REVIEW ARTICLE

What's new in High Frequency Oscillatory Ventilation in Neonates?

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ABSTRACT

High Frequency Oscillatory (HFO) ventilation, mostly used as a rescue strategy in neonates with worsening of respiratory failure on conventional mechanical ventilation, is also proposed as a lung protective strategy due to its generation of low tidal volumes and supraphysiological frequencies that facilitate gas exchange. Most of the studies have failed to show any advantage of HFO ventilation over conventional ventilation, probably due to the large fluctuations of tidal volumes produced in HFO ventilation. Modes for targeting tidal volumes in HFO ventilation are currently available in the newer ventilators. The effects of volume targeting in HFO ventilation were reviewed from the literature. Six studies were identified as eligible for this review. Targeting tidal volumes in HFO ventilation seemed feasible and offered some stability of ventilation parameters like high frequency tidal volumes (VTHf) delivered, minute ventilation (MV) produced, partial pressure of carbon dioxide (pCO2) in blood, and diffusion coefficient of carbon dioxide (DCO2) in preterm infants ventilated for respiratory distress. Better stability of oxygen saturation (SpO2) levels was also reported in one of the studies. None of the reviewed studies could however demonstrate better stability of haemodynamic parameters including heart rate, perfusion index, pleth variability index and mean arterial blood pressure levels. Follow-up data were also not available in any of the studies reviewed. The quality of evidence from the papers reviewed based on their study designs, study quality and directness in judging the quality of evidence is very low and the strength of the evidence is considered weak. However, this mode of ventilation appears promising and needs to be evaluated in well-designed future trials.

INTRODUCTION

High Frequency Oscillation (HFO) Ventilation is being used now for more than three decades as a rescue ventilation strategy when conventional ventilation fails to achieve effective gas exchange in preterm neonates with worsening of respiratory distress. As HFO makes use of supraphysiologic frequencies and small tidal volumes lesser than the anatomic dead space,[1] HFO ventilation has the potential of being considered as a lung protective

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strategy in mechanical ventilation.[2] However, some of the earlier studies have shown an increase in the incidence of brain injury probably due to hypocarbia and fluctuations of pCO2 in preterm infants ventilated on HFO ventilation.[3] One of the reasons why most of the studies have failed to show any advantage of HFOV over conventional ventilation may be related to the large fluctuations of tidal volumes produced in HFO ventilation.

Following publication of feasibility studies from normal and surfactant depleted neonatal lungs of animals, targeting tidal volumes has now become possible in neonates ventilated on HFO mode of ventilation in certain ventilators.[4] Average of total exhaled volume of gas and pressure amplitude generated per second is used to calculate high frequency tidal volume (VTHf) in these machines. Accurate measurements of tidal volumes by sophisticated flow sensors have revealed that the VTHf generated in HFO ventilation is generally much higher than the anatomical dead space of these infants.[5] The uncontrolled tidal volumes generated during HFO ventilation could be the reason why HFO Ventilation mode did not prove more beneficial than conventional ventilators in the prevention of lung injury. As the same delta P may cause different levels of chest oscillations and wide fluctuations in VThf in the same neonate as the lung condition changes, carbon dioxide (CO_2) elimination in HFO Ventilation is likely to vary in the same baby if VTHf is not kept constant.

Targeting tidal volumes in HFO mode is now available in newer ventilators like Dräger VN500, Fabian HFO, Leoni Plus and SLE 6000 ventilators.[6] The mechanism of CO_2 removal in VTHf targeted HFOV mode is a complex phenomenon. As the cycling frequency in HFO ventilation is very high, it is impractical to adjust peak inspiratory pressure (PIP) of each breath. Instead, to target VTHf in HFO, the machines average the delta P and exhaled volume over 1 second and adjust the settings accordingly. High frequency tidal volume (VThf) generated is in fact proportional to the fluctuations of delta P around the mean airway pressure (MAP) and inversely proportional to the frequency. Other factors that influence the VThf generated are the endotracheal tube size and lung compliance.[7] Pressure swings (delta P) created around the MAP produces tidal volumes (VTHf) that may be less than or equal to the anatomical dead space volume in HFO ventilation, thus potentially reducing ventilation induced lung injury (VILI) in this mode of ventilation.

While targeting tidal volume is the widely accepted the current strategy to prevent hypocarbia and improve outcomes in preterm infants ventilated on conventional modes of ventilation[8,9] it is not yet clear if the same strategy of targeting tidal volumes will improve the outcomes in HFO ventilation. There are very few studies available in the literature on the benefits of targeting tidal volumes in HFO ventilation. Modes that target high frequency tidal volume (VThf) like the volume guarantee mode (VG mode) is now available on HFO ventilation in some of the newer ventilators. In VG mode, VTHf is maintained by continuous modification of the amplitude (delta pressure) and any increase in the frequency will result in further increase in ventilation parameters like DCO_2, unlike in HFO ventilation without VG. This review aimed to evaluate the current evidence available in the literature on the feasibility and efficacy of volume targeting modes in HFO ventilation.

METHODS

The research question "is volume targeting feasible and more effective than non-volume targeted mode in high frequency oscillatory ventilation in preterm infants?" was evaluated in the review. While designing the review it was hypothesized that the use of volume targeted HFO was feasible and as compared to non-volume targeted HFO ventilation, it would result in more stable pCO2 levels and other ventilation parameters in preterm infants mechanically ventilated for treatment of RDS.

An extensive search of literature looking for trials published up to April 2019 that assessed the effects of volume targeting modes of HFO ventilation on the stability of ventilation and physiologic parameters, neonatal morbidity parameters and long term outcome in preterm infants. The primary objectives of the review were the evaluation of the feasibility and efficacy of targeting tidal volumes in HFO ventilation. The outcomes reviewed for evaluating the feasibility of targeting tidal volumes were the high frequency tidal volumes (VThf) delivered and the minute ventilation (MV) produced. The efficacy of VG mode was evaluated by reviewing the stability of ventilation parameters like the stability of ventilation parameters like partial pressures of carbon dioxide (pCO_2) levels in blood and diffusion coefficient of carbon dioxide (DCO_2). The other outcomes reviewed also included stability of physiological parameters like oxygen saturation (SpO_2) levels and haemodynamic parameters like heart rate, perfusion index, pleth variability index and mean arterial blood pressure levels. An attempt was also made to review neonatal morbidity parameters like the duration of ventilation required, incidence of CLD of prematurity and brain injury in the forms of grade 3 - 4 IVH and any IVH and periventricular leukomalacia (PVL). Literature was further reviewed for other short term outcomes and subsequent neurodevelopmental and long term outcomes when VG mode was used in HFO mode of ventilation in preterm infants.

RESULTS

The topic being a relatively new concept, not many studies were available in the literature. Even though a meta-analysis was planned on the feasibility and efficacy of targeting tidal volumes in HFOV, a detailed literature review revealed that no meta- analysis was feasible on the topic due to paucity of literature. Of the 2911058 studies found from the various data bases, 77 trials were relevant to the topic. Of these,

Table 1. Population and Outcome Studied

Paper	Title	Population Studied	Outcomes studied
1. (10)	Impact of Volume Guarantee on High-Frequency Oscillatory Ventilation in Preterm Infants: A Randomized Crossover Trial	Preterm infants born at 24 -32 weeks' gestation, ventilated in the first 6 hour of life	Feasibility of volume targeting (HFO with VG), Stability of VTHf and pCO2 levels
2.(11)	Effect of Volume Guarantee in Preterm Infants on High-Frequency Oscillatory Ventilation: A Pilot Study	Extreme low birth weight preterm infants born at 22 and 23 weeks' gestation, ventilated with HFOV for more than 28 days of age	Fluctuations of HR and SpO2 and the proportion of time with SpO2 <80%
3.(12)	Using very high frequencies with very low lung volumes during high-frequency oscillatory ventilation to protect the immature lung. A pilot study	30 newborn infants with severe respiratory insufficiency on HFOV.	Feasibilty of using very low VTHf using very high frequency and comparison of pCO2, delta pressure and tidal volumes in each mode
4.(13)	High-frequency oscillatory ventilation with volume guarantee: a single-centre experience	17 neonates ventilated continuously with HFO with VG mode for a minimum of 12 hours selected from a convenience sample of 90 infants ventilated with HFO VG in the NICU	Fluctuation of VTHf and correlation of VTHf and DCO2 with pCO2 levels
5.(4)	High-Frequency Oscillatory Ventilation Combined with Volume Guarantee in a Neonatal Animal Model of Respiratory Distress Syndrome	Six 2- day old Landrace-large white newborn piglets with a mean (±standard deviation (SD)) body weight of 2.57 ± 0.26 kg	Effect of adjusting VThf settings instead of ΔPhf on PaCO2 levels and The stability of VThf and PaCO2 using HFO VG during lung disease
6.(14)	Effect of the I/E ratio on CO2 removal during high-frequency oscillatory ventilation with volume guarantee in a neonatal animal model of RDS	Five healthy 2-day-old Landrace-large white piglets with a mean (±standard deviation (SD)) body weight of 2.97 ± 0.34 kg	Effect of I/E ratio on pCO2 levels during HFO ventilation using VG

43 studies were identified after removing the duplicates. Volume targeting being a new mode in HFO ventilation, only six studies could be finally found eligible for the review. The population and outcome studied in the included trials are summarized in **Table 1.**

Babylog VN500 (Drager, Lubeck, Germany) was the ventilator used in all reviewed trials. Active inspiration and expiration is allowed in this ventilator to create a sinusoidal pressure wave around the set mean airway pressure (MAP). Volume targeting mode (called VG mode in this ventilator) is achieved in this ventilator by a microprocessor that generates a VTHf by adjusting the amplitude (delta pressure) based on the inputs received from the flow sensor regarding VTHf and leak present during the previous breaths.

Stability of ventilation parameters was not the primary outcome in few of these trials selected even though they had evaluated the fluctuation of various ventilation parameters like arterial blood pCO_2 levels, delivered VTHf, MV produced and DCO_2 levels on volume targeting mode in HFO ventilation. All the six studies (including the two animal trials) were included anyway in the review due to the paucity of literature on the topic and the novelty of the concepts reported in some of these trials. Paper 1, the only randomized short term cross-over clinical study reported the feasibility of delivering stable VTHf and achieving stabile ventilation parameters like pCO_2 and DCO_2 levels when VG mode was used in HFO ventilation.[10] Paper 2, an observational study suggested that VG mode in HFO attenuates fluctuations of pCO_2, $DCO_2$and SpO_2 levels in extreme preterm infants.[11] Paper 3, another prospective observational study suggested the feasibility of delivering lower tidal volumes and higher frequencies to minimize lung injury in VG mode.[12] Paper 4, a retrospective observational study from a single centre found significant inverse correlation between weight corrected VTHf and DCO_2 levels with blood pCO_2 levels when VG mode was used in HFO ventilation.[13] Paper 5 reported feasibility of delivering stable VThf levels and producing stable pCO_2 levels in HFO ventilation when VG mode was used in an animal model.[4] Paper 6, another animal study primarily reported stable CO_2 elimination when I/E ratios of 1:1 and 1:2 were used in HFO ventilation with VG mode turned on unlike when VG mode was turned off.[14]

DISCUSSION

Use of volume targeted ventilation was found feasible in HFO ventilation from most of the papers reviewed. Analysis of the trials revealed that use of volume targeting modes by volume guarantee (VG) mode in HFO ventilation seemed to prevent fluctuations and provide some stability to various extents for parameters like VTHf delivered, MV produced, pCO_2 levels, and DCO_2 levels in preterm infants or the animal models ventilated for respiratory distress. While two studies reported that even when the lung compliance changes rapidly in the first few hours of life, stable tidal volume was delivered in HFO VG ventilation, stability of minute ventilation was reported in another study. Two other trials had different study designs but their findings also suggested the stability of VTHf levels when VG mode was used in HFO ventilation. One of the trails reported that when VG mode was used in HFO ventilation, VTHf and DCO2 levels correlated well with pCO_2 levels only when weight correction was done. The pCO_2 levels in blood, a true measure of effective ventilation, as measured in arterial blood or monitored transcutaneously was reported to be more stable when VG mode of ventilation was used in three of these trials reviewed. The effect of a mode of ventilation on the alveolar ventilation is also represented by DCO_2 levels in addition to blood pCO_2 levels in HFO ventilation. DCO2 is calculated as $VTHf^2$ x frequency (ml^2/ sec) and depicted on the measured panel of the ventilator. Lesser fluctuations of DCO2 levels were reported when VG mode was used in HFO ventilation in five of the six trials. Also, the use of I/E ratios of 1:1 and 1:2 were reported to result in no fluctuations in the arterial pCO2 levels at different frequencies when VG mode was used unlike when VG mode was not used in HFO ventilation in a trial on an animal model. Even though, stability of oxygen saturation (SpO_2) levels when VG mode was used in HFO ventilation was reported in one of the trials reviewed, this effect was not reported in the other trials.

Based on the study designs, study quality and directness in judging the quality of evidence, the quality of evidence gathered from all these trials is low and the strength of recommendations is weak for recommending targeting of VTHf in preterm infants requiring HFO ventilation to achieve any of the positive outcomes reported in these trials. Also, none of the reviewed trials could demonstrate significant stability of haemodynamic parameters like heart rate, perfusion index, pleth variability index and mean arterial blood pressure levels in HFO ventilation with VG mode as compared to without VG mode.

For any intervention to have an impact on the clinical practice, follow up data are essential. None of the reviewed trials had evaluated any short term outcomes like duration of ventilation required, incidence of chronic lung disease of prematurity and brain injury (IVH and PVL) and long term outcomes like neurodevelopmental outcomes. This makes the clinical significance of these trials even more uncertain. Hence, even though the use of volume targeting mode in HFO ventilation seems to offer some stability of ventilation parameters and hence possibly could affect the subsequent outcomes positively, it can be concluded that any estimate of effect is very uncertain for recommending volume targeting mode when HFO ventilation is used in preterm neonates at present as the standard of care without further studies.

In summary, targeting tidal volumes seems to be a potentially beneficial strategy to stabilize ventilation and physiological parameters and possibly improve outcome in preterm infants requiring HFO ventilation. As the relevance of lung protective ventilation strategies increase with the survival of more and more extreme preterm neonates and the evidence for this strategy is very limited, time is ripe for carrying out further research in this field. It is recommended to have well-designed multicentric randomized controlled trials with large number of preterm infants to confirm these suggested benefits of the use of volume targeting mode in preterm infants ventilated on HFO ventilation.

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