What are the respiratory requirements for the treatment of COVID-19 pneumonia?

Background

What happens in the lungs during COVID-19 pneumonia?

Patients may require support of their breathing by having ventilatory assistance for a range of reasons, but patients who are seriously affected by COVID-19 will primarily develop pneumonia which may progress to acute respiratory distress syndrome, (ARDS), in which there is extreme inflammation with damage and fluid accumulation within the small gas-exchange sacs of the lungs, (alveoli). These patients require specialised ventilation strategies to prevent hypoxia (oxygen depletion of their tissues) which have been well defined, and which are known to deliver optimum therapy.

How is ventilatory assistance conventionally delivered?

Since the first positive pressure devices were introduced in the 1950s, it has become conventional to ventilate the lungs, in a wide variety of disease, by delivering positive pressure ventilatory support, either via a tightly-fitting face mask (CPAP), or through a cuffed endo-tracheal tube using positive pressure ventilators (PPV). These devices have become increasingly sophisticated and a whole generation of anaesthetists/intensivists have become expert in their use.

However, before this method was introduced there was a long history of using negative pressure ventilation, (NPV), by placing the patient’s body within a chamber with their head outside, with a seal at the neck. The lungs were inflated by creating a negative pressure in the chamber or tank, (the “iron lung”). NPV mimics and enhances natural respiration. The
change from NPV to PPV was not a planned decision related to their relative evidence or efficacy, but occurred because of the convenience of not having to manage a patient inside a large tank, and ironically, a shortage of these large and expensive devices during the polio epidemics of the 1950s.

**Could NPV have a role in COVID-19 infection?**

There is substantial evidence that NPV can deliver treatment to patients with ARDS as well, or superior to, conventional PPV. To compare these modalities, it is important to define what is required from the ventilatory support system to deliver optimum gas exchange, namely:
- Prevention of areas of lung collapsing (atelectasis) at the end of expiration
- A controlled (≤4-6 ml/kg) tidal volume of air/oxygen to deliver inspiration
- A sufficient breathing frequency to maintain a normal partial pressure of carbon dioxide, (PCO₂)
- A sufficient inspired oxygen concentration to deliver an adequate partial pressure of oxygen to the arterial blood, (PaO₂)

  The way in which atelectasis is reduced is to continue to apply a positive end-airway pressure (PEEP) throughout expiration, so instead of the lungs being inflated from atmospheric pressure to say +20 cmH₂O, they are inflated from say +8 cmH₂O at rest to +28 cmH₂O.

**We must consider the heart as well as the lungs.**

In addition, the importance of maintaining the patient’s heart function must be measured as the cardiac index (CI, output of blood from the heart, litres/min/m²) so that the arterial blood can optimally deliver oxygen to the tissues. The deleterious effects of COVID-19 on the cardiovascular system have been
stressed in much of the recent COVID-19 literature from China, Italy and USA.\textsuperscript{9-17} Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects host cells through ACE2 receptors, leading to coronavirus disease (COVID-19)-related pneumonia, while also causing acute myocardial injury and chronic damage to the cardiovascular system. Therefore, particular attention should be given to cardiovascular protection during treatment for COVID-19.

An unfortunate potential consequence of using PPV is that by forcing air into the lungs, which share the same expansile but limited space within the chest, it inevitably increases the pressure on (squeezes) the heart and the major veins leading to it. Positive pressure reduces preload on the right ventricle (RV) by decreasing the venous return and increases afterload on the RV, both of which reduce the CI. Negative pressure maintains RV preload by drawing venous blood as well as air into the thorax and does not tend to increase RV afterload, thus tending to increase CI. The cardiac index needs to be considered when comparing PPV with NPV, as well as oxygen and carbon-dioxide transfer.

\textbf{History.}

PPV was introduced during the 1950s when the commonest ventilatory support requirement was to assist patients paralysed by the polio virus. These patients typically had normal healthy lungs, but reduced muscular power to breathe, so all that was required then was to inflate their relatively compliant lungs and allow them to deflate spontaneously under their own elastic recoil. At that point in time therefore, both PPV and NPV were only required to inflate the lung and then ‘switch off’. Since then medicine has moved on and different categories of patients, (notably those with ARDS), have posed challenges
that have been managed mainly with increasingly sophisticated CPAP, BiPAP and IPPV devices. Hence, PPV technology has been developed while for most centres NPV has ‘stood still’. However, important advances have been made with various forms of NPV delivery in some centres, which will be discussed. Before that, there are some important practical considerations below about ventilating people in negative pressure devices.

**Ventilation involving the whole-body, torso, or just the front of the chest?**

The original iron lungs developed in the late 1920s were whole-body chambers that enclosed the entire awake patient below the neck. A seal was achieved around the neck by soft rubber. The practicalities of this arrangement were difficult. Managing the patient’s continence was problematic requiring them to have their bladders catheterised and needing opening side-windows to pass bed-pans in and out. In addition it was difficult to access their limbs to measure blood pressure, deliver intravenous therapies, let alone deal with washing, etc. More recently much smaller chambers have been used for the cuirass-style negative pressure chambers (‘the knight’s breast-plate’), but these tend to splint the chest wall and typically only contribute minimal ventilatory support\(^{18}\). Some experimental NPV studies have been performed with the whole thorax, or the abdomen and thorax, enclosed within a negative-pressure chamber which have shown important cardiovascular advantages (discussed below). Ventilator designs which only deliver the negative pressure to the torso will provide optimal ventilatory and cardiac advantages and will also allow access to manage the patient’s bladder and bowels as well as access to their lower limbs for medical procedures.

**Efficacy and complications of PPV versus NPV**
Cardiac index

Animal data  The impact of PEEP on the CI has been of concern for a long period and the animal evidence was reviewed in 1983, when it was confirmed that it substantially and consistently reduced CI\textsuperscript{19}. Later this was clarified in dogs that had their lungs deliberately damaged with oleic acid. Each animal was then ventilated sequentially by both PPV and NPV with the equivalent lung inflation pressures (positive or negative), ending with the same level of either PEEP, or negative end-expiratory pressure (NEEP), the same tidal volumes, and the same inspired O2 concentrations. The CI in dogs was 16\% higher during NPV that with PPV due to a reduction in venous return with PPV and an increase with NPV\textsuperscript{20}. More recently it was shown that this difference was far greater if the lung-damaged animals, (rabbits), only had the NPV delivered to the chest and upper abdomen\textsuperscript{21}.

Human evidence  The 1983 review of animal evidence also referenced four human reports which supported the case that the potential of PPV reducing the CI was probably also true in man\textsuperscript{19}. In 1995, fifteen unconscious adults who were ventilated after road accidents were ventilated with PPV and each was studied without any PEEP, with PEEP, and with an equivalent NEEP pressure being applied to the chest during ventilation and their responses measured. The CI fell when PEEP was applied and rose when NEEP was used, such that it was 24.5\% higher with NEEP than with PEEP, and this was equally true for those 9 patients with damaged lungs and the 6 without\textsuperscript{22}. A similar study was reported in 1998 in 9 adults with acute lung injury\textsuperscript{23}. A 20\% increase in CI was also shown in a 2015 study of 6 intubated and sedated adults with ARDS who were exposed to no PEEP and to equivalent PEEP and NEEP pressures\textsuperscript{24}. 
**Oxygenation**

**Animal data**  As part of the lung-damaged rabbit study described above, it was shown that for equivalent pressure settings the oxygen transfer was significantly greater with NPV than with PPV\(^2^1\). This was shown not to be linked to variations in the distribution of pulmonary blood flow patterns within the lungs, but reflected NEEP being better than PEEP at preventing atelectasis and keeping the lung tissue more evenly ventilated. Not only were the lungs more evenly inflated, but they had higher end-expiratory volumes, and on serial CT scans were shown to be consistently aerated during inspiration and expiration, while cyclical expiratory atelectasis was obvious with PVP+PEEP.

**Human data**  The three studies in which each patient was treated with both PPV and NPV at equivalent settings all showed clinically important increases in arterial oxygenation expressed as a 19.9% increase in oxygen delivery\(^2^2\), a fall in the fractional inspired oxygen (FIO\(_2\)) required to maintain an oxygen saturation (SO\(_2\)) of >90%\(^2^3\), or as an higher partial pressure of arterial oxygen to fractional inspired oxygen ratio (P/F) at 345 vs 256 mmHg\(^2^4\).

**Clinical experience**  As early as 1976, an adult with severe alveolar disease (ARDS) who had NEEP added to their ventilation regimen rapidly reduced their oxygen requirement\(^2^5\), and in 1985 another patient on PPV+PEEP with ARDS had her hypoxemia reversed by the use of NEEP\(^5\). Since then there have been reports of over 3,000 patients treated for acute exacerbations of chronic obstructive pulmonary disease (COPD) often due to secondary infections\(^6^-^8\).
Ventilator-associated lung injury

Animal data  It has been known that PPV may increase lung inflammation, and that in animals this may be reduced by the addition of PEEP\(^3\). This is also associated with increased levels of cytokines and a higher risk of multiple-organ-failure developing which has again become a prominent feature of the most recent COVID-19 research literature\(^26\). In the paired rabbit experiments described above, some animals had lung histology examined after periods of PPV+PEEP and NPV+NEEP. Both had lung damage as they had had saline lung lavage to wash out their surfactant, but this was significantly more extensive in those exposed to positive pressures\(^21\). The PPV animals’ lungs were also heavier due to more extensive oedema.

Human data  A large prospective randomised controlled trial of high versus low tidal volumes in adults undergoing PPV for ARDS measured the interleukin-6 concentrations in the plasma to determine the level of inflammatory responses between these groups. The group with higher tidal volumes were ventilated at higher positive peak pressures, had significantly higher interleukin-6 levels, and had a higher mortality which led to the trial being stopped early\(^2\).

Pneumothorax risk  The incidence of pneumothorax among ARDS patients treated with PPV is reported to be 8%\(^4\). This complication has only been reported in one of over 3,000 patients on NPV, in a man with COPD who required intermittent NPV for over six months\(^27\), which is not an uncommon incidence for that condition.

Summary
General principles suggest that expanding the lungs by moving the chest under negative pressure is more physiological than inflating them by pumping in air under positive pressure, both in terms of the mechanism by which they change their shape, the recruitment of all lung segments, expiration and in terms of the effects on the cardiovascular system. Multiple studies have demonstrated that PPV significantly reduces the CI, whilst NPV significantly increases it, which can create a benefit of around 20% by using NPV.

D. Martin, BMJ article, 9th May 2020, writing about novel approaches to intensive care medicine proposed that high levels of positive end expiratory pressure increase intra-thoracic pressure, reducing venous return to the heart and may be a factor in the increasing incidence of thromboembolic events in the lungs28.

Sui Huang et al, 26th May 202029, reported in vitro studies showing that expression of ACE2 in alveolar cells is increased following mechanical stretch and inflammation. Critically ill Covid-19 patients have often required prolonged mechanical ventilation with positive pressure devices, which can cause mechanical stress to lung tissue. They analyzed transcriptome datasets of 480 (non-COVID-19) lung tissues in the GTex tissue gene expression database. They found that mechanical ventilation of the tissue donors increased the expression of ACE2 by more than two-fold (p<10^-6. They also proposed that mechanical ventilation of patients with COVID-19 pneumonia may eo ipso facilitate viral propagation in the lung, further accelerating the pulmonal pathology that has necessitated mechanical ventilation in the first place. Their findings support the call for gentler ventilation methods and protocols.

Negative pressure ventilation can also significantly improve oxygen transfer into the arterial blood compared to PPV, increasing tissue oxygen delivery and producing less lung damage and inflammatory responses. These statements arise
from detailed human studies, clinical case reports, and large case-series, where the addition of NEEP to PPV, or the use of NPV+NEEP has been shown to demonstrate the same benefits as seen in animals, and to be clinically beneficial. We are constantly learning more about the different phenotypes resulting from COVID-19 infection and we cannot be sure of the precise benefit that will be obtained in patients who are in the Green and Yellow phases as defined in the UK CPAP guidelines\textsuperscript{30}. However, there is certainly a body of previous research data, as indicated above, which would justify a clinical trial using continuous negative extra-thoracic pressure, (CNEP), initially combined with facemask or nasal prong oxygen, in a similar manner to the administration of CPAP or HFNO\textsubscript{2}. There would be the possibility of introducing NPV as a non-invasive addition in an awake patient. We wish to assess whether NPV will prevent escalation of a proportion of patients with worsening indices, thus avoiding endotracheal intubation and IPPV treatment.

Physicians moved from using NPV to PPV in the 1960s, largely related to nursing issues and the availability of smaller positive pressure devices. Consequently NPV has been largely disregarded since then, so there are a whole generation of anaesthetists and intensivists who are unaware of the research and continuing use in children and adults of all ages. The scientific and clinical evidence shows that a modern NPV device with a torso-only cabinet may provide a treatment alternative to CPAP with the additional possibility of preventing escalation of the patient requiring intubation and PPV. The ease of manufacture, use of readily available parts (not in competition with PPV devices), low cost and easy nursing and medical management, including in the prone position, are all additional advantages.

**Prone Positioning.**

Ng Z, Tay WC, et al\textsuperscript{31}, assessed awake prone positioning for non-intubated oxygen dependent COVID-19 pneumonia
patients and concluded that with critical care teams globally facing resource depletion, awake prone positioning can be a low-risk, low-cost manoeuvre, helping patients with COVID-19 pneumonia and reducing the need for intensive care.

Bastoni D, Poggiali E et al\textsuperscript{32} recently reported their experience of prone ventilation in selected patients treated with helmet non-invasive ventilation, NIV, continuous positive airway pressure, CPAP, for acute respiratory failure in COVID-19 pneumonia. 4 out of 10 patients who attempted proning with helmet NIV CPAP failed due to lack of compliance of the patients, despite pain control. Patients in the Exovent can undertake their own spontaneous proning without difficulty, adjust their position themselves and the neck and hip seals allow them to wipe their faces or rub any irritated areas of skin giving them a feeling of complete control, in contrast to a positive pressurised system.

It is to be hoped that clinical trials of the Exovent during this COVID-19 pandemic can be undertaken as soon as possible.

References


29. Sui Huang MD, PhD¹, Arja Kaipainen Ph.D.¹, Michael Strasser PhD¹, Sergio Baranzini PhD² Mechanical ventilation stimulates expression of ACE2 the receptor for SARS-Cov-2, Doi:10.20944/preprints20.2005.0429.v1

