**On – line Supplementary material**

**Validation of a proposed algorithm for assistance titration during Proportional Assist Ventilation with load adjustable gain factors.**

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**Methods.**

We respectively analyzed the recordings of twenty-six patients with respiratory failure of different causes participated in three previous research protocols. Patients were mechanically ventilated through either a cuffed endotracheal (no 7) or tracheotomy tube and were clinically stable. Based on the original protocols patients were recorded at different levels of assist and were instrumented with esophageal and gastric balloons. As part of the individual research protocols, fifteen patients were studied with and without an artificial increase in elastic work of breathing (application of sandbags to the entire surface of the chest and abdominal wall). Each patient at different experimental condition was considered as an an individual experimental case (EC).

 **Data analysis**

1. **Assessment of physiological variables**(see also Supplementary Table 1)

In each experimental case at least ten breaths over a period of three minutes were randomly analyzed and averaged to give the breath variables for the corresponding EC. Breaths with low-quality Pdi signal were excluded. For each selected breath, Pdi was defined as the highest value of Pdi during inspiration 1, 2.

*Assessment of inspiratory effort*

The Inspiratory effort per breath (PTP-Pdi) was quantified by measuring the area under the Pdi signal, from the beginning inPdi increase to the point at which Pdi started to decline rapidly. The PTP-Pdi per minute (PTP-Pdi/min) was calculated as the product of PTP-Pdiper breath multiplied with the respiratory frequency (f)1, 2.

*Breath characteristics*

Neural (TIn) was measured as the time interval from the beginning in the Pdiincrease to its peak value and mechanical inspiratory time(Tim) as the time interval between the onset of neural inspiration to the time of negative flow signal. The difference between Tim and TIn(Δt) was calculated. Delay triggering time (Td),was measured as the time interval from the beginning in the Pdi increase to the nadir value of Paw during inspiration 1, 2

 The rate of the rise of Pdi (dp/dt) was calculated as the ratio of change of Pdi during the inspiration to neural inspiratory time 1, 2.

In each collected breath, we also measured the PEEPi and assessed the presence of expiratory muscle activity and the relative contributions of the diaphragm and inspiratory rib cage muscles to the inspiratory effort.

Expiratory muscle activity was confirmedin the presence of a continuing increase in gastric pressure during the expiration 3.

The relative contribution of the diaphragm and inspiratory rib cage muscles to the inspiratory effort was assessed as previously described. Considering that Peos and Pgas represent an estimate of the total inspiratory muscleou tputand diaphragmatic activity respectively,the relative contributions of the diaphragm and inspiratory rib cage muscles to the inspiratory effort was estimated by the ratio of the change in gastric pressure (Pgas) to change in Peos(ΔPgas/ΔPeos) during inspiration. ΔPgas was measured as the difference from the beginning of an effort to its maximum value, andΔPeoswas measured from the starting of the effort to its nadir value. As expiratory musclecontraction may increase Peos and Pgas, when expiratory activity was identified, the riceofgasduringthe preceded breath was subtracted from, Peos and Pgas to obtain the corrected measurements. ΔPgas/ΔPes ratio yields values <-1 in healthy subjects and >1 in the case of total diaphragmatic inactivity. A ratio range between <-1to 1 is indicative of impairment diaphragmatic activity,greater contribution of accessory muscles related to diaphragm or combination of the above3.

**b.Calculation of PmusPeak and PTP-PmusPeak**

 The PmusPeak and the estimated inspiratory effort (pressure time product of PmusPeak-PTP-PmusPeak) were calculated using the formulas proposed by Carteaux et al.4as follow:

PmusPeak = (Paw peak–PEEP)x100-gain/gain

 (wherePawpeak = is the Peak inspiratory airway pressure, PEEP the end-expiratory positive airway pressure and gain the level of assist)

PTP-PmusPeak = PmusPpeak x TIm/ 2x f (where TIm is the mechanical inspiratory time and f the respiratory frequency).

The difference between PmusPeak and Pdi (dΡ), and between PTP-Peakmus/min and PTP-Pdi/min (ΔPTP) were calculated. dΡ and ΔPTP/min were also expressed as the percentage of Pdi (dΡ%Pdi) and PTP-Pdi/min (ΔPTP/min% PTP-Pdi/min)respectively.

**c. Assessment of correlations**

A Spearman’s rank correlation coefficient was computed to assess the association between PmusPeak, PTP-PmusPeak, dP and ΔPPT and possible confounding physiological factors. Each of the above variables was tested using as independent variables, the dp/ dt, the PEEPi, the presence of expiratory muscle activity (+/-), the ΔPga/ ΔPes ratio, the triggering delay time, and the time difference between TIm and TIn (Δt). Correlation coefficient is shown in Table S3.

**d. Validation of the proposed algorithm**

According to the proposed algorithm the adjustment of the gain was set as PmusPeak to range between 5-10 cmH2O as follow:

If PmusPeak ranged between 5-10cmH2O, the estimated inspiratory effort was assumed to range within the acceptable values (50-150 cmH2O.sec/min) , the level of assist was considered as adequate, and no adjustment in gain was performed.

If PmusPeak was <5 cmH2O ,the estimated inspiratory effort was assumed to be < 50cmH2O.sec/min, the level of assist was considered excessive, and the gain was decreased until PmusPeak to reach the target range.

If PmusPeak was >10 H2O, the estimated inspiratory effort was considered to be >150 cmH2O.sec/min , the level of assist was considered as insufficient, and the gain was increased until PmusPeak to reach the target range.

The validation of the algorithm was performed by assessing the accuracy of PmusPeak in the prediction of the actual range of the inspiratory effort, determined by the measured PTP-Pdi. In each EC we assessed whether the value of PTP-Pdi was within the predicted range by the PmusPeak inspiratory effort(<50,50-150 <150cmH2O.sec/min for PmusPeak<5, 5-10, >10 cmH20 respectively ). Validation was performed in the total of ECs by contacting a ROC analysis and in three subgroups, determined by the value of PmusPeak as follow:

*Subgroup 1* included the ECs in which PmusPeak was <5-cmH2O

*Subgroup 2* included the ECs in which PmusPeak was 5-10cmH2O

*Subgroup 3*included the ECs in which PmusPeak was>10cmH2O

 **Results**

The recordings of twenty-six difficult-to-wean patients (median age 72y,IQR 64-74 )were retrospectively analyzed. The mediandurationon mechanical ventilation at the time of the study was 12 days (IQR = 6.25-18.75 ). Assist level, patient’sdemographic andclinical characteristics are shown in Table S1.

Sixty-three different experimental cases were identified, and atotal of 725 sufficient breaths were available for analysis.

**Breathing characteristics**

The median tidal volume was 0.39(IQR 0.33-0.50).The median mechanical (TIm )and neural inspiratory time were 0.97 (IQR 0.81-1.17) and 0.65(IQR 0.49-0.91)respectively. TIm was significantly higher than TIn (median= **0.33** ), z= 06.44, p<0.0001),Fig S2. In two ECs TIn was higher that TIm.

Triggering delay (median0.17 sec, IQR: 0.13-0.2) was inversely correlated with dp/pt ( rho -0.41, p<0.001), suggesting an increase in triggering delay with a decreasein respiratory drive. Respiratory drive expressed by the dp/dt ratio ( median 13.86,IQR:8.43-23.53) was decreased with the increase in ventilator assistance. The median external Positive end-expiratory pressure was 9 cmH2O. PEEPi was identified in all but two EC (median 0 cmH2O, IQR 0.530-1.8).

## Expiratory muscle activity detected in 14 of the 63 (%) was ECs. In all but three ECs, Pgas /Peos ratio yield values between -1to +1, indicating an impaired diaphragmatic activity or /an and increased rib case muscle activity. In three ECs (pertained to the same patient) the Pgas /Peos ratio was > +1 ( 1.32) suggesting total diaphragmatic inactivity.

**References**

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**Table . S1 Patient’s demographics and characteristics .**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient(No) | Sex(M/F | Age (years) |  Days on MV | Diagnosis on ICU admission |
| 1234567891011121314151617181920212223242526Median (IQR) | MMFMMMMFΜFMMMMMFMMMM FMFMMM | 7464637047707275537572748176774371722573706165737472**72****64-74** | 355561826154411262191512175619714716127619**12****6.25-18.75** | SepsisAECOPD-PneumoniaPolyneuromyopathyCHFLymphomaAECOPDAspiration pneumoniaPneumoniaARDSAECOPDCHF- AECOPDCOPD SepsisAECOPDAECOPDAspiration pneumoniaCHF- sepsis Trauma - sepsisARDS sepsisAECOPDTrauma-ARDSARDS -sepsisARDS sepsisTrauma-ARDSARDS -sepsisARDS  |

**MV;** mechanical ventilation, **ARDS;** acute respiratory distress syndrome ,**CHF;** congestive heart failure , **AECOPD;** acute exacerbation of chronic obstructive pulmonary disease

**Table S2. Synoptic description of the different physiological variables their meaning and the method of measurement**

|  |  |  |
| --- | --- | --- |
| Variable | **Physiologic meaning** |  **Measurement** |
| **Pressure Time Product (PTP**) | An estimation of Inspiratory Muscle Effort per breath |  Calculated as the Area under muscle Pressure waveform over neural inspiratory time (from the beginning in muscle pressure increase to the point at which Pressure starts to decline rapidly ) |
| **PTP/min** | An estimation of Inspiratory Muscle Effort per minute |  Calculated as the product of PTP per breath and respiratory frequency |
| **TIn** | Neural inspiratory time | Time interval from the beginning in the Pdi increase to its peak value |
| **TIm** | Mechanical inspiratory time | Measured as the time interval between the beginning of mechanical inspiration to the time of negative flow signal |
| **Δt** | Patient Ventilator Asynchrony | Difference between Tim and TIn |
| **Td** | Delay triggering time |  Measured as the time interval from the beginning in the Pdi increase to the nadir value of Paw during inspiration  |
| **dp/dt** | Estimation of patient’s respiratory drive |  Calculated as the ratio of change of Pdi during the inspiration to neural inspiratory time.  |
| **PEEPi** | Presence of elastic recoil pressure  |  Measured as the value of Pdi corresponding to the time at the zero flow crossing |
| **Expiratory muscle activity** | Presence of expiratory muscle activity |  Indicated by the continuing in increase of gastric pressure during the expiration |
| **ΔPgas/ΔPeos** |  Estimation of relative contributions of the diaphragm and inspiratory rib cage muscles to the inspiratory effort | Calculated as the ratio of the change in gastric pressure (Pgas) to change in the Peos(ΔPgas/ΔPeos) during inspiration |
| **ΔPgas** | Difference in gastric pressure | Difference in gastric pressure from the beginning of the effort to its maximum value |
| **ΔPeos** | ΔP in eosophageal pressure | Eosophageal pressure measured from the starting of the effort to its nadir value |

**Table S3**. **Spearman rank correlation coefficients (rho).**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable**  | **Confounding factors**  |  **rho** | **p -value** |
| **PmusPeak- PTP/min** | dp/dt | 0.25 | **0.04** |
|  | Δt | -0.18 | 0.15 |
|  | Expiratory activity | -0.1 | 0.43 |
|  | Td | 0.13 | 0.30 |
|  | ΔΡgas/ΔΡeos | 0.18 | 0.21 |
|  | PEEPi | 0.16 | 0.19 |
| **PmusPeak** |  | **rho** | **p-value** |
|  | dp/dt | 0.42 | **0.0006** |
|  | Δt | -0.08 | 0.56 |
|  | Expiratory activity | -0.24 | 0.0576 |
|  | Td | 0.02 | 0.84 |
|  | ΔΡgas/ΔΡeos | 0.29 | **0.03** |
|  | PEEPi | 0.16 | 0.21 |
| **ΔPTP** |  | **rho** | **p-value** |
|  | dp/dt | -0.07 | 0.54 |
|  | Δt | 0.25 | **0.04** |
|  | Expiratory activity | 0.13 | 0.29 |
|  | Td | 0,18 | 0.15 |
|  | ΔΡgas/ΔΡeos | 0.25 | 0.07 |
|  | PEEPi | 0.15 | 0.14 |
| **dΡ** |  | **rho** | **p-value** |
|  | dp/dt | -0.39 | **0.0014** |
|  | Δt | 010 | 0.4 |
|  | Expiratory activity | 0.14 | 0.27 |
|  | Td | 0.22 | 0.11 |
|  | ΔΡgas/ΔΡeos | 0.04 | 0.14 |
|  | PEEPi | 0.14 | 0.26 |

***PmusPeak***; the calculated (from the formula) peak inspiratory pressure, ***PTP-PmusPeak/min*** ; the calculated pressure time product of PmusPeak per min ,***PTP- Pdi /min;*** pressure time product per min of Pdi, ***dP;*** the difference between PmusPeak and Pdi, **ΔPTP**; the difference between PmusPeak-PTP and Pdi-PTP, ***dp/dt***; the rate of the rise of trans-diaphragmatic pressure (Pdi) ,***Δt***;the difference between mechanical (TIm) and neural (TIn) inspiratory time ,***Td***; Delay triggering time, ***ΔΡgas/ΔΡeos;*** the ratio of change in gastric Pgas to changes in esophageal (Peos) pressure during inspiration, ***PEEPi***; intrinsic positive end-expiratory pressure.

**Figure Supplementary 1**. **Scatterplot with a fitted regression line, showing the relationship between PmusPeak and Pdi (A) and PTP-PmusPeak and PTP-Pdi (B) .***R2: Coefficient of determination.*



**Figure Supplementary 2. Calculation of PTP-Pdi/breath in a representive patient at different experimental conditions.**

**A :** PTP-Pdi in a representive patient whenPdi is exressesd in **A** convex shape (PTP-Pdi= area A+B ,15.10 cmH2O.sec )and in the theoretical case of linear increase of Pdi (PTP-Pdi =Area B, 12.13cmH2O\*sec) . Notice that for the same Pdi max value and inspiratory time ,the PTP-Pdi depends upon the shape of Pdi. **B**: PTP-Pdi in the same patient, assuming the same Pdimax, and calculated using the neural inspiratory time (PTP-Pdi =Area A , 15.10 cmH2O.sec) and mechanical inspiratory time (PTP-Pdi =Area A+B, 24.36 cmH2O\*sec). TIn; neural inspiratoty time, TIm; mechanical inspiratoty time



**Figure Supplementary 3**. Box- and whiskers plots representing comparisonof mechanical,(A panel) and Neural inspiratory time (B). The lower and upper edges of the box are the 25th and 75th percentiles, respectively. Median values are shown by the linewithin the box. Whiskers represent adjacent values. Markers denote outliers. (\*):p<0.05. **TIm**: Mechanical inspiratory time; **TIn**: Neural inspiratory time



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