The mechanisms of severe COVID-related ARDS are heterogeneous and still not well understood. However, COVID-19 appears to be associated with a strong activation of respiratory drive and excessive inspiratory effort. Many Covid-19 patients exhibit a very strong respiratory drive – either as a consequence of their hypoxemia or – potentially – a direct influence of the virus on the respiratory control center. Covid-19 patients might therefore be particularly vulnerable to develop P-SILI and their respiratory drive should be monitored.

Excessive respiratory drive and effort is believed to be an important factor for the disease progression in COVID-19 patients in several ways, potentially leading to a transition from phenotype L to H and further to F, as postulated by Tonelli et al.

Years ago, Takeshi Yoshida et al. already demonstrated in histologic examinations that when lung injury is already present/severe, excessive spontaneous breathing can lead to worsening of the injury.

High Drive and Effort may lead to:
- P-SILI
- NIV failure
- prolonged disease/ventilation
- pathogenic stress/strain
- high transpulmonary pressures, transvascular stress & pulmonary oedema
- diaphragm injury
- asynchronies
COVID-19 RELATED ARDS – EXCESSIVE RESPIRATORY DRIVE AND EFFORT. FACTORS FOR DISEASE PROGRESSION?

POST INTUBATION

In addition, excessive drive and effort can lead to relapse of respiratory failure in critically ill and mechanically ventilated patients with COVID-19 as described in a study by Esnault et al.15 In this study, P0.1 and ΔPocc were measured to estimate resp. drive and effort. The following cut-off values were identified: P0.1 ≥ 4cmH₂O and ΔPocc ≤15cmH₂O. 0% of patients with P0.1 of less than 4cmH₂O and with a Pocc of greater than -15cmH₂O had a relapse. Patients with a higher P0.1 and very negative Pocc had a 62.5% risk of relapse. This demonstrates the impact of respiratory effort, resulting in the call for close monitoring of respiratory drive and inspiratory effort18.

Read more in our clinical whitepaper on assisted spontaneous breathing and weaning. Click here to download.

Measuring Respiratory Drive and Effort

As respiratory drive and effort have been described as factors driving disease progression in COVID-19 patients by potentially causing P-SILI, it seems important to monitor these factors. They should also be considered in the decision on the respiratory support strategy for each individual patient, be that in the decision for intubation and subsequent invasive ventilation or in the process of weaning invasively ventilated patients.

There are various methods of measuring respiratory drive and effort at different levels. Different ways of clinical observation to estimate respiratory effort that can be applied even without any technical support.
Clinical Score to evaluate respiratory effort

<table>
<thead>
<tr>
<th>Element</th>
<th>Method</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate</td>
<td>By Counting (bpm)</td>
<td>≤ 20 = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21-25 = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26-30 = 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 30 = 4</td>
</tr>
<tr>
<td>Nasal Flaring (inspiration)</td>
<td>By Observation</td>
<td>1</td>
</tr>
<tr>
<td>Sternocleidomastoid Use</td>
<td>By Palpation</td>
<td>1</td>
</tr>
<tr>
<td>(expiration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Muscles Use</td>
<td>By Palpation</td>
<td>1</td>
</tr>
<tr>
<td>(expiration)</td>
<td></td>
<td></td>
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</tbody>
</table>


Clinical observations in non-intubated patients
Apigo and colleagues introduced a scoring system to evaluate respiratory effort by clinical observation of 19:
- Respiratory Rate
- Nasal Flaring
- Sternocleidomastoid muscle use strain
- Abdominal muscle use during expiration

This score provides an uncomplicated way to get an indication of the respiratory effort to estimate if a patient is prone to P-SILI potentially requiring invasive respiratory support. The authors conclude that their data suggest that patients with COVID-19 associated pneumonia can be supported for extended periods using High-Flow Nasal Cannulae (HFNC) despite tachypnea, provided there is only infrequent or modest use of respiratory accessory muscles, corresponding to a WOB scale ≤4 and prompting closer assessment for possible intubation when WOB scale is >4. However, data from a larger cohort of patients is awaited for further proof of this concept. 19 One thing to keep in mind here is that in this concept, the respiratory rate in particular is a “parameter” that reacts rather late in patients developing hypoxemia and hypercapnia. 22

Ventilatory parameters in assisted ventilation
When assisted ventilation is applied, a set of measures can be monitored to evaluate respiratory drive and breathing effort:
- Tidal volume
- Respiratory rate
- P0.1 Maneuver
- \([Esophageal Pressure P_{es}]\)

Tidal volume may act as good value helping to identify patients who fail on non-invasive ventilation requiring intubation. Carteaux et al. identified a tidal volume of 9.5ml/kg/iBW as a cut off. Patients with tidal volumes ≥9.5ml/kg/iBW run a higher risk of failing on NIV and requiring invasive ventilation, as these patients make a great breathing effort indicating high respiratory drive. 20

But there is one thing to be kept in mind when looking at tidal volume: The human body has a fairly high tolerance of increased breathing as a response to decreasing \(\text{PaO}_2\). Minute ventilation is more or less unaffected unless \(\text{PaO}_2\) has dropped to 60mmHg. 21 But when \(\text{PaCO}_2\) increases, the first value to react is tidal volume at about 42mmHg, and only later, when \(\text{CO}_2\) increases further, the frequency will be increased at about 51mmHg. So these ventilatory parameters react late, with tidal volume coming first. 22
As already described above, $P_{es}$ can serve as an indicator for respiratory effort in spontaneously breathing patients, but is rather cumbersome to apply in non-invasively ventilated patients. However, the P0.1 Maneuver is another interesting measure for respiratory drive, not effort. For the P0.1 Maneuver, the ventilator measures the negative pressure generated in the first 100ms of inspiration, thought to be largely independent from total inspiratory effort, but a better reflection of respiratory drive.

**Dissociation of respiratory drive and effort**

When deciding on the measurements to be applied, it may be worth remembering that respiratory drive and breathing effort are not necessarily the same.

While respiratory drive is the neural output, breathing effort is the mechanical output, which in the end is likely to contribute to lung damage as described in the concept of patient self-induced lung Injury (P-SILI). Normally the ventilation (l/min) desired by the brain for a given $PaCO_2$ (translated into respiratory drive) exactly matches the ventilation actually achieved at a given $PaCO_2$ as a result of respiratory effort. But these two measures can also be dissociated if high elastance / low compliance restricts the respiratory system to deliver the brain’s demand. Also, sedation and fatigue may cause a dissociation of drive and effort. Therefore it might be sensible to measure drive and effort to identify excessive effort potentially leading to P-SILI and disease progression or relapse, but also fatigue.
Technical parameters monitoring drive and effort

In assisted ventilation, the following parameters may be used to monitor drive and effort in addition to the above mentioned ventilatory parameters:
- Esophageal Pressure (P_{es})
- Occlusion Pressure (P_{occ})
- P:01 Maneuver

Esophageal Pressure in COVID-19 patients may predict NIV failure

Another way of measuring respiratory effort is performing an occlusion maneuver to estimate muscle pressure (P_{musc}). The swing in airway pressure generated by respiratory muscle effort under assisted ventilation when the airway is briefly occluded (ΔP_{occ}) is a highly feasible technique to evaluate respiratory effort. ΔP_{occ} correlates well with the total muscle pressure, the muscle pressure being 0.75% of the measured ΔP_{occ} \text{24}.

The above described parameters represent values that seem to correlate well with respiratory drive and effort and that may contribute to lung damage and thus disease progression or relapse. However, the assessment of the lung condition is a crucial support in the decision for individualized therapy decisions, e.g. in inhomogeneous lungs. Computed tomography of the lung is the gold standard to assess the lungs condition but it requires transport. Bedside tools for lung imaging might be of help in the decision for the right respiratory support measures.

In our article on ventilating patients with COVID-19-associated ARDS, we reviewed relevant literature and four current guidelines to provide a practical overview. For references and details, please visit our website: www.draeger.com/covid-ventilation

Esophageal pressure as a surrogate for transpulmonary pressure can be used to estimate respiratory effort. P_{es} swings of >15cmH_{2}O represent excessive work of breathing potentially requiring mechanical ventilation or even sedation. In the above mentioned study by Tonelli and colleagues, only the patients with reduced ΔP_{es} successfully avoided intubation, whereas only those who did not improve their ΔP_{es} failed NIV and required
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