CHEST

Initiation of Noninvasive Ventilation for Sleep Related Hypoventilation Disorders

Advanced Modes and Devices

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Although noninvasive ventilation (NIV) has been used since the 1950s in the polio epidemic, the development of modern bilevel positive airway pressure (BPAP) devices did not become a reality until the 1990s. Over the past 25 years, BPAP technology options have increased exponentially. The number of patients receiving this treatment both in the acute setting and at home is growing steadily. However, a knowledge gap exists in the way the settings on these devices are adjusted to achieve synchrony and match the patient's unique physiology of respiratory failure. This issue is further complicated by differences in pressure and flow dynamic settings among different types of NIV devices available for inpatient and home care.

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Prevalent alveolar and sleep related hypoventilation disorders include patients with COPD presenting with acute-on-chronic hypercapnic respiratory failure, overlap syndrome (COPD plus OSA), obesity hypoventilation syndrome (OHS), and progressive restrictive pulmonary disorders, such as thoracic cage abnormalities and neuromuscular disease (NMD). Careful selection of NIV mode and settings should be based on the patient's distinctive needs and level of acute illness. This review focuses on providing a practical approach to NIV in prevalent stable sleep-related alveolar hypoventilation syndromes, both in non-ICU hospital settings and at home, with emphasis on customizing NIV settings to the patient's unique physiology of respiratory failure.

Noninvasive ventilation (NIV) is used widely in hospitalized patients with COPD presenting with acute-on-chronic hypercapnic respiratory failure,[1,2] overlap

ABBREVIATIONS: ABG = arterial blood gas; ALS = amyotrophic lateral sclerosis; AVAPS = average volume-assured pressure support; AVAPS-AE = average volume-assured pressure support with auto-expiratory positive airway pressure; BPAP = bilevel positive airway pressure; CMS = Centers for Medicare & Medicaid Services; EPAP = expiratory positive airway pressure; FOT = forced oscillation technique; iPAP = inspiratory positive airway pressure; iPEEP = inspiratory positive end-expiratory pressure; iVAPS = intelligent volume -assured pressure support; NIV = noninvasive ventilation; NMD = neuromuscular disease; OHS = obesity hypoventilation syndrome; PAP = positive airway pressure; PC = pressure assist control mode; PS = pressure support; PSG = polysomnography; RR = respiration rate; S = spontaneous; ST = spontaneous timed; $TcCO_2$ = transcutaneous CO_2; Ti = inspiratory time; Ti max = maximal inspiratory time; Ti min = minimal inspiratory time; Va = alveolar ventilation; VAPS = volume-assured pressure support; V_T = tidal volume; V_{Te} = expiratory tidal volume

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syndrome (COPD plus OSA)[3], and OHS, the latter being defined as obesity (BMI > 30 kg/m^2) and daytime hypercapnia ($Paco_2$ > 45 mm Hg), when other causes of chronic alveolar hypoventilation have been ruled out.[4-6] It is also frequently used in other causes of hypoventilation syndrome related to opioid and sedative use, as well as progressive restrictive pulmonary disorders such as thoracic cage abnormalities and NMD.[7-9]

A thorough understanding of NIV modes and settings is crucial to guarantee an uneventful transition from hospital to home for patients with chronic respiratory disease, but a knowledge gap exists about advanced NIV modes.[10] Although most pulmonary and critical care practitioners are comfortable with the use of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), other setting options are misunderstood and frequently ignored. Settings such as trigger and cycle sensitivity, rise time, and inspiratory time (Ti) are poorly understood and are usually left in the factory's default mode. The purpose of this review is to provide a practical approach to NIV in prevalent stable sleep-related alveolar hypoventilation syndromes, both in the non-ICU hospital setting and at home, with emphasis on customizing NIV settings to the patient's unique physiology of respiratory failure.

Bilevel Positive Airway Pressure Devices: What Is in the Box?

Hardware

In minimally monitored hospital areas and at home, the most common NIV devices being used are bilevel positive airway pressure (BPAP) devices exclusively designed to interact with a mask. They are basically composed of a blower (or turbine), a respiratory circuit (generally a single limb), heated humidity, and a mask. Based on flow and pressure sensors located in the device, a microprocessor-based controller is constantly adjusting the turbine speed (dynamic blower) to reach a preset device output (positive pressure).[11] The mask, which contains an obligatory leak to minimize CO_2 rebreathing, is the point of interface between the device (mechanical pump) and the patient (respiratory pump) (Fig 1A).[12] In highly monitored areas of the hospital (predominantly the ICU), other ventilator options (and circuits) are available for NIV, such as mechanical ventilators (MVs) with a capability to deliver NIV and hybrid mechanical ventilators (Table 1).

Software

1) Modes in BPAP—fixed vs self-adjusting (targeted) pressure: By definition, NIV encompasses BPAP devices that are capable of separately adjusting IPAP and EPAP.

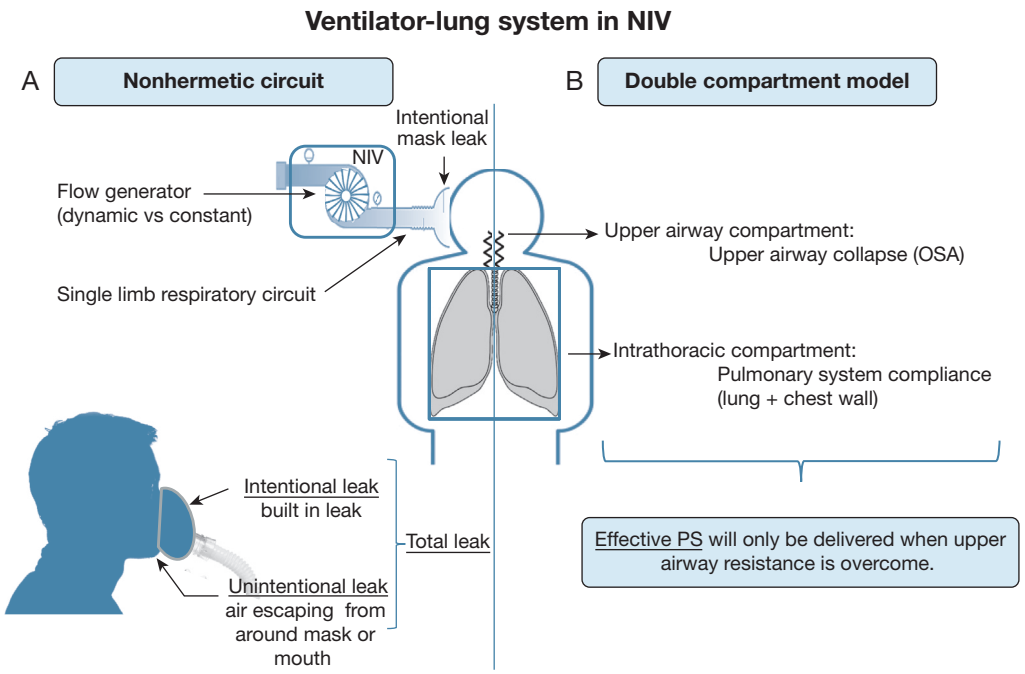


Figure 1 – *Ventilator-lung system in NIV. NIV = noninvasive ventilation; PS = pressure support.*

TABLE 1] Noninvasive Ventilation: What Is in the Box?

What Is in the Box?			
Hardware	Ventilator Options	Respiratory assist device (RAD) Devices designed to be used only for NIV	Manufactured either for specific use in the ICU (eg the Respironics V60) or for specific use at home (eg, the ResMed S10 VPAP ST-A). These devices include many different modes and software options that will perform differently
		Mechanical ventilator (MV) Devices designed for critical care use, predominantly for ventilation in combination with an invasive interface	These devices can also be used with noninvasive interfaces Many devices include options for preset NIV modes (eg, the Siemens SERVO-i)
		Hybrid MVs Devices are hybrids between typical MV and RADs and are designed for both home and critical care use	They offer the largest range of options for modes and settings for both invasive and noninvasive styles of ventilation
	Pneumatic systems	Piston	Pneumatic system generally found in conventional MVs
		Turbine	Dynamic blower systems are variable- speed (fast) turbines that change speed to reach a preset flow
			Constant-revolution blower systems are constant-speed turbines in which flow output is regulated by opening and closing of proportional valves
	Respiratory circuits	Active/double-lumen circuit Circuit designed for inhalation (oxygen rich) from 1 limb (tube) and exhalation (CO_2 rich) through another	This is designed as a closed system with no intentional leak This circuit is used in delivering NIV through an MV Compensation for circuit compliance and resistance occurs either automatically (calibration) or by choosing circuit configuration (eg, the Philips Respironics Trilogy 100/200)
		Passive/single-lumen circuit Circuit designed for continuous flow (inhaling and exhaling)	CO_2 is cleared through an exhalation port This intentional leak can occur through an integrated tubing valve or on the mask itself Because of the intentional leak, inspiratory and expiratory tidal volume are not measured directly but are calculated by propriety algorithms based on information from proximal sensors in the device

NIV = noninvasive ventilation.

The EPAP is set to maintain upper airway patency and the IPAP/EPAP difference provides pressure support (PS) to sustain/augment the patient's tidal volume (V_T). Depending on the device manufacturer and mode, the blower may provide either a fixed BPAP (BPAP mode) or a BPAP with self-adjustment pressure capability to

support the patient's ventilation (volume-assured pressure support mode [VAPS]). VAPS devices have the capability to sense changes in the patient's respiratory flow over several breaths and to proportionally adjust the positive pressure during inhalation (IPAP/PS) to reach a respiratory target. These respiratory targets could be either expiratory tidal volume (VTE) (Respironics, AVAPS [average VAPS]), or alveolar ventilation (ResMed, iVPAS [intelligent VAPS]).[13,14] Using the iVAPS device, the calculation of target alveolar ventilation (Va) can be done by the device itself using the patient's height and targeted backup rate. The clinician can then increase or decrease the programmed target Va until he or she is comfortable with the VTE average estimates. If the device is not available, the laboratory titration software can provide the same information (Table 2).

Due to the absence of tracheal or endotracheal tubes and the noninvasive nature of these devices, upper airway patency is not guaranteed. Therefore, effective ventilation should be conceptualized in a double-compartment respiratory model, in which EPAP will achieve the upper compartment patency (upper airway patency) needed to allow the effective delivery of PS to the lower compartment (lower airways)[15] (Fig 1B). Therefore, the auto-EPAP algorithm has been introduced in few devices with VAPS capability (eg, Respironics AVAPS-AE) to address the upper airway resistance (OSA) and improve ventilation (Table 2), In the AVAPS-AE device, a forced oscillation technique (FOT) is used to measure the airway resistance. If the upper airway is patent, the FOT sinusoidal signal (5 Hz, 1 cm H_2O amplitude) during EPAP will result in flow oscillations. However, if the airway is obstructed, flow oscillations will be smaller, and EPAP will be increased by 1 cm H_2O after the analysis of 10 breaths. The algorithm will continue testing FOT for changes in airway resistance.[16-18]

Depending on the device's interaction with the patient's spontaneous breath, or lack of it, BPAP can be delivered in spontaneous mode (S), spontaneous timed (ST) mode, or pressure assist control mode (PC) (Table 2). The device may also contain a timed (T) mode. As this mode does not allow for patient synchrony, it is only rarely used, and it will not be discussed in this review.

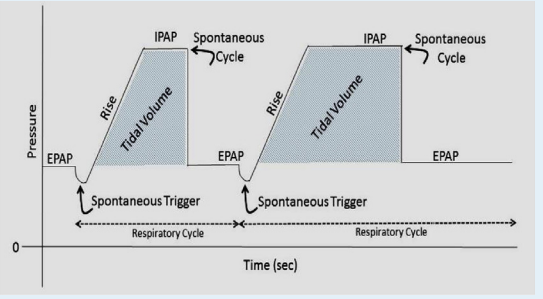
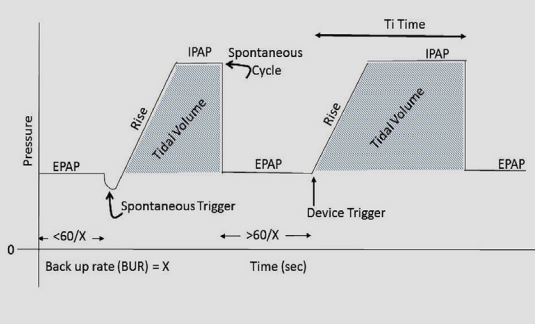
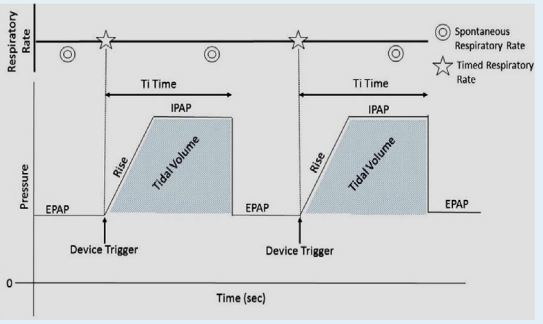
2) Advanced Settings in BPAP: Anatomy of a Pressure Waveform: In NIV, a positive pressure breath can be characterized by its three main phase variables during the respiratory cycle: the trigger, the target, and the cycle (Table 3, e-Table 1). Based on these inspiratory phase variables, the following advanced settings in BPAP devices in ST or PC mode can be adjusted:

Trigger sensitivity sets the level of inspiratory flow change (generated by the patient's inhalation effort) above which the device switches from EPAP (exhalation) to IPAP (inhalation). It applies to spontaneous breaths and is measured by either pressure or flow changes detected by the device. Changes in trigger sensitivity should be customized to the patient's pathophysiology and assessed at the bedside.[19,20] In some devices, a software product determines the trigger without the physician needing to adjust the setting manually (eg, Auto-Trak by Respironics).[20] The use of the standard Auto-Trak assumes normal diaphragmatic strength; therefore, it may be associated with premature cycling in patients with neuromuscular disease (NMD) and trigger insensitivity in patients with COPD.[21] A newer version of the software (sensitive Auto-Trak) allows adults with weakness or children to more easily trigger breaths, although this function has not been developed or tested in patients with NMD. Clinically, a highly sensitive trigger (less effort needed to trigger IPAP) may be used in patients with NMD to improve synchrony (Table 3).

Rise time sets the time (in milliseconds) it takes the device to transition from EPAP to IPAP (pressurization time). A slower rise can be helpful in those with bulbar disease or chest wall stiffness. A faster rise time may be helpful to improve comfort in those with "air hunger" or muscle weakness (Table 3).[22]
Inspiratory time (Ti) sets the time limit spent on IPAP (s). Apart from PS, Ti is the main setting driving the size of the exhaled VT. The longer the time spent in inhalation, the larger the VT (assuming constant pulmonary mechanics). Depending on the manufacturer and device model, Ti may either apply to mandatory breaths (Respironics) or to spontaneous (S) as well as mandatory breaths (ResMed) in ST mode (Table 3). In PC mode, all devices will deliver a fixed Ti in response to all breaths (Table 2).

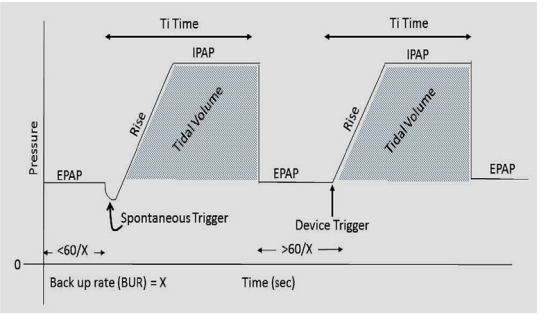
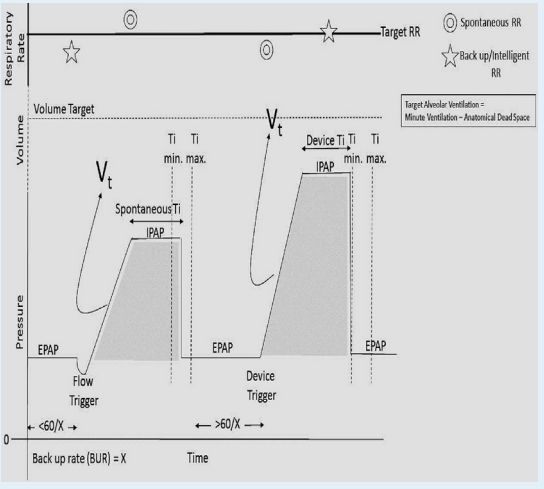
Cycle sensitivity sets the cycle out of IPAP. Completion of inhalation may be determined by flow decay (percentage of decrement in flow compared with the peak inspiratory flow noted at the initiation of inhalation) or by time (Ti). When the cycle is determined by the percentage of peak flow, the lower it is set, the later the inhalation supported by IPAP

TABLE 2] Software in the Box: Most Common Modes Available in ICU/Ambulatory Care

Software in the Box: Most Common Modes Available		
S Mode (spontaneous)		The device senses the patient's inspiratory effort and triggers IPAP in response to an increase in flow, and cycles into EPAP at the end of inspiration. In this mode, the breath will last as long as inspiratory flow is noted. The breath rate and the respiratory pattern will be determined by the patient. Clinical: applicable to any clinical scenario in which the proper minute ventilation can be sustained based on the patient's natural respiration rate
ST mode (spontaneous/timed) BIPAP-ST (Respironics) VPAP-ST (ResMed)		The device augments (provides PS) any breath initiated by the patient (spontaneous [S]), but will also apply to device-delivered breaths (timed [T] breath) should the patient's breath rate fall to less than the clinician's set "backup" rate In contrast to S breaths, IPAP in T breaths will persist for the entire Ti time programmed as part of the device settings. This may cause the tidal volume to be reduced or uneven between S and T breaths. *This may vary by manufacturer.* Clinical: in the setting of COPD, this uneven tidal volume may be beneficial by assisting ventilation without facilitating air trapping/ hyperinflation that may limit tolerance for NIV
T mode (timed)		The fixed breath rate and the fixed inspiration time set by the clinician are applied regardless of patient effort. Clinical: rarely used in clinical practice

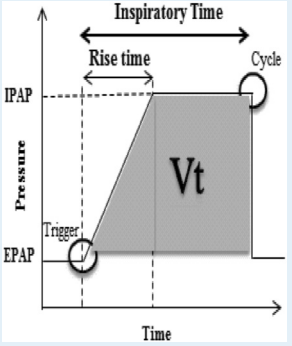
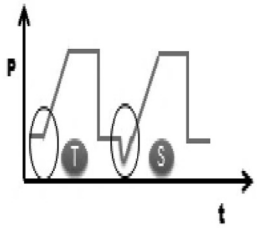
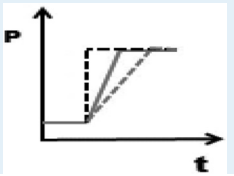
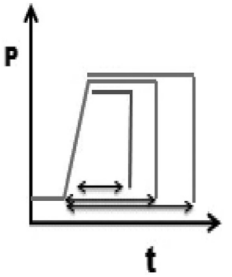
(Continued)

TABLE 2] *(Continued)*

Software in the Box: Most Common Modes Available		
PC mode (pressure control)		The distinction between ST and PC mode centers on the programmed Ti. Although the inspiration can be triggered spontaneously (S) or timed (T), there is no flow cycling out of IPAP. As opposed to ST, when Ti is applied only in timed breaths, in PC mode the programmed Ti time is applied to every breath. This will even out tidal volume on a breath-to-breath basis. Clinical: a consistently applied fixed Ti is adventitious in the setting of NMD when diaphragmatic fatigue will drive otherwise short Ti time
Volume-assured pressure support modes (VAPS) AVAPS (assured volume assured pressure support; ResMed) targets expiratory tidal volume iVAPS (intelligent volume assured pressure support ResMed) targets alveolar ventilation (minute ventilation minus death space ventilation)		It is designed to maintain a preset target ventilation by monitoring ventilation, adjusting the PS, and providing a backup breath automatically VAPS technology is add-on software, which can be used with NIV in either ST or PC mode The settings include a range of PS values that are automatically adjusted to reach a targeted tidal volume. The EPAP is also programed using a range of settings to allow for automatic adjustments, targeting EPAP to prevent upper airway obstruction. Regarding backup rate, iVAPS "intelligent" backup shifts between two-thirds of set rate during spontaneous breathing and set rate during period of apnea. In AVAPS devices, backup rate can be fixed or autoset, which is 2 bpm less than the average rate of the most recent six spontaneous breaths. Clinical: not inferior to BPAP-ST in management of OHS, COPD and NMD.

BPAP = bilevel positive airway pressure; EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; max = maximum; min = minimum; NMD = neuromuscular disease; OHS = obesity hypoventilation syndrome; PC = pressure control; PS = pressure support; RR = respiration rate; ST = spontaneous times; Ti = inspiratory pressure. See Table 1 legend for expansion of other abbreviations.

TABLE 3] Advanced Settings in Bilevel Positive Airway Pressure: Anatomy of a Pressure Waveform

Pressure Wave for Basic and Advanced NIV Settings			
Settings	Waveforms	Definitions/Actions	Comments
Respiratory phase variables in a pressure-time waveform		*EPAP* is device's lowest pressure set during exhalation *Trigger* is the switch from EPAP to IPAP (initiation of supported inhalation) *Rise time* is the time it takes the device to transition from EPAP to IPAP (pressurization time) *Inspiratory time* is the time the device spends in IPAP *Cycle* is the switch from IPAP to EPAP *IPAP* is the device's highest pressure set during inhalation	EPAP is needed to eliminate exhaled air (CO_2) from a single-lumen circuit, stent open the upper airway, improve small airway recruitment (oxygenation), and improve triggering in high intrinsic PEEP (eg, COPD) EPAP in some devices is referred to as CPAP or PEEP The higher the IPAP and the longer it lasts, the larger the resultant inhaled tidal volume
Inspiratory trigger (Who decides when to take a breath?)		*Trigger* may be initiated by patient (spontaneous breath) or by the device ("mandatory" breath) *Spontaneous breath* (flow triggered): flow above which the device changes from EPAP to IPAP *Trigger sensitivity* sets the level of inspiratory flow change above which the device switch to IPAP *Mandatory breath* (timed triggered) is initiated by the device based on preset backup respiration rate (RR) *Spontaneous timed* (ST)	Goal of trigger: ↓ Muscular effort ↓ Delay between patient's initiation of breath and the start of the device's delivered breath
Rise time (How quickly can IPAP be reached?)		*Rise time* is the time it takes the device to transition from EPAP to IPAP (pressurization time) Manufacturers' differences: ResMed measures in ms Respironics uses a qualitative measure (the lower the setting the faster the rise)	↓ Rise time (fast pressurization) may be needed to: Match patient's high respiratory drive Accelerate inhalation in COPD Slow rise is helpful in patients with bulbar disease Fast rise time helpful in diaphragmatic dysfunction
Inspiratory Time (Ti) (How long is the IPAP maintained?)		*Ti* is the set time limit to support inhalation by IPAP Manufacturer differences: Respironics: Ti limit may apply only to mandatory (timed) breaths, being variable during spontaneous breaths (S) ResMed: Ti limit may apply to both mandatory and spontaneous breaths	Assuming constant pulmonary mechanics: The longer the Ti, the larger is the tidal volume By applying Ti in timed and spontaneous breaths, a more constant tidal volume and minute ventilation may be reached (ResMed) In the I:E cycle, Ti will influence time spent in exhalation, and it will depend on respiration rate

(Continued)

TABLE 3] (Continued)

Pressure Wave for Basic and Advanced NIV Settings

Settings	Waveforms	Definitions/Actions	Comments
Inspiratory cycle (What decides when to switch from inhalation to exhalation?)		Cycle is set to limit inhalation support by IPAP Flow cycle: when the device detects the termination of patient's breath by flow reduction. Cycle sensitivity sets the level of inspiratory flow (peak flow) below which the device changes from IPAP to EPAP Manufacturer differences: Respironics: all spontaneous breaths are flow cycle ResMed: any breath in which inspiratory time lasts longer than Ti min but shorter than Ti max Time cycle: based on Ti settings Manufacturer differences: Ti (Respironics) Ti min set to secure a minimal inhalation time. Ti max set to avoid a prolonged inhalation time (safety limit variable) (ResMed).	Between the maximal and minimal Ti settings (time cycle), inspiratory termination is determined by flow reduction in ResMed devices Flow termination criteria are defined by: Percentage of peak inspiratory flow 10% (late termination of inspiration) recommended in NMD 25% (default) 50% (early termination of inspiration) recommended in COPD to increase time in exhalation In Respironics machine, this is flow triggered (L/min) or "Auto-Trak" High levels of unintentional leak may interfere with flow-based expiratory cycle

I:E = inspiratory to expiratory ratio; PEEP = positive end-expiratory pressure. See Table 2 legend for expansion of other abbreviations.

will terminate (eg, in NMD it may be set at 8%-15% or "very low," and in COPD it can be set at 35% or "very high"). Otherwise, the inhalation supported by IPAP may terminate by reaching the Ti limit in an assisted breath (inhalation initiated by patient but cycled by the device) or a mandatory breath (inhalation initiated and terminated by the device). In comparison with the BIPAP device (Respironics), the VPAP device (ResMed) cycles out of IPAP in a window period. This cycle window is defined by a Ti min, which guarantees a minimal time in inhalation so that a short shallow breathing pattern will not develop in those with NMD. Ti max limits the maximal time in IPAP, providing a safety protection against hyperinflation in those with COPD or against late cycling in those with a large unintentional pressure leak from the mask. Between these two time-limit parameters ("time window"), the patient's spontaneous breath may cycle by flow (Table 3).

Effective Ventilation by Synchronization With NIV Devices

The effective ventilation of a patient is attained only by reaching a synchronous interaction between the "mechanical pump" (settings) and the "respiratory pump" (the patient's ability and desire to breathe). Effective synchrony requires optimized mask fitting to reduce flow and other comfort features such as heat and humidity adjustments. Finally, synchrony requires the respiratory specialist to harmonize settings to the unique features of each patient's physiology.

NIV for Sleep-Related Alveolar Hypoventilation in Non-ICU Hospital Settings/Sleep Laboratory and at Home

Selection of the appropriate mode of NIV and the adjustment of NIV settings are of crucial importance to reach optimal synchronization with the patient.[23] However, hospital or sleep laboratory initiation and titration of BPAP devices in patients with complex cardiopulmonary comorbidities could be challenging. Therefore, it is recommended that this titration (modes/settings) be performed in a monitored environment (monitored bed in a hospitalized patient or sleep laboratory setting for chronic sleep related hypoventilation syndromes), in a stepwise fashion under the supervision of trained heath-care providers with a systematic approach to intervene for initial problems and for careful follow-up.[24-27] Among other monitoring

tools (eg, arterial blood gas [ABG] monitoring, overnight oximetry, polysomnography [PSG]), it is recommended that adequately calibrated transcutaneous CO_2 ($TcCO_2$) or end-tidal P_{CO_2} be used to adjust NIV settings in otherwise hemodynamically stable patients with chronic alveolar hypoventilation. A critical requirement for obtaining reliable $TcCO_2$ measurements is appropriate handling and knowledge of the equipment and procedure. In circumstances in which NIV treatment is initiated and adjusted empirically in the outpatient setting based on clinical judgment, a close follow-up of serial NIV download reports or PSG, or both, should be used (if and when possible) to confirm that the final NIV settings are effective or to make adjustments as necessary.[27,28]

COPD

Depending on stability (compensated vs exacerbation), severity stage (mild vs severe), and comorbidities (OSA, congestive heart failure, myocardial infarction), COPD may require different levels of NIV intervention (Tables 4, 5). Qualification for NIV in COPD is based on Centers for Medicare & Medicaid Services (CMS) regulations and guidelines (e-Table 2, part 1).

In the acute care/ICU setting, decompensated patients with hypercapnic respiratory failure from acute COPD exacerbation are usually treated with BPAP or VAPS in the ST mode.[1,5,29] Several publications have shown that patients with COPD treated with NIV for hypercapnic respiratory failure secondary to COPD exacerbation at the time of hospitalization had lower inpatient mortality, a shorter length of stay, and lower costs compared with those treated with mechanical ventilation.[1,29] Once the COPD exacerbation is resolved, noninvasive positive pressure ventilation for the treatment of severe stable chronic COPD may be considered.

In the non-ICU hospital setting/sleep laboratory, nocturnal NIV for chronic severe COPD is commonly titrated under PSG and guided by oximetry, $TcCO_2$, ABG analysis, or a combination. Patients with COPD with an OSA comorbidity (overlap syndrome) may benefit from the use of CPAP or BPAP-S, with adjustment of EPAP pressure to eliminate apneic events. In overlap syndrome, CPAP has proved to improve survival and decrease first-time hospitalization from COPD exacerbation.[3,30-32] Conversely, in those patients with severe COPD in compensated hypercapnic respiratory failure without OSA, the usual BPAP therapy (low PS) has proved ineffective (low-intensity BPAP).[33-36] In this population, emerging literature supports benefits from high-intensity therapy, with high IPAP/PS adjusted to achieve total control of the patient's spontaneous breathing, with near abolition of diaphragmatic activity.[37] In these studies, not yet replicated in the United States, PS (and respiration rate [RR]) were adjusted to decrease arterial tension CO_2 by 20% or to achieve a value lower than 48 mm Hg by reaching IPAP $>$ 18 cm H_2O, achieving mortality improvement without affecting sleep quality[38-40] (Tables 4, 5). In comparison with low-intensity BPAP therapy, VAPS has shown an equal improvement of nocturnal gases (pH, P_{aCO_2} levels, and nocturnal

TABLE 4] Clinical Spectrum of COPD for NIV Intervention

COPD	COPD/OSA Overlap	Severe COPD	COPD Exacerbation	COPD "Plus"
Clinical presentation	Baseline PaO_2 and P_{aCO_2} are normal PSG demonstrates sleep apnea Spirometry: mild to moderate obstruction	Chronic need for supplemental oxygen Chronic P_{aCO_2} $>$ 52 mm Hg Would benefit from the use of NIV in both the ICU and at home	At baseline *may* not have hypercapnia or hypoxemia Is in the midst of an acute episode with high WOB/CO_2 and hypoxemia, with need for inpatient NIV	COPD plus means that NIV may be more helpful for hospitalized patients with: ↙ COPD + MI ↙ COPD + HF ↙ COPD + CAP
Clinical risks	Pulmonary hypertension	Readmission mortality	Intubation risk	Worsening of underlying disease (eg, HF)
Device	CPAP therapy	Bilevel (S/ST) or VAPS Oxygen supplementation	Bilevel (S/ST) or VAPS Oxygen bleed in	Bilevel (ST/S) Oxygen bleed in

CAP = community acquired pneumonia; HF = heart failure; MI = myocardial infarction; PSG = polysomnography; VAPS = volume-assured pressure support; WOB = work of breathing. See Table 1, 2, and 3 legends for expansion of other abbreviations.

TABLE 5] Matching NIV Settings to Patient's Respiratory Mechanics

Pathophysiology/ Device Settings	Chronic OHS (Compensated)	Chronic COPD (Compensated)	Chronic NMD (Compensated)
Respiratory mechanics	↑ Muscle load (↑ UA resistance, 90% OHS) Increased resistance from chest and abdominal wall ↓ FRC due to obesity (expiratory flow limitation, airway closure, V/Q mismatch) ↓ Respiratory drive (leptin resistance, 10% OHS)	↑ Muscle load (↑ Lower airway resistance in COPD) ↓ Muscle capacity (diaphragm atrophy, mechanical disadvantage)	↓ Muscle capacity ↑ Chest wall resistance
Target volume (cc)	Target tidal volume 8 cc/kg ideal body weight	Target tidal volume 8 cc/kg ideal body weight	Target tidal volume 8 cc/kg ideal body weight
	To adjust PS (BPAP-ST), expiratory tidal volume (AVAPS), or Va (iVAPS) based on ABG (pH, $Paco_2$), $TcCO_2$, or a combination		
IPAP (cm H_2O)	High IPAP BPAP-ST: adjust IPAP to a PS for goal tidal volume (average PS, 8-10 cm H_2O) VAPS: allow a large IPAP max/IPAP min difference to reach target expiratory tidal volume or Va	High IPAP (or best tolerated) BPAP: adjust IPAP to a PS for goal tidal volume (or best tolerated) Allow large IPAP max/IPAP min difference to reach target expiratory tidal volume or Va as tolerated	Intermediate IPAP (or best tolerated) Adjust IPAP to a PS for tidal volume goal in BPAP-ST. (average PS, 6 cm H_2O) Allow IPAP min at a higher baseline
EPAP (cm H_2O)	High EPAP in OHS/OSA Adjust to eliminate obstructive apneas (average 8-12 cm H_2O) or snoring	Adjust to eliminate obstructive apneas if present If ineffective trigger, increase EPAP to overcome high iPEEP (first-line therapy)	Low EPAP to reduce work of breathing and improve triggering
Respiration rate (bpm)	To adjust to goal minute ventilation based on ABGs or $TcCO_2$, or both		
Trigger sensitivity[a]	Respironics: Auto-Trak or flow trigger 2-3 L/min ResMed: trigger from medium to low	Respironics: Auto-Trak or flow trigger 4-5 L/min ResMed: trigger medium	High trigger sensitivity to support a weak respiratory muscular effort Respironics: flow trigger at 1-3 L/min ResMed: trigger high or very high
Rise time (ms)	Default or slow rise time Respironics: 3 (300 ms)-6 (600 ms) ResMed: 500-900 ms	Fast rise time	Default or slow rise time Respironics: 3 (300 ms)-6 (600 ms) ResMed: 500-900 ms

(Continued)

TABLE 5 *(Continued)*

Pathophysiology/ Device Settings	Chronic OHS (Compensated)	Chronic COPD (Compensated)	Chronic NMD (Compensated)
Ti (ms)	Long Ti or long Ti min to maximize tidal volume and gas exchange by (↑ I:E) Ti/Ttot 50%	Short Ti or short Ti max to increase expiratory time and minimize iPEEP (↓ I:E) Ti/Ttot 25% in patients with BMI > 30	Long Ti or long Ti min to maximize tidal volume and gas exchange (↑I:E) Ti/Ttot 50%
Cycle Sensitivity[a]	Default or low cycle sensitivity Respironics: Auto-Trak or manual at 10%-15% of peak flow ResMed: Cycle medium to low	Default or high cycle sensitivity (early cycle) to provide a longer exhalation time (↓ I:E) Respironics: Auto-Trak or manual at 30%-50% of peak flow ResMed: Cycle sensitivity medium to high	Default or low cycle sensitivity (late cycle) to provide a longer inhalation time (maximize tidal volume and gas exchange by high I:E) Respironics: Auto-Trak or manual at 10%-15% of peak flow ResMed: Cycle low

ABG = arterial blood gas; AVAPS = average volume-assured pressure support; FRC = functional residual capacity; iPEEP = intrinsic PEEP; iVAPS = intelligent volume-assured pressure support; $TcCO_2$ = transcutaneous CO_2; TI/Ttot = inspiratory time to total time of respiratory cycle ratio; Ttot = total time of respiratory cycle; Ttot = xxx; UA = upper airway; Va = alveolar ventilation; V/Q = ventilation-perfusion. See Table 1, 2, and 3 legends for expansion of other abbreviations.

[a]Respironics has automatic adjustments of trigger and cycle sensitivity called Auto-Trak sensitivity (this function also adjusts for mask leak).

oxygenation), health-related quality of life, sleep efficiency, and compliance in stable patients with chronic COPD.[41,42]

Obesity Hypoventilation Syndrome

Most patients with OHS are characterized by a primary increase in respiratory load from OSA (severity of OSA greater than time spent in sustained oxygen desaturation) on a background of impaired CO_2 clearance and elevated CO_2 production.[43,44] Because of this, approximately 60% of patients with OHS will respond to CPAP by unloading the upper airway resistance and markedly abolishing inspiratory positive end-expiratory pressure (iPEEP) while supine.[45] The remainder of patients will require BPAP therapy to fully support their ventilation needs.[46] Qualification for NIV in OHS is based on CMS guidelines (e-Table 2, part 1).

In a non-ICU hospital setting/sleep laboratory, nocturnal NIV is usually titrated under PSG and guided by oximetry, $TcCO_2$, ABG analysis, or a combination. CPAP is generally considered the initial (first-line) therapy in patients with OHS and compensated hypercapnic respiratory failure with a predominant OSA component.[45,47] If persistent sleep hypoventilation or sustained desaturations remain after elimination of upper airway obstruction by CPAP, a trial of BPAP-S is indicated.[48] When compared with CPAP, BPAP-S was equally effective in improving daytime hypercapnia and quality of life and was superior in improving subjective sleep quality in a subgroup of patients with OHS without severe nocturnal hypoxemia.[47,49] However, in those patients with OHS with a predominant lack of respiratory drive despite BPAP-S therapy (severity of OSA less than time spent in sustained oxygen desaturation), a trial of BPAP-ST or VAPS is recommended.[46,48] The target respiratory volume could be set at 8 cc/kg of ideal body weight, and it should be adjusted based on results from ABG measurements or $TcCO_2$, or both. However, unlike overlap syndrome settings, OHS may require a higher EPAP to overcome usually more severe OSA and a larger PS or target volume (VTE or Va) to overcome the restrictive respiratory system physiology in morbid obesity. If optimal CPAP is available as a reference, EPAP could be set at or 2 cm H_2O above the optimal CPAP setting. In these patients, stabilization of the upper airways is crucial to deliver effective ventilation. In ST mode, and in a stepwise fashion, increments in rise time (500-900 ms or "3-6"), prolongation of Ti (prolonged Ti, or Ti min, or Ti/total time of respiratory cycle (Ttot), 50%), or lowering cycle sensitivity ("low" or

"10%-15%"), or both, will increase the inhalation time, favoring a larger V_T and improvement of gas exchange in these patients. In the United States, CMS qualifying guidelines for an NIV home ventilator may apply to those patients with OHS in medical need of BPAP-ST or VAPS (e-Table 2, part 2). Current limited data suggest that both AVAPS (Respironics) and iVAPS (ResMed) are equally effective in treating chronic hypercapnic respiratory failure compared with BPAP-ST.[50,51] In comparison with BPAP, VAPS has been shown to provide a greater improvement of $Paco_2$ levels and an equal improvement in nocturnal oxygenation, sleep quality, and health-related quality of life.[50,52,53] In only one study has VAPS shown worse sleep quality (less total sleep time, decreased stage 2 sleep, and increased awakening) in comparison with BPAP.[54] When compared with CPAP in patients with OHS and severe OSA, AVAPS has shown a larger improvement in health-related quality of life, spirometric values, and 6-min walk distance despite reaching no difference in improvement of $Paco_2$ and bicarbonate levels between groups.[51] In OHS, high maximal IPAP or PS and low minimal IPAP or PS will allow a wide range of pressures to reach the target volume (eg, 8 cc/kg of ideal body weight). Although EPAP will be adjusted (manually or automatically) to the severity of OSA, the backup RR target may be set 2 to 3 bpm less than the patient's spontaneous respiratory frequency. Ideally, the patient's minute ventilation should be adjusted based on clinical response, the device's download report, $TcCO_2$, or ABG analysis during a polysomnographic study and at the follow-up visit (Table 5).

Neuromuscular Disorders

Respiratory failure in patients with progressive NMD is due to respiratory muscle weakness with increased respiratory load, leading to ineffective ventilation. This can occur in an acute manner or in the setting of myasthenia gravis crisis or Guillain-Barre syndrome, or it can develop over time in progressive motor neuron disease or muscular dystrophy.[55-57]

In both circumstances, the first line of therapy should be initiation of NIV, resulting in the subsequent decrease of the respiratory system load, increase in minute ventilation, and decrease in physiological dead space. It should be noted that in some patients with these acute presentations, severe bulbar disease may limit the ability to use NIV given the increased risk for aspiration. Qualification for NIV in NMD is based on CMS guidelines (e-Table 3).

In the non-ICU hospital setting, the use of noninvasive ventilation in progressive neuromuscular respiratory failure has been well established.[7] Although BPAP-ST is considered the first line of therapy based on extensive clinical experience, VAPS in ST or PC modes may be an acceptable alternative. A goal target V_T of no less than 8 cc/kg and minute ventilation should be very closely monitored and adjusted based on ABG or $TcCO_2$ results, or both. Due to diaphragmatic weakness, it is essentially important to make sure the patient can trigger ventilation effectively[58] (Table 5).

In the home setting for patients with motor neuron disease, the decision for noninvasive ventilation is based on the combination of symptoms (eg, frequent arousals, morning headaches, excessive daytime sleepiness), objective evidence of sleep related hypoventilation (eg, an elevated diurnal CO_2 level, abnormal nocturnal oximetric measurements), and the rate of disease progression. Based on CMS/National Institute for Health and Care Excellence guidelines, there are four objective criteria that can be used to guide the initiation of noninvasive ventilation: (1) forced vital capacity $< 50\%$ of predicted (upright or supine), (2) maximal inspiratory pressure ≤ 60 cm H_2O or sniff nasal pressure < 40 cm H_2O (upright or supine), (3) $Paco_2 > 45$ mm Hg, and (4) overnight nocturnal desaturation $< 88\%$ for 5 min. If a patient meets *any* of these criteria, it is appropriate to initiate noninvasive ventilation.[9,59] BPAP with backup rate (BPAP-ST or VAPS) and home-based ventilation are commonly used.[53,60] Most extensively studied in amyotrophic lateral sclerosis (ALS) populations, NIV has been proved to improve quality of life as well as survival in this population, particularly in those compliant with ≥ 4 hours of NIV each day and without severe bulbar dysfunction (although benefits may still be seen in bulbar-onset ALS).[61-64] Compared with BPAP, VAPS has been shown to deliver a lower median IPAP and to improve compliance by reaching equal improvement in nocturnal gas exchange (pH, $Paco_2$, nocturnal oxygenation), sleep quality, and respiratory muscle strength.[21,53] Due to issues with mobility and positioning, it is common to initiate patients with NMD on noninvasive ventilation without formal titration; therefore, close clinical follow-up to assess the effectiveness of ventilation is required. Beyond compliance data, the device's data download provides information about ventilatory support (eg, average pressures required to generate a tidal volume and the average minute ventilation), and progression of disease (eg, percentage of breaths spontaneously

triggered and cycled). Although NIV has the capability of meeting a desired targeted V_T, whether this is appropriate for the patient's ventilation needs will need to be assessed separately. A finding of a rising total respiratory rate or an increasing assisted rapid shallow breathing index may suggest an ineffective level of respiratory support. An alternative objective evaluation for oxygenation and ventilation after the initiation of therapy could be performed in the home-based setting with either pulse oximetry or $TcCO_2$ recording[21] (Table 5).

As NMD is progressive, there comes a time at which nocturnal support is not enough, and patients will require daytime ventilation support. A home mechanical ventilator with internal battery and portability can be used with mask ventilation or mouthpiece/sip ventilation or through a tracheostomy. Mouthpiece or sip ventilation allows a patient to take ventilatory support as needed, usually through a straw or angled mouth piece. When a patient requires full ventilatory support 24 hours a day, tracheostomy is not a mandatory requirement, unless there are additional issues with the inability to clear secretions or mental status changes. Long-term use of 24-hour NIV has now been reported by several authors.[65-68]

Troubleshooting Asynchronies

Multiple asynchronies may emerge during titration of NIV devices. Similar to invasive mechanical ventilation, these asynchronies could be identified at initiation of inhalation (eg, ineffective inspiratory effort, double triggering or auto-triggering), or at the end of it (eg, premature or late cycling). Before adjusting any setting on the device, a thorough mask fitting should take high priority toward minimizing any pressure leak. If not compensated, a mask leak may (1) increase or decrease the trigger sensitivity (missed trigger efforts or auto-triggering, respectively), (2) compromise the EPAP, with a subsequent increase in upper airway resistance and ineffective PS delivery (ventilation), or (3) prevent the device's cycling by preventing the inspiratory peak flow decay (e-Table 3), or a combination.

Conclusions

In the past 2 decades, the role of NIV in the management of acute and chronic sleep-related alveolar hypoventilation syndromes has dramatically changed medical practice in hospitals as well as in outpatient settings. However, a growing knowledge gap exists in the way to adjust these devices' settings to achieve synchrony and match the patient's unique respiratory failure physiology. Unfortunately, there are several shortcomings in this area. In the NIV literature, the objective testing (bench research) in technical performance and reliability of these devices is limited, as is the scientific evidence of effectiveness and clinical benefits. In summary, careful selection of NIV mode and settings should be based on the patient's unique needs and level of acute illness. However, further clinical trials and national guidelines on NIV therapy in prevalent sleep-related alveolar hypoventilation syndromes are well overdue. Future trials will need to address optimal ventilator setup strategies in new modes of ventilation, the impact of asynchrony in the patient-NIV interaction, the role of PSG in NIV titration protocols, and the safety and cost-effectiveness of outpatient vs inpatient setup to initiate and titrate NIV.

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