SUPPLEMENTAL DIGITAL CONTENT

Bedside adjustment of proportional assist ventilation to target a predefined range of respiratory effort

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Patients and Methods

This was a prospective multicenter observational study involving five university hospitals, four in France (Angers, Créteil, Nice, Rouen) and one in Spain (Barcelona). The study was approved by the Ethics Committee of the Société de Réanimation de Langue Française (French society of intensive care medicine) and the Ethics Committee of Hospital de Sant Pau, Barcelona.

Measurements

The following data were recorded at inclusion under assist-control ventilation (ACV):

- Demographic data: age, gender, height, weight, ICU admission date, intubation date, co-morbidities, mean reason for intubation, SAPS II [1] at ICU admission and at inclusion.

- Hemodynamic data: arterial blood pressure, heart rate, dose of vasopressor (if any).

- Respiratory data: FiO₂, PEEP, inspiratory flow, tidal volume, preset respiratory rate, measured respiratory rate (RR), minute ventilation (Vₑ), P₀.₁ (average of three consecutive measures).

- Respiratory mechanics: static compliance and resistance of the respiratory system were measured using a tele-inspiratory occlusion.

- Arterial blood gases (ABG).

- RASS score [2], dose of sedative drugs (if any).

During the study, the following parameters were recorded each morning under PAV+:

- Hemodynamic data: arterial blood pressure, heart rate, dose of vasopressor (if any).

- Respiratory data: FiO₂, PEEP, Gain, Pₘₚ₈ₚ, expired tidal volume (Vₑ), insufflation time (Ti), measured respiratory rate (RR), minute ventilation (Vₑ).

- ABG,
- RASS score, dose of sedative drugs (if any),
- Number of gain adjustments and whether they had been made according to the standard settings or to the additional settings (see below).
- When a weaning trial was performed, its result was reported.

In 45 of the 53 patients, a laptop was connected to the ventilator, using a dedicated software that allowed all the ventilator data to be output every minute throughout the duration of PAV+ ventilation. These data, which were converted into Excel datasets (Microsoft Excel, Microsoft Corporation, Redmond, WA) for subsequent analysis, included: FiO₂, PEEP, Gain, peak airway pressure ($P_{aw,\text{Peak}}$), mean airway pressure ($P_{aw,\text{Mean}}$), respiratory rate (RR), expired tidal volume (Vte), insufflation time (Ti).

**Gain adjustment during PAV+**

A Puritan-Bennett 840 ventilator (Covidien, Galway, Ireland) was used to deliver PAV+. The protocol to adjust the gain was designed to maintain the patient within a normal range of respiratory effort. The respiratory muscles pressure-time product ($PTP_{\text{mus}}$) is a reliable measure of respiratory effort [3]. A $PTP_{\text{mus}}$ of between 50 and 150 cmH₂O.s.min⁻¹ can be considered as a reasonable and acceptable effort during assisted mechanical ventilation [3-4]. However, as the $PTP_{\text{mus}}$ was not measurable at the bedside, we used its major component, the peak muscle pressure ($P_{\text{mus,Peak}}$), as a surrogate. In fact, in PAV+, it is possible to calculate the $P_{\text{mus,Peak}}$ at the bedside. PAV+ uses the equation of motion of the respiratory system to work [5]. During assisted mechanical ventilation, this equation can be written as follows:

$$P_{\text{tot,\text{app}}} = P_{\text{aw,\text{app}}} + P_{\text{mus,\text{app}}} = R_q + R \times V_{i,\text{app}} + E \times V_{e,\text{app}} \quad \text{[Equation 51]}$$
Where $P_{tot}(t)$: total pressure, $P_{aw}(t)$: airway pressure, $P_{mus}(t)$: muscle pressure, $P_0$: starting pressure (corresponding to the total PEEP), $R$: resistance of the respiratory system, $E$: elastance of the respiratory system, $V'(t)$: instantaneous flow, $V(t)$: instantaneous volume.

During PAV+, the resistance and elastance of the respiratory system are regularly measured by means of tele-inspiratory micro-occlusions [6-7], while the instantaneous flow and volume are continuously monitored. The assistance delivered by the ventilator is then in proportion to this instantaneous flow, volume and respiratory load. Hence, during PAV+, the total pressure needed to inflate the respiratory system is known, and only a proportionality factor – the gain – needs to be set by the clinician.

\[ P_{aw}(t) = \text{Gain} \times P_{tot} \quad [\text{Equation S2}] \]

The gain represents the percentage of the total pressure that is assumed by the ventilator, the remaining pressure being assumed by the patient’s respiratory muscles. By simply combining equations S1 and S2, we obtain the relation between $P_{aw}(t)$ and $P_{mus}(t)$ in PAV+, showing how the assistance is in proportion to the muscle pressure:

\[ P_{aw}(t) - \text{PEEP} = P_{mus}(t) \times \frac{\text{Gain}}{100 - \text{Gain}} \quad [\text{Equation S3}] \]

Given the equation S3, it is possible to calculate the peak muscle pressure ($P_{mus,Peak}$) breath by breath from the values of the PEEP, the gain, and the $P_{aw,Peak}$ pressure, which are continuously monitored on the ventilator screen:

\[ P_{mus,Peak} = (P_{aw,Peak} - \text{PEEP}) \times \frac{100 - \text{Gain}}{\text{Gain}} \quad [\text{Equation S4}] \]

The target range of $P_{mus,Peak}$ was based on the following reasoning: by assuming that the muscle pressure waveform has a triangular shape, and that the end of the inspiratory effort is at the peak muscle pressure, then the $PTP_{mus}$, which is the area under the muscle pressure curve during the inspiration, can be calculated over a minute (in cmH₂O.s.min⁻¹) as follows (Fig 2):
Where Ti is the inspiratory time and RR the respiratory rate.

Based on this equation, we considered that with usual Ti and RR values, a $P_{\text{mus,Peak}}$ between 5 and 10 cmH$_2$O should allow the $PTP_{\text{mus}}$ to remain between 50 and 150 cmH$_2$O.s.min$^{-1}$. We therefore designed a protocol to adjust assistance during PAV+ that first aimed to keep the $P_{\text{mus,Peak}}$ between 5 and 10 cmH$_2$O.

Consequently, the protocol for setting the ventilator and especially adjusting the gain in PAV+ has been designed as follows:

1. **Initiation of PAV+ ventilation:**
   - **Alarms settings:**
     - Airway pressure alarm: 40 cmH$_2$O
     - Respiratory rate alarm: 40 cycles/ minute
     - Maximum expired tidal volume: 10 ml/kg of predicted body weight
     - Minimum expired tidal volume: 0 ml/kg
     - Maximum minute ventilation alarm: 20 l/min
     - Minimum minute ventilation alarm : 7 l/min
   - **Ventilatory parameters settings :**
     - FiO$_2$ and PEEP were adjusted according to the standard practice in each participating center.
     - Gain: 50%
     - Inspiratory trigger: 1 l/min

After starting PAV+ ventilation, the gain was immediately adjusted from the 50% starting gain according to the instructions below. The $P_{\text{mus,Peak}}$ was then estimated at least every 8 hours and the gain was adjusted if needed.
2. **Algorithm to adjust the gain:**

**A. P\textsubscript{mus}-settings:**

P\textsubscript{mus}-settings were based on the measure of \( P_{\text{mus,Peak}} \) at the bedside, using the grid designed for this purpose (Fig 1). In case of a high breath-by-breath variability, the value of the \( P_{\text{mus,Peak}} \) was obtained by averaging five consecutive measures of the \( P_{\text{mus,Peak}} \). The aim of the P\textsubscript{mus}-settings was to adjust the gain to target the \( P_{\text{mus,Peak}} \) range (between 5 and 10 cmH\textsubscript{2}O).

- If \( P_{\text{mus,Peak}} < 5 \text{ cmH}_2\text{O} \): decrease the gain in steps of 10\% until the \( P_{\text{mus,Peak}} \) exceeds 5 cmH\textsubscript{2}O.

- If \( P_{\text{mus,Peak}} > 10 \text{ cmH}_2\text{O} \): increase the gain in steps of 10\% until the \( P_{\text{mus,Peak}} \) decreases to below 10 cmH\textsubscript{2}O.

- If \( 5 \text{ cmH}_2\text{O} \leq P_{\text{mus,Peak}} \leq 10 \text{ cmH}_2\text{O} \): the \( P_{\text{mus,Peak}} \) target range is reached, do not modify the gain.

**B. Additional settings:**

Additional settings had to be used if any of the following appeared despite a \( P_{\text{mus,Peak}} \) within the target range:

- In case of clinical signs of respiratory distress (RR > 40/min, use of accessory respiratory muscles, dyspnea expressed by an awake patient) lasting for more than 5 min, and/or
- A V\textsubscript{te} < 5 ml/kg of predicted body weight, and/or
- The diagnosis of a respiratory acidosis on the ABG:
  - Reassess first the FiO\textsubscript{2} and the PEEP. If they are considered optimal:
  - Increase the gain in steps of 10\% until the disappearance of the above signs.
- In case of V\textsubscript{te} > 10 ml/kg of predicted body weight, and/or
- The appearance of a respiratory alkalosis on the AGB:
o Look for and treat any other cause of hyperventilation that can generate over-assistance (such as pain, anxiety or metabolic acidosis). If no other cause is found:

o Decrease the gain in steps of 10% until the above signs disappear.

3. **Ventilatory criteria that mandate a switch to ACV mode:**

   Independently of the clinical condition, the PAV+ had to be switched to ACV if it was needed to increase:

   - The gain above 85%, and/or
   - The FiO₂ above 70%, and/or
   - The PEEP above 10 cmH₂O.

4. **Weaning from mechanical ventilation:**

   All patients underwent a daily screening to identify whether they were ready for a weaning trial. The criteria for this trial were:

   - The disease causing the need for intubation was controlled
   - No clinical sign of respiratory failure
   - FiO₂ ≤ 50% and PEEP ≤ 5 cmH₂O
   - SaO₂ ≥ 90%
   - RASS score ≥ -2, without continuous sedation (analgesics permitted)
   - Hemodynamic stability without vasopressor

   The weaning trial consisted of 1 hour of pressure support ventilation with a pressure support level at 7 cmH₂O and no PEEP.

   Extubation required all of the following conditions:

   - SpO₂ ≥ 90% with a FiO₂ ≤ 50%
   - RR ≤ 35/min
   - Adequate response to simple commands
- Acceptable cough capacity
- No need for frequent suctioning
- Hemodynamic stability without vasopressor
- No worsening on the ABG if performed (not mandatory)

**Quality control**

All the investigators reviewed and approved the case report form before the first patient was included, thus ensuring a strict and homogenous method of data collection. Before the start of this study, medical teams at all participating centers received the same specific training in the protocol. This training was based on a specially designed tool to adjust the gain during PAV+. This tool consisted of a slideshow specifically developed for this purpose. During the study, telephone assistance from the coordinating center (Henri Mondor Hospital) was available 24h/d. The collected data were entered into a database (Microsoft Excel; Microsoft Corporation, Redmond, WA) and then reviewed for inconsistencies and data entry errors by one investigator (GC).

**Statistics**

Statistical analyses were performed with Statistical Package for the Social Sciences (version 16.0, SPSS, Chicago, IL, USA). Continuous data are expressed as the median (25th, 75th percentile). Continuous data were compared before and after the start of PAV+ ventilation using a Wilcoxon signed-rank test. Comparisons between patients that were or were not extubated at the end of the PAV+ ventilation were made using a Mann-Whitney U test. A two-sided p-value of 0.05 or less was considered statistically significant.
REFERENCES


