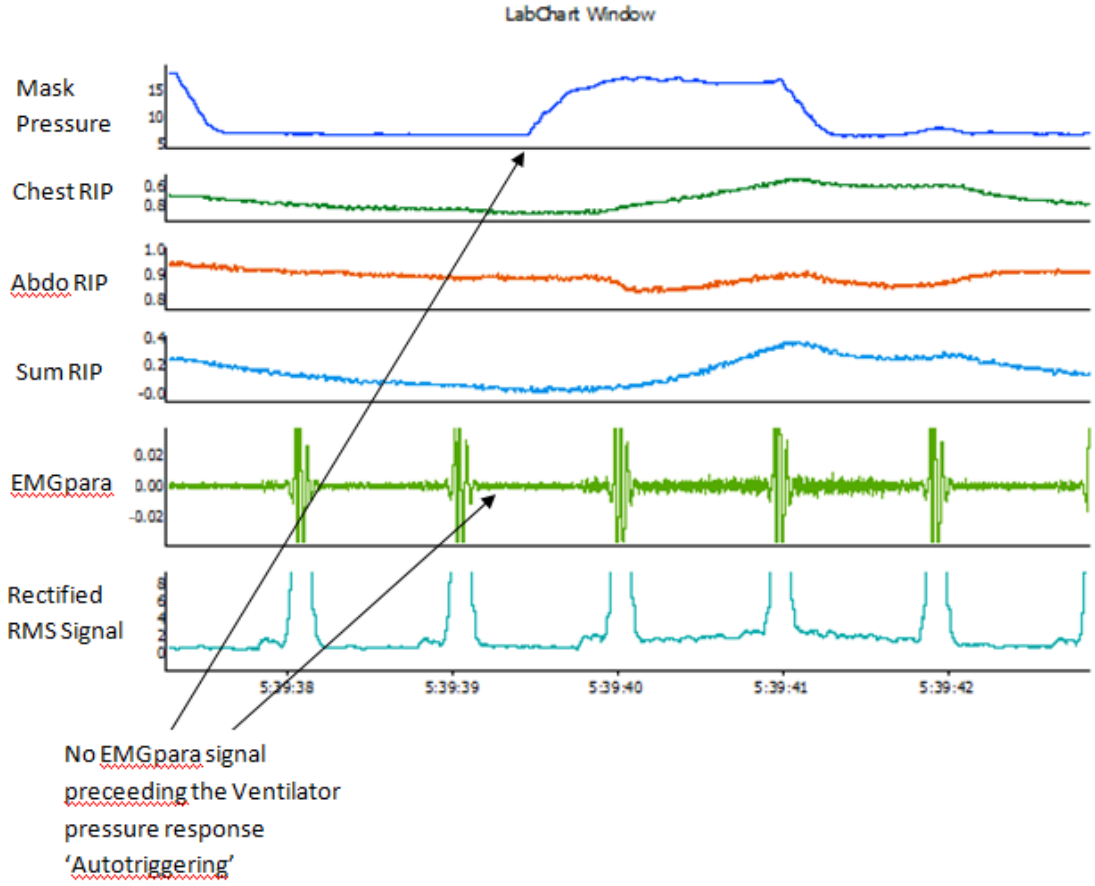
Abbreviations: Chest RIP = chest respiratory inductance plethysmography, Abdo RIP= abdominal respiratory inductance plethysmography and EMGpara = parasternal intercostals electromyography

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

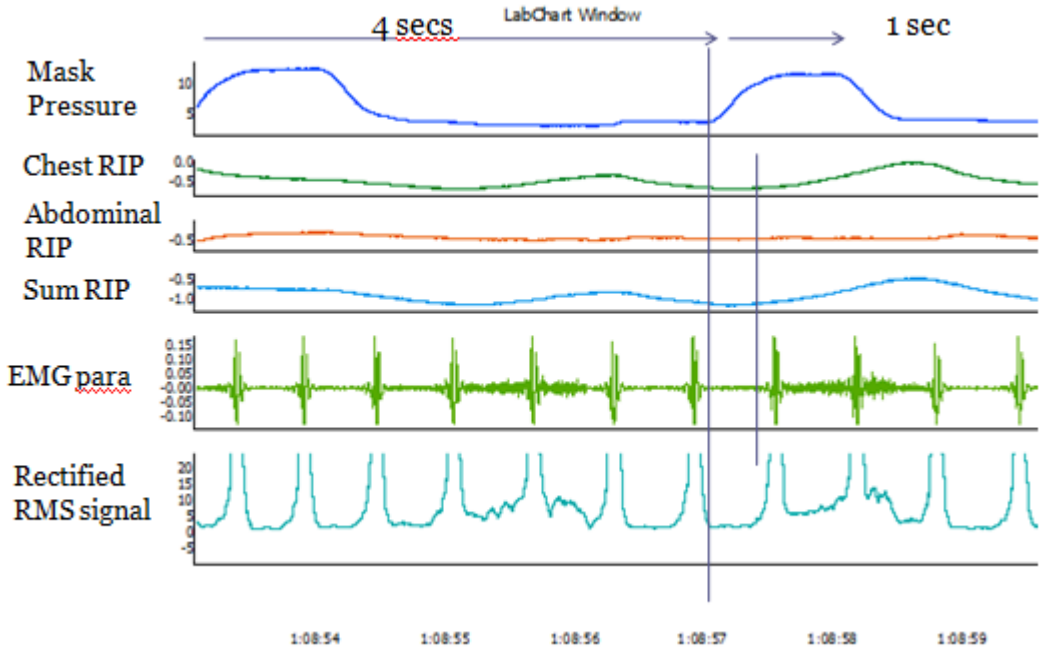
With a pressure supported ventilator delivered breath, the asynchrony occurs without a preceding sEMGpara signal and with delayed chest and abdominal movement after the onset of pressure delivered by the ventilator. To confirm this, the inspiratory time will be different to set back-up inspiratory time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

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



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.

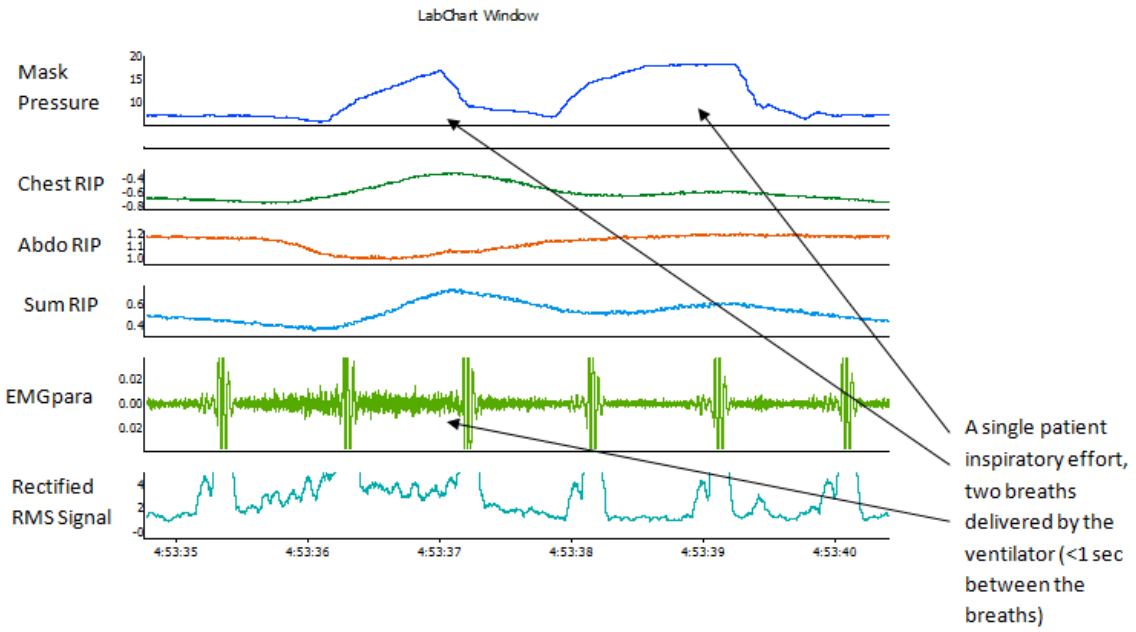
Figure E3: A representative trace of an *auto-triggered pressure controlled ventilator delivered breath*



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).

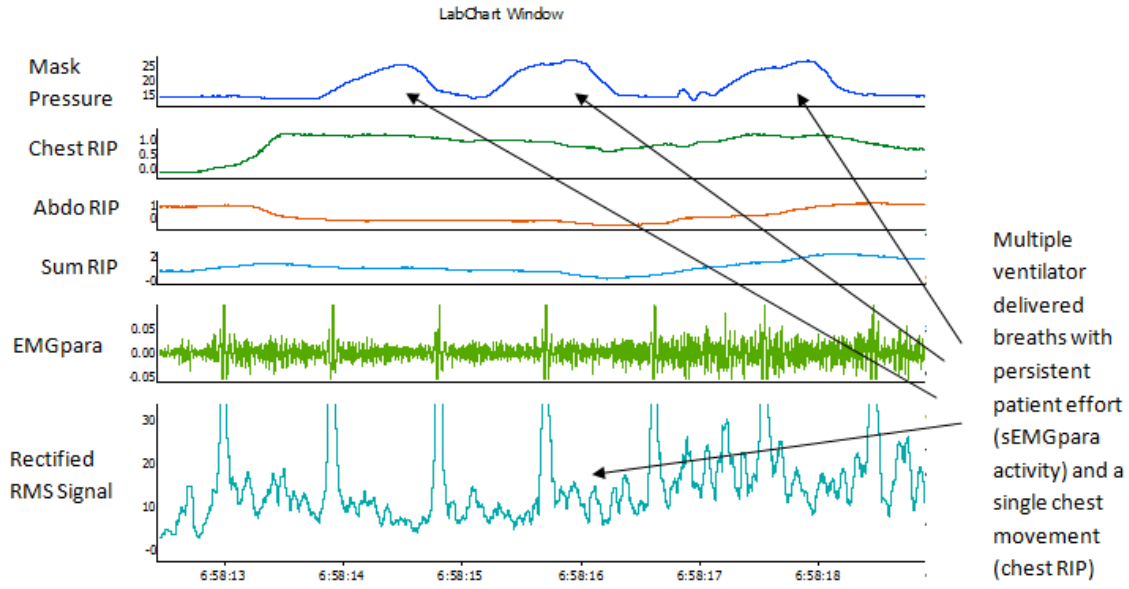
Figure E4: A representative trace of *'double triggering'*



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'*



CYCLING ASYNCHRONY

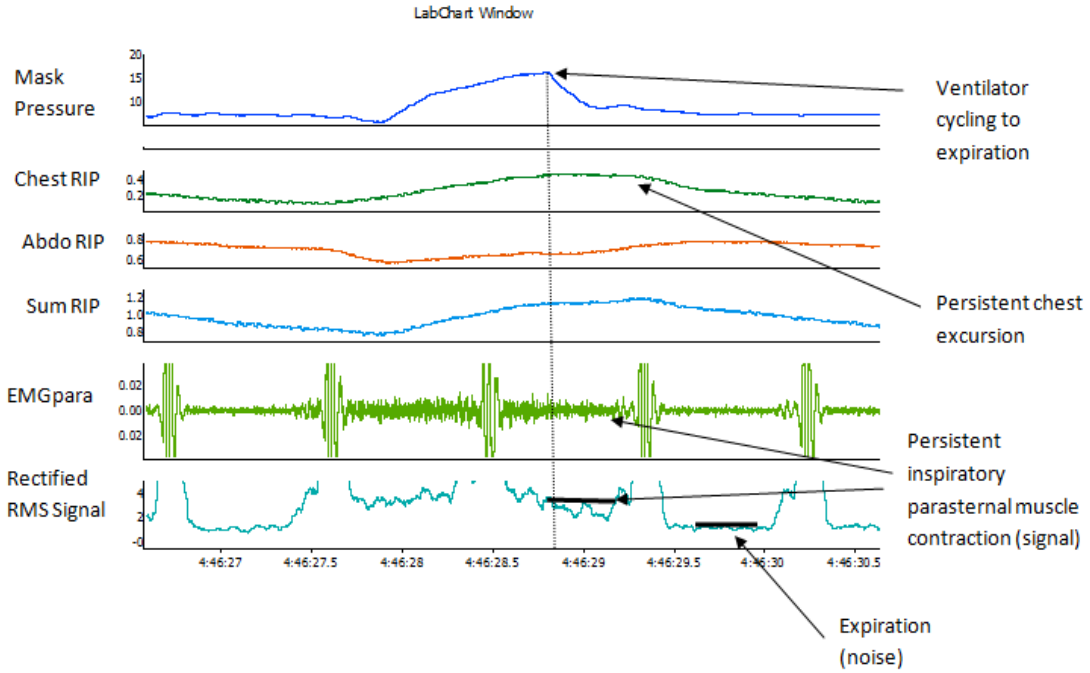
Premature expiratory cycling asynchrony

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:

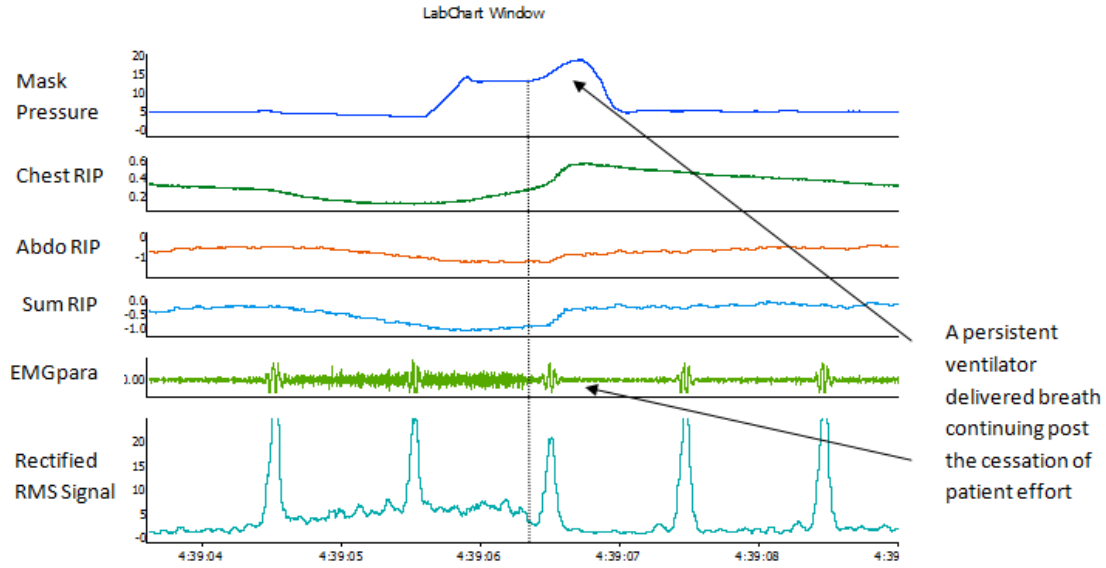
1) sEMGpara activity ceases 20ms prior to the expiratory phase

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.

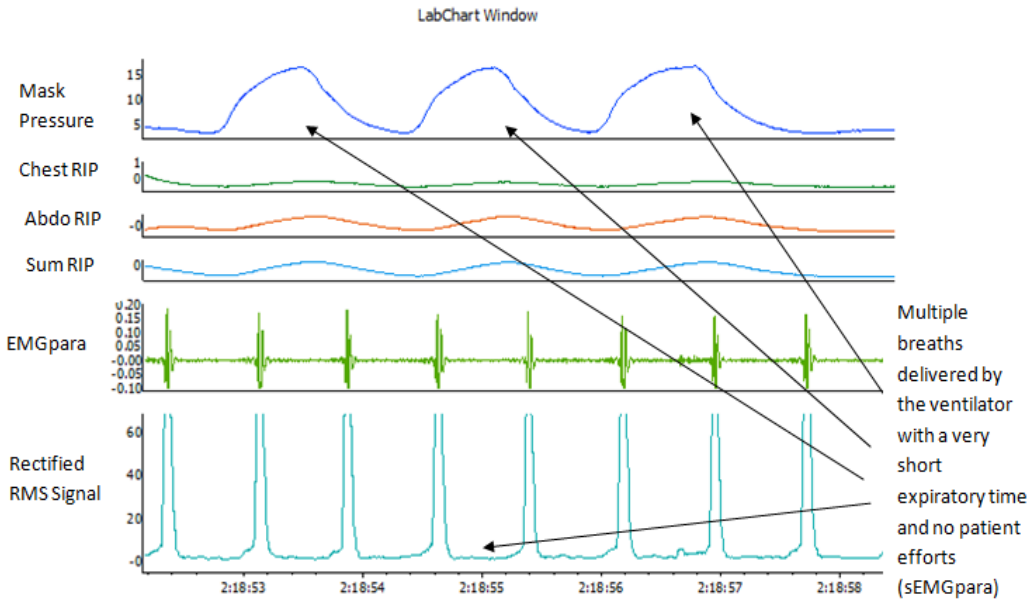
Figure E7: A representative trace of *delayed expiratory cycling*



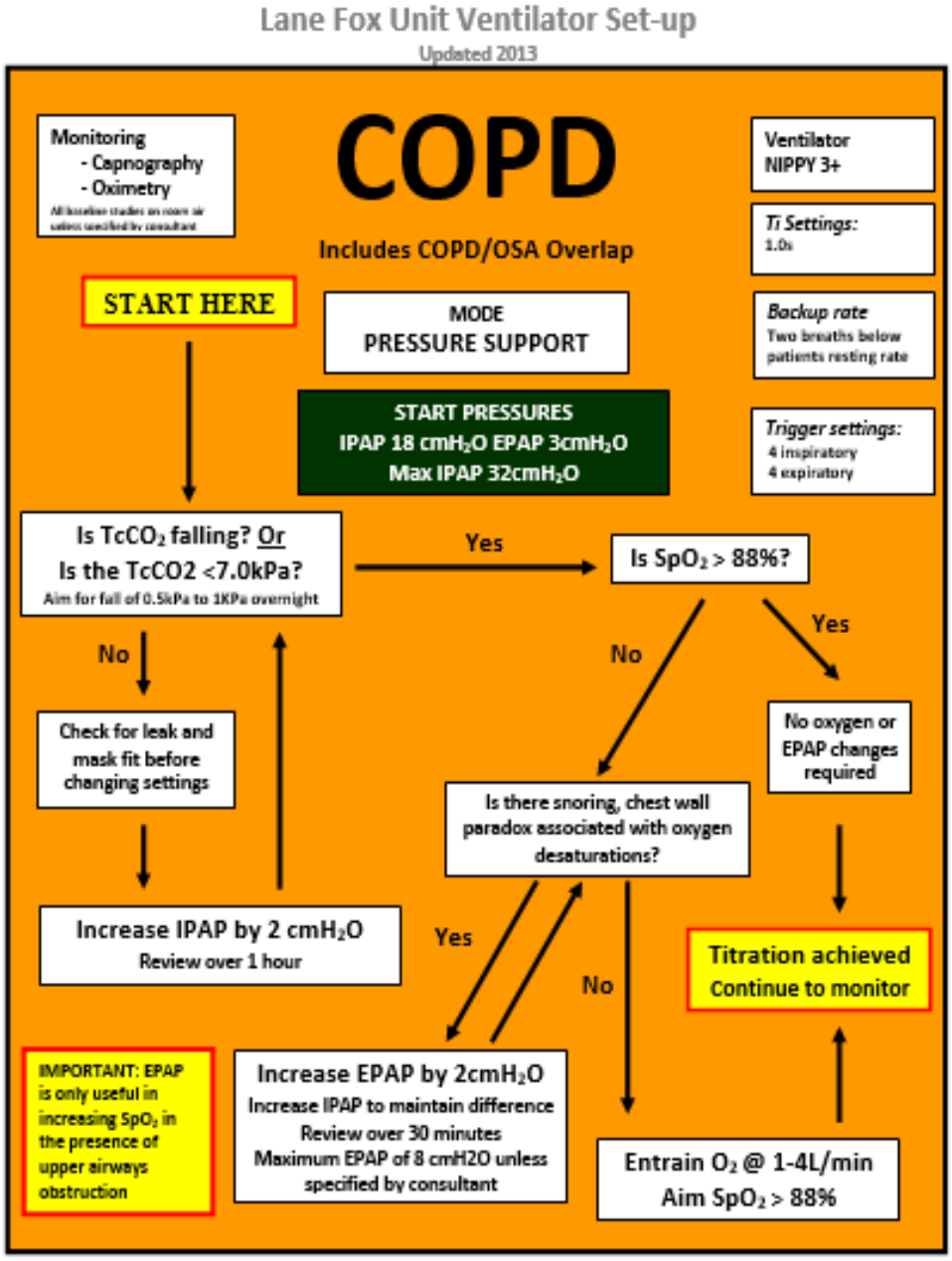
Autocycling

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).

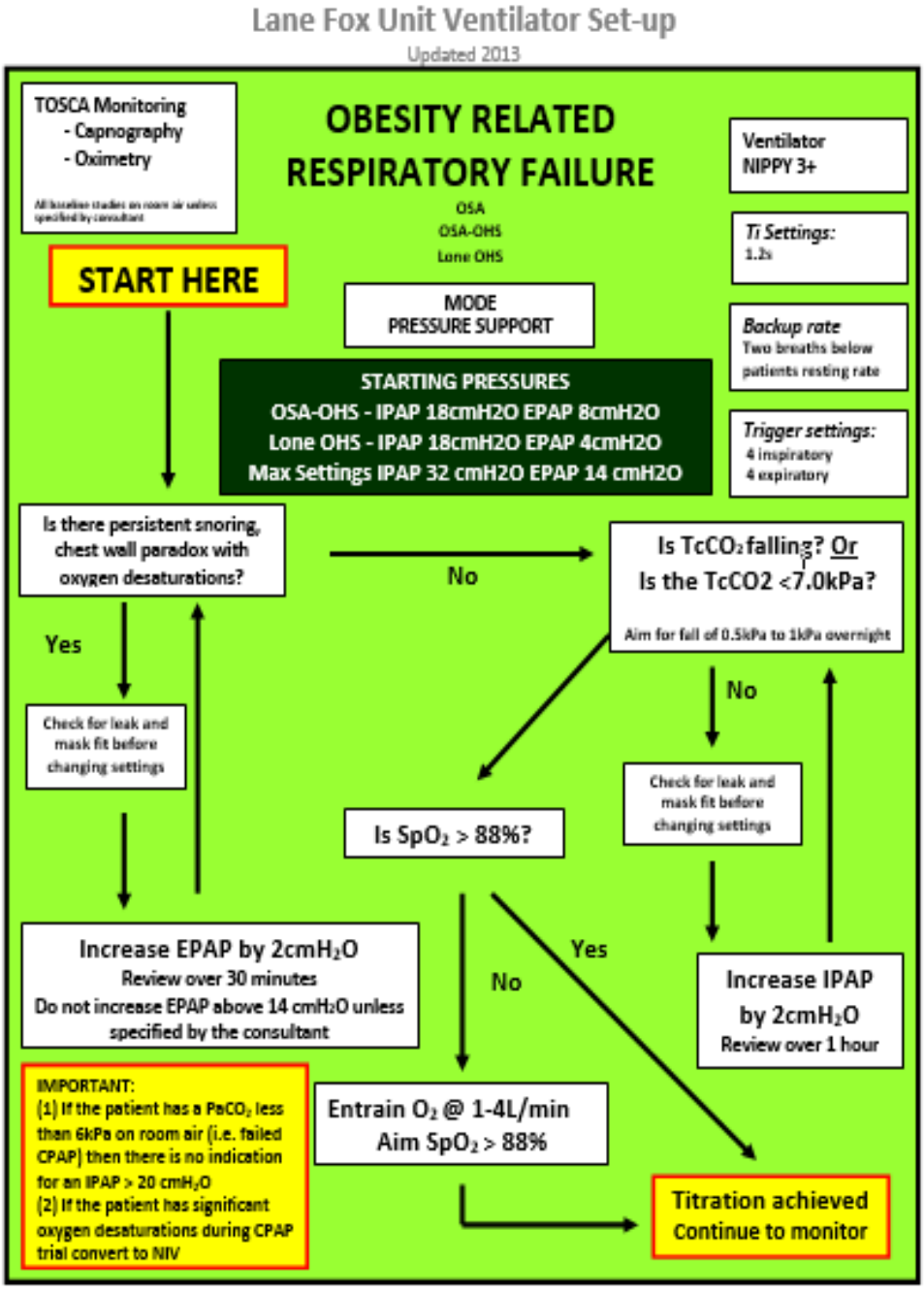
Figure E8: A representative trace of 'autocycling'



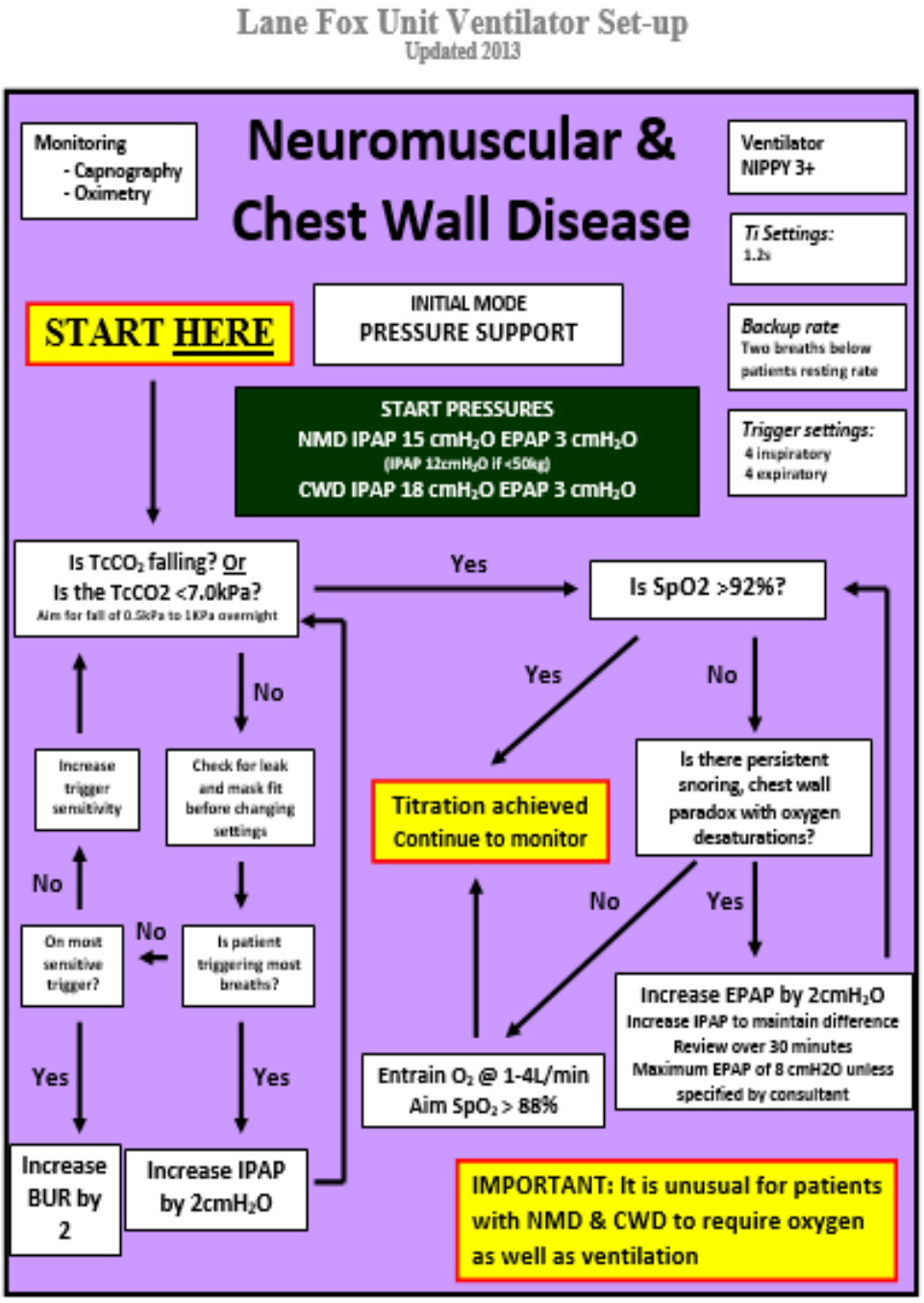
APPENDIX E2a: Protocolised set-up of home mechanical ventilation for patients with chronic obstructive pulmonary disease (COPD) used at the Lane Fox Respiratory Unit, St. Thomas' Hospital, London UK



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



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



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