

Continuous assessment of neuro-ventilatory drive during 12 hours of pressure support ventilation in critically ill patients

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Research

Keywords: mechanical ventilation, assisted modes of ventilation, pressure support ventilation (PSV)

Posted Date: September 14th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-52434/v2>

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Version of Record: A version of this preprint was published on November 20th, 2020. See the published version at <https://doi.org/10.1186/s13054-020-03357-9>.

Abstract

Introduction: Pressure support ventilation (PSV) should allow spontaneous breathing with a “normal” neuro-ventilatory drive. Low neuro-ventilatory drive puts the patient at risk of diaphragmatic atrophy while high neuro-ventilatory drive may causes dyspnea and patient self-inflicted lung injury. We continuously assessed for 12 hours the electrical activity of the diaphragm (EAdi), a close surrogate of neuro-ventilatory drive, during PSV. Our aim was to document the EAdi trend and the occurrence of periods of “Low” and/or “High” neuro-ventilatory drive during clinical application of PSV.

Method: In 16 critically ill patients ventilated in the PSV mode for clinical reasons, inspiratory peak EAdi peak ($EAdi_{PEAK}$), pressure time product of the trans-diaphragmatic pressure per breath and per minute ($PTP_{DI/b}$ and $PTP_{DI/min}$, respectively), breathing pattern and major asynchronies were continuously monitored for 12 hours (from 8 a.m. to 8 p.m.). We identified breaths with “Normal” ($EAdi_{PEAK}$ 5 - 15 mV), “Low” ($EAdi_{PEAK} < 5$ mV) and “High” ($EAdi_{PEAK} > 15$ mV) neuro-ventilatory drive.

Results: Within all the analyzed breaths (177.117), the neuro-ventilatory drive, as expressed by the $EAdi_{PEAK}$, was “Low” in 50.116 breath (28 %), “Normal” in 88.419 breaths (50 %) and “High” in 38.582 breaths (22 %). The average times spent in “Low”, “Normal” and “High” class were 1.37, 3.67 and 0,55 hours, respectively ($p < 0.0001$), with wide variations among patients. Eleven patients remained in the “Low” neuro-ventilatory drive class for more than one hour, median 6.1 [3.9 - 8.5] hours and 6 in the “High” neuro-ventilatory drive class, median 3.4 [2.2 – 7.8] hours. The asynchrony index was significantly higher in the “Low” neuro-ventilatory class, mainly because of a higher number of missed efforts.

Conclusions: We observed wide variations in EAdi amplitude and unevenly distributed “Low” and “High” neuro ventilatory drive periods during 12 hours of PSV in critically ill patients. Further studies are needed to assess the possible clinical implications of our physiological findings.

Introduction

Compared to controlled mechanical ventilation, mechanical assistance to spontaneous ventilation has the potential to improve gas exchange, hemodynamics, diaphragmatic function and comfort in most critically ill patients [1–3]. Pressure support ventilation (PSV) is the most used assisted mode of ventilation [4]. During PSV, the ventilator applies a constant (operator set) level of positive pressure throughout patient’s spontaneous inspiration and the inspiratory flow results from the interplay between patient’s inspiratory effort, assistance level and respiratory system impedance (mainly, resistance and elastance). Cycling to the expiratory phase occurs when the instantaneous inspiratory flow decays below a pre-definite threshold, usually an adjustable percentage of peak inspiratory flow [5]. Theoretically, PSV should support the respiratory muscles allowing spontaneous breathing with a “normal” neuro-ventilatory drive [6–8]. Over-assistance would result in low neuro-ventilatory drive putting the patient at risk of diaphragmatic atrophy [9,10] while, on the other hand, under-assistance would result in high neuro-ventilatory drive, dyspnea [11], diaphragmatic fatigue and patient self-inflicted lung injury (P-SILI) [12].

Assessing the neuro-ventilatory drive would be pivotal to set and monitor PSV, but, unfortunately, is difficult to realize in clinical practice [13]. Accordingly, respiratory rate (RR), tidal volume (VT), patient-ventilator synchrony and gas exchange are taken into account to set PSV in the clinical setting [14–17]. To our knowledge, the neuro-ventilatory drive has not been continuously assessed during a prolonged period of PSV in critically ill patients.

The electrical diaphragmatic activity (EAdi) is the temporal sum of the electromyographic potentials of the crural diaphragm recorded by an array of electrodes mounted on the wall of a nasogastric tube [18,19]. A dedicated software (Servo i, Getinge, Solna, SW) integrates and converts into a single amplitude/time signal the signals recorded by each electrode pair, taking into account the inspiratory displacement of the diaphragm [20]. The EAdi is a close surrogate of the neuro-ventilatory drive [13,21–23] and is proportional to work of breathing [24].

In this study, we continuously assessed for 12 hours the neuro-ventilatory drive (as expressed by the EAdi) in critically ill patients ventilated in the PSV mode. Due to different anatomical characteristics between patients, it is difficult to establish absolute reference EAdi values [25–27]. Nevertheless, in order to favor data analysis, based on previous studies [7,25,28,29] we identified periods of “Normal” ($EAdi_{PEAK}$ 5 - 15 mV), “Low” ($EAdi_{PEAK} < 5$ mV) and “High” ($EAdi_{PEAK} > 15$ mV) neuro-ventilatory drive. Our aim was to document the occurrence and entity of periods of “Low” and/or “High” neuro-ventilatory drive during clinical PSV application.

Methods

Patient selection

Patients admitted over a period of six months to the ICUs of the University of Bari and Ferrara Academic Hospitals were considered for enrollment in the study. The study was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Policlinico di Bari (protocol no. 257) and of the Arcispedale Sant’Anna hospital, Ferrara, Italy (protocol no. 131084). Informed consent was obtained from each patient according to local regulations. The study was conducted between January 2016 and July 2016 in accordance with the Declaration of Helsinki. A physician not involved in the study was always present for patient care.

Patients were eligible for the study if they were older than 18 years and excluded if they were affected by neurological or neuromuscular pathologies, had known phrenic nerve dysfunction or any contraindication to the insertion of a naso-gastric catheter (for example: recent upper gastrointestinal surgery, esophageal varices).

Measurements

Patients were studied in the semi-recumbent position. All the patients were ventilated with a Servo i ventilator (Maquet Critical Care, Solna, Sweden) equipped with the neurally adjusted ventilatory assist (NAVA) software that includes the “neuro-ventilatory tool” for EAdi measurement. At the beginning of the study, the standard naso-gastric tube was replaced with a 16 Fr, 125 cm, EAdi catheter (Maquet Critical Care, Solna, Sweden) unless an EAdi catheter was already in place. The EAdi catheter was first positioned according to the corrected nose-ear lobe-xiphoid distance formula and subsequently through the EAdi catheter position tool (Servo i, NAVA software) [30].

Peak airway opening pressure ($P_{AO\ PEAK}$) and positive end-expiratory pressure (PEEP) were measured from the P_{AO} signal. Tidal volume (VT) was measured as the integral of the inspiratory flow. Mechanical respiratory rate (RR), inspiratory and expiratory time ($T_{i,MECH}$ and $T_{e,MECH}$, respectively) were measured by the flow and P_{AO} signals. The inspiratory EAdi peak ($EAdi_{PEAK}$), the slope of the EAdi from the beginning of inspiration to the peak ($EAdi_{SLOPE}$) and the neural inspiratory time ($T_{i,NEUR}$) were measured from the EAdi waveform.

The inspiratory pressure generated by the diaphragm (trans-diaphragmatic pressure, P_{DI}) was calculated according to the method recently validated by Bellani and coworkers [7,18,21,31]. Briefly, we first calculated the diaphragmatic neuro-muscular efficiency (NME) as the ratio between the negative deflection peak in P_{AO} during a spontaneous inspiratory effort (recorded during a brief end-expiratory occlusion lasting 5-10 s) and the corresponding peak in the EAdi curve. The NME measures the diaphragmatic neuro-mechanical coupling, and can be used to convert the EAdi into P_{DI} ($P_{DI} = EAdi * NME$) [31] [32]. The inspiratory P_{DI} pressure-time product per breath (PTP_{DI}/b) was calculated as the area under the P_{DI} signal. The inspiratory P_{DI} pressure-time product per minute (PTP_{DI}/min) was calculated as:

$$PTP_{DI}/min = PTP_{DI}/b * RR.$$

The breathing pattern and EAdi- parameters, obtained from the RS232 port of the Servo i ventilator at a sampling rate of 100 Hz, were stored in a personal computer (NAVA tracker software, Maquet Critical Care, Solna, Sweden) for subsequent analysis (ICU Lab automatic analysis software, Kleistek Engineering; Bari, Italy).

Study protocol

Patients were admitted to the study within 24 hours after the shift in the PSV mode. At the beginning of the study, the PSV level was carefully titrated to obtain a VT between 5 and 8 ml/Kg predicted body weight (PBW) and a RR between 20 and 30 breaths/min [6,34,35]. The inspiratory trigger was set in the flow-by mode, sensitivity level 5 (Servo i arbitrary units); the expiratory trigger was set at 30 % of the peak inspiratory flow. Clinical PEEP and FiO₂ levels were left unchanged. Starting from the end of the PSV titration phase, patients were studied for 12 hours, from 8 a.m. to 8 pm.

Data analysis

In order to continuously assess the neuro-ventilatory drive throughout the 12 hours study period, the EAdi waveforms were analyzed through the automatic EAdi analysis software, a dedicated function of the ICU Lab software (Kleistek Engineering; Bari, Italy). This software identifies the EAdi peaks corresponding to each single breath and transfers the EAdi related data ($EAdi_{PEAK}$, $EAdi_{SLOPE}$, Ti_{NEUR}) in an excel sheet.

Since the breathing pattern parameters (VT, RR, PaO_{PEAK} , Ti_{MECH}) could not be examined continuously by the software, for each patient we analyzed manually the first 30 consecutive breaths available for each neuro-ventilatory drive class through the dedicated function of the Kleistek software.

Based on previous studies [7,25,28,29] and on the manufacturer instructions (Maquet Critical Care AB, NAVA flow chart MX-6462 Rev 02/2015), we pre-defined three neuro-ventilatory drive classes: “Low”, for breaths with $EAdi_{PEAK}$ below 5 mV; “Normal”, for breaths with $EAdi_{PEAK}$ between 5 and 15 mV and “High” for breaths with $EAdi_{PEAK}$ higher than 15 mV.

Patient-ventilator asynchronies were assessed by taking into account in the first 20 consecutive min, for each EAdi class, based on the method proposed by Thille and coworkers [36]. Asynchronies were classified into six types: a) ineffective triggering (missed effort); b) ineffective inspiratory triggering; c) double-triggering; d) auto-triggering; e) prolonged cycle; f) short cycle [36]. The Asynchrony Index (AI) was calculated as:

$AI = \text{Total number of asynchronies} / (\text{mechanical cycles} + \text{missed efforts}).$

Statistical analysis

We assessed the number the percentage of time spent in each of the three pre-defined $EAdi_{PEAK}$ classes (i.e. “Low”, “Normal” and “High”). Differences between percentages were analyzed through the chi-square test. In order to estimate the average time spent in each of the three EAdi classes, we applied the Generalized Estimated Equation (GEE) model [37]. In the GEE model the single breath is the first level unit, the time of each breath is the dependent variable, the class of EAdi is the independent variable and, finally, the patient is the second level unit. Pairwise comparisons between the estimate times spent in each of the three neuro-ventilatory drive classes were adjusted according to Tukey.

Normally distributed continuous data are expressed as means and standard deviation (SD) and non-normally distributed data are expressed as median and interquartile range (IQR). Normality of continuous data was tested through the Kolmogorov–Smirnov test. The ANOVA or the Friedman repeated measure analysis of variance was used as appropriate. Pairwise comparisons were adjusted according to Tukey.

A multivariable multinomial logistic model for ordinal variables and repeated measures was applied to evaluate the effect of Ti_{MECH} , Pao_{PEAK} , VT/PBW, RR and PS level on the probability of being in one of the three $EAdi_{PEAK}$ classes. All the statistical tests were two-tailed, and p -values of less than 0.05 were considered statistically significant. Statistical analysis was performed by software SAS 9.4 (SAS Institute, Cary NC).

Results

Of the 155 patients admitted in the study period, 31 were eligible to the study. Five of them declined to participate and 26 were enrolled. Ten were dropped out from the study: in 6 the ventilation mode was changed during the 12 h study period and in 4 the $EAdi$ trace was not reliable (Figure 1). The demographical and clinical characteristics of the 16 studied patients are shown in Table 1.

Taking all the patients as a whole, 177.117 breaths were collected throughout the study period. The neuro-ventilatory drive was “Low” in 50.116 breaths (28 %), “Normal” in 88.419 breaths (50 %) and “High” in 38.582 breaths (22 %) (chi-square = 45; $p = 0.0001$) (Figure 2). The GEE model showed a significant difference between the time spent in the three different $EAdi$ classes and estimated an average time of 1.37 hours for the “Low”, 3.67 hours for the “Normal” and 0,55 hours for the “High” class ($p < 0.0001$). The difference between the average time spent in the “Normal” and “High” class was statistically significant ($p = 0.019$). The intra-patient variability (\pm standard error) was 0.025 ± 0.104 , while the residual variability was 0.908 ± 0.192 . Accordingly, the intra-class correlation coefficient was low (2.7%) and not statistically significant, indicating that, among the patients, the time spent in each neuro-ventilatory drive class was heterogenous.

Figure 3 and 4 show, respectively, the individual trend of the neuro-ventilatory drive throughout the study and the percentage of study time in which each patient remained in the “Low”, “Normal” and “High” neuro-ventilatory drive class. Eleven patients remained in the “Low” neuro-ventilatory drive class for more than one hour, median 6.1 [3.9 - 8.5] hours. Six patients remained in the “High” neuro-ventilatory drive class for more than one hour, median 3.4 [2.2 - 7.8] hours.

Table 2 reports the breathing pattern, $EAdi$ and work of breathing parameters referred to the three neuro-ventilatory drive classes. Compared to the “Low” class, tidal volume was significantly higher in the “Normal” and “High” neuro-ventilatory drive class. Both PTP_{DI}/b and PTP_{DI}/min significantly increased going from the “Low” to the “High” class.

Table 3 shows the major patient-ventilator asynchronies in the three classes. The asynchrony index was significantly higher in the “Low” neuro-ventilatory class, mainly because of a higher number of missed efforts.

Figure 5 shows that, according to the multivariable multinomial logistic model, the risk of being in the “High” neuro-ventilatory drive class increased exponentially with VT (Panel A) and with RR (Panel B). The odds ratio of being in a neuro-ventilatory drive class different than “Normal” increased by 1.41 [CI

95%, 1.16 – 1.70], $p = 0.0019$, for each deviation of 1 ml/Kg PBW from the median VT (7.4 ml/Kg PBW) and by 1.1 [CI 95%, 1.0 – 1.24], $p = 0.0472$, for each deviation of 1 breath/min from the median RR (18.5 breaths/min). T_{inspMECH} , P_{aoPEAK} and the PSV level were not included in the model because not significant at the univariate analysis.

Discussion

By monitoring for 12 hours the EAdi in critically ill patients ventilated in the PSV mode, we observed unevenly distributed periods of “Low” and/or “High” neuro-ventilatory drive.

By amplifying the patient’s breathing effort, mechanical assistance should normalize the neuro-ventilatory drive when the respiratory muscles are challenged by an absolute or relative increase in workload [16,38,39]. However, the PSV algorithm leaves to the clinician the task of setting the level of assistance and, therefore, of estimating patient’s neuro-ventilatory drive [17,40,41]. Physiological observations during stepwise PSV titration suggest that excessive or insufficient assistance (over and under-assistance, respectively) are associated with peculiar breathing patterns. Briefly, low VTs (i.e. lower than 5 ml/Kg PBW) and high RRs (i.e. higher than 30 breaths/min) denote under-assistance, whereas high VTs (i.e. higher than 8 ml/Kg PBW) and low RRs (i.e. lower than 20 breaths/min) denote over-assistance [17,42,43]. In this study, according to these physiological observations and to a consolidated clinical protocol [6,34,44], we titrated PSV to a VT between 5 and 8 ml/PBW and a RR between 20 and 30 breaths/min. The fact that we found wide variations in neuro-ventilatory drive since the beginning of the study, challenges the “classical” approach to PSV setting (Figure 3). Despite our study was physiologically oriented and conducted in a small cohort of patients, we believe that these findings could be of clinical interest for studies aiming at more physiological protocols for setting the assistance level during PSV.

As reviewed elsewhere [8,11,26], the neuro-ventilatory drive originates from the respiratory centers, a network of interconnected neurons in the pons and medulla and is modulated by gas exchange, physical exercise, sleep, emotional and behavioral inputs, pain, discomfort, sedation and analgesia. In pathological conditions, air trapping, decreased lung and/or chest wall compliance, increased airway resistance and/or respiratory muscle weakness may alter the coupling between patient’s effort and diaphragmatic excursion (neuro-ventilatory coupling), increasing the neuro-ventilatory drive [16,45–47]. In our patients, we observed wide variations in neuro-ventilatory drive despite the sedation level was kept constant throughout the study period (i.e. RASS score between 0 and – 1) [33]. To explain these findings, one can hypothesize that our patients underwent to subclinical episodes of discomfort or pain, able to increase the neuro-ventilatory drive, or, on the contrary to excess of sedation or sleep able to decrease the neuro-ventilatory drive. Indeed, sleep rhythm and architecture are disrupted in critically ill patients [48–50]. These variations in neuro-ventilatory drive would have been “primary”, i.e. independent from the ventilatory assistance. Another possible hypothesis, however, is that the metabolic status and/or the mechanical workload posed on the respiratory muscles varied during the study and the PSV mode was not able to appropriately “satisfy” the changing patient’s requirements. In the latter case it would have

been appropriate to classify the “Low” and “High” neuro-ventilatory drive periods as over or under-assistance, respectively [38]. Unfortunately, our study design does not allow to outline if the neuro-ventilatory drive varied for a primary or a secondary mechanism and, accordingly, we are not able to classify as over or under-assistance the “Low” or “High” neuro-ventilatory drive episodes recorded in our patients.

It is worth remarking that during PSV the assistance level is fixed and it has been shown that the response to a sudden metabolic [51] or elastic load [16] is “not physiologically oriented” (i.e. rapid shallow breathing). At variance with PSV, during the neurally adjusted ventilatory assist mode (NAVA) the assistance is proportional to the EAdi [19,52], during the proportional assist ventilation *plus* mode (PAV) the assistance is proportional to the patient’s inspiratory effort [38,39,53] and during the adaptive support mode (ASV) the ventilator adapts the assistance according to a closed loop algorithm to optimize the WOB through the Otis Equation [54,55]. Thus, an attracting hypothesis is that the “proportional” modes or the ASV would stabilize more the neuro-ventilatory drive than PSV [28,56].

During PSV, a “Low” neuro-ventilatory drive puts the patients at risk of diaphragmatic atrophy and patient-ventilator asynchrony [10,57,58]. Interestingly, we found an asynchrony index of 20.6 ± 3.5 % during the “Low” neuro-ventilatory drive periods (Table 3), well above the 10 % threshold, that predicts prolonged weaning and ICU length of stay [36,59]. On the other hand, an “High” neuro-ventilatory drive may induce diaphragmatic dysfunction and patient self-inflicted lung injury [13,60–62]. Previous data from our group suggest that a prolonged PSV period (48 hours) does not improve diaphragmatic efficiency [7]. Based on the present data, we speculate that the concurrence of “Low” and “High” neuro-ventilatory drive periods could explain our previous findings.

Overall, our physiological data support the idea that the neuro-ventilatory drive should be continuously monitored during PSV in critically ill patients. The EAdi tool may represent a reasonable approach, since the EAdi is a “close” peripheral surrogate of the neuro-ventilatory drive, but there are several drawbacks that must hamper any over-enthusiasm. First, the relation between EAdi amplitude and breathing effort is not linear but depends from the neuro-ventilatory coupling [38]. For example, in case of diaphragmatic atrophy, the EAdi signal may be detectable in the absence of detectable pneumatic breathing efforts [63]. Second, the EAdi tool is commercially available in one ventilator only. Third, in several patients it is technically difficult or even impossible to obtain a reliable EAdi monitoring, even in experienced hands [7]. In the present study, we were not able to obtain a readable EAdi signal in 4 out of 26 patients (15.4 %), despite our groups are experienced in clinical EAdi monitoring (Figure 1). This suggests caution when trusting on the EAdi monitoring in the clinical context. According to the expert’s opinion, monitoring the breathing effort through esophageal manometry or estimating it through diaphragmatic echography could be an alternative [13,26,27,42]. However, it should be kept in mind that EAdi amplitude and breathing effort convey different information [25].

We must acknowledge the following study limitations. First: the $EAdi_{PEAK}$ thresholds applied in the present study to classify the neuro-ventilatory drive are empirical, although based on previous studies

[7,25,28,29] and on the manufacturer's instructions (Maquet Critical Care AB, NAVA flow chart MX-6462 Rev 02/2015). Indeed, the EAdi signal is burdened by interindividual variability [64]. Nevertheless, we identified a rather broad "Normal" EAdi_{PEAK} range similar to the one recently observed by Piquilloud and coworkers in healthy volunteers supported with different level of PSV [25] and by Liu and coworkers in patients [65]. Another important issue in favor of our approach is that in our patients the median PTP_{DI}/min (a parameter of work of breathing) was 110 [73-164] cmH₂O/s/min in the "Normal" EAdi class (Table 2), largely within the normal PTP_{DI}/min range identified by classical physiological studies, i.e. between 50 and 150 cmH₂O/s/min [66]. On the other hand, despite the absolute EAdi thresholds are debatable, our data clearly document a wide EAdi variability over time in otherwise clinically stable patients during PSV (Figure 3) and therefore, despite the absolute EAdi thresholds remain debatable, our study effectively quantified the neuro-ventilatory drive trend during PSV **Second:** an important issue to interpret our results is how the PSV level was set. As discussed above, our intent was to reproduce the "real life" in the clinical scenario [67–69]. However, we cannot exclude that different approaches to PSV setting would have a different impact on the neuro-ventilatory drive [28]. **Third:** ours was a physiologically oriented study and thus we have no data on the impact of the neuro-ventilatory drive patterns on diaphragmatic and pulmonary functions.

Conclusions

We observed wide variations in EAdi amplitude and unevenly distributed "Low" and "High" neuro ventilatory drive periods during 12 hours of PSV in critically ill patients. Further studies are needed to assess the possible clinical implications of these physiological findings.

Declarations

Ethics approval and consent to participate

This study was approved both by the ethics committee of the Azienda Ospedaliero-Universitaria Policlinico di Bari (protocol no. 257) and by the ethics committee of the Arcispedale Sant'Anna hospital, Ferrara, Italy (protocol no. 131084). All patient enrolled in this study or their next of kin signed an informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Available

Availability of supporting data

The study dataset used is available upon a justified request.

Competing interest

Salvatore Grasso in the past two years received fees for lectures and board membership from: Getinge Critical Care (Solna SW), Estor Critical Care (Pero, Milan Italy). The other authors declare that they have no competing interest.

Funding

This work was supported by the grant number GR-2013-023555391: “Diaphragmatic dysfunction in critically ill patients undergoing mechanical ventilation” from the Italian Ministry of Health (Bando Ricerca Finalizzata 2013).

Authors Contribution

RDM participated in the study design, carried out the measurements and data analysis and drafted the manuscript; **SS** participated in the study design, carried out the measurements and drafted the manuscript; **CAV** participated in the study design and revised the manuscript; **NB** performed the statistical analysis, helped to carry out the data analysis and helped to review the manuscript; **PT** performed the statistical analysis, helped to carry out the data analysis and helped to review the manuscript; **FS** participated in the study design, helped to review the manuscript and carried out the data analysis; **LP** participated in the data analysis and reviewed the manuscript; **RI** participated in the data analysis and reviewed the manuscript; **LD** participated in the study design and reviewed the manuscript; **FM** participated in the study design, carried out the measurements and data analysis and drafted the manuscript; **SG** conceived and coordinated the study, participated in designing and drafting the manuscript.

All the authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank all the nurses and caregivers for their active involvement in the management of patients during this study.

Abbreviations

PSV: pressure support ventilation

EAdi: electrical activity of the diaphragm

EAdi_{PEAK}: Peak EAdi

PTP_{DI}/b: pressure-time product of the P_{DI} per breath

PTP_{DI}/min: pressure-time product of the P_{DI} per minute

P-SILI: patient self-induced lung injury

RR: respiratory rate

VT: tidal volume

NAVA: neurally adjusted ventilatory assist

P_{AO} : pressure airway opening

$P_{AO\ PEAK}$: Peak airway opening pressure

PEEP: positive end-expiratory pressure

$T_{i,MECH}$: mechanical inspiratory time

$T_{e,MECH}$: mechanical expiratory time

$T_{i,NEUR}$: neural inspiratory time

NME: neuro-muscular efficiency

RASS: Richmond agitation sedation scale

PBW: predicted body weight

FiO_2 : oxygen inspiratory fraction

AI: Asynchrony Index

GEE: Generalized Estimated Equation

PAV: proportional assist ventilation

References

1. Putensen C, Hering R, Wrigge H. Controlled versus assisted mechanical ventilation. *Curr Opin Crit Care*. 2002;8:51–7.
2. Putensen C, Muders T, Varelmann D, Wrigge H. The impact of spontaneous breathing during mechanical ventilation. *Curr. Opin. Crit. Care*. 2006. p. 13–8.
3. Tobin MJ, Jubran A, Laghi F. Critical Care Perspective Patient – Ventilator Interaction. 2001;163:1059–63.
4. Esteban A, Ferguson ND, Meade MO, Frutos-Vivar F, Apezteguia C, Brochard L, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med*. 2008; 170_170-177.

5. MacIntyre NR. Respiratory function during pressure support ventilation. *Chest* [Internet]. The American College of Chest Physicians; 1986;89:677–83.
6. Brochard L, Pluskwa F, Lemaire F. Improved efficacy of spontaneous breathing with inspiratory pressure support. *Am Rev Respir Dis*. 1987; 136:411-5.
7. Di mussi R, Spadaro S, Mirabella L, Volta CA, Serio G, Staffieri F, et al. Impact of prolonged assisted ventilation on diaphragmatic efficiency: NAVA versus PSV. *Crit Care* [Internet]. *Critical Care*; 2016;20:1–12.
8. Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D. Respiratory drive in critically ill patients pathophysiology and clinical implications. *Am J Respir Crit Care Med*. 2020; 201(1):20-32.
9. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med*. 2011;183:364–71.
10. Hudson MB, Smuder AJ, Nelson WB, Bruells CS, Levine S, Powers SK. Both high level pressure support ventilation and controlled mechanical ventilation induce diaphragm dysfunction and atrophy. *Crit Care Med*. 2012; 40(4):1254-60
11. Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia is Baffling to Physicians. *Am J Respir Crit Care Med* [Internet]. 2020;0:1–20.
12. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am. J. Respir. Crit. Care Med*. 2017; 195(4):438-422.
13. Bertoni M, Spadaro S, Goligher EC. Monitoring Patient Respiratory Effort during Mechanical Ventilation: Lung and Diaphragm-Protective Ventilation. *Crit Care*. *Critical Care*; 2020;24.
14. Betensley AD, Khalid I, Rrt JC, Pensler RA, Digiovine B. Patient Comfort During Pressure Support and Volume Controlled-Continuous Mandatory Ventilation. 2008;C:897–902.
15. M. de Wit. Monitoring of Patient-Ventilator Interaction at the Bedside Marjolein de Wit MD MSc. 2011;61–72.
16. Grasso S, Puntillo F, Mascia L, Ancona G, Fiore T, Bruno F, et al. Compensation for increase in respiratory workload during mechanical ventilation: Pressure-support versus proportional-assist ventilation. *Am J Respir Crit Care Med*. 2000; 161:819-26
17. Macintyre NR, Leatherman NE. Ventilatory muscle loads and the frequency-tidal volume pattern during inspiratory pressure-assisted (pressure-supported) ventilation. *Am Rev Respir Dis*. 1990; 141:327-31
18. Stripoli T, Spadaro S, Di mussi R, Volta CA, Trerotoli P, De Carlo F, et al. High-flow oxygen therapy in tracheostomized patients at high risk of weaning failure. *Ann Intensive Care* [Internet]. Springer International Publishing; 2019;9.
19. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. *Nat. Med*. 1999. 5:1433-6.

20. Beck J, Sinderby C, Lindström L, Grassino A. Influence of bipolar esophageal electrode positioning on measurements of human crural diaphragm electromyogram. *J Appl Physiol*. 1996; 81:1434-49
21. Di mussi R, Spadaro S, Stripoli T, Volta CA, Trerotoli P, Pierucci P, et al. High-flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease. *Crit Care*. *Critical Care*; 2018;22:1–11.
22. Beck J, Sinderby C, Lindström L, Grassino A. Effects of lung volume on diaphragm EMG signal strength during voluntary contractions. *J Appl Physiol*. 1998; 85:1123-34.
23. Doorduyn J, Van Hees HWH, Van Der Hoeven JG, Heunks LMA. Monitoring of the respiratory muscles in the critically ill. *Am J Respir Crit Care Med*. 2013; 187:20-7
24. Rozé H, Lafrikh A, Perrier V, Germain A, Dewitte A, Gomez F, et al. Daily titration of neurally adjusted ventilatory assist using the diaphragm electrical activity. *Intensive Care Med*. 2011; 37:1087-94
25. Piquilloud L, Beloncle F, Richard JCM, Mancebo J, Mercat A, Brochard L. Information conveyed by electrical diaphragmatic activity during unstressed, stressed and assisted spontaneous breathing: a physiological study. *Ann Intensive Care* [Internet]. Springer International Publishing; 2019;9:1–14.
26. Spinelli E, Mauri T, Beitler JR, Pesenti A, Brodie D. Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions. *Intensive Care Med* [Internet]. Springer Berlin Heidelberg; 2020; 46(4):606-618.
27. Spadaro S, Marangoni E, Ragazzi R, Mojoli F, Verri M, Longo L, et al. A methodological approach for determination of maximal inspiratory pressure in patients undergoing invasive mechanical ventilation. *Minerva Anestesiol*. 2015; 81:33-8.
28. Beloncle F, Piquilloud L, Rittayamai N, Sinderby C, Rozé H, Brochard L. A diaphragmatic electrical activity-based optimization strategy during pressure support ventilation improves synchronization but does not impact work of breathing. *Crit Care* [Internet]. *Critical Care*; 2017;21:1–8.
29. Barwing J, Pedroni C, Olgemöller U, Quintel M, Moerer O. Electrical activity of the diaphragm (EAdi) as a monitoring parameter in difficult weaning from respirator: A pilot study. *Crit Care*. 2013;17.
30. Barwing J, Ambold M, Linden N, Quintel M, Moerer O. Evaluation of the catheter positioning for neurally adjusted ventilatory assist. *Intensive Care Med*. 2009; 35:1809-14
31. Bellani G, Mauri T, Coppadoro A, Grasselli G, Patroniti N, Spadaro S, et al. Estimation of patient's inspiratory effort from the electrical activity of the diaphragm. *Crit Care Med*. 2013;41:1483–91.
32. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Respir Dis*. 1982;126:788–91.
33. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal P V., Keane KA, et al. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002; 166:1338-44
34. Coisel Y, Chanques G, Jung B, Constantin JM, Capdevila X, Matecki S, et al. Neurally adjusted ventilatory assist in critically ill postoperative patients: A crossover randomized study. *Anesthesiology*. 2010;113:925–35.

35. Berger KI, Sorkin IB, Norman RG, Rapoport DM, Goldring RM. Mechanism of relief of tachypnea during pressure support ventilation. *Chest* [Internet]. The American College of Chest Physicians; 1996;109:1320–7.
36. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med.* 2006; 32:1515-22.
37. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika.* 1986;
38. Younes M. Proportional Assist Ventilation and Pressure Support Ventilation: Similarities and Differences. 1991.
39. Younes M. Proportional assist ventilation, a new approach to ventilatory support: Theory. *Am Rev Respir Dis.* 1992; 145:114-20.
40. Nava S, Bruschi C, Fracchia C, Braschi A, Rubini F. Patient-ventilator interaction and inspiratory effort during pressure support ventilation in patients with different pathologies. *Eur Respir J.* 1997; 10(1):177-83
41. Brochard L, Harf A, Lorino H, Lemaire F. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. *Am Rev Respir Dis.* 1989; 139:513-21
42. Spadaro S, Grasso S, Mauri T, Dalla Corte F, Alvisi V, Ragazzi R, et al. Can diaphragmatic ultrasonography performed during the T-tube trial predict weaning failure? The role of diaphragmatic rapid shallow breathing index. *Crit Care.* 2016; 28;20:305.
43. Berger KI, Sorkin IB, Norman RG, Rapoport DM, Goldring RM. Mechanism of relief of tachypnea during pressure support ventilation. *Chest.* 1996; 109:1320-7.
44. Yonis H, Crognier L, Conil JM, Serres I, Rouget A, Virtos M, et al. Patient-ventilator synchrony in Neurally Adjusted Ventilatory Assist (NAVA) and Pressure Support Ventilation (PSV): A prospective observational study. *BMC Anesthesiol* [Internet]. *BMC Anesthesiology*; 2015;15:1–9.
45. Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte F Della, Navalesi P. Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. *Intensive Care Med.* 2008; 34:2010-8.
46. Younes M, Riddle W. Relation between respiratory neural output and tidal volume. *J Appl Physiol Respir Environ Exerc Physiol.* 1984;56:1110-9.
47. Younes M. Load responses, dyspnea, and respiratory failure. *Chest.* 1990.
48. Alexopoulou C, Kondili E, Plataki M, Georgopoulos D. Patient-ventilator synchrony and sleep quality with proportional assist and pressure support ventilation. *Intensive Care Med.* 2013; 39:1040-7
49. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest.* 2000; 117:809-18
50. Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. *Intensive Care Med.* 2004. 30(2):197-206.
51. Ranieri VM, Giuliani R, Mascia L, Grasso S, Petruzzelli V, Puntillo N, et al. Patient-ventilator interaction during acute hypercapnia: Pressure- support vs. proportional-assist ventilation. *J Appl Physiol.* 1996; 81(1):426-36

52. Terzi N, Piquilloud L, Rozé H, Mercat A, Lofaso F, Delisle S, et al. Clinical review: Update on neurally adjusted ventilatory assist—report of a round-table conference. *Crit. Care.* 2012. 20;16(3):225.
53. Younes M, Puddy A, Roberts D, Light RB, Quesada A, Taylor K, et al. Proportional assist ventilation: Results of an initial clinical trial. *Am Rev Respir Dis.* 1992. 145:121-9
54. Iotti GA, Polito A, Belliato M, Pasero D, Beduneau G, Wysocki M, et al. Adaptive support ventilation versus conventional ventilation for total ventilatory support in acute respiratory failure. *Intensive Care Med.* 2010;
55. Arnal JM, Wysocki M, Nafati C, Donati S, Granier I, Corno G, et al. Automatic selection of breathing pattern using adaptive support ventilation. *Intensive Care Med.* 2008;
56. Chen C, Wen T, Liao W. Neurally adjusted ventilatory assist versus pressure support ventilation in patient-ventilator interaction and clinical outcomes: a meta-analysis of clinical trials. *Ann Transl Med.* 2019; 17(16):382
57. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med.* 2008; 358:1327-35
58. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med.* 2011; 183:364-71
59. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med.* 2015; 41:633-41.
60. Petrof BJ, Jaber S, Matecki S. Ventilator-induced diaphragmatic dysfunction. *Curr. Opin. Crit. Care.* 2010;16(1):19-25.
61. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of diaphragm thickness during mechanical ventilation: Impact of inspiratory effort. *Am J Respir Crit Care Med.* 2015; 192(9):1080-8.
62. Yoshida T, Fujino Y, Amato MBP, Kavanagh BP. Fifty years of research in ARDS spontaneous breathing during mechanical ventilation risks, mechanisms, and management. *Am. J. Respir. Crit. Care Med.* 2017;195:985-922
63. Mortamet G, Proulx F, Crulli B, Savy N, Jouvret P, Emeriaud G. Diaphragm electrical activity monitoring as a breakpoint in the management of a tetraplegic child. *Crit. Care.* 2017;26;21:116.
64. Goligher EC, Dres M, Patel BK, Sahetya SK, Beitler JR, Telias I, et al. Lung and Diaphragm-Protective Ventilation. *Am J Respir Crit Care Med.* 2020;1–43.
65. Liu L, Liu H, Yang Y, Huang Y, Liu S, Beck J, et al. Neuroventilatory efficiency and extubation readiness in critically ill patients. *Crit Care.* 2012; 31;16:R143
66. Sassooun CSH, Light RW, Lodia R, Sieck GC, Mahutte CK. Pressure-time product during continuous positive airway pressure, pressure support ventilation, and T-piece during weaning from mechanical ventilation. *Am Rev Respir Dis.* 1991;

67. Yoshida T, Roldan R, Beraldo MA, Torsani V, Gomes S, De Santis RR, et al. Spontaneous effort during mechanical ventilation: Maximal injury with less positive end-expiratory pressure. *Crit Care Med*. 2016; 44:e678-88.
68. Lindqvist J, Van Den Berg M, Van Der Pijl R, Hooijman PE, Beishuizen A, Elshof J, et al. Positive end-expiratory pressure ventilation induces longitudinal atrophy in diaphragm fibers. *Am J Respir Crit Care Med*. 2018; 198(4):472-485.
69. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, et al. Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med*. 2016;42:1360-73.

Table 3

Pt #	Age	Sex	PBW (Kg)	SAPS II	Causes of ARF	MV (Days)	PSV level (cmH2O)	PEEP (cmH2O)	FiO2 %	RASS	NME (cmH2O/ μ V)	ICU Outcome
1	70	M	70	63	Septic shock	10	8	13	40	0	0,62	Alive
2	70	M	67	35	Acute post-operative respiratory failure	11	10	7	40	-1	1,66	Alive
3	71	M	66	39	Trauma	13	8	8	50	0	1,58	Dead
4	71	M	53	39	Septic shock	2	10	6	50	0	1,92	Alive
5	69	F	60	49	Thoracic Injury	2	13	7	40	0	1,76	Dead
6	70	M	68	31	Hemorrhagic stroke	8	10	8	40	-1	2,41	Alive
7	85	M	71	40	Drowning	5	13	7	35	-1	1,01	Dead
8	75	F	53	43	Septic shock	7	8	5	40	-1	0,9	Alive
9	59	M	57	27	Hemorrhagic shock	12	9	10	30	-1	1,74	Alive
10	61	M	53	33	Septic shock	11	9	10	50	-1	3,2	Alive
11	78	M	79	46	COPD exacerbation	5	14	5	50	0	3,45	Alive
12	84	M	67	30	Community acquired pneumonia	4	10	5	40	0	1,89	Alive
13	49	M	64	36	Septic shock	11	11	10	30	-1	2,52	Alive
14	73	F	48	38	Acute post-operative respiratory failure	8	10	5	40	0	3,77	Alive
15	80	M	66	40	COPD exacerbation	11	9	8	50	-1	0,98	Dead
16	70	M	70	45	Septic shock	7	18	10	50	0	2,05	Alive

Mean 70.18 63.25 39.12 7.9 10.65 7.76 43.24 -0.5 1,96

SD 9.38 8,4 8.64 3.5 2.60 2.28 8.09 0.52 0,9

TABLE 1: baseline demographic and clinical characteristics of the patients.

Abbreviations: PBW = predicted body weight; SAPS II =Simplified Acute Physiology score II. The score can range from 0 to 163, with higher scores indicating a higher probability of death; ARF = acute respiratory failure; MV: mechanical ventilation; PSV level = Pressure Support Ventilation level; PEEP = positive end-expiratory pressure; FiO₂ = inspiratory oxygen fraction; RASS= Richmond Agitation Sedation Scale; ICU = intensive care unit; COPD = chronic obstructive pulmonary disease.

TABLE 2: physiological parameters, referred to the three EAdi-defined neuro-ventilatory drive classes

	“Low” Class (EAdi _{PEAK} < 5 μV)	“Normal” Class (EAdi _{PEAK} 5 - 15 μV)	“High” Class (EAdi _{PEAK} > 15 μV)
VT/PBW (ml/Kg)	7.2 [6.2-8.3]	7.5 [6.3-9.2] *	8.8 [6.9-9.5] *
RR (breaths/min)	19.7 [15.0-28.9]	19.1 [15.8-22.7] *	15.6 [14.8-21.7] **
PEEP (cmH₂O)	6.2 [5.2-9.9]	7.2 [5.9-8.0]	7.8 [6.7-12.1]
Pao_{PEAK} (cmH₂O)	17.5 [14.4-20.9]	18.0 [16.8-18.7]	19.3 [18.0-20.0] **
Ti_{MECH} (s)	0.97 [0.76-1.18]	1.02 [0.86-1.17]	1.01 [0.80-1.14] **
Ti_{NEUR} (s)	1.05 [0.81-1.27]	1.17 [0.93-1.41]	1.13 [0.83-1.38] **
EAdi_{PEAK} (μV)	3.2 [2.1-4.1]	8.0 [6.5-10.1]	19.9 [17.2-28.5] **
EAdi_{SLOPE} (μV/s)	2.6 [1.9-3.7]	6.4 [5.1-9.3] *	21.1 [14.7-27.8] **
PTP_{DI}/b (cmH₂O/s)	2.2 [1.4-3.4]	6.6 [3.8-9.3] *	12.4 [8.0-17.3] **
PTP_{DI}/min (cmH₂O/s/min)	46 [29-76]	110 [73-164] *	213 [160-309] **

Data expressed as median and Interquartile Range [IQR]

Abbreviations: EAdi = diaphragmatic electrical activity; VT = tidal volume; PBW = predicted body weight; RR = respiratory rate; PEEP = positive end expiratory pressure; Pao_{PEAK} = peak airway opening pressure; Ti_{MECH} = mechanical inspiratory time; Ti_{NEUR} = neural inspiratory time; EAdi_{PEAK} = peak diaphragmatic electrical activity; EAdi_{SLOPE} = slope from the beginning of inspiration to EAdi_{PEAK}; PTP_{DI}/b = inspiratory pressure-time product of the diaphragm, per breath; PTP_{DI}/min = inspiratory pressure-time product of the diaphragm, per minute

*) p < 0.05 compared to the “Low” EAdi Class

#) p < 0.05 compared to the “Normal” EAdi Class

Due to technical limitations Table 3 is available as a download in the Supplementary Files.

Figures

Figure 1

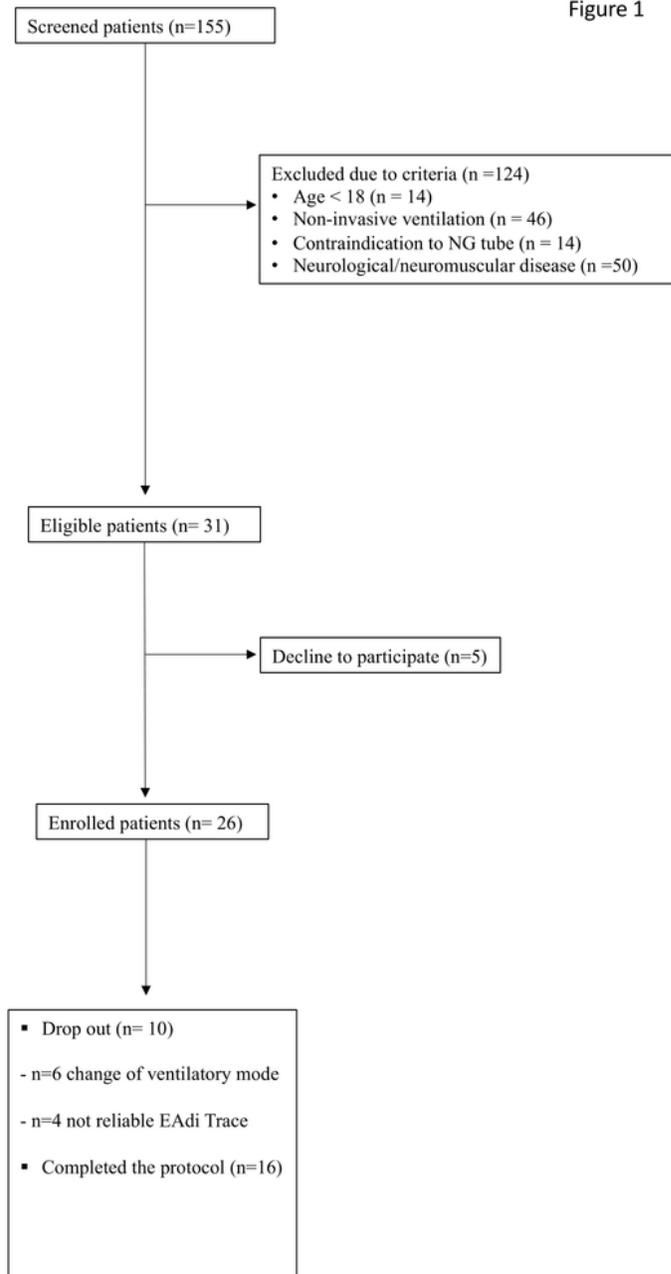


Figure 1

flow diagram of patient's enrollment. Abbreviations: NG = naso-gastric. EAdi = electric diaphragmatic activity.

Figure 2

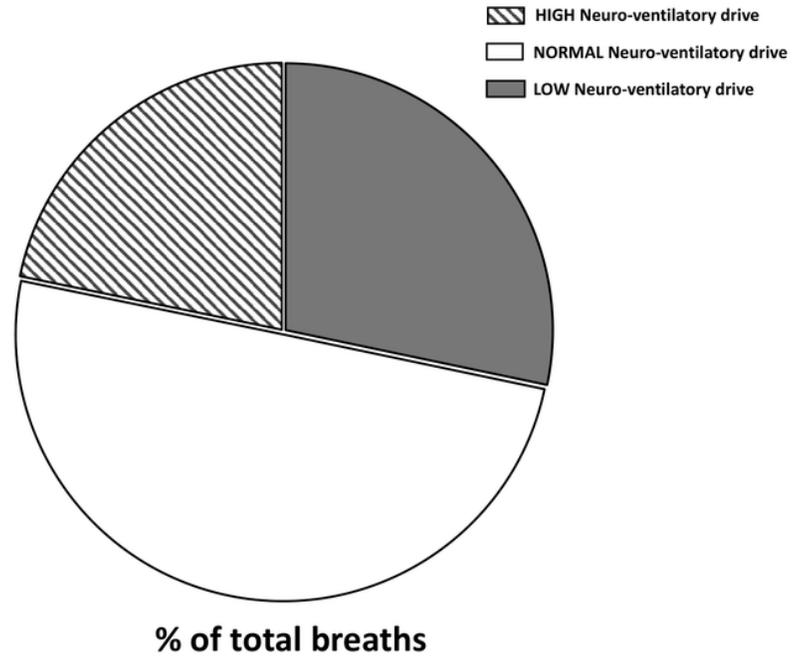


Figure 2

percentage of the collected breaths (including all the patients and the whole study period) belonging to the “Low” (28 %), “Normal” (50 %) and “High” (22 %) neuro-ventilatory drive class (chi-square = 45; p = 0.0001).

Figure 3

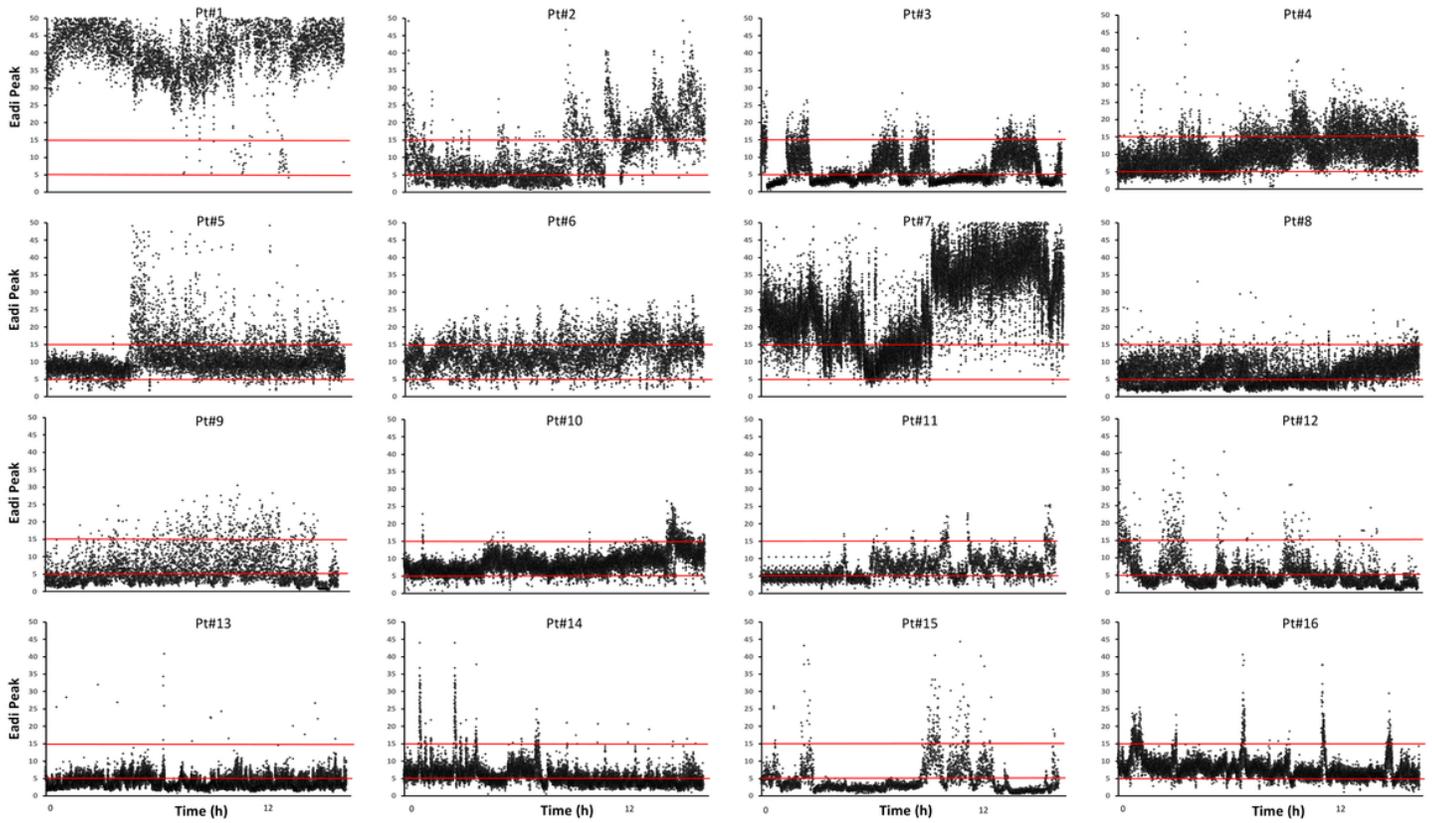


Figure 3

individual neuro-ventilatory drive trend throughout the study. Each point represents the electric diaphragmatic activity peak (EAdiPEAK) of a single breath. The two red lines represent the 5 - 15 μ V EAdiPEAK range depicting the “Normal” neuro-ventilatory drive.

Figure 4

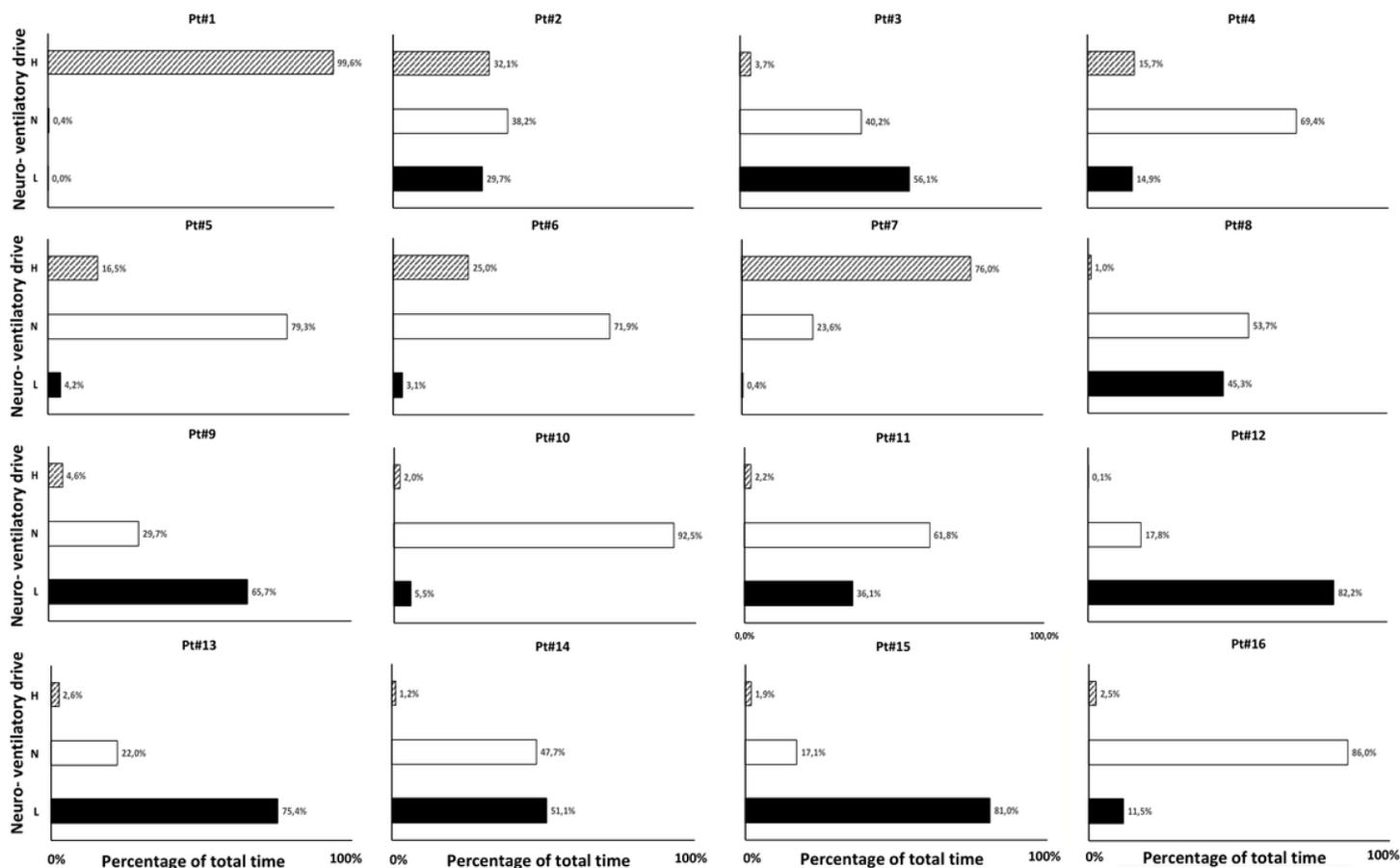


Figure 4

individual percentage of study time in which each patient remained in the “Low”, “Normal” and “High” neuro-ventilatory drive class. Eleven patients remained in the “Low” neuro-ventilatory drive class for more than one hour, median 6.1 [3.9 - 8.5] hours. Six patients remained in the “High” neuro-ventilatory drive class for more than one hour, median 3.4 [2.2 – 7.8] hours.

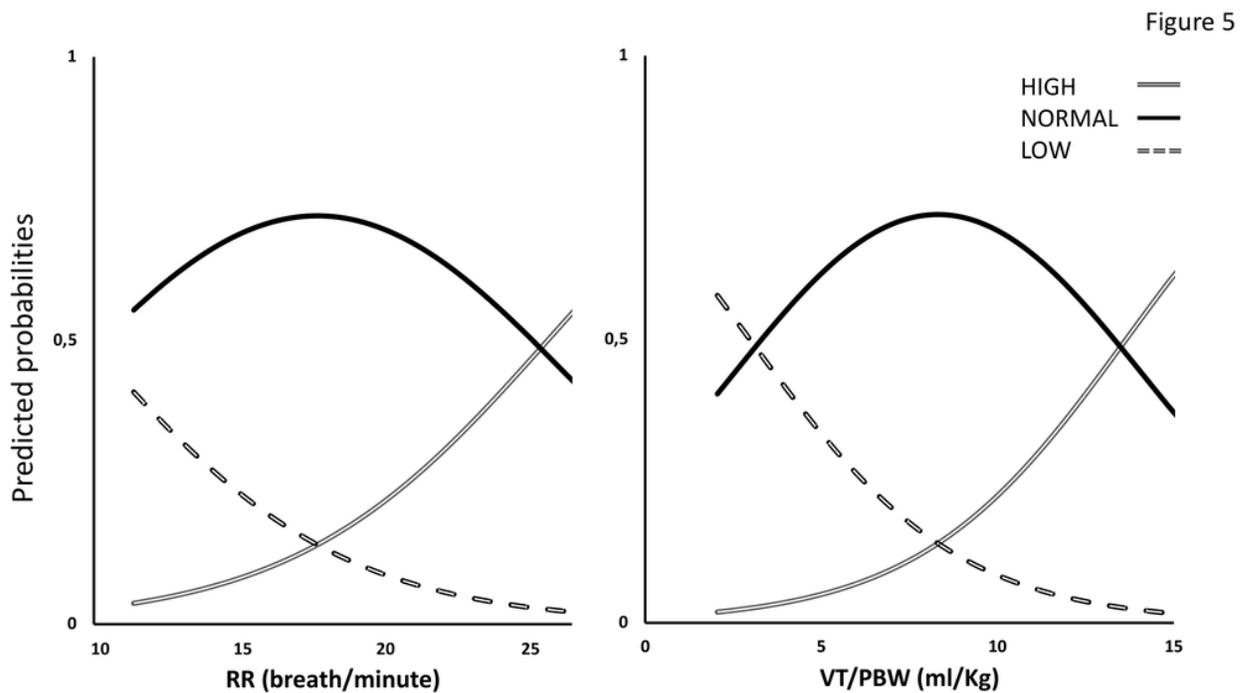


Figure 5

according to the multivariable multinomial logistic model, the risk of being in the “High” neuro-ventilatory drive class increased exponentially with respiratory rate (RR, Left Panel) and tidal volume/predicted body weight (VT/PBW, Right Panel).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TABLE3.pdf](#)