A proposed lung ultrasound and phenotypic algorithm for the care of COVID-19 patients with acute respiratory failure

Proposition d’un algorithme basé sur l’échographie pulmonaire et le phénotype physiologique pour la prise en charge des patients atteints de la COVID-19 souffrant d’insuffisance respiratoire aiguë

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Abstract

Pulmonary complications are the most common clinical manifestations of coronavirus disease (COVID-19). From recent clinical observation, two phenotypes have emerged: a low elastance or L-type and a high elastance or H-type. Clinical presentation, pathophysiology, pulmonary mechanics, radiological and ultrasound findings of these two phenotypes are different. Consequently, the therapeutic approach also varies between the two. We propose a management algorithm that combines the respiratory rate and oxygenation index with bedside lung ultrasound examination and monitoring that could help determine earlier the requirement for intubation and other surveillance of COVID-19 patients with respiratory failure.

Résumé

Les complications pulmonaires du coronavirus (COVID-19) constituent ses manifestations cliniques les plus fréquentes. De récentes observations cliniques ont fait émerger deux phénomènes : le phénotype à elastance faible et le phénotype à elastance élevée.

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Two phenotypes for one pathophysiology

Two phenotypes have recently been suggested to describe the clinical features of respiratory failure in COVID-19—a low elastance (L-type) phenotype and a high elastance (H-type) phenotype. As the elastance is the inverse of the compliance, the L-type indicates high compliance, and the H-type the opposite. The phenotype’s differing presentations are based on viral load timing, comorbidities, and likely genetic determinants of the response to hypoxemia. The L-type is the most common phenotype (> 50%). Those patients present with hypoxemia and hypocapnia but without dyspnea. They have normal respiratory system mechanics, hence the reported term by several emergency physicians of “happy hypoxic COVID” because, despite significant oxygen desaturation, the patient remains alert and able to talk. While some may keep a normal respiratory drive, others may exhibit a significantly increased respiratory drive, which could induce a patient self-inflicted lung injury (P-SILI). Hypoxemia in the L-type phenotype is thought to result from a ventilation-perfusion mismatch and loss of hypoxic vasoconstriction leading to shunt fraction up to 50%. As reported in the acute respiratory system (ARDS), the severity seems to correlate with the difference between the end-tidal carbon dioxide and the arterial partial pressure of carbon dioxide (PaCO₂), which is an indirect measure of dead-space. The CT and chest radiographs reveal well-aerated compartments, patchy disease and ground-glass opacities with some peripheral involvement.

The high elastance (H-type) is more consistent with a classical picture of ARDS from non-COVID-19 settings. Hypoxemia in those patients is a result of shunting through the consolidated regions of the lung, which is more...
important than in the L-type. As those clinical manifestations are different, the treatment will vary according to the predominant pattern. Notably, a transition from L-type to H-type may evolve because of progression of COVID-19 pneumonia, injurious mechanical ventilation, and/or P-SILI.\textsuperscript{14-18} Regression from an H-type to L-type or gradual normalization has also been observed with CT during recovery (Fig. 1).\textsuperscript{20,21}

**Fig. 1** A) Computed tomography scan in a 68-yr-old coronavirus disease (COVID-19) patient with progressive dyspnea and oxygen saturation of 86% on room air. A L-type phenotypic pattern is shown. Lung ultrasound revealed a small right pleural effusion, several anterior subpleural consolidations, and B-lines in the posterior region. While in the intensive care unit, the patient experienced fever and progressive respiratory deterioration requiring intubation after 24 hr. The peripheral pulse oximetry remained at 87% despite a fraction of inspired oxygen (F\textsubscript{IO2}) at 100%, positive end-expiratory pressure titration of 10 cmH\textsubscript{2}O, and inhaled nitric oxide of 10 ppm. Blood gas revealed a pH of 7.37, partial pressure of carbon dioxide (PCO\textsubscript{2}) of 43.4 mmHg, and oxygen partial pressure (PaO\textsubscript{2}) of 63.8 mmHg. After 15 min of prone positioning, the SaO\textsubscript{2} increased to 95% and on the following blood gas assessment, the PaO\textsubscript{2}/F\textsubscript{IO2} ratio was 268 with a compliance of 53 mL-cmH\textsubscript{2}O. B) A repeat CT scan in the same patient was done on day 4 to rule-out a pulmonary embolism. A transition to the H-type is observed. C) Transition in a 49-yr-old man recovering from COVID-19 respiratory failure. His phenotype changed from an H-type to an (D) L-type (courtesy of Dr. Emmanuel Charbonney and Dr. Lawrence Leroux)

**Proposed management algorithm**

Figure 2 outlines a proposed management algorithm for a rational approach to ventilatory support of COVID-19 patients with acute respiratory failure. Although it will need careful prospective clinical evaluation, it can be considered an “outside the box” perspective in this new clinical frontier. Its purpose is to help clarify the importance in ventilation strategies, which will be very different for the two ARDS phenotypes seen in COVID-19.

**Ventilation strategies for different phenotypes**

We propose that the algorithm be initiated when oxygen therapy is needed to correct symptomatic hypoxemia in COVID-19 patients with acute respiratory failure—e.g., when hypoxemia occurs that is refractory to oxygen...
therapy with a high-flow nasal cannula (HFNC) with an increased fraction of inspired oxygen (FIO2). Traditionally, the response to oxygen therapy is assessed with the oxygen partial pressure (PaO2)/FIO2 ratio22 or alternatively, when using peripheral pulse oximetry (SpO2), the SpO2/FIO2.23 Even though these ratios are well documented, they do not take into account the underlying respiratory workload. A PaO2/FIO2 ≤ 150 mmHg is considered a severe hypoxemic state and mandates close clinical supervision and intervention. The medical community is now supporting the use of HFNC as a clinically accepted adjunct approach to treating hypoxemia in COVID-19 patients.24 The

Fig. 2 COVID-19 respiratory failure management. Following clinical and ultrasound examination to determine the L-type (low elastance) or H-type (high elastance) pattern, oxygen therapy is initiated. There can be progression or regression from one type to the other. The respiratory rate and oxygenation (ROX) index can be used, calculated, and monitored along with lung ultrasound to help in the process of deciding if and when to intubate. Mechanical ventilation settings include the tidal volume (TV), the respiratory rate (RR), and the degree of positive end-expiratory pressure (PEEP), which will vary according to the L or H phenotype. * Indicates that the decision to intubate is based on oxygenation and ventilation failure or compromised airway patency before initiating mechanical ventilation. ARDS = acute respiratory distress syndrome; CT = computed tomography; ECMO = extracorporeal membrane oxygenation; ETCO2 = end-tidal carbon dioxide; FIO2 = inspired oxygen; P = pressure; PaO2 = oxygen partial pressure; PAP = pulmonary artery pressure; PBW = predicted body weight; Pplat = plateau pressure; ROX index; SpO2 = pulse oxygen saturation; V/Q = ventilation perfusion. Adapted in part from Gattinoni et al.11, 13 and Marini et al.27
literature from HFNC technology proposes a novel index, validated as a prognostic outcome of short-term HFNC therapy. This respiratory rate and oxygenation (ROX) index is based on the traditional \( \frac{\text{PaO}_2}{\text{FIO}_2} \) ratio, but is then coupled with the respiratory rate.\(^{23,25}\) For practical bedside use, \( \text{PaO}_2 \) is substituted for \( \text{SpO}_2 \), so the ROX index is defined as the \( \left( \frac{\text{SpO}_2}{\text{FIO}_2} \right) / \text{respiratory rate} \). It can be calculated using an online tool (https://qxmd.com/calculate/calculator_724/rox-index-to-predict-risk-of-intubation).

As an example, a patient with an \( \text{SpO}_2 \) of 80\%, an \( \text{FIO}_2 \) of 0.8, and a respiratory rate of 35/min \( \left( \frac{80/0.8}{35} \right) \) will have a ROX index of 2.8. As the respiratory condition deteriorates, the ROX index decreases.

Roca et al. have suggested various ROX index cut-off values that are associated with the need for intubation.\(^{23}\) Values below 2.85, 3.47, and 3.85 are the cut-off values used at two, six, and twelve hour, respectively. No predictive index is perfect, and a gray zone obviously exists between 3.85 and 4.88, in which it is difficult to firmly conclude what the optimal management should be. However, monitoring the ROX index over time, with emphasis from the 12th hour onwards, suggests that if the ROX index is \( \geq 4.88 \), then the patient has a high chance of avoiding intubation. If the ROX index is \( < 3.85 \), then the risk of HFNC failure is high. In the initial study of the ROX index\(^{23}\) among patients in this zone, the ROX index...
could be repeated one or two hours later. If the score has increased, the patient should be considered with a higher likelihood of avoiding intubation. If it has decreased, then intubation has a higher likelihood to be necessary. If the score is unchanged, then reassessment should be performed after one or two more hours. The ROX index has recently been implemented by one of the authors (N.P.) and is being considered, along with advice from other experts in mechanical ventilation, by the French Ministry of Health, who have arbitrarily decided to re-assess the ROX index every 30 min. They have chosen a change in the ROX index of 0.5 to monitor the rapid onset of symptoms in the average COVID-19 patient compared with the usual ARDS patient. Therefore, a reduction of the ROX index by 0.5 from baseline over 30 min is considered significant and may suggest imminent need for intubation. Indeed, such a strategy obviously requires a prospective evaluation.

The sensitivity and specificity of lung ultrasound findings for COVID-19 remains to be determined. Nevertheless, based on several case series, editorials/commentaries, a recent narrative review, and the authors own experience, four basic ultrasound patterns can be observed: 1) normal pattern (A lines and < 3 B-lines); 2) mild disease: ≥ 3 B-lines with some of them being confluent (waterfall or beam like) and thickened pleura suggestive of an L-type; 3) broken pleural lines; and 4) severe disease with subpleural consolidation and a typical ARDS picture. The fourth pattern is more suggestive of an H-type. In H-type, ultrasound examination will often reveal some L-type features, such as loss of aeration and overlapping areas of peripheral or subpleural consolidation, but pathological lesions will mostly be seen in the posterior region of the lung. Management and triage would be different in patients with more extensive disease. Nevertheless, it is possible that the extent of any abnormal lung ultrasound pattern might be more important than the actual pattern or type of pathology itself. A large number of abnormal regions would correlate with the severity of lung

**Role of lung ultrasound monitoring**

Following the initiation of mechanical ventilation, it becomes important to discriminate between type-L vs type-H ARDS phenotypes for proper ventilator strategies as proposed by Marini et al. This is where lung ultrasound can be useful.

**Fig. 4** Computed tomographic and lung ultrasound correlation in a COVID-19 patient with subpleural consolidation. (Courtesy of Dr. Stéphan Langevin and Mr. Jacques Cadorette) (Video 4 available as Electronic Supplementary Material)
inflammation. Pleural effusions have been uncommonly observed and were present in only 4.7% of patients in a series by Lomoro et al. and in 10% of patients in a separate report by Xing et al. The reduction or absence of a vascular Doppler signal in the areas of peripheral or subpleural consolidation (Fig. 1D,1F) is common in COVID-19 and could represent peripheral segmental lung infarction through a microangiopathy, as described recently by autopsies from the United States. Coronavirus disease could be associated with an increased incidence of thrombotic complications such as pulmonary embolism.

Fig. 5 Examples of various COVID-19 complications detected using bedside ultrasound. Pulmonary hypertension with a trans-tricuspid pressure gradient (PG) of 45 mmHg in a patient developing right ventricular failure. B) Transthoracic short-axis aortic valve view showing a dilated right ventricular outflow tract (RVOT) of 35 mm and pulmonary artery in a patient with pulmonary embolism. C) Deep venous thrombosis of the femoral vein. D) Abnormal hepatic vein flow (HVF) Doppler velocity suggestive of right ventricular diastolic dysfunction. E) Renal venous congestion pattern-II associated with right ventricular dysfunction. F) Enlarged optic nerve sheath (ONS) in a patient with severe encephalopathy and extra-pyramidal signs. (Courtesy of Dr. Caroline Gebhard and Stephan Langevin.). AR = atrial reversal HVF; D = diastolic HVF; S = systolic HVF. (Video 5B, 5C available as Electronic Supplementary Material.)

As with any patients in the intensive care unit, COVID-19 patients can also develop other pulmonary complications. These include superimposed bacterial pneumonia, cardiogenic pulmonary edema related to myocardial dysfunction, right ventricular dysfunction and pulmonary hypertension due to pulmonary embolism, pleural effusions, and pneumothoraces. As suggested by Volpicelli et al., the bilateral patchy distribution of multiform clusters, alternating with “spared areas” is typical of the disease. Any other ultrasound signs should be considered at intermediate probability and should lead to further testing.

Bedside ultrasound could be useful in detecting associated pulmonary complications or non-pulmonary complications such as cardiac dysfunction that can occur in such patients. Combining heart, lung, deep veins examination and whole-body ultrasound can identify the mechanism, risk factors, and life-threatening conditions in patients with respiratory symptoms (Fig. 5). Lung ultrasound can also impact clinical decision-making in patients with acute respiratory failure and provide comprehensive monitoring of regional lung aeration changes that could be used to predict response to prone positioning with improved right
ventricular function (Figs 6 and 7) or higher positive end-expiratory pressure strategy. Newer modalities such as strain and speckle tracking could eventually be used to detect early abnormal peripheral pulmonary stress. The authors strongly advocate ultrasound as the key to rapid repeated progress imaging (rather than CT, which is more expensive and has logistical difficulties) and hence a decision to intubate would clearly be influenced by a rapidly deteriorating set of ultrasound images.

Repeated ultrasound imaging over time can allow for accurate determination of the progression of lung pathology and can strongly influence a decision to institute early mechanical ventilation. Such repeated ultrasound imaging would be logistically convenient at the bedside without transporting the patient to the radiology department and would not involve any radiation dosing. Nevertheless, although lung ultrasound outperforms chest radiograph, it cannot be as comprehensive as CT since any lung pathology not involving the surface of the lung (and therefore covered by some aerated lung) cannot be detected by ultrasound. Lung ultrasound can be performed with a wide range of ultrasound machines, including handheld devices. The advantage of the handheld devices is that they can be fully enclosed in a plastic sheath, thereby reducing the risk of equipment contamination and spread of infection between patients. The performance and interpretation of lung ultrasound is much simpler than other imaging modalities such as transthoracic echocardiography as the images are easy to acquire and there are a limited number of patterns to interpret. Education can be scaled to meet the COVID-19 crisis through online courses (e.g., https://www.iteachu.com/courses/covid-19-lung-ultrasound/) simulation, and peer-to-peer mentoring.

**Other management modalities and limitations**

Other important elements in deciding whether to intubate is the work of breathing. This can also be monitored clinically by observing the use of accessory muscles or by measuring or estimating changes in pleural pressure. Once mechanical ventilation is initiated, tidal volume, respiratory rate, positive-pressure ventilation, prone positioning and veno-venous extracorporeal membrane oxygenation, sedation, and neuromuscular blockade will be adjusted differently depending on the phenotype and in accordance to ARDS management guidelines.

Finally, there are still several unanswered questions and uncertainties regarding COVID-19 respiratory infections and the role of bedside ultrasound. We are still on an
ascending learning curve regarding this new medical condition. Our proposed algorithm, which reflects the current understanding of COVID-19 respiratory failure, is likely to evolve as new information becomes available. The Table summarizes key questions on respiratory complications and management in COVID-19 patients with the use of lung ultrasound.

Table Undetermined issues in the respiratory complications and use of lung ultrasound in COVID-19 patients

1) What are the sensitivity and specificity of the ultrasound findings in determining the severity and type of lung disease phenotypes?
2) What is the sensitivity and specificity of the ROX index in predicting requirement for intubation and how does it correlate with ultrasound findings?
3) What is the mechanism of hypoxia in the early phase or L-type phenotype?
4) What are the performances of the various lung ultrasound scoring systems?
5) What are the role of the new modalities such as strain and speckle tracking in detecting early abnormal peripheral pulmonary stress?
6) What are the case-based or population-based outcomes related to specific lung ultrasound findings?
7) Can we determine response to prone positioning with lung ultrasound?
8) Does the routine use of lung ultrasound improve the care of COVID-19 patients?
9) What is the outcome of a different lung strategy with or without lung ultrasound for the L-type and H-type phenotypes?

COVID-19 = coronavirus disease; ROX = respiratory rate and oxygenation

Fig. 7 Cardiac examination and portal vein interrogation before (A–B) and after (C–D) prone positioning. Note the reduction in the size of the right ventricle (RV) in relation to the left ventricle (LV) and the improved portal velocities and reduction in the portal vein pulsatility index (PVPI). (Courtesy of Dr. Stéphan Langevin.) (Videos 7A and 7C available as Electronic Supplementary Material.)
contribute to understanding more about the two suggested phenotypes described by Gattinoni et al.\textsuperscript{11,13} It might also be used to confirm or challenge the aforementioned phenotypes categorization.\textsuperscript{69,70} Bedside lung ultrasound can help identify severity of lung involvement and response to therapy, as part of evaluation for ventilation as well as during the recovery and weaning process. With the implementation of this emerging information, clinical management may be somewhat distinct from that of other evidence-based interventions. As a result, clinical trials will be required to determine the best ventilation strategies for the different lung-involvement phenotypes seen in hypoxic COVID-19 patients.

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