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REVIEW Open Access

Caution about early intubation and mechanical ventilation in COVID-19

Martin J. Tobin*, Franco Laghi and Amal Jubran

A fear of ventilator shortage with COVID-19 panicked politicians into demanding automakers to branch into ventilator manufacture.

Some experts have argued that mechanical ventilation should be employed early in order to prevent COVID-19 patients progressing from mild disease to more severe lung injury. This viewpoint has been expressed most forcefully by Marini and Gattinoni in a *JAMA Editorial* [1], where they attest that vigorous spontaneous inspiratory efforts can rapidly lead to patient self-induced lung injury (P-SILI).

P-SILI is thought to parallel ventilator-induced lung injury (VILI), an entity supported by decades of experimentation and randomized trials [2]. In contrast, P-SILI has surfaced only in the past 4–5 years [3]. Two research studies are commonly cited by authors warning about P-SILI [1, 3–5].

To induce hyperventilation, Mascheroni et al. [6] infused salicylate into the brainstem of spontaneously breathing sheep. The authors claim that the consequent ~ threefold increase in minute ventilation produced lung injury, and this was prevented by mechanical ventilation. Tidal volume (the focus of authors warning about P-SILI) [1, 3–5] increased from 178 to 235 ml. The proportional tidal volume in healthy humans would be 502 ml—much less than experienced by healthy pregnant women.

In a non-blinded, observational study, patients with acute respiratory failure who failed noninvasive ventilation had higher tidal volume than successfully managed patients. Carteaux et al. [7] concluded that high tidal volume predicted need for endotracheal intubation. Patients ultimately intubated were significantly sicker than non-intubated patients: more frequent immunosuppression (37.5% v 6.7%), higher SAPS II (41 v 30), and lower PaO_2/FiO_2 (122 v 177). Need for intubation was more likely precipitated by severity of underlying illness than tidal-volume size (which was found to be a marginal predictor). Tidal volumes in these two studies do not constitute a sound scientific basis for occurrence of P-SILI in patients with COVID-19.

Based on the P-SILI hypothesis, Gattinoni and coauthors advocate radical changes to ventilator management of patients with COVID-19. They claim that noninvasive options are of "questionable" value [5], "intubation should be prioritized", [4] and delayed intubation will cause a P-SILI vortex that induces more severe ARDS [1].

They view heightened respiratory drive in COVID-19 patients as maladaptive, and recommend deliberate lowering of respiratory drive in these patients [1]. They claim that "near normal compliance … explains why some of the patients present without dyspnea" [5]. If a COVID-19 patient is severely hypoxic, normal lung compliance will not prevent dyspnea. Concurrently some COVID-19 patients are free of dyspnea despite substantial hypoxemia (dubbed "silent-happy hypoxia") [8]. This arises because the level of hypoxemia per se is not sufficiently low to induce increased respiratory motor output and accompanying $PaCO_2$ levels blunt the hypoxic response [2, 9].

To assess patient effort, Gattinoni and coauthors recommend inserting an esophageal balloon as a "crucial" step [5]. They specify that when esophageal-pressure swings increase above 15 cmH_2O, "the risk of lung injury increases and therefore intubation should be performed

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as soon as possible" [5]. No experimental data exists to justify this assertion. Expressing vague and ill-defined concepts in mathematical terms gives them a specious air of respectability that cloaks lack of knowledge and perpetuates confusion. Equally important, manipulations of the upper airway while inserting an esophageal balloon in a dyspneic COVID-19 patient will escalate the risk for endotracheal intubation.

We are not recommending a desultory approach to instituting mechanical ventilation or saying that numbers are not important. When we learn that a patient is acutely and persistently hypoxemic despite supplemental oxygen, we immediately consider steps to institute assisted ventilation. But it is not possible to pick an oxygen saturation breakpoint at which the benefits of mechanical ventilation will decidedly outweigh its hazards across all patients [2]. To recommend instituting mechanical ventilation based on esophageal-pressure swings above 15 cmH_2O [5] amounts to playing with fire.

Mechanical ventilation is lifesaving in severe respiratory failure, and few medical therapies equal its power [2]. While some COVID-19 patients can be managed with supplemental oxygen, patients with the most severe respiratory failure demand insertion of an endotracheal tube [8]. An endotracheal tube facilitates control over an unstable airway and enables precise regulation of oxygen, pressure and volume [10]. But the endotracheal tube brings in its wake a slew of complications [2]. Each day of mechanical ventilation exposes patients to complications and increases mortality [2].

Recommendations based on P-SILI for discontinuation of mechanical ventilation in COVID-19 patients are particularly radical. Marini and Gattinoni recommend that "weaning should be undertaken cautiously" [1]. Numerous studies demonstrate that physicians are unnecessarily cautious in assessing patients for weaning [2, 10]. To advocate "spontaneous trials only at the very end of the weaning process" [1] is a formula to increase mortality in COVID-19 patients—especially when an insufficient supply of ventilators is feared and some authorities recommend connecting four patients to a single ventilator.

The process of transforming thoughts about a new biological entity into material things (reification) takes years. Once existence of a new entity is corroborated through additional research, it acquires substance and is gradually accepted as approximating truth. History is replete with entities once viewed as real, now considered fiction (status lymphaticus, visceroptosis). At this time, the existence of P-SILI is based only on the shakiest of circumstantial evidence and has yet to be exposed to the acid-wash of experimental testing by differing scientists. Yet P-SILI is being promoted as a *raison d'etre* for a radical approach to mechanical ventilation in the time of the COVID-19 pandemic.

The true impact of mechanical ventilation in COVID-19 will never be known. It depends on whether intubated patients truly required mechanical ventilation or whether they could have been sustained with oxygen supplied by less drastic methods [8]. It is difficult to determine how many physicians have been influenced by P-SILI as a justification for preemptive mechanical ventilation as a preventive measure.

Even if high tidal volume and P-SILI play some role in the progression of respiratory failure in COVID-19 patients—for which there is no convincing evidence—this would not provide justification for liberal use of endotracheal intubation, for which there are decades of research documenting fatal complications.

Abbreviations

VILI: Ventilator-induced lung injury; P-SILI: Patient self-induced lung injury; SAPS II: Simplified Acute Physiology Score II.

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LETTER TO THE EDITOR

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Spontaneous breathing, transpulmonary pressure and mathematical trickery

Luciano Gattinoni[1*], John J. Marini[2], Mattia Busana[1], Davide Chiumello[3] and Luigi Camporota[4]

Dear Editor,

We read with interest the review by Tobin, Laghi and Jubran on mechanical ventilation in COVID-19 [1]. Rather than a balanced review of the literature, the authors have chosen their sources (mostly opinion pieces) selectively to challenge our interpretation of the data and approach to the problem. Their contention is that patient-self-inflicted lung injury (P-SILI) may be inconsequential to the amplification of lung injury and is not a justification for the 'liberal use of endotracheal intubation …[which leads to] …fatal complications..'

Having spent large portions of our investigative careers in addressing lung injury and respiratory mechanics, imagine our dismay to learn from them that very few persons require intubation, that P-SILI is a figment of our imaginations, that oesophageal balloons have little value, and that we are using the smoke and mirrors of mathematics to mislead our colleagues. A re-reading of our cited papers has caused us to puzzle why such grave contentions were made by our critics. These deserve a detailed response.

For the reader unaware of the controversial debate on this issue, we summarize our view: patients with COVID-19 acute hypoxaemic respiratory failure (AHRF) often present with profound hypoxaemia paired with unusually good compliance, preserved lung gas volume on CT chest imaging, and substantial increases of respiratory drive and minute ventilation. The excessive drive may amplify the risk of lung damage through P-SILI. If oxygen, HFNC, CPAP, and NIV are unable to subdue vigorous inspiratory efforts even after resolution of hypoxaemia, mechanical ventilation should be applied (i.e., we advocate avoiding delayed intubation—rather than early intubation *per se*). This statement derives from the observation of hundreds of patients in Italy and United Kingdom.

Tobin et al., as a criticism to our approach, maintain that P-SILI is a recent invention, not substantiated by adequate literature [1]. In fact, in 1938 Barach exploited spontaneous breathing to induce experimental lung oedema [2]. Since then, multiple papers in high-tier journals document regional damage from vigorous breathing efforts [3, 4], including a recently published study demonstrating that the median oesophageal pressure swing in patients with moderate or severe AHRF undergoing an NIV trial was 34 cmH_2O [5]. Reduction in oesophageal pressure swings (DP_{es}) was a clear indicator of NIV success and improved chest radiology [5].

In addition, vigorous respiratory efforts increase central blood flow and the likelihood of oedema forming in fluid-permeable lungs. In any case, the argument that the increased tidal volumes seen in heathy pregnant women do not lead to P-SILI cannot be applied to those with injured and diseased lungs. In this context, the study by Mascheroni et al. is cited misleadingly [1, 6]: The primary trigger for VILI is repeated strain associated with excessive transpulmonary pressure, however generated (ventilator or respiratory muscles). Therefore, using the oesophageal pressure swing to quantify the inspiratory effort is not a contributor to "vague and ill-defined concepts, expressed in mathematical terms". At the pressure we suggested of 15 cmH_2O, experimental and clinical data indicate that the strain exceeds 1, indicating that tidal volume is, at least, as big as resting lung volume. It is difficult to understand why instituting invasive

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ventilation when DP_{es} >15 cmH_2O, admittedly inexact, is equivalent to "playing with fire". Actually, employing mathematical thresholds to guide treatment is not unknown to the inventor of the rapid shallow breathing index and the advocate of a numerical plateau pressure threshold for VILI. Indeed, the same authors published that DP_{es} is a logical method to monitor weaning, as large DP_{es} are poorly tolerated.

As far as intubation timing, it is far too early to come to a conclusion as to the optimal approach in COVID-19. However, this disease has been characterized by sudden deterioration and lengthy time course [7]. The existing COVID-19 literature reports rates of invasive ventilation ranging from 21 to 90% of all patients with hypoxaemia and ARDS, with mortality rates from 16.7% up to 88–97% of completed episodes [8]. Tobin et al. [9] use this to suggest that invasive ventilation is fatal. However, institutions that adopted an early invasive ventilation strategy have one of the lowest mortality rates reported from the USA. The alternative argument may be that patient selection and a delayed timing of intubation may have played a role. The latter concern has been expressed by Chinese physicians reporting the Wuhan experience [7] and in their expert consensus on COVID-19 [10].

Regarding weaning, we agree with the authors that clinicians often delay extubation. Yet, premature liberation without adequate COVID resolution has led to high reintubation rates (up to 50%). This approach has obvious disadvantages: increased morbidity, mortality and hazard to healthcare staff.

In the end, we thank the authors for their epistemological lesson: finally, we have learned that to prove and disprove something is the basis of scientific progress (Karl Popper would feel gratified). It is possible, then, that future data will disprove the non-existence of spontaneously induced lung injury or prove the tragic consequences of ignoring a growing volume of solid experimental and observational data.

Authors' contribution

All authors contributed to writing and editing the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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LETTER TO THE EDITOR

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P-SILI is not justification for intubation of COVID-19 patients

Martin J. Tobin*, Franco Laghi and Amal Jubran

Dear Editor,

We thank Dr. Gattinoni and colleagues for their interest in our article and their thought-provoking comments [1, 2].

They are correct in observing we quoted opinion articles: three were by Gattinoni et al. We will not point out all instances where Gattinoni et al. misquoted our article, but two need to be addressed. One, they claim we communicated "very few persons require intubation"—we never said that. Two, they state "Tobin et al.…use this to suggest that invasive ventilation is fatal." On the contrary, we wrote "Mechanical ventilation is lifesaving in severe respiratory failure, and few medical therapies equal its power" [2].

In reference to experimental evidence supporting the existence of patient self-induced lung injury (P-SILI), Gattinoni and colleagues note that "Barach exploited spontaneous breathing to induce experimental lung oedema" [1]. On the contrary, Barach et al. are explicit in stating that they were "unable to confirm…that a pathologically elevated negative pressure was responsible for the occurrence of pulmonary edema" (page 770). It is true that pulmonary edema can result from large pleural pressure swings, such as consequent to upper airway obstruction. Patients with acute severe asthma develop large pleural pressure swings, yet autopsy studies in patients dying because of status asthmaticus are remarkable for the absence of pulmonary edema [3].

We are unsure what Gattinoni et al. [1] mean when they claim we cited the study of Mascheroni et al. misleadingly. In addition to previously highlighted problems, we add that 31% of hyperventilating sheep died without life-threatening hypoxemia, that surfactant properties in afflicted sheep were equivalent to control animals, the absence of a control group of sheep ventilated with ventilator settings that mimicked the breathing pattern of the non-intubated sheep, and *en passant* dismissal of neurogenic pulmonary edema. These flaws need to be underscored about a study regarded as an experimental foundation for the existence of P-SILI.

Gattinoni et al. [1] claim that the study by Tonelli et al. supports the existence of P-SILI. It does not. Tonelli et al. did record large swings in esophageal pressure (ΔPes), but did not document regional lung damage. If inspiratory efforts were causing P-SILI, one would expect a decrease in tidal volume-to-transpulmonary pressure swing ratio ($V_T/\Delta P_L$)—a surrogate of lung compliance. $V_T/\Delta P_L$ remained constant across 24 h of noninvasive ventilation (see Supplement: Figure E2, panel C in Tonelli et al). Worsening chest radiographs at 24 h cannot be linked mechanistically to P-SILI (or failure of noninvasive ventilation) because the radiographs were taken following intubation (to which a radiologist cannot be blinded).

Gattinoni and colleagues [1] note that frequency-to-tidal volume (f/V_T) is expressed with a threshold value. The f/V_T threshold was derived by first analyzing a training data set, and then accuracy of that f/V_T threshold was tested prospectively in a subsequent validation data set [4]. We used the same approach in our Pes weaning study [5]. This rigorous approach differs fundamentally from picking ΔPes of 15 cmH_2O based on theoretical rationalization without any experimental testing.

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Gattinoni and colleagues' recommendations regarding intubation in COVID-19 patients were explicit, without caveats: "intubation should be prioritized", and when ΔPes increases above 15 cmH_2O, "intubation should be performed as soon as possible" [2]. We are relieved they no longer recommend early intubation. They now "advocate avoiding delayed intubation"—but delayed intubation is a diagnosis that can be made only in hindsight.

We are pleased that Gattinoni et al. [1] have reversed their advice on weaning of COVID-19 patients and no longer recommend that "weaning should be undertaken cautiously" [2]. It is true that the rate of intubation and mortality in COVID-19 patients exhibits a broad range. All the more reason to avoid issuing explicit directions based on binary alliterative (H, L) ARDS phenotypes—as yet untested.

To help readers better understand the importance of P-SILI in influencing intubation and ventilator weaning in COVID-19 patients, we hope that Gattinoni and colleagues will answer the following questions:

(a) What *experimentum crucis* has been undertaken in humans to demonstrate that vigorous inspiratory efforts cause P-SILI?
(b) What calculus can they provide for the tradeoff between decades of documented complications consequent to intubation and mechanical ventilation versus the hypothesized existence of P-SILI?

We are not saying that P-SILI is an uninteresting hypothesis. We are concerned about recommendations for intubation and ventilator weaning during the COVID-19 pandemic based on an untested hypothetical entity.

Abbreviations
COVID-19: Coronavirus Disease 2019; f/V_T: Frequency-to-tidal volume; Pes: Esophageal pressure; P-SILI: Patient self-induced lung injury; $V_T/\Delta P_L$: Tidal volume-to-transpulmonary pressure swing ratio; ΔPes: Tidal swings in esophageal pressure.

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