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"Evaluation of Different Inspiratory Efforts in a Pediatric Model of Healthy Lung and Pediatric Acute Respiratory Distress Syndrome During Optimized Pressure Support Ventilation and Proportional Assist Ventilation Plus (PAV+): A Bench Study

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ABSTRACT

Introduction: While proportional ventilator modes have gained popularity in adult patients' ventilatory management, Proportional Assist Ventilation (PAV+) use in pediatric patients with Pediatric Acute Respiratory Distress Syndrome (PARDS) remains unexplored. This study aims to evaluate the effects of optimized PSV and PAV+ on patient-ventilator interaction and respiratory pattern in two pediatric simulated lung models.

Methods: The study utilized an active lung simulator to replicate two pediatric lung models: one healthy and one with mild PARDS. Each model was ventilated using PAV+ and optimized PSV at four different levels, assessing simulated patient-ventilator interaction and mechanical response to increase inspiratory effort.

Results: In terms of simulated patient-ventilator interaction, in a healthy and mild PARDS lung model and all setting tested, the optimized PSV presented the better patient-ventilator interaction with the shortest values of Inspiratory trigger delay ($Delay_{trinsp}$), Pressurization time ($Time_{press}$) and Expiratory trigger delay ($Delay_{trexp}$) and the highest values of Synchrony time ($Time_{synch}$). Only in the lung model with PARDS, during high assistance levels and high Pmus, no significant differences were found in terms of patient ventilation interaction between the two modalities.

Conclusions: In a healthy lung model, optimized PSV allows optimal simulated patient-ventilator interaction and assistance levels compared to PAV+. On the contrary, in a simulated lung with mild PARDS, PAV+ appears as a valid alternative to PSV, especially under conditions of intense inspiratory effort and high assistance levels.

1 | Introduction

Partial ventilatory support modes are widely used in ventilatory management, both in adult and pediatric patients. Pressure Support Ventilation (PSV) is the most common mode of partial ventilatory support; during PSV, the ventilator applies a preset level of pressure to assist the patient's inspiration. It is known that asynchrony phenomena are frequent and probably related to multiple factors, including mechanical characteristics and performance of the mechanical ventilator, as well as physiological factors influencing neural respiratory drive, such as muscle strength and respiratory mechanics of the patient [1]. These latter two components are particularly crucial in neonates and children, where respiratory system characteristics and a respiratory pattern, characterized by high respiratory rates, can interact negatively with flow-based ventilator algorithms, especially in difficult-to-wean patients who often exhibit a high rate of asynchrony [2, 3].

Several studies have shown that worse patient-ventilator synchrony is associated with increased mechanical ventilation length and, consequently, a higher risk of developing Ventilator-Associated Pneumonia (VAP) and other infections [4–11]. These issues are particularly relevant for the pediatric population affected by Pediatric Acute Respiratory Distress Syndrome (PARDS).

In recent years, new ventilatory modes have been implemented to optimize patient-ventilator synchrony by acting on both timing and the level of support provided proportionally to the respiratory effort generated by the pediatric patient. Ventilatory modes such as Proportional Assist Ventilation Plus (PAV +) and Neurally Adjusted Ventilatory Assist (NAVA) have been shown to providesynchronized support with the respiratory cycle of both adult and pediatric patients.

In particular, PAV+ provides ventilatory support proportional to the patient's respiratory effort. Inspiratory pressure is delivered in proportion to both flow variation (resistive unloading) and tidal volume variation (elastic unloading), and the clinician can adjust the amount of amplification of the patient's generated effort to be used [12].

PAV+ is effective in treating acute respiratory failure (ARF) of various etiologies [13–23] in the adult population. Indeed, several studies have demonstrated the advantages of PAV+ over other modes of assisted ventilation, especially in terms of patient-ventilator interaction and mechanical ventilation tolerance. To our knowledge, no study has compared the effect of PAV+ and optimized PSV on patient-ventilator interaction in the pediatric population with both healthy lungs and restrictive lung mechanics typical of PARDS.

The purpose of our bench study was to evaluate the effects of optimized PSV and PAV+ on simulated patient-ventilator interaction and mechanical response to increased inspiratory effort in a healthy pediatric lung model and a pediatric patient model with mild Acute Respiratory Distress Syndrome (PARDS).

2 | Methods and Materials

2.1 | Bench Model

This study was conducted at the Respiratory Mechanics Laboratory (Ventil@b) of the Catholic University of Rome, Italy. Optimized PSV and PAV+ were delivered to an active lung simulator (ASL 5000 Ingmar Medical, Pittsburgh, USA), connected to a Puritan Bennett 840 mechanical ventilator Tyco HealthCare, Pleasanton, USA, via a cuffed endotracheal tube (6 mm diameter). The simulator was set to mimic a 30 Kg healthy pediatric patient and with PARDS. Specifically, the respiratory mechanics characteristics of the "healthy patient" were:

- Compliance (Crs) 1.1 mL/cmH_2O/kg,
- Airway resistance (Rrs) 10 cmH_2O/L/s,
- Respiratory rate (RR) 25 breaths/min,
- Initial muscle pressure (Pmus) was set at 8 cmH_2O and subsequently increased to 12, 16, and 20 cmH_2O for each ventilatory mode.

The "pediatric patient with mild PARDS" was simulated with the following respiratory mechanics characteristics:

- Compliance (Crs) 0.5 mL/cmH_2O/kg,
- Respiratory rate (RR) 40 breaths/min,
- Initial muscle pressure (Pmus) was initially set at 8 cmH_2O then increased to 12 and 16 cmH_2O for each ventilatory mode.

For each tested Pmus, four increasing levels of optimized PSV (10, 14, 18, 22 cmH_2O) were applied sequentially alternated with four levels of PAV+ (50, 60, 70, and 80%) chosen in such a way as to obtain the same pressures applied to the airways during the corresponding four levels of optimized PSV. Positive End-Expiratory Pressure (PEEP) was kept constant at 5 cmH_2O. The PSV trial was optimized using a fast pressurization ramp and an expiratory trigger at 40%. This was done after evaluating simulated Pmus and respiratory simulated pattern [24].

The decision to test PAV+ and optimized PSV in a simulated setting of healthy pediatric lungs and mild PARDS is driven by their potential to manage respiratory mechanics with partial or proportional support in clinical practice. In contrast, in cases of moderate or severe PARDS with more severe restrictive mechanics, these modes are rarely used, as the focus shifts to preventing PSILI from aggravating an already critically inflamed lung condition, which is challenging to manage with mechanical ventilation.

2.2 | Measurements

Airflow (V′) was measured using a pneumotachograph (Fleish No.1, Metabo, Epalinges, Switzerland), while airway pressure (Paw) was measured by a pressure transducer with a differential pressure of $\pm$100 cmH2O (Digima Clic-1, ICULab system; KleisTek Engineering, Bari, Italy), placed distally to the pneumotachograph. All signals were acquired, amplified, filtered, and digitized at 100 Hz, then recorded on a dedicated personal computer and analyzed through specific software (ICULab 2.7; KleisTek). The inspiration and expiration time of the ventilator (respectively mechanical inspiration time and mechanical expiration time) and the cycling speed of the ventilator were determined by flow curve analysis. The inspiratory duty cycle (mechanical Ti/Ttot) was calculated as the ratio of mechanical inspiration time to the total duration of the mechanical respiratory act (Ttot). Airflow (V′) and tidal volume (Vt) delivered to the simulator, airway opening pressure (Paw), and inspiratory muscle effort were displayed online on the computer screen. Signals obtained with the ASL 5000 were transmitted to a Host PC via Ethernet 10/100MBit, sampled, and processed in real-time using specific software (Lab View, Ingmar Medical). Signals obtained with the ASL 5000 were integrated with ICULab system signals using a specific ICULab application (ICULab 2.7, KleisTek). Numerical integration of flow over time determined mechanical tidal volume (Vt_{mech}). The amount of tidal volume provided to the simulator during active inspiration (i.e., neural tidal volume, Vt_{neu}) was calculated as the volume generated from the beginning of the negative deflection of inspiratory muscle effort to its nadir. During the study, Vt_{neu}/Vt_{mech} was calculated and is defined as the time during which the patient inspiratory effort and the ventilatory assistance are in phase and as the percentage of Vt delivered during patient inspiration, respectively.

Simulated patient-ventilator interaction was assessed by measuring:

1. Pressurization time ($Time_{press}$), is defined as the time required to reach the preset level of pressure support from the baseline value.
2. Inspiratory trigger delay ($Delay_{trinsp}$) is calculated as the time interval between the onset of the negative deflection of inspiratory muscle effort and the onset of ventilatory support (e.g., positive deflection on the Paw curve).
3. Expiratory trigger delay ($Delay_{trexp}$), is evaluated as the delay between the end of inspiratory effort and the end of mechanical inspiration (i.e., deflection on the flow curve).
4. Synchrony time ($Time_{synch}$), is defined as the time during which simulated patient inspiratory muscle effort and Paw are in phase (ideally at 100%).
5. Vt_{neu}/Vt_{mech} intended as the percentage of VT delivered during the negative deflection of inspiratory muscle effort.
6. Wasted effort, is defined as ineffective inspiratory efforts not assisted by the ventilator.
7. Auto-triggering, is an act of mechanical inspiration delivered in the absence of neural inspiratory effort.
8. $Times_{ynch}/Ti_{neu}$, defined as the time during which simulated respiratory effort and mechanical ventilatory support are synchronized, indexed to Ti_{neu} [25–27].

For each level of PS, PAV + , and Pmus applied, the existing correlation in each ventilation mode between increased inspiratory effort and volume increase, at constant support delivered, respectively in optimized PSV and PAV + , was assessed.

2.3 | Statistical Analysis

Continuous variables with a normal distribution were expressed as means and standard deviations (SD) and evaluated using the Student's *t*-test. Continuous variables with non-normal distributions were expressed as medians and interquartile ranges (IQR) and evaluated using the Mann-Whitney test. Frequencies were compared using the chi-square test or the exact Fisher test, depending on the cases. Analysis of variance (ANOVA) for repeated measures was performed to detect significant differences among individual experiences. *P* values < 0.05 were considered statistically significant. The statistical software MedCalc version 14.12.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) was used for statistical analysis.

3 | Results

In Table 1, data on simulated patient-ventilator interaction in the bench setting of "healthy pediatric patient" are presented, during the comparison of optimized PSV and PAV+ with corresponding levels of respiratory assistance and increasing Pmus levels.

In terms of simulated patient-ventilator interaction, in the bench setting of "Simulated pediatric patient with healthy lungs" at all levels of optimized PSV and PAV+ tested, with increasing Pmus, $Delay_{trinsp,}$ and $Delay_{trexp}$ were always significantly shorter with the Pressure Support mode compared to PAV+ ($p < 0.05$). In terms of $Time_{press}$ and $Time_{synch}$, optimized PSV presented consistently longer values compared to PAV+ at all levels of assistance and Pmus tested ($p < 0.05$). The Pressure Support mode showed significantly higher $Time_{synch}$,$/Ti_{neu}$ values compared to PAV+ ($p < 0.05$) during all settings tested in the simulated "pediatric patient with healthy lungs."

In Table 2, data on simulated patient-ventilator interaction in the bench setting of "pediatric patient with mild PARDS" are presented, during the comparison of optimized PSV and PAV+ with corresponding levels of respiratory assistance and increasing Pmus levels.

During the setup of optimized PSV 10 cmH_2O and PAV + 50%, PSV optimized showed significantly shorter values of $Delay_{trexp}$ and $Time_{press}$, while the values of $Delay_{trinsp}$ ($p < 0.05$) at higher Pmus (16–20 cmH_2O) were reduced, and the levels of $Time_{synch}$ were higher ($p < 0.05$) at increasing Pmus.

At optimized PSV 14 cmH_2O and PAV + 60% setting, $Delay_{trinsp}$ and $Delay_{trexp}$ values were significantly shorter in optimized PSV ($p < 0.05$) only at high Pmus (12 and 16 cmH_2O), while no difference was highlighted in terms of $Time_{press}$ and $Time_{synch}$.

At higher assistance levels, both in optimized PSV and PAV+ (18 cmH_2O/70% and 22 cmH_2O/80%), no statistically significant differences were found at all tested Pmus, in terms of $Delay_{trinsp}$, $Time_{press}$, and $Time_{synch}$, except for $Delay_{trexp}$ values, which were significantly shorter ($p < 0.05$) during optimized PSV compared to PAV + .

During all tested settings in the simulated patient with mild PARDS, no statistically significant differences were found in terms of $Time_{synch}/Ti_{neu}$.

Tables 3 and 4 compare, with the same inspiratory effort (Pmus), the effects on the respiratory pattern of different levels of optimized PSV and PAV + , respectively, in healthy pediatric patients and those with mild PARDS.

In both simulations, with the same Pmus, Ti_{mech} was significantly longer during optimized PSV than during PAV+ ($p < 0.05$), while

TABLE 1 | Effects, in a simulated pediatric "healthy" lung model, of different levels of PAV+ and optimized PSV at the same inspiratory effort (Pmus), on patient-ventilator interaction.

RR 25 breaths/min		"Healthy" simulated lung model $Delay_{trinsp}$ (s)	$Delay_{trexp}$ (s)	$Time_{synch}$ (s)	$Time_{synch}/Ti_{neu}$
Pmus 8 cmH_2O	PAV 50%	0.18 ± 0.01	0.37 ± 0.01	0.27 ± 0.01	0.61 ± 0.01
	PS 10 cmH_2O	0.14 ± 0.01**	0.37 ± 0.01	0.31 ± 0.01**	0.69 ± 0.02*
	PAV 60%	0.18 ± 0.00	0.41 ± 0.06	0.24 ± 0.00	0.57 ± 0.01
	PS 14 cmH_2O	0.14 ± 0.01**	0.39 ± 0.01	0.32 ± 0.01**	0.69 ± 0.01**
	PAV 70%	0.19 ± 0.01	0.45 ± 0.00	0.24 ± 0.001	0.57 ± 0.03
	PS 18 cmH_2O	0.13 ± 0.01**	0.43 ± 0.01	0.34 ± 0.01**	0.72 ± 0.01**
	PAV 80%	0.18 ± 0.01	0.51 ± 0.01	0.25 ± 0.01	0.57 ± 0.01
	PS 22 cmH_2O	0.15 ± 0.02**	0.45 ± 0.00**	0.33 ± 0.01**	0.68 ± 0.02*
Pmus 12 cmH_2O	PAV 50%	0.16 ± 0.01	0.39 ± 0.02	0.27 ± 0.02**	0.62 ± 0.02
	PS 10 cmH_2O	0.12 ± 0.01*	0.34 ± 0.00*	0.34 ± 0.01	0.74 ± 0.02*
	PAV 60%	0.18 ± 0.01	0.42 ± 0.01	0.26 ± 0.01**	0.60 ± 0.03
	PS 14 cmH_2O	0.12 ± 0.01**	0.37 ± 0.01**	0.35 ± 0.00	0.74 ± 0.01**
	PAV 70%	0.18 ± 0.01	0.48 ± 0.01	0.25 ± 0.01	0.59 ± 0.02
	PS 18 cmH_2O	0.13 ± 0.02*	0.39 ± 0.01*	0.34 ± 0.01**	0.73 ± 0.03**
	PAV 80%	0.18 ± 0.01	0.52 ± 0.01	0.25 ± 0.01**	0.57 ± 0.01
	PS 22 cmH_2O	0.12 ± 0.00**	0.44 ± 0.01**	0.33 ± 0.01	0.73 ± 0.01**
Pmus 18 cmH_2O	PAV 50%	0.18 ± 0.02	0.41 ± 0.01	0.25 ± 0.01	0.58 ± 0.03
	PS 10 cmH_2O	0.11 ± 0.00**	0.38 ± 0.01*	0.31 ± 0.00**	0.74 ± 0.01**
	PAV 60%	0.16 ± 0.01	0.46 ± 0.01	0.27 ± 0.01	0.62 ± 0.02
	PS 14 cmH_2O	0.11 ± 0.01**	0.38 ± 0.01**	0.33 ± 0.01**	0.74 ± 0.01**
	PAV 70%	0.17 ± 0.01	0.46 ± 0.01	0.26 ± 0.01	0.61 ± 0.01
	PS 18 cmH_2O	0.11 ± 0.01**	0.40 ± 0.01**	0.32 ± 0.01**	0.74 ± 0.02**
	PAV 80%	0.18 ± 0.01	0.51 ± 0.01	0.25 ± 0.01	0.58 ± 0.02
	PS 22 cmH_2O	0.11 ± 0.01**	0.40 ± 0.01**	0.35 ± 0.01**	0.76 ± 02**

Abbreviations: $Delaytr_{exp}$, expiratory trigger delay; $Delaytr_{insp}$, inspiratory trigger delay; PAV+, proportional assist ventilation plus; PS, pressure support; RR, respiratory rate; $Time_{synch}$, time of synchrony.
*$p < 0.05$; **$p < 0.01$.

Ti/Ttot was significantly longer during PAV+ than optimized PSV ($p < 0.05$).

At low Pmus, the delivered Vt_{mech} during PAV+ was significantly lower than the Vt_{mech} during optimized PSV ($p < 0.01$). However, at high Pmus and high levels of optimized PSV and PAV + , the delivered Vt_{mech} was significantly higher in PAV+ than in optimized PSV ($p < 0.01$).

With the same optimized PSV and PAV+ delivered, increasing Pmus from 8 to 16 cmH_2O increased Vt_{mech} and Vt_{neu} ($p < 0.01$) (Figures 1 and 2) both in healthy subjects and in patients with PARDS. This increase for low Pmus resulted in a significant increase in Vt_{mech} and Vt_{neu} in optimized PSV ($p < 0.01$), while at high Pmus (16 cmH_2O), the increase in Vt_{mech} and Vt_{neu} was significantly greater in PAV + , both in the model of healthy pediatric patients and in those with PARDS.

The analysis of Vt_{neu}/Vt_{mech} showed that at low levels of assistance and Pmus, there were no significant variations between PAV+ and optimized PSV. By increasing both Pmus and the level of PSV optimized and PAV+ in both tested clinical conditions, a significant increase in Vt_{neu}/Vt_{mech} ($p < 0.05$) was observed, greater in optimized PSV than in PAV+ ($p < 0.05$).

Statistical analysis of the data obtained in the two different tested clinical conditions (healthy patients and patients with ARDS) showed that, with the same Pmus and support delivered in optimized PSV and PAV + , the Vt_{mech} produced during PARDS was significantly lower than in healthy patients ($p < 0.05$). The increase in Pmus in the simulated patient with PARDS resulted in a significant increase in Vt_{mech} at increasing levels of PAV+ and optimized PSV. It is important to emphasize that at high levels of Pmus and support, the delivered Vt_{mech} in PAV+ was significantly higher than in optimized PSV ($p < 0.05$).

4 | Discussion

The results of this study demonstrated the applicability of a mode of proportional closed-loop ventilation (PAV+) and how optimized PSV can improve simulated patient-ventilator

TABLE 2 | Effects, in a simulated lung model of mild PARDS (Pediatric Acute Respiratory Distress Syndrome), of different levels of PAV+ and optimized PSV at the same inspiratory effort (Pmus), on patient-ventilator interaction.

		Mild PARDS simulated lung model			
RR 25 breaths/min		**Delay$_{trinsp}$ (s)**	**Delay$_{trexp}$ (s)**	**Time$_{synch}$ (s)**	**Time$_{synch}$/Ti$_{neu}$**
Pmus 8 cmH_2O	PAV 50%	0.12 ± 0.00	0.26 ± 0.01	0.170.0 ± 1	0.58 ± 0.01
	PS 10 cmH_2O	0.13 ± 0.01	0.23 ± 0.01*	0.16 ± 0.01	0.52 ± 0.02
	PAV 60%	0.12 ± 0.00	0.30 ± 0.01	0.14 ± 0.00	0.54 ± 0.01
	PS 14 cmH_2O	0.13 ± 0.01	0.25 ± 0.01*	0.15 ± 0.01	0.53 ± 0.01
	PAV 70%	0.14 ± 0.01	0.28 ± 0.01	0.16 ± 0.01	0.54 ± 0.02
	PS 18 cmH_2O	0.13 ± 0.01	0.30 ± 0.01	0.14 ± 0.01*	0.51 ± 0.01
	PAV 80%	0.13 ± 0.01	0.33 ± 0.01	0.15 ± 0.01	0.53 ± 0.02
	PS 22 cmH_2O	0.14 ± 0.00	0.29 ± 0.01*	0.15 ± 0.00	0.52 ± 0.02
Pmus 12 cmH_2O	PAV 50%	0.11 ± 0.01	0.27 ± 0.00	0.17 ± 0.00	0.60 ± 0.01
	PS 10 cmH_2O	0.12 ± 0.01	0.21 ± 0.01*	0.18 ± 0.01	0.60 ± 0.02
	PAV 60%	0.14 ± 0.01	0.28 ± 0.01*	0.15 ± 0.01	0.51 ± 0.02
	PS 14 cmH_2O	0.12 ± 0.01	0.24 ± 0.01	0.16 ± 0.01	0.58 ± 0.01*
	PAV 70%	0.12 ± 0.01	0.30 ± 0.01*	0.17 ± 0.02	0.57 ± 0.03
	PS 18 cmH_2O	0.11 ± 0.01	0.25 ± 0.01	0.18 ± 0.01	0.61 ± 0.02
	PAV 80%	0.13 ± 0.01	0.33 ± 0.00*	0.16 ± 0.01	0.54 ± 0.02
	PS 22 cmH_2O	0.12 ± 0.01	0.28 ± 0.03	0.16 ± 0.02	0.58 ± 0.02
Pmus 16 cmH_2O	PAV 50%	0.14 ± 0.01	0.27 ± 0.01	0.14 ± 0.00	0.51 ± 0.01
	PS 10 cmH_2O	0.10 ± 0.00**	0.21 ± 0.01**	0.19 ± 0.01**	0.65 ± 0.01**
	PAV 60%	0.14 ± 0.00	0.28 ± 0.01	0.15 ± 0.01	0.51 ± 0.01
	PS 14 cmH_2O	0.12 ± 0.01*	0.23 ± 0.01*	0.15 ± 0.01	0.55 ± 0.03
	PAV 70%	0.12 ± 0.01	0.30 ± 0.00	0.17 ± 0.01	0.57 ± 0.02
	PS 18 cmH_2O	0.11 ± 0.01	0.24 ± 0.02*	0.17 ± 0.02	0.60 ± 0.04
	PAV 80%	0.13 ± 0.01	0.34 ± 0.00	0.15 ± 0.01	0.52 ± 0.02
	PS 22 cmH_2O	0.12 ± 0.01	0.25 ± 0.04*	0.18 ± 0.03	0.60 ± 0.04*

Abbreviations: Delaytr$_{exp}$, expiratory trigger delay; Delaytr$_{insp}$, inspiratory trigger delay; PAV+, proportional assist ventilation plus; PS, pressure support; RR, respiratory rate; Time$_{synch}$, time of synchrony.
*$p < 0.05$; **$p < 0.01$.

interaction in two bench settings of pediatric respiratory mechanics, namely "pediatric patient with normal respiratory mechanics," referred to as "healthy," and "pediatric patient with mild Pediatric Acute Respiratory Distress Syndrome (PARDS)."

Although widely studied in adults [28–30], the clinical application of PAV+ in the pediatric field has been poorly evaluated, except in small cohorts of newborns for short periods, focusing more on feasibility rather than on prospective randomized controlled trials (RCTs) [12, 30].

Clinical studies conducted on PAV+ in the pediatric field have shown short-term benefits in newborns with Respiratory Distress Syndrome (RDS) and evolving Bronchopulmonary Dysplasia (BPD), in terms of maintaining gas exchange stability and lower oxygenation index with lower mean airway pressures (MAP) compared to other assisted ventilation modes [8, 30–32]. To date, no long-term physiological or clinical studies or RCTs have been conducted in both neonatal and pediatric settings that could evaluate important outcomes such as the development of BPD and/or duration of mechanical ventilation.

Despite clear theoretical advantages, the practical application of PAV+ has been severely limited by the need for continuous knowledge of the Compliance and Resistance values of the respiratory system in patients with active respiratory muscles and dynamic flow conditions.

Pediatric applications have been further limited by even greater difficulties related to the dynamic calculation of Crs (Compliance) and Rrs (Resistance) values, which have been overcome by PAV+ software equipped with continuous respiratory mechanics calculation and adjustable "gain" factors as the load varies. Indeed, the closed-loop system of PAV+ has been effective in varying the delivered volume according to the magnitude of inspiratory effort generated by the patient.

In terms of patient-ventilator interaction in the bench setting of healthy pediatric patients, the results of our study differ from those found in comparative studies between PAV+ and PSV (Pressure Support Ventilation) in adult patients or newborns with acute respiratory problems.

TABLE 3 | Effects, in a simulated pediatric "healthy" lung model, of different levels of PAV+ and optimized PSV at the same inspiratory effort (Pmus), on Ti_{mech}, Ti/Ttot flow, Vt_{mech}, and Vt_{neu}/Vt_{mech}.

		"Healthy" simulated lung model			
RR 25 breaths/min		**Ti_{mech} (s)**	**Ti/Ttot flow (%)**	**Vt_{mech} (ml)**	**Vt_{neu}/Vt_{mech} (%)**
Pmus 8 cmH_2O	PAV50%	0.64 ± 0.00	31%	276.00 ± 1.73	60%
	PS 10 cmH_2O	0.68 ± 0.01**	31%	371.00 ± 0.00**	57%
	PAV60%	0.65 ± 0.06	32%	318.00 ± 0.00	50%
	PS 14 cmH_2O	0.70 ± 0.01	32%	451.33 ± 1.15**	57%
	PAV70%	0.69 ± 0.01	34%	366.33 ± 6.35	47%
	PS 18 cmH_2O	0.76 ± 0.01**	35%*	535.00 ± 3.61**	55%*
	PAV80%	0.76 ± 0.01	36%	433.00 ± 0.00	40%
	PS 22 cmH_2O	0.78 ± 0.01	35%*	614.00 ± 1.73**	49%**
Pmus 12 cmH_2O	PAV50%	0.66 ± 0.01	32%	366.00 ± 3.46	51%
	PS 10 cmH_2O	0.68 ± 0.01*	31%*	437.00 ± 2.00**	60%**
	PAV60%	0.68 ± 0.00	33%	457.67 ± 4.04	47%
	PS 14 cmH_2O	0.72 ± 0.01**	32%*	517.00 ± 0.00**	58%**
	PAV70%	0.73 ± 0.01	35%	527.33 ± 4.04	43%
	PS 18 cmH_2O	0.73 ± 0.01	33%*	593.00 ± 0.00**	55%**
	PAV80%	0.76 ± 0.01	37%	620.00 ± 8.00	38%
	PS 22 cmH_2O	0.76 ± 0.01	35%*	669.33 ± 1.15**	50%**
Pmus 16 cmH_2O	PAV50%	0.67 ± 0.02	32%*	501.33 ± 4.04	54%
	PS 10 cmH_2O	0.69 ± 0.01*	31%	502.00 ± 1.15	54%
	PAV60%	0.72 ± 0.01	34%	582.33 ± 0.58	48%
	PS 14 cmH_2O	0.71 ± 0.00*	32%**	575.00 ± 0.00**	56%**
	PAV70%	0.72 ± 0.00	34%	661.00 ± 0.00	44%
	PS 18 cmH_2O	0.72 ± 0.02	33%*	644.00 ± 7.94*	52%**
	PAV80%	0.76 ± 0.00	37%	765.33 ± 5.77	39%
	PS 22 cmH_2O	0.75 ± 0.01	34%**	727.00 ± 1.73**	55%**

Abbreviations: PAV+, proportional assist ventilation plus; PS, pressure support; RR, respiratory rate; Ti_{mech}, inspiratory mechanical time; Ti/Ttot flow, mechanical respiratory pattern; Vt_{mech}, mechanical tidal volume; Vt_{neu}, neural tidal volume.
*$p < 0.05$; **$p < 0.01$.

In the case of the bench setting of healthy pediatric patients, optimized PSV always showed better patient-ventilator interaction than PAV+, at any level of support and Pmus (muscle pressure) tested, as demonstrated by low $Delay_{trinsp}$ and $Delay_{trexp}$ values and significantly higher $Time_{synch}$ and $Time_{synch}/Ti_{neu}$ values.

Our results demonstrate how Pressure Support optimized on a simulated patient's respiratory mechanics and respiratory pattern can determine a better patient-ventilator interaction and a higher level of assistance even compared to a ventilation mode proportional to the patient's effort.

In this bench test, the expiratory trigger and pressurization ramp chosen during each optimized PSV setting were deliberately faster to better match the simulated pediatric patient's respiratory mechanics and high respiratory rates by analyzing the Pmus tracing used.

During the bench test on pediatric patients with mild PARDS, in terms of simulated patient-ventilator interaction, the results of our study differ from the study by Bath et al. [33] conducted on a population of preterm infants undergoing mechanical ventilation for 1 week. In their study, Bath et al. demonstrated that the application of PAV+ compared to ACV (Assist Control Ventilation) in this specific premature infant population results in a statistically significant reduction in both oxygenation index and respiratory effort after 1 h of application.

Our results show that PS mode, at low levels of assistance and Pmus, has better-simulated patient-ventilator interaction than PAV + , as evidenced by significantly lower $Delay_{trexp}$ and $Delay_{trinsp}$ values. Conversely, with increasing assistance in both optimized PSV and PAV + , and especially with increasing Pmus, PAV+ proved to be an alternative to optimized PSV in assisting simulated pediatric patients with mild PARDS, as demonstrated by the absence of statistically significant differences in terms of $Delay_{trinsp}$, $Delay_{trexp}$, and $Time_{synch}$.

The results obtained, with the application of high levels of assistance both in PAV+ and in optimized PSV at high Pmus, tend to confirm the results presented in the work of Costa et al.

TABLE 4 | Effects, in a simulated lung model of mild PARDS (Pediatric Acute Respiratory Distress Syndrome), of different levels of PAV+ and optimized PSV at the same inspiratory effort (Pmus), on Ti_{mech}, Ti/Ttot flow, Vt_{mech}, and Vt_{neu}/Vt_{mech}.

		Mild PARDS simulated lung model			
RR 40 breaths/min		**Ti_{mech} (s)**	**Ti/Ttot flow (%)**	**Vt_{mech} (ml)**	**Vt_{neu}/Vt_{mech} (%)**
Pmus 8cmH_2O	PAV 50%	0.43 ± 0.01	32%	136.00 ± 0.58	49%
	PS 10 cmH_2O	0.38 ± 0.01**	30%**	171.67 ± 0.58**	51%
	PAV 60%	0.44 ± 0.01	34%	152.00 ± 0.00	38%
	PS 14 cmH_2O	0.41 ± 0.01**	31%**	212.33 ± 0.58**	46%
	PAV 70%	0.45 ± 0.01	34%	178.67 ± 0.58	45%
	PS 18 cmH_2O	0.44 ± 0.01*	33%*	252.00 ± 0.00**	39%
	PAV 80%	0.48 ± 0.01	36%	205.67 ± 2.31	36%
	PS 22 cmH_2O	0.44 ± 0.01**	34%**	289.67 ± 1.15**	40%
Pmus 12 cmH_2O	PAV 50%	0.44 ± 0.00	33%	202.00 ± 0.00	48%
	PS 10 cmH_2O	0.38 ± 0.01**	29%**	207.33 ± 1.15**	57%
	PAV 60%	0.42 ± 0.01	32%	230.67 ± 0.58	48%
	PS 14 cmH_2O	0.40 ± 0.01**	31%*	245.00 ± 2.00**	52%
	PAV 70%	0.47 ± 0.01	35%	265.33 ± 1.15	42%
	PS 18 cmH_2O	0.42 ± 0.01**	32%**	286.00 ± 0.00**	53%*
	PAV 80%	0.49 ± 0.01	37%	297.33 ± 1.15	37%
	PS 22 cmH_2O	0.44 ± 0.01**	33%**	323.00 ± 1.73**	45%*
Pmus 16 cmH_2O	PAV 50%	0.41 ± 0.01	31%	252.67 ± 1.15	47%
	PS 10 cmH_2O	0.40 ± 0.00**	30%*	242.33 ± 1.15**	56%*
	PAV 60%	0.42 ± 0.01	32%	286.00 ± 0.00	47%
	PS 14 cmH_2O	0.38 ± 0.01**	29%**	277.67 ± 2.52**	53%
	PAV 70%	0.47 ± 0.01	35%	340.33 ± 2.89	43%
	PS 18 cmH_2O	0.41 ± 0.01**	32%**	315.00 ± 0.00**	53%**
	PAV 80%	0.49 ± 0.01	37%	378.00 ± 3.46	36%
	PS 22 cmH_2O	0.43 ± 0.01**	32%**	351.00 ± 1.73**	49%**

Abbreviations: PAV+, proportional assist ventilation plus; PS, pressure support; RR, respiratory rate; Ti_{mech}, inspiratory mechanical time; Ti/Ttot flow, mechanical respiratory pattern; Vt_{mech}, mechanical tidal volume; Vt_{neu}, neural tidal volume.
*$p < 0.05$; **$p < 0.01$.

[32] on adult patients, especially in terms of the mechanical volume delivered in phase with the mechanical inspiration.

As described in the results, during PAV + , in both bench setting conditions, an increase in inspiratory effort corresponds to a linear increase in volume and pressure applied to the airways; moreover, at the same level of assistance and inspiratory effort, the system correctly applies lower absolute volume and pressure values in the restrictive model, suggesting its applicative safety (even in the presence of alarm systems and overpressure limitation) in the pediatric field. These data are substantially in line with the results reported by Kondili et al. [34] in a study conducted on adult critical patients, where the short-term response of respiratory output was observed starting from a resting condition to which a viscoelastic load was added during both PAV+ and PS modes. In 10 patients, respiratory work was increased, and the compensatory respiratory load pattern was examined during both support modes. Airway and transdiaphragmatic pressures, volume, and flow were measured with each breath. Without load, both modes provided equal support, as indicated by the pressure-time product generated by the diaphragm for each breath, each minute, and for each liter of ventilation. With the load, these values were significantly lower ($p < 0.05$) with PAV+ compared to PS (5.1 ± 3.7 vs. 6.1 ± 3.4 cmH_2O.s, 120.9 ± 77.6 vs. 165.6 ± 77.5 cmH_2O.s/min, e 18.7 ± 15.1 vs. 24.4 ± 16.4 cmH_2O.s/l, respectively).

Unlike PS, with PAV + , the ratio between tidal volume (Vt) and the pressure-time product generated by the diaphragm for each breath (neuroventilatory coupling index) remained relatively independent of the load. With PAV + , the magnitude of reduction in Vt induced by the load and the increase in respiratory rate were significantly lower than during PS.

In critical patients, therefore, short-term compensation for respiratory load was effective during Proportional Assist Ventilation with adjustable "gain" factors compared to PS mode.

The experimental situation described in this study has some limitations. The first is the applicability of PAV+ software only to the field of invasive ventilation in intubated patients, dictated by the need for a closed system that can make the mechanism of

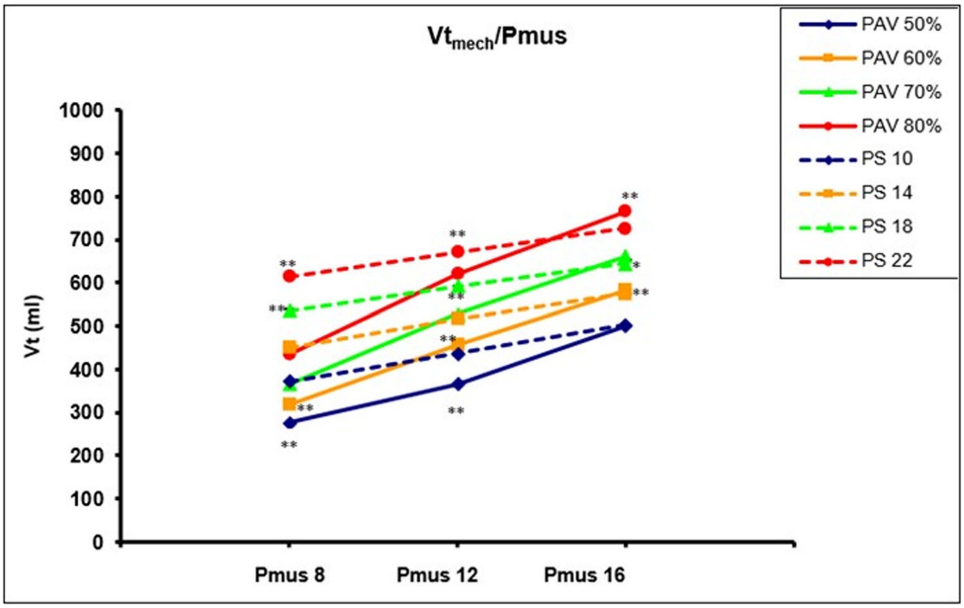

FIGURE 1 | Mechanical tidal volume (Vt_{mech}) and inspiratory effort (Pmus) ratio in a simulated pediatric "healthy" lung model, with two different ventilation modalities (PAV+ and optimized PSV). Vt: tidal volume; PS: pressure support, PAV: proportional assist ventilation, Pmus: muscle pressure. *: $p < 0.05$; **: $p < 0.01$. [Color figure can be viewed at wileyonlinelibrary.com]

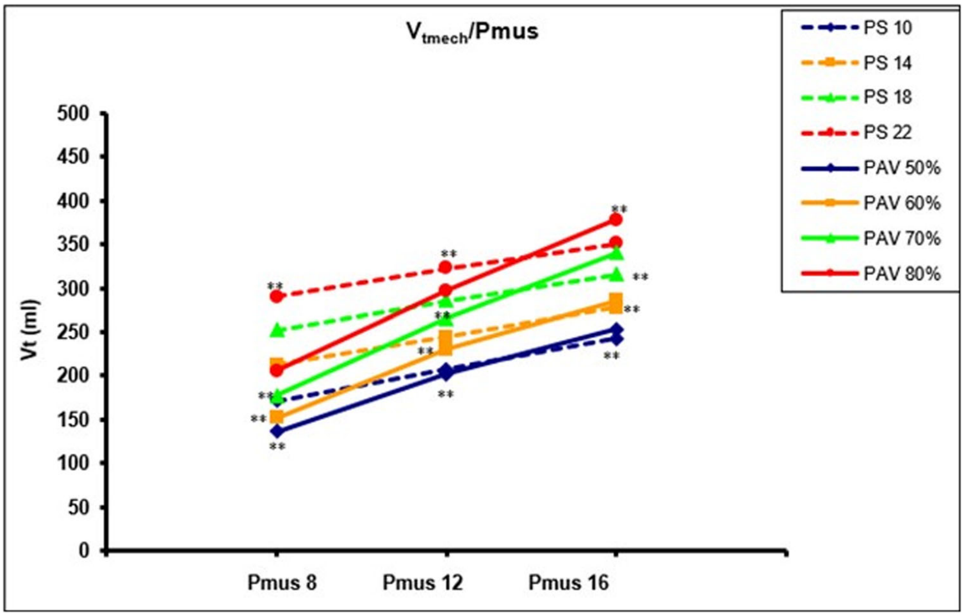

FIGURE 2 | Mechanical tidal volume (Vt_{mech}) and inspiratory effort (Pmus) ratio in a simulated lung model of mild PARDS (Acute Respiratory Distress Syndrome), with two different ventilation modalities (PAV+ and optimized PSV). Vt: tidal volume; PS: pressure support, PAV: proportional assist ventilation, Pmus: muscle pressure. *: $p < 0.05$; **: $p < 0.01$. [Color figure can be viewed at wileyonlinelibrary.com]

serial tele-inspiratory and tele-expiratory occlusions operative necessary for the automatic calculation of respiratory mechanics variables. The second is the need to apply the software only in patients with intact respiratory drive and effective inspiratory efforts (as during PSV). The third is performing a test under ideal conditions without air leaks. In fact, in the presence of air leaks, the flow and volumes applied to the patient would lose linear dependence on inspiratory effort in PAV + , and therefore, the pressure applied to the airways would no longer be correlated with Pmus.

5 | Conclusions

In conclusion, our results demonstrate that in simulated pediatric patients with normal respiratory mechanics, the optimized Pressure Support Mode, when properly set in terms of cycling off and pressurization ramp, allows more optimal patient-ventilator interaction and assistance levels not inferior even to proportional techniques such as PAV + . On the contrary, in simulated pediatric patients with mild PARDS respiratory mechanics, PAV+ appears as a valid alternative to PS mode, especially under conditions of intense inspiratory effort and high assistance levels. Obviously, these experimental data obtained from bench conditions constitute only a prerequisite for the realization of confirmatory physiological studies first, and clinical studies later, in pediatric patients with acute respiratory failure.

Author Contributions

G. Spinazzola: conceptualization, project administration, writing – original draft. **G. Ferrone:** conceptualization, writing – review and editing, writing – original draft. **R. Costa:** conceptualization, writing – review and editing. **O. Festa:** data curation, methodology. **M. Piastra:** visualization, supervision. **G. Bello:** supervision. **M. F. Amato:** visualization. **M. Rossi:** visualization. **G. Conti:** conceptualization, methodology, writing – review and editing.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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