Why do we wish to re-introduce Negative-pressure Ventilation for the treatment of many forms of respiratory failure, both acute and chronic?

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

What happens in the lungs during COVID-19 pneumonia?

Patients who are unwell enough and are admitted to hospital may require support of their breathing 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 lung (alveoli).[1] These patients require specialised ventilation strategies to treat and prevent hypoxia (oxygen depletion of their tissues) which have been well defined[2,3], and which are known to deliver optimum therapy[4].

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 respiratory disease, by delivering positive pressure ventilatory support, either non-invasively (NIV), via pressurised oxygen through a tightly-fitting face mask, CPAP,[5], BiPAP, or by high flow nasal oxygen treatment (HFNOT).

Non-invasive Ventilatory Support

HFNOT provides warmed, humidified gases at flows of up to 60 litre/min, with inspired oxygen concentrations of up to 100%.[6] The use of HFNOT is well validated in neonatal populations but is not currently widely used in COVID-19 patients, based on lack of efficacy, oxygen use and infection spread.

NIV with BiPAP is usually not needed in those with previously normal lungs and should be reserved for those with hypercapnic acute on chronic ventilation problems.

Continuous Positive Airway Pressure (CPAP), is currently the preferred form of non-invasive ventilatory support in the management of hypoxaemic COVID-19 patients. Lung compliance is often maintained in the initial stages in COVID-19 patients. CPAP use does not replace invasive mechanical ventilation (IMV), but early application may prevent escalation to IMV. The response to CPAP is assessed with regular monitoring and clinical review. Where there is no adequate response initially, where clinical decline continues, or where patient tolerance of CPAP limits its use, early intubation and mechanical ventilation may be needed. Excessive work of breathing may be the prime indicator if patients become exhausted despite CPAP support.

Potential Disadvantages of CPAP
CPAP devices have saved countless lives but CPAP masks and hoods can be distressing for patients by causing claustrophobia, upper airway drying, facial skin breakdown and ulceration. The use of low doses of agents to improve comfort and tolerance can be considered. Opioids may be used in appropriate doses to help reduce the sensation of breathlessness, reduce respiratory rates and control high tidal volumes – which may drive on-going patient-induced lung injury (PILI).

Strict hygiene precautions are necessary in a ward environment though the risk of infection to staff when using CPAP is not thought to be high with appropriate use of personal protective equipment (PPE) according to the latest Public Health England PPE guidance. Patients can be monitored using continuous peripheral arterial oxygen saturation (SpO2) with an appropriate level of nursing support. Arterial lines/blood gases are not needed unless there are reasons to suspect CO2 retention.

The choice between HFNOT, CPAP, BiPAP or early intubation and mechanical ventilation in COVID-19 patients has been, and remains, controversial.

Negative Pressure non-invasive ventilatory support - a brief history

Before positive pressure devices were introduced, there was a long history of using negative pressure ventilation (NPV). John Mayow, an English scientist and physician built the first external negative pressure ventilatory device in 1673[7]. The unit used a bellows and bladder to expel the air and Mayow described this as mimicking the action of the respiratory muscles. The first tank type respirator was described by a Scottish doctor, John Dalziel, in1832[8]. Dalziel thought that by applying a negative pressure to the body rhythmically, in phase with inspiration, he might be able to prevent the deaths of patients who were suffering from respiratory failure. Numerous other negative pressure devices were designed and used in the late eighteenth and early nineteenth century but negative pressure ventilation became a reliable clinical reality in 1928 with the development of the iron lung, which was initially designed and built by Philip Drinker, an engineer, Charles McKhann, a paediatrician and Louis Shaw, a physiologist[9,10]. This was the first reliable method of prolonged respiratory support and had taken several years of work in the Department of Ventilation, Illumination and Physiology at Harvard Medical School. Although subsequently associated with the polio epidemic, it was initially designed for the Consolidated Gas Company of the USA, who needed resuscitation and respiratory support equipment for a substantial number of workers who were being injured by electric shock, carbon monoxide gas and smoke inhalation.

The lungs were inflated by creating a negative pressure in the chamber or tank (the "iron lung"). NPV has a potential major advantage as it mimics and enhances natural respiration. Physiological responses to NPV differ from responses to PPV, in ways that may have clinical advantages in the management of respiratory failure in general, and specifically in COVID-19.

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 and nurse a patient inside a large tank, and ironically, a shortage of these large and expensive devices during the polio epidemics of the 1940's and 1950s.

At that time the commonest ventilatory support requirement was to assist patients with the paralytic form of polio, who typically had normal healthy lungs, but reduced muscle 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 PPV devices. Hence, PPV technology has been developed while for most centres NPV has 'stood still'. 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. However, important advances have been made with various forms of NPV delivery in some centres and the science and clinical aspects will be discussed. Before that, there are some important practical considerations below about ventilating people in negative pressure devices.

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.[11-13] 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 (PCO_2)
- A sufficient inspired oxygen concentration to deliver an adequate partial pressure of oxygen to the arterial blood (PaO_2)

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 cmH_2O, they are inflated from say +8 cmH_2O at rest to +28 cmH_2O.

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/m^2) 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[14-22]. 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. Thus, CI needs to be considered when comparing PPV with NPV, as well as oxygen and carbon dioxide transfer. Cresti et al in 2020[23], reviewed the data and stated that myocardial injury may complicate COVID-19 infection in more than a quarter of patients and, due to the wide a range of possible insults, cardiac imaging plays a crucial diagnostic and prognostic role. They suggested that large-scale registries and studies are needed to understand the independent prognostic role of cardiac injury.

Whole-body, torso, or the front of the chest?

The original iron lungs 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 bedpans 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[24]. 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 (see below). A design which only delivers 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 to their lower limbs for medical procedures.

Efficacy and complications of PPV versus NPV

Cardiac index

Animal data The impact of PEEP on the cardiac index (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[25]. 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 than with PPV due to a reduction in venous return with PPV and an increase with NPV[26]. 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[27].

Human evidence The 1983 review of animal evidence also referenced four reports in humans which supported the case that the potential of PPV to reduce the CI was probably also true in man[25.]. 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[28]. A similar study was reported in 1998 in 9 adults with acute lung injury[29]. A 20% increase in CI was also shown in a 2012 study of 6 intubated and sedated adults with ARDS who were exposed to no PEEP and to equivalent PEEP and NEEP pressures[30].

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[27]. 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.

The clear conclusion from this study is that **negative-pressure ventilation results in superior oxygenation** that is unrelated to lung perfusion and may be explained by more effective inflation of lung volume during both inspiration and expiration.

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[28], a fall in the fractional inspired oxygen (FIO_2) required to maintain an oxygen saturation (SO_2) of >90%[29], or as a higher partial pressure of arterial oxygen to fractional inspired oxygen ratio (P/F) at 345 vs 256 mmHg[30].

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[31], and in 1985 another patient on PPV+PEEP with ARDS had her hypoxemia reversed by the use of NEEP[32]. 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 [11-13].

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[33]. 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[27]. The PPV animals' lungs were also heavier due to more extensive oedema.

Human data The 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[34], 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 and in terms of the effects on the cardiovascular system. Multiple studies have demonstrated that PPV can significantly reduce the CI, whilst NPV significantly increases it, which can create a benefit of around 20% by using NPV.

Dan Martin, in his BMJ article, 9th May 2020,[35] on 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 lungs.

Sui Huang et al, later that month [36,] 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 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. They also proposed that mechanical ventilation of patients with COVID-19 pneumonia may *eo ipso* facilitate viral propagation in the lung, further accelerating the pulmonary pathology that had 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[37]. 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. There would be the possibility of introducing NPV as a non-invasive addition in an awake patient, who would be able to talk, drink and eat. We wish to assess whether NPV will prevent escalation of a proportion of patients with worsening indices, thus avoiding endotracheal intubation and IPPV treatment. It may be additionally useful to treat patients with comorbidities which currently exclude them from consideration of mechanical ventilation on ICU.

Physicians moved from using NPV to PPV in the 1960s, largely due to nursing issues and the availability of smaller positive pressure devices. Consequently, NPV has been largely disregarded since then so there is 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 to 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. Ng Z, Tay WC, et al[38,] 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 to delay and reduce the need for intensive care.

It is to be hoped that clinical trials of the Exovent can be undertaken as soon as possible.

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