PROTOCOL

TITLE	High Frequency Oscillatory Ventilation Combined with Intermittent Sigh Breaths in Neonate: Effect on Carbon Dioxide Level
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Keywords	Carbon Dioxide, High-Frequency Ventilation, Sigh Breath, Newborn

Background and rationale

Pulmonary disease continues to be the major cause of morbidity and mortality in very preterm infants.[1] Neonatal intensive care units (NICU) across the world have successfully used conventional ventilation (CV), high-frequency oscillatory ventilation (HFOV), and high-frequency jet ventilation (which is currently not available in Thailand) to manage respiratory failure in newborn.[2] Non-synchronized CV, the earliest mode of ventilation used in neonates, was designed to emulate tidal respirations typical of newborns.[3] Synchronized ventilation improves gas exchange; increases patient comfort with decreased need for sedation and muscle relaxation; reduces airway pressures; decreases work of breathing, risk of barotrauma and volutrauma; and provides faster weaning from mechanical ventilation.[4]

In order to avoid distortion of the lung caused by the large swings in pulmonary pressures during CV at rates of 30 to 80 breaths per minute, HFOV at rates of 600 to 800 breaths per minute with very small tidal volume (TV) was developed (**Figure 1**). HFOV allows for low TV, and minimizing volutrauma and shear force injury by using of TVs that are smaller than physiologic dead space (<3 mL/kg) that oscillate around a set mean airway pressure (MAP) at rates ranging from 300 to 900 breaths per minute (5–15 Hz).[4] Gas exchange occurs from multiple processes, including Taylor dispersion, molecular diffusion, regional variation in turbulent and laminar flow, and pendelluft movement of air. Exhalation on HFOV is active, in contrast to the passive exhalation seen with high-frequency jet ventilation, and adjustments in amplitude, frequency, and MAP can modulate infant oxygenation and ventilation.[4]

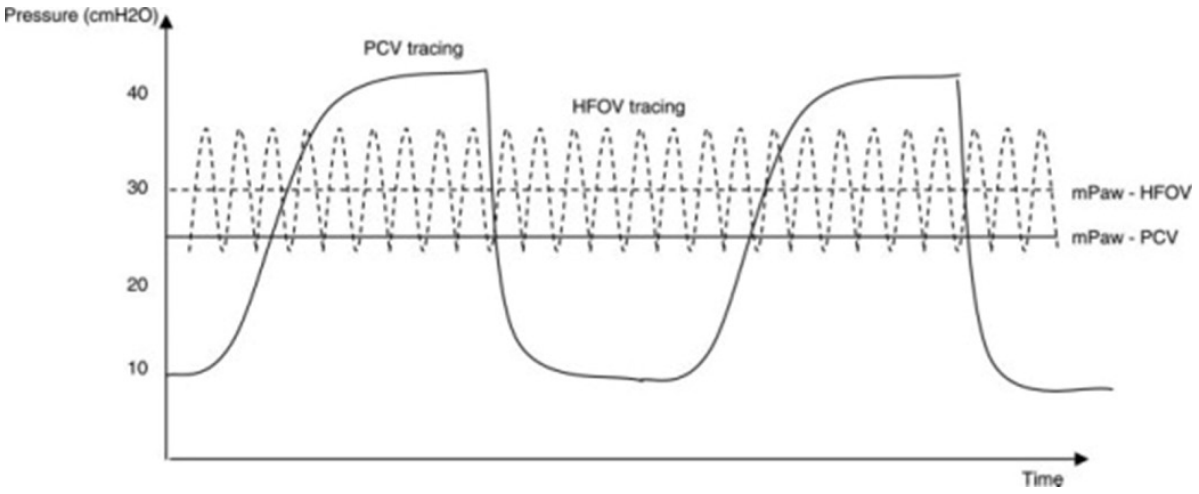


Fig. 1 Schematic representation of the purported waveforms of HFOV and conventional pressure-controlled ventilation in the distal airways. The large pressure swings present in the proximal circuit during HFOV (perhaps up to twice the mean airway pressure, depending on the set ΔP) are significantly attenuated in the distal airways. The degree of attenuation is dependent on frequency, ETT size, and inspiratory/expiratory time ratio.

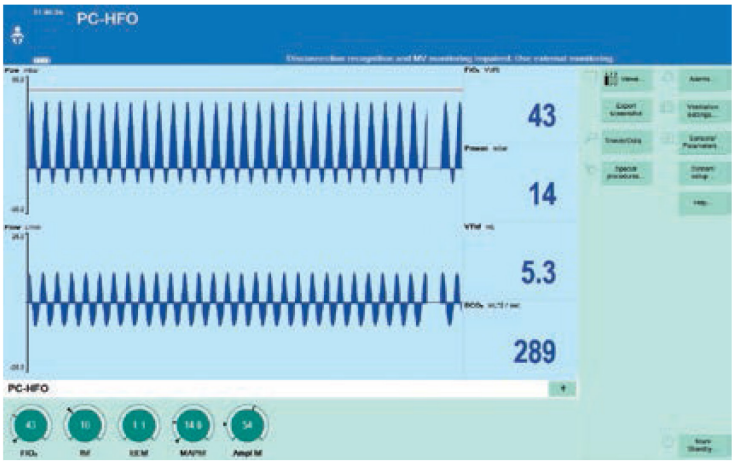
Comparison 1. HFOV versus CV (all trials)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death by 28 to 30 days	10	2148	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.88, 1.34]
2 Mechanical ventilation at 28 to 30 days in survivors	3	767	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.86, 1.35]
3 Oxygen at 28 to 30 days in survivors	6	1043	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.10]
4 CLD at 28 to 30 days (O_2 + x-ray) in survivors	4	820	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.74, 1.01]
5 Death or CLD at 28 to 30 days	5	1160	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.85, 1.04]
6 Death by 36 to 37 weeks or discharge	17	3329	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.10]
7 CLD at 36 to 37 weeks PMA or discharge in survivors	17	2786	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.78, 0.96]
8 Death or CLD at 36 to 37 weeks PMA or discharge	17	3329	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.97]
9 Any pulmonary air leak	13	2854	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.05, 1.34]
10 Gross pulmonary air leak	11	2185	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.88, 1.45]
11 Intraventricular haemorrhage - all grades	12	3084	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.95, 1.14]
12 Intraventricular haemorrhage - grades 3 or 4	18	4069	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.95, 1.27]
13 Periventricular leukomalacia	17	3983	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.81, 1.31]
14 Retinopathy of prematurity (stage 2 or greater) in survivors	12	2781	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.70, 0.93]

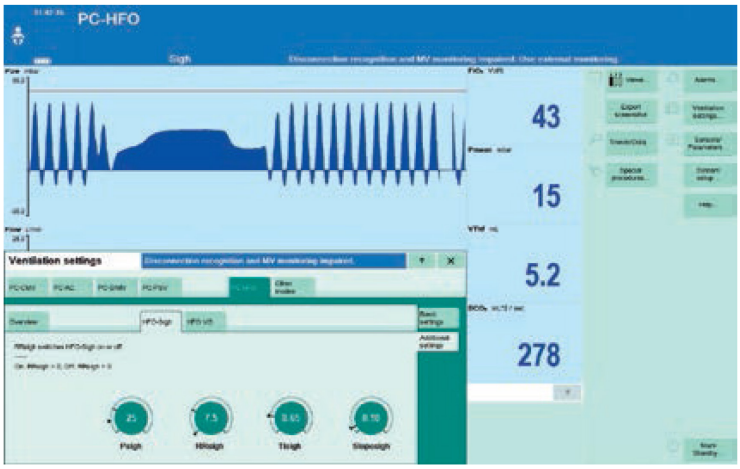
Fig. 2 Results from meta-analysis compared clinical outcomes between elective high-frequency oscillatory ventilation (HFOV) versus conventional ventilation (CV)

Recent a meta-analysis in 2015, 19 eligible studies involving 4096 preterm infants were included in **Figure 2**. Meta-analysis comparing elective HFOV with CV, bronchopulmonary dysplasia (BPD) and severe retinopathy of prematurity in survivors at term equivalent gestational age or discharge was significantly reduced with the use of HFOV. There was no evidence of effect on mortality at 28 to 30 days of age or at approximately term equivalent age. Pulmonary air leaks, defined as gross air leaks or pulmonary interstitial emphysema, occurred more frequently in the HFOV group but no difference in only gross air leaks. However, pulmonary air leaks were not different between HFOV and CV when subgroup analyses by age at randomization, routine surfactant use or not, type of high frequency ventilator (oscillator versus flow interrupter), inspiratory to expiratory (I:E) ratio of high frequency ventilator (1:1 versus 1:2) and CV strategy (lung protective or not).[1]

Previous physiologic studies in non-intubation, Sighs are spontaneous deep inspirations characterized in infants by a biphasic pattern with an inspiratory reinforcement occurring at the end of an inspiration ('breath on the top of a breath'). Sighs were more frequent in preterm than in term infants and more so during Rapid eye movement (REM) sleep than non-REM sleep.[5] Sighs in the preterm infant without lung disease were similar frequency in normal full-term infants (1.5 sighs per 10 minutes).[6, 7] Therefore, sigh frequency in preterm infants increased with the degree of prematurity at birth and severity of BPD.[6] Sigh breaths were much more frequent in infants than in adults.[8]



3A



3B

Fig. 3 True oscillation generated by the HFO option is sinusoidal; expiration is supported by active expiration to prevent air trapping. The result is smooth, precise, and gentle oscillation (3A). HFO-Sigh helps avoid atelectasis and can be triggered at preset intervals or performed manually as required, following suctioning maneuvers for example (3B).

Previous physiologic studies in intubated adults, sigh may improve lung function through improved lung elastance (increased gas exchange and lung volume, and decreased the respiratory drive)[9] and enhance regional lung protection (decreased regional lung strain and intra-tidal ventilation heterogeneity).[10] In an animal study, large inflations or sighs increased release of active surfactant.[11]

In intubated animal study, rat took a spontaneously deep (sigh) breath which resulted in a rapid fall of pCO_2 (from 30 to 26 mm Hg).[12] In intubated pediatric patients after major surgery, arterial pCO_2

decreased from pressure support ventilation (PSV, 39.3 ± 3.3 mm Hg) to "PSV + sigh" group (34.3 ± 4.6 mm Hg; p <0.001)[13] while arterial pCO_2 was not significantly different in neonatal patients (PSV vs. PSV + sigh, mean ± SD 42.3 ± 3.7 vs 40.4 ± 5)[14] and adult patients (PSV vs. PSV + sigh, median [interquartile ranges] 44 [38, 49] vs. 43 [39, 47] mm Hg, p = 0.70).[15]

Besides pCO_2 level, sigh breaths improved oxygenation and lung mechanics in neonate. In crossover randomized controlled trial (RCT) from 11 neonates (median age 11.5 [8.7–74] days) after cardiac surgery, PSV + sigh mode significantly increased PaO_2/FiO_2, inspiratory time and tidal volumes, and decreased oxygenation index and respiratory rate compared to PS mode.[14] In 48 healthy preterm infants (weight at study 2,042 ± 316 g and postconceptional age 36.6 ± 2.0 weeks), mean ± SD. functional residual capacity (FRC) after sigh breaths, after apneic pauses, and neither a sigh nor an apneic pause was found 26.0 ± 6.9, 20.0 ± 6.8, and 24.0 ± 7.7 mL/kg, respectively, FRC after sigh breaths and neither a sigh nor an apneic pause was significantly higher than after apneic pauses.[16]

Knowledge gap

Due to the lack of data and complexity of ventilator management trials, a clear consensus for the optimum mode of initial mechanical ventilation for neonate does not exist. The ventilation strategies used for this population vary significantly. However, HFOV is increase used as an initial ventilatory strategy especially in preterm infants including our center. Study in HFOV combined with intermittent sigh breaths in neonate is limited especially on arterial carbon dioxide level.

There were only two active but not recruiting studies which compared between HFOV with intermittent sigh breaths (HFOV-sigh) and HFOV in ClinicalTrial.gov (https://clinicaltrials.gov/ct2/results?cond=High+frequency+oscillatory+ventilation+with+intermittent+sigh+breaths+&term=&cntry=&state=&city=&dist=, **Figure 4**)[17, 18] Both registered trials focus on preterm neonates (gestational age 24–36 weeks), sigh PIP 30 cm H_2O for 1 hour, and measured lung mechanics (electric tomography impedance) and blood oxygenation.[17, 18] While this study fulfils this intervention by enrolled preterm and term infants (gestational age 24–41 weeks), lower sigh PIP (MAP+5, maximum sigh PIP 30 cm H_2O; usually MAP in HFOV 8–25 cm H_2O) for 2 hours, and focus on blood ventilation.

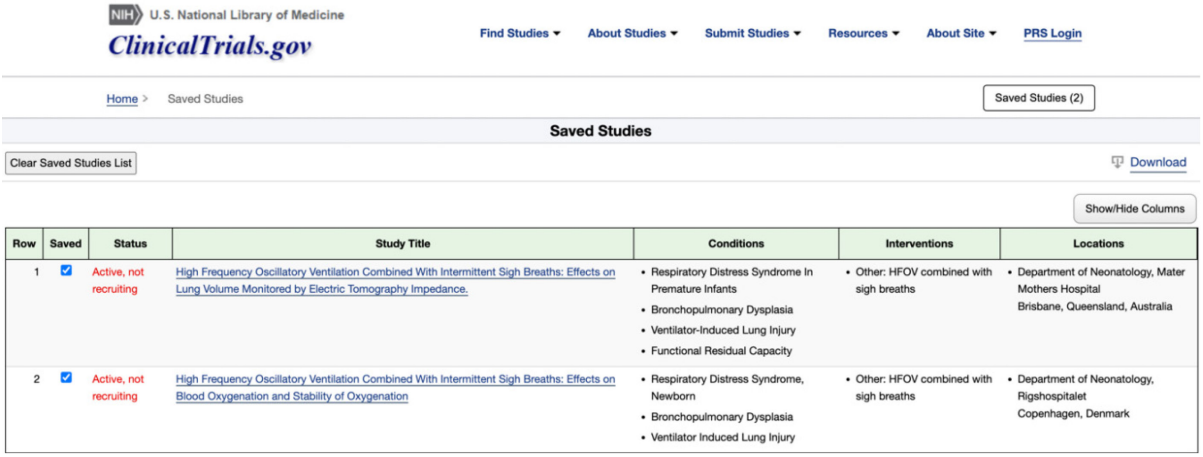


Fig. 4 Studies registered in ClinicalTrial.gov which compared "High frequency oscillatory ventilation with intermittent sigh breaths (HFOV-sigh)" with "High frequency oscillatory ventilation (HFOV)"

Objectives

Comparing the pCO_2 level after 2 hours of HFOV-sigh mode (after intervention) compared with HFOV mode (before intervention)

Conceptual framework

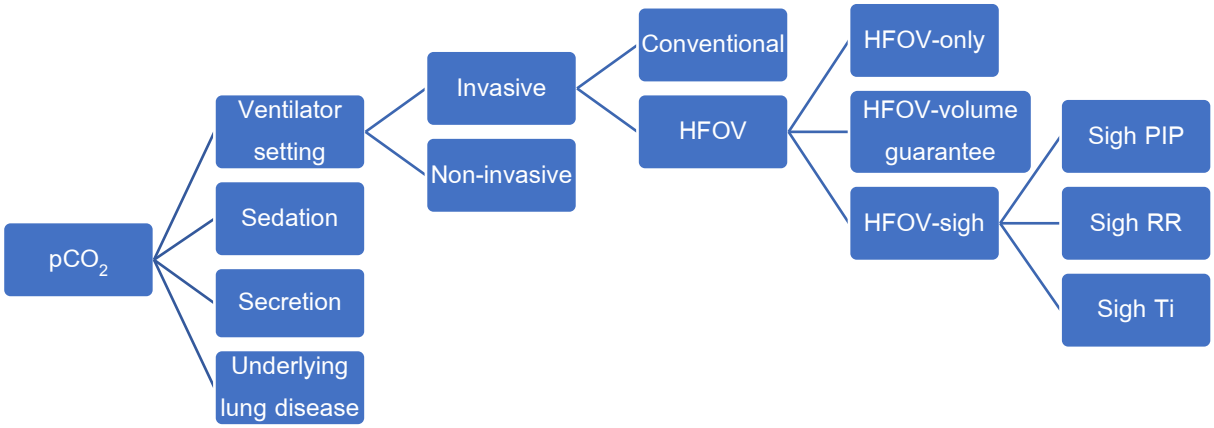


Fig. 5 Factors affect arterial pCO_2 level in ventilated neonates

(HFOV = High frequency oscillatory ventilation; PIP = Peak inspiratory pressure; RR = Respiratory Rate; Ti = inspiratory time)

Literature review

High-frequency oscillatory ventilation (HFOV) is a type of ventilator that can reduce barotrauma, achieve adequate alveolar ventilation with small tidal volumes. In recent years, HFOV versus conventional ventilation for acute pulmonary dysfunction in preterm infants had has been highly debated issue about effectiveness in many systemic reviews, meta-analyses, and randomized controlled trials.[1, 19, 20] From meta-analysis, It revealed HFOV could reduce chronic lung disease or death rather than conventional ventilation.[1]

Sighs are spontaneous deep inspirations characterized in infants by a biphasic pattern with an inspiratory reinforcement occurring at the end of an inspiration ('breath on the top of a breath'). Sighs were more frequent in preterm than in term infants and more so during Rapid eye movement (REM) sleep than non-REM sleep.[5] Sighs in the preterm infant without lung disease were similar frequency in normal full-term infants (1.5 sighs per 10 minutes).[6, 7] Therefore, sigh frequency in preterm infants increased with the degree of prematurity at birth and severity of bronchopulmonary dysplasia.[6] Sigh breaths were much more frequent in infants than in adults.[8]

Previous physiologic studies in intubated adults, sigh may improve lung function through improved lung elastance (increased gas exchange and lung volume, and decreased the respiratory drive)[9] and enhance regional lung protection (decreased regional lung strain and intratidal ventilation heterogeneity).[10] In an animal study, large inflations or sighs increased release of active surfactant.[11]

Sigh breaths may improve CO_2 clearance,[13] oxygenation and lung mechanics[14, 16] in neonate. Currently, only 4 studies in HFOV-sigh mode were conducted. The first and second studies were registered in Clinical trial.gov.[17, 18] Preterm (gestational age 24–36 weeks) neonates were enrolled to crossover RCT between HFV and HFV-sigh groups to compare oxygenation and lung volume in both periods. The sigh peak inspiratory pressure (PIP) was set at 30 cm H_2O. Both trials have still been active studies and outcome data not reported in the clinicaltrial.gov. The third study in Japan was a practical advice in preterm (especially for infants born at less than 28-week gestation). They applied sigh breaths (2-3 times per minute, 0.7-1.0 seconds in duration) with sigh PIP at 5 cm H_2O above the current mean airway pressure (MAP).[21] The final study compared HFJV with or without sigh breath in neonate with respiratory distress syndrome (RDS) and meconium aspiration syndrome (MAS).[22]

We hypothesized that sigh breaths augment restoring lung volume and ventilation in intubated neonate with HFOV. In neonatal studies, the results from HFOV combined with intermittent sigh breaths have never reported (active 2 studies and review 1 study).[17, 18, 21] This study, therefore, was designed to examine the short-term effects of sigh breaths during HFOV in neonate undergoing mechanical ventilation.

Methods

Study design: before-after interventional, non-randomized trial, study

Study setting: Neonatal Intensive Care Unit (NICU), Songklanagarind Hospital

Target population: NICU admitted neonate

Study population: Intubated neonate

Inclusion criteria:

- Preterm and term neonate (gestational age 24-41 weeks) with postnatal age less than 28 days
- Already ventilated with high frequency ventilation at least 1 hours
- An umbilical or peripheral arterial catheterization was available

Exclusion criteria

- Previous or current pulmonary air leaks (pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, and pneumopericardium)
- Heterogeneous lung disease including MAS, congenital diaphragmatic hernia
- Suspected lung hypoplasia
- Suspected or confirmed intraventricular hemorrhage grade III-IV
- Suspected or confirmed hypoxic ischemic encephalopathy or 5-min Apgar score less than 3
- Hemodynamic instability despite using inotrope(s)
- Arterial pCO_2 level less than 45 mm Hg or more than 70 mm Hg before intervention
- Need a new arterial puncture for samples both before and after interventions
- Moribund status
- Parents' decision not to participate

Subject withdrawal criteria

- Develop air leak syndrome during intervention
- Worsening respiratory distress with increasing HFO setting (changed Hz, MAP, delta pressure, increased FiO_2 more than 0.1, and need to suction or positive pressure ventilation via self-inflating bag or T-piece resuscitation) during study
- Hemodynamic instability and need to increase dose or add new inotrope during intervention
- Parents' decision not to participate during study

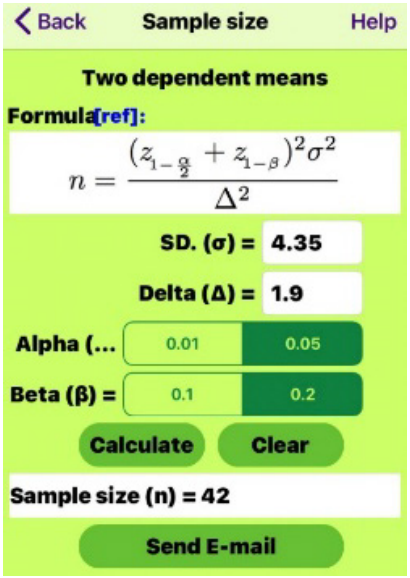
Study termination criteria

- During or after intervention within 24 hours, more than 5 neonates will develop new pulmonary air leaks (10% of 50 participants; because pulmonary air leaks occurred in HFOV 27.7% [392/1,415] in meta-analysis[1] so we use 10% of sample size calculation to terminate study for safety).
- The second sample after add sigh breath, more than 10 neonates have pCO_2 <35 mm Hg neonates (20% of 50 participants).

Sample size calculation

Primary outcome: Compare arterial pCO_2 level between HFOV (before) and HFOV-sigh (after)

- No previous study was compared the pCO_2 level between neonates who were on HFOV mode and HFOV + sigh mode.
- From Bonacina 2019,[14] neonates who were on invasive PSV and PSV + sigh mode. The pCO_2 levels in PSV and PSV + sigh were 42.3 ± 3.7 mm Hg and 40.4 ± 5.0 mm Hg (Delta = 1.9 mm Hg, SD. = 4.35), respectively.



- Study design was before and after intervention. The dependent outcome was pCO_2 level (continuous variable) In two dependent mean data, the calculated sample size was 42 neonates (alpha = 0.05, beta = 0.2, Delta = 1.9, SD. = 4.35), then increase 20% (if possible) for increased power. Finally, the targeted sample size was 50 neonates. We plan to recruit for one year, then preliminary analysis will do. If the result was significant differences, the study may be considered to terminate.

Operational definition

- Dependent variable = Arterial pCO_2 level
- Independent variables = Sigh breaths

Procedure

- Neonates who were ventilated with HFOV would be informed consent to the parents by the neonatal fellow (Dr. Kulthida Baingam). After informed consent, the first arterial blood gas was drawn after on HFOV at least 1 hour. Then, participants would be switched on HFOV-sigh mode (the same setting of HFOV mode and add only sigh breath). The second arterial blood gas was drawn (2 hours to 2 hours 15 minutes after start HFOV-sigh). After that sigh breaths would be switched off then on only HFOV mode.
- The ventilator in NICU had 4 brands (SLE6000, Drager, Fabian, and Sensor medic); however, sigh mode was only available in SLE6000 infant ventilators (United Kingdom) and Drager Babylog VN500 (Germany).
- HFOV-sigh setting both SLE6000 and Drager Babylog VN500: setting (Hz, MAP, delta pressure) same as HFOV, set sigh RR 3 breath/min, Sigh Ti = 1 sec, Sigh PIP = (MAP+5, maximum 30) cm

H_2O, Slope sigh 0.5. No change in Hz, MAP, delta pressure, and increased FiO_2 less than 0.1 occurred between intervention.

- Currently, only 3 studies in HFOV-sigh mode were conducted (**Table 1**). We set sigh RR 3 breath/min and Sigh Ti = 1 sec (similar to previous studies[17, 18, 21]), Sigh PIP = (MAP+5,[21] maximum 30[17, 18]) cm H_2O. While HFJV combined with higher sigh PIP (set at 27 and 37 cm H_2O in RDS and MAS) resulted in excessive tidal volume.[22]

Table 1. Review sigh breaths in neonates, children, and adults with HFOV

Author	Population	Mode of ventilator	Sigh setting			Sigh Duration
			Sigh PIP (cm H_2O)	Sigh RR (/min)	Sigh Ti (sec.)	
Heiring[17, 18]	Preterm neonate	HFOV	30	3	1	1 h
Nakanishi[21]	Preterm neonate	HFOV+VG	MAP+5	2-3	0.7-1.0	N/A
Romo[22]	Preterm and Term neonates	HFJV	27 (RDS) 37 (MAS)	6	0.3-0.4	N/A
Bonacina[14]	Neonate and infant	PSV	30	1	3	240 breaths
Nacoti [13]	Children undergoing major surgery	PSV	30	1	0.5	1 h
Mauri [10]	Adult with ARDS	PSV	35	2,1,0.5	N/A	20 min
Mauri[15]	Adult with ARDS	PSV	30	1	N/A	30 min
Badet[23]	Adult with ARDS	A/C	<40, 2*TV	2-3	N/A	1 h

A/C= assist controlled, HFJV = high-frequency jet ventilation; HFOV = High frequency oscillatory ventilation; VG = Volume guarantee; MAP = Mean airway pressure, MAS = Meconium aspiration syndrome; N/A = not available; PIP = peak inspiratory pressure; PSV = pressure support ventilation; RDS = Respiratory distress syndrome; RR = Respiratory rate; Ti = Inspiratory time; TV = tidal volume

- The monitoring during HFOV and HFOV-sigh monitoring was vital signs (systolic, diastolic, mean arterial pressure, heart rate, SpO_2 were collected every 15 minutes during intervention for 2 h and after intervention for 1 h) by neonatal fellow (Dr. Kulthida Baingam) and nurse, clinical manifestations, respiratory distress, umbilical arterial blood gas during study, and chest X-ray within 24 hours after intervention or immediately if clinical conditions deteriorate. The first blood gas was obtained after HFOV mode at least 1 hour with stable participants. After HFOV-sigh, the blood gas was obtained after 2 hours (no more than 2 hours 15 minutes) in this setting.

Data collection

Participant's data and blood gas's result will be recorded in record form.

Data management

EpiData entry is used for data entry and data documentation. The data will be safe and private collected; moreover, only principal investigator and recorder will access.

Data analysis

Parametric continuous variables are presented as mean (standard deviation, SD) and paired t-test was used to compare paired samples. Nonparametric continuous variables are presented as median (interquartile range, IQR) and the Wilcoxon signed rank test with continuity correction was used to compare paired samples. Subgroup analysis for gestational age less than 37 and 32 weeks.

Ethical issues

For Safety, the intermittent sigh breaths generated low sigh RR, optimal sigh PIP and Ti from previous studies. For 2 hours, neonatal fellow will monitor clinical conditions and then 24 hours after intervention. Risk of sigh breath may be air leak syndrome because this mode may increase PIP sigh and ventilation. In meta-analysis in neonate, neonates who on HFOV mode developed pulmonary air leaks 27.7% (392/1,415).[1] However, neonate with risk of air leak syndrome (previous or current pulmonary air leaks e.g., pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, and pneumopericardium. Heterogeneous lung disease including MAS, congenital diaphragmatic hernia, and suspected lung hypoplasia) will be excluded and the participants will be closed-monitored during and 24 hours after intervention (clinical and radiographic conditions). Some neonates may expose X-ray (increase 1 time) more than routine care to monitor safety. However, some neonate may need follow X-ray by clinical condition of each neonate within 24 hours, this neonate will not be repeat more X-ray.

The blood gases were drawn for 2 times, more than routine care. The arterial blood gases were only drawn through umbilical or peripheral arterial catheter for reducing pain from direct artery puncture. Each time used approximately 0.2 mL of blood (Total blood 0.4 mL). Arterial blood gases were needed to evaluate patient's ventilation. In case of lowest birth weight 500 g neonate, total blood loss was about 0.8 mL/kg/day (< 2.5 mL/kg). The methods of arterial blood gas drawing were firstly the doctor would draw blood containing heparin from umbilical artery catheter to the first syringe by sterile technique then the tuberculin syringe was secondly drawing from umbilical artery catheter to be analyzed for arterial blood gas. Thirdly, the blood from the first syringe was returned to the patient and finally the blood was clear from umbilical or peripheral arterial catheter by 0.5 mL flushing with normal saline. The maximum allowable blood draw volumes were shown in **Figure 6**.

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Maximum allowable blood draw volumes:

PATIENT'S WEIGHT		TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW	MAXIMUM mL IN A 30-DAY PERIOD
Kg	lbs	mL	2.5% of total blood vol	5% of total blood vol
1	2.2	100	2.5	5
2	4.4	200	5	10
3	3.3	240	6	12
4	8.8	320	8	16
5	11	400	10	20

Fig.6 Maximum allowable blood draw volumes

The record form was unidentifiable enrolled patients; therefore, name or hospital number would not be filled in the record form. The data would be kept in secret files and only principal investigators and recorders could access to these data.

Enrolled participants may be not directly profitable from this thesis; nevertheless, the enrolled participants would be evaluated pCO_2 level and ventilation monitoring

The social benefit was the published study in neonate that evaluate sigh breaths in HFOV that may lead to further investigation and application in general practice.

Informed consent process

The parents of intubated neonates with available umbilical artery catheter would be pursued to enrolled in this study by NICU fellows within a few days after intubation. The parents would receive informative documents with explaining the entire data about 30 to 60 minutes or until the parent were crystal clear about the study detail by NICU fellows. If the parents allowed the patients to enroll in the study, they would sign the signature in the informed consent's document.

The resigned data would be recorded in the recorded form and informed consent's document. It would record date of resignment and signature of both parents and doctors.

Time table 1st October 2022 ถึง 30th June 2024

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