Volume Guaranteed Ventilation During Neonatal Transport*

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Objectives: To compare tidal volumes, inflating pressures and other ventilator variables of infants receiving synchronized intermitted mandatory ventilation with volume guarantee during emergency neonatal transport with those of infants receiving synchronized intermitted mandatory ventilation without volume guarantee.

Design: Retrospective observational study.

Setting: A regional neonatal emergency transport service.

Patients: We enrolled 77 infants undergoing emergency neonatal transfer. Forty-five infants were ventilated with synchronized intermittent mandatory ventilation with volume guarantee and 32 with synchronized intermitted mandatory ventilation without volume guarantee.

Interventions: Infants received synchronized intermitted mandatory ventilation with or without volume guarantee during inter-hospital emergency neonatal transport using a Fabian + nCPAP evolution neonatal ventilator (Software Version: 4.0.1; Acutronic Medical Instruments, Hirzel, Switzerland).

Measurements and Main Results: We downloaded detailed ventilator data with 0.5 Hz sampling rate. We analyzed data with the Python computer language and its data science packages. The mean expiratory tidal volume of inflations was lower and less variable in infants ventilated with volume guarantee than in babies ventilated without volume guarantee (group median 4.8 vs 6.0 mL/kg; $p = 0.001$). Babies ventilated with synchronized intermittent mandatory ventilation with volume guarantee had on average lower and more variable peak inflating pressures than babies ventilated without volume guarantee (group median 15.5 vs 19.5 cm H_2O; $p = 0.0004$). With volume guarantee, a lower proportion of the total minute ventilation was attributed to ventilator inflations rather than to spontaneous breaths between inflations (group median 66% vs 83%; $p = 0.02$). With volume guarantee, babies had fewer inflations with tidal volumes greater than 6 mL/kg and greater than 8 mL/kg (group medians 3% vs 44% and 0% vs 7%, respectively; $p = 0.0001$). The larger tidal volumes in the non-volume guarantee group were not associated with significant hypocapnia except in one case.

Conclusions: During neonatal transport, synchronized intermittent mandatory ventilation with volume guarantee ventilation reduced the occurrence of excessive tidal volumes, but it was associated with larger contribution of spontaneous breaths to minute ventilation compared with synchronized intermitted mandatory ventilation without volume guarantee. (*Pediatr Crit Care Med* 2019; 20:1170–1176)

Key Words: carbon dioxide; neonatal; synchronized intermittent mandatory ventilation; tidal volume; volume guaranteed ventilation

Volume guaranteed (VG) ventilation, also known as volume-targeted ventilation, is an adaptive ventilation mode. During VG mode the clinician sets a target tidal volume (VT) and the ventilator's computer uses a feedback algorithm to adjust the peak inflating pressure (PIP) for the next inflation to try to achieve an expiratory (1) or leak-compensated expiratory (2) VT as close to the target as possible. In a systematic review VG, compared with time-cycled pressure-limited

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ventilation, has been shown to improve several short and long-term neonatal outcomes including pneumothorax, hypocapnia, days of ventilation, neonatal mortality, bronchopulmonary dysplasia, and periventricular leukomalacia (3).

Over the last decade, VG has been increasingly used on neonatal ICUs (NICUs) worldwide (4, 5). A target VT range of 4–6 (6–8) or 4–8 mL/kg (9) has been recommended by several reports and reviews and is generally used as a guideline for NICUs. However, there has been no report on the use of VG during neonatal transport. In a recent report, 40% of infants ventilated with pressure-limited ventilation during interhospital transport had their VTs outside the 4–6 mL/kg target range for greater than 50% of time (10).

We hypothesized that using VG ventilation during neonatal transport would result in lower and less variable VTs compared with pressure-controlled ventilation. To investigate this, in this study, we compared infants ventilated using pressure-controlled synchronized intermittent mandatory ventilation (SIMV) with or without VG during interhospital neonatal transport.

MATERIALS AND METHODS

Patients

Clinical and ventilator data were collected from all 300 infants transferred by the Neonatal Emergency and Transport Service of the Peter Cerny Foundation (Budapest, Hungary) over a 17-month period (between March 20, 2017, and August 20, 2018) who received invasive or noninvasive respiratory support during interhospital transport using a Fabian +nCPAP evolution neonatal ventilator (Software Version: 4.0.1; Acutronic Medical Instruments, Hirzel, Switzerland). The cohort comprised 29% of all transfers requiring respiratory support in the period (n = 1,018). The transport team comprised a fully trained neonatologist with experience in neonatal transport and an experienced neonatal transport nurse practitioner. Respiratory management including the choice of ventilator mode and settings was at the discretion of the transport team without an explicit guideline. The study was approved by the Scientific and Medical Research Council Ethics Committee of Hungary (reference number: 40158/2018/EKU).

Of the 300 infants, 145 received ventilation via an endotracheal tube during the transport for longer than 15 minutes and were considered for inclusion in this study (**Fig. 1**). Infants were intubated with un-cuffed and nonshouldered endotracheal tubes; tubes were routinely cut to reduce dead space. Volume triggering was used for synchronization in all cases. During volume triggering a synchronized inflation is delivered if the VT of the patient's respiratory effort reaches a particular volume, expressed as percentage of the expired VT of the previous inflation; the user can set the percentage between 10% and 25%. We included infants who received at least 15 minutes of pressure-controlled SIMV either with VG (SIMV-VG) or without VG (SIMV) during the transfer. We excluded infants whose postmenstrual age was greater than 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.

Data Retrieval and Analysis

We downloaded ventilator data using a data logger developed by the ventilator manufacturer for research purposes. The software downloads all ventilator variables and settings including peak inspiratory pressure, positive end-expiratory pressure (PEEP), inspiratory and expiratory VT, inspiratory and expiratory time, F_{IO_2} at a 0.5 Hz sampling rate. Data were retrieved with millisecond time stamps and exported as text files. The ventilator variables correspond to the last inflation that occurred before the time stamp. Minute volume is reported by the ventilator as a rolling mean over 30 seconds. Clinical data were collected from electronic healthcare records. Blood gases were obtained via capillary sampling using heel-pricks in all cases, as babies did not have arterial catheters.

Data were analyzed using Python (Version 3.7.1, https://www.python.org) and its add-on packages. Anaconda (Continuum Analytics, http://docs.continuum.io/anaconda/pkg-docs) was installed on a MacBook Pro 2014 Version, 2.6 GHz i5 processor and 8GB random access memory (Apple, London, UK). Programming was done using Jupyter Notebook (Version 7.2.0, http://ipython.org/notebook.html). Data were represented, manipulated, and analyzed using the NumPy (Version 1.15.4, http://www.numpy.org) and pandas (Version 0.23.4, http://pandas.pydata.org). Statistical analysis was performed using SciPy (Version 1.1.0, www.scipy.org). For each ventilator variable, arithmetic mean and SD was determined for each recording. As these aggregate values were not normally distributed within the cohorts, the two groups were compared using nonparametric Mann-Whitney U tests. Correction for multiple testing was done using the Benjamini-Hochberg method with a false discovery rate of 5%. Visualization was done using matplotlib (Version 3.0.2, http://matplotlib.org). All software is open-source and freely available. The Jupyter notebooks containing and explaining all steps of data processing and statistical analysis can be viewed on GitHub code repository at https://github.com/belteki/transport_VG.

RESULTS

We studied infants receiving SIMV with VG (n = 45) or without VG (n = 32) during neonatal transport. 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 (11, 12) of the infants ventilated with or without VG was not significantly different at the beginning or at the end of the transfer (**Table 1**).

We determined the mean and SDs of ventilator variables in each recording (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B51—**legend**, Supplemental Digital Content 4, http://links.lww.com/PCC/B54; and **Supplementary Table 2**, Supplemental Digital Content

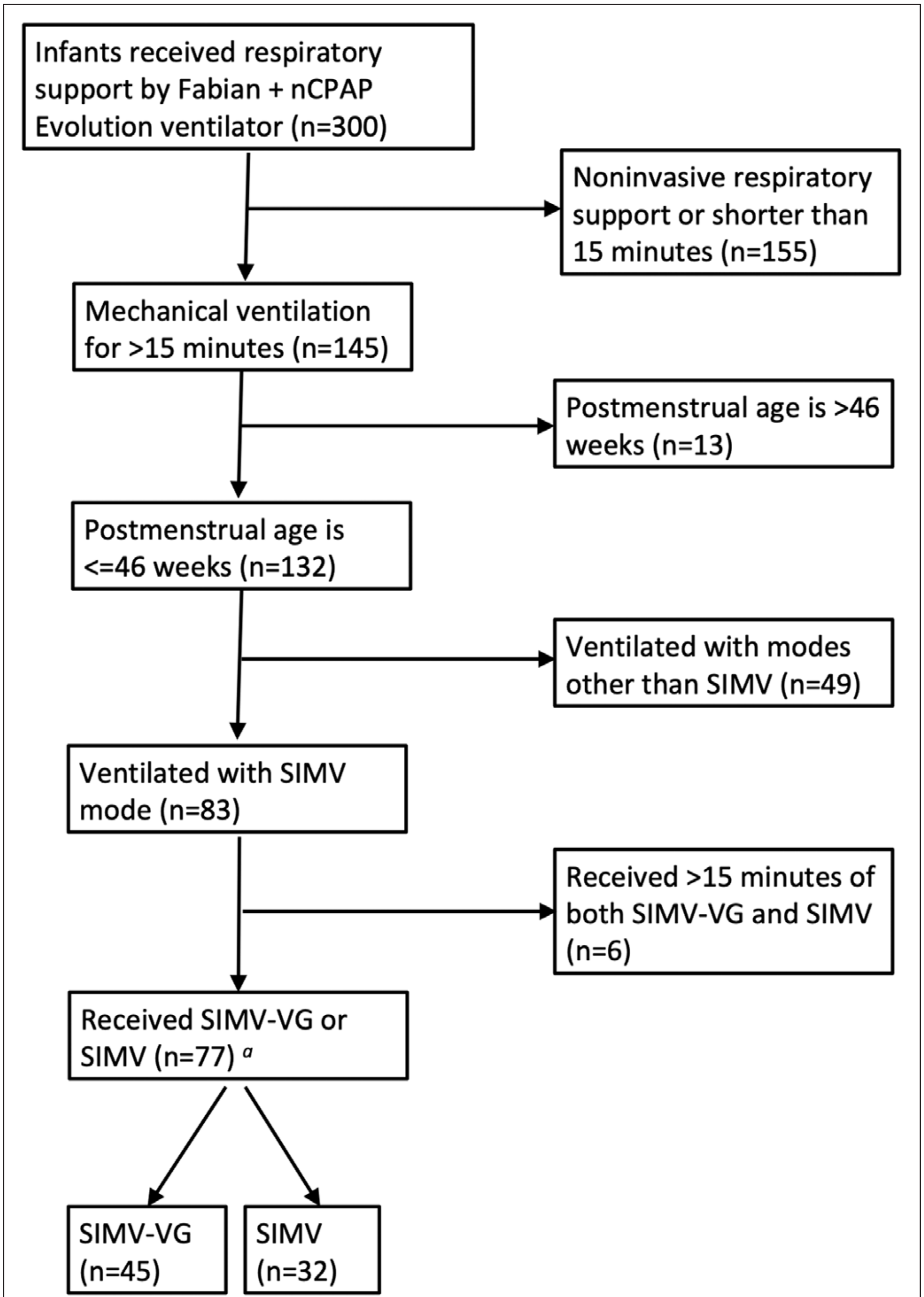

Figure 1. Diagram showing the selection of patients included in the study. [a]Patients who received both synchronized intermittent mandatory ventilation with volume guarantee (SIMV-VG) and synchronized intermittent mandatory ventilation without volume guarantee (SIMV) modes during transport, but one of them for less than 15 min were included, but these short periods were removed from analysis.

2, http://links.lww.com/PCC/B52—legend, Supplemental Digital Content 4, http://links.lww.com/PCC/B54) and compared the two groups. Results are shown in **Tables 2** and **3**.

The mean expiratory VT of ventilator inflations (VTemand) was lower in infants ventilated with VG than in babies ventilated without VG (group median 4.8 vs 6.0 mL/kg; $p = 0.001$). The variability of VTemand was also significantly lower in the group with VG. Babies receiving SIMV-VG had, on average, lower and more variable PIP (group median 15.5 vs 19.5 cm H_2O; $p = 0.0004$). There were no significant differences in the ventilatory rate, minute volume, FIO_2, and the percentage of endotracheal tube 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% vs 83%; $p = 0.02$), meaning their spontaneous breathing between the SIMV inflations contributed more to the total minute volume. The VT 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.

We determined the proportion of inflations with expiratory VTs outside the recommended 4–6 (6–8) or 4–8 mL/kg (9) ranges. Overall, when using VG, the expiratory VT was greater than 6 mL/kg in 17,675 of 106,765 ventilator inflations (16.5%). Without VG, this occurred in 55% (30,691/56,032 inflations, see **Fig. 2*A***). Expiratory VTs greater than 8 mL/kg occurred only in 2.4% of inflations with VG but in 25.8% without VG. The percentage of inflations exceeding 6 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 Fig. 2, B and C). Without VG, 15 of 32 babies (47%) received an average VTemand of greater than 6 mL/kg (e.g., see **Supplementary Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/PCC/B53; legend, Supplemental Digital Content 4, http://links.lww.com/PCC/B54), whereas with VG this occurred only in five of 45 babies (11%). Without

TABLE 1. Basic Clinical Details and Ventilator Settings of the Patients Included in the Study

Variables	Synchronized Intermittent Mandatory Ventilation With Volume Guarantee			Synchronized Intermittent Mandatory Ventilation (Without Volume Guarantee)			*p*
Number of cases	45			32			
Clinical details	Mean	SD		Mean	SD		*p*[a]
Gestational age (wk)	34.3	5.4		34.5	5.6		0.88
Corrected gestational age (wk)	35.3	4.9		35.7	5.5		0.71
Birth weight (g)	2,368	1,053		2,469	1,210		0.70
Current weight (g)	2,467	1,050		2,558	1,199		0.73
Primary reason for transfer	*n*			*n*			
Respiratory	22			13			
Cardiac	4			5			
Surgical	5			4			
Neurology	14			10			
Respiratory severity score[b]	Median	IQR		Median	IQR		*p*[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 (min)	Median	Range	Total	Median	Range	Total	*p*[c]
	80	20–237	3,559	47	15–136	1,868	0.007
Ventilator settings[d]	Median	IQR		Median	IQR		*p*[c]
Set inspiratory time (s)	0.36	0.35–0.38		0.35	0.34–0.38		0.19
Set ventilatory rate (1/min)	35	27–40		34	28–41		0.32
Set positive end-expiratory pressure (cm H_2O)	6	5–6		5	5–6		0.05
Set peak inflating pressure (cm H_2O)	NA	NA		20	17–21		NA
Maximum allowed inflating pressure (cm H_2O)	22	20–28		NA	NA		NA
Target tidal volume (mL/kg)	4.8	4.4–5.2		NA	NA		NA

IQR = interquartile range, NA = not applicable.

[a]Student *t* test (two-tailed).

[b]Respiratory severity score is the product of F_{IO_2} and mean airway pressure (MAP) (F_{IO_2} × 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 variable was calculated. Data shown in the table are group medians and IQRs of these mean values.

VG, six received (19%) on average greater than 8 mL/kg VTemand while this did not occur in the VG group. The mean PIP of the six recordings with a mean VTemand greater than 8 mL/kg ranged between 17 and 24 cm H_2O.

In the VG group, the average VT of ventilator inflations was considerably below 4 mL/kg in four cases. In one the maximum inflating pressure (Pmax) was set too low to deliver the set expiratory VT. In three cases, the target VT was set at less than 4 mL/kg by the clinical team. In the non-VG group, the set PIP was too low to deliver a VTemand greater than 4 mL/kg in four cases.

The capillary P_{CO_2} values immediately after the transfer were similar in the VG and non-VG groups (group means 6.99 kPa [52.4 mm Hg] vs 7.53 kPa [56.5 mm Hg]; $p = 0.39$). Only six babies had a P_{CO_2} less than 5 kPa (37.5 mm Hg) (two in the VG group and four in the non-VG group), and one infant without VG had a P_{CO_2} less than 4 kPa (30 mm Hg).

DISCUSSION

To our knowledge, this is the first report of using VG ventilation during neonatal transport. We found that babies ventilated with VG had lower and less variable VTs than babies ventilated without VG. Without VG infants frequently received inflations with expiratory VT greater than 6 mL/kg or some greater than 8 mL/kg; this occurred much less frequently during VG.

TABLE 2. **Comparison of the Averages of Ventilation Variables**

Ventilator variable	Synchronized Intermittent Mandatory Ventilation With Volume Guarantee Median (IQR)	Synchronized Intermittent Mandatory Ventilation (Without Volume Guarantee) Median (IQR)	p[a]
Peak inflation pressure (cm H_2O)	15.5 (10.3–18.4)	19.5 (16.7–21.2)	0.0004
Inspiratory tidal volume of ventilator inflations (mL/kg)	5.1 (4.8–5.6)	6.5 (5.5–7.9)	0.0011
Expiratory tidal volume of ventilator inflations (mL/kg)	4.8 (4.5–5.3)	6.0 (4.9–7.6)	0.0011
Percentage of minute volume attributed to ventilator inflations rather than spontaneous breaths between ventilator inflations	66.5 (53.5–83.6)	82.7 (69.3–96.8)	0.0215
Positive end-expiratory pressure (cm H_2O)	5.9 (5.0–6.1)	5.1 (4.9–6.0)	0.0819
Expiratory tidal volume of the spontaneous breaths not associated with ventilator inflations (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
Mean airway pressure (cm H_2O)	7.2 (6.2–8.5)	7.8 (6.8–8.9)	0.1215
F_{IO_2} (%)	29.3 (21.8–35.4)	34.3 (21.3–52.3)	0.1527
Minute volume (L/min/kg)	0.25 (0.21–0.31)	0.27 (0.23–0.35)	0.2060

IQR = interquartile range.

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

For each patient, the arithmetic mean of each ventilator variable was calculated in each recording. Data shown in the table are group medians and IQRs of these mean values for both the SIMV-VG and the SIMV groups.

TABLE 3. **Comparison of the Variability of Ventilation Variables**

Ventilator Variable	Synchronized Intermittent Mandatory Ventilation With Volume Guarantee Median (IQR)	Synchronized Intermittent Mandatory Ventilation (Without Volume Guarantee) Median (IQR)	p[a]
Peak inflation pressure (cm H_2O)	2.7 (2.0–3.8)	1.3 (0.6–1.5)	0.0000002
Expiratory tidal volume of ventilator inflations (mL/kg)	0.8 (0.6–0.9)	1.3 (0.9–1.8)	0.0004
Mean airway pressure (cm H_2O)	0.9 (0.6–1.2)	0.6 (0.4–0.9)	0.0628
Inspiratory tidal volume of ventilator inflations (mL/kg)	0.8 (0.6–1.7)	1.2 (0.9–1.9)	0.0637
Minute volume (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
Percentage of minute volume attributed to ventilator inflations rather than spontaneous breaths between ventilator inflations	9.9 (8.0–14.1)	8.6 (6.0–11.8)	0.1548
Expiratory tidal volume of the spontaneous breaths not associated with ventilator inflations (mL/kg)	1.0 (0.8–1.4)	1.2 (0.7–1.6)	0.2993
Positive end-expiratory pressure (cm H_2O)	0.4 (0.2–0.7)	0.3 (0.3–0.6)	0.4348
F_{IO_2} (%)	2.6 (0.0–5.0)	1.8 (0.0–5.5)	0.4354

IQR = interquartile range.

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

For each patient, the SD of each ventilator variable was calculated in each recording. Data shown in the table are group medians and IQRs of these SD values for both the synchronized intermittent mandatory ventilation with volume guarantee and the synchronized intermittent mandatory ventilation (without volume guarantee) groups.

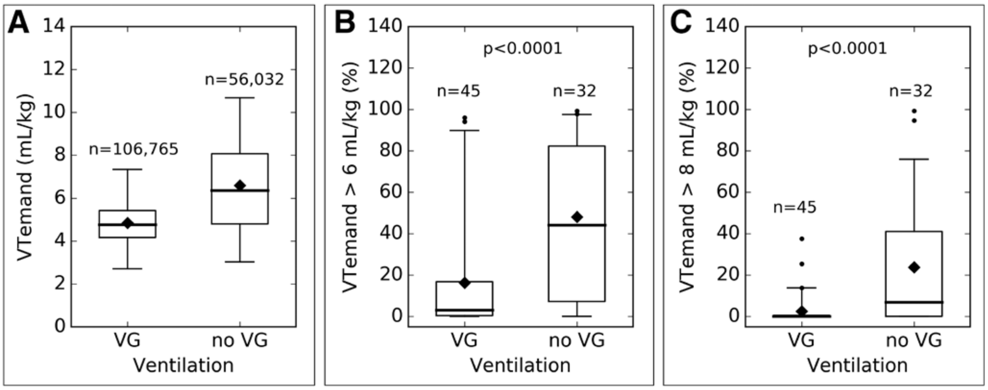

Figure 2. Comparison of tidal volumes in infants ventilated with or without volume guarantee. **A**, *Boxplots* showing the distribution of the expiratory tidal volumes of ventilator inflations (VTemand) in all recordings combined. Synchronized intermittent mandatory ventilation with volume guarantee (SIMV-VG) ($n = 106{,}765$) and synchronized intermittent mandatory ventilation without volume guarantee (SIMV) ($n = 56{,}032$) inflations are compared. Due to the very large sample sizes, statistical significance testing would not be appropriate. **B** and **C**, *Boxplots* showing the distribution of the percentage of inflations with tidal volumes greater than 6 mL/kg (**B**) or greater than 8 mL/kg (**C**) in the individual recordings. Inflations with tidal volumes over 6 mL/kg or greater than 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 5–95th centiles (*error bars*) are shown. Outliers are shown as *filled circles*.

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 cm H_2O. It has been suggested that high VTs more than a high inflating pressure are associated with neonatal lung injury (13, 14). However, clinicians may be misled by thinking that if they ventilate infants without VG but use PIP they consider low (e.g., < 20 cm H_2O), large VTs could not occur. It has also been established that even brief hypocapnia is associated with adverse neurodevelopmental outcome both in term and preterm babies (15, 16). The P_{CO_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 VTs do not necessarily cause over-ventilation and hypocapnia.

A limitation of our study is that we cannot comment on the clinical significance of larger VTs occurring during transport without VG because we did not collect data on clinical outcomes. The relatively short duration of ventilation during transport (the longest was < 4 hr) may limit the effect of large VTs on long-term outcomes. However, animal data suggest that even short periods of moderately high VTs can result in lung injury. In rats, mechanical ventilation with large VTs for 30 minutes did not cause histologic changes in the lung but changed the expression of several genes involved in inflammation and stress response (17). In ventilated preterm lambs even a 15-minute period of ventilation with 6–7 mL/kg increased early markers of lung injury and inflammation (18). In a recent article, extremely preterm infants receiving mask ventilation with VTs greater than 6 mL/kg had a significantly higher occurrence rate of intraventricular hemorrhage (19).

During synchronized ventilator inflations VT delivery results from the combination of the baby's breathing effort and the ventilator's inflating pressure. When the baby has strong breathing effort during VG ventilation, the ventilator's PIP is quickly reduced to just above the PEEP level, making the ventilator's driving pressure (PIP–PEEP) and hence contribution to the work of breathing minimal (6). Without VG, the set PIP results in larger VTs than it would have done in an apneic baby. However, it has not been established that the large VTs achieved this way are as damaging as the ones delivered to an apneic baby (17–19). Clinical studies will be required to clarify the significance of these large VTs.

The total minute ventilation during SIMV is the sum of ventilator inflations (synchronized 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 ventilatory rate was similar. In a short crossover study of infants ventilated with SIMV-VG and SIMV on a NICU, Herrera et al (20) 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. This may be due to larger spontaneous VTs or faster spontaneous breathing rate or both. Indeed, the VTespon 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 VTs 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.

Another possible limitation of our study is that we used volume triggering rather than flow triggering and most NICUs and clinicians use flow triggering rather volume triggering. However, we do not think using volume triggering has significantly influenced our data or reduced the generalizability of our findings as all infants in both groups had volume triggering.

A strength of our study is the use of computational data download with high sampling rate (one in 2 s). Therefore, our data are not affected by observational bias and are based on greater than 150,000 data points. The processing of these large datasets using the open-source Python computer language and its data packages allows for reproducible data analysis.

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.

CONCLUSIONS

VTs greater than 6 mL/kg and even greater than 8 mL/kg frequently occur during neonatal transport using SIMV without VG and using VG helps to avoid them. SIMV-VG is associated with a larger contribution of spontaneous breaths to minute ventilation compared with SIMV without VG.

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