Combined oscillatory and mandatory ventilation in newborn infants

Infants who fail to respond to intermittent mandatory ventilation (IMV) and/or high frequency oscillatory ventilation (HFOV) alone, can benefit from a combination of HFOV and IMV known as combined oscillatory and mandatory ventilation (COMV). This article reviews the available evidence on the effectiveness and safety of COMV, including animals studies. The author's experience of the effect of COMV in both preterm and term infants who did not respond to IMV or HFO is described and operational guidance regarding management of COMV is given.

Keywords
COMV; HFOV; IMV; oxygenation; gas exchange

Key points
1. Several studies have shown COMV can facilitate alveolar recruitment and improve oxygenation in infants failing to improve on IMV and/or HFOV alone.
2. Combining two components (IMV and HFO) with similar principles and physical and mechanical characteristics provides a two pronged approach by improving both oxygenation and CO₂ elimination.
3. In the author's study, COMV improved oxygenation and gas exchange in newborn infants and appeared to be safe as a rescue treatment.
4. There are no randomised controlled trials on the effectiveness and safety of COMV.

When intermittent mandatory ventilation (IMV) and/or high frequency oscillatory ventilation (HFOV) fails to improve respiratory failure, the imposition of HFOV during IMV has been shown to facilitate alveolar recruitment and improve oxygenation. This mode of ventilation has been referred to as combined oscillatory and mandatory ventilation (COMV) or high frequency oscillation-intermittent ventilation (HFO-IMV) or combined high frequency ventilation (CHFV). It will be referred to as COMV in this article.

Literature review
Boynton and colleagues reported improved pulmonary gas exchange by combining HFOV and IMV to treat neonates with severe respiratory failure. COMV was used in 12 neonates (gestation 24-40 weeks) with inadequate gas exchange (mean PaO₂ 32 mmHg, PaCO₂ 60 mmHg) on conventional IMV with mean airway pressure (MAP) 16 cmH₂O, FiO₂ 1.0. Within 10 hours of beginning COMV, improvements were seen in the mean arterial PCO₂ (60±5 to 38±2 mmHg), IMV rate per minute (96±8 to 17±4), the mean arterial-alveolar oxygen tension ratio (0.05±0.01 to 0.09±0.01) and MAP (16±2 to 10±3 cmH₂O). The authors concluded that in some neonates with respiratory failure who fail to respond to IMV, COMV can be successful.

Another study reported that a heterogeneous group of 45 neonates (gestation 25-43 weeks) with severe pulmonary disease and inadequate gas exchange on IMV (MAP 17 cmH₂O, FiO₂ 1.0, rate 78 per minute) was successfully treated with COMV. During COMV, CO₂ removal improved significantly in almost all patients except in infants with aspiration. Radiographic and clinical improvement/resolution of pre-existing air leaks was noted. A positive oxygenation response in the first six hours of treatment was related to a much higher chance of survival and patients with active air leaks responded most favourably to COMV. COMV failed to improve ventilation in neonates with diaphragmatic hernia/hypoplastic lungs. Complications during COMV included increased pulmonary secretions, worsening or recurrence of pre-existing air leaks, or occurrence of new air leaks. Twenty-four patients died, 18 due to a respiratory cause. The authors concluded that initiation of COMV earlier in the course of the disease may improve survival.

Murthy and Petros suggested that COMV mode offers significant improvement as a rescue mode for neonates and infants with severe respiratory failure. COMV was used as a rescue mode in 10 neonates and infants aged one day to 17 months, who were receiving maximal conventional ventilation. FiO₂ was reduced from 0.90 to 0.55 at six hours and 0.44 at 12 hours on COMV. There was also an improvement in gas exchange with complete haemodynamic stability.

Using the same method, El Baz and colleagues reported successful treatment of severe hypoxaemia in adults suffering from adult respiratory distress syndrome with
death imminent, despite maximum ventilatory support with intermittent positive pressure ventilation. Only slight improvement of PaO₂ was noted with high frequency positive pressure ventilation (HPPV) at the rate of 250 breaths/min. HFO ventilation improved oxygenation but there was progressive CO₂ retention and respiratory acidosis. Administration of HPPV simultaneously with HFO provided adequate oxygenation by accelerated gas diffusion and CO₂ elimination by convection, and successfully treated the hyperoxaemia of respiratory failure in all patients. The technique was well tolerated by the patients and cardiac output was also adequately maintained during the treatment.

Blanco and coauthors reported that the combination of HFOV and IMV is advantageous in improving pulmonary gas exchange in rabbit saline-lavaged lungs. Oscillations were continuously superimposed upon ventilator breaths and MAP was measured at the end of endotracheal tube, through a catheter alongside the tube. HFO-IMV produced a significant improvement in PaO₂, PaCO₂ and ventilatory index at a lower MAP.

In the study by Obara and colleagues the effects on lung tissue of HFOV combined with IMV were compared with those of conventional mechanical ventilation (CMV) by matching the mean tracheal pressure. Pulmonary alveolar type 2 cells and subcellular organelles from rabbit lung were morphometrically examined by electron microscopy. The volume and surface densities of lamellar bodies in alveolar type 2 cells from the animals ventilated with CMV were decreased significantly compared with those from the animals either ventilated with CMV or breathing spontaneously (control group). The cell surface to volume ratio in the HFO-IMV group showed a significant increase compared with the CMV groups, whereas other variables showed no differences between the three groups. These results suggest that secretion of surfactant from alveolar type 2 cells was enhanced in COMV-treated animals compared with CMV-treated and control groups.

Walsh and Carlo studied the impact of inflation during HFOV by applying sustained inflation at pressures of 5, 10, 15 cm H₂O above MAP for 3, 10 and 30 seconds to 15 rabbits after saline lavage to induce surfactant deficiency. Arterial PO₂ compliance of the respiratory system and functional residual capacity increased after sustained inflation at pressure levels of at least 10 cmH₂O and 10 seconds duration. As the pressure or duration of the sustained inflation was increased, oxygenation improved (p<0.005). Sustained inflations of 5 cmH₂O above MAP of 3 seconds duration were ineffective. The authors concluded that either a critical pressure or duration of sustained inflation is needed to improve oxygenation and pulmonary mechanics during HFOV.

The Medway experience

Patients and methods

The effects of COMV ventilation in 30 infants, mean gestation 26 weeks (23-42), mean birthweight 1,000g (370-3180g) were reviewed retrospectively over a four year period. COMV was started due to poor oxygenation with or without hypercapnia and five infants had pulmonary air leak syndrome. Primary diagnoses included surfactant deficiency disease, pneumonia, meconium aspiration syndrome and pulmonary hypoplasia. The oxygenation index (OI), a function of FiO₂ requirements and MAP to maintain adequate oxygenation, was used to predict those infants who had received maximal conventional ventilation therapy and who might benefit from extracorporeal membrane oxygenation (ECMO).

Oscillations (10Hz) were delivered during both the inspiratory and expiratory phases of the ventilator cycle using the SLE2000 HFO ventilator. The same MAP was used initially in all infants and the delta pressure (delta P, amplitude, oscillatory pressure) was increased until chest wall bounce was clearly seen. Neotrend sensors were used in most of the infants for continuous arterial blood gas measurement and tidal volume (TV) was measured by Florian (Neonatal Respiration Monitoring, SLE) in all infants (FIGURE 1). (COMV ventilation and tidal volume monitoring is now available in one machine, the SLE 5000.) Arterial blood

![FIGURE 1](image1.png) Measurement of tidal volume using the Florian (Neonatal Respiration Monitoring SLE).

![FIGURE 2](image2.png) Changes in MAP (cmH₂O), FiO₂, OI and PaCO₂ (kPa) after COMV treatment.

<table>
<thead>
<tr>
<th>MAP(cmH₂O)</th>
<th>FiO₂</th>
<th>OI</th>
<th>PaCO₂(kPa)</th>
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<tbody>
<tr>
<td>Pre-COMV</td>
<td>15</td>
<td>0.85</td>
<td>24</td>
</tr>
<tr>
<td>+ 4 hours</td>
<td>12</td>
<td>0.45</td>
<td>12</td>
</tr>
<tr>
<td>+ 24 hours</td>
<td>12</td>
<td>0.45</td>
<td>11</td>
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TABLE 1 Mean values for MAP, FiO₂, oxygenation index (OI) and PaCO₂ immediately before and after four and 24 hours of COMV treatment.
gases were measured routinely at four hour intervals and also immediately prior to starting COMV. Recordings were made immediately prior to, at four and 24 hours after starting COMV.

Results
The effect of COMV treatment in the 30 infants is shown in TABLE 1 and FIGURE 2. At four hours, 23 of the 30 (77%) infants showed improved oxygenation and in 21(70%) infants, TV improved and PaCO$_2$ was <4.5 requiring rate reduction in the conventional component. During the treatment three infants developed pulmonary air leak syndrome, no other complications were noted. Overall mortality was 33%(10) including five of the seven infants who failed to improve oxygenation at four hours after COMV.

Among the 30 survivors, mean duration for COMV was four days and eight infants developed chronic lung disease. One had post haemorrhagic ventricular dilatation and one had unilateral porencephalic cyst.

Conclusions
COMV improved oxygenation and gas exchange in newborn infants and also appeared to be safe when used as rescue treatment when IMV, with or without HFOV, failed. Our numbers are small; however, the results are encouraging for further clinical and physiological studies.

Operational guidance and settings of COMV
The characteristic feature in COMV is the imposition of HFO at a fixed frequency but of variable Delta pressure in both inspiratory and expiratory phases of standard conventional ventilation. The oscillator’s sinusoidal pressure waveform is superimposed on all IMV breaths (FIGURE 3).

Commencing COMV
After attempting lung recruitment by surfactant administration, plus maximum HFOV and/or IMV depending on the unit ventilation guidelines, COMV can be commenced as detailed below (FIGURE 4).

IMV component
IMV is commenced with peak inspiratory pressure settings (PIP) usually at 20-24 cmH$_2$O associated with satisfactory chest wall excursion and positive end-expiratory pressure settings (PEEP) at 4-5 cmH$_2$O. The rate is usually set between 30-60 per minute initially and is adjusted as necessary depending on the blood gases, in particular carbon dioxide levels. By using the same PIP and rate as the previous IMV alone, imposition of HFO would provide the same MAP. Inspiratory time (IT) is usually set between 0.34-0.5 seconds. Altering the IMV rate will affect IE ratios and this in turn will affect MAP hence oxygenation, if inspiratory:expiratory ratios are not kept constant. Recordings of PIP (cmH$_2$O), PEEP (cmH$_2$O), MAP (cmH$_2$O), rate (bpm), IT (seconds), IE ratio FiO$_2$ (%/decimal) are made regularly or when changes are instituted.

Oscillatory component
HFOV is commenced at the starting oscillation frequency of 10 Hz with delta P sufficient to produce optimal visible chest vibratory movement, usually starting at 10 cmH$_2$O up to a maximum of 30 cmH$_2$O. Delta P is increased by 2-4 cmH$_2$O increments until vibrations are clearly visible but not excessive. Chest wall bounce should thereafter be recorded as frequently as vital signs and any change occurring independently of ventilator settings should be investigated and relevant adjustments or interventions made. MAP is adjusted prior to switching from IMV to achieve a high frequency tidal volume of 2-3 mL/kg. FiO$_2$ is maintained at the same concentration. Frequency (Hz), oscillator/delta pressure (cmH$_2$O) and MAP (cmH$_2$O) are recorded regularly or with any changes made.

Other measures
Once gases are stable chest X-ray is performed to monitor lung inflation – optimum inflation occurs when the diaphragm is positioned between the seventh and eighth ribs posteriorly. Arterial blood gases are measured according to the clinical status of the patient and chest radiographs are obtained at least daily. During surfactant administration, oscillation is stopped immediately before administration and IMV mode only is used for 10 minutes thereafter.

Standard sedation guidelines are effective during COMV. Paralysis may only been necessary if gross pulmonary air leaks are present. Contrary to the situation with oscillation, issues surrounding airway care are no different to managing infants undergoing conventional ventilation. Disconnections are well tolerated in the stable infant. There is usually no need to temporarily increase PIP/MAP.

Management of COMV based on gas exchange and oxygenation
Carbon dioxide elimination during oscillation is dependent on frequency x TV, however it is limited at frequencies more than 15 Hz due to intrinsic characteristics of lung tissues. Optimum frequencies correspond closely to the resonant frequency of neonatal lung tissue; 6-12 Hz. In COMV, just as in conventional ventilation, adjusting PIP will have an effect on TV and thus CO$_2$ removal. Therefore the major determinant of CO$_2$ removal is TV which is controlled by changes in delta P during oscillation and PIP in COMV. In COMV, as in IMV, oxygenation depends on MAP and inspired oxygen concentration. Increments in MAP directly affect lung volume via alveolar recruitment. Oxygenation is independent of delta P and rate in COMV except at very low lung volumes.

After checking endotracheal tube patency and excluding pneumothorax, hypercapnia is treated by increasing delta P by 4 cmH$_2$O increments to achieve adequate chest wall vibrations. When delta P reaches a maximum usually by 30 cmH$_2$O, CMV rate is increased by increments of five to a maximum of 60/min, followed by an increase in PIP by 1-2 cmH$_2$O. Hypoxia can be due to under or over-inflation of lungs and PIP is adjusted according to chest X-ray findings.

Weaning from COMV
Ventilator settings are adjusted to wean IMV components first by decreasing rate, PIP and MAP while maintaining acceptable oxygenation and ventilation. COMV is very effective in CO$_2$ removal therefore IMV rate and Delta P may need to be weaned before other components for hypocapnia. IMV rate is reduced in steps of five per minute to a minimum of 30 per minute and then delta P is reduced by 4 cmH$_2$O decrements to a minimum of
**Combined Oscillatory and Mandatory Ventilation (COMV)**

**Oscillation component**
- Frequency $\rightarrow$ 10Hz
- Delta $P$ $\rightarrow$ 10 cmH$_2$O $\rightarrow$ ($\uparrow$ by 2-4 cmH$_2$O until vibrations visible) $\rightarrow$ maximum 30 cmH$_2$O

**IMV component**
- PIP $\rightarrow$ 18 cmH$_2$O, PEEP $\rightarrow$ 4 cmH$_2$O
- Rate $\rightarrow$ 60 bpm, Ti $\rightarrow$ 0.4sec

**Blood gas management of COMV**
- $\uparrow$ CO$_2$ $> 6.5kPa$, $\downarrow$ CO$_2$ $< 4.5kPa$
- Check ETT patency/exclude pneumothorax
- $\uparrow$ delta $P$ by 4 cmH$_2$O $\rightarrow$ max 30 cmH$_2$O
- CMV rate by 5/time $\rightarrow$ 30/min
- $\uparrow$ IMV rate by 5 $\rightarrow$ max 60/min
- delta $P$ by 4 cmH$_2$O/time $\rightarrow$ 6 cmH$_2$O
- $\uparrow$ PIP by 1-2 cmH$_2$O
- ? Need CXR
- $\uparrow$ O$_2$ $> 10kPa$, $\downarrow$ O$_2$ $< 6kPa$
- $\downarrow$ FiO$_2$ $\rightarrow$ 0.3
- $\uparrow$ FiO$_2$
- by 1-2 cmH$_2$O (2-4 hourly)
- Repeat CXR
- Underinflated
- Overinflated
- $\uparrow$ PIP
- $\downarrow$ PIP

**Weaning from COMV**

**Principles:**
- Wean IMV component first
- If CO$_2$ removal very rapid, $\downarrow$ delta $P$ and IMV rate first
- Maintain Ti $> 0.3$ sec while on COMV
- $\downarrow$ FiO$_2$ $\rightarrow$ 0.3
- $\downarrow$ IMV PIP by 1-2 cmH$_2$O until MAP $< 7$ cmH$_2$O
- $\downarrow$ IMV rate to maintain normocapnia: (If hypocapnia $\rightarrow$ $\downarrow$ delta $P$ & IMV rate)
- $\downarrow$ delta $P$ 4 cmH$_2$O/time when IMV rate 30/min
- Stop oscillation when delta $P$ of 6 cmH$_2$O tolerated

**FIGURE 4** Flow chart – management of COMV (adapted from Ghaus & Bignall).
6 cmH$_2$O. Oscillation is stopped once a delta P of 6 cmH$_2$O is tolerated with no increase in CO$_2$. When PaO$_2$ is high or normal FiO$_2$ is reduced to 0.3 (30%) and if it is tolerated, PIP (hence MAP) is reduced in a stepwise manner by 1 cmH$_2$O 2-4 hourly until MAP <7 cmH$_2$O.

**Discussion**

**HFO/IMV versus COMV**

Gas exchange during HFOV represents a complex phenomenon including diffusive dispersive and convective (bulk) transport mechanisms. The significance of the different mechanisms supposedly involved, such as conventional mixing due to turbulence, augmented diffusion, pendelluft and inter-regional gas mixing, remains unclear and may vary in different regions of the lung. HFOV may promote augmented diffusion and enhance inter-regional gas mixing. Oxygenation is related to MAP and if the MAP is too low in terminal lung units, they may collapse with resulting ventilation-perfusion inequality; if the airway pressure is too great, pulmonary blood flow may decrease. A combination of IMV with continuous HFO can facilitate adequate gas exchange in certain critically ill neonates who are hypoxic or hypercapnic with IMV. COMV may improve oxygenation by reducing airway pressure in terminal lung units thus improving pulmonary blood flow.

HFOV actively withdraws the inspired volume during the expiratory phase of the respiratory cycle avoiding gas trapping and carbon dioxide retention. However, the lower MAP achieved with HFOV in terminal lung units can lead to basal atelectasis and ventilation/perfusion mismatch. The addition of IMV prevents basal airway closure and ventilation perfusion mismatch, a complication of HFOV. Chan and Greenough reported impairment of oxygenation even with increasing MAP on transfer to HFOV in some patients and attributed this to inadequate MAP level to recruit sufficient alveoli. Addition of IMV to HFOV might be more helpful in this regard. COMV may not only prevent alveolar collapse but also recruit atelectatic alveoli and decrease ventilation perfusion mismatch. In the severely diseased lung it improved CO$_2$ removal, lessened the requirement for positive pressure ventilation and resulted in a more stable clinical course.

HFO combined with a sustained inflation was shown in an animal study to increase mean lung volumes and to improve oxygenation. The addition of IMV to HFO probably provided adequate opening forces for the recruitment of more alveoli with improvement of oxygenation. The efficient elimination of CO$_2$ during COMV also probably contributed slightly to higher alveolar PaO$_2$ levels. A minimum IMV rate seems necessary to prevent atelectasis and COMV improves CO$_2$ exchange in all patients. Elimination of CO$_2$ depends on delta pressure but is not usually responsive to frequency changes between 15-30 Hz. A possible explanation is that CO$_2$ exchange is related to minute volume. Tidal volume through the endotracheal tube falls with increasing oscillatory frequency but the minute volume remains constant at frequencies between 15 and 30 Hz. Increasing delta pressure increases TV and minute volume. CO$_2$ elimination is dependent on a critical convection flow (TV) in excess of that delivered during HFO. The delivered TV during HFO is determined by the driving gas pressure, the resistance of the HFO tubes and the insufflation time. The higher the frequency, the shorter the insufflation time and the smaller the TV. Carbon dioxide elimination during IMV is thought to be dependent on the product of tidal volume and frequency, however, at higher rate frequencies (900 breaths/min) CO$_2$ elimination is independent of the frequency but dependent on the delivered TV.

**HFO-IMV system**

Kapotic and colleagues described a system for HFOV and IMV in neonates in which the oscillator’s sinuoidal pressure wave (equal inspiratory and expiratory time per cycle) is superimposed on all IMV breaths. The oscillatory pulses are fixed in the continuous mode which prevents them from being applied solely between or at phases of the IMV breaths. Unlike IMV alone, COMV can produce a large difference in peak to peak pressures between the proximal airway connector and the distal trachea. IMV rate, inspiratory time and pressures are calculated independent of the oscillatory waveform. PEEP and PIP are determined as the mean of the superimposed oscillations. At frequencies of 20 to 30 Hz, the oscillatory volume diminished from 27 mL at the vibrator to 7-14 mL at the airway connector, to 0.1-2.3 mL at the tip of the ET tube.

Air leak and COMV

COMV can provide ventilation at lower conventional ventilator rates and lower peak and mean airway pressures which is ideal in air leak syndrome. Radiographic and clinical improvement/resolution of pre-existing air leaks are due to the fact that ventilation at much higher frequencies and lower PIP than with conventional ventilation reduces intraluminal peak pressures and pressure swings and provides lesser (tidal) volume to air leaks. This allows over distended lung areas to heal, minimises barotraumas in normal lung areas and allows a more rapid resorption of interstitial air. However, the continuation of IMV breaths or sighs during HFO could impair the resolution of air leaks and/or contribute to their (re) occurrence, therefore more rapid and marked reduction in the PIP, even at the expense of a less significant improvement in arterial blood gases, is important.

**Surfactant and COMV**

The pattern of mechanical ventilation has been shown to affect the release of pulmonary surfactant into alveoli. The study of Massaro and Massaro using electronic microscopy and morphometry showed that periodic deep breaths inflating the lung with four times the tidal volume every five minutes for one hour were potent stimuli of surfactant secretion. In Obara’s study, IMV was superimposed as an intermittent sigh to prevent atelectasis produced by continuous HFOV for long periods of time. The same PIP was used for IMV during HFO. However, volume and surface densities of the lamellar bodies in the COMV group were significantly different from the control and IMV groups.

As airway pressure from the large airways to the alveoli increases during HFOV and the degree of lung inflation increases progressively with increased ventilation frequency, there would be differences in lung volume and alveolar pressure even if mean airway pressures were matched in IMV and COMV groups. Increased minute ventilation during COMV would also produce an augmented surfactant release into the alveolar spaces.

**Sustained inflation**

Sustained inflation (SI), hyperinflation or regular sighs are needed to prevent atelectasis and this can be achieved by
combining HFOV with IMV\(^{12}\). SI is a method that has been utilised to recruit atelectatic alveoli and augment lung volume thereby improving gas exchange and the mechanics of the respiratory system during HFOV. Oxygenation in static compliance improves along with changes in functional residual capacity, suggesting a beneficial effect of volume recruitment. The optimal magnitude and duration of SI are unknown. SIs of short duration and minimum magnitude are ineffective in improving oxygenation. SIs of intermediate (10 cmH\(_2\)O above MAP) and high (15 cmH\(_2\)O above MAP) magnitude were effective at both 10 and 30 seconds. As SI pressure or duration is increased; oxygenation is improved but hypercarbia occurs as SI is prolonged. Furthermore, transient changes in blood pressure and the risk of pneumothorax argue for conservative use of high pressure, long duration SIs. An SI of 15 cmH\(_2\)O above MAP of 10 cmH\(_2\)O produced the greatest increase in oxygenation, compliance and functional residual capacity without associated hypercarbia.

Conclusions

COMV provides a differentiated gas exchange (a two pronged approach) with HFOV providing oxygenation by augmentation of gas diffusion and pendelluft, while IMV independently achieves adequate CO\(_2\) elimination by convection. COMV has been shown to maintain all the advantages of HFOV over IPPV with a lower MAP and PIP plus a low incidence of barotrauma. The significant reduction of intrapulmonary shunting during COMV indicates efficient recruitment of the alveoli and an overall improvement of lung ventilation and perfusion. There are certain advantages in combining two components (IMV and HFOV) with similar principles and physical and mechanical characteristics. From our own experience, COMV improved oxygenation and gas exchange in newborn infants and also appears to be safe when used as rescue treatment when IMV and/or HFOV alone have failed. However, there are no randomised controlled trials on the effectiveness and safety of COMV.

References