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Proportional assist ventilation with load-adjustable gain factors in critically ill patients: comparison with pressure support

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Abstract *Objectives:* It is not known if proportional assist ventilation with load-adjustable gain factors (PAV+) may be used as a mode of support in critically ill patients. The aim of this study was to examine the effectiveness of sustained use of PAV+ in critically ill patients and compare it with pressure support ventilation (PS). *Design and setting:* Randomized study in the intensive care unit of a university hospital. *Methods:* A total of 208 critically ill patients mechanically ventilated on controlled modes for at least 36 h and meeting certain criteria were randomized to receive either PS (n = 100) or PAV+ (n = 108). Specific written algorithms were used to adjust the ventilator settings in each mode. PAV+ or PS was continued for 48 h unless the patients met predefined criteria either for switching to controlled modes (failure criteria) or for breathing without ventilator assistance. *Results:* Failure rate was significantly lower in PAV+ than that in PS (11.1 vs. 22.0%, P = 0.040, OR 0.443, 95% CI 0.206–0.952). The proportion of patients exhibiting major patient–ventilator dyssynchronies at least during one occasion and after adjusting the initial ventilator settings, was significantly lower in PAV+ than in PS (5.6 vs. 29.0%, $P <$ 0.001, OR 0.1, 95% CI 0.06–0.4). The proportion of patients meeting criteria for unassisted breathing did not differ between modes. *Conclusions:* PAV+ may be used as a useful mode of support in critically ill patients. Compared to PS, PAV+ increases the probability of remaining on spontaneous breathing, while it considerably reduces the incidence of patient–ventilator asynchronies.

Keywords Controlled modes · Assisted modes · Patient–ventilator interaction

Introduction

The early reinstitution of spontaneous breathing in mechanically ventilated critically ill patients has become an important therapeutic option to avoid the various complications associated with controlled mechanical ventilation and facilitate the weaning process [1, 2]. It is recommended that mechanically ventilated critically ill patients should be switched to assisted modes even during the acute course of their illness as soon as they meet certain criteria [3, 4]. Pressure support (PS) is a widely used mode of assisted mechanical ventilation [5, 6]. In this mode the ventilator, once triggered by the patient effort, provides a pre-set level of constant pressure until a cycling-off criterion is reached [7]. As a result, the patient, by altering the pressure generated by respiratory muscles, may change the inspiratory flow and thus have partial control over the mechanical breath. This ability, however, is seriously compromised in the presence of abnormal respiratory system mechanics [8].

Proportional-assist ventilation (PAV) is a mode of support in which the ventilator pressure is proportional to instantaneous flow and volume and hence to pressure generated by the respiratory muscles [9]. Numerous studies have shown that PAV improves the synchrony between patient and ventilator and may decrease sleep disruption compared with PS [10–14]. The necessity of regular measurements of respiratory system mechanics, however, imposes a major obstacle to the widespread use of this mode. For this reason, methods of non-invasive determination of resistance and elastance of the respiratory system when patients are ventilated with PAV have been described [15, 16]. Based on these methods, a software has been developed (PAV+) which automatically adjusts the flow assist and volume assist so that they always represent constant fractions of the measured values of resistance and elastance of the respiratory system [17].

Although PAV+ has been successfully applied in critically ill patients for a limited time [17, 18], it is not known whether this mode could be used as the main mode of assisted mechanical ventilation. Apart from the well-known advantages of PAV in terms of patient–ventilator synchrony [10–14, 19], PAV+ by providing semi-continuous respiratory system mechanics [17] may help the caregiver to follow the patient status and recognize various complications associated with the process of mechanical ventilation. The aim of this study was to compare the effectiveness of sustained use of PS and PAV+ in critically ill patients immediately upon meeting certain criteria for assisted mechanical ventilation.

Methods

Detailed methods are available in the Electronic supplementary material (ESM).

Patients

This study was conducted in a medical–surgical intensive care unit (ICU). The study was approved by the Hospital Ethics Committee and signed informed consent was obtained from each patient or next of kin.

Patients under mechanical ventilation for at least 36 h and ventilated with a controlled mode (CMV, volume or pressure control) were screened for eligibility. Inclusion criteria were: ability to trigger the ventilator at a satisfactory rate (>10 breaths/min); $PaO_2 > 60$ mmHg, with fractional concentration of inspired O_2 (FIO_2) < 65%; total [extrinsic ($PEEP_E$) and intrinsic (PEEPi)] positive end-expiratory airway pressure ($PEEP_{TOT}$) < 15 cmH_2O; no severe acidemia (pH > 7.30); no severe hemodynamic instability; no severe bronchospasm; and a stable neurological status.

Study protocol

As soon as inclusion criteria were met, the patients were allocated at random to receive proportional assist (PAV+ group) or pressure support (PS group) ventilation using Puritan-Bennett 840 ventilators (Nellcor Puritan Bennett LLC, Gosport, UK). Randomization was concealed and stratified by disease severity using the APACHE II score. Specific pre-defined written algorithms were used to adjust the ventilator settings in each mode (see ESM). PAV+ or PSV was continued for 48 hours unless the patients met pre-defined criteria either for switching to CMV (failure criteria, Table 1) or for breathing without ventilator assistance (see ESM).

If, during the 48-h study period, the primary physician decided that the patient needed a procedure that necessitated heavy sedation and CMV, the protocol was temporarily interrupted. In this patient, PAV+ or PS was re-instituted after the end of the procedure when the inclusion criteria were met again.

In both groups identical algorithms for sedation and analgesia titration were followed [20, 21]. Remifentanyl was used for analgesia and propofol for sedation. Vasoactive drugs (mainly noradrenaline) were given following usual clinical guidelines [22].

Measurements

During the study the following parameters were measured:

(1) Gas exchange data: PaO_2, $PaCO_2$, PaO_2/F_IO_2, and pH
(2) Respiratory data: Tidal volume (V_T), ventilator rate (F_{rvent}), minute ventilation (V'_E), patient respiratory rate (F_{rpat}), peak (P_{peak}) and mean (P_{mean}) airway pressures, end-inspiratory alveolar pressure (P_{plat}), respiratory system resistance (R_{rs}) and compliance (C_{rs}), $PEEP_E$, $PEEP_i$ and $PEEP_{TOT}$. Major patient–ventilator dyssynchronies (ineffective efforts, double triggering and auto-triggering) were evaluated by measuring the difference between F_{rvent} and F_{rpat} [14, 23, 24]. Expiratory asynchrony and triggering delay were not systematically examined. P_{plat}, R_{rs}, C_{rs} and $PEEP_i$ were measured during CMV (within 8 h before randomization, in all patients) [23, 24] and during PAV+ (only in patients randomized to PAV+) [15–17].
(3) Hemodynamic data: Arterial and central venous pressures and heart rate.

Table 1 Failure criteria

At least one of the following
1 Respiratory distress[a] despite adjustment of $PEEP_E$ and/or assist level[b]
2 Hypoxemia ($SaO_2 < 90\%$) despite adjustment of F_IO_2 and/or $PEEP_E$ and/or assist level[b]
3 Hypercapnia with acidemia (pH < 7.35 or pH < 7.30 in patients with pre-existing metabolic acidosis) despite adjustment of sedation level and/or $PEEP_E$ and/or assist level[b]
4 Severe hemodynamic instability[c] or arrhythmias
5 Acute ischemic heart disease
6 Increased need for sedation for medical reasons (i.e. CNS disease, agitation, fighting the ventilator) that results in depressed respiratory drive
7 The need for re-intubation in less than 48 h after extubation in patients in whom extubation was performed within the 48-h study period (extubation failure)

F_IO_2 Fractional concentration of inspired O_2, *$PEEP_E$* external positive end-expiratory airway pressure, *CNS* central nervous system

[a] Definition of respiratory distress: at least 2 of the following: 1) Heart rate > 120% of the usual rate for >5 min and/or systolic arterial blood pressure (SAP) >180 or <90 mmHg and/or SAP changes >20% of the previous value for >5 min; (2) Respiratory rate > 40 breaths/min for >5 min; (3) Marked use of accessory muscles; (4) Diaphoresis; (5) Abdominal paradox; (6) Marked complaint of dyspnea (in conscious patients)

[b] See Figures S1–S6 in the ESM for adjustment of F_IO_2, $PEEP_E$ and assist level

[c] Need for norepinephrine > 0.5 μg/kg per h

Endpoints

The primary endpoint was the proportion of patients meeting failure criteria in each mode during the 48-h study period. Secondary endpoints were: (1) the proportion of patients meeting criteria for unassisted breathing, (2) the proportion of patients exhibiting major patient–ventilator dyssynchronies, and (3) the total amount of sedative, analgetic and vasoactive drugs during the 48 h of observation.

Statistical analysis

We estimated that the failure rate in patients ventilated with PS would be 25% [4], and calculated a need to enrol at least 100 patients in each arm, to detect a 15% difference in failure rate between modes using a two-sided test, a type I error of 0.05, and a power of 80%. Results are given as medians (25th–75th interquartile ranges), unless stated otherwise. Proportions were compared using the χ^2 test or the Fisher exact test when required. Continuous variables were compared with Wilcoxon or Mann–Whitney tests, as appropriate. The cumulative probability of remaining on spontaneous breathing was analyzed by the Kaplan–Meier method, and a log-rank test was used to assess differences. A stepwise logistic regression analysis was performed to identify prognostic baseline indices of failure on assisted modes. $P < 0.05$ was considered significant.

Results

For detailed results see also ESM.

Patients were enrolled from May 2006 to March 2008. During this period 984 patients were screened for eligibility and 208 of them were randomized: 100 to PS and 108 to PAV+ (Fig. 1).

Patients' characteristics and baseline variables (during CMV) are shown in Table 2. The two groups were similar for most characteristics and variables. The study was temporarily interrupted in 17 patients in PAV+ group and in 14 in PS group. Mortality in the ICU was 23.0 in PS and 17.6% in PAV+ (P = 0.39), but no patients died during the 48-h study period. Hospital mortality was 30.0 in PS and 23.1% in PAV+ (P = 0.28).

The initial assist averaged 70 ± 5% (mean ± SD) in PAV+ and 23.5 ± 2.4 cmH_2O (total pressure) in PS. The proportion of patients meeting failure criteria and switched to CMV during the 48 h of observation was significantly lower in PAV+ group than in PS group (Fig. 1, Fisher's exact test, P = 0.040, OR 0.443, 95% CI 0.206–0.952). The main reason for the lower failure rate with PAV+ was a lower rate of hypoxemia (Table 3). The probability of remaining on spontaneous breathing (assisted or unassisted) is shown in Fig. 2 and was significantly increased with PAV+ (Long-rank, P = 0.041). The proportion of patients meeting criteria for unassisted breathing and placed on t-piece did not differ between modes (53.7% in PAV+ group vs. 46.0% in PS group, P = 0.33, OR 0.73, 95% CI 0.43–1.27).

During CMV P_{peak}, P_1 (the end-inspiratory airway pressure, immediately after rapid airway occlusion), P_{plat} and $PaCO_2$ were significantly higher and PaO_2/F_IO_2 and pH significantly lower in patients who failed than in patients who succeeded (see ESM). None of the other patients' characteristics and baseline variables differed significantly between failure and success patients. The variables that differed significantly between failure and success patients as well as the mode of support were included in a stepwise logistic regression analysis which showed that only P_1 (χ^2 10.42, $P < 0.001$) and the mode of support (χ^2 4.24, $P <$ 0.04) served as independent predictors of failure.

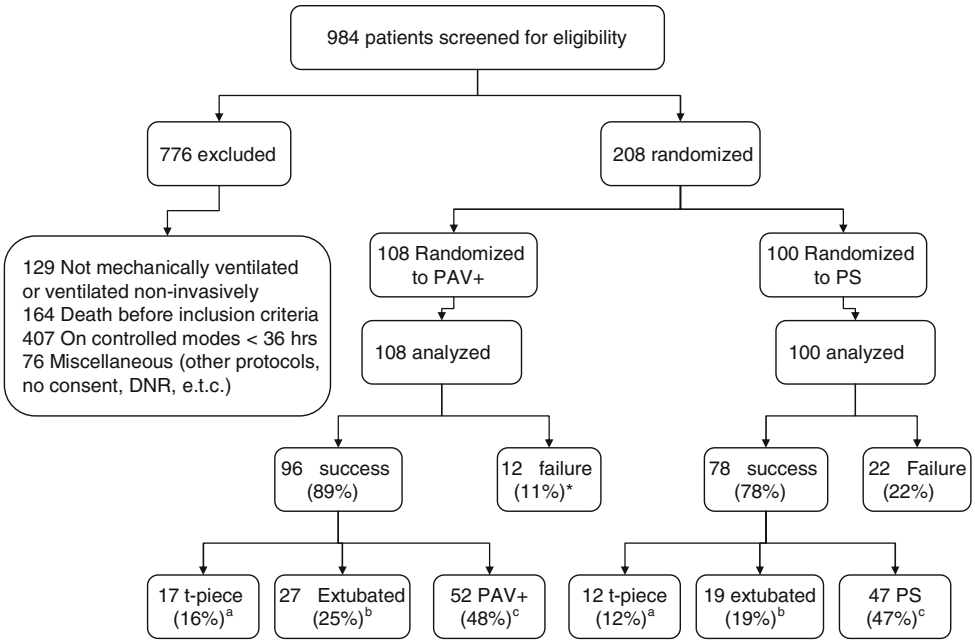

Fig. 1 Flow chart of the study. *Parentheses* indicate percentage of total patients randomized to each group. *PAV+* Proportional assist ventilation with load adjustable gain factors, *PS* pressure support. *Significantly different from PS group. [a]Patients placed on t-piece and remained on t-piece throughout the study. [b]Patients successfully extubated. [c]Patients either being on assisted spontaneous breathing throughout or placed intermittently on t-piece

The proportion of patients exhibiting major patient–ventilator dyssynchronies was significantly lower in the PAV+ group than that in the PS (5.6 vs. 39.0%, $P < 0.001$, OR 0.1, 95% CI 0.04–0.251). The difference remained significant even after excluding measurements at initial assist level which was chosen rather arbitrary (5.6 vs. 29%, $P < 0.001$, OR 0.144, 95% CI 0.057–0.365). In the PS group, from a total of 696 measurements, 95 (13.6%) revealed a difference between patients' breathing frequency and ventilator rate (Fig. 3). With PS ineffective efforts were the type of major asynchrony observed in all but two measurements. In two patients and on two occasions double triggering was identified. From these measurements, considerable patient–ventilator dyssynchronies (>10% of patient's respiratory efforts) were observed in 67 (9.6% of the total measurements). In the PAV+ group, from a total of 744 measurements, 21 (2.8%) revealed a difference between patients' breathing frequency and ventilator rate, while considerable dyssynchrony was observed in 10 (1.3% of the total). With PAV+ only ineffective efforts were observed.

The total amount of sedative and vasoactive (noradrenaline) drugs received within the 48 h of study period, was slightly but non-significant lower in the PAV+ group (see ESM). This difference was entirely due to the higher number of patients who failed on PS and received increased doses of vasopressors and sedatives when they were switched to control modes. The total amount of analgetics was similar between the groups.

In PS, immediately upon switching to assisted modes, V_T, V'_E, P_{peak} and P_{mean} were significantly higher and F_{rvent} significantly lower than the corresponding values in PAV+ (see ESM). Thereafter, these variables did not differ between modes.

Individual examination of P_{plat} during PAV+ ($P_{plat_{PAV+}}$) showed that from a total of 744 measurements only on 9 occasions (1.2%) and in 5 patients (4.6%) $P_{plat_{PAV+}}$ was above 30 cmH_2O (highest value 35.2 cmH_2O). Three out of these five patients failed on PAV+ and were switched to controlled mechanical ventilation relatively early. In 94% of the measurements, $P_{plat_{PAV+}}$ was below 26 cmH_2O (see ESM).

Hemodynamic data did not differ either between modes or as a function of time (see ESM).

Discussion

The main finding of this study is that PAV+ may be used as a mode of support in critically ill patients meeting certain criteria for assisted modes. Compared to PS, during the 48-h period of observation, patients ventilated with PAV+ exhibited: (1) increased probability of remaining on assisted or un-assisted spontaneous breathing and (2) better patient–ventilator synchrony.

The probability of remaining on spontaneous breathing during the study period was significantly increased in patients ventilated with PAV+ when compared with PS. The failure rate observed in the PS group was remarkably similar to that reported by Cereda et al. [4] who studied only patients with ALI/ARDS and used similar inclusion criteria to ours. It is not clear why patients ventilated with PAV+ exhibited a lower failure rate than those ventilated

Table 2 Baseline characteristics of the study patients

	PS (n = 100)	PAV+ (n = 108)	P value
Age	63 (49–72)	59 (36–73)	0.14
Sex, male/female (n)	66/34	72/36	0.99
APACHE II at admission	19.5 (14.5–25.0)	19.0 (14.0–24.0)	0.58
APACHE II at randomization	16.0 (11.0–20.0)	15.0 (11.0–18.5)	0.47
Admission diagnosis, n (%)			0.83
ALI/ARDS/sepsis/MODS	32 (32.0)	32 (29.6)	
Trauma (excluding CNS damage)	10 (10.0)	14 (13.0)	
Traumatic CNS disease	18 (18.0)	23 (21.3)	
CNS disease (excluding trauma)	14 (14.0)	10 (9.3)	
CHF/cardiogenic shock	6 (6.0)	4 (3.7)	
AECOPD	6 (6.0)	4 (3.7)	
Post-operative ARF	7 (7.0)	9 (8.3)	
Cardiac arrest	2 (2.0)	5 (4.6)	
Others	5 (5.0)	7 (6.5)	
Days on CMV	4.0 (3.0–6.0)	4.0 (3.0–6.0)	0.87
V_T (ml/kg)	6.7 (6.0–7.4)	6.6 (6.0–7.1)	0.41
F_r (breaths/min)	23.0 (20.0–26.5)	23.0 (20.0–25.5)	0.69
V'_E, (l/min)	10.0 (8.6–11.6)	9.9 (8.5–11.2)	0.50
$PEEP_E$ (cmH_2O)	6.5 (5.0–7.8)	7.0 (6.0–8.0)*	0.046
$PEEP_i$	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.07
$PEEP_{TOT}$ (cmH_2O)	7.0 (6.0–8.8)	7.0 (6.0–9.0)	0.94
F_IO_2	0.40 (0.35–0.48)	0.40 (0.35–0.50)	0.75
PaO_2/F_IO_2 (mmHg)	242 (187–296)	215 (177–295)	0.52
$PaCO_2$ (mmHg)	40.0 (36.0–44.5)	40.0 (37.0–43.5)	0.95
Arterial pH (units)	7.44 (7.40–7.47)	7.44 (7.40–7.47)	0.69
P_{peak}[a]	31.5 (27.0–36.0)	31.0 (28.0–36.0)	0.45
P_1[a]	21.0 (18.0–24.5)	21.0 (18.0–23.0)	0.88
P_{plat}[a]	18.0 (15.0–20.0)	18.0 (15.0–20.0)	0.43
$C_{rs_{CMV}}$[a] (ml/cmH_2O)	40.0 (32.5–51.0)	44.0 (34.0–51.0)	0.69
R_{min}[a] (cmH_2O/l per s)	10.0 (8.0–13.0)	10.0 (8.0–14.0)	0.54
R_{max}[a] (cmH_2O/l per s)	14.0 (11.0–16.0)	13 (11.0–17.0)	0.97
HR (beats/min)	87 (72–100)	85 (71–99)	0.42
MAP (mmHg)	84 (77–93)	84 (76–92)	0.88
CVP (mmHg)	11.0 (8–13)	10.0 (8–12)	0.76

Values are expressed as medians (interquartile range) or numbers (percentage)

* Significantly different from PS group

[a] Values obtained within 8 h before randomization

PAV+ proportional assist ventilation with load adjustable gain factors; *PS* pressure support; *ALI* acute lung injury; *ARDS* acute respiratory distress syndrome; *MODS* multiple organ dysfunction syndrome; *CNS* central nervous system; *AECOPD* acute exacerbation of chronic obstructive lung disease; *CHF* congestive heart failure; *ARF* acute respiratory failure; *CMV* controlled mechanical ventilation; V_T tidal volume; F_r ventilator rate; V'_E minute ventilation; $PEEP_E$, $PEEPi$, $PEEP_{TOT}$ external, intrinsic and total positive end-expiratory airway pressures, respectively; F_IO_2 fractional concentration of inspired O_2; P_{peak}, P_1, P_{plat} dynamic and static end-inspiratory airway pressures; $C_{rs_{CMV}}$ static end-inspiratory respiratory system compliance, measured on CMV; R_{min}, R_{max} minimum (airways) and maximum respiratory system resistance, measured on CMV; *HR* heart rate; *MAP*, *CVP* mean arterial and central venous pressures, respectively

with PS. The strict pre-defined algorithms for ventilator and analgo-sedation management, as well as the pre-set criteria for failure, indicate that clinical decisions are unlikely to play an important role for the observed difference. Patient–ventilator asynchrony could be a factor, since considerable asynchrony was observed with PS but not with PAV+. A high incidence of asynchrony during assisted ventilation is associated with a longer duration of mechanical ventilation [25], while it may affect sleep quality, an important and often unrecognized determinant of outcome of mechanical ventilation [26, 27]. Nevertheless, further studies are needed to resolve if sleep quality and patient–ventilator asynchrony may underscore the observed difference between modes.

The end-inspiratory airway pressure, immediately after rapid airway occlusion during CMV (P_1) and the mode of support, independently predicted the occurrence of failure. P_1 at constant ventilator settings and $PEEP_{TOT}$, depends on time-constant inequalities and compliance [23]. Since ventilator settings, $PEEP_{TOT}$ and respiratory system compliance did not differ between success and failure patients, the dependency of the main outcome on P_1 indicates that time-constant inequalities may, to some extent, determine the outcome. The high incidence of gas exchange deterioration in failure patients supports this assumption, since time-constant inequalities is an important determinant of gas exchange properties of the lung [28, 29]. Finally, the stepwise logistic regression analysis suggests that, for a

Table 3 Causes of failure[a]

	PAV+	PS	*P*
Respiratory distress	8 (7.4)	10 (10.0)	0.507
Extubation failure[b]	2 (1.9)	2 (2.0)	1.00
Hypoxemia	3 (2.8)	10 (10.0)*	0.043
Hypercapnia	2 (1.9)	3 (3.0)	0.673
Hemodynamic instability[c]/arrhythmias	2 (1.9)	6 (6.0)	0.158
Acute ischemic heart event	0 (0.0)	1 (1.0)	0.481
Increased need of sedation	3 (2.8)	3 (3.0)	1.00
Inappropriate increase in sedation[d]	3 (2.8)	1 (1.0)	0.622

Values are numbers (% of randomized patients)
PAV+ proportional assist ventilation with load adjustable gain factors, *PS* pressure support
* Significantly different from PAV+ group
[a] Some patients met more than one failure criteria
[b] In all patients, re-intubation was performed within the 48-h study period. In three patients (2 in PAV+ and 1 in PS) re-intubation was performed within 1 h of extubation due to upper airway obstruction. In the remaining patient (PS group) re-intubation was performed several hours later for respiratory distress, hypoxemia and hemodynamic instability
[c] Need for norepinephrine > 0.5 μg/kg per h
[d] Protocol violation

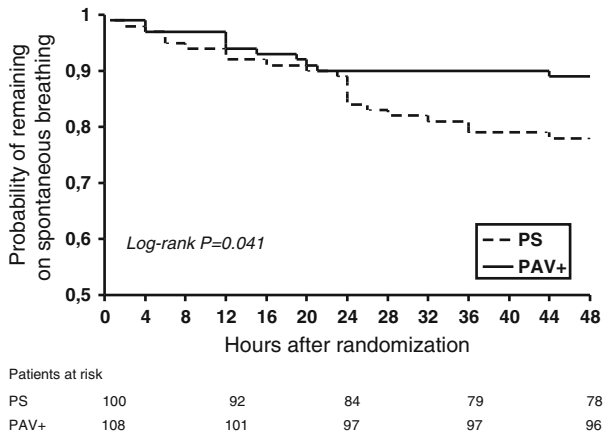

Fig. 2 Kaplan–Meier estimates of probability of remaining on spontaneous breathing (assisted or unassisted) in patients randomized to PS and PAV+. *PAV+* Proportional assist ventilation with load adjustable gain factors, *PS* pressure support

given P_1, patients randomized to PAV+ were at lower risk for failure than these randomized to PS.

The breathing pattern immediately upon switching to assisted modes differed significantly between PAV+ and PS. With PS, V_T was significantly higher and ventilator rate significantly lower than the corresponding values with PAV+. The lower ventilator rate was due to the considerable number of ineffective efforts, whereas the higher V_T to the inability of the patients to compensate for the high assist dialled initially. It follows that with PS, the breathing pattern was highly dependent on the level of assist and thus, on the caregiver. On the other hand, with PAV+ the level of assist did not significantly influence either the V_T or ventilator frequency, the patients being able to maintain the desired breathing pattern over a considerable range of assist. The inability of the patients to compensate the high PS level may cause non-synchrony with the ventilator [14], unstable breathing [19] and sleep disturbances [26].

Previous studies demonstrated that ineffective efforts are common during PS [14, 25]. Our study confirmed this and showed that PAV+ is associated with a significant decrease in the incidence of ineffective efforts. Multiple factors related to patient characteristics, depth of sedation, ventilator settings and operational ventilator principles, cause this type of asynchrony [30]. In our study, patients' characteristics, sedation management and standard ventilator settings such as $PEEP_E$ and flow threshold for triggering did not differ between modes. It follows that the ventilator operational principles between modes is the key factor for the observed difference in the incidence of patient–ventilator asynchrony [31]. With PS there is a dissociation between inspiratory effort and V_T; V_T may be adequate or excessive (if assist is high) even with very low inspiratory effort [13]. On the other hand, with PAV+ the patient retains the ability to maintain V_T constant over a wide range of assist, while there is a tight link between inspiratory effort and V_T since the patient's inspiratory effort drives the ventilator [9, 13]. With PS the observed dependency of V_T on the assist level (high V_T with high assist) and the possible uncoupling between inspiratory effort and V_T (relatively high V_T with low inspiratory effort) [13] may interfere with the triggering

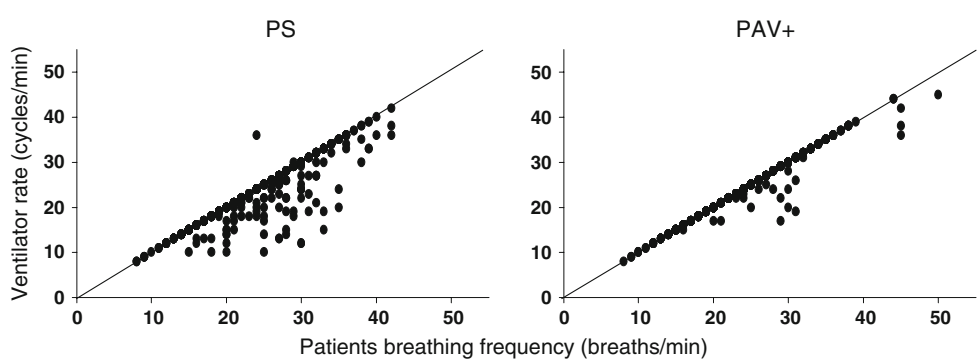

Fig. 3 Relationship between patients' breathing frequency and ventilator rate during PS and PAV+. *Solid lines* identity lines. Each *closed circle* represents a measurement at a particular time during the 48-h period. PS: 696 measurements, PAV+: 744 measurements. *PAV+* Proportional assist ventilation with load adjustable gain factors, *PS* pressure support

process and increase the risk of ineffective efforts [31]. We believe that both factors play a role in determining the difference in the incidence of ineffective efforts between modes. At initial assist the higher V_T with PS may contribute to ineffective efforts by increasing $PEEP_i$ [25, 32]. On the other hand at lower assist, since V_T and breathing frequency did not differ between modes, the PS-induced uncoupling between effort and V_T may cause ineffective efforts [33]. Expiratory asynchrony, an issue with PS but not with PAV+, could be a factor in some patients [32, 34]. However, since neither respiratory muscle activity was evaluated nor $PEEP_i$ during PS was measured, we cannot further comment on the factors that determine the occurrence of ineffective efforts. Nevertheless, contrary to PAV+ with PS, attention should be given to (1) assist level, (2) neuroventilatory coupling (V_T/inspiratory effort ratio) and (3) expiratory asynchrony if avoidance of ineffective efforts is desired. Studies have demonstrated that high assist, high V_T/inspiratory effort ratio and low flow threshold criterion for cycling off may cause ineffective efforts [11, 25, 32, 34]. We should also note that notwithstanding that recognition of major patient–ventilator asynchronies necessitates some skills [33], the achievement of synchrony may not be always feasible [32]. Indeed, in our study, although every effort was undertaken to improve patient–ventilator synchrony during PS, several patients continued to exhibit, although to a lesser extent, ineffective efforts (see Table S3 in ESM). In addition in approximately 10% of the patients new dyssynchronies (either ineffective triggering or double triggering) were identified in various occasions during the study, necessitating an action from the caregiver. It is of interest to note that the difference in the incidence of ineffective efforts between the two modes decreased during the 2nd day of the study (see Table S3). This was likely due to two reasons. First, during this period some patients with ineffective efforts failed on pressure support and were placed on controlled modes. Second, in several patients pressure support was reduced as a function of time and this reduction decreased the risk of ineffective effort [25, 32].

Theoretically, since with PAV+ the patient determines both the V_T and the ventilator pressure, overdistension due to excessive end-inspiratory alveolar pressure might be a risk, particularly at high assist and in patients with high respiratory drive not related to load per se (i.e. patients with CNS disease or with metabolic acidosis). Our study clearly showed that this is not the case. Independent of the percentage assist, airway pressure obtained 300 msec after end-inspiratory occlusion ($P_{plat_{PAV+}}$) remained below 30 cmH_2O in 98.2% of measurements and below 26 in 94%. These findings agree with earlier observations reported by Younes [35]. It is recommended that during controlled mechanical ventilation, static end-inspiratory airway pressure (P_{plat}) should be maintained at less than 30 cmH_2O to minimize the risk of ventilator-induced lung injury [36]. Furthermore, recent data have shown that in ARDS patients, P_{plat} should be less than 28 cm H_2O (and even less than 26 cmH_2O) to guarantee lung protection [37]. Therefore, patients ventilated with PAV+ even at high assist, were able to maintain a V_T that resulted in end-inspiratory alveolar pressure well below the recommended threshold. This is likely due to the presence of neural reflexes (i.e. Hering–Breuer) that inhibit inspiratory muscle activity if lung distension exceeds a certain threshold that is well below total lung capacity [38]. PAV+ does not interfere with the operation of these reflexes, since with this mode inhibition of inspiratory muscle activity results in an automatically termination of pressure delivery [9].

In four patients (3 in PAV+ and 1 in PS) an inappropriate increase in sedation resulted in depressed respiratory drive and failure on assisted modes. Although this may be considered a medical error and protocol violation, we did not exclude these patients from analysis because medical error is part of everyday practice, particularly in the critically ill patients [39]. Nevertheless, we should note that patients on PAV+ may be more vulnerable to the side effects of sedation as far as respiratory drive is concerned, since with this mode there is no guarantee either for pressure or for volume once the ventilator is triggered [9]. Particular attention should be given in patients with CNS disease in whom tight control of $PaCO_2$ is desirable.

Four limitations of the study should be acknowledged. First, this work was performed in a single center with research experience on PAV. Therefore, these results may not pertain to other ICUs. However, we believe that the algorithms used for ventilator management are self-explanatory and easily applicable. Second, PAV+ was applied for 48 h and some patients who needed ventilatory support beyond that period were placed on other modes. We chose this time period because of limited number of PAV+ ventilators in our unit. Thus, the design of this study does not permit any comment regarding weaning time between the two modes. Third, this type of study presents the difficulty for a correct blinding of the investigators that might lead to bias. Although, in order to overcome this, we predefined the criteria for all relevant interventions and clinical decisions to be made, this bias could not be entirely excluded. Fourth, major patient–ventilator asynchronies were evaluated non-invasively using the flow-time waveform. Although esophageal pressure would have ensured greater accuracy in detecting major asynchrony, this method is invasive and not practical for long-term evaluation of patient–ventilator interaction. Nevertheless studies found an excellent agreement between major asynchronies detected from flow and from esophageal pressure signals [14, 25, 32], and thus we feel confident that errors, if any, in detecting asynchronies based on flow-time waveform should be minimal and without clinical significance.

In conclusion, our study showed that PAV+ is a safe and efficient ventilator mode that may support the majority of the critically ill patients meeting criteria for assisted ventilation. Compared to PS, PAV+ increases the probability of remaining on assisted or un-assisted spontaneous breathing, while it considerably reduces the incidence of patient–ventilator asynchronies.

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