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Patient–ventilator interaction in ARDS patients with extremely low compliance undergoing ECMO: a novel approach based on diaphragm electrical activity

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Abstract *Purpose:* Patients with acute respiratory distress syndrome (ARDS) requiring extracorporeal membrane oxygenation (ECMO) usually present very low respiratory system compliance (Cst_{rs}) values (i.e., severe restrictive respiratory syndrome patients). As a consequence, they are at high risk of experiencing poor patient–ventilator interaction during assisted breathing. We hypothesized that monitoring of diaphragm electrical activity (EAdi) may enhance asynchrony assessment and that neurally adjusted ventilatory assist (NAVA) may reduce asynchrony, especially in more severely restricted patients. *Methods:* We enrolled ten consecutive ARDS patients with very low Cst_{rs} values undergoing ECMO after switching from controlled to pressure support ventilation (PSV). We randomly tested (30 min) while recording EAdi: (1) PSV30 (PSV with an expiratory trigger at 30 % of flow peak value); (2) PSV1 (PSV with expiratory trigger at 1 %); (3) NAVA. During each step, we measured the EAdi-based asynchrony index (AI_{EAdi}) = flow-, pressure- and EAdi-based asynchrony events/EAdi-based respiratory rate × 100. *Results:* AI_{EAdi} was high during all ventilation modes, and the most represented asynchrony pattern was specific for this population (i.e., premature cycling). NAVA was associated with significantly decreased, although suboptimal, AI_{EAdi} values in comparison to PSV30 and PSV1 ($p < 0.01$ for both). The PSV30–NAVA and PSV1–NAVA differences in AI_{EAdi} values were inversely correlated with patients' Cst_{rs} ($R^2 = 0.545$, $p = 0.01$ and $R^2 = 0.425$, $p < 0.05$; respectively). *Conclusions:* EAdi allows accurate analysis of asynchrony patterns and magnitude in ARDS patients with very low Cst_{rs} undergoing ECMO. In these patients, NAVA is associated with reduced asynchrony.

Keywords Mechanical ventilation · Extracorporeal membrane oxygenation (ECMO) · Acute respiratory distress syndrome (ARDS) · Diaphragm electrical activity (EAdi) · Neutrally adjusted ventilator assist (NAVA) · Asynchrony

Introduction

Extracorporeal membrane oxygenation (ECMO) ensures viable blood gases while allowing protective mechanical ventilation (MV) in patients with severe acute respiratory distress syndrome (ARDS) [1, 2]. Recent studies showed that ECMO is safe and that an ECMO-based treatment strategy may improve survival without disability [3–6].

During the first days of ECMO, controlled MV is usually implemented with tidal volumes (V_t) significantly lower than those adopted before ECMO [7]. The initial V_t reduction allowed by ECMO may be particularly beneficial in severe ARDS patients with more serious lung injury and extremely low static respiratory system compliance (Cst_{rs}) [8, 9]. After this phase, protective assisted MV may improve respiratory muscle function and gas exchange, decrease sedation and aid weaning from the ventilator [10–12]. However, Cereda et al. [13] showed that pressure support ventilation (PSV) may be difficult to implement in ARDS patients with low Cst_{rs}, likely because peak inspiratory flow is reached rapidly and the flow-based expiratory phase of PSV starts while patient is still inspiring (premature expiratory cycling). Thus, ARDS patients with low Cst_{rs} undergoing ECMO are at high risk of patient–ventilator asynchrony [14]. Asynchrony represents a serious threat, as higher asynchrony is associated with iatrogenic injury and delayed weaning from the ventilator [15–17].

Diaphragm electrical activity (EAdi) can be monitored during any assisted MV mode (e.g., during PSV) and represents a clinically reliable monitor of the respiratory center's neural activity [18]. EAdi monitoring increases accuracy in the assessment of patient–ventilator asynchrony [19], and neurally adjusted ventilatory assist (NAVA) is another assisted MV mode based on the EAdi and designed to improve synchrony [18, 20, 21]. To date, only a few pilot reports exist on the use of NAVA in severe ARDS patients undergoing ECMO, none of which systematically analyzed patient–ventilator interaction: (1) Bein et al. [22] reported the case of one severely injured soldier transported with pumpless ECMO and NAVA; (2) a study on six patients showed auto-regulation of EAdi and NAVA in the presence of reduced ECMO support [23]; (3) our group reported the successful application of NAVA in one severe ARDS patient undergoing ECMO, which generated the hypothesis of the present study [14].

In the present study, we monitored EAdi continuously while delivering NAVA and PSV, the latter at two different expiratory criteria (i.e., pre-set by the manufacturer and the one that allows the longest inspiratory time) in ARDS patients with extremely low Cst_{rs} undergoing ECMO. We evaluated asynchronies during each ventilation mode and calculated an EAdi-based asynchrony index (AI_{EAdi}). We hypothesized that: (1) EAdi monitoring would enhance asynchrony assessment; (2) NAVA would decrease patient–ventilator asynchrony; (3) the decrease in asynchrony during NAVA would be more evident in patients with lower Cst_{rs} values.

Materials and methods

Study setting

The present study was performed in a ten-bed university hospital general intensive care unit (ICU), part of the Italian ECMOnet system [24], specialized in treatment of severe ARDS patients unresponsive to conventional therapy, including the use of ECMO [25].

Study population

Between June 2010 and February 2011, we enrolled ten consecutive ARDS patients [26] with low Cst_{rs} values (as reported by the attending physician) undergoing ECMO (for patients' clinical management see the online data supplement) within 48 h after switching from controlled ventilation to PSV. Exclusion criteria were: age <18 years, hemodynamic instability and contraindications to inserting a NAVA dedicated nasogastric tube (NGT) (e.g., nasal bleeding). Informed consent was obtained from each subject or next of kin before enrollment. The Institutional Review Board approved the study.

After enrollment, all patients were connected to a mechanical ventilator that could deliver both PSV and NAVA (SERVO-i®; MAQUET GmbH & Co. KG, Rastatt, Germany). EAdi was recorded during all study phases using a dedicated NGT with an array of electrodes placed at its distal end (EAdi catheter; MAQUET GmbH & Co. KG, Rastatt, Germany). Correct EAdi catheter positioning was checked using the appropriate built-in ventilator function and following the manufacturer's instructions [18].

Data collection

Sex, age, predicted body weight, body mass index (BMI), Simplified Acute Physiology Score II (SAPS II) values [27], duration of mechanical ventilation and days on ECMO, total patient's O_2 consumption and the proportion granted by ECMO, and the Sepsis-related Organ Failure Assessment (SOFA) Score [28] and Lung Injury Score (LIS) [29] were recorded at enrollment. We also recorded in-hospital mortality.

Study protocol

We randomly applied the following assisted ventilation strategies for 30 min each: (1) PSV30: PSV with expiration cycling time set at 30 % of the flow peak value (i.e., pre-set on SERVO-i® ventilators by the manufacturer); (2) PSV1: PSV with expiration cycling time set at 1 % (i.e., the least allowed by SERVO-i® ventilators); (3) NAVA: NAVA with gain set between 0.5 and 2 $cmH_2O/\mu V$ to obtain, on average, the same V_t as during pre-study clinically set PSV and with expiratory cycling pre-set by the manufacturer at 70 % of EAdi peak value (non-modifiable). All other PSV settings were left as clinically set, because they likely indicate a thoughtful selection of

the "optimal" PSV level in each patient. Thus, during all phases, we left the following unchanged: (1) PSV level (i.e., set to obtain V_t = 3–5 ml/kg with peak inspiratory pressure below 30 cmH_2O and respiratory rate $\leq$35 breaths/min); (2) PSV and NAVA pressure- or flow-based inspiratory triggers (set at −2 cmH_2O or at 2–5 l/min); (3) PSV inspiratory rise time (set at 0.15–0.25 s); (4) NAVA EAdi-based inspiratory trigger (set at 0.5–0.8 μV: NAVA starts inspiration on a first come-first serve criteria between flow- and EAdi-based inspiratory triggers); (5) PEEP and FiO_2 levels; (6) ECMO blood and gas flows.

At the end of the study, patients were sedated, paralyzed and switched to volume assist/control ventilation in order to measure Cst_{rs} value by means of end-expiratory and end-inspiratory holds.

Data acquisition and analysis

Each ventilator was connected through its serial port to a personal computer that recorded continuous waveforms of airway pressure, flow, volume and EAdi during all study phases. After the study was completed, by offline visual inspection of airway pressure, flow, volume and EAdi waveforms recorded during the last 5 min of each phase, we calculated AI_{EAdi} as the number of flow-, pressure- and EAdi-based asynchrony events divided by patients' EAdi-based respiratory rate:

$$AI_{EAdi} = \text{number of flow -, pressure- and EAdi-based asynchrony events/number of positive EAdi deflections} \times 100.$$

We defined four different asynchrony patterns [30, 31]: (1) ineffective triggering: one positive EAdi deflection with or without airway pressure drop not followed by an assisted breath; (2) double triggering: two assisted breaths delivered during a single positive EAdi deflection; (3) auto-triggering: a mechanically delivered breath without an associated positive EAdi deflection and without airway pressure drop; (4) premature cycling: an assisted breath with expiration starting before the end of patient's effort as assessed by EAdi (i.e., before EAdi peak or right after it) and/or with biphasic expiratory flow waveform (Figs. 1, 2).

Positive EAdi deflections not related to patients' breathing efforts (e.g., heart activity) were visually recognized by standardized criteria (e.g., very low amplitude and/or very different shape in comparison to preceding and subsequent EAdi deflections) and not included in the asynchrony analysis.

From the same time period, we also calculated: the time between the onset of ventilator inspiratory flow and the beginning of the expiratory one (ventilator inspiratory time, Ti); the mean time between the beginning of each positive EAdi deflection and the onset of ventilator inspiratory flow (inspiratory delay, ID); the mean time between EAdi peak and the beginning of the expiratory flow (cycle-off time, CT). CT values were negative (i.e., early cycle-off) if the expiratory flow of the ventilator started before the EAdi peak (Fig. 1).

Right after the end of each study phase and immediately prior to the next, we also collected: ventilator settings, arterial blood gas analysis, patient's respiratory rate measured by mechanical ventilator, mean peak EAdi value ($EAdi_{peak}$), the pressure generated by the patient during the first 0.1 s of a normal inspiratory act (p0.1, a measure of patient's central respiratory drive obtained by end expiratory breath hold) [32] and hemodynamics.

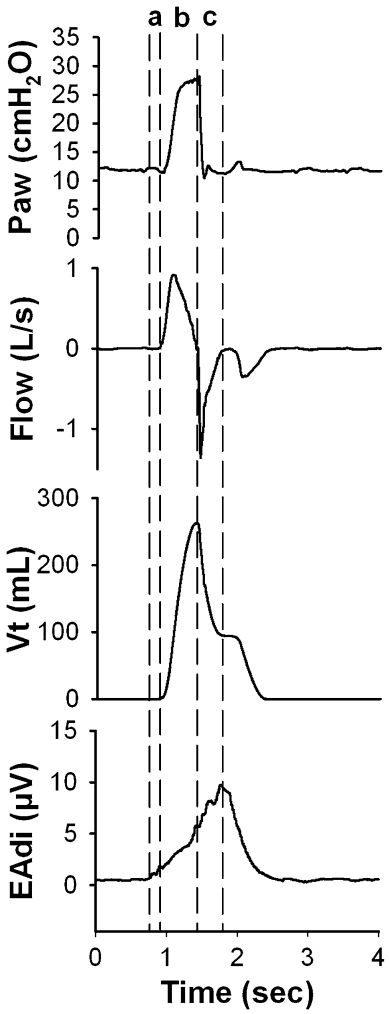

Fig. 1 Airway pressure (Paw), airway flow (Flow), tidal volume (V_t) and diaphragm electrical activity (EAdi) from one representative ARDS patient with extremely low respiratory system compliance undergoing ECMO during pressure support ventilation with expiration cycling set at 1 % of peak inspiratory flow (PSV1). The asynchrony pattern present in this breath is premature cycling (see text for details). *a* Inspiratory delay (ID); *b* ventilator inspiratory time (Ti); *c* early cycle-off time (CT)

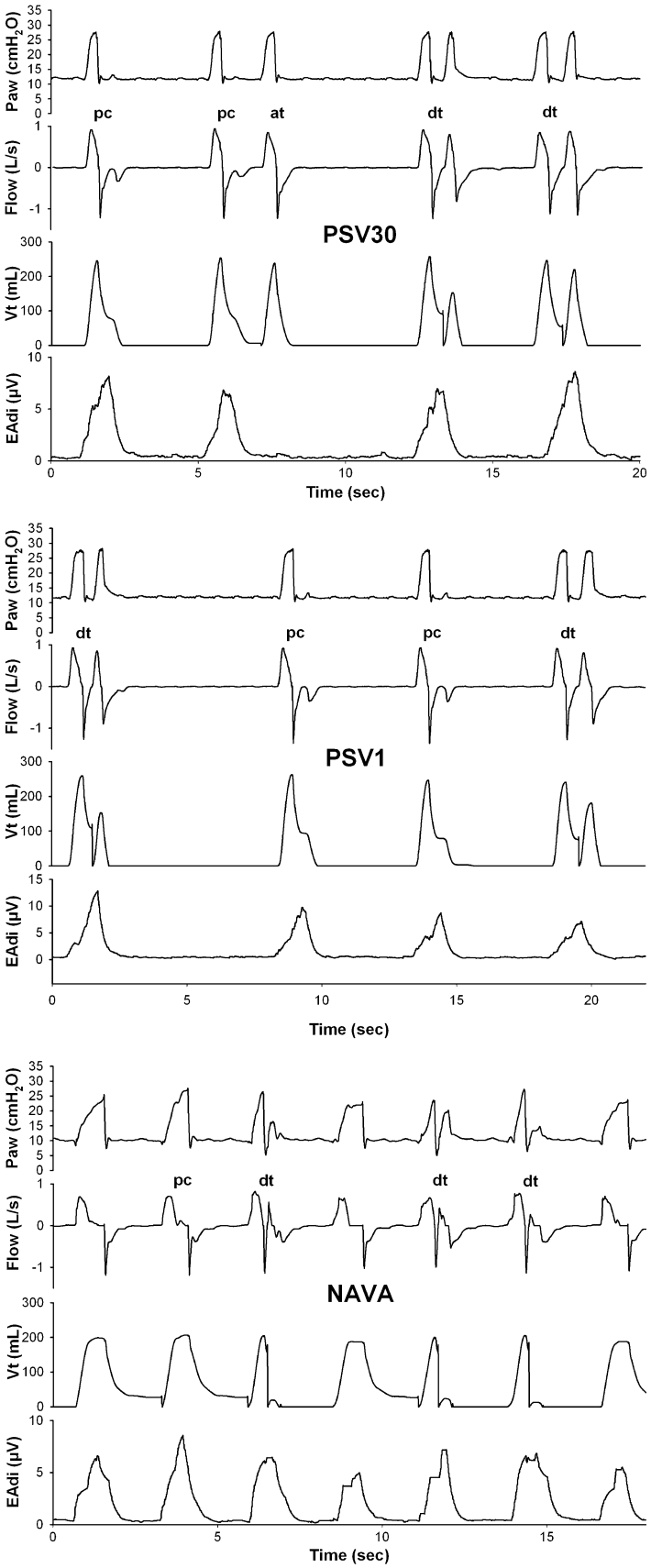

Fig. 2 Representative tracings from different ARDS patients with extremely low respiratory system compliance undergoing ECMO during different assisted mechanical ventilation modes. PSV30: clinical pressure support ventilation (PSV) with expiration cycling time set at 30 % of flow peak value; PSV1: clinical PSV with expiration cycling time set at 1 % of flow peak value; NAVA: neurally adjusted ventilatory assist (NAVA) with gain set to obtain same tidal volume as during pre-study clinical PSV (the expiration cycling time during NAVA is pre-set at 70 % of EAdi peak value). Asynchrony was high during all study phases, with presence of premature cycling (pc), double triggering (dt) and auto-triggering (at). EAdi tracings enable recognition of premature cyclings of ventilator while the patient is still inspiring. During NAVA, asynchrony decreased but remained non-optimal as premature cyclings and double triggerings were present. Interestingly, double triggering during NAVA seems to be generated by biphasic EAdi waveforms (see [21])

Statistical analysis

Our study was powered to detect a 30 ± 30 % decrease in AI between PSV30 and NAVA [14], at a level of significance of 0.05 and power of 80 %. The sample size was similar to previous studies, too [33]. To detect possible carry-over effects, variables measured during different study phases were compared by two-way analysis of variance (ANOVA) for repeated measures with study phase as within-subject and randomization sequence as between-subject factors, or (for categorical variables) chi-square or Fisher's exact test, as appropriate. If the ventilation strategy effect was statistically significant, a post hoc analysis was performed comparing the three treatments at each step (Tukey method). Association between two variables was assessed by linear regression. A level of $p < 0.05$ (two-tailed) was considered as statistically significant. Data are indicated as mean ± standard deviation, unless otherwise indicated. Statistical analyses were performed by SigmaPlot 11.0 (Systat Software Inc., San Jose, CA, USA) and IBM SPSS Statistics 19 (International Business Machines Corp., Armonk, NY, USA).

Results

Patient characteristics

Table 1 and Table E1 (online data supplement) report the main patient characteristics. The study was performed after 23 ± 17 days of MV but, at the time of the study, all patients still fulfilled ARDS criteria, LIS values were high, and Cst_{rs} was very low (18 ± 8 mL/cmH_2O). Only PaO_2/FiO_2 ratios were artificially high (245 ± 118 mmHg (Table 2) because of the increase in mixed venous oxygen content related to ECMO support. All ECMOs were veno-venous, except for one veno-arterial ECMO.

Effect of randomization sequence on studied parameters

Table E2 (online data supplement) reports the randomization sequence of different study phases for each patient. Statistical analysis did not disclose any significant interaction between randomization order and ventilation phase for any of the variables considered ($p > 0.05$ for all).

Effects of different assisted MV strategies on physiological parameters

During all study phases, patients' global physiological parameters did not change significantly (Table 2): gas exchange and hemodynamics were not affected by the implementation of PSV30, PSV1 and NAVA.

Assessment of patient–ventilator synchrony

EAdi-based analysis of asynchrony showed that ineffective triggering was the least represented pattern during PSV, while premature cycling was the most frequent (Table 3; Fig. 2). During NAVA, incidence of premature cyclings decreased, and all patterns became more equally represented (Table 3). As a consequence, high PSV-related AI_{EAdi} values significantly decreased during NAVA ($p < 0.01$, Fig. 3). Switching from PSV to NAVA, Ti was longer, ID significantly decreased, and CT

Table 1 Main characteristics of the ten severe ARDS patients undergoing ECMO enrolled in the study

Patient	Age (years)	Gender	Severe ARDS etiology	Hospital outcome	Cst_{rs} (ml/cmH_2O)	LIS	Days on MV	PSV level (cmH_2O)	NAVA gain (cmH_2O/μV)
1	20	M	Pulmonary tuberculosis	S	7	3.00	57	12	0.5
2	59	M	Acute exacerbation of idiopathic pulmonary fibrosis	NS	7	3.00	7	12	2.0
3	59	M	Post-pneumonectomy lung injury	NS	11	2.25	38	14	0.8
4	44	F	Post-pneumonectomy lung injury	NS	12	2.75	25	14	1.0
5	44	F	Pneumonia	S	24	2.50	23	10	1.0
6	41	M	Pneumonia	S	21	1.50	10	12	2.0
7	48	M	Pneumonia	NS	25	3.25	6	10	0.5
8	66	M	Pneumonia	NS	20	2.00	6	14	0.9
9	47	M	Pneumonia	S	31	3.75	30	11	0.8
10	34	F	Pneumonia	S	23	1.50	32	10	1.5
Mean ± SD	46 ± 13	7 M/3 F	–	5 S/5 NS	18 ± 8	2.55 ± 0.74	23 ± 17	12 ± 2	1.1 ± 0.6

M male, *F* female, *ARDS* acute respiratory distress syndrome, *S* survivor, *NS* non-survivor, *Cst_{rs}* static respiratory system compliance, *LIS* Lung injury score, *MV* mechanical ventilation, *PSV* pressure support ventilation, *NAVA* neutrally adjusted ventilatory assist

Table 2 Effect of different assisted MV strategies on patients' global physiologic parameters

Parameter	PSV30	PSV1	NAVA	*p* value[a]
PaO_2/FiO_2 (mmHg)	245 ± 118	244 ± 116	244 ± 117	0.83
FiO_2	0.55 ± 0.20	0.55 ± 0.20	0.55 ± 0.20	–
$PaCO_2$ (mmHg)	44.1 ± 5.5	44.6 ± 4.5	44.9 ± 4.9	0.21
pH	7.440 ± 0.039	7.433 ± 0.034	7.430 ± 0.038	0.06
HR (b/min)	101 ± 15	99 ± 14	100 ± 14	0.59
mABP (mmHg)	73 ± 13	72 ± 11	70 ± 14	0.70
CVP (mmHg)	6 ± 2	6 ± 3	6 ± 3	0.31
mPAP (mmHg)	24 ± 7	23 ± 7	24 ± 5	0.62
PAOP (mmHg)	10 ± 4	11 ± 5	10 ± 4	0.46
CO (L/min)	7.9 ± 2.2	7.6 ± 2.0	8 ± 2.4	0.53

Data are expressed as mean ± SD

PaO_2 partial oxygen arterial tension, *FiO_2* inspired O_2 fraction (we left pre-study FiO_2 levels unchanged during each phase), *$PaCO_2$* partial carbon dioxide arterial tension, *HR* heart rate, *mABP* mean arterial blood pressure, *CVP* central venous pressure, *mPAP* mean pulmonary arterial pressure, *PAOP* pulmonary arterial occlusion pressure, *CO* cardiac output, *PSV30* clinically set pressure support ventilation (PSV) with expiration cycling time set at 30 % of flow peak value, *PSV1* clinically set PSV with expiration cycling time set at 1 % of flow peak value, *NAVA* neurally adjusted ventilatory assist (NAVA) with gain set between 0.5 and 2 $cmH_2O/\mu V$ to obtain same tidal volume as during pre-study clinical PSV; the expiration cycling time during NAVA is pre-set at 70 % of the EAdi peak value

[a] Variables were compared by two-way analysis of variance (ANOVA) for repeated measures with study phase as within-subject and randomization sequence code as between-subject factors

improved ($p < 0.01$, $p < 0.05$ and $p < 0.01$; respectively, Table 3).

Determinants of asynchrony severity

AI_{EAdi} was inversely correlated, during all study phases, with Ti ($R^2 = 0.179$, $p < 0.05$) and, more closely, with CT ($R^2 = 0.548$, $p < 0.05$). ID, instead, was not correlated with asynchrony severity. The decrease in AI_{EAdi} values between PSV30 and NAVA and between PSV1 and NAVA were inversely correlated with patients' Cst_{rs} values ($R^2 = 0.545$, $p = 0.01$ and $R^2 = 0.425$, $p < 0.05$; respectively) (Fig. 4).

Effects of different assisted MV strategies on patients' respiratory variables

V_t did not change along different study phases, but P_{peak} was lower during NAVA ($p = 0.05$, Table 4). RR displayed by ventilator significantly decreased during NAVA in comparison to PSV30 and PSV1 ($p < 0.01$), but patients' EAdi-based neural RR didn't change (Table 4).

Table 3 Effects of different assisted MV strategies on patient–ventilator synchrony

Parameter	PSV30	PSV1	NAVA	*p* value[a]
ID (ms)	74 ± 27	61 ± 24	41 ± 29	0.07
CT (ms)	−218 ± 234*	−84 ± 183**	113 ± 42	<0.01
Ti (ms)	440 ± 100*	530 ± 160*	810 ± 280	<0.01
Flow/pressure/EAdi-based				
Double triggering (b/min)	5 ± 7	3 ± 6	1 ± 1	0.22
Auto triggering (b/min)	3 ± 7	3 ± 5	1 ± 1	0.90
Ineffective triggering (b/min)	0 ± 0	0 ± 1	0 ± 1	0.86
Premature cycling (b/min)	13 ± 15	8 ± 12	1 ± 2	0.11
AI_{EAdi} (%)	103 ± 61*	74 ± 43*	20 ± 13	<0.01

Data are expressed as mean ± SD

ID inspiratory delay, *CT* cycle-off time, *Ti* ventilator inspiratory time, *AI_{EAdi}*, EAdi-based AI (see text for details), *PSV30* clinically set pressure support ventilation (PSV) with expiration cycling time set at 30 % of flow peak value, *PSV1* clinically set PSV with expiration cycling time set at 1 % of flow peak value, *NAVA* neurally adjusted ventilatory assist (NAVA) with gain set between 0.5 and 2 $cmH_2O/\mu V$ to obtain same tidal volume as during pre-study clinical PSV; the expiration cycling time during NAVA is pre-set at 70 % of EAdi peak value

* $p < 0.01$ vs. NAVA (post hoc Tukey method)

** $p < 0.05$ vs. NAVA (post hoc Tukey method)

[a] Variables were compared by two-way analysis of variance (ANOVA) for repeated measures with study phase as within-subject and randomization sequence code as between-subject factors

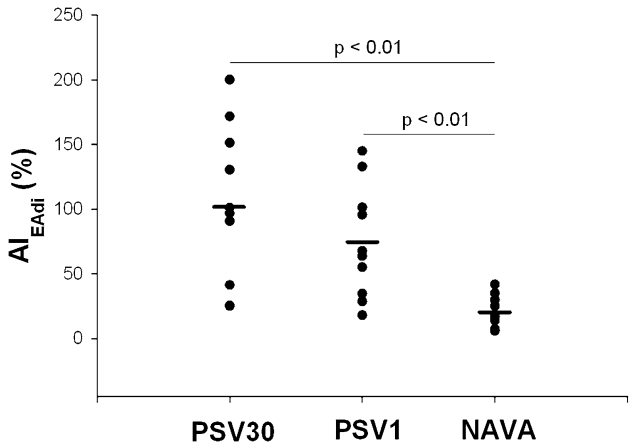

Fig. 3 EAdi-based AI (AI_{EAdi}) significantly decreased during NAVA. AI_{EAdi} = number of EAdi-based asynchrony events/number of positive EAdi deflections × 100. *Horizontal solid lines* represent mean values. *p* values refer to differences between PSV30 or PSV1 and NAVA (Tukey method)

Discussion

In the present study we described that in ARDS patients with very low Cst_{rs} undergoing ECMO: (1) short inspiratory time and low Cst_{rs} values lead to premature ventilator expiratory cycling and cause high patient–ventilator asynchrony; (2) EAdi monitoring allows specific and accurate assessment of patient–ventilator interaction; (3) NAVA is associated with improved, although still suboptimal, patient–ventilator interaction in comparison to PSV.

We assessed patient–ventilator interaction during PSV delivered by pre-set and prolonged cycle-off settings in ARDS patients with very low Cst_{rs} undergoing ECMO. Previously, Cereda et al. [13] observed a 21 % incidence of failure of PSV in ARDS patients. PSV failure is often due to poor patient–ventilator interaction that can lead to patients' discomfort, respiratory distress, barotrauma, prolonged intubation, muscular exhaustion and, possibly, increased mortality [15–17, 34]. The main reason for poor interaction during PSV is a mismatch between patient's and ventilator's inspiration and expiration, which is more likely to happen in patients with decreased Cst_{rs} values (or with increased airway resistance) [13, 14]: in Cereda's study, indeed, the presence of low Cst_{rs} was associated with PSV failure. In the present study, patients' Cst_{rs} was extremely low, and implementation of both PSV modes yielded poor results. EAdi-based measure of asynchrony, indeed, was extremely high, with premature cycling being the most represented pattern. Premature cycling, which has already been described in two different patient populations undergoing volume-controlled and non-invasive ventilation [31, 35], was the asynchrony pattern that we expected to be predominant in our population because of the PSV flow-based early expiration trigger (see "Introduction") [13]. Thus, EAdi monitoring during PSV might yield accurate and specific assessment of patient–ventilator interaction in ARDS patients with low Cst_{rs}. Still, the fact that changing PSV expiratory trigger decreased asynchrony only to a limited extent may seem in contrast with previous findings by Chiumello et al. [36]. The discrepancy between our findings and previous results may be due to the clinical characteristics of our study population: in Chiumello's paper patients' mean Crs_{st} was 61 ± 38 ml/cmH_2O as compared to 18 ± 8 ml/cmH_2O in ours (i.e., milder vs. severe restrictive ARDS patients) [36].

NAVA delivers ventilatory assist in proportion to EAdi [18]. This prompts ventilation that should more closely reflect patient's central respiratory neural output and should be less influenced by the mechanical properties of patients' respiratory system [37]. NAVA, in previous studies, reduced inspiratory and expiratory trigger mismatch, minimized wasted inspiratory efforts and reduced asynchrony in comparison to PSV [20, 21]. When we implemented NAVA in our patient population, asynchrony decreased and, as we hypothesized, the decrease was mainly due to a reduced presence of premature cyclings. In fact, NAVA's longer Ti matched patient and ventilator breathing patterns more closely. These results were even more evident in patients with the lowest Cst_{rs} and shortest Ti during PSV, who are at higher risks of developing elevated plateau pressure and ventilation injury during controlled MV and, therefore, might benefit more from switching to assisted ventilation [38]. However, asynchrony during NAVA decreased only to suboptimal values, and we tried to better analyze this finding. We observed that: (1) NAVA expiration cycling criteria in some patients are reached too early, causing premature ventilator cycling (as during PSV), but, at variance to PSV, the expiration trigger cannot be modified in NAVA mode; (2) auto-triggerings during NAVA are mainly due to unstable basal EAdi activity; (3) double triggering during NAVA happened in the presence of biphasic EAdi deflections, as already described by Piquilloud et al. [21]: the ventilator interprets the second rise as a new inspiratory effort and a new breath is delivered (Fig. 2). In conclusion, suboptimal asynchrony values obtained during NAVA are better than those obtained during PSV and might further improve with changes in ventilator pre-set algorithms.

Piquilloud et al. [21] compared the flow- and pressure-based asynchrony index during PSV and NAVA in intubated acute respiratory failure patients apparently not affected by ARDS and with Cst_{rs} values in the normality range. Piquillod's study showed that, in such patients, asynchrony significantly decreased during NAVA: thus, our data are in line with their result, albeit ours were obtained in a very peculiar and difficult to study patient population.

Our study presents a few major limitations: (1) it is a single-center crossover physiologic study, and we cannot

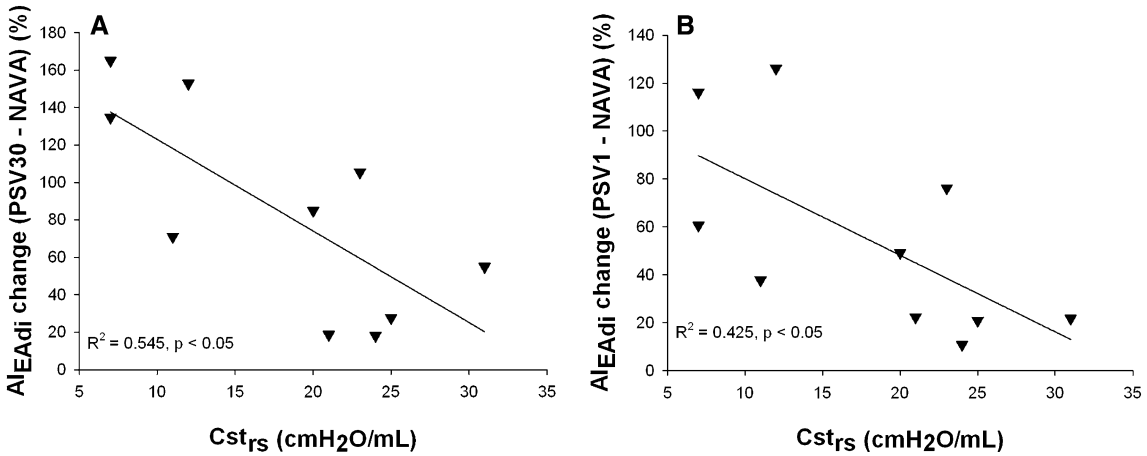

Fig. 4 Respiratory system compliance (Cst_{rs}) values were correlated with differences in EAdi-based asynchrony index (AI_{EAdi}) values between PSV30 and NAVA (**a**) and between PSV1 and NAVA (**b**). Sicker ARDS patients undergoing ECMO may benefit more from longer NAVA-associated inspiratory time

Table 4 Effects of different assisted MV strategies on patients' respiratory variables

Parameter	PSV30	PSV1	NAVA	*p* value[a]
PSV level (cmH_2O)	12 ± 2	12 ± 2	–	–
NAVA gain ($cmH_2O/\mu V$)	–	–	1.1 ± 0.6	–
V_t (ml/kg)	3.8 ± 1.1	3.9 ± 1.0	3.9 ± 1.5	0.50
P_{peak} (cmH_2O)	23 ± 4*	22 ± 4**	20 ± 5	0.05
Ventilator RR (b/min)	24 ± 6*	23 ± 8**	18 ± 5	0.01
MVe (l/min)	5.3 ± 1.2	5.1 ± 1.1	4.3 ± 1.4	0.09
p0.1 (cmH_2O)	3.0 ± 2.4	2.0 ± 1.6	1.4 ± 1.0	0.07
EAdi-based neural RR (b/min)	20 ± 7	19 ± 7	19 ± 6	0.96
$EAdi_{peak}$ (μV)	8.6 ± 6.1	8.6 ± 6.1	9.6 ± 6.7	0.37

Data are expressed as mean ± SD

V_t, tidal volume, P_{peak} peak inspiratory airway pressure, *RR* respiratory rate, *MVe* expired minute ventilation, *p0.1*, pressure drop during the first 0.1 s of inspiration with occluded airways, *EAdi* diaphragm electrical activity, *PSV30* clinically set pressure support ventilation (PSV) with expiration cycling time set at 30 % of flow peak value, *PSV1* clinically set PSV with expiration cycling time set at 1 % of flow peak value, *NAVA* neurally adjusted ventilatory assist (NAVA) with gain set between 0.5 and 2 $cmH_2O/\mu V$ to obtain same tidal volume as during pre-study clinical PSV; the expiration cycling time during NAVA is pre-set at 70 % of EAdi peak value

* $p < 0.01$ vs. NAVA (post hoc Tukey method)

** $p < 0.05$ vs. NAVA (post hoc Tukey method)

[a] Variables were compared by two-way analysis of variance (ANOVA) for repeated measures with study phase as within-subject and randomization sequence code as between-subject factors

draw definitive conclusions regarding clinical outcomes associated with asynchrony and/or NAVA use in severe ARDS patients undergoing ECMO (e.g., MV-free days). However, the analysis of patient–ventilator interaction during PSV and NAVA might give some indications on the potential clinical benefits of NAVA; (2) each study phase lasted only 30 min: this was the minimal time to obtain stable NAVA and PSV ventilation pattern based on previous data; (3) we studied PSV delivered only in two conditions, while other settings might have been changed (e.g., different inspiratory rise time or other expiratory trigger criteria). We chose PSV30 as it is the one pre-set by the manufacturer, thus likely being the one most widely adopted. PSV1, instead, was chosen to increase inspiratory time, likely to reduce asynchrony in sicker severe ARDS patients with lowest Cst_{rs} values. The attending physician chose all other settings, thus implying an optimization process before the protocol start in each patient. Leaving these settings unchanged throughout the study allowed us to focus on the correlation among Ti, Cst_{rs} and asynchrony, which was the object of this study. However, we must acknowledge that Ti could have also been modified by the application of different inspiratory rise times [36] and that the clinical choice of flow- versus pressure-based inspiratory triggers might yield, respectively, a higher incidence of auto- versus ineffective triggerings [39].

Conclusions

ARDS patients with very low Cst_{rs} values undergoing ECMO experience high asynchrony during assisted MV. EAdi monitoring enhances recognition of asynchrony severity and of specific asynchrony patterns (i.e., premature cycling). In comparison to PSV, EAdi-based NAVA ventilation reduces patient–ventilator asynchrony to suboptimal levels. Reduced asynchrony during NAVA is more relevant in sicker patients, as defined by lower Cst_{rs} values. Although preliminary, our findings seem to suggest that NAVA could be more appropriate than PSV when switching ARDS patients with very low compliance from controlled to assisted ventilation. However, adequately powered long-term studies are needed to confirm these hypotheses.

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