New noninvasive modalities in long-term pediatric ventilation: a scoping review

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Abstract

Long-term noninvasive ventilation modalities for the pediatric population have undergone a continuous evolution. Hybrid noninvasive ventilation modalities have been recently introduced in clinical practice. Combining the advantages of conventional ventilation, hybrid modes use algorithms that automatically adjust the ventilator's settings to achieve a predefined ventilation target. Most of the recommendations on the use and settings of hybrid noninvasive ventilation modalities in children are derived from adult experience. Therefore, there is a lack of evidence on its implementation in pediatric chronic respiratory diseases. This scoping review aims to map the existing information regarding the use of hybrid ventilation modalities in the pediatric population and identify knowledge or research gaps. We performed a literature search using MEDLINE and PubMed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews. We included 13 studies (10 studies on average volume-assured pressure-support ventilation, 2 studies on intelligent volume-assured pressure-support ventilation, and 1 study on adaptive servoventilation). The use of new noninvasive ventilation modes in the pediatric population has been applied for the treatment of neuromuscular and hypoventilation syndromes as an alternative therapeutic option in the case of the failure of conventional noninvasive ventilation. Their widespread use has been hampered by the limited evidence available. Longitudinal studies on a larger number of patients are needed to confirm their effectiveness and evaluate their long-term clinical and functional outcomes.

Introduction

Long-term noninvasive ventilation (NIV) use in the pediatric population has increased over the last few decades, as a result of better clinical outcomes among children with chronic respiratory medical conditions. Improvements in NIV technology and patient-tailored interfaces have offered significant clinical advantages [1].

Hybrid NIV modalities have been recently introduced in clinical practice. Combining the advantages of conventional ventilation, hybrid modes use algorithms that automatically adjust the ventilator's settings to achieve a predefined ventilation target. This offers several advantages, such as the ability to compensate for tidal volume changes occurring at different sleep stages or in case of lung compliance modifications.

The volume-assured pressure support ventilation (AVAPS) debuted in 1992 with the aim of combining the benefits of conventional volume- and pressure-controlled ventilation [2]. Since then, other volume-targeted systems have been developed [3], trying to

ensure the average level of a predetermined tidal volume (Vt) or alveolar ventilation (Va). The intelligent AVAPS (iVAPS) ventilation is a new hybrid mode (iVAPS®; ResMed Inc., Sydney, Australia) that relies on automatically targeting Va by adjusting inspiratory pressure and respiratory rate (RR). The target Va is calculated through an algorithm that subtracts the estimated anatomical dead space from minute ventilation [4,5]. The adaptive servo-ventilation (ASV) is a servo-controlled/pressure-controlled flow-cycled mode, which allows a variable support during the inspiratory phase, superimposed on a fixed or automatic level of expiratory positive airway pressure (EPAP). Its algorithm mirrors the patient breath-by-breath, continuously calculating a target minute ventilation and dynamically customizing the pressure support (PS) delivered. It aims to avoid transient episodes of central hypopnea/apnea after hyperventilation and associated hypocapnia [6].

Although hybrid modes were initially conceived for invasive mechanical ventilation [3], they have been applied in adult patients with chronic respiratory conditions, such as neuromuscular diseases (NMD), obesity hypoventilation syndrome, and chronic obstructive pulmonary disease. Most of the recommendations on the use and settings of hybrid NIV modalities in children are derived from adult experience. Therefore, there is a lack of evidence on its implementation in pediatric chronic respiratory diseases.

Moreover, the variety of labels, algorithms, and parameter setups might be misleading for physicians. This scoping review aims to map the existing information regarding the use of hybrid ventilation modalities in the pediatric population and identify knowledge or research gaps to be further evaluated. An overview of the hybrid ventilation modes' function and settings is also given.

Methods

The review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [7].

For this review, we searched MEDLINE and PubMed for preclinical and clinical studies on hybrid NIV modalities used in infants (≤1 year old) and children (≤16 years old). Our search included studies published from inception to January 31, 2023. We excluded articles in languages other than English. We used the following keywords: "Noninvasive ventilation", "NIV", "Noninvasive positive pressure ventilation", "NIPPV", "volume-assured pressure-controlled ventilation", "Volume targeted pressure controlled ventilation", "average volume-assured pressure-support ventilation", "AVAPS", "intelligent volume-assured pressure support", "iVAPS", "adaptive servoventilation", "ASV", "pediatric", "children" as exact phrases and a combination of broad subject headings according to databases' syntax.

No limitations were imposed for specific contexts, with the aim of including both in-hospital and home care settings. Case series, case reports, reviews, randomized controlled trials, and non-randomized studies (both prospective and retrospective) were included. Abstracts and conference proceedings were excluded.

Two authors (MP and GM) independently performed the search. Differences in selections were solved by consensus, with the help of a third author (CG). Reference lists of the included articles were screened for other relevant articles or reviews not retrieved by the database search. None of the studies were excluded from the review based on quality assessment.

We collected data regarding the type of study, setting, population characteristics, ventilator settings, and outcomes (adherence to therapy). Data were then tabulated for appropriate presentation. Meta-analysis was not performed due to limited data, mainly deriving from case series. Table 1 synthesizes the main characteristics of new NIV modalities in the children population, with reference to specific devices. Table 2 summarizes the main settings used in the studies retrieved. Table 3 gives an overview of the diagnostic categories, indications for NIV treatment, findings, and limitations of the reviewed studies.

Results

The initial search identified 220 results. Following screening of titles and abstracts and after duplicates removal, 22 full-text articles were evaluated. Among these, we selected and included 13 articles. The details on the inclusion/exclusion process are provided in the PRISMA flow diagram (*Supplementary Figure 1*) [8]. No randomized controlled trials nor non-randomized studies were retrieved. We found 3 case series [9-11], and 10 case reports [12-21], for a total of 50 patients.

Among the retrieved studies, 10 studies analyzed AVAPS application [9,12-20], 2 iVAPS [10,11], and only 1 ASV [21]. A description of all the included studies is provided with details in Tables 2 and 3.

The largest case series of pediatric AVAPS use published to date is a retrospective single-center study [9], which compares AVAPS to conventional bilevel support in improving hypercarbia in a cohort of 19 pediatric patients (11 boys; median age 10.5 years, range 1 to 20 years) with nocturnal hypoventilation. In these cases, AVAPS was applied only if hypoventilation was not controlled by conventional bilevel ventilation. Included patients were affected by NMD (n=9), obstructive hypoventilation (n=5), parenchymal lung diseases (n=4), and congenital central hypoventilation syndrome (CCHS) (n=2). The AVAPS modality was used in ST mode in 16 patients and PC mode in the remaining 3 patients. Patients included in this study demonstrated significant improvement in peak transcutaneous carbon dioxide measurement ($TcCO_2$) (63±14 mmHg *vs.* 57±9 mmHg, p=0.009), mean $TcCO_2$ (55±10 mmHg *vs.* 49±7 mmHg, p=0.001), total sleep time with $TcCO_2$ >50 mmHg (54±2 mmHg *vs.* 47±1 mmHg, p=0.02), and mean $TcCO_2$ in REM sleep (54±2 mmHg *vs.* 47±1 mmHg, p=0.02). Compared to conventional bilevel ventilation, AVAPS delivered higher Vt (165±100 mL *vs.* 135±104 mL, p=0.04) using similar pressures. The set mean Vt was 221.8±115.6 mL. The set mean RR was 21±6.4 breaths/min. The inspiratory positive airway pressure (IPAP) ranged from 11 to 20 mmHg (mean ± standard deviation, 16±2 cmH_2O), and the EPAP ranged from 4 to 6 cmH_2O (5±1 cmH_2O).

Among the included case reports, three described the potential reliability of AVAPS as an alternative to conventional NIV in infants with CCHS [12-14], one in severe bronchopulmonary dysplasia in an extremely premature infant [15], three in the treatment of obstructive sleep apnea (OSA) refractory to continuous positive airway pressure (CPAP) [16-18], two in hypoventilation conditions related to pediatric neuromuscular disorders [19,20].

There are only two published studies on the use of iVAPS in the children population [10,11].

Khayat *et al*. conducted a retrospective study of 8 CCHS patients who underwent both a titration polysomnography (PSG) with standard bilevel ventilation (BiPAP) in ST mode and a consecutive follow-up study with iVAPS mode, with the purpose of determining if iVAPS was more effective at controlling hypercarbia than conventional BiPAP ventilation [10]. They found a significant difference between the two BPAP modes in terms of peak non-REM $tcCO_2$ [43.0 (40.0-46.0) mmHg *vs.* 46.5 (45.0-48.0) mmHg for standard ST mode; p<0.05].

Table 1. Main characteristics of new long-term noninvasive pediatric ventilation modalities.

	ASV	AVAPS	iVAPS
Definition	Servo-controlled/pressure-controlled ventilation allowing a variable support during the inspiratory phase according to: - a preset Ve (S9 AutoSet CS PaceWaveTM Resmed®) - Relative Ve (Somnovent CRTM® Weinmann) - Peak Inspiratory flow (System One BiPAP autoSV AdvancedTM Respironics/Philips®)	Servo-controlled/pressure-controlled targeting Vt in a flow cycling or time cycling breath (*i.e.*, AVAPS®; Bilevel Synchrony Trilogy EVO, Phillips/Respironics; Vt Smart Eove, Air Liquid; volume-control plus, PB540/560 Medtronic; Volume guaranteed in ST/T mode, Vivo 45LS/65 Breas®, Volume guaranteed in S/ST mode, Prisma 40/50® Weinmann)	Servo-controlled/pressure-controlled ventilation targeting Va(iVAPS, ResMed)
Control variable	Minimal and maximal inspiratory pressure*	Minimal and Maximal Inspiratory Pressure*	Minimal and maximal inspiratory pressure**
Baseline variable	EPAP or Auto-EPAP	EPAP or auto-EPAP	EPAP or auto-EPAP
Trigger variable	- Flow trigger with active patient - Time (BURR) in passive respiration Respironics/Philips® BURR: default setting 5/breaths/min + adaptation in a moving window or manually set) Resmed® BURR: default setting 15/breaths/min + adaptation in a moving window, no manually setWeinmann® BURR: default setting: 80% of average breathing rate with highest weight on last breaths (can be manually fixed)	- Flow trigger with active patient - Time (BURR) linked to algorithm (*i.e.*, Auto-Trak/Auto-Trak sensitive, Respironics/Philips®)	- Flow trigger with active patient - Time or flow trigger in passive patient
Cycling variable	A percentage of inspiratory flow threshold decay (according to manufacturer's algorithm)	A percentage of inspiratory flow threshold (according to manufacturer's algorithm) or a given inspiratory time. Vt may also be forced, in some ventilators or between a Ti min and Ti max	A percentage of inspiratory flow threshold is always the first cycling factor. Time cycling depends also on a given set Ti min or Ti max
Target	Minute or relative Ve or peak inspiratory flow	A minimum average Vt is maintained	Va
Pressure ramp profile	Not available	Settable	Settable
Unintentional leak compensation	Good for mild to moderate leaks	Good for mild to moderate leaks	Good for mild to moderate leaks
Advantages	Guarantees a constant target Ve or a target peak flow	Guarantees a minimal average Vt	Guarantees a minimal average Va
Disadvantages	Problems related to fixed back up rate in some models	- Vt under- or over-estimation - Overshooting	- Va under- or over-estimation - Less likelihood of overshooting
Used circuits	Intentional leak "vented" circuit	Intentional leak "vented" circuit	Intentional leak "vented" circuit

ASV, adaptive servo-ventilation; AVAPS, average volume assured pressure support; BURR, backup respiratory rate; EPAP, end positive expiratory airway pressure; IPAP, inspiratory airway pressure; min, minimal; max, maximal; iVAPS, intelligent volume assured pressure support; Ti, inspiratory Time; min, minimal; max, maximal; Va, alveolar ventilation; Ve, minute ventilation; Vt, tidal volume. All ventilators in "vented" intentional leak configuration have a default level of EPAP. *Pmax is equal to (IPAP – EPAP) or (IPAP + EPAP) depending on the manufacturer's algorithm; **Pmax is always equal to (IPAP + EPAP).

Table 2. Ventilator settings and adherence to noninvasive ventilation treatment.

	Author	IPAPmin or PSmin (cmH_2O)	IPAPmax or PSmax (cmH_2O)	EPAP (cmH_2O)	Respiratory rate (RR-breaths per minute)	Ti (sec)	Inspiratory trigger	Rise time	AVAPS rate (cmH_2O per min)	Target tidal volume (mL)	Chosen tidal volume (mL/kg body weight)	Adherence
AVAPS												
	Vagiakis *et al.*	4	19	4	16	NA	NA	NA	NA	450	8	NA
	Saddi *et al.*	10	14	4	21	1.3	Autotrack sensitive	NA	5	80	9	NA
	Paglietti *et al.*	10	NA	3	16	NA	NA	NA	NA	NA	NA	NA
	Saddi *et al.*	12	20	5	30	0.5	NA	NA	NA	60	10	NA
	Stowe *et al.*	16	26	11	12	NA	NA	NA	NA	500	NA	NA
	Diaz-Abad *et al.*	4	17	5 to 16	20	1.5	NA	3	NA	390	8	Average night use 6.4 hours
	Veeravigrom *et al.*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Gentin *et al.*	11	17	4	22	1	NA	NA	2	80	8	Average night use 5.5 hours
	Lovejoy *et al.*	20	4	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Saddi *et al.*	11	20	4 to 6	21 ± 6.4	NA	NA	NA	NA	221.8±115.6	NA	% of use for >4 h/30 days 81±30 days

	Author	PSmin (cmH_2O)	PSmax (cmH_2O)	PS median (cmH_2O)	EPAP (cmH_2O)	Respiratory rate (RR-breaths per minute)	Ti min (sec)	Ti max (sec)	Alveolar target volume (ml)	Chosen tidal volume (ml/kg body weight)	Mean average daily usage (hours)	Median average daily usage (hours)
iVAPS												
	Khayat *et al.*	5.5 (4.5-7.5)	13 (12.5-19)	12.2 (10.2-13)	5.5 (4.5-6)	20 (17-20)	1.1 (1-1.25)	1.3 (1.2-1.4)	4.5 (3.3-5.3)	6.5 (5.9-7.7)	8 (5.4-9.1)	8 (6-9.5)
	Sunkonkit *et al.*	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.4±1.6	8.6±1.4
ASV	Tabone *et al.*	3	8	NA	5 to 8	NA	NA	NA	NA	NA	9	NA

AVAPS, average volume assured pressure support; iVAPS, intelligent volume-assured pressure support; ASV, adaptive servo-ventilation; IPAP, inspiratory airway pressure; min, minimal; max, maximal; PSmin, minimal pressure support; PSmax, maximal pressure support; Ti min, minimal inspiratory time; Ti max, maximal inspiratory time; RR, respiratory rate.

Table 3. Review of the studies on new long-term noninvasive pediatric ventilation modalities.

	Author	Study design	Population	Indications for NIV	Results	Limitations
AVAPS						
	Vagiakis *et al.*	Case report	16-year-old patient	CCHS/tracheostomy	Successful transition to noninvasive AVAPS from tracheostomy ventilation	Case report, retrospective study design
	Saddi *et al.*	Case report	10-month-old infant	CCHS	AVAPS was associated with a consistent transcutaneous CO_2 ($tcCO_2$) reduction when compared to conventional bilevel ventilation	Case report, retrospective design of the study
	Paglietti *et al.*	Retrospective observational study	2-month-old infant	CCHS/tracheostomy	Successful transition from IMV (PCV) to NIV and decannulation	AVAPS settings not available
	Saddi *et al.*	Case report	24-week-old premature infant	Severe BPD	More efficient control of hypoventilation, tracheostomy avoided	Single case report
	Stowe *et al.*	Case report	11-year-old patient	ROHHAD	CPAP and bilevel ST mode unsuccessful, AVAPS mode demonstrated to improve adherence, ventilation and pulmonary hypertension	Sigle case report
	Diaz-Abad *et al.*	Case report	8-year-old patient	OSA	Reduction of AHI from very severe (138.2) to moderate levels (9.7), avoidance of tracheostomy, good compliance and clinical response to NIV treatment	Single case report
	Veeravigrom *et al.*	Retrospective observational study (of pediatric PSG results)	1/166 PSG studies (age unknown), 17 PAP titration studies	OSA/CCHS	Seventeen PAP titration studies were performed: AVAPS titration was conducted in a CCHS case	Study on prevalence of sleep disorders, with no data on ventilation modalities applied
	Gentin *et al.*	Case report	3-year-old patient	Multiminicore myopathy, nocturnal hypoventilation	High NIV tolerance, no recurrence of pneumonia episodes, better gas exchanges	Single case report
	Lovejoy *et al.*	Case report	11-year-old patient	Perioperative ventilation optimization in a patient with Ullrich congenital muscular dystrophy	No perioperative anesthesiologic/ respiratory complications	Single case report, no other studies on perioperative paediatric AVAPS use
	Saddi *et al.*	Case series	19 patients (mean age 10.5 years)	NMD (9 patients), obstructive hypoventilation (5 patients), parenchymal lung disease (4 patients), CCHS (2 patients)	AVAPS demonstrated significant improvement in peak $TcCO_2$, mean $TcCO_2$, total sleep time with $TcCO_2$ >50 mmHg and mean $TcCO_2$ in REM sleep	Single-center non blinded retrospective study design; no standardized protocol; long time interval between conventional BPAP and studies (difficult direct comparison)
iVAPS						
	Khayat *et al.*	Retrospective observational study	8 patients (median age 10.6)	CCHS	PSG showed improvements when iVAPS was used (better reduction of $TcCO_2$)	Single center retrospective study design
	Sunkonkit *et al.*	Prospective observational study	20 patients (mean age 14.1±3.4)	NMD	AVAPS may guarantee better adherence to ventilation therapy as compared to when S/T mode is used (increase in mean and median daily usage hours and median percentage of usage ≥ 4 h)	Single center study, no ventilator settings provided, results are not generalizable to younger children with NMD (only for body weight >30kg), exclusion bias (2 patients excluded due to poor NIV tolerance)
ASV						
	Tabone *et al.*	Case report	11-year-old patient	Severe-mixed SAS	Normalization of the AHI (1 event/hour), correction of nocturnal hypoventilation and improvement of daytime symptoms	Single case report, no other studies on paediatric ASV

AHI, apnea-hypopnea index; ASV, adaptive servo-ventilation; AVAPS, average volume assured pressure support; BPD, bronchopulmonary displasia; CCHS, congenital central hypoventilation syndrome; IMV, intermittent mandatory ventilation; iVAPS, intelligent volume-assured pressure support; NIV, noninvasive ventilation; NMD, neuromuscular disease; OSA, obstructive sleep apnea; PAP, positive airway pressure; PSG, polysomnography; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation; SAS, sleep apnea syndrome; $TcCO_2$, transcutaneous carbon dioxide measurement.

In their prospective observational study, Sunkonkit *et al*. compared the adherence and efficacy of iVAPS *vs.* standard ST mode in a cohort of 20 children with NMD, finding a mean average daily usage and a median daily usage for iVAPS mode and ST mode of 8.4±1.6 *vs.* 7.2±2.5 h (p=0.012) and 8.6±1.4 *vs.* 7.8±2.1 h (p=0.022), respectively [11]. Unfortunately, the author did not provide details on ventilator settings.

The ASV modality has only been reported in one case [21], where its use was associated with correction of a severe mixed-sleep apnea syndrome (SAS) in an 11-year-old patient (body mass index 19 kg/m^2) with a metastatic diencephalon anaplastic ganglioglioma. The patient developed a severe mixed-SAS with central and obstructive respiratory events, and nocturnal alveolar hypoventilation. The use of ASV mode resulted in a reduction of apnea episodes (1 event/hour), the correction of nocturnal hypoventilation, and the improvement of daytime symptoms.

Discussion

Conventional NIV has been the mainstay treatment for children with NMD and hypoventilation syndromes, both in acute and chronic settings. The optimal ventilatory support is usually determined after a thorough clinical evaluation and polysomnographic study, in order to reach the optimal target of gas exchanges and airway patency. However, many patients need varying respiratory support through the day, in relation to pulmonary impedance variations related to body positions, variations in pulmonary mechanics, and different sleep stages. As an example, minute ventilation in children with CCHS can vary significantly due to differences in the control of breathing during REM and non-REM sleep. This often results in higher pressure settings during the first half of the night, when non-REM sleep predominates, and subsequent hyperventilation during the second half of the night when REM sleep is predominant [10].

In addition, conventional NIV modes are not able to auto-titrate the degree of respiratory support with disease progression, as can be seen in NMD. These issues may explain the suboptimal adherence rates to conventional NIV [22], resulting in frequent pulmonary exacerbations with subsequent hospitalizations, prolonged intensive care unit stays, and multiple clinic visits. Moreover, unintentional leaks must be considered as one of the major issues in NIV. Single-circuit ventilators with calibrated intentional leaks (vented configuration) have demonstrated better compensation for unintentional leaks [3,23] than non-vented configurations.

Compared to conventional NIV, hybrid modes allow the clinician to set variable PS that self-adjusts to maintain target Vt despite varying respiratory mechanics, ventilatory control, upper airway patency, and respiratory muscle recruitment [2].

Despite their theoretical advantages, the use of hybrid NIV modes in children is uncommon. The inconsistency of pediatric clinical indications for AVAPS must be related to the small number of cases reported, which hampers the assessment of its effectiveness and safety. Neither prospective randomized controlled trials nor specific guidelines have been issued yet, and the suggested settings for the pediatric population are derived from the manufacturer's indications and previous adult studies.

Hybrid mode function and settings

The working principle of AVAPS is based on the ability to provide a pre-set target Vt (dependent variable) by automatically adjusting the IPAP (independent variable) within a pre-set range (IPAP max - IPAP min), with a backup RR (BURR). These ventilators cycle between an IPAP and an EPAP, where the peak pressure (Pmax) is equal to IPAP - EPAP. However, some manufacturers adopt a different setup, where Pmax is equal to IPAP + EPAP.

Inspiration is initiated in a pressure-controlled flow-cycled mode (independent variable) that can be forced, in some software, between a preset minimal (Tmin) and maximal inspiratory (Tmax) time. A breath-to-breath feedback loop adjustment of the inspiratory pressure allows the ventilator to reach the pre-set Vt, following a pre-set or adjustable speed rate, averaging inspiratory pressure over several breaths, and according to respiratory effort, lung compliance, and resistance. If the delivered Vt is above the pre-set target, this mechanism is deactivated and the inspiratory pressure does not change [2,24] (Table 1).

"Overshooting" is one of the main drawbacks of Vt targeting. This is defined as the inadequate increase in Vt>20% [25-28] related to the inability of the ventilator algorithm to promptly respond to abrupt changes in unintentional leaks or to respiratory impedance amelioration [25,29,30]. Overshooting may be responsible for hyperventilation, as both RR and Va are not controlled: hypocarbia and hyperinflation may decrease the patient's respiratory effort, with consequent patient-ventilator asynchrony, periodic breathing, microarousals [6], and potential gastric distension [25,31].

The EPAP value should be fixed by the operator on a clinical basis or decided following sleep studies, using polygraphy or PSG. Alternatively, some ventilators automatically adjust the EPAP (AutoEPAP) between two pre-set levels (EPAPmin and EPAPmax), aiming at upper airway patency [32]. Principal characteristics are shown in Table 1.

iVAPS is a new hybrid mode of NIV (iVAPS®; ResMed Inc., Sydney, Australia) which relies on automatically targeting Va by adjusting inspiratory pressure and RR.

In this setup, the inspiratory pressure is labelled as PS and Pmax equals IPAP + EPAP. To reach target Va, the inspiratory pressure (within minimal and maximal PS) is continuously adjusted during the inspiration phase breath-to-breath, and instead of a fixed backup rate, the iVAPS intelligent backup rate (iBR) shifts automatically between two limits. The cycling variable is the percentage of inspiratory flow decay, both for spontaneous or controlled breaths, forced between a Tmin and Tmax.

The target Va is calculated through an algorithm that subtracts the estimated anatomical dead space (automatically calculated by the device using the patient's height) from minute ventilation [4,5]. The target patient rate, which defines the upper boundary of iBR, is set to match the patient's average spontaneous breath rate. During spontaneous ventilation, the iBR is reduced to 2/3rds of the target patient rate by the device, giving the opportunity to trigger the ventilator. In case of trigger failure, or when ventilation is below the target or in the occurrence of apnea episodes, the iBR increases from its background frequency to the target rate (within 4-5 breaths), bringing the patient back to the target. A single spontaneous breath resets the iBR to its background rate until needed [33,34].

In case the Va falls 50% below the target, pressure increases of 0.35 cmH_2O per second. Conversely, pressure decreases of 0.5 cmH_2O per second occur when the delivered Va overtakes the target for more than 200%.

The EPAP level can be set at a fixed value or automatically adjusted within two levels (minimal and maximal) decided by the operator. The EPAP is chosen on a flow curve analysis. In addition, iVAPS allows a "learning" ST mode during which the software computes a target minute ventilation at a given setting, by measuring the patient's RR and Vt [33,34]. It is necessary to remember that S or ST modes use a "below EPAP" setup, while iVAPS mode uses

an "above EPAP" setup. This means that, when switching from the "S or ST learning mode" to iVAPS, the inspiratory pressure should be reduced to the same Pmax obtained during the "learning mode".

The ASV modality is a servo-controlled/pressure-controlled flow-cycled mode ("above EPAP" setup), which allows a variable support during the inspiratory phase, superimposed on a fixed or automatic level of EPAP. Its primary indication was to provide the hydrostatic benefits of low levels of EPAP while directly suppressing central sleep apnea (CSA) or Cheyne-Stokes respiration, without causing over-ventilation in patients with stable congestive heart failure. This mode was later applied in OSA patients experiencing emergent or persistent CSA under CPAP use [35,36]. In complex forms of sleep disorders (CSA mixed□SAS or mixed□SAS) and complex sleep apneas (complex□SAS) refractory to CPAP [35], ASV counterbalances the patient's ventilatory instability, reducing respiratory-event related arousals, and at the same time stabilizes minute ventilation and arterial blood gases by modulating the level of PS and EPAP.

The ASV mode algorithm (based either on target ventilation or peak flow) mirrors the patient breath-by-breath, continuously calculating a target minute ventilation and dynamically customizing the PS delivered. It aims to avoid transient episodes of central hypopnea/apnea after hyperventilation and associated hypocapnia [6].

The operator sets a minimum and a maximum value of inspiratory pressure. During normal breathing, the device delivers the minimum value of support. On a breath-by-breath basis, the peak flow is captured and monitored over a 3-minute moving window. At every point within this 3-minute window, an average peak flow is calculated, and the peak flow target is established around that average, with respect to the patient's needs.

In case the patient's drive is absent, the device will increase the inspiratory support to a maximum pressure of 20-25 cmH_2O, in order to maintain the target ventilation [37,38]. When the patient resumes his spontaneous effort, the inspiratory pressure drops back gradually to the minimum set value. When ventilation exceeds 90% of the target, the PS stays at the minimum pressure level. BURR can be manually adjusted in some devices (Table 1).

While the inspiratory support increases in response to the reduction of minute ventilation, EPAP increases in response to flow limitation/snoring. The EPAP can be set manually or in AUTO mode. In this last case, two levels of EPAP can be set, the lower being at least 4 cmH_20. Assessment of "Flow Limitation" is based on the analysis of flow-shape after single breaths or after a spike-pressure delivery. If minute ventilation remains above the dynamic target despite flow limitation/snoring, the ventilator increases EPAP only. During apneas, PS increases as minute ventilation drops below the dynamic target. If there is little or no patient ventilation during this period, the apnea is classified as obstructive. The algorithm detects obstructive events, as increases in PS do not stabilize minute ventilation. Once spontaneous breathing resumes, it increases EPAP in proportion to the severity of the event, with the aim of preventing further apneas from occurring.

In addition to the above-mentioned hybrid NIV modes, the intermittent abdominal pressure ventilation is worth a special mention. This is an unconventional noninvasive modality consisting of a portable ventilator and a corset equipped with an internal bladder as an interface. The cyclic inflation and deflation of the bladder guarantees the passive movement of the diaphragm, thus ensuring the expiratory phase (the diaphragm is dislocated upwards to expel air up to the functional residual capacity) and the inspiratory phase (the abdominal viscera and the diaphragm are lowered by gravity, and inspiration occurs due to the elastic recoil of the lungs and chest). This modality might be a valid alternative both to daytime and nighttime conventional NIV in patients affected by NMD with advanced respiratory failure, avoiding early tracheostomy and acute respiratory exacerbations [39,40].

Pediatric settings

There are no specific pediatric indications for hybrid NIV use and setting, and most of the recommendations derive from manufacturers' indications and previous experience with adult patients. Ventilator settings need to be independently titrated on an individual basis, according to the patient's underlying disease. IPAP and BURR should be titrated to provide an appropriate ventilatory support, while EPAP needs to be adjusted to stabilize the upper airway and/or increase the functional residual capacity.

The target Vt in the retrieved studies varies between 6.5 and 10 mL/kg of body weight (Table 2), in accordance with common indications to ensure a target Vt of at least 6-10 mL/kg [41,42]. The ideal body weight (IBW) is usually considered for the calculation of the target Vt, deriving from studies on obese adult patients. In the case of pediatrics, there is no consensus on IBW calculation [18], and hybrid NIV is used regardless of children's obesity.

As a consequence, the pre-set maximal inspiratory pressure should be decided to prevent the ventilator from not attaining the target Vt (*e.g.*, unintentional leaks, reduced inspiratory effort, or modifications of respiratory impedance) [41], with higher values in restrictive lung conditions.

As suggested by the manufacturer, iVAPS and ASV can be used in children weighing more than 30 kg. In the case of iVAPS, where the ventilation target is Va (defined as the minute ventilation minus anatomical dead-space ventilation), this has been estimated considering the anatomical dead space approximated by the patient's height [120 × (height/175)] [10]. Due to age cut-offs, iVAPS and ASV have limited application among older patients (10.6 median age and 14.1 mean age for iVAPS, 11 years for ASV in retrieved studies). No age limitation has been identified with AVAPS use, which has also been applied in premature infants [15].

Conclusions

The use of new NIV modes (AVAPS, iVAPS, ASV) in the pediatric population has been applied for the treatment of CCHS, NMD, severe obesity complicated by OSA, rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation, bronchopulmonary dysplasia, and CSA. Although limited availability of preliminary data, these new modes should be considered as an alternative therapeutic option in the case of conventional NIV failure. The quality of available evidence is low, and longitudinal studies on a larger number of patients are needed to confirm their effectiveness and to evaluate their long-term clinical and functional outcomes.

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Online supplementary material:

Supplementary Figure 1. PRISMA flowchart. Modified from Page et al. *(2021).*