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Volume Targeted Algorithms. Are they a one-size-fits-all approach to noninvasive ventilation?

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Abstract

Noninvasive ventilation (NIV) has rapidly expanded as the principle respiratory support strategy in a variety of disease states ultimately resulting in respiratory insufficiency including COPD, overlap syndrome (COPD + comingled sleep disordered breathing), obesity hypoventilation syndrome (OHS), motor neuron diseases, such as amyotrophic lateral sclerosis (ALS), as well as various muscular dystrophies to list just a few examples. In recent years, NIV technology and algorithms have experienced rapid development aimed at improving performance, reliability, comfort, portability, titration efficiency, and treatment outcomes. One specific algorithmic advancement of NIV has been the development of volume targeting algorithms and the creation of new, hybrid modes of NIV. The fundamental feature of volume targeted algorithms is the automation of the inspiratory positive airway pressure (IPAP) or pressure support (PS). In recent years, volume targeted modes have grown in popularity and often are the preferred method of implementing NIV in the home.

There are important differences between manufacturer's proprietary algorithms that should be understood by the clinician when implementing NIV or when evaluating patient response to NIV. This article will identify some of the unique characteristics of commercially available volume targeted modes and will provide an overview of recent findings in specific cohorts.

Keywords: non-invasive ventilation (NIV), volume-targeted ventilation, volume assured pressure support, chronic obstructive pulmonary disease (COPD), neuromuscular disorders (NMD)

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Introduction

Noninvasive ventilation (NIV); the delivery of positive pressure to the lungs without the placement of an endotracheal or tracheostomy tube, has been widely adopted as the principal intervention to treat both acute and chronic respiratory failure in a variety of disease states and patient profiles.[1,2] The technology associated with NIV has experienced rapid advancements in both features and algorithms. One specific algorithmic advancement replaces fixed pressure support, with a pressure support range and a controller configured to dynamically adjust the pressure support level to maintain a tidal volume target. In recent years, volume targeted ventilation (TgV) has been widely adopted as the primary mode of NIV ventilation to treat respiratory insufficiency in the home setting. [3]

Annals of TgV Modes

The first TgV pressure mode of NIV to be introduced to the market was AVAPS by manufacturer Philips which received 510K clearance in 2007. AVAPS; which stands for Average Volume Assured Pressure Support, was designed to maintain a stable average tidal volume in adult patients with respiratory insufficiency. Other proprietary TgV modes were subsequently developed such as iVAPS; Intelligent Volume-Assured Pressure Support, from ResMed, and more recently the TgV modes by Breas. Subsequent iterations of the original algorithms have added additional features such as an automated expiratory positive pressure (EPAP), adjustable rates of pressure change, automatic backup rates, and automatic inspiratory time algorithms. Collectively, these TgV pressure modes; used with or without an auto EPAP feature, have grown in popularity and have become a common way of implementing NIV across a variety of disease states and patient profiles in the homecare setting.

Functional Intent of TgV Modes

There are a variety of disease states associated with hypoventilation, which is often exacerbated during sleep. TgV algorithms were designed to provide stable tidal volumes and to improve gas exchange in respiratory insufficiency by mitigating sleep-related hypoventilation. TgV algorithms are available in a variety of modes depending on the ventilator platform being utilized. Although algorithms vary, the basic function of a TgV algorithm is to compare exhaled tidal volume (V_{TE}) to the volume target set by the clinician. Based on this feedback loop, the controller adjusts the delivered inspiratory pressure in a bi-directional manner to maintain a stable delivered tidal volume. In the case of ResMed's iVAPS algorithm, exhaled tidal volume is replaced by an alveolar ventilation target using a calculation to estimate and subtract anatomical dead space. In addition to modulating pressure support, iVAPS also delivers timed breaths to reach the alveolar minute ventilation target. AVAPS-AE, an iteration of AVAPS, also has an automated backup breath rate feature designed to maintain a consistent frequency that closely mirrors the patient's eupneic rate based on a preset evaluation window at the initiation of therapy.

Specific to the stable, chronic respiratory failure COPD cohort, debate continues within the clinical community as to the optimal way to implement and manage NIV to realize optimal patient outcomes. NIV implementation strategies have included both targeting lower levels of pressure support (low intensity NIV or LIT-NIV), as well as targeting higher levels of pressure support (high intensity NIV or HIT-NIV) aimed at unloading the respiratory muscles and normalizing the partial pressure of carbon dioxide values in arterial blood ($PaCO_2$). [4] Based on promising evidence, titration of pressure support targeted to achieve a substantial reduction of $PaCO_2$ is generally considered the standard of care when implementing NIV in the stable, chronic respiratory failure COPD cohort. [5] TgV ventilation has been identified as a possible tool to improve the efficiency and accuracy of NIV implementation and decrease the time in the hospital to initiate the therapy and facilitate an accurate titration of NIV setting. [6]

TgV and Auto EPAP

TgV modes may be used with or without an auto EPAP feature. The primary role of an auto EPAP feature is to improve upper airway patency and decrease the occurrence and frequency of sleep disordered breathing events. Significant upper airway obstruction that occurs during sleep disordered breathing events (SDB) may limit the ability of the TgV algorithm to adequately modulate the pressure support to meet and subsequently maintain the volume target. A consideration when determining whether to employ or not employ an auto EPAP algorithm feature is the specific cohort or patient profile that is being treated with NIV. OHS is defined by the presence of significant sleep disordered breathing (AHI > 5), as is overlap syndrome (COPD + OSA). Neuromuscular disease (NMD) is associated with sleep disordered breathing; however, the site of obstruction may not be the same location and should be factored in the decision. Insufficient research has been performed regarding the use of automated EPAP modes to treat various forms of NMD and there remain unanswered questions regarding implementation and adjustment of EPAP when upper airway obstruction exists. Pharyngo-laryngeal muscle impairment predisposes an individual for having sleep disordered breathing and the presence of obstructive apneas have been negatively correlated with poor survival in ALS when not addressed. [7]

Adjusting EPAP levels, as a means to splint the upper airway, is the primary mechanism to eliminate or control obstructive apneas, however increased levels of EPAP may be poorly tolerated by some individuals with ALS. One study evaluating an automatic EPAP algorithm as compared to manually titrated EPAP in a cohort of individuals with chronic respiratory failure did include individuals diagnosed with a neuromuscular disease. In this study the auto EPAP algorithm was found to be non-inferior to manually titrated EPAP. [8] Still, caution should be undertaken when determining whether an auto EPAP feature is employed to address upper airway (UA) instability and obstruction in NMD. If an automated EPAP feature is chosen when implementing NIV, careful monitoring of the subject includes an evaluation of the degree of obstructive apnea control, patient ventilator asynchrony, interface leaks, as well the risk of aspiration when an inability to protect the airway exists.

Comparison of TgV Design and Algorithmic Differences

Although designed with similar intended functions, TgV algorithms have unique differences that include unique settings and contrasting responses to conditions. This article is not meant to be a deep dive in TgV algorithm comparisons, nor is it meant to highlight a specific algorithm as being superior. Rather the article is intended to illustrate that TgV modes are inherently different and to inform the clinician as to some of the unique algorithmic differences between NIV platforms. Understanding how an algorithm may respond to a specific event or condition, may help a clinician initially determine what TgV algorithm is better suited for a specific patient profile, or may aid in identifying when a patient is not responding as expected to a TgV mode.

Target Volume by Breas

Breas has developed a TgV that can be combined with traditional modes of NIV. The TgV feature was designed to be used with a circuit that has a built-in leak/exhalation port. According to the user manual and product specification sheets, TgV is available in the following ventilator modes and feature combinations:

- PSV(TgV) – Pressure Support Ventilation with Target Volume
- PSV(TgV+AE) – Pressure Support Ventilation with Target Volume and Auto EPAP
- PCV(TgV) – Pressure Controlled Ventilation with Target Volume
- PCV(A+TgV) – Assisted Pressure Controlled Ventilation with Target Volume
- PCV(A+TgV+AE) – Assisted Pressure Controlled Ventilation with Target Volume and Auto EPAP

Breas TgV + NIV modes operate using a user-defined target volume which is compared to the delivered volume on a breath-by-breath basis. When measured V_T < 5% of set TgV, the pressure controller will increase IPAP by 0.5 cmH_2O for the next delivered breath. Conversely, when measured V_T > 5% of set TgV, the pressure controller will decrease IPAP by 0.5 cmH_2O for the next delivered breath. The controller does not modulate IPAP when the measured V_T stays within an acceptable range that is between 95-105% of the set TgV. Pressure adjustment is bounded by the min and max pressure limits. Figure 1 demonstrates the TgV pressure support response to a reduction in lung compliance in a bench model.

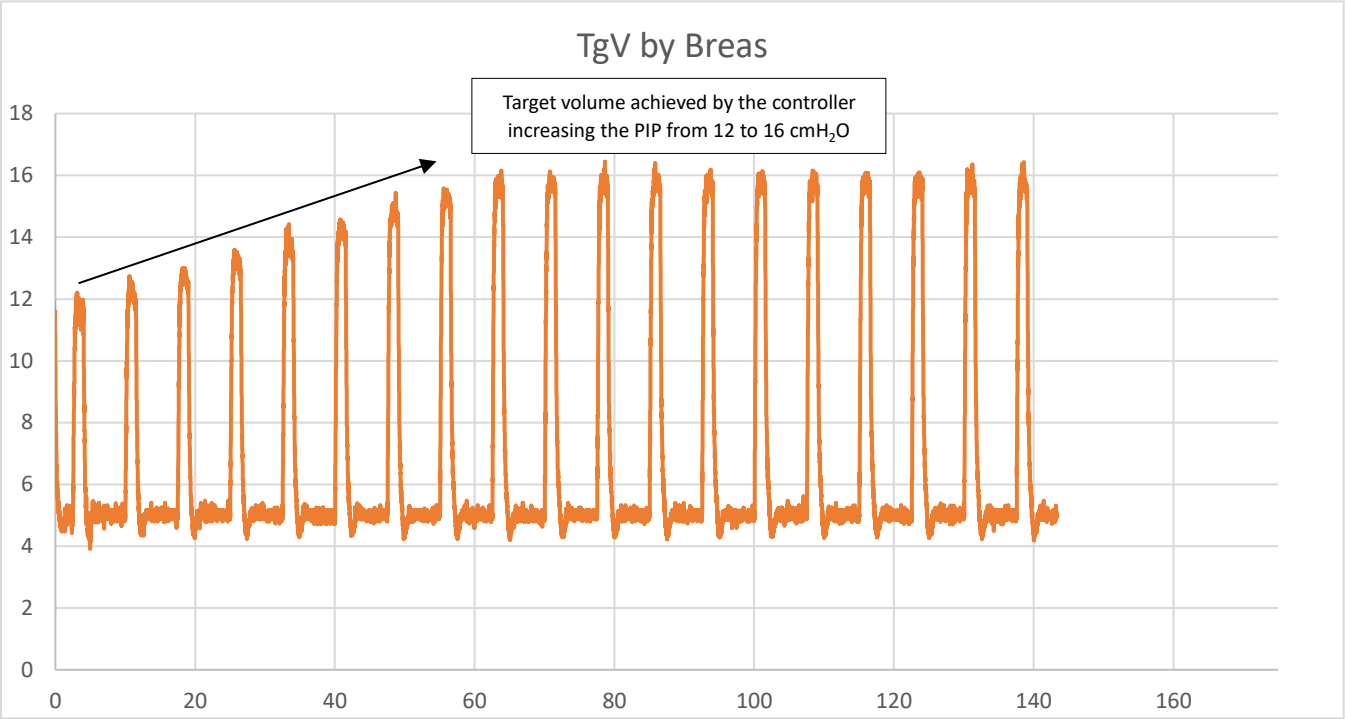

Figure 1: Breas Vivo 45 LS platform. Mode: PCV/A-TgV – Adult, Target Volume: 800 mL, Inspiratory P - 15 cmH2O, PEEP - 5 cmH2O, Rate - 8 bpm, TI - 1.5 sec, Rise Time – 2, Insp Flow Trigger – 2, Max Pressure - 40 cmH2O, Min Pressure - 9 cmH2O, Leak Circuit, Pre-Use Circuit Test Completed. TTL dual lung set to R5 and C 0.1, after a stable period was achieved without changes in pressure support, compliance was decreased to 0.6 and the following pressure support changes were observed. The Vivo 45 LS demonstrated a consistent 0.5 cmH2O change per breath as indicated in the user manual achieving an average peak inspiratory pressure of 16 cmH2O to achieve the target volume of 800 mL after the change in compliance was introduced.

AVAPS and AVAPS-AE by Philips

Average Volume Assured Pressure Support (AVAPS) is a feature that can be enabled in multiple pressure modes (S/T, PC, PSV, and A/C-PC) of ventilation depending on the ventilator model. Once the feature is enabled, a clinician can set a target tidal volume and an IPAP minimum and maximum range. Exhaled tidal volume (V_{TE}) is compared to the target V_T, IPAP is increased if V_{TE} < Target V_T, conversely IPAP is decreased when if V_{TE} > Target V_T. Iterations of the original AVAPS feature have added in new elements such as an adjustable rate of change (1-5 cmH_2O) that limits the maximum pressure that the algorithm may increase in a minute. Average Volume Assured Pressure Support with Auto EPAP (AVAPS-AE) includes an automated EPAP, automated backup rate, as well as an automated inspiratory time and expiratory time algorithms and is presented as an independent mode of NIV in the Trilogy range of ventilators. While the AVAPS component of AVAPS-AE is reactive in nature; responding to changes in exhaled volume, the auto EPAP algorithm was designed to be proactive in nature using a 1 cmH_2O, 5 Hz forced oscillation (FOT) signal to identify changes in upper airway resistance. The EPAP controller compares resistance profiles to changes in EPAP to determine the optimal EPAP level. EPAP is proactively increased as part of a high-pressure search (Popt) and decreased (Pcrit) designed to maintain the lowest possible EPAP while maintaining a patent upper airway. Delivered EPAP is constrained by the EPAP min and EPAP max settings which are set by the user. Leak compensation is a feature described in the user manual to improve the accuracy of measured volumes. The leak compensation feature is restricted to passive, active flow, and dual limb circuits. Leak compensation is not an available feature in the active PAP circuit configuration. Leak compensation limits are not publicly disclosed by the manufacturer.

According to the manufacturer, both the AVAPS feature, and AVAPS-AE mode are contraindicated for patients weighing less than 10 kilograms.

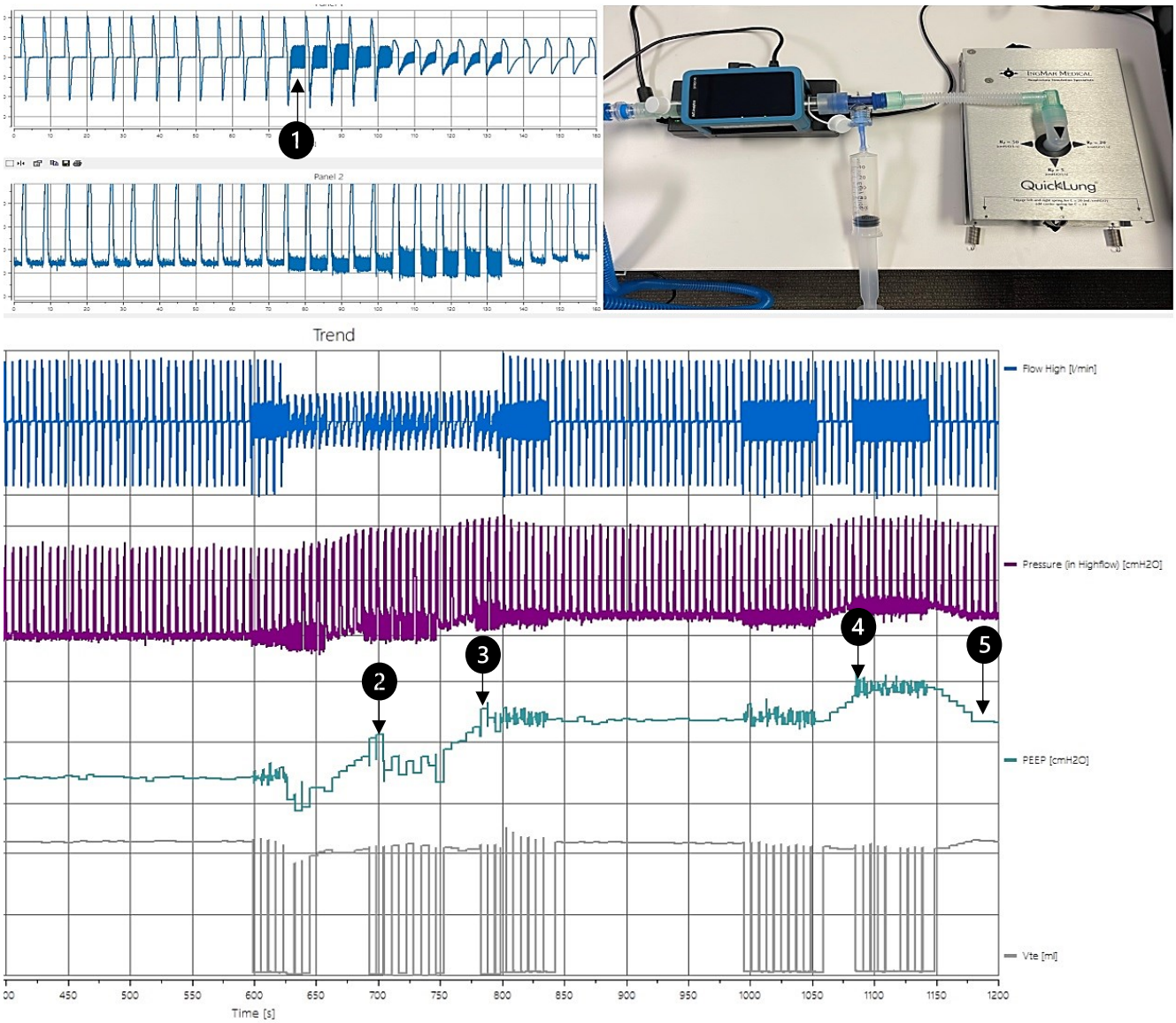

Figure 2: Illustrates an example of the pressure support response to changes in exhaled volume as well as the EPAP response to changes in simulated upper airway resistance in a bench test setup using Philips AVAPS-AE algorithm. An upper airway model was created using a rigid outer lumen with a compressible inner lumen that can be opened or closed using a 50mL syringe. A passive exhalation circuit was connected to the ventilator and the IMT flow analyzer. The upper airway was placed in between the IMT flow analyzer and an IngMar Medical Quick Lung. FOT signal being introduced to measure resistance in the upper airway (1) which is the primary input for the auto EPAP controller. Proactive increases in EPAP (Popt search) can be seen at points (2), (3), and (4), after an introduction of ↑ resistance by partially closing the UA model, followed by a Pcrit search at point (5) after making the UA model patent and ↓ resistance.

AVAPS-AE settings: AVAPS Rate: 5 cmH_2O, Tidal Volume: 500 mL, Maximum Pressure: 30 cmH_2O, Pressure Support Max: 15 cmH_2O, Pressure Support Min: 5 cmH_2O, EPAP Max Pressure: 15 cmH_2O, EPAP Min Pressure 5 cmH_2O, Breath Rate: Auto, Trigger Type: Auto-Trak, Rise Time: 2

iVAPS and iVAPS-AE by ResMed

iVAPS or Intelligent Volume Assured pressure support by Resmed (Poway CA, USA) is a mode of noninvasive ventilation that is indicated for individuals weighing ≥ 30kg. iVAPS modulates pressure support by comparing actual or delivered ventilation to an alveolar ventilation target. Alveolar ventilation is physiological dead space subtracted from tidal volume which is then multiplied by frequency. Approximately 1/3rd of each breath inspired remains in the conducting zones of the lungs and does not take part in gas exchange. There are two functions for a clinician to set the alveolar ventilation target, one is a learn feature that will automatically calculate an alveolar ventilation target and backup rate during

stable breathing and the other is a calculation based on an individual's height, resting respiratory rate, and previously device-measured tidal volume or minute ventilation values. The algorithm is associated with faster pressure support changes (Figure 3) as compared to the other models evaluated in this article with a rate of change that can equal 0.7 cmH_2O per second. According to the manufacture, the pressure support changes typically do not exceed 3 cmH_2O per breath. iVAPS also has an automated backup rate algorithm labeled iBR for intelligent back up rate. The iBR target is intended to be set close to the individual's eupneic frequency. iBR operates using two limits, the target breath rate; representing the upper frequency boundary, and the background frequency, which is approximately 2/3^{rds} of the rate target and is designed to encourage spontaneous breaths. iVAPS also has an automated EPAP feature that can respond to partial or complete upper airway closure. Use of a single limb circuit with intentional leak provides a leak compensated estimation of flow and exhaled tidal volume; however, the leak compensation threshold is not specified by the manufacturer for the Astral 100 and 150 ventilator platforms. The user manual provides a warning that measurement of exhaled gas volume may be affected by a leak (Astral 100/150 user manual, English pg. 11). An alert to an excessive leak condition may be in part facilitated by activating one or more ventilation alarms that include leak alarm, low pressure alarm, low PEEP alarm, and a circuit disconnection alarm.

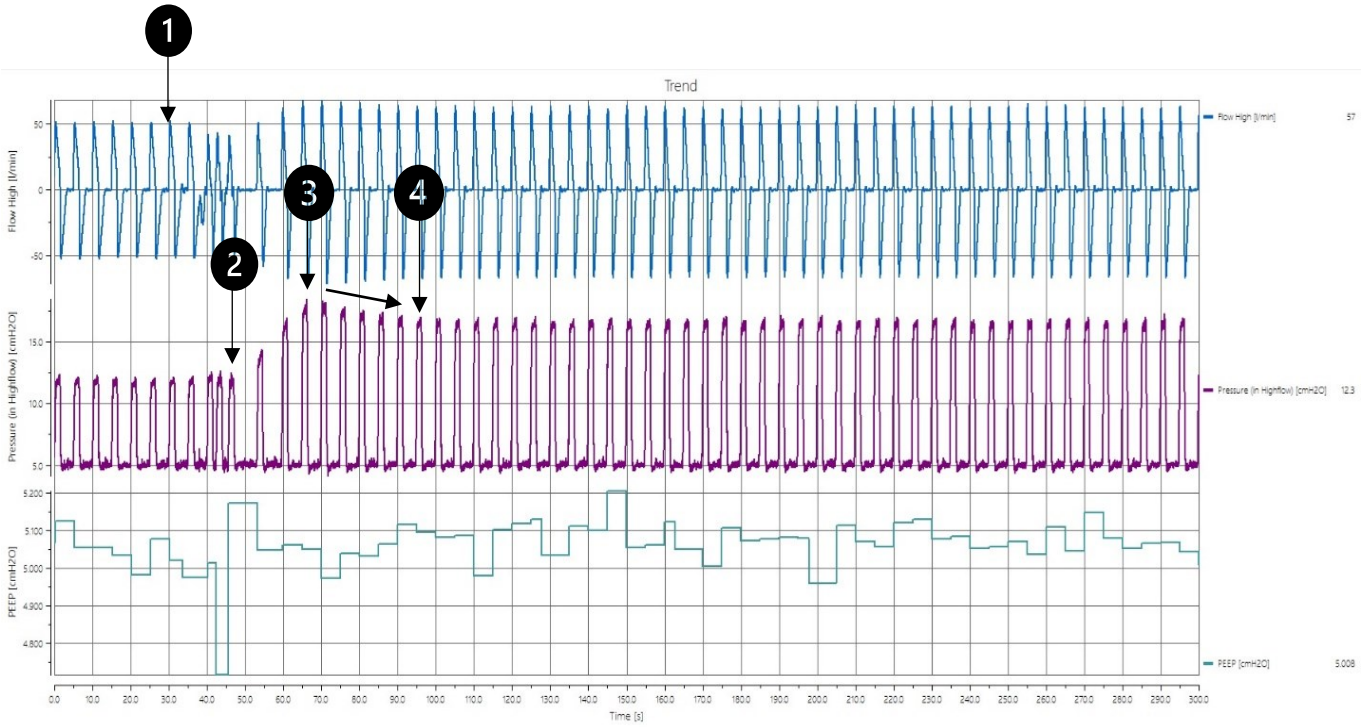

Figure 3: A passive exhalation circuit was connected to the Astral 100 ventilator and the IMT® flow analyzer. A single TTL® lung was initially set to a R5, C 0.1 normal lung model. After stabilization of PIP to 12 cmH_2O occurred (1), compliance was decreased to 0.6 (2) to evaluate the pressure support controller's response. Pressure support was increased rapidly from 12 cmH_2O to a PIP of 17.5 cmH_2O within three breaths (3). The controller initially overshot the alveolar ventilation target and proceeded to settle to a PIP of 16.4 cmH_2O (4) for the remainder of the evaluation period.

iVAPS settings: Patient Height: 68 inches, Target Rate: 12 bpm, Target V_A: 9 lpm, EPAP 5 cmH_2O, Auto EPAP: OFF, PS Min: 4 cmH_2O, PS Max: 40 cmH_2O, Rise: 300 msec, T_I Min: 1.5 sec, T_I Max: 2.0 sec, Trigger: Low, Cycle %: 25. Circuit Test was performed and passed before testing scenario initiated.

Volume Targeted Ventilation by React Health

React Health manufacturers multiple ventilator configurations that offer three TgV ventilation modes: Vol-Targeted-PS, Vol-Targeted-PC, and Vol-Targeted-SIMV. In all three modes a set tidal volume is delivered by adjusting the pressure controller target on a breath-by-breath basis. The initial breath is delivered as a pressure control breath at the set pressure minimum. The ventilator then calculates the amount of pressure required to deliver the set tidal volume and adjusts delivered pressure on subsequent breaths. Clinicians are able to adjust the rate of pressure adjustment made in TgV ventilation modes by setting the Pres. Adj. Rate Control to a setting of slow or fast. The slow setting will allow a

pressure change maximum of 1 cmH_2O per breath, while the fast setting will allow a pressure change maximum of 3 cmH_2O per breath. The maximum pressure is limited to 50 cmH_2O or 5 cmH_2O below the High-Pressure alarm setting, whichever is lowest. The V*Home ventilator and other ventilator configurations by React Health are rated to provide leak compensation up to 175 lpm at 20 cmH_2O according to the clinical manual. Robust leak compensation is an important aspect of a ventilator's ability to deliver an accurate volume and maintain patient-ventilatory synchrony in the presence of moderate to large unintentional leaks. TgV modes can be used with leak and valveless circuit configurations. Figure 4 demonstrates the pressure modulation when the "Fast" pressure adjustment setting was selected.

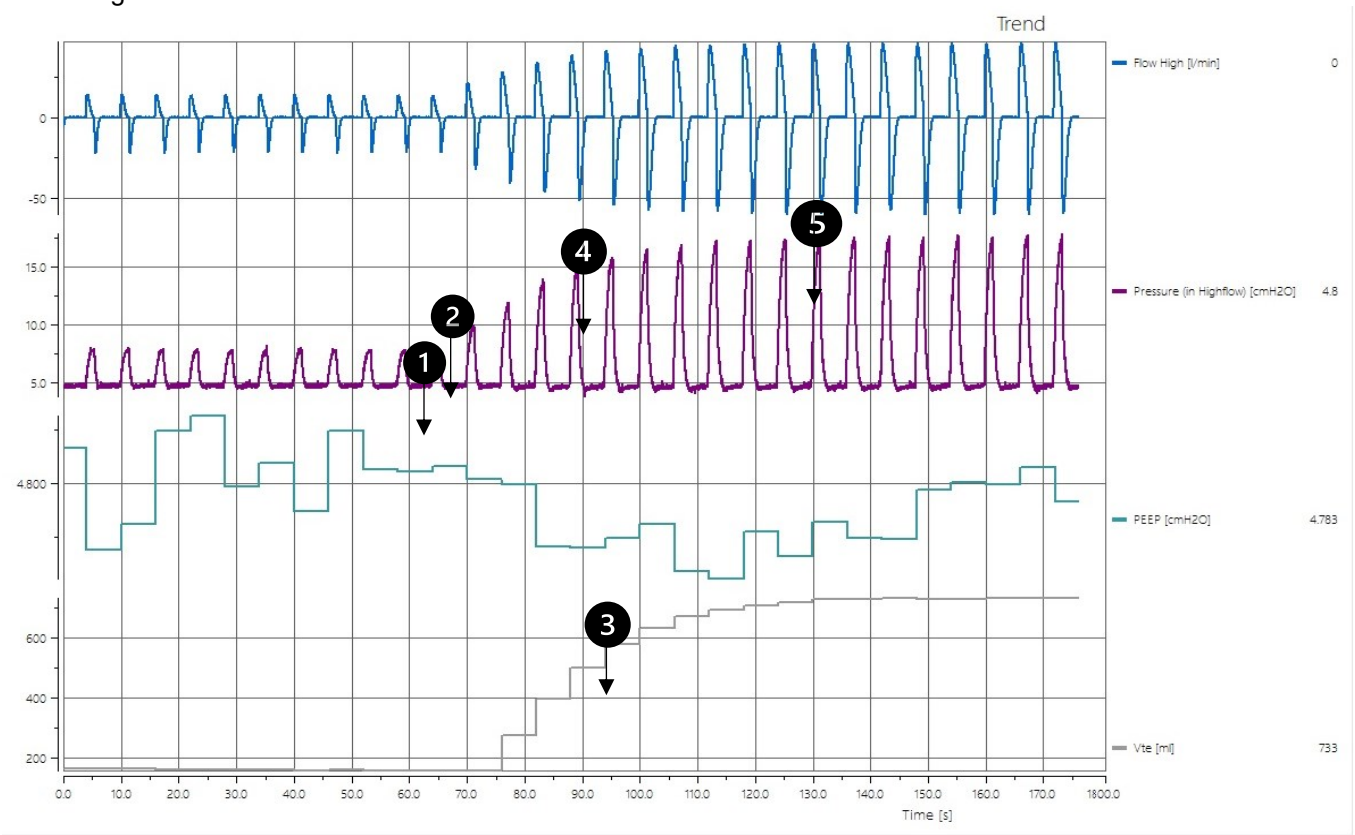

Figure 4: A passive exhalation circuit was connected to the V+C ventilator and the IMT® flow analyzer. A single TTL® lung was initially set to a R5, C .05 restrictive lung model. After stabilization of VT_E and PIP to approximately 7.7 cmH_2O occurred (1), the TgV was changed from 200 mL to 800 mL (2) to evaluate the pressure support controller's response. The increase in VT_E corresponding to the pressure change with each machine triggered breath is demonstrated in the VT_E trend (3). Pressure changes were larger in the initial breaths to a maximum of 2.2 cmH_2O, however not using all the available per breath pressure bandwidth of 3 cmH_2O. Pressure changes became more granular decreasing to < 0.5 cmH_2O per breath as the gap between VT_E and the TgV decreased (4) a design to prevent an overshoot of the volume target. PIP increased from 7.7 cmH_2O to a stable PIP of 17.3 cmH_2O over 11 breaths (5) with a △ P of 9.6 cmH_2O.

V+C settings: Mode: Vol-Targeted-PS, TgV start: 200 mL, Test TgV: 800 mL, Rate: 10 bpm, PEEP 5 cmH_2O, PS Min: 2 cmH_2O, PS Max: 45 cmH_2O, T_I Min: 1.5 sec, Flow Trigger: 3, Flow Cycle: 25% Time Cycle 1.5 sec, Rise Time 4. Circuit Test was performed using a passive (leak) circuit configuration, which passed before the testing scenario was initiated.

TgV NIV and the Clinical Evidence

In the following section, a snapshot of the characterizations of the disease is followed by a summary of the findings of more recently available clinical evidence surrounding TgV based NIV featuring the described cohort.

COPD and Overlap Syndrome

COPD is associated with airways inflammation, alveolar wall destruction, a reduction in alveolar capillary exchange area, increased physiologic dead space, and dynamic lung hyperinflation. Dynamic hyperinflation imposes an inspiratory load burden that may negatively impact diaphragmatic contraction

resulting in increased reliance on accessory muscle use. Rapid Eye Movement (REM) sleep inhibits accessory muscle contraction which may result in clinically significant impairment of gas exchange during sleep. [9] In addition to sleep-related hypoventilation, comingled sleep disordered breathing may also be present in the COPD patient profile and is often termed *overlap syndrome*. Muscle relaxation in addition to the supine position exacerbates upper airway obstruction potentially worsening hyperinflation and sleep-related hypoventilation. [9] Improving nocturnal gas exchange may be accomplished through a combination of pressure support to help stabilize lung volume, EPAP to splint the upper airway and mitigate airflow obstruction; when sleep disordered breathing is present, and a backup rate to ensure a clinically viable minimum minute ventilation threshold.

TgV has been clinically evaluated in COPD and overlap syndrome patient profiles. A summary of the more recent findings is presented in Table 1.

Obesity Hypoventilation Syndrome (OHS)

Obesity Hypoventilation Syndrome or OHS is characterized by respiratory impairment; including both respiratory mechanics and ventilatory drive, that is associated with the presence of daytime hypoventilation, morbid obesity (BMI > 40kg/m^2), and comingled sleep disordered breathing - of which 90% is caused by obstructive apneas and hypopneas (AHI > 5 per hr). [14] Hallmark features of OHS include: decreased lung volumes, decreased chest wall compliance, increased airways resistance, increased work of breathing and the potential for small airway closure during the exhalation phase creating intrinsic PEEP and adding to the inspiratory load burden. [14]

Normalizing gas exchange through nocturnal ventilatory support is further complicated by the need to ensure upper airway patency as well as the nocturnal occurrence of periodic marked decreases in respiratory system compliance secondary to the supine body position and excessive weight. Key findings related to TgV in the OHS Cohort are summarized in Table 1.

Neuromuscular Disorders (NMD)

Neuromuscular diseases (NMD) refer to an umbrella of broadly defined clinically and genetically heterogenous disorders affecting the peripheral nervous system, the synapse between motor neurons and muscle fibers (neuromuscular junction), and skeletal muscles; that in many cases, lead to progressive muscle weakness, atrophy, and wasting. NMD can be acquired or genetic, with the disease onset presenting in a range of ages from infant through adult. NMDs are estimated to affect approximately 1 in 1,000 individuals globally with varying lengths of survivability. [20] When the NMD is associated with respiratory muscle weakness and respiratory imbalance, NIV and airway clearance are principle respiratory interventions aimed at slowing the decline of forced vital capacity, correction of alveolar hypoventilation, improvement of blood gases, mitigating respiratory infections, supporting phonation, and improving quality of life and length of survivability. Table 1 provides a summary of clinical evidence investigating the role of TgV in the ventilatory support strategy.

Conclusion

TgV modes represent an exciting step forward in the continuous evolution in noninvasive ventilation algorithms and modes. TgV have shown promise in improving certain aspects in the clinical management of NIV and patient outcomes such as increased efficiency for the clinician to implement, more stable volume delivery over time despite disease state progression, and in some cohorts, improved adherence over static pressure NIV modes. Arguably more work is needed to improve TgV algorithms as the clinical evidence has yet to show a clear superiority to standard fixed-pressure NIV modes in critically important areas including gas exchange, hospitalizations, quality of life, and survivability.

Although TgV modes are generally viewed as an efficient way to implement NIV for disease states such as OHS, COPD, and NMD, it is important to note that algorithms performance and response to input signals vary between manufacturers. Some manufacturers take a more conservative approach to modulating pressure support changes, others allow for a much more aggressive approach to pressure support rates of change. Rapid versus slower pressure support changes in response to changes in tidal volume may have an impact on sleep architecture, comfort, and even possibly adherence. Leak compensation and triggering also vary between platforms. Interface leaks can be a common occurrence during noninvasive ventilation, so it is incumbent upon a clinician to consider triggering performance of the various home ventilator platforms and always be aware of the potential for patient ventilator asynchrony (PVA) as part of the ongoing management of the patient's ventilatory support regimen.

Use of an auto EPAP algorithm may be a beneficial tool to ensure that the presence of comingled sleep disordered breathing is addressed and does not prevent the stable delivery of tidal volume over time. Evaluation of patient and upper airway responses to automated pressure changes are still necessary, especially in cases of bulbar dysfunction and vocal cord spasticity.

Finally, TgV modes should not be simply viewed as one-size-fits-all approach to ventilation that somehow replaces the need for careful implementation and ongoing patient evaluation and management. As recent clinical evidence has demonstrated in a cohort of severe COPD, not all individuals who were treated with NIV were “responders”. Clearly defined clinical goals, appropriately set pressure levels, and minimum levels of daily adherence appear to be very important aspects contributing to improved patient outcomes when implementing and managing NIV in the home setting. [24]

Table 1: summary of clinical evidence investigating the role of TgV in the ventilatory support strategy

Year	Cohort	Summary of Key Findings	Reference
2014	COPD	1. Sleep quality, the control of nocturnal hypoventilation, daytime hypercapnia, overnight ventilation patterns, subjects' tolerance, health-related quality of life, lung function, and exercise capability were all similar in subjects who underwent HI-NIV and target V(T) NIV. 2. Nevertheless, target V(T) NIV might offer some physiological advantages in breathing pattern and might be beneficial in some individual patients.	Storre et al [10]
2014	COPD	1. Domiciliary va-NIV and pp-NIV have similar effects on physiological outcomes in COPD patients with CVF and both are well tolerated. 2. Patients allocated va-NIV spent fewer days in hospital initiating therapy 3.3 (1.6) versus 5.2 (2.8) (P 0.02). 3. Both groups showed significant improvements in $PaCO_2$ and $mSpO_2$ after three months treatment.	Oscroft et al [6]
2020	COPD	1. VAPS mode had similar efficacy as the pressure-support (PS) mode. 2. VAPS could significantly improve the patients’ subjective feelings.	Zhang et al [11]
2021	COPD (*AE-COPD*)	1. There were no significant differences between two modes (*iVAPS, N = 26 or BPAP S/T, N = 56*) with respect to demographics such as age, gender, presence of comorbidity, usage of long-term oxygen therapy or NIV, and the baseline ABG parameters. 2. Both modes were similarly effective in the management of appropriately selected patients with hypercapnic respiratory failure caused by AECOPD.	Söyler et al [12]
2022	COPD	1. Application of AVAPS mode results in more rapid and steady improvement in patients of COPD as compared to BiPAP (S/T) mode. 2. Management through non-invasive ventilation AVAPS mode should be considered in patients with acute exacerbation of COPD with type 2 respiratory failure.	Maheshwari et al [13]
2006	OHS	1. Both standard NIV and TgV NIV improved oxygenation, sleep quality, and health-related quality of life (HRQL). 2. TgV (AVAPS) was demonstrated to provide a more efficient decrease in $PtcCO_2$, however did not provide further benefit sleep quality and HRQL.	Storre et al [15]
2012	OHS	1. Improvements in $PaCO_2$ and severe respiratory insufficiency questionnaire (SRI) were seen in both standard and TgV with no statistical differences. 2. Improvement in physical activity and reduction in fat mass were observed in both groups without statistical difference.	Murphy et al [16]
2018	OHS	1. TgV (AVAPS-AE) compared to NIV using an ST mode at 2 months had similar impact on sleep quality and gas exchange. 2. TgV may offer a benefit of reduction in time associated with implementing home NIV.	Patout et al [17]
2020	OHS without severe OSA	1. Hospitalization days were similar between the control and NIV groups. 2. NIV therapy, in contrast with the control group, produced significant longitudinal improvement in $PaCO_2$, pH, bicarbonate, quality of life, and daytime sleepiness. 3. Moreover, per-protocol analysis showed a statistically significant difference for the time until the first ED visit favoring NIV.	Masa et al[18]

2023	OHS	1. The study demonstrated no difference in medium-term cost-effectiveness. 2. Both interventions were associated with similar clinical effectiveness, between outpatient and inpatient NIV setup.	Murphy et al [19]
2017	ALS	1. In ALS, VAPS achieves a more reliable V_T than PS, and is associated with significantly less rapid shallow breathing. 2. No differences in patient compliance were found between VAPS and PS. 3. Irrespective of the mode of PS, patients with ALS demonstrate decreased spontaneous breath cycling.	Nicholson et al [21]
2021	Pediatric NMD	1. Improved adherence was observed in the VAPS (TgV) mode group as compared to the S/T mode group in pediatric NMD patients. 2. No differences in gas exchange, sleep architecture, or parent proxy reports of NIV intolerance between the groups.	Sunkonkit et al [22]
2023	NMD & ALS	1. Baseline NIV usage was lower in the ST group versus the VAPS (TgV) group. 4. VAPS (TgV) mode was associated with increased ventilation sustained over time as compared to ST mode.	Orr et al [23]

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