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Using applied lung physiology to understand COVID-19 patterns

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Identifying patterns in observations has led to some of the most important scientific discoveries, such as the workings of the solar system (Copernicus), natural selection (Darwin), the periodic table (Mendeleev), and plate tectonics (Wegener). Drawing parallels and building models to explain observations are inherent modes of brain functioning to comprehend the world.[1] As stated by Charbonneau and colleagues,[1] 'Patterns give rise to scientific discovery; a break from an expected pattern or a newly recognized pattern demands to be explored, clarified, and understood. Connecting seemingly unrelated patterns can also lead to scientific discoveries … When scientists begin to see a series of patterns that all support the same conclusion, they can form a hypothesis that they can test by collecting more data and looking for more patterns'.

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Medicine is no exception, and there are countless examples on how observations were used to infer causal hypotheses, most notably for the mode of transmission of cholera by Snow in 1854, the discovery of blood types by Landsteiner in 1901, or the interpretation of the laws of inheritance and genetics by Mendel in 1865. When faced with a new, complex, or poorly understood disease, we look for patterns and diseases that relate (e.g. comparing heat stroke and malignant hyperthermia), or how seemingly related pictures diverge (e.g. differences between cerebral salt wasting syndrome and the syndrome of inappropriate antidiuretic hormone). Sometimes, the comparison may appear far-fetched but nonetheless valuable into highlighting disease mechanisms (e.g. muscle disuse in astronauts in space and ICU-acquired weakness[2]). Patterns cannot only lead to discovery, but also to prediction and action. Improving water sanitation in 19th century England had clear effects on cholera epidemics, and understanding the major blood types proved crucial for transfusions during World War I.

Since December 2019, coronavirus disease 2019 (COVID-19) has rapidly swept across the world. Efforts came from all corners to try to improve our understanding and management of this highly challenging disease, and unsurprisingly, a vast number of hypotheses and suggestions have arisen, based on the patterns of diseases, identifying phenotypes, or drawing parallels with occasionally seemingly disconnected clinical pictures. To list just a few examples, it has been suggested that COVID-19 had two major lung phenotypes[3,4]; that it was related to high-altitude pulmonary oedema[5]; and that it was linked with vitamin C[6] or D,[7] ultraviolet index,[8] melatonin,[9] or nicotine.[10] Some of these hypotheses have generated heated debates amongst scientists. Gattinoni and colleagues[3] describe explicitly the process of seeking patterns in their COVID-19 patients: 'These severely hypoxaemic patients despite sharing a single aetiology (SARS-CoV-2) may present quite differently from one another: normally breathing ("silent" hypoxaemia) or remarkably dyspnoeic; quite responsive to nitric oxide or not; deeply hypocapnic or normo/hypercapnic; and either responsive to prone position or not. Therefore, the same disease actually presents itself with impressive non-uniformity'. Similar remarks can be found online, for example, from an emergency physician in New York: 'You get used to seeing certain patterns, and the patterns I was seeing did not make sense'.[11] Identifying patterns in COVID-19 patients can have clear consequences on predicting future behaviour of a patient or informing clinical decision. For example, recommendations on mechanical ventilation for COVID-19 patients moving away from the strict ARDSnet protocol have been proposed.[3,4]

In this issue of the *British Journal of Anaesthesia*, Ottestad and Søvik[12] compare COVID-19 patients to high-altitude exposure. The authors argue that the acute exposure to altitude in otherwise healthy subjects leads to profound hypoxaemia with relatively little respiratory distress (the so-called 'silent hypoxia' or 'happy hypoxia'), and a decrease in P_{ACO_2} from compensatory hyperventilation, both phenomena also commonly observed in COVID-19 patients. By exposing healthy subjects to acute hypobaric hypoxia, the authors elegantly show how hypocapnia significantly shifts the oxygen–haemoglobin dissociation curve and improves blood oxygen saturation. The approach taken by Ottestad and Søvik[12] of examining the disease behaviour through the lens of applied lung physiology is very insightful and can be taken one notch further. A deep understanding of the clinical picture of COVID-19 patients can be gained by analysing the science behind respiratory failure and what drives the minute ventilation.[13–15]

In a steady state, the minute ventilation requirement of a patient is given by

$$\dot{V}E = \frac{\dot{V}P_{CO_2}}{(1 - \frac{VD}{VT}) \cdot Pa_{CO_2} \cdot k}$$

where $\dot{V}E$ is the minute ventilation (L min^{-1}), $\dot{V}P_{CO_2}$ is the CO_2 production (L min^{-1}), $VD/VT$is the ratio of physiological dead space to tidal volume, Pa_{CO_2} is the partial pressure of CO_2 in arterial blood, and k is a dimensional constant. This equation demonstrates that minute ventilation requirement is determined by only three factors: CO_2 production, VD/VT, and P_{ACO_2}.

It is important, yet under-recognised, that ventilation requirements (as elaborated by the preceding equation) and increased work of breathing are more potent drivers of subjective dyspnoea than hypoxaemia.[14] This underappreciation may result from the fact that, in most clinically encountered diseases with severe hypoxaemia, there is concomitant increased work of breathing, leading to confounding of separate but related processes. The physical loads on the respiratory system responsible for high work of breathing in disease states fall into four main categories: (i) elastic loads impeding tidal excursions (e.g. from parenchymal or pleural disease, or skeletal deformities, such as kyphoscoliosis), (ii) resistive loads on airflow (e.g. from bronchospasm, or airway secretions or stenosis), (iii) inertial mass of the respiratory system (e.g. an obese body habitus, the effects of which are exacerbated by recumbency), and (iv) minute ventilation requirements.[14,16] Minute ventilation requirements magnify the work of breathing: a doubling of minute ventilation doubles the other summative mechanical workloads on the respiratory system. Therefore, if gas exchange abnormalities in some patients with COVID-19 occur earlier than increases in mechanical loads, patients may not experience marked subjective dyspnoea despite low arterial oxygen saturations. If they were previously healthy, their dyspnoea may become apparent only after progression of the disease and development of severe and unsustainable mechanical loads. But, how exactly might respiratory workloads affect the development of dyspnoea and respiratory distress in COVID-19?

Most patients with COVID-19 have elevated minute ventilation, sometimes marked, as a result of increased dead space ventilation,[17] increased CO_2 production from the inflammatory response, or both. However, a very high minute ventilation, up to 50% of the 15 s maximal voluntary ventilation (approximately 65 L min^{-1} in young adults, or roughly a tidal volume of 1.5 L at a ventilatory frequency of 45 bpm), can be sustained indefinitely in otherwise healthy persons.[13,18] Thus, just like asymptomatic hypoxia, absence of subjective dyspnoea despite high minute ventilation should not be surprising.

In obese patients, the inertial mass of the respiratory system is increased, and this effect is more pronounced when patients are supine and recumbent. When combined with high minute ventilation, the loads imposed by obesity may raise the work of breathing sufficiently to cause symptoms. Although obesity appears to be an important risk factor for COVID-19 clinical illness and poor outcomes from it,[19] whether this reflects the effects of obesity on the respiratory system or other

factors remains to be determined.[20] To date, early in the course of illness, neither prominent secretions nor bronchospasm have been reported in COVID-19.[21,22] Therefore, resistive loads on the respiratory system do not appear to be significant, at least early in the illness.

This leaves us with the highly contested issue of respiratory system compliance in COVID-19 as a contributor to work of breathing and dyspnoea. It would be curious indeed if hypoxaemia, increased minute ventilation, and markedly reduced respiratory system compliance did not result in significant subjective dyspnoea in COVID-19, as it does in other causes of acute respiratory distress syndrome (ARDS). This exposes the possibility that, at least early in the course of illness, lung compliance in COVID-19 is not markedly reduced (and by extension, elastic loads increased), as Gattinoni and colleagues[3] have suggested. In a large cohort of patients receiving mechanical ventilation for COVID-19, mean respiratory system compliance was similar to that in ARDS patients in clinical trials spanning more than two decades.[17]

It is important to note two things about the reported mean compliance in ARDS in patients with COVID-19 (so-called CARDS[4]). First, patients on mechanical ventilation may have the highest illness severity, and thus the lowest respiratory system compliance. In patients in whom the disease has progressed from a normal compliance state without dyspnoea to a low compliance one with significant dyspnoea, dyspnoea itself may have precipitated intubation and mechanical ventilation, and mechanical ventilation may be a surrogate marker for low compliance in COVID-19. Experience and anecdotal reports suggest that there are many patients with hypoxaemia commensurate with typical mechanically ventilated ARDS cohorts, but who are spontaneously breathing comfortably in non-ICU settings on high concentrations of supplemental oxygen, such as high-flow nasal cannula. What is the lung compliance of these patients with severe gas exchange abnormalities, who, in previous cohorts, might have been intubated? Second is that the lung compliance in spontaneously breathing patients with COVID-19 is difficult to measure and has not yet been reported. One worry, and an ongoing controversy in the management of these patients, is the possibility of patient self-induced lung injury (P-SILI), whereby high transpulmonary pressures from air hunger and vigorous ventilatory efforts in spontaneously breathing patients induce and exacerbate existing lung injury.[4,17] According to this line of thinking, patients who begin with relatively normal compliance may, because of marked air hunger resulting in high transpulmonary pressure gradients and ventilatory frequencies, self-inflict lung injury that reduces compliance as they continue to breathe spontaneously while generating high mechanical power.[4,23] In the context of the work of breathing scheme presented, their low compliance measured on the ventilator later in the course of the disease is a consequence of lack of dyspnoea at the outset, which, in other diseases, would have precipitated intubation and mechanical ventilation with lung-protective mechanical ventilation much earlier. Proponents of P-SILI thereby recommend earlier intubation with lung-protective mechanical ventilation utilising low tidal volumes to prevent ongoing self-induced lung injury.[4,24] Because of the protracted course of COVID-19,[21,22] it remains to be seen whether the benefits of such a strategy outweigh the known costs of prolonged sedation and paralysis required to achieve reduced mechanical power that would theoretically prevent P-SILI.[25,26] Important to consider with this strategy is the increased stress on finite ICU resources, namely, ventilators, beds, and staff.[26]

Whilst it is possible that COVID-19 results in a unique subset or phenotype of ARDS, it is at least as likely that the COVID-19 pandemic has created an unusually large but otherwise usual population of patients with ARDS. The controversies surrounding phenotypes of ARDS in COVID-19 will take several years and reams of data to settle. Until then, it may be useful to utilise this opportunity to reflect on how the symptomatic presentation and course of COVID-19 differ from or conform to our expectations, and what any discrepancies may teach us about the underlying physiological principles. Ottestad and Søvik[12] have pointed us in the right direction for reflection on the pathophysiology as additional data become available. Hopefully, the insights we gain can inform us not only about COVID-19, but about respiratory failure in general. Meanwhile, we should be cautious in intervening on the basis of hypoxaemia and tachypnoea alone, without associated subjective dyspnoea and respiratory distress.[15]

Authors' contributions

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Editing of first draft: both authors.
Approval of final version: both authors.

Declarations of interest

The authors declare that they have no conflicts of interest.

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An ethical algorithm for rationing life-sustaining treatment during the COVID-19 pandemic

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