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Analysis of neonatal ventilator performance and patient-ventilator interactions – a big data approach

Thesis

Doctor of the Hungarian Academy of Sciences

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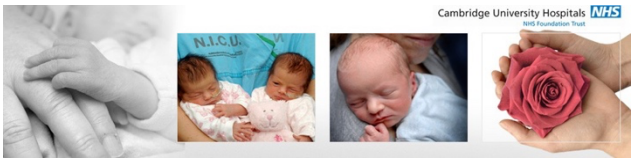

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2. List of abbreviations

AARC	American Academy of Respiratory Care
AC	Assist control
Amplmax	Maximum allowed pressure amplitude during HFOV
ANOVA	Analysis of variance
ATC	Automatic tube compensation
AV	Alveolar ventilation
BE	Base excess
BPD	Bronchopulmonary dysplasia
CDP	Continuous distending pressure
CI	Confidence interval
CMV	Controlled mandatory ventilation
CO_2	Carbon dioxide
csv	Comma separated value
DCO_2	Diffusion coefficient of carbon dioxide
DCO_2corr	Weight-corrected diffusion coefficient of carbon dioxide
deltaP	Pressure amplitude during HFOV
ECMO	Extracorporeal membrane oxygenation
ELBW	Extremely low birth weight
ET-CO_2	End-tidal carbon dioxide
ETT	Endotracheal tube
FiO2	Fraction of inspired oxygen
FRC	Functional residual capacity
g	gram
GUI	Graphical user interface
HFFI	High frequency flow interruption
HFJV	High frequency jet ventilation
HFOV	High frequency oscillatory ventilation
HFOV-VG	High frequency oscillatory ventilation with volume guarantee
HFV	High frequency ventilation
Hz	Hertz
ICD	International classification of diseases
IEC	International Electro-technical Commission
IQR	Interquartile range
IVH	Intraventricular haemorrhage
kg	kilogram
kPa	kilopascal
L	Litre
MAP	Mean airway pressure
MAS	Meconium aspiration syndrome
min	Minute
mL	Millilitre
MMV	Mandatory minute ventilation
msec	milliseconds
MV	Minute ventilation / minute volume
MVe	Expired minute ventilation
MVi	Inspired minute ventilation
MVmand	Minute ventilation contributed by the mandatory ventilator inflations
MVresp	Percentage of minute ventilation contributed b ventilator inflations
MVspon	Minute volume contributed by the spontaneous breaths
NAVA	Neurally adjusted ventilator assist
NETS-PCA	Neonatal Emergency and Transport Service of the Peter Cerny Foundation
NICU	Neonatal intensive care unit
NS	Not significant
OCR	Optical character recognition
$paCO_2$	Arterial partial pressure of carbon dioxide (in blood)
paO_2	Arterial partial pressure of oxygen (in blood)
PAV	Proportional assist ventilation
pCO_2	Partial pressure of carbon dioxide in blood

PEEP	Positive end expiratory pressure
PEEPset	The set positive end expiratory pressure
PICU	Paediatric intensive care unit
Pinfl	Inflating pressure (= PIP – PEEP)
PIP	Peak inspiratory pressure / Peak inflating pressure
PIPmand	Peak inspiratory pressure of mandatory ventilator inflations
PIPset	Set peak inspiratory pressure
PIPspon	Peak inspiratory pressure of pressure-supported spontaneous breaths
Pmax	Maximum allowed peak inspiratory pressure
pCO_2	Partial pressure of oxygen in blood
Pphar	Pharyngeal pressure
PPHN	Persistent pulmonary hypertension of the neonate
PRT	Pressure rise time / slope time
PS	Pressure support
PSV	Pressure support ventilation
PSV-VG	Pressure support ventilation with volume guarantee
Ptrach	Tracheal pressure
PVI	Patient-ventilator interaction
PV	Pressure-volume (loop)
PVL	Periventricular leukomalacia
r	Correlation coefficient
RCT	Randomised control trial
RDS	Respiratory distress syndrome
ROC	Receiver operator characteristic
ROP	Retinopathy of prematurity
RR	Respiratory rate
RRdiff	Difference between actual and set respiratory rate
RRmand	Rate of the mandatory ventilator inflations
RRset	Respiratory rate
RRspon	Rate of the spontaneous breaths
SD	Standard deviation
SIMV	Synchronised intermittent mandatory ventilation
SIMV-PS	Synchronised intermittent mandatory ventilation, pressure support on spontaneous breaths
SIMV-VG	Synchronised intermittent mandatory ventilation with volume guarantee
SIMV-VG-PS	Synchronised intermittent mandatory ventilation with volume guarantee, pressure support on spontaneous breaths
SIPPV	Synchronised intermittent positive pressure ventilation
SIPPV-VG	Synchronised intermittent positive pressure ventilation with volume guarantee
SpO_2	Oxygen saturation of the blood
$tcCO_2$	Transcutaneous carbon dioxide
Ti	Inspiratory time
Timand	Inspiratory time of ventilator inflations
Tispon	Inspiratory time of spontaneous breaths
Timax	Maximum allowed inspiratory time (during PSV mode)
VD	Dead space volume
VG	Volume guarantee
VT	Tidal volume
VTe	Expired tidal volume
VTemand	Expired tidal volume of mandatory ventilator inflations
VTespon	Expired tidal volume of spontaneous breaths
VTi	Inspired tidal volume
VTimand	Inspired tidal volume of ventilator inflations
VTispon	Inspired tidal volume of spontaneous breaths
VTlc	The volume of leak compensation (estimated expiratory leak)
VTmand	Leak-compensated expired tidal volume of mandatory ventilator inflations
VTset	Target tidal volume during VG
VTspon	Leak-compensated expired tidal volume of spontaneous breaths
VThf	“Tidal” volume of high frequency oscillation
VTV	Volume targeted ventilation

3. Introduction

3.1. The role of mechanical ventilation in today's neonatology

Despite recent advances in non-invasive respiratory support and less invasive surfactant administration, mechanical ventilation remains important on neonatal intensive care unit (NICUs) (1, 2) Babies born at the threshold of viability (22-25 weeks of gestation) frequently require mechanical ventilation for longer periods, sometimes for several weeks (3). Threshold of viability is arguably defined as the smallest and most immature babies who can be successfully intubated and mechanically ventilated after birth. Babies born at higher gestation or at term may also require mechanical ventilation for lung immaturity, infection, meconium aspiration syndrome (MAS), congenital airway, lung or heart malformations or hypoxic ischaemic encephalopathy (HIE). Finally, mechanical ventilation is provided for babies during and after surgical procedures. Busy NICUs frequently have >1,500 ventilator days yearly. Despite all technological development, mechanical ventilation via an endotracheal tube remains a high-risk intervention, and is associated with short and long-term complications (4, 5).

3.2. Evolution of neonatal ventilators

Originally developed in the Sixties and Seventies, neonatal ventilators were initially simple devices, comprising only mechanical parts and powered by pressurised medical gases with no reliance on electricity (6, 7). In the absence of any electric or digital components, they could only provide controlled mandatory ventilation (CMV) with some basic parameters clinicians were able to set, e.g., peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), respiratory rate (RR), inspiratory time (Ti) and fraction of inspired oxygen (FiO_2). They saved many babies' lives as they were capable of providing positive pressure ventilation and lung inflations to infants with respiratory distress syndrome (RDS) who could not be treated with supplemental oxygen alone. However, the use of constant ventilator rate and inflating pressure (the difference between PIP and PEEP) resulted in under- or over-ventilation when the infant's lung mechanics changed, unless ventilator parameters very reviewed frequently. Even then, there was a large breath-to-breath variability in the delivered tidal volume (VT), as the infant was breathing sometimes in synchrony and sometimes against the ventilator. The resultant patient-ventilator asynchrony also caused significant distress to babies and led to fluctuations in intrathoracic and cerebral perfusion pressures which were associated with an increased risk of intraventricular haemorrhage (IVH) (8).

Such simple ventilators are not in use any more for neonatal ventilation in developed countries except during neonatal transport where they are also being replaced by modern ventilators. They have re-emerged in some places during the Covid-19 pandemic to alleviate the shortage of ventilators as they can be produced quickly and cheaply (9).

Beginning in the Eighties, newer models of ventilators were supplied with increasingly sophisticated and powerful computers and digital technology (10). The current models are equipped with ventilator displays which turns them essentially into touch-screen computers (**Figure 1**). Modern ventilators also detect and respond to patient signals and provide adaptive ventilator modes (6, 11, 12, 13).

Besides all their benefits, the availability of complex ventilator screens and adaptive ventilator modes have also made the use of modern mechanical ventilators more challenging for clinicians. Most neonatal units in Europe do not have dedicated respiratory therapists and neonatologists need to look after many other aspects on neonatal critical care including cardiovascular issues, nutrition, infection, metabolism, neurology and parental communication. Therefore, little time is left for reviewing ventilator screens. Data and trends displayed by the ventilator are frequently disregarded and novel complex ventilation modes are frequently not used (14, 15). There is also limited evidence for the use of several adaptive ventilator modes with high-quality clinical studies lacking.

Figure 1: Display of the Dräger Babylog™ VN500 neonatal ventilator. Pressure, flow and volume waveforms are shown in real time. Ventilator settings and some of the ventilator parameters are also displayed. The user can change settings using the touch screen. The display can also be customised to show pressure-volume and flow-volume loops, other ventilator parameters, parameter trends or the alarm log. Other neonatal ventilator models have similar displays and functionalities.

3.3. Adaptive features of modern neonatal ventilators

Adaptive features of modern neonatal ventilators can be grouped in three categories:

(1) Delivering ventilator inflations in synchrony with the baby's own respiratory effort.

(2) Adapting the power of ventilator inflations to the strength of the infant's respiratory effort, so that a stronger breathing effort results in either more powerful ventilator inflations (e.g., proportional assist ventilation, PAV or neurally adjusted ventilator assist, NAVA) or, on the contrary, in less powerful the ventilator inflations (volume targeted ventilation, VTV, also known as volume guarantee, VG).

(3) Maintaining the ventilator's performance during significant leak around the endotracheal tube (ETT).

Recognition of baby's respiratory effort can happen via detecting the inward flow through the endotracheal tube generated by the infant (or the resultant inspired volume). The pressure drop in the ventilator's circuit generated by the inspiratory effort can also be detected. There is evidence that flow triggering is superior to pressure triggering and most modern neonatal ventilators use the former (16, 17). More recently, neural triggering detecting the neuro-muscular activity associated with respiratory effort has also become available for clinical use with NAVA (17, 18).

3.3.1. Flow sensors

Flow sensors employing hot wire anemometers and placed at the proximal end of the ETT are widely used to detect the baby's inspiratory effort and to calculate tidal volumes.

3.3.1.1. Detection of patient effort

Proximal flow sensors detect the baby's inspiratory effort more sensitively than sensors placed inside the ventilator, as the performance of the latter is reduced by the dampening effect the ventilator circuit, which is significant due to the relatively low flow rates generated by infants (19). Modern flow sensors can detect as low as 0.1 – 0.2 L/minute inspiratory flow and modern ventilators can trigger inflations with <50 milliseconds triggering delay (**Figure 2**). However, their performance depends on regular calibration and prevention of soiling by airway secretions or condensed water in the ventilator's circuit.

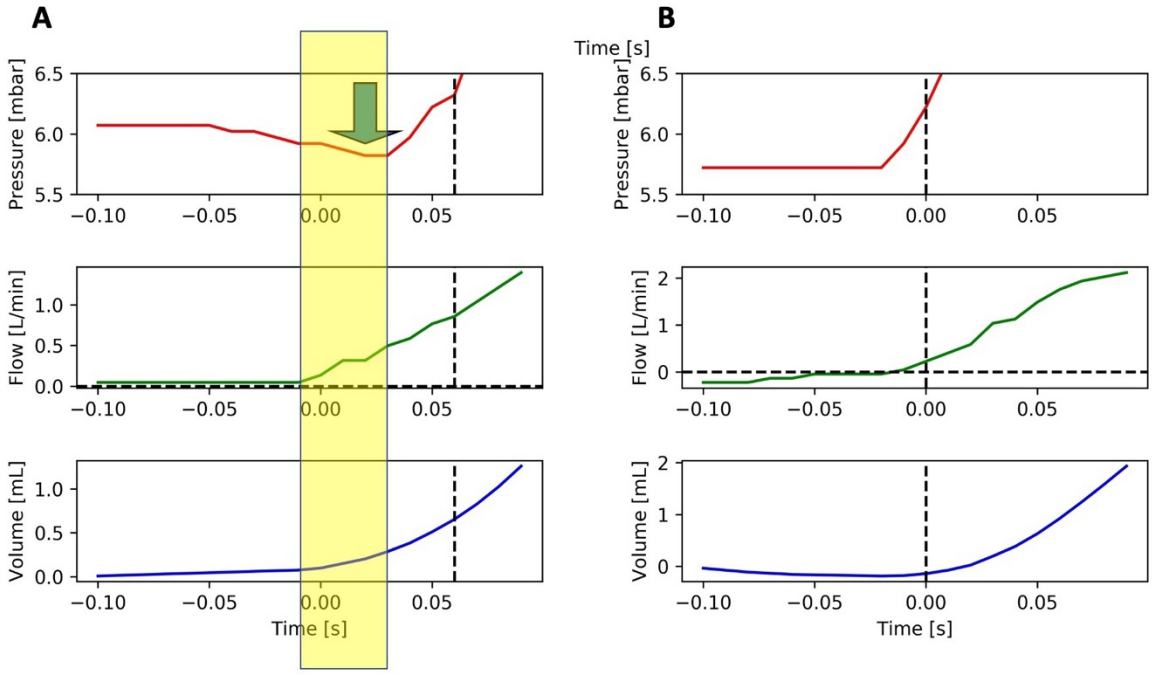


Figure 2: Triggering delay. Pressure (red), flow (green) and volume (blue) waveforms at the beginning of **(A)** a synchronized ventilator inflation triggered by the patient and **(B)** a backup inflation initiated by the ventilator. During patient triggering, the inspiratory (positive) flow generated by the baby is followed by the transient slight pressure drop (blue arrow) due to the patient breathing in from the ventilator's circuit. This is followed by a pressure rise once the ventilator has been triggered. The triggering delay (~0.03 seconds) is marked by the yellow rectangle. During the ventilator triggered backup inflation (B) pressure is rising first followed by inspiratory flow. Modified from (20).

3.3.1.2. Determination of tidal volume

No volume measurement takes place in modern neonatal ventilators; tidal volumes are calculated by time integration of the flow values obtained at a high sampling rate (7). Ventilators can only calculate the volume from the flow detected by the flow sensor, that is, the flow entering the lungs or returning from the lungs via the ETT. If there is significant leak

around the ETT, the inspired and expired tidal volumes calculated by the ventilator will be different from the actual tidal volume (see **section 3.3.3**).

3.3.2. Adaptive ventilation modes

3.3.2.1. Synchronised ventilation

Before flow sensors and computerised ventilators became available, the only way to achieve patient-ventilator synchrony had been to set the ventilator's rate to match the baby's own respiratory rate in a 1:1 or, during weaning, in a 1:2 or 1:3 ratio. However, as the baby's own respiratory rate changed quickly, frequent changes is ventilator rate were required.

Modern ventilators can synchronise the ventilator's inflations with the baby's own respiratory effort. Compared to CMV, synchronised ventilation in newborns has been shown to shorten the duration of mechanical ventilation and to reduce the risk of air leaks in a meta-analysis, although it has not been shown to influence long-term clinical outcomes (21). However, some of the studies included in the meta-analysis were relatively old and used earlier ventilator models with less sensitive flow sensors and less sophisticated triggering algorithms. In addition, the control groups ventilated with CMV were also not completely asynchronous as clinicians had been trying to ensure synchrony via the method described above with variable success, thereby reducing the effect size of the automatic synchronisation.

Synchronised ventilation modes can have different ventilator logic as to how many ventilator inflations are triggered and how ventilator inflations are cycled, that is, how inspiration ends (7, 13, 19). Current neonatal ventilators usually offer three basic synchronised ventilation modes differing in these characteristics: (1) synchronised intermittent positive pressure ventilation (SIPPV), also known as assist-control (AC); (2) synchronised intermittent mandatory ventilation (SIMV); and (3) pressure support ventilation (PSV).

3.3.2.1.1. Synchronised intermittent positive pressure ventilation (SIPPV)

During SIPPV, most breathing attempts of the infant that exceed the set trigger threshold will trigger ventilator inflations (**Figure 3**). The set ventilator rate (RRset) is only a minimum rate, which will be delivered if the baby is apnoeic or if his or her breathing rate is lower than RRset. Preterm babies with RDS usually breathe fast and can trigger >60/min ventilator inflations during SIPPV (22). Term babies suffering from HIE may also trigger frequent ventilator inflations.

To avoid a very high ventilator rate, most ventilator manufacturers include in their SIPPV algorithm a refractory period (usually 0.12 – 0.14 seconds) after each ventilator inflation, when a further inflation cannot be triggered (Thomas Krüger, Dräger, personal communication). Therefore, ventilator rates >120/min are almost always caused by auto-triggering (usually by condensed water in the circuit) or by a technical fault of the ventilator.

In babies with consistent breathing effort, ventilator rate can be safely reduced to below the baby's own breathing rate. This will improve patient-ventilator synchrony as it will leave more time for the baby to trigger ventilator inflations (22). However, the set ventilator rate should

be high enough to provide sufficient ventilation even if the infant unexpectedly stops breathing (e.g., at least 30-40/min).

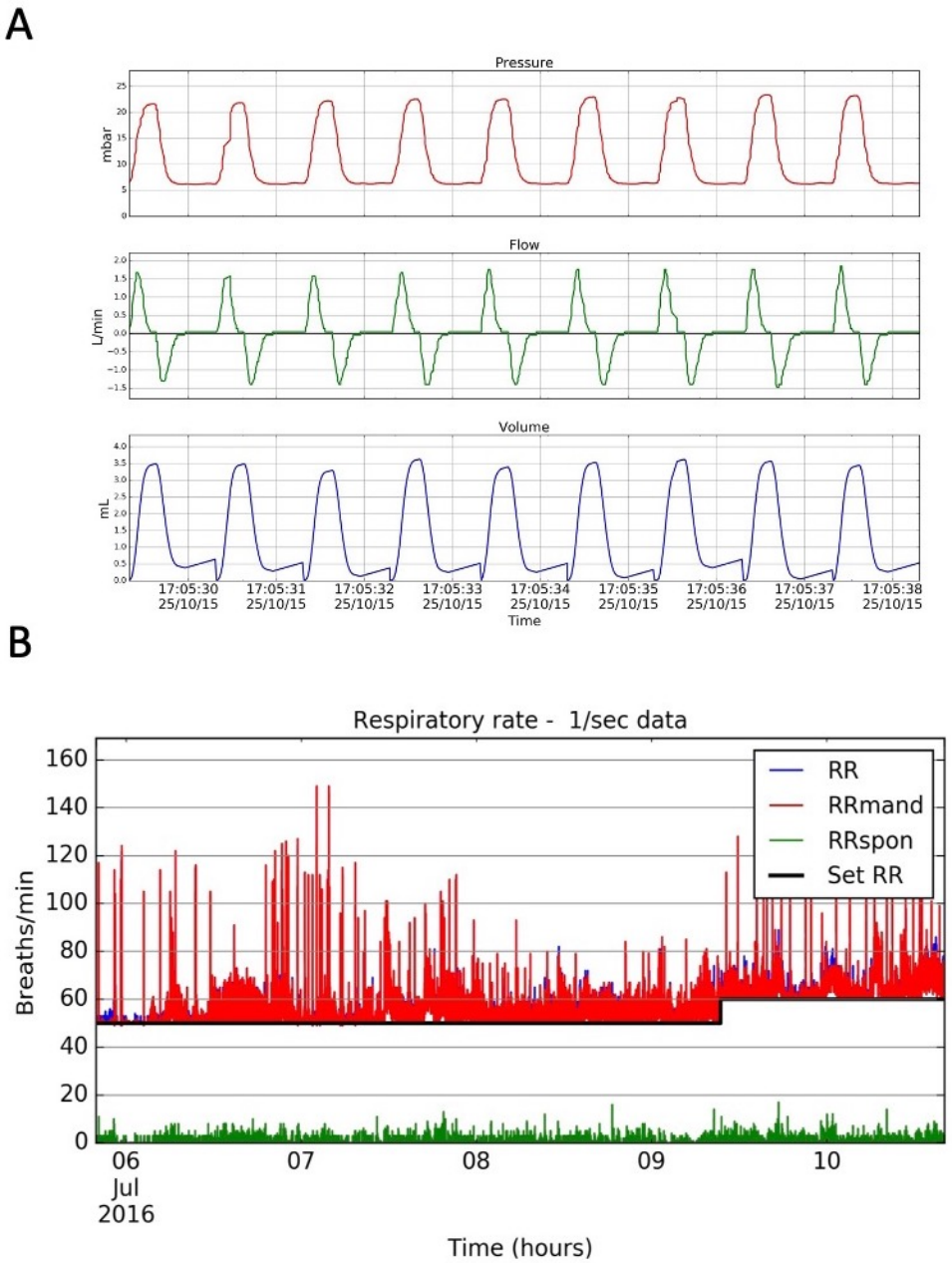


Figure 3: Synchronised intermittent positive pressure ventilation (SIPPV). A. Pressure (red), flow (green) and flow (blue) waveforms over a period of ~9 seconds. There are no spontaneous breaths between ventilator inflations because during SIPPV most breathing attempts of the baby trigger a synchronised ventilator inflation. **B.** Trends of respiratory rate during SIPPV over a period of ~6 days. Data has been collected with 1 Hz (1 per second) sampling rate. During SIPPV the set ventilator rate (black) is only a minimum rate; the infant can trigger more ventilator inflations (RRmand, red). Here the ventilator rate was set at 50/min (increased to 60/min later) but the baby triggered more ventilator inflations, sometimes exceeding 70/min. There were few (<10/min) spontaneous breaths (RRspon, green). They were either weak respiratory attempts not reaching the triggering threshold or they occurred very soon (<0.12 seconds) after a previous ventilator inflation, during the refractory period of the ventilator.

3.3.2.1.2. Synchronised intermittent mandatory ventilation (SIMV)

During SIMV, only a set number of ventilator inflations will be delivered, either triggered by the baby or initiated by the ventilator, if the infant is apnoeic or has a low respiratory rate. Between ventilator inflations, the infant can breathe spontaneously from the continuous flow of the ventilator's circuit (**Figure 4**). The spontaneous breaths can be optionally pressure supported, SIMV-PS, see **Figure 5**). The use of pressure support on spontaneous breaths essentially converts those to pressure limited positive pressure inflations. However, they are flow cycled (see **section 3.3.2.1.3.)** rather than time cycled and hence their Ti is variable.

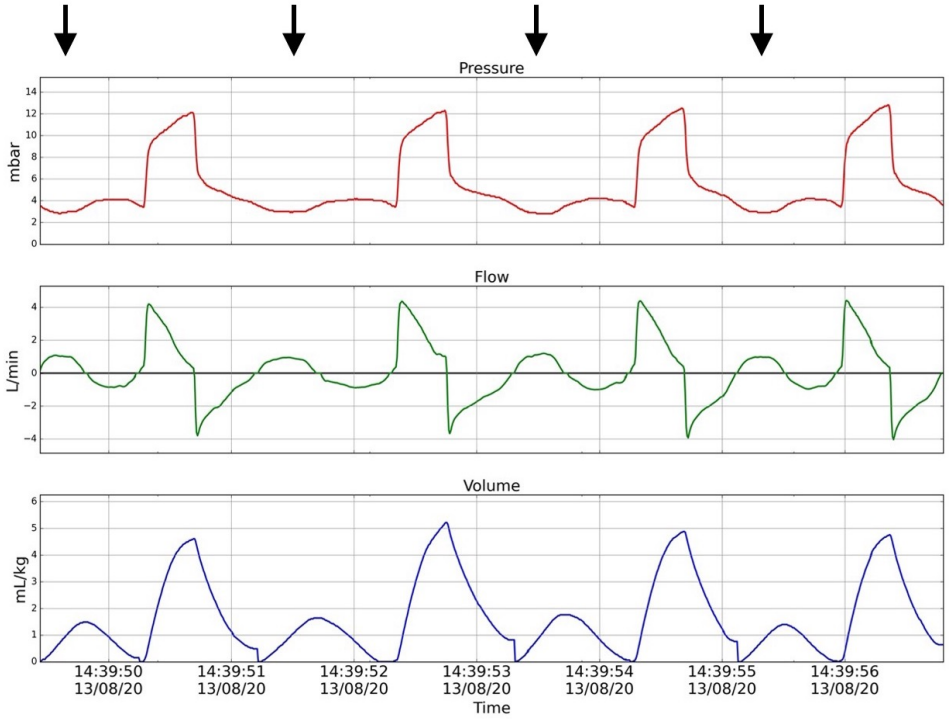


Figure 4: **Synchronised intermittent mandatory ventilation (SIMV).** Pressure (red), flow (green) and volume (blue) waveforms over a period of ~7 seconds. Ventilator inflations and spontaneous breaths alternate. No pressure support is used for spontaneous breaths; therefore, they are characterised by some negative deflections of the pressure in the ventilator's circuit during inspiration (arrows). Spontaneous breaths are associated with much lower inspiratory (positive) and expiratory (negative) flow than ventilator inflations and their tidal volume is approximately 1/3 of the VT of ventilator inflations (1.5 mL/kg vs. 5 mL/kg).

3.3.2.1.3. Pressure support ventilation

SIPPV and SIMV are time-cycled modes, that is, ventilator inspiration ends and pressure returns to PEEP level after the set inspiratory time, which is determined by the clinician. In contrast, pressure support ventilation is flow-cycled, and inspiration ends when the inspiratory flow drops down to a low level (**Figure 6**), usually 5-20% of the peak inspiratory flow (this "termination criterion" can be set on some ventilators). The inspiratory time is determined by the respiratory mechanics and it is not constant. Clinicians can set a maximum inspiratory time (Timax), which cannot be exceeded and after which inspiration ends irrespective of the flow. Similar to SIPPV, during PSV the set ventilator rate is also only a minimum rate and the baby can trigger more inflations.

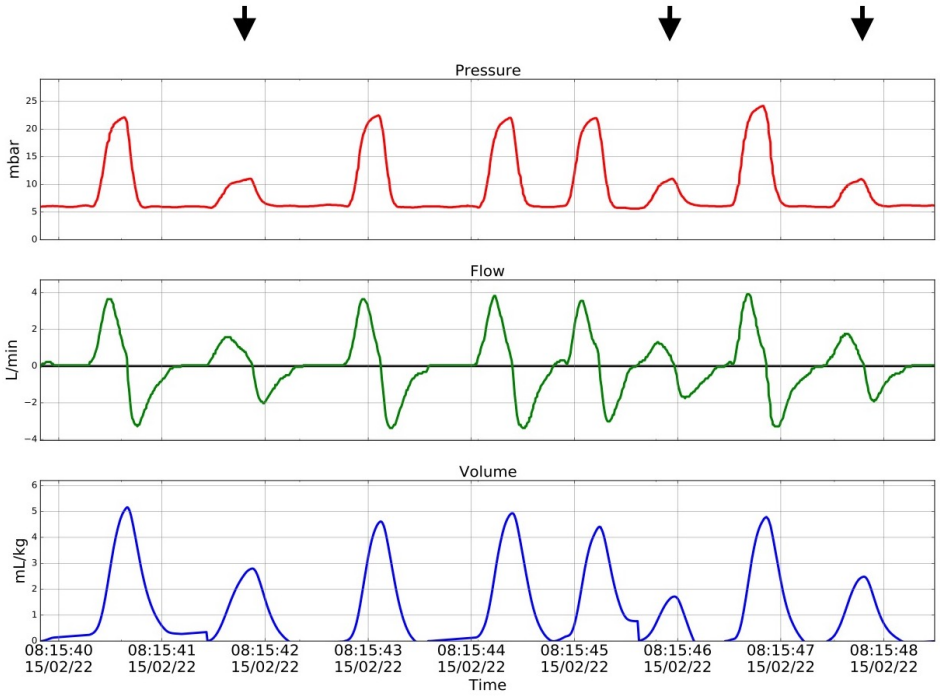


Figure 5: **Synchronised intermittent mandatory ventilation with pressure support on spontaneous breaths (SIMV-PS).** Pressure (red), flow (green) and volume (blue) waveforms over a period of ~9 seconds. Spontaneous breaths (arrows) occur between ventilator inflations, and they receive pressure support. Pressure support level is 5 mbar above PEEP which was 6 mbar. Pressure supported spontaneous breaths had lower inspiratory and expiratory flow and lower tidal volume than ventilator inflations. Note that PIP of ventilator inflations is variable as volume targeted ventilation was used.

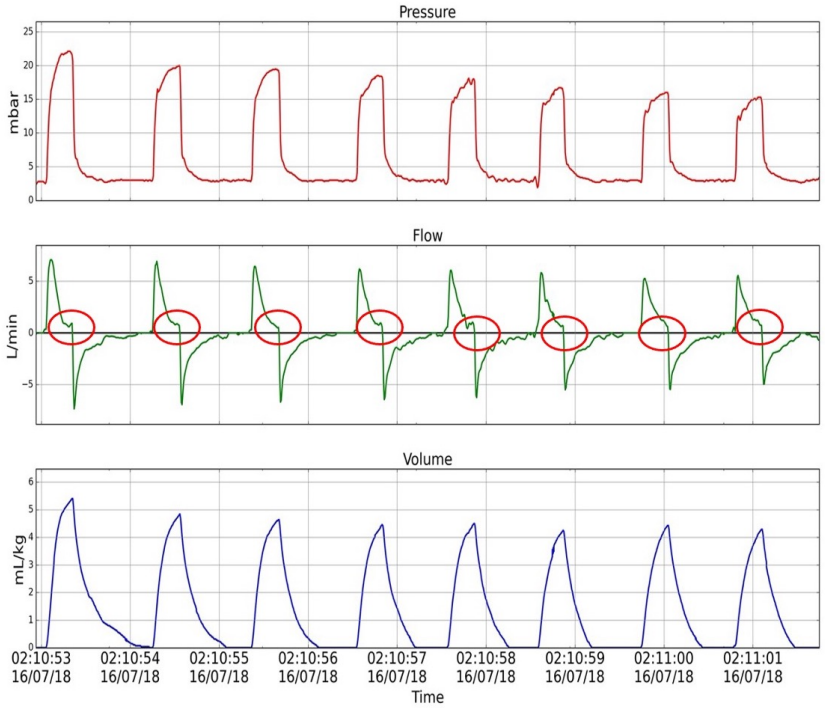


Figure 6: Pressure support ventilation (PSV). Pressure (red), flow (green) and volume (blue) waveforms over a period of ~9 seconds. Inspiration ends and airway pressure drops to PEEP when inspiratory flow has decreased to 15% of the peak inspiratory flow (red circles). The inspiratory time is slightly variable. Note that PIP is being gradually decreasing during the consecutive inflations. This is because VG was also used (PSV-VG).

3.3.2.1.4. The impact of pressure rise time on ventilator waveforms

Pressure rise time (PRT, also known as slope time) is the time from the beginning of pressure rise to the point when the PIP is reached. The duration of the PRT influences the shape of the pressure waveform (**Figure 7**). PRT is determined by the level of continuous flow in the ventilator circuit ("circuit flow"): the higher the circuit flow, the faster the pressure rise and the shorter the PRT. On some ventilators the circuit flow, rather than PRT, can be set and PRT is determined implicitly.

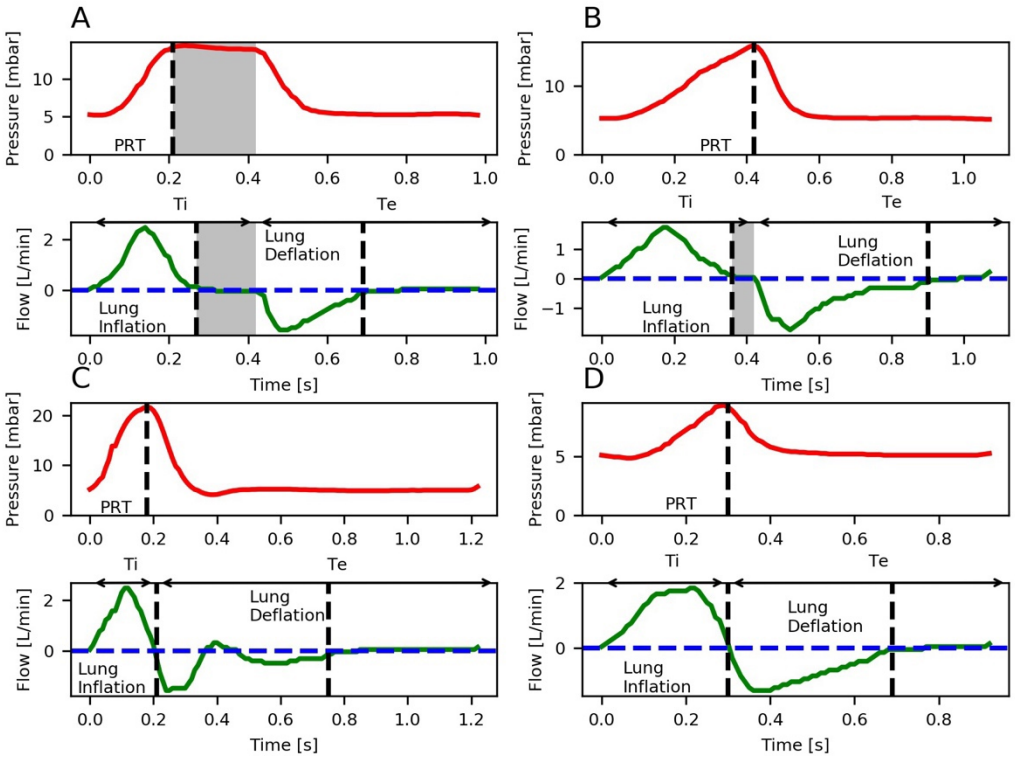


Figure 7. Ventilator pressure and flow waveforms, with different pressure rise times during SIPPV-VG and PSV-VG modes. On the pressure waveforms the end of pressure rise is marked by a dashed vertical line; pressure plateau, if present, is highlighted by shading. On the flow waveforms the end of lung inflation and lung deflation are marked by dashed vertical lines; inspiratory hold, if present, is highlighted by shading. Inspiratory and expiratory times are showed by arrows above the waveforms. **A-B.** SIPPV-VG ventilation with an inspiratory time of 0.4 s but with a short pressure rise time (0.08 s) in **A**, or long (0.40 s) in **B**. In **A**, the short PRT results in a pressure plateau (shaded area) and when that is reached, the flow quickly drops down to zero resulting in a long inspiratory hold of ~0.2 s (shaded area), lasting until the end of the 0.4 s inspiratory time. In **B** with the long PRT, the inflating pressure rises gradually during almost the whole inspiration. There is only a very short inspiratory hold lasting for <0.05 s (shaded area). **C-D.** PSV-VG ventilation. The PRT in **C** is set at 0.08 s in **D** at 0.4 s; Timax is 0.6 s in both cases. During PSV-VG ventilator inflation stopped when inspiratory flow decreased to 15% of the peak flow; therefore, there is no inspiratory hold and Ti is variable. A longer PRT is associated with longer Ti. In **C** the baby continues to breathe in during the expiratory part of the ventilator cycle. Please note the actual PRTs delivered by the ventilator do not always correspond exactly to the set values. Adapted from (23)

Changing the PRT affects ventilator inflations during time-cycled and flow-cycled modes differently. During time-cycled modes (SIPPV or SIMV), a short PRT (high circuit flow rate) is thought to be associated with improved oxygenation as it is associated with higher mean airway pressure (MAP) with increased area under the pressure curve (24). During flow-cycled

ventilation a shorter PRT is expected to lead to shorter inspiratory times although this has not been reported from human studies. However, a short PRT (high circuit flow) might also contribute to lung damage and possibly bronchopulmonary dysplasia due to the increased tissue shear (rheotrauma). A study done in sheep found that increased circuit flow rate (corresponding to short PRT) caused lung damage, but only at flow rates of 18 or 28 L/min, considerably higher than the <10 L/min usually used by neonatal ventilators during conventional ventilation (25, 26). In a follow-up study in human infants, ventilator flow rates between 4-8 L/min did not alter cytokine release in tracheal aspirates (27). However, the effect of using different PRTs on ventilator parameters and blood gases has not been studied in infants prior to the work presented in this thesis and an associated paper (23).

3.3.2.1.5. Comparison and indications of synchronised ventilation modes

Studies with long term clinical outcomes comparing the different synchronised ventilation modes are lacking. Most studies were small, included a heterogenous group of patients and ventilation protocols, were of short duration and only looked at short term physiologic and clinical outcomes. In systematic reviews, ventilation modes supporting all breaths (SIPPV and PSV) were associated with shorter duration of ventilation than SIMV (21, 28). However, there was no significant difference in the prevalence of BPD or other long-term outcomes. A systematic review comparing flow-cycled (PSV) and time cycled (SIPPV and SIMV) ventilation modes concluded that there was insufficient evidence to decide whether one of them offers benefits over the other for babies (29).

Of note, babies included in most of these studies were bigger and more mature than the extremely low birth weight (ELBW) infants who frequently require mechanical ventilation today. The ventilators were also older models, and flow sensors and synchronisation algorithms have improved significantly since then. It is possible that synchronised ventilation using today's ventilator models offers more clinical benefit over CMV than reported in the published studies. Currently most neonatal units use synchronised ventilation modes in all cases.

During SIMV, clinicians frequently use PS to reduce the work of the breathing imposed on the baby by breathing through a narrow endotracheal tube (30, 31). In a randomized trial, infants ventilated with SIMV-PS required fewer days of mechanical ventilation than babies receiving SIMV only (32). The PS level is usually set as a fraction (e.g., 50% or 75%) of the peak inflating pressure during SIMV inflations (33). While there is no evidence-based recommendation to set PS at a particular level, it has been shown that the use of PS, and its level, influence several ventilator and physiological parameters. Gupta *et al* reported an increase in MAP and MV and a decrease in the total respiratory rate with increasing PS levels (34). In another study, Osorio *et al.* found that using PS with SIMV increased not only MAP and MV but also the total respiratory rate (35). However, in this study, the set SIMV rate was reduced when PS was used and the increase in respiratory rate may have been compensatory to that.

3.3.2.2. Volume targeted ventilation (volume guarantee)

3.3.2.2.1. The logic of volume targeted ventilation

Besides synchronisation, the other way of adapting ventilator inflations to the patient's needs is to change the driving pressure of ventilator inflations in response to the baby's respiratory effort. During volume targeted ventilation (VTV, also known as volume guarantee, VG), the ventilator calculates the expired tidal volume (VTemand) of each ventilator inflation by integrating flow sensor data, and adjusts the PIP of the next inflation in order to keep VTemand as close as possible to the target VT (VTset), set by clinicians (**Figure 8**) (7, 36). If VTemand is less than the target, PIP is increased gradually until a maximum allowed value (Pmax), which is also set by the user (**Figure 9)**. If VTemand is above the target, e, PIP is progressively reduced to as low as the PEEP level **(Figure 10)**.

The PIP required to deliver the target VTset depends on lung mechanics, the leak around the ETT and the infant's breathing effort. In babies with no respiratory effort and no leak, the ventilator's inflating pressure (Pinfl, the difference between PIP and positive end-expiratory

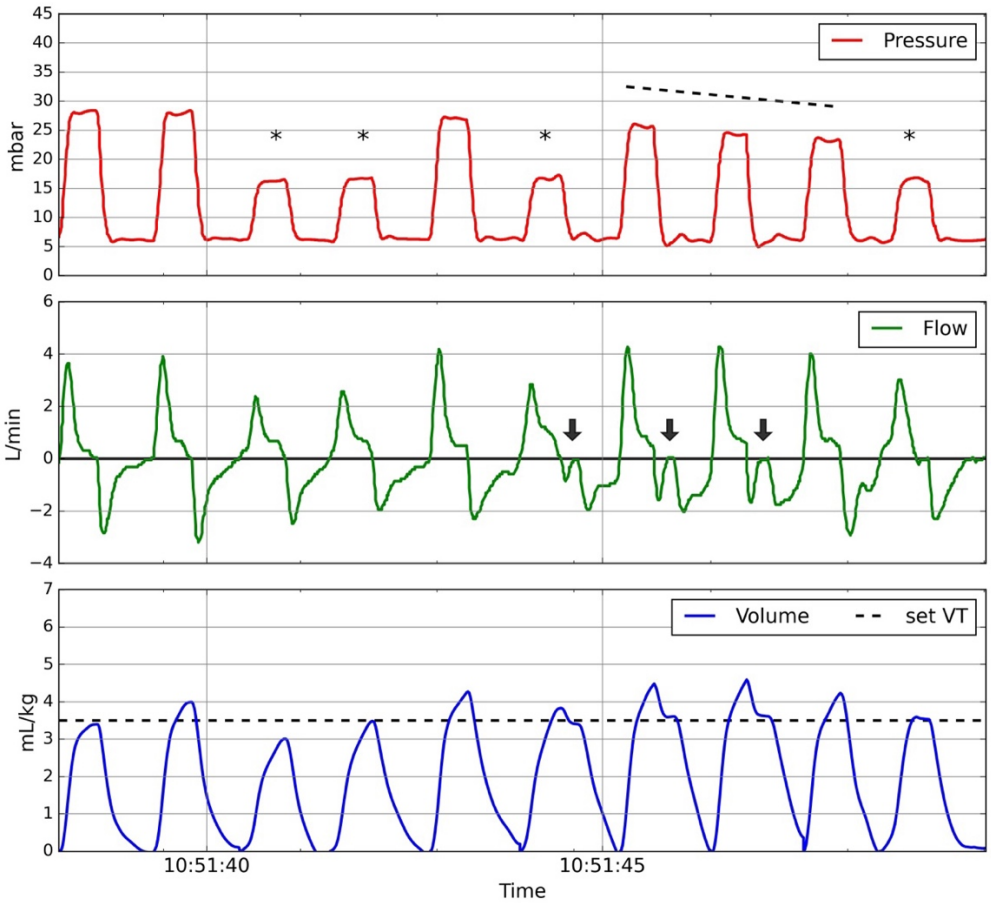


Figure 8: Volume targeted ventilation. Pressure, flow and volume waveforms from a 14-second recording of a term infant ventilated with SIPPV-VG mode containing 10 inflations, 4 of them triggered (synchronised, marked with asterisks), and 6 untriggered (backup). The triggered inflations have PIPs ~17 mbar and the untriggered inflations PIPs ~28 mbar. During triggered inflations the infant has contributed to the VT with her own inhalations. The tidal volume was close to the targeted 3.5 mL/kg (dashed line) during both triggered and untriggered inflations. As the tidal volumes of inflations 7-9 were above the target, the PIP was gradually reduced (marked with dashed line). Towards the end of the recording the baby takes small breaths, shown by the arrows, which interrupt the ventilator's expiratory flow. Figure adapted from (7).

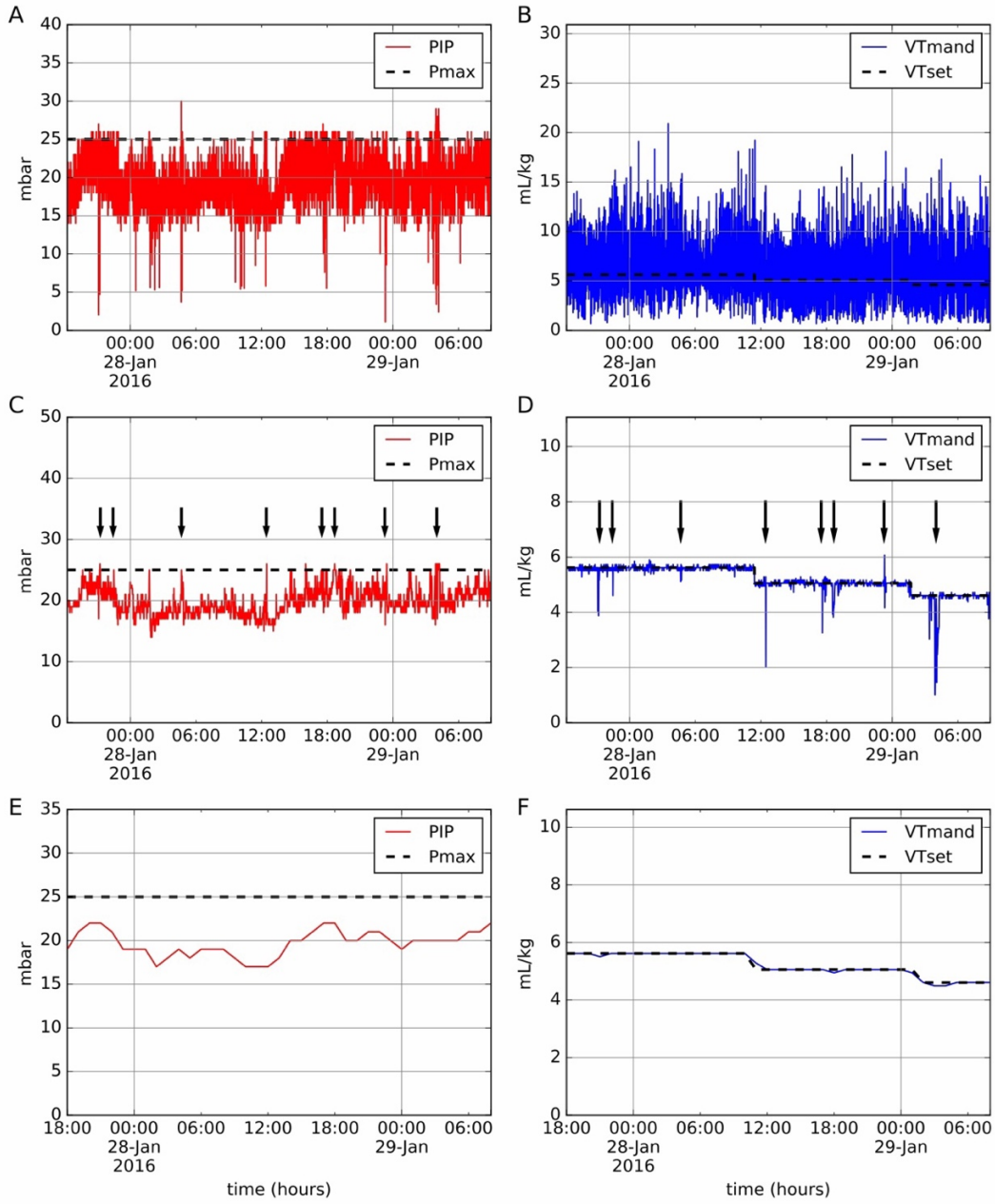


Figure 9: **Short and long-term variability of peak inspiratory pressure and tidal volume during SIPPV-VG.** **A**: Variability of PIP. The ventilator was sampled with 1 Hz over a period of 38.5 hours; therefore, this graph is based >130,000 data points but due to resolution of the image and the pressure measurements, not every data point is shown separately. The median PIP of this recording was 5 mbar below the Pmax. However, due its variability, the PIP frequently reached Pmax when inflation stopped, and delivery of tidal volume could have been limited. **B**: Variability of the mandatory leak-compensated tidal volume (VTmand) in the same recording, sampled with 1 Hz frequency. The target VT is also shown (dashed line). VTmand is highly variable and sometimes exceeds 10 mL/kg due to the infant taking deep breaths. **C**: Graph showing median of the PIP aggregated over 1-minute periods. Each data point represents the median of 60 measurements taken at 1 Hz sampling rate, removing most of short-term variability. However, occasionally even the 1-minute median values of PIP reached Pmax (arrows). **D**: Graph showing median VTmand aggregated over 1-minute periods. It shows that on average the VG delivered the set VT very well. When Pmax was reached, tidal volume delivery was also limited. **E**: 1-hour medians of PIP demonstrate long-term changes in PIP. Over a longer time, the median PIP remained well below the Pmax. **F**: 1-hour medians of VTmand. The long-term average of the tidal volume is very close to the targeted value. Adapted from (37).

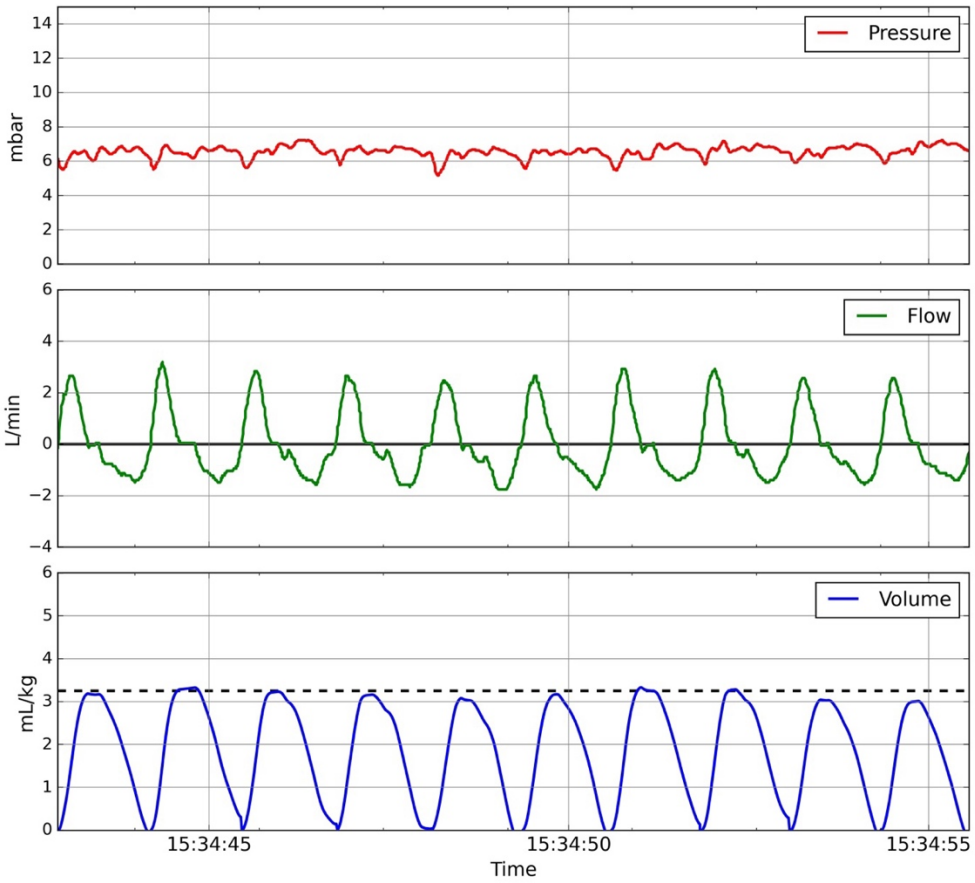


Figure 10: Ventilator recording of a term infant suffering from hypoxic ischaemic encephalopathy and ventilated with SIMV-VG. PIP is low, just above the PEEP. This infant had normal lungs and had fast and deep breaths trying to lower the $PaCO_2$ as a response to the metabolic acidosis. The target expired tidal volume (VTset) was at 3.25 mL/kg (dashed line). As the infant generated VTset alone, the VG algorithm reduced PIP of the triggered ventilator inflations to the PEEP level. Please note that the RRset was 30/min. The infant's breathing rate here is ~60/min. Triggered SIMV inflations and spontaneous breaths cannot be distinguished from each other on the graph. The $PaCO_2$ was in the normal range. Figure adapted from (7).

pressure, PEEP) required to deliver a particular VTset is a function of the respiratory system's compliance and the airway resistance, as described by the equation of motion (38). Decreasing respiratory system compliance or increasing airway resistance requires a higher inflating pressure to deliver the same tidal volume and vice versa.

Volume targeted ventilation is conceptually different from volume-controlled ventilation which is frequently used in adults and older children. Volume controlled ventilation uses constant or linearly decelerating inspiratory flow to deliver the set *inspired* tidal volume for each inflation, that is, its primary control variable is flow or volume. During VG, individual inflations are pressure controlled and inspiratory flow is variable. Volume targeting is achieved by the ventilator's computer adjusting the PIP breath-to-breath. As a result, the delivered VTe is usually somewhat different from the set target. As the baby can freely breathe in from the continuous flow of the ventilator circuit, tidal volume can also exceed the target set by the clinician.

3.3.2.2.1.1. The role of the maximum allowed inspiratory pressure (Pmax) during volume guarantee ventilation

During VG a maximum inflating pressure (Pmax) is set to prevent the PIP going inadvertently high (see section **3.3.2.2.1 and Figure 9).** If Pmax is set too low, it limits the PIP and tidal volume delivery and causes frequent "low tidal volume" alarms (39). If Pmax is set too high, there may be a delay in recognizing important clinical events such as slippage of the endotracheal tube, pneumothorax or change in the lung's compliance. It has been recommended Pmax should initially be set about 5 mbar above the "working PIP" used to deliver VTset and if VTset is not reached Pmax should be increased in small steps (40). In another review an initial Pmax of ~25-30 mbar was recommended with a later adjustment to at least 5-10 mbar above the "working PIP", allowing the ventilator flexibility to deliver the target VTset during variable spontaneous breaths, changing ETT leaks or untriggered inflations (36). A problem with setting Pmax is that although there had been data about accuracy of the delivered tidal volume during VG ventilation (41, 42, 43), details of how PIP varies as a baby breathes, cries, splints against an inflation, as the ETT position, or leak around it, changes and the effect of the P_{max} has been unknown. It has also been unclear, how well a Pmax can be determined by observing the baby and ventilator because there are limited data about the variation in PIP during VG (41, 42). In a study included in this thesis we sought answers to these questions (37).

3.3.2.2.2. Evidence for use of volume targeted ventilation

Compared with pressure-controlled ventilation, VG is associated with more stable tidal volumes and pCO_2 levels, shorter duration of mechanical ventilation and fewer pneumothoraces. In addition, VG has been shown to improve several long-term clinical outcomes in systematic reviews (44, 45). Babies receiving VG did better in terms of the combined outcome of death or bronchopulmonary dysplasia (BPD). There was also a lower risk of severe (grade 3 or 4) IVH and periventricular white matter lesions. Due to these benefits, VG has been increasingly used on NICUs, although its introduction to routine clinical care has been hindered by lack of knowledge about this complex ventilator mode and how to set the target tidal volume (46).

Most studies investigating VG recruited very preterm infants and the benefits of VG ventilation in term babies are much less well established. In a randomized study of 40 infants born at >34 weeks of gestation Bhat *et al.* found fewer episodes of hypocapnia during VG but no other benefits (47). There was also no publication about the effects of volume-targeted ventilation during emergency neonatal transport, prior to the work presented in this thesis and the associated publication (48).

3.3.2.2.3. Combination of ventilation modes with volume guarantee

Volume guarantee can be combined with SIPPV, SIMV and PSV. If the infant becomes apneic during these synchronized modes, volume targeting is still maintained for the backup inflations which are delivered at the set ventilator rate. During SIMV-VG with pressure support on the spontaneous breaths (SIMV-VG-PS), only the mandatory (SIMV) inflations are volume-targeted; the pressure supported spontaneous breaths are positive pressure inflations with a set PIP which equals the PEEP plus the pressure support level (PS). Therefore, in this mode, the

relationship between the PIP of the volume guaranteed inflations (PIPmand) and the PIP of the pressure supported spontaneous breaths (PIPspon) is not fixed, because the VG algorithm alters the PIPmand breath-to-breath in response to the expired tidal volume of the previous inflation, while the PS level (and consequently, PIPspon) remains the same, unless it is changed by clinicians (**Figure 11**). This may result in a variable ratio of the mandatory and spontaneous tidal volumes and their contribution to total minute ventilation. However, there were no published reports about the use of SIMV-VG-PS in neonatology prior to the work presented in this thesis and the associated publication.

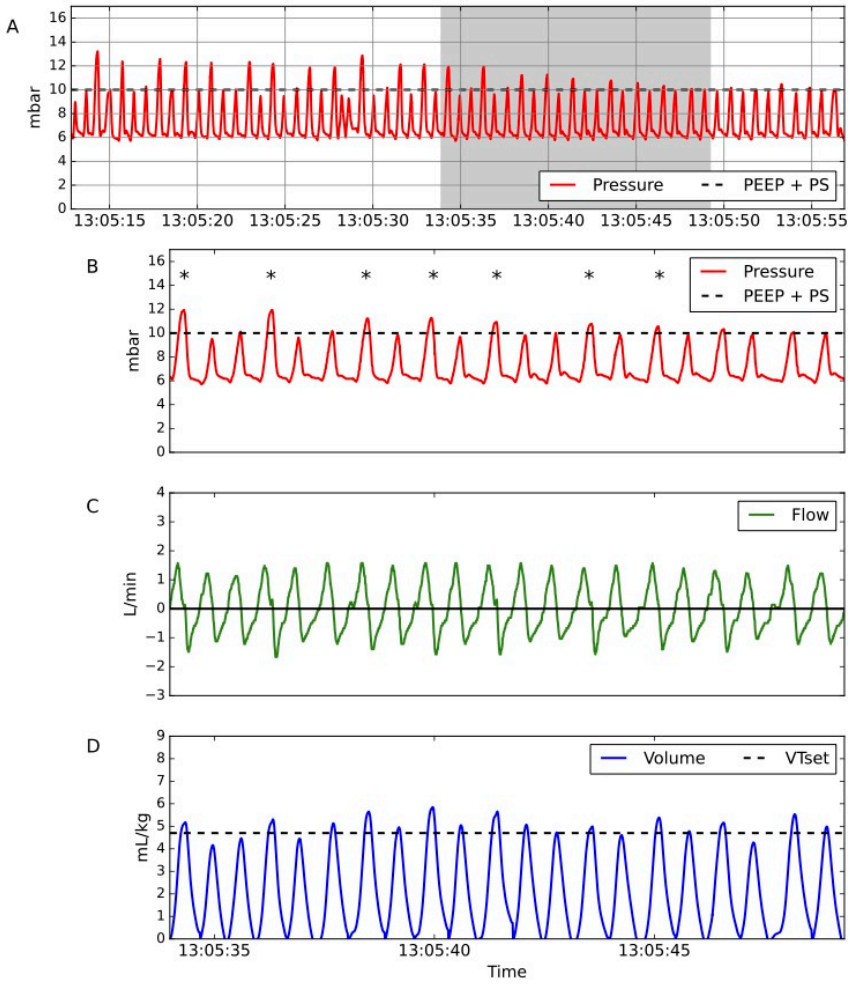


Figure 11. Ventilator waveforms of a 25-weeker preterm infant ventilated using SIMV-VG-PS for respiratory distress. Ventilator rate of VG inflations was 35/min, their inspiratory time was 0.3 seconds, pressure rise time was 0.15 seconds. **A.** Pressure waveforms over a period of ~45 seconds. Volume-targeted mandatory ventilator inflations (asterisks) alternate 1:1 or 1:2 with pressure supported spontaneous breaths. The total (mandatory plus spontaneous) respiratory rate is ~85/min. The peak inspiratory pressure of mandatory inflation (PIPmand) is variable. Pressure support level (PS) was set at 4 mbar, positive end expiratory pressure (PEEP) at 6 mbar; therefore, the peak inspiratory pressure of spontaneous breaths (PIPspon = PEEP + PS) is 10 mbar (dashed line). **B.** Pressure, flow and volume waveforms for the period marked by shading on A. Tidal volumes of the volume guaranteed ventilator inflations (asterisks) were larger than the target VT which was 4.7 mL/kg (dashed line over the volume waveform), therefore their peak inspiratory pressure is progressively reduced by the VG algorithm until they become indistinguishable from the pressure supported spontaneous breaths. Note that flow waveforms indirectly suggest the presence of intrinsic PEEP as there is no flow-free interval between expiration and inspiration (49).

3.3.2.2.4. Volume targeted ventilation in babies with strong respiratory effort

During VTV, if the baby is breathing, his or her effort contributes to lung inflations during triggered ventilator cycles or coincidentally also during non-triggered ones. In this case the VTV algorithm reduces PIP to avoid VT exceeding its target. In infants with strong spontaneous breathing this can result in very low ventilator inflating pressures, when the PIP is just above the PEEP (see **Figure 10** and reference (50)). It has been suggested that this could lead to cycles of exhaustion with fluctuations of the partial pressure of carbon dioxide in the blood (pCO_2), and that the intermittent drop in mean airway pressure may contribute to intracranial haemorrhage and atelectasis (51), but there are no published studies about this. In a study included in this thesis and in the associated paper (52) we investigated how frequently low PIP occurs in babies ventilated with VG and how it impacts on other ventilator parameters and blood gases. In another paper we also investigated ventilator parameters during VTV in infants suffering from HIE, because these babies frequently hyperventilate to compensate for their metabolic acidosis (53).

3.3.2.3. Proportional assist ventilation and neurally adjusted ventilator assist

During VG, the ventilator's contribution shows an inverse relationship with the baby's own respiratory effort: when the baby takes deeper breaths, less contribution is required from the ventilator to achieve the target VTset, and the ventilator's algorithm gradually reduces the PIP of the ventilator inflations. In contrast, during PAV and NAVA, the ventilator's contribution is proportional to the infant's respiratory effort, that is, a stronger breathing infant will receive higher inspiratory pressures and more ventilator support. These ventilator modes allow for selective unloading of the resistive work of breathing (calculated from the level of inspiratory flow) and of the elastic work of breathing (calculated from the speed of change in lung volume) (54).

While PAV uses flow signals for triggering ventilator inflations, NAVA is triggered by the neuromuscular activity of the diaphragm. During NAVA, triggering delay is shorter than during flow triggering and there is less patient-ventilator asynchrony (17). However, NAVA is dependent on placement of nasogastric tube containing the sensor to detect diaphragm activity, which is invasive and expensive and it is limiting its routine clinical use (14, 46). In addition, there is a need for clinical studies to assess if it improves long-term clinical outcomes.

3.3.3. Leak compensation

The third adaptative feature of modern ventilators is to limit the impact of leakage around the ETT on patient-ventilator interactions and respiratory mechanics. Unlike adults or older children, babies are usually intubated with un-cuffed endotracheal tubes, because cuffed tubes have not been available in small sizes and they were associated with increased risk of tracheal damage (55). More recently, micro-cuffed tubes have become available from size 3.0 mm internal diameter, although they still have a reduced internal diameter and increased resistance when compared to un-cuffed tubes (56). There is usually a significant and often variable leak around un-cuffed tube.

When there is leak around the ETT, the VTe (determined from flow data detected by the flow sensor) is less the VTi (**Figure 12A**). The actual tidal volume is between the inspired and expired tidal volume, but much closer to the expired tidal volume, because the pressures in the trachea and the lungs are higher during inspiration than during expiration and therefore there is more leak during inspiration (57, 58). However, the value of the actual tidal volume cannot be determined from flow data, only estimated using physical principles (57).

Leak around the ETT was one of the main reasons while primary volume-controlled ventilation has not become widely used in neonates: volume controlled ventilation usually delivers a set *inspired* tidal volume, but in case of a large leak, the baby would receive only a variable fraction of it. However, leaks can also interfere with other aspects of ventilator performance including synchronisation, cycling, lung pressurisation and tidal volume delivery. Modern computerised ventilators and their algorithms have built-in mechanisms to reduce the impact of leaks.

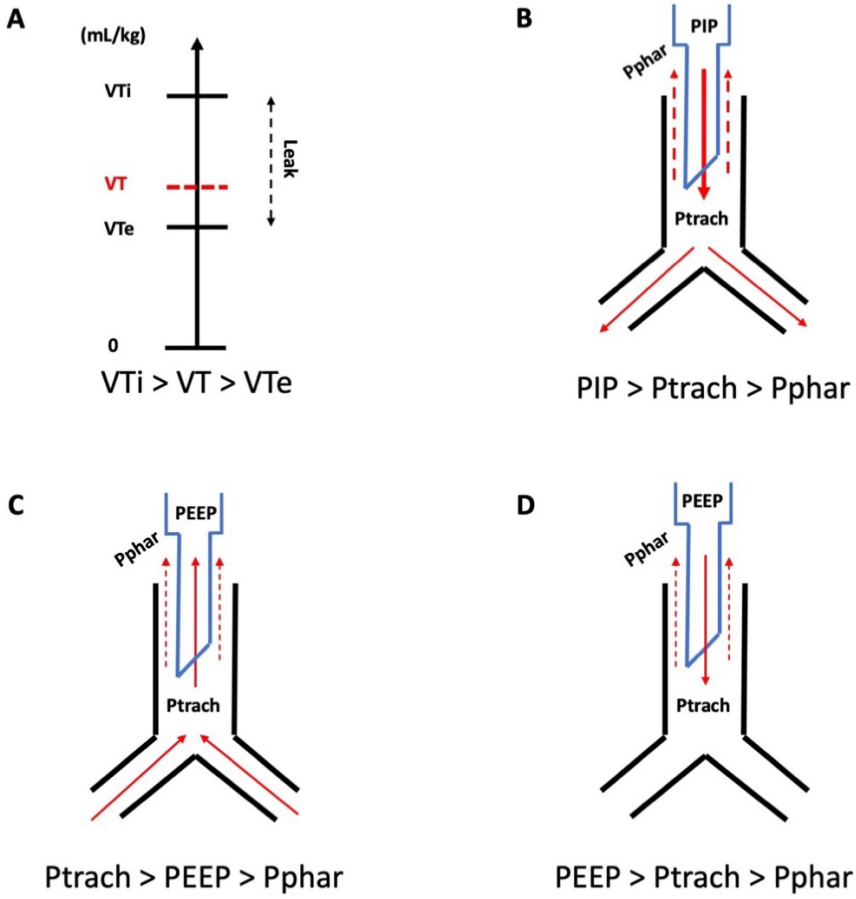


Figure 12: A. Relationship between the inspired (VTi) and expired (VTe) tidal volumes calculated from flow sensor data and the actual, effective tidal volume (VT). VT is closer to VTe than to VTi as there is more leak during inspiration due to the larger pressure difference between the tracheal end of the ETT and the pharynx. VT cannot be determined directly from flow sensor data, only estimated using flow and pressure data together with endotracheal tube and ventilator circuit characteristics. **B-D**. Schematic drawings showing pressures and gas flow (arrows) in case of a significant leak around the ETT during inspiration (**B**), during expiration (**C**) and between ventilator inflations (**D**). The thickness of the arrows is proportional to the rate of flow. The leak is larger during inspiration than during expiration because the pressure in the trachea at the distal end of the tube (Ptrach) is higher. The leak between ventilator inflations results in ongoing inward flow through the tube which may cause auto-triggering of the ventilator unless effective leak adaptation is used. PIP and PEEP are the peak inspiratory pressure and the positive end-expiratory pressure, respectively, measured at the proximal end of the ETT. Pphar is the pressure in the pharynx, approximately equal to the atmospheric pressure.

3.3.3.1. Limiting the impact of leaks on synchronisation and cycling

Leak around the ETT may result in auto-triggering of the ventilator even when the baby has no respiratory effort. PEEP is invariably used during neonatal ventilation. Due to PEEP, there is an ongoing outward gas flow through the leak between ventilator inflations, because the pressure in the trachea is always higher than the atmospheric pressure of the pharynx (see **Figure 12D**). The resultant loss of gas in the trachea is replaced by an inward flow through the ETT, which may be misinterpreted by the ventilator as respiratory attempt made by the baby and delivery of "synchronised" ventilator inflations may follow (59, 60). Modern ventilators frequently include a mechanism (called "leak adaptation" or "leak compensation"), when the flow trigger's threshold is increased automatically in case of a large leak to avoid auto-triggering (**Figure 13**) (61, 62). These changes in triggering threshold are usually hidden from clinicians, who can continue using sensitive flow trigger settings (i.e., 0.1-0.2 L/min) without the risk of frequent auto-triggering.

The ongoing inward flow between ventilator inflations with significant leak can also interfere with flow cycling during pressure support ventilation, as inspiratory flow may not drop to the level where the ventilator's computer would normally "cycle", that is, end inspiration and return pressure to PEEP level (60). To avoid this, during modern flow cycling algorithms the cycling threshold is also automatically increased when there is a significant ETT leak (**Figure 13**).

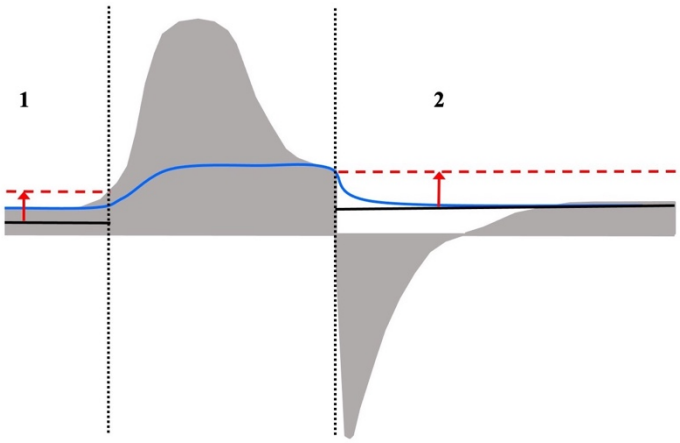


Figure 13: Leak adaptation to avoid leak-related auto-triggering or delayed cycling. Flow waveform is shown as measured by the flow sensor at the proximal end of the ETT. Leak flow is indicated by blue line. Inspiratory phase of the ventilator inflation is between the dotted vertical lines, expiration is after the second dotted line. *Prevention of auto-triggering (1):* In the absence of leak adaptation, a ventilator inflation would be triggered immediately without any patient effort as the set trigger threshold (horizontal black line) is lower that the ongoing flow between ventilator inflations. During leak adaptation, the ventilator's algorithm increases the trigger threshold to a higher level (red arrow and red dashed line); triggering will only occur if flow is increased further by the patient effort. *Prevention of delayed cycling (2):* During this flow-cycled inflation, cycling (termination) of ventilator inspiration would be delayed as leak flow remains higher than termination sensitivity (horizontal black line). Automatic increase of termination sensitivity (red arrow and line) ensures that cycling is not delayed. Drawing is not to scale.

3.3.3.2. Limiting the impact of leaks on lung pressurisation and maintenance of airway pressure

With a large leak around the ETT, larger inspiratory flow is required for the pressure in the trachea and the lungs to increase to the PIP level, because some of the gas entering through the tube is immediately leaking out next to it to the pharynx. Modern ventilators automatically increase the flow in the ventilator circuit in case of the large leak to ensure enough flow is

available for the pressure to build up within the same time. Somewhat confusingly, this is also called “leak compensation” (63, 64, 65, 66).

Even with leak compensation, the pressure in the trachea is still below PIP at the end of inspiration and below PEEP during the end of expiration (67, 68). This is because there is an inward flow through the ETT to replace the volume escaping through the leak, and this means that there is also a pressure drop through the tube (see **Figure 12)** (69). The PIP and PEEP displayed by the ventilator represent measurements in the circuit proximal to the ETT; the relevant pressures in the lungs are lower than that. Leak compensation mechanisms cannot fully eliminate this and the resultant suboptimal lung inflation or lung collapse may be responsible for the desaturation and increased FiO_2 requirement seen infants who have sick lungs and large leak around the ETT. The automatic tube compensation (ATC) function estimates the pressure drop through the ETT using the length and the internal diameter of the tube and the flow through it and increases the pressure at the proximal end of the tube to ensure that the set PIP is achieved at the distal end of the tube during inspiration (70). ATC is also active between lung inflations when the pressure at the proximal end of the tube is at the PEEP level. Therefore, in principle, it could also compensate for the loss of PEEP. However, although ATC is available on some neonatal ventilators, its neonatal use has not been reported yet.

3.3.3.3. Limiting the impact of leaks on tidal volume delivery during volume guarantee ventilation

During volume targeted ventilation, the ventilator is trying to maintain the *expired* tidal volume close to the target VT set by the clinician. However, if there is a very large leak, this cannot be achieved, even when PIP is progressive increased to the level of Pmax, resulting in frequent or constant alarming of the ventilator and the risk of alarm fatigue (see **section 3.7**.). It has been held anecdotally that this occurs when leak is significantly >50% but there had been no reported studies about this prior to work presented in this thesis and the associated publications (58, 71). Of note, the effective tidal volume and the blood CO_2 level may still be acceptable even in this situation because it is higher than the expired VT (**Figure 12A**).

The VN series of the Dräger Babylog™ neonatal ventilators (VN500, VN600 and VN800), allow the user to target the “leak compensated expired tidal volume” (VTmand) instead of the expired VT (VTemand) during volume targeted ventilation (**Figure 14**). This includes the leak during expiration (which gas was present in the lungs at the end of inspiration and therefore participated in gas exchange, see **Figure 12**), and thereby it is approximating the effective (actual) tidal volume. The expiratory leak cannot be determined from flow sensor data, only estimated from the pressure and flow data and the ETT’s diameter using physics principles. The Dräger ventilator’s manual refer to this as “leak compensation”, although it is very different from the “leak compensation” mechanisms offered by other ventilators as detailed above. There have been no reports about the use of this mode except the work presented in this thesis (58).

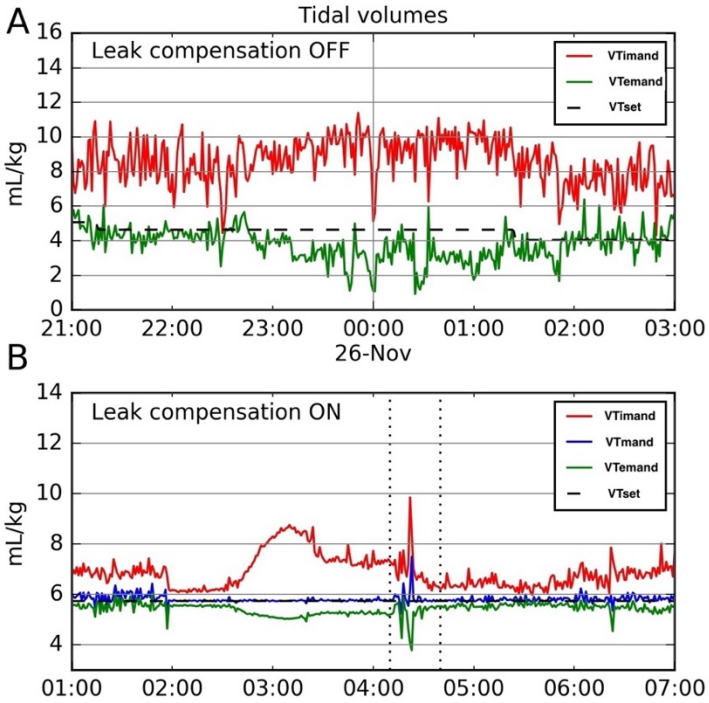


Figure 14: Volume targeted ventilation with or without leak compensation. Two illustrative cases showing VG ventilation using the Dräger Babylog™ VN500 ventilator with variable ETT leak for six hours. Each data point on graph is the average of 60 measurements collected with 1 Hz sampling rate. **A**. No leak compensation, the expired tidal volume (VTemand) is the target tidal volume. Between 23:00 – 01:00 the large difference between the VTimand and VTemand was due to a large (>50%) leak and so VTemand remained below the target VTset (dashed line). **B**. Leak compensation on, VTmand is the targeted at the set level. VTmand is calculated as VTemand plus the estimated ETT leak during expiration, so with a leak VTmand is larger than VTemand. In this recording the VTmand is maintained very close to VTset throughout the recording, even when there is >50% leak around 03:00 to 04:00. Adapted from (58).

3.4. High frequency oscillatory ventilation (HFOV)

High frequency ventilation (HFV) is an alternative mode of respiratory support which has been available in neonatology for more than 40 years (72, 73). During HFV, lower gas volume enters the lungs at a time than during conventional ventilation but it happens at a much higher rate. Due to high frequency of respiratory cycles, expiration cannot happen passively as during spontaneous breathing or conventional mechanical ventilation, but it needs to be assisted actively by the ventilator.

There are three kinds of HFV used in newborn: high frequency jet ventilation (HFJV), high frequency flow interruption (HFFI) and high frequency oscillatory ventilation (HFOV). Of them, HFOV has been used most extensively in newborns.

3.4.1. Basic principles of HFOV

During HFOV, pressure oscillations are generated by the ventilator using various mechanisms (piston, membrane, etc.) at a frequency of 5-20 Hz (300–1200 per minute), **Figure 15**. These pressure oscillations are centred around a continuous distending pressure (CDP) maintained in the ventilator's circuit and in the lungs; in case of fully symmetrical pressure oscillations (which is rarely the case), MAP is the same as CDP. Gas movement is generated by these pressure oscillations.

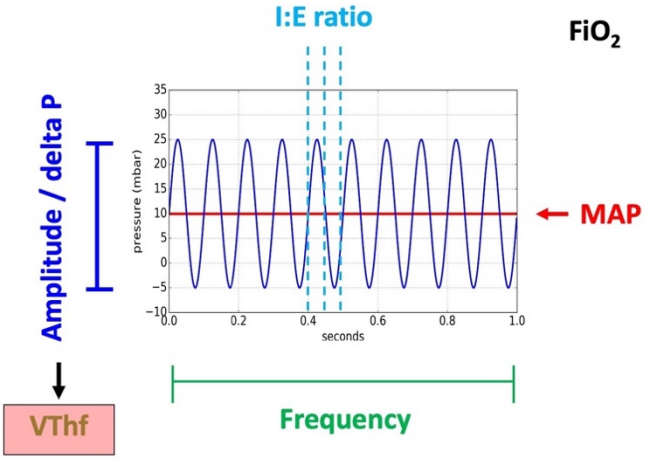


Figure 15: Ventilator parameters during high frequency oscillatory ventilation (HFOV). See main text for more details.

3.4.2. Ventilator parameters during HFOV

During HFOV, clinicians set FiO_2, MAP, frequency, the amplitude of pressure oscillations (also known as "deltaP"), and the ratio of the inspiratory time and expiratory time ("I:E ratio"), see **Figure 15.** Modern oscillators also display the "tidal volume" of oscillations, abbreviated as VThf, which is a misnomer as HFOV is not considered traditionally as "tidal ventilation". During HFOV-VG (see later) VThf can be set by the user. Modern oscillators also display the diffusion coefficient of carbon dioxide (DCO_2) which is the main indicator of CO_2 elimination during HFOV (see **section 3.4.3.4.).**

3.4.3. Gas exchange during HFOV

3.4.3.1. Mechanisms of gas exchange during HFOV

During conventional ventilation, gas enters the lungs during each respiratory cycle (ventilator inflation or spontaneous breath). This is called "tidal ventilation" and its volume is called the "tidal volume" (VT). It has been held traditionally, that only part of the VT, which exceeds the equipment and anatomic dead space volume (VD), participates in alveolar gas exchange (74, 75). The equipment dead space includes the volume of the endotracheal tube, flow sensor and capnography sensor, if used. Anatomic dead space includes the trachea and the large airways where gas exchange does not happen. Alveolar ventilation (AV), which is the main determinant of CO_2 elimination, can be calculated as AV = RR x (VT – VD). It is always lower than minute ventilation (MV), which is calculated at the proximal airway opening as RR x VT. In addition to equipment and anatomic dead space, physiologic dead space can also be present due to ventilation-perfusion mismatch (76, 77).

Traditionally, it is been held that HFOV uses oscillation volumes (VThf) less than the anatomic dead space; therefore, gas exchange would not be possible based on the concept of tidal ventilation alone. Additional mechanisms have been proposed to account for gas exchange during HFOV. They include asymmetric flow profiles, Taylorian dispersion, "pendelluft", cardiogenic mixing and molecular diffusion (72, 78). However, more recent studies and data presented in this thesis have demonstrated that "tidal volumes" during HFOV can be as high

as 3 mL/kg and conventional "tidal" ventilation may indeed be in part responsible for gas exchange (79, 80). It has also been demonstrated that extremely low birth weight infants weighing <800 g can also be ventilated with ~5 mL/kg VT during conventional ventilation, although it is less than the sum of the equipment and anatomic dead space for them (81). This suggests that the above gas exchange mechanisms also play a role during at conventional ventilator rates (82).

3.4.3.2. Control of oxygenation during HFOV

As during conventional ventilation, oxygenation during HFOV is determined by FiO_2 and MAP. Unlike conventional ventilation, MAP can be set directly during HFOV, rather than being implicitly defined by other settings. Lung recruitment manoeuvres by gradually increasing MAP are essential during HFOV to ensure that the alveoli become and remain open, making gas exchange possible (83, 84).

3.4.3.3. Control of carbon dioxide elimination during HFOV

During conventional ventilation, CO_2 elimination is proportional to minute ventilation, which is the product of tidal volume and respiratory rare (MV = VT x RR). During HFOV, CO_2 elimination is determined by the diffusion coefficient of carbon dioxide (DCO_2), which is frequency x $VThf^2$ (72). The fact that CO_2 elimination during HFOV shows a linear relationship with frequency but a quadratic relationship with VThf has significant implications as to how changing ventilator parameters affect CO_2 elimination.

First, small changes in VThf (e.g., 0.1-0.2 mL/kg) may have significant impact on blood CO_2 levels, much larger than changes in frequency. Second, during HFOV (unless HFOV-VG is used), VThf and frequency are not independent. When using the same pressure amplitude (deltaP), a lower frequency results in higher VThf and *vice versa*, as more volume can be delivered in the lungs over longer periods using the same pressure amplitude (85). Because the change in VThf has a quadratic impact on CO_2, while the impact of frequency is only linear, reducing the frequency during HFOV (without VG) will paradoxically increase CO_2 elimination and *vice versa*. Of note, the higher the HFOV frequency, the more attenuation of the pressure amplitude will happen along the airways and the lower shearing forces alveoli will be exposed to (86). It is arguable to use the highest possible HFOV frequency allowed by patient characteristics, severity of lung illness and lung mechanics.

3.4.3.4. Interpretation of the diffusion coefficient of carbon dioxide (DCO_2) during HFOV

Modern ventilators display DCO_2 values during HFOV. Changes in DCO_2 over time in the same patient may inform clinicians about changes in CO_2 elimination and may predict blood gas CO_2 levels. However, DCO_2 values across different patients cannot be compared.

In this thesis and in an associated paper I present evidence that weight-correction of DCO_2 by dividing it with the square of the body weight improves its predictive value and allows for direct comparison of DCO_2 values obtained from different patients (87).

3.4.4. Evidence for use of HFOV

Neonatal HFOV has been used both as primary mode of ventilation and as rescue modality in babies in whom either conventional ventilation failed to provide adequate gas exchange or high ventilator parameters (FiO_2, MAP or MV) were required.

When used as a rescue treatment in preterm infants with respiratory distress, the early studies provided inconclusive results, with some studies reporting an increased risk of air leak syndromes, while in others the risk of pneumothoraces was reduced (88, 89). The risk of IVH was also increased in some, but not all studies. However, in a systematic review performed in 2000, only one study passed quality assessment; which showed no increased risk of air leaks but an increased risk of IVH (90). There was no difference in long term outcomes.

Several randomised control trials (RCT) used HFOV as primary ventilation mode in preterm infants. A systematic review of 19 RCTs was performed in 2015, and it found an overall higher risk of air leaks and lower risk of retinopathy of prematurity (ROP) in the HFOV group (91). There was also a significant reduction in BPD in some of the studies when HFOV was used but it was not consistent across all trials. There was no change in the risk of IVH or periventricular leukomalacia (PVL) or in mortality and neurodevelopmental outcome.

In a long-term follow-up study of a large RCT using HFOV as primary mode in preterm infants, respiratory function was significantly better in the HFOV arm at 11-14 years of age (92) but this was not maintained at 16-19 years of age (93). There was no consistent difference in neurodevelopmental outcome (92).

HFOV was also used in term infants suffering from respiratory failure, both as rescue mode or as primary therapy. Some studies have shown improvements in clinical outcomes. Meta-analysis of them has been difficult due to the diverse pathology underlying respiratory failure and heterogeneity of the HFOV settings used. In a systematic review performed in 2009, only two trials met quality criteria and they demonstrated no effect on mortality, air leaks, pulmonary or neurodevelopmental outcome (94). There was also no difference in the number of extracorporeal membrane oxygenation (ECMO) referrals.

However, the findings of HFOV studies performed more than 10-15 years ago and their meta-analyses should be interpreted with caution. Most of them used the Sensormedics ventilator, while in the last two decades HFOV mode has become available on almost all neonatal ventilators, using different oscillation generating mechanisms. Moreover, although the conventional ventilation modes used in the control groups have been available for several decades, they have improved significantly in the last 20 years with the emergence of computerised ventilators. Finally, synchronised conventional ventilation has become gold standard and volume targeted ventilation has been increasingly used, while neither of them was used in the control groups of the early studies.

In summary, early HFOV studies fail to inform us on the use of HFOV in neonates. They neither confirm nor rule out benefits of HFOV in a subgroup of patients with particular characteristics and clinical problems. In fact, more recent studies have shown benefits of HFOV in some clinical scenarios (95).

3.4.5. HFOV with volume guarantee (HFOV-VG)

On the latest generation of neonatal ventilators, volume-targeted HFOV, also known high frequency oscillatory ventilation with volume guarantee (HFOV-VG), has become available.

3.4.5.1. Ventilator parameters and gas exchange during HFOV-VG

During HFOV-VG, clinicians set a target volume and the ventilator is constantly changing the applied pressure amplitude (deltaP), in order to maintain VThf as close to the target as possible (96). The user also sets a maximum allowed pressure amplitude (Amplmax), which cannot be exceeded even if the target VThf cannot be achieved (**Figure 16)**.

Oxygenation during HFOV-VG can be controlled the same way as during HFOV. However, controlling CO_2 is different. As oscillations volumes (VThf) are guaranteed during HFOV-VG, VThf is maintained, even if the frequency is increased, although it requires a higher amplitude to deliver the same VThf at a higher frequency. Consequently, during HFOV-VG there is no inverse relationship between the frequency and CO_2 elimination, unlike during HFOV without VG (see **section 3.4.3.3.**) (85). During HFOV-VG, increasing the frequency improves CO_2 elimination, provided the set Amplmax is not reached by the deltaP and the target VThf can be delivered.

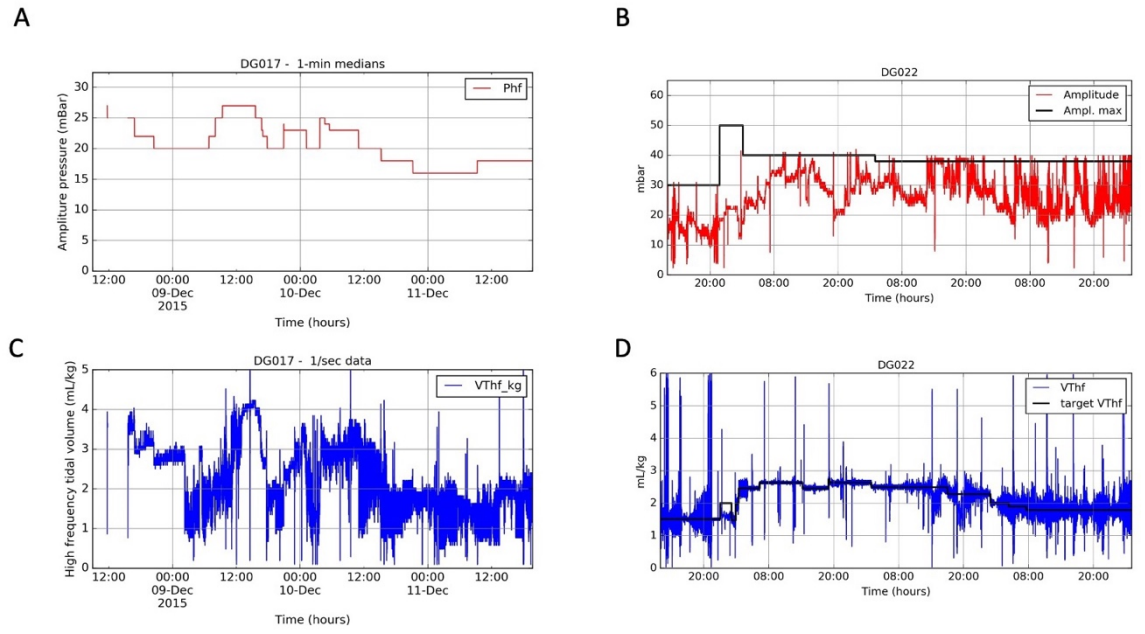


Figure 16. Comparison of HFOV and HFOV-VG. Recordings from an infant ventilated with HFOV (A & C) and with HFOV-VG (B & D). Graphs show the pressure amplitudes (A & B) and oscillation volumes (VThf, C & D) in each case. Recording duration was ~90 hours in both cases. For each minute the average of the ventilator parameter was calculated and these are shown on the graphs. During HFOV without VG, pressure amplitude (**A)** remained the same until it was changed by clinicians; during HFOV-VG (**B**), amplitude changes automatically, up to a maximum value (Amplmax, black line) set by the user. During HFOV without VG, VThf is highly variable, sometimes <1 mL/kg and at one point exceeding 4 mL/kg. With HFOV-VG, VThf remains between 1 and 3 mL/kg and usually close to the target (black line).

3.4.5.2. Evidence of benefits of HFOV-VG

The use of VG during HFOV has been shown to reduce variability of both VThf and pCO_2 and to help avoiding hypocapnia (97, 98, 99, 100, 101). It reduced duration of mechanical ventilation after neonatal cardiac surgery (101). The use of HFOV-VG as part of a quality improvement program reduced the risk of BPD (95). However, no prospective study has been reported so far on clinical outcomes when using HFOV-VG versus HFOV without VG. Despite this, HFOV-VG has been increasingly used on NICUs, as it is generally available on the latest neonatal ventilator models and clinicians have already experience with the use of VG during conventional ventilation.

On our NICU in Cambridge we started to use HFOV-VG for clinical care in 2015, and we were one of the first units to publish our experience with it after analysing data downloaded from the ventilators. This work is presented in this thesis and in an associated publication (80).

3.5. Assessment of ventilator performance

The performance of ventilators can be assessed in bench studies using lung models in a respiratory lab. It can also be tested *in vivo*, either by ventilating experimental animals in the lab or by ventilating human infants on the NICU during clinical care or as part of a research study.

3.5.1. Bench studies

Ventilators are thoroughly tested by ventilator manufacturers during their development and even after their marketing before software updates. Providing data on bench testing is required for approval by medical device regulatory agencies. In addition, neonatal ventilators have been bench-tested by academic investigators as part of research, when frequently the performance of several different ventilator models are compared (65, 102, 103, 104, 105, 106, 107, 108, 109).

Bench testing is usually done using standardised conditions and sophisticated lung models. These models can be configured by setting respiratory physiology parameters (i.e., compliance, resistance, inductance) and mimicking different human lung conditions. Different levels of leakage can also be set and leak compensation mechanisms of neonatal or adult ventilators have been tested using such models (57, 61, 110).

The main benefit of ventilator bench testing is that experimental conditions can be tightly controlled, which is particularly useful when comparing different ventilators. In addition, more sensors can be used and more extensive data collection can be done without interfering with lung function or clinical care. Finally, performance under extreme conditions rarely or not normally occurring in humans can also be tested.

The main limitation of ventilator bench studies is that they are unable to mimic the complexity of patient-ventilator interactions regularly occurring during clinical care, unless the infant is fully sedated or muscle relaxed, which is rare. In addition to breathing with or against the ventilator, the baby may turn the head, cough or splint the chest. These events result in short-

term (breath-to-breath) changes in respiratory mechanics which cannot be modelled on the bench.

3.5.2 *In vivo* studies

Ventilators can also be tested *in vivo*, that is, ventilating living organisms, either experimental animals or human infants.

Neonatal ventilators have been tested in studies using experimental animals (106, 111, 112). Testing on animals offers many of the benefits of bench studies, such as testing a broad range of ventilator parameters under standardised conditions, while also taking advantage of some of the benefits of testing ventilators on actual lungs, e.g., patient-ventilator interactions. On the other hand, respiratory physiology of experimental animals is rarely a good model for human lungs and animals usually need to be significantly sedated during the experiment due to technical feasibility and for animal welfare reasons.

More recently, studies testing neonatal ventilator performance during clinical care have also been reported (43, 58, 71, 113). Some of these studies form part of this thesis and the associated publications. The main benefit of such testing is that is evaluates these devices under the circumstances they are actually used. Ventilator performance can be assessed in babies with different demographic and clinical characteristics, lung mechanics, sedation level and breathing effort.

The main limitation of ventilator performance assessment on NICU is that testing conditions cannot be standardized. These studies are observational, as changing ventilator parameters only for the sake of the study would be unethical. However, ventilator performance assessment can be "piggybacked" by reusing ventilator data collected during *bona fide* ventilator research studies testing different ventilator modes or settings.

A further limitation is that ventilator performance, that is, how well the ventilator maintains its parameters close to their target, depends on the baby and his or her clinical characteristics. Babies with more advanced gestational or postnatal age or receiving no or little sedative medication will breathe more and interact with the ventilator in a more complex way. This will make maintenance of ventilator parameters for the ventilator more difficult. Due to this, data obtained from individual babies cannot be directly compared and performance of different ventilator models used on different NICUs or even on the same unit can only be compared if the units look after similar babies in general and sufficient number of babies have been studied.

Finally, *in vivo* ventilator assessment studies on NICUs require ventilator data to be collected at a high sampling rate and without interfering with clinical care. Although this has been increasingly available (see next section), it usually requires additional equipment such a laptop, to which data are being streamed, which may be difficult on some unit due to spatial constraints. I anticipate that in the future ventilator data will be collected in an unintrusive way, for example from electronic health care records or wirelessly from the ventilators directly (114).

3.5.3. The impact of physical forces on ventilator performance

Inter-hospital neonatal transport is essential for providing high quality neonatal care for a geographical region. *In utero* transfer of mothers with impending very preterm delivery has been considered good practice for decades (115). However, as preterm birth or critical illness of infants is not always predictable (116), and *in utero* transfer is not always possible (117), some sick infants are delivered in district hospitals and need to be transferred to level 3 neonatal intensive care units (NICUs) or specialist centres. The increasing centralization of neonatal services is also dependent on availability high-quality neonatal transport.

Neonatal ground transport is associated with significant vibration and acceleration due to road and traffic conditions (118, 119, 120, 121, 122). It has been suggested that both vibration (acceleration whose magnitude and direction changes periodically with high frequency) and "sustained" acceleration (changes in the ambulance's speed or it's direction due to the vehicle speeding up, slowing down, or turning left or right) during transfer may impact on the infant's condition (123, 124). Animal studies described the adverse health implications of vibration on respiratory and cardiovascular systems (125). In population-based studies, survival of extremely preterm infants born in hospitals equipped with level 3 NICUs was better than survival of infants transferred to these centres postnatally (126, 127). Severe intraventricular haemorrhage is also more frequent after *ex utero* transport (128), although it is uncertain whether this reflects the impact of postnatal transport or better initial stabilization in level 3 centres (129).

Critically ill infants frequently require mechanical ventilation during transport. Vibration and sustained acceleration during transfer can potentially influence mechanical ventilation via multiple mechanisms. These physical forces may affect the ventilator's performance, increase variability of the peak inflating pressure (PIP) and the tidal volume (VT) or their deviation from set target values. They might trigger physiological responses in the infant, resulting in changes in respiratory rate, breathing effort and minute ventilation. Finally, they may affect ventilator-patient interactions, resulting in irregular ventilator waveforms and loops. However, the impact of the ambulance's sustained acceleration and vibration on mechanical ventilation has not been reported. In a study described in this thesis and the associated paper (130) we investigated the impact of these physical forces on ventilator parameters and patient-ventilator interactions during inter-hospital neonatal transfers.

3.6. Retrieval and analysis of "Big Data" obtained from neonatal ventilators

Over the last 10-15 years the amount of data collected and stored by humanity has been increasing exponentially. Most of this increase is due to data obtained from "internet-of-things" which are physical objects with sensors, processing ability and software allowing them to stream data to storage devices (131). The availability of this "Big Data" has generated significant challenges as to storage, analysis and interpretation, but at the same time it has also offered novel opportunities as to data insight, algorithm development, and automation of the relevant physical technologies.

3.6.1. What is Big Data?

The term "Big Data" is used to describe data sets which are so large and complex that they become awkward to work with using standard statistical software. A more formal and widely used definition has been provided by data analyst Doug Laney: "Big data is *high-volume*, *high-velocity* and/or *high-variety* information assets that demand cost-effective, innovative forms of information processing that enable enhanced insight, decision making, and process automation" (no formal reference found). This is sometimes referred to as the "3V". Data can now be collected from mechanical ventilators and other pieces of medical equipment which fulfil all three criteria for Big Data.

3.6.2. "Big Data" collected in neonatal intensive care

Doctors have collected data about patients and their illnesses since ancient times. In some respect, modern medicine emerged at the end of the 19th century when doctors started to collect data from their patients by other means than simple physical observation (e.g., X-rays, electrocardiogram, biochemical tests on body fluids, microbiology testing etc.). Neonatal intensive care (and more broadly, intensive care) has been made possible because of the availability of patient monitors continuously reporting physiologic data such as temperature, heart rate, respiratory rate, blood pressure, oxygen saturation etc. However, until recently, data from NICU monitors were only recorded manually by nurses and doctors on flow sheets at a low frequency, e.g., at every 10-15 minutes. This data collection did not capture the range and variability of these parameters and most information present in these data was lost. Moreover, manual data collection is also prone to observer's bias; for example, nurses tend to record oxygen saturation values when they are higher (132).

On today's NICUs, patient monitors and medical devices are frequently connected to electronic health care systems. However, despite the opportunity to stream data at high sampling rate to storage, usually data are still only stored at a low sampling rate and sometimes only when the nurse or doctor requests that a data point is stored. This approach also results in low sampling rate and observer bias. Very recently, streaming and storage of high throughput multimodal monitoring data has become routine on some NICUs, predominantly for research purposes (133, 134). I envision that such data collection and storage will become a standard part of clinical care in near future.

Data collected in intensive care fall into three categories: (1) physiologic data collected by monitors and sensors of medical equipment; (2) free-text data written by clinical staff; and (3) imaging data (still images and videos) obtained by imaging technologies (X-ray, ultrasound, magnetic resonance imaging) (135). They require different methods for processing and analysis. In this thesis I will focus on data obtained by sensors of neonatal mechanical ventilators.

3.6.3. Data availability from neonatal ventilators

Ventilators have displayed some parameters since the beginning of the technology. Initially this was limited to the pressure, flow and inhaled oxygen concentration. With increasing sophistication and incorporation of electric components and computers, other parameters such as ventilator rate, inspiratory and expiratory time, tidal volume and minute ventilation have

also been displayed. However, there was no opportunity to download or store these data, and ventilation research studies used intermittent manual data collected by researchers reading and recording data displayed on ventilator screens (81, 102, 136, 137, 138). However, this approach only allowed data collection with a low sampling rate and it was also prone to observation bias.

Later, download of ventilator data with a low sampling rate (e.g., one random or aggregated data point every 10 seconds to - 5 minutes) became available and was used in clinical research studies (42, 50, 139). Higher sampling rate was only available in the research lab and or, if used in clinical research, it required continuous presence of dedicated research personnel, allowing only for short study periods (31, 65, 111, 140, 141, 142). Until the last decade there was no opportunity to download ventilator data from infants during clinical care with a high sampling rate *and* over longer periods at the same time. This hindered research because to quantitatively analyse ventilator performance during clinical use of ventilators, the majority of ventilator inflations needs to be captured in an unbiased way, requiring ~1 Hz sampling of PIP and VT. To characterise and quantify patient-ventilator interactions, waveform level analysis is required, necessitating ≥100 Hz sampling of pressure and flow data.

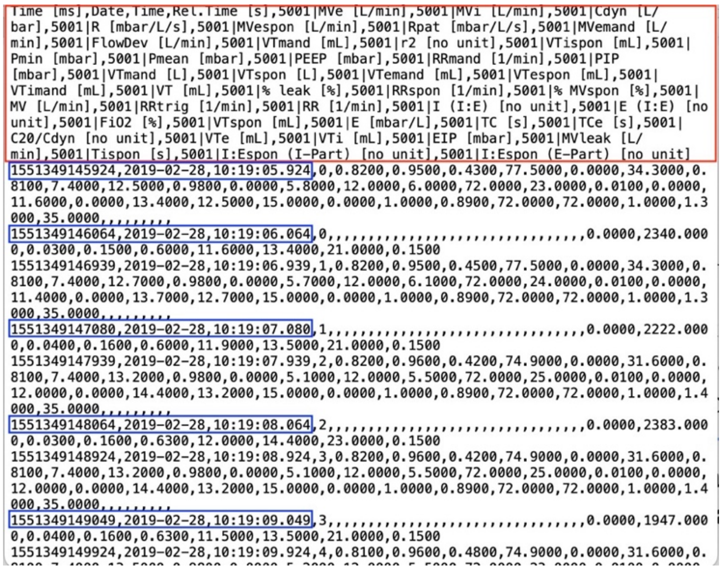
Recently, continuous download of data at a high sampling rate has been increasingly becoming available on various neonatal ventilators models, which allowed for studies assessing ventilator performance and patient-ventilator interactions during clinical use in unprecedented details. Some of the first studies using such data are included in this thesis.

3.6.4. Computational tools for analysing neonatal ventilator data

The high throughput data retrieved from modern neonatal ventilators present novel challenges for data processing and analysis. Ventilator data are two-dimensional time series data where one axis is time and the other axis is the different ventilator parameters (**Figure 17).** Data are usually presented as tabular data and exported as comma-separated or tab-delimited text files. During clinical research such data are usually imported, processed and analysed by spread sheet programs such as Microsoft Excel™. However, if ventilator data collected at a high sampling rate and over long periods, the volume of the data exceeds what can be reproducibly analysed using spread sheet programs. For example, a data collection over 3 days and with a 100 Hz sampling rate results in a table with 3 days * 24 hours/day * 3,600 seconds/hour * 100 data points/second, that is a total of 25,920,000 rows. To analyse such “Big Data”, the use of scripting computer programming languages has been adopted. The languages most frequently used for data science are Python, R and Matlab. For the research presented in this thesis Python was used.

3.6.4.1. The Python computer language

Python (https://www.python.org) is a freely available general-purpose computer language that was initially developed in 1996 but has been continuously expanded and further developed by a large community of users and developers. It’s easy-to-understand code and shallow learning curve makes it accessible and attractive to people without formal programming training and background. By today it has become the most frequently used computer language in the world.



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Time [ms],Date,Time,Rel.Time [s],5001|MVe [L/min],5001|MVi [L/min],5001|Cdyn [L/
bar],5001|R [mbar/L/s],5001|MVespon [L/min],5001|Rpat [mbar/L/s],5001|MVemand [L/
min],5001|FlowDev [L/min],5001|VTmand [mL],5001|r2 [no unit],5001|VTispon [mL],5001|
Pmin [mbar],5001|Pmean [mbar],5001|PEEP [mbar],5001|RRmand [1/min],5001|PIP
[mbar],5001|VTmand [L],5001|VTspon [L],5001|VTemand [mL],5001|VTespon [mL],5001|
VTimand [mL],5001|VT [mL],5001|% leak [%],5001|RRspon [1/min],5001|% MVspon [%],5001|
MV [L/min],5001|RRtrig [1/min],5001|RR [1/min],5001|I (I:E) [no unit],5001|E (I:E) [no
unit],5001|FiO2 [%],5001|VTspon [mL],5001|E [mbar/L],5001|TC [s],5001|TCe [s],5001|
C20/Cdyn [no unit],5001|VTe [mL],5001|VTi [mL],5001|EIP [mbar],5001|MVleak [L/
min],5001|Tispon [s],5001|I:Espon (I-Part) [no unit],5001|I:Espon (E-Part) [no unit]
1551349145924,2019-02-28,10:19:05.924,0,0.8200,0.9500,0.4300,77.5000,0.0000,34.3000,0.
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1551349149049,2019-02-28,10:19:09.049,3,,,,,,,,,,,,,,,,,,,,,,,,,,,,,0.0000,1947.000
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1551349149924,2019-02-28,10:19:09.924,4,0.8100,0.9600,0.4800,74.9000,0.0000,31.6000,0.
```

Figure 17. **Format of data downloaded from the Dräger Babylog™ VN500 ventilator**. Data are presented as comma separated values (csv). The first line of the file (broken into multiple physical lines in this view, marked by red rectangle) contains the parameter names. The subsequent lines start with timestamps of millisecond precision (blue rectangles) followed by ventilator data. During long recordings file sizes can reach several gigabytes.

3.6.4.2. Python data analysis tools for tabular data

The recent popularity of Python has been largely due to its excellent data analysis packages. *NumPy* (http://www.numpy.org) is a python package suitable for representing, processing and analysing numerical data, including high-dimensional data. It is based on fast algorithms written in C and Fortran languages. It allows for vectorized computation, making it particularly useful for analysing the tabular data obtained by monitors and sensors of medical equipment. *pandas* (http://pandas.pydata.org) is a high-level Python package based on *NumPy*. Originally developed for analysing financial data, *pandas* has become the standard tool for processing time series data, including medical data. Statistical analysis is possible using the *SciPy* (www.scipy.org) and *statmodels* (https://www.statsmodels.org) Python packages which can directly handle data processed by *pandas* or *NumPy*. *Matplotlib* (http://matplotlib.org) and *seaborn* (https://seaborn.pydata.org) are Python-based visualisation libraries which can produce both simple plots and advanced graphics (e.g., three-dimensional or interactive graphs) and publication quality images.

The emergence of large datasets has facilitated the development and use of machine learning and (more recently) deep learning algorithms for predictive analytics. The *scikit-learn* (https://scikit-learn.org) machine learning library and the *TensorFlow* (https://www.tensorflow.org) and *PyTorch* (https://pytorch.org) deep learning libraries are all Python-based and interface well with NumPy and pandas.

In the last decade, the use of Python for data science has been made easier by the emergence of interactive coding interfaces, particularly the Jupyter Notebook (https://jupyter.org). Jupyter uses a web browser interface hosted locally, although online versions such as Google's Colab (https://colab.research.google.com) have also become freely available. These notebooks contain packets of executable Python code and annotating text, both presented as boxes in a browser window. The code can be executed interactively, step-by-step. The user can generate interactive data analysis pipelines, including data import, analysis, export, in-line visualisation. It also supports rich annotation of the code using the *markdown* mini-language **(Figure 18)**.

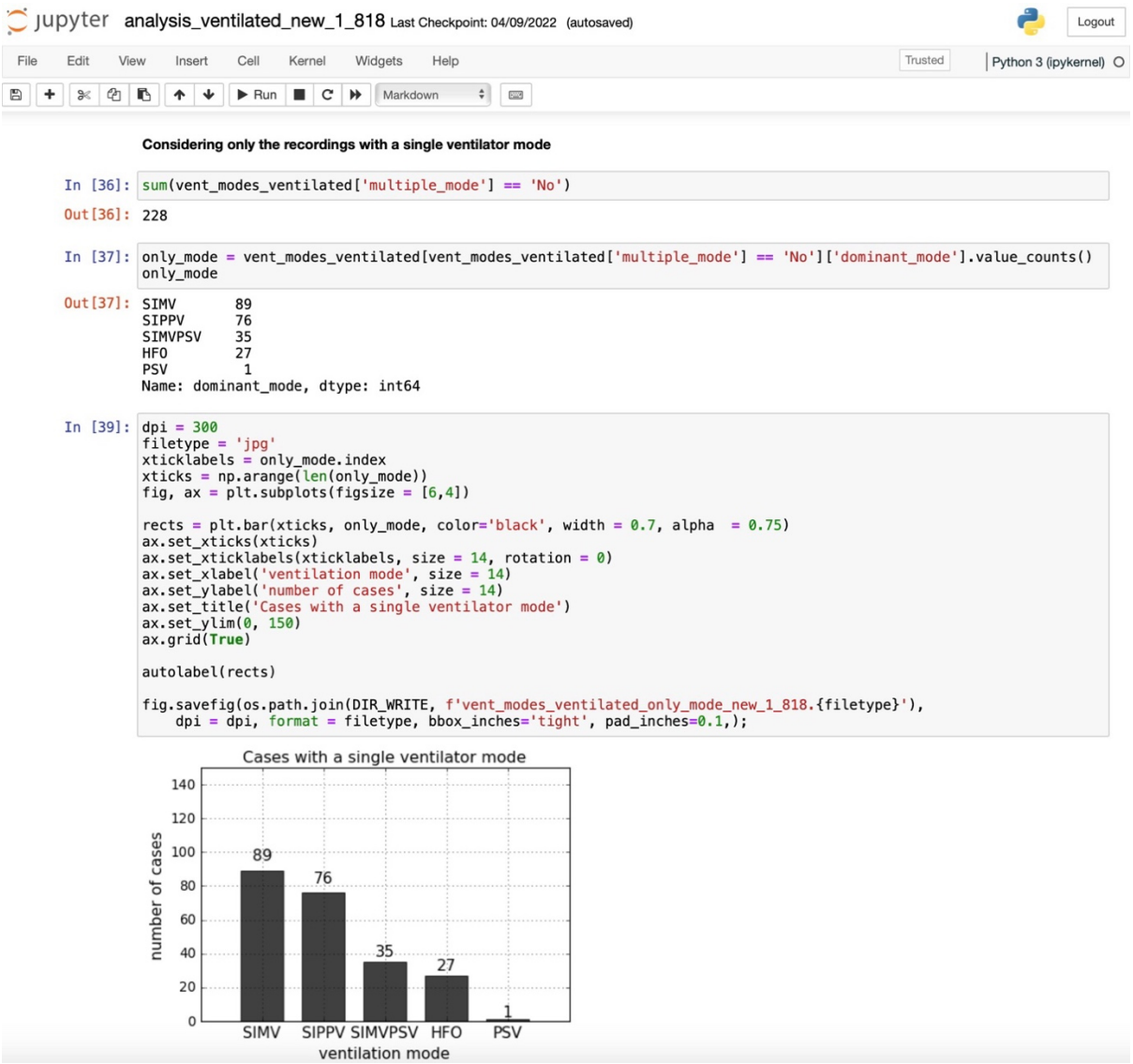

Figure 18. Screenshot of a Jupyter Notebook containing Python code for interactive scripting. Code can be executed in blocks and results are shown immediately after the block. In-line plotting and code annotation by rich text is also shown.

3.7. Ventilator alarms

Despite all technological development, mechanical ventilation requires frequent and significant clinician input. Ventilator parameters need to be changed regularly based on clinical findings, patient monitor readings (e.g., oxygen saturation, end-tidal or transcutaneous carbon dioxide levels) and blood gases. Sometimes ventilated babies require immediate attention due to a technical problem with the ventilator, an acute complication of mechanical ventilation, or rapid change in the clinical condition of the patient.

Ventilators have been equipped with alarms since the advent of the technology for safety reasons. Some alarms report failure of gas supply, disconnection or obstruction of ventilation circuit, flow sensor problems, etc. Others occur when a parameter (e.g., tidal or minute volume, peak inspiratory pressure or respiratory rate) is outside the range set by the user. Frequent alarms may occur if the limits have been set inappropriately. Ventilation with inappropriate settings even for short periods may cause long-term morbidities (143). Over-ventilation and

hypocapnia are associated with cerebral white matter injury and poor neurodevelopmental outcome (144). Some ventilator alarms (e.g., minute volume low and high alarms) are mandatory and are required for regulatory approval of a device for clinical use.

Unfortunately, the increasing complexity of ventilators has been associated with increasing number and complexity of their alarms. The proliferation of ventilator alarms has not been accompanied by development of a standardized terminology amongst manufacturers. Different ventilator alarms have different importance and urgency. Most neonatal ventilators conform to the IEC (International Electro-technical Commission) 60601-1-8 general standard which is a global guideline for ventilator alarms (145). The AARC (American Academy of Respiratory Care) classes alarms as high, medium and low priority (146). This grading of alarms is commonly used by most ventilator manufacturers, although there is much variability in this as well (147).

The abundance of ventilator alarms results in frequent audible alarming which may affect developmental care, particularly when several ventilated babies are in the same room (148). Studies across several NICUs demonstrated that exposure to frequent alarms negatively affected the time staff took to respond to even critical alarms (149). Desensitisation to alarms is called “alarm fatigue” and it may result in staff eventually missing or ignoring important alarms (150). Frequent alarms may also make the clinicians set alarms limits too widely and the alarm loses its role of protecting against clinical incidents. There is a trade-off between setting a too narrow target range (associated with too frequent triggering and alarm fatigue) and a too wide range (potentially compromising patient safety). ECRI (Emergency Care Research Institute), a not-for-profit organisation researching approaches to improving patient care, declared ventilator alarms as one of the top 10 health technology hazards in 2017 (151).

Among the many ventilator alarms, some of them are redundant or difficult to interpret. Many alarms only assess one ventilator parameter. Due to normal variability of ventilator parameters, it can be difficult to set alarm limits correctly. The future is to develop “smart” ventilator alarms which consider input from multiple ventilator and monitor parameters, temporal trends and context. These intelligent alarms will potentially reduce false alarms and alarm fatigue and will also represent a step towards automation of mechanical ventilation.

In order to develop such intelligent alarms, as a first step, the prevalence and causes of ventilator alarms in the NICU need to be quantitatively studied and understood. Large-scale audits of patient monitor alarms have been performed on intensive care units by downloading patient monitor data (150, 152). However, auditing ventilator alarms from neonatal units has not been reported. A study on a paediatric intensive care unit (PICU) did not report ventilator alarms systematically because of difficulties with obtaining time-stamped data (153). Another study included ventilators in their alarm audit on a NICU; however, it focused on appropriate equipment use and did not analyse alarm data (154). Moreover, manual data collection of ventilator alarms is labour-intensive, introduces observational bias, data loss and is unreliable. In this thesis and the associated publication, I provide the first quantitative report on neonatal ventilator alarms using data downloaded from ventilators over many days and their computational analysis.

3.8. Patient-ventilator interactions (PVIs) and asynchronies

In modern neonatology, deep sedation and muscle relaxation is limited to the most severe cases (155). Breathing babies interact with the ventilator in a complex way, for example, coughing, splinting the chest, breathing out during ventilator inflation, breathing in when the ventilator has just finished inflation (114, 156). Modern ventilators are able to recognize patient signals and respond by adapting their output to the baby's needs (see **section 3.3.2**). Nonetheless, complex and adverse patient-ventilator interactions and asynchronies still occur frequently during neonatal ventilation.

3.8.1. Recognition of PVIs by analysis of ventilator waveforms and loops

Ventilators do not report quantitatively how frequently PVIs occur, but their displays show waveforms and loops from which these asynchronies can be identified. However, interpreting abnormal ventilator waves and loops requires both significant experience and time. Busy clinicians frequently ignore ventilator waveforms or only review them for very short periods (157). As these data are not routinely downloaded or stored, they cannot be reviewed later. Adverse PVIs frequently go unnoticed, cause significant discomfort to babies and, if abundant, they may contribute to short- and long-term neonatal morbidities, although this has only been examined systematically in adults, in whom frequent asynchronies also associated with increased mortality (158).

An alternative to inspecting ventilator screens for long periods would be to develop computational methods to study the effectiveness of mechanical ventilation and the occurrence of individual PVIs. This approach requires access to raw ventilator data (airway pressure and flow) at a sampling rate high enough to computationally re-generate and analyse waveforms and loops. To interpret these raw data, as a first step, they need to be split into individual ventilator inflations which can then be further segmented into sub-phases (i.e., lung inflation, inspiratory hold, lung deflation etc.). Identification and separation of these segments enables statistical analysis of their characteristics over longer periods and automatic detection, characterisation and quantitative analysis of patient-ventilator interactions during different phases of the respiratory cycle.

Recently, several different approaches have been reported to computationally analyse adult ventilator data and characterize patient-ventilator interactions (114, 159, 160, 161, 162, 163, 164, 165). There are also some, albeit fewer, reports from children (166, 167). Unfortunately, analysis of PVIs in neonates is lagging behind the adult or even the paediatric field. Most of the few available reports studied triggering asynchronies during NAVA ventilation (168, 169); however, NAVA is still only used by a minority of NICUs. Data obtained in adults or in children are of limited relevance due to differences in neonatal respiratory mechanics and the ventilation modes used. For example, babies are breathing much faster than adults and their tidal volumes are much smaller, particularly when compared to the equipment dead space. Moreover, babies are usually intubated with un-cuffed ETT and there is frequently significant and often variable leak around the tube. Finally, while adults and older children are frequently ventilated with primary volume-controlled ventilation using constant flow, babies are ventilated with pressure limited ventilation using variable flow, with the increasing use of volume guarantee.

In this thesis and an associated paper, we describe and validate a novel computational approach to split high-throughput raw data downloaded from the ventilators of critically ill babies into individual ventilator inflations and to further segment the inflations into different sub-phases.

4. Aim and objectives

4.1. Aims

The overarching aim of the work presented in this thesis and in the associated original publications was to gain insight into the performance of mechanical ventilators when providing respiratory support to critically ill infants. An additional aim has been to develop novel tools and approaches which can provide clinicians and ventilator manufacturers with quantitative information about ventilator performance and patient-ventilator interactions. I envision that such information could help to provide better respiratory care for babies, to develop neonatal ventilators further and, in the longer term, to automate neonatal mechanical ventilation.

4.2. Specific objectives

1. Develop novel computation tools and methods to process and analyse high throughput data retrieved from neonatal ventilators.

2. Analyse how well a neonatal ventilator model (the Dräger Babylog™ VN500) maintains the tidal volume close to its target during volume targeted ventilation on the neonatal intensive care unit.

3. Analyse how well the fabian™+ncpap neonatal ventilator model maintains their tidal volume during volume targeted ventilation and whether movement of the ambulance and the transport environment impact on the ventilator's performance.

4. Investigate how the Dräger Babylog™ VN500 and fabian™+ncpap ventilators respond to leak around the endotracheal tube and how effective their leak compensation mechanisms are.

5. Investigate how two under-appreciated and frequently overlooked ventilator settings, the pressure rise time (PRT) and the maximum allowed inspiratory pressure (Pmax) impact on neonatal ventilator performance.

6. Investigate how Dräger Babylog™ VN500 and fabian™+ncpap ventilators perform in challenging situations such in babies with little sedation, strong respiratory effort or hyperventilation. Assess if the use of volume targeted ventilation is feasible in this situation.

7. Analyse the performance of the Drager Babylog™ VN500 ventilator during a novel ventilation mode, high frequency oscillatory ventilation with volume guarantee (HFOV-VG). Also provide data on the range of the ventilator parameters characterising this novel mode. Provide insight as to how to interpret the diffusion coefficient of carbon dioxide (DCO_2) during HFOV or HFOV-VG.

8. Perform a quantitative analysis of neonatal ventilator alarms in the NICU by analysing a large number of ventilated infants and long ventilation periods. Investigate the occurrence, duration and causes of ventilator alarms.

9. Develop a computer software to recognise, isolate, visualise and characterise individual respiratory cycles (ventilator inflations or spontaneous breaths) in high-throughput data downloaded from neonatal ventilators.

5. Methods

5.1. Patients

The results presented in this thesis are all based on data collected from infants who received mechanical ventilation via endotracheal tube as part of their clinical care, either on neonatal intensive care units or during emergency inter-hospital neonatal transfers.

5.1.1. Babies ventilated on the NICU

5.1.1.1. Observational studies on the NICU, Cambridge, UK

Clinical and ventilator data were collected from a total of 316 infants admitted to the NICU of Rosie Hospital, Cambridge, UK between September 2015 and December 2022. The unit is a large tertiary regional NICU with ~800 admission and 1,500 ventilator days yearly. All babies receive conventional mechanical ventilation or HFOV using a Dräger Babylog™ VN500 ventilator (Dräger Medical, Lübeck, Germany) which is the only ventilator model used on the Unit, except the occasional use of Sensormedics for HFOV.

Babies requiring mechanical ventilation are intubated with uncuffed and unshouldered endotracheal tubes, the position of which is routinely checked by a chest X-ray. The NICU's guideline is to ventilate preterm or term infants who have respiratory distress using SIPPV-VG mode. Babies with normal lungs (i.e., ventilated for neuromuscular or airway issues) are ventilated with SIMV-VG mode without pressure support. The use of leak compensation during VG was introduced in 2016. The Unit's guideline is to use 4-6 mL/kg target VT initially, which is adjusted later based on blood gases, done 4-6 hourly during the first week of life and less frequently in chronically ventilated babies. Pmax is set initially at 30 mbar and then adjusted to keep it 5-10 mbar above the usually occurring PIP. High frequency oscillatory ventilation is used as a rescue mode. However, respiratory management of individual cases is decided by the attending consultant neonatologist.

During mechanical ventilation, the target pCO_2 (whether capillary or arterial) was 5-8 kPa in term infants and in preterm babies during the first week of life. After the first week of life pCO_2 levels up to 10-11 kPa were tolerated, provided the pH was >7.25, or in cases of severe pulmonary interstitial emphysema or evolving BPD, >7.20.

For the observational data collection all babies requiring mechanical ventilation via an ETT were considered eligible, unless (1) extubation was planned within 24 hours; (2) the infant was receiving palliative care; (3) parents did not consent to their baby's participation study; or (4) the clinical team disagreed with the inclusion.

The study was approved by the Bromley (London) Research Ethics Committee of the Health Research Authority of the United Kingdom. All procedures were performed in accordance with the ethical standards of the Research Ethics Committee and the amended Helsinki Declaration (1983). Informed consent was obtained from parents, using deferred consenting. Ventilator data collection was started as soon as it was feasible after admission without interfering with the first hour care or clinical procedures. The study was strictly observational: no aspect of ventilation or clinical care changed due to the study. Parents were approached for informed consent later but prior to the baby's discharge from the Unit. Clinical data were only collected

after parental consent had been given. If parents had declined the baby's participation, the ventilator data previously collected were deleted.

The individual observational studies included in this thesis used sub-groups of these patients based on additional selection criteria relevant for the particular study. They are described for each study in the Results section of the thesis.

5.1.1.2. Observational studies on the NICU, Debrecen, Hungary

Clinical and ventilator data were collected from a total of 52 infants admitted to the NICU of the Department of Paediatrics, University of Debrecen, Debrecen, Hungary between September 2021 and December 2022. The unit is a regional tertiary NICU, admitting both in-born and out-born infants. All babies receive conventional mechanical ventilation or HFOV using a Dräger Babylog™ VN500 ventilator, which is the only ventilator model used on the Unit, except the occasional use of Sensormedics for HFOV. The Unit's guideline is to use SIMV-VG-PS mode for all babies receiving conventional ventilation. For the observational data collection all babies requiring mechanical ventilation via an ETT were considered eligible, unless (1) extubation was planned in the near future; (2) the infant was receiving palliative care; (3) parents did not consent to their baby's participation study; or (4) the clinical team disagreed with the inclusion.

The study was approved by the Research Ethics Committee of the University of Debrecen, Hungary (reference: DE KREB/IKEB 5830-2021). All procedures were performed in accordance with the ethical standards of the Research Ethics Committee and the amended Helsinki Declaration (1983). Informed consent was obtained from parents, using deferred consenting. Ventilator data collection was started as soon as it was feasible. The study was strictly observational: no aspect of ventilation or clinical care was changed due to the study. Parents were approached for informed consent later but prior to the baby's discharge from the Unit. Clinical data were only collected after parental consent was given. If parents declined the baby's participation, the ventilator data already collected were deleted.

For the study presented in this thesis, data from a subset of this patient population was used. See **section 6.1.1.1.3.** for more details.

5.1.1.3. Interventional study on the NICU, Cambridge, UK

To analyze the effect of the flow rate in the ventilator's circuit on ventilation parameters, an interventional study was performed. This study was approved by the Cambridge East Research Ethics Committee of the Health Research Authority of the United Kingdom. Informed consent was obtained from the parents in all cases prior to any intervention or data collection. The inclusion criteria were birth weight <2,000 grams and mechanical ventilation using SIPPV-VG mode. Babies were excluded if (1) their respiratory condition was unstable (FiO_2 >50%, $PaCO_2$ >8.5 kPa or <5 kPa in the previous 12 hours); (2) their extubation was planned within 12 hours; (3) they had a surgical procedure in the previous 12 hours or were planned to have one in the following 12 hours; (4) they had a pneumothorax with a chest drain; (5) they had a >50% leak around the endotracheal tube; (6) they did not have an arterial line; (7) their parents did not give consent; and (8) where the clinical care team did not agree. The study has been registered on ClinicalTrials.gov (ID: NCT03306524).

5.1.2. Babies ventilated during neonatal transport, NETS-PCA, Budapest, Hungary

The Neonatal Emergency and Transport Service of the Peter Cerny Foundation (NETS-PCA, Budapest, Hungary) covers a geographical area in central Hungary with a population of ~5 million. The transport team comprises a fully trained neonatologist with experience in neonatal transport and an experienced neonatal transport nurse practitioner. Ambulance drivers are professional drivers with several years' experience in driving neonatal ambulances. Emergency transfers are completed using blue lights, siren and ambulance priority.

Clinical management during transport is based on formally approved local guidelines; however, ventilator management of the individual cases, including the choice of ventilator mode and settings, is at the discretion of the transport team. The transport service started to use a fabian™ +nCPAP evolution neonatal ventilator (Vyaire Medical, Mettawa, IL, US) in 2015 which was replaced in 2020 by fabian™ HFO neonatal ventilator. Volume guaranteed ventilation was introduced in 2016 after formal staff training sessions but without an explicit guideline at that time.

Clinical and ventilator data were collected from 1,575 infants transferred between March 2017 and February, 2023 by NETS-PCA. For the observational data collection all babies were considered eligible if they received invasive or noninvasive respiratory support during inter-hospital transport by fabian™ neonatal ventilators (Vyaire Medical, Mettawa, IL, US). The study was approved by the by the Scientific and Medical Research Council Ethics Committee of Hungary (reference number: 40158/2018/EKU). The need for informed consent was waived in light of the non-interventional nature of the study and the anticipated difficulties of getting informed consent in transport settings. No aspect of ventilation or clinical care was changed due to the study.

The individual observational studies included in this thesis used sub-groups of these patients based on additional selection criteria as relevant for the particular study. They are described for each study in the Results section of the thesis.

5.2. Interventions

All research presented in this thesis except the study analysing the impact of pressure rise time and circuit flow rate (**see section 6.1.3.)** were observational with no change in clinical care which followed the local guidelines and was co-ordinated by the attending neonatologist of the NICU or the transport neonatologist.

During the pressure rise time study, total time for each study was 210 minutes and a dedicated research nurse was continuously present. Infants were ventilated with Dräger Babylog™ VN500 ventilators during their clinical care and the study. The study started with a period of 30 minutes with the ventilator parameters used by clinical care team including a PRT of 0.08 sec that is currently recommended for clinical care by the local guideline. Infants were then ventilated using five different PRTs between 0.08 and 0.40 sec both with SIPPV-VG and with PSV-VG (**Table 1**). During PSV-VG Timax was set at 0.6 sec. Each of the 10 epochs lasted for 15 minutes and their order was randomized in each subject to avoid bias due to carry-over effects from preceding epochs. We used the random sequence generating function of the NumPy package to randomize the sequence of interventions in each patient. Study interventions were followed by a 30-minute cool-down period using the original ventilator

parameters. An arterial blood gas was done from indwelling umbilical or peripheral artery catheters before the first and after the last study intervention. Throughout the study, the target tidal volume, the backup ventilator rate and the Pmax remained as the clinical team had set them prior to the study. The FiO_2 was adjusted by the clinical nurse looking after the baby (who was different from the dedicated research nurse responsible for the study) to maintain the oxygen saturation (SpO_2) in the target range of 90-95%.

The primary outcome of the study was difference in mean end-tidal CO_2 (ET-CO_2) levels between the different epochs. The standard deviation (SD) of ET-CO_2 was not known to us; however, assuming an SD of 0.5 kPa, 18 subjects would have been required to prove equivalence (defined as ET-CO_2 difference <0.5 kPa) with 90% confidence and 80% power. Secondary outcomes were changes in other ventilator parameters including tidal volume, PIP, MAP, FiO_2, and Ti.

Table 1. Interventions of the study analyzing the impact to different pressure rise times during SIPPV-VG and PSV-VG ventilation. In each subject the order of the interventions was randomized. The target tidal volume was 5 mL/kg in all cases.

Intervention	Duration (min)	Mode	Pressure rise time (s)	Set inspiratory time [max]* (s)
1	15 min	SIPPV-VG	0.08	0.40
2	15 min	PSV-VG	0.08	[0.60]
3	15 min	PSV-VG	0.16	[0.60]
4	15 min	SIPPV-VG	0.16	0.40
5	15 min	SIPPV-VG	0.24	0.40
6	15 min	PSV-VG	0.24	[0.60]
7	15 min	PSV-VG	0.32	[0.60]
8	15 min	SIPPV-VG	0.32	0.40
9	15 min	SIPPV-VG	0.40	0.40
10	15 min	PSV-VG	0.40	[0.60]

* Set Ti during SIPPV-VG and maximum allowed inspiratory time (Timax) during PSV-VG.

5.3. Data collection

5.3.1. Clinical data

5.3.1.1. Babies ventilated on the NICU, Rosie Hospital, Cambridge, UK

Clinical data were collected from electronic health care records of the Hospital. Data included gestational, postnatal and postmenstrual age, birth weight and weight at the start of the recording, endotracheal tube size and insertion length, list of clinical problems and medications used. Blood gases done as part of clinical care using a cobas b 221™ point of care blood gas system (Roche) were also retrieved from electronic records. In addition, for the interventional study (see **section 6.1.3.**) side-stream end-tidal capnography with a microstream sampling line designed for neonates was used to measure ET-CO_2 using a Capnostream™ 20p patient monitor (Medtronic, Watford, UK). ET-CO_2, pulse rate and oxygen saturations were downloaded with 1 Hz sampling rate via a USB port as csv files.

5.3.1.2. Babies ventilated on the NICU, Debrecen, Hungary

Clinical data were collected from electronic health care records. Data included gestational, postnatal and postmenstrual age, birth weight and weight at the start of the recording, endotracheal tube size and insertion length, list of clinical problems and medications used. Blood gases done as part of clinical care using were also retrieved from electronic records. Transcutaneous carbon dioxide ($tcCO_2$) data were downloaded from TCM5™ monitor (Radiometer, Copenhagen, Denmark) with 1 Hz sampling rate via a USB port as csv files.

5.3.1.3. Babies ventilated during neonatal transport, NETS-PCA, Budapest, Hungary

Clinical data were collected computationally from medical and nursing transport records scanned using optical character recognition (OCR). Data included gestational, postnatal and postmenstrual age, birth weight and weight at the time of the transport, list of clinical problems with International Classification of Diseases (ICD) codes and blood gases. In case of therapeutic hypothermia, blood gases were temperature corrected. Values outside the ranges usually found in neonates were manually verified and, if found to be due to erroneous OCR of handwritten notes, amended or excluded. Data on medications used during transport were collected manually from scanned records.

5.3.2. Ventilator data

5.3.2.1. Dräger Babylog™ VN500 ventilator

A total of 2,419 days of ventilator data have been collected from 368 babies ventilated using the Dräger Babylog™ VN500 ventilator on two tertiary NICUs.

Ventilator data were downloaded to laptop computers via a cable attached to one of the serial communication ports of the ventilator using a recording software developed by the "Technology and Intellectual Property" Department of Dräger Medical. It is for experimental and scientific purposes only and is not commercially available. Downloaded data carry a timestamp with millisecond precision and are exported into comma-separated value (csv) text files.

The software retrieves airway pressure, flow and volume data with 100 Hz sampling frequency. Airway pressure is measured by the ventilator's sensors. Flow is measured by the proximal flow sensor connected at the proximal end of the ETT. Volume data are generated by the ventilator using time integration of the flow data. The 100 Hz sampling rate is sufficient for waveforms of individual breaths and inflations to be reconstructed (20). As the recording software was designed to be compatible with paediatric and adult ventilators using larger tidal volumes, due to bandwidth limitations the smallest difference in tidal volume that can be retrieved was 1.35 mL, which is too large for neonatal studies. Therefore, we reconstructed volume waveforms computationally from the flow data.

The software also downloads all calculated ventilator parameters at 1 Hz sampling frequency, including mandatory, spontaneous, inspiratory, expiratory tidal and minute volumes, PIP, MAP, PEEP, Ti and Te, FiO_2 etc. The parameters obtained are those of the last full inflation applied to the patient or made spontaneously by the patient before the timestamp. Minute

ventilation is directly calculated from the ventilator flow data with appropriate low pass filters. The percentage of leakage around the endotracheal tube is calculated at each second from the minute volumes as 100 x ($MV_i - MV_e$) / MV_i (%).

During HFOV, VThf is calculated by the ventilator from flow measurements and is leak-compensated. The ventilator internally has a sampling frequency of one in 5.2 milliseconds with a low pass filter. VThf values are averaged by the ventilator's computer over 1 second periods; these averaged values are displayed by the ventilator and were downloaded. VThf does not include tidal volumes of spontaneous breaths during HFOV, but it can be influenced by them. DCO_2 values are calculated as frequency * $Vthf^2$ from the averaged VThf over a 1-second period.

The recording tool also retrieves alarm data with a timestamp when an alarm was triggered and again when the issue triggering the alarm has been resolved. Changes in ventilator and alarm settings are recorded with a timestamp showing the time the changes were made.

5.3.2.2. fabian™ +nCPAP evolution and fabian™ HFO ventilators

A total of 1,720 hours of ventilator data have been collected from 1,575 babies receiving invasive or non-invasive respiratory support using fabian™ neonatal ventilators during their inter-hospital neonatal transport. Until October 2020 data were collected from a fabian™ +nCPAP evolution ventilator, after that data were collected from a Fabian™ HFO ventilator model.

Ventilator data were downloaded to a laptop computer via a cable attached to one of the serial communication ports using a data logger developed by the ventilator manufacturer for research purposes. The laptop computer was integrated into the transport trolley and connected to the ventilator permanently. Ventilator data download started automatically when the ventilator was switched on and continued until it was turned off.

The software downloads airway pressure, flow and volume data at 125 Hz sampling frequency. It also downloads ventilator parameters (e.g., PIP, VT, RR, MV, FiO_2 etc.) with 0.5 Hz sampling rate (1 data point every 2 seconds). Ventilator settings, their changes and ventilator alarms were also recorded. All data are retrieved with millisecond time stamps and exported as text files. The ventilator parameters retrieved at 0.5 Hz sampling rate correspond to the last inflation or spontaneous breath (as appropriate) that occurred before the time stamp. Minute ventilation is calculated as rolling mean over 30 seconds and it includes both ventilator inflations and spontaneous breaths, if present. During SIMV mode, the software does not record the number of spontaneous breaths between SIMV inflations; however, their contribution to the total minute ventilation is reported as percentage.

5.3.3. Ambulance acceleration and vibration data

Emergency vehicles were all Mercedes-Benz™ Sprinter vans with air suspension, equipped and used as dedicated neonatal ambulances. The transport incubator was Dräger TI 5400™ (Dräger, Lübeck, Germany), fixed on a bed using a hydraulic anti-vibration system (Hydro-Soft™, Fahrtec, Germany). The infant was placed on a Vacuum Pillow™ vacuum mattress (AB Germa, Sweden). Movement periods of the ambulance were retrieved from an iTrack™ GPS

tracking system (iDATA Ltd, Hungary, https://www.idatatelematics.com) and were also verified by reviewing patient records.

Ambulance acceleration data were collected using a freely available software (Accelerometer Analyzer, version 16.11.27, https://chipapk.com/app/39720) installed on a mobile phone, which was fixed on the top of the transport incubator, correctly aligned with the direction of travel. The internal clocks of the accelerometer and the ventilator were synchronized to the minute before each transfer. The accelerometer's sensor collects acceleration data with 100 Hz sampling rate along three dimensions: front-back (X), left-right (Y) and up-down (Z), see **Figure 22**. The sensor's resolution is 0.009 m/sec^2, its maximum range is 39 m/sec^2 and its minimum delay is 10 milliseconds. Acceleration data were exported as comma separated values (csv) in text files.

5.4. Data processing and analysis

5.4.1. Processing and analysis of ventilator data

5.4.1.1. Processing and descriptive statistics

Ventilator data were processed and analysed using Python and its data science libraries (see **section 3.6.4**. for more details on these tools). All software used in this thesis is open source and freely available. Computer programming was done in Jupyter Notebooks using the free version of Anaconda distribution (170), installed on MacBook Pro personal computers, 2014 and 2019 versions. Jupyter notebooks containing and explaining all steps of data processing and analysis can be accessed as GitHub code repositories at **https://github.com/belteki**. The *Ventiliser* software (see **section 5.4.2.)** was developed as part of the work presented in this thesis and it is also freely available at **https://pypi.org/project/ventiliser**.

Ventilator data were represented, manipulated and analysed using the *pandas* (171) package and *NumPy* arrays as underlying data structures. Data from the Dräger™ ventilators were downloaded as comma-separated value (csv) files and directly imported into *pandas* DataFrames. Data from Fabian™ ventilators were downloaded as key/value pairs (0.5 Hz ventilator parameters, settings and alarms) or as hexadecimal data (125 Hz pressure, flow and volume data). Python scripts were written for converting them into tabular data which could then be imported as *pandas* DataFrames.

Descriptive statistics, handling of missing data and artifact removal was done using *pandas*. As the exact filtering and outlier removal steps differed in the specific projects, they will be presented together with the individual studies in the Results section. *pandas* was also used to generate aggregate values (average and spread) of the ventilator data over longer periods (e.g., 1 minute or longer). For ventilator parameters showing normal distribution, arithmetic mean and SD were calculated for each period, for parameters with non-parametric distribution, median and interquartile range (IQR) were calculated. Inferential statistics, correlation and regression analysis was done using *SciPy*.

To determine ventilator parameters associated with blood gases, we used aggregated data as they are more representative than single readings. We calculated the mean or median of the ventilator parameters obtained with 1 Hz sampling rate over specific periods before each blood gas measurement. We excluded the last two minutes before the gas analysis, because the blood

had already been collected and placed in the analyser during that period (**Figure 19**).

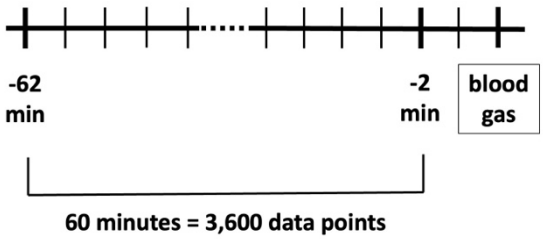

Figure 19. Calculating aggregate values of ventilator parameters before blood gases over longer periods. Mean and SD (for normally distributed parameters) or median and IQR (for parameters with non-parametric distribution) were calculated from ventilator data obtained at each second. The last two minutes before the time of the blood gas was excluded. The figure shows an averaging period of 60 minutes corresponding to 3,600 data points. Aggregating over shorter or longer periods was done similarly. Adapted from (52).

5.4.1.2. Inferential statistics

For inferential statistics during the observational studies, the specific statistical tests used for the different studies varied and are presented in the Results section.

During statistical analysis of the interventional pressure rise time study, for each 15-minute epoch, the mean value of each ventilator parameter was calculated for each patient. For physiologic parameters (ET-CO_2 and SpO_2) only the second half of each epoch was averaged, to leave time for the set PRT to affect them. Group means and SDs were calculated from these aggregated values. One-way repeated measures analysis of variance (ANOVA) was used to compare epochs with different PRTs for each ventilator mode separately. Correction for multiple testing was done using the Benjamini-Hochberg method with a false discovery rate of 5%; a corrected $p<0.05$ was considered as statistically significant. For ventilator parameters where a significant difference was seen among the different epochs using repeated measures ANOVA, a linear mixed model approach was used to account for the non-independence of measurements because parameters were measured on the same neonate in each epoch over 10 epochs. Briefly, this involves simple linear regression with PRT as independent variable and the relevant ventilator as dependent variable with an additional neonate-specific term for both slope and intercept, thus enabling a linear estimate of the response of a ventilator parameter to PRT for each individual neonate. Equivalence testing for ET-CO_2 was done with 90% confidence, considering a difference of <0.5 kPa as equivalent. To use data which were more representative than single readings, we calculated the mean of 600 values obtained during 10 minutes starting 12 minutes before and ending at 2 minutes before each blood gas measurement. We omitted the last two minutes before the gas analysis because the blood had already been collected and placed in the analyzer during this period (see **Figure 19**).

5.4.1.1. Visualizations

Data visualization and production of the figures in this thesis and in the associated publications was done using *matplotlib* and *seaborn*. To investigate how irregular pressure-volume loops become at different vibration levels, all inflations and breaths over 1-minute periods were plotted on the same chart. Irregularity of these composite loops was quantitated as the number of pressure-volume data pairs occurring over the 1-minute period. The 1-minute periods with

the lowest and the highest median vibration for each recording were then compared. The graphical user interface of the *Ventiliser* package was built using the *PyQt5* (https://www.riverbankcomputing.com/software/pyqt/) and *pyqtgraph* (http://www.pyqtgraph.org/).

5.4.2. Development of the Ventiliser package

To develop the *Ventiliser* package, phases and subphases of the respiratory cycle needed to be defined first unambiguously. Subsequently, flow and pressure states associated with the subphases also needed to be determined. Finally, an algorithm segmenting the respiratory cycles into subphases based on flow and pressure states needed to be implemented.

5.4.2.1. Definition of a ventilator cycle and its phases and sub-phases

Before implementing the algorithm, we defined the concept of a ventilator cycle and its phases and sub-phases (**Table 2**). The start of a ventilator cycle was defined as the time from the start of the positive (inward) flow which is accompanied by a ventilator-assisted and ventilator-cycled positive pressure inflation. The ventilator cycle can be triggered by the baby and synchronized when the increase in flow precedes the start in pressure rise (trigger delay) or it can be a ventilator-initiated backup cycle when the airway pressure increases first, rapidly followed by the appearance of positive flow (**Figure 20**). A ventilator cycle lasts until the start of the next ventilator cycle (commencement of next positive flow). In some modes (e.g., SIMV), there can be unassisted or pressure-supported spontaneous breaths between ventilator inflations. The inspiratory phase of the cycle includes the period when the lungs are being inflated (lung inflation time) and the inspiratory hold, which, if present, corresponds to inflated lungs with the airway pressure being maintained at the PIP level and with no air flow. The expiratory phase comprises the lung deflation time, the period when the lungs are deflating to the level of the functional residual capacity (FRC), and the time with the lungs at FRC and the airway pressure at the PEEP (expiratory hold or pause).

Table 2. Phases and subphases of a ventilator cycle defined by direction and change in airway flow. Inspiratory hold may be absent depending on the ventilator modes and settings used.

Phase	Subphase	Start	End
Inspiration	Lung inflation	Start of ventilator cycle[a]	Inspiratory flow ends
	Inspiratory hold	Inspiratory flow ends	Expiratory flow starts
Expiration	Lung deflation	Expiratory flow starts	Expiratory flow ends
	Expiratory hold	Expiratory flow ends	Start of next ventilator cycle

[a] Start of a ventilator cycle was defined by the beginning of the positive (inward) flow both in case of triggered and backup ventilator inflations.

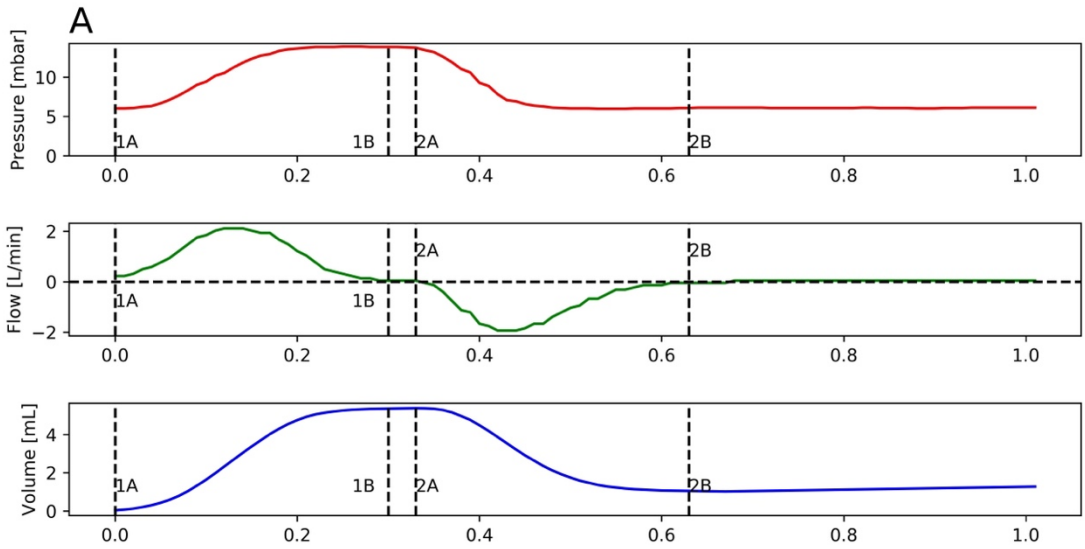

Figure 20. Phases and subphases of a ventilator cycle. Ventilator waveforms reconstructed from pressure and flow data obtained at 100 Hz sampling rate. Ventilator mode was SIPPV-VG. Subphases of the inflation are demarcated by dotted line and numbered as follows: 1A. Lung inflation; 1B. Inspiratory hold; 2A. Lung deflation; 2B. Expiratory hold. The failure of the tidal volume wave form to return to zero at the end of expiration indicates the presence of some leak around the endotracheal tube. This was a backup ventilator inflation without any patient contribution; patient-ventilator interactions make waveforms more complex and difficult to segment into subphases. Modified from (20).

5.4.2.2. Definition of pressure and flow states associated with the subphases of ventilator cycles

After defining ventilator subphases, we also defined flow and pressure states associated with them (**Tables 3 & 4**). To reduce noise and processing time, the raw time series was then discretised by associating flow and pressure states with these subphases. Mapping states to raw time series was achieved by piecewise aggregate approximation using mean and standard deviation with a window size of 3 data points (30 milliseconds). The mean ($Wmean_i$) and standard deviation ($Wstd_i$) of each segment (W_i) was then compared to the next one (W_{i+1}). Stationary states were determined by comparing the difference in mean between windows ($\Delta Wmean = Wmean_{i+1} - Wmean_i$) against $Wstd_i$. If $\Delta Wmean < 2\ Wstd_i$ or $\Delta Wmean <$ a threshold (T) then the state is stationary and if not, it is non-stationary (moving). T is defined as 0.1 L/min for flow and 10% of set PEEP for pressure. The type of the non-stationary states is determined by the sign of ΔWmean with positive flow and pressure states being "Inspiration initiation", "Expiration termination" and "Pressure rise" respectively, and negative flow and pressure states being "Inspiration termination", "Expiration initiation" and "Pressure drop" respectively. For stationary flow states, the "Peak inspiratory flow" state has positive $Wmean_i$, the "Peak expiratory flow" state has negative $Wmean_i$, and the "No flow" state has $Wmean_i$ within ±0.1 L/min of 0 L/min. For stationary pressure states, the average between the previous PIP and the set PEEP was used, such that if $Wmean_i <$ the average, it was state PEEP and if not, it was state PIP. Details can be seen on **Figures 21** & **22.**

Table 3: Flow states identified by *Ventiliser.*

Label	Flow state	Flow direction[a]	Flow change	Subphase(s) when occur[b]
0	No flow	No flow	N/A	Inspiratory hold Expiratory hold
1	Inspiration initiation	Positive	Increasing	Lung inflation
2	Peak inspiratory flow	Positive	No change	Lung inflation
3	Inspiration termination	Positive	Decreasing	Lung inflation
4	Expiration initiation	Negative	Increasing	Lung deflation
5	Peak expiratory flow	Negative	No change	Lung deflation
6	Expiration termination	Negative	Decreasing	Lung deflation

[a] Positive flow corresponds to inward flow normally present during inspiration. Negative flow corresponds to outward flow normally present during expiration.
[b] See **Table 2** for definition of subphases of a ventilator cycle.

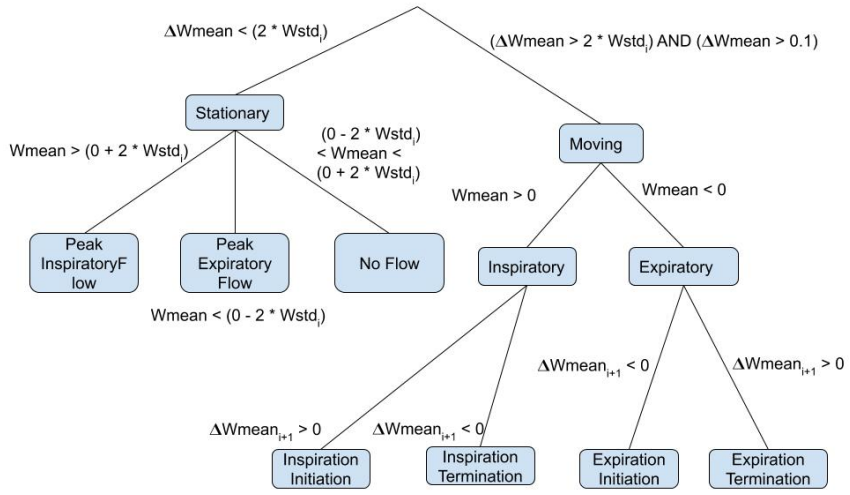

Figure 21.: Schema for the logic used to segment flow time series data. $Wmean_i$ refers to the mean flow within the i^{th} window. $\Delta Wmean$ refers to the difference between $Wmean_{i+1}$ and $Wmean_i$. $Wstd_i$ refers to the standard deviation of the flow within the i^{th} window. For detailed explanation regarding stationary and moving (non-stationary) states see main text.

5.4.2.3. Segmentation algorithm

After discretisation, breaths were demarcated into inspiration-inspiration intervals, determined by encountering an "Inspiration initiation" or "Peak inspiratory flow" state and also fulfilling the following two criteria: (1) having already encountered an expiratory state ("Expiration initiation", "Peak expiratory flow" or "Expiration termination"); or (2) having encountered an "Inspiratory hold" or "Expiratory hold" state of more than 50 time units (=500 milliseconds with the 100 Hz sampling rate data). This allows *Ventiliser* to recognise the start of a new ventilator inflation even after positive flow was previously encountered without any negative flow, which may be due to a very large (>90%) leak around the endotracheal tube or a ventilator artefact. Inflations with <500 millisecond expiratory time will still be missed but the user can set this value differently. There is also an optional post-processing step which merges adjacent

breaths if they are discovered to have significantly different inspiratory and expiratory volumes, which further reduces artefacts, but also combines breaths with large leaks around the endotracheal tube in to one (default value is 66%).

Table 4. Pressure states identified by *Ventiliser.*

Label	Pressure state	Pressure level	Pressure change	Subphase(s) when can occur[a]
0	PEEP	PEEP	No change	Lung deflation[b] Expiratory hold
1	Pressure rise	Between PEEP and PIP	Increasing	Lung inflation
2	PIP	PIP	No change	Lung inflation[b] Inspiratory hold
3	Pressure drop	Between PIP and PEEP	Decreasing	Lung deflation

[a] See **Table 2** for definition of subphases of a ventilator cycle.
[b] Due to airway resistance, during inspiration airway pressure rises to PIP level some time before inspiratory flow ends and during expiration pressure drops down to PEEP level some time before expiratory flow ends.

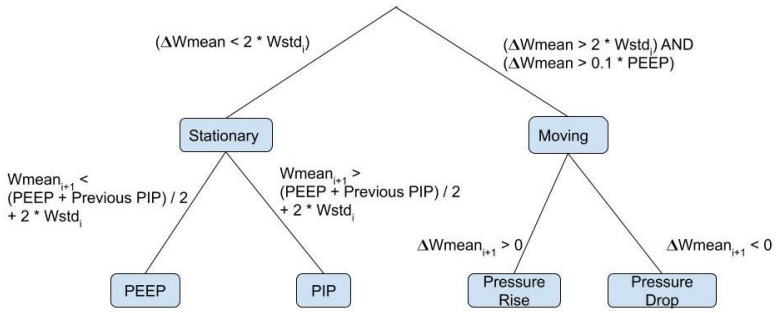

Figure 22. Schema for the logic used to segment airway pressure time series data. $Wmean_i$ refers to the mean pressure within the i^{th} window. $\Delta Wmean$ refers to the difference between $Wmean_{i+1}$ and $Wmean_i$. $Wstd_i$ refers to the standard deviation of the i^{th} window. PEEP is the positive end expiratory pressure set by the user. "Previous PIP" refers to the peak inspiratory pressure during the previous ventilation cycle. For detailed explanation regarding stationary and moving (non-stationary) states see main text.

Identifying inflation subphases is further complicated by the fact that in many cases the pressure and flow waveforms of ventilated infants do not show the regular shapes presented in **Figure 20,** due to spontaneous breathing effort, splinting, coughing or movement of the baby and artefacts due to kinking of the ETT or condensed water in the ventilator circuit. Therefore, an actual subphase is frequently not a contiguous series of consecutive single flow and pressure states as shown in **Tables 3 & 4**. Instead, it may be a region dominated by one particular state and interspersed with others. For example, an inflation may start with an "Inspiration initiation" flow state but if the patient is splinting the chest or is trying to breathe out briefly, inspiratory flow will decrease or even stop, resulting in "Peak inspiratory flow" or "Inspiration termination" flow states, respectively, before increasing again to reach the true peak inspiratory flow. To address this, *Ventiliser* iterates over the set of ordered states (flow or pressure) and finds the split along the time axis that maximises the information gain of the current state with

respect to all other states. Each subsequent split is performed on the data after the previous split to ensure order.

5.4.3. Processing and analysis of ambulance acceleration and vibration data

Vehicle acceleration and vibration data were downloaded as comma-separated value (csv) text files and imported into *pandas* DataFrames. Descriptive statistics, handling missing data and artifact removal was done using *pandas*.

For accelerometer data, we subtracted the gravitational acceleration (9.81 m/sec^2) from the vertical (Z) acceleration measurements (**Figure 23)**. To separate high-frequency vibration and low-frequency "sustained" acceleration (due to the ambulance accelerating, decelerating or turning left or right), we used the *scipy.signal.butter()* function of *Scipy* to apply third order Butterworth high-pass and low-pass filters, respectively (172). Cut-off frequency was 0.5 Hz in both cases.

For each minute and along each axis (X, Y & Z), we calculated the median of the absolute value (the quantity without the sign) of the vibration and of the sustained acceleration vectors during the minute. To determine the overall acceleration or vibration (irrespective of direction) we calculated the Euclidean length (173) (also known as L2 norm) of the vectors as square root of ($X^2 + Y^2 + Z^2$), see **Figure 23**.

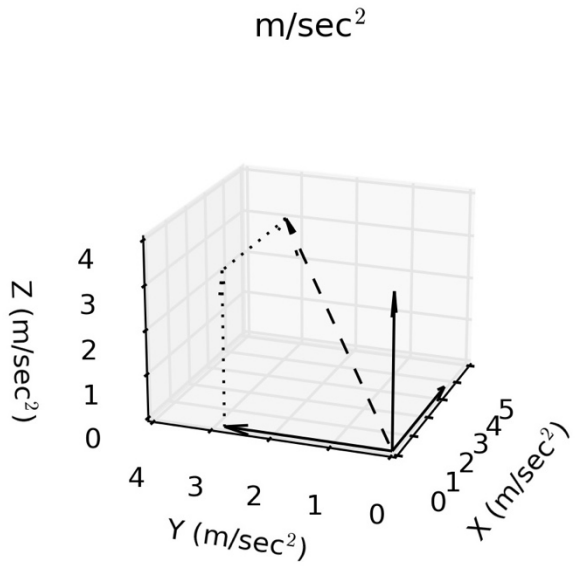

Figure 23. The three components of the acceleration vector: X (front-back), Y (side-to-side), Z (up-down) accelerations. The ambulance is moving in X direction. The graph only shows positive accelerations but acceleration can also be negative when the ambulance is slowing down (X), turn to the right (Y) or during vertical vibration (Z). Absolute value of an acceleration component is its distance from zero, that is, its value without a sign. The dashed arrow shows the length (Euclidean norm) of the acceleration vector, see main text for more details.

6. Results

6.1. Analysis of ventilator performance

6.1.1. Ventilator parameters and maintenance of tidal volume during volume targeted ventilation

6.1.1.1. On the neonatal intensive care unit

6.1.1.1.1. The tidal volume terminology of the Dräger Babylog™ VN500 ventilator

The general terms for inspiratory and expiratory tidal volume are VTi and VTe, respectively. They refer to both spontaneous breaths or ventilator inflations. During SIPPV almost all inflations are mandatory. The inspiratory tidal volume delivered during mandatory ventilator inflations is called VTimand. The expired tidal volume exiting the ETT during mechanical ventilation is called the VTemand. When the leak compensation mode is enabled the leak-compensated expiratory tidal volume is called VTmand. The tidal volume set during VG ventilation is called VTset. In leak-compensated mode the ventilator aims to maintain VTmand at VTset. Without leak compensation VTemand is maintained at VTset. We calculated the difference (VTdiff) between the delivered tidal volume (VTmand in leak compensated mode and VTemand without leak compensation) and the VTset. We also calculated the volume used for leak compensation (VTlc), that is, the ventilator estimated expiratory leak around the ETT, as VTmand - VTemand. On the VN500 ventilator low tidal volume alarms are triggered if the VTemand or VTmand are <90% of the VTset for more than 8 consecutive inflations.

6.1.1.1.2. The impact of leak compensation during volume targeted ventilation

6.1.1.1.2.1. Ventilator parameters with or without leak compensation

For this study (58), we analysed ventilator recordings from 30 infants ventilated in NICU, Rosie Hospital, Cambridge. All recordings were >12 hours long and babies were ventilated with SIPPV-VG. The NICU started to use the leak compensated mode on the ventilators during the data collection, therefore 11 recordings had no leak compensation and 19 were leak compensated. Summary statistics for included infants are shown in **Table 5**.

Table 5. Baseline characteristics of the infants. Groups were compared using Mann-Whitney U-Test.

	Leak compensation ON (n= 19)	**Leak compensation OFF (n=11)**	**P value**
	median (range)	**median (range)**	
Gestational age at birth(weeks)	27 (24-40)	32 (24-40)	0.172
Weeks of gestation, n (%)			
23-28 weeks	10 (52.6%)	4 (36.4%)	0.466
28-32 weeks	6 (31.6%)	2 (18.2%)	0.672
33-36 weeks	1 (5.3%)	1 (9.1%)	>0.999
>36 weeks	2 (10.5%)	4 (36.4%)	0.156
Gestational age at study (weeks)	28 (24-42)	32 (24-43)	0.141
Birth weight (g)	760 (520-3052)	795 (550-4250)	0.281
Current weight (g)	940 (520-4185)	1736 (640-4300)	0.132

We recorded 3,376,158 leak-compensated inflations from 19 patients and 1,202,595 non-leak-compensated inflations from 11 patients. In 0.029% of the inflations tidal volume was >20 mL/kg and in 0.026% VTlc was negative. They were considered as artifacts possibly due to flow measurement errors and excluded from further analysis.

Overall, there was no significant difference in the FiO_2, PIP, ventilator rate, inspiratory and expiratory tidal volumes, Pmax and VTset between the leak compensated and uncompensated recordings (**Table 6**). The minute volume and percentage of the leak were significantly higher with leak compensation.

Table 6. Group statistics with leak compensation on or off. For each recording averages of the various ventilatory parameters were calculated: arithmetic mean for parametrically distributed data and median for non-parametric distribution. These averages were compared between the 2 groups by Mann-Whitney U Test. Data are presented as group medians with interquartile ranges and ranges.

Ventilator parameter	Leak compensation ON (n = 19)			Leak compensation OFF (n = 11)			P value
	median	IQR	Range	median	IQR	Range	
FiO_2 (%)	29	16	21 - 89	24	13	21 - 59	0.161
PIP (mbar)	18	6	14 - 33	21	4	17 - 26	0.195
Pmax (mbar)	30	8	22 - 39	30	6	25 - 38	0.389
Pdiff (Pmax-PIP) (mbar)	10	6	4 - 20	7	7	2 - 19	0.333
MAP (mbar)	10	3	8 - 12	10	1	9 - 23	0.415
RR (/min)	61	10	45 - 79	57	11	45 - 64	0.091
VTimand (mL/kg)	4.86	1.02	3.82 - 6.87	4.99	0.91	3.74 - 8.42	0.333
VTemand (mL/kg)	4.49	0.91	3.14 - 6.01	4.56	0.93	3.57 - 5.33	0.457
VTmand (mL/kg)	4.61	0.98	3.53 - 6.31	n/a	n/a	n/a	n/a
VTset (mL/kg)	4.58	0.92	3.35 - 6.23	4.48	0.60	3.78 - 5.37	0.281
VTdiff (mL/kg)	0.00	0.02	-1.54 - 0.32	0.00	0.01	-0.87 - 0.20	0.349
Leak (%)	12	14	0 - 37	0	0	0 - 55	0.005
Minute volume of leak (L/kg/min)	0.04	0.03	0.01 - 0.11	0.01	0.03	0.00 - 0.23	0.002

6.1.1.1.2.2. Maintenance of tidal volume during large leak with or without leak compensation

The percentage of leak was <20% in 73% of leak-compensated inflations (**Figure 24A**). The volume of leak compensation was <1 mL/kg in 97.3% of inflations (**Figure 24B**). There was positive correlation between leak compensation volume and the percentage leak. With leaks ≥90% the mean leak compensation volume was 1.8 mL/kg but with large variability (**Figure 24C**).

We investigated inflations where the leak was >50% (105,207 inflations, 2.3%). While there was no difference in most ventilator parameters between recordings with or without leak compensation, VTdiff was significantly less with leak compensation: 0.15 mL/kg compared with 1.15 mL/kg without leak compensation, ($p<0.001$) (**Table 7).** Without leak compensation, the mean VTemand fell progressively below the VTset as the leak increased >50% (**Figure 25**). With leak compensation, the mean VTmand was maintained close to the VTset at all leaks until >80% when some overshoot occurred. However, VTdiff in both groups was highly variable and frequently positive, that is, the delivered VT frequently slightly exceeded VTset.

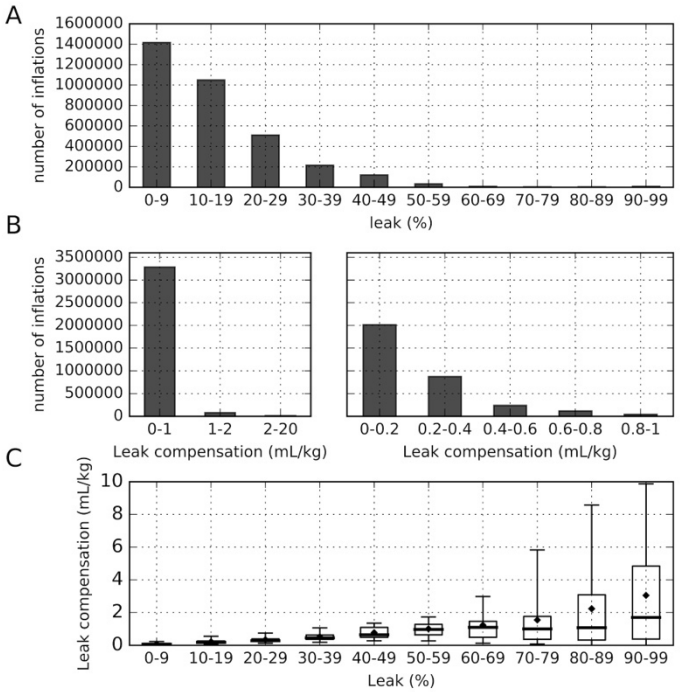

Figure 24: A: Histograms showing the number of leak-compensated inflations according to ranges of endotracheal tube leak. For the majority of the >3 million inflations the leak was less than 20%. **B:** Histograms showing the number of leak-compensated inflations according to the volume of leak compensation (VTlc). The first shows leak compensation volumes up to 20 ml/kg, the second shows details of the commonest leak compensation volumes 0 to 1 mL/kg. VTlc was <1 mL/kg in 97.3% of the inflations and <2 mL/kg in 99.6% of the inflations. **C:** Boxplots showing VTlc according to percentage of leak. Leak compensation increases with increasing leak. With leaks ≥90% the median VTlc was 1.8 mL/kg with a large variability. Median (line), mean (diamond), interquartile range (box) and 5th-95th centiles (error bars) are shown.

Table 7. Group statistics for inflations with >50% leak, comparing leak compensation on or off. For each recording averages of the various ventilatory parameters were calculated: arithmetic mean for parametrically distributed data, median in case of non-parametric distribution (VTdiff). These averages were then compared between the groups by Mann-Whitney U Test. Data are presented as group medians, interquartile ranges and ranges.

Ventilator parameters	Leak compensation ON (n = 19)			Leak compensation OFF (n = 11)			P
	median	IQR	Range	median	IQR	Range	
FiO_2 (%)	30	15	21 to 99	23	17	22 to 62	0.114
PIP (mbar)	20	5	15 to 39	23	2	17 to 28	0.028
Pmax (mbar)	30	7	22 to 40	30	6	25 to 36	0.373
Pdiff (Pmax-PIP) (mbar)	9	5	1 to 18	6	4	2 to 13	0.043
MAP (mbar)	10	2	9 to 13	11	2	9 to 14	0.081
RR (/min)	74	14	48 to 90	67	13	49 to 80	0.019
VTimand (mL/kg)	7.46	2.72	3.95 to 11.33	7.14	0.71	4.88 to 9.47	0.201
VTmand (mL/kg)	4.94	1.42	2.75 to 6.98	3.40	n/a	n/a	n/a
VTemand (mL/kg)	3.03	0.93	2.13 to 4.43	3.40	0.46	1.09 to 4.03	0.232
VTset (mL/kg)	4.65	0.91	3.35 to 6.23	4.48	0.57	3.89 to 5.47	0.207
VTdiff (mL/kg)	-0.15	0.58	-1.97 to 1.06	-1.15	0.61	-3.27 to 0.67	<0.001

6.1.1.1.2.3. Effect of leak on peak inspiratory pressure and low tidal volume alarms

Without leak compensation, the difference between Pmax and PIP (Pdiff) decreased progressively as the leak increased because with increasing leak the ventilator increases the PIP to try to deliver the VTset. Interestingly, at >70% leak the Pdiff increased again. We speculate that this is because with very large leaks the ventilator is not able to increase the PIP to the level needed to deliver the VTset. With leak compensation Pdiff remained stable irrespective of the amount of leak (**Figure 25**).

The number of “low tidal volume” alarms was less in recordings with leak compensation (medians: 1.73 vs 4.13 per hour) although this difference was not statistically significant (p=0.09, Mann-Whitney U-test) because of the highly variable number of these alarms due to large differences in Pmax settings in different recordings.

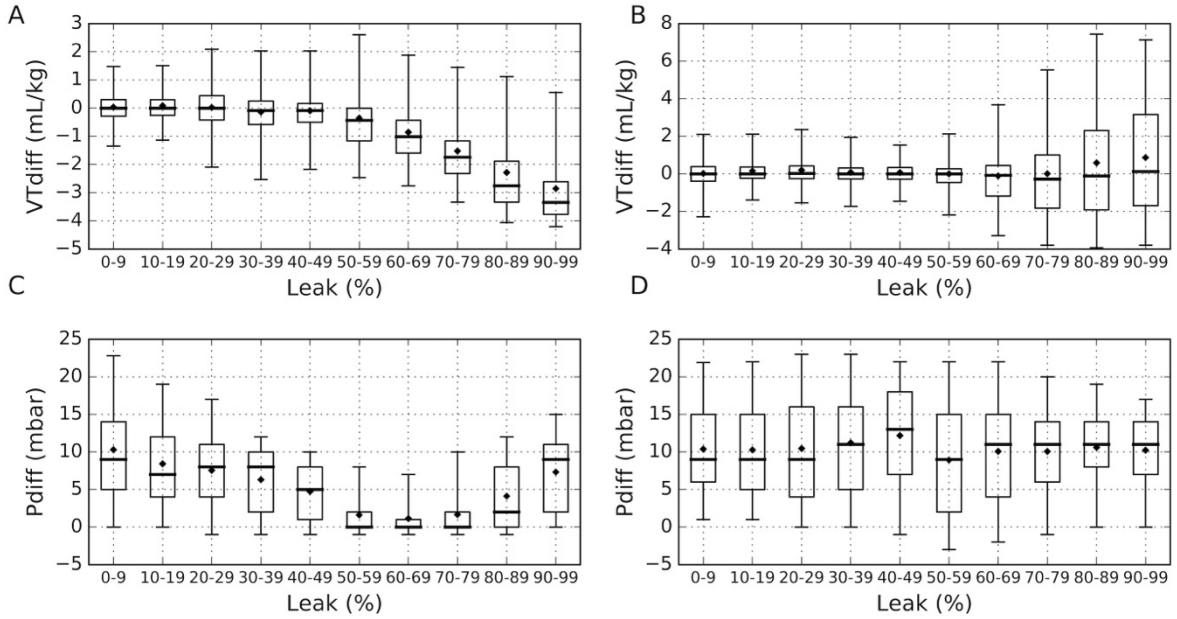

Figure 25: A-B Boxplots representing the difference (VTdiff) between the actual and target tidal volumes at different levels of leak. **A:** No leak compensation. When leak exceeds 50% the VTdiff is increasing progressively with increasing leak, that is, the target tidal volume is not achieved. **B:** Leak compensation. The set tidal volume is achieved consistently at all levels of leak but with increasing variation as the leak increased. **C-D:** Boxplots representing the difference (Pdiff) between the Pmax and the PIP. **C:** No leak compensation. With increasing leak Pdiff is decreasing progressively as the ventilator increases the PIP to maintain the expiratory tidal volume. When leak is >70% Pdiff increases again. **D:** Leak compensation. Pdiff remains stable at all levels of leak.

6.1.1.1.2.4. Arterial and capillary carbon dioxide levels

The VTset was similar at 4.58 mL/kg and 4.48 mL/kg in the leak-compensated and non-leak compensated groups, respectively. When all pCO_2 measurements were compared (capillary and arterial, n = 247) the median pCO_2 was slightly higher with leak compensation than without it: 54.0 mmHg [IQR 47.3-64.5] vs. 51.8 [45.8-57.0] mmHg, (7.2 kPa [6.3-8.6] vs 6.9 kPa [6.1-7.6], p=0.037, Mann-Whitney U-test). When only arterial measurements were compared (n=108), the results were 52.0 mm Hg [IQR 49.5-60.0] vs. 50.3 [45.0-56.3] mmHg (7.0 [6.6-8.0] vs. 6.7 [6.0-7.5] kPa, p = 0.037). The pCO_2 was expected to be higher with leak compensation because when using the same VTset the ventilator delivers a slightly lower effective tidal volume with leak compensation than without since the computed value for the expiratory leak is taken into account.

6.1.1.1.3. Analysis of SIMV-VG-PS ventilation mode

During this study (49) 137 days analysed ventilator data were collected from 16 infants ventilated in SIMV-VG-PS mode (see **section 3.3.2.2.3**.) in the Neonatal Intensive Care Unit, Department of Paediatrics, University of Debrecen, Hungary. The Unit uses this mode with active leak compensation as the main mode of invasive ventilation. The local recommendation is to set PS level so that PIPspon is ~66% of the working PIPmand required during VG inflations. Clinical details of the babies are shown in **Table 8**. The median recording duration after excluding periods with ventilation modes other than SIMV-VG-PS was 3 days (0.6 – 28 days).

Table 8. Basic clinical and ventilation details of the infants studied

Demographics (n=16)	**Median**	**Range**
Gestational age at birth (weeks)	26.7	23.3 – 38.0
Post-menstrual age (weeks)[a]	27.8	23.4 – 38.1
Birth weight (grams)	935	500 – 3,700
Number of patients		
Birth weight >2000 grams	3	
Birth weight 1000 – 2000 grams	4	
Birth weight <1000 grams	9	

[a] At the start of the recording

We excluded respiratory cycles when the PIP was lower than the PEEP, as this can only occur during spontaneous breaths without pressure support (0.19%). We also excluded inflations and spontaneous breaths when the leak compensated expired VT (VTmand or VTspon) was >25 mL/kg (0.38%), periods when the MV was >1 L/min/kg (0.3%) or when the total respiratory rate (RR) was >130/min (0.4%). These events do not normally occur during conventional ventilation and they likely represent artefacts, e.g., when the ventilator circuit was open or when condensed water in the circuit caused auto-triggering. We also removed data points when one or more of these parameters were missing. Altogether, we excluded a total of 705,974 data points out of the initial 13,452,646 (5.2%).

For each minute of recording, we calculated the average (mean) of ventilator parameters separately for VG ventilator inflations and for spontaneous breaths with PS. These mean values were then compared. Minutes when there were no spontaneous breaths between VG inflations have been excluded. To characterize these ventilator parameters over the whole recordings (or for the longitudinal analysis, in each quarter of the recordings), median of the 1-minute means or their ratios was calculated in each recording, as these aggregate values themselves were not normally distributed within the recordings. Mann-Whitney test was used to compare these groups. For longitudinal analysis of ventilator parameters, Friedman's test was used. P values <0.05 were considered as statistically significant. The mean transcutaneous CO_2 ($tcCO_2$) was calculated by averaging over 10-minute periods. 10-minute periods when the range of $tcCO_2$ readings exceeded 15 mmHg (2 kPa) were disregarded, in order to exclude periods of calibration, artefacts or rapidly changing CO_2.

PIPmand was highly variable in all recordings, while the PS level was changed infrequently by clinicians and hence PIPspon also changed infrequently. **Figure 26A** shows the recording from a baby for the whole ventilation time. The ratio of PIPspon to PIPmand differed considerably from the local recommendation of 0.66 (group median: 0.80, range: 0.50–1.00, see **Table 9** &

Figure 27A). Most recordings had minutes when the average PIPspon exceeded the average PIPmand.

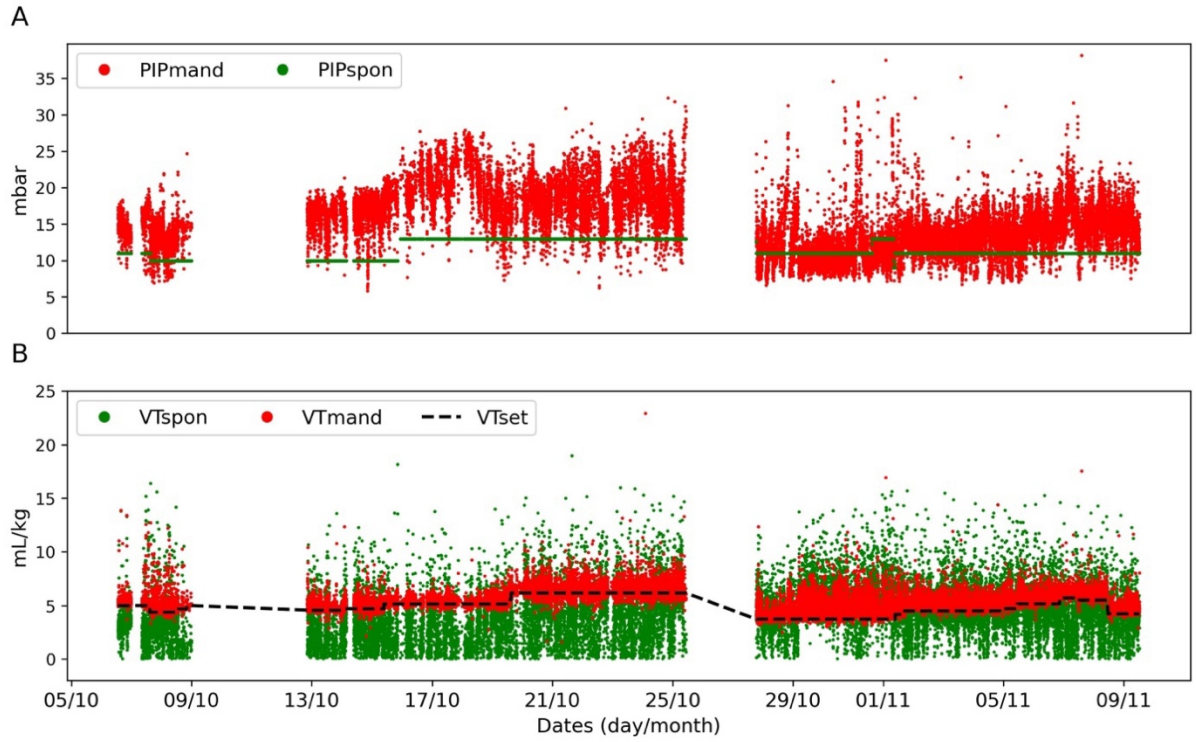

Figure 26: Peak inflating pressures (**A**) and tidal volumes (**B**) of volume-targeted inflations and pressure supported spontaneous breaths from a 25-weeker baby (LVD002) ventilated for respiratory distress during the first month of life. The baby had two periods of extubation lasting for ~4 and 2.5 days, respectively. Each dot in A and B corresponds to the mean PIP or the mean expired VT calculated over a minute, respectively. Parameters for volume targeted mandatory ventilator inflations and pressure supported spontaneous breaths are shown separately. During the last third of the recording (between 29/10 and 09/11), peak inflating pressures of volume targeted inflations were frequently lower than the peak inflating pressure of pressure supported spontaneous breaths. In this period the expired tidal volume of volume-targeted inflations usually exceeded the set target (dashed line), but the tidal volume of pressure supported spontaneous breaths was frequently even larger. Adapted from (49).

VTspon and its proportion to the VTmand (VTspon/VTmand) were also highly variable during the recordings (group median: 0.75, range: 0.30 – 1.1, see **Table 9**, **Figure 26B** and **Figure 27B**). In two infants, the median VTspon exceeded VTmand. The proportion of spontaneous and mandatory respiratory rates (RRspon/RRmand) and their contribution to minute ventilation were also highly variable in each recording. To analyse longitudinal trends in ventilator parameters, we compared the ratios of spontaneous and mandatory ventilator parameters during the four quarters of each recording (**Figure 28**). The ratios of PIPspon/PIPmand, VTspon/VTmand, RRspon/RRmand and MVspon/MVmand were all increasing significantly during the course of recordings.

Table 9: Group median and range of ventilator parameters characterising volume guaranteed ventilator inflations and pressure supported spontaneous breaths.

Ventilator parameter or ratio	Group median	Group range
PIPmand [mbar]	14.2	8.1 - 23.1
PIPspon [mbar]	11	8 - 15
PIPspon/PIPmand	0.8	0.5 - 1
VTmand [mL/kg]	5.6	4.3 - 7
VTspon [mL/kg]	4.2	1.7 - 6.2
VTspon/VTmand	0.75	0.3 - 1.1
RRmand [1/min]	32.8	20 - 44.8
RRspon [1/min]	20.6	5.2 - 57.8
RRspon/RRmand	0.6	0.1 - 2.8
MVmand [L/min/kg]	0.17	0.11 - 0.26
MVspon [L/min/kg]	0.07	0.03 - 0.19
MVspon/MVmand	0.44	0.10 - 1.38
Timand [s]	0.33	0.28 - 0.35
Tispon [s]	0.25	0.2 - 0.4
Tispon/Timand	0.83	0.63 - 1.2

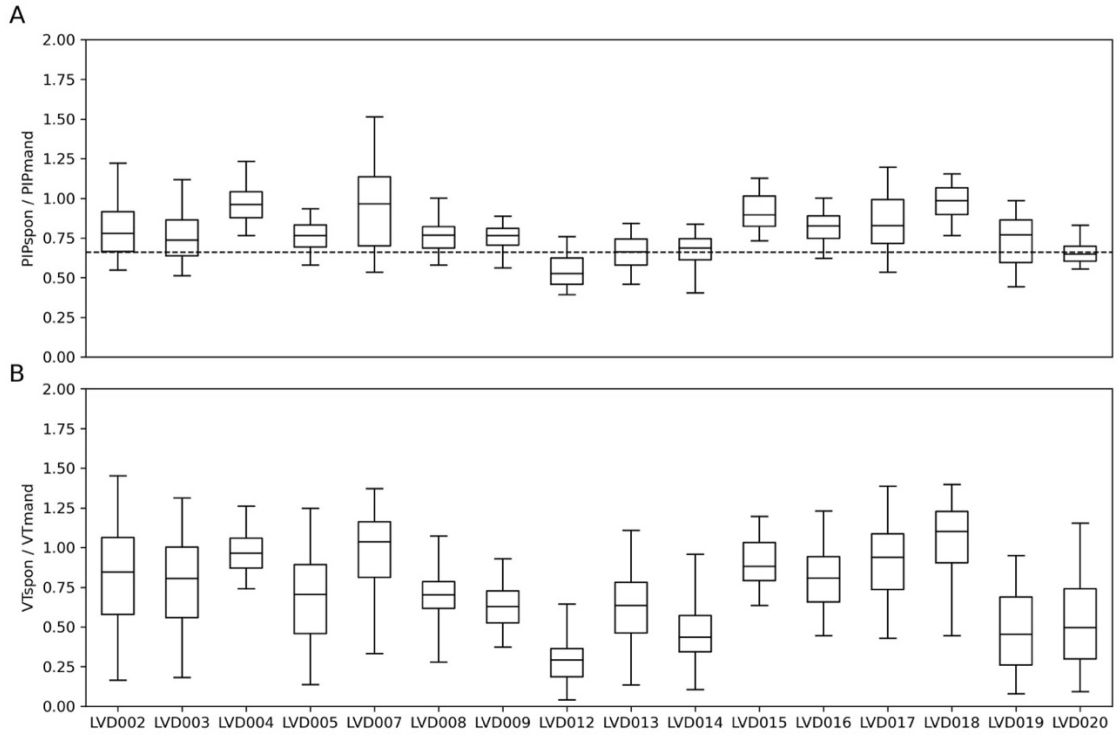

Figure 27: Ratio of peak inflating pressures (**A**) and leak compensated expired tidal volumes (**B**) of volume-targeted inflations and pressure supported breaths in each study subject. For each minute of each recording, the mean peak inflating pressure (PIPspon and PIPmand) and the mean expired tidal volume (VTspon and VTmand) were calculated separately for pressure supported spontaneous breaths and for volume targeted mandatory ventilator inflations. Their proportion was also determined for each minute, and its distribution in each recording are shown on this graph. Boxes represent interquartile ranges; whiskers show 5th and 95th centiles. Median is shown as a horizontal line. **A.** Ratio of the peak inflating pressures (PIPspon / PIPmand). The local guideline was to set the pressure support level to ensure a ratio of 0.66 (dashed line). In most patients the median ratio considerably deviated from this target and in three babies (LVD004, LVD007 and LVD018) it was >0.9. **B.** Ratio of the leak compensated expired tidal volumes (VTspon/VTmand). The median tidal volume of pressure supported spontaneous breaths reached or exceeded that of volume targeted inflations in two cases (LVD007 and LVD018). Adapted from (49).

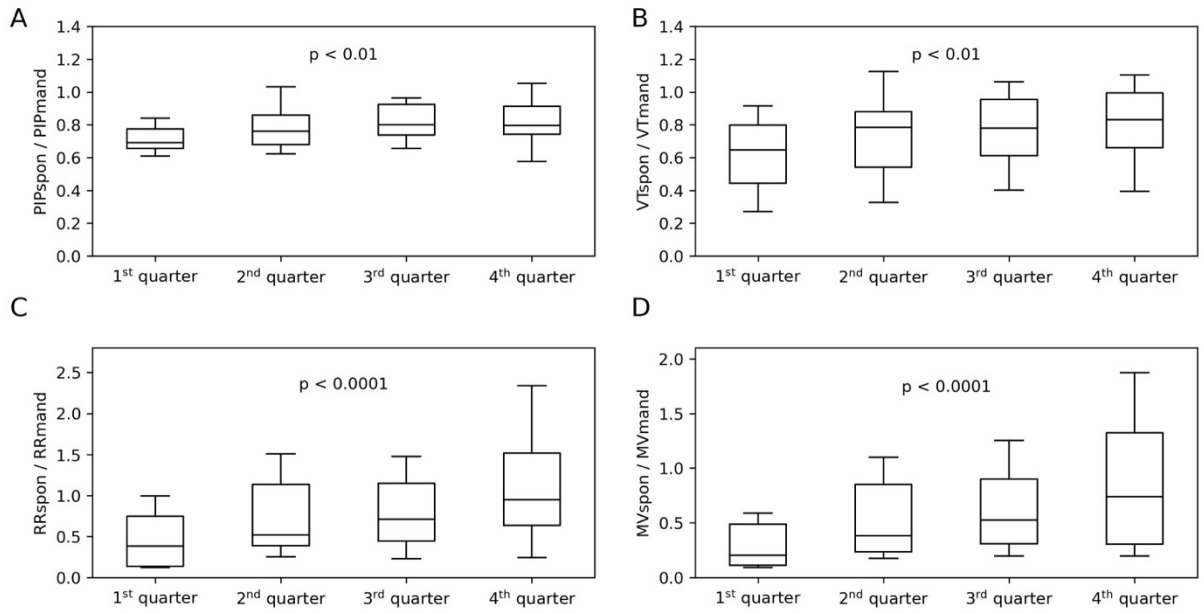

Figure 28: Longitudinal analysis of pressure supported spontaneous breaths and volume guaranteed mandatory inflations in ventilated infants. Boxplots showing the proportions of spontaneous and mandatory (A) peak inflating pressures, (B) expired tidal volumes, (C) respiratory rates, and (D) minute ventilation in each quarter of the recordings. Horizontal lines represent medians, boxes represent interquartile ranges, whiskers correspond to 5th and 95th centile spread of the data. P values (Friedman's test) are also shown. Adapted from (49).

To assess the impact of relatively low or high PS levels on spontaneous breathing and blood carbon dioxide levels, we analysed 10-minute periods. When PS level and consequently PIPspon were relatively high compared with PIPmand (PIPspon/PIPmand >0.66), the tidal volume of spontaneous breaths was also significantly higher than when PIPspon/PIPmand was <0.66 (**Table 10**). These periods were also characterized by significantly higher spontaneous respiratory rates, although the rate of the mandatory ventilator inflations was not significantly different. Contribution of pressure supported spontaneous breaths to MV were also higher during these periods. However, there was no difference seen in transcutaneous carbon dioxide levels. Even when 1-hour periods were considered, a relatively high PS level and PIPspon/PIPmand ratio were associated with higher RRspon and no difference in $tcCO_2$ during the last 10 minutes of the hours (data not shown).

To see if computationally matching the level of PS to the actual PIP required during VG inflations would have reduced VTspon and the VTspon/VTmand ratio, we have separately analysed only those 1-minute periods when PIPspon/PIPmand was between 0.6 and 0.72. During these periods, the median VTspon was significantly (p=0.03) lower (group median: 3.2 mL/kg, range: 2.1 – 4.7 mL/kg), than during the whole recordings (4.2 mL/kg, range 1.7 – 6.2 mL/kg, see Table 2). The median VTspon/VTmand ratio was also lower during these periods (group median: 0.61, range: 0.35 – 0.79) than during the whole recording (group median: 0.75, range: 0.30 – 1.1) but the difference was not statistically significant (p=0.06).

The inspiratory time of the flow-cycled and pressure-supported spontaneous breaths showed large variability (group median: 0.25 second, range: 0.20 – 0.40 second) and was significantly (p=0.0003) shorter than the set Ti of the time cycled ventilator inflations (group median: 0.33 second, range: 0.28 – 0.40 second, see **Table 9**).

Table 10. Comparison of 10-minute periods with low or high ratio of inflating pressures for pressure supported breaths and volume targeted inflations (PIPspon/PIPmand). Changes in this ratio were mostly due to changes in the PIPmand required to deliver the target VT as pressure support level was changed only infrequently by clinicians.

Ventilator parameter	PIPspon / PIPmand < 0.66 median (IQR)	PIPspon / PIPmand > 0.66 median (IQR)	P value[a]
VTspon [mL/kg]	1.76 (1.36, 2.51)	4.37 (3.83, 4.85)	0.0001
VTmand [mL/kg]	5.8 (5.3, 6.25)	5.71 (5.31, 6.21)	0.86
VTspon/VTmand	0.35 (0.22, 0.44)	0.73 (0.61, 0.88)	0.0001
RRspon [1/min]	4.83 (3.68, 12.63)	23.09 (14.77, 36.87)	0.0001
RRmand [1/min]	40.05 (35.01, 40.52)	34.98 (30.1, 40.17)	0.06
RRspon /RRmand	0.13 (0.1, 0.35)	0.71 (0.38, 1.14)	0.0001
MVspon [L/min/kg]	0.015 (0.01, 0.02)	0.09 (0.06, 0.11)	0.0001
MVmand [L/min/kg]	0.186 (0.15, 0.21)	0.17 (0.14, 0.2)	1.00
MVspon/MVmand	0.1 (0.06, 0.16)	0.5 (0.32, 0.77)	0.0001
$tcCO_2$ [mmHg][b]	60.8 (54.9, 61.7)	58.0 (53.9, 62.6)	0.64

[a]Mann-Whitney U-test
[b]Transcutaneous CO_2 data were available from 8 patients only

6.1.1.2. During neonatal transport

For these studies (48, 71), infants were considered (n=145) if they were transferred between 20/03/2017 and 20/08/2018, they required mechanical ventilation via an endotracheal tube and the ventilation recording was longer than 15 minutes after excluding the periods before departure of the transport team from the referring hospital and after arrival to the receiving hospital.

To evaluate maintenance of the target tidal volume by the ventilator, we studied ~107 hours of ventilator data the from 83 infants who received VG ventilation (using modes SIPPV-VG, SIMV-VG and SIMV-VG-PS) for >15 minutes. As ventilator data were recorded once every 2 seconds, our analysis is based on ~194,000 data points. Cumulative statistics on clinical details and ventilator setting and parameters in **Table 11.**

To compare ventilation with or without volume guarantee during transport, we included infants who received >15 minutes of either SIMV-VG or SIMV without VG during neonatal transport. We excluded infants whose postmenstrual age was >46 weeks (n=13), who were mechanically ventilated with modes other than SIMV (n=49) or who received both SIMV and SIMV-VG for longer than 15 minutes during the transport (n=6). Applying these inclusion and exclusion criteria resulted in a group of 45 infants receiving SIMV-VG ventilation and 32 receiving SIMV without VG. The two groups were similar in gestational age at birth, corrected age at the time of transport, birth weight, weight at transfer and clinical problems but the recordings in the VG group were significantly longer. The respiratory severity score (174, 175) of the infants ventilated with or without VG was not significantly different at the beginning or at the end of the transfer (**Table 12**).

Table 11. Summary clinical details (n=83), ventilator settings and parameters.

Recording duration (minutes)	**Median**	**Range**
	74	20 – 237
Clinical details	**Median**	**Range**
Gestational age (weeks)	35	23 – 41
Postnatal age (hours)	5.22	1.32 – 3,179
Corrected gestational age (weeks)	36	23 – 48.9
Birth weight (grams)	2,400	450 – 4,650
Weight at transfer (grams)	2,400	560 – 4,700
Ventilator modes	**Recordings***	**Number of data points**
SIMV-VG	56	121,566
SIMV-VG-PS	4	8,193
SIPPV-VG	32	64,268
Ventilator settings**	**Median**	**IQR**
FiO_2 (%)	30	21 – 40
VTset (mL/kg)	4.8	4.3 - 5.4
PEEPset (cmH_2O)	6	5 – 6
Pmax (cmH_2O)	22	20 – 25
RRset (1/min)	38	30 – 43
Ti (s)	0.36	0.35 - 0.38
Te (s)	1.22	1.02 - 1.62
Circuit flow, inspiratory (L/s)	8	7.5 – 10
Circuit flow, expiratory (L/s)	4	4 – 4
Trigger sensitivity (1-10)	1	1 – 1
Ventilator parameters**	**Median**	**IQR**
PIP (cmH_2O)	16.1	10.3 - 20.0
PEEP (cmH_2O)	5.9	5.0 - 6.1
MAP (cmH_2O)	7.9	6.3 - 9.4
VTimand (mL/kg)	5.1	4.4 - 6.3
VTemand (mL/kg)	4.5	3.8 - 5.6
Endotracheal tube leak (%)	0	0 – 0
MV (L/min/kg)º	0.27	0.22 - 0.33
VTdiff (= VTemand – VTset, mL/kg)	-0.06	-0.30 to 0.27
Absolute value of VTdiff (mL/kg) ºº	0.29	0.11 – 0.79
Pdiff (= Pmax – PIP, cmH_2O)	6.9	2.7 – 11.7

* Nine patients received more than one ventilation mode during the transport.
** Statistics was performed on all the ~194,000 data points.
º MV includes both ventilator inflations and spontaneous breaths.
ºº Absolute value of a number is its distance from zero, that is, its value without a sign.

6.1.1.2.1. Maintenance of tidal volume and the impact of leakage around the tube

Overall, VTdiff was close to zero: its mean was -0.04 mL/kg (median: -0.06 mL/kg, interquartile range (IQR): -0.30 – 0.27 mL/kg). The absolute value of VTdiff was also low: its mean was 0.72 mL/kg (median: 0.29 mL/kg, IQR: 0.11 – 0.79 mL/kg). 80% of inflations were within 1 mL/kg of the target and 40% were within 0.2 mL/kg (**Figure 29A-B**).

Endotracheal tube leaks affected tidal volume delivery significantly: when the leak was ≥50%, the VTemand decreased progressively below the target and PIP increased to Pmax (**Figure 30**).

Table 12. Basic clinical details and ventilator settings of the patients included in the study

	SIMV-VG			SIMV			
Number of cases	45			32			
Clinical details	**mean**	**SD**		**mean**	**SD**		**p value** [a]
Gestational age (weeks)	34.3	5.4		34.5	5.6		0.88
Corrected gestational age (weeks)	35.3	4.9		35.7	5.5		0.71
Birth weight (grams)	2,368	1,053		2,469	1,210		0.70
Current weight (grams)	2,467	1,050		2,558	1,199		0.73
Respiratory severity score (RSS) [b]	**median**	**IQR**		**median**	**IQR**	**p value** [c]	
At the beginning of transfer	2.3	1.4-3.2		2.7	1.7-3.9	0.06	
At the end of transfer	2.0	1.4-2.5		2.6	1.6-4.5	0.07	
Recording durations (minutes)	**median**	**range**	**total**	**median**	**range**	**total**	**p value** [c]
	80	20 - 237	3559	47	15 - 136	1868	0.007
Ventilator settings [d]	**median**	**IQR**		**median**	**IQR**		**p value** [c]
Ti (sec)	0.36	0.35 - 0.38		0.35	0.34 - 0.38		0.19
RRset (1/min)	35	27 - 40		34	28 - 41		0.32
PEEPset (cmH_2O)	6	5 - 6		5	5 - 6		0.05
PIPset (cmH_2O)	n/a	n/a		20	17 - 21		n/a
Pmax (cmH_2O)	22	20 - 28		n/a	n/a		n/a
VTset (mL/kg)	4.8	4.4 - 5.2		n/a	n/a		n/a

[a] Student T-test (two-tailed)
[b] Respiratory severity score is the product of FiO_2 and MAP (FiO_2 x MAP). See main text for more details and references.
[c] Mann-Whitney U-Test. Correction for multiple testing was done using the Benjamini-Hochberg method with a false discovery rate of 5%
[d] For each patient, the arithmetic mean of each ventilator parameter was calculated. Data shown in the table are group medians and interquartile ranges (IQR) of these mean values.

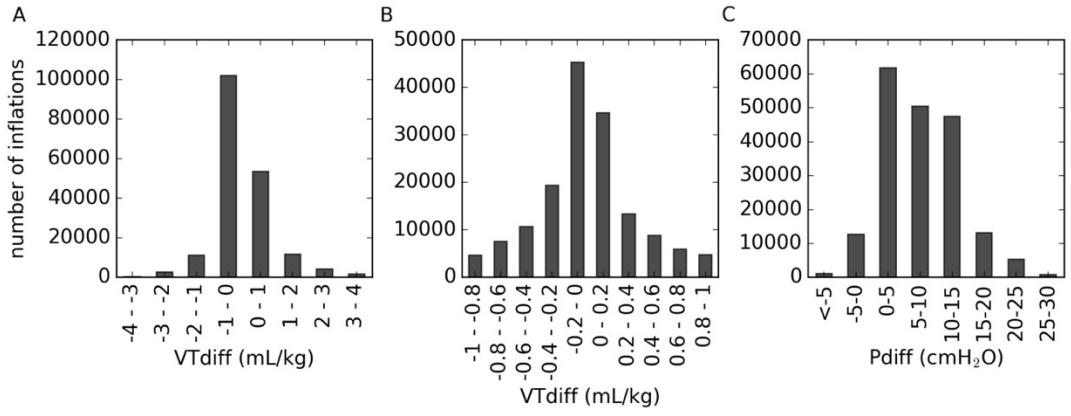

Figure 29. Histograms showing the distribution of the VTdiff and Pdiff in infants ventilated with volume guaranteed ventilation. VTdiff is the difference between the target and actual expiratory tidal volume of ventilator inflations (VTemand–VTset). Pdiff is the difference between the highest allowed inflating pressure and the actual inflating pressure (Pmax–PIP). **A-B:** The actual tidal volume was within 1 mL/kg of the target in 80% of the inflations and very close to it (within 0.2 mL/kg) in 40% of them. **C:** PIP was on average 7 cmH_2O below the Pmax but with significant variability. Adapted from (71).

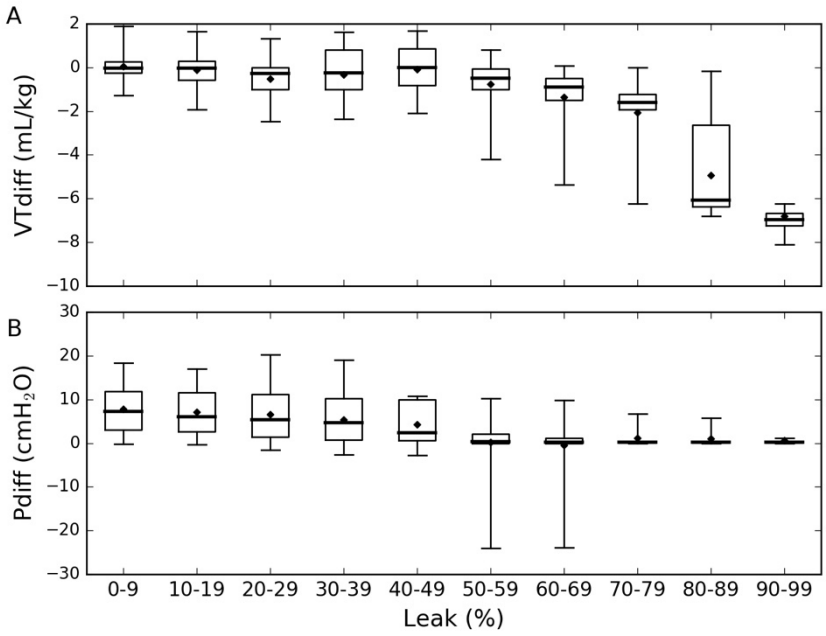

Figure 30. Boxplots showing the distributions of VTdiff (**A**) and Pdiff (**B**) for different levels of ETT leak. Medians (bold lines), means (diamonds) interquartile ranges (boxes) and 5th–95th centiles (error bars) are shown. **A:** VTemand shows significant variability at each level of leak but on average it is maintained close to the target when leak is <50%. With >50% leak, VTemand progressively falls below the target (VTdiff becomes negative). **B:** With progressively increasing leak the PIP gets closer to Pmax and reaches it more frequently (Pdiff becomes zero). Adapted from (71).

In babies weighing <1000 g, the delivered VTemand was well below the target in a considerable proportion of inflations due to endotracheal tube leak and/or PIP reaching Pmax (**Figure 31A-B**). However, when inflations with ≥50% leak or when the Pmax was reached were excluded, VTemand was below target by >1 mL/kg in less than 12% of inflations in each weight category (**Figure 31C-D**). Importantly, VTemand sometimes exceeded the target by more than 2 mL/kg due to the baby's large inspirations during ventilator inflations. There was no difference in VTdiff among the three modes used.

6.1.1.2.2. Inflating pressures during volume targeted ventilation

The median difference between Pmax and PIP was 7.1 cmH_2O (IQR: 2.7 – 11.7 cmH_2O, **Figure 30B**). PIP reached Pmax in only 7.2% of inflations despite Pmax being set relatively low in most cases (mean Pmax of the cases ranged between 14.5 – 46 cmH_2O, group median: 22 cmH_2O).

6.1.1.2.3. Ventilation volumes and capillary CO_2

We analysed the relationship between capillary pCO_2 levels and the tidal and minute volumes averaged over a 10-minute period before the blood gas as described in **section 5.4.1.1.** VTemand showed a weak inverse correlation with pCO_2 levels (r = -0.34, p = 0.0022, **Figure 32A**). The correlation between MV and pCO_2 was also weak (r = -0.22, p = 0.0567, **Figure 32B**). Interestingly, only 52% (28/54) of the normocapnic blood gases with pCO_2 between 5-8 kPa, (37.5-60 mmHg) were associated with VTemand in the range of 4-6 mL/kg; 31% (17/54) had a VTe <4 mL/kg and 17% (9/54) >6 mL/kg. The target tidal volumes did not correlate with pCO_2 (data now shown).

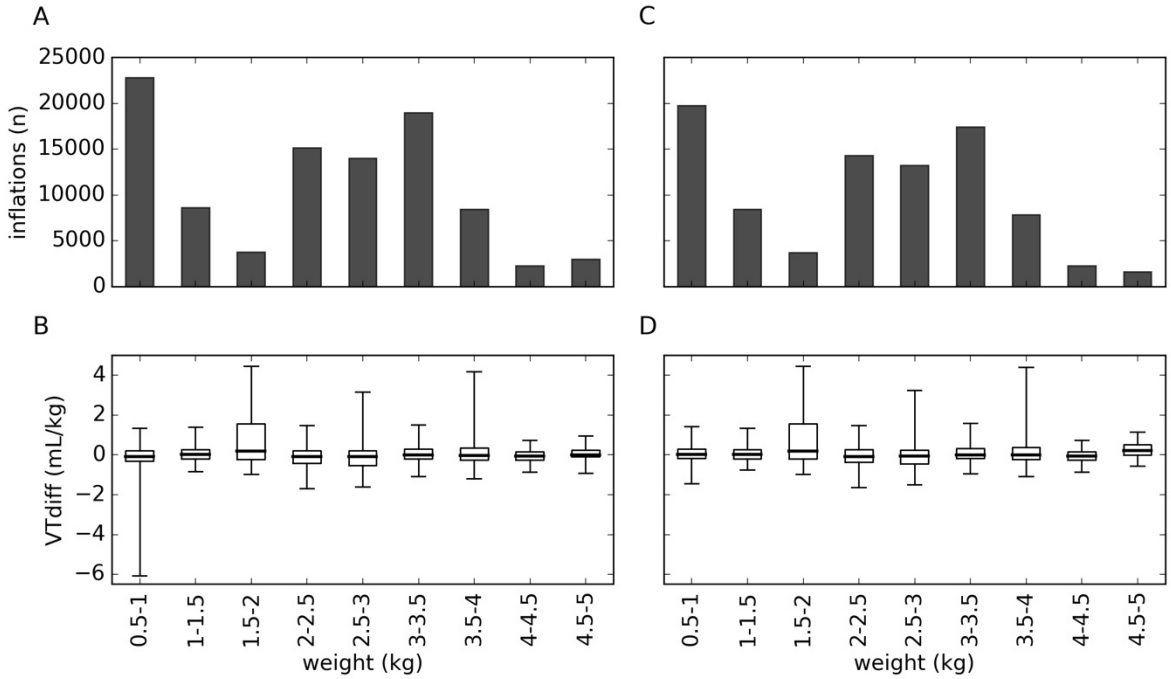

Figure 31. Tidal volume delivery in babies of different weight. **A-B:** All ventilator inflations are included. **A:** Bar plots showing the number of inflations analyzed for the various weight categories. **B:** In babies weighing less than 1000 g the expiratory tidal volume frequently fell considerably below target. **C-D:** Only ventilator inflations when leak was <50% and Pmax was not reached are included. **C:** Bar plots showing the number of inflations analyzed for the various weight categories. **D:** The delivered tidal volume is close to the target in each weight category (VTdiff is close to 0). The boxplots show medians (bold lines), interquartile ranges (boxes), and 5th–95th centiles (error bars). Adapted from (71).

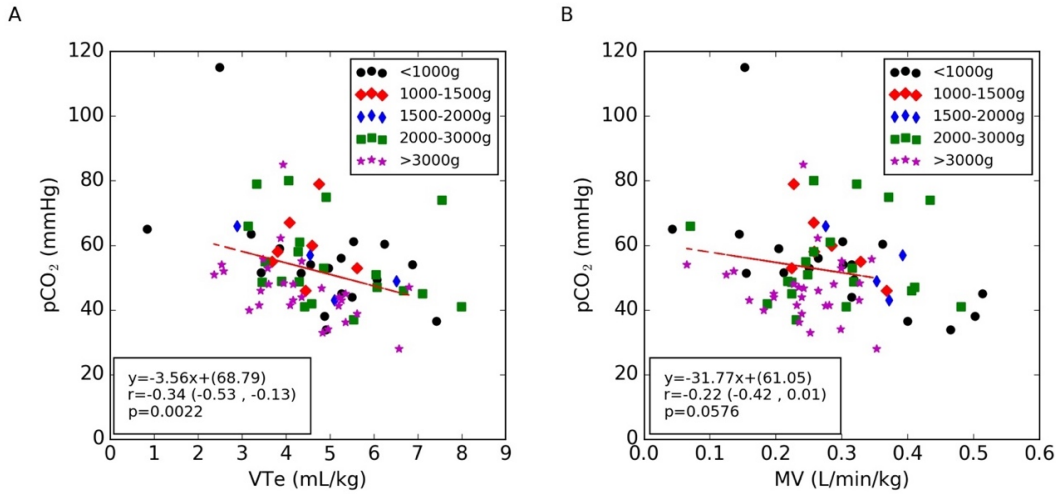

Figure 32. Correlation between expiratory tidal volume (**A**) or minute volume (**B**) before blood gases, and pCO_2. The inverse correlation is poor although statistically significant in both cases. Weight-corrected tidal and minutes volumes fall in the same range for all weight categories. Adapted from (71).

6.1.1.2.4. Comparison of ventilator parameters during SIMV with or without VG in neonatal transport

VTemand was lower in infants ventilated with VG than in babies ventilated without VG (**Table 13.**). The variability of VTemand was also significantly lower in the group with VG **(Table 14**). Babies receiving SIMV-VG had, on average, lower and more variable PIP. There were no significant differences in the ventilator rate, minute volume, FiO_2 and the percentage of ETT leak between the two groups. Interestingly, in babies receiving VG, a lower percentage of total minute volume was provided by the ventilator inflations (group median 66% versus 83%, p=0.02), meaning their spontaneous breathing between the SIMV inflations contributed more to the total minute volume. The tidal volume of the spontaneous breaths (VTespon) was higher in the VG group but this was not statistically significantly different from the non-VG group. The downloading software did not report the number of spontaneous breaths.

Table 13: **Comparison of the *averages* of ventilation parameters**. For each patient, the arithmetic mean of each ventilator parameter was calculated in each recording. Data shown in the table are group medians and interquartile ranges (IQR) of these mean values for both the SIMV-VG and the SIMV groups.

Ventilator parameter	SIMV-VG	SIMV	
	median (IQR)	median (IQR)	p value [a]
PIP (cmH_2O)	15.5 (10.3 - 18.4)	19.5 (16.7 - 21.2)	0.0004
VTimand (mL/kg)	5.1 (4.8 - 5.6)	6.5 (5.5 - 7.9)	0.0011
VTemand (mL/kg)	4.8 (4.5 - 5.3)	6.0 (4.9 -7.6)	0.0011
MVresp (%)	66.5 (53.5 - 83.6)	82.7 (69.3 - 96.8)	0.0215
PEEP (cmH_2O)	5.9 (5.0 - 6.1)	5.1 (4.9 - 6.0)	0.0819
VTespon (mL/kg)	3.0 (1.7 - 4.0)	2.3 (0.5 - 3.4)	0.1091
Leak (%)	0.3 (0.1 - 1.8)	0.7 (0.2 - 2.0)	0.1201
MAP (cmH_2O)	7.2 (6.2 - 8.5)	7.8 (6.8 - 8.9)	0.1215
FiO_2 (%)	29.3 (21.8 - 35.4)	34.3 (21.3 - 52.3)	0.1527
MV (L/min/kg)	0.25 (0.21- 0.31)	0.27 (0.23 - 0.35)	0.2060

[a] Mann-Whitney U-Test. Correction for multiple testing was done using the Benjamini-Hochberg method with a false discovery rate of 5%.

Table 14: **Comparison of the *variability* of ventilation parameters**. For each patient, the standard deviation (SD) of each ventilator parameter was calculated in each recording. Data shown in the table are group medians and interquartile ranges (IQR) of these SD values for both the SIMV-VG and the SIMV groups.

Ventilator parameter	SIMV-VG	SIMV	
	median (IQR)	median (IQR)	p value [a]
PIP (cmH_2O)	2.7 (2.0 - 3.8)	1.3 (0.6 -1.5)	0.0000002
VTemand (mL/kg)	0.8 (0.6 - 0.9)	1.3 (0.9 - 1.8)	0.0004
MAP (cmH_2O)	0.9 (0.6 - 1.2)	0.6 (0.4 - 0.9)	0.0628
VTimand (mL/kg)	0.8 (0.6 - 1.7)	1.2 (0.9 - 1.9)	0.0637
MV (L/min/kg)	0.04 (0.02 - 0.05)	0.05 (0.03 - 0.07)	0.0766
Leak (%)	2.4 (1.3 - 5.7)	3.8 (2.2 - 6.0)	0.1313
MVresp (%)	9.9 (8.0 - 14.1)	8.6 (6.0 - 11.8)	0.1548
VTespon (mL/kg)	1.0 (0.8 - 1.4)	1.2 (0.7 - 1.6)	0.2993
PEEP (cmH_2O)	0.4 (0.2 - 0.7)	0.3 (0.3 - 0.6)	0.4348
FiO_2 (%)	2.6 (0.0 - 5.0)	1.8 (0.0 - 5.5)	0.4354

[a] Mann-Whitney U-Test. Correction for multiple testing was done using the Benjamini-Hochberg method with a false discovery rate of 5%.

6.1.1.2.5. Tidal volumes outside the recommended range occur less frequently when using VG in transport setting

We determined the proportion of inflations with expiratory tidal volumes outside the recommended 4-6 mL/kg (50, 51, 81) or 4-8 mL/kg (142) ranges. Overall, when using VG, the VTemand was >6 mL/kg in 17,675 of 106,765 ventilator inflations (16.5%). Without VG this occurred in 55% (30,691 of 56,032 inflations, see **Figure 33A**). VTemand >8 mL/kg occurred only in 2.4% of inflations with VG but in 25.8% without VG. The percentage of inflations exceeding 6 mL/kg or 8 mL/kg in the individual recordings was lower in the VG group than the group without VG (group medians 3% vs. 44%, p=0.0001 and 0% vs. 7%, p=0.0001, respectively, see **Figure 33B-C**). Without VG, 15/32 babies (47%) received an average VTemand of >6 mL/kg, while with VG this occurred only in 5/45 babies (11%). Without VG, 6 (19%) received on average >8 mL/kg VTemand, while this did not occur in the VG group. The mean PIP of the 6 recordings with a mean VTemand >8 mL/kg ranged between 17 and 24 cmH_2O.

In the VG group the average VTemand was considerably below 4 mL/kg in 4 cases. In one the Pmax was set too low to deliver VTset. In three cases the target tidal volume was set at <4 mL/kg by the clinical team. In the non-VG group, the set PIP was too low to deliver a VTemand >4 mL/kg in 4 cases.

6.1.1.2.6. pCO_2 on arrival was similar in infants ventilated with or without VG during transport

The capillary pCO_2 values immediately after the transfer were similar in the VG and non-VG groups (group means: 6.99 kPa (52.4 mmHg) vs. 7.53 kPa (56.5 mmHg), p=0.39. Only 6 babies had a pCO_2 <5 kPa (37.5 mmHg) (2 in the VG group and 4 in the non-VG group) and one infant without VG had a pCO_2 <4 kPa (30 mmHg).

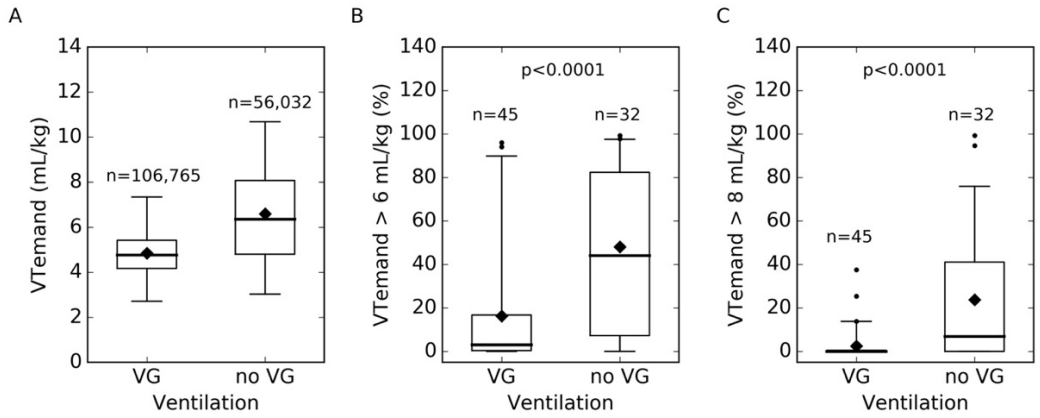

Figure 33. A. Boxplots showing the distribution of VTemand in all recordings combined. SIMV-VG (n = 106,765) and SIMV (n = 56,032) inflations are compared. Due to the very large sample sizes, statistical significance testing would not be appropriate. **B-C.** Boxplots showing the distribution of the percentage of inflations with tidal volumes >6 mL/kg (**B**) or >8 mL/kg (**C**) in the individual recordings. Inflations with tidal volumes over 6 mL/kg or >8 mL/kg occur significantly more frequently in cases ventilated without volume guarantee (p=0.0001). Medians (lines), means (filled diamonds), interquartile ranges (boxes), and 5^{th}–95^{th} centiles (error bars) are shown. Outliers are shown as filled circles. Adapted from (48).

6.1.1.3. In infants suffering from hypoxic-ischaemic encephalopathy

In this study (53) we considered babies who were born after 36 completed weeks of gestation, received therapeutic hypothermia for HIE and were ventilated via an ETT during interhospital transfer which lasted for at least 15 minutes (n=49). Eligibility criteria for introducing therapeutic hypothermia was in accordance with the Total Body Hypothermia for Neonatal Encephalopathy trial protocol (176). Prior to transfer all infants received passive hypothermia at the referring unit which included reducing or turning off the heat source of the incubator or the resuscitation equipment and monitoring the rectal temperature.

We excluded two infants who had major congenital abnormalities and one atypical case where hypothermia and transfer happened after a postnatal collapse at 20 hours of age. Of the remaining 46 infants, we analyzed clinical and ventilator data from those receiving SIMV with VG (n=28) or without VG (n=8). The transport service's guideline suggests the use of SIMV in infants suffering from HIE; the choice of whether to use VG or not was left to the clinician during the study period. When VG was used, the guideline was to use 4-6 mL/kg as target tidal volume, but clinicians could reduce that below 4 mL/kg if needed to avoid or reduce hypocapnia. The 10 infants ventilated with other modes (SIPPV with or without VG or SIMV-VG with pressure support) were excluded. Hypocapnia was defined as pCO_2 below 35 kPa (4.65 mmHg) (177).

The two groups were not significantly different for gestation, postnatal age, birth weight and basic clinical characteristics including Apgar score, respiratory severity score (178) or sedation (**Table 15**). Some infants received passive cooling by reducing the transport incubator's temperature; their proportion and temperatures were not different between the groups. The median duration of ventilator recordings was 81 minutes and 55 minutes in the SIMV-VG and SIMV group, respectively, with a total duration of 46.8 hours.

Table 15. Demographic and clinical details of the infants receiving SIMV-VG or SIMV ventilation. For parametric variables arithmetic mean and standard deviations (SD) are shown. For non-parametric variables, median and interquartile range (IQR) are given.

Ventilation mode	**SIMV-VG**	**SIMV**	
Number of cases	**count**	**count**	
	28	8	
Duration of recordings (minutes)	**median (IQR)**	**median (IQR)**	**p[1]**
	81 (57 - 101)	55 (37 - 74)	0.12
Demographic details	**mean (SD)**	**mean (SD)**	**p[2]**
Gestational Age (weeks)	38.9 (1.4)	38.9 (1.3)	0.92
Birth Weight (grams)	3463 (584)	3342 (474)	0.60
Postnatal Age (hours)	2.8 (2.4)	2.2 (1.7)	0.53
Apgar score	**median (IQR)**	**median (IQR)**	
At 5 minutes	4 (3 - 4)	5 (3-5)	
At 10 minutes	7 (4-7)	7 (6 - 8)	
Respiratory illness	**median (IQR)**	**median (IQR)**	**p[1]**
Respiratory severity score (RSS)[5]	1.7 (1.1 - 2.1)	1.7 (1.5 - 3.3)	0.05
Capillary blood gas at the beginning of transfer	**Median (IQR)**	**Median (IQR)**	**p[1]**
pH	7.08 (6.98 - 7.20)	7.07 (7.02 - 7.13)	0.37
pCO_2 (mmHg)	48.6 (39.6 - 61.2)	48.9 (36.2 - 59.5)	0.29
Actual base excess (mmol/L)	-15.0 (-21.5 to -11-1)	-16.0 (-18.6 to -11.0)	0.46
Therapeutic hypothermia during transport	**count**	**count**	**p[3]**

Active cooling	22	6	0.99
Passive cooling[4]	6	2	
Rectal temperature	**mean (SD)**	**mean (SD)**	**p[2]**
At the start of transport	34.8 (1.6)	34.8 (1.6)	0.41
At the end of transport	34.1 (0.7)	33.9 (0.9)	0.39
Sedative medication[6]	**count (%)**	**count (%)**	**p[3]**
None	8 (29%)	2 (25%)	0.99
Opioid (Fentanyl / Morphine)	20 (71%)	5 (63%)	
Benzodiazepine (Midazolam)	1 (4%)	2 (25%)	
Anticonvulsant	**count (%)**	**count (%)**	**p[3]**
None	19 (68%)	7 (88%)	0.4
Phenobarbital	9 (32%)	1 (13%)	
Muscle relaxants	**count (%)**	**count (%)**	**p[3]**
None	25 (89%)	5 (63%)	0.17
Atracurium / Rocuronium	3 (11%)	3 (38%)	

[1] Mann-Whitney U-test
[2] Student's T-test
[3] Fisher's exact test
[4] Passive cooling included reducing or turning off the heat source of the incubator or the resuscitation equipment with monitoring of deep rectal temperature
[5] The respiratory severity score is calculated as FiO_2 × MAP (178).
[6] Some of the infants received more than one sedative medication

6.1.1.3.1. Ventilator parameters in babies suffering from HIE

VTemand was significantly (p=0.01) lower in the group receiving SIMV-VG (median: 4.9 mL/kg, IQR: 4.6-5.3 mL/kg) than in the group receiving SIMV without VG (median: 7.1 mL/kg, IQR: 5.3-8.0 mL/kg), see **Table 16**. Babies receiving SIMV-VG had significantly (p=0.02) lower PIP with a larger variation (median: 10.7 cmH_2O, IQR: 7.8-17.2 cmH_2O) than those ventilated without VG (median: 17.5 cmH_2O, IQR: 16.6-19.4 cmH_2O).

Spontaneous breathing between the SIMV inflations contributed considerably to the total minute ventilation in both groups: its contribution to the total minute ventilation during SIMV-VG was 39% (IQR: 18-52%) and 30% (IQR: 20-38%) during SIMV without VG (p=0.29). The target tidal volume, ventilator rate, minute ventilation, FiO_2, PEEP and MAP were not different between the two groups. In both groups, the majority of infants were ventilated with FiO_2 <40% and MAP <10 cmH_2O.

6.1.1.3.2. VG during transport had no impact on pCO_2 on arrival

There was no significant difference between the two groups in capillary pCO_2 at the end of the transport: the median [IQR] pCO_2 was 46 [26-55] mmHg and 49 [27-59] mmHg for the SIMV-VG and SIMV groups (p=0.42), respectively. Only 5 (18%) infants ventilated with SIMV-VG and 2 (25%) infants ventilated with SIMV had an arrival pCO_2 <35 mmHg (4.65 kPa). An arrival pCO_2 <30 mmHg (4 kPa) was only seen in 3 infants, 2 in the SIMV-VG group and 1 in the SIMV group. The change in pCO_2 during transport was also not significantly different between the groups: the median [IQR] difference was 0.5 [-9.0 – 8.0] mmHg for SIMV-VG recordings and -6.4 [-12.3 – 4.6] mmHg for the SIMV recordings (p=0.21). Babies with severe hypo- or hypercapnia at the beginning of transport tended to have larger changes in their pCO_2.

Table 16: Comparison of ventilators parameters in infants with hypoxic ischaemic encephalopathy during SIMV ventilation with or without volume guarantee. For each patient, the mean (VTemand, VTset, PIP, PEEP, MAP,

RR, MV) or median (FiO_2, MVspon) of ventilator parameter was calculated in the individual recordings. Data shown in this table are group medians and interquartile ranges (IQRs) of these aggregate (mean or median) values.

Parameter	SIMV-VG	SIMV	
	Group median (IQR)	Group median (IQR)	p value[1]
VTemand (mL/kg)	4.9 (4.6-5.3)	7.1 (5.3-8.0)	0.01
VTset (mL/kg)	4.4 (3.9-4.8)	n/a	n/a
PIP (cmH_2O)	10.7 (7.8-17.2)	17.5 (16.6-19.4)	0.02
MVspon (%)	42 (14-59)	32 (18-42)	0.29
FiO_2 (%)	21 (21-26)	21 (21-46)	0.29
MAP (cmH_2O)	6.2 (5.1, 7.7)	7.0 (6.7-8.1)	0.08
MV (L/kg/min)	0.25 (0.21-0.29)	0.23 (0.19-0.28)	0.38
PEEP (cmH_2O)	5.1 (5.0-6.0)	5.8 (5.0-6.0)	0.20
RR (1/min)	25.3 (18.7-34.6)	23.2 (16.9-27.3)	0.25

[1] Mann-Whitney U test. P values <0.05 were considered as significant, after correcting for multiple comparisons using the Benjamini-Hochberg method.

6.1.1.3.3. Maintenance of tidal volumes when using VG in babies with HIE

We further analyzed the SIMV-VG recordings to explore how close the actual expired tidal volumes were to the target values. The group median [IQR] of the mean VTdiff was 0.33 [-0.12 – 1.27] mL/kg. The mean VTdiff was >1 mL/kg in 9 (32%) recordings. The median Pdiff of the recordings ranged between -1.9 – 27.9 cmH_2O). There were only 2 (7%) recordings when the Pmax was within 5 cmH_2O of the PIP.

6.1.1.3.4. Low inflating pressures in babies with strong spontaneous breathing effort

Among the babies ventilated with SIMV-VG there was a moderate but statistically significant inverse linear correlation between the contribution of the spontaneous breaths to the total minute ventilation and the mean PIP of the volume targeted ventilator inflations (**Figure 34**).

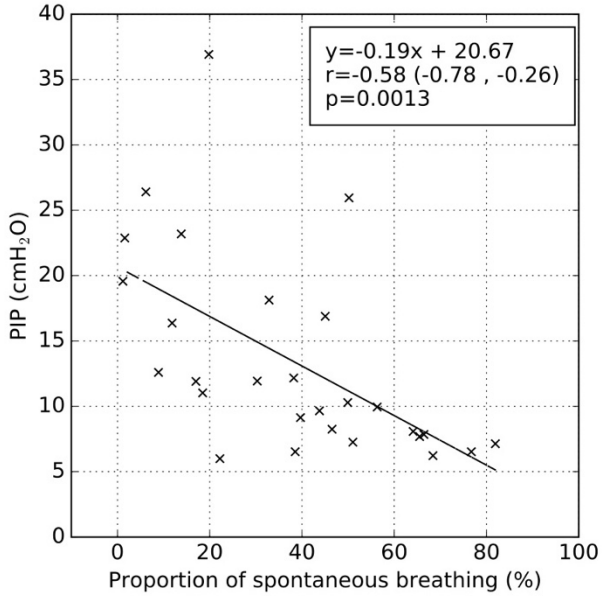

Figure 34: Pearson's correlation between the infants' contribution to the total minute ventilation (MV) and the mean peak inflating pressure (PIP) during the transport in infants receiving SIMV-VG ventilation. Most babies whose spontaneous breathing accounted for over 50% of the total minute ventilation had very low (<10 cmH_2O) PIP. Regression line, correlation coefficient (r) and its 95% confidence interval are also shown. Adapted from (53).

Babies who had >50% of the total MV from spontaneous breathing (n=9) had lower average PIP (group median: 7.7 cmH_2O, IQR:

7.1-8.1 cmH_2O) than babies (n=19) who had <50% of the MV from spontaneous breaths (group median: 12.2 cmH_2O, IQR: 10.0-18.9 cmH_2O, p<0.01). In babies with PIP <10 cmH_2O (n=13), the VTemand and VTdiff were significantly (p<0.01) larger than in babies with PIP >10 cmH_2O (n=15) (**Figure 35A-B**). Interestingly, 11 (85%) of these infants received sedation during or shortly before the transfer and 2 (15%) had also received muscle relaxant before the transport. These babies did not have adverse clinical events during transport and their pCO_2 and pH immediately after transport was not different than that of the babies with higher (>10 cmH_2O) mean PIP (**Figure 35C-D**).

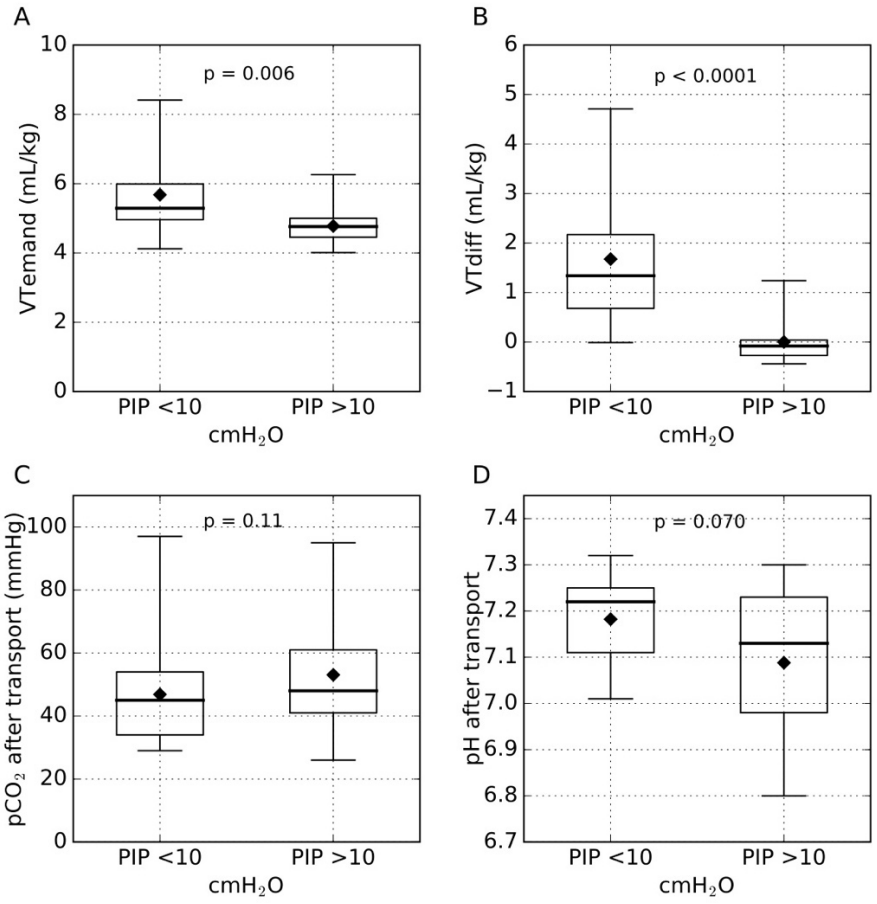

Figure 35: Comparison of ventilator parameters and blood gases in babies suffering from HIE and receiving SIMV-VG ventilation during transport with mean PIP <10 cmH_2O and >10 cmH_2O. **A.** The expired tidal volume of ventilator inflations (VTemand). **B.** The difference between the actual and targeted expired tidal volume (VTdiff). **C.** pCO_2 and **D.** pH immediately after the transport. Babies with low PIP had significantly higher VTemand and VTdiff and did not develop hypercapnia or acidosis during the transport. Horizontal lines represent medians, boxes represent interquartile ranges, whiskers show full range of values. Mean values are shown by black diamonds. Adapted from (53).

6.1.1.4. In infants requiring low inflating pressures during volume guarantee ventilation

In this study (52), infants were considered if they received only conventional ventilation on the NICU in Cambridge during the recording period (n=250). Recordings, or parts of recordings, with ventilation modes other than SIPPV-VG or SIMV-VG, or when leak compensation was turned off were disregarded. Recordings were also excluded if after clean-up they were shorter than 12 hours. This resulted in a final set of 195 infants and 968 days of mechanical ventilation and included term, preterm and extremely preterm babies with a full spectrum of problems requiring neonatal intensive care (**Table 17**). 162 infants received SIPPV-VG ventilation, 22 were ventilated with SIMV-VG. In 11 infants both modes were used during the recording period.

Table 17. Basic clinical and ventilation details of the infants studied

Demographics (n=195)	**Median**	**Range**
Gestational age at birth (weeks)	27.9	22.3 – 42.3
Post-menstrual age (weeks)	29.4	22.4 – 47.3
Birth weight (grams)	980	391 – 4,750
Actual weight (grams)	1,130	450 – 4,750

Respiratory cycles were excluded from analysis when the PIP was lower than the PEEP, as this can only occur during spontaneous breaths (0.08%). Ventilator inflations were also excluded when VTmand was >25 mL/kg (0.03%), or periods when the minute volume was >1 L/min/kg (0.08%). These events do not normally occur during conventional ventilation, and they probably represent artefacts, e.g., when the ventilator circuit was open or when condensed water in the circuit caused auto-triggering. Periods with a ventilator rate was >130/min were also disregarded (0.03%). During SIPPV, the ventilator rate can be higher than the set rate; however, to prevent very fast ventilator rates, the VN500 ventilator does not start another ventilator inflation within 0.12 seconds after a previous inflation. Therefore, even with the shortest inspiratory times used on our Unit (0.33 seconds), rates >130/min cannot occur, and these data probably represent auto-triggering due to condensed water in the ventilation circuit. Data points were also removed when one or more of these parameters were missing. Altogether, a total of 1,866,096 data points were excluded out of the initial 83,635,965 (2.23%).

To analyse ventilator parameters before blood gases, the mean (for parameters showing normal distribution) or the median (for parameters with non-parametric distribution) of the parameter was calculated over periods of variable length (15 minutes, 30 minutes, 1, 2, 4, 6, 12 and 24 hours) before each blood gas (n=3,599), as described in **section 5.4.1.1.** and on **Figure 19**. For each period the median inflating pressure (Pinfl) was calculated as the median of PIP – PEEP of all ventilator inflations during the period. Pinfl was considered low when it was less than 5 mbar.

We considered three clinical scenarios: (1) Very preterm infants (born before 32 completed weeks of gestation) ventilated during the first week of life using SIPPV-VG; (2) Very preterm infants ventilated after the first week of life using SIPPV-VG; (3) term infants suffering from hypoxic ischaemic encephalopathy (HIE) and ventilated with SIMV-VG.

6.1.1.4.1. Periods with low inflating pressure occur frequently in infants receiving volume targeted ventilation

When averaged over the 1-hour period before each blood gas (n=3,371), the median Pinfl of the ventilator inflations ranged between 0.3 and 43 mbar (group median 14 mbar). The range was similar for shorter or longer averaging periods (between 15 minutes and 24 hours, see **Figure 36**). 109 infants (56%) had blood gases with a median Pinfl <10 mbar over the 60 minutes before the gas, and in 59 infants (30%) 1-hour periods with median Pinfl <5 mbar occurred. The latter group included both preterm and term infants, although more mature infants with encephalopathy or airway malformation and normal lungs, were over-represented, data not shown). During periods when the median Pinfl was <5 mbar, short periods of higher Pinfl usually occurred (**Figure 37**).

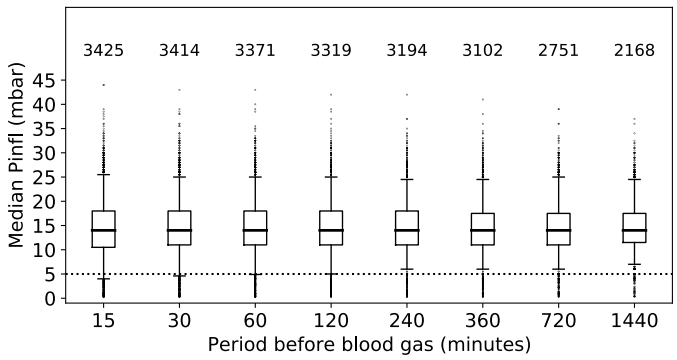

Figure 36. Boxplots showing the distribution of the median inflating pressure (Pinfl = PIP – PEEP) over different periods before blood gases. Periods between 15 minutes and 1,440 minutes (=24 hours) are shown on the horizontal axis. Boxes represent interquartile range; group median is shown as horizontal line, whiskers correspond to 5th and 95th centile, respectively, outliers outside this range are shown as dots for individual data points. The median Pinfl was <5 mbar (dotted line) prior to ~5% of the gases, even when aggregated over a period of 12 hours. The number of blood gases analysed for each interval are shown above the boxes. Longer aggregating periods have fewer blood gases analysed, because for gases done soon after the start of a recording only shorter periods of ventilator data are available. Adapted from (52).

6.1.1.4.2. Low inflating pressures are frequently associated with tidal volumes exceeding the target and high respiratory rate

The periods when the median Pinfl was <5 mbar, were associated with significantly lower target tidal volumes in preterm infants ventilated with SIPPV-VG during the first week of life and in term infants ventilated with SIMV-VG. However, the actual VTmand significantly ($p<0.0001$) exceeded the VTset in all three groups and did not differ from the VTmand obtained during periods with higher Pinfl (**Tables 18-20**).

Preterm infants triggered significantly ($p<0.0001$) more ventilator inflations on SIPPV-VG when the median Pinfl was <5 mbar, while term infants with HIE had more and deeper spontaneous breaths between SIMV inflations. The minute ventilation was not different at different levels of Pinfl in any of the three groups. In term infants with HIE, FiO_2 was significantly lower when the median Pinfl was <5 mbar than when Pinfl was higher.

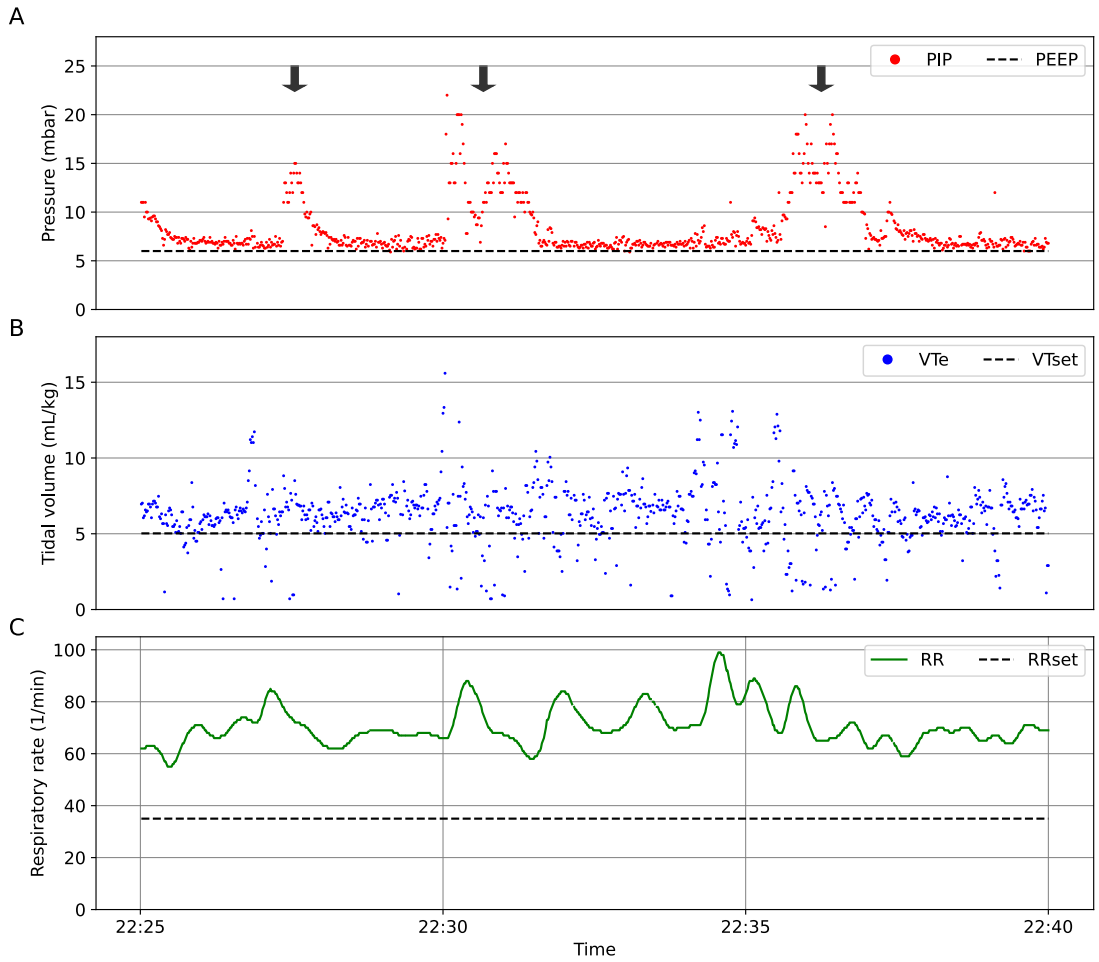

Figure 37. Peak inspiratory pressure (PIP), leak-compensated expired tidal volume (VTmand) and respiratory rate (RR) in a 1-month- old infant born at 30 weeks of gestation, collected over a period of 15 minutes. The baby required intubation and mechanical ventilation for micrognathia and airway obstruction. On A and B, dots correspond to the PIP and VTmand of individual ventilator inflations; on C, RR calculated as moving mean over 20-second periods are shown. Ventilation mode during this period was SIPPV-VG. **A**. PIP was just above the set PEEP of 6 mbar (dotted line) for the majority of ventilator inflations, but there were 3 short (1-2 minutes) periods when higher PIP was recorded (arrows). **B**. VTmand was considerably larger than the targeted 5 mL/kg (VTset, dotted line) for most inflations. These large tidal volumes were generated predominantly by the infant's breathing. **C.** The baby also triggered more ventilator inflations than the set backup rate of 35 minute (RRset, dotted line), with the ventilator rate sometimes exceeding 80 per minute. Adapted from (179).

Table 18. Ventilator parameters and blood gases in very preterm infants receiving SIPPV-VG ventilation during the first week of life. Ventilator parameters were collected during 60-minute periods before blood gases and grouped according to different levels of median Pinfl. For parameters showing normal distribution (marked with asterisks), the mean of the data points collected over the 60 minutes with 1 Hz sampling rate was calculated. For other ventilator parameters the median was calculated similarly. As these aggregate data are not normally distributed, the table shows group medians and interquartile ranges (IQRs) of them. The median (IQR) of selected blood gas parameters is also shown in the blood gases associated with these periods.

Pinfl [mbar]:	0-4.9	5-9.9	10-14.9	15-19.9	20-24.9	≥25	KW p value[1]	post hoc p value[2]
Blood gases [n]	23	127	498	298	44	13		
VTemand [mL/kg]*	5.31 (5.09-6.07)	5.15 (4.8-5.52)	5.29 (5.02-5.58)	5.5 (5.06-5.88)	5.55 (5.15-5.98)	5.55 (5.39-5.92)	<0.001	NS
VTset [mL/kg]*	4.5 (4.46-4.58)	4.95 (4.49-5.01)	5 (4.9-5.5)	5.47 (5.0-5.67)	5.54 (5.04-5.96)	5.94 (5.55-6.0)	<0.0001	<0.0001
VTdiff [mL/kg]	0.47 (0.27-0.97)	0.12 (0.0-0.22)	0 (0.0-0.0)	0 (0.0-0.0)	0 (-0.12-0.0)	-0.13 (-0.35-0.0)	<0.0001	<0.0001
RR [1/min]	66 (62.0-73.0)	63 (60.0-68.0)	60 (56.0-63.0)	60 (54.0-62.0)	57 (52.0-60.0)	60 (60.0-60.0)	<0.0001	<0.001
RRset [1/min]	50 (50.0-57.5)	50 (50.0-60.0)	60 (50.0-60.0)	60 (50.0-60.0)	55 (50.0-60.0)	60 (60.0-60.0)	<0.001	NS
RRdiff [1/min]	13 (11.0-21.0)	10 (6.0-15.5)	3 (1.0-7.0)	2 (0.0-4.0)	0 (0.0-2.5)	0 (0.0-0.0)	<0.0001	<0.0001
RRtrig [1/min]	42 (29.75-58.0)	38.5 (23.0-58.0)	11 (2.0-29.5)	7 (0.0-22.0)	1 (0.0-16.0)	0 (0.0-0.0)	<0.0001	<0.0001
MV [L/min/kg]*	0.33 (0.31-0.37)	0.32 (0.29-0.36)	0.32 (0.29-0.35)	0.33 (0.3-0.35)	0.33 (0.27-0.34)	0.32 (0.31-0.33)	NS	
FiO_2 [%]	25 (22.0-29.0)	24 (21.0-29.5)	24 (21.0-28.0)	26 (23.0-32.0)	26 (23.75-30.25)	30 (25.0-45.0)	<0.0001	NS
pH	7.25 (7.22-7.28)	7.28 (7.25-7.32)	7.27 (7.24-7.31)	7.27 (7.23-7.31)	7.28 (7.21-7.32)	7.21 (7.18-7.23)	0.035	NS
pCO_2 [kPa]	6.7 (6.14-7.4)	6.7 (6.25-7.2)	6.7 (6.2-7.4)	6.7 (6.1-7.42)	6.6 (6.07-7.5)	6.7 (5.8-7.5)	NS	
BE [mmol/L]	-4.6 (-6.95 -3.3)	-4.2 (-5.85 - -1.45)	-4.25 (-6.0 - -2.4)	-4.3 (-6.48 - -2.52)	-5.25 (-7.02 - -2.12)	-9 (-9.5- -7.2)	<0.001	NS
Lactate [mmol/L]	2.1 (1.3-3.4)	1.5 (1.16-2.1)	1.6 (1.2-2.58)	1.9 (1.3-3.2)	2.6 (1.3-3.3)	3.9 (2.8-12.8)	<0.0001	NS

[1]: Kruskal-Wallis test comparing all groups with Bonferroni correction
[2]: Mann-Whitney U-test comparing the group with inflating pressure <5 mbar versus all other data, with Bonferroni correction

Table 19. Ventilator parameters and blood gases in very preterm infants receiving SIPPV-VG ventilation after the first week of life. See the legend of **Table 18** for more details.

Pinfl [mbar]:	0-4.9	5-9.9	10-14.9	15-19.9	20-24.9	≥25	KW p value[1]	post hoc p value[2]
Blood gases [n]	37	141	507	518	305	139		
VTemand [mL/kg]*	5.4 (4.62-6.03)	5.4 (4.62-6.03)	5.65 (5.0-6.11)	5.4 (4.79-6.07)	5.43 (4.79-6.33)	5.83 (4.86-7.14)	0.015	NS
VTset [mL/kg]*	5 (4.14-5.35)	5 (4.14-5.35)	5.17 (4.74-5.69)	5.47 (4.9-6.07)	5.43 (4.75-6.04)	5.95 (5.0-7.23)	<0.0001	NS
VTdiff [mL/kg]	0.33 (0.12-0.56)	0.33 (0.12-0.56)	0.06 (0.0-0.17)	0 (0.0-0.11)	0 (0.0-0.11)	0 (-0.12-0.0)	<0.0001	<0.0001

RR [1/min]	65 (61.0-71.0)	65 (61.0-71.0)	60 (55.0-64.0)	60 (51.25-61.0)	57 (50.0-61.0)	60 (51.0-60.0)	<0.0001	<0.0001
RRset [1/min]	50 (50.0-55.0)	50 (50.0-55.0)	50 (50.0-60.0)	50 (50.0-60.0)	50 (50.0-60.0)	60 (50.0-60.0)	<0.0001	<0.001
RRdiff [1/min]	13 (9.0-18.0)	13 (9.0-18.0)	6 (2.0-12.0)	2 (0.0-6.0)	1 (0.0-4.0)	0 (0.0-1.0)	<0.0001	<0.0001
RRtrig [1/min]	46 (33.5-55.5)	46 (33.5-55.5)	22 (6.0-42.0)	6 (0.0-24.0)	3 (0.0-15.0)	0 (0.0-2.0)	<0.0001	<0.0001
MV [L/min/kg] *	0.33 (0.28-0.38)	0.33 (0.28-0.38)	0.32 (0.28-0.38)	0.31 (0.28-0.36)	0.3 (0.26-0.35)	0.32 (0.27-0.41)	<0.0001	NS
FiO_2 [%]	30 (25.0-42.0)	30 (25.0-42.0)	30 (24.0-38.0)	35 (28.0-45.0)	39 (30.0-50.0)	45 (37.0-55.0)	<0.0001	NS
pH	7.31 (7.24-7.36)	7.31 (7.24-7.36)	7.32 (7.28-7.36)	7.32 (7.27-7.36)	7.33 (7.28-7.37)	7.33 (7.29-7.36)	NS	
pCO_2 [kPa]	7.65 (6.78-8.68)	7.65 (6.78-8.68)	7.5 (6.7-8.3)	7.4 (6.55-8.3)	7.4 (6.6-8.4)	7.3 (6.35-8.5)	NS	
BE [mmol/L]	0.9 (-2.58-3.72)	0.9 (-2.58-3.72)	0.7 (-2.2-3.6)	0.2 (-2.8-2.4)	0.9 (-1.6-4.4)	0.7 (-1.1-4.15)	0.021	NS
Lactate [mmol/L]	1.2 (0.8-1.6)	1.2 (0.8-1.6)	1.3 (1.0-1.9)	1.3 (0.9-2.0)	1.2 (0.9-1.7)	1.1 (0.9-1.6)	0.048	NS

Table 20. Ventilator parameters and blood gases in term infants suffering from hypoxic ischaemic encephalopathy and receiving SIMV-VG ventilation. See the legend of **Table 18** for more details.

Pinfl [mbar]:	**0-4.9**	**5-9.9**	**10-14.9**	**15-19.9**	**KW p value[1]**	**post hoc p value[2]**
Number of blood gases [n]	37	39	48	7		
VTe [mL/kg]*	4.33 (3.88-4.83)	4.33 (4.01-4.64)	4.51 (3.99-5.01)	5 (4.08-5.49)	NS	
VTset [mL/kg]*	4 (3.8-4.35)	4 (3.91-4.52)	4.51 (3.99-5.0)	5.01 (4.27-5.51)	0.006	0.035
VTdiff [mL/kg]	0.48 (0.14-1.32)	0.03 (0.0-0.13)	0 (0.0-0.0)	0 (-0.19-0.02)	<0.0001	<0.0001
VTspon [mL/kg]*	4.27 (3.35-5.32)	2.05 (1.15-3.22)	0.15 (0.04-1.31)	0.15 (0.04-2.6)	<0.0001	<0.0001
RR [1/min]	53 (40.0-68.0)	45 (35.0-52.5)	45 (33.75-50.0)	60 (42.5-63.0)	NS	
RRset [1/min]	20 (15.0-25.0)	30 (27.0-40.0)	40 (30.0-50.0)	35 (32.5-55.0)	<0.0001	<0.0001
RRspon [1/min]	30 (19.0-44.0)	15 (7.0-29.0)	3 (1.5-46.25)	16 (0.0-32.5)	<0.0001	<0.0001
RRtrig [1/min]	20 (19.5-27.0)	26 (16.0-30.0)	7 (0.0-20.0)	15 (7.0-27.0)	0.006	NS
MV [L/min/kg]*	0.2 (0.18-0.25)	0.17 (0.14-0.2)	0.18 (0.15-0.27)	0.25 (0.2-0.32)	0.044	NS
MVspon [%]	53 (43.0-60.0)	7 (0.5-25.5)	0 (0.0-1.0)	0 (0.0-7.5)	<0.0001	<0.0001
FiO_2 [%]	21 (21.0-22.0)	21 (21.0-25.0)	23 (21.0-25.5)	31 (30.0-37.5)	0.006	0.029
pH	7.37 (7.33-7.4)	7.37 (7.32-7.4)	7.36 (7.3-7.4)	7.36 (7.35-7.38)	NS	
pCO_2 [kPa]	5 (4.47-5.75)	6.1 (5.4-6.55)	5.6 (5.18-6.28)	5.8 (5.05-6.5)	NS	
BE [mmol/L]	-4.8 (-7.05 - -0.25)	-1.5 (-3.95 - 1.65)	-2.4 (-4.43 - -1.32)	-3 (-4.75 - 0.95)	NS	
Lactate [mmol/L]	2.2 (1.62-3.18)	1.4 (1.24-2.0)	1.75 (1.42-2.4)	2.5 (2.4-2.6)	0.004	0.036

6.1.1.4.3. Periods with low inflating pressures are not associated with changes in blood gases

Inflating pressures <5 mbar during the 1-hour period before blood gases were not associated with significant changes of the blood gases in any of the three clinical groups (**Tables 18-20**). pCO_2 and base excess were also not different in preterm or term babies immediately after 1-hour periods when the median Pinfl was <5 mbar compared to periods when the Pinfl was higher. Lactate levels were also not different in preterm infants but term infants with HIE had significantly higher lactate levels when Pinfl was <5 mbar. Averaging ventilator data over shorter (15 or 30 minutes) or longer (2, 4, 6, 12 or 24 hours) periods before each blood gas gave similar results (data not shown).

6.1.2. The impact of the set maximum allowed inspiratory pressure (Pmax) on ventilator performance

In this study (37), we analysed data from 25 neonates receiving SIPPV-VG with leak-compensation continuously for at least 12 hours (**Table 21**). The local guideline recommends keeping Pmax 5 mbar above the "working PIP" but without specific instructions as to how to adjust it. The pressure rise time was set at 0.08 second in all cases and the inspiratory time was 0.33 seconds or longer. Therefore, tidal volume delivery could not be limited by the inspiratory time only by Pmax.

Table 21. Summary clinical details

Clinical parameters	median (range)
Gestational age (weeks)	27.4 (23.7-39.9)
Weeks of gestation, n (%)	
23-27 weeks	15 (60%)
28-32 weeks	5 (20%)
33-36 weeks	3 (12%)
>36 weeks	2 (8%)
Gestational age at study (weeks)	28.6 (24.1-47.3)
Birth weight (g)	760 (420-3,052)
Current weight (g)	1,008 (480-4,185)

The median recording time was 50 hours with a total of 60 ventilator days recorded. We collected data on >5 million inflations. For 1.7% of inflations data on one or more ventilator parameters were missing and for 0.09% the tidal volume was over 20 mL/kg or the respiratory rate was over 125/min. They likely represent an open circuit or flow sensor problem, so these data were excluded.

6.1.2.1. Variability of peak inspiratory pressure

In most recordings the PIP showed large breath-by-breath variability as it was changed by the VG algorithm in response to fluctuations in spontaneous tidal volumes, patient-ventilator interactions or variable ETT leak. Pmax was between 20-30 mbar in 8 recordings (32%), between 30-40 mbar in 14 recordings (56%) and >40 mbar in 3 recordings (12%). In some cases when Pmax was set at 40 mbar or higher, the working pressure was high and so the high Pmax was required; moreover, it was still frequently reached by the PIP. In other cases, the

Pmax was set at >15 mbar above the usual PIP. In recordings when PIP frequently reached Pmax, the median VTmand was significantly below the target value for longer periods.

The median Pdiff ranged between 5-20 mbar in the individual recordings (group median: 11 mbar) despite the unit's guideline to keep Pmax 5 mbar above the working PIP. Overall, Pdiff was <10 mbar in 43.1% of inflations, <5 mbar in 16.1 % and the PIP reached Pmax in 5.2% (**Figure 38A**). Therefore, despite keeping the Pmax >10 mbar above PIP overall in most recordings, the PIP reached Pmax in many inflations. These data illustrate that due to large variation in PIP during VG ventilation it is not easy for clinicians to define a "working pressure" and use it to set the Pmax.

6.1.2.2. Effect of Pmax on tidal volume delivery and low tidal volume alarms

The tidal volume varied from breath to breath as each baby breathed and the ventilator adjusted the PIP. However, when averaged over long periods, VTmand was very close to the set target: the median VTdiff was <0.5 mL/kg in each recording. Tidal volume delivery was stable even when Pmax was substantially higher than the PIP: the median VTdiff was <0.1 mL/kg and VTdiff had similar variability for all ranges of Pdiff <20 mbar. When Pdiff was >20 mbar, the median of VTdiff was still only 0.45 mL/kg but its variability was larger (**Figure 38B**). During inflations where VTmand was larger than VTset the PIP was relatively low (**Figure 38C-D**), suggesting the large breaths were due to the baby actively breathing from the circuit and so the VG reduced the PIP.

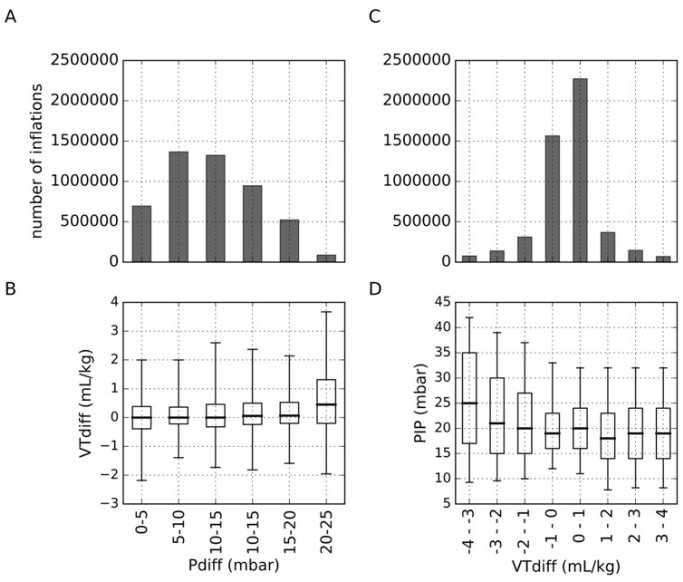

Figure 38. A: Histogram showing the number of inflations for different levels of Pdiff in the >5 million inflations analysed in the 26 recordings. **B:** Boxplots showing the distribution of VTdiff for inflations with different Pdiff ranges. Median VTdiff was close to zero for all ranges of Pdiff less than 20 mbar. **C:** Histogram showing the number of inflations for different levels of VTdiff. The actual VTmand deviates from the targeted VTset by less than 1 mL/kg in >80% of the inflations. **D:** Boxplots showing the distribution of PIP for various levels of VTdiff. When VTdiff is large (the VTmand exceeds the targeted value), PIP is usually relatively low. Horizontal lines mark median values. Boxes represent interquartile range; error bars represent 5th and 95th centiles.

When PIP reached the Pmax, VTmand was frequently lower than the target. The proportion of inflations where Pmax limited tidal volume delivery by >1 mL/kg varied between 0% and 8.5% in the recordings. The percentage of inflations limited by Pmax in each recording showed inverse correlation with the median Pdiff (Spearman's correlation: r = -0.79, 95% confidence interval (CI): -0.91, -0.58, p < 0.001). During the recordings Pmax was changed infrequently (median: 0.65 times daily) and the frequency of changes was not closely related to the PIP variability.

The number of low tidal volume alarms ranged between 0.1/hour and 22.5/hour. Their frequency had a strong inverse correlation with Pdiff (r = -0.71, 95% CI: -0.86, -0.44, p < 0.001). Therefore, the lower the Pmax, the more inflations failed to reach the target tidal volume due to PIP being limited by Pmax, and more low tidal volume alarms sounded.

6.1.2.3. How to set Pmax level and effect of how often to change it

We were interested how the proportion of inflations reaching Pmax would be affected by the frequency of staff adjusting Pmax and also by the level Pmax was set above this observed PIP. To investigate this, we considered a range of scenarios for adjusting Pmax between 2-hourly to once a day. We also considered scenarios of Pmax being 5 to 15 mbar above the most frequently observed PIP (the statistical mode of PIP) over the observation period. These were modelled from our recordings by building 11 x 12 = 131 computational models and analysing how frequently Pmax would have been reached in each case. Some of the results are shown on **Figure 39**. When Pmax was 5 mbar above the mode of PIP, Pmax limited >10% of the inflations. Increasing Pmax to 10 mbar above the mode of PIP reduced the number of such inflations. The number of inflations limited by Pmax did not change significantly whether the Pmax setting was adjusted 2 hourly or 12-hourly. In other words, reviewing and adjusting Pmax more frequently would not have reduced the proportion of inflations when Pmax is reached.

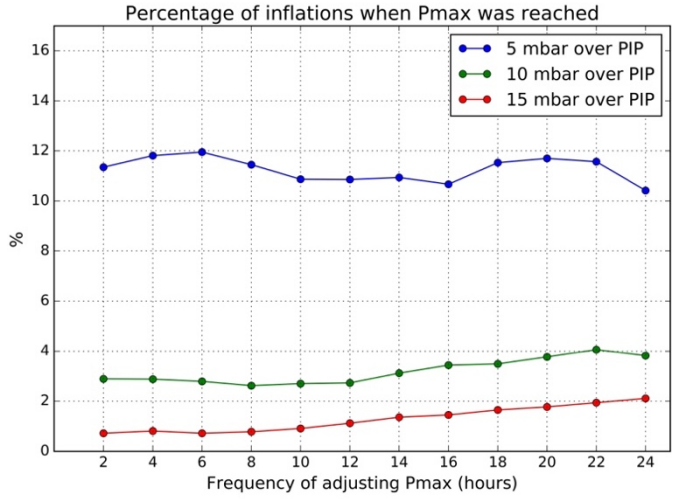

Figure 39: A calculation of the percentage of inflations which would reach Pmax when it was set at 5, 10 or 15 mbar over the observed PIP and also the influence of changing the Pmax at different intervals between 2-24 hours. Graph was produced by computational modelling using the collected ventilator data and hypothetical Pmax levels.

6.1.3. The impact of pressure rise time on ventilator parameters

We wanted to understand the effect of different PRTs on ventilator parameters and gas exchange. We hypothesized that while changing the PRT may affect MAP, and during PSV-VG the inspiratory time as well, it does not affect delivery of the target tidal volume or CO_2 elimination. To investigate this, we performed a crossover study in infants ventilated with different PRTs during SIPPV-VG and PSV-VG ventilation (23).

There were 229 ventilated babies on the NICU over the study period. The majority could not be recruited due to lack of availability of the research nurse, birth weight >2000 g, early

extubation or lack of arterial access. 19 infants were considered for the study. One developed intestinal perforation before consenting, 1 had >50% leak around the ETT and in 5 cases parents declined consent. Twelve infants were recruited and all of them completed the study without any clinical deterioration or adverse event. The mean gestational age of participants at birth was 26.5 (range: 23.7 – 31.0) weeks, their mean postnatal age was 3.25 (range: 1 – 7) days. Their weight at the time of the study ranged between 515 – 1,720 g (mean: 904 g). All infants were ventilated for respiratory distress syndrome; none had confirmed sepsis or congenital malformations.

6.1.3.1. Effect of pressure rise time and ventilation mode on ventilator parameters

Group means and SDs of ventilator settings and measurements are shown in **Table 22.**

Table 22. Ventilator settings and measurements during SIPPV-VG and PSV-VG modes with five different pressure rise times. The mean values of each ventilator parameter have been calculated for each epoch in each patient. The data in the table are group means and standard deviations of these averages (n=12).

Ventilation parameters	SIPPV-VG					p [1]	PSV-VG					p [1]
PRT (s)	0.08	0.16	0.24	0.32	0.40	n/a	0.08	0.16	0.24	0.32	0.40	n/a
Ti (s)	0.40	0.40	0.40	0.40	0.40	n/a	0.21 (0.02)	0.28 (0.03)	0.34 (0.03)	0.38 (0.01)	0.46 (0.03)	<0.0001
VTset (mL/kg)	5.00	5.00	5.00	5.00	5.00	n/a	5.00	5.00	5.00	5.00	5.00	n/a
VTmand (mL/kg)	5.31 (0.68)	5.23 (0.63)	5.25 (0.49)	5.33 (0.42)	5.29 (0.54)	0.79	5.14 (0.49)	5.24 (0.54)	5.31 (0.70)	5.25 (0.47)	5.26 (0.62)	0.95
VTdiff (mL/kg)	0.45 (0.53)	0.23 (0.26)	0.26 (0.18)	0.33 (0.20)	0.23 (0.42)	0.79	0.22 (0.24)	0.24 (0.34)	0.31 (0.84)	0.25 (0.19)	0.26 (0.37)	0.96
RRset (1/min)	55.0	55.0	55.0	55.0	55.0	n/a	55.0	55.0	55.0	55.0	55.0	n/a
RR (1/min)	64.7 (6.95)	67.0 (10.7)	63.8 (6.91)	63.5 (5.85)	69.0 (15.3)	0.79	71.5 (11.3)	66.8 (8.51)	64.2 (6.84)	68.0 (12.4)	63.5 (5.22)	0.24
MV (L/kg/min)	0.34 (0.06)	0.34 (0.06)	0.34 (0.05)	0.32 (0.03)	0.33 (0.04)	0.79	0.37 (0.08)	0.36 (0.08)	0.33 (0.04)	0.34 (0.04)	0.32 (0.04)	0.18
PIP (mbar)	16.5 (2.59)	18.3 (4.08)	18.2 (4.59)	17.3 (4.46)	15.2 (4.61)	0.09	19.8 (3.78)	19.7 (3.69)	18.6 (4.10)	16.8 (3.64)	15.6 (3.84)	0.003
Pmax (mbar)	31.25 (3.61)	31.25 (3.61)	31.7 (4.25)	31.7 (4.25)	31.7 (4.25)	n/a	31.25 (3.61)	31.7 (4.25)	31.7 (4.25)	31.7 (4.25)	31.7 (4.25)	n/a
MAP (mbar)	9.21 (0.98)	9.52 (1.40)	9.21 (1.60)	8.67 (1.31)	8.32 (1.51)	0.001	8.66 (1.07)	8.86 (1.18)	8.90 (1.26)	8.82 (1.23)	8.98 (1.42)	0.95
FiO_2 (%)	25.6 (3.61)	26.1 (5.43)	26.0 (5.13)	25.42 (3.49)	27.0 (6.29)	0.95	25.8 (4.94)	26.0 (5.02)	25.4 (4.41)	25.4 (5.57)	25.7 (4.02)	0.95
SpO_2 (%)	88.1 (6.13)	90.0 (4.48)	91.3 (4.37)	91.8 (3.80)	92.3 (4.11)	0.09	92.2 (3.16)	92.17 (2.79)	91.0 (4.35)	89.7 (4.53)	92.2 (3.18)	0.23
ET-CO_2 (kPa)	5.26 (0.70)	5.32 (0.67)	5.34 (0.76)	5.53 (0.70)	5.67 (0.74)	0.40	5.60 (0.58)	5.49 (0.58)	5.52 (0.57)	5.59 (0.66)	5.67 (0.69)	0.72

[1] p value using one-way repeated measures ANOVA from *statsmodels* package corrected for multiple testing by Benjamini-Hochberg method allowing for a false discovery rate of 5%.

During PSV-VG, an increasing PRT was associated with significantly longer ventilator inspiratory times (p<0.0001, **Figure 40A**); this was not seen during SIPPV-VG where the Ti was always set at 0.4 s. With SIPPV-VG the there was no significant change in PIP with increasing PRT but there was a small but significant reduction in MAP (p=0.001) (**Figure 40C**). During PSV-VG, increasing PRT was associated with significantly lower PIP (p=0.003) (**Figure 40B**) although MAP was not significantly different. With a short PRT (0.08 s), the PIP

was higher during PSV-VG than SIPPV-VG (19.8 mbar versus 16.5 mbar, p=0.042). VTmand was maintained within 0.5 mL/kg of targeted value with all PRTs both during SIPPV-VG and PSV-VG. There were no differences in minute ventilation, respiratory rate and FiO_2 among the epochs with different PRTs in any of the ventilator modes.

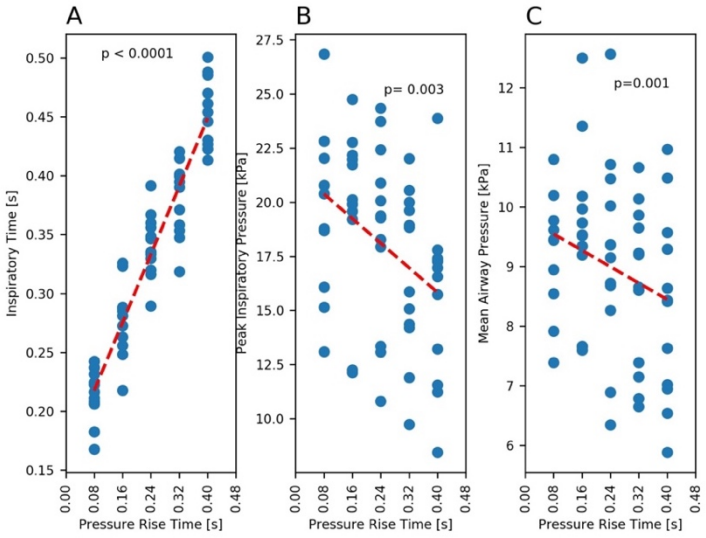

Figure 40. Mixed linear regression models inspiratory time, peak inspiratory pressure and mean airway pressure changing significantly when using different pressure rise times. **A.** Inspiratory time (Ti) during PSV-VG ventilation. **B.** PIP during PSV-VG. **C.** MAP during SIPPV-VG.

6.1.3.2. The effect on gas exchange

During SIPPV-VG SpO_2 increased slightly with increasing PRT (**Figure 41A**) but this was not statistically significant when analyzed using one-way repeated measures ANOVA corrected for false discovery (0.092). There was no consistent change in SpO_2 during PSV-VG.

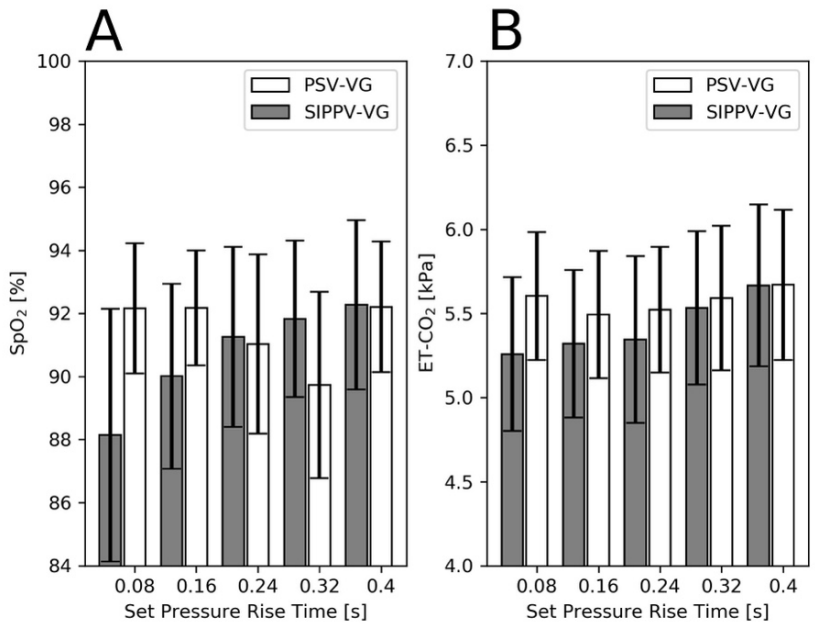

Figure 41. Effect of different pressure rise times on inspiratory time, SpO_2 and ET-CO_2 during SIPPV-VG and PSV-VG modes. **A.** Peripheral oxygen saturations. **B.** ET-CO_2. For each epoch, mean values of ventilator parameters were calculated in each patient. Bars show group means and its 95% confidence interval from the 12 patients.

ET-CO_2 levels showed good correlation with P_aCO_2 levels in arterial blood gases (r = 0.79, p<0.001). On average, mean ET-CO_2 was 1.42 kPa lower than P_aCO_2 (range: -0.098 – 2.57). During SIPPV-VG, ET-CO_2 levels increased slightly with longer PRTs but the change was not statistically significant (p = 0.402, **Figure 41B**). There was no change in ET-CO_2 during PSV-VG. The largest difference between any epoch was between a PRT of 0.40 and 0.08 s during SIPPV-VG (0.41 kPa, 90% confidence interval: 0.112 - 0.586 kPa). As we considered a <0.5 kPa difference as clinically equivalent, the equivalence in terms of CO_2 elimination cannot be proven with 90% confidence from our dataset.

6.1.4. Ventilator performance during high frequency oscillatory ventilation with volume guarantee

We retrospectively analysed ventilator data from a convenience group of 17 babies who were ventilated with HFOV-VG for >12 hours as part of their clinical care (80). Their median corrected gestation at the time of recording was 28 weeks (range 24-40 weeks). Their weights ranged between 515 and 3,476 g (median: 1,100 g). Seven infants weighed <1 kg, 7 were between 1-2 kg and 3 were >2 kg. They were ventilated for various neonatal problems including RDS, MAS, sepsis, PPHN, pneumothorax, BPD, and necrotizing enterocolitis.

6.1.4.1. HFOV-VG protocol

We used HFOV as rescue ventilation mode. HFOV-VG was initiated the same way as HFOV without VG. MAP was initially set at the level of the MAP delivered during the preceding conventional ventilation and then increased gradually until FiO_2 decreased to <50% or the clinician felt that the lungs were sufficiently recruited. MAP was then gradually reduced until FiO_2 started to rise again. A chest X-ray was performed approximately 1 hour later to confirm the position of the diaphragm at the level of the 8^{th}-9^{th} posterior rib. We used an I:E ratio of 1:1 in each case. Frequency ranged between 7-12 Hz. Pressure amplitude was set initially at a level that resulted in appropriate chest oscillations in the subjective opinion of the senior clinician. $tcCO_2$ monitoring was used in babies receiving HFOV. When a blood gas confirmed that the pCO_2 was in the target range for the particular infant, VG was started using the current VThf set as the target value. Amplmax (the largest allowed amplitude) was usually set 10 mbar above the amplitude being used. Later, VThf was weaned by no more than 0.1 mL/kg at a time based on blood gases and $tcCO_2$ data. Infants were usually extubated when the MAP was <10 mbar, FiO_2 <40%, sedation had been weaned and the baby was breathing and was cardiovascularly stable. Some infants were changed to conventional ventilation prior to extubation.

6.1.4.2. Maintenance of tidal volume during HFOV-VG

We analyzed in detail ~3.2 million seconds (36.7 days) of HFOV-VG ventilation with a sampling rate of 1/sec (1 Hz). Data were partially missing for 6,986 seconds (0.22%) and these times were excluded from analysis. We also excluded data when the VThf was over 6 mL/kg (1,420 data points, 0.04%) as these values most likely reflect artefact due to disconnection of the ventilator circuit. Overall, the median VThf was 1.93 mL/kg (IQR: 1.64-2.45 mL/kg). VThf was between 1.5 and 2 mL/kg in 42% of the recorded period and between 2 and 2.5 mL/kg in 24% (**Figure 42A**). For all the data the difference between the set and delivered tidal volume

was <0.2 mL/kg 83% of the time and <0.5 mL/kg in 93% of the recording time (**Figure 42B**).

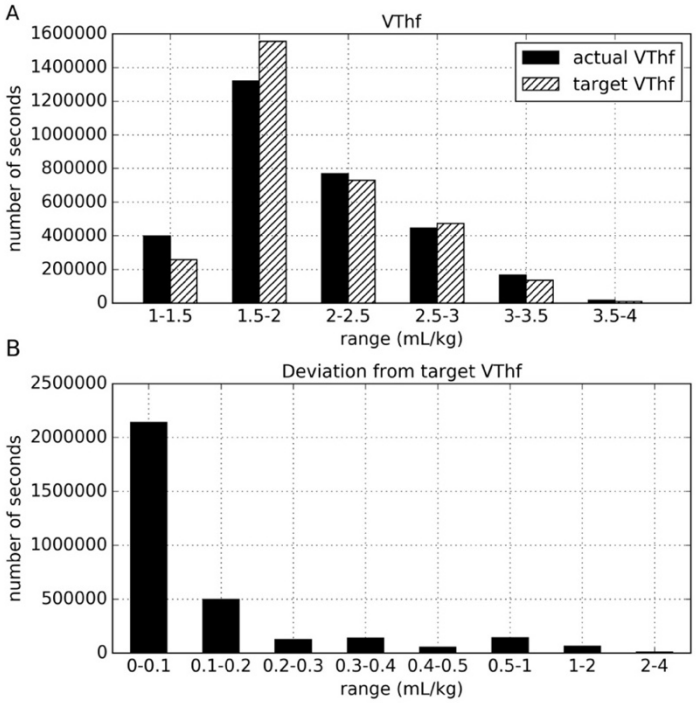

Figure 42. Histograms showing the distribution of targeted and actual tidal volumes (VThf) and their difference during high frequency oscillatory ventilation. **A:** Actual delivered and targeted tidal volumes **B:** Absolute value of the difference between and actual and target VThf.

Table 23. Actual and targeted tidal volumes during HFOV-VG. VThf was recorded once every second. Median values are shown together with 5th and 95th percentile values. The deviation of VThf from the targeted value was calculated as the absolute value of the difference between the target and actual VThf calculated for each second. Abbreviations: Mo: Morphine sulphate, F: Fentanyl, P: Pancuronium bromide, V: Vecuronium bromide, A: Atracurium besylate.

Patient	Duration (hours)	Weight (g)	Sedative / muscle relaxant medication	Actual VThf (mL/kg) Median (5th - 95th centile)	Target VThf (mL/kg) Median (5th - 95th centile)	Deviation from target VThf (mL/kg) Median (5th - 95th centile)
DG005	29.1	1995	Mo, V, P	1.9 (1.3 - 1.9)	1.8 (1.6 - 1.8)	0.05 (0.55 - 4.06)
DG006	24.1	650	Mo, F, A	2.8 (2.5 - 3.1)	2.8 (2.3 - 3.1)	0 (0.15 - 2.62)
DG009	43.6	1080	Mo, F	2.7 (1.4 - 3.4)	2.9 (2.5 - 2.9)	0.28 (1.39 - 3.15)
DG018	37.7	755	Mo, P	3.3 (3 - 3.8)	3.3 (3 - 3.6)	0 (0.13 - 3.71)
DG020	27.9	2250	Mo	1.5 (1.3 - 1.9)	1.5 (1.3 - 1.9)	0 (0.13 - 4.22)
DG022	83.7	2850	Mo, A, P	2.1 (1.5 - 2.6)	2.3 (1.5 - 2.6)	0.04 (0.42 - 4.49)
DG025	65.1	515	Mo	1.9 (1.4 - 2.3)	1.9 (1.8 - 1.9)	0.19 (0.58 - 3.88)
DG032	36.7	940	Mo	2 (0.7 - 2.6)	2 (1.8 - 2)	0.21 (1.17 - 4.04)
DG038	110.6	1100	Mo	2.5 (1.4 - 2.8)	2.4 (2.3 - 2.7)	0.09 (1.09 - 3.73)
DG040	47.6	570	Mo	1.8 (1.4 - 2.6)	1.9 (1.6 - 2.5)	0 (0.35 - 3.86)
DG046	46.3	1180	Mo	1.4 (1.2 - 1.9)	1.4 (1.2 - 1.9)	0 (0.17 - 3.47)
DG049	72	520	Mo	1.9 (1.7 - 2.5)	1.9 (1.9 - 2.3)	0 (0.38 - 4.04)
DG050	41.3	1490	Mo	1.6 (1.3 - 1.7)	1.6 (1.3 - 1.6)	0 (0.27 - 4.56)
DG053	28.5	3476	Mo	2.5 (2 - 2.7)	2.6 (2 - 2.7)	0 (0.09 - 2.85)
DG056	68	1950	Mo	1.5 (1.2 - 1.8)	1.5 (1.4 - 1.8)	0.05 (0.36 - 4.15)
DG069	38.8	830	Mo, A	1.7 (1.2 - 2.2)	1.7 (1.7 - 1.7)	0.12 (0.72 - 4.22)
DG077	77.6	1660	Mo, A	2 (1.8 - 2.4)	1.9 (1.9 - 2.4)	0 (0.18 - 3.86)

We analyzed the distribution of VThf and other respiratory parameters in each recording (**Table 23**). The median VThf of the individual recordings ranged between 1.44 and 3.31 mL/kg. Despite the VG mode, some recordings had significant variability of VThf, with the actual VThf deviating from the target by >1 mL/kg in 5% of the recording time. This occurred sometimes in babies receiving little sedative medication and no muscle relaxants and may have been due to ventilator-patient interactions similar to that seen in conventional ventilation with VG (180). It is illustrated in the recordings of two babies on **Figure 43A-B**. However, when the median was calculated over 5-minute periods, VThf was always very close to the target value (**Figure 43C-D**). The pressure amplitude varied both in the short and long term, the latter probably reflecting changes in spontaneous breathing patterns or respiratory mechanics (**Figure 43E-F**). When there was a rapid increase in chest compliance, the amplitude was weaned automatically by the VG algorithm to ensure the VThf was well maintained (**Figure 44A-B**)

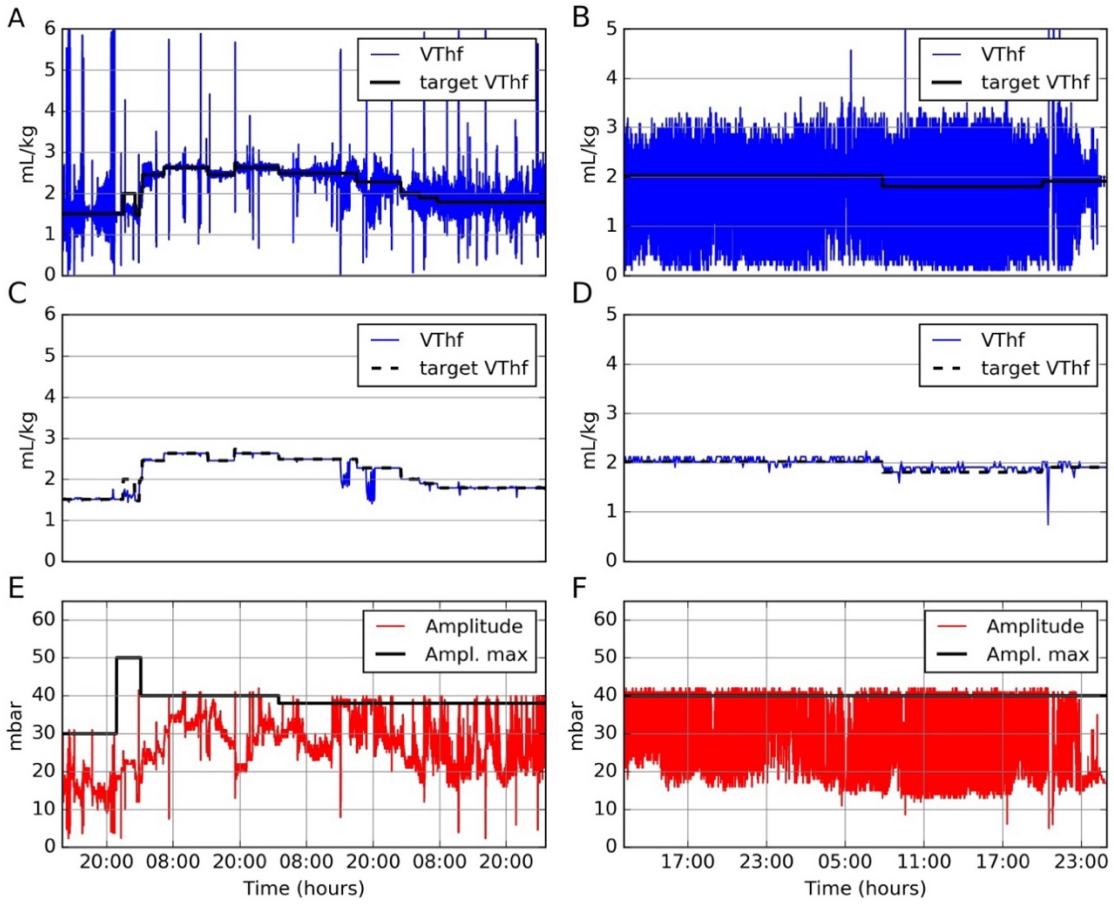

Figure 43. Detailed analysis of VThf and pressure amplitude in infants ventilated with HFOV-VG using 1/sec data sampling. The graphs have been built from >100,000 data points. **A.** This infant (DG022) received 30 µg/kg/hour Morphine sulphate and 480 µg/kg/hour Atracurium (muscle relaxant) intravenously during this ~84-hour long recording. The actual tidal volume is very close to the target. **B.** This infant (DG032_2) received only 10 µg/kg/hour Morphine sulphate for sedation. VThf shows large variability despite the VG mode possibly due to spontaneous breathing and patient-ventilator interactions. **C-D.** VThf averaged over 5-minute periods: each data point represents the median of 300 VThf values obtained with 1Hz sampling rate. During both recordings, the median VThf was maintained very close to the target value even though there was significant short-term variability. **E.** The pressure amplitude shows significant long-term variability even in this patient receiving muscle relaxation. **F.** In this baby with more short-term variability of VThf, the variability of the pressure amplitude is much larger.

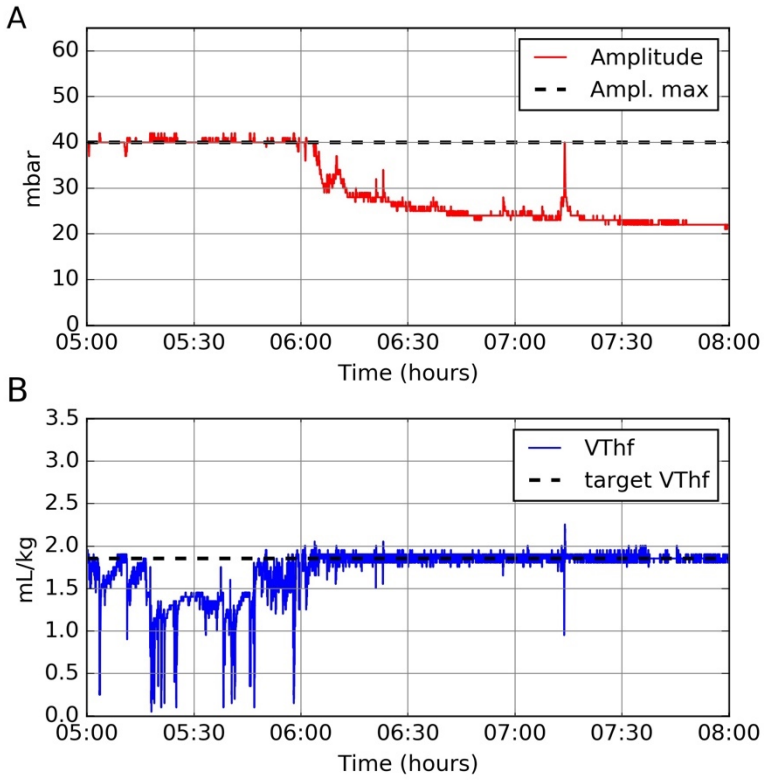

Figure 44. A-B. Auto-weaning of the pressure amplitude during HFOV-VG with improving chest compliance. This infant had severe bronchopulmonary dysplasia with hypoxic spells associated with severe desaturations. The target VThf could not be delivered as the pressure amplitude reached the allowed limit. Shortly after 06:00 a dose muscle relaxant was given. Amplitude pressure dropped significantly within 10 minutes and VThf was well maintained, probably because the chest wall splinting causing the hypoxic spells was prevented.

6.1.4.3. Correlation of VThf and DCO_2 with pCO_2 during HFOV-VG

In addition to VThf, the ventilator calculates and displays DCO_2, calculated as frequency x $VThf^2$. We analyzed the correlation of VThf and DCO_2 with pCO_2 in each recording and across all recordings. We calculated the median of these ventilator parameters over 10-minute periods before each blood gas as described in **section 5.4.1.1**.

Of the 243 blood gases, pCO_2 was <5 kPa in 27 (11%) and >8 kPa in 53 (22%). After weight correction, VThf and DCO_2 showed negative (inverse) correlation with pCO_2 values, which were all very weak, although statistically significant (**Table 24, Figure 45**). The correlation remained weak even when only arterial blood gas measurements were used. VThf or DCO_2 not corrected for body weight showed no inverse correlation with pCO_2. A VThf of >2.5 mL/kg AND a blood gas with a pCO_2 >8 kPa together were seen only with 6 blood gases (2.5%). A VThf of ≥2.5 mL/kg predicted a pCO_2 <8 kPa with a positive predictive value of 87%. However, the negative predictive value was only 25%, and many infants required much less VThf to avoid hypercapnia. Even within the individual recordings the inverse correlation between VThf and pCO_2 was variable, and sometimes the same VThf and frequency settings resulted in substantially different pCO_2 values.

Table 24: Pearson's correlation analysis between VThf, DCO_2 (with or without weight correction) and pCO_2 across all recordings. Weight-corrected values show a weak but statistically significant inverse correlation, uncorrected data do not correlate with pCO_2.

Parameter	All blood gases (n=243)			Arterial blood gases (n=130)		
	r	95% CI	p	r	95% CI	p
DCO_2/kg^2	-0.184	-0.303, -0.059	0.004	-0.108	-0.275, 0.066	0.222
VThf/kg	-0.162	-0.282, -0.037	0.011	-0.109	-0.276, 0.065	0.218
DCO_2	0.126	0.001, 0.248	n/a	0.202	0.031, 0.362	n/a
VThf	0.168	0.043, 0.288	n/a	0.222	0.052, 0.380	n/a

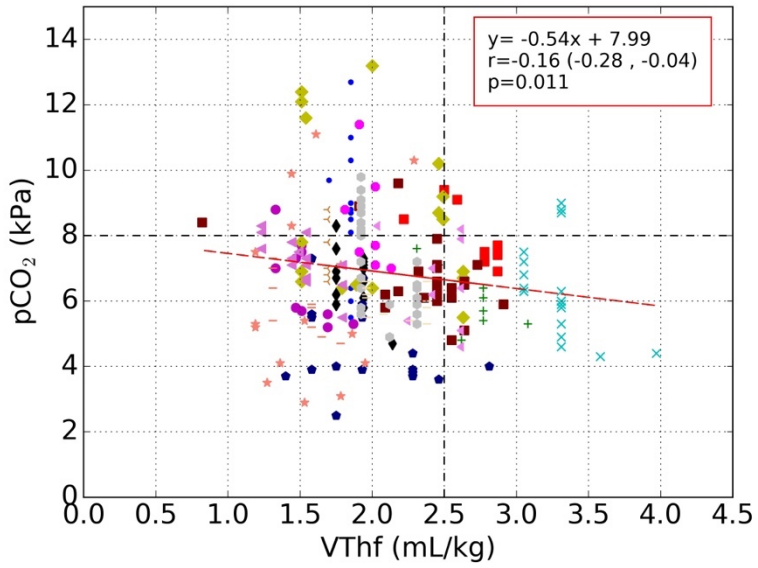

Figure 45. Pearson's correlation between the VThf of HFOV oscillations corrected to the body weight (mL/kg) and blood gas pCO_2 data. There is a very weak but statistically significant inverse correlation. Data from different patients are marked with different markers and different colors. For some patients the same VThf was associated with very different pCO_2 in the consecutive blood gases.

6.1.5. How to interpret DCO_2 during HFOV

For this report we re-analysed data from a subset of infants who were ventilated with HFOV (87). There were 18 recordings obtained from 14 infants. The combined duration of recordings was 952.5 hours (approximately 39.7 days). There were 254 blood gas measurements during the recordings, of which, 106 (42%) were arterial.

To use DCO_2 values which were more representative than single readings we calculated the mean of 600 DCO_2 values obtained during 10 minutes as described in **section 5.4.1.1**. We corrected DCO_2 data for the body weight by dividing by the square of the body weight in kilograms (DCO_2corr).

6.1.5.1. Weight correction improves correlation between DCO_2 and pCO_2

When all the blood gases were considered together, uncorrected DCO_2 values showed no inverse correlation with pCO_2 data (**Figure 46A**). The range of DCO_2 values was very wide (between 5.5 – 570 mL^2/sec) and DCO_2 readings from different patients "clustered" in different parts of the graph. This clustering and the lack of inverse correlation were also observed if only arterial blood gases were considered (**Figure 46B**).

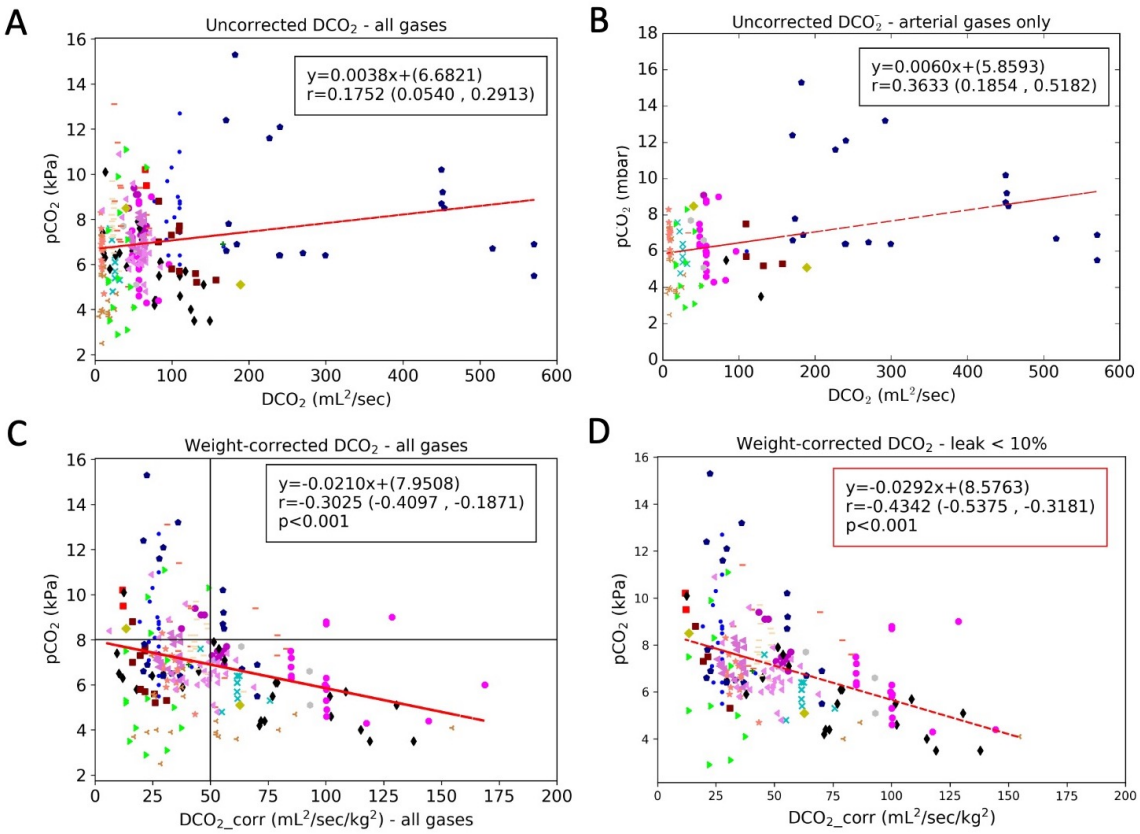

Figure 46. Correlation between DCO_2 and pCO_2. Scatterplots with data obtained from different patients shown with different markers. "r" represents Pearson's correlation coefficient with 95% confidence intervals. **A**. Graph showing all blood gas pCO_2 (arterial and capillary) data plotted against uncorrected DCO_2. There is no inverse correlation between DCO_2 and pCO_2, and data obtained from the individual patients tend to cluster. **B**. In this graph only arterial $paCO_2$ data are plotted against uncorrected DCO_2. There is no inverse correlation between DCO_2 and $paCO_2$. **C**. Graph showing all blood gas pCO_2 (arterial and capillary) data plotted against DCO_2 corrected for the square of the body weight (DCO_2corr). There is statistically significant inverse correlation between DCO_2corr and pCO_2. **D.** Relationship between DCO_2corr and in blood gases when the endotracheal tube leak was <10%. The inverse correlation is stronger than when all gases were considered.

DCO_2corr values showed significantly less variability, the range was between 5.2 – 169 $mL^2/sec/kg^2$, (**Figure 47A**). Unlike DCO_2, DCO_2corr from different patients showed an inverse correlation with pCO_2 values (**Figure 46C**). This was weak (r = -0.3025, 95% confidence intervals: -0.4097, -0.1871) but statistically significant ($p<0.001$). Also, the graph shows less clustering of values from individual patients. When only arterial blood gas measurements were considered, there was also an inverse correlation but it was not statistically significant because of the small numbers (data not shown).

We analyzed the individual patient slopes of the correlation between DCO_2corr and pCO_2, where at least 10 blood gases were available (14 out of the 18 recordings). All except two showed an inverse correlation between DCO_2corr and PCO_2 although it was only just statistically significant ($p<0.05$) in 6 out of 14 cases (**Table 25**). This is likely to be due to the smaller number of blood gas samples in individual cases. Also, weight-correction improved the inter-individual comparability of DCO_2 values. Therefore, a significant correlation on the whole cohort is still useful.

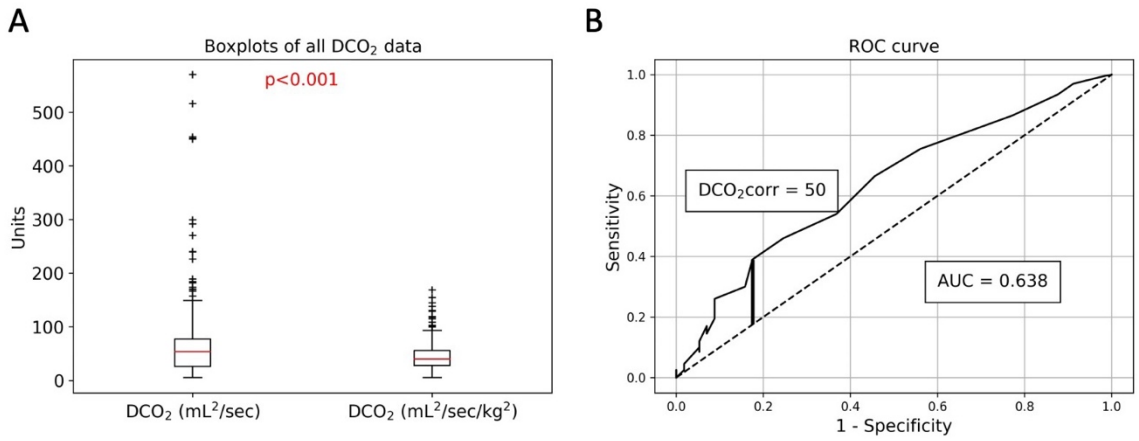

Figure 47. **A**. Boxplots of DCO_2 and weight-corrected DCO_2corr values obtained from all patients. DCO_2corr shows significantly less variability than uncorrected DCO_2. **B.** Receiver operating characteristic (ROC) analysis of DCO_2corr values to predict a pCO_2 less than 8 kPa. The optimal cut-off is shown at 50 mL/s/kg^2 (sensitivity: 0.390, specificity: 0.82, Youden score = 0.215).

Table 25: Characteristics of the individual pCO_2 –DCO_2corr curves

Patient	Equation	r (95% CI)*	p value
DG005	y=-0.0176x+10.1310	-0.1671 (-0.5775 , 0.3107)	p=0.4942
DG006	y=-0.1515x+9.9216	-0.6002 (-0.8925 , 0.0474)	p=0.0666
DG009	y=-0.0932x+13.4458	-0.7588 (-0.9337 , -0.2916)	p=0.0068
DG017	y=-0.0245x+7.5918	-0.7013 (-0.8586 , -0.4236)	p=0.0001
DG018	y=-0.0210x+7.5859	-0.1894 (-0.5926 , 0.2897)	p=0.4373
DG020	y=-0.0380x+10.8140	-0.7170 (-0.9278 , -0.1593)	p=0.0196
DG022	y=-0.0063x+10.8582	-0.3180 (-0.6747 , 0.1593)	p=0.1846
DG025	y=-0.4691x+10.9389	-0.5458 (-0.8014 , -0.1218)	p=0.0156
DG032	y=-0.0420x+10.2766	-0.3346 (-0.7229 , 0.2144)	p=0.2229
DG038	y=-0.0460x+9.3383	-0.5297 (-0.7443 , -0.2159)	p=0.0022
DG038	y=0.0127x+6.6313	0.1438 (-0.3190 , 0.5513)	p=0.5452
DG040	y=-0.0218x+4.9033	-0.1893 (-0.5926 , 0.2898)	p=0.4375
DG040	y=-0.1963x+11.5732	-0.4855 (-0.7833 , -0.0063)	p=0.0482
DG046	y=0.0592x+4.0290	0.3173 (-0.2328 , 0.7136)	p=0.2491

* Pearson's correlation coefficient with 95% confidence intervals

To investigate if using time windows for DCO_2 averaging other than 10 minutes leads to better results, we performed the same analysis using different time windows between 2 and 20 minutes. DCO_2corr data obtained over 2, 5 and 15-minute windows also showed inverse correlation with pCO_2 albeit somewhat weaker than 10-minute data (data not shown). Data obtained with 20-minute time windows showed no inverse correlation.

6.1.5.2. The impact of leak on correlation between DCO_2 and pCO_2

Leak was calculated, similarly to DCO_2, using the mean value of the 600 data points during 10 minutes before the blood gas was taken. Pragmatically, we divided the leak into two groups: <10% (209 blood gases) and ≥10% (45 blood gases). With <10% leak the correlation between DCO_2corr and pCO_2 improved further ($r = -0.4342$, 95% confidence intervals: -0.5375, -0.3181 and $p<0.0001$, see **Figure 46D**), although the inverse correlation remained weak. In addition, the inverse correlation was statistically significant even when only arterial pCO_2 values were used (not shown). In the subset with ≥10% leak there was no correlation between DCO_2corr or and PCO_2 or $paCO_2$.

6.1.5.3. Predictive value of DCO_2 to avoid hypercapnia

Analyses were done to determine whether DCO_2corr value could be used to predict avoidance of hypercapnia (pCO_2 >8 kPa or 60 mmHg). Receiver operating characteristic curve (ROC) analysis together with Youden's statistic showed that the optimal cutoff was DCO_2 ≥50 $mL^2/sec/kg^2$ which predicted a pCO_2 ≤8 kPa with a positive predictive value of 0.886 and a negative predictive value of 0.278 (specificity = 0.825, sensitivity = 0.39, Youden score = 0.215, area under the curve = 0.638), see **Figure 47B**. Moreover, of the 57 DCO_2corr values >60 $ml^2/sec/kg^2$ (from 9 patients), only 5 were associated with a pCO_2 value >8 kPa. Therefore, we suggest that DCO_2corr values >60 $mL^2/sec/kg^2$ should not be routinely targeted unless hypercapnia persists.

6.1.6. The impact of ambulance acceleration and vibration on ventilator performance

We analyzed accelerometer and ventilator data from 113 infants undergoing emergency neonatal transfer (130). All infants had a net journey time >10 minutes after removing periods when baby was ventilated with the transport ventilator before departure or after arrival or when the transport incubator was moved between the neonatal unit and the ambulance or vice versa. We excluded 4 infants whose postmenstrual age was >46 weeks (n=109). Basic clinical data of the infants are shown in **Table 26**. The total duration of recordings was 82.4 hours.

Table 26. Summary clinical details, ventilator modes used and duration of recordings

Clinical details	**Median (range)**
Gestational age (weeks)	36 (22 – 41)
Postnatal age (hours)	6.0 (1.6 – 1644)
Postmenstrual age (weeks)	37 (22 – 45.8)
Birth weight (grams)	2,840 (400 – 4,900)
Weight at transfer (grams)	2,880 (400 – 4,900)
Recording duration (minutes)	44 (11 – 106)
Ventilator modes	**Patients (n)**
SIMV	63
SIMV-PS	4
SIPPV	34
More than one mode	8
VG on*	97
VG off*	17

* In some cases, VG was turned on or off during the transfer.

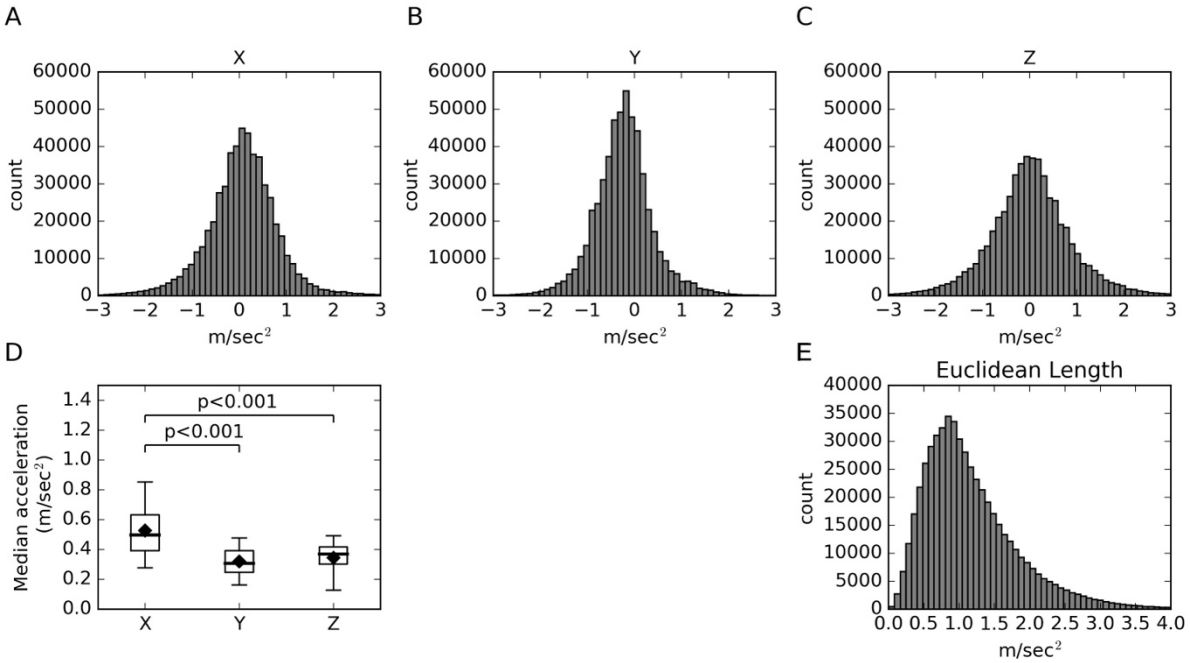

Figure 48. Acceleration of ambulance in the three directions of space. **A-C.** Histograms showing the distributions of acceleration measurements during transfer of a preterm infant born at 30 weeks and weighing 950 g. Acceleration vector reading counts are shown separately in the front-back (X), left-right (Y) and up-down (Z) directions. Sampling rate was 100 Hz. Only acceleration readings up to 3 m/sec^2 are shown, although rarely higher values also occurred. **D.** Boxplots showing the distribution of the median absolute acceleration of the recordings in each direction. The largest acceleration occurred in the front-back (X) direction, significantly larger than in the left-right (Y) or up-down (Z) directions. Group medians are marked by horizontal line, means by black diamonds. Boxes represent interquartile range; error bar correspond to 95% range. **E.** Distribution of the length (Euclidean norm) of the acceleration vector for the same recording as shown in A-D. See Methods (**section 5.4.3**.) for more details.

6.1.6.1. Vibration is responsible for most of ambulance acceleration

We plotted the median sustained acceleration against the median vibration for each minute in each direction (**Figure 49A-C).** During most minutes there was significant vibration in all directions. However, in the X (front-back) and Y (side-to-side) directions there were also minutes characterized by significant sustained acceleration but with little vibration; they likely represent periods when the ambulance was increasing or decreasing its speed on a relatively smooth surface (direction X), or turned left or right (direction Y). As expected, in vertical direction (Z) there was only vibration (**Figure 49C** & **Figure 50**).

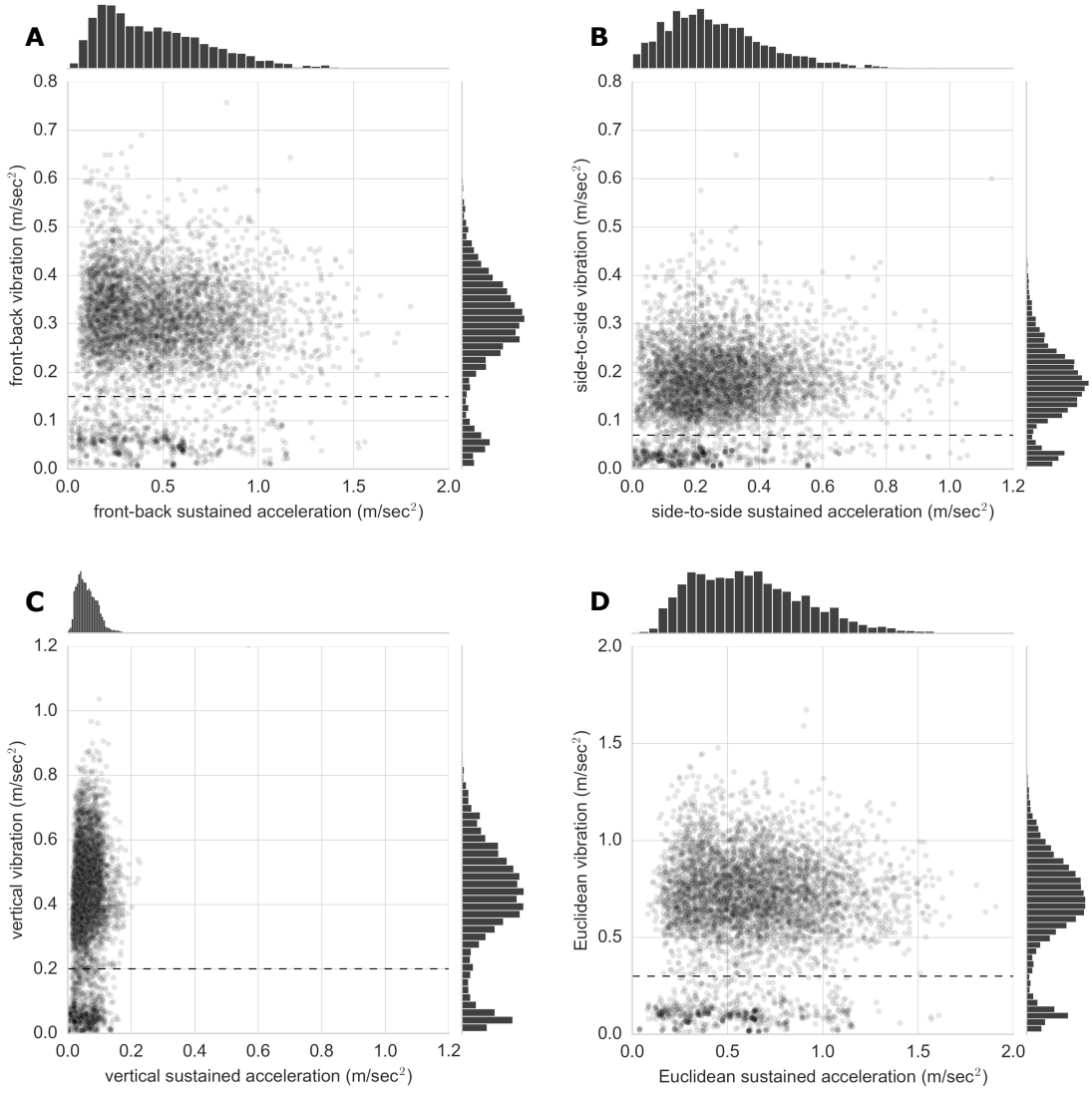

Figure 49. Scatterplots showing the median vibration during each 1-minute period plotted against the median sustained acceleration over the same period. Histograms for each variable are shown along the axes. **A-C:** Acceleration and vibration along the front-back (X), left-right (Y) and up-down (Z) axes, respectively. **D.** Euclidean length of the acceleration and vibration vector for each minute. Minutes when vibration was >0.3 m/sec^2 (area above the dashed lines on D**)** were considered as periods of vibration (with or without sustained acceleration). Minutes when the sustained acceleration was high but there was no vibration likely correspond to periods when the ambulance changed its speed or direction frequently while travelling on a smooth road surface. In vertical direction (C) only vibration was possible.

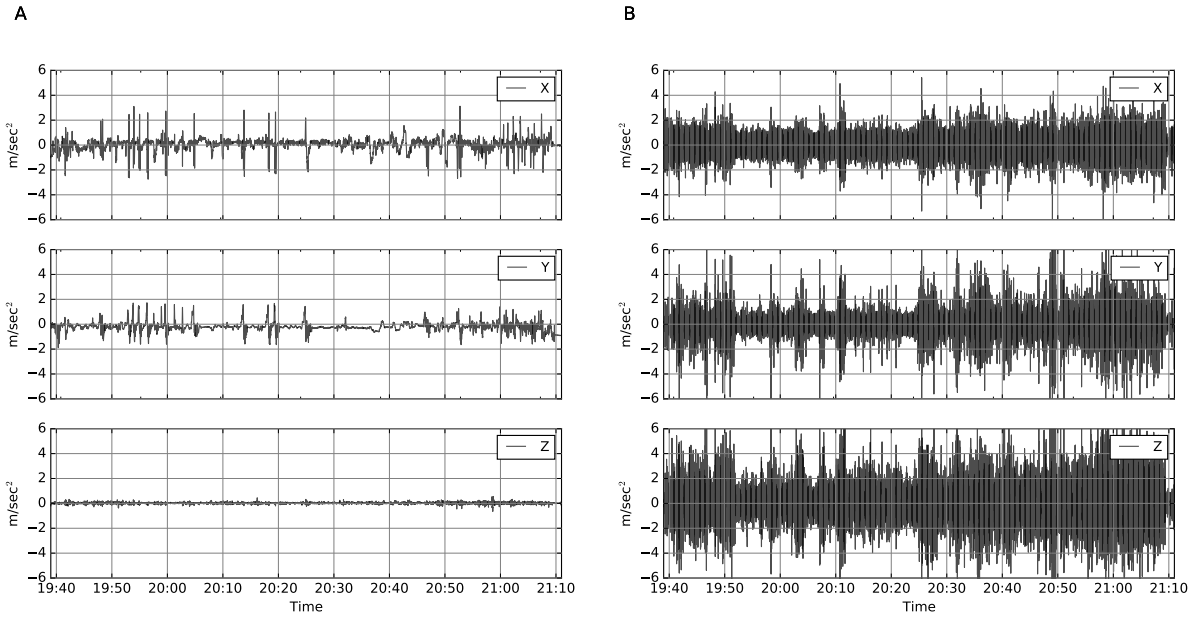

Figure 50. Time series graphs showing sustained acceleration (**A**) and vibration (**B**) during transfer of a preterm infant. Sustained acceleration and vibration data were separated by a low-pass and a high-pass frequency filter, respectively, as described in Methods. Most acceleration is due to vibration; however, there were periods without vibration but significant sustained acceleration either in the front-to-back (X) direction (vehicle speeding up or slowing down), or in the side-to-side (Y) direction (vehicle turning left or right). In the vertical (Z) direction only vibration was possible.

6.1.6.2. Neither vibration nor sustained acceleration significantly affect ventilator parameters

There was no alignment between periods of high or variable acceleration and variability of tidal or minute volume, peak inflating pressure and fraction of inspired oxygen (**Figure 51**).

As they represent different physical forces and potentially impact differently on the ventilator and the baby, we studied the impact of vibration and sustained acceleration separately. We considered minutes as periods of vehicle vibration when the median vibration was >0.3 m/sec^2 (**Figure 49D**). Minutes when vibration was <0.3 m/sec^2 were considered as periods of no vibration, although significant sustained acceleration occurred during some of them.

We compared ventilator parameters during the minute with the highest and the lowest vibration in each recording (**Table 27**). There was no difference in the average expired tidal volume, peak inflating pressure, minute ventilation and fraction of inspired oxygen between these periods. The variability of these parameters was also not affected by vibration (data not shown). No differences were seen even in extremely preterm infants. During volume guaranteed ventilation, the tidal volume was maintained equally well during periods of high vibration compared with periods of low vibration; during pressure-controlled ventilation the PIP was delivered as set by the user. In SIPPV, infants did not trigger more inflations during the vibration periods.

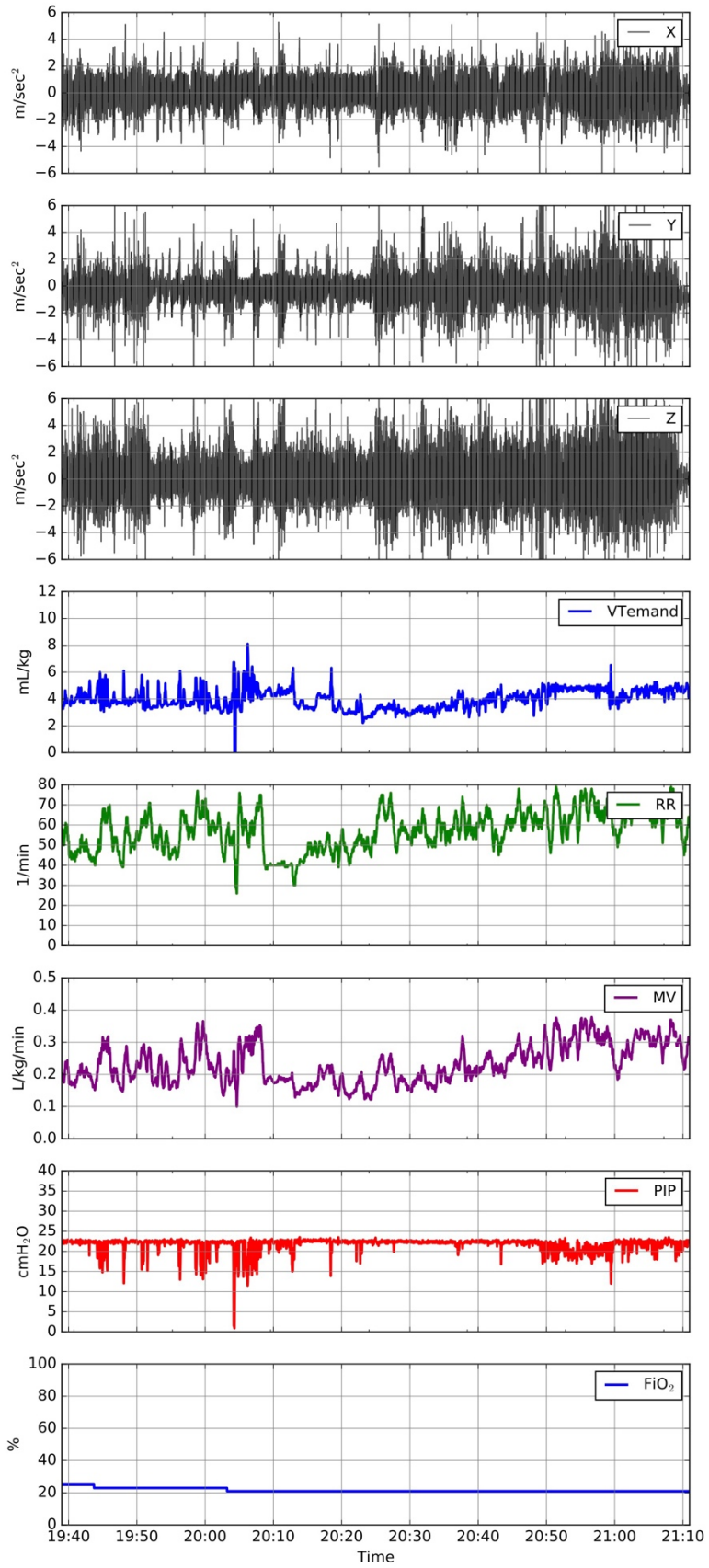

Figure 51. Time series graphs of the acceleration measurements and selected ventilator parameters of a very preterm infant. Acceleration readings are shown separately in the front-back (X), left-right (Y) and up-down (Z) directions. Sampling rate was 100 Hz; therefore, this ~90-minute-long recording contained ~540,000 acceleration measurements. Periods of high accelerations occurred in each direction and they frequently coincided with each other, likely representing periods of vibration. Occasionally, acceleration readings exceeded 5 m/sec^2. Ventilator data were sampled at 1 Hz. The baby was ventilated with SIPPV without volume guarantee. The VTemand, respiratory rate (RR) and MV all show significant variability during the 90-minute-long transfer but they do not coincide with high acceleration periods. The PIP shows some variability, particularly during the end of the transfer, despite the pressure-controlled ventilation mode. This is likely due to patient-ventilator interactions. FiO_2 was only changed twice during the transport team and remained <30% throughout the transfer.

Table 27. Comparison of ventilator parameters during periods of low and high vibration. For each minute of recording, the median acceleration and the mean of the ventilator parameters were calculated. For each recording, the 1-minute periods with lowest and highest vibration were chosen. Group statistics of these data are shown in table.

	Minute with lowest vibration	**Minute with largest vibration**	
All transfers (n=109)			
	Group mean (SD)	**Group mean (SD)**	**P value** *
Acceleration (m/sec^2) &	0.49 (0.26)	1.5 (0.25)	<0.0001
VTemand (mL/kg)	5.14 (1.84)	5.27 (1.83)	0.20
MV (mL/kg/min)	0.28 (0.12)	0.29 (0.11)	0.40
PIP (cmH_2O)	18.2 (7.4)	18.1 (6.6)	0.89
FiO_2 (%)	37.3 (22.3)	36.2(21.6)	0.12
Volume guarantee ventilation (n=97) £			
	Group mean (SD)	**Group mean (SD)**	**P value** *
Acceleration (m/sec^2) &	0.51 (0.27)	1.5 (0.24)	<0.0001
VTemand (mL/kg)	5.08 (1.64)	5.23 (1.68)	0.12
PIP (cmH_2O)	18.0 (7.7)	17.9 (6.9)	0.75
	Group median (range)	**Group median (range)**	**P value** +
VTdiff (mL/kg)	0.5 (0.02 – 5.85)	0.41 (0.03 – 5.11)	0.32
Pdiff (cmH_2O)	12.7 (0.3 – 32.9)	12.4 (0.2 – 31.4)	0.18
Pressure limited ventilation (n=17) £			
	Group mean (SD)	**Group mean (SD)**	**P value** *
Acceleration (m/sec^2) &	0.45 (0.21)	1.44 (0.27)	<0.0001
VTemand (mL/kg)	5.64 (2.69)	5.54 (2.39)	0.70
PIP (cmH_2O)	18.6 (3.6)	18.7 (3.4)	0.88
	Group median (range)	**Group median (range)**	**P value** +
Pdiff (cmH_2O)	0.3 (0.2 – 1.7)	0.4 (0.3 – 0.6)	0.58
SIPPV mode (n=34)			
	Group mean (SD)	**Group mean (SD)**	**P value** *
Acceleration (m/sec^2) &	0.47 (0.28)	1.51 (0.26)	<0.0001
RR (1/min)	59.0 (15.6)	60.7 (15.5)	0.10
	Group median (range)	**Group median (range)**	**P value** +
RRdiff (1/min)	11.2 (0 – 55)	15.5 (0 – 56)	0.18
SIMV mode (n=63)			
	Group mean (SD)	**Group mean (SD)**	**P value** *
Acceleration (m/sec^2) &	0.50 (0.25)	1.46 (0.22)	<0.0001
VTemand (mL/kg)	5.51 (2.17)	5.45 (2.16)	0.69
VTespon (mL/kg)	2.26 (2.36)	2.39 (2.72)	0.49

*: Two-tailed paired Student T-test; + Wilcoxon signed rank test; &: Euclidean length of acceleration vector (see Methods); £ During some transfers volume guarantee was turned on only for part of the transfer.

We also compared ventilator parameters during the minutes with the highest and lowest sustained (front-back or side-to-side) acceleration but without significant vibration, and found no differences in these parameters or in their variability either (**Table 28**).

Table 28. Comparison of ventilator parameters during periods of low and high sustained acceleration. For each minute, the median acceleration and the mean of the ventilator parameters were calculated. For each recording, the 1-minute period with lowest and highest sustained acceleration was chosen. Only cases where the lowest acceleration was <0.6 m/sec^2 and the highest acceleration was >0.6 m/sec^2 have been included (n=41). Group means and standard deviations of these data are shown in table.

	Minute with lowest vibration	Minute with largest vibration	
	Group mean (SD)	**Group mean (SD)**	**P value** *
Acceleration (m/sec^2) &	0.39 (0.15)	0.83 (0.19)	<0.0001
VTemand (mL/kg)	4.98 (1.50)	5.15 (1.44)	0.34
MV (mL/kg/min)	0.30 (0.10)	0.29 (0.10)	0.20
PIP (cmH_2O)	19.3 (6.7)	19.0 (6.7)	0.55
FiO_2 (%)	40.9 (26.4)	40.3 (25.2)	0.55

*: Two-tailed paired Student T-test; &: Euclidean length of acceleration vector (see Methods).

6.1.6.3. Impact of vibration on pressure-volume loops

Vibration frequently made the pressure-volume (PV) loops more irregular (**Figure 52**). Overall, the complexity (expressed as the number of pressure-volume data pairs during a period) of the PV loops was higher during the 1-minute period with the highest vibration than during the minute with lowest vibration. The median (IQR) number of pressure-volume data pairs were 2522 (1928 - 3148) and 2740 (2029 - 3418), respectively (p<0.0001, Wilcoxon signed rank test).

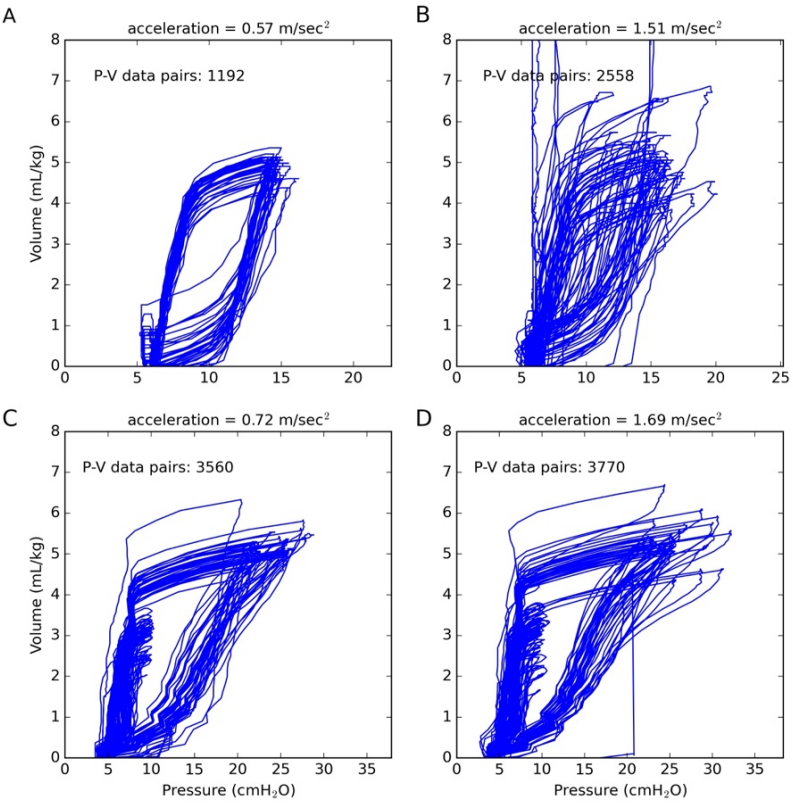

Figure 52. Composite pressure-volume loops over 1-minute periods with low and high vibration. The graphs show the loops of all respiratory cycles (mandatory or spontaneous) occurring during the minute. Median vibration is shown above the graphs. The number of pressure-volume (P-V) data pairs occurring during the period are shown in the chart area. Higher number of P-V data pairs correspond to more irregular loops. **A-B:** P-V loops of an infant born at 26 weeks of gestation who was 32 days old and weighed 1325 grams at the time of the transfer. **C-D:** P-V loops from a baby born at 36 weeks of gestation and transferred on the first day of life. During the period of intense vibration, PV loops became more irregular in both cases, with the number of P-V data pairs increasing.

6.2. Analysis of neonatal ventilator alarms

6.2.1. Patients included in the study

We collected and analysed ventilator alarms computationally from 50 infants mechanically ventilated using Dräger Babylog™ VN500 ventilators (157). The clinical team was aware of the study but not its purpose. The median gestational age was 28.5 weeks (range 23 - 42 weeks). The mean weight during the recordings was 1810 grams (range: 515 – 4,300g). Four babies had data collected for <12 hours and were excluded from analysis. Average duration of recordings was 2.5 days (range 22 to 165 hours). Total data collection was 116 days. Thirty-four babies (74%) received SIPPV, 14 (30%) SIMV, 14 (30%) HFOV, and 3 (6%) PSV. VG was used, at least part of the time, in 45. Many received more than one mode during the recording period.

6.2.2. Causes of frequent neonatal ventilator alarms

There were 27,751 alarms recorded, on average, 603 per patient, 238 per 24 hours of recording, ~10 alarms per patient per hour (range: 0.75 – 57.2). Cumulative statistics about number and duration of the frequent alarms are shown in **Table 29**. The type, frequency and duration of alarms varied between infants. Alarms of a similar kind were frequently clustered, sometimes >100/hour (**Figure 53A**). Some babies had over 10% of their recording time with one or more alarm active (**Figure 53B**). Alarms fell into 22 categories, of which, 8 caused ~99% of all alarm events (**Table 20**).

Table 29. Number and duration of the 8 most frequent ventilator alarms during the whole study, ordered by frequency. They represent over 99% of all alarm events.

Alarm category	Number	Number per 24 hours of recording	Duration per 24 hours of recording	Median alarm duration	Minimum alarm duration	Maximum alarm duration
Minute volume < low limit	7792	66.7	25.5 min	14.0 sec	1.0 sec	35 min
Tidal volume < low Limit	7734	66.3	16 min	6.0 sec	0.9 sec	24 min
Volume not constant	3676	31.5	18 min	10.0 sec	0.9 sec	1.8 hrs
Respiratory rate > high limit	2760	23.6	13.5 min	21.0 sec	1.0 sec	23 min
Tube obstructed	2437	20.9	1.7 min	3.0 sec	0.9 sec	216 sec
Minute volume > high limit	2376	20.4	11.6 min	10.0 sec	1.0 sec	4.33 hrs
Disconnection ventilator	476	4.1	100 sec	6.0 sec	1.0 sec	22.5 min
Check neonatal flow sensor	195	1.7	34 min	70.0 sec	2.0 sec	13.47 hrs

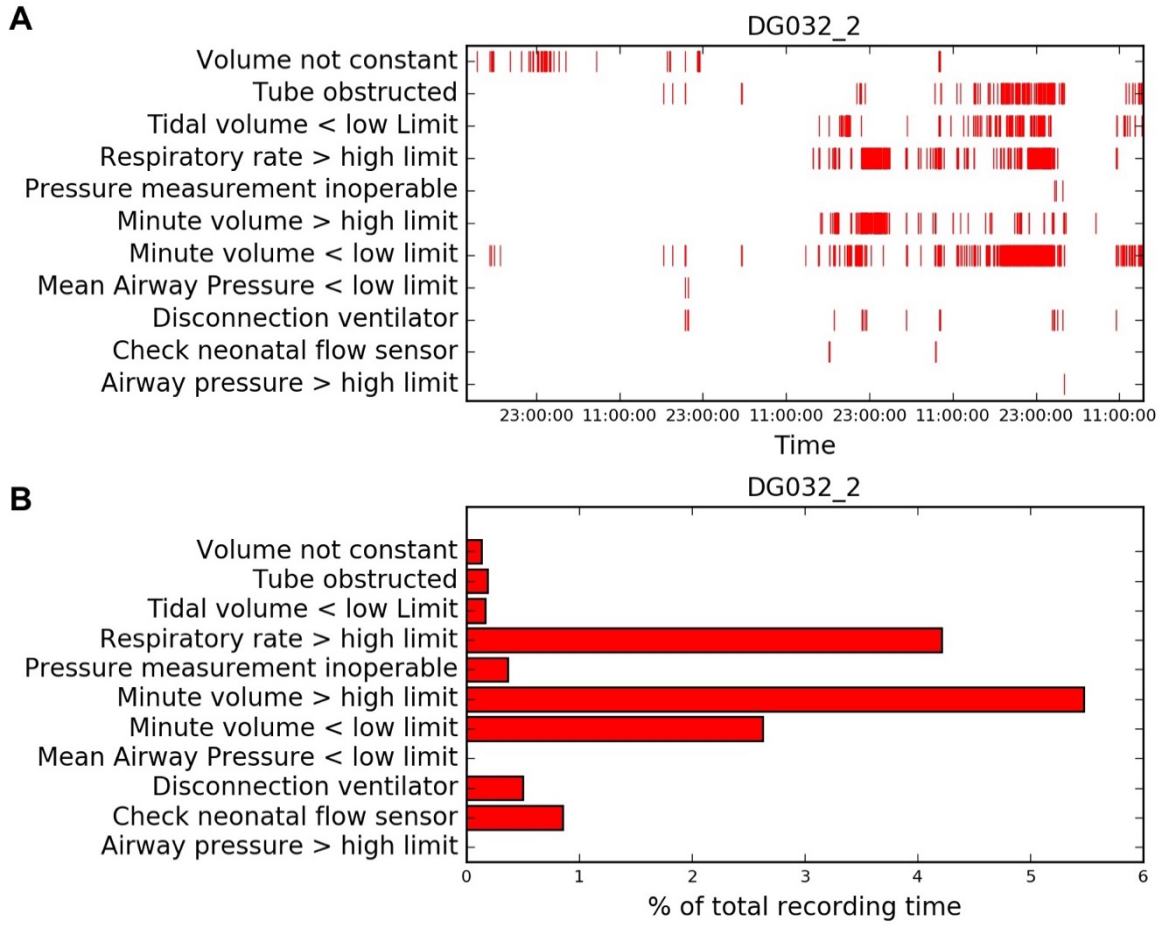

Figure 53. Individual alarm events from one baby' recording (DG032-2) over ~90 hours. Each small vertical line represents one alarm event. The horizontal labels on the left show the type of alarm. Some alarms occurred much more commonly than others and tended to cluster. **B:** This shows the proportion of the recording when different alarms were active.

6.2.2.1. Minute volume and respiratory rate alarms

Three alarms, where the user sets the alarm limits accounted for 46.5%: "minute volume < low limit" (7792 (28%) events), "minute volume > high limit" (2376 (8.6%) events)" and "respiratory rate > high limit" (2760 (9.9%) events).

The number of "minute volume > high limit" ("MV high") alarm events varied widely for different babies, even when normalised for 24-hour periods. In some it was uncommon, either because the MV hardly varied due to deep sedation or muscle relaxation, or because the alarm limit was set inappropriately high, sometimes even >1 L/kg/min in conventionally ventilated babies. In other cases, when the MV high alarm was set at an apparently physiologically meaningful level *and* there was significant variability in the MV, the alarm was triggered hundreds of times (**Figure 54A**). Interestingly, arterial blood gases during the two recordings with the highest number of high MV alarms did not show severe hypocapnia (lowest $PaCO_2$ were 4.8 kPa (36 mmHg) and 4.7 kPa (35 mmHg) respectively), but the blood gas measurements may not have coincided exactly with the high MV periods. The alarm triggering sometimes prompted staff to increase the alarm limit to very high levels. HFOV has a higher measured MV than conventional ventilation but occasionally the high alarm limit was not changed when the mode changed to conventional.

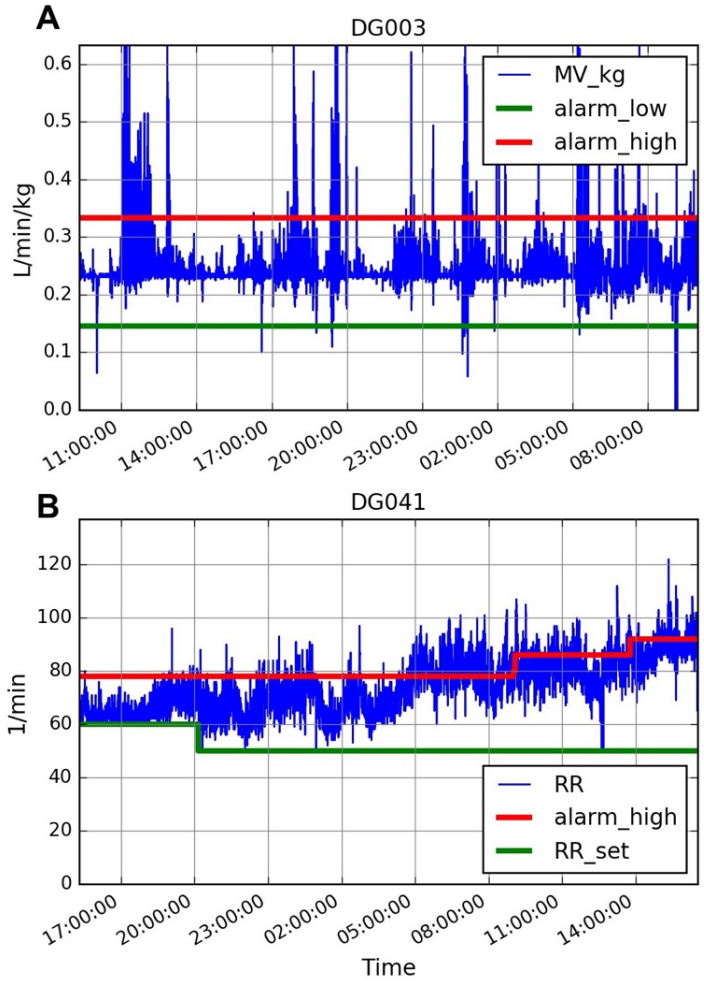

Figure 54. A: Recording of the minute volume for baby DG003 for ~24 hours. It also shows the upper and lower alarm limits set by the clinical team. When the minute volume went above or below those limits the alarm sounded. It can be seen there were many occasions when the MV was above the upper alarm limit. **B:** shows the variability of the respiratory rate for baby (DG041) ventilated with SIPPV mode over ~ 24 hours. It also shows the upper respiratory rate alarm limit and the set minimum (backup) respiratory rate, and how these were changed by the clinical team. When the respiratory rate went above or below those limits the alarm occurred. It can be seen the respiratory rate was frequently higher than the upper alarm limit.

There were cases when the "MV low" alarm was triggered over a hundred times. Sometimes, this was due to inappropriately high settings, e.g., set at >0.2 L/min/kg. In other cases, the MV variability was high, or fell below 0.2 L/min/kg. As many recordings were with VG mode and appropriate back-up rates, the expired tidal volume (VTe) must have been reduced during these periods. The "tidal volume < low limit" alarm often coincided with the MV low alarm (see **Figure 53A**).

The "respiratory rate > high limit" ("RR high") alarm was frequently triggered when an infant's breathing was over the set RR (**Figure 54B**). This occurred during both SIPPV and SIMV modes, even when the RR high alarm limit was >100/min. Some may have been triggered by condensed water moving in the circuit imitating spontaneous breathing.

6.2.2.2. Tidal volume <low limit alarms

Three frequent alarms were related to the set VTe not being achieved. The "tidal volume < low limit" (7734 (27.9%) events) occurred if the VTe was <90% of the set VTe for 8 consecutive inflations. The "volume not constant" (3676 (13.2%) events) and the "tube obstructed" (2437

(8.8%) events) alarms also refer to the VTe not being achieved and may sometimes refer to the same clinical event. These three alarms accounted for 49.9% of all alarm events and sometimes dominated the recording, or part of it. Failure to achieve the targeted VTe occurs with the VG mode and may be due to: (1) excessive leak around the endotracheal tube, (2) a low set Pmax so the pressure cannot increase enough to deliver the set VTe, (3) the baby splinting the abdominal muscles against an inflation and obstructing gas flow.

6.2.2.3. Other frequent alarms

The other two frequent alarms were: "disconnection ventilator" (476 (1.7%) events) and "check neonatal flow sensor" (195 (0.7%) events). While the disconnection alarm may signal accidental disconnection, in most cases it was triggered by ventilator circuit disconnection during endotracheal tube suctioning. The "check neonatal flow sensor" alarm can mean any flow sensor malfunction but it is usually caused by either corrupted calibration data that can be remedied by sensor recalibration, or the sensor is contaminated.

6.2.3. Duration of ventilator alarms

The median (IQR) alarm duration was 10 (4 to 21) seconds, defined as when alarm was active, irrespective of whether it was silenced or not. 26,106 (94.1%) alarms lasted <1 minute and 13,516 (48.7%) lasted <10 seconds (**Figure 55**). The median duration was very different for different alarms ranging from 1 to 277 seconds (**Table 29** and not shown). Of the seven frequent alarms, only the "Check neonatal flow sensor" alarm had a median time >30 seconds. The minute volume, ventilator rate, and tidal volume alarms were typically frequent and short and activated and inactivated usually before a clinician intervened.

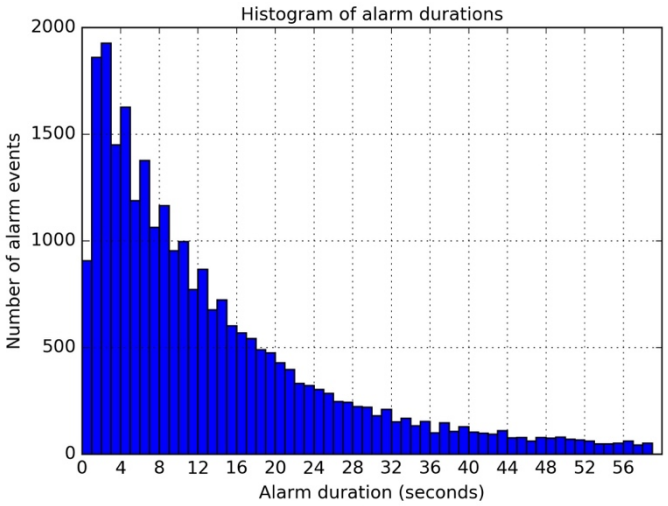

Figure 55. Histogram of alarm durations. Most alarm were short, lasting for less than 20 seconds. Alarms were considered active when the event triggering the alarm was present even if the alarm sound was silenced. Alarms longer than 1 minute are not shown on this graph but they are discussed in the text.

6.2.3.1 Very prolonged alarms

The duration of 86 alarm events was >10 minutes and 17 lasted >1 hour (**Table 30**). For example, the "minute volume > high limit" alarm of recording DG032 was continuously active for ~4 hours 20 minutes. This happened after the ventilator had been changed to HFOV mode but the high MV alarm limit stayed at 0.45 L/min/kg, the level used for conventional ventilation. This was much less than the >1 L/min/kg MV used during HFOV. Staff responded about 4 hours later by increasing the MV high alarm limit to 1.7 L/min/kg. This showed that

NICU staff can "adapt" to persistent alarms, with a potential risk to patient safety.

Ten out of the 17 alarms lasting for >1 hour were flow sensor alarms. This is a problem as an accurate flow-sensor is essential for correct VTe measurement during VG ventilation. It is therefore important to educate staff to respond promptly to these alarms.

Table 30. Alarm events lasting for more than 1 hour.

Rank	Recording	Alarm	Duration (seconds)
1	DG037	Check neonatal flow sensor	48496
2	DG007	Check neonatal flow sensor	43266
3	DG010	Check neonatal flow sensor	34963
4	DG037	Check neonatal flow sensor	28918
5	DG033	Check neonatal flow sensor	26796
6	DG017	Check neonatal flow sensor	23123
7	DG032	Minute volume > high limit	15579
8	DG015	Check neonatal flow sensor	12101
9	DG026	Check neonatal flow sensor	10472
10	DG042	Check neonatal flow sensor	6873
11	DG026	Check neonatal flow sensor	6486
12	DG022	Volume not constant	6408
13	DG050	Minute volume > high limit	6148
14	DG045	Check neonatal flow sensor	4926
15	DG040	Minute volume > high limit	4516
16	DG038	Volume not constant	4474
17	DG005	Volume not constant	4076

6.3. Computational analysis of neonatal waveforms and loops

6.3.1. The *Ventiliser* package

We developed *Ventiliser (20)*, a computational pipeline for segmenting neonatal ventilator data into individual inflations, their phases and sub-phases (see **Figure 20**). Spontaneous breaths between ventilator inflations are also recognized, if present. *Ventiliser* uses a rule-based algorithm as described in the Methods (**section 5.4.2**). *Ventiliser* generates reports in table format exported as csv files. The reports list all identified ventilator inflations and spontaneous breaths with start time and duration of the various flow and pressure states and sub-phases. Additional parameters such as inspiratory and expiratory time, lung inflation and deflation time, peak inspiratory and expiratory flow, inspiratory and expiratory tidal volumes are also reported. The timing of sub-phases allows the user to distinguish between synchronised and backup inflations (see **Figure 2**). The correlation coefficient between pressure and flow is also reported; spontaneous breaths between ventilator inflations (if present) are characterised by absent or negative correlation as in their case the positive inspiratory flow is associated with no increase or even some decrease of the pressure from PEEP level, unless they are pressure-supported.

Ventiliser also has an evaluation module which a user with appropriate programming skills can use for quality control of *Ventiliser's* output. It also includes a graphical user interphase (GUI)

capable of importing raw ventilator data. The GUI shows pressure and flow waveforms in a time window set by the user. The user can manually identify and label transition points between the flow and pressure states. The manual annotation can be exported and stored as a .csv file and compared with computational annotation provided by the pipeline. *Ventiliser* can be run on a mid-range personal computer with an approximate speed of 2 minutes per ventilation day (corresponding to 8.64 million data points) and the running time scales linearly with duration of the recording.

6.3.2. Algorithm validation

To evaluate the performance of the algorithm, three random 5-minute samples were extracted from longer recordings of three infants; two were with SIMV-VG and with SIPPV-VG. In all three the infant had spontaneous breathing effort and therefore interacted with the ventilator in a complex way. These recordings were not used during the development of *Ventiliser* (out-of-sample validation). The samples were manually annotated by a medical student using the GUI after receiving formal training about ventilator waveforms. The algorithm successfully identified >97% of the manually labelled flow and pressure states with a mean error between 10 and 40 milliseconds (representing 1 to 4 data points) for all except the expiratory hold start key point which had a mean error of 49.4 milliseconds (**Table 31**). Overall, the difference between the mean duration of sub-phases identified by the two methods was <50 milliseconds in 83.33% (25/30) of the tests.

Table 31. Overall performance of *Ventiliser* against manual annotations. This table has been compiled from annotation data of three different recordings from three patients.

	Number identified by algorithm	Number of manually annotated	% identified	Mean error (msec)
inspiration_initiation_start	924	934	98.93	14.4
peak_inspiratory_flow_start	926	938	98.72	12.1
inspiratory_hold_start	925	936	98.82	20.5
expiration_initiation_start	920	936	98.29	16.1
peak_expiratory_flow_start	920	932	98.71	22.1
expiratory_hold_start	905	916	98.8	49.4
pressure_rise_start	808	825	97.94	36.8
pip_start	804	824	97.57	17.8
pressure_drop_start	805	824	97.69	30.4
peep_start	793	814	97.42	23.8

6.3.2. Processing and in-depth analysis of neonatal ventilator data using Ventiliser

To demonstrate the utility of *Ventiliser* we present analysis of a 39-hour long ventilator recording obtained from a term infant ventilated using SIPPV-VG mode. The respiratory parameters calculated and displayed by the ventilator (i.e., respiratory rate, tidal volume, peak inspiratory pressure) are shown in data-rich time series plots (**Figure 56A-C**).

From the 14,044,274 pressure and flow data points *Ventiliser* identified 143,260 respiratory cycles: 128,663 ventilator inflations (mean: 55/min) and 14,597 unsupported spontaneous breaths. As the actual ventilator rate was between 60-65/min over the whole recording (**Figure 56A**), *Ventiliser* detected ~85-90% of ventilator inflations overall. We further analysed two 1-hour periods of the recording in more detail (**Table 32**). During period 1 the baby had some breathing effort, but the majority of inflations were initiated by the ventilator as the high back-up rate allowed only a short time window for the baby to trigger inflations by generating inspiratory (positive) flow. During period 2 stronger breathing effort appeared, there were more synchronised inflations and some unsupported spontaneous breaths also appeared. Moreover, during period 2 ventilator waveforms and loops became more variable and irregular (**Figure 57**).

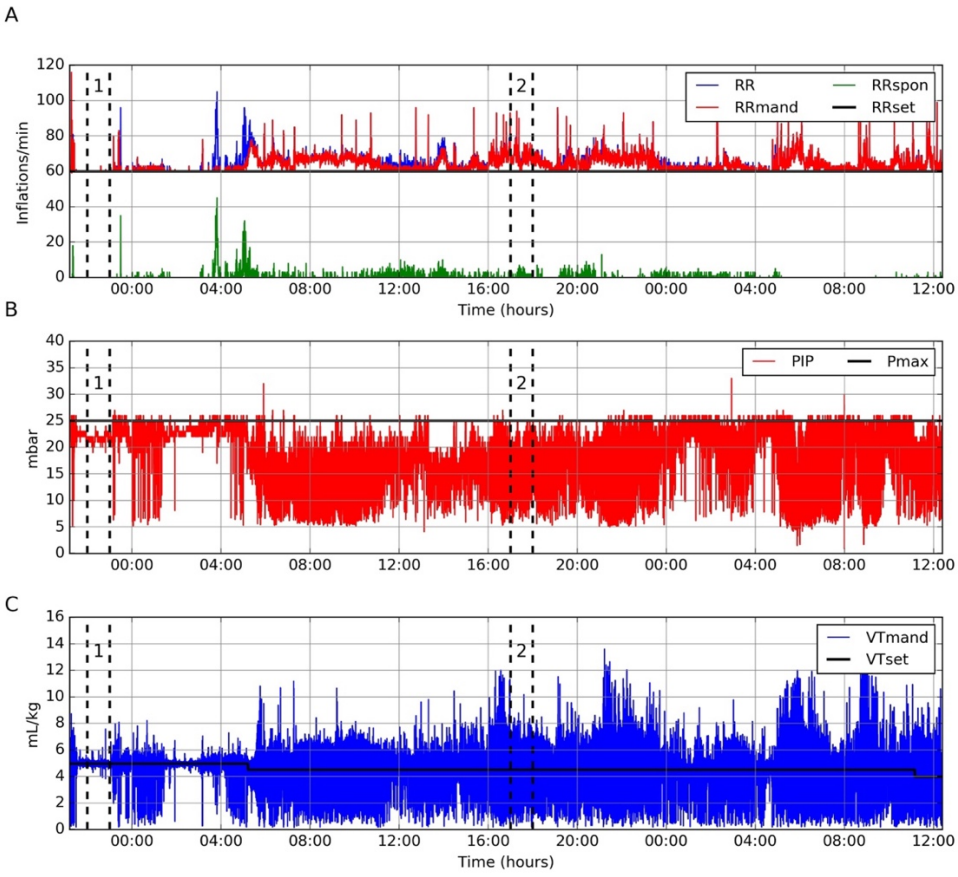

Figure 56. Reconstruction of ventilator trends from ventilator parameter data downloaded with 1 Hz sampling rate. Data were downloaded from a term infant ventilated for respiratory distress. The infant was ventilated with SIPPV-VG mode. Time series plots of ventilator rate (**A**), pressures (**B**) and tidal volume (**C**). After the first 4 hours the baby triggered more ventilator inflations (RRmand) than the ventilator backup rate (RRset). A few spontaneous breaths (RRspon) also appeared. These were ones which did not reach the trigger threshold (0.2 L/min) or fell to the refractory period of 0.12 seconds after a previous inflation (A). As this was VG ventilation the PIP shows large short-term variability, particularly when spontaneous breathing effort appeared (B). The leak compensated expired tidal volume (VTmand) also shows significant short-term variability and deviations from its target (VTset) when the infant was breathing, with tidal volumes <2 mL/kg and >10 mL/kg occurring frequently (C). Dashed lines and numbers show the two time periods studied in more detail.

Segmentation of inflations into sub-phases allowed for quantitative analysis of these sub-phases over the period (**Table 32**). For example, we have found that the actual pressure rise time was on average longer than the set value (80 milliseconds). During period 2, the median time spent with the pressure at the PIP level was significantly shorter and the pressure drop to PEEP level and lung deflation time were also significantly shorter. In accordance with this, during period 1 a larger number of inflations had an inspiratory hold (pressure at the PIP level with no air flow). Also, during period 1 more inflations had no expiratory hold, that is, the next inflation started immediately after deflation of the lung.

Table 32. **Characterization of ventilation inflations in a 39-hour long recording and in two 1-hour periods**. Periods are the same as on the graph of **Figure 56**. The respiratory rate increased, and more synchronised inflations appeared during period 2 when stronger spontaneous breathing effort was present.

	Whole recording	**Period 1 22:00-23:00**	**Period 2 17:00 – 18:00**
Duration (hours)	39.2	1	1
Ventilator settings			
Ventilator mode	SIPPV-VG	SIPPV-VG	SIPPV-VG
Set respiratory rate (1/min)	60	60	60
Inspiratory time (msec)	400	400	400
pressure rise time (msec)	80	80	80
Statistics returned by Ventiliser			
Number of respiratory cycles			
All cycles (n)	143,260	3,622	3,902
Synchronised inflations (n, %)	55,696 (39%)	1,496 (41%)	1,709 (44%)
Backup inflations (n, %)	72,967 (51%)	2,126 (59%)	1,590 (41%)
Spontaneous breaths (n, %)	14,597 (10%)	0 (0%)	6,03 (15%)
Duration of inflation sub-phases [a]	**Median (5^{th} - 95^{th} centile)**	**Median (5^{th} - 95^{th} centile)**	**Median (5^{th} - 95^{th} centile)**
Pressure rise time (msec)	210 (150 – 240)	210 (180 – 210)	210 (120 - 270)
PIP time* (msec)	150 (30 – 210)	180 (150 - 210)	150 (30 - 240)
Pressure drop time* (msec)	210 (120 – 240)	210 (210 - 240)	180 (30 - 210)
PEEP time (msec)	390 (150 – 480)	390 (360 - 420)	390 (90 - 480)
Lung inflation time (msec)	360 (270 – 420)	330 (300 - 390)	360 (210 - 450)
Total inspiratory time (msec)	360 (270 – 420)	360 (300 - 390)	360 (210 - 450)
Lung deflation time* (msec)	600 (360 – 690)	630 (540 - 690)	510 (300 - 660)
Total expiratory time (msec)	630 (360 – 720)	630 (600 - 690)	600 (300 - 720)
Occurrence and duration of inspiratory hold and expiratory hold			
Number of inflations with inspiratory hold** (n, %)	19,117 (15%)	1,783 (49%)	613 (19%)
Inspiratory hold duration (msec)	30 (30 - 120)	30 (30 - 90)	60 (30 - 150)
Number of inflations with expiratory hold** (n, %)	49,435 (38%)	1,014 (28%)	1,634 (50%)
Expiratory hold duration (msec)	60 (30 - 210)	60 (30 - 120)	90 (30 - 220)

[a] Only ventilator inflations (synchronized and backup) are included. Spontaneous breaths have been excluded as their timing is not controlled by the ventilator. Inflation sub-phases are defined in Tables 1 & 2.
* $p < 0.0001$ using Mann-Whitney U test, when comparing period 1 and 2.
** $p < 0.0001$ using Chi-squared test, when comparing period 1 and 2.

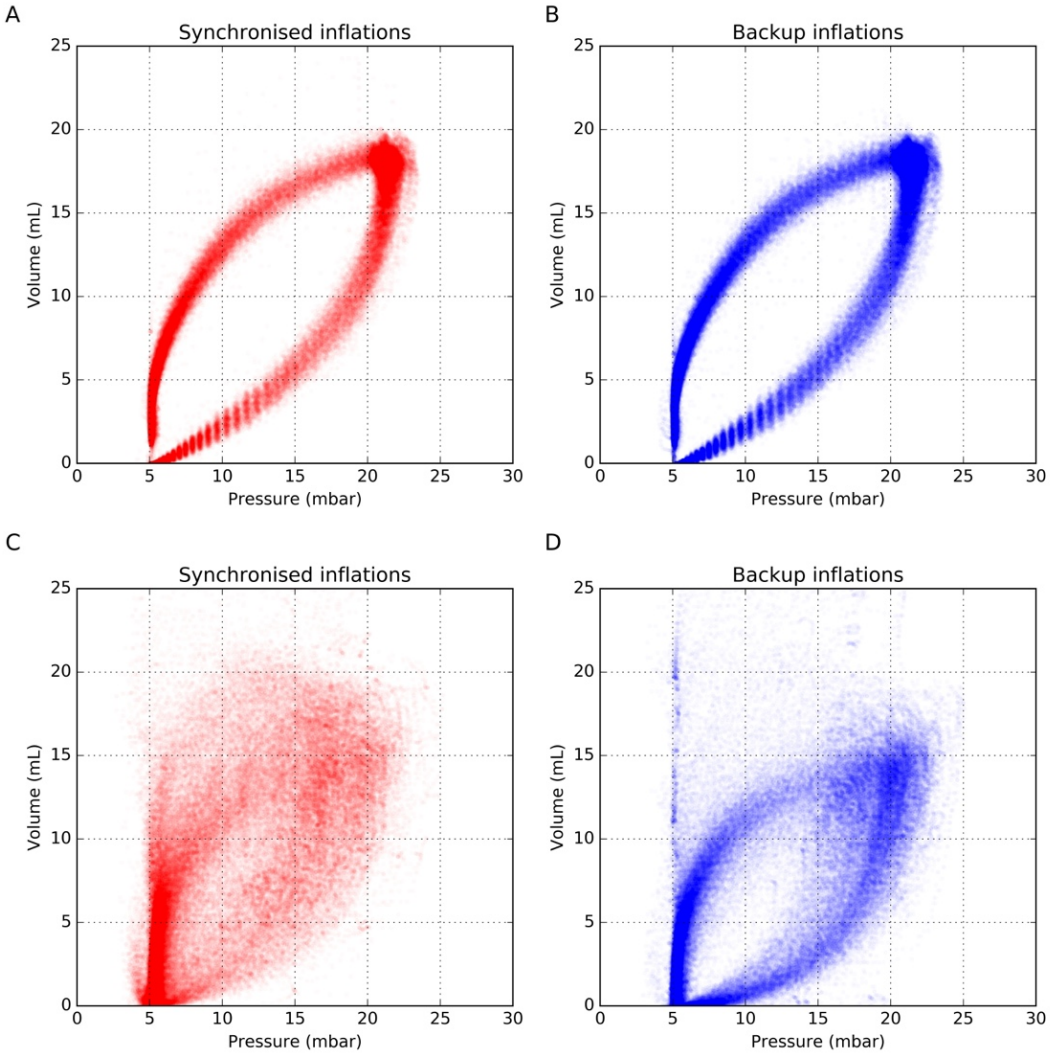

Figure 57. Reconstruction of ventilator loops and waveforms from downloaded ventilator flow and pressure data sampled at 100 Hz. Composite pressure-volume loops over two 1-hour periods. Each data point represents a single pressure-volume data pair. **A-B**. During period 1 regular pressure-volume loops are produced with little variability both for synchronised and for backup inflations. **C-D**. With stronger breathing effort of the baby (period 2) the waveforms become more irregular, there are more synchronized inflations requiring lower inflating pressures.

7. Discussion

7.1. Neonatal ventilator performance studies

We tested two different neonatal ventilator models (the Dräger Babylog™ VN500 ventilator and the fabian™ +ncpap ventilator) during their clinical use, on the neonatal unit and during emergency neonatal transport, respectively. We analysed how closely these ventilators maintain the expired tidal volume to the set target during VG ventilation in babies with different clinical characteristics. We also analysed ventilator performance in challenging situations, such as in hyperventilating infants or when there was a large leak around the ETT or when there was significant acceleration or vibration due to movement of the ambulance vehicle. We investigated how the user's choice of Pmax impacted of ventilator performance during VG ventilation.

We also studied some features which are ubiquitously available on modern neonatal ventilators but have not been studied in clinical research. One of them was the pressure rise time (PRT) which can be set in one way or other on all ventilators but there has been very little data published about it. We also reported on a complex adaptive ventilator mode (SIMV-VG-PS) frequently used on NICUs without any paper published about it.

The main strength of our studies is that they are based on patient population typically encountered on tertiary NICUs and that we used computational data retrieval with a high sampling rate. Our data collection method overcomes several limitations inherent to collecting data manually and/or with a low sampling rate, namely, observer's bias and failure to capture the complexity of these adaptive ventilator modes and patient-ventilator interactions. In addition, we have developed a computational pipeline using the Python computer language to process and analyse these data. This is important, as the amount of data analysed in our studies could not have been reproducibly processed with spread sheet program such as Microsoft Excel™.

The main limitation of the studies presented in this thesis is that they were observational. It is difficult to perform interventional studies in ventilated infants. Parents are less likely to give consent to interventional trials than to observational ones, particularly in critically ill babies Moreover, consent for interventional studies usually needs to be obtained before the inclusion and it is difficult and sometimes controversial to approach parents for consents soon after delivery of a very preterm or critically ill baby (181). In our observational studies on NICUs we used the deferred consent model (182) and ~85% of parents consented to continuation of ventilator data collection and to collecting clinical data. For the studies during emergency neonatal transport, the Research Ethics Committee waived the need for consent as it would not have been ethical to approach parents who were understandably distressed due to the planned emergency transfer of their baby, and contacting them in retrospect would have likely resulted in a low response rate.

Another limitation of our studies is that we did not look at clinical outcomes, similarly to most other neonatal ventilation studies (21). Studying clinical outcomes, particularly long-term outcomes such a BPD or neurodevelopmental outcome, requires significant human and financial resources, and there is usually considerable attrition rate. In addition, larger numbers of study participants are required for such studiers to have sufficient statistical power, because multiple factors influence long-term morbidities and the impact of individual factors such as respiratory management is limited. Finally, a particular concern regarding ventilator studies is

that by the time data about long-term outcomes become available (several years or even decades), the technology will have developed significantly and the results are not necessarily applicable to babies ventilated with the latest generation of ventilators.

Despite the limitations listed above, there is merit in ventilator performance studies on NICUs and during neonatal transfers because they provide clinicians with information about equipment and technology that they need to use every day, despite the lack of clinical evidence. Without such information available, busy clinicians have limited time to observe and study their ventilators and their knowledge in terms of the details of the complex and adaptive ventilator modes such is VG is limited (46). Without sufficient knowledge and time, they are unable to distinguish ventilator malfunctions from normal functioning, e.g., when the VT is significantly different from its target during VG ventilation (183). With the increasing availability of high sampling rate data from ventilators, I envision that the number of similar studies will increase.

7.1.1. Maintenance of tidal volume during volume guarantee ventilation

7.1.1.1. During conventional ventilation modes with VG

A study presented in this thesis was the first to analyse the VG function of the Dräger Babylog™ VN500 ventilator at the level of individual inflations (58); for the fabian™ ventilators, ours was the first study overall in infants (71). In both cases we found that, overall, the expired tidal volume was very close to the target VT, irrespective of the weight of the infant and whether the ventilator mode was SIPPV-VG or SIMV-VG. However, VTmand showed considerable short-term variability and in some cases even the average value was well below or above the targeted volume.

Different ventilators use different algorithms for VG; therefore, how well they maintain the tidal volume in principle may be different. In our studies with the Dräger Babylog™ VN500 and the fabian™ ventilators we found that the mean VTdiff was 0.6-0.7 mL/kg (58, 71), albeit with significant variability among recordings. In a study using SLE5000 ventilators with two different algorithms and combining SIMV and SIPPV inflations, the mean absolute value of VTdiff for the V4 algorithm was 0.4 mL/kg and for the V5 algorithm 0.3 mL/kg (43). The authors did not report their Pmax settings or effect of ETT leak. However, different levels of leak and different Pmax policies on different units make the comparison of ventilator performance in patients difficult as these factors influence significantly how well tidal volume can be maintained during VG modes (see **section 7.1.2**. and **7.1.3**.). Moreover, irrespective of the set parameters, the tidal volume can exceed the target value significantly if the baby takes large breaths from the ventilator circuit during synchronised inflations (see **section 7.1.4**.).

In our study with fabian™ ventilator there was only weak correlation between tidal volume and blood pCO_2 values. This is explained in part by the different ventilator rates at the time of different blood gases. However, the correlation between minute ventilation (that included both ventilator and spontaneous breaths) and pCO_2 was also weak and statistically not significant. One factor affecting the correlation between ventilator parameters and blood gases is that we used capillary blood gases and capillary CO_2 levels may not accurately reflect the arterial $PaCO_2$ in all cases. However, several papers have also reported no correlation or only poor inverse correlation of VT or MV with pCO_2 values in ventilated infants even when only arterial blood gases were used (43, 184, 185, 186). This is not surprising, as alveolar ventilation is

affected by anatomical and functional dead space and uneven lung perfusion. Finally, there is evidence that the current simple physical model of bulk gas flow may not fully explain CO_2 elimination even during conventional ventilation, because very small babies (<800 grams) can be ventilated using tidal volumes less than the anatomic dead space, and they still have normal pCO_2 (184, 187). Interestingly, only in half of the cases were the expired tidal volume within the generally accepted 4-6 mL/kg range even when pCO_2 was normal.

7.1.1.1.1. The complex case of SIMV-VG-PS

SIMV-VG-PS is arguably the most complex ventilation mode routinely available on today's neonatal ventilators. During SIMV-VG-PS, two different kinds of respiratory cycles co-exist: (1) time-cycled and volume targeted mandatory ventilator inflations (triggered by the baby or initiated by the ventilator), and (2) pressure-supported spontaneous breaths which are patient-triggered, flow-cycled and pressure-controlled cycles (see **section 3.3.2.2.3.)**. SIMV inflations have a fixed Ti, set by the user, while the pressure supported spontaneous breaths have variable Ti determined by respiratory mechanics. The PIP of SIMV-VG inflations (PIPmand) is variable, adjusted by the ventilator to deliver a target expired VT, while with PS support the peak inspiratory pressure of spontaneous breaths (PIPspon) is fixed, as set by the clinician. The respiratory rate of SIMV inflations is fixed, while babies can have variable number of pressure-supported spontaneous breaths between them.

During SIMV-PS without VG, the ratio of PIPspon and PIPmand is fixed, although the expired tidal volume can be highly variable for both, due to patient-ventilator interactions, variable leaks around the ETT and changes in lung mechanics. During SIMV-VG-PS, the VG algorithm automatically reduces PIPmand if the expired tidal volume exceeds the set target (see **Figure 11**). As the PS level is not weaned automatically, and it is usually only infrequently changed by clinicians, the PIPspon/PIPmand ratio varies, with resultant changes in the ratio of spontaneous and mandatory tidal volumes.

We found that in daily clinical routine it is not possible to consistently link the PS level to the PIP of VG inflations by manual adjustments. PIPspon/PIPmand was highly variable, and sometimes the PIP of pressure supported spontaneous breaths exceeded the PIP of ventilator inflations. The VT of the spontaneous breaths was also frequently larger than the VT of VG inflations. This suggests that tidal volume control during SIMV-VG-PS is worse than during SIPPV-VG or PSV-VG, when essentially all respiratory cycles are volume targeted, although this has not been tested in clinical studies.

The other concern about SIMV-VG-PS is that clinicians may not notice when the set PS level results in higher PIPspon and VTspon than the PIPmand and VTmand of VG inflations, respectively. In this situation, if the set mandatory ventilator rate is reduced, e.g., in response to hypocapnia, minute ventilation will paradoxically increase and pCO_2 may drop further.

Interestingly, when we considered only those minutes when PIPspon/PIPmand ratio was close to 66%, VTspon and VTspon/VTmand ratio were lower, but their variability remained considerable. This is most likely due to the breath-to-breath variability in the baby's breathing effort and interactions with the ventilator.

In adults, progressively decreasing PS levels were associated with increasing breathing rate but no change in pCO_2 (188), and similar findings have also been reported in neonates (34). For

adults, a proprietary automated weaning protocol (SmartCare™, Dräger, Lübeck, Germany) has been developed to adjust PS level based on respiratory rate and $tcCO_2$, and it has been shown to reduce the duration of mechanical ventilation (189, 190). In our study, when PIPmand was low compared to the PS level, babies had a higher respiratory rate. During these periods babies also had larger spontaneous tidal and minute volumes but their CO_2 was not different. One possible explanation is that the respiratory rate increased as the babies were "under-supported", that is, did not receive high enough PIP and VT during the mandatory VG inflations. However, the rate and depth of spontaneous breaths also depend on other factors such as the level of sedation and neuromuscular maturity of the infant (191). It is also possible that the lower PIPmand was secondary in babies who had primarily a strong respiratory effort.

Flow-cycled pressure supported spontaneous breaths had significantly shorter Ti than time-cycled mandatory ventilator inflations. The significance of this is uncertain. During time-cycling, when the set Ti is longer than the time required for lung inflation, gas flow stops, resulting in end-inspiratory hold, with the pressure maintained at the PIP level. The presence of end-inspiratory hold increases mean airways pressure, and there may be continued gas movement within the lung between alveoli with different time constants (192). However, the impact of inspiratory hold on gas exchange has not been reported.

In summary, we found that during SIMV-VG with PS, it is difficult to manually adjust the PS level to the automatically controlled PIP of VG inflations and to achieve stable tidal and minute volumes. Clinicians should consider using SIPPV or PSV with VG, where the VG algorithm controls the tidal volume of almost all respiratory cycles (see **section 3.3.2.1**.). SIPPV is associated with lower work of breathing than SIMV with or without PS (33). SIPPV or PSV are also associated with shorter duration of mechanical ventilation in neonates than SIMV (21, 28).

7.1.1.2. During HFOV-VG

Ours was the first paper reporting a detailed analysis of ventilation parameters when using HFOV-VG over long periods, with millions of data points collected and analyzed. We found, as expected, that during HFOV-VG the ventilator tightly controls VThf while the pressure amplitude varies widely. The tight control of VThf and auto-weaning of the amplitude may be particularly useful when the respiratory mechanics changes rapidly such as after surfactant therapy, drainage of a pneumothorax or treatment with sedation and muscle relaxation (see **Figure 44**). Without VG these events could lead to excessive oscillations and hypocapnia, unless the clinical team responds and reduces the amplitude promptly.

Our data show that despite the good overall VThf control there is frequently significant short-term variability of oscillation volumes during HFOV-VG. As previous studies collected data with much lower sampling rate, most of this variability was not captured (97, 98). In our experience this short-term variability of VThf depended more on the presence or absence of patient-ventilator interactions, that is, the baby's spontaneous breathing activity or movements than on whether volume guarantee was used or not.

The range of VThf used during our observational study was wide. Traditionally, HFOV is thought to operate with tidal volumes less than the dead space by using other physical mechanism than bulk flow (193, 194). In some of our recordings VThf >3 mL/kg was used during HFOV-VG with normal arterial CO_2 levels. This suggests that tidal volumes during

HFOV and conventional ventilation represent a continuum and they may share some of the physical mechanisms of gas exchange, as reported by others (82).

We found that in babies with a wide range of weight, even weight-corrected VThf and DCO_2 (see **section 6.1.5**.) showed only weak inverse correlation with pCO_2. Spontaneous breathing during HFOV may have contributed to gas exchange to a different extent in different babies. Correlation between VThf and pCO_2 was sometimes poor even in gases from the same patient. This may have been caused by variable spontaneous breathing effort or lung disease progression or recovery during the consecutive blood gases. Because of this we think close monitoring of CO_2 using transcutaneous probes and regular blood gases remains important during HFOV-VG.

Interestingly, in our study there was no significant difference between the correlation coefficients for VThf and DCO_2, even though traditionally DCO_2 is considered to be the best predictor of CO_2 elimination during HFOV. This may be in part due to the limited range of frequency used in our recordings (7-12 Hz). Targeting a weight-corrected DCO_2 (see **section 6.1.5**. and (87) may be a better option when using a wide range of frequency settings. However, clinicians may be more familiar with controlling tidal volumes rather than DCO_2. Based on our data, we suggest starting HFOV-VG with 2-2.5 mL/kg VThf with close monitoring of CO_2 levels, as many infants will actually require VThf lower than 2 mL/kg. VThf can then be weaned in small steps (by no more than 0.1 mL/kg at a time), as it is still more closely related to pCO_2 than the amplitude during traditional HFOV.

Volume guaranteed conventional ventilation has been shown to reduce death or bronchopulmonary dysplasia as well as several complications (e.g., hypocapnia, pneumothorax, neurological damage) in preterm infants (44). While this does not necessarily mean the VG during HFOV offers similar advantages, it is feasible that by controlling the tidal volumes and pCO_2 better, it protects the lung and the cerebral circulation. In fact, clinicians using “traditional” HFOV are aware of the importance of tidal volumes, and develop a “semi-quantitative” strategy by setting the amplitude at a level where they believe the chest oscillations are deemed “adequate”. Pragmatically, using HFOV-VG automates the control of the amplitude and prevents rapid changes in ventilation and CO_2 clearance.

Since publication of our paper (80), HFOV has become more frequently used on NICUs, although there are still no published studies showing that it actually improves clinical outcomes. Nonetheless, as such information is difficult to obtain and it is rarely available for other ventilation modes either (see **section 3.3.2.1.5.**), in the author’s opinion, it is justifiable to use HFOV-VG routinely during clinical care.

Recently, HFOV-VG has been used with very high frequencies (>15 Hz) in very preterm infants with RDS as primary mode of mechanical ventilation (95, 195). As small babies require small tidal volumes (in absolute measures, that is, in mL), the low VThf can be delivered with very high frequency even by the modern ventilators, whose physical oscillation performance is usually week compared to the Sensormedics ventilator which was traditional used for HFOV (104). As part of a quality improvement program, this strategy has improved long-term pulmonary outcomes; however, the program also included other interventions, which could have contributed to the better outcomes (95). More clinical studies will need to clarify if the use of HFOV-VG is associated with improved long-term clinical outcomes.

7.1.1.2.1. How to interpret DCO_2

DCO_2 is ventilator parameter calculated as frequency x VThf x VThf, available on modern oscillator displays (see **section 3.4.3.3.**). During HFOV, DCO_2 has been considered to be an indicator of CO_2 elimination the same way as minute ventilation during conventional ventilation (72). However, there have been no studies about how to interpret DCO_2 values from different babies.

In a study presented in this thesis (87), we found no correlation between uncorrected DCO_2 and pCO_2. However, when DCO_2 was corrected to the square of body weight, there was a significant, albeit weak, inverse correlation. When analysing gas exchange during HFOV in rabbits, Boynton *et al* also used weight-corrected tidal volumes and found an inverse correlation between $paCO_2$ and DCO_2, see Figure 3 in (193). However, papers describing HFOV and DCO_2 in neonates have used uncorrected VThf and DCO_2 (97, 98, 195).

We found that if the DCO_2corr was >50 $mL^2/sec/kg^2$, the probability of significant hypercapnia (pCO_2 >8 kPa, that is, >60 mmHg) was 17.5% and if DCO_2corr was >60 $mL^2/sec/kg^2$ it was <10%. Therefore, when starting HFOV, clinicians should not routinely use settings resulting in DCO_2corr >60 $mL^2/sec/kg^2$. Moreover, we found an inverse correlation between $VThf^2$ and even VThf and pCO_2, even though the HFOV frequency in our recordings varied between 7-12 Hz. Despite using a different ventilator model to deliver HFOV, our results are in line with the findings of Dimitriou *et al* (196), suggesting that VThf >2.5 mL/kg is rarely needed to avoid hypercapnia.

The inverse correlation between DCO_2corr and pCO_2 was weak. There are several possible explanations for this. The DCO_2 formula was originally developed based on experiments done in dogs (197), rabbits (193) and mathematical calculations (198). It is possible that the "true" DCO_2 correlating well with pCO_2 should be calculated as $DCO_2 = (Hz)^x$ x $(VThf)^y$ where x and y are different from 1 and 2, respectively, and they may be fractions (108, 198, 199). Moreover, x and y may be different for different oscillators and can also vary among different patients depending on their weight or lung pathology. The instrumental and anatomic dead space account for approximately half of the tidal volume during conventional ventilation, which means that with the lower oscillation volumes (VThf), a large proportion of alveolar CO_2 will not be immediately exhaled. A baby needing HFOV may have inhomogeneous alveolar ventilation and ventilation-perfusion mismatch, so it is expected that the correlation between DCO_2 and pCO_2 will not be good. The movement of gas in the lung is very different between conventional ventilation and HFOV and this is likely to influence the relationship between VThf and pCO_2 and the correlation between DCO_2 and pCO_2.

Although using weight-adjusted VThf and DCO_2 would be preferable on neonatal ventilator displays this may not be practical without significant changes to ventilator "checks and balances" to ensure that the correct weight is entered. However, when a particular DCO_2 value is interpreted or targeted by clinicians, weight-correction using the square of the current body weight should be used, as it is in conventional ventilation, when tidal volumes are interpreted as mL/kg. New research studies should report DCO_2 as weight corrected.

7.1.2. The impact of pressure rise time

We analysed how different pressure rise times change the pressure waveforms, alter ventilator parameters and affect blood gases. We found that our primary outcome, ET-CO_2, was not significantly different during short or long PRTs. Our findings are not in line with those of Hurley & Keszler who, in a bench experiment, using the same ventilator model as us found that a shorter PRT and the associated higher flow rate resulted in better CO_2 elimination than a longer PRT and the associated lower flow rate (82). There are several possible explanations for this.

On older ventilator models PRT is controlled implicitly by setting the circuit flow rate ("bias flow") that is maintained throughout the whole respiratory cycle. On the VN500 ventilator, the PRT ("slope time") can be set directly. In this case PRT is controlled by two factors: the flow during inspiration and the expiration valve. During the pressure rise from PEEP to PIP, the ventilator increases the circuit flow as needed to reach the pressure plateau within the PRT. When PIP is reached, the circuit flow automatically returns to the base flow of 6L/min for the rest of inspiration and for the whole expiration. However, if the 6 L/min baseline circuit flow results in a shorter PRT than as set by the user, the expiratory valve closes more slowly to allow for a longer PRT rather than the flow decreasing below 6 L/min (Thomas Krueger, Dräger Medical, personal communication). Moreover, we do not know the circuit flow during the pressure rise, only the average circuit flow obtained with 1 Hz sampling rate. Therefore, we cannot compare our findings with those Hurley & Keszler who used set flow rates.

It is also possible that the duration of epochs (15 minutes) was not long enough for the ET-CO_2 to rise or to drop significantly. However, it has been shown that ET-CO_2 changes very quickly with changes in ventilation or cardiac physiology, e.g., during cardiac arrest or return of circulation after resuscitation (200). Moreover, we did not find a consistent increase or decrease in ET-CO_2 during any of the epochs. Another possibility is that the measured ET-CO_2 underestimated $paCO_2$ as it can happen particularly with the high (>60/min) respiratory rates observed in our study (201). However, the ET-CO_2 values showed a good correlation with $paCO_2$ before the interventions.

Finally, during SIPPV-VG the ET-CO_2 did increase with increasing PRT: it was 0.41 kPa higher with 0.4 s PRT than with 0.08 s. There was also a small increase in SpO_2. Due to the small number of the participants, our study may have been underpowered to demonstrate that these increases are statistically significant. The standard deviation of ET-CO_2 was larger than the expected 0.5 kPa, ranging between 0.57 – 0.76 kPa. In a similar group of preterm infants but using main stream capnography, Lin *et al*. found an even higher variability in ET-CO_2 values: the SD was 0.95 kPa before surfactant treatment and 1.24 kPa after surfactant (202). Assuming a SD of 0.76 kPa it would have required a sample size of 29 to demonstrate that the obtained 0.41 kPa difference is significantly different at the $p<0.05$ level, and it would have required a sample size of 40 to demonstrate equivalence with 90% confidence and with a power of 80%.

We also analysed the effect of different PRTs on ventilator parameters. The targeted tidal volume was reliably delivered at each different PRT: the mean difference between the actual and targeted leak compensated expired VT was <0.5 kPa in each epoch in each mode. This was most likely because the VG mode was being used to help deliver the set tidal volumes. There was also no difference in respiratory rate or minute volume. This was probably because SIPPV and PSV are modes that trigger inflations with every patient breath reaching the triggering

threshold. Therefore, the ventilator rate is largely determined by the baby's respiratory rate if they are frequently breathing faster than the set backup rate. In PSV-VG mode, shorter inspiratory times were observed during short PRTs and were associated with higher peak inflating pressures, presumably due to larger inflating pressure being required to deliver the targeted tidal volume in less time in volume guaranteed mode. This was not seen during SIPPV-VG as the set Ti was 0.4 s in each epoch. However, during SIPPV-VG with a short PRT, the 0.4 s Ti was frequently associated with an inspiratory hold as shown on **Figure 7A.**

During SIPPV-VG, mean airway pressure was higher during shorter PRTs. This was most likely due to the rapid rise in pressure with the same Ti resulting in a higher MAP, which equals the area under the pressure curve, as has also been suggested by others (24). There was no difference in MAP during PSV-VG despite the short PRTs being associated with higher PIPs, because they were also associated with shorter Ti and hence the area under the pressure curve corresponding to MAP was not larger overall. We argue that during volume guarantee ventilation the relationship between PRT (or circuit flow) and MAP is complex, as the PIP is modulated by the VG algorithm in order to achieve the set tidal volume, and the required PIP is influenced by the circuit flow and, in the case of PSV-VG, the variable inspiratory time.

A limitation of our study is that it did not examine long-term outcomes, only ventilator parameters and blood gases. We did not observe any clinical deterioration or adverse event with any of the PRTs in any mode. We have not found any original reports investigating the clinical consequences of using different PRT or flow rates in human infants. The lamb experiments of Bach *et al* (25) found evidence of lung injury only at a much higher inspiratory flow rate (18L/min) than what is achieved in human infants even with very short PRTs (<0.1 second) and circuit flow rates between 4-8 L/min did not alter cytokine release in tracheal aspirates of ventilated babies (27). Therefore, we feel that we cannot make an evidence-based recommendation to avoid short PRTs or to use a particular PRT value.

Our study provides evidence, however, that neonatologists can safely use considerably longer PRTs than the frequently used ~0.1 seconds which results in square-like pressure waveform. There is a theoretical concern that a long PRT and the associated low inspiratory flow rate could result in insufficient lung inflation. In case of SIPPV-VG mode, if the lungs were insufficiently inflated, the target tidal volume would not be delivered, and the ventilator would increase the PIP. We found that even with a PRT being as long as the set Ti (0.4 seconds), the PIP was not higher (see Table 2). We also showed that during PSV-VG an increasing PRT (and hence decreasing the inspiratory flow rate) results in a longer Ti and lower PIP as it has also been found in lambs by others (26). Increasing the Ti by increasing the PRT could allow clinicians to avoid the very short inspiratory times sometimes seen during PSV, particularly in babies with stiff lungs.

7.1.3. The impact of Pmax during volume guarantee ventilation

In our study (37) we showed that PIP fluctuates significantly during VG as the babies breathe. Due to this variability the "working PIP" can be difficult to determine and a local protocol of keeping Pmax 5 mbar over the working PIP can be difficult to implement even if the Pmax is reviewed frequently. Moreover, we showed that if Pmax is set only 5 mbar above what is clinically considered to be the working PIP, delivery of tidal volume will be limited frequently and low tidal volume alarms will be triggered. These effects can be considerably reduced by increasing the Pmax higher above the working PIP.

However, there are several concerns about keeping the Pmax at a higher level. Some clinicians are cautious because they are concerned about barotrauma. It is now considered that volutrauma and atelectotrauma are more damaging to the lungs than barotrauma and that a high PIP with a VT in the normal range is unlikely to injure the lungs (203, 204, 205, 206, 207, 208). With VG the PIP only increases when the VT is below the target. Our analysis showed that on average, the VT is very close to the target (within 0.1 mL/kg) even for those inflations when the Pmax is 15-20 mbar above actual PIP. In addition, during VG the Dräger Babylog™ VN500 ventilator has a safety program which stops ventilator inflation immediately if the VTi is >130% of the target VT (40). For these reasons, during VG a high PIP is very unlikely to cause a high tidal volume. When the tidal volume does rise significantly above the target VT this is due to the baby actively taking a breath that is higher than VTset. When it happens during consecutive inflations, the VG protocol of the ventilator progressively reduces the PIP; therefore, most inflations with high tidal volume are associated with low PIP not a high one (36, 41).

Another potential concern is that as VTV usually targets the expired tidal volume, if there is a large leak around the endotracheal tube the effective tidal volume (volume in the lungs at the end of inflation) will be somewhat larger than VTset due to the expiratory component of the leak (40). Some clinicians may want to avoid this by keeping Pmax relatively low. However, this will result in frequent ventilator alarms as the PIP will quickly reach Pmax if VTmand is below VTset due to excessive leak. In our study this was not a concern as we used the leak-compensated mode of the VN500 ventilator (58). However, leak-compensated volume targeting may not be available on other ventilators or they may use different algorithms.

The most significant concern about setting Pmax at a high level is potentially delayed recognition of significant clinical events such as slippage or obstruction of the ETT, pneumothorax or worsening lung compliance. The recommendation of keeping Pmax 5 mbar above working PIP is not based on safety studies or clinical evidence and in the absence of clinical outcomes our study also cannot make recommendations as to a particular Pmax level. There will always be a trade-off between potentially delayed recognition of clinical events on one side and limited tidal volume delivery and frequent alarms on the other. Frequent alarms represent a clinical risk due to alarm fatigue and staff failing to address the cause of the alarm (157). We suggest that Pmax level has to be determined by local protocol with consideration given to NICU setup, nurse numbers and usual patient population. Moreover, it is unlikely that one single recommendation would be ideal for all NICU patients as older preterm babies with evolving or established bronchopulmonary dysplasia are prone to splinting of the chest and have more variable PIP than preterm infants on the first couple days of life (36, 81, 209). If PIP frequently reaches Pmax, clinicians should assess the baby and the ventilator to see if there are correctable reasons for a high PIP. If no cause is found, other than very stiff lungs, then the Pmax can be increased.

7.1.4. The impact of leak around the endotracheal tube

Traditionally, it has been held that neonatal volume guaranteed ventilation can be continued with leaks <50% (36), because with more leak around the ETT, the expired tidal volume remains below VTset and PIP is progressively increased to the level of Pmax, resulting in constant ventilator alarms (**see section 3.3.3.3.**). However, this has not been studied quantitatively in ventilated babies.

We analysed how two neonatal ventilators for their performance during VG modes with significant leak around the ETT (58, 71). We found that fabian™ +nCPAP evolution ventilator indeed maintained the target tidal volume up to 50% leak (**see Figure 30**). For the Dräger Babylog™ VN500 ventilator, without leak compensation the limit was also 50%. However, with leak-compensation, the VTset was maintained at all leaks until >80% when some overshoot occurred (**Figure 25**).

Leak compensation is not unique to the Dräger ventilators but it is offered by most modern neonatal ventilators. However, the leak compensation mechanisms used by different ventilators and manufacturers are very different (see **section 3.3.3.3**.). Targeting the leak-compensated expired tidal volume during VG is unique to Dräger ventilators, and it may be responsible for the better performance of the VG during >50% leakage.

Interestingly, our analysis of the Dräger Babylog™ VN500 ventilator showed that when leak compensation was not used and the leak was >70%, the Pdiff was progressively increasing rather than decreasing, as initially expected (**see Figure 25C**). We speculate that with excessive leak and VTmand below VTset, the ventilator's algorithm is still trying to generate a pressure as high as Pmax to deliver the target VT; however, without leak compensation it may be unable to generate this pressure due to the excessive leak. With leak compensation the Pdiff remained stable even in the presence of large leak.

The pCO_2 values were marginally higher with leak compensation but we think this finding has little clinical significance. In principle, the pCO_2 is expected to be higher with leak compensation because when using the same VTset the ventilator delivers a slightly lower effective tidal volume with leak compensation than without since the computed value for the expiratory leak is taken into account. However, this finding needs to be interpreted with caution because CO_2 exchange is influenced by several factors. Of note, the groups were not matched for clinical characteristics and collection of blood gases was based on the decision of attending clinicians. Thus, sicker infants may have had disproportionally more blood gas samples.

We also analysed the impact of leak during HFOV. Correlation between weight-corrected DCO_2 and pCO_2 was better if we only included blood gases when leak around the ETT was <10% (**see Figure 46**). We speculate that leak may impact on HFOV in different ways: it may impair its gas exchange mechanisms but it may also improve CO_2 elimination by washing out the equipment dead space as described (210). In any case, even weight-corrected DCO_2 values need to be interpreted with caution if there is a significant ETT leak.

7.1.4.1. How to manage babies with a large leak around the tube

If an infant remains stable with a large (>50%) endotracheal tube leak with low FiO_2 requirement, normal blood gases and consistent breathing effort, this author argues that there is a significant chance that the baby can be successfully extubated and treated with non-invasive respiratory support, although this has not been tested in published studies. However, it also needs to be considered if the baby will be able to maintain an open airway after extubation, for example in cases of craniofacial anomalies. In babies who deteriorate in case of a large leak with desaturations and/or require high FiO_2, reintubation with a larger endotracheal tube is recommended. Again, consideration needs to be given if the previous intubation was difficult as smaller than optimal tubes are sometimes inserted after multiple

unsuccessful attempts. If intubation is expected to be difficult, tolerating a larger leak even with high FiO_2 requirement may be preferable until specialist help arrives. Sometimes, advancing a tube a little will reduce the large leak a bit, but it is important to avoid selective intubation of the right main bronchus. Of note, accidental extubation with the ETT tip in the pharynx can also mimic a very large leak and should always be ruled out.

7.1.5. The impact of patient respiratory effort during mechanical ventilation

Infants breathe spontaneously by intermittently lowering the pressure in their pleural cavity below the atmospheric pressure (or below the actual PEEP, if PEEP is used). Without ventilator support (i.e., self-ventilating or on CPAP) they do all the work of breathing. The ventilator can contribute to the work of breathing by providing positive pressure (above the actual PEEP level) at the airway opening intermittently. The work of breathing done by the ventilator is directly proportional to the difference between the PIP and the PEEP (inflating pressure, Pinfl), and it is also directly proportional to the number of ventilator cycles per minute.

During adaptive ventilation modes, which detect and respond to patient signals, the ventilator can adjust its contribution to the work of breathing along two axes independently: (axis 1) by changing its inflating pressure in response to patient signals and/or (axis 2) by changing the number of respiratory cycles it contributes to in response to patient signals. The ventilator can respond by changing its inflating pressure in response to changes in the strengths of the patient's breaths. Similarly, the number of cycles the ventilator is responding to may be related to the frequency of patient's breathing effort. However, more sophisticated signal-response relationships are also possible, such as mandatory minute ventilation (MMV) (111, 211).

The relationship between patient breathing and ventilator contribution during different ventilation modes can be positive, absent or negative along both axes. For the inflating pressure, a positive relationship means that the stronger effort the baby is generating, the higher inflating pressure is used by the ventilator; a negative relationship means the opposite. For the respiratory rate, a positive relationship means that the higher the patient's own respiratory effort, the more breaths are assisted by the ventilator using a positive inflating pressure.

Ventilator modes can be characterised and classified according to their relationship to the patient's breathing effort along these two axes (**Table 33** and **Figure 58**).

Modes with positive relationship in both domains or with positive relationship in one and absent relationship in the other (PPS, PAV, NAVA, SIPPV, PSV, SIMV-PS) aim at providing more support to babies with more or stronger signals, assuming that the stronger signals may represent increased work of breathing due to an underlying lung process or hypercapnia. These modes try to take over more work of breathing from the baby in these situations. However, a strong breathing effort may also be due to other causes such as encephalopathy or metabolic acidosis. In these situations, the use of these modes may potentially lead to over-ventilation and hypocapnia, unless the ventilator algorithm includes limits on this positive relationship. However, this has not been thoroughly assessed in clinical studies.

Table 33: Classification of various ventilator modes according to the two axes. See text for more details.

Ventilator mode	Relationship along axis 1 (depth of patient breaths and ventilator inflating pressure)	Relationship along axis 2 (number of patient breaths and number of cycles contributed to by ventilator)
CMV, IPPV, IMV	Absent	Absent
SIPPV / AC / PTV	Absent	Positive
SIMV	Absent	Absent
SIMV-PS	Absent	Positive
PSV	Absent	Positive
SIPPV-VG / AC-VG / PTV-VG	Negative	Positive
SIMV-VG	Negative	Absent
SIMV-VG-PS	Negative*	Positive
PSV-VG	Negative	Positive
PPS / PAV	Positive	Positive
NAVA	Positive	Positive
MMV	Negative	Negative
MMV-PS	Negative*	Ambiguous**

* Only partially, as the negative relationship only holds for mandatory ventilator inflations. Spontaneous breaths will still remain pressure supported
** Ambiguous because increasing respiratory rate will reduce the number of mandatory inflations via the MV feedback loop. However, if the spontaneous breaths are pressure supported, the ventilator still contributes to them.

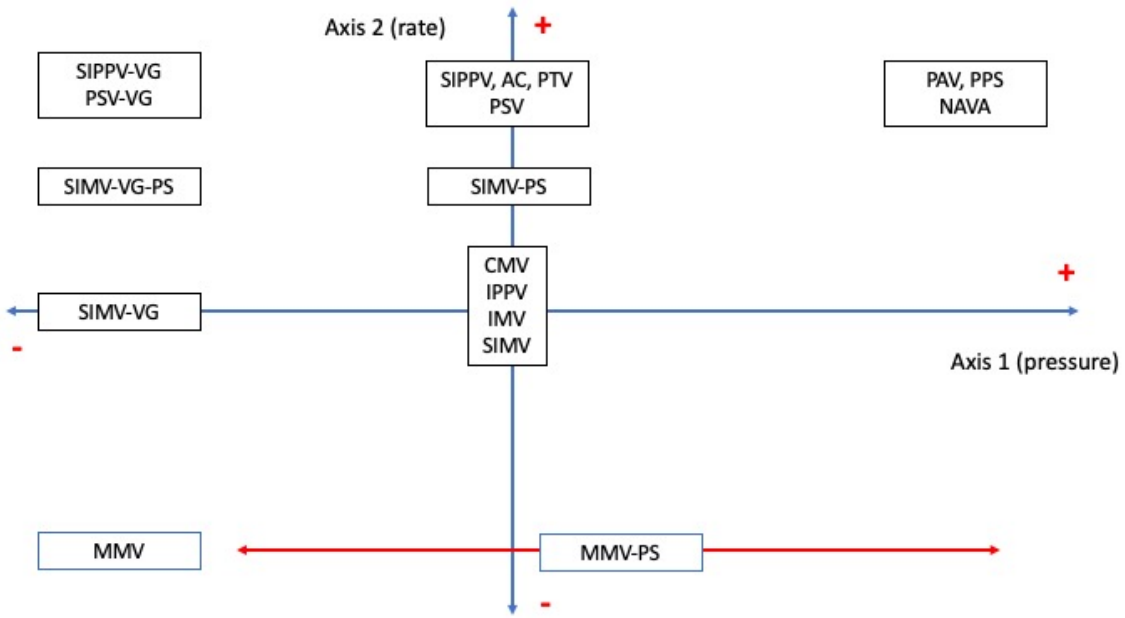

Figure 58: Graph showing the position of various ventilator modes along the two axes. See text for details.

Modes with negative relationship in one or both domains (SIPPV-VG, SIMV-VG, PSV-VG, MMV) aim at making babies do as much of the work of breathing as they can and provide support for the rest. These modes assume that babies are breathing stronger or a lot because they are able to do it and not because they are not getting enough support from the ventilator. This assumption proves correct in babies with normal lungs and/or with encephalopathy. However, there is a theoretical risk that in infants with sick lungs and weak respiratory muscles, the ventilator will leave the baby under-supported (e.g., when VG ventilation is using a PIP close to the PEEP level). It has been argued in review articles that continuing with the VG with the same tidal volume would lead to exhaustion and acidosis (51), but no original research data have been presented to support this hypothesis so far.

If there is negative relationship in the pressure domain (axis 1), a strongly breathing infant will do all the work of breathing, even if in the rate domain (axis 2) the relationship is absent or positive. This is the case in case of SIPPV-VG or PSV-VG: even though the ventilator would assist all breathing attempts, its "assist" means using PIP very close to PEEP. In that sense SIMV-VG-PS or MMV-PS are different as the negative relationship of the pressure domain (axis 1) only relates to mandatory ventilator inflations and spontaneous breaths will still be pressure supported.

7.1.5.1. What is significance of low inflating pressures during volume guarantee?

We analysed ventilation parameters and blood gases in infants receiving volume targeted ventilation with episodes of very low (<5 mbar) ventilator inflating pressures (52). We found that while these episodes were more frequent in term infants with encephalopathy, they occurred in 30% of all infants, including many preterm babies.

The minute ventilation during periods with median Pinfl <5 mbar was not different from the MV obtained during periods with higher inflating pressures in either preterm or term babies, despite clinicians setting lower target tidal volumes during these periods. This is due to the fact that during these periods babies exceeded the target VT and the set respiratory rate, either by triggering more inflations (during SIPPV-VG) or breathing deeper and more frequently between them (during SIMV-VG). There was no difference in blood gases between periods when inflating pressure was <5 mbar or when it was higher, except in the lactate levels, which were higher when median Pinfl was <5 mbar in term babies with hypoxic-ischaemic encephalopathy and it probably reflects the perinatal lactic acidosis present in these infants.

It has been suggested that low inflating pressures are associated with episodes of exhaustion, hypercapnia or acidosis (51). From our data we cannot either confirm or fully rule out the occurrence of these periods as we did not record acid-base parameters (pH, pCO_2, base excess and lactate) continuously, only analysed data from blood gases collected during clinical care.

When the Pinfl is just above the PEEP, the ventilator barely contributes to the work of breathing and the baby is responsible for most of it. The situation is sometimes compared to endotracheal continuous positive airway pressure (ET-CPAP); however, it can be argued that this is only a superficial similarity. During ET-CPAP, all respiratory work is done by the baby. During VG, the ventilator's algorithm compares the actual expired tidal volume with the target VT after each inflation and if the baby is getting tired, that is, the generated VT is below the target, the PIP of the following ventilator inflation is increased, resulting in the ventilator contributing

more to the work of breathing. When reviewing ventilator waveforms, intermittent periods with higher inflating pressures can usually be identified in these infants (**see Figure 37**).

We argue that most babies who consistently require only low Pinfl during volume targeted ventilation can be successfully extubated unless they have airway obstruction or inconsistent respiratory effort. If clinicians want to continue mechanical ventilation in this situation, they could consider providing more support to the baby by increasing the target tidal volume with careful monitoring of blood gases. Sometimes clinicians use deep sedation or turn off volume targeting and ventilate the infant with just pressure limited ventilation. However, using deep sedation interferes with developmental care, makes recognition of neurologic abnormalities difficult in babies with hypoxic-ischaemic encephalopathy and prolongs weaning from mechanical ventilation. Turning off volume targeting will potentially cause high tidal volumes and hypocapnia. In addition, it may lead to excessive transpulmonary pressures (the sum of the ventilator's inflating pressure and the pressure gradient generated by the baby's breathing effort), potentially resulting in patient self-inflicted lung injury (212), although this has not been studied in neonates and it is arguable that due to hypocapnia the patient's respiratory effort could be reduced or absent.

A limitation of the study is that CO_2 levels were not monitored continuously and therefore very rapid fluctuations of them cannot fully be ruled out. Most blood gases were capillary gases rather than arterial. A relatively high set respiratory rate (~50-60/min) was used during SIPPV, which could have resulted in worse patient-ventilator synchrony than a lower backup rate. Further limitations are that physiologic parameters were not monitored and clinical outcomes were not examined. However, periods with low inflating pressures are more likely to occur in babies with specific pathologies such as hypoxic-ischaemic encephalopathy, which would have confounded such analysis.

7.1.5.2. Volume guarantee ventilation in babies with hypoxic ischaemic encephalopathy

In a retrospective study (53) we analyzed ventilator parameters and blood gases during VG ventilation in infants undergoing therapeutic hypothermia for HIE; we compared babies receiving SIMV-VG with babies ventilated with SIMV only. To our knowledge this is the first report of VG ventilation in babies with HIE. Dassios *et al* studied ventilator parameters in babies with HIE and therapeutic hypothermia (213); however, the authors did not discuss if the infants received volume targeted or pressure limited ventilation and their analysis was based on eight observations recorded manually over a 72-hour period. We collected data computationally with 0.5 Hz sampling rate; therefore, our analysis is based on a dataset with thousands of data points.

VG ventilation of babies with HIE is potentially difficult for two reasons. First, these babies frequently hyperventilate to compensate for metabolic acidosis caused by the asphyxia and may develop hypocapnia. During VG ventilation the ventilator stops an inflation if the inspiratory tidal volume significantly exceeds the target VT; however, babies can continue breathing from the continuous flow in the ventilator circuit (19). Despite this, we found the babies ventilated with VG had lower tidal volumes and maintained their average tidal volume close to the target value.

Despite the lower tidal volumes, minute ventilation and pCO_2 at the end of transfer was not different between the groups. There are several possible explanations for this. First, during

SIMV babies can breathe spontaneously between the ventilator inflations, particularly if the ventilator rate is set low. The tidal volumes of these spontaneous breaths are controlled solely by the infant even when VG is used. In our dataset the SIMV rate was <30/minute for most babies. We found that in some babies, spontaneous breaths contributed more than 50% to the total minute ventilation even when sedation was used. Therefore, the lower tidal volumes of ventilator inflations during SIMV-VG may have had a limited effect. However, using a higher SIMV rate or using SIPPV ventilation mode (which delivers a ventilator inflation with each attempted breath) would have been likely to result in a higher minute ventilation and lower pCO_2 irrespective whether VG is used or not. Second, it has been reported during SIMV-VG infants breathe more between ventilator inflations than during SIMV with the same rate but without VG (214). Third, the study was short, limited to the transport period. Finally, our study may have been underpowered to detect the potential benefit of VG on pCO_2 at the end of transport. Based on data from another study from the same transport service (215), and assuming the variability of pCO_2 seen in our data, even if there was a 50% reduction in hypocapnia after of transport, it would have required a balanced sampled size of 120 patients.

The second concern with VG ventilation in term infants with HIE and strong breathing effort is that the VG algorithm lowers the PIP to try and maintain the VTemand near the set level and hence the ventilator's inflating pressure and contribution to the work of breathing in these babies is frequently minimal, as discussed in the previous section (**section 7.1.5.2).** In our dataset we found that PIPs below 10 cmH_2O (inflating pressure <4-5 cmH_2O) occurred mostly in babies whose spontaneous breathing contributed to their ventilation by more than 50%. These babies frequently exceeded VTset due to hyperventilation and did not develop hypercapnia or acidosis. However, based on these data we cannot rule out these adverse events during longer ventilation periods or in babies with different clinical characteristics (e.g., in preterm infants).

The main strength of our study is the prospective computational data collection. Moreover, our cohort was uniform as all recordings happened on the first day of life during *ex utero* transfer to a cooling center. A limitation of our study is that it was a retrospective analysis, the sample size was relatively low, and it was limited to the duration of interhospital transfer lasting no more than 1-2 hours. Also, we had only two capillary gases for each transfer (one at the beginning and one the end) rather than serial arterial blood gases. Capillary pCO_2 values may have been significantly higher than arterial pCO_2 values in babies who had peripheral vasoconstriction due to therapeutic hypothermia. Although there was no difference between the groups in the number of babies receiving sedation, the actual level of sedation and spontaneous breathing effort could have been different. Finally, no clinical or long-term outcomes have been studied. The use of VG ventilation in these babies needs to be established in future clinical studies.

7.1.6. Using volume guarantee ventilation during transport

Analysing ventilator data from babies ventilated during neonatal transport, we found that babies ventilated with VG had lower and less variable tidal volumes than babies ventilated without VG (48). Without VG, infants frequently received inflations with expiratory tidal volume >6 mL/kg or some >8 mL/kg; this occurred much less frequently during VG. Importantly, babies who were ventilated without VG did not receive high inflation pressures.

Although the median PIP of the non-VG group was significantly higher than the median PIP in the VG group it was still only 19.5 cmH_2O. It has been suggested that high tidal volumes rather than high inflating pressures are associated with neonatal lung injury (206, 216). However, clinicians may be misled by thinking that if they ventilate infants without VG but use PIP which they consider low (e.g., <20 cmH_2O), large tidal volumes could not occur. It has also been established that even brief hypocapnia is associated with adverse neurodevelopmental outcome both in term and preterm babies (177, 217). The pCO_2 values obtained immediately after the transport were similar in the two groups and severe hypocapnia occurred only in one case. Therefore, when not using VG during neonatal transport, the higher tidal volumes do not necessarily cause over-ventilation and hypocapnia.

A limitation of our study is that we cannot comment on the clinical significance of larger tidal volumes occurring during transport without VG because we did not collect data on clinical outcomes. The relatively short duration of ventilation during transport (the longest recording was <4 hours) may limit the effect of large tidal volumes on long-term outcomes. However, animal data suggest that even short periods of moderately high tidal volumes can result in lung injury. In rats, mechanical ventilation with large tidal volumes for 30 minutes did not cause histological changes in the lung but changed the expression of several genes involved in inflammation and stress response (218). In ventilated preterm lambs even a 15-minute period of ventilation with 6-7 mL/kg increased early markers of lung injury and inflammation (219). In a recent paper, extremely preterm infants receiving mask ventilation with tidal volumes >6 mL/kg had a significantly higher incidence of intraventricular haemorrhage (220).

During synchronized ventilator inflations tidal volume delivery results from the combination of the baby's breathing effort and the ventilator's inflating pressure. Without VG, the set PIP results in larger tidal volumes in breathing babies than it would have done in an apnoeic baby. However, it has not been established that the large tidal volumes achieved this way are as damaging as the ones delivered to an apnoeic baby (218, 220, 221). Clinical studies will be required to clarify the significance of these large tidal volumes.

The total minute ventilation during SIMV is the sum of ventilator inflations (synchronised or backup) and the spontaneous breaths. An interesting finding was that a larger proportion of the total minute ventilation was due to spontaneous breaths in babies ventilated SIMV-VG than in infants ventilated with SIMV without VG even though the set ventilator rate was similar. In a short crossover study of infants ventilated with SIMV-VG and SIMV on a NICU, Herrera *et al.* also reported that during SIMV-VG infants had enhancement of the spontaneous respiratory effort with larger minute volumes of their spontaneous breaths between the SIMV inflations (214). This may be due to larger spontaneous tidal volumes or faster spontaneous breathing rate or both. Indeed, the tidal volume of the spontaneous breaths was ~25% larger in the VG cohort but this was not statistically significant. Unfortunately, the downloading software we used did not retrieve the rate of spontaneous breaths. We speculate that with lower tidal volumes from inflations the infants took larger breaths in between. The clinical significance of this is uncertain but clinicians need to be aware of this as the baby may be doing proportionally more work of breathing.

A limitation of our work is that it was not a randomized prospective study. To minimize inclusion bias and to improve generalizability, data were downloaded from all patients ventilated using the ventilator with data download capabilities over a long period and we included all patients who received SIMV ventilation unless their postmenstrual age was over

46 weeks. The clinical characteristics of SIMV-VG and SIMV without VG groups were similar.

7.1.7. The impact of ambulance acceleration and vibration on ventilation

In this study we found that during most minutes there was significant vibration, with or without significant change the speed of vehicle or its direction (130). We also found that even significant vibration or sustained acceleration did not affect ventilator parameters or ventilator performance. As vibration is largely influenced by road surface and vehicle speed, our findings highlight the importance of preferring roads with even surface and limiting the speed of the ambulance, rather than simply avoiding quick acceleration, deceleration or turning.

A strength of our study is that we studied a large number of babies requiring emergency transport for reasons which are representative of the activities of most neonatal transport services. Ventilation and acceleration data were collected prospectively and computationally, eliminating the biases and limitations associated with manual data collection.

Our study has some limitations. It was observational rather than a randomized controlled trial; however, exposing babies to higher acceleration and vibration than absolutely necessary would be unethical. We did not record and analyze physiological parameters such as oxygen saturation, heart rate or blood pressure which could have provided more information about clinical instability or distress in these infants. As we used the ventilator's sensors for measuring ventilator performance, our experimental setup did not detect potential sensor errors. Finally, as the clocks of the ventilator and the accelerometer were manually synchronized, our data were not suitable to detect instantaneous and specific responses to acceleration shorter than 1 minute.

Acceleration and vibration levels inside emergency vehicles are affected by road conditions, traffic, driving style, vehicle make, model and suspension. Moreover, the acceleration transferred to the transport incubator and to the infant also depends on how the incubator is fixed within the ambulance and how the infant's position is stabilized within the incubator. In our ambulances the incubator was mounted on a pneumatic anti-vibration system, while in some ambulances a solid mechanical fixation is used, potentially resulting in more vibration transferred to the incubator and to the baby. Despite all these variables, the acceleration values obtained in our study are similar to those obtained by others (121, 222). Finally, we fixed the accelerometer to the top wall of the transport incubator, while in some studies it was attached directly to the infant (122); however, babies probably faced similar acceleration and vibration levels as measured because they were stabilized by a vacuum mattress inside the incubator.

We used the fabian +nCPAP evolution™ neonatal ventilator. Our findings may not necessarily generalize to all neonatal ventilators. The ventilator is not registered for inter-hospital neonatal transfer by its manufacturer; however, it is used by several neonatal transport services after integration into transport trolleys by third party services, as in our case (Andreas Waldmann, Vyaire, personal communication). Nonetheless, our work provides evidence that modern ventilation modes such as synchronized ventilation and volume targeting can be used safely during neonatal transport without significant interference from the physical forces arising during the journey.

Despite stability of ventilator parameters, we found that intense vibration made the pressure-volume loops more irregular and complex, although the extent of this was variable. This phenomenon may be due to the direct physical effect of vibration on the ventilator-patient unit or it may reflect physiological responses of the baby. The latter can be influenced by gestation and weight, postnatal age, critical illness and sedation. The large number of potential co-variates may be responsible for the variable impact of vibration in different recordings. Nonetheless, our paper provides the first evidence that vibration during transport may affect ventilator-patient interactions in some critically ill infants.

7.2. Ventilator alarms

Although ventilator alarms are frequent and known to disturb babies, parents and staff, the topic has been under-researched and ours was the first report to computationally analyse thousands of ventilator alarms downloaded from ventilators (157). We showed that neonatal ventilator alarms on average occur at a rate of 10 per hour. We also found that nearly half of the alarms were caused by physiological variability in the respiratory rate or minute volume, or inappropriate setting of relevant alarm limits. While most alarms lasted for <1 minute and frequently only for a couple seconds, sometimes alarms were accepted by staff for very long periods. These results can be used to educate staff how to set alarm limits and respond to different alarms. It should also help ventilator manufacturers, and regulators by informing them about the usefulness of various alarms in clinical practice. We hope such data will be routinely available from future neonatal ventilators.

In infants with spontaneous breathing effort, MV changes from minute to minute, leading to frequent and short alarms. To avoid this, staff may set “MV low” and “MV high” alarm limits at non-physiological values, e.g., as <0.1 L/min/kg and >0.5 L/min/kg, respectively, which can lead to delayed recognition of significant clinical events. We recommend setting the MV low and high alarm limits at 20-30% below and above the currently observed values, and to revise the limits regularly as the baby’s condition changes. In addition, some ventilators (e.g., the Dräger Babylog™ VN500 ventilator) have the option of delaying MV alarms by 10-15 seconds; using this strategy on our unit has resulted in a significant reduction in alarms without clinical incidents (unpublished observation).

Clinicians also need to set the limit of the “Respiratory rate high” alarm. While preterm infants usually have respiratory rates between 40-60/min, sometimes their rate is >80/min, but rarely >100/min. However, term babies with HIE and metabolic acidosis sometimes breathe more than 100/min. The respiratory rate may also frequently vary, making it difficult to set alarm limits. To avoid too many alarm events, we recommend setting the respiratory rate high alarm to 20-30% higher than the actual rate. Ventilator rates >130/min usually reflect auto-triggering due to condensed water bubbling in the ventilator circuit. To prevent this, the water traps need to be emptied regularly or use a circuit where water vapour can pass through the circuit wall.

During HFOV, carbon dioxide elimination is determined by DCO_2 (see **section 3.4.3.4**.). Although minute ventilation is not relevant for HFOV, MV alarm limits still need to be set on most ventilators during HFOV. HFOV is associated with large “minute ventilation” (i.e., >1 L/kg/min) and the “MV high” alarm limit needs to be increased significantly, or there will be a continuous “MV high” alarm. When ventilation mode is changed back to conventional, clinicians need to remember reducing the MV alarm limits.

There were many "low tidal volume" alarms where the Pmax limited the peak inflating pressure and prevented the ventilator from delivering sufficient pressure to ensure VTset was delivered. We suggest the Pmax should be set at a high level where it is unlikely to trigger alarms frequently but where clinicians need to know the ventilator is using a high peak pressure so they can assess what is happening to the ventilator and baby and whether any clinical intervention or changes in ventilation is needed (see **section 7.1.3**.).

A frequent cause of alarms were flow sensor issues, and flow sensors alarms were sometimes tolerated by staff for several hours. An operational flow sensor is essential for synchronized ventilation. The flow sensor is also required for calculating tidal volumes which are in turn essential for VG ventilation. Flow sensors need regular calibrations, and if they get soiled by condensed water or medications, they may need replacing.

7.3. Computational analysis of neonatal waveforms and loops

We have developed and validated a computer program (*Ventiliser*) that identifies and characterizes individual inflations from airway pressure and flow data downloaded from neonatal ventilators (20). The software was developed and initially tested with raw data obtained from the Dräger Babylog™ VN500 ventilator; however, as the input to our programs is platform agnostic, requiring only flow and pressure data in a tabular data format and obtained at a high sampling rate, *Ventiliser* can be used with any neonatal ventilator from which flow and pressure data can be downloaded at high sampling rate. We have also successfully used *Ventiliser* on data obtained from the fabian +nCPAP evolution™ neonatal ventilator (Belteki *et al*, unpublished observations).

Existing software solutions for ventilation waveform analysis have used adult ventilator data and primarily focused on detection of specific adverse patient- ventilator interactions (such as double triggering or ineffective respiratory efforts) via a rule-based algorithm (114), hidden Markov model (159) or machine learning (160). Furthermore, most of them are not freely available (159, 160) or may be tied to specific ventilator platforms (114). None of these methods has been validated in neonates. The physiology of adult and neonatal ventilation is significantly different: neonates are usually intubated with un-cuffed endotracheal tubes and have some leak around the tube, can breathe during ventilation, the ventilator modes and settings used are different from those used in adults, and patient ventilator interactions are also different.

Recently BreathMetrics (161), a program written in Matlab programming language, sought to address the issue of providing a flexible but standard way to perform basic processing and analysis of respiratory waveforms. However, it was developed for the purpose of analysing spontaneous breathing in mice and adult humans from nasal respiration data. Moreover, the program does not use airway pressure, only air flow and the Matlab software is not freely available. *Ventiliser* uses Python, a popular computer language and its freely available data science libraries, it itself is freely available to clinicians and researchers. The use of Python also enables the possibility for interfacing with existing open-source platforms such as ventMap (114) and installation on devices such as the RaspberryPi™ to enable real-time distributed processing and data collection at the bedside.

Ventiliser uses a rule-based rather than a machine learning algorithm. Machine learning models frequently perform better when tested on new data not seen during algorithm development

(223). However, supervised machine learning methods require a training dataset that can only be produced via manual annotation by domain experts. As ventilator data are complex and noisy due to patient-ventilator interactions, thousands of inflations would need to be manually annotated by clinicians having significant expertise in neonatal ventilation. In addition, manufacturers and regulators of high-risk technologies such as life support equipment are reluctant to adopt and approve "black box" models such as machine learning algorithms.

Despite its rule-based algorithm, *Ventiliser* correctly identified >97% of inflations and their sub-phases in three short samples which were not used during algorithm development. *Ventiliser* can be used for benchmarking more complex or sophisticated segmentation algorithms developed in the future and its GUI can be used for producing a manually annotated training dataset.

Our out-of-sample validation on manually annotated samples also showed that *Ventiliser* was able to identify the inflation key points (boundaries between sub-phases) with good accuracy. The length of each sub-phase is determined by the interval between key points, and hence the error from the prediction of key points is summed when identifying sub-phase lengths as seen in **Table 32**. The expiration termination and expiratory hold sub-phases had considerable deviation from manual annotation (>50 milliseconds in some cases). This probably reflects the more variable nature of the expiratory phase in infants with spontaneous breathing effort which means trying to fit them to an ideal expiration is more challenging.

The pressure rise time (PRT, also known as slope time) calculated by *Ventiliser* was significantly longer than the one set by the clinician. We cannot tell if our algorithm overestimates the pressure rise time or if the actual PRT is longer than the set value due to patient-ventilator interactions or other factors. In the manually annotated samples, the PRTs returned by *Ventiliser* were close to the manually identified values which were also longer than the set slope time (80 milliseconds); however, these were only short samples. The clinical significance of different PRTs in neonatal ventilation is uncertain (23).

We have also found that a significant proportion of ventilator inflations during SIPPV-VG ventilation contain periods of inspiratory hold, the occurrence and significance of which in neonates are not known as there are few studies analysing short periods (224). *Ventiliser* allows for quantitative analysis of inflations over long periods and will facilitate such studies in future.

7.4. Future directions

Over the last decade, non-invasive respiratory support with rescue surfactant administration has become widely accepted standard of care for extremely preterm infants (2). Moreover, it has been argued that neonatal mechanical ventilation is a therapeutic relic and eventually will become obsolete (225). However, despite all improvement in non-invasive respiratory care, the vast majority of smallest and most immature infants still require mechanical ventilation, sometimes for several weeks (3), and the incidence of bronchopulmonary dysplasia did not decrease among them (226). In fact, one can argue that one of the factors determining the threshold of viability (currently at 22-23 weeks) is what is the earliest gestation when adequate gas exchange can be provided by mechanical ventilation. Based on this logic, the most immature babies will always require ventilation until completely novel therapies become available to provide gas exchange for them (227). In addition, term babies with respiratory morbidity, HIE and surgical condition also require mechanical ventilation.

As mechanical ventilation causes lung damage and is associated with short and long-term complications, it is desirable to further improve ventilators and ventilation modes to limit the impact of unavoidable mechanical ventilation on babies. As I discussed in **section 3.3.2.1.5.**, there is limited evidence as to which ventilation modes and what ventilator parameters to use, despite the thousands of clinical studies performed and published. At the same time, ventilators as medical devices have gone through very significant development over the last 2-3 decades. It is arguable that the development of modern and sophisticated mechanical ventilators has contributed more to minimising lung injury in ventilated babies than the clinical research about which ventilation mode to use in which baby.

Ventilator development is done mostly by ventilator manufacturers and it is complicated by intellectual property rights, lack of clinical expertise and lack of access to clinical and ventilator data. On the other hand, clinicians who the end users of ventilators, are usually unaware of the details of modern ventilation modes and sometimes also of many features and options modern ventilators offer. To improve clinicians' understanding of their ventilators, objective data is required to inform them about the performance of their ventilators and ventilation modes during clinical care, rather than in bench experiments or in short controlled studies. Obtaining such data was the main motivation of the studies presented in this thesis. In the following sections I briefly discuss where further ventilator development may lead and what benefits it could potentially offer.

7.4.1. Continuous data streaming and processing from neonatal ventilators

As discussed in **section 3.5.**, traditionally neonatal ventilator studies used manually collected data or data collected computationally but at low sampling frequency. The studies forming the basis of this thesis and also recent work by others (43, 113) have used ventilator data downloaded with high enough frequency to study each ventilator inflation or spontaneous breath in detail and to detect and analyse patient-ventilator interactions. Currently ventilator data downloading programs are research tools, only provided to selected users by ventilator manufacturers, and the obtained data can only be used for research purposes rather than during clinical care. Without such dedicated software clinicians can usually only download averaged ventilator data retrospectively from the ventilator usually via a universal serial bus (USB) port. In addition, the downloading software usually requires a dedicated computer to be placed next to the ventilator and connected to it via a serial port, which is difficult on some NICUs due to space constraints. Finally, ventilator data download needs to be manually started and stopped which requires human resources.

I argue that continuous streaming and download of ventilator data should be part of the clinical operation of modern neonatal ventilators. The technology could use unintrusive devices (e.g., Raspberry Pi computers) as done by others studying adult ventilation (114). Alternatively, data could be streamed wirelessly to storage devices. Due to the significant drop in the price of external data storage devices, storing high sampling rate ventilator data is not expensive. During our data collection from the Dräger Babylog™ VN500 ventilator with a 100 Hz (100 data points per second) sampling rate produced ~700 Mbyte data for each day of ventilation. All ventilator data produced by a busy tertiary NICU ventilating 2,000 days in a year can be stored on a 2 Terabyte external hard drive costing ~£150. The data can then be used for quality improvement, teaching and retrospective research.

To process and interpret such high-throughput ventilator data, computational tools are required, similar to the one described in this thesis (see **section 5.4**.). These tools are open source and freely available but clinicians are rarely familiar with them. This author argues that using these tools for analysing medical data should receive more focus in graduate and postgraduate medical training in the future, because similar "big data" are becoming ubiquitous in most areas of clinical medicine. There is also a need to increase the number of data scientists working in healthcare research and to improve integration and communication between clinical and data science teams.

7.4.2. Smart ventilator alarms

As discussed in the previous sections, currently there is a multitude of different ventilator alarms, but many of them are redundant, difficult to interpret or clinically meaningless. Many alarms only assess one ventilator parameter, such as minute volume or respiratory rate, and clinicians need to set a particular alarm limit which remains the same until they change it. However, in ventilated breathing babies there is considerable short-term variability of ventilator parameters such as respiratory rate and minute volume, and they also change over time with changes in disease process, respiratory mechanics, postnatal maturation and sedation level of the infant. Clinicians revise alarm limits infrequently and even when they do, alarm limits cannot be set at physiologically appropriate levels without causing significant alarm activity due to the short-term variability of these parameters. Therefore, the value of these alarms, in their current format, is questionable.

The future is to develop "smart" ventilator alarms which consider input from multiple ventilator parameters and their temporal trends, rather than looking at single data points or averages over short periods (228, 229). Smart alarms will also have input from physiologic parameters such as oxygen saturation and transcutaneous or end-tidal CO_2. They will use artificial intelligence to predict adverse events and the need to alarm, although the concerns about black-box machine learning models and interpretable artificial intelligence (230) need to be addressed before they can be introduced in routine clinical use. However, in the long term, these intelligent alarms will likely be able to reduce false alarms and the risk of alarm fatigue. They will also represent a significant step towards automation of mechanical ventilation (see **section 7.4.4.**).

7.4.3. Quantitative analysis of neonatal ventilator patient interactions

The occurrence and significance of patient-ventilator interactions in ventilated newborns is largely unknown and this author believes that they represent the "dark matter" of neonatal ventilation. Textbooks and review articles usually present idealised ventilator waveforms and loops as illustrations, produced by either hand-drawing or photographing the ventilator screen at the "right time". They show theoretical respiratory cycles with no patient interaction, or idealised patient-ventilator interactions rarely seen during clinical practice. Modern ventilator displays show ventilator-waveform and loops real-time, but busy clinicians rarely have the time to observe ventilator screens over longer periods. Therefore, the complexity of neonatal ventilator waveforms and the frequency of patient-ventilator interactions is severely under-appreciated.

In adults, frequent ventilator asynchronies are associated with poor clinical outcome (158). It is arguable that their clinical significance is even larger in newborns whose immature lungs are more susceptible to injury and who usually receive less sedation during mechanical ventilation than adults. However, the inability to quantify patient-ventilator interactions over longer period hinders quantitative studies investigating the association of neonatal PVIs with clinical outcomes.

Downloading ventilator pressure and flow data with high enough sampling rate (100 Hz more) allows for detailed visualisation of individual respiratory cycles as shown in several figures of this thesis. PVIs can then be identified in the visualised ventilator waveforms and loops by manual inspection and annotation, although it requires significant work by clinicians with a good understanding of neonatal ventilation. Such manually produced annotated data sets could in turn be used for training supervised machine learning algorithm capable of recognising PVIs automatically. With such algorithms, the prevalence of the individual PVIs could be determined over long periods and their association with clinical outcomes can be studied quantitatively. Eventually, ventilators could also be developed to inform clinical care teams about the frequency and trends of patient-ventilator interactions and asynchronies in ventilated babies.

7.4.4. Automation of neonatal mechanical ventilation

Despite all its development, mechanical ventilation has remained a semi-automated technology. Clinicians set various ventilator parameters which the ventilator is then trying to maintain at or close to the target level. The clinical team is continuously monitoring oxygen saturation and, more recently, carbon dioxide levels via transcutaneous or end-tidal CO_2 monitoring. Blood gases are done intermittently. Based on them ventilator parameters are revised and changed by the clinicians when they feel it is required.

Because of the availability of computerised ventilators and feedback from continuously monitored physiologic variables, mechanical ventilation could potentially be automated. Full automation would include (at least) three components: (1) automatic control of oxygenation based on feedback from oxygen saturation; (2) automatic control of carbon dioxide elimination based on feedback from continuously monitored carbon dioxide levels; (3) continuous monitoring of adverse patient-ventilator interactions and automatically adjusting ventilator settings to minimise them.

Of the above tasks, so far only automatic control of oxygenations has been implemented and found its way to clinical practice. Several algorithms have been developed to adjust FiO_2 levels in order to maintain oxygen saturation levels in a target range (231). Some are based on explicit rules, others use machine learning. It has been proven that their performance to maintain saturations in range exceeds that of nurses and doctors (232). However, their disadvantage is that they only consider FiO_2 as a factor to manipulate oxygenation and they disregard the role of mean airway pressure and lung recruitment.

Software has also been developed for automation of carbon dioxide elimination, such as automatic weaning protocols and mandatory minute ventilation (233, 234), and they are available on some modern ventilators. In adults and children, they have been shown to reduce duration of mechanical ventilation (190). However, they have not been used in neonatology, except in small research studies (211). Moreover, their implementation is more difficult and

they are less successful than automatic FiO_2 control. The major reason for this is that the relationship between ventilator parameters and pCO_2 is more complex than between FiO_2 and oxygen saturation. For example, the correlation between minute ventilation and CO_2 elimination is poor even when consecutive blood gases from same infant are considered, as discussed in **section 7.1.1.1.** However, it is feasible that using large amount of detailed ventilator and physiological data, more complex features can be derived with better predictive power of CO_2 elimination than minute ventilation. Availability of high sampling rate ventilator data is essential for such approaches.

Finally, the aim of modern neonatal ventilation is not only to ensure normality of oxygen saturation and blood gases, but also to provide comfort for the ventilated baby without the need of excessive sedation. This can only be achieved by setting and changing ventilator parameters to ensure that the baby remains comfortable, that is, by minimising adverse patient-ventilator interactions. Automatic detection and recognition of these asynchronies by the ventilator is required for development of such protocols.

8. Most significant findings of the thesis

1. I developed computational pipelines to analyse data downloaded from neonatal ventilators with a high sampling rate. These tools allowed the study ventilator performance at high resolution and over long periods at the same time.

2. I also developed a software (*Ventiliser*) that automatically annotates ventilator data by recognising ventilator inflations, spontaneous breaths and their sub-phases. I demonstrated that the program was capable of analysing millions of ventilator inflations and breaths quantitatively. I made the software open source and freely available.

3. I studied performance of two neonatal ventilators (the Dräger Babylog™ VN500 and the fabian™+ncpap ventilators) during clinical care using data downloaded at high enough sampling rate (1 Hz) to capture almost all respiratory cycles. Prior to my studies there was only one similar study and that tested a different neonatal ventilator model.

4. I demonstrated that during volume targeted ventilation both above ventilators maintain the expired tidal volume close (<1 mL/kg) to the target most of the time, despite the significant short-term variability in peak inspiratory pressure and tidal volume.

5. I studied how the two ventilators perform in volume guarantee mode when there is a significant leak around the endotracheal tube. I found that the fabian™+ncpap ventilator performs well up to 50% leak and found the same results for the Dräger Babylog™ VN500 ventilator, unless leak compensation mode was used.

6. I was the first to study leak-compensated volume targeting on the Dräger Babylog™ VN500 ventilator which is its unique feature. I showed that in leak compensation mode tidal volumes are well maintained even with endotracheal tube leaks >50%, although with increased variability.

7. I analysed how the choice of the maximum allowed peak inspiratory pressure (Pmax) impacted on maintenance of tidal volume during volume guarantee ventilation. I demonstrated that if the general recommendation of keeping the Pmax 5 mbar above the working PIP is followed, it will frequently result in failure to deliver the tidal volume and it causes frequent ventilator alarms.

8. I provided the first report as to how choosing different pressure rise times impact on ventilator parameters and blood gases during neonatal volume guarantee ventilation. I showed that it is safe to use a wide range of pressure rise times without the risk of clinical deterioration or significant changes in blood gases.

9. I was the first to report on ventilator parameters during neonatal SIMV-VG ventilation with pressure support on spontaneous breaths. I showed that the automatic weaning of the peak inspiratory pressure during periods of strong patient effort resulted in a complex and paradoxical situation when pressure-supported spontaneous breaths received more ventilator contribution than mandatory volume guaranteed ventilator inflations.

10. I studied the frequently debated scenario when in babies with strong spontaneous breathing effort, the peak inspiratory pressure is reduced close to the level of PEEP

during volume guarantee ventilation. I demonstrated that this scenario does not result in patient exhaustion or hypercapnia or acidosis as suggested previously.

11. I analysed volume guarantee ventilation in babies in babies with hypoxic-ischaemic encephalopathy. I showed that the use of volume guarantee in these babies reduces tidal volumes and frequently results in very low inflating pressures without affecting blood carbon dioxide levels.

12. I performed the first details analysis of ventilator parameters during high frequency oscillatory ventilation with volume guarantee (HFOV-VG), a relatively new ventilator mode which is getting into widespread clinical use. I showed that there is a significant short-term variability of the oscillation volumes but on average they are maintained close to their target. I also provided data what oscillation volumes are required to maintain blood carbon dioxide levels in the target range.

13. I demonstrated that weight-correction of the diffusion coefficient of the carbon dioxide (DCO_2) improves its correlation with blood carbon dioxide and its predictive value of those during HFOV.

14. I provided the first report on the use of volume targeted ventilation during neonatal transport. I demonstrated that although there was no difference in blood gases at the end of the transfers, during volume targeted ventilation tidal volumes were maintained more stringently and excessive tidal volumes were avoided.

15. I analysed how acceleration and vibration during neonatal transport affected ventilator performance and patient-ventilator interactions. I found that ventilator parameters were well maintained even during periods of high vibration or acceleration, although ventilator waveforms and loops became more complex and disorganised.

16. I collected and analysed computationally thousands of ventilator alarms. I showed that in most cases there are frequent alarms, on average one in every six minutes. I also showed that sometimes clinical staff sets the alarm limits at inappropriate levels or tolerates alarms for several hours without rectifying the underlying problem.

17. I showed that a limited number of alarm types were responsible for the majority of ventilator alarms. I demonstrated that frequent minute volume and respiratory rate alarms were due to the normal variability of these parameters present in most ventilated babies. I highlighted that it may not possible to set these alarms' limits so that frequent alarms are avoided but the alarm limits still remain clinically meaningful and safe.

9. References

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10. List of publications

10.1. Publications included in this thesis

1. Panayiotou E, Spike K, Morley C, **Belteki G**. Ventilator respiratory graphic diagnosis of hiccupping in non-ketotic hyperglycinaemia. *BMJ Case Rep*. 2017 Aug 9;2017:bcr2017220267.

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12. Mitra N, **Belteki G**. Fifteen-minute consultation: How to interpret and manage ventilator alarms in the neonatal intensive care unit. *Arch Dis Child Educ Pract Ed*. 2021 Oct;106(5):269-277.

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10.2. Other publications since PhD thesis

1. **Belteki G**, Smith GC. Single versus multiple antenatal steroids in threatened preterm delivery: more benefit or harm? *Arch Dis Child Fetal Neonatal* Ed. 2009 Jan;94(1):F5-7.

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10.3. Publications included in PhD thesis

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10.4. Book chapters

1. **Bélteki G**. "Veleszületett rendellenességek, anyagcsere-betegségek," in *Tabularium paediatriae*, 2000, pp. 29–34.

2. Kálmánchey R., **Bélteki G.**, "Chromosoma rendellenességek és dysmorphiás szindrómák," in *Gyermekneurológia*, Medicina, 2000, pp. 111–126.

3. Balla L, Baranyi É, Bécsi A, **Bélteki G,** Erdős G, Gerő G., Götze Á, Bérczi V, Gyenes G., Kaiser G., Káli G., Körmendy M., Masszi T., Laki A., Mihalik P., Pék L., Péter Z., Rókusz L., Szűcs J., Tremmel A., Kovács G. P., Balla L., Kaizer G., and Makara M., Rövidítések az orvosi gyakorlatban. Budapest: Melánia Kiadó, 1999.

10.5. Scientometrics

MTMT közlemény és idéző összefoglaló táblázat				
Bélteki Gusztáv adatai (2023.07.28)				
Közlemény típusok	**Száma**		**Hivatkozások[1]**	
Tudományos közlemények	Összes	Részletezve	Független	Összes
I. Tudományos folyóiratcikk	38	---	---	---
külföldi kiadású szakfolyóiratban idegen	---	37	940	1058
külföldi kiadású szakfolyóiratban magyar	---	0	0	0
hazai kiadású szakfolyóiratban idegen nyelven	---	0	0	0
hazai kiadású szakfolyóiratban magyar	---	1	0	0
II. Könyvek	1	---	---	---
a) Könyv, szerzőként	1	---	---	---
idegen nyelvű	---	0	0	0
magyar nyelvű	---	1	0	0
b) Könyv, szerkesztőként[2]	0	---	---	---
idegen nyelvű	---	0	---	---
magyar nyelvű	---	0	---	---
III. Könyvrészlet	2	---	---	---
idegen nyelvű	---	0	0	0
magyar nyelvű	---	2	0	0
IV. Konferenciaközlemény folyóiratban vagy konferenciakötetben	1	---	---	---
idegen nyelvű	---	1	0	0
magyar nyelvű	---	0	0	0
Közlemények összesen (I.-IV.)	42	---	940	1058
Absztrakt[3]	19	---	0	0
Kutatási adat	0		0	0
További tudományos művek[4]	4	---	4	4
Összes tudományos közlemény	65	---	944	1062
Hirsch index[5]	13	---	---	---
Oktatási művek	0	---	---	---
Felsőoktatási művek	0	---	---	---
Felsőoktatási tankönyv idegen nyelvű	---	0	0	0
Felsőoktatási tankönyv magyar nyelvű	---	0	0	0
Felsőoktatási tankönyv része idegen nyelven	---	0	0	0
Felsőoktatási tankönyv része magyar nyelven	---	0	0	0
Oktatási anyag	0	---	0	0
Oltalmi formák	0	---	0	0
Alkotás	0	---	0	0

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Ismeretterjesztő művek	0	---	---	---
Folyóiratcikk		0	0	0
Könyvek	---	0	0	0
További ismeretterjesztő művek	---	0	0	0
Közérdekű vagy nem besorolt művek[6]	0	---	0	0
További közlemények[7]	0		0	0
Egyéb szerzőség[8]	3	---	298	352
Idézők szerkesztett művekre	---	---	0	0
Idézők disszertációban, egyéb típusban	---	---	0	0
Összes közlemény és összes idézőik	68	---	1242	1414

Megjegyzések
A táblázat számai hivatkozások is. A számra kattintva a program listázza azokat a műveket, amelyeket a cellában összeszámlált.
--- : Nem kitölthető cella
[1] A hivatkozások a disszertáció és egyéb típusú idézők nélkül számolva. A disszertáció és egyéb típusú idézők összesítve a táblázat végén találhatók.
[2] Szerkesztőként nem részesedik a könyv idézéséből
[3] Csak a tudományos jellegű absztraktok.
[4] Minden további még el nem számolt tudományos mű (kivéve alkotás vagy oltalmi forma), ahol a szerző: szerző, szerkesztő, kritikai vagy forráskiadás készítője szerzőségű.
[5] A disszertációk és egyéb típusú idézők nélkül számolva. A sor értéke az "Összes tudományos közlemény" sor idézettségi adatait veszi alapul.
[6] Minden Közérdekű, Nem besorolt jellegű közlemény, ahol a szerző nem egyéb szerzőségű szerző.
[7] Ide értve minden olyan művet, mely a táblázat más, nevesített soraiban nem került összeszámlálásra.
[8] Minden olyan egyéb szerzőségű mű, ahol a szerző nem: szerző, szerkesztő, kritikai vagy forráskiadás készítője szerzőségű.

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