Pulsehaler™ - A Novel Pulsating Air Pressure Device for Treatment of COVID-19

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**Background**

The need for ventilator support in COVID, with attendant critical care staff, for a large number of patients, is overwhelming the medical system capacity\(^1\). Furthermore, evidence from the UK setting shows that nearly 50% of COVID patients entering ICU as of March 26, 2020 have died\(^2\).

COVID-19 virus reaches the distal airways and may cause severe bilateral pneumonia\(^3, 4\), leading to oxygen transfer disorder and the need for ventilator support, and in some cases even the need to use ECMO (extracorporeal membrane oxygenation). Recent data\(^5\) based on 55,924 COVID-19 cases in China indicate that in over 1/3 of COVID-19 cases, patients experience sputum production. Autopsies performed on COVID-19 victims in China\(^6\), as well as radiologic analysis\(^7\), revealed that there is thick, sticky mucus present in the lower, small airways\(^8\). The leading professor from the Tongji Medical College autopsy team in Beijing reported that they found “a large amount of mucus in the lungs”. In an interview with Bloomberg he stated\(^9\): “The secretion is very sticky. It attaches to the lung like paste. You must know what the pathological change is and give targeted treatment. Otherwise it will be useless like **delivering oxygen through a blocked path.**” This was echoed by others in China who in the past led the battle against SARS. Zhong Nanshan, an academician of the Continental Academy of Engineering, stated that “**there is no severe fibrosis and there is a lot of mucus.**” The lungs of patients with COVID-19 are different from those infected by the SARS virus.\(^10\)

We believe that our Pulsehaler technology, described below, can help the war on COVID-19 in 3 ways:

1. **delaying or even preventing** the progression of moderate/serious COVID-19 patients (who do not yet require mechanical ventilation) to a state where they require ICU ventilation
2. **improving lung function and reducing residual effects** of infection by treating COVID-19 patients post infection
3. **reducing the need for hospitalization or the risk of secondary infection**, by pre-treating high risk COPD patients at home prior to infection.

Much has been published about the use of external chest oscillations and other vibrating devices to mobilize mucus secretions (eg. King et al, 1983\(^11\), Gross et al, 1985\(^12\), Konstan et al., 1994)\(^13\). Such oscillations have been applied via external vests which has to some extent replaced chest physiotherapy airway clearance techniques. Data on efficacy of these devices has been mixed\(^14\), with some showing improvements in lung function but not in exercise capacity\(^15\). The vibrations from these devices are highly attenuated as they travel through the chest wall to the lung itself. Furthermore, these devices oscillate at a single frequency, limiting their effectiveness.
Other passive devices, called oscillating positive expiratory pressure devices (OPEP) (eg. Acapella, Aerobika, Flutter, Lung Flute), have also been employed to provide airway clearance. However, these devices require vigorous blowing to activate, which is difficult for lung-compromised patients. As well, because they allow negative pressures during inspiration, these devices contribute to airway re-collapse during each breathing cycle, which disrupt the cilia synchronization required to move mucus up the airway. Cilia dis-synchrony has been found to contribute to slower mucus movement in human coronavirus\textsuperscript{16}. They also work at a limited frequencies, and have not demonstrated significant lung function or exercise improvements.

**Pulsehaler\textsuperscript{TM}**

Respinova Ltd., an Israeli company, has developed a new oscillatory airway pressure device called Pulsehaler\textsuperscript{TM}. Pulsehaler\textsuperscript{TM} administers sequences of multi-frequency positive air pressure pulsations throughout a patient’s breathing cycle. Pulsehaler\textsuperscript{TM} generates a pre-programmed protocol of pressure pulsations which have specific frequencies, waveform, pressure amplitude, and duration. It delivers these pressure pulses directly to the airway via a mouthpiece.

Pulsehaler\textsuperscript{TM} is the first device to combine pressure pulses at a wide variety of frequencies, with its own positive pressure generator, and a unique method of air pressure pulse generation via air chopping.

The initial trial\textsuperscript{17} of Pulsehaler\textsuperscript{TM}, conducted at Hadassah Medical Center, Israel was conducted on COPD patients. This trial demonstrated a significant improvement in exercise capacity (\textit{more than 2.5x the minimum clinical important difference}\textsuperscript{18}), inspiratory capacity, and FVC, as well as Borg Dyspnea Score and Mastery Score.

Although the Pulsehaler COPD study didn’t specifically measure mucus production, investigators observed in many subjects a substantial increase in mucus production and decrease in mucus viscosity, together with improvement in mucus color. Pulsehaler\textsuperscript{TM}’s pulsating positive pressure air waves at these frequencies appear to help restore the proper function of respiratory cilia responsible for moving mucus out of the airway, and reduce mucus viscosity in the small airways. Furthermore, use of continuous positive pressure during the breathing cycle prevents airway closure, allowing the cilia the time they require to resynchronize.
We conducted a second trial of Pulsehaler at Asaf Harofe Hospital in Israel, again on COPD patients. This trial demonstrated, via SPECT-CT imaging, that Pulsehaler™ caused closed airways to reopen all the way to the periphery of the lung. (See figure).

COVID-19 patients presenting respiratory symptoms may typically deteriorate into bi-lateral pneumonia. Data from SARS, which appears to create pulmonary infections with some similarities to COVID-19, showed positive effects of noninvasive positive pressure ventilation in treating acute respiratory failure. However, the data from COVID-19 also shows, unlike SARS, a significant mucus component blocking small airways. Based on this finding, and the data from our COPD studies, we hypothesize that Pulsehaler™’s multi-frequency pulsating positive pressure waves can complement other therapies used to treat moderate COVID-19 patients. We also hypothesize that using Pulsehaler™ can improve oxygenation, and reduce the thick mucus evident in these patients. We believe it may also reduce the risk of secondary infection, and reduce the risk of deterioration to a state requiring full mechanical ventilator support.

Pulsehaler™ (actual device shown in the figure) consists of a Base Unit and Hand Unit, connected via a hose. The Base Unit generates continuous positive pressure via a built-in turbine. The hand unit contains a rotating disc that chops the air flow into pressure pulses at a series of predefined frequencies, over a 20 minute treatment. Chopping the airflow in this way produces pulse shapes, pressure amplitudes, and harmonic frequencies that have been demonstrated clinically to open airways, improve exercise capacity, and decrease breathlessness. In our COPD trial, the investigators observed enhancement of mucus clearance, although the degree was not quantified in this study. Mucus viscosity is affected by Pulsehaler™ through a thixotropic effect, whereby viscosity of a liquid can be changed by shaking or vibration (like shaking a ketchup bottle to make it more liquid).
Furthermore, cilia must beat synchronously to move mucus. They cannot beat in synchrony in an airway that is collapsed due to mucus, inflammation, or loss of tethering forces, all of which are seen in COVID-19 patients. Pulsehaler™ provides positive pressure throughout the breathing cycle, thus enabling cilia to resynchronize and beat effectively to move the mucus up the airway.

**Comparison to Current State of the Art**

COVID-19 patients are at present being treated in hospital when they have symptoms of breathing difficulty. Treatment can include oxygen, or as patients progress, transition to BIPAP or in worst case scenario, to full mechanical ICU ventilation. Current treatments do not appear to slow down the progression and the risk of transition from moderate to critical.

Pulsehaler™ has numerous advantages over other treatment devices, including other oscillation devices, CPAP, and BIPAP:

1. **Relies on patient’s normal breathing** – Other airway oscillation devices require the patient to generate high flows and pressures to achieve oscillations, which would be difficult for COVID-19 respiratory-compromised patients. Pulsehaler enables the patient to receive treatment using normal relaxed breathing.

2. **Positive Pressure Support** – By using a built-in turbine blower, rather than relying on patient-generated pressure, Pulsehaler™ provides positive pressure support to the patient during treatment, while the oscillations re-open closed airways and clear mucus.

3. **Demonstrated Clinical Efficacy for Re-opening airways** – Pulsehaler™ has been clinically demonstrated to re-open airways, and to improve mucus clearance. BiPAP and CPAP have been not been found to re-open collapsed airways, nor are they useful for mucus clearance. In fact, in our sham-controlled study, the sham device was a simple BiPAP without the Pulsehaler oscillations. In the trial, BiPAP failed to reach the threshold of the Minimum Clinically Important Difference, while Pulsehaler™ exceeded MCID by 2.5x. As compared to external vests, Pulsehaler™ provides the oscillations at multiple frequencies, and without the attenuation cause to external pulsation methods.

4. **Easy for Patients to self-administer** – awake patients can easily use Pulsehaler™ with a few minutes of training, and can use the device at home to prevent or slow the need for treatment in hospital.

5. **Multi-Patient Use** – All patient contact parts and the patient filter can be removed and retained by patients, while the Base Unit and Hand Unit can be disinfected with viracide wipe-down. Pulsehaler™ is being adapted for use in COVID-19 to contain an exhalation filter to prevent virus spread.

6. **Reduced Cost / Increased Effectiveness** – Our estimate for the price of a Pulsehaler™ compares very favorably to the cost of ventilators ($10K-50K) and other therapies. Also, each Pulsehaler™ can be used in the hospital setting to treat multiple patients because of its short treatment time, thus further spreading the per-patient cost. Using Pulsehaler™ in the home setting to pre-treat high risk COPD patients can reduce hospital burden costs and the number of patients that need to be admitted.
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Development Status

Pulsehaler™ is undergoing final design refinements. To expedite completion, we are also conducting certain laboratory tests required for FDA / CE in parallel to these refinements. Tooling for many components is complete for transition to large scale production. Other tools are out for quotation currently.

Regulatory Status

Pulsehaler is a Class II device in the USA and Class IIa in Europe. Testing to FDA / CE / ISO recognized standards is ongoing. Materials have already passed the first biocompatibility tests. Our team is investigating Emergency Use Authorization for Pulsehaler™ in several jurisdictions.

About Respinova Ltd.

Respinova Ltd. is a SME located in Israel. Its team has over 150 years of collective experience in commercializing novel medical devices, from concept to manufacturing scale-up and distribution. Cliff Ansel, Respinova’s CEO, has extensive experience in developing medical devices for defense and pandemic situations. Prior to Respinova, he was the CEO of a US Marine Corps / Navy / Army contractor, Thornhill Medical. Under Mr. Ansel’s guidance, his former firm developed the MOVES® SLC™ portable ICU, and MADM™ Anesthesia system, which are now the standard of care in USMC critical care, and is currently being deployed in the fight against COVID-19. We have extensive medical device manufacturing contacts in the US, Canada, Europe, Asia, and Israel, and we are able to partner with one or more of them to speed up full scale manufacturing deployment of Pulsehaler™.
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References

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