Next Step™ Resuscitator as a Novel Device for Providing Volume-Targeted Ventilation in the Delivery Room

by

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ABSTRACT

Approximately 13-26 million newborns worldwide require breathing assistance at birth. Positive pressure ventilation (PPV) is the cornerstone of neonatal resuscitation. The purpose of PPV is to help the newborn develop a functional residual capacity by delivering an adequate tidal volume (V_T). Traditional neonatal resuscitation devices, i.e., the self-inflating bag (SIB) and T-Piece devices are pressure-limited. This mode of ventilation provides a constant inspiratory flow to deliver a set inspired V_T. However, if a constant volume of air is being delivered, this can result in volutrauma as the infant's lung mechanics will fluctuate post-delivery. Modern mechanical ventilators, such as the Dräger VN500, Fabian™ HFO, and Leoni Plus use flow sensors to deliver volume-targeted ventilation, which is a mode of ventilation that delivers a stable V_T by varying the PIP on a breath-by-breath basis. Recently, a new ventilator was developed called the Next Step™ Resuscitator. Compared to the other ventilators, the Next Step™ has not been extensively studied. In this thesis, the Next Step™'s performance in providing PPV and its internal properties (i.e., power usage and the time it takes to deliver a target oxygen concentration) were examined in a series of animal and observational studies.

First, using a neonatal piglet model, we compared the Next Step™ to different ventilation strategies: self-inflating bag (SIB) only, SIB+respiratory function monitor (RFM), T-Piece only, T-Piece+RFM, and Fabian™ HFO, to examine which device/strategy can maintain the most consistent V_T at ~0.5 cmH_2O and ~1.5 cmH_2O compliance levels. The Next Step™ and Fabian™ HFO provided the most stable V_T during PPV (5.10 and 4.76 mL/kg at ~0.5 cmH_2O compliance; 5.22 and 4.43 mL/kg at ~1.5 cmH_2O compliance, respectively) with no significant differences between the two devices, at all compliance levels tested.

Second, we examined the amount of time it takes for the Next Step™ to achieve changes in oxygen (O_2) concentration compared to the Dräger VN500, Leoni Plus, and T-Piece resuscitators (GE, Neo-Tee and NeoPuff). Providing excessive oxygen (100% O_2) to the preterm infant can cause oxidative stress whilst providing too little O_2 can prevent them from reaching an optimal O_2 saturation level, increasing their risks of death and intraventricular hemorrhage. The mean ± SD time required to achieve FiO_2 changes at 10 L/min was 32±1 s, 25±3 s and 36±2 s for the Leoni Plus, Next Step™, and Dräger VN500, respectively, at a V_T of 4 mL/kg. At a V_T of 6 mL/kg, the mean ± SD time required to achieve FiO_2 changes at 10 L/min for the Leoni Plus, Next Step™, and Dräger VN500 was 32±1 s, 28±3 s and 35±2 s, respectively. As for the GE T-Piece, Neo-Tee and NeoPuff, the mean ± SD time required to achieve changes at 10 L/min was 15±2 s, 17±1 s and 19±1 s, respectively. Overall, there was a lag time of approximately 30 s for the ventilators at a V_T of 4 mL/kg and 6 mL/kg. For the T-Pieces, there was a lag time of approximately 20 s.

Third, we compared the amount of electrical power the Next Step™ uses compared to the Dräger VN500, Fabian™ HFO, and the Leoni Plus when providing PPV and continuous positive airway pressure (CPAP). A barrier to the installation and use of mechanical ventilators in developing countries is access to electricity. In this study, we found that the Next Step™ used the least amount of power when providing PPV regardless of changes to the respiratory rate and positive end expiratory level (range): 18.47-21.04 W for the Next Step™ versus 89.6-96.1 W for the Dräger VN500, 64.56-65.04 W for the Leoni Plus, and 27.37-29.34 W for the Fabian™ HFO. Similarly, the Next Step™ used the least amount of power when providing CPAP: range: 9.95-11 W for the Next Step™ versus 98.6-98.6 W for the Dräger VN500, 64.35-65.25 for the Leoni Plus and 22.7-23.45 W for the Fabian™ HFO.

PREFACE

This thesis consists of a research project that has received research ethics approval from the University of Alberta Research Ethics Board, including: i) "Neonatal Porcine Model of Hypoxemic Respiratory Failure," (AUP00004124), March 28, 2023. This thesis is modified from our published work "Tran, K.H., Ramsie, M., Law, B., et al. (2024) Comparison of positive pressure ventilation devices during compliance changes in a neonatal ovine model. *Pediatr Res.* 10.1038/s41390-024-03028-3."

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TABLE OF ABBREVIATIONS

Bpm – Breaths per Minute

CI – Confidence Interval

CoSTR – Consensus of Science and Treatment Recommendations

CPAP – Continuous Positive Airway Pressure

DR – Delivery Room

FIB – Flow Inflating Bag

FiO_2 – Fraction of Inspired Oxygen Concentration

FRC – Functional Residual Capacity

ILCOR – International Liaison Committee on Resuscitation

iPPV – Intermittent Positive Pressure Ventilation

NICU – Neonatal Intensive Care Unit

NRP – Neonatal Resuscitation Program

OR – Odds Ratio

$PaCO_2$ – Partial Pressure of Carbon Dioxide

PEEP – Positive End Expiratory Pressure

PIP – Peak Inspiratory Pressure

PLV – Pressure Limited Ventilation

PPV – Positive Pressure Ventilation

RFM – Respiratory Function Monitor

RR – Relative Risk

SIB – Self-Inflating Bag

SpO_2 – Oxygen Saturation

TLC – Total Lung Capacity

V_T – Tidal Volume

V_{Te} – Expired Tidal Volume

V_{Ti} – Inspired Tidal Volume

VTV – Volume Targeted Ventilation

Chapter 1. Introduction

1.1 Lung aeration at birth

Before birth, the neonate's airways are fluid-filled and do not participate in gas exchange.[1] These liquids help the infant's lungs stay in a distended state and prevent their lungs from collapsing during fetal development.[2] However, in order for the infant to breathe and establish a functional residual capacity (FRC), these fluids need to be displaced and replaced by air.

During labor, as the mother's uterine muscles contract, this increases the transpulmonary pressure (pressure across the airway wall) within the infant, creating an upward pressure gradient that forces the diaphragm into the chest, and consequently expelling liquid out of the infant's trachea, nose, and mouth.[3] Another mechanism, proposed by Hooper *et al*[4] suggests that during inspiration, a large transpulmonary pressure is generated which acts as a hydrostatic pressure gradient that drives liquid into the surrounding pulmonary tissues.

Many infants can successfully transition from fetal to neonatal life without help, dispel these liquids from their lungs and breathe spontaneously. However, approximately 10–20% (~13–26 million newborns worldwide) require breathing assistance at birth.[5] The International Liaison Committee on Resuscitation (ILCOR) provides a consensus of science and treatment recommendations (CoSTR), while national resuscitation councils such as the European Resuscitation Council, provide guidelines on resuscitating newborn infants.[6,7] They all agree that positive pressure ventilation (PPV) is integral to neonatal resuscitation.[6,7] PPV aims to create a FRC by delivering an adequate tidal volume (V_T) to initiate spontaneous breathing and facilitate gas exchange.[8] PPV is provided by using a ventilation device, i.e., flow-inflating bag (also known as an anesthesia bag), self-inflating bag (SIB), or T-Piece resuscitator, and an interface, i.e., facemask, laryngeal mask, nasal prong, or endotracheal tube.

1.2 Oxygen transition at birth

Post-delivery, the oxygen saturation (SpO_2) of newborns is as low as 30% which then increases over the next 7-10 minutes to 85–95%.[9] The goal of a successful resuscitation for preterm infants is to facilitate the transition from intrauterine low SpO_2 levels to accepted post-transitional neonatal ranges, i.e., 65% for 2 minutes after birth and 85% for 5 minutes after birth.[5–7]

Several animal and human studies have shown that a high fraction of inspired oxygen (FiO_2) is toxic to lung tissue. In a systematic review and meta-analysis conducted by Davis *et al*,[10] which comprised of five trials and 1302 newborns, the authors reported that resuscitation with air (21% O_2) resulted in lower risks of mortality [relative risk (RR) (95% CI): 0.71(0.54–0.94)] compared to 100% O_2. Preterm infants are particularly vulnerable to the free radical oxygen species generated by high concentrations of O_2 because their antioxidant mechanisms are not fully developed until the third trimester, which begins around the 28th week of pregnancy.[11] Gladstone *et al*[12] analyzed lung lavage fluid in neonates ventilated for respiratory distress syndrome and found that a $FiO_2 > 0.4$ was associated with a significant increase in protein bound carbonyl (a marker of oxidative injury). Furthermore, prolonged exposure to hyperoxia (high concentrations of O_2) has also been linked to leukocyte activation and sequestration in the neonatal rat lung.[13] Similarly, using asphyxiated term piglets, Munkeby *et al*[14] reported that 30 minutes of exposure to 100% O_2 resulted in a significant increase in inflammatory markers. Thus, using high oxygen concentrations during neonatal resuscitation can result in acute lung injury, especially in very preterm infants.

Interestingly, a recent meta-analysis[15] of 10 randomized trials and four cohort studies, which included 5,697 preterm newborns <32 weeks' gestation comparing low fraction of

inspired oxygen (≤0.5) versus high (>0.5), reported very low certainty of evidence for all outcomes: short term mortality: [RR (95% CI): 0.83 (0.50–1.37); long-term mortality (1–3 years): [RR(95% CI): 1.05(0.32–3.39)]; long-term neurodevelopmental impairment (at 1–3 years): [RR (95% CI): 1.14 (0.78–1.67)]; bronchopulmonary dysplasia: [RR (95% CI): 1.00 (0.71–1.40)]; and grade 3 and 4 intraventricular hemorrhage: [RR (95% CI): 0.96 (0.61–1.51)]. These results suggest that the use of a lower FiO_2 does not lead to positive clinical outcomes as previously suggested. Based on the above meta-analysis, the current CoSTR recommends <65% as the initial O_2 concentration in preterm infants.[16]

A recent individual patient analysis of randomized trials reported that 46% of preterm infants resuscitated with initial lower oxygen concentration did not reach SpO_2 of 80% at 5 minutes.[17] If resuscitation was initiated with a FiO_2 <0.3, this was associated with a decreased likelihood of reaching an SpO_2 of 80% [OR (95% CI): 2.63 (1.21–5.74)], and consequently, an increased risk of major intraventricular hemorrhage [adjusted OR (95% CI): 2.04 (1.01–4.11)] and a higher risk of death [OR (95% CI): 2.66 (1.45–4.87)].[17] These data suggest that the initial use of lower oxygen concentrations can also be harmful for the infant. As a result, O_2 delivery should be regularly monitored and titrated using pulse oximetry to meet SpO_2 target ranges, corresponding to those of spontaneously breathing, healthy full-term infants.[16]

1.3 Ventilation Devices

Flow-inflating bag (FIB), self-inflating bag (SIB) or a T-Piece resuscitator are the most commonly used PPV devices (see summary in Table 1.1). The SIB is the most popular modality because it is inexpensive and does not require a compressed gas source while the FIB and T-Piece require a compressed gas source. An advantage to the T-Piece resuscitator is that it can provide a set peak inflation pressure (PIP) and positive end-expiratory pressure (PEEP), while a

SIB provides variable PIP, even with an attached PEEP valve.[18] Similarly, a FIB can produce variable PIP and PEEP,[18–21] in addition to being difficult to maneuver, especially for inexperienced operators.[22,23] Using a FIB can also result in a higher median (range) delivered tidal volume (V_T) [8.5 (5.3–11.4)] mL/kg compared to a T-piece [5.6 (4.3–7.9)] mL/kg ($p<0.0001$).[24]

In a large cohort study, Guinsburg *et al*[25] reported that survival to hospital discharge without major morbidities (i.e., bronchopulmonary dysplasia, periventricular leukomalacia, and severe intraventricular hemorrhage) was 47% with the T-Piece compared to 35% with the SIB in preterm infants <33 weeks' gestation. Logistic regression adjusted for maternal characteristics, obstetric, and neonatal morbidities demonstrated that PPV using a T-piece increased the chance of survival to hospital discharge without major morbidities [odds ratio (OR) (95% CI):1.38 (1.06–1.80)]. While these results are very encouraging, two studies comparing a T-piece resuscitator with a SIB did not confirm these findings.[26,27] Dawson *et al*[26] reported that there was no significant difference in the median SpO_2 at five minutes after birth between T-Piece and SIB groups (61% versus 55%, respectively), or rate of endotracheal intubation and administration of surfactant. Jayaram *et al*[27] also reported that the use of a T-Piece over a SIB did not produce a difference in the 1-min ($p=0.77$) and 5-min ($p=0.11$) Apgar scores (a proxy used to measure neonate's initial status and response to resuscitation) or the need for use of chest compressions or epinephrine in the delivery room (DR).

However, in a randomized study conducted by Szyld *et al*[28], the authors reported significantly reduced rates of intubation in those ventilated with a T-Piece compared to a SIB (14% versus 23%, $p=0.008$); mean (standard deviation) maximum PIP was significantly greater with a T-Piece compared to self-inflating bag (26(2) cmH_2O versus 8(2) cm H_2O, $p<0.001$).

Similarly, in a randomized trial conducted by Thakur *et al*[29], the authors reported significantly lower intubation rates with a T-Piece compared to a self-inflating bag (15% versus 34%, p=0.04). Furthermore, the median [interquartile range (IQR)] duration of PPV was significantly shorter when a T-Piece was used compared to a self-inflating bag [30 (30-60) seconds versus 60 (30-90) seconds, p<0.001].[29]

A recent systematic review reported that PPV provided with a T-piece significantly decreased the duration of PPV (mean difference: -19.8 seconds, 95% CI: -27.7 to -12.0 seconds) as well as the risk of bronchopulmonary dysplasia [RR (95% CI): 0.64 (0.43–0.95)].[30] These data suggest that a T-piece has the potential to improve neonatal survival outcomes by delivering a more consistent PIP and PEEP. The current resuscitation guidelines also recommend the use of a T-piece resuscitator over a self-inflating bag during PPV; however, a self-inflating bag should always be available as a backup in the event of loss of compressed gas.

Table 1.1: Summary of PPV Devices

Self-inflating bag (SIB)	Flow-inflating bag (FIB)	T-piece Resuscitator
Advantages		
Does not require a compressed gas source.	Easy visual detection of a poor mask seal.	Delivers PIP and PEEP at set levels.[18–20,31]
Relatively inexpensive.	Relatively inexpensive.	Can be used to maintain prolonged inflations in contrast to the SIB even when a PEEP valve is attached.[18]
Can deliver PEEP with PEEP-valve attached.[32]		"rPAP™" uses fluidic-flip technology, with lower expiratory resistance compared to Neopuff T-Piece Resuscitator.[33] This then lowers the imposed work of breathing for the neonate, reducing their subsequent need for intubation.[34]
Disadvantages		
Some SIBs have a forward valve leakage design, in which the expiratory flow exit	Difficult to maneuver using intermittent PPV with PEEP.	Requires a compressed gas source.

lip does not seal completely, preventing effective V_T delivery.		
Some SIBs are unable to deliver V_T of <2.5-5 mL.[35]	Requires a compressed gas source.	If gas flow rate is changed, PIP and PEEP can inadvertently increase or decrease.[36–39]
Delivered PIP could be above the Pop-off safety-valve limit of 45 cmH_2O.[35]	Inconsistent delivery of PIP and PEEP.[35]	Unable to detect changes in compliance.[40,41]
Some SIBs do not deliver a volume until >50% of total bag compression distance is reached.[35]	Requires a manometer to measure delivered PIP and PEEP.	

Abbreviations: FIB=flow-inflating bag; PIP=peak inflation pressure; PEEP=positive-end expiratory pressure, SIB=self-inflating bag; V_T=tidal volume.

1.4 Facemask as an interface for PPV

Facemasks are available in various shapes and sizes and should cover the infant's mouth and nose but not their eyes and chin (see summary in Table 1.2).[42,43] O'Shea *et al*[43] reported that a facemask with a 35mm diameter are suitable for preterm infants <29 weeks' gestation or <1,000g birth weight, while a 42mm diameter mask would be appropriate for infants 27–33 weeks' gestation or 750–2,500g. Whereas 50mm diameter masks are too large for many preterm infants. Two randomized trials compared the Fisher & Paykel (Fisher & Paykel, Auckland, New Zealand) and Laerdal (Laerdal, Stavanger, Norway) round mask in infants <33 weeks' gestation and reported no difference in mask leak between both masks.[44,45] Lorenz *et al*[46] examined a novel suction mask, which aims to improve the seal around the infant's face by creating a vacuum. However, the suction mask did not reduce mask leak and resulted in higher rates of transient skin discoloration/bruises on the infant's face compared to the round silicone mask.

1.5 Nasal prongs or nasopharyngeal tubes

An alternative approach to facemasks is using a nasal prong or nasopharyngeal tube positioned into one or both of the newborn's nostrils.[47] Cohort studies in the DR reported that infants who received respiratory support via nasal prongs had lower rates of intubations compared to a facemask (16% versus 47%).[48] Similarly, Lindner *et al*[49] and te Pas *et al*[50] compared a combination of interventions, which included nasopharyngeal tubes, sustained inflations, and PEEP to conventional interventions (i.e., providing immediate intubation or ventilation via a SIB), and reported reduced rates of intubations and bronchopulmonary dysplasia. These data suggest a potential advantage of using a nasal interface over a facemask during PPV in the DR.

However, a recent meta-analysis comprising of five trials and 873 infants, reported no

statistical difference in in-hospital mortality [RR (95% CI): 0.98 (0.63–1.52)] or DR intubations [RR (95% CI): 0.63 (0.39–1.02)].[47] It is important to note that the largest trial to date by Donaldson *et al,*[51] in which the authors reported a significant reduction in DR intubations (32% with nasal prongs and a new respiratory system versus 44% with a facemask), was not included in the meta-analysis.

Table 1.2: *Types of interfaces*

Round Facemask	Teardrop/Anatomical-shaped Facemask	Suction Mask	Nasal Prongs
		Advantages	
Sizes range from 35–50 mm, which makes it suitable for most preterm infants.	Fits the contours of large term infants' face better than round facemasks.[16]	Mask leak is significantly lower with suction mask compared to round facemasks: 0.7% vs. 12.1%, p=0.00.[52]	Allows better visualization of infant's face and mouth.[53]
Relatively easy to clean.[54]	Masks do not exert pressure on the infant's eyes.[55]		Infant can be repositioned more easily without affecting the distending pressure.[53]
Can create effective seal on a small infant's face.	Mask's function is unaffected the way it is held/rotated.[55]		Theoretically less likely to activate trigeminocardiac reflex (a reflex that can cause sudden decrease in heart rate or apnea).

			No difference in rates of apnea, breathing rates, and heart rates compared to face masks[56,57]
			Lower rates of intubation compared to facemask[48,49]
Disadvantages			
Challenging to maintain good seal with infant's head in a correct position to maintain a patent airway.[58]	Increased mask leak once air cushion rim is deflated (27% to 52%, p=0.02).[55]	Delivers lower PIP (27.2 cmH_2O vs. 30.4 cmH_2O, $p<0.05$) and PEEP (3.7 cmH_2O versus 5.1 $cmH_2Op<0.05$) compared to round facemasks and can cause mild bruising and discolorations.[46]	Infants might develop nasal injury (incidence of injuries range from 37.16–67.86%).[59,60]
			No difference in in-hospital mortality or major morbidities compared to round facemasks.[47,61,62]

Abbreviations: PIP=peak inflation pressure; PEEP=positive-end expiratory pressure.

1.6 Mask Leak

A seal between the face and mask is an important determinant of successful PPV, as large leaks could result in ineffective ventilation by delivering an inadequate V_T.[63,64] Manikin study reported that resuscitators are unaware of large and variable mask leaks.[65,66] Observational DR studies reported mask leak range from 0–100% during PPV and that resuscitators were unaware of the extent of their leaks.[63,64]

Different approaches to reduce mask leak have been suggested: i) using corrective steps (i.e., MR.SOPA, Figure 1.1),[6,67] ii) a two-person mask hold technique,[68] iii) simulation training using a Respiratory Function Monitor (RFM),[69] and iv) adding a RFM during mask ventilation in the DR.[70–72] A RFM displays the leak around the facemask as graphical and numerical outputs.[73] The operator can then adjust the facemask's position and how it is held to minimize leak.[73] Tracy *et al*[68] reported that using the two-person mask hold technique reduced mask leak from 22% to 13% compared to the standard one-person mask ventilation method.

Using manikins, O'Curain *et al*[69] randomized 400 participants to mask ventilation training either with a RFM present or without. In both groups, the pre-training mask leak was not different; however, the post-training mask leak was significantly lower in the training group with a RFM present (i.e., mask leak decreased from 63% to 23% in the RFM visible group versus 51% to 35% in the RFM masked group).[69] While this is reassuring, no study has examined if simulation training using a RFM can result in improved mask ventilation technique in the DR.

Three randomized trials compared whether having a RFM displayed can reduce mask leak during PPV in preterm infants in the DR.[70–72] Overall, the trials had mixed results, with two trials reporting a significant reduction in mask leak when a RFM was visible,[71,72] and one trial

reporting no difference in mask leak.[70] These data suggest that a RFM can reduce mask leak during training, but during DR resuscitation, a RFM might not reduce mask leak. Since PPV requires facemasks to deliver air and oxygen to the infant, mask leak can affect the peak inflation pressure (PIP), positive-end expiratory pressure (PEEP) and V_T being delivered to the infant.

M	Mask adjustment	Reapply the mask. Consider the two hands technique
R	Reposition of the airway	Place head neutral or slightly extended
Try PPV and reassess chest movement		
S	Suction the mouth and nose	Use a bulb syringe or suction catheter
O	Opening the mouth	Open the mouth and lift the jaw forward
Try PPV and reassess chest movement		
P	Pressure increase	Increase pressure in 5 to 10 cmH_2O increments, max 40 cmH_2O
Try PPV and reassess chest movement		
A	Airway alternative	Place an endotracheal tube or laryngeal mask
Try PPV and assess chest movement and breath sounds		

Figure 1.1. MR. SOPA Corrective Steps

1.7 Oxygen Saturation

Immediately following birth, the oxygen saturation (SpO_2) of newborns is as low as 30%, which then increases over the next 7–10 minutes to 85%–95%. Preterm infants have slightly lower oxygen saturation (SpO_2) than term infants. In the neonatal intensive care unit (NICU), oxygen (O_2) therapy is provided to infants based on their blood gas values, color, transcutaneous O_2

monitoring and SpO_2 levels measured with a pulse oximeter.[74] Since 2010, the International Liaison Committee on Resuscitation has suggested using pulse oximetry to guide oxygen therapy in the delivery room to avoid hyperoxia (excessive O_2) and hypoxia (low levels of O_2) because it is non-invasive and can monitor SpO_2 continuously.[75,76]

In most NICUS, the infant's fraction of inspired oxygen (FiO_2), which is the concentration of oxygen in the gas mixture,[77] is titrated to maintain SpO_2 within a target range. This range may differ among NICUs and countries. Traditionally, 100% oxygen was provided to newborns. However, this has been associated with increased neonatal mortality. Vento *et al*[78–80] and Saugstad *et al*[81–84] reported that the use of high O_2 concentrations during resuscitation is associated with short- and long-term morbidity, such as oxidative stress, inflammation, and bronchopulmonary dysplasia. However, using low O_2 concentrations can also lead to adverse effects. Oei *et al*[17] reported that 46% of preterm infants resuscitated with initial low oxygen concentration did not reach SpO_2 of 80% at 5 minutes and this was associated with an increased risk of major intraventricular hemorrhage and a higher risk of death.

The optimal concentration at which oxygen concentration should be delivered for newborns is still a topic of debate. Welsford *et al*[15] conducted a meta-analysis of 10 randomized trials and four cohort studies, which included 5,697 patients in preterm newborns <32 weeks' gestation comparing low fraction of inspired oxygen (≤0.5) versus high (>0.5). The authors reported very low certainty of evidence for all outcomes: short term mortality, long-term mortality (at 1-3 years), long-term neurodevelopmental impairment (at 1-3 years), bronchopulmonary dysplasia, and grade III and IV intraventricular hemorrhage. Based on this meta-analysis, the current CoSTR recommends <65% as the initial oxygen concentration in preterm infants.[16] More recently, the American Heart Association recommends 21% O2 for newborns ≥ 35 weeks'

gestation and 21-30% for newborns ≤ 35 weeks' gestation with subsequent O_2 titration based on pulse oximetry.[85] Since achieving an optimal SpO_2 is a crucial step in neonatal resuscitation, it is important to deliver the targeted FiO_2 in a timely manner to a preterm infant who is apneic or asphyxiated. In the delivery room (DR), several ventilation devices are used to deliver O_2 to the infant, i.e., self-inflating bag (SIB), T-Piece resuscitator, and mechanical ventilators such as the Dräger VN500. However, compared to the T-Piece and mechanical ventilators, the SIB delivers an imprecise amount of flow of oxygen[86] and can overdeliver the target FiO_2.[87,88] As a result, the SIB is seldom used for O_2 therapy if a T-Piece resuscitator or a mechanical ventilator are available. In a study conducted by Follett *et al,*[89] the authors reported a lag time of approximately 30 seconds to achieve the desired FiO_2 from the oxygen blender to the facemask using a GE T-Piece.

1.8 Peak Inflation Pressure (PIP)

Peak inspiratory pressure (PIP) is the highest pressure measured during the respiratory cycle and is the combination of alveolar pressure and airway pressure.[90] PIP is essential for PPV because it determines the pressure gradient of between the beginning and end of inspiration, therefore it affects V_T (amount of air that moves in and out of the lungs within one cycle of respiration) and minute ventilation (amount of air that enters the lungs per minute).[90] At the physiological level, an increase in PIP increases V_T. An increase in PIP also increases mean airway pressure which will improve oxygenation.[90]

Current resuscitation guidelines recommend an initial PIP of 20-25 cm H_2O in preterm infants.[5] However, the PIP required to deliver an appropriate V_T depends on gestational age, disease state, delivery mode (caesarian section versus vaginal), and degree of lung aeration.[91,92] Even in the same infant, lung compliance and the corresponding PIP needed to deliver an appropriate V_T varies greatly within the first minutes after birth.[91–93] In the DR, PPV is commonly

provided via a pressure-limited device T-Piece resuscitator, where a static PIP is arbitrarily chosen, with the assumption that this will deliver an adequate V_T.[5,6] However, the delivered V_T is rarely measured, therefore PIPs are not adjusted to optimize V_T delivery.[63]

Studies demonstrated that excessive PIP results in barotrauma, volutrauma, extensive damage to the lung parenchyma, and cause alveolar cellular dysfunctions.[94–98] As lung compliance improves as the lung aerates, the delivered V_T will vary if a static/constant PIP is used.[99] Therefore, healthcare professionals should adjust the PIP in a dynamic manner—adjusting and titrating the levels of PIPs as needed—when using a facemask to provide PPV to prevent excessive V_T delivery.

1.9 Tidal Volume (V_T)

Tidal volume (V_T) is physiologically defined as the amount of air that moves in or out of the lungs with each respiratory cycle and it measure around 4-6 mL/kg for neonates.[100,101] V_T is critical to ventilation because it affects the amount of oxygen being delivered to the alveoli as well as removal of CO_2. When providing mechanical ventilation, it is important to deliver an optimal amount of V_T based on the patient lung's compliance and the extent to which their lungs are already aerated to prevent volutrauma or barotrauma. Volutrauma occurs when large V_T are delivered, causing the alveoli to overdistend as well as repetitive opening of collapsed alveoli. These events consequently trigger an inflammatory cascade that causes lung permeability, pulmonary edema, and alteration of surfactant.[100] Barotrauma on the other hand occurs when the alveoli rupture (due to excessive V_T) and air is subsequently released into the mediastinum or pleural cavity.[100]

The volume difference between FRC and total lung capacity (TLC) is small in very preterm infants.[102] Vilstrup *et al*[102] reported that term infants have a total lung capacity of 43–52 mL/kg.

In contrast, by 10 hours of age, preterm infants with respiratory distress symptom had a FRC of approximately 11 mL/kg and a TLC of only 19 mL/kg (almost two times less than a term infant).[103] Lung compliance and the corresponding PIP needed to deliver an appropriate V_T vary greatly in the first minutes after birth. Therefore, relying on a fixed PIP and subjective assessment (i.e., observing the infant's chest rise) may result in harm by either under- or over-ventilation. It is, therefore, necessary to measure and adjust the V_T delivered during PPV at birth.

DR studies reported that the delivered V_T during PPV ranges from 0–31 mL/kg.[26,63] This is extremely concerning for the neonate as high V_T delivery is associated with lung injury.[104,105] Björklund *et al*[106] reported that just 6 manual inflations with a V_T of 30 mL/kg decreased the effectiveness of subsequent surfactant treatment and induced lung injury within two minutes of starting ventilation. However, if V_T was controlled to avoid lung over-distention, little or no injury occurred.[106] Animal studies have also demonstrated that performing PPV with a V_T >8 mL/kg resulted in lung injury.[107,108] The infliction of lung injury soon after birth contributes to the development of chronic lung changes, resulting in bronchopulmonary dysplasia, which has significant implications on long term lung function, mortality, and neurodevelopment. As a result, a V_T of <8 mL/kg is recommended when providing PPV to preterm infants and should be targeted accordingly.

However, it is important to note that a low V_T can prevent the infant's lung from being adequately aerated and oxygenated, as well as increase their work of breathing. Patel *et al*[109,110] reported that a V_T of 4 mL/kg was associated with a significantly higher work of breathing compared to a V_T of 5 mL/kg ($p=0.003$) and a V_T of 6 mL/kg ($p<0.001$) for pre-term infants being weaned from mechanical ventilation as well as those suffering from acute respiratory distress. This excessive WOB may predispose the infants to fatigue,[111] prolong their duration of weaning, and

increase their risks of failing extubation.[112] Based on the 2021 European Resuscitation guidelines, an expired V_T of 5–8 mL/kg should be the target of ventilation in newborn infants.[7]

1.10 Positive-End Expiratory Pressure (PEEP)

Positive end expiratory pressure (PEEP) is defined as the positive pressure that remains in the airways at the end of the respiratory cycle (end of expiration).[113] Studies reported that PEEP improves oxygenation, prevents collapse of alveoli, promotes recruitment of collapsed alveoli, decreases the work of breathing, and conserves surfactant.[114–116] Guinsburg *et al*[25] reported that the survival rate to hospital discharge without major morbidities was 47% in infants receiving PPV with a T-Piece + PEEP compared to 35% in infants receiving ventilation via a SIB without a PEEP-valve. Although a T-Piece provides the most consistent PEEP, if healthcare providers increase or decrease the set gas flow, the PEEP will inadvertently increase or decrease, which might be harmful for the neonate.[36]

Currently, the optimal PEEP level for promoting lung recruitment in preterm neonates is unknown. There is an ongoing clinical trial (POLAR trial) that examines the incidence of bronchopulmonary dysplasia or death among infants born <28 weeks' gestation comparing the effects of static PEEP (5-6 cmH_2O) versus dynamic PEEP (titrating PEEP levels between 8-12 cmH_2O).[117] However, in the most recent CoSTR, a PEEP level of 5 cmH_2O is recommended when providing PPV as most studies comparing PEEP to no PEEP for preterm infants used this value.[5]

1.11 Respiratory Function Monitor

A flow sensor placed between an interface and a ventilation device can be used to assess mask leak, airway obstruction, and V_T delivery during PPV. An RFM such as the Florian and Monivent systems, measures and displays airway pressures, gas flow, mask leak, and V_T.

Simulation studies have shown reduced mask leak when an RFM was available (23% versus 35% for RFM non-visible group)[69] as well as improvements in volume targeting (i.e., maintaining the target V_T and inflation time) at different compliance levels (0.2–0.34 mL/cmH_2O)[118]. Additionally, single center trials comparing a visible RFM versus masked RFM reported less mask leak and adequate V_T delivery in the pre-specified target range of 4-8 mL/kg when the RFM was visible.[71,72] Most resuscitators support the use of RFM and consider it helpful in making resuscitation more effective.[119]

However, the impact of RFM on neonatal resuscitation in the DR is still unclear. Milner *et al*[120] reported that the usefulness of an RFM during neonatal resuscitation is dependent on the operator's level of experience. For example, only 59% of the participants would alter the inflation pressure based on the V_T displayed on the RFM and when SpO_2 was <85% at 1 min, no senior trainee, but 50% of the junior trainees would increase the inspired O_2.[120] Moreover, the MONITOR trial randomized 288 preterm infants to either a RFM visible or masked during PPV and reported no difference in mask leak (visible 24.9% vs. masked 20.7%) or V_T delivery between 4–8 mL/kg (visible 30% vs. masked 30%).[70] A recent meta-analysis of three trials enrolling 443 infants reported that the pooled analysis showed no difference in rates of death before discharge with a RFM versus no RFM [RR (95%CI): 0.98 (0.64–1.48)].[121] However, the pooled analysis suggested a significant reduction in brain injury (a combination of intraventricular hemorrhage and periventricular leukomalacia) [RR (95%CI): 0.65 (0.48–0.89), p=0.006)] and intraventricular hemorrhage [RR (95%CI): 0.69 (0.50–0.96), p=0.03)] in infants receiving PPV with a RFM in contrast to no RFM. While the reduction in brain injury is encouraging, none of the individual trials were powered for this outcome, warranting the need for additional studies.

1.12 What is volume-targeted ventilation?

Historically, traditional ventilators were time cycled and pressure limited where several respiratory parameters, i.e., flow rate, inflation time, inspired oxygen concentration, PIP, and ventilator rate, were set by healthcare providers and delivered through an endotracheal tube.[122] The PIP was arbitrarily chosen (based on protocol or experience) to push an unknown V_T into the infant's lungs. The PIP was then adjusted based on the infant's chest wall movements, breathing efforts, and measured arterial blood gasses.[123] With these monitoring techniques, there is a high level of subjectivity, which could result in over- or underventilation. More importantly, the ventilators at the time were unable to measure V_T and control it. In addition, the endotracheal tubes used were uncuffed, making the potential for mask leak high, which consequently, affects the delivered V_T. The ventilation rate used was also asynchronous with the spontaneous breaths made by the infant between inflations. This was associated with a higher risk for pneumothorax.[124] As a result, muscle relaxants, such as pancuronium, were administered to stop the babies from breathing spontaneously. However, this led to a higher PIP being used, causing the infant to become edematous and unresponsive, making it difficult to determine when they can be weaned from mechanical ventilation.[123] In a 2005 Cochrane review conducted by Cools *et al*[125] which comprised of six trials (486 preterm infants), the authors did not recommend the routine use of pancuronium or any other neuromuscular blocking agent in ventilated newborn infants due to limited knowledge on their long-term pulmonary and neurologic effects. However, in a recent systematic review and meta-analysis comprising of 253 neonates conducted by Gupta *et al,*[126] the use of succinylcholine (another muscle relaxant) is justified in certain clinical scenarios such as managing difficult airways and controlled endotracheal intubation in the NICU. The authors reported that neonates who received succinylcholine required less intubation

attempts than those who did not [OR (95% CI): 0.24(0.13–0.44), p<0.00001]; with no significant differences between groups in the incidences of bradycardia and hypertension.

In contrast, modern mechanical ventilators have microprocessor technology and sensitive flow sensors at the outer end of the endotracheal tube, to help them detect the onset of a baby's breath and accurately measure inspiratory and expiratory V_T.[123,127] This then allows the ventilators to adjust the valves/turbines in real time to deliver the desired ventilation output.[123,127] This mode of ventilation is called VTV or also known as "volume-guaranteed ventilation." Its purpose is to prevent a high V_T from being delivered to the infant to minimize the risks of ventilator-induced lung injury.

VTV is different from volume-controlled ventilation. For the latter, a constant inspiratory flow is used to deliver the set inspired V_{Ti}, which is calculated by integrating the flow data measured from the proximal flow sensor.[123] This mode of ventilation works best when the endotracheal tubes are cuffed (to prevent leak). However, babies were commonly intubated with uncuffed tubes because cuffed tubes can increase the work breathing (their smaller internal diameter can increase airway resistance) and damage the trachea.[128,129] These uncuffed tubes are associated with variable leaks, and as a result, the baby's actual V_T might be considerably less than the delivered V_{Ti}.[123]

VTV on the other hand is pressure controlled for each inflation. Gas flow ends when the PIP needed to reach the set expired V_T (V_{Te}) is reached. The ventilator's microprocessor determines the infant's V_{Te} (measured from the peripheral flow sensor) and compares it to the set target V_{Te}. If the infant's measured V_{Te} is lower than the target V_{Te}, the PIP of the subsequent inflation is increased and vice versa.[123] The ventilator also has algorithms to decrease or increase

the PIP if the infant is also breathing spontaneously, to prevent excess delivery of V_T.[123] For example, during a triggered inflation (where the infant's inspiratory efforts are contributing to the V_{Ti} for that inflation), the PIP will be reduced compared to untriggered inflation (where the infant is apneic and is not contributing to the V_{Ti} for that inflation), the PIP will be increased. It is important to note that there is significant breath-to-breath variability for V_{Te} and PIP because the baby can breathe more or less from one inflation to the next.[123] However, VTV algorithms prevent the PIP from changing more than a few cmH_2O across each inflation and the average difference between the set and actual V_{Te} recorded for several neonatal ventilator models was < 1 mL/kg.[130–133] For example, using the Dräger Babylog 8000 (one of the most commonly used neonatal ventilators), McCallion *et al*[134] reported that the PIP was 4 cmH_2O lower during triggered inflation versus untriggered inflations, with no differences between the expired tidal volumes (103% versus 101% of the set V_{Te}, respectively).

Moreover, with VTV, the operator has no control over each PIP used except for setting a maximum PIP (P_{max}), which cannot be exceeded, even if the target V_{Te} cannot be reached with a lower PIP.[123] VTV also targets V_{Te} instead of V_{Ti}. This is because some of the V_{Ti} can be lost if there is leak around the interface providing PPV. Several reviews have recommended the use of 4-6 mL/kg as the target V_{Te} for most babies;[135,136] however, the latest European resuscitation guidelines suggest to use a V_{Te} of 5-8 mL/kg. Evidently, the optimal range of V_{Te} to use for neonates remains undefined due to the limited number of randomized-controlled trials as well as the fact that infants with certain clinical conditions may require a larger delivered V_T (i.e., bronchopulmonary dysplasia or meconium aspiration syndrome).[137,138]

1.13 Why volume-targeted ventilation?

Initially, ventilator induced lung injury (VILI) was thought to be cause by high pressure (barotrauma). However, animal and clinical studies have demonstrated that it is the large V_T that contributes to VILI in infants. Using rats, Dreyfuss *et al*[104] reported that exposure to high V_T and high PIP caused pulmonary edema and structural abnormalities whereas exposure to normal V_T and high PIP caused no pathologic lung changes for the animals. This suggests that exposure to high V_T is the cause for the ventilator-induced pulmonary edema and not high PIP, *per se*. In another study conducted by Hernandez *et al*,[95] the authors ventilated two groups of young rabbits with a PIP of 15, 30, and 45 cmH_2O, with one group having their chest wall movement restricted via a full body plaster case and the other with free chest wall movements. The capillary filtration coefficient was used to evaluate microvascular permeability (a marker of lung damage). As PIP increased from 15 cmH_2O to 30 cmH_2O and 45 cmH_2O, the capillary filtration coefficient increased to 31% and 430%, respectively, for the animals with free chest wall movement.[95] Conversely, the group with restricted inspiratory volume had no significant increases in their capillary filtration coefficient at any of the PIP values used.[95] These data suggest that distension of the lung instead of high PIP is responsible for the microvascular damage in the immature rabbit lung. Adkins *et al*[139] also reported that younger rabbits had higher capillary filtration coefficient (91% at a PIP of 15 cmH_2O and 440% at a PIP of 45-55 cmH_2O) compared to adult rabbits. Pressure-volume loops indicated that young rabbits had more compliant lungs (which allows greater distension of the lungs) than adult rabbits, which made them more susceptible to the development of ventilator induced microvascular permeability. In another study, Björklund *et al*[106] reported that just 6 manual inflations with a high V_T of 30 mL/kg decreased the

effectiveness of subsequent surfactant treatment and resulted in increased inflammatory lung injury markers. However, when V_T was controlled for, little to no injury occurred.

Numerous studies and reviews of VTV compared with pressure limited ventilation (PLV) using human participants have been published. In a systematic review and meta-analysis conducted by Peng *et al*[140], the authors reported that VTV resulted in a reduction in the incidence of bronchopulmonary dysplasia [RR (95% CI): 0.61 (0.46–0.82)]; grade 3 or 4 intraventricular hemorrhage [RR (95% CI): 0.55 (0.39–0.79)], periventricular leukomalacia [RR (95% CI): 0.33 (0.15–0.72) and pneumothorax [RR (95% CI): 0.52 (0.29–0.93)]. However, there was no evidence that infants ventilated with VTV modes had reduced deaths compared to infants ventilated with PLV modes [RR (95% CI): 0.73 (0.51–1.05)]. Wheeler *et al*[141] on the other hand reported that using VTV resulted in a reduction in the combined outcome of death or bronchopulmonary dysplasia [RR (95% CI): 0.73 (0.57–0.93)]. An explanation for this discrepancy could be that Wheeler *et al*[141] only included nine trials in their meta-analysis whereas Peng *et al*[140] included 18 trials; and the outcome death and bronchopulmonary dysplasia was combined for Wheeler *et al* [141]but separated for Peng *et al*[140]. However, in a Cochrane review conducted by Klingenberg *et al*[142], the authors found no difference in the primary outcome death before hospital discharge between VTV modes versus PLV modes [RR (95% CI): 0.75 (0.53–1.07)] but reductions in other secondary outcomes such as rates of pneumothorax, grade 3 or 4 intraventricular hemorrhage, and mean days of mechanical ventilation. These results suggest that VTV may not lead to a reduction in death rates for infants requiring PPV but can lead to an improvement in other clinical outcomes, that can ultimately lower their risks for mortality and morbidity.

1.14 Current ventilators that provide VTV

Currently, there are several ventilators that can provide the VTV mode: 1) Dräger Babylog 8000 and VN500 (Dräger, Lübeck, Germany), 2) SLE 5000 infant ventilator (SLE systems, UK), 3) Stephanie pediatric ventilator (F. Stephan Biomedical, Germany), 4) V.I.P Bird gold (Viasys Healthcare, USA), 5) and Fabian^{TM} ventilators (Vyaire, Mettawa, IL, United States). Several bench and clinical studies have reported positive clinical outcomes with these ventilators, but most of the available literature is on the Dräger ventilators.

In a randomized-controlled trial conducted by Lista *et al*[143], the authors reported that using the VTV mode on Dräger Babylog 8000 significantly reduced inflammatory markers (interleukin-6 and interleukin-8) that are associated with respiratory distress syndrome in preterm infants ($p<0.05$). Keszler *et al*[144] also reported that when using VTV mode on the Dräger Babylog 8000, the target partial pressure of carbon dioxide ($PaCO_2$) levels was 20% below the target compared to 36.3% for assist/control ventilation only (where the PIP is manually adjusted by the operator as clinically indicated). 15.1% of the breaths were also above the target V_T for VTV compared to assist/control ventilation only (25.4%). This suggests that using the VTV mode on the Dräger Babylog 8000 reduced hypocarbia and large V_T delivery.

Khashaba *et al*[145] also reported that using VTV allowed preterm infants to wean from mechanical ventilation faster than infants receiving no VTV ($p=0.02$), as well as decreased the number of days of hospitalization ($p=0.01$) and rates of extubation failure ($p=0.04$). The Dräger line of ventilators has also been shown to be more reliable with its V_T delivery compared to other ventilators. For example, Hawks *et al*[146] reported that when the Hamilton T1 transport ventilator (Hamilton T1, Reno, NV) and Dräger VN500 were set to deliver a V_T of 6 mL/kg, the former delivered excessive V_T (~16 mL/kg) for 8-10 breaths whereas Dräger VN500 maintained the set

V_T. The Hamilton also reported lower V_T (~2 mL) than what was delivered to the lung model whereas the Dräger was within 1 mL. However, the authors noted that the Dräger had greater accuracy than the Hamilton when used for extremely low birthweight testing ($p<0.05$) but lower accuracy when used for term newborn testing ($p<0.05$).

There are also several limitations to existing VTV ventilators. Abbasi *et al*[147] reported that the respiratory values displayed on neonatal VTV ventilators can be inaccurate, often underestimating or overestimating the actual expired V_T and lung compliance. Using test lung models, the authors reported 4 out of the 5 ventilators they studied underreported the expired V_T by ~1–12% across all lung conditions (normal-to-low compliance).[147] Similarly, using surfactant-deficient juvenile rabbits, DiBlasi *et al*[148] reported that the measured V_T accuracy was 2.6–14% within the pre-set value for several VTV ventilators [Dräeger Babylog VN500, Avea (CareFusion, Yorba Linda, California) and Servo-I (Maquet, Solna, Sweden)]. Additionally, using a test lung model, Jaecklin *et al*[149] reported that the Dräger Babylog 8000, SLE 5000 and V.I.P Gold could overshoot the V_T by 115–188% following rapid increase in compliance. In comparative study conducted by Sharma *et al*[150], the Dräger Babylog 8000 delivered the highest mean airway pressure and PIP at all set V_T (5 mL/kg and 10 mL/kg) and inflation time (0.35 and 0.50 seconds) compared to the SLE 5000, Stephanie pediatric ventilator, and V.I.P. Bird gold. However, there were no significant differences in delivered V_{Ti} for all four devices tested. Interestingly, the V.I.P Bird Ventilator delivered only half of the set V_T, i.e., if 20 mL was the set V_T, only 10 mL was delivered. According to the manufacturer, when VTV is used, only half of the set V_T will be delivered due to the "loss of volume from compression of gases within the ventilator circuit." These results suggest that depending on the ventilator design, VTV modes

vary in terms of how they measure and control V_T delivery, and further standardization of measurement and computation methods are needed.

1.15 Next Step™ Resuscitator

The Next Step™ resuscitator (KM Medical, Auckland, New Zealand) is a novel prototype that provides VTV. It is portable and does not require a compressed gas source to function and has the capacity to deliver supplementary oxygen if connected to a gas tank or oxygen outlet. In a manikin study conducted by Solevag *et al,*[151] the authors reported that as compliance increased from 0.5 mL/cmH_2O to 2.0 mL/cmH_2O, V_T increased 3-4 folds for the SIB, Neo-Tee disposable T-Piece resuscitator, Neopuff infant T-Piece resuscitator, and Giraffe stand-alone infant resuscitation system T-Piece, except for the Next Step™, which was able to maintain a consistent V_T (near the target of 5 mL/kg). There were no significant differences in ventilation rate for all devices tested. In another study conducted by Solevag *et al,*[152] the Next Step™ delivered the most consistent V_T at all compliance levels tested (0.5, 1.0 and 2.0 mL/cmH_2O), and was rated as the most preferred device as well as easiest to be used amongst 25 registered Neonatal Resuscitation Program (NRP) healthcare professionals. These results suggest that the Next Step™ is a promising new device for neonatal resuscitation because it can deliver a consistent V_T (which reduces the risks of volutrauma) but it also reduces the stress of NRP providers when working in the DR. However, there are currently limited studies on the Next Step™, with previous studies using exclusively manikin models[151,152] and done on the bench side.[153–156]

1.16 PPV in low-and-middle income countries (LMICs)

Approximately 14.8 million pre-term deliveries are made annually, with more than 81% of pre-term births occurring in Asia and sub-Saharan Africa.[157] However, this has not been matched with positive survival outcomes. In some LMICs, the mortality rates of neonates admitted to the neonatal units range from 4.4 to 22.5%[158] and it is estimated that 3.6 million neonatal deaths occur worldwide each year, with 99% of these occurring in LMICs.[159,160] Reasons for this include inadequate tools and trained staff for providing essential newborn care, i.e., temperature maintenance and neonatal resuscitation.

For the majority of LMICs, the SIB is the most commonly used ventilation device because it does not require a compressed gas source, it is inexpensive, and does not require electricity to function. However, a SIB provides variable PIP even with an attached PEEP valve,[18] which can consequently affect the delivered V_T, leading to under- or overventilation for the infant. Consequently, this can increase the infant's risks of developing bronchopulmonary dysplasia and intraventricular hemorrhage.

Mechanical ventilators on the other hand, such as the Dräger VN500, Leoni Plus, and Fabian^{TM} HFO can provide a set V_T and PIP via volume-targeted ventilation (VTV), reducing the risks of volutrauma and associated comorbidities. However, these ventilators are expensive, require electricity to function and most hospitals in LMICs lack the infrastructure to house and maintain these devices. In LMICs, especially in remote regions, where access to electricity can be difficult and unreliable, access to an affordable neonatal resuscitator that uses limited energy is critical.

1.17 Thesis Overview

The purpose of this thesis is to examine the internal properties of the Next Step™ resuscitator as well as its capacity to provide PPV in contrast to other interfaces used in the DR and NICU. The studies presented in this thesis consist of one randomized animal study and two observational studies.

The first study examines whether the Next Step™ resuscitator can deliver a set V_T with changing airway compliance in a neonatal piglet model against several commonly used neonatal resuscitation devices (SIB, T-Piece and Fabian™ HFO). Studies using a lung simulator and manikins reported that healthcare providers are unable to adjust to compliance changes by just observing chest rise regardless of using a self-inflating bag (SIB) or a T-Piece; warranting the need of a more objective assessment.[40,161] The second study compares the amount of time it takes for the Next Step™, Dräger VN500, Leoni Plus, and other T-Piece devices to reach a desired FiO_2 target, as excessive delivery of FiO_2 during PPV can harm the infant. The third study compares how much power the Next Step™ uses versus the Dräger VN500, Leoni Plus, and Fabian™ HFO ventilators during PPV and continuous positive airway pressure (CPAP). Several hypotheses were formed for this project, including:

- The Next Step™ resuscitator will deliver the most consistent V_T compared to all other ventilation devices with a changing lung compliance level.
- The Next Step™ resuscitator will take the same amount of time as other ventilation devices commonly used in the DR to deliver a target FiO_2.
- The Next Step™ will use less power than the other three ventilators (Dräger VN500, Leoni Plus, and Fabian™ HFO) because of its compact size.

This thesis consists of four chapters. Chapter one provides background information about the research project, including an overview of PPV and associated devices/techniques. Chapter two describes the methodological approach and framework used to address the core research questions which constitute this thesis work. Chapter three explains results of the three individual studies: i) the Next Step™'s capacity to deliver a consistent V_T with changing compliance levels against three other ventilation devices, ii) the time it takes for the Next Step™ to titrate the concentration of FiO_2 against several ventilation devices, and iii) how much power the Next Step™ uses in contrast to three other neonatal ventilators. Chapter four is a discussion of the results and presents the conclusions and future directions for this research project.

Chapter 2: Methods

2.1 Methods for Study #1 comparing PPV devices during compliance changes in a neonatal ovine model

2.1.1 Ethic Approval and Animals

Ten neonatal mixed breed piglets were obtained on the day of experimentation from the University Swine Research Technology Centre in Edmonton, Alberta, Canada. There were no exclusion criteria. Experiments were conducted after the approval of the Animal Care and Use Committee, University of Alberta (AUP00004124) and reported according to the ARRIVE guidelines.[162] A graphical display of the study protocol is presented in Figure 2.1.1.

2.1.2 Randomization

Randomization was done using a computer-generated randomization program (http://www.randomizer.org). A numbered, sealed brown envelope was opened just before the commencement of PPV containing the group allocation.

2.1.3 Sample size and power estimates

We hypothesized that the Next Step™ will deliver the most consistent V_T at 5mL/kg. In previous simulation studies comparing SIB, T-Piece, and the Next Step™, the targeted V_T of 5mL/kg (±10%) with the SIB was 20%, 22% with the T-Piece and 65% with the Next Step™.[151,152] We hypothesized that the Next Step™ will improve targeted V_T delivery at 5mL/kg (±10%). A sample size of 10 per group would be sufficient to detect the improved targeted V_T delivery at 5mL/kg (±10%) from 20% to 65% with 90% power and a 2-tailed alpha error of 0.05.

2.1.4 Blinding

It was not possible to blind the team to the allocated intervention due to the nature of the intervention. However, the statistical analysis was blinded to group allocation.

2.1.5 Animal preparation

Piglets were instrumented as previously described with modifications.[163–165] Following the induction of anesthesia using isoflurane, piglets were intubated via tracheostomy. Pressure-controlled ventilation (Sechrist Infant Ventilator Model IV-100; Sechrist Industries, Anaheim, California) was commenced at a respiratory rate of 16–20 breaths/min and a pressure of 20/5 cmH_2O. Oxygen saturation was kept within 90–100%, glucose level and hydration were maintained with an intravenous infusion of 5% dextrose at 10 mL/kg/hr. During the experiment anesthesia was maintained with intravenous propofol 5–10 mg/kg/hr and morphine 0.1 mg/kg/hr. Additional doses of propofol (1–2 mg/kg) and morphine (0.05–0.1 mg/kg) were also given as needed. The piglet's body temperature was maintained at 38.5–39.5°C using an overhead warmer and a heating pad.

2.1.6 Hemodynamic parameters

A 5-French Argyle® (Klein-Baker Medical Inc. San Antonio, TX) double-lumen catheter was inserted via the right femoral vein for administration of fluids and medications. A 5-French Argyle® single-lumen catheter was inserted above the right renal artery via the femoral artery for continuous arterial blood pressure monitoring in addition to arterial blood gas measurements.

Piglets were placed in a supine position and allowed to recover from surgical instrumentation until baseline hemodynamic measures were stable (minimum of one hour). Ventilator rate was adjusted to keep the partial pressure of arterial CO_2 between 35–45 mmHg as determined by periodic arterial blood gas analysis. Blood gases were collected every 15 minutes during stabilization. Mean systemic arterial pressure, systemic systolic arterial pressure, heart rate, and percutaneous oxygen saturation were continuously measured and recorded throughout the experiment with a Hewlett Packard 78833B monitor (Hewlett Packard Co., Palo Alto, CA).

2.1.7 Ventilation Devices

We used a self-inflating bag (SIB) (Preterm model, Laerdal Silicone Resuscitator, Laerdal Medical, Stavanger, Norway) with no PEEP valve or manometer attached and PPV was provided at a rate of 50/min and inspiration time of 0.3 sec. A Neopuff infant T-piece (Fisher & Paykel, Auckland, New Zealand) with default setting of a PIP of 24 cmH_2O, PEEP of 5 cmH_2O, rate of 50 breaths/min. The Fabian™ HFO ventilator (Acutronic Medical System AG, Hirzel, Switzerland) with default settings of maximum pressure (P_{max}) of 40 cmH_2O, PEEP of 5 cmH_2O, rate of 50 breaths/min, set V_T of 5 mL/kg and inspiration time of 0.3 sec. The Next Step™ Neonatal Resuscitator (KM Medical, Auckland, New Zealand) with default settings of maximum pressure (P_{max}) of 40 cmH_2O, PEEP of 5 cmH_2O, rate of 50 breaths/min, set V_T of 5 mL/kg and inspiration: expiration ratio of 1:3. The Next Step™ delivers V_T with an accuracy of 0.1–0.3 mL (according to the manufacturer), it also controls ventilation rate and monitors airway pressure. None of the devices were connected to heated/humidified gas.

2.1.8 Respiratory parameters

An RFM (NM3, Respironics, Philips, Andover, MA) was placed between the SIB or T-Piece to measure respiratory rate, V_T, airway pressures, and gas flow.[166] The NM3 flow sensor has a fixed orifice pneumotach, which uses the pressure difference to calculate the gas flow passing through the sensor, which is then translated into the inspiratory and expiratory V_T.[166] The Next Step™ and the Fabian™ HFO use a hot-wire anemometer flow sensor, which measures direction and speed of gas flow by measuring heat loss of an electrically heated wire, which is then translated into inspiratory and expiratory V_T.[73]

2.1.9 Experimental protocol

As piglets have already undergone fetal-to-neonatal transition, compliance changes were simulated by placing a strap around the piglet's chest, which covered up to ½ of the piglet's chest. The strap was tightened to achieve the desired airway compliance. We aimed to study two compliance levels: ~0.5 mL/cmH_2O and ~1.5 mL/cmH_2O. The NM3 was used to measure the piglet's airway compliance for all testing conditions, except for the Fabian^{TM} HFO which was able to measure its own airway compliance.

The sequence of the devices used for PPV was randomized: SIB, SIB+RFM, T-Piece, T-Piece+RFM, Next Step^{TM}, Fabian^{TM} HFO and PPV was performed for 1 minute with each of the six devices. Each intervention was repeated once, to increase the number of recordings. All six interventions were completed with the ~0.5 mL/cmH_2O compliance followed by ~1.5 mL/cmH_2O compliance in all piglets, this was not randomized. After each PPV period, a washout period of 1 min in between each testing device was used to readjust the strap and measure the compliance.

During ventilation with the SIB and T-Piece without the RFM, V_T delivery was judged by assessing chest rise. Once the RFM was added for the SIB and T-Piece, the RFM was used to assess V_T delivery.

During PPV with the SIB+RFM, the operator could adjust the squeeze of the SIB and during PPV with the T-Piece+RFM, the PIP could be adjusted to deliver the target V_T of 5 mL/kg. At the end of experimentation, piglets were euthanized with an intravenous dose of Euthanyl (240 mg/mL).

2.1.10 Data collection and statistical analysis

For the SIB and T-Piece interventions, airway pressures, gas flow, and V_T were measured and analyzed using Flow Tool Physiologic Waveform Viewer (Philips Healthcare, Wallingford, CT). The Next Step™ and Fabian™ HFO screens were captured by a video camera, during the experiment (Iphone 14 Pro Max, California, United States). KHT reviewed the video recordings frame by frame and stopped the recording every 2 seconds to record PIP, PEEP, rate, and V_T.

The data was tested for normality (Shapiro-Wilk and Kolmogorov-Smirnov test) and compared using ANOVA for repeated measures using Bonferroni post-test. Fisher's exact test was used for categorical variables. The data are presented as mean (standard deviation-SD) for normally distributed variables and median (interquartile range-IQR) for skewed variables. P-values are 2-sided and $p<0.05$ was considered statistically significant. Statistical analyses were performed with Stata version 18 (StataCorp LLC, Texas, USA).

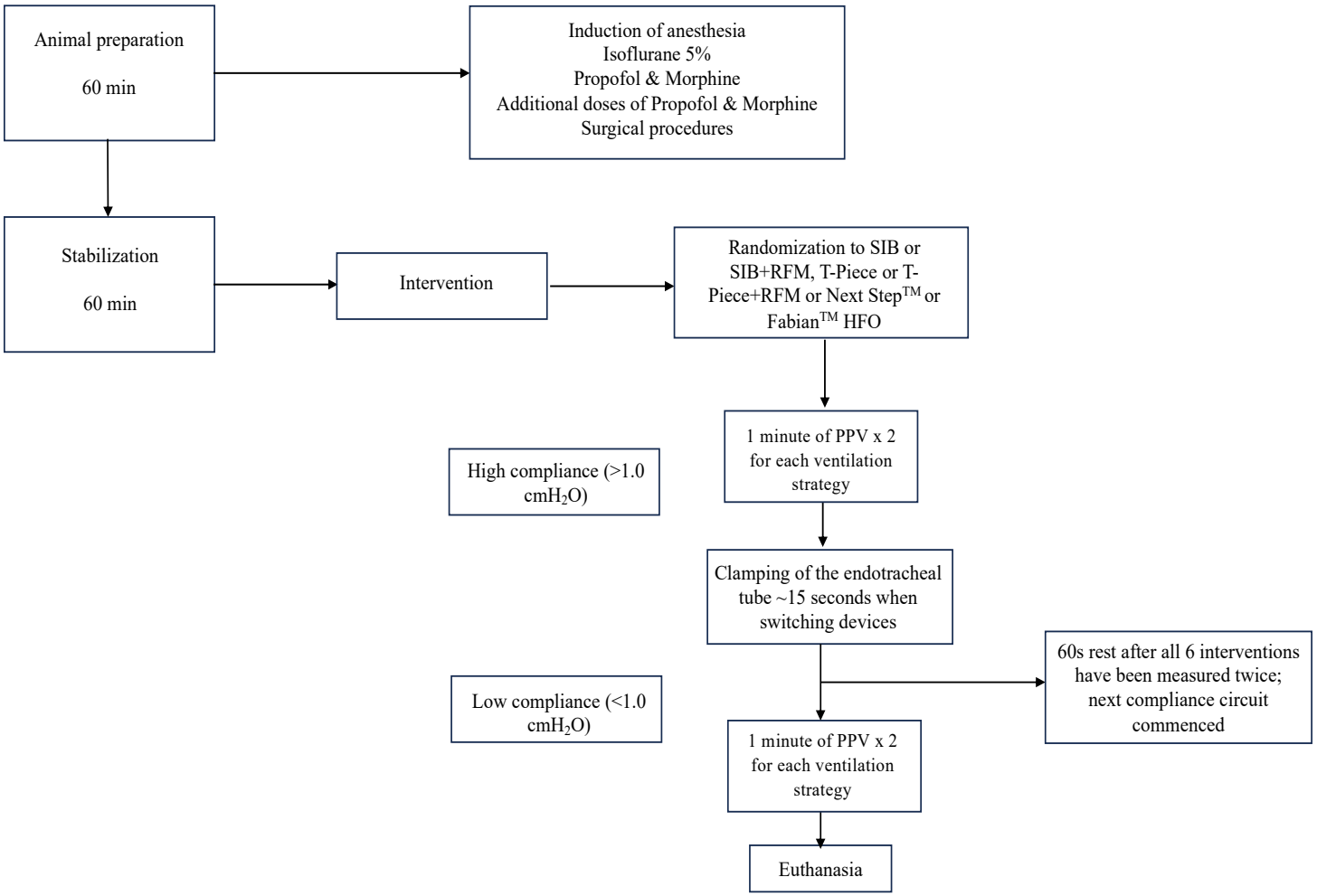

Figure 2.1.1 Study flow chart

Figure 2.1.2 Self-inflating bag with RFM condition. A cloth was placed around the piglet's chest to increase or decrease its airway compliance. A Respiratory function monitor was used to monitor the piglet's respiratory parameters.

Figure 2.1.3 T-Piece with RFM condition. A cloth was placed around the piglet's chest to increase or decrease its airway compliance. A Respiratory function monitor was used to monitor the piglet's respiratory parameters. The endotracheal tube was clamped for ~15 seconds when we switched ventilation devices to prevent the piglet's lung from depreciating.

Figure 2.1.4 Fabian™ HFO ventilator monitor displaying several respiratory parameters. An inflation time of 0.30 seconds, FiO_2 of 21%, V_T of 5 mL/kg, P_{max} of 40 cmH_2O and PEEP of 5 cmH_2O were used.

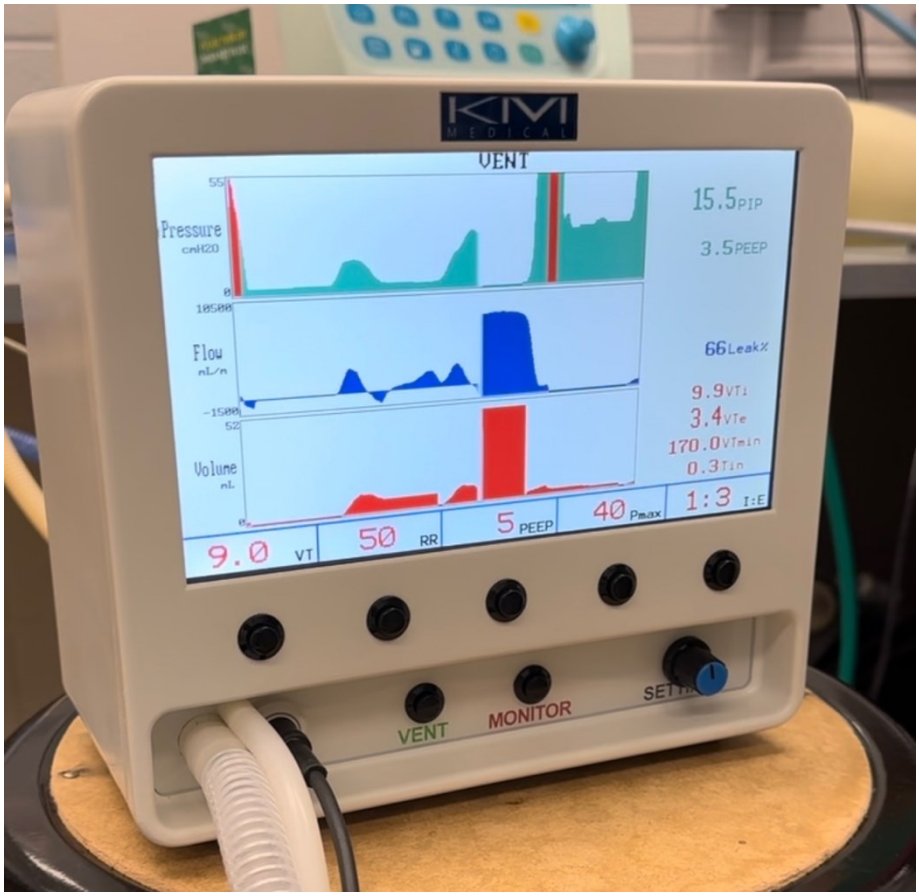

Figure 2.1.5 Next Step™ resuscitator displaying several respiratory parameters. A V_T of 5 mL/kg, PEEP of 5 cmH_2O, respiratory rate of 50 breaths per minute, P_{max} of 40 cmH_2O and inspiration: expiration ratio of 1:3 were used.

2.2 Methods for Study #2 assessing the time needed to achieve changes in oxygen concentration during PPV amongst several PPV devices

2.2.1 Ventilation Devices

A 2 mL test lung was attached to the Dräger VN500, the Next Step™ resuscitator and Leoni Plus ventilator. A T-piece device is a continuous flow, pressure limited device with a built-in manometer and a positive end expiratory pressure valve. A NeoPuff infant T-piece (Fisher & Paykel, Auckland, New Zealand) with default setting of a PIP of 30 cmH_2O and PEEP of 5 cmH_2O and rate of 50 breaths/min. Similar respiratory parameters were used for the disposable T-Piece resuscitator Neo-Tee (Mercury Medical, Clearwater, FL, USA) and the GE T-Piece (Giraffe Warmer, GE Health Care, Canada). The Next Step™ Neonatal Resuscitator (KM Medical, Auckland, New Zealand) with default settings of maximum pressure (P_{max}) of 30 cmH_2O, PEEP of 5 cmH_2O, rate of 50 breaths/min, set V_T of 4 mL/kg and 6 mL/kg and inspiration: expiration ratio of 1:3. The Dräger VN500 ventilator (Dräger, Lübeck, Germany) with default settings of maximum pressure (P_{max}) of 30 cmH_2O, PEEP of 5 cmH_2O, rate of 50 breaths/min, set V_T of 4 mL/kg and 6 mL/kg and inspiration time of 0.3 sec. The Leoni Plus ventilator (Heinen + Löwenstein GmbH, Bad Ems, Germany) with default settings of maximum pressure (P_{max}) of 30 cmH_2O, PEEP of 5 cmH_2O, rate of 50 breaths/min, set V_T of 4 mL/kg and 6 mL/kg, flow of 10 L/min and inspiration: expiration ratio of 1:3.

2.2.2 Experimental Protocol

PPV was provided according to default settings for the three ventilation devices. In all trials, a gas flow rate of 10 L/min was used. During PPV, the FiO_2 at the oxygen blender was changed from 0.21 to 1.0 to 0.21, with stepwise increase and decrease in increments of 0.1 or 0.2. The duration (in seconds) until the set oxygen concentration was achieved at the test lung

was recorded using an iPhone 14 Pro Max (Apple, California, United States). The MaxO2® OM-25ME oxygen analyzer (Maxtec, Salt Lake City, USA) was calibrated before the experiments and the ventilation devices were connected to the MaxO2® OM-25ME to measure the oxygen concentration. The oxygen analyzer has an accuracy of ±3% according to manufacturer data.

For the Dräger VN500, Leoni Plus, and Next Step™ ventilators, two V_T were used: one trial with a V_T of 4 mL/kg and one with a V_T of 6 mL/kg. The pressure-control assist-control (PC-AC) plus volume-guaranteed mode was used for the Dräger VN500 whereas the AC mode was used for the Leoni Plus. The volume-guaranteed "vent" mode was used for the Next Step™. All data were recorded onto a spreadsheet. For each ventilation device, two recordings were made for each, and all had a test lung attached and no leak.

2.2.3 Statistical Analysis

All data were analyzed using IBM SPSS software for Windows Version 26.0 (SPSS 26.0) (IBM Corp., Armonk, NY, USA), and were reported as mean ± standard deviation (SD) for parametric tests. Data were compared using paired samples t-test and ANOVA for repeated measures with a Bonferroni post-test. P values are two sided and $p<0.05$ was considered statistically significant.

2.3. Methods for Study #3 assessing the power usage amongst several PPV devices during PPV and CPAP

2.3.1 Ventilation Devices

We used the Next Step™ Neonatal Resuscitator (KM Medical, Auckland, New Zealand), Dräger VN500 (Dräger, Lübeck, Germany), Leoni Plus ventilator (Löwenstein Medical, Bad Ems, Germany), and Fabian™ HFO ventilator (Vyaire, Mettawa, IL, United States). For the Next Step™, the following default settings were used to provide PPV: maximum pressure (P_{max}) of 30 cmH_2O, PEEP of 4–10 cmH_2O (starting at 4 cmH_2O and increasing it by an increment of 2 cmH_2O, up to a maximum of 10 cmH_2O), respiratory rate of 30–60 breaths/min (starting from 30 and increasing it by an increment of 10 breaths/min, up to a maximum of 60 breaths/min), set V_T of 3–8 mL/kg (starting from 3 mL/kg and increasing it by an increment of 1 mL/kg, up to a maximum of 8 mL/kg), and inspiration: expiration ratio of 1:3.

As for the Leoni Plus, Dräger VN500 and Fabian™ HFO ventilator, similar default settings were used. Moreover, the pressure-control assist-control (PC-AC) plus volume-guaranteed mode was used for the Dräger VN500 whereas the assist-control (AC) mode was used for the Leoni Plus ventilator, as well as an inspiratory flow and expiratory flow of 10 L/min. For the Fabian™ HFO, the intermittent PPV (iPPV) mode was used whereas the volume guaranteed "vent" mode was used for the Next Step™ (see Figures 2.3.1, 2.3.2 and 2.3.3).

For the CPAP testing, the respiratory rate was set to 0.5 breaths per minute and PEEP was increased from 4 cmH_2O to 10 cmH_2O (at an increment of 1 cmH_2O per trial up to a maximum of 10 cmH_2O) for the Dräger VN500. For the Next Step™, similar settings were used. As for the Leoni Plus, the "nCPAP" mode was used with a flow of 10 L/min. PEEP was started from 4 cmH_2O

and increased up to 10 cmH_2O (at an increment of 1 cmH_2O per trial). Similarly, the nCPAP mode was used for the Fabian™ HFO. Two recordings were made for all devices.

A 50 mL test lung (Dräeger, Lübeck, Germany) was attached to the Dräger VN500, Leoni Plus, and Fabian™ HFO whereas a 50 mL test lung (KM Medical, Auckland, New Zealand) was attached to the Next Step™ resuscitator. The Next Step™, Leoni Plus, Fabian™ HFO and the Dräger VN500 all use a hot-wire anemometer flow sensor, which measures direction and speed of gas flow by measuring heat loss of an electrically heated wire, which is then translated into inspiratory and expiratory V_T.[73]

2.3.2 Experimental Protocol

A RioRand Plug Power Meter Energy Monitor (Richmond, British Columbia, Canada) was used to measure the voltage of the Next Step™, the Leoni Plus, the Fabian™ HFO, and the Dräger VN500. For the Next Step™, Leoni Plus, Fabian™ HFO, and the Dräger VN500, we started at a respiratory rate of 30 breaths per minute and PEEP of 4 cmH_2O. The V_T was then increased from 3 mL/kg to 8 mL/kg, where two recordings were made for each trial. Once the voltage used by a V_T of 8 mL/kg was recorded, we then increased the respiratory rate to 40 breaths per minute (at an increment of 10 breaths per minute) and PEEP to 6 cmH_2O (at an increment of 2 cmH_2O) and reset the V_T back to 3 mL/kg. We then repeated the same steps, i.e., increasing V_T and keeping respiratory rate and PEEP constant. Once recordings for the respiratory rate of 60 breaths per minute, V_T of 8 mL/kg and PEEP of 10 cmH_2O were made, we stopped the experiment. PPV was performed for one minute per trial and an iPhone 14 Pro Max (Apple, California, United States) was used as the timer. The data were then entered onto a spreadsheet.

2.3.3 Statistical Analysis

Statistical analysis was descriptive. The data are presented as mean (standard deviation (SD)) for normally distributed continuous variables and median (interquartile range (IQR)) when the distribution was skewed. Statistical analyses were performed with IBM SPSS software for Windows Version 26.0 (SPSS 26.0).

Figure 2.3.1 The Fabian^{TM} HFO ventilator was connected to the RioRand Plug Power Meter Energy Monitor, where voltage was recorded. The "iPPV" mode was used with P_{max} of 30 cmH_2O, inspiratory time of 0.3 s, varying levels of PEEP, respiratory rate, and V_T.

Figure 2.3.2 An example of the respiratory parameters tested on the Leoni ventilator. The RioRand Plug Power Meter Energy monitor (not pictured here) was connected to the ventilator in the back. The "AC" mode was used with a P_{max} of 30 cmH_2O, flow of 10 L/min, inspiratory time of 0.3 s, varying levels of PEEP, respiratory rate, and V_T.

Figure 2.3.3 An example of the respiratory parameters tested on the Dräger VN500. The RioRand Plug Power Meter Energy monitor (not pictured here) was connected to the ventilator in the back. The "PC-AC" mode was with a Pmax of 30 cmH_2O, an inspiratory time of 0.3, varying levels of PEEP, respiratory rate, and V_T.

Chapter 3. Results

3.1. Results for Study #1 comparing PPV devices during compliance changes in a neonatal ovine model

3.1.1 Tidal volume

Ten neonatal mixed breed piglets (1-3 days old, weight between 1.8-2.4 kg) were obtained on the day of the experiment. All respiratory parameters are summarized in Table 3.1.1 for ~0. 5 mL/cmH_2O and ~1. 5 mL/cmH_2O compliance.

The delivered V_T at ~0.5 mL/cmH_2O and ~1.5 mL/cmH_2O compliance is presented in Table 3.1.1 and Figure 3.1.1 (~0.5 cmH_2O compliance) and Figure 3.1.2 (~1.5mL/cmH_2O compliance).

The Next Step™ and the Fabian™ HFO delivered the targeted V_T of 5 mL/kg most accurately at both compliance levels (Figure 3.1.1 and 3.1.2 and Table 3.1.2). At ~0.5 mL/cmH_2O compliance, the Next Step™ and Fabian™ HFO delivered 69% and 76% of inflations within the target range, while the other approaches where less than 50% (Table 3.1.2). However, the percentage of inflations within target range increased for both SIB and T-Piece when an RFM was used (Table 3.1.2).

Similarly, at ~1.5 mL/cmH_2O compliance, the Next Step™ and Fabian™ HFO delivered 68% and 62% of inflations within the target range, while the other approaches where less than 30% (Table 3.1.2). When an RFM was available, the percentage of inflations within target range increased for T-Piece but not SIB (Table 3.1.2)

3.1.2 Peak Inflation Pressure

At ~0.5 mL/cmH_2O compliance, the PIP was significantly lower for the Next Step™ and Fabian™ HFO compared to all other devices (Table 3.1.1) with no difference between the Next

Step™ and Fabian™ HFO. At ~1.5 mL/cmH_2O compliance, there were no differences between the PIP for all devices (Table 3.1.1). During PPV with the SIB+RFM, the squeeze of the SIB was adjusted to aim for V_T of 5 mL/kg. During PPV with the T-Piece+RFM, PIP was decreased 13 times and increased 4 times at ~0.5 mL/cmH_2O compliance; and decreased 29 times and increased four times at ~1.5 mL/cmH_2O compliance.

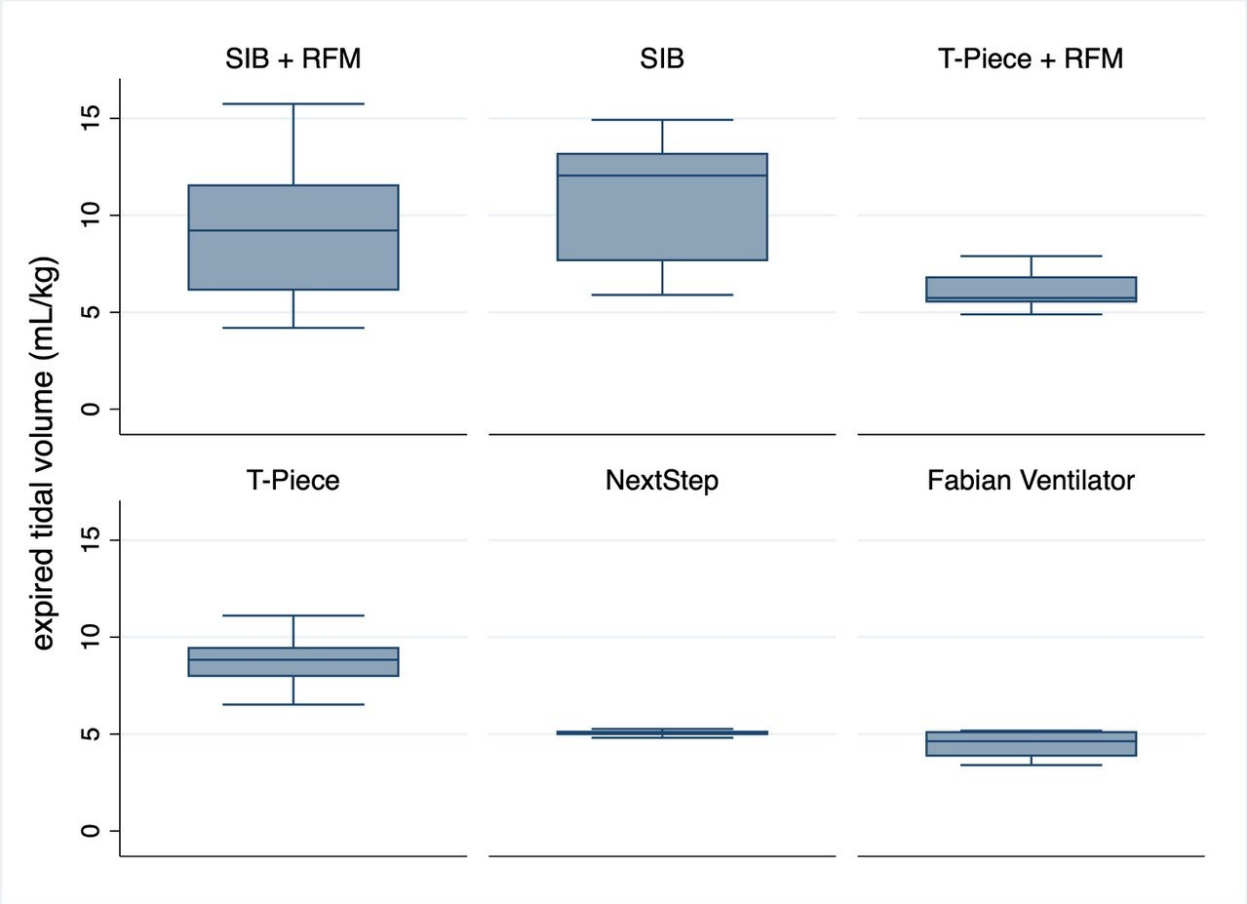

Figure 3.1.1 Comparison of expired tidal volume between SIB with RFM (SIB+RFM), SIB only, T-Piece with RFM (T-Piece+RFM), T-Piece only, Next Step™, and Fabian™ HFO ventilator at ~0.5 cmH_2O compliance.

Abbreviations: RFM=respiratory function monitor; SIB=self-inflating bag.

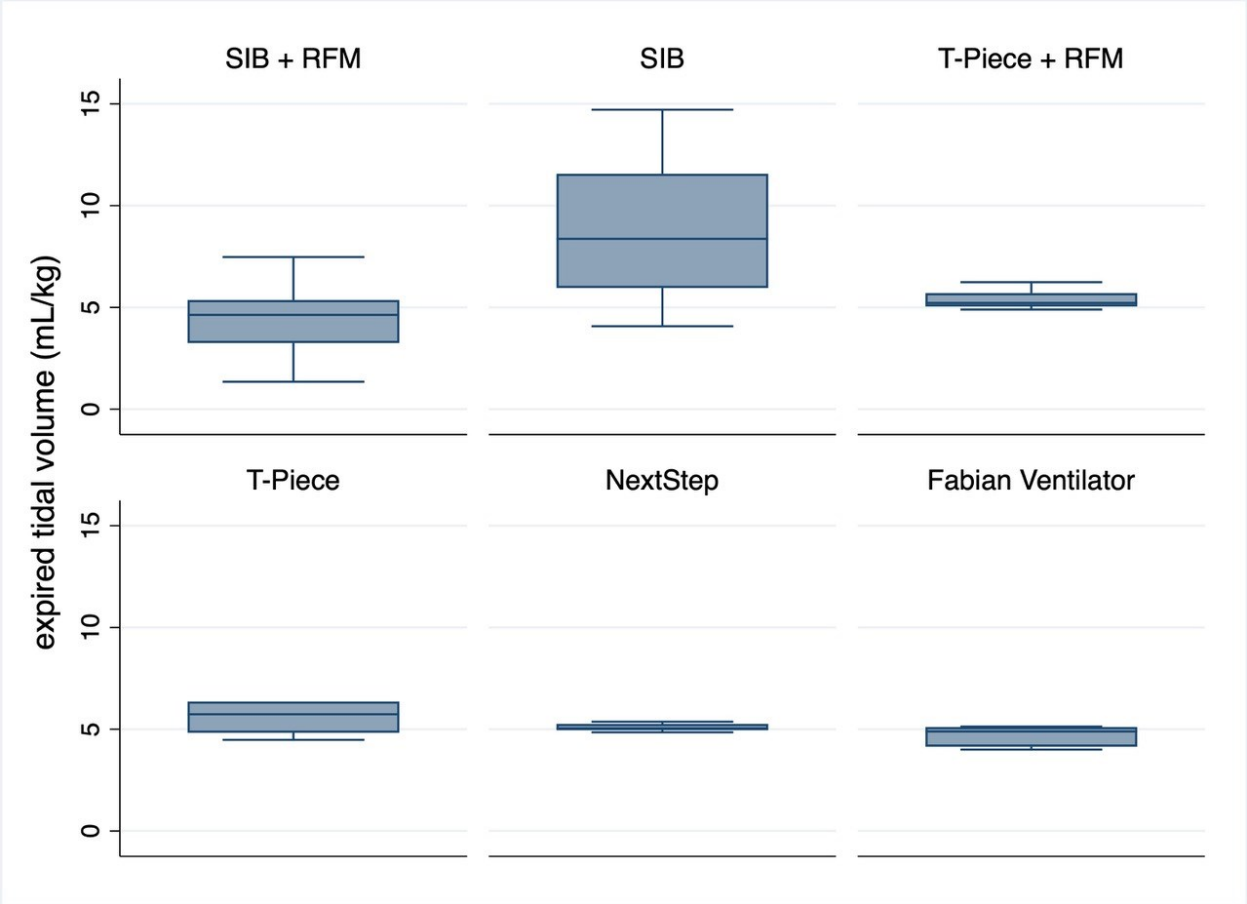

Figure 3.1.2 Comparison of expired tidal volume between SIB with RFM (SIB+RFM), SIB only, T-Piece with RFM (T-Piece+RFM), T-Piece only, Next Step™, and Fabian™ HFO ventilator at ~1.5 cmH_2O compliance.

Abbreviations: RFM=respiratory function monitor; SIB=self-inflating bag.

Table 3.1.1 Respiratory Parameters with all ventilation devices at ~0.5 cmH_2O and ~1.5 cmH_2O compliance

Intervention	SIB	SIB+RFM	T-Piece	T-Piece+RFM	Next Step™	Fabian™ HFO
~0.5 cmH_2O compliance						
Expired V_T (mL/kg)	8.9 (3.6)	4.5 (1.8)	7.4 (4.3)	6.4 (3.1)	5.1 (0.2)	4.8 (0.5)
Respiratory rate (/min)	51.3 (7.2)	51.9 (5.1)	50.3 (8.3)	49.7 (1.5)	50 (1)	50 (1)
PIP (cmH_2O)	28.3 (6.6)	24.9 (3.9)	23.7 (5.8)	23.8 (5.8)	14.0 (2.8)	13.8 (3.2)
PEEP (cmH_2O)	0 (0-0)	0 (0-2.45)	4.8 (2.4-5.2)	4.8 (0-5.3)	5 (5-5)	6.05 (5.75-6.5)
PIF (mL/min)	5.8 (1.8)	3.8 (1.6)	4.3 (1.9)	4.2 (2.0)		
PEF (mL/min)	-8.0 (2.8)	-5.0 (2.5)	-6.0 (3.0)	-6.0 (2.6)		
~1.5 cmH_2O compliance						
Expired V_T (mL/kg)	12.1 (5.3)	9.4 (3.9)	8.6 (1.5)	6.5 (1.6)	5.2 (0.6)	4.4 (0.7)
Respiratory rate (/min)	49.5 (4.2)	51.1 (1.9)	47.7 (4.2)	49.4 (2.4)	50 (1)	50 (1)
PIP (cmH_2O)	23.6 (7.6)	21.4 (4.9)	19.1 (2.2)	16.0 (3.9)	22.2 (3.9)	19.8 (4.9)
PEEP (cmH_2O)	1.3 (2.1)	0.8 (1.8)	4.2 (1.7)	4.3 (1.8)	4.9 (0.3)	5.0 (0.2)
PIF (mL/min)	7.7 (2.9)	6.2 (2.1)	4.2 (1.0)	4.4 (1.2)		

PEF (mL/min)	-8.5 (3.2)	-7.9 (2.9)	-5.6 (1.0)	-4.6 (1.9)

Data are reported as mean (standard deviation) unless indicated [#]median (interquartile range).

Abbreviations: PEEP=positive-end-expiratory pressure; PEF=peak expiratory flow; PIF=peak inspiratory flow; PIP=peak inflation pressure; RFM=respiratory function monitor; SIB=self-inflating bag; V_T=tidal volume.

Table 3.1.2 Number of inflations delivered with target V_T of 5 mL/kg and ±10% of target V_T at ~0.5 cmH_2O and ~1.5 cmH_2O compliance

Intervention	SIB	SIB+RFM	T-Piece	T-Piece+RFM	Next Step™	Fabian™ HFO
~0.5 cmH_2O compliance						
V_T 4.5 mL/kg & 5.5 mL/kg	38 (7%)	131 (20.5%)	162 (31%)	259 (49%)	527 (69%)	513 (76%)
$V_T \leq 4.4$ mL/kg	97 (17%)	274 (43%)	113 (22%)	65 (12%)	92 (12%)	154 (23%)
$V_T \geq 5.6$ mL/kg	410 (75%)	233 (36.5%)	241 (47%)	209 (39%)	148 (19%)	5 (1%)
~1.5 cmH_2O compliance						
V_T 4.5 mL/kg & 5.5 mL/kg	85 (12%)	67 (10%)	27 (5%)	171 (30%)	511 (68%)	453 (62%)
$V_T \leq 4.4$ mL/kg	101 (14%)	152 (22%)	74 (14%)	60 (10%)	73 (10%)	274 (37.5%)
$V_T \geq 5.6$ mL/kg	521 (74%)	463 (68%)	424 (81%)	346 (60%)	163 (22%)	4 (0.5%)

Data are reported as n(%)

Abbreviations: RFM=respiratory function monitor; SIB=self-inflating bag; V_T=tidal volume

3.2 Results for Study #2 assessing the time needed to achieve target FiO_2

3.2.1. Time required to achieved FiO2 changes amongst the three ventilators

At a V_T of 4 mL/kg and linear increase or decrease of 0.21 to 1.0 or 1.0 to 0.21, there were no significant differences between groups (p=0.42 and p=0.53, respectively). At a V_T of 4 mL/kg and stepwise increase of 0.21 to 1.0 in 0.1 increments, there were no significant differences between groups (p=0.21) (see Table 3.2.1). However, for a stepwise decrease of 1.0 to 0.21 in 0.1 increments, there were significant differences between groups (p=0.03), with the Next Step™ taking less time to reach the desired FiO_2 concentration compared to Dräger VN500 (p<0.001) and Leoni Plus (p<0.001) (see Table 3.2.2). At a V_T of 4 mL/kg and stepwise increase or decrease of 0.21 to 1.0 or 1.0 to 0.21 in 0.2 increments, there were no significant differences between groups (p=0.07 and p=0.92, respectively). Overall, the mean ± SD time required to achieve FiO_2 changes at 10 L/min was 32±1 s, 25±3 s and 36±2 s for the Leoni Plus, Next Step™, and Dräger VN500, respectively, at a V_T of 4 mL/kg (see Table 3.2.1).

At a V_T of 6 mL/kg and a linear increase or decrease of 0.21 to 1.0 or 1.0 to 0.21, there were no significant differences between groups (p=0.42 and p=0.38) (see Table 3.2.3). At a V_T of 6 mL/kg and stepwise increase or decrease of 0.21 to 1.0 or 1.0 to 0.21 in 0.1 increments, there were no significant differences between groups (p=0.73 and p=0.99, respectively). At a V_T of 6 mL/kg and stepwise increase of 0.21 to 1.0 in 0.2 increments, there were significant differences between groups (p=0.01). However, post-hoc analysis with a Bonferroni adjustment indicated that there was no significant difference between Leoni Plus and Next Step™ resuscitator (p=0.12). Similarly, there were no significant difference between the Leoni Plus and Dräger VN500 ventilator (p=0.07) and Next Step™ and Dräger VN500 (p=1.00) (see Table 3.2.4). At a V_T of 6 mL/kg and stepwise decrease of 0.21 to 1.0 in 0.2 increments, there were no

significant differences between groups (p=0.08). Overall, at a V_T of 6 mL/kg, the mean ± SD time required to achieve FiO_2 changes at 10 L/min for the Leoni Plus, Next Step™, and Dräger VN500 was 32±1 s, 28±3 s and 35±2 s, respectively.

As for the T-Pieces, there were no significant differences between groups with a linear increase or decrease of 0.21 to 1.0 or 1.0 to 0.21 (p=0.22 and p=0.61, respectively). From a stepwise increase of 0.21 to 1.0 in 0.1 increments, there were significant differences between groups (p=0.02) (see Table 3.2.5). However, post-hoc analysis with a Bonferroni adjustment indicated that there was no significant difference between the GE T-Piece and NeoPuff T-Piece (p=0.27). Similarly, there were no significant difference between the GE T-Piece and NeoTee T-Piece (p=1.00) and NeoPuff versus Neo-Tee (p=0.53) (see Table 3.2.6). Similarly, from a stepwise decrease of 1.0 to 0.21 in 0.1 increments, there were no significant differences between groups (p=0.71). From a stepwise increase of 0.21 to 1.0 in 0.2 increments, there was a significant difference between groups (p=0.02). However, post-hoc analysis with Bonferroni adjustment revealed no significant differences between the T-Pieces (see Table 3.2.6). Similarly, from a stepwise decrease of 1.0 to 0.21 in 0.2 increments, there were no significant differences between groups (p=0.59). Overall, the mean ± SD time required to achieve changes at 10 L/min was 15±2 s, 17±1 s and 19±1 s for the GE T-Piece, Neo-Tee T-Piece and NeoPuff T-Piece, respectively.

Table 3.2.1 Overall time to reach oxygen concentrations (s) using an oxygen flow rate of 10 L/min and V_T of 4 mL/kg

Change in fraction of inspired oxygen	Ventilation Device			Overall significance
	Leoni Plus	Next Step™	Dräger VN500	
0.21 to 1.0	29±1	33±2	42±1	0.42
1.0 to 0.21	52±1	38±1	48±2	0.53
0.21 to 1.0 in 0.1 increments	17±1	16±6	23±1	0.21
1.0 to 0.21 in 0.1 increments	37±3	17±7	35±6	0.03
0.21 to 1.0 in 0.2 increments	19±1	23±8	27±1	0.07
1.0 to 0.21 in 0.2 increments	37±1	23±8	39±4	0.92

Data presented as mean±SD

Abbreviations: s=seconds; sd=standard deviation

Table 3.2.2 Multiple comparisons between ventilation devices using an oxygen flow rate of 10L/min and V_T of 4 mL/kg

Change in fraction of inspired oxygen	Ventilation Device		
	Next Step™ vs. Leoni Plus	**Next Step™ vs. Dräger VN500**	**Leoni Plus vs. Dräger VN500**
0.21 to 1.0	-	-	-
1.0 to 0.21	-	-	-
0.21 to 1.0 in 0.1 increments	1.00	0.003	0.003
1.0 to 0.21 in 0.1 increments	<.001	<.001	1.00
0.21 to 1.0 in 0.2 increments	0.47	1.00	0.11
1.0 to 0.21 in 0.2 increments	0.01	0.003	1.00

Bonferroni correction has been applied for the p-values reported

Table 3.2.3 Overall time to reach oxygen concentration (s) using an oxygen flow rate of 10 L/min and V_T of 6 mL/kg

Change in fraction of inspired oxygen	Ventilation Device			Overall significance
	Leoni Plus	Next Step™	Dräger VN500	
0.21 to 1.0	27±1	44±2	42±1	0.42
1.0 to 0.21	53±1	43±1	48±1	0.38
0.21 to 1.0 in 0.1 increments	16±1	21±7	24±1	0.73
1.0 to 0.21 in 0.1 increments	38±3	16±6	33±6	0.99
0.21 to 1.0 in 0.2 increments	18±1	27±7	27±1	0.01
1.0 to 0.21 in 0.2 increments	39±2	19±7	34±2	0.08

Data presented as mean±SD

Abbreviations: s=seconds; sd=standard deviation

Table 3.2.4 Multiple comparisons between ventilation devices using an oxygen flow rate of 10L/min and V_T of 6 mL/kg

Change in fraction of inspired oxygen	Ventilation Device		
	Next Step™ vs. Leoni Plus	Next Step™ vs. Dräger VN500	Leoni Plus vs. Dräger VN500
0.21 to 1.0	-	-	-
1.0 to 0.21	-	-	-
0.21 to 1.0 in 0.1 increments	0.05	0.92	0.01
1.0 to 0.21 in 0.1 increments	<.001	<.001	0.23
0.21 to 1.0 in 0.2 increments	0.12	1.00	0.07
1.0 to 0.21 in 0.2 increments	<.001	0.02	0.62

Bonferroni correction has been applied for the p-values reported

Table 3.2.5 Overall time needed to reach oxygen concentration (s) using an oxygen flow rate of 10 L/min

Change in fraction of inspired oxygen	Ventilation Device			Overall significance
	GE	Neo-Tee	NeoPuff	
0.21 to 1.0	22±1	26±2	18±1	0.22
1.0 to 0.21	21±1	24±1	26±1	0.61
0.21 to 1.0 in 0.1 increments	13±5	13±3	12±1	0.02
1.0 to 0.21 in 0.1 increments	8±1	9±1	21±3	0.71
0.21 to 1.0 in 0.2 increments	16±4	16±3	13±1	0.02
1.0 to 0.21 in 0.2 increments	11±2	12±3	22±1	0.59

Data presented as mean±SD

Abbreviations: s=seconds; sd=standard deviation

Table 3.2.6 Multiple comparisons between T-Pieces using an oxygen flow rate of 10 L/min

Change in fraction of inspired oxygen	Ventilation Device		
	GE vs. Neo-Tee	GE vs. NeoPuff	Neo-Tee vs. NeoPuff
0.21 to 1.0	-	-	-
1.0 to 0.21	-	-	-
0.21 to 1.0 in 0.1 increments	1.00	0.27	0.53
1.0 to 0.21 in 0.1 increments	1.00	<.001	<.001
0.21 to 1.0 in 0.2 increments	1.00	0.11	0.27
1.0 to 0.21 in 0.2 increments	1.00	<.001	<.001

Bonferroni correction has been applied for the p-values reported

3.3. Results for Study #3 assessing the power usage amongst several PPV devices

3.3.1 Power Consumption during PPV

At a PEEP of 4 cmH_2O, the mean (SD) power used by the Next Step™ was 18.5 (0.21) W compared to 96.1(4.96) W for the Dräger VN500, 64.6 (0.45) W for the Leoni Plus and 27.4 (2.45) W for the Fabian™ HFO. As the respiratory rate increased from 30-60 breaths per minute and V_T increased from 3 mL/kg to 8 mL/kg, the power consumed ranged from 18.3–18.8 W for the Next Step™ compared to 89.6–100.1 W for the Dräger VN500; 64.1–65.2 W for the Leoni Plus and 24.6–30.0 W for the Fabian™ HFO (see Figure 3.3.1).

At a PEEP of 6 cmH_2O, the mean (SD) power used by the Next Step™ was 19.6 (0.85) W compared to 89.6 (0) W for the Dräger VN500, 64.8 (0.52) W for the Leoni Plus and 29.3 (1.27) W for the Fabian™ HFO. As the respiratory rate increased from 30-60 breaths per minute and V_T increased from 3 mL/kg to 8 mL/kg, the power consumed ranged from 18.9–20.8 W for the Next Step™, whereas for the Dräger VN500, the power consumed stayed consistently at 89.6 W. As for the Leoni Plus, its power consumption ranged from 64.3–65.4 W while the Fabian™ HFO's power consumption ranged much less from 28.1–30.5 W (see Figure 3.3.2).

At a PEEP of 8 cmH_2O, the mean (SD) power used by the Next Step™ was 19.9 (0.18) W compared to 89.6 (0) W for the Dräger VN500, 65.0 (0.40) W for the Leoni Plus and 28.6 (1.08) W for the Fabian™ HFO. As the respiratory rate increased from 30-60 breaths per minute and V_T increased from 3 mL/kg to 8 mL/kg, the power consumed ranged from 19.9–20.1 W for the Next Step™, whereas for the Dräger VN500, the power consumed stayed consistently at 89.6 W. However, for the Leoni Plus and Fabian™ HFO, their power consumption ranged from 64.6–65.2 W and 27.8–30.2 W, respectively (see Figure 3.3.3).

At a PEEP of 10 cmH_2O, the mean (SD) power used by the Next Step™ was 21.0 (0.97) W compared to 89.6 (0) W for the Dräger VN500, 64.9 (0.45) W for the Leoni Plus and 28.3 (0.83) W for the Fabian™ HFO. As the respiratory rate increased from 30-60 breaths per minute and V_T increased from 3 mL/kg to 8 mL/kg, the power consumed ranged from 20.5–22.4 W for the Next Step™, whereas for the Dräger VN500, the power consumed stayed consistently at 89.60 W. However, for the Leoni plus and Fabian™ HFO, their power consumption ranged from 64.4–65.3 W and 27.5–29.4 W, respectively (see Figure 3.3.4).

3.3.2 Power Consumption during CPAP

At a PEEP of 4 cmH_2O, the mean (SD) power used by the Next Step™ was 9.95 (0.21) W compared to 98.6 (0) W for the Dräger VN500, 65.3 (0.21) W for the Leoni Plus and 22.6 (0.21) W for the Fabian™ HFO. At a PEEP of 5 cmH_2O, the mean (SD) power used by the Next Step™ was 10.3 (0.21) W compared to 98.6 (0) W for the Dräger VN500, 65.0 (0.21) W for the Leoni Plus and 23.5 (1.48) W for the Fabian™ HFO. At a PEEP of 6 cmH_2O, the mean (SD) power used by the Next Step™ was 10.3 (0.21) W compared to 98.6 (0) W for the Dräger VN500, 64.8 (0) W for the Leoni Plus and 22.9 (0.21) W for the Fabian™ HFO. At a PEEP of 7 cmH_2O, the mean (SD) power used by the Next Step™ was 10.6 (0.21) W compared to 98.6 (0) W for the Dräger VN500, 64.8 (0) W for the Leoni Plus and 22.7 (0) W for the Fabian™ HFO. At a PEEP of 8 cmH_2O, the mean (SD) power used by the Next Step™ was 10.6 (0.21) W compared to 98.6 (0) W for the Dräger VN500, 64.5 (0) W for the Leoni Plus and 22.7 (0) W for the Fabian™ HFO. At a PEEP of 9 cmH_2O, the mean (SD) power used by the Next Step™ was 10.7 (0) W compared to 98.6 (0) W for the Dräger VN500, 64.4 (0.21) W for the Leoni Plus and 22.7 (0) W for the Fabian™ HFO. At a PEEP of 10 cmH_2O, the mean (SD) power used by the

Next Step™ was 11.0 (0) W compared to 98.6 (0) W for the Dräger VN500, 64.4 (0.21) W for the Leoni Plus and 22.7 (0) W for the Fabian™ HFO (see Figure 3.3.5).

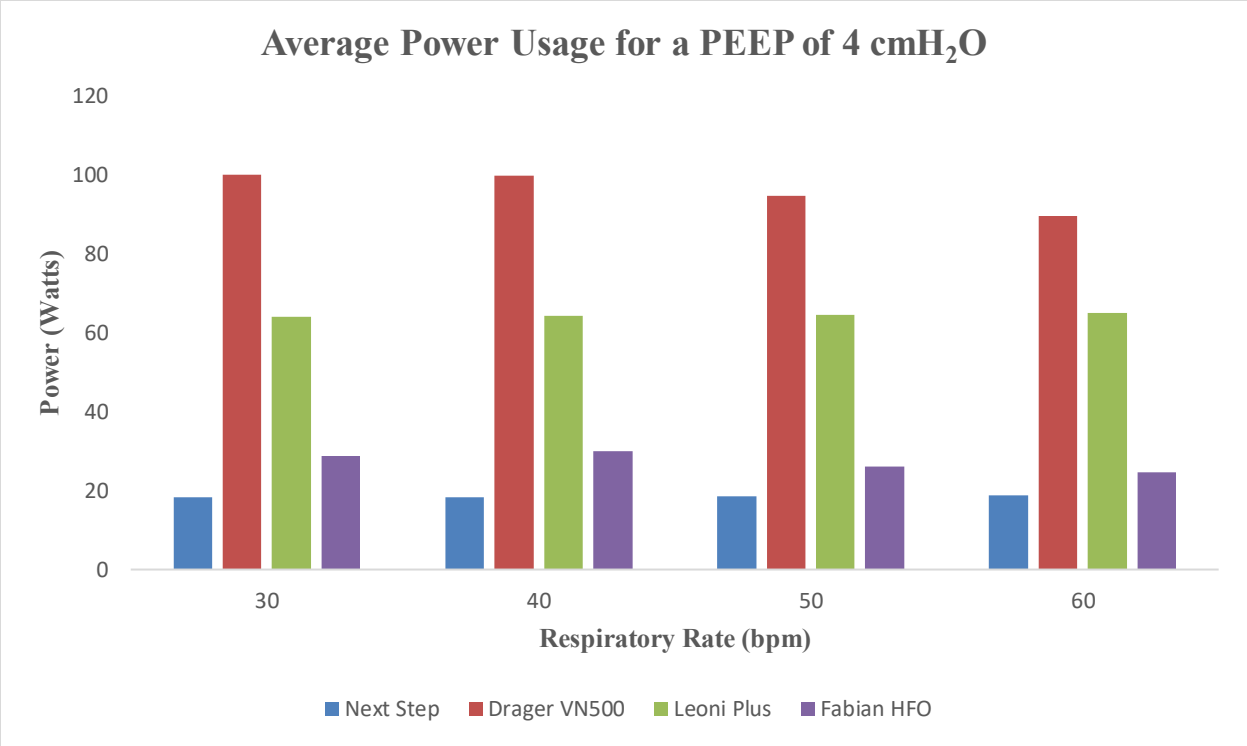

Figure 3.3.1 Average power consumption amongst the Next Step™, Dräger VN500, Leoni Plus and Fabian™ HFO at a PEEP of 4 cmH_2O.

Abbreviations: bpm=breaths per minute.

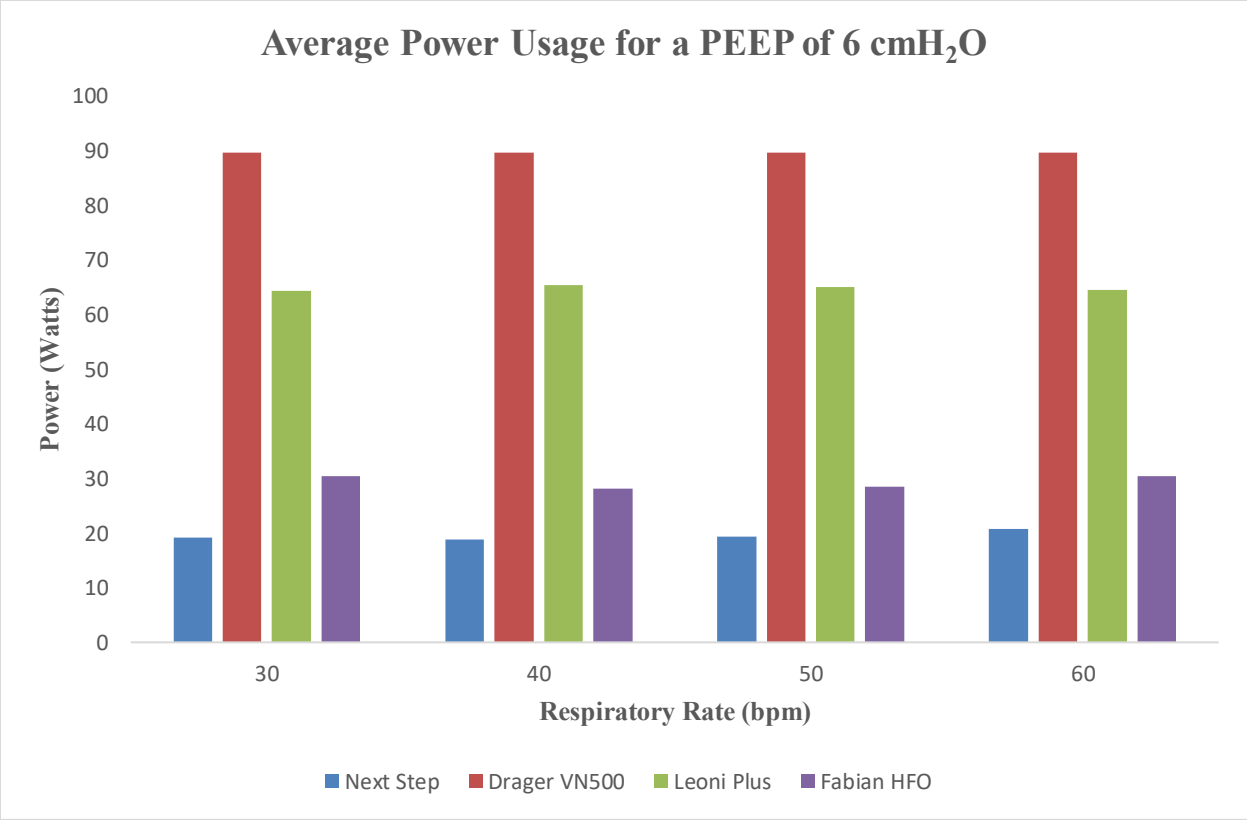

Figure 3.3.2 Average power consumption amongst the Next Step™, Dräger VN500, Leoni Plus and Fabian™ HFO at a PEEP of 6 cmH_2O.

Abbreviations: bpm=breaths per minute.

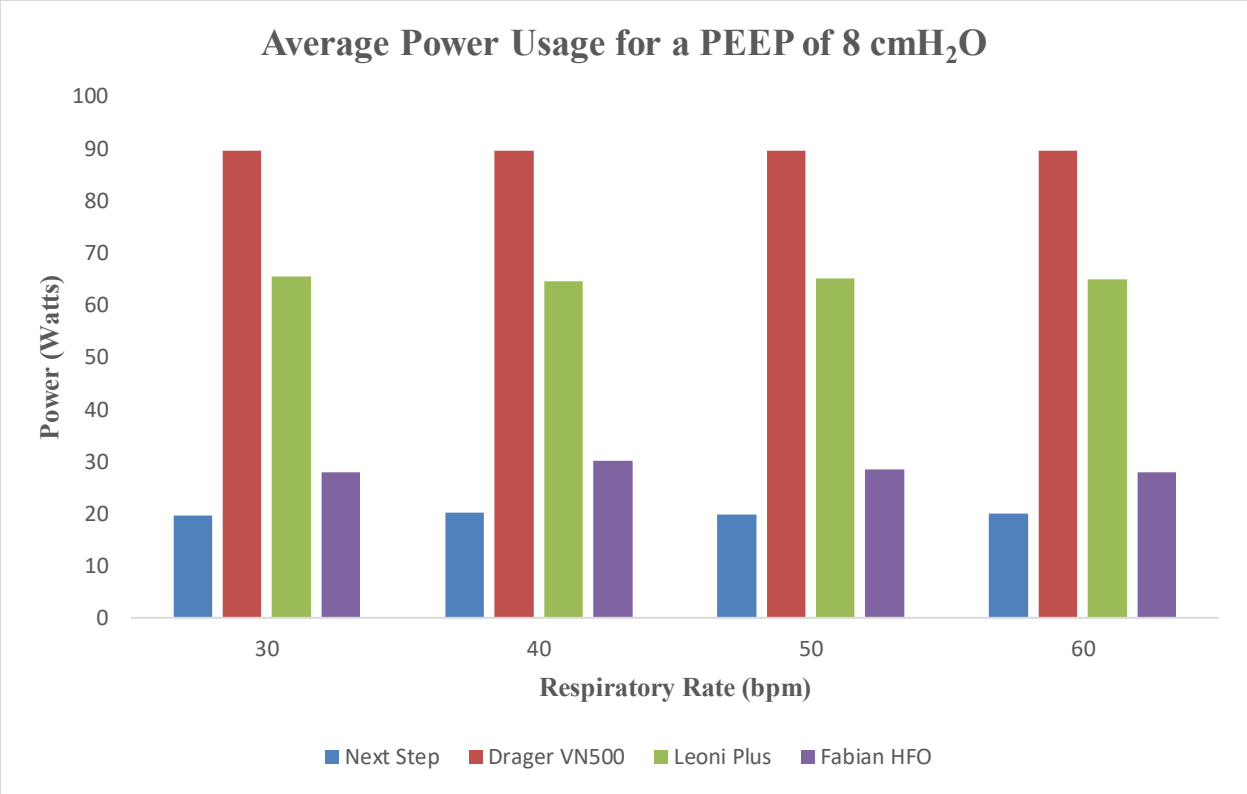

Figure 3.3.3 Average power consumption amongst the Next Step™, Dräger VN500, Leoni Plus and Fabian™ HFO at a PEEP of 8 cmH_2O.

Abbreviations: bpm=breaths per minute.

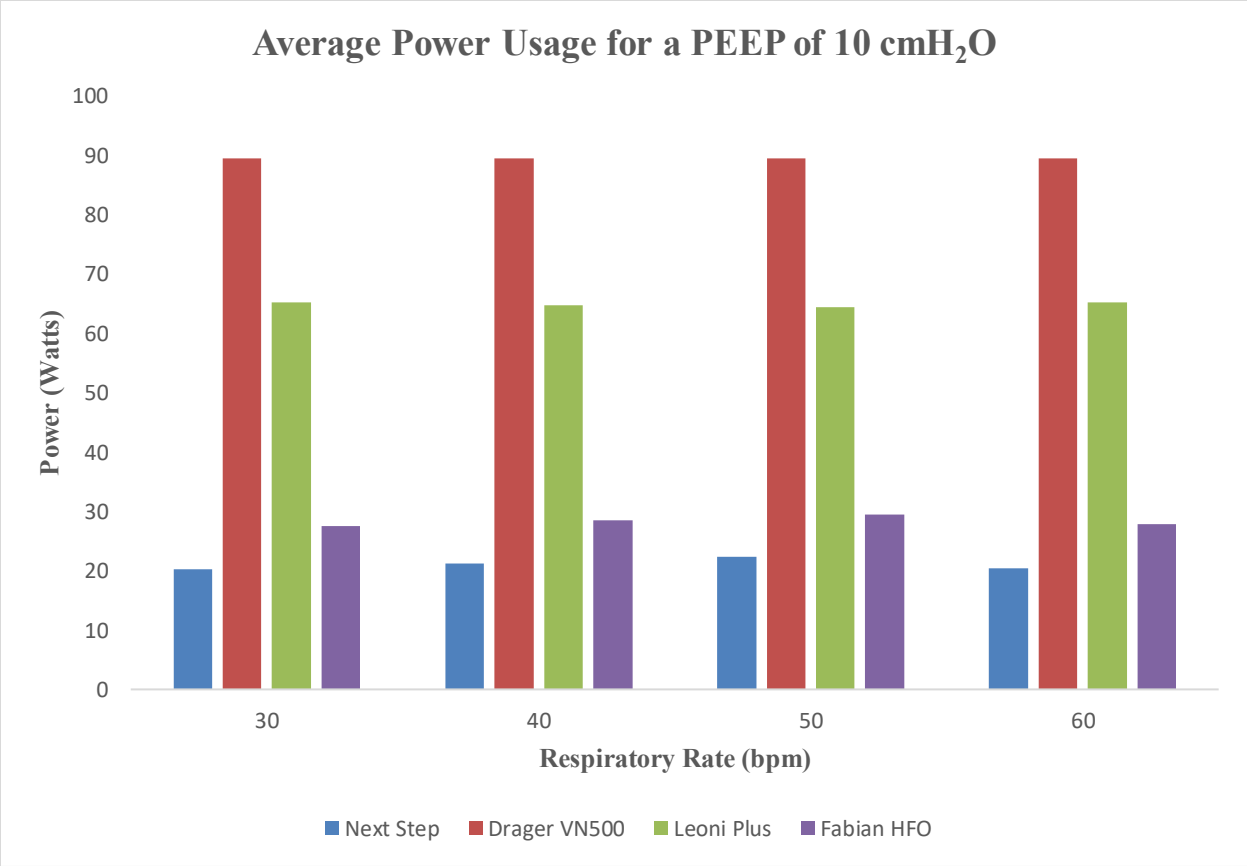

Figure 3.3.4 Average power consumption amongst the Next Step™, Dräger VN500, Leoni Plus and Fabian™ HFO at a PEEP of 10 cmH_2O.

Abbreviations: bpm=breaths per minute.

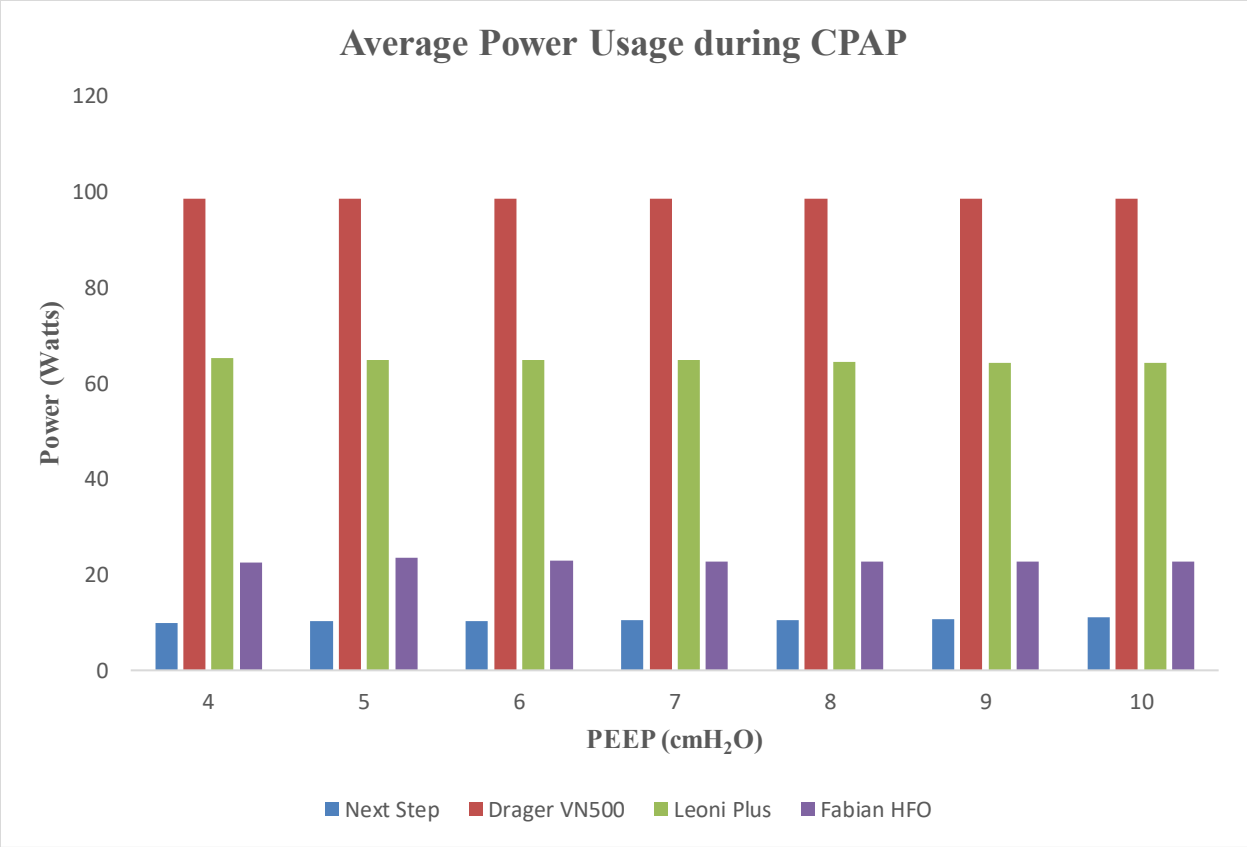

Figure 3.3.5 Average power consumption amongst the Next Step™, Dräger VN500, Leoni Plus and Fabian™ HFO during CPAP.

Abbreviations: PEEP=positive-end expiratory pressure

Chapter 4: Discussion

4.1. Next Step™ resuscitator can deliver a target V_T

In the delivery room, PPV is routinely delivered using pressure-controlled devices (i.e., SIB or T-piece), which either delivers a variable PIP (SIB) or a set PIP (T-Piece). With these devices, an assumption is made that the used PIP will deliver an adequate V_T. However, the delivered V_T is not routinely measured and can range between 0-30 mL/kg.[26,63] The current approach to monitor the delivered V_T includes observing changes in heart rate and chest rise.[167] An RFM can be used to adjust the PIP and monitor V_T delivery. However, randomized trials comparing V_T delivery with and without and RFM have had contradicting results.[70–72] In contrast, VTV is routinely used in the NICU to deliver a set V_T, which has resulted in improved survival and reduction in intraventricular hemorrhage and bronchopulmonary dysplasia.[142] However, routine use of VTV has not been translated into the delivery room.

Our study is the first to compare V_T delivery at different airway compliances with routinely used ventilation devices (with or without RFM guidance) to the Fabian™ HFO ventilator and the Next Step™, using a neonatal piglet model. The results of the study can be summarized as followed: i) V_T was statistically significantly lower for the Next Step™ and Fabian™ HFO compared to the four other ventilation strategies at ~1.5 mL/cmH_2O compliance, with no significant differences at ~0.5 mL/cmH_2O compliance (Table 3.1.1 & Figure 3.1.1); ii) the Next Step™ and Fabian™ HFO required statistically significantly lower PIP at ~0.5 mL/cmH_2O compliance. In contrast, there was no difference in delivered PIP between groups at ~1.5 mL/cmH_2O compliance (Table 3.1.1); iii) the Next Step™ and Fabian™ HFO had the highest proportions of inflations delivering within the target V_T range of 5 mL/kg (±10%) at both compliance levels (Table 3.1.2).

As the lung-air interface moves distally during PPV and thereby aerating the lung, the compliance is rapidly changing, which affects the delivered V_T. A recent study by Breseti *et al*[168] reported that the V_T almost doubled from 4.4 to 7.8 mL/kg when compliance increased from 0.2 to 0.4 mL/cmH_2O. Similarly, Kattwinkel *et al*[40] reported a significant increase in V_T when compliance increased from 0.2-0.5 mL/cmH_2O to 1.2-1.8 mL/cmH_2O during PPV of a lung simulator. Furthermore, Huynh *et al*[169] reported when compliance increased from 0.5 to 1.0 mL/cmH_2O, V_T increased 3-folds with a SIB. Solevag *et al*[151,152] compared a SIB and the T-Piece with the Next Step™ in a mannequin and reported that the V_T increased 3-4 folds as compliance increased. In the current study, we observed a similar trend: higher V_T was delivered with the SIB and T-Piece as compliance increased. With the addition of an RFM, the V_T was reduced for these devices. The high V_T delivered is concerning as animal studies reported that V_T >8 mL/kg results in lung and brain injury.[170,171] Interestingly, the delivered V_T with the Next Step™ and the Fabian™ HFO was similar and unaffected by the compliance changes. It is important to note that in the current study we used compliances of ~0.5 and ~1.5 mL/cmH_2O, whereas previous studies have used lower compliances, which might have affected our results.[40,161]

An RFM can be used to adjust the delivered PIP to prevent the delivery of high V_T as compliance changes. Randomized trials have reported that an RFM helped reduce the delivery of high V_T delivery by up to 25%.[70–72] Adding an RFM to either a SIB or T-Piece to adjust PIP to guide V_T delivery could reduce high V_T delivery by up to 50% (Table 3.1.1). While this percentage is twice as high as clinical trials reported, it might be due to the laboratory settings (which is less stressful than the DR) and the fact that a single operator (GMS) was providing PPV for all groups, which is different compared to the heterogenous staff in the DR. However, despite the increased percentage of target range V_T delivery with RFM use, a substantial number of inflations were still

delivered with a too high V_T, while the Next Step™ did not have many inflations with excessive V_T, suggesting a potential role for this device in reducing volutrauma and thereby lung and brain injury.

There are caveats to using an RFM, which include lack of experience and knowledge about the displayed waveforms which may lead to misinterpretation of the signals and the diversion of attention of healthcare professions away from the baby and towards the RFM monitor.[73,172,173]

In terms of limitations, the piglets in our study were intubated with a tightly sealed endotracheal tube to prevent leak. However, this is not always feasible in the delivery room. We muscle relaxed the piglets at the start of the experiment to allow for more accurate assessment of the compliance. However, this is not done in human infants. For the analysis we used a 10% variation in V_T as our target range as indicated by the Next Step™'s manufacturer.[174] Similarly, the Fabian™ HFO only delivers ~80% of inflations within 1 mL/kg of set V_T.[132] Since the Next Step™ is a prototype, we used the Fabian™ HFO as gold standard for comparison of ventilation parameters. Lastly, the Fabian™ and Next Step™ use a hot wire anemometer in their flow sensor while the NM3 uses a fixed orifice pneumotach, both of which exhibit differences in the accuracy of their measured V_T.[175] However, the accuracy of the used flow sensors are within clinically acceptable deviations in volume measurements.[176]

4.2. Time required to achieve a target FiO_2

According to the latest European Resuscitation guidelines, room air (21% O_2) should be used for infants at 32 weeks' gestation or more, 21-30% of inspired O_2 at 28-31 weeks' gestation, 30% for infants <28 weeks' gestation[7]. The concentration should be titrated to achieve saturations of ≥ 80% at 5 minutes of age. In addition, if there is no increase in heart rate despite

effective ventilation or if oxygenation (guided by SpO_2) remains unacceptable, a higher fraction of FiO_2 should be used.[7] However, in order for supplementary oxygen to be effective, effective ventilation (lung aeration and the establishment of a FRC) needs to be established prior[8,74,93]. Follett *et al*[89] previously reported that there was a lag time of approximately 30 s to achieve the FiO_2 at the facemask for the GE T-Piece. However, there is no published data for other ventilation devices commonly used in the delivery room and NICU.

Our study shows that on average, it takes approximately 30 s for the Leoni Plus, Next Step™, and Dräger VN500 to deliver the desired FiO_2 concentration at a V_T of 4 and 6 mL/kg. As for the GE T-Piece, Neo-Tee and Neopuff, it takes them approximately 20 s to deliver the desired FiO_2 concentration at the facemask. Our T-Piece's results are slightly less than the values reported by Follett *et al*[89] and Dekker *et al*[177], who reported that it takes approximately 30 s for the GE T-Piece and NeoPuff T-Piece resuscitator to deliver the FiO_2 concentration at the facemask. However, in Follett *et al's* study, the authors used three different flow rates (5, 8, and 10 L/min) whereas for our study we only used one flow rate (10 L/min), which could explain the discrepancy in our results (Follett *et al*[89] *reported* a mean of 33±12 s and 34±10 s going from 0.21 to 1.0 O_2 and vice versa, whereas in our study, we observed a delay of 22±12 s and 21±1 s, respectively). In addition, the authors also had two other conditions in their study: one where there was a 50% leak to mimic the leak often seen in neonatal resuscitation, and one where the test lung was not connected to the T-Piece to simulate continuous positive airway pressure[89]. In our study, there was no leak for all testing conditions, which could contribute to the variation in the average time reported. As for Dekker *et al*[177], the authors used a 50 mL test lung whereas for our study we used a 2 mL test lung; the authors also included a 50% leak trial in their study and their stepwise increase or decrease of O_2 titrations was done in 0.2 increments instead of 0.1.

Goos *et al*[178] also reported that there are considerable variations of SpO_2 target ranges within the first minutes after birth due to inability to control the SpO_2, i.e., techniques used or face mask leaks, which could further explain the discrepancy in our results from Follett *et al*'s and Dekker *et al's*.

There are several limitations to our study. For example, we used a different length of tubing for gas for the ventilators compared to the T-Pieces, as well as using only one flow rate instead of multiple. In addition, we did not have leaks in our trials, which is different from the setting of the DR where there is often mask leak during PPV. Nevertheless, our findings indicate that there is a delay in the change in oxygen exposure at the oxygen blender to the facemask for the Next Step™, Leoni Plus, Dräger VN500, GE T-Piece, Neo-Tee T-Piece and NeoPuff T-Piece.

4.3 Power Consumption

In LMICs, access to mechanical ventilators can be difficult due to limited resources, lack of infrastructure, and access to stable electricity. Our study is the first to compare electricity usage between the Next Step™, the Dräger VN500, Leoni Plus, and Fabian™ HFO ventilators. The findings can be summarized as followed: 1) Power usage was 0.5-5 times higher for the Dräger VN500, Leoni Plus, and Fabian™ HFO compared to the Next Step™ resuscitator across all testing conditions; 2) as respiratory rate and/or PEEP increased for the Next Step™, its power consumption remained relatively low between 18.47-21.04 W compared to 89.60-100.1 W for the Dräger VN500 (equivalent to running a 100W lightbulb), 64.1-65.53 W for the Leoni Plus, and 24.63-30.5 W for the Fabian™ HFO; and 3) when providing CPAP, the Next Step™ used 9.95-10.7 W with increasing levels of PEEP, whereas the Dräger VN500 used 98.6W, and the

Leoni Plus and Fabian™ HFO used 64.35-65.25 W and 22.55-23.45 W, respectively. This suggests that using the Next Step™ can help reduce electricity usage by almost 0.5-10 folds, depending on whether you are providing PPV or CPAP.

Most adult and pediatric intensive care units (ICUs) in LMICS are in located in cities, making it challenging for rural patients to access.[179] In addition, in underdeveloped countries like Uganda and Nepal, there is only 1.0 and 16.7 ICU beds per one million population, respectively, highlighting the lack of infrastructure and resources available to critical care for patients in these regions.[179] Several studies have reported that access to reliable electricity is positively correlated with positive health outcomes. In a multi-country longitudinal study, Wang *et al*[180] reported significantly lower infant and under 5 mortality rates in urban areas with reliable access to electricity compared to areas with unreliable access. Van de Poel *et al*[181] also found that urban-rural differences in access to electricity account for 9% of the gap in infant mortality between urban versus rural regions in six countries in Africa. Moreover, in a longitudinal study conducted by Apenteng *et al*,[182] the authors reported that for every day that there is a power outage of 2 or more hours, this was significantly associated with the risk of in-facility mortality of up to 43% in Ghana. In certain LMICs, power outages can almost occur as often as daily.[183] For example, in a systematic review conducted by Moore *et al*,[184] the authors reported that in South Asia and sub-Saharan Africa, the average power outages were 25.5 and 8.9 per month, respectively. These results suggest that in LMICs, access to electricity can be unreliable, which can affect the health outcomes of the individuals in these regions.

It is important to note that there is also the potential for mortality associated with mechanical ventilation use in infants. For example, Mokhtar *et al*[185] reported that 48.3% of neonates they had in their study passed away from receiving mechanical ventilation, with

ventilator-associated pneumonia being the biggest contributor to these infants' deaths. However, 240 of the infants enrolled had were considered critically ill: 28.3% had respiratory distress syndrome, 16.7% had congenital pneumonia, 16.7% had sepsis, and 10% had apnea and a multivariate regression analysis was not performed to control for these factors. Other studies have reported similar mortality rates from 43.3% to 74%, albeit all these studies used pressure limited ventilation instead of VTV.[186–188] Conversely, several studies have reported favorable outcomes associated with VTV use, such as decrease in the incidence of grade 3 or 4 intraventricular hemorrhage and bronchopulmonary dysplasia. In a systematic review conducted by Wheeler *et al*[141], the authors reported that utilization of VTV resulted in a reduction in combined outcome of death or bronchopulmonary dysplasia [RR(95% CI): 0.73(0.57-0.93)], and the combined outcome of periventricular leukomalacia or grade 3-4 intraventricular hemorrhage [RR(95% CI): 0.48(0.28-0.84)]. In another systematic review conducted by Klingenberg *et al,*[142] similar results were reported: VTV modes reduced the rates of grade 3 or 4 intraventricular hemorrhage [RR(95% CI): 0.53(0.37-0.77)] and death or bronchopulmonary dysplasia at 36 weeks' gestation [RR(95% CI): 0.73(0.59-0.89)].

In terms of limitations for the current study, the Dräger VN500 and Leoni Plus were connected to an oxygen source whereas the Next Step™ resuscitator and the Fabian™ HFO ventilator were not. However, 21% O_2 (room air) was the oxygen concentration used for all ventilators therefore this should not have an impact on the results. In addition, the data reported is based on a 120V supply voltage and 60 Hz (which Canada operates under). The results might differ for regions of the world that use a different voltage setting.

4.4. Future Directions

Since the studies conducted here were observational and performed on a neonatal ovine model, future studies could be performed in the delivery room as well as on human preterm infants. The delivery room is a stressful environment where quick decisions have to be made and healthcare professionals must have good judgement, psychomotor, and cognitive skills to respond to the situation under intense time pressure.[189] This situation often leads to human errors and deviations from resuscitation algorithms, as high as 90%.[190,191] Moreover, some studies have reported that healthcare providers commit errors as high as 55% of the time in simulated neonatal resuscitation.[192,193] Thus, it is important to use the Next Step™ in real-life environments such as the DR and NICU to determine if the findings reported here are translatable to a clinical setting.

In addition, in study #2 where we analyzed the amount of time it takes to achieve a target FiO2 level amongst several PPV devices, future studies should incorporate other ventilation devices such as the Fabian™ HFO, Dräger Babylog 8000, SLE 5000 infant ventilator, and V.I.P Bird gold; as well as use test lung models where there is leak to mimic the mask leak often seen in neonatal resuscitation. Different flow rates should be also used, i.e., 5 L/min and 8 L/min to determine how this affects the time required to achieve the desired FiO_2 level. Lastly in study #3, we compared the power usage against several neonatal ventilators. In our study, we only used the Fabian™ HFO, Dräger VN500 and Next Step™. Future studies should incorporate other ventilation devices such as the Dräger Babylog 8000, SLE 5000 infant ventilator, and V.I.P Bird gold. In addition, different voltages should be used, i.e., 220V, to see how the results might differ.

4.5. Conclusions

In this thesis, I examined the internal properties of the Next Step™ resuscitator, namely its power usage and the time it takes to deliver a targeted FiO_2 level, in addition to maintaining a target V_T level despite changes to lung compliance. While these studies were observational, they demonstrated positive results, highlighting the potential applications of the Next Step™ as a novel ventilation device in the DR and NICUs.

In study #1, the Next Step™'s capacity to maintain a target V_T with changing lung compliance levels was explored. At either low (~0.5 mL/cmH_2O) or high compliance (~1.5 mL/cmH_2O), the Next Step™ mean expired V_T was closest to the target V_T of 5 mL/kg, in contrast to the four other ventilation strategies (SIB-only, SIB+RFM, T-Piece only, and T-Piece+RFM). The Next Step™ also performed similarly to the Fabian™ HFO in maintaining the target V_T. This study demonstrates that the Next Step™ has the capacity to perform PPV similarly to an established and routinely used neonatal ventilator.

Moreover, in study #2 and #3, the internal properties of the Next Step™ were examined, mainly its capacity to deliver a targeted FiO_2 and its power consumption. Compared to the Leoni Plus and Dräger VN500, the Next Step™ took a similar amount of time (~30 s) to deliver the desired FiO_2 level under low (4 mL/kg) and high V_T (6 mL/kg) settings. This was slightly higher than the average time observed for the T-Pieces (~20 s). A potential discrepancy for this is the length of tubing used to provide gas supply for the ventilators and the T-Pieces. However, in terms of power usage, the Next Step™ used the least amount of power during PPV under increasing levels of PEEP, respiratory rate, and V_T compared to other ventilation devices, even when in CPAP mode. For example, the Next Step™ used 0.5-5 times less power than certain ventilators during PPV and CPAP. These studies demonstrate that the Next Step™'s functional capacities are similar to other ventilation devices commonly used in the DR and its minimal

power consumption could help advance neonatal care in LMICs where access to electricity is limited and unreliable.

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