Effect of Nitric Oxide Delivery Device on Tidal Volume Accuracy During Mechanical Ventilation at Small Tidal Volumes

Courtney D Ranallo, Tracy L Thurman, Shirley J Holt, Summer G Frank-Pearce, Michael P Anderson, and Mark J Heulitt

BACKGROUND: Inhaled nitric oxide (INO) is used in infants as a therapy for elevated pulmonary vascular resistance. When INO is delivered at low tidal volumes, displayed inspiratory and expiratory volumes vary widely. We hypothesize that volume is removed by the sampling line during the ventilation cycle, and this results in a net volume loss at low tidal volumes. This study aimed to measure the volumes delivered and to assess the accuracy of displayed ventilator values using a test lung. METHODS: A test lung was connected to a ventilator and an INO delivery system. All tests were performed with stable mode settings across volumes of 18, 30, 42, and 60 mL. Flow measured with a pneumotachometer attached between the test lung and the circuit assessed the percent error between inspiratory and expiratory volumes measured by the pneumotachometer measured and displayed on the ventilator under various INO/sample line conditions to determine where and how much volume was being displaced. RESULTS: Displayed and measured inspiratory volumes had small variations between the INO/sample line conditions and baseline. However, expiratory volumes, with the sample line connected, exhibited large percent error values that increased (−14, −20, −27, and −34) as tidal volume decreased (60, 42, 30, and 18 mL) and error was significantly larger compared to baseline in all tidal volumes ($P < .01$) with and without INO delivery. CONCLUSIONS: We concluded that inspiratory volumes were not affected by INO delivery, but additional removal of volume in the expiratory phase of the breath cycle by the sampling line results in a large error in the displayed expiratory volume.
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Introduction

Inhaled nitric oxide (INO) causes selective pulmonary vasodilation by increasing cyclic guanosine monophosphate levels that relax smooth muscles. The Food and Drug Administration has approved the use of INO for persistent pulmonary hypertension in newborns, but there are numerous off-label uses of INO, including pulmonary hypertension related to ARDS and congenital heart disease. INO can be safely delivered to infants and children with effective local pulmonary vasodilation without systemic effects.[1-3] Although the survival benefits of INO in acute lung injury remain controversial, the use of INO has been shown to reduce pulmonary artery pressure in patients with

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pulmonary hypertension, reduce pulmonary hypertension crises in high-risk patients after congenital heart defect surgery, and shorten duration of mechanical ventilation in patients with hypoxic respiratory failure.[4-6] Therefore, INO delivery will continue to have a clinical indication in infants and requires safe delivery practices at low tidal volume (V_T).

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Safe delivery of INO requires continuous monitoring of oxygen, NO, and NO_2 concentrations.[7-9] During INO delivery with the INOMax DSIR (Mallinckrodt, Staines-upon-Thames, United Kingdom), NO is added by the injector module in proportion to the INO setting and the circuit flow to the inspiratory limb of the ventilator circuit prior to the humidifier, and the sample line continuously removes gas (0.23 L/min) for monitoring near the Y of the endotracheal tube, a distance that is required to allow for adequate mixing.[10,11] At the bedside, we have observed that measured inspiratory and expiratory volumes vary widely when INO is being used at low V_T. This discrepancy raises concern about the accuracy of the volume being delivered to the patient, especially at times when precise ventilation and oxygenation are imperative. Volumes introduced by INO and removed by sampling are estimated by the manufacturer (Ikaria) and would predict a net positive volume balance at high V_T (ie, 500 mL predicts a net change of 0.2 L/min).[12] However, clinically observed expired volumes are much less than inspired volumes, indicating a net negative volume balance. The manufacturer-provided formula (Net change = [INOMax dose × minute ventilation/INOMax concentration – INOMax dose] – 0.23 L/min) used with low volumes predicts a net volume loss. Therefore, we hypothesize that removal of volume by the sampling line during the respiratory cycle results in a net volume loss at low V_T. Furthermore, given the location of the sampling line in the inspiratory limb, it is unclear whether the net volume loss occurs during the inspiratory phase, equally throughout the cycle, or during the expiratory phase, and how this net volume loss affects the minute ventilation of the patient. This was an in vitro study designed to measure the net volume difference at low V_T to predict the effects of INO on minute ventilation. The primary outcome is the difference between the ventilator-displayed V_T (inspiratory and expiratory V_T) and pneumotachometer-measured V_T (proximal inspiratory and expiratory V_T).

QUICK LOOK

Current knowledge

Inhaled nitric oxide (INO) delivery devices interface with the ventilator circuit to deliver NO safely. Volume changes during INO delivery are more relevant at low tidal volumes and have not been studied. Infants receiving INO during mechanical ventilation have displayed volumes that vary widely and cause concern for accuracy of delivered volumes and the effects on minute ventilation at low tidal volumes.

What this paper contributes to our knowledge

On the basis of volumes measured by the ventilator, it would appear that there is a considerable net loss of volume with the INO delivery device, but in fact the patient receives a tidal volume very close to that which is prescribed, and the apparent net loss only occurs during expiratory phase sampling. This is due to continuous removal of volume by the sample line, the bulk of which occurs during the expiratory phase of the respiratory cycle.

Methods

This project was conducted at Arkansas Children's Hospital Research Institute. A test lung (Bio-Tek Ventilator Tester, Fluke Biomedical, Everett, Washington) with the infant side was used for all tests. The test lung with compliance of 0.02 L/cm H_2O and resistance of 8 cm H_2O/0.5 L/s) was connected to the Servo-I ventilator (Maquet, Bridgewater, New Jersey) and the INOMax DSIR. The test lung was ventilated using pressure-regulated volume control ventilation, set PEEP of 5 cm H_2O, set V_T of 18, 30, 42, and 60 mL, and set breathing frequency of 30 breaths/min. The INO dose was set at 20 ppm for all test conditions. Measurements of respiratory flow and pressure waveforms were acquired using the Biopac MP100 System (Biopac Systems, Santa Barbara, California). A 0–35 L/min pneumotachometer (Hans Rudolph, Shawnee, Kansas) was utilized for data collection. The pneumotachometer was attached directly to the test lung in line with the ventilator circuit and the INO sample line (Fig. 1). Flow was calibrated using a flow meter. Volume measurements were obtained through the computer by integrating the flow signal. Volume was verified with a calibrated syringe (Hans Rudolph, Kansas City, Missouri). To monitor pressure, the pneumotachometer was equipped with a pressure hose and a barb-type port that allowed airway-pressure sampling. Pressure was calibrated with a manometer. All output signals were routed via an analog channel box into the Biopac MP100 data acquisition unit to convert them into digital signals that could then be processed by a computer.

Data were collected for each of the 4 V_T settings in each of the 4 conditions: (A) baseline (ie, ventilator only); (B) ventilator with INO and without the sample line; (C) ventilator with the sampling line and without INO; and (D) the

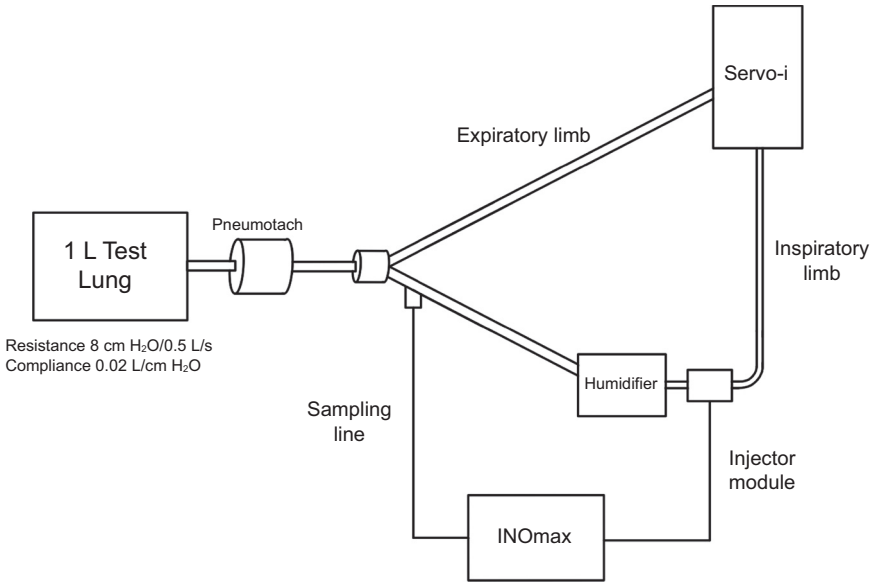

Fig. 1. Test lung model with Servo-i, INOMax, and pnuemotachograph.

clinical scenario (ie, ventilator with INO and sampling line). Flow waveforms obtained with the pneumotachometer were analyzed to measure inspiratory and expiratory V_T for 10 consecutive breaths. Values for inspiratory and expiratory V_T that were displayed by the ventilator were matched timewise and compared to measurements obtained with the pneumotachometer. Displayed measurements were collected from the ventilator via a memory card.

The primary outcome of differences between the ventilator-displayed inspiratory and expiratory V_T and the pneumotachometer-measured inspiratory and expiratory V_T were compared in terms of the inspiratory V_T percent error and expiratory V_T percent error between INO/sample line categories at each V_T, where percent error = ([displayed V_T – measured V_T]/Measured V_T) × 100.

The inspiratory and expiratory V_T levels were not normally distributed; therefore, the Kruskal-Wallis test was used to identify differences by INO/sample line category within each tested V_T level and by V_T within each INO/sample line category. Where the omnibus Kruskal-Wallis test identified a difference between the groups, pairwise comparisons were made with the Steel-Dwass adjustment for multiple comparisons between the categories and the reference (control) group.

For comparisons between INO/sample line categories within each V_T, the control group was the baseline situation (ie, ventilator only, without INO and without the sampling line) and the primary group of interest was the clinical situation seen in practice (ie, ventilator with INO and sampling line). For comparisons between V_T within each INO/sample line category, the control group was the V_T = 60 mL because it is the highest volume. An alpha of 0.05 was used to assess the significance of all statistical tests. Data were analyzed with SAS 9.3 (SAS Institute, Cary, North Carolina) and JMP 11 (SAS Institute, Cary, North Carolina).

Results

Overall, the differences in volume during the inspiratory phase were small regardless of whether the sampling line was connected, whereas expiratory volume differences were significantly larger when the sampling line was connected.

Table 1 presents the displayed and measured volumes during the inspiratory phase. During inspiration, there was very little difference between displayed and measured V_T and within each V_T for the 4 conditions. When INO was added to the ventilator circuit (ie, condition B), the increase in V_T became proportionally larger (ie, 20.5, 34, 47, and 66.8 mL, respectively) as INO gas was added to the circuit flow proportionally to deliver the desired INO concentration. This outcome was expected, thus increasing the percent error from baseline (Fig. 2). The conditions with the sampling line connected exhibited a V_T closer to the ventilator-displayed V_T, indicating the removal of a small amount of gas during the inspiratory phase of the ventilation cycle (ie, 1.5–2 mL). Steel-Dwass analysis revealed no significant difference in inspiratory V_T percent error between the condition D (ie, INO and sample line) and the baseline condition (ie, ventilator only), except for condition D at V_T of 18 mL ($P = .032$) (Table 1).

During the expiratory phase of ventilation, larger errors were noted between the volumes measured with the pneumotachometer and those displayed on the ventilator (Table 2). There was a statistically significant difference in percent

Table 1. Summary of Displayed and Measured Inspiratory V_T Measurements

V_T, mL	Conditions		No.	Displayed Inspiratory V_T	Measured Inspiratory V_T	Inspiratory V_T Error, %	P^*
	INO	Sample Line					
18	A: Without INO	Disconnected	10	18.0 (18.0–18.0)	2.0 (19.0–21.0)	−7.4 (−14.3 to −5.3)	Control
	B: With INO	Disconnected	10	18.0 (18.0–18.0)	20.5 (2.0–21.0)	−12.1 (−14.3 to −1.0)	.42
	C: Without INO	Connected	10	18.0 (18.0–18.0)	18.5 (18.0–19.0)	−2.6 (−5.3 to 0.0)	.02
	D: With INO	Connected	10	18.0 (18.0–19.0)	19.0 (18.0–2.0)	−2.5 (−5.0 to 0.0)	.032
30	A: Without INO	Disconnected	10	3.0 (3.0–3.0)	33.0 (32.0–34.0)	−7.5 (−11.8 to −6.3)	Control
	B: With INO	Disconnected	10	3.0 (3.0–3.0)	34.0 (33.0–35.0)	−11.7 (−14.3 to −9.1)	.13
	C: Without INO	Connected	10	3.0 (3.0–3.0)	31.0 (3.0–32.0)	−1.6 (−6.3 to 0.0)	.005
	D: With INO	Connected	10	3.0 (3.0–3.0)	32.0 (31.0–33.0)	−4.6 (−9.1 to −3.2)	.16
42	A: Without INO	Disconnected	10	42.0 (42.0–43.0)	46.0 (45.0–47.0)	−7.6 (−8.5 to −6.7)	Control
	B: With INO	Disconnected	10	42.0 (41.0–42.0)	47.0 (46.0–48.0)	−11.7 (−14.6 to −8.7)	.08
	C: Without INO	Connected	10	42.0 (42.0–42.0)	44.0 (43.0–45.0)	−4.5 (−6.7 to −2.3)	.03
	D: With INO	Connected	10	42.0 (42.0–43.0)	45.5 (44.0–47.0)	−6.5 (−8.5 to −4.5)	.78
60	A: Without INO	Disconnected	10	6.0 (6.0–61.0)	65.0 (64.0–66.0)	−6.9 (−9.1 to −6.3)	Control
	B: With INO	Disconnected	10	6.0 (6.0–6.0)	67.0 (66.0–68.0)	−9.8 (−11.8 to −9.1)	.037
	C: Without INO	Connected	10	6.0 (6.0–61.0)	63.0 (62.0–64.0)	−4.7 (−4.8 to −3.2)	.01
	D: With INO	Connected	10	6.0 (6.0–6.0)	65.0 (64.0–66.0)	−6.9 (−9.1 to −6.3)	> .99

Data are presented as median (interquartile range).
* Steel-Dwass analysis.
V_T = tidal volume
INO = inhaled nitric oxide

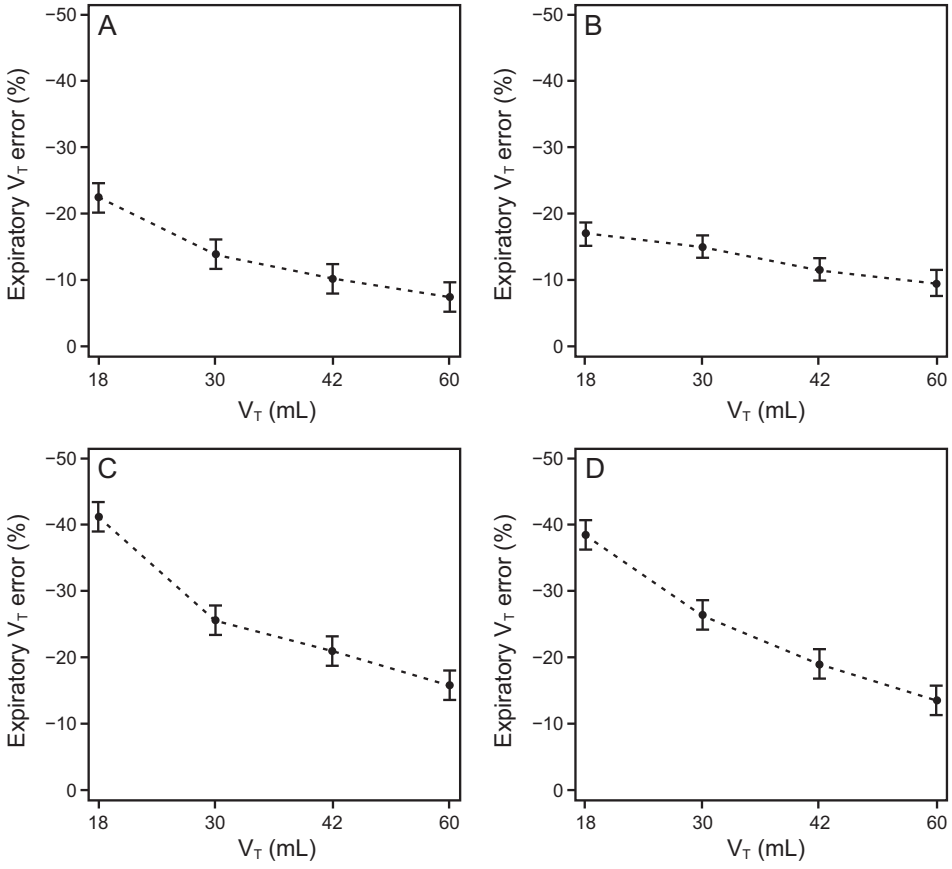

Fig. 2. Comparisons of the 4 conditions of inspiratory V_T error. A: Baseline condition. B: INO delivery without sample line. C: Sampling line without INO delivery. D: Clinical INO delivery. There were no significant differences between tidal volumes or conditions. V_T = tidal volume.

Table 2. Summary of Displayed and Measured Expiratory V_T Measurements

V_T, mL	Conditions		No.	Displayed Expiratory V_T	Measured Expiratory V_T	Expiratory V_T Error, %	P^*
	INO	Sample Line					
18	A: Without INO	Disconnected	10	16.0 (16.0–17.0)	20.5 (2.0–21.0)	−23.8 (−23.8 to −15.0)	Control
	B: With INO	Disconnected	10	17.0 (16.0–18.0)	20.5 (2.0–21.0)	−17.0 (−23.8 to −1.0)	.52
	C: Without INO	Connected	10	11.0 (11.0–12.0)	18.5 (18.0–19.0)	−40.5 (−42.1 to −33.3)	.002
	D: With INO	Connected	10	12.0 (12.0–13.0)	19.0 (18.0–2.0)	−34.2 (−4.0 to −27.8)	.008
30	A: Without INO	Disconnected	10	28.0 (27.0–28.0)	32.5 (32.0–33.0)	−15.2 (−16.1 to −12.5)	Control
	B: With INO	Disconnected	10	29.0 (29.0–29.0)	33.5 (33.0–34.0)	−14.7 (−14.7 to −12.1)	.61
	C: Without INO	Connected	10	22.0 (22.0–23.0)	30.5 (3.0–31.0)	−27.8 (−29.0 to −23.3)	.001
	D: With INO	Connected	10	23.0 (23.0–24.0)	31.5 (31.0–33.0)	−26.5 (−28.1 to −25.8)	.93
42	A: Without INO	Disconnected	10	4.0 (4.0–41.0)	45.5 (45.0–46.0)	−13.0 (−13.0 to −10.9)	Control
	B: With INO	Disconnected	10	40.5 (4.0–42.0)	46.0 (45.0–46.0)	−12.0 (−13.0 to −8.7)	.92
	C: Without INO	Connected	10	33.5 (33.0–34.0)	43.0 (43.0–43.0)	−22.1 (−23.3 to −20.9)	<.001
	D: With INO	Connected	10	36.0 (36.0–36.0)	44.5 (44.0–45.0)	−20.0 (−20.0 to −18.2)	<.001
60	A: Without INO	Disconnected	10	58.0 (58.0–58.0)	63.0 (63.0–63.0)	−7.9 (−7.9 to −7.9)	Control
	B: With INO	Disconnected	10	6.0 (6.0–61.0)	65.0 (65.0–65.0)	−7.7 (−7.7 to −7.6)	.14
	C: Without INO	Connected	10	51.0 (5.0–51.0)	6.0 (59.0–61.0)	−15.8 (−16.4 to −13.6)	<.001
	D: With INO	Connected	10	54.0 (53.0–55.0)	63.0 (63.0–63.0)	−14.3 (−15.9 to −12.7)	<.001

Data are presented as median (interquartile range).
* Steel-Dwass analysis.
V_T = tidal volume
INO = inhaled nitric oxide

error between the clinical scenario (ie, condition D) and the baseline condition at all V_T settings (all Steel-Dwass $P <$ .001). Thus, the expiratory V_T percent error increased (−14%, −20%, −26%, and −34%) as V_T decreased (60, 42, 30, and 18 mL), respectively, because the amount of volume removed by the sampling line remained closely fixed and thus had a proportional effect (Table 2). When comparing condition C (ie, sampling line connected without INO) to baseline, the expiratory V_T percent error was significantly higher for all V_T settings ($P = .008$, .001, .001, and .001 for V_T of 18, 30, 42, and 60 mL, respectively). As V_T decreases, the effect of having the sample line connected shows a significantly steeper increase in the expiratory V_T percent error than when the sample line is disconnected and capped. When INO was added without the sampling line connected (ie, condition B), the expiratory V_T percent error was not significantly different than baseline across all V_T settings (Fig. 3).

Discussion

Mechanical ventilation and delivery of INO at low V_T has its challenges. No previous studies have looked at the volume changes with INO administration at low V_T. Continuous sampling would be expected to have a proportionally greater impact at lower V_T than at higher V_T. Although continuous sampling occurs, our data demonstrate that volume removal is not equally distributed between the inspiratory phase and the expiratory phase of the ventilator cycle. There is a net loss of volume for each respiratory cycle, as predicted by the manufacturer's formula, but most of that loss occurs during the expiratory phase. Therefore, the volume delivery to the patient is closer to the prescribed inspiratory V_T than previously expected and would not expect to have dramatic effects on minute ventilation.

We found that the difference in the volume added by the introduction of INO into the ventilator circuit and the removal of volume by the sampling system resulted in a net gain of volume to the patient during the inspiratory phase of the breath cycle. We noted that there was a difference in displayed V_T (18, 30, 42, and 60 mL) and V_T measured at baseline, which resulted in a larger V_T delivered to the test lung (20, 33, 46, and 65 mL, respectively). This baseline inspiratory V_T error was not significant but represents an underestimation by the ventilator.

When examining the effect of the sampling line in isolation (ie, the difference in volume between condition A and condition C), the mean volume removed was 1.5–2 mL across all V_T settings tested. During the expiratory phase, 7.5–9 mL were removed for sampling. However, at baseline an error of 3–4 mL was detected. Thus, even when accounting for the baseline error, the remaining volume removed by the sampling line was larger than the volume removed during the inspiratory phase. Therefore, the removal of additional volume in the expiratory phase of the breath cycle by the sampling system results in a percent error between the displayed expiratory V_T and the

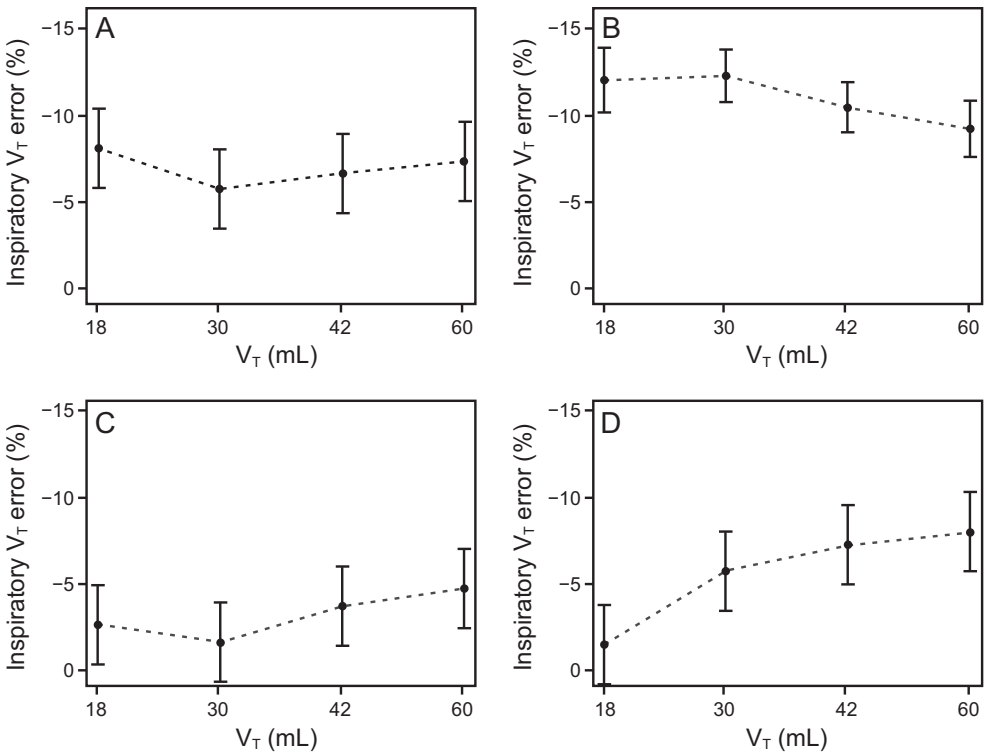

Fig. 3. Comparisons of the 4 conditions of expiratory V_T error (%). When the sample line is attached, as in (C) and (D), there is a statistically significant larger error in volume than when it is not attached, as in (A; baseline condition) and (B). V_T = tidal volume.

measured expiratory V_T that is larger than the inspiratory V_T percent error. This is due to unequal sampling during the phases of the respiratory cycle. Sampling during inspiratory flow allows detection of F_{IO_2}, NO_2 production in the humidifier, and NO delivery, which is necessary for safe delivery. However, sampling during expiration makes quantifying endotracheal leaks more difficult.

The manufacturer's formula would predict a volume removal of 210 mL/min at V_T = 18 mL (breathing frequency = 30 breaths/min), resulting in a loss of circuit volume of approximately 40%. However, our measurements indicate a removal of ~135 mL/min (ie, 4.5 mL/cycle at the same breathing frequency). For the largest V_T studied (ie, 60 mL), the measured volume removed per cycle was 180 mL/min, which was closer to the predicted value of 184 mL/min based on the formula and the predicted percent of loss (ie, 11%).

Therefore, the patient receives a V_T close to the prescribed V_T during inspiration because the baseline error, the addition of INO volume, and the volume removed from the sampling line result in delivered volumes close to the displayed inspiratory V_T. During the expiratory cycle, volume is removed again after it leaves the patient and before it reaches the expiratory cassette. Therefore, the displayed expiratory V_T does not indicate loss of prescribed inspiratory V_T alone, but accounts for the total volume removed during the whole respiratory cycle, with the expiratory phase contributing to the majority of the lost volume.

We chose an in vitro design to isolate the volume changes with the addition of INO and the removal of volume by the sampling line. The use of a test lung allowed us to have consistent conditions in which to measure flows that would be expected to change during changes in resistance and compliance. We chose V_T settings that would deliver 6 mL/kg to pediatric subjects with a weight of 3 kg, 5 kg, 7 kg, or 10 kg, which represents a clinical range in the population of interest. Our goal was to determine the volume change accuracy compared to the manufacturer-provided formula because there have been no previous studies examining net balance of volume at low V_T settings. We also set out to determine whether continuous sampling resulted in equal volume removal across the respiratory cycle, which does appear to be the case according to our data.

This study has its limitations. We used only one ventilator, the Servo-I; other mechanical ventilators, modes of ventilation, and circuit designs may allow for different flow and sampling patterns that were not evaluated in our model. In addition, changes in a patients resistance and compliance may alter the pressures required for flow delivery and thus may allow for changes in sampling volumes taken by the sampling line.

Conclusions

Safe and effective use of INO at low V_T requires understanding of volume changes that occur with INO proportional injection and continuous sampling. Proximal flow sensors may be the best way to ensure volume accuracy given our data in using a proximal pneumotachograph. More studies on this topic are warranted.

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