RESEARCH ARTICLE

Positive Pressure Ventilation for Respiratory Disease – a flawed, non-physiological solution. Further evidence from COVID-19

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ABSTRACT

"Modern" larger mammals developed over the last 65 million years, after the demise of the dinosaurs. All mammals, including hominids, breathe by negative pressure.

Between 1928 and the 1950's negative-pressure ventilation using so-called "iron lungs" saved countless poliomyelitis epidemic patients, but during the 1950s, when these devices were in short supply, they were largely replaced by smaller, practical, positive pressure ventilation devices and techniques. These had been used previously for thirty years by anaesthetists in operating theatres to enable general anaesthesia for surgery.

However, positive pressure ventilation for longer term respiratory support was quickly recognised to have disadvantages, including the need for intubation and sedation, reduction of cardiac output from reduced systemic venous return, ventilator acquired pneumonia, and ventilator-induced lung injury. Subsequently, lower tidal volumes and plateau inspiratory pressures were introduced to reduce mortality. There is an extensive publication history of these disadvantages over the last 60 years.

Additionally, the limitations of positive pressure ventilation have been further starkly revealed in COVID-19 pneumonia, a condition where the incidences of pneumothorax and pneumomediastinum have been especially prominent and where mechanical ventilation has been shown to stimulate the expression of angiotensin-converting enzyme-2 (ACE2; the receptor for the SARS-Cov-2 virus in the lung). Mechanical ventilation of patients with COVID-19 pneumonia has been shown to facilitate viral propagation in the lung, further accelerating the pulmonary pathology that had necessitated mechanical ventilation in the first place.

The deleterious effects of COVID-19 on the cardiovascular system have been stressed in much of the recent COVID-19 literature worldwide. Acute myocardial injury and chronic damage to the cardiovascular system have been reported. A potential consequence of using positive pressure ventilation is that by forcing air into lungs, which share the space within the chest, it inevitably increases the pressure on the heart and the major veins leading to it. High levels of positive end-expiratory pressure increase intrathoracic pressure, reducing venous return to the heart and decreasing the cardiac index.

The question, therefore, is whether we should continue to pursue development of positive pressure ventilation methods alone, or, whether respiratory medicine needs to re-investigate and develop negative pressure ventilation, the physiological way that the mammalian cardiorespiratory system evolved to function optimally.

Introduction

Current scientific research suggests that *Brasilodon quadrangularis*, a shrew-like creature that lived 225 million years ago is, at present, the oldest mammal ever identified.[1] "Modern" larger mammals developed over the last 65 million years, after the demise of the dinosaurs. All mammals, including hominids, breathe by negative pressure. Hominids actually have the ability to breathe by a form of positive pressure injection of air into the lungs called glossopharyngeal breathing (GPB, glossopharyngeal insufflation, or frog breathing). The technique was first described by Dail in 1951[2]

The technique involves the use of the oropharyngeal, laryngeal and neck muscles to positively inject boluses of air into the lungs. The glottis closes with each "gulp". Numerous training videos are available,[3,4] Many individuals cannot master glossopharyngeal breathing as they are unable to seal off the nose by elevating their soft palate and it is physically tiring and inefficient, except for short periods of time. If this had been the preferred system of ventilation then millions of years of mammalian and hominid evolution would have developed it. All mammals inhale by contracting the diaphragm downward and contracting the intercostal muscles between the ribs, pulling the rib cage upward and outward. This creates a negative pressure in the chest cavity, which results in lung expansion and influx of air.

John Mayow, an English scientist and physician built the first external negative pressure ventilatory device in 1673.[5] This 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, in 1838.[6] Throughout most of the 19th century and the first half of the 20th century, negative pressure ventilatory devices were those most used to provide ventilatory assistance. A common misconception amongst the present generation of anaesthetists, critical care doctors, and nurses, is that this form of respiratory support was only useful for the well-known polio epidemics of the 20th century. This view is incorrect.

Between 1928 and the 1960's negative-pressure ventilation (NPV) certainly saved countless poliomyelitis epidemic patients, but most clinicians are unaware that Macintosh used the Both cabinet respirator in 1940 to manage postoperative surgical patients and demonstrate the prevention of postoperative atelectasis.[7] This was an initial example of critical care medicine providing respiratory support and paved the way for the establishment of Critical Care units. In 1960, Kelleher[8] introduced a modified iron lung, which rotated 180°. This automatic turning helped to treat or prevent atelectasis, and he used it successfully for the treatment of Guillain–Barre syndrome, in addition to polio.

As antibiotic therapy became more widely used in the 1950s and 1960s, patients recovered from devastating infections but were left persistently dyspnoeic and hypercapnic. With the limited availability of new positive pressure devices, some hospitals reused NPV tank ventilators that were still available to treat chronic respiratory failure and relieve intractable dyspnoea in other disorders such as kyphoscoliosis, post-tuberculous thoracoplasty, pulmonary fibrosis, bronchiectasis, other neuromuscular disorders and chronic obstructive pulmonary disease (COPD). It is important to note that even at that time it was felt that this form of ventilation was more physiological, and that further lung damage was less likely with NPV. When respiratory muscles were still too weak, or the chest walls less compliant, the benefit from NPV would be its reduction in the work of breathing, while supporting gas exchange and relieving dyspnoea.[9] These are all relevant considerations in many of the patients requiring ventilatory support in COVID-19 pneumonia.

The severe poliomyelitis epidemic in Copenhagen, Denmark, in 1952 became a turning point for the treatment of respiratory paralysis. Lassen[10] described how the Blegdam Hospital in Copenhagen had 2722 admissions for acute poliomyelitis in a 19-week period, 866 of the paralytic type, necessitating ventilation in 316 patients. On a single day, 70 patients needed a ventilator at the same time, when only one tank and six cuirasses were available. A similar situation to this was seen with the COVID-19 pandemic in many countries. Lassen[10] reported that intermittent positive pressure ventilation (IPPV) was a more versatile method of artificial respiration at that time when negative pressure devices were in short supply. His anaesthetist colleague, Bjorn Ibsen developed the technique of tracheostomy and manual IPPV. The requirements in the COVID-19 pandemic were those of a new lethal virus but this was not an entirely new situation. The irony was a shortage, or absence, of negative pressure devices in many countries.

Methods

Narrative review based on systematic literature research. Data sources: Google Scholar and Pub Med for NPV; Covid -19; provided key publications, which were combined with relevant literature related to complications of positive pressure mechanical ventilation (PPV) in the previous seven decades and during the COVID-19 pandemic. A total of 60 papers have been included in this review and analysis.

Results

THE CHANGE FROM NPV TO PPV

Until the 1950s NPV was the only way of ventilating patients for extended periods of time and NPV with tank ventilators saved the lives of many polio patients from the 1920s to the 1950s[11-13] Negative pressure ventilation developed in the late 1920s were whole-body chambers enclosing the entire awake patient below the neck and a seal was achieved around the neck by a collar of soft rubber but the practicalities of this arrangement could be difficult. In some versions managing the patient's continence was problematic, requiring bladder catheterisation and side-windows through which to pass bedpans. In addition, it was difficult to access the patient's limbs to measure blood pressure, deliver intravenous therapies, let alone deal with washing, etc. The tank ventilators were expensive, in short supply in the few countries fortunate enough to have them, bulky, cumbersome, heavy and space consuming.

Smaller chambers were used for the cuirass-style negative pressure chambers ('the knight's breastplate'), but these tended to splint the chest wall and were often unable to adequately ventilate patients because of poor fit, obesity, or poor performance.[14] However, in a landmark paper in 1955, Pask[15] postulated that further development of the cuirass respirator would occur because this design could potentially produce less compromise of the circulation than positive pressure respirators, but it needed to be made comfortable for use over long periods for awake patients and capable of adequate ventilation. Pask proposed modification so that it would be possible to nurse the patient in the prone position and believed that in the future this type of respirator would be important, comments from 1955, which are still pertinent today.

Positive pressure ventilation, (PPV), had been used by anaesthetists for most operations from the 1920's. After the establishment of intensive care units, (ICU), in the 1950s, various technical developments allowed the use of PPV devices to ventilate patients for extended periods. It is important to note that this change from NPV to PPV was *not* based on research evidence or outcome measures of superiority. The anaesthetists running the early ICUs were familiar with the PPV machines from their operating theatre practice, and thus NPV gradually fell out of favour.

With the success of the polio vaccine, there was a dramatic reduction in the need for negative pressure ventilators resulting in them being stored or discarded. The ventilator assistance for polio victims, who typically had normal healthy lungs but reduced power to breathe, simply required inflation of their relatively compliant lungs, allowing them to deflate spontaneously under their own elastic recoil. Both PPV and NPV were only required to inflate the lung and then "switch off." Since then, different categories of patients, notably those with acute respiratory distress syndrome (ARDS), have posed challenges that have been managed mainly with increasingly sophisticated, and increasingly expensive, continuous positive airway pressure (CPAP), bi-level positive airway pressure, (BiPAP) and PPV devices. Positive pressure ventilation technology has been developed while negative pressure ventilation has largely been forgotten.

It was simply a matter of time before physicians saw the potential use of so called "non-invasive" positive pressure support in other settings. The on-going development of positive pressure devices meant that few continued to advocate the use of NPV in the acute stages of respiratory disease. As a consequence, a whole generation of anaesthetists and critical care doctors have been trained with little knowledge or experience of the potential benefits of negative pressure devices.

Unknown to many modern critical care, respiratory medicine and anaesthetic hospital units, for over 50 years a few doctors have remained active in the use of negative pressure non-invasive ventilation, and some have made their own version of tank ventilators. Sauret et al[16] working in Barcelona, Spain and Corrado and Gorini [17-20] in Florence, Italy continued to assess NPV and PPV for both acute and chronic respiratory failure. Corrado and Gorini[18] summarized the literature on the use of both negative and positive forms of ventilation in 2002. The primary end points in their assessment were progression to intubation or tracheostomy. Their research showed no difference between negative and positive modalities and no difference in mortality. Raymondos et al[21] from Hannover, Germany compared 2 hours of continuous external negative pressure ventilation (CENPV) in intubated patients with ARDS in a tank respirator with 2 hours of continuous positive pressure ventilation (CPPV). Continuous external negative ventilation with a tank respirator improved gas exchange in patients with ARDS at lower transpulmonary, airway and intra-abdominal pressures and initially improved haemodynamics.

SEVEN DECADES OF INCREASING KNOWLEDGE OF THE COMPLICATIONS OF POSITIVE PRESSURE VENTILATION. WHAT HAPPENED DURING COVID-19?

Ventilator Induced Lung Injury:

Positive pressure mechanical ventilation can produce physiological and morphological alterations in the lung, producing ventilator-induced lung injury (VILI). Acute Respiratory Distress Syndrome (ARDS) was first described by Ashbaugh et al in 1967[22] and only 3 years later in 1970, Mead et al developed the conceptual basis for VILI[23]. They suggested that the forces acting on lung parenchyma are actually much greater than those applied to the airway and suggested that the pressure to expand an atelectatic region at a transpulmonary pressure of 30 cm H_2O, surrounded by fully expanded lung, would be around 140 cm H_2O, contributing to lung haemorrhage and lesions. Since then, hundreds of research papers have highlighted several potential drawbacks and complications of PPV contributing to morbidity and mortality. A State-of-the-Art review by Pingleton[24] as far back as 1988 discussed these complications in detail. De Prost et al[25] further reviewed the situation in 2011 and the clinical implications of VILI from positive pressure devices continue to be debated to the present day.

Barotrauma, pneumo-mediastinum, pneumothorax and extra-thoracic dissection:

In 1979 Johnson and Altmann[26] reported that the radiographic detection of pulmonary interstitial gas in patients receiving PEEP therapy for severe respiratory failure was a key indicator for progression to barotrauma, pneumomediastinum, pneumothorax and extra-thoracic dissection. The limitations of PPV have been further revealed starkly in COVID-19 pneumonia, a condition where the incidence of pneumothorax and pneumomediastinum have been especially prominent [27-29]. Lemmers et al[29] found a seven-fold increase of pneumomediastinum/subcutaneous emphysema compared with a group of non-COVID ARDS patients treated in their unit over the previous five years, despite the use of low tidal volumes (5.9±0.8 mL·kg^{-1} ideal body weight) and low airway pressure (plateau pressure 23±4 cmH_2O). This is in enormous contrast to the very rare incidence of pneumothorax in the many thousands of patients treated by NPV for a wide variety of respiratory failure over many decades and often for many years.[30]

A recent major review of the adverse effects of positive pressure ventilation by van Egmond and Booij[31] thoroughly examines the role of pleural pressure in relation to pneumothorax and other associated complications. Indeed, whilst "non-invasive" (NIV) CPAP and BiPAP ventilation are so-called because they avoid intubation, the fact that positive pressure is the key factor in producing pneumothorax is confirmed by its occurrence during CPAP administration in COVID-19 patients[32] and previously in 2003 in SARS patients with an incidence of between 6 and 15%.[33-35]

Non-invasive Ventilation:

Karagiannidis et al[36] reviewing the changes in utilization and outcomes of a national cohort of 17,023 COVID-19 patients treated by PPV and NIV in Germany concluded that the utilization of NIV rapidly increased during the second autumn wave, which was associated with a reduced usage of intubation and positive pressure mechanical ventilation, but not with overall mortality. High non-invasive failure (NIV-F) rates were associated with increased mortality, particularly in late NIV-F. They stated "global current practices of mechanical ventilation (MV) widely differ, also depending on COVID-19-associated resource limitations. Therefore, the role of NIV remains a matter of uncertainty and discussion, especially with regard to the balance between the NIV benefits and the risk of NIV failure (NIV-F)". CPAP also requires more oxygen than invasive ventilation or a facemask. During the pandemic there were worldwide concerns about oxygen supplies.

Research papers reporting patients' views on NIV Helmet CPAP treatment during the COVID-19 pandemic are few[37] and, whilst recognising that this was a potentially life-saving treatment and their need to be resilient, the patients recounted many negative aspects including the helmet application, communication problems, feeling entrapped, mental confusion and fear of dying. Complaints of excessive noise, gas flow turbulence, choking sensation and thirst were very common.

Viral propagation:

Sui Huang et al[38] proposed that PPV of patients with COVID-19 pneumonia may *eo ipso* facilitate viral propagation in the lung, further accelerating the pulmonary pathology.

Neurotoxicity, neurocognitive impairment:

Positive pressure mechanical ventilation may induce neurotoxicity which can initiate or increase chronic cognitive disorders, but this remains controversial.[39,40] The relationship between MV and neurocognitive impairment was first reported in 1999 in MV-treated ARDS patients.[41] Multiple preclinical and clinical studies suggest that MV induces harmful effects on neurocognitive functions but whether these changes are due to direct MV-induced damage or as result of the perioperative/critical care environment and pre-existing frailty remains debated.[42]

Intubation and Laryngo-tracheal trauma and stenosis:

Prolonged intubation has long been shown to produce laryngo-tracheal trauma and is the commonest cause of airway stenosis, which can produce significant morbidity and precipitate life-threatening airway compromise.[43] Prior to the COVID-19 pandemic, rates of post-intubation and post-tracheostomy airway stenosis ranged from 10 to 22%, with prolonged intubation being the primary risk factor.[45] Patients intubated for longer than 10 days have an increased risk for developing airway trauma and stenosis. A multi-institutional case–control study.[45] showed that each additional day of intubation increased the odds by 21%. Throughout the pandemic, the median duration of endotracheal intubation in COVID-19 survivors was estimated to be 17 days.[46] When controlled for length of intubation, COVID-19 patients, nevertheless, have a greater reported incidence and severity of airway complications. Fiacchini et al compared 30 COVID-19 patients and 45 non-COVID-19 patients who underwent prolonged positive pressure mechanical ventilation. Detailed endoscopic airway examination showed 47% of COVID-19 patients had complications compared to 2% of the control group.[47]

COVID-19 affecting the cardiovascular system:

The deleterious effects of COVID-19 on the cardiovascular system were rapidly recognised early in 2020 and were immediately reported in the COVID-19 literature from China[30] and subsequently worldwide. Acute myocardial injury and chronic damage to the cardiovascular system have been reported in systematic reviews and meta-analyses.[(48-49)] A potential consequence of using PPV is that by forcing air into the lungs, which share the limited space within the chest, it inevitably increases the pressure on the heart and the major veins leading to it. High levels of positive end expiratory pressure (PEEP) increase intrathoracic pressure, reducing venous return to the heart and may be a factor in the increasing incidence of thromboembolic events in the lungs.[50]

The impact of PEEP:

The impact of PEEP on the cardiac index, (CI), has been of concern for over 40 years and the animal evidence was reviewed in 1983, when it was confirmed that it substantially and consistently reduced the CI.[51] 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. In 1995, fifteen unconscious adults after road accidents were ventilated with PPV and each was studied without PEEP, with PEEP, and with an equivalent NEEP pressure being applied to the chest during ventilation. 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.[52] Similar studies were reported in 1998 and 2015 in adults with acute lung injury.[21,53]

The million dollar question:

During the COVID- 19 pandemic Torjesen[54] in a BMJ News Analysis stated that when to start invasive ventilation was the "million dollar question" in COVID-19 care. The article underlined the many serious problem for intensive care doctors and the following statements were made in good faith by leaders in Critical Care in the frontline: -

> *"We haven't really had good data to tell us what the right thing to do is"*
> *"We've all adopted CPAP and non-invasive ventilation (NIV) on no evidence"*
> *"Lots of patients with injuries to their lungs just from the non-invasive mask"*
> *"There's definitely a group of patients to whom we are doing harm and we should be moving earlier towards intubating them, I think"*
> *"Persist (with NIV) for a long time may mean the heavy breathing might cause lung damage of its own"*
> *"There are still one or two hospitals that still adamantly say that you need to invasively ventilate everybody and that you shouldn't be non-invasively ventilating"*
> *"No good evidence exists from clinical trials on the use of non-invasive respiratory support such as high flow nasal oxygen outside critical care settings"*
> *"When is the right time to start invasive ventilation?"*

The results of this review just briefly outline the many problems of PPV over the last seven decades.

CAN WE AVOID INTUBATION AND LIMIT THE USE OF PPV IN FUTURE PANDEMICS?

NPV has been used for >100 years across a range of clinical conditions including polio, ARDS, acute respiratory failure in chronic obstructive pulmonary disease patients, a range of neuromuscular disorders, chest wall disease, and post-cardiothoracic and spinal surgery. Some of the potential benefits of NPV may include improved ventilation, decreased lung damage, improved haemodynamics, ease of proning and prevention of escalation to intubation. Physicians

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moved from using NPV to PPV in the 1950s and 60's for many reasons including lack of supply of the large, cumbersome, costly negative pressure tank devices, nursing issues and the familiarity of anaesthetists with smaller, increasingly developed positive pressure devices from the operating theatre.[30]

It is important to stress in these days of "Evidence Based Medicine" that this change was not due to comparative studies demonstrating superiority of PPV over NPV, nor improved outcome measures, but because anaesthetists who became the initial intensive care specialists already had over three decades of experience of using intubation and positive pressure to ventilate patients in the operating theatre.[(55)] NPV has been largely ignored since then and there are now a generation of anaesthetists and intensivists who are largely unaware of the continuing research into NPV in both children and adults over the last 50 years.[18,21,56,57] Recent scientific and clinical evidence show that a modern CNEP/ NPV device with a torso-only cabinet may provide a non-invasive ventilation alternative to CPAP, with the additional possibility of preventing escalation of the patient to intubation and PPV.[56,57] Our research and aims for the future should be to look again and carefully re-evaluate negative pressure device development, alongside positive pressure devices.

CAN WE STUDY THE PAST AND DIVINE THE FUTURE OF RESPIRATORY SUPPORT?
Confucius 551BCE-479BCE "Study the past if you would divine the future"

It is certainly an important philosophical, physiological and practical point to question whether we, *Homo Sapiens*, can ignore more than 200 million years of evolutionary development of mammalian ventilation that has negative pressure as its basic principle. Have the events of the last 70 years shown positive pressure devices to be an outstanding improvement, or do they indeed have many problems? The review of the literature shows that to be the case.

There are many examples of where studying the past has produced change and potential benefit. The first electric vehicle origins date back to the early 19th century.[58] Robert Anderson invented the first crude electric carriage between 1832-1839. In 1884 Gustave Trouvé, demonstrated a working three-wheeled electric vehicle at the International Exposition of Electricity in Paris. In 1884 Thomas Parker, known for electrifying the London Underground, built the first fully electric production car in the UK, which had many principles in common with today's electric cars. The first gasoline-powered vehicle was not introduced until 1885 by Carl Benz.[59] Over the last 130 years gasoline-powered vehicles have made a major contribution to transport and development, but with the relentlessly increasing disadvantages of pollution, climate change and effects on health, all now demonstrated by scientific investigation and leading to the increased adoption of modern electric vehicles.

FUTURE WORLDWIDE RESPIRATORY SUPPORT
The COVID -19 pandemic once again showed the huge differences in healthcare between countries worldwide. The rich countries dominated events with their facilities, but even they, in many cases, were short of respiratory support and had serious problems with oxygen supply. Treatment outcomes were relatively poor, even in centres of excellence.

Achieving equity in health and wellbeing outcomes is something we should all strive towards and be strong advocates for vulnerable groups and poorer nations.[60] Negative pressure devices are potentially easier to manufacture and use readily available parts (not in competition with PPV devices), can be low cost and with easier nursing and medical management.[30] Crucially they could be much more easily manufactured and used in LMIC countries.

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