BMC Pediatrics

RESEARCH

Open Access

Evaluating tidal volume stability in extremely preterm infants on high-frequency oscillatory ventilation with volume guarantee

Saleh S. Algarni[2,3], Omar M. Almutairi[1], Mohammed Sufyani[1], Saad Alshreedah[1], Naif Alotaibi[1], Sami S. Alanazi[1], Abeer H. Alharthi[1], Ibrahim Alanazi[1], Abadi Ghazwani[1], Ibrahim Ali[1], Abdulaziz Homedi[1], Saif Alsaif[1,2,3] and Kamal Ali[1,2,3*]

Abstract

Background High Frequency Oscillatory Ventilation (HFOV) combined with volume guarantee (HFOV-VG) represents an innovative ventilation mode designed for managing respiratory failure in neonates. This study aimed to assess the stability of High Frequency tidal volume (VThf) in extremely preterm infants ventilated on HFOV with VG during the first 48 h of life. Additional objectives included examining the correlations between VThf, Diffusion Coefficient of Carbon Dioxide (DCO_2) and key respiratory markers.

Methods This retrospective, single-center study included 22 extremely preterm infants treated with HFOV-VG as the primary mode of ventilation at King Abdulaziz Medical City. Data were collected directly from the ventilator every minute for the first 48 h of life. Blood gases were analyzed every 4–6 h to maintain normocapnia (PCO_2 40–55 mmHg). The distribution of continuous variables was assessed using the Shapiro-Wilk test for normality. As most data were found to be non-normally distributed, results are presented as medians with interquartile ranges (IQR). The Kruskal-Wallis test was used to compare non-normally distributed continuous variables across groups. The Spearman's rank correlation coefficient (Spearman's rho) was used to evaluate correlations between key clinical and ventilatory variables. All statistical analyses were conducted using Stata software (version 17; StataCorp LLC, College Station, TX), with statistical significance set at $p < 0.05$.

Results Twenty-two infants had a median gestational age of 26.5 weeks (IQR 24–28) and a median birth weight of 830 g (IQR 600–1300). The median set VThf per kilogram was 2.2 mL/kg [IQR 2,2.6], which was consistent with the measured VThf. Significant correlations were observed between weight-corrected DCO_2 and VThf (spearman rho = 0.8089, $p < 0.0001$), and between measured amplitude and weight corrected DCO_2 (spearman rho = 0.6497p < 0.0001). Raw DCO_2 correlated with measured amplitude (spearman rho = 0.1364, $p < 0.0001$). PCO_2 showed no significant correlation with raw DCO_2 ($p = 0.4813$) and weight-corrected DCO_2 ($p = 0.4845$). Notable variations in FiO_2, frequency, and MAP were identified between different PCO_2 levels ($p < 0.01$) as well as the weight corrected DCO_2 ($p = 0.04$).

*Correspondence:
Kamal Ali
alika@ngha.med.sa

Full list of author information is available at the end of the article

Conclusions HFOV-VG effectively stabilized VThf in extremely preterm infants with fluctuations in amplitude, providing consistent ventilation support during the early critical period. The weight-corrected DCO_2 correlated strongly with VThf and measured amplitude, underscoring its potential as a reliable marker for CO_2 clearance. These findings highlight the utility of HFOV-VG in managing respiratory needs in extreme preterm infant.

Keywords HFOV, Volume guarantee, Preterm infants, Tidal volume, Carbon dioxide

Introduction

Although the use of non-invasive ventilation methods is increasing, a considerable proportion of extremely preterm infants with respiratory distress syndrome (RDS) still require intubation and mechanical ventilation. High-frequency oscillatory ventilation (HFOV) is commonly used in treating infants with respiratory distress syndrome (RDS) [1, 2]. One of the potential benefits of HFOV compared to conventional mechanical ventilation is its use of smaller tidal volumes and the ability to safely maintain higher mean airway pressures than what is typically applied in conventional ventilation methods [3]. Although several mechanisms contribute to gas exchange in HFOV, the tidal volume generated during HFOV (VThf) plays a critical role in carbon dioxide removal. This VThf is primarily produced by fluctuations in the pressure (ΔPhf) around the mean airway pressure, as well as the oscillation frequency [4]. Factors such as endotracheal tube size and lung compliance also influence the VThf [5]. These factors can cause significant variations in VThf and CO_2 clearance, which may impact the overall effectiveness of HFOV [6].

HFOV combined with volume guarantee (HFOV-VG) represents an innovative ventilation mode designed for managing respiratory failure in neonates. Theoretically, HFOV-VG is anticipated to lower the risk of lung injury by minimizing fluctuations in VThf. It also aims to reduce out-of-target PCO_2 levels and decrease episodes of hypoxia compared to traditional HFOV [7, 8]. With HFOV-VG, clinicians are able to set a target VThf, and the ventilator automatically adjusts the amplitude pressure to deliver the desired VThf. This precise regulation of VThf, combined with automatic amplitude adjustments, is especially advantageous in situations where respiratory mechanics change quickly [7, 9]. Research has shown that during HFOV-VG, VThf may fluctuate momentarily, but overall, it remains consistently close to the set target over time [10]. The Diffusion Coefficient of Carbon Dioxide (DCO_2) is recognized as an essential marker for tracking CO_2 clearance, but the level needed to maintain normocapnia can differ between individuals. Weight-corrected DCO_2 ([mL/kg] ^{2}/s) has been proposed as a method to minimize variability between patients [8].

This study builds upon existing literature by specifically evaluating the stability of VThf over the first 48 h in extremely preterm infants ventilated with HFOV with VG. While previous studies have explored the general performance of HFOV-VG, there remains a gap in understanding how VThf fluctuations relate to key respiratory markers such as weight-corrected DCO_2, PCO_2, and measured amplitude. By examining these relationships, this study offers new insights into the effectiveness of HFOV-VG in maintaining stable ventilation and optimizing CO_2 clearance in extremely preterm infants.

The primary aim of this study was to evaluate the stability of VThf over the first 48 h in extremely preterm infants ventilated with HFOV using VG. Additionally, the study aimed to explore the correlations between VThf and key respiratory markers, including the weight-corrected DCO_2, PCO_2, and measured amplitude. Furthermore, the study aimed to examine the differences in ventilatory settings across varying levels of PCO_2, to provide insights into optimizing respiratory support in this high-risk population.

Methodology

This retrospective, single-center study was conducted on twenty-two extremely preterm infants born at less than 28 weeks' gestation between January 2024 to October 2024. The study was conducted at King Abdulaziz Medical City, and ethical approval was obtained from the King Abdullah International Medical Research Centre (KAIMRC) before the commencement of the study. The inclusion criteria were infants born at less than 28 weeks gestational age who were ventilated on HFOV with VG and inborn at the facility. The exclusion criteria included infants who were outborn or had major congenital anomalies or congenital heart disease.

In this study, all 22 infants included in this study were intubated at birth for respiratory distress syndrome (RDS) and remained ventilated for at least 48 h. HFOV-VG was initiated soon after admission to the NICU as the primary mode of ventilation. No infants were intubated later for other indications, ensuring a uniform study population. The ventilator used was the Dräger VN600, specifically chosen for its HFOV-VG capabilities. The VN600 ventilator produces a sinusoidal pressure waveform centered around a designated mean airway pressure (MAP), incorporating both active inspiration and expiration phases. In volume-guarantee (VG) mode, this ventilator targets a specific VThf by using a microprocessor that monitors the VThf of the previous breath—adjusted for any air leak—and then modulates the delta pressure to maintain the set VThf target. For these infants, the MAP

was initially set at 10 mbar, and then gradually increased in increments of 2 mbar every 2–3 min until an optimal pressure for lung recruitment was achieved. This critical pressure point was defined by improved oxygenation or a fraction of inspired oxygen (FiO_2) requirement below 40% with an arterial oxygen saturation target of 90–94%. Once the optimal opening pressure was identified, the MAP was reduced stepwise by 2 mbar to find the closing pressure, followed by re-opening the lung to the critical pressure level. Finally, the MAP was set 2 mbar above the closing pressure to maintain continuous lung inflation and stability, allowing for optimal respiratory function. In this approach, the lung recruitment maneuver was tailored and carefully monitored to prevent overdistension and ensure minimal lung injury, offering a protective strategy in the early respiratory management of these preterm infants. Surfactant was administered soon after admission to the NICU for all infants included in the study.

The amplitude limit was set approximately 10–15% higher than the required average amplitude to achieve target VThf, which was adjusted in increments of 0.1–0.2 mL/kg to maintain the target $PaCO_2$ range. Blood gas analyses were performed at regular intervals (4–6 h or as needed) to ensure the infants maintained normocapnia, defined as $PaCO_2$ levels between 40 and 55 mmHg. These blood gas results guided ventilator setting adjustments, ensuring that each infant received individualized respiratory support based on their physiological needs. FiO_2 levels were adjusted to maintain oxygen saturation (SpO_2) between 90 and 94%, using pulse oximetry for continuous monitoring.

Data were continuously collected for the first 48 h of life. Key ventilatory parameters—including set and measured VThf, amplitude, MAP, frequency, and the FiO_2—were recorded directly from the ventilator every minute. For each infant, 2,880 ventilator measurements were captured over the study period, resulting in a detailed dataset for in-depth analysis. In addition to the ventilatory parameters, the study monitored the diffusion coefficient of carbon dioxide (DCO_2), which is a critical measure of the efficiency of CO_2 removal. To allow for accurate comparisons, DCO_2 and VThf were corrected for each infant's weight, accounting for variations in weight. The PCO_2 data were paired with ventilator data by extracting ventilator parameters recorded 10 min before each blood gas sampling. This interval was selected to allow for physiological stabilization following any ventilatory adjustments and to ensure that the recorded ventilatory settings accurately reflect the conditions influencing the measured PCO_2.

Maternal characteristics recorded included a history of premature rupture of membranes (PROM) > 18 h, hypertensive disorders (chronic hypertension and pregnancy-induced hypertension), diabetes (gestational and pregestational), chorioamnionitis, and the use of antenatal steroids. Chorioamnionitis was defined clinically based on the presence of maternal fever (≥ 38.0 °C) along with one or more of the following criteria: uterine tenderness, maternal or fetal tachycardia, foul-smelling amniotic fluid, or purulent vaginal discharge, following the guidelines recommended by the American College of Obstetricians and Gynecologists [11]. PROM was defined as rupture of membranes persisting for more than 18 h before delivery. Additionally, antenatal steroid administration was reported for any administration of steroids, including both partial and full courses, with dexamethasone being the corticosteroid of choice at our center. Baseline demographics for each infant included gestational age, birth weight, gender, Apgar scores at 5 min, and mode of delivery. Additionally, the duration of ventilation to extubation and the occurrence of pulmonary air leaks were documented.

Statistical analysis

Data were collected directly from the ventilator every minute for the first 48 h of life, resulting in a total of 2,880 observations per patient. The distribution of continuous variables was assessed using the Shapiro-Wilk test for normality. As most data were found to be non-normally distributed, results are presented as medians with interquartile ranges (IQR). Categorical variables are presented as absolute numbers and percentages.

The Kruskal-Wallis test was used to compare non-normally distributed continuous variables across groups, such as the comparison of $PaCO_2$ levels (hypocarbia, normocarbia, and hypercarbia). Categorical variables were compared using the chi-square test. The Spearman's rank correlation coefficient (Spearman's rho) was used to evaluate correlations between key clinical and ventilatory variables, such as the relationships between measured tidal volume and DCO_2, or between amplitude and PCO_2, due to the non-parametric nature of the data. All statistical analyses were conducted using Stata software (version 17; StataCorp LLC, College Station, TX), with statistical significance set at $p < 0.05$.

Results

Table 1 shows that the study population had a median gestational age of 26.5 weeks and birth weight of 830 g. Maternal risk factors included hypertension (23%), premature rupture of membranes (32%), and chorioamnionitis (14%). Antenatal steroids were given in 73% of cases. Most infants (64%) were delivered via cesarean section and all received surfactant. No mortality was reported (Table 1).

Table 2 presents key respiratory parameters measured in 22 extremely preterm infants ventilated on HFOV with

Table 1 Maternal and infant's characteristics

	(*n* = 22)	
Maternal Hypertension	5 (23)	
Maternal Diabetes	2 (9)	
Maternal Premature Rupture of the Membrane	7 (32)	
Maternal Chorioamnionitis	3 (14)	
Antenatal Steroids	16 (73)	
Gestational Age in weeks	26.5 [24,28]	
Birth weight in grams	830 [600,1300]	
Gender	Male	13 (59)
	Female	9 (41)
Apgar score at 5 min	8 [7,8]	
Mode of delivery	Spontaneous vaginal Delivery	8 (36)
	Caesarean section delivery	14 (64)
Surfactant Therapy	22(100)	
Pneumothorax	1 (4.5)	

Table 2 Ventilatory and blood gas parameters in preterm infants ventilated with HFOV and volume guarantee

Variable	Median (IQR)
Set Amplitude	27 [24–30]
Measured Amplitude	16 [14–20]
Set VThf (ml/kg)	2.2 [2-2.6]
Measured VThf (ml/kg)	2.2 [2-2.6]
Raw DCO_2 (ml^2 /s)	38 [27–69]
Weight corrected DCO_2 ($mL/kg^2/s$)	55.5 [41-69.7]
Set Frequency (Hz)	10 [9–12]
Set Mean Airway Pressure (MAP)	12 [10–14]
Set Fraction of Inspired Oxygen (FIO_2)	40 [32–55]
pH	7.26 [7.2–7.3]
PCO_2	50 [42–59]
PaO_2	62 [44–83]
HCO_3	22 [19.6–24.4]
Oxygenation Index (OI)	9.7 [6.5–13.2]

VG. The median set amplitude was 27 [IQR 24,30], while the measured amplitude was 16 [IQR 14,20]. Both the set and measured tidal volumes (VThf) were 2.2 mL/kg [IQR 2,2.6]. The median raw DCO_2 was 38 mL^2/s [IQR 27,69], and the weight-corrected DCO_2 was 55.5 $mL/kg^2/s$ [IQR 41,69.7]. The set frequency was 10 Hz [IQR 9,12], and the set mean airway pressure (MAP) was 12 cmH_2O [IQR 10,14]. (Table 2).

The scatter plot in Fig. 1 demonstrates a strong correlation between Set and Measured VThf with the regression line ($y = 0.11 + 0.96x$) indicating a near 1:1 relationship. The R^2 value (0.844) suggests that the majority of the variance in measured VThf is attributed to the set values, highlighting the consistency of VG in HFOV. Most data points cluster tightly along the regression line, indicating that the ventilator effectively maintains tidal volume delivery within the intended range. However, some variability is evident, particularly at lower and mid-range VThf values, where measured values deviate slightly from set values. (Fig. 1).

Figure 2 illustrates a comparison between set and measured VThf (ml/kg) for 22 infants ventilated on HFOV with VG over the first 48 h. The set VThf (ml/kg) (blue bars) generally ranges between 2 and 3 ml/kg for most infants. Overall, the measured VThf (ml/kg) aligns closely with the set VThf (ml/kg), indicating that the volume guarantee function was generally effective in maintaining the targeted VThf across the cohort (Fig. 2).

Table 3 presents correlations between various respiratory parameters. There was a strong, statistically significant positive correlation between weight-corrected DCO_2 and VThf (spearman rho = 0.8089, $p < 0.0001$), which aligns with the mathematical relationship between these variables. However, the strength of this correlation in a clinical setting reinforces the role of VThf in CO_2 elimination, supporting the use of weight-corrected DCO_2 as a reliable surrogate for ventilation efficiency in extremely preterm infants. There was also a statistically significant positive correlation between VThf and measured amplitude (spearman rho = 0.2217, $p < 0.0001$). The PCO_2 did not correlate with VThf (Spearman

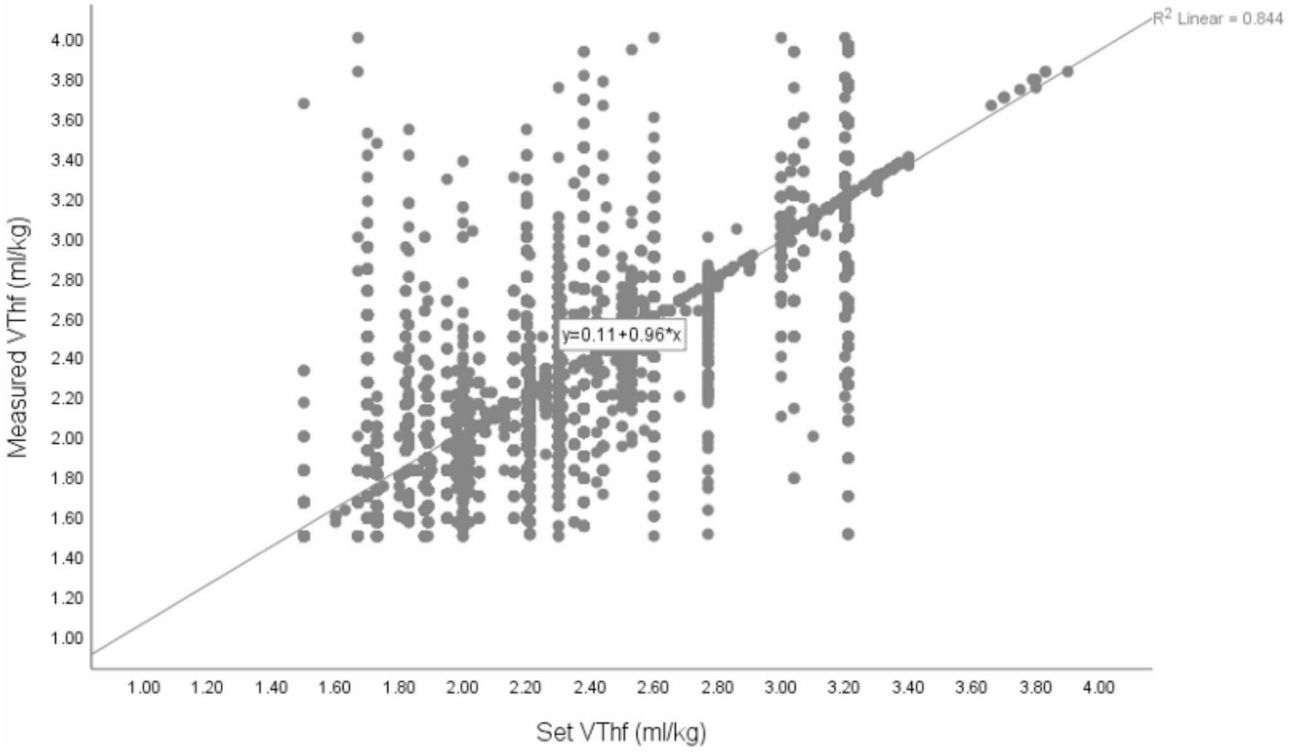

Fig. 1 Scatter plot pf set and measured VThf (ml/kg)

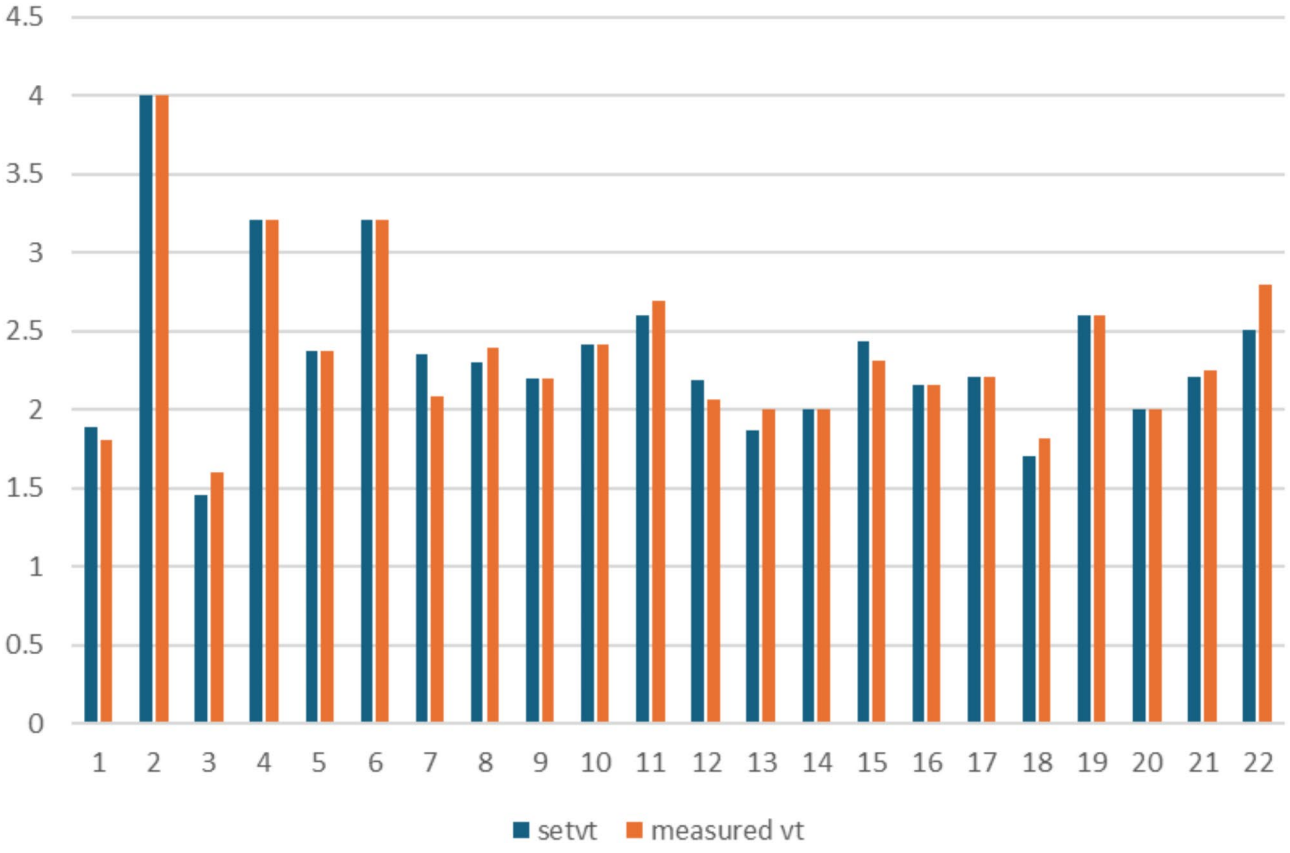

Fig. 2 Comparison of set and measured tidal volumes per kilogram across 22 infants ventilated on HFOV with VG Over the first 48 h

Table 3 Correlation of ventilatory parameters: DCO2, tidal volume, amplitude, and PCO2 in infants ventilated on HFOV with VG over the first 48 h

Variable	Variable	Spearman's rho	*p*-value
VThf (ml/kg)	Weight corrected DCO_2 ($mL/kg^2/s$)	0.8089	< 0.0001
VThf (ml/kg)	Measure amplitude	0.2217	< 0.0001
VThf (ml/kg)	PCO_2	0.0304	0.7049
Raw DCO_2 (ml^2 /s)	PCO_2	-0.0564	0.4813
Weight corrected DCO_2 ($mL/kg^2/s$)	PCO_2	0.0560	0.4845
Measured Amplitude	Weight corrected DCO_2 ($mL/kg^2/s$)	0.6497	< 0.0001
Measured Amplitude	Raw DCO_2 (ml^2 /s)	0.1364	< 0.0001

Table 4 Comparison of HFOV/VG settings and $PaCO_2$ levels in 22 infants over 48 h

Parameter	Hypocarbia (*n* = 53)	Normocarbia (*n* = 55)	Hypercarbia (*n* = 55)	*p*
Measured amplitude	17 [15,24]	19 [14,21]	18 [12,24]	0.97
Fraction of Inspired Oxygen (FiO_2)	40 [30,55]	45 [35,65]	50 [41,89]	< 0.01
Frequency (Hz)	10 [8,11]	10 [10,13]	10 [9,11]	< 0.01
Mean Airway Pressure (MAP)	12 [10,15]	11 [10,15]	13 [10,14]	0.24
Measured VThf (ml/kg)	2.3 [2,2.6]	2.2 [2,2.6]	2.4 [2,3]	0.53
Raw DCO_2 (ml^2 /s)	56 [27,128]	40 [24,161]	41 [29,75]	0.89
Weight corrected DCO_2 ($mL/kg^2/s$)	47 [39,66]	59 [48,70]	55 [42,80]	0.04

rho = 0.0304, $p = 0.7049$), raw DCO_2 (ml^2/s) (Spearman rho = -0.0564, $p = 0.4813$) or weight-corrected DCO_2 ($mL/kg^2/s$) (Spearman rho = 0.0560, $p = 0.4845$). The lack of correlation between PCO_2 and DCO_2 indicates that CO_2 elimination through the ventilator may not directly correspond to PCO_2 levels. Measured amplitude correlated positively with both weight-corrected DCO_2 (spearman rho = 0.6497, $p < 0.0001$) and raw DCO2 (spearman rho = 0.1364, $p < 0.0001$), suggesting that higher amplitude settings are associated with better CO_2 clearance. (Table 3).

Table 4 provides a comparison of ventilatory parameters across three groups of infants ventilated on HFOV with VG categorized by their levels of PCO_2: hypocarbia ($PCO_2 < 40$mmHg) ($n = 53$), normocarbia (PCO_2 40-55mmHg) ($n = 55$), and hypercarbia ($PCO_2 > 55$mmHg) ($n = 55$). The measured amplitude showed no significant difference between the groups ($p = 0.97$). The FiO_2 demonstrated a statistically significant increase, starting from a median of 40 [30–55] in the hypocarbia group to 45 [35–65] in the normocarbia group and reaching 50 [41–89] in the hypercarbia group ($p < 0.01$). The frequency also showed significant variation, with the normocarbia group having a higher median frequency of 10 [10, 11, 12, 13] Hz compared to 10 [8, 9, 10, 11] Hz in the hypocarbia group and 10 [9, 10, 11] Hz in the hypercarbia group ($p < 0.01$). The MAP had no statistically significant difference ($p = 0.24$). The VThf was also not significantly different between groups ($p = 0.53$). While the raw DCO_2 values did not show significant differences ($p = 0.89$), the weight-corrected DCO_2 was significantly different, with medians of 47 [39–66] in the hypocarbia group, 59 [48–70] in the normocarbia group, and 55 [42–80] in the hypercarbia group ($p = 0.04$) (Table 4).

Discussion

In this study, we retrospectively investigated 22 extremely preterm infants born at less than 28 weeks' gestation. Our objective was to assess the stability of tidal volume delivery in infants ventilated on HFOV with VG over the first 48 h of life.

Our findings show that the set and measured VThf were highly consistent in both median values and interquartile range (IQR), indicating that the ventilator settings effectively achieved the desired VThf levels. Clinically, the set and measured VThf values were closely aligned, as demonstrated in our scatter plot analysis, confirming that VThf remained stable and within the target range. However, despite this strong correlation, some variation between set and measured VThf was observed. This variability is likely influenced by several factors. First, adjustments in amplitude occur stepwise rather than continuously. The ventilator modifies amplitude in discrete increments in response to deviations from the set VThf, which may result in transient mismatches between the set and measured tidal volume. Second, if the maximum allowable amplitude is set too low, the ventilator may not generate sufficient pressure to fully achieve the set VThf, particularly in cases of increased impedance or airway resistance. Third, the presence of an air leak around the endotracheal tube may lead to a loss of delivered volume, reducing the measured VThf despite automatic ventilator adjustments. These factors may

explain the observed minor deviations while demonstrating the overall stability and reliability of VG in HFOV.

In our study, infants were ventilated at a median frequency of 10 Hz, with a set amplitude range of 25–30, while the measured amplitude consistently ranged between 14 and 20. There is evidence from previous studies that the increase in amplitude required to maintain a stable VThf, measured at the airway opening, becomes progressively dampened as it moves through the airways to the alveoli. This attenuation effect is especially pronounced at higher oscillatory frequencies, where the pressure gradually reduces, reaching its lowest point at the system's resonant frequency, as shown in multiple studies [9, 12, 13]. The ideal frequency is influenced by the lung's condition; higher frequencies are particularly beneficial for lung diseases with low compliance and short time constants, such as respiratory distress syndrome (RDS) in preterm infants [10, 13]. There is evidence from animal studies that employing very high frequencies (20 Hz) with a reduced VThf significantly decreased histological lung injury when compared to conventional mechanical ventilation (CMV) and HFOV at more typical frequencies (10 Hz) [13, 14]. Recently, Zannin et al. showed that in preterm infants, increasing the oscillatory frequency while adjusting amplitudes to sustain a stable DCO_2 resulted in VThf values that were consistently lower [15].

In this study we have also examined the correlations between DCO_2, VThf, amplitude, and PCO_2. Our findings showed a strong correlation between weight-corrected DCO_2 and VThf, which aligns with the mathematical relationship between these variables. However, the strength of this correlation in a clinical setting reinforces the role of VThf in CO_2 elimination, supporting the use of weight-corrected DCO_2 as a reliable surrogate for ventilation efficiency in extremely preterm infants. The lack of correlation between DCO_2 and PCO_2 in our study suggests that while DCO_2 is a useful marker of ventilation efficiency, it may not fully predict gas exchange adequacy as reflected in blood gas parameters. This discrepancy can be attributed to several factors, including individual variability in lung compliance, dead space ventilation, and pulmonary perfusion, all of which influence the relationship between ventilation and arterial PCO_2. Additionally, metabolic factors such as CO_2 production and perfusion status may impact PCO_2 levels independently of ventilation settings. The timing of blood gas measurements, which provide intermittent assessments, compared to the continuous monitoring of DCO_2, could also contribute to the weak correlation observed. Moreover, ventilator settings are often adjusted based on blood gas results rather than DCO_2 trends alone, further influencing the relationship. These results imply that in clinical practice, reliance on DCO_2 alone might not suffice, and a more individualized approach—potentially incorporating frequent blood gas assessments and real-time ventilator monitoring—may improve outcomes for extremely preterm infants during the critical early phase of respiratory support.

In comparing the infants based on their PCO_2 levels (hypocarbia, normocarbia, and hypercarbia), we found that infants with hypercarbia required significantly higher FiO_2 levels, possibly reflecting compromised gas exchange in hypercarbic states. Frequency settings also differed across the PCO_2 groups, implying that adjusting oscillatory frequency may help in managing CO_2 levels. Additionally, weight-corrected DCO_2 differed significantly across groups, underscoring its value as an indicator of ventilation efficacy in relation to PCO_2 levels. The lower weight-corrected DCO_2 observed in hypocapnic infants may be explained by several factors. Hypocapnia in preterm infants often results from an increased minute ventilation relative to metabolic CO_2 production rather than enhanced ventilatory efficiency. While DCO_2 is a recognized marker of CO_2 elimination in HFOV, it is influenced by both tidal volume and frequency. In hypocapnic states, clinicians may have reduced ventilatory support, particularly by lowering the frequency, leading to a paradoxical reduction in DCO_2 despite lower PCO_2 levels. Additionally, hypocapnic infants might have better lung compliance, allowing for more effective CO_2 elimination at lower ventilatory pressures, thereby requiring less DCO_2 to maintain normocapnia. Another potential explanation is that the relationship between DCO_2 and PCO_2 is not entirely linear, as other factors such as changes in metabolic demand, fluctuations in cardiac output, and alterations in pulmonary perfusion can influence CO_2 clearance. Consequently, in some cases, a lower DCO_2 may still be sufficient to achieve hypocapnia, reinforcing the need for individualized ventilatory adjustments rather than relying solely on DCO_2 as a surrogate for gas exchange adequacy. Interestingly, MAP and tidal volume remained relatively constant across all PCO_2 groups, indicating that these parameters might not require significant adjustments based solely on PCO_2 levels. This could reflect the inherent stability of certain ventilatory settings even as gas exchange requirements change.

In a retrospective study of 53 preterm infants less than 32 weeks' gestation with severe RDS, researchers evaluated VThf and DCO_2 required to achieve normocapnia during HFOV-VG. The study reported that a VThf of around 1.64 mL/kg was necessary to maintain normocapnia across the cohort. No significant correlation was observed between PCO_2 levels and either VThf or DCO_2corr, though VThf was slightly lower at a frequency of 12 Hz compared to 10 Hz [16]. Compared to our findings, which involved 22 extremely preterm infants under

28 weeks' gestation, we have also found no correlation between VThf, DCO_2 and PCO_2. Of note that VThf in our study was larger at 2.2 ml/kg. Both studies reinforce the recommendation for individualized HFOV-VG settings to meet patient-specific needs, particularly through continuous PCO_2 monitoring and frequent setting adjustments.

In another prospective, randomized crossover study, researchers compared HFOV with VG to HFOV alone in 20 preterm infants under 32 weeks' gestation with RDS. Their results indicated that HFOV with VG produced higher VThf and DCO_2 compared to HFOV alone. Additionally, the VG feature allowed for more consistent VThf maintenance within the target range and led to fewer instances of hypo- and hypercarbia compared to HFOV alone. The authors noted that, despite these findings, the study's small sample size and crossover design limit broader conclusions [7]. Our study differs in its focus and scope, evaluating 22 extremely preterm infants under 28 weeks' gestation ventilated solely on HFOV with VG over a continuous 48-hour period. Similar to the crossover study, we observed that VG helps stabilize tidal volumes, though our extended tracking allowed for insights into dynamic respiratory parameters across a larger set of minute-by-minute data points.

In another retrospective study, investigators analyzed the performance of HFOV-VG in 17 infants. They collected approximately 3.2 million seconds of ventilator data, evaluating the stability of the VThf and its effect on ventilation parameters and blood gas measurements. The study found a median VThf of 1.93 mL/kg, with the delivered VThf closely matching the set target within 0.2 mL/kg for 83% of the time. Though there were moment-to-moment fluctuations in VThf, it aligned well with the target value when averaged over 5-minute intervals. A weak inverse correlation was observed between weight-corrected DCO_2 and $PaCO_2$, while uncorrected values showed no correlation [10]. Our findings align with this study in that HFOV-VG maintained VThf close to target settings. In our study, we did not observe a correlation between PCO2 and both raw and weight-corrected DCO2 contrary to this study. Both studies underscore HFOV-VG's efficacy in providing consistent tidal volume but also highlight the need for individualized settings for optimal respiratory support in neonates.

Building on the findings of previous studies, this study expands our understanding of HFOV-VG by evaluating VThf stability and its relationship with key respiratory parameters over the first 48 h in extremely preterm infants. While prior research has assessed VThf and DCO_2 in relation to normocapnia or ventilation stability, our study provides a continuous minute-by-minute analysis, offering a more detailed perspective on VThf fluctuations. Additionally, while some studies reported correlations between DCO_2 and PCO_2, we did not observe a significant relationship between PCO_2 and both raw and weight-corrected DCO_2, suggesting that DCO_2 alone may not fully capture ventilation efficiency. Our findings also emphasize variations in ventilatory settings across different PCO_2 levels, particularly in frequency adjustments and FiO_2 requirements. By continuously assessing HFOV-VG performance in extremely preterm infants under 28 weeks' gestation, this study provides meaningful data to refine respiratory management strategies in this high-risk population.

The study has some strengths and limitations. A key strength is the continuous monitoring of ventilatory parameters every minute over the first 48 h. This detailed dataset allowed us to assess the stability of tidal volume highlighting the capability of HFOV with VG to provide consistent respiratory support in this high-risk group. Additionally, the exclusive focus on infants born at less than 28 weeks' gestation ensures that the findings are particularly relevant for those at the highest risk of respiratory complications.

The study's limitations include a relatively small sample size of 22 infants, which may affect the generalizability of the results. Moreover, being a single-center study, the findings may not fully apply to other NICU settings with different equipment or ventilation protocols. Another limitation of this study is the lack of data on endotracheal tube (ETT) leak, which may have influenced the accuracy of volume-targeting. Future studies incorporating continuous monitoring of ETT leak would be valuable in evaluating its effect on volume-targeted high-frequency ventilation and ensuring more precise delivery of set tidal volumes in extremely preterm infants. Lastly, the lack of a control group ventilated without VG limits the ability to make direct comparisons, which could have added further depth to the conclusions. Noteworthy, we acknowledge that the findings of our study are specific to the VN600 ventilator and apply primarily to preterm infants with RDS, a condition characterized by relatively homogeneous lung disease.

Conclusions

In conclusion, this study provides valuable insights into the performance of HFOV-VG in extremely preterm infants, emphasizing its effectiveness in maintaining stable tidal volumes and consistent respiratory support over the first 48 h of life. Our findings showed significant correlations between weight-corrected DCO_2 and tidal volume, indicating that weight-adjusted DCO_2 may serve as a useful indicator of ventilation efficiency in this population. Additionally, the lack of a strong correlation between DCO_2 and $PaCO_2$ suggests that multiple parameters should be considered when optimizing respiratory support. Overall, HFOV-VG appears to be a promising

lung-protective ventilation strategy, with the potential for improved outcomes through individualized monitoring and tailored adjustments based on real-time data. Further multi-center studies with larger sample sizes are needed to validate these findings.

Abbreviations

HFOV	High-Frequency Oscillatory Ventilation
VG	Volume Guarantee
NICU	Neonatal Intensive Care Unit
RDS	Respiratory Distress Syndrome
VThf	High-Frequency Tidal Volume
MAP	Mean Airway Pressure
ΔPhf	Amplitude Pressure Fluctuations
FiO2	Fraction of Inspired Oxygen
SaO2	Arterial Oxygen Saturation
DCO2	Diffusion Coefficient of Carbon Dioxide
PaCO2	Partial Pressure of Carbon Dioxide
PaO2	Partial Pressure of Oxygen
IQR	Interquartile Range

Acknowledgements
The authors would like to acknowledge the assistance of the personnel in the Neonatal Intensive Care Department (NICD) at King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

Author contributions
KA, SG, OM, SS and IA were involved in the concept and design of the study, supervision, and made significant contributions to the writing and critical review of the manuscript. KA and SG performed the statistical analysis of the data, had full access to all the data in the study, and take responsibility for the integrity and accuracy of the data analysis. KA, OM, MS, SS, NO, IA, SA, AG and AH were involved in the data acquisition, analysis, interpretation of data, and critical review of the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

Funding
No funding was provided.

Data availability
Data is available from the corresponding author on reasonable request.

Declarations

Ethical approval
King Abdullah International Medical Research Centre (KAIMRC) ethics committee approved the project with IRB number: IRB/0341/24.

Human ethics and consent to participate
This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the Institutional Review Board of King Abdullah International Medical Research Centre (IRB approval number: IRB/0341/24). As this study involved retrospective analysis of data collected as part of routine clinical care, the requirement for informed consent was waived by the ethics committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Author details
[1]Neonatal Intensive Care Department, (Neonatal Medicine), King Abdulaziz Medical City-Riyadh, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia
[2]Department of Respiratory Therapy, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[3]King Abdullah International Medical Research Center, Riyadh 11481, Kingdom of Saudi Arabia

Received: 14 November 2024 / Accepted: 19 March 2025
Published online: 31 March 2025

References

1. van Kaam AH, et al. Ventilation practices in the neonatal intensive care unit: a cross-sectional study. J Pediatr. 2010;157(5):767–71. e1-3.
2. Clark RH, et al. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics. 1992;89(1):5–12.
3. Rehan VK, et al. Mechanism of reduced lung injury by high-frequency nasal ventilation in a preterm lamb model of neonatal chronic lung disease. Pediatr Res. 2011;70(5):462–6.
4. Slutsky AS, Drazen JM. Ventilation with small tidal volumes. N Engl J Med. 2002;347(9):630–1.
5. Singh R, et al. Respiratory mechanics during high-frequency oscillatory ventilation: a physical model and preterm infant study. J Appl Physiol (1985). 2012;112(7):1105–13.
6. Zimova-Herknerova M, Plavka R. Expired tidal volumes measured by hot-wire anemometer during high-frequency Oscillation in preterm infants. Pediatr Pulmonol. 2006;41(5):428–33.
7. Iscan B, et al. Impact of volume guarantee on High-Frequency oscillatory ventilation in preterm infants: A randomized crossover clinical trial. Neonatology. 2015;108(4):277–82.
8. Belteki G, Lin B, Morley CJ. Weight-correction of carbon dioxide diffusion coefficient (DCO(2)) reduces its inter-individual variability and improves its correlation with blood carbon dioxide levels in neonates receiving high-frequency oscillatory ventilation. Pediatr Pulmonol. 2017;52(10):1316–22.
9. Sanchez-Luna M, et al. New ventilator strategies: High-Frequency oscillatory ventilation combined with volume guarantee. Am J Perinatol. 2018;35(6):545–8.
10. Belteki G, Morley CJ. High-frequency oscillatory ventilation with volume guarantee: a single-centre experience. Arch Dis Child Fetal Neonatal Ed. 2019;104(4):F384–9.
11. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 2010;37(2):339–54.
12. Pillow JJ, et al. Dependence of intrapulmonary pressure amplitudes on respiratory mechanics during high-frequency oscillatory ventilation in preterm lambs. Pediatr Res. 2002;52(4):538–44.
13. Venegas JG, Fredberg JJ. Understanding the pressure cost of ventilation: why does high-frequency ventilation work? Crit Care Med. 1994;22(9):S49–57.
14. Gonzalez-Pacheco N, et al. Use of very low tidal volumes during high-frequency ventilation reduces ventilator lung injury. J Perinatol. 2019;39(5):730–6.
15. Zannin E, et al. Effect of frequency on pressure cost of ventilation and gas exchange in newborns receiving high-frequency oscillatory ventilation. Pediatr Res. 2017;82(6):994–9.
16. Tuzun F, et al. Volume guarantee High-Frequency oscillatory ventilation in preterm infants with RDS: tidal volume and DCO(2) levels for optimal ventilation using Open-Lung strategies. Front Pediatr. 2020;8:105.

Publisher's note