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

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Two recent *ERJ* articles demonstrate dramatic benefit with CPAP in COVID-19 patients, highlighting problems with the landmark trial of CPAP (and related guidelines) and illustrating the danger of believing that trials capture the truth of clinical practice https://bit.ly/3pVp78e

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Coronavirus disease 2019 (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 intensive care unit (ICU).

In this issue of the journal, Brusasco *et al.* [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 (P_{aO_2}/F_{IO_2}) of 119 mmHg (interquartile range 99–153), and many satisfied criteria of acute respiratory distress syndrome (ARDS). Of the 11 (17.2%) non-responders, seven underwent endotracheal intubation and four died.

Recently, Oranger *et al.* [2] reported that six of 14 patients managed by supplemental oxygen underwent endotracheal intubation and two died (combined unfavourable outcome, 57.1%). Following implementation of CPAP, nine 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 *et al.* [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 *et al.* [5].

Why do the Genoa-Paris findings differ from the RCT of Delclaux *et al.* [5]? It is overly simplistic to say it was determined largely by the nature of underlying diseases. Rather, the results raise fundamental

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epistemological questions. Epistemology being the study of the very basis on which our knowledge rests, *i.e.* 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 intrinsic positive end expiratory pressure, 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 *et al.* [2] employed CPAP for as little as 2 h twice daily, whereas patients in the RCT of Delclaux *et al.* [5] were required to use CPAP for at least 6–12 h a day.

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 *et al.* [5] are necessarily 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: $P_{aO_2}/F_{IO_2} \leq 300$ mmHg and bilateral infiltrates [5]. Whether patients exhibited signs of increased respiratory effort is not reported. Some patients had P_{aO_2}/F_{IO_2} 283 mmHg, which equates to P_{aO_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 [1] and Paris [2] were managed on general and pulmonology wards, whereas patients in the RCT of Delclaux *et al.* [5] were managed in ICUs by intensivists. A decision for intubation in Genoa and 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 per 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 per min (upper limit of normal range) [12].

Authors reporting series of COVID-19 patients communicate that their decisions about intubation were heavily influenced by World Health Organization (WHO) guidelines. The guidelines caution that noninvasive ventilation "should only be used in selected patients" and warn of a high likelihood of failure [13]. The Emory COVID-19 Quality and Clinical Research Collaborative [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 are apparently based on experience with coronavirus-induced Middle East respiratory syndrome (MERS). MERS is mentioned nine times in the WHO guidelines of 28 January, 2020, whereas pathophysiological principles get no coverage [13]. Published experience with MERS is based on 12 ICU patients who received mechanical ventilation, five 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 and Research Centre (ICNAARC) reveal that 28-day mortality of COVID-19 patients admitted to the ICU decreased from 43.5% (95% CI 41.6–45.5%) for the time period 1 February to 28 March, to 34.4% (95%

CI 32.3–36.2%) for time period 16 April to 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 [1] and Paris [2] 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 Hickling *et al.* [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 the retrospective report of Hickling *et al.* [17], not the RCT published 20 years later.

To return to the epistemological question: are the findings from Genoa [1] and Paris [2] believable? They certainly have the ring of truth: death and endotracheal intubation are concrete events. The Genoa and 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 *et al.* [5] true? Yes, under the circumstances. But "circumstance" is the all-important ingredient in this situation. The circumstances under which Delclaux *et al.* [5] 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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References

1 Brusasco C, Corradi F, Di Domenico A, *et al.* Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure. *Eur Respir J* 2021; 57: 2002524.
2 Oranger M, Gonzalez-Bermejo J, Dacosta-Noble P, *et al.* Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study. *Eur Respir J* 2020; 56: 2001692.
3 Bahl A, Van Baalen MN, Ortiz L, *et al.* Early predictors of in-hospital mortality in patients with COVID-19 in a large American cohort. *Intern Emerg Med* 2020; 15: 1485–1499.
4 Rochwerg B, Brochard L, Elliott MW, *et al.* Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; 50: 1602426.
5 Delclaux C, L'Her E, Alberti C, *et al.* Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. *JAMA* 2000; 284: 2352–2360.
6 Magee B. The Story of Philosophy. London, Dorling Kindersley, 1998.
7 Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. *Am J Respir Crit Care Med* 2020; 201: 1319–1320.
8 Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. *Ann Intensive Care* 2020; 10: 78.
9 Tobin MJ. Principles and Practice of Mechanical Ventilation. 3rd Edn. New York, McGraw Hill, 2013.
10 Tobin MJ. Generalizability and singularity. The crossroads between science and clinical practice. *Am J Respir Crit Care Med* 2014; 189: 761–762.
11 Carlile PV, Gray BA. Effect of opposite changes in cardiac output and arterial PO_2 on the relationship between mixed venous PO2 and oxygen transport. *Am Rev Respir Dis* 1989; 140: 891–898.
12 Società Italiana di Malattie Infettive e Tropicali (SIMIT). Vademecum per la cura delle persone con malattia da COVI-19. Edizione 2.0, 13 marzo 2020. www.eahp.eu/sites/default/files/covid19_vademecum_2.0_13_marzo_2020.03_11.pdf Date last accessed: 16 Nov 2020
13 World Health Organization. Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (2019-nCoV) Infection is Suspected: Interim Guidance 28 January 2020 https://apps.who.int/iris/bitstream/handle/10665/330893/WHO-nCoV-Clinical-2020.3-eng.pdf?sequence=1&isAllowed=y. Date last accessed: 21 Oct 2020
14 Hernandez-Romieu AC, Adelman MW, Hockstein MA, *et al.* Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. *Crit Care Med* 2020; 48: e1045–e1053.
15 Arabi YM, Arifi AA, Balkhy HH, *et al.* Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014; 160: 389–397.
16 Doidge JC, Mouncey PR, Thomas K, *et al.* Trends in intensive care for patients with COVID-19 in England, Wales and Northern Ireland. *Preprints* 2020; preprint [https://doi.org/10.20944/preprints202008.0267.v1].
17 Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 1990; 16: 372–377.
18 Kuhn TS. The Structure of Scientific Revolutions. 3rd Edn. Chicago, University of Chicago Press, 1962; p. 24.