Intensive Care Med
DOI 10.1007/s00134-012-2601-5

PEDIATRIC ORIGINAL

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Impact of volume guarantee on synchronized ventilation in preterm infants: a randomized controlled trial

Received: 20 January 2012
Accepted: 27 April 2012

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Abstract *Purpose:* The aim of this randomized controlled trial was to assess whether the addition of volume guarantee (VG) to triggered ventilation decreases the duration of ventilation in very low birth weight (VLBW) infants with respiratory distress syndrome (RDS). *Methods:* Infants were randomized into two groups to initially receive either assist/control (A/C) or A/C plus VG ventilation and then weaned with synchronized intermittent mandatory ventilation (SIMV) or SIMV plus VG. *Results:* Forty-five infants were included in the study. The demographic and clinical characteristics, values of tidal volume (VT), peak inspiratory pressure (PIP), fraction of inspired oxygen, carbon dioxide tension, and pH were similar for all participating infants initially. During the follow-up, the VT levels were more stable, and the PIP levels were significantly decreasing in the VG group. Although the duration of ventilation was shorter in the VG group, this trend was not statistically significant. The incidences of death and bronchopulmonary dysplasia (BPD) were not significantly different, but the combined outcome of death or BPD was lower in the VG group. Although the VG group experienced less frequent BPD, periventricular leukomalacia, and intraventricular hemorrhage, these differences were not statistically different. *Conclusion:* The VG option, when combined with A/C (in the acute phase of RDS) and SIMV (in the weaning), reduced VT variability, and may have shortened the duration of ventilation in VLBW infants. Overall mortality and BPD rates did not change, but their combined outcome was significantly improved in infants treated with VG modes as compared to those treated with synchronized pressure-limited modes alone.

Keywords Volume guarantee · Mechanical ventilation · VLBW · RDS · Bronchopulmonary dysplasia · Premature

Introduction

Despite a shift towards non-invasive respiratory support, pressure-limited ventilation (PLV) strategies, especially synchronized intermittent mandatory ventilation (SIMV) and assist/control (A/C) modes, continue to be the primary methods of invasive ventilation in preterm infants [1].

Volume-targeted ventilation (VTV) strategies have been developed, which aim to deliver a consistent VT. A recent meta-analysis of randomized controlled trials of neonatal VTV versus PLV found that VTV significantly reduced the rates of death, bronchopulmonary dysplasia, pneumothorax, hypocarbia, and severe cranial ultrasound abnormalities [2]. Depending on the ventilator design,

Published online: 23 May 2012

VTV modes vary in terms of how they measure and control VT delivery. On the basis of the aforementioned meta-analysis, neonatal VTV using the Bird VIP infant ventilator is probably the most widely studied mode. Volume guarantee (VG) ventilation is a VTV mode that is only available on the Drager Babylog 8000 plus and the VN500 ventilators and can be combined with any of the standard synchronized ventilator modes [A/C, SIMV, and pressure support ventilation (PSV)] [2].

We hypothesized that the addition of VG ventilation to PLV may result in a reduction of the duration of mechanical ventilation in premature infants with respiratory distress syndrome (RDS). The secondary objective was to evaluate the effects of VG on the incidence of mortality and morbidities, such as bronchopulmonary dysplasia (BPD), air leak syndromes, patent ductus arteriosus (PDA), and intraventricular hemorrhage (IVH).

Materials and methods

Study design and interventions

This randomized, controlled, prospective trial was conducted in the level III neonatal intensive care unit (NICU) at Dokuz Eylul University Hospital in Izmir, Turkey, between January 2006 and December 2008. All of the participants were inborn and ventilated from the time of admission to the NICU by a positive pressure ventilator (Babylog 8000 plus, Draeger, Lubeck, Germany) that allows the clinician to combine synchronized pressure-limited modes with VG. All 58 enrolled infants were initially ventilated using the A/C mode and all of them received surfactant (Survanta®, 100 mg/kg) in the delivery room or in the NICU, depending on where endotracheal intubation was performed.

Infants were randomized to either the PLV group (group I) or the VG group (group II) using a block randomization with random block sizes. Blinding was not possible due to the nature of the intervention, so the random selected block sizes were chosen to help maintain balance in terms of treatment assignment and reduce the potential for selection bias. The envelopes containing instructions were sequentially numbered and opaque.

Patients

Forty-five inborn premature infants at 23–31 weeks gestation who required tracheal intubation within the first hour of life and mechanical ventilation for at least the first 24 h of life owing to severe RDS were considered eligible for the study. Twenty-six infants were excluded owing to the presence of major congenital anomalies (two infants), absence of parental consent (five infants), unavailability of the study ventilator (six infants), or extubation before 24 h (six infants from group I and seven infants from group II; more specifically, three patients in each group were self-extubated in the first 3 h and were then treated with non-invasive ventilation). The study conforms to the conditions of the Declaration of Helsinki 1995 and the 2004 revisions and was approved by the Committee on Human Experimentation at Dokuz Eylül University in Izmir, Turkey.

Ventilation strategies

For the PLV group, the ventilator settings remained unchanged from that selected by the clinical team at the time of intubation. The ventilator strategy in both groups was similar: the peak inspiratory pressure (PIP) or VT for the VG group was set at the minimal level to provide normal excursion of the chest. Because the chest excursion is an insensitive parameter used to assess adequate VT, we also checked the VT levels delivered by the initial PIP on ventilator monitor, and the peak pressure was set to obtain an initial VT of 4–6 ml/kg even in the A/C mode. FiO_2 was given as needed to achieve an arterial oxygen saturation (SpO_2) between 88 and 93 % by pulse oximetry. Inspiratory time and positive end-expiratory pressure were set by the clinical team for both groups at 0.3–0.4 (min–max) s and 4–6 (min–max) cmH_2O, respectively. In the A/C mode, the PIP was adjusted by increments of 1–2 cmH_2O by the clinical team to keep the PCO_2 values inside the target range. During the first 24 h of life, the target range for PCO_2 and pH values were 40–60 mmHg and 7.25–7.40, respectively, in both groups.

In the VG mode, the VT was set at 4 ml/kg initially on the basis of our clinical experience. The PIP limit was set at 15–20 % above the average PIP needed to achieve the target VT. Subsequently, the set VT was adjusted by the clinical team by increments of 0.5 ml/kg as frequently as necessary when the PCO_2 was outside the target range. Arterialized capillary blood gases were measured on admission, at the 1st and 4th hour after randomization, and then at 4–6 h intervals or more often as needed. The infants were switched from the A/C to the SIMV mode for weaning when the need to increase or decrease the PIP in the PLV group or the VT in the VG group ceased on the basis of each infant's blood gases and clinical status. The ventilatory rate was then reduced using the SIMV mode of the ventilator and starting at an SIMV rate of 40 bpm. If the blood gas analyses taken 4 h after a change were within normal limits during the weaning process, we continued with these settings for 4 h until new blood gas measurements were taken. Thereafter, the rate was reduced in a stepwise fashion with a prolonged expiratory time (1, 2, 3, and 5 s). At 18 bpm, all infants were put on aminophylline. Those babies who were treated with

$FiO_2 < 30$ % and tolerated an expiratory time of 5 s were then extubated to nasal continuous positive airway pressure (CPAP). The reintubation criteria were the same in both groups, and included at least one of the following: a pH < 7.25 and $PCO_2 > 60$ mmHg, $SpO_2 < 88$ % on $FiO_2 < 60$ %, more than two episodes of apnea per hour [defined as cessation of breathing for 20 or <20 s if associated with cyanosis and/or bradycardia (heart rate <100 per min)], or any episode of apnea that did not respond to tactile stimulation and required bag and mask ventilation.

Data acquisition and analysis

The selected outcome variables included differences and variables derived from the VT, mean airway pressure (MAP), and PIP (the working pressure in the VG group). Variables were recorded continuously at 10-s intervals using proprietary software called Babyview1 (Draeger, Inc., Lubeck, Germany). The data were then exported into a spreadsheet (Microsoft Excel, Microsoft Corp., Redmond, WA) for analysis. The data were averaged over 10-min periods, and the mean values were compared between the groups at the 1st, 2nd, 4th, 8th, 12th, 16th, and 24th hours of intubation. Infants were monitored using pulse oximetry and blood pressure measurements. The blood gas analysis (BGA) of arterialized capillary samples (i.e., from the warmed heel) were performed at admission and at the 1st, 4th, 8th, 12th, 16th, and 24th hours after randomization using a blood gas analyzer (ABLTM 700 Radiometer, Copenhagen, Denmark).

We also recorded the duration of ventilation and the incidence of PDA (required treatment), air leaks, IVH, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP, stage > 2), necrotizing enterocolitis (NEC—at least Bell stage 3), BPD (oxygen dependency at 36 weeks of postconceptional age), and postnatal steroid treatment. Maternal and neonatal demographic and clinical characteristics were also recorded. The diagnosis of chorioamnionitis was accomplished both clinically and histologically [3].

Statistics

Unpaired data were compared using the chi-square test for categorical variables and the Student's *t* test or the Mann–Whitney test for continuous variables as appropriate. Changes in the mean MAP, FiO_2, PCO_2, VT, and PIP levels over various times in each study group were analyzed using repeated measures ANOVA with a Greenhouse–Geisser correction. The repeated measures ANOVA generated an *F* statistic that is used to determine statistical significance. If the ANOVA was statistically significant for repeated measures, we then ran post hoc tests (i.e., Bonferroni) to discover which specific means differed. A *p* value less than 0.05 was considered significant. Herein, values are presented as mean ± SD if the data are normally distributed and assessed by the Kolmogorov–Smirnov test or the median with quartiles. Statistical analyses were performed using the SPSS software package for Windows (SPSS, Inc., Chicago, IL).

Our previous experiences with conventional ventilation mode showed that 80 % of the infants failed to extubate at the 48th postnatal hour. From this experience, a sample size calculation determined that 22 babies per group would be needed to show a 50 % difference between the two groups in terms of extubation failure at the 48th postnatal hour with a two-sided alpha of 0.05 and 80 % power.

Results

Forty-five infants ventilated for RDS were included in the study. Twenty-two of the infants were randomly assigned to the PLV group, whereas 23 of them were randomly assigned to the VG group during the first hour of life. No significant differences were observed between the two groups in terms of the antenatal glucocorticoid treatment and other recorded antenatal characteristics. None of these infants required cardiac massage or drugs during resuscitation at birth. Thirty-nine infants were intubated and administered surfactant in the delivery room, whereas the remaining six infants (two infants in the PLV, and four infants in the VG group) were intubated and received surfactant within the first hour of life. The requirement for repeated surfactant instillations was not significantly different between the two groups ($p = 0.67$). In the repeat surfactant-treated infants, two infants in both groups were given three doses, whereas the others received two doses. Endotracheal tube leaks in all enrolled infants were persistently below 30 % of the expiratory VTs. The average degree of leak was equivalent in the two groups. The demographic and clinical characteristics of the infants in the two groups were similar as seen in Table 1.

The comparative values of the mean VT, PIP, MAP, FiO_2, pH, and PCO_2 at the initiation of the study for each mode are summarized in Table 2. No difference was found between the two groups in terms of the initial data. The number of successfully extubated patients within 48 postnatal hours was higher in the VG group, but the difference was not statistically significant ($p = 0.315$) (Fig. 1).

No difference was observed between groups in terms of mean MAP, FiO_2, VT, and PIP at any time. MAP and FiO_2 significantly decreased over time during the first 24 h in both the PLV and VG groups ($F = 9.5$, $p < 0.0001$ and $F = 10.6$, $p < 0.001$, respectively). VT means for each time point were not significantly different

Table 1 Demographic data and delivery room management

	PLV (n = 22)	VG (n = 23)	p values
Birth weight (g)[a]	975.5 ± 294.3	1,055.8 ± 236.3	0.33
Gestation (weeks)[a]	27.6 ± 2.1	27.8 ± 1.7	0.70
Antenatal steroids	16/22	17/23	0.82
Chorioamnionitis	2/22	3/23	0.67
SGA	4/22	4/23	0.94
Balloon–mask ventilation in delivery room	20/22	21/23	0.68
Intubation in delivery room	20/22	19/23	0.31
Repeat surfactant administration	6/22	5/23	0.67

SGA small for gestational age
[a] Values are presented as mean ± SD

Table 2 Initial ventilatory data and blood gases

	PLV (n = 22)	VG (n = 23)	p values
Initial ventilatory data			
Inspired oxygen (%)[a]	69.51 ± 21.82	60.5 ± 24.4	0.18
Peak inspiratory pressure (cmH_2O)[a]	16.60 ± 3.70	15.21 ± 3.82	0.21
Mean airway pressure (cmH_2O)[a]	7.91 ± 1.81	7.54 ± 1.92	0.46
Tidal volume (ml/kg)[a]	3.80 ± 1.80	3.90 ± 0.28	0.52
Transition period to the SIMV (h)[b]	6 (3–9.5)	4 (3–8)	0.51
Initial blood gases			
pH[a]	7.31 ± 0.06	7.31 ± 0.07	0.81
PCO_2[a]	53.91 ± 8.62	54.62 ± 10.61	0.80

[a] Mean ± SD
[b] Median (interquartile range/25–75 %)

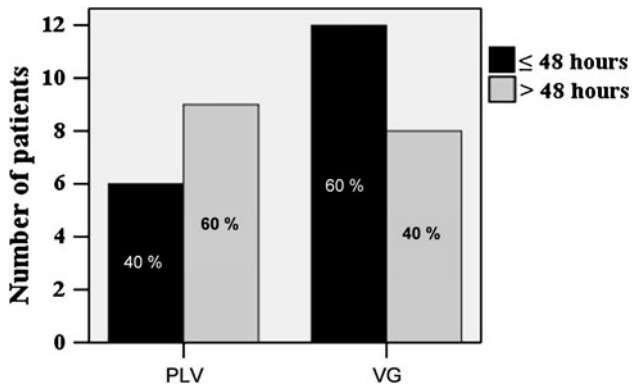

Fig. 1 Extubation success of the infants in the two groups within 48 h of birth ($p = 0.315$)

between the groups, but a repeated measures ANOVA determined that the mean VT levels differed significantly between time points in the PLV group ($F = 4.9$, $P = 0.015$). Post hoc analysis detected a significant difference in VT levels from the 0th to the 1st hour ($p = 0.04$). Mean VT measurements were not significantly different between time points in the VG group ($F = 2.1$, $p = 0.71$). Additionally, mean PIP levels did not significantly vary between time points in the PLV group ($F = 0.4$, $p = 0.733$), but a significant reduction was detected in the VG group over the course of time ($F = 4.4$, $p < 0.001$). Post hoc tests revealed that the VG option was associated with a significant reduction in the PIP levels from the 0th to the 4th hour ($p = 0.04$). The PCO_2 levels of the two groups at all time points were similar. The mean PCO_2 measurements were not significantly different between time points in the PLV and VG groups ($F = 1.1$, $p = 0.398$ and $F = 2.1$, $p = 0.07$, respectively) (Figs. 2, 3).

The incidence of death and BPD in the two groups were similar, but their combination was significantly lower in the VG group as compared to group I (relative risk 0.42, CI 0.19–0.94, $p = 0.005$). Two infants in the PLV group, and one infant in the VG group required home oxygen therapy ($p = 0.68$). Moreover, no differences were observed in the incidence of postnatal steroid therapy, pneumothorax, PDA requiring medical treatment, IVH, PVL, ROP, and NEC (Table 3).

Discussion

This is the first randomized, controlled, prospective clinical study that compared AC, followed by SIMV during weaning, with and without VG in infants with acute RDS. The most frequently used ventilation mode in our practice prior to this study was A/C followed by SIMV. The mean duration of ventilation in preterm

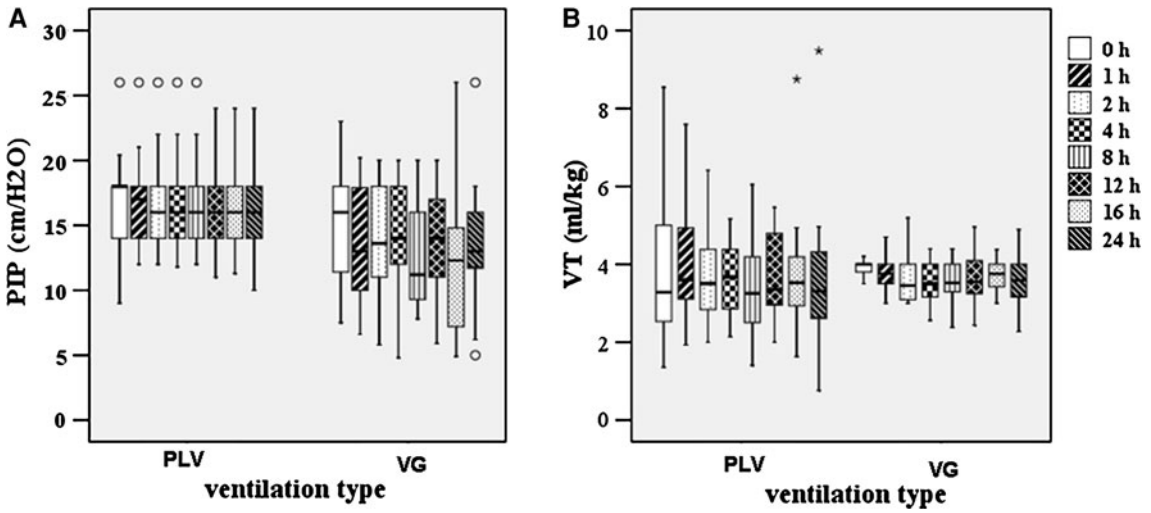

Fig. 2 **a** Evolution of peak inspiratory pressure over time in PVL and VG groups ($F = 0.4$, $p = 0.733$; $F = 4.9$, $p = 0.015$, respectively). **b** Evolution of tidal volumes (VT, ml/kg) over time in PLV and VG group ($F = 4.9$, $P = 0.015$; $F = 2.1$, $p = 0.7$, respectively). The *lower* and *upper margins* of each box correspond to quartiles (i.e., percentiles 25 and 75), the *line* in the *middle* of the box corresponds to the median, the *whiskers* correspond to percentiles 10 and 90, *circles* beyond the *whiskers* correspond to outliers (cases with values between 1.5 and 3 box lengths from the *upper or lower edge* of the box), and *stars* correspond to extremes (cases with values beyond 3 box lengths from the edge of the box)

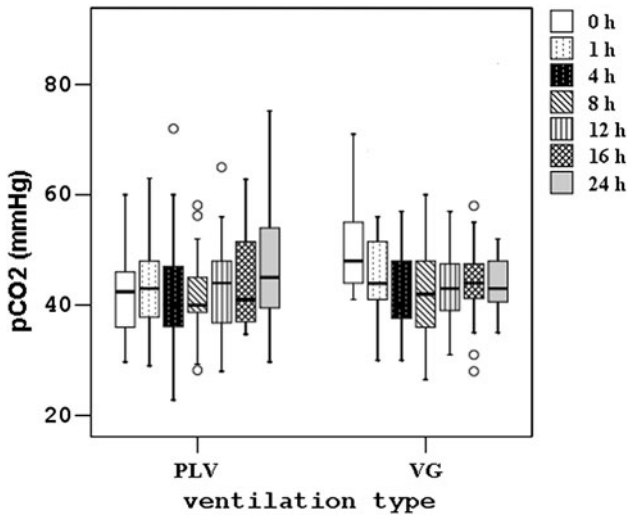

Fig. 3 Evolution of blood gas PCO_2 levels over time in PVL and VG groups. Mean PCO_2 measurements were not different significantly between time points in PLV and VG group ($F = 1.1$, $p = 0.398$ and $F = 2.1$, $p = 0.07$, respectively). See Fig. 2 for further explanation

infants with RDS was 4.7 + 7.3 days for survivors and 8.9 + 11 days for infants who died as recorded in our previous report [4].

Although VG was found to be less effective when combined with SIMV as compared to A/C in a previous crossover study [5], the transition from A/C to the SIMV mode during weaning has long been implemented in our unit. Therefore, we prefer weaning with the SIMV plus VG mode as presented in the present study. The VT was more stable, and PIP levels decreased over time significantly in the VG group during the first 24 h. The lower PIP, fewer excessively large VTs, or more stability in the VT during the VG periods as compared to that of the A/C or SIMV alone have also been demonstrated by previous short-term crossover trials [6, 7]. The transition time to SIMV and the duration of ventilation were shorter in the VG group in the present study, but none of the differences were statistically significant.

In the first 24 h, the PCO_2 and the pH levels for all blood gases were not significantly different between the two groups. In the first randomized controlled trial of VG, the authors demonstrated that VG combined with A/C maintained PCO_2 and VT within the target range more consistently than A/C alone during the first 72 h of life in preterm infants with RDS [8]. We initially used a target VT of 4 ml/kg with the VG mode in accordance with our previous practices, showing that higher VT goals may lead to hypocarbia. Similarly, Dawson and Davies [9] demonstrated that 4 ml/kg VT provides an acceptable range of PCO_2 and less hypocarbia with SIMV plus VG. However, extremely low birth weight infants may need higher VT values for normocapnia during the first 3 weeks of life as shown recently by Keszler et al. [10]. Nafday et al. [11] compared SIMV with PSV plus VG in a randomized study in preterm infants with RDS during the first 24 h of life. Although they did not find a difference in the time of extubation or other important clinical outcomes, the PSV plus VG group achieved weaning by utilizing a smaller number of blood gases as compared to the SIMV group.

Table 3 Important outcomes of neonates in the two groups

	PLV (n = 22)	VG (n = 23)	p values
Duration of ventilation for all infants (h)[a]	79 (38–294)	39 (25–117)	0.19
Duration of ventilation for survivors (h)[a]	96 (48–240)	36 (24–108)	0.51
Duration of hospitalization (days)[b]	54.2 ± 22.5	47.5 ± 22.9	0.43
BPD among survivors	6/15 (40)	3/20 (15)	0.09
BPD among all	7/22 (32)	3/23 (13)	0.13
Postnatal steroid	4/22 (18)	2/23 (9)	0.41
Death	7/22 (32)	3/23 (13)	0.13
BPD or death	14/22 (64)	6/23 (26)	0.005
Pneumothorax	2/22 (9.1)	2/23 (8.7)	0.68
PDA (requiring treatment)	14/22 (64)	14/23 (61)	0.50
NEC (>stage 1)	3/22 (14)	2/23 (9)	0.53
IVH (Papile grade 3 or 4)	7/22 (32)	3/23 (13)	0.13
PVL	4/22 (18)	2/23 (9)	0.41
ROP (>stage 2)	1/22 (5)	2/23 (9)	0.58

Data are presented as n (%) unless otherwise specified
[a] Median (interquartile range/25–75 %)
[b] Mean ± SD

Lista et al. [12] also compared a VG mode with a non-VG mode with the same ventilator in a similar population and reported the same outcomes as the present study. In fact, they demonstrated the most convincing evidence to date about the potential benefits of volume-targeted ventilation. One main difference between these two studies is that Lista et al. described lung inflammatory response as the main outcome. Additionally, Lista et al. used the PSV mode, not the AC/SIMV mode like the present study.

The body of literature on VG ventilation continues to expand rapidly, but none of the studies had sample sizes sufficiently large enough to unequivocally demonstrate the ultimate benefit of this approach. The Cochrane review, which was last updated in 2010, included 12 randomized trials in the meta-analysis and included 793 preterm infants [2]. Only three of these trials were primarily designed to compare the efficacy and safety of VG and conventional modes in RDS treatment [8, 11, 13]. The combined outcome of death or BPD was included in five trials [8, 12, 14–17]. No individual trial reported a difference in the combined outcome of death or BPD, but the pooled meta-analysis revealed a reduction in this combined outcome (typical RR 0.73 [95 % CI 0.57–0.93], typical RD 0.12 [95 % CI 0.21–0.03], NNT 8 [95 % CI 5–33]). Even though our sample size is not sufficiently large to supply adequate power, the reduction of this combined outcome in our results was compatible with this meta-analysis [2].

The major limitation of our study is the small sample size. With the increased use of non-invasive ventilation techniques over the last few years, the use of invasive mechanical ventilation has decreased dramatically [18], which is also the case in our practice as expected. The exclusion of babies who did not require endotracheal intubation within the first hour of life or needed a shorter duration of ventilation (i.e., <24 h) further reduced the number of eligible patients for our study.

In conclusion, our results support the findings of previous short-term studies, which demonstrated the reduction of PIP and VT variability. No statistically significant differences were observed in the incidence of air leak syndromes, PDA, IVH, PVL, ROP, and NEC, but the number of cases of these issues was lower in the VG group. A trial with a larger sample size is needed to derive sufficient power to examine differences in these outcomes. Further investigations with different combined VG modes and different VTs are needed in order to derive more precise instructions for clinical practice.

Conflicts of interest No sponsor was involved in the study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the paper for publication. The first draft of the manuscript was written by Dr. Nuray Duman and nobody received any kind of payment to produce the manuscript.

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