The development of clinical data on COVID-19 has been very rapid, resulting in a large amount of data being generated in a very short time. However, hard evidence still appears to be scarce. This article has been written to the best of our knowledge based on selected literature and opinions of clinical experts. It does not represent a summary of all available literature and therefore does not claim to be exhaustive. As COVID-19 is a very complex disease, you should always refer to the original literature mentioned in this article, other relevant literature and the circumstances of the individual case when deciding on the right ventilation strategy for your patients. It is also strongly advised to follow your national/local guidelines and standards.

The mechanisms of severe COVID-related ARDS are heterogeneous and still not well understood.[15] However, COVID-19 appears to be associated with a strong activation of respiratory drive and excessive inspiratory effort.[16]

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.[16]

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.[13]

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.[16]

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

!

PRE-INTUBATION

In non-invasively ventilated patients, monitoring the inspiratory effort by the means of Esophageal pressure (P_{es}) helps identify success and failure. Tonelli et al. showed that reduced inspiratory effort under NIV measured by reduced P_{es} swings was a predictor for success, whereas persistent inspiratory effort indicated by less pronounced reduction in P_{es} swings predicted failure, and patients were more likely to require invasive support. NIV reduced P_{es} swings and resulted in less inspiratory effort within the first 2 hours of NIV. Negative impact of high P_{es} swings on the lung were also shown in radiologic changes. Even though this is an interesting finding, measuring P_{es} in non-invasively ventilated patients may not always be practicable in daily clinical work.[17]

Read more in our clinical whitepaper on non-invasive respiratory support.
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!

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 ΔP_{occ} were measured to estimate resp. drive and effort. The following cut-off values were identified: P0.1 ≥ 4cmH_2O and ΔP_{occ} ≤15cmH_2O. 0% of patients with P0.1 of less than 4cmH_2O and with a P_{occ} of greater than -15cmH_2O had a relapse. Patients with a higher P0.1 and very negative P_{occ} 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 effort[18].

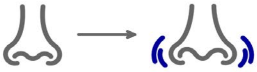
Read more in our clinical whitepaper on assisted spontaneous breathing and weaning.
Click here to download.

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

	Element	Method	Points
	Respiratory Rate	By Counting (bpm)	≤ 20 = 1 21-25 = 2 26-30 = 3 > 30 = 4
	Nasal Flaring (inspiration)	By Observation	1
	Sternocleidomastoid Use (inspiration)	By Palpation	1
	Abdominal Muscles Use (expiration)	By Palpation	1

Apigo M, Schechtman J, Dhliwayo N, Al Tameemi M, Gazmuri RJ. Development of a work of breathing scale and monitoring need of intubation in COVID-19 pneumonia. Crit Care. 2020 Jul 31;24(1):477. doi: 10.1186/s13054-020-03176-y. PMID: 32736637; PMCID: PMC7393620.

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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 PaO_2. Minute ventilation is more or less unaffected unless PaO_2 has dropped to 60mmHg.[21] But when $PaCO_2$ increases, the first value to react is tidal volume at about 42mmHg, and only later, when 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.[23] **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 as a surrogate for transpulmonary pressure can be used to estimate respiratory effort. P_{es} swings of >15cmH_2O 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

Esophageal Pressure in COVID-19 patients may predict NIV failure

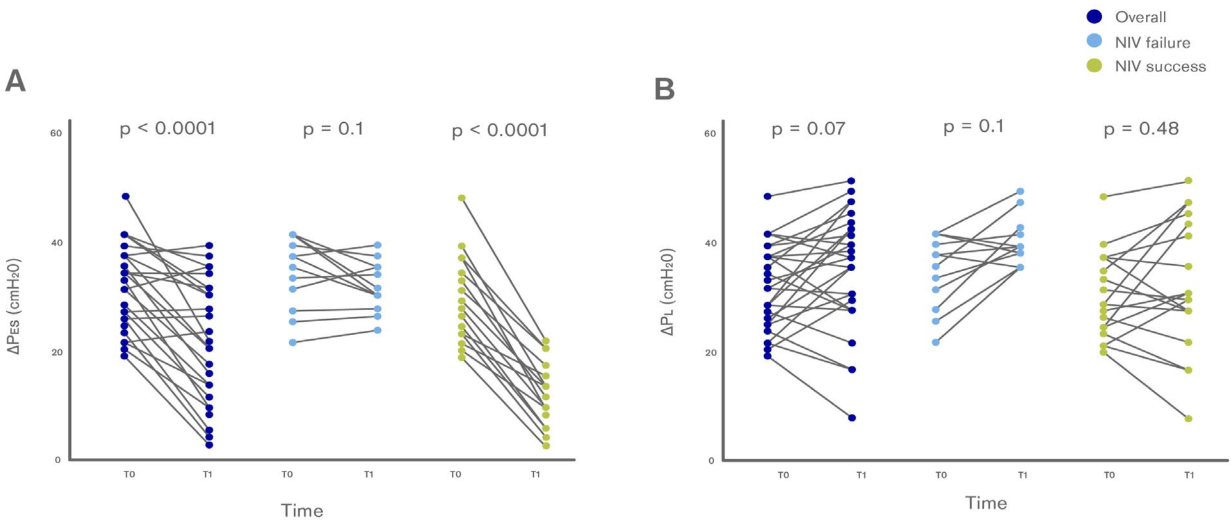

Figure 2
(A) ΔPes changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours. (B) ΔPL changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours. ΔPes = tidal change in esophageal pressure; ΔPL = tidal change in transpulmonary pressure; NIV = noninvasive mechanical ventilation.

Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, Della Casa G, D'Amico R, Girardis M, Nava S, Clini EM, Marchioni A. Early Inspiratory Effort Assessment by Esophageal Manometry Predicts Noninvasive Ventilation Outcome in De Novo Respiratory Failure. A Pilot Study. Am J Respir Crit Care Med. 2020 Aug 15;202(4):558-567. doi: 10.1164/rccm.201912-2512OC. PMID: 32325004; PMCID: PMC7427381.

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}[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

REFERENCES

1. Williams GW et al, Anesthesiology 2021;134:270; Pfortmueller CA et al, Best Practice & Research Clinical Anaesthesiology 2020; https://doi.org/10.1016/j.bpa.2020.12.011
2. Gattinoni L et al, COVID-19 Does Not Lead to a "Typcial" Acute Respiratory Distress Syndrom; Am J Respir Crit Care Med. 2020 May 15;201(10):1299-1300. doi: 10.1164/rccm.202003-0817LE.
3. Grasselli G et al., Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study, Lancet Respir Med. 2020 Dec;8(12):1201-1208. doi: 10.1016/S2213-2600(20)30370-2. Epub 2020 Aug 27.
4. Chiumello D et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. Intensive care medicine. 2020:1-10. doi:10.1007/s00134-020-06281-2
5. Ferrando C. et al., Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS, Intensive Care Med. 2020 Dec;46(12):2200-2211. doi: 10.1007/s00134-020-06192-2. Epub 2020 Jul 29.
6 Cummings M. J. et al., Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study, Lancet. 2020 Jun 6;395(10239):1763-1770. doi: 10.1016/S0140-6736(20)31189-2. Epub 2020 May 19.
7. Botta M. et al., Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study, Lancet Respir Med. 2021 Feb;9(2):139-148. doi: 10.1016/S2213-2600(20)30459-8. Epub 2020 Oct 23.
8. Gattinoni L. et al., COVID-19 pneumonia: different respiratory treatments for different phenotypes?, Intensive Care Med. 2020 Jun;46(6):1099-1102. doi: 10.1007/s00134-020-06033-2. Epub 2020 Apr 14.
9. Marini JJ et al., Integrating the evidence: confronting the COVID-19 elephant, Intensive Care Med. 2020 Oct;46(10):1904-1907. doi: 10.1007/s00134-020-06195-z. Epub 2020 Jul 25
10. Gattinoni L et al., The Respiratory Drive: An Overlooked Tile of COVID-19 Pathophysiology, Am J Respir Crit Care Med. 2020 Oct 15;202(8):1079-1080. doi: 10.1164/rccm.202008-3142ED
11. Younes Zaid et al, Platelet reactivity to thrombin differs between patients with COVID-19 and those with ARDS unrelated to COVID-19, Published online 2021 Jan 27. , doi: 10.1182/bloodadvances.2020003513
12. Chalmers JD et al, Eur Resp J, Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline, Apr 15;57(4):2100048. doi: 10.1183/13993003.00048-2021. Print 2021 Apr.
13. Tonelli R et al., Spontaneous Breathing and Evolving Phenotypes of Lung Damage in Patients with COVID-19: Review of Current Evidence and Forecast of a New Scenario, J Clin Med. 2021 Mar; 10(5): 975. Published online 2021 Mar 2. doi: 10.3390/jcm10050975
14. Osuchowski MF et al., The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity, Lancet Respir Med. 2021 May 6;S2213-2600(21)00218-6. doi: 10.1016/S2213-2600(21)00218-6. Online ahead of print
15. Esnault P at al, High Respiratory Drive and Excessive Respiratory Efforts Predict Relapse of Respiratory Failure in Critically Ill Patients with COVID-19, Am J Respir Crit Care Med. 2020 Oct 15; 202(8): 1173–1178. Published online 2020 Oct 15. doi: 10.1164/rccm.202005-1582LE
16. Takeshi Y et al, CCM 2013;41:536-545
17. Tonelli R et al., Early Inspiratory Effort Assessment by Esophageal Manometry Predicts Noninvasive Ventilation Outcome in De Novo Respiratory Failure A Pilot Study, Am J Respir Crit Care Med. 2020 Aug 15;202(4):558-567. doi: 10.1164/rccm.201912-2512OC
18. Gattinoni L et al., The Respiratory Drive: An Overlooked Tile of COVID-19 Pathophysiology, Am J Respir Crit Care Med. 2020 Oct 15;202(8):1079-1080. doi: 10.1164/rccm.202008-3142ED
19. Apigo et al. Crit Care. 2020 Jul 31;24(1):477
20. Carteaux G et al., Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume, Crit Care Med. 2016 Feb;44(2):282-90. doi: 10.1097/CCM.0000000000001379
21. Tobin MJ et al., Am J Respir Crit Care Med. 2020 Aug 1;202(3):356-360. doi: 10.1164/rccm.202006-2157CP.)
22. Vaporidi K et al., Am J Respir Crit Care Med. 2020 Jan 1;201(1):20-32. doi: 10.1164/rccm.201903-0596SO
23. Spinelli E et al., Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions, Intensive Care Med. 2020; 46(4): 606–618. Published online 2020 Feb 3. doi: 10.1007/s00134-020-05942-6
24. Bertoni M et al., A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation, Crit Care. 2019 Nov 6;23(1):346. doi: 10.1186/s13054-019-2617-0
25. Tomasino S et al, Semin Cardiothorac Vasc Anesth 2020;24:287-292
26. Morais CCA et al. Bedside electrical impedance tomography unveils respiratory "chimera" in COVID-19. Am J Respir Crit Care Med. 2021;203(1):120-1
27. Kotani T et al., Roles of Electrical Impedance Tomography in Determining a Lung Protective Strategy for Acute Respiratory Distress Syndrome in the Era of Coronavirus Disease 2019, JAMA J. 2021;4(2):81-85. DOI: 10.31662/jmaj.2021-0014
28. Gattinoni L. et al., COVID-19 and ARDS: the baby lung size matters, Intensive Care Med. 2021; 47(1): 133–134.Published online 2020 Dec 4. doi: 10.1007/s00134-020-06324-8
29. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators et al., 'Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial', JAMA, 27 September 2017, https://doi.org/10.1001/jama.2017.14171
30. Zhao Z et al., 'Positive End-Expiratory Pressure Titration with Electrical Impedance Tomography and Pressure–Volume Curve in Severe Acute Respiratory Distress Syndrome', Annals of Intensive Care 9, no. 1 (December 2019): 7, https://doi.org/10.1186/s13613-019-0484-0

31. Zarantonello F et al., 'Prone Position and Lung Ventilation/Perfusion Matching in Acute Respiratory Failure Due to COVID-19', American Journal of Respiratory and Critical Care Medicine, 21 May 2020, rccm.202003-0775IM, https://doi.org/10.1164/rccm.202003-0775IM
32. Guérin C et al., 'A Prospective International Observational Prevalence Study on Prone Positioning of ARDS Patients: The APRONET (ARDS Prone Position Network) Study', Intensive Care Medicine 44, no. 1 (2018): 22–37, https://doi.org/10.1007/s00134-017-4996-5.
33. Wiggermann N et al, 'Proning Patients With COVID-19: A Review of Equipment and Methods', Human Factors, 16 August 2020, 0018720820950532, https://doi.org/10.1177/0018720820950532
34. German S3 Guideline – Recommendations for the therapy of hospitalised patients with COVID-19, Version 4.1, February 2021
35. Surviving Sepsis Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First Update; March 2021; doi: 10.1097/CCM.0000000000004899.
36. ERS Guideline for the Management of hospitalized adults with coronavirus disease 2019 (COVID-19): A European Respiratory Society living guideline, January 2021, DOI: 10.1183/13993003.00048-2021
37. Australian guideline for clinical care of people with COVID-19, National COVID-19 Clinical Evidence Taskforce (Link)
38. Grieco DL et al., Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial, JAMA. 2021 May 4;325(17):1731-1743. doi: 10.1001/jama.2021.4682
39. Perkins GD et al., RECOVERY- Respiratory Support: Respiratory Strategies for patients with suspected or proven COVID-19 respiratory failure; Continuous Positive Airway Pressure, High-flow Nasal Oxygen, and standard care: A structured summary of a study protocol for a randomised controlled trial, Trials. 2020 Jul 29;21(1):687. doi: 10.1186/s13063-020-04617-3
40. Patel BK et al., Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial, JAMA. 2016 Jun 14;315(22):2435-41. doi: 10.1001/jama.2016.6338
41. Leasa D et al., Knowledge translation tools to guide care of non-intubated patients with acute respiratory illness during the COVID-19 Pandemic, Crit Care. 2021 Jan 8;25(1):22. doi: 10.1186/s13054-020-03415-2
42. Papoutsi E et al, Crit Care 2021;25:121
43. Raoof S et al., High-Flow, Noninvasive Ventilation and Awake (nonintubated) proning in Patients with Coronavirus Disease 2019 with Respiratory Failure, Chest. 2020 Nov;158(5):1992-2002. doi: 10.1016/j.chest.2020.07.013. Epub 2020 Jul 15.]
44. Carteaux G et al., Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume, Crit Care Med. 2016 Feb;44(2):282-90. doi: 10.1097/CCM.0000000000001379
45. Pisano A et al., Indications for Tracheal Intubation in Patients With Coronavirus Disease 2019 (COVID-19), J Cardiothorac Vasc Anesth. 2021 May; 35(5): 1276–1280
46. Roca O at al., An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy, Am J Respir Crit Care Med. 2019 Jun 1;199(11):1368-1376. doi: 10.1164/rccm.201803-0589OC
47. Ricard JD et al., Use of nasal high fow oxygen during acute respiratory failure, Intensive Care Med. 2020 Sep 8 : 1–10. doi: 10.1007/s00134-020-06228-7
48. Zucman N et al., Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure, Intensive Care Med. 2020 Jul 15 : 1–3. doi: 10.1007/s00134-020-06177-1
49. Duan J et al., Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients, Intensive Care Med. 2017 Feb;43(2):192-199. doi: 10.1007/s00134-016-4601-3. Epub 2016 Nov 3.]
50. Brault C et al, AJRCCM 2020, doi 10.1164/rccm.202005-2025LE
51. Telias I et al., 'Airway Occlusion Pressure As an Estimate of Respiratory Drive and Inspiratory Effort during Assisted Ventilation', American Journal of Respiratory and Critical Care Medicine 201, no. 9 (1 May 2020): 1086–98, https://doi.org/10.1164/rccm.201907-1425OC.
52. Positionspapier zur praktischen Umsetzung der apparativen Differenzialtherapie der akuten respiratorischen Insuffizienz bei COVID-19: Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP), https://www.researchgate.net/publication/340865640_Positionspapier_zur_praktischen_Umsetzung_der_apparativen_Differenzialtherapie_der_akuten_respiratorischen_Insuffizienz_bei_COVID-19_Deutsche_Gesellschaft_fur_Pneumologie_und_Beatmungsmedizin_eV_DGP
53. Rose L et al., 'Automated versus Non-Automated Weaning for Reducing the Duration of Mechanical Ventilation for Critically Ill Adults and Children', Cochrane Database Syst Rev 6 (2014).
54. Lellouche F et al., 'A Multicenter Randomized Trial of Computer-Driven Protocolized Weaning from Mechanical Ventilation', American Journal of Respiratory and Critical Care Medicine 174, no. 8 (15 October 2006): 894–900, https://doi.org/10.1164/rccm.200511-1780OC.
55. Taenaka H. et al., Individualized ventilatory management in patients with COVID-19-associated acute respiratory distress syndrome, Respir Med Case Rep. 2021; 33: 101433. Published online 2021 May 31. doi: 10.1016/j.rmcr.2021.101433
56. Zhao Z. et al., The use of electrical impedance tomography for individualized ventilation strategy in COVID-19: a case report, BMC Pulm Med. 2021; 21: 38. Published online 2021 Jan 22. doi: 10.1186/s12890-021-01411-y

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