RESPIRATORY CARE Paper in Press. Published on February 16, 2016 as DOI: 10.4187/respcare.04400

The Ratio of Inspiratory Pressure Over Electrical Activity of the Diaphragm Remains Stable During ICU Stay and Is Not Related to Clinical Outcome

Giacomo Bellani MD PhD, Andrea Coppadoro MD, Matteo Pozzi MD, Alfio Bronco MD, Daniela Albiero MD, Nilde Eronia MD, Valeria Meroni MD, Giacomo Grasselli MD, and Antonio Pesenti MD

BACKGROUND: We previously described an index, defined as the ratio between the inspiratory muscle pressure (P_{mus}) and the electrical activity of the diaphragm (E_{di}) (P_{mus}/E_{di} index). In the present work, we describe the trend of P_{mus}/E_{di} index over time, investigating whether it could be an indicator of muscular efficiency associated with risk factors for diaphragmatic injury and/or clinical outcomes. METHODS: This work is a retrospective analysis of subjects with measurements of P_{mus}/E_{di} index obtained, on different days, during assisted ventilation. Effects of P_{mus}/E_{di} index absolute value on clinical outcomes were investigated dividing subjects into those with P_{mus}/E_{di} index higher or lower than the median. Effects of P_{mus}/E_{di} index trend over time were analyzed, distinguishing between subjects with P_{mus}/E_{di} index increasing or decreasing. RESULTS: Mean P_{mus}/E_{di} index was 1.04 ± 0.67, and the median (interquartile range) was 1.00 (0.59–1.34), without a systematic trend over the days. Demographic, ventilator, or outcome data did not significantly differ between subjects with P_{mus}/E_{di} index higher or lower than the median. Similarly, we did not find relevant differences in subjects with P_{mus}/E_{di} index increasing or decreasing over time. CONCLUSIONS: The P_{mus}/E_{di} index value remained constant in each subject over time, although the inter-individual variability was high. Neither the P_{mus}/E_{di} index nor its trends appeared to be associated with ventilatory variables or clinical outcome. *Key words: pressure support; weaning; diaphragm; electromyography; muscle pressure; neutrally adjusted ventilator assist.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

In recent years, a growing body of evidence has demonstrated a potentially detrimental effect of mechanical ventilation on diaphragm contractility.[1] Patients undergoing short periods of ventilation might develop a ventilator-induced diaphragmatic dysfunction,[2] a condition associated with atrophy and loss of function of muscle fibers,[3] with prolonged weaning from the ventilator and worse patient outcome.[4] The possibility of monitoring the extent of ventilator-induced diaphragmatic dysfunction would be of great clinical value both for diagnostic purposes and to follow the patient's diaphragm status over time. Moreover, ventilator-induced diaphragmatic dysfunction could be an

Drs Bellani, Pozzi, Bronco, Eronia, Meroni, and Pesenti are affiliated with the Department of Health Science, University of Milan-Bicocca, Monza, Italy. Drs Bellani, Pozzi, Bronco, Eronia, and Pesenti are also affiliated with the Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy. Dr Coppadoro is affiliated with the Department of Emergency and Intensive care, A. Manzoni Hospital, Lecco, Italy. Dr Albiero is affiliated with the Humanitas Research Hospital, Rozzano (MI), Italy.

This work was supported by institutional funds. The Department of Health Science, University of Milan-Bicocca, received funds for research from Draegerwerk AG, Lubeck, Germany, not directed to this study. The authors have disclosed no conflicts of interest.

Correspondence: Giacomo Bellani MD PhD, University of Milan-Bicocca, Department of Medicine and Surgery, Via Cadore 48, 20900 Monza (MB), Italy. E-mail: giacomo.bellani1@unimib.it.

DOI: 10.4187/respcare.04400

RESPIRATORY CARE Paper in Press. Published on February 16, 2016 as DOI: 10.4187/respcare.04400

end point to evaluate the efficacy of novel therapeutic approaches aimed to preserve diaphragm function during mechanical ventilation. However, whereas a formal ventilator-induced diaphragmatic dysfunction diagnosis requires an invasive muscular biopsy,[4,5] the bedside tools to monitor diaphragmatic dysfunction are quite limited. Maximal inspiratory pressure[6] is easily obtainable in cooperative patients, but it has a low specificity and evaluates only the maximum force that the inspiratory muscles are able to generate[7]; in contrast, the measurement of diaphragmatic twitch following magnetic stimulation of the phrenic nerve[8] is more cumbersome. Finally, novel data suggest a possible role of diaphragm ultrasound.[9]

In a previous work,[10] we described the ratio between the pressure developed by the inspiratory muscles (P_{mus}) and the root mean square signal of the electrical activity arising from the crural diaphragm (E_{di}),[11,12] measured by electrodes placed on a nasogastric tube by a commercially available ventilator.[13] We defined this ratio as the P_{mus}/E_{di} index; briefly, the P_{mus}/E_{di} index expresses how much pressure (in cm H_2O) the inspiratory muscles generate for 1 μV of E_{di}. We have shown that P_{mus}/E_{di} index calculated during an expiratory hold (in which the pressure drop in the occluded airways equals P_{mus}) closely reflects the P_{mus}/E_{di} index value obtained during tidal ventilation, when P_{mus} is measured by esophageal pressure; as a consequence, esophageal pressure measurement might no longer be necessary to calculate P_{mus} once an E_{di} signal is available.[13,14]

Other investigators have previously used the term neuromuscular efficiency to describe the ratio between the pressure generated by the diaphragm and the corresponding electrical activity, albeit the formula applied was not identical in the different studies.[15,16] The use of the term efficiency has a positive connotation, somewhat suggesting that a diaphragm with a higher P_{mus}/E_{di} index (ie, higher neuromuscular efficiency) would have a better performance in terms of contractility and force development. If this is the case, we hypothesized that a higher or lower P_{mus}/E_{di} index would be associated with different risk factors for ventilator-induced diaphragmatic dysfunction (eg, duration of controlled ventilation) or clinical outcomes and that an increase in P_{mus}/E_{di} index during the subject's course might indicate an improvement of the muscle function.

The purpose of this preliminary observational study was to describe, in a mixed population of subjects undergoing spontaneous assisted breathing after a prolonged period of mechanical ventilation, the average value of P_{mus}/E_{di} index and its variability as well as the potential association of the P_{mus}/E_{di} index value (and of its trend over time) with certain relevant clinical variables and outcomes.

QUICK LOOK

Current knowledge

Inspiratory muscle pressure (P_{mus}) and electrical activity of the diaphragm (E_{di}) are linked by a correlation coefficient (P_{mus}/E_{di} index), which indicates how much pressure (in cm H_2O) the diaphragm generates for each microvolt. This index, which can be calculated by means of a single expiratory hold at the bedside, can be used to calculate P_{mus} from E_{di} during tidal ventilation.

What this paper contributes to our knowledge

The P_{mus}/E_{di} index has a marked variability between subjects but did not show any systematic trend during a subject's recovery after a period of mechanical ventilation. There is no evidence of an association between the P_{mus}/E_{di} index and any relevant ventilator variables, duration of ventilation, or clinical outcome.

Methods

This was an observational retrospective clinical study. The study was approved by our ethical committee, and subjects' consent was waived due to its retrospective nature.

Subjects

We retrospectively selected subjects admitted in our ICU in 2012 and 2013, in whom we had obtained at least one measurement of the P_{mus}/E_{di} index in the first 48 h of transition from controlled to assisted spontaneous breathing and at least one in the last 48 h before separation from the ventilator. Exclusion criteria were: observation period of $<$48 h, neuromuscular diseases, age $<$18 y, or pregnancy. Some of these subjects had been included in previously published studies, whereas in other subjects, the E_{di} catheter had been placed for clinical reasons, and the measurement was obtained with the purpose of monitoring P_{mus} from E_{di}.

Measurements

In each subject, the P_{mus}/E_{di} index had been measured, as shown in Figure 1, by pushing the freeze screen button of the ventilator immediately after the expiratory hold, as the average value of 3 triplicate measurements. After performing an expiratory hold, the freeze screen button of the ventilator allows the display of a 20 s recording. A cursor can be used to scroll through the waveforms and display the numerical values of the signals at the selected time points. All subjects were undergoing either pressure sup-

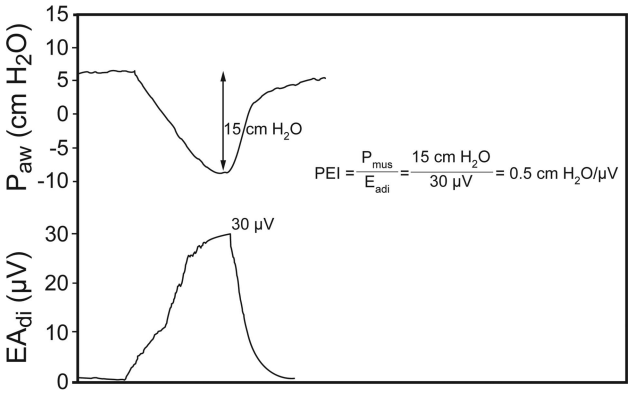

Fig. 1. Maneuver used to measure the ratio of inspiratory muscle pressure over electrical activity of the diaphragm (P_{mus}/E_{adi} index; PEI). During an expiratory occlusion, the pressure generated by the inspiratory muscles causes a drop in airway pressure (P_{aw}), which is then divided by the corresponding E_{di}.

port ventilation or neurally adjusted ventilatory assist, whose parameters were adjusted by the ICU physicians.

For each subject, we also collected from medical records the main demographic variables on admission, duration of controlled ventilation prior to transition to assisted ventilation, and duration of deep sedation (defined as a Richmond Agitation-Sedation Scale score of <-2). Moreover, during the period between the first and the last measurement of P_{mus}/E_{di} index available, we collected on a daily basis main ventilator variables, arterial blood gases, and biochemistry. We calculated the peak inspiratory E_{di}-derived P_{mus} as the product of E_{di} and P_{mus}/E_{di} index divided by 1.25. This factor was introduced and validated previously,[13] in order to take into account the different properties of the diaphragm during quasi-isometric contraction (expiratory hold) and during shortening (tidal ventilation). Due to the large variability of the observation period and the lack of some values on given days (since they were not collected for clinical purposes), it was virtually impossible to make between-patient comparisons at prefixed time points or by comparing the time courses. We thus decided, for variables collected longitudinally, to average the measurements, obtaining a single mean value for each subject, which was used in the comparisons. Finally, we collected the ICU and hospital outcome as well as the number of ventilator-free days in the first 28 d since the beginning of invasive ventilation (considered equal to zero for the non-survivors).

Statistics

Normality of data was tested by the Kolgomorow-Smirnoff test; normally distributed variables are presented as mean ± SD, whereas not normally distributed variables are presented as median (interquartile range); *t* test (paired or unpaired where appropriate) was used for the normally distributed variables, whereas the Mann-Whitney U test was used for unpaired variables.

Table 1. General Characteristics of the Study Population

Parameters	Median (IQR)
Age, y	60 (48–73)
SAPS II	47 (41–55)
ICU LOS, d	16 (10–25)
Hospital LOS, d	36 (22–51)
Ventilator-free days in the first 28 d, d	15 (4–22)
Duration of deep sedation, d	6 (2–16)
Duration of controlled ventilation, d	4 (1–8)

IQR = interquartile range
SAPS II = Simplified Acute Physiology Score II
LOS = length of stay

Results

By reviewing our charts, we found and included in this study 41 subjects, who were followed up for a mean of 6.9 ± 4.1 d. The characteristics of the subject population are reported in Table 1. Five of the 41 subjects (12%) died in the ICU but were included in the analysis with the available data. The mean P_{mus}/E_{di} index was 1.04 ± 0.67 cm $H_2O/\mu V$, and the median (interquartile range) was 1.00 (0.59–1.34) cm $H_2O/\mu V$. We did not find differences between males and females (1.43 ± 0.76 vs 1.21 ± 0.74, $P = .38$), subjects admitted with septic shock or not (1.25 ± 0.66 vs 1.43 ± 1.02, $P = .52$), or ICU survivors and non-survivors (1.28 ± 0.74 vs 1.30 ± 0.87, $P = .98$). In our population, we did not find a systematic trend in P_{mus}/E_{di} index, which did not show significant differences between the first and last day of the recording (1.38 ± 0.94 vs 1.30 ± 0.79 cm $H_2O/\mu V$, $P = .57$ Fig. 2). Moreover, in the subgroup of subjects with >4 measurements available, we plotted the values of P_{mus}/E_{di} index as a function of the progressive day on which the recording was obtained, but we could not find any significant correlation (data not shown).

In view of the lack of a systematic change of the P_{mus}/E_{di} index during the study period, we calculated for each subject the mean P_{mus}/E_{di} index over the period studied, and we then divided the population into 2 subject groups, characterized by a P_{mus}/E_{di} index lower or higher than the median (0.69 ± 0.22 and 1.85 ± 0.79 cm $H_2O/\mu V$, respectively, $P < .001$), which was exactly 1.00 cm $H_2O/\mu V$. Table 2 shows the comparison of clinical characteristics between the 2 groups. We found no significant difference, either in the demographic, ventilator, or outcome data, except for a longer hospital stay in subjects with a lower P_{mus}/E_{di} index ($P = .02$); in this analysis, we included only subjects

RESPIRATORY CARE Paper in Press. Published on February 16, 2016 as DOI: 10.4187/respcare.04400

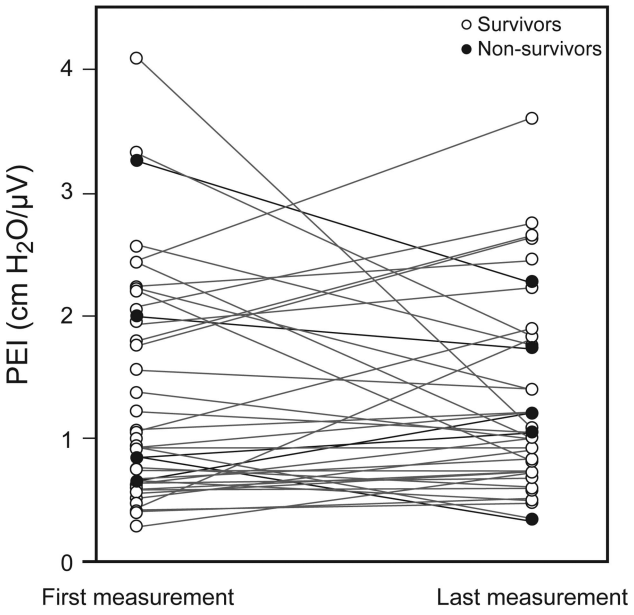

Fig. 2. The values of ratio of inspiratory muscle pressure over electrical activity of the diaphragm (P_{mus}/E_{di} index; PEI) for individual subjects. There was a large inter-individual variability, without a systematic trend between the first and the last measurement day.

who survived until the hospital discharge. Moreover, the subjects with a P_{mus}/E_{di} index <1 μV/cm H_2O also had significantly higher values of $P = .1$, with a difference that was statistically significant, albeit not clinically relevant.

When we divided the subject population based on the temporal trend of the P_{mus}/E_{di} index, we found 16 subjects in whom P_{mus}/E_{di} index decreased over time by $35 \pm 22\%$ and 21 subjects in whom it increased over time by $40 \pm 34\%$. When we compared these 2 groups (Table 3), we found that subjects in whom P_{mus}/E_{di} index decreased over time had higher levels of P_{aCO_2} and plasmatic bicarbonates, without significant differences in pH. Moreover, they had higher levels of hemoglobin. No differences in any of the outcome parameters were found between subjects within these 2 groups.

Discussion

The main findings of this paper can be summarized as follows. In a mixed population of ICU subjects, the P_{mus}/E_{di} index averages (and also has a median value of) 1 cm $H_2O/\mu V$, without a systematic trend of variation over time, except for a slight decrease in some subjects and a slight increase in others. However, neither a P_{mus}/E_{di} index higher or lower than the median nor an increase or decrease over time appeared to be associated with relevant clinical variables or outcomes.

In a previous article,[10] we described the use of P_{mus}/E_{di} index as a tool to convert the E_{di} into the pressure generated by the respiratory muscle. The latter value has an important clinical implication, since it is becoming more evident that spontaneous breathing during mechanical ventilation can have both negative and positive consequences,[17] whose balance probably depends on the severity of lung injury[18] and the level of assistance, since both over- and underassistance of patients can be associated with adverse consequences. Whereas overassistance is associated with the risk of elevated tidal volumes and asynchronies,[19] an insufficient assist level results in large negative pressure swings that can severely injure the lungs[18,20] or the diaphragm itself[21] and cause increased oxygen consumption.[22] Moreover, had the P_{mus}/E_{di} index value been relatively constant among all different subjects, one could calculate the P_{mus} just from the E_{di}, without the need of an occluded airway pressure measurement (eg, in non-intubated subjects). However, the value proved to be quite variable in the subjects included in this study, with a median of 1 but an interquartile range varying from 0.59 to 1.34 cm $H_2O/\mu V$. This finding suggests that without calculating the P_{mus}/E_{di} index factor, it is virtually impossible to derive the P_{mus} only from the E_{di}. We can use the borders of the interquartile range to make some examples: for the same level of peak E_{di} (eg, 10 μV), one quarter of the subjects (left of the 25th percentile of P_{mus}/E_{di} index) will have a P_{mus} <10 $\mu V \times 0.59$ cm $H_2O/\mu V/1.25 = 4.7$ cm H_2O, and one quarter will have a P_{mus} >10 $\mu V \times 1.34/1.25$ cm $H_2O/\mu V = 10.7$ cm H_2O. However, the relative stability of the index in the population allows one to follow the trend of P_{mus} in a given patient, even after the extubation, simply relying on the value measured just before extubation. In this work, we also defined for the first time the expected ranges of P_{mus}/E_{di} index for a mixed population of critically ill ventilated subjects, which does not necessarily translate to the general population. These values cannot be considered normal, since neither high nor low P_{mus}/E_{di} index values appeared to be associated with any relevant clinical outcome.

With the intent of identifying possible associations between different values of P_{mus}/E_{di} index and some relevant clinical outcomes, we arbitrarily divided the subject population into 2 subgroups characterized by a mean P_{mus}/E_{di} index value higher or lower than the median value of the entire population, which turned out to be exactly 1.0 cm $H_2O/\mu V$. Since no normal values for P_{mus}/E_{di} index are reported in the available literature, we thought that applying this selection criterion was the most reasonable and conservative approach to perform a robust analysis of our data. Liu et al[16] demonstrated a remarkable difference in the values of neuromuscular efficiency (an index analogous to the P_{mus}/E_{di} index) between subjects who failed or succeeded a spontaneous breathing trial. In our study, we did not systematically assess weanability by a daily spontaneous breathing trial, but rather, as surrogate indi-

RESPIRATORY CARE Paper in Press. Published on February 16, 2016 as DOI: 10.4187/respcare.04400

Table 2. Comparison of Characteristics of Subject With a Value of PEI Lower or Higher Than the Population Median

Parameters	Lower PEI	Higher PEI	*P*
Age, median (IQR) y	62 (49–75)	56 (48–70)	.46
SAPS II, median (IQR)	45 (40–55)	49 (43–55)	.92
ICU LOS, median (IQR) d	16 (11–37)	16 (8–25)	.27
Hospital LOS, median (IQR) d	48 (26–66)	28 (17–46)	.02
Ventilator-free days in the first 28 d, median (IQR) d	15 (0–22)	16 (5–21)	.27
Duration of deep sedation, median (IQR) d	7 (2–17)	6 (3–12)	.20
Duration of controlled ventilation, median (IQR) d	5 (1–15)	3 (1–6)	.22
Gas exchange, mean ± SD			
P_{aO_2}/F_{IO_2}, mm Hg	234 ± 64	245 ± 53	.56
P_{aCO_2}, mm Hg	44 ± 4	46 ± 6	.45
pH	7.4 ± 0.03	7.4 ± 0.02	.91
HCO_3^- mmol/L	27 ± 3	28 ± 4	.41
Metabolic variables			
Cholesterol, median (IQR) mg/100 ml	127 (91–165)	113 (98–146)	.28
Albumin, mean ± SD mg/100 ml	2.99 ± 0.37	3 ± 0.39	.96
Lactates, median (IQR) mmol/L	1.2 (0.9–1.7)	1.4 (1–1.9)	.88
Hemoglobin, mean ± SD g/100 mL	10.6 ± 0.79	10.5 ± 0.9	.58
Blood glucose, mean ± SD mmol/L	130 ± 22	133 ± 22	.58
Ventilatory variables			
Set pressure support, median (IQR) cm H_2O	6 (5.3–8)	7 (5.7–8.7)	.47
Minute ventilation, mean ± SD L/min	9.6 ± 1.54	9 ± 1.64	.22
Tidal volume, mean ± SD mL	462 ± 64	444 ± 73	.42
Breathing frequency, mean ± SD breaths/min	21 ± 4	21 ± 4	.77
Set PEEP, median (IQR) cm H_2O	9 (7–10)	9 (8–10)	.42
$P_{0.1}$, median (IQR) cm H_2O	1.7 (1.3–2)	1.3 (1.1–15)	.035
Negative inspiratory force, mean ± SD cm H_2O	28 ± 8	27 ± 9	.90
E_{di}-derived P_{mus}, mean ± SD cm H_2O	8 ± 4	9 ± 6.1	.92

PEI = P_{mus}/E_{di} index
IQR = interquartile range
SAPS II = Simplified Acute Physiology Score II
LOS = length of stay
E_{di} = electrical activity of the diaphragm
P_{mus} = inspiratory muscle pressure

cators of a subject's conditions with respect to weaning, we considered other clinical outcomes, such as the duration of mechanical ventilation during ICU stay and outcome. Indeed, in the same paper,[16] another parameter, the neuro-ventilatory efficiency, which also takes into account the mechanical properties of the respiratory system, had a better predictive value than the neuromuscular efficiency, stressing the multifactorial etiology of weaning failure.

In our study, we did not have an independent way to assess the presence and extent of ventilator-induced diaphragmatic dysfunction, but due to its preliminary nature, we relied on clinical data, such as the previous duration of controlled ventilation, a parameter known to impact the extent of ventilator-induced diaphragmatic dysfunction; moreover, we looked at the maximal inspiratory pressure as indicator of muscle strength. However, we reasoned that if a low P_{mus}/E_{di} index was indicative of a compromise in muscular function, it should translate into a worse subject outcome[5] or the need for higher ventilator assistance. The lack of any association between the value of P_{mus}/E_{di} index (or its temporal trends) and clinical variables, like ventilator-free days, duration of controlled ventilation, and average level of assistance, might suggest that neither the absolute value of P_{mus}/E_{di} index nor its trend over time is likely to be a good indicator of muscular health status.

This work has some relevant limitations that should be acknowledged. The study was not prospectively designed to a specific end point, with the relative calculation of a sample size, mainly due to the fact that the P_{mus}/E_{di} index has not been the object of specific research, and we aimed to describe its normal values and variability in the general population. Second, we did not use specific protocols for ventilator titration and spontaneous breathing trials for weaning from mechanical ventilation. Rather, we observed the ongoing clinical practice in our ICU, where weaning is commonly performed by decreasing the level of pressure support. Finally, we did not prospectively enroll a cohort

RESPIRATORY CARE Paper in Press. Published on February 16, 2016 as DOI: 10.4187/respcare.04400

Table 3. Comparison of Characteristics of Subject With a Value of PEI Increasing or Decreasing During the Observation Period.

Parameters	Decreasing PEI	Increasing PEI	*P*
Age, median (IQR) y	62 (49–70)	52 (41–73)	.32
SAPS II, median (IQR)	44 (38–53)	52 (45–58)	.051
ICU LOS, median (IQR) d	16 (11–47)	21 (14–39)	.39
Hospital LOS, median (IQR) d	46 (21–51)	44 (27–72)	.23
Ventilator-free days in the first 28 d, median (IQR) d	11 (0–16)	17 (4–21)	.39
Duration of deep sedation, median (IQR) d	13 (3–16)	7 (2–12)	.41
Duration of controlled ventilation, median (IQR) d	7 (3–16)	4 (1–8)	.30
Gas exchange, mean ± SD			
P_{aO_2}/F_{IO_2}, mm Hg	240 ± 51	245 ± 58	.78
P_{aCO_2}, mm Hg	48 ± 6	43 ± 4	.006
pH	7.41 ± 0.02	7.40 ± 0.03	.34
HCO_3^- mmol/L	30 ± 3.6	27 ± 2.8	.003
Metabolic variables			
Cholesterol, median (IQR) mg/100 ml	142 (99–176)	111 (85–147)	.72
Albumin, mean ± SD mg/100 ml	3.0 ± 0.3	3.0 ± 0.4	.78
Lactates, median (IQR) mmol/L	1.3 (1.1–1.6)	1.3 (0.9–1.9)	.57
Hemoglobin, mean ± SD g/100 mL	10.9 ± 0.9	10.2 ± 0.6	.01
Blood glucose, mean ± SD mmol/L	132 ± 19	133 ± 23	.91
Ventilatory variables			
Set pressure support, median (IQR) cm H_2O	7 (5.5–8.8)	7.3 (5.7–8.3)	.46
Minute ventilation, mean ± SD L/min	9.1 ± 1.6	9.5 ± 1.6	.49
Tidal volume, mean ± SD mL	435 ± 69	458 ± 68	.31
Breathing frequency, mean ± SD breaths/min	21 ± 3	21 ± 5	.99
Set PEEP, median (IQR) cm H_2O	8 (7–10)	9 (8–10)	.83
$P_{0.1}$, median (IQR) cm H_2O	1.4 (1.2–1.7)	1.5 (1.2–2)	.28
Negative inspiratory force, mean ± SD cm H_2O	29 ± 10	28 ± 9	.70
E_{di}-derived P_{mus}, mean ± SD cm H_2O	8.3 ± 3.3	8.3 ± 5.9	.94

PEI = P_{mus}/E_{di} index
IQR = interquartile range
SAPS II = Simplified Acute Physiology Score II
LOS = length of stay
E_{di} = electrical activity of the diaphragm
P_{mus} = inspiratory muscle pressure

of consecutive subjects undergoing mechanical ventilation but rather those in whom an E_{di} catheter was in place either for research or clinical purpose, potentially selecting a population of subjects with respiratory issues.

Conclusions

In this preliminary observational study, we have shown that the median value of the P_{mus}/E_{di} index is 1 cm $H_2O/\mu V$, but with a rather high inter-individual variability. However, the value tended to remain fairly constant within a given subject during the ICU stay. Neither the P_{mus}/E_{di} index nor its trends appeared to be associated with relevant ventilator variables, duration of ventilation, or clinical outcome (except for a possible association with hospital stay), making P_{mus}/E_{di} index not a very promising candidate to track ventilator-induced diaphragmatic dysfunction at the bedside.

REFERENCES

1. Jaber S, Jung B, Matecki S, Petrof BJ. Clinical review: ventilator-induced diaphragmatic dysfunction: human studies confirm animal model findings! Crit Care 2011;15(2):206.
2. Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 2004;169(3):336-341.
3. Bruells CS, Smuder AJ, Reiss LK, Hudson MB, Nelson WB, Wiggs MP, et al. Negative pressure ventilation and positive pressure ventilation promote comparable levels of ventilator-induced diaphragmatic dysfunction in rats. Anesthesiology 2013;119(3):652-662.
4. 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(13):1327-1335.
5. 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(3):364-371.
6. Nemer SN, Barbas CS, Caldeira JB, Guimarães B, Azeredo LM, Gago R, Souza PC. Evaluation of maximal inspiratory pressure, tracheal airway occlusion pressure, and its ratio in the weaning outcome. Journal of critical care 2009;24(3):441-446.

7. Savi A, Teixeira C, Silva JM, Borges LG, Pereira PA, Pinto KB, et al. Weaning predictors do not predict extubation failure in simple-to-wean patients. J Crit Care 2012;27(2):221.e1-8. doi: 10.1016/j.jcrc.2011.07.079.
8. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, et al. Diaphragm dysfunction on admission to the intensive care unit: prevalence, risk factors, and prognostic impact: a prospective study. Am J Respir Crit Care Med 2013;188(2):213-219.
9. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax 2014;69(5):423-427.
10. Bellani G, Pesenti A. Assessing effort and work of breathing. Curr Opin Crit Care 2014;20(3):352-358.
11. Sinderby C, Beck J, Spahija J, Weinberg J, Grassino A. Voluntary activation of the human diaphragm in health and disease. J Appl Physiol 1998;85(6):2146-2158.
12. Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, Sinderby C. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am J Respir Crit Care Med 2001;164(3):419-424.
13. 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(6):1483-1491.
14. Bellani G, Coppadoro A, Patroniti N, Turella M, Arrigoni Marocco S, Grasselli G, et al. Clinical assessment of auto-positive end-expiratory pressure by diaphragmatic electrical activity during pressure support and neurally adjusted ventilatory assist. Anesthesiology 2014;121(3):563-571.
15. Ciavaglia CE, Guenette JA, Langer D, Webb KA, Alberto Neder J, O'Donnell DE. Differences in respiratory muscle activity during cycling and walking do not influence dyspnea perception in obese patients with COPD. J Appl Physiol 2014;117(11):1292-1301.
16. 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;16(4):R143.
17. Marini JJ. Spontaneously regulated vs. controlled ventilation of acute lung injury/acute respiratory distress syndrome. Curr Opin Crit Care 2011;17(1):24-29.
18. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. The comparison of spontaneous breathing and muscle paralysis in 2 different severities of experimental lung injury. Crit Care Med 2013;41(2):536-545.
19. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006;32(10):1515-1522.
20. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. Crit Care Med 2012;40(5):1578-1585.
21. Kallet RH. Patient-ventilator interaction during acute lung injury, and the role of spontaneous breathing: part 1: respiratory muscle function during critical illness. Respir Care 2011;56(2):181-189.
22. Bellani G, Foti G, Spagnolli E, Milan M, Zanella A, Greco M, et al. Increase of oxygen consumption during a progressive decrease of ventilatory support is lower in patients failing the trial in comparison with those who succeed. Anesthesiology 2010;113(2):378-385.