Volume-targeted ventilation in newborn infants

Mechanical ventilation via an endotracheal tube remains a 'standard of care' for infants with severe respiratory failure. Ventilation saves lives but can also cause lung injury and evidence suggests that excessive or inadequate tidal volume delivery causes more lung injury (volutrauma) than unregulated inspiratory pressure delivery (barotrauma). Volume-targeted ventilation (VTV) has been shown to produce better short-term outcomes than pressure-targeted ventilation and is used to aim to minimise lung injury. However, data are limited with regards to medium- and long-term outcomes and there are no published data comparing efficacy and safety of different modes of VTV.

Helen Chitty[1]
MBBS, MRCPCH, PGCertClinEd
Clinical Research Fellow in Neonatology

Sunil Sinha[1,2]
MD, PhD, FRCP, FRCPCH
Professor of Paediatrics and Neonatal Medicine
sunil.sinha@stees.nhs.uk

[1]Department of Neonatology, James Cook University Hospital, Middlesbrough
[2]The University of Durham

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Key points

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1. Volume-targeted ventilation (VTV) is a newer modality of ventilation designed to minimise ventilator-induced lung injury.
2. Systematic reviews of the evidence to date have shown that VTV is associated with improved short-term outcomes in neonates.
3. There are several different modes of VTV in clinical use but no evidence regarding comparison of modes.
4. Neonatal staff must have a thorough working knowledge of the mode used in their unit in order to ensure that VTV is delivered in an optimal and safe manner.

While non-invasive methods of respiratory support are now commonly used,[1] mechanical ventilation via an endotracheal tube remains the 'gold standard' for treatment of infants with severe respiratory failure.[2] Different types of volume-targeted ventilation (VTV), aimed at monitoring and delivering desired tidal volumes to the infant, are now being used widely.[3] This review aims to discuss the reasons for recommending the use of VTV and to describe commonly used modes of VTV.

Respiratory distress syndrome

Respiratory distress syndrome (RDS) is a common cause of respiratory failure in preterm infants, although some term infants are also affected. It occurs due to a combination of factors including surfactant deficiency or inactivation, and structural immaturity of the lungs.[4] Surfactant, produced by type II pneumocytes, lines the alveoli and reduces surface tension while maintaining the functional residual capacity (FRC) of the lungs. Surfactant insufficiency leads to loss of FRC, collapse of the alveoli and atelectasis. The infant has to make a greater inspiratory effort to open the alveoli on inspiration, causing fatigue and further atelectasis. This leads to hypoventilation and hypoperfusion followed by hypoxaemia, hypercarbia and acidosis. With the ensuing endothelial and epithelial damage and leakage of plasma proteins there is further requirement for ventilation,[4] thus becoming a part of the pulmonary injury sequence (**FIGURE 1**).[5]

The diagnosis of RDS is made by a

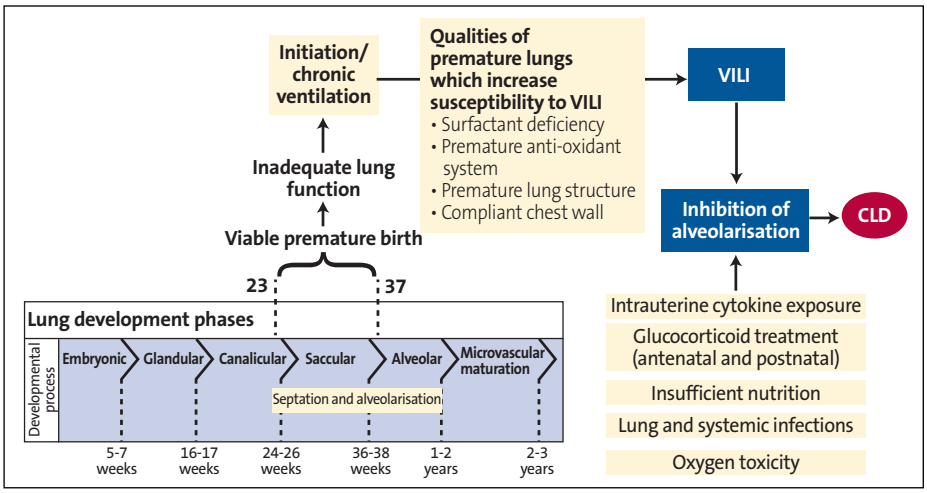

FIGURE 1 Mechanisms of ventilator-induced lung injury and chronic lung disease in preterm infants. Reprinted from Attar and Donn[5] with permission from Elsevier. Key: VILI = ventilator-induced lung injury, CLD = chronic lung disease.

composite of clinical assessment, blood gas analysis and radiographic changes. RDS typically starts in the first few hours of life and usually peaks in severity within 48 hours. Many infants recover from RDS without any initial clinical sequelae. However, there is evidence to show that lung injury can occur even within the first few ventilated breaths.[6] Infants ventilated for several days or weeks develop lung injury due to one or a combination of factors including prolonged ventilation, oxygen toxicity and infection, on a background of structural lung immaturity. Histologically, there are fewer and larger alveoli with reduced or absent septation. This is known as chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) and is defined clinically by most as oxygen dependency and/or the need for artificial respiratory support at 36 weeks' postconceptional age.[7,8] The different mechanisms of lung injury are summarised in **TABLE 1**.

	Cause	Effects
Barotrauma	Excessive inspiratory pressure delivery	Alveolar damage, pulmonary oedema, pulmonary air leak
Volutrauma	Excessive inspiratory tidal volume delivery	Disruption of alveolar cells and epithelial and endothelial layers
Atelectrauma	Repeated recruitment and derecruitment of lung units due to inadequate PEEP and positive pressure ventilation	'Shearing' effect on alveoli during reopening of lung units Over-expansion of some lung units due to inability to deliver the inspiratory volume to other closed lung units
Biotrauma	Inflammation or infection	Ongoing lung inflammation
Rheotrauma	Inappropriate airway flow	Excessive flow: turbulence, excessive PEEP, lung over-inflation Insufficient flow: air hunger, increased work of breathing

TABLE 1 The different types of lung injury.[2,5] Key: PEEP = positive end expiratory pressure.

Ventilator-induced lung injury

Conventional ventilation can be divided into two modalities:[9]
1) pressure-targeted ventilation
2) volume-targeted ventilation.
Ventilation can lead to complications if it is not optimised or is prolonged. One such complication is ventilator-induced lung injury (VILI) which is multifactorial in origin (**FIGURE 1**).[5]

Barotrauma

Barotrauma was originally thought to be the main cause of VILI.[10] High-pressure ventilation can cause pulmonary oedema and structural damage in animal models.[10] However, subsequent work has shown that the majority of VILI is likely to be caused by excessive tidal volumes.[11]

Volutrauma

Volutrauma is the result of the delivery of excessive inspiratory volume to the alveoli. This may be due to a shearing effect which causes disruption of the alveolar type I cells (which line the alveoli and are responsible for gas exchange) and the epithelial and endothelial layers.[11] The compliant chest wall of preterm infants increases the risk of VILI as it allows the lungs to expand more for any given pressure. Excessive tidal volumes are associated with low lung compliance, reduced ventilator efficacy and high protein leak,[12] as well as reduced response to surfactant[5] in animal models.

A study published in 1989 compared varying degrees of positive inspiratory pressure (PIP) – 15, 30 and 45cmH_2O – on three different groups of rabbit models.[11] In the first group, the lungs were removed and ventilated in isolation (the lack of a chest wall meant that lung expansion had no external restriction). In the second group, rabbits were ventilated with intact chest walls that expanded normally during inspiration, allowing for normal lung inflation. In the third group, rabbits were placed in thoraco-abdominal casts in order to prevent expansion of the chest wall during ventilation. The casts prevented an increase in tidal volumes during lung inflation despite the use of increasing PIPs. The researchers found that the isolated lungs showed the greatest evidence of VILI even at the lowest PIP level (15cmH_2O). The lungs of rabbits with intact chests showed significant evidence of damage when ventilated at 30 and 45cmH_2O. However, the lungs of rabbits with tidal volumes restricted by the thoraco-abdominal casts showed no evidence of lung injury, even at the highest PIP levels.

These results support the argument that it is the alveolar 'stretch' caused by excessive tidal volume delivery rather than damage due to excessive pressure delivery that leads to VILI in newborn infants.[7]

Atelectrauma

In contrast to volutrauma, atelectrauma is caused by under-expansion of alveoli leading to atelectasis.[5] Infants with RDS have unequal areas of lung expansion and collapse meaning that both volutrauma and atelectrauma can occur simultaneously. Although the clinician may target a particular tidal volume using a ventilator, this volume will not be delivered to closed lung units and therefore may lead to the over-expansion of the remaining open lung units (causing volutrauma).[5]

Biotrauma

Exposure to inflammatory mediators as a result of *in utero* or postnatal infection, oxidative stress or mechanical ventilation can lead to ongoing lung inflammation that may contribute to BPD.[2]

Rheotrauma

It is not only the amount of tidal volume but also the way in which the volume flows to the lungs that also contributes to lung injury. Excessive gas flow causes lung over-inflation and unintentional positive end expiratory pressure (PEEP), whereas insufficient gas flow leads to air hunger and increased work of breathing.[9]

It is likely that all four mechanisms of injury contribute to VILI in a preterm infant. However, volutrauma and atelectrauma due to over- and under-expansion of the alveoli seem to contribute to most of the damage.

Evidence to support the use of VTV

Does the importance of maintaining tidal volume delivery within a specific range in order to prevent VILI translate into improved clinical outcomes? A recent Cochrane review[13] and meta-analysis[14] by Wheeler and colleagues, comparing VTV with pressure-targeted ventilation, combined the results from 12 and nine trials respectively. VTV was associated with a reduction in the combined outcomes of

death and CLD (number needed to treat = 8) as well as reductions in the rates of pneumothoraces, duration of ventilation, hypocarbia, and the combined outcomes of periventricular leukomalacia (PVL) or grade III-IV intraventricular haemorrhage (IVH). Another more recent meta-analysis reviewed 18 studies and reported similar findings but found no difference in the incidence of death.[15] These results support the use of VTV in infants in reducing short- and medium-term complications associated with mechanical ventilation.

Different modes of VTV

Volume-targeted modes of ventilation allow the clinician to control the volume of gas delivered to the infant. The different modes deliver and maintain this volume in different ways but all share the common goal of aiming to deliver either a specific volume, or a volume within a specific range, to the infant. The differences in tidal volume delivery, flow and inspiratory pressure are summarised in **TABLE 2**.

Volume-controlled ventilation

When using volume-controlled ventilation (VCV) the primary aim is to keep the expired tidal volume within a desired range. The expired tidal volume is measured using a flow sensor situated as close to the endotracheal tube (ETT) as possible. The flow sensor monitors airway pressures, tidal volumes and gas flows passing between the infant and the ventilator.[2]

The clinician sets a volume of gas that the ventilator delivers to the infant whenever the infant takes a breath (or according to the pre-set mandatory respiratory rate if the infant is apnoeic). The ventilator aims to deliver this volume irrespective of the lung compliance or PIP required to deliver it. The gas is delivered at a constant flow rate that is also set by the clinician.[2]

However, not all of the set volume of gas that leaves the ventilator ultimately reaches the infant's lungs. Much of it remains within the circuit between the ventilator and the infant and is referred to as 'compressible volume loss'.[2] Some is also lost due to the leak around the uncuffed ETT. The compressible volume loss increases as lung compliance decreases (the stiffer the lungs, the smaller the volume of gas that reaches them). The clinician intermittently adjusts the set volume manually on the ventilator to aim to deliver a volume to the infant's lungs that is within a desired range and achieves acceptable gas exchange.[2]

In this mode, although the clinician can aim to keep the expired tidal volume within a desired range it is often not practically possible to achieve specific tidal volumes with each breath. Therefore the volume of gas that actually reaches the

Ventilatory mode	Mechanism of action
Volume-controlled ventilation (VCV)	• Inspiratory volume set by clinician • Flow rate set by clinician to provide continuous inspiratory flow • PIP and maximum inspiratory volume increase during, and peak at the end of, inspiration • Inspiratory time depends on the set inspiratory volume and flow • PIP varies automatically according to lung compliance
Volume guarantee (VG) ventilation	• Inspiratory volume, inspiratory time and maximum PIP limit set by clinician • Inspiratory flow rate is variable and determined by the ventilator • Peak inspiratory flow occurs early in inspiration, then decelerates throughout the remainder of inspiration • PIP and maximum inspiratory volume peak early in inspiration • The ventilator adjusts PIP on a breath-by-breath basis to target the set volume • The ventilator uses the VTe of the previous breath as a reference for adjustment of PIP • The working PIP will not exceed the maximum PIP limit
Pressure-regulated volume controlled (PRVC) ventilation	• Inspiratory volume and maximum PIP limit set by clinician • Inspiratory flow rate is variable and determined by the ventilator • Peak inspiratory flow occurs early in inspiration, then decelerates throughout the remainder of inspiration • Initial PIP is delivered at 10cmH_2O above the set PEEP – this is used as a reference to calculate the pressure needed to achieve the set inspiratory volume during further breaths • Next three breaths delivered using a PIP of 75% of the calculated PIP • Further adjustments in PIP are made in 3cmH_2O increments or decrements • The working PIP will not exceed a threshold higher than 5cmH_2O below the maximum PIP limit
Volume-assured pressure support (VAPS) ventilation	• Relies on the infant breathing spontaneously in order to 'trigger' the ventilator to deliver breaths • Inspiratory volume set by the clinician • Inspiratory flow accelerates and decelerates according to patient effort and ventilator variables (similar to PSV) • When flow decelerates to a minimum value the delivered volume is measured • If the delivered volume exceeds the set inspiratory volume the breath is terminated and cycled into expiration (similar to PSV) • If the set inspiratory volume is not achieved flow is continued and inspiratory time increased until the volume is achieved (similar to VCV) • Working pressure may also be increased by the ventilator in order to achieve the set volume

TABLE 2 Differences between different modes of VTV.[2] Key: PIP = peak inspiratory pressure, VTe = expired tidal volume. PSV = pressure support ventilation, VCV = volume-controlled ventilation.

infant is dependent both on lung compliance, which can vary rapidly and frequently, and the clinician who may not keep up with the rapid changes in lung compliance. The ventilator will generate whatever PIP is necessary to deliver the pre-set tidal volume (although this can be limited by the clinician for safety reasons) and there is therefore an increase or reduction in the generated PIP as lung compliance deteriorates or improves respectively. However regulation of PIP is not controlled by the ventilator as in the case with the other volume-targeted modes.[2]

VCV was associated with improved short- to medium-term clinical outcomes when compared to pressure-targeted ventilation in previous clinical trials[16-19] but has not been compared to other modes of VTV.

Hybrid modes

These modes are primarily pressure modes of ventilation but aim to achieve the same goal as VCV by targeting a specific volume of gas. This is facilitated by the use of microprocessor technology and a servocontrolled mechanism to up- or down-regulate tidal volumes. The microprocessor is contained within a flow sensor that monitors tidal volumes with each breath. It then feeds back to the ventilator to enable adjustments of pressure or flow to be made with the next breath in order to achieve the desired tidal volume.[2] These modes include volume guarantee (VG), pressure-regulated volume control (PRVC), volume-assured pressure support (VAPS), and newer emerging modes which require further evaluation.

Volume guarantee ventilation

When using VG the clinician sets the desired tidal volume. The flow sensor measures the infant's expired tidal volume and the ventilator uses this as a reference to adjust the PIP up or down over the next few breaths to aim to deliver the set tidal volume. Adjustments to the PIP are made in small increments to avoid large fluctuations in volume delivery. The gas flow rate is variable and occurs more rapidly at the beginning of an inspired breath. This mechanism aims to overcome the problem of compressible volume loss.[2,9]

However this mode is sensitive to ETT leak – the higher the leak, the less reliable the technology is in accurately measuring tidal volumes.[20] The PIP is altered in small increments so it may take several breaths before the desired tidal volume is achieved. A maximum pressure limit can be selected above which the ventilator will not generate peak pressures. This is useful in instances such as partial ETT obstruction when an increasing peak pressure is related to a mechanical problem rather than poor lung compliance. However, the clinician needs to ensure that the limit is set high enough above the working PIP so that the ventilator can deliver the desired tidal volume, particularly if lung compliance is worsening.

VG is a commonly used mode of VTV but it still requires further scientific evaluation in clinical trials powered to detect differences in long-term outcomes.[21] Its use has been associated with improvements in short-term clinical outcomes, such as

- less variability (better control) of tidal volumes[22-25]
- fewer episodes of hypocarbia[24-26]
- shorter duration of ventilation[27]
- a reduction in markers of lung inflammation.[28,29]

However, methodological limitations of some studies restrict the application of their results to clinical practice. None of the studies compare VG to a different mode of VTV.

Pressure-regulated volume control ventilation

PRVC is similar to VG in that it uses variable gas flow and a servocontrolled mechanism to target tidal volumes. The clinician sets the desired tidal volume and a maximum pressure limit. The ventilator delivers the first breath using a PIP that is 10cmH_2O above the PEEP and measures the actual tidal volume that is achieved in order to calculate the PIP needed to deliver the desired tidal volume. It will then deliver the next three breaths using a PIP that is 75% of that calculated. If the desired volume is not reached, the PIP is increased by 3cmH_2O until it is achieved.[21] Likewise, if an excessive tidal volume is delivered the PIP is decreased by 3cmH_2O until the desired volume is reached.[2] Unlike VG, in which the working PIP is adjusted on a breath-by-breath basis, an average of four breaths is used to adjust the PIP during PRVC ventilation.

There are few neonatal clinical trials comparing PRVC with other modes. One study demonstrated a significantly shorter time to extubation in infants weighing <1,000g[30] when compared with time-cycled pressure-limited ventilation but this was derived from a post hoc analysis and there was no difference between the two modes in the study population as a whole.

Volume-assured pressure support

Pressure support ventilation (PSV) is a flow-cycled, variable flow mode. Being a pressure type of ventilation, it does not guarantee the amount of volume delivered to the infant. However VAPS is a hybrid mode that combines aspects of PSV with VCV to aim to control volume delivery. Flow accelerates rapidly at the start of inspiration (acceleration is affected by the extent of the infant's spontaneous inspiratory effort) and cycles into expiration if the desired volume is reached or exceeded (similar to PSV). If it is not achieved, the inspiratory flow continues (and the inspiratory time is extended) until the desired volume is reached (similar to VCV). PIP is augmented if the volume is well below the target value.[2]

There are no published neonatal trials comparing VAPS to another mode of ventilation.

Differing patterns of gas flow

The patterns of gas flow in VCV and hybrid modes of VTV are different and they may have different effects on the underlying lung mechanics. In VCV, the clinician selects a specific flow rate at which the volume should be delivered so that gas flow is constant throughout inspiration and therefore the maximal tidal volume and PIP are reached at the end of inspiration. In VG and PRVC the flow is variable and maximal at the beginning of inspiration meaning that PIP and tidal volume are achieved earlier in inspiration.[2] When the designated PIP has been achieved the gas flow rate decreases during the remainder of inspiration. VAPS is unique in that it changes the flow pattern breath by breath if the machine detects that the tidal volume is not going to be achieved – it starts in the same way as in VG or PRVC unless the preset tidal volume is not achieved at which point flow continues as it would in VCV.

One area for future research is to determine whether the variable flow rate provided by a hybrid mode of VTV or the constant flow rate provided by VCV is more advantageous in certain clinical situations, such as in infants with early RDS or ventilator-dependent infants with evolving BPD.

Conclusion

VTV is no longer considered an experimental treatment and is now used widely in neonatal intensive care units. It is considered to be safe and effective and has short-term advantages such as reduction in the duration of ventilation and its associated complications. Data regarding longer term clinical outcomes are lacking and large multi-centre trials will be needed to investigate these outcomes. However, these trials may prove to be difficult to achieve because of the introduction of several newer devices that have not been compared in clinical trials and because of the varying ventilation strategies practised between units. In the meantime, clinicians must familiarise themselves with the modes and device used to deliver VTV on their unit in order to ensure that volume-targeting is achieved safely and optimally.

References

1. **Garg S., Sinha S.** Non-invasive ventilation in premature infants: based on evidence or habit. *J Clin Neonatol* 2013;2:155-59.
2. **Sinha S.K., Donn S.M.** Volume-targeted ventilation. In: Goldsmith J.P., Karotkin E.H. (eds.) *Assisted Ventilation of the Neonate*. 5th ed. St. Louis, Mo: Elsevier Saunders; 2011. p.186-99.
3. **Klingenberg C., Wheeler K.I., Owen L.S. et al.** An international survey of volume-targeted neonatal ventilation. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F146-48.
4. **Hamvas A.** Pathophysiology and management of respiratory distress syndrome. In: Martin R.J., Fanaroff A.A., Walsh M.C. (eds.) *Fanaroff and Martin's Neonatal-Perinatal Medicine. Diseases of the Fetus and Infant*. 9th ed. St. Louis, Mo: Elsevier Mosby; 2011. p.1106-16.
5. **Attar M.A., Donn S.M.** Mechanisms of ventilator-induced lung injury in premature infants. *Semin Neonatol* 2002;7:353-60.
6. **Björklund L.J., Ingimarsson J., Curstedt T. et al.** Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997;42:348-55.
7. **Jobe A.H., Bancalari E.** NICHD/NHLBI/ORD Workshop Summary: Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;162:1723-29.
8. **Korones S.B.** Complications. In: Goldsmith J P., Karotkin E.H. (eds.) *Assisted Ventilation of the Neonate*. 5th ed. St. Louis, Mo; Elsevier Saunders; 2011. p.389-425.
9. **Donn S.M., Sinha S.K.** Assisted ventilation and its complications. In: Martin R.J., Fanaroff A.A., Walsh M.C. (eds) *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 9th ed. St. Louis, Mo: Elsevier Mosby; 2011. p1116-140.
10. **Dreyfuss D., Saumon G.** Barotrauma is volutrauma, but which volume is the one responsible? *Int Care Med* 1992;18:139-41.
11. **Hernandez L.A., Peevy K.J., Moise A.A., Parker J.C.** Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. *J App Physiol* 1989;66:2364-68.
12. **Wada K., Jobe A.H., Ikegami M.** Tidal volume effects on surfactant treatment responses with the initiation of ventilation in preterm lambs. *J App Physiol* 1997;83:1054-61.
13. **Wheeler K., Klingenberg C., McCallion N. et al.** Volume-targeted versus pressure-limited ventilation in the neonate. *Cochrane Database of Syst Rev* 2010;11:CD003666.
14. **Wheeler K.I., Klingenberg C., Morley C.J., Davis P.G.** Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Neonatology* 2011;100:219-27.
15. **Peng W., Zhu H., Shi H., Liu E.** Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F158-65.
16. **Sinha S.K., Donn S.M., Gavey J., McCarty M.** Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child* 1997;77:F202-05.
17. **Singh J., Sinha S.K., Clarke P. et al.** Mechanical ventilation of very low birth weight infants: is volume or pressure a better target variable? *J Peds* 2006;149:308-13.
18. **Singh J., Sinha S.K., Alsop E. et al.** Long-term follow-up of very low birth weight infants from a neonatal volume versus pressure mechanical ventilation trial. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F360-62.
19. **Hummler H.D., Engelmann A., Pohlandt F., Franz A.R.** Volume-controlled intermittent mandatory ventilation in preterm infants with hypoxemic episodes. *Int Care Med* 2006;32:577-84.
20. **Donn S.M., Boon W.** Mechanical ventilation of the neonate: should we target volume or pressure? *Respir Care* 2009;54:1236-43.
21. **Grover A., Field D.** Volume-targeted ventilation in the neonate: time to change? *Arch Dis Child Fetal Neonatal Ed* 2008;93:F7-9.
22. **Abubakar K.M., Keszler M.** Patient-ventilator interactions in new modes of patient-triggered ventilation. *Pediatr Pulmonol* 2001;32:71-75.
23. **Herrera C., Gerhardt T., Claure N. et al.** Effects of volume-guaranteed synchronized intermittent mandatory ventilation in preterm infants recovering from respiratory failure. *Pediatrics* 2002;110:529-33.
24. **Keszler M., Abubaker K.** Volume guarantee: stability of tidal volume and incidence of hypocarbia. *Pediatr Pulmonol* 2004;38:240-45.
25. **Scopesi F., Calevo M.G., Rolfe P. et al.** Volume targeted ventilation (volume guarantee) in the weaning phase of premature newborn infants. *Pediatr Pulmonol* 2007;42:864-70.
26. **Cheema I., Sinha A., Kempley S., Ahluwalia J.S.** Impact of volume guarantee ventilation on carbon dioxide tension in newborn infants: a randomised controlled trial. *Early Hum Dev* 2007;83:183-89.
27. **Guven S., Bozdag S., Saner H. et al.** Early neonatal outcomes of volume guaranteed ventilation in preterm infants with respiratory distress syndrome. *J Matern Fetal Neonatal Med* 2013;26:396-401.
28. **Lista G., Colnaghi M., Castoldi F. et al.** Impact of targeted-volume ventilation on lung inflammatory response in preterm infants with respiratory distress syndrome (RDS). *Pediatr Pulmonol* 2004;37:510-14.
29. **Lista G., Castoldi F., Fontana P. et al.** Lung inflammation in preterm infants with respiratory distress syndrome: effects of ventilation with different tidal volumes. *Pediatr Pulmonol* 2006;41:357-63.
30. **Piotrowski A., Sobala W., Kawczyński P.** Patient-initiated, pressure-regulated, volume-controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomised study. *Int Care Med* 1997;23:975-81.