



Early View

Editorial

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Noninvasive strategies in COVID-19: epistemology, randomised trials, guidelines, physiology

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COVID-19 is producing seismic changes in society at large and the action of doctors is receiving greater attention from the public than ever in our lifetime. The medical care provided to millions of patients suffering from a single disease constitutes an experiment of nature of extraordinary proportions. The release of voluminous data into medical journals provides the spur to meditate on long-held assumptions about the way we interpret clinical research.

Two studies published in the *European Respiratory Journal* reveal dramatic benefits with use of continuous positive airway pressure (CPAP) in COVID-19 patients managed outside the ICU.

Brusasco and colleagues [1] report that 53 of 64 (82.8%) patients recovered with CPAP. The patients had severe hypoxaemia, arterial oxygen tension-to-fractional inspired oxygen ratio ($\text{PaO}_2/\text{F}_i\text{O}_2$) of 119 mmHg (IQR 99-153), and many satisfied criteria of acute respiratory distress syndrome (ARDS). Of the 11 (17.2%) non-responders, 7 underwent endotracheal intubation and 4 died.

Oranger and colleagues [2] report that 6 of 14 patients managed by supplemental oxygen underwent endotracheal intubation and 2 died (combined unfavourable outcome, 57.1%). Following implementation of CPAP, 9 of 38 (23.7%) patients were intubated and none died.

Given that COVID-19 patients managed by invasive ventilation have experienced mortality rates of up to 90% (and higher) [3], the findings of the Genoa [1] and Paris [2] groups with use of CPAP are striking. In reporting their findings, Oranger and colleagues [2] remark that unprecedented pressure on ICUs made the “avoidance of intubation a critical issue.” They also note that Guidelines do not recommend the use of noninvasive ventilation in ARDS [4] and that use of CPAP is problematic because efficacy was not demonstrated in the randomised controlled trial (RCT) of Delclaux and colleagues [5].

Why do the Genoa-Paris findings differ from the RCT of Delclaux and colleagues? It is overly simplistic to say it was determined largely by the nature of underlying diseases. Rather, the results raise fundamental epistemological questions. Epistemology being the study of the very basis on which our knowledge rests—specifying the conditions for knowing as such—and it is always lurking a layer or two deeper than any question in science [6].

It has become part of medical dogma that information gained through an RCT represents the gold-standard for clinical practice. The RCT is a superb experimental design for testing the benefit of a pharmacological agent such as streptomycin. But many therapies differ in fundamental ways from pharmacological compounds. In the case of COVID-19, RCTs provide no guidance as to when to insert an endotracheal tube—the single most important decision in these patients [7, 8]. That decision is based on clinical judgment, gestalt and tacit knowledge [9]—information that cannot be captured in an RCT.

Use of CPAP is a clinical art: an experienced physician enacts multiple and rapid adjustments at the bedside depending on patient response. Refinements involve trial and error, combined with improvisation (as with jazz). Each patient warrants individualised care [10]. When, for example, CPAP produces an increase in oxygenation but is accompanied by mental dulling, an astute clinician suspects a decrease in cardiac output and revives mentation by titrating CPAP downwards [11]. Or a patient may be oxygenating satisfactorily on CPAP, but repeated ineffective efforts are visible on the monitor screen. A canny physician suspects auto-PEEP, and by increasing CPAP eliminates the ineffective efforts [9]. The number of hours that CPAP is used varies from one patient to the next. Oranger and colleagues [2] employed CPAP for as little as 2 hours twice daily, whereas patients in the RCT of Delclaux and colleagues were required to use CPAP for at least 6-12 hours a day [5].

It is axiomatic to undertaking an RCT that investigators must meticulously follow a series of uniform protocolised steps. Heterogeneity among investigators is inimical to its purpose. An RCT aspires to

nothing less than emulating the scientific precision achieved during an experiment on the laboratory bench. By imposing a rigid protocol that curtails a doctor's freedom to improvise in response to a patient's physiological performance, the RCT no longer mirrors what a doctor is actually doing. Clinical practice is not science, nor is science clinical practice—yet RCTs are seen as reflecting clinical practice.

The steps performed by Delclaux and colleagues [5] are necessary staged and do not evince how an expert clinician extemporises and adapts to changing circumstance. Two criteria were used to enter patients into the RCT: $\text{PaO}_2/\text{F}_i\text{O}_2 \leq 300$ mmHg and bilateral infiltrates [5]. Whether patients exhibited signs of increased respiratory effort is not reported. Some patients had $\text{PaO}_2/\text{F}_i\text{O}_2$ 283 mmHg, which equates to PaO_2 73.6 mmHg at F_iO_2 0.26. An experienced physician would never entertain use of CPAP in such a patient. In short, the RCT does not mirror the truth of real-life clinical practice.

The patients in Genoa and Paris were managed on general and pulmonology wards whereas patients in the RCT of Delclaux and colleagues were managed in ICUs by intensivists. A decision for intubation in Genoa-Paris entailed transfer of a patient to another physician team, which was not the case with the RCT. Given the shortage of ICU beds consequent to COVID-19, there was greater incentive to avoid intubation than in the RCT. For example, some Genoa patients had respiratory rates of 38 breaths/min (or higher) [1]—an expected physiological response to trachea-bronchial inflammation, producing stimulation of irritant, stretch, and J receptors [7]. Some Guidelines recommended endotracheal intubation as soon as respiratory rate rose above 22 breaths/min (upper limit of normal range) [12].

Authors reporting series of COVID-19 patients communicate that their decisions about intubation were heavily influenced by WHO Guidelines. The Guidelines caution that noninvasive ventilation “should only be used in selected patients” and warn of a high likelihood of failure [13]. Emory authors [14] report that WHO Guidelines steered them away from noninvasive strategies and towards intubation. Authors

from Detroit [3] specify that they were influenced by WHO Guidelines encouraging early intubation and cautioning against the use of noninvasive strategies.

What is the science on which the WHO Guidelines are founded? The strong warnings against use of noninvasive strategies is apparently based on experience with coronavirus-induced Middle East Respiratory Syndrome (MERS). MERS is repeated nine times in the WHO Guidelines of January 28, 2020, whereas pathophysiological principles get no coverage [13]. Published experience with MERS is based on 12 ICU patients who received mechanical ventilation, 5 of whom were judged to have failed noninvasive ventilation [15]; not one data point is reported on the reason that noninvasive strategies was judged to have failed.

Use of noninvasive strategies, such as CPAP, as opposed to endotracheal intubation is of major importance in COVID-19 patients because of numerous life-threatening complications associated with intubation and mechanical ventilation [7-9]. Emerging data from the Intensive Care National Audit & Research Centre (ICNAARC) reveal that 28-day mortality of COVID-19 patients admitted to the ICU decreased from 43.5% (95% CI 41.6% to 45.5%) for the time period 1 February-28 March to 34.4% (95% CI 32.3% to 36.2%) for time period 16 April-21 May, 2020 [16]. Over the same period, the rate of intubation (and mechanical ventilation) decreased from 75.9% to 44.1% [16]. We will never know how many physicians were steered away from use of noninvasive strategies (such as CPAP) because Guidelines discouraged their use.

Another characteristic of the Genoa-Paris reports is their retrospective design. Retrospective reports are judged inferior *ipso facto* to prospective studies. Advance in science, however, is determined by the novelty of a hypothesis (conjuring of an idea not previously thought) and reporting findings that will be judged convincing by subsequent investigators. Use of low tidal-volume ventilation in ARDS was first tendered in a retrospective report of 50 patients by Keith Hickling [17]. In his seminal *The Structure of*

Scientific Revolutions [18], Thomas Kuhn divided science into paradigm shifts and normal science (Kuhn also termed the latter “mopping-up operations”). The paradigm shift in ARDS management was enunciated in Hickling’s retrospective report, not the RCT published twenty years later.

To return to the epistemological question: are the Genoa-Paris findings believable? They certainly have the ring of truth—death and endotracheal intubation are concrete events. The Genoa-Paris authors are relaying what they saw: use of a noninvasive strategy avoided intubation in COVID-19 patients and saved lives. Are the findings of Delclaux and colleagues [5] true? Yes, under the circumstances. But “circumstance” is the all-important ingredient in this situation. The circumstances under which Declaux and colleagues employed CPAP are extremely different from its use in Genoa [1] and Paris [2], and the RCT does not capture the truth of real-life clinical practice—independent of differences in underlying disease states. The patients in Genoa and Paris were fortunate that their doctors employed a therapy that contravened a landmark RCT [5] and related Guidelines.

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