Physiological response to intrapulmonary percussive ventilation in stable COPD patients

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Summary Intrapulmonary percussive ventilation (IPV) is a ventilatory technique that delivers bursts of high-flow respiratory gas into the lung at high rates, intended for treating acute respiratory failure and for mobilization of secretions. We performed a study, aimed at assessing the physiological response to IPV, on patients’ breathing pattern, inspiratory effort, lung mechanics and tolerance to ventilation.

Ten COPD patients underwent randomized trials of IPV through a face mask at different pressure/frequency combinations (1.2 bar/250 cycles/min; 1.8/250; 1.2/350; 1.8/350), separated by return to baseline (SB), using the IMP2 ventilator. In 5 patients we have also compared the physiological changes of IPV with those obtained during pressure support ventilation (PSV).

Minute ventilation did not vary among the trials, but tidal volumes (VT) were significantly greater during 1.2/250, 1.2/350 and 1.8/350 compared to SB. The pressure time product of the diaphragm per minute (PTPdi/min) estimate of the diaphragm oxygen expenditure was also significantly reduced during 1.2/250 and 1.8/250 (209 cmH2O × s/min for SB vs. 143 and 125 for 1.2/250 and 1.8/250, respectively P<0.05), as well as dynamic intrinsic end-expiratory pressure (PEEPi,dyn). Similar reduction in PTPdi/min were obtained also during PSV. Tolerance to ventilation and oxygen saturation were satisfactory and did not change during the different trials. In 5 normal subjects a prolonged apnea trial lasting >2 min was also performed, without any significant decrease in SaO2 or subjective discomfort. In conclusion, IPV was able to guarantee an adequate ventilation, while inducing a significant unloading of the diaphragm during the "low-frequency" trials.

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Introduction

Intrapulmonary percussive ventilation (IPV) is a ventilatory technique that delivers small bursts of high-flow respiratory gas into the lung at high rates,\(^1\) intended for mobilization of secretions that has been employed in several pathologies, characterized by excessive secretion, both in adults and children.\(^2\)–\(^5\) In a very recent randomized-controlled study\(^6\) conducted in ICU and performed in COPD patients with initial respiratory acidosis, IPV has been shown to prevent the deterioration of acute exacerbation, avoiding therefore the use of invasive mechanical ventilation. Potential mechanisms of actions include enhanced alveolar recruitment, improved mucus clearance, and/or a direct high-frequency oscillatory ventilation like effect.\(^1\) Surprisingly, so far no study has been performed to evaluate the physiological changes induced by IPV. In order to better understand the effects of this modality of ventilation, we describe the changes of IPV on breathing pattern, diaphragmatic function, respiratory mechanics and patient’s tolerance in stable COPDs with chronic respiratory failure, and we compared, in a subset patients, those effects with the ones obtained during non-invasive pressure support ventilation (PSV). We also verify the potentiality of IPV in providing effective ventilation during a prolonged apnea trial in a group of normal subjects.

Materials and methods

Patients

Ten severe COPD patients, with minimal mucus hypersecretion (\(<10\text{ml/d}\)) naïve to ventilation, and affected by chronic hypercapnic respiratory failure were studied during a phase of clinical stability during sessions of IPV. Clinical stability was defined as the absence of exacerbations of their respiratory disease in the preceding 3 months. The patients were admitted to the hospital for a scheduled short control of their clinical conditions. The quantity of mucus secretion was assessed asking the patients to collect their sputum in a box for the 48 h preceding the experimental trial. Collection and quantification of sputum weight was performed every 12 h. Patients’ characteristics are illustrated in Table 1. All the patients were on long-term oxygen therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.2 ± 6.7</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/2</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 0.02</td>
</tr>
<tr>
<td>(P_{aCO_2}) (mmHg)</td>
<td>52.3 ± 8.1</td>
</tr>
<tr>
<td>(P_{aO_2}) (mmHg)</td>
<td>53.1 ± 7.0</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>89 ± 11</td>
</tr>
<tr>
<td>FEV(_1) (% predicted)</td>
<td>31 ± 9</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>35 ± 8</td>
</tr>
</tbody>
</table>

Intervention

IPV is a ventilatory versatile form of high-frequency ventilation (HFV) that delivers bursts of high-flow respiratory gas in the lung at high respiratory rates. HFV techniques have three essential common elements: a high-pressure flow generator, a valve for flow interruption, and a breathing circuit for connection to the patients. Many variants of this definition were further developed as flow interruption ventilation (HFFI), high-frequency oscillation (HFO) and high-frequency positive pressure ventilation (HFPPV) based on the specific techniques that discriminate them. Similar to HFV, IPV delivers subphysiologic tidal volumes \((V_T)\) at rapid rates. Unique to the IPV is the presence of a sliding venturi system (phasitron), powered by compressed gas that can be changed from 0.8 up to 3.5 bar and that generates the oscillations in the range of 80–650 cycles/min.\(^7\) During this ventilation a continuous positive pressure is maintained, while a high-velocity percussive inflow opens airways and enhances intra-bronchial secretion mobilization. During IPV the high pressures generated by the ventilator are mostly dissipated in the mask and in the upper airways. IPV was delivered with a specific ventilator (IMP2, Breas Medical Mölnlycke, Sweden) through a full face mask. The inspiration-to-expiration time \((I/E\) ratio\) was adjusted to 1/2.5 and the proximal expiratory pressure was set to 3 cmH\(_2\)O. The \(I/E\) ratio of the administered oscillatory flow pattern generated by the device (that is independent of the patient’s breathing pattern) was set at 1/2.5 because this was the setting used in the only clinical study performed in COPD patients with respiratory failure.\(^6\) Indeed, since the setting of the \(I/E\) ratio influences the mean airway pressure, it was recommended by the distributors of the device, the use of a 1/2.5 ratio in COPD patients, to avoid pressure higher than 30 cmH\(_2\)O.

Protocol

First trial

As illustrated in Fig. 1, upper part, 10 COPD patients were randomly assigned to 4 sessions of
IPV, at different pressure/frequency combinations lasting 10 min each and separated by return to spontaneous breathing (SB) for 15 min. This time was always long enough to allow a complete return to baseline conditions of the main physiological variables (see “Results”), and therefore to avoid any carry-over effect. The following sessions were performed by the trained respiratory therapist: frequency of percussion of 250/min using a driving pressure of the apparatus of 1.2 bar (1.2/250) and 1.8 bar (1.8/250), respectively, and frequency of percussion of 350/min using a driving pressure of 1.2 bar (1.2/350) and 1.8 bar (1.8/350). Changing the driving pressure from 1.2 to 1.8 bar will increase the airways pressure generated during each percussion, where a decrease in frequency will increase the volume of air delivered by the machine during each pulsation. The patients were instructed by the respiratory therapist to relax, but not to try to keep the frequency of the ventilator.

**Second trial**

As shown in Fig. 1 middle part, 5 of 10 patients underwent also an additional experimental procedure at the end of the first trial. They were randomly assigned to 2 sessions of IPV (1.2/250 and 1.8/250) and 1 of non-invasive PSV lasting 10 min each and separated by return to SB for 15 min. Non-invasive PSV was delivered using the same face mask, while the experimental apparatus (i.e. location of the pneumotach and pressure transducers) was kept constant. The level of end-expiratory pressure was maintained constant at 3 cmH2O, while the inspiratory pressure was set according to the patient’s tolerance (14.2 ± 2.1 cmH2O).

Oxygen was eventually supplied to those patients with an SpO2 < 90%, directly into the mask to maintain an oxygen saturation (SpO2) > 90% and was kept constant throughout the experimental procedure.

**Third trial**

Five normal volunteers (2 females and 3 males, mean age = 38.8 ± 4.1) were also studied, during 2 periods of apnea obtained with a breath-holding, lasting at least 2 min, separated by 15 min of SB (Fig. 1, lower part). The apnea trials were performed during 2 sessions of IPV (1.2/250 and 1.8/250) delivered in random order. The trials were performed without oxygen supply.

**Measurements**

The physiological variables were continuously displayed on a PC screen. SpO2 and heart rate were also continuously monitored with a portable device.

Flow at the airway opening was measured with a heated pneumotachograph (Hans-Rudolf 3700, Kansas, USA) and a differential pressure transducer (Honeywell ± 300 cmH2O; Freeport, IL, USA) placed

<table>
<thead>
<tr>
<th>First Trial</th>
<th>(n=10 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>10 min</td>
</tr>
<tr>
<td>S.B</td>
<td>1.2/250</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second Trial</th>
<th>(n=5 patients of the previous 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>10 min</td>
</tr>
<tr>
<td>S.B</td>
<td>1.2/250</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Third Trial</th>
<th>(n=5 normal volunteers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>APNEA &gt; 2 min</td>
</tr>
<tr>
<td>S.B</td>
<td>1.2/250</td>
</tr>
</tbody>
</table>

All the IPV trials were performed in random order.

**Figure 1** Protocol of the study. The COPD patients underwent 2 different trials (first and second trial), while the normal volunteers were studied during the third trial. SB = spontaneous breathing, 1.2/250 = frequency of percussion of 250/min and driving pressure of 1.2 bar, 1.8/250 = frequency of percussion of 250/min and driving pressure of 1.8 bar, 1.2/350 = frequency of percussion of 350/min and driving pressure of 1.2 bar, 1.8/350 = frequency of percussion of 350/min and driving pressure of 1.8 bar.
between the mask and the ventilator tubings. \( V_T \) was obtained by digital integration of the flow using the trapezoidal rule.\(^9\)

Airway pressure (Honeywell \( \pm 300 \text{cmH}_2\text{O}; \) Freeport, IL, USA) was measured from a side port between the pneumotachograph and the face mask.

Esophageal and gastric pressures were measured with a balloon–catheter system. To this aim, an esophageal balloon positioned at the lower third of the esophagus, filled with 0.5 ml of air and a gastric balloon filled with 1 ml of air. The proper position of the balloon was verified using the occlusion test.\(^9\)

Transdiaphragmatic pressure (Pdi) was calculated as the difference between gastric (Pga) and esophageal (Pes) pressure.\(^9\)

The pressure time integrals of the diaphragm was calculated per breath (PTPdi/b) and per minute (PTPdi/min).\(^10\)

Respiratory mechanics were assessed using Mead and Wittenberger’s technique.\(^11\) Inspiratory pulmonary resistance \( (R_L) \) and elastance \( (E_L) \) were calculated by fitting the equation of motion of a single-compartment model using multilinear regression.

Dynamic PEEPi (PEEPi,dyn) was measured according to Appendini et al.\(^12\)

Expiratory muscle recruitment during the different trials was assessed by measuring the rise in Pga during expiration from its end-inspiratory level to the maximum at end-expiration.\(^13,14\)

The patient’s tolerance to ventilation was evaluated on a visual analogue scale. This scale has been used and validated in previous studies\(^15,16\) and has 5 scores: 1, bad; 2, poor; 3, sufficient; 4, good; 5, very good. The patients were asked by the respiratory therapist to answer the following question: “How do you feel your breathing is at this moment”? For each condition tested, the patient placed a finger on the number that best represented the intensity of his or her dyspnoea.

The study was approved by the local Ethical Committee and written informed consent was obtained from the patients and normal subjects.

**Statistics**

Results are presented as mean \( \pm \) standard deviation (SD) for continuous variables, as frequency or percentage for the nominal variables and as median (quartiles or range) for the ordinal variables. Comparisons for each sequence and each continuous variable were performed with one-way ANOVA for repeated measures. Post hoc comparisons between sequences were performed by using Duncan’s test. Comparisons between the different SB measurements were performed using the Kruskall–Wallis analysis of variance.

To compare repeated measures for an ordinal variable (patient tolerance) the Friedman test was used, while internal comparisons were performed using a non-parametrical test for multiple post hoc comparisons.

All tests were two-sided. A \( P \) value < 0.05 was considered statistically significant.

**Results**

All the patients and normal subjects tolerated the experimental procedure well, except for 2 patients who could not stand the 1.2/350 trial and the 1.2/350 and 1.8/350. \( \text{SpO}_2 \) was kept also constant throughout the trials, without changing the \( \text{FiO}_2 \) set at SB. No statistical difference was observed in all the physiological variables recorded between the different periods of SB lasting 15 min.

Ten minutes of IPV were able to induce a homogeneous breathing pattern in our patients, as already described in this population of stable patients by another study using other types of ventilatory support.\(^17\)

**First trial**

**Figure 2**, upper part, is a recording from a representative COPD patient.

**Table 2** shows the main physiological changes induced by IPV in the first experimental trial. Minute ventilation was not statistically different from SB during the IPV trials, since while \( V_T \) was significantly increased, respiratory rate decreased even though not significantly. The PTPdi/min and PTPdi/b, estimate of the diaphragm energy expenditure was reduced, compared to SB, in all the IPV trials, but significantly so only during those at low frequency (1.2/250 and 1.8/250). Similar changes were observed for the amount of PEEPi,dyn.

Lung compliance and resistance did not significantly change during the various ventilatory trials. Tolerance to ventilation was not statistically significant among the trials, but a larger proportion of patients ranked the low-frequency trials (1.2/250 and 1.8/250) as ”good” or ”very good”.

The expiratory muscle recruitment was minimal in most of the patients with actually only 2/10 subjects showed a rise in Pga during expiration \( > 1 \text{cmH}_2\text{O} \) at 1.8/350.

**Second trial**

**Figure 3** shows the individual changes (different symbols) in PTPdi/min at SB, 1.2/250,1.8/250 and
during non-invasive PSV in the 5 patients undergoing an additional trial with this latter mode of ventilation. No significant differences were observed between the IPV trials and PSV session, for the PTPdi/b, and all the other physiological recordings, as illustrated in Table 3.

Third trial

The apnea trial was well tolerated by all the normal subjects, and lasted on average 139 ± 18 s without any significant decrease in SaO2 under IPV.
Figure 1, lower part, illustrates the apnea trial in a typical normal subject. Complete absence of SB can be depicted by the pressures traces.

Discussion

IPV is one stand-alone technique of HFV, that was initially employed for treating acute respiratory failure due to different pathologies like burns, smoke inhalation, closed head injury, hyaline membrane disease and ARDS. More recently, it has been also successfully and increasingly used in those patients with cystic fibrosis, Duchenne muscular dystrophy and other neuromuscular diseases and exacerbated COPD, as a primary treatment for mobilizing and clearing secretions.

Apart from an „in vitro” investigation that assessed changes in flow, volume and pressure waveforms after modification of resistance and elastance, while maintaining the same ventilatory settings, no study has systematically assessed the „in vivo” physiological changes using the parameters commonly used during the non-invasive treatment.

In order to avoid potential confounders, the study was performed on stable patients with minimal mucus production, since despite the randomized nature of the trial, the mobilization of massive secretion potentially induced by the initial application of IPV, may have altered the mechanical properties of the respiratory system, influencing therefore the following runs with a carry-over effect.

As a matter of fact both pulmonary compliance and resistances were maintained constant during the experimental procedures.

We have chosen to study COPD patients with chronic respiratory failure since in this latter population, it was recently demonstrated, during an episode of exacerbation requiring ICU admission, that IPV may prevent further deterioration, avoiding therefore the need for invasive mechanical ventilation.

In that study, several mechanisms of action for IPV were postulated. Apart from the effect on mucus clearance, it was suggested that an external positive end-expiratory pressure (PEEP_e) effect and/or an HFV-like effect were possible. IPV maintains an intrapulmonary pressure to stabilize the airway patency during the whole respiratory cycle, so that this mechanism may counterbalance the inspiratory load necessary to start inspiration when a positive end-expiratory pressure is present in COPD patients. As a matter of fact the amount of PEEPI_dyn was significantly reduced during 1.2/250 and 1.8/250, suggesting a direct effect of IPV. Indeed, no indirect signs of hyperinflation, such as a „notching” in the expiratory phase of Pdi, were observed during the IPV trials.

Despite during an acute exacerbation of COPD, the portion of energy expenditure of the diaphragm (PTPdi), due to the presence of PEEPI_dyn is very

<table>
<thead>
<tr>
<th>Variable</th>
<th>SB</th>
<th>1.2/250</th>
<th>1.8/250</th>
<th>PSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_e ) (l/m)</td>
<td>7.58±3.1</td>
<td>8.81±4.4</td>
<td>9.0±3.9*</td>
<td>9.6±4.2*</td>
</tr>
<tr>
<td>PTPdi/b (cmH(_2)O x s)</td>
<td>7.7±4.8</td>
<td>5.8±3.9*</td>
<td>5.5±4.0*</td>
<td>4.9±3.6*</td>
</tr>
<tr>
<td>PEEPI_dyn (cmH(_2)O)</td>
<td>2.8±1.2</td>
<td>1.5±1.0*</td>
<td>1.2±0.8*</td>
<td>1.1±0.9*</td>
</tr>
<tr>
<td>( R_e ) (cmH(_2)O/l x s)</td>
<td>8.3±3.3</td>
<td>8.4±2.9</td>
<td>7.8±2.2</td>
<td>7.9±2.3</td>
</tr>
<tr>
<td>( C_L ) (cmH(_2)O/l/s)</td>
<td>0.08±0.02</td>
<td>0.07±0.04</td>
<td>0.08±0.03</td>
<td>0.07±0.05</td>
</tr>
<tr>
<td>Sa(_O)_2 (%)</td>
<td>95.4±1.4</td>
<td>96.8±2.6</td>
<td>96.2±1.9</td>
<td>96.5±2.0</td>
</tr>
</tbody>
</table>

See Table 2 for abbreviations.

*P<0.05 from SB.
consistent\textsuperscript{11} (~40% of the total), in stable COPD, like those included in the present study, it is definitively less.\textsuperscript{23}

Therefore the marked and statistically significant decrease in PTPdi both per breath and per minute, observed during IPV must be due also to a direct "ventilatory effect". The PTPdi depends on the time of inspiration and the tidal transdiaphragmatic pressure (Pdi) generated during each inspiration. Since IPV did not significantly influence the respiratory timing, the decrease in the metabolic consumption was presumably due to the use of a lower portion of Pdi, as repeatedly demonstrated during any form of invasive or non-invasive mechanical support of ventilation.\textsuperscript{23,24}

Indeed the physiological changes induced by IPV were very similar to those obtained in 5 patients during the most commonly used mode of non-invasive ventilation (i.e. PSV).\textsuperscript{23,24} The comparison of different modes of ventilation must be anyhow taken with caution, since the matching of the physiological variables (i.e. $V_T$, mean airways pressure or minute ventilation) is very difficult to achieve.

Having said that, IPV could be considered a form of full ventilatory support. To confirm this all the 5 normal subjects enrolled for the prolonged apnea trial without oxygen supply, could successfully sustain the breath holding for more than 2 min without any drop in SaO\textsubscript{2}. It may be therefore suggested that IPV may be safely used also in those tracheotomized patients with absent or minimal ventilator autonomy (i.e. spinal cord injury or amyotrophic lateral sclerosis), when they need to be disconnected from their usual ventilator in order to mobilize their secretions.

Last, IPV was well tolerated, but overall the low-frequency trials were better accepted. Indeed, it has also been suggested that the application of a continuous positive intrapulmonary pressure, may increase the activation of the expiratory muscles.\textsuperscript{25} This was not the case in the large majority of our patients (8/10), that did not show a significant increase in the tidal transdiaphragmatic pressure (Pdi) generated during expiration.\textsuperscript{13,14}

The assessment of the clinical usefulness of IPV in stable COPD and its potential fields of application were beyond the aim of this physiological study, so that further studies are clearly needed to confirm the potential role of IPV to manage patients undergoing an acute exacerbation of their chronic obstructive disease.

In this first physiological study performed in stable COPD patients with chronic respiratory failure, we have demonstrated that the application of IPV is associated with a significant reduction of the diaphragm energy expenditure, probably mediated by a "true ventilatory" effect. Indeed, it is safe, and overall well tolerated, especially with the lower frequencies. Further studies may be needed to extrapolate these results to more acute patients.

References


