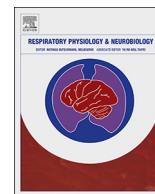




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Inspiratory effort and breathing pattern change in response to varying the assist level: A physiological study



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ABSTRACT

Aim: To describe the response of breathing pattern and inspiratory effort upon changes in assist level and to assess if changes in respiratory rate may indicate changes in respiratory muscle effort.

Methods: Prospective study of 82 patients ventilated on proportional assist ventilation (PAV+). At three levels of assist (20%–50%–80%), patients' inspiratory effort and breathing pattern were evaluated using a validated prototype monitor.

Results: Independent of the assist level, a wide range of respiratory rates (16–35br/min) was observed when patients' effort was within the accepted range. Changing the assist level resulted in paired changes in inspiratory effort and rate of the same tendency (increase or decrease) in all but four patients. Increasing the level in assist resulted in a 31% (8–44%) decrease in inspiratory effort and a 10% (0–18%) decrease in respiratory rate. The change in respiratory rate upon the change in assist correlated modestly with the change in the effort ($R = 0.5$).

Conclusion: Changing assist level results in changes in both respiratory rate and effort in the same direction, with change in effort being greater than that of respiratory rate. Yet, neither the magnitude of respiratory rate change nor the resulting absolute value may reliably predict the level of effort after a change in assist.

1. Introduction

Assisted mechanical ventilation aims to assure adequate ventilation by assisting and partially unloading the respiratory muscles (Pierson, 2002). Ideally, the level of assist should not only result in normal or near-normal arterial blood gases but also to normal or near-normal levels of inspiratory effort, to prevent both over- and under-assistance induced injury of the diaphragm (Schepens et al., 2019; Schepens and Goligher, 2019). Setting the level of ventilator assist in everyday practice relies mostly on the clinical estimation of inspiratory effort, as indicated by the breathing pattern -tidal volume (VT) and respiratory rate (RR)- and clinical signs of respiratory distress (Boles et al., 2007; Hansen-Flaschen, 2000; Hess, 2001; Ray et al., 2006). However, the relationship between ventilatory assist and inspiratory effort, tidal volume, and respiratory rate is complicated and multifactorial, affected by the patient's respiratory drive, ability to generate alveolar ventilation, and the mode of support (Vaporidi et al., 2020). Therefore, although tidal volume and respiratory rate are commonly used in everyday practice to titrate the level of assist, the scientific evidence guiding assist titration to the patient effort is limited, derived from studies with

a relatively small number of patients (Berger et al., 1996; Carteaux et al., 2016; Giannouli et al., 1999; Marantz et al., 1996) and do not consider the random/normal variability in breathing pattern, unrelated to the level of assist.

The aim of this study was to 1) characterize the responses of respiratory drive, respiratory effort, and breathing pattern to changing levels of ventilatory assist in critically ill patients and 2) assess if changes in respiratory rate may indicate changes in respiratory drive and effort. To this end, during proportional assist ventilation with adjustable gain factors (PAV+), noninvasive measurements of respiratory drive, effort (as indicated by inspiratory muscle pressure) were obtained at different levels of assist, using a validated prototype monitor (PVI) (Kondili et al., 2010; Younes et al., 2007). Contrary to conventional modes of assisted mechanical ventilation, PAV+ permits the patients to select their desired breathing pattern as determined by feedback mechanisms of control of breathing (Younes, 1992).

2. Methods

This study was conducted in the medical-surgical ICU of the

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University Hospital of Heraklion between January 2011 and July 2012 after approval by the Hospital Ethics Committee (11118). Since the study protocol does not involve a therapeutic intervention and clinical or diagnostic interventions, it was considered as carrying no more than minimal risks, and informed consent was waived. Patients were included in the study after at least 48 h of mechanical ventilation, when they fulfilled standard criteria for initiation of weaning from controlled mechanical ventilation (hemodynamic stability, reversal of cause of respiratory failure). Exclusion criteria were: age under 18 years, pregnancy, severe muscle weakness or cervical spine injury, uncontrolled pain, fever, or delirium, readiness for spontaneous breathing trial, and when PVI monitor was unavailable. The study was interrupted if the patient could not trigger the ventilator, developed respiratory distress, or became for any reason unstable (increase in vasopressor requirements, deterioration of oxygenation, etc.).

2.1. Study protocol

At the time of the study, all patients were ventilated on assisted modes (pressure support or PAV+). All patients were studied on PAV+ at three different levels of assist 20 %, 50 %, and 80 % at the PEEP set by the treating physician. Each level of assist, applied randomly, was maintained for 10 min. Moreover, recordings were obtained for 10 min at the mode selected by the treating physician (PS or PAV+) before and immediately after PAV+. Arterial blood gases were obtained during the last minute of low (20 %) and high (80 %) level of assist.

2.2. Measurements

The pressure generated by the inspiratory muscles per breath (P_{mus}) was evaluated as an index of effort and calculated on a breath-by-breath basis by a research prototype monitor (PVI Monitor, YRT Limited, Winnipeg, Canada) using a method described in detail previously. Briefly, the inputs required by the monitor to calculate P_{mus} are the airway pressure (P_{aw}) and flow (V'), whereas volume (V) was obtained by V' integration. At least two points during expiration that satisfied passive conditions (i.e., flow was driven by the elastic recoil pressure) were automatically identified by the monitor. At these points, the equation of motion was applied, and elastance (E_{rsPVI}) and resistance (R_{rsPVI}) of the respiratory system were calculated. Using these values and the equation of motion, P_{mus} was calculated in each breath. Further fine-tuning of E_{rsPVI} and R_{rsPVI} was performed to eliminate artifacts derived from the P_{mus} waveform. PVI monitor connected in line with the ventilator circuit has been validated to provide non-invasively measurement of P_{mus} , as well as of tidal volume and respiratory rate in breath by breath basis (Kondili et al., 2010; Younes et al., 2007).

Patient mechanical inspiratory time (T_i) was measured as the interval between the beginning of P_{mus} increase and the point at which P_{mus} started to decline rapidly. Patient mechanical expiratory time was measured as the remainder of the respiratory cycle. The rate of rise of P_{mus} (dp/dt_i) was calculated as the change in P_{mus} during inspiration divided by T_i and was used as an index of respiratory drive. The level of PEEPi during the different levels of assist was measured as the positive deflection of P_{mus} from the onset of mechanical inspiration to the point of zero flow.

Additionally, the following data were collected: severity score on admission, etiology of respiratory failure, days on mechanical ventilation, ICU, and hospital length of stay and outcome.

2.3. Data and statistical analysis

The output of PVI monitor data was processed before analysis to optimize data quality (e.g., artifact rejection). From each 10-min period, the 7th to 10th min of the recording was selected for analysis. In each patient, for each variable and a given level of assist, the

Table 1
Patients characteristics.

Demographics	Male n (%)	49 (57)
	Age (mean, SD)	63 ± 17
	APACHE-II on admission (mean, SD)	20 ± 8
Comorbidities n (%)	COPD	27 (32)
	Heart Failure	25 (29)
Admission Diagnosis	Acute respiratory failure	31 (36)
	Sepsis/ septic shock	20 (23)
	Brain Injury	17 (20)
	Post-arrest	7 (8)
	Trauma	6 (7)
Characteristics at inclusion	Days on MV	8.6 ± 6.5
	Tracheostomy	47 (55)
	PaO ₂ /FiO ₂ (mean ± SD)	230.5 ± 71.5
ICU outcome	ICU stay (days)	20 ± 13
	ICU mortality	24 %

APACHE: Acute physiology and chronic health evaluation, COPD: Chronic obstructive pulmonary disease, MV: Mechanical ventilation, PaO₂/FiO₂: the ratio of arterial to inspired oxygen fraction.

distribution of values was evaluated. Means and SD were calculated after examining for normal distribution. The calculated means in each variable were used for comparisons among patients. Between groups of patients or levels of assist, differences in continuous variables were compared using paired-samples *t*-test or repeated-measures analysis of variance and post-hoc comparisons with Tukey's test. Pearson's test was used to examine the correlation between continuous variables.

As determined by the study design, at the end of the study period (30 min), patients were placed again on the same ventilator settings used by the treating physician. Thus, in each patient, recordings were available with the same ventilator settings at approximately 30 min apart, while the patient's condition was considered stable (pre- and post-study). An analysis of ventilation variables in the pre- and post-study recordings was used to determine the variability (range of difference) of each variable in the 'stable' critically ill patient. We used IBM SPSS Statistics for Windows version 25 (Armonk, NY) for analysis.

3. Results

During 18 months, 82 critically ill patients were included in the study. The patients' characteristics are presented in Table 1. Patients were studied on the 8 ± 6 day of mechanical ventilation; the baseline measurements from the ventilator and the PVI monitor are presented in Table 2. In the analysis of single patient data (3-min breath by breath analysis), and for all PVI variables, a normal distribution was found in more than 90 % of cases, and thus, the mean values were used for comparison among patients. Results were qualitatively similar when median values were used (data not shown).

Table 2
PVI measurements at baseline (pre-study) and after the end of the study in the same mode (post-study).

	Pre-study	Post-study	Pre-post study change [5–95 range]
VT (ml/kg)	6.7 ± 1.7	6.7 ± 1.7	0 [-0.9–0.9]
RR (br/min)	27 ± 6	27 ± 6	0 [-6–6]
P_{mus} peak (cmH ₂ O)	15 ± 10	15 ± 8	0 [-3–6]
Elastance _{PVI} (cmH ₂ O/L)	26 ± 13	25 ± 13	0 [-5–7]
Resistance _{PVI} (cm ₂ O/L/sec)	11 ± 6	12 ± 7	0 [-5–3]
PEEPi (cmH ₂ O)	2 ± 1	2 ± 1	0 [-2–2]

VT: Tidal volume, RR: Respiratory rate, P_{mus} peak: Inspiratory muscle pressure calculated by PVI, PEEPi: Intrinsic positive end-expiratory pressure. A Paired-samples *t*-test was used to evaluate differences between the two conditions.

3.1. Breathing pattern during the pre- and post-study period

Ventilatory variables in the pre- and post-study period were not different (Table 2). This was true when the two ventilation modes (PS, PAV+) were examined independently (data not shown). Arterial blood gases were also not different before and after the study. The variability in tidal volume and respiratory rate, indicated by the coefficient of variation (Tobin et al., 1988), was 9% and 13 %, respectively. The 5–95 range of change in each variable was calculated as an indicator of the variability in breathing pattern that can be expected in a relatively stable critically ill patient when ventilation settings have not been modified (Table 2).

3.2. Respiratory drive, effort, and breathing patterns

We subsequently analyzed, independently of the level of assist, the correlation between indices of respiratory drive (dP/dt), effort (Pmus_{peak}), and breathing pattern (tidal volume - VT and respiratory rate - RR). A very strong linear correlation was observed between respiratory drive and Pmus_{peak} at each level of assist ($r = 0.9$). Respiratory drive correlated weakly with respiratory rate ($r = 0.4$), but not with tidal volume. When respiratory drive and Pmus_{peak} were within the accepted 'target' range for mechanically ventilated patients (Schepens and Goligher, 2019), a broad range of respiratory rate (R_{5-95} : 16–35 br/min) was observed (Fig. 1).

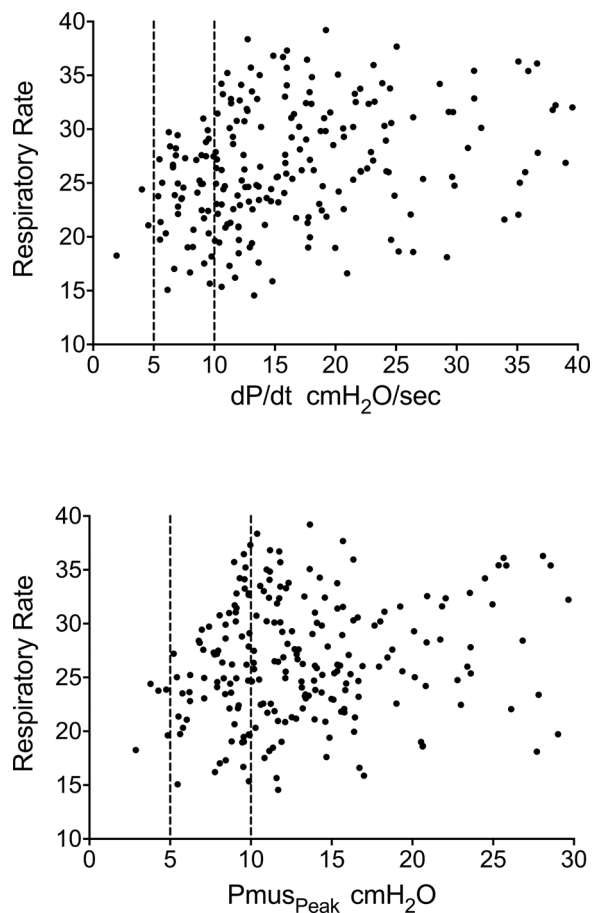


Fig. 1. Respiratory rate (RR) vs. respiratory drive and effort indicated by dP/dt and Pmus_{peak}, respectively, irrespective of assist level. Vertical dotted lines indicate the target range for each value for critically ill mechanically ventilated patients.

Table 3

Ventilation variables at the three different levels of assist.

Variable	PAV + Assist Level		
	20 %	50 %	80 %
VT (ml/kg)	7 ± 2	7 ± 2	8 ± 2 ^{##}
RR br/min	28 ± 6 ^{**}	27 ± 6 [^]	26 ± 6 ^{###}
Pmus _{PVI} (cmH ₂ O)	17 ± 8 ^{***}	15 ± 10 [^]	14 ± 10 ^{###}
dP/dt (cmH ₂ O/sec)	20 ± 13 ^{***}	18 ± 15 [^]	16 ± 9 ^{###}
Elastance _{PVI} (cmH ₂ O/L)	22 ± 11 [*]	23 ± 12 [^]	26 ± 16 ^{###}
Resistance _{PVI} (cm ₂ O/L/sec)	10 ± 7	10 ± 7	11 ± 8 ^{##}
PEEPi (cmH ₂ O)	2 ± 2	2 ± 2	2 ± 2

Values represent means ± SD and differences were calculated using repeated-measures analysis of variance with Tukey post test. P-values: * < 0.05, ** < 0.01, *** < 0.001 for PAV20 % vs. PAV50 %; ^ < 0.05, ^^ < 0.01, ^^ < 0.001 for PAV50 % vs. PAV80 %; ## < 0.01, ### < 0.001 for PAV20 % vs. PAV80 %. PAV: Proportional assist ventilation, VT: Tidal volume, RR: Respiratory rate, Pmus_{PVI} Inspiratory muscle effort calculated by PVI, dP/dt Respiratory drive estimated using the Pmus_{PVI} to neural inspiratory time ratio.

3.3. Changes in respiratory drive, effort and breathing pattern in response to the change in assist

Finally, we examined the patterns of change of respiratory drive, Pmus_{peak}, RR, and VT in response to changes in the level of assist. With increasing assist, small but statistically significant changes were observed in all variables (Table 3). The change in effort, in response to change in assist, was greater than the change in respiratory rate (Fig. 2). Respiratory drive decreased as assist increased, and this change correlated strongly with the change in the effort ($R = 0.8$), but moderately with the change in respiratory rate ($R = 0.5$), and not with the change in tidal volume. The patterns of response to assist increase were characterized by a concomitant increase in tidal volume and decrease in respiratory rate, yet, these changes were mostly within the expected range of variation, and not specific for the change in effort (Fig. 3). Moreover, increasing assist resulted in most patients (67 %) in the decrease of both effort and rate (Fig. 4). A significant change in respiratory rate, opposite to that of effort, was observed only in four patients (5%). The sensitivity and specificity of a decrease in respiratory rate to predict a decrease in effort was 88 % and 71 %, respectively, with a positive predictive value of 90 %. Yet, the change in respiratory rate correlated only modestly with the change in effort ($R = 0.5$) and the resulting inspiratory effort at high assist ($R = 0.4$, Fig. 4). In some patients ($n = 16$, 20 %), effort did not decrease with increasing assist. The development of intrinsic PEEP due to increase in tidal volume (12 cases) and the presence of high respiratory drive due to metabolic acidosis (7 cases) were the most common causes of this phenomenon.

4. Discussion

This study in critically ill patients in the post-acute phase examined the changes in breathing pattern, respiratory drive and effort and their correlations, induced by changes of the level of assist. Patients were studied using PAV+, a mode that permits patients to choose their breathing pattern and monitored with PVI, a prototype monitor validated to estimate inspiratory muscle pressure (Kondili et al., 2010; Younes, 1992; Younes et al., 2007). The main findings of the study are: 1) patients respond to changes in ventilatory assist mainly by changing effort per breath; 2) when respiratory drive and/or effort are normal, a wide range of respiratory rate is observed; 3) although respiratory rate changes towards the same direction as effort, neither the magnitude of change, nor the resulting value of respiratory rate are related to the level of effort, suggesting the limited role of respiratory rate in titrating assist to a target level of effort.

In this study the correlation of indices of respiratory drive (dP/dt) and effort (Pmus) was, as expected, very strong (de Vries et al., 2018;

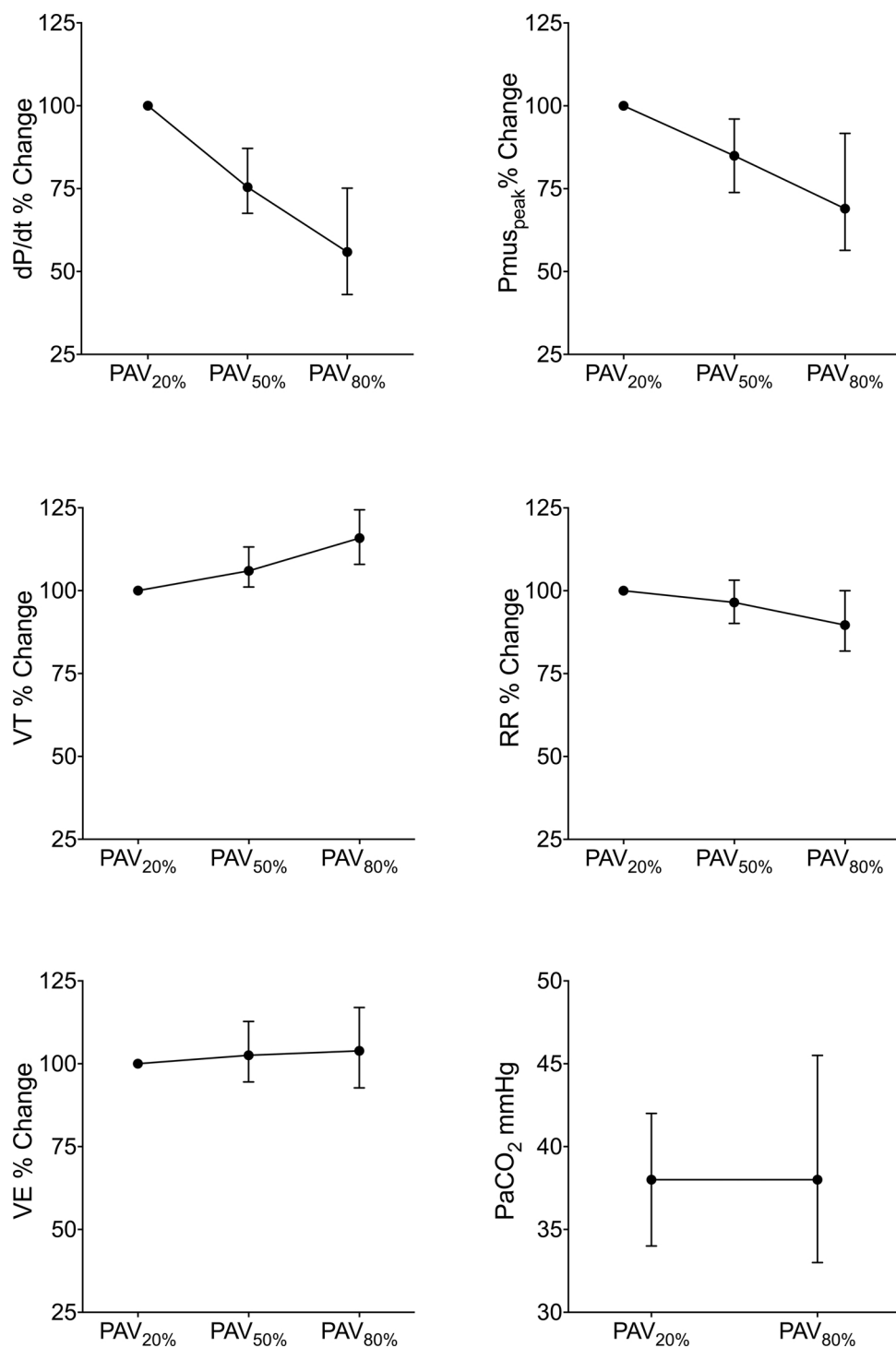


Fig. 2. Change in respiratory drive (dP/dt), effort (P_{mus}_{peak}), tidal volume (VT), respiratory rate (RR), minute ventilation (VE), and PaCO₂, induced by a change in assist from PAV20 % to PAV50 % and PAV80 %, expressed as a percent of the value at PAV20 % for all ventilation variables, and in mmHg for PaCO₂.

Mauri et al., 2016; Vaporidi et al., 2020). Respiratory rate correlated weakly with respiratory drive, and most importantly, a wide range of breathing frequencies was observed in patients with relatively normal respiratory drive and effort. Tachypnea was present in several patients with normal respiratory drive and P_{mus}, and, although no patient exhibited hypoxemia, hyperactive delirium or fever at the time of the study, other causes of tachypnea, such as systemic inflammation, receptor stimulation or cortical stimulation could not be excluded (Telias et al., 2018; Vaporidi et al., 2020). In addition, in our study, respiratory drive was estimated using the rate of increase of P_{mus}, which in the

presence of neuromuscular weakness underestimates the actual respiratory drive (the rate of increase of electrical activity of the respiratory center output). Therefore, at the presence of neuromuscular weakness, respiratory center activity during inspiration may be high causing an increase in respiratory rate despite normal inspiratory pressure during inspiration. This observation is in line with several studies showing a higher than normal respiratory rate in critically ill patients (Akoumianaki et al., 2019; Giannouli et al., 1999; Marantz et al., 1996). Moreover, a low respiratory rate was not uncommon, despite a high respiratory drive and effort, highlighting the inadequacy

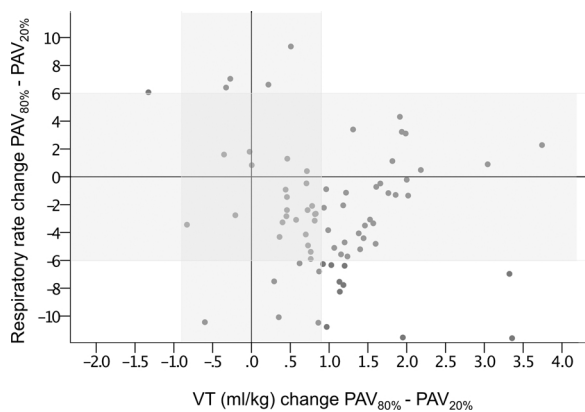


Fig. 3. Changes in breathing pattern- respiratory rate (RR) and tidal volume (VT)-, when assist changed from PAV20 % to PAV80 %, Gray shaded areas indicate the expected variability in RR and VT, which is the range of change observed with unchanged ventilator settings and arterial blood gases.

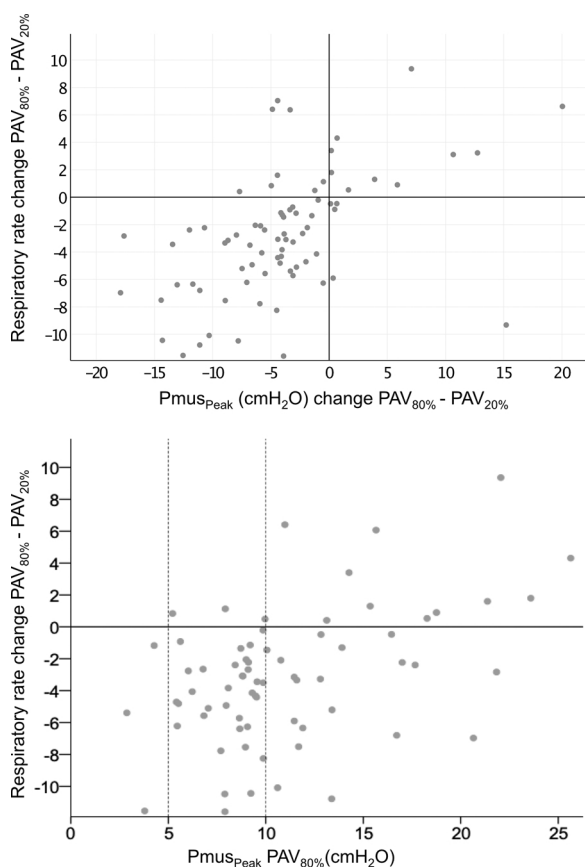


Fig. 4. Change in respiratory rate when assist changed from PAV20 % to PAV80 % vs. the corresponding change in $P_{musPeak}$ in the upper panel, and the absolute value of $P_{musPeak}$ at PAV80 % in the lower panel; vertical dotted lines indicate the target range for critically ill mechanically ventilated patients.

of respiratory rate as an indicator of respiratory drive and effort. This is not an unexpected finding as the respiratory rate in critically ill patients may be affected by several factors, most commonly sedation and opioid analgesia, which were also present in these patients (Grap et al., 2012; McGrane and Pandharipande, 2012; Vaporidi et al., 2020).

The response of critically ill patients to changes in assist was characterized overall by a decrease in respiratory drive, effort and respiratory rate, and an increase in tidal volume. Patients changed their effort more often and to a greater extent than their respiratory rate

upon change of assist and drive. This pattern of response is the same as the one observed in healthy subjects (Duffin et al., 2000). In our study in most patients, these changes of RR and VT were within the range of variability observed without a change in ventilator settings. Moreover, this variability, for both rate and tidal volume, was found higher in the critically ill than in healthy individuals (Tobin et al., 1988).

In mechanically ventilated patients a decrease in the respiratory rate in response to the increasing level of assist is usually considered as indicative of respiratory muscle unloading (Esteban et al., 1997, 1999; Sellares et al., 2012; Yang and Tobin, 1991). This study identified that, indeed, a decrease in respiratory rate has a positive predictive value of 90 % to predict a decrease in the inspiratory effort. However, this study also identified that it is only the direction of change and not the magnitude of the effect that can be predicted. Thus, these results indicate that, although a change in effort in response to a change in assist can be predicted by the change in respiratory rate with reasonable accuracy, neither the absolute value of respiratory rate nor its change can indicate if the resulting effort is low, normal or high.

Some methodological issues and limitations of this study should be considered in the interpretation of results. First, the changes in breathing pattern were studied while the patients were ventilated only in PAV + mode. Therefore, different changes in breathing pattern in response to changes in ventilator assist may be present during ventilation on PSV. Yet, a previous study has shown similar changes in patients' neural respiratory rate in response to varying the assist level between PAV and PSV (Giannouli et al., 1999). Second, the estimation of inspiratory effort and respiratory drive was performed using the measurement of $P_{musPeak}$, instead of the gold standard method of trans-diaphragmatic pressure (Pdi). However, we have previously shown that $P_{musPeak}$ derived by PVI monitor provides an accurate estimation of inspiratory effort (Kondili et al., 2010). At different levels of assist during ventilation on PAV+, $P_{musPeak}$ was compared with trans-diaphragmatic pressure (Pdi), and the pressure developed by all respiratory muscles (P_{mus}) -calculated with the Campbell diagram and using chest wall mechanics measured at active and passive ventilation. No significant difference between $P_{musPeak}$, and Pdi and P_{mus} , in terms of timing, magnitude, shape, and the rate of pressure increase.

5. Clinical and physiological relevance of the study findings

Setting the level of ventilator assist aims in adequate unloading of the respiratory muscles. In everyday clinical practice, the titration of assist usually aims to achieve a tidal volume of 6–8 ml/kg and a respiratory rate of 15–25 breaths/min. Moreover, automated systems have been introduced to facilitate titration of assist, relying on measurements of tidal volume and respiratory rate. It is widely believed that high breathing rate may be indicative of excessive work of breathing, and that a decrease in respiratory rate with increasing the level of assist indicates unloading of respiratory muscles and thus adequate assist level. However, it has been shown that frequently tachypnea may be due to factors unrelated to respiratory load. The results of this study emphasize that respiratory rate is not a sensitive indicator of the patient's effort and that neither the magnitude nor the absolute change in the respiratory rate in response to varying the level of assist reflects the changes in inspiratory effort accurately. It is, therefore important, in clinical practice to avoid oversimplifications and assumptions such as that a relatively normal respiratory rate assures a normal level of inspiratory effort. During the recent Covid-19 epidemic, it has been reported that patients with severe disease 'surprisingly' did not develop tachypnea and respiratory distress, an observation which is in line with the findings of this study, and not at all unexpected.

6. Conclusion

In conclusion, the present study, in mechanically ventilated patients on the recovery phase of acute illness, showed that changing the assist

level results in changes of inspiratory effort in more patients and to a greater magnitude, than of respiratory rate, though both effort and rate change almost always in the same tendency (either increase or decrease). Yet, neither the magnitude of change nor the absolute value of respiratory rate can be used to quantitatively estimate the resulting respiratory effort after a change in the level of assist.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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