Prevalence and Prognosis Impact of Patient–Ventilator Asynchrony in Early Phase of Weaning according to Two Detection Methods

Camille Rolland-Debord, M.D., Côme Bureau, M.D., Tymothee Poitou, M.D., Lisa Belin, Ph.D., Marc Clavel, M.D., Sébastien Perbet, M.D., Nicolas Terzi, M.D., Ph.D., Achille Kouatchet, M.D., Thomas Similowski, M.D., Ph.D., Alexandre Demoule, M.D., Ph.D.

ABSTRACT

Background: Patient–ventilator asynchrony is associated with a poorer outcome. The prevalence and severity of asynchrony during the early phase of weaning has never been specifically described. The authors' first aim was to evaluate the prognosis impact and the factors associated with asynchrony. Their second aim was to compare the prevalence of asynchrony according to two methods of detection: a visual inspection of signals and a computerized method integrating electromyographic activity of the diaphragm.

Methods: This was an ancillary study of a multicenter, randomized controlled trial comparing neurally adjusted ventilatory assist to pressure support ventilation. Asynchrony was quantified at 12, 24, 36, and 48 h after switching from controlled ventilation to a partial mode of ventilatory assistance according to the two methods. An asynchrony index greater than or equal to 10% defined severe asynchrony.

Results: A total of 103 patients ventilated for a median duration of 5 days (interquartile range, 3 to 9 days) were included. Whatever the method used for quantification, severe patient–ventilator asynchrony was not associated with an alteration of the outcome. No factor was associated with severe asynchrony. The prevalence of asynchrony was significantly lower when the quantification was based on flow and pressure than when it was based on the electromyographic activity of the diaphragm at 0.3 min^{-1} (interquartile range, 0.2 to 0.8 min^{-1}) and 4.7 min^{-1} (interquartile range, 3.2 to 7.7 min^{-1}; $P < 0.0001$), respectively.

Conclusions: During the early phase of weaning in patients receiving a partial ventilatory mode, severe patient–ventilator asynchrony was not associated with adverse clinical outcome, although the prevalence of patient–ventilator asynchrony varies according to the definitions and methods used for detection. **(ANESTHESIOLOGY 2017; 127:989-97)**

PATIENT–VENTILATOR asynchrony is defined as a mismatch between the patient and ventilator inspiratory and expiratory times.[1,2] There is now a body of literature suggesting that patient–ventilator asynchrony during mechanical ventilation is frequent[3] and associated with increased need for sedation,[4] prolonged duration of mechanical ventilation,[5] increased need for tracheostomy,[6] and increased mortality.[7]

Most studies have quantified patient–ventilator asynchrony at heterogeneous time points[4] and during variable periods of time.[6,7] In addition, these studies were generally of a single-center type and therefore did not integrate the heterogeneity of practices in terms of mechanical

What We Already Know about This Topic

- Asynchrony between patient and ventilator is widely believed to be associated with poor outcome, but the significance of asynchrony in early ventilator weaning is unknown. In addition, the detection of asynchrony with airway pressure (or flow) patterns and electrical activity of the diaphragm have been compared in a large population.

What This Article Tells Us That Is New

- In 103 patients, asynchrony was assessed every 12 h after switching from full to partial ventilator support. Asynchrony was not associated with adverse outcome, and its incidence was less if monitoring airway pressure (and flow) patterns compared with electrical activity of the diaphragm.

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 915. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication November 3, 2016. Accepted for publication July 11, 2017. From the Intensive Care Unit and Respiratory Division (Département "R3S"), Groupe Hospitalier Pitié-Salpêtrière Charles Foix, AP-HP, 75013, Paris, France (C.R-D., C.B., T.P., T.S., A.D.) and Biostatistics, Public Health and Medical Information Department (L.B.), Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Paris, France; INSERM and UPMC, University Paris 6-Pierre et Marie Curie, UMR_S 1158, "Neurophysiologie Respiratoire Expérimentale et Clinique", Paris, France (C.R.-D., C.B., T.P., T.S., A.D.), Sorbonne Universités, University Paris 6-Pierre et Marie Curie, Paris, France (L.B.); Intensive Care Unit, CHU Limoges, 87042 Limoges Cedex, France (M.C.); Intensive Care Unit, Department of Anesthesiology, Critical Care and Perioperative Medicine, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France (S.P.); R2D2 EA-7281, Université d'Auvergne, Clermont-Ferrand, France (S.P.); CHU de Caen, Department of Intensive Care, Caen, France (N.T.); Medical ICU, Angers University Hospital, Angers, France (A.K.).

 Anesthesiology 2017; 127:989-97

<zdoi;10.1097/ALN.0000000000001886>

ventilation.[3,8,9] Finally, the detection of patient–ventilator asynchrony was mostly achieved with visual inspection of the airway flow and pressure signals.[3,4,6] The electromyographic activity of the diaphragm (EAdi), which provides a reliable insight into patient inspiratory and expiratory time and may subsequently be considered by nature as a gold standard, has rarely been used to detect asynchrony.[9–11] Altogether, these points may explain why the prevalence and consequences of patient–ventilator asynchrony vary widely across studies.[3,6–8,12,13]

To overcome these various limitations, we performed an ancillary study of a multicenter, randomized controlled trial in which patient–ventilator asynchrony was quantified homogeneously during the early phase of weaning. We chose this period specifically because it is characterized by its lability, with many clinical instabilities (state of consciousness, respiratory mechanics, gas exchange changes, and hemodynamic variations). Our first aim was to evaluate the prognosis impact and the factors associated with severe patient–ventilator asynchrony at this specific moment of the mechanical ventilation process. We decided as a precaution to use two detection methods: first, an analysis restricted to the inspection of airway flow and pressure signal and, second, a computerized method integrating EAdi as a surrogate of patient inspiratory time that may be considered by nature as a gold standard. Our second aim was therefore to compare the respective prevalence of patient–ventilator asynchrony according to the two methods of detection.

Materials and Methods

This is an ancillary study of a multicenter, randomized controlled trial that aimed to compare neurally adjusted ventilatory assist (NAVA) to pressure support ventilation (PSV) in mechanically ventilated patients in 11 intensive care units (ICUs) in France (clinical trial registration No. NCT02056093).[14] The present study focuses on secondary measures and outcomes that have not yet been published. The study protocol was approved for all of the centers by the Comité de Protection des Personnes Ile de France 6, according to French law. Written informed consent was obtained from the patients or their surrogates before inclusion in the study. A detailed description of the study design has been published previously.[14]

Patients

Patients receiving endotracheal mechanical ventilation for more than 24 h for acute respiratory failure of respiratory cause (*de novo* hypoxemic respiratory failure, acute cardiogenic pulmonary edema, or acute-on-chronic respiratory failure) were eligible when they met the following criteria: ability to sustain PSV for at least 30 min with a total level of inspiratory pressure less than 30 cm H_2O; estimated remaining duration of mechanical ventilation greater than 48 h; level of sedation less than or equal to 4 on the Ramsay scale in the absence of a medical decision to increase the level of sedation; fraction of inspired oxygen less than or equal to 50% with a positive end-expiratory pressure less than or equal to 8 cm H_2O; and absence of administration of high-dose vasopressor therapy defined by norepinephrine greater than 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or dopamine greater than 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Exclusion criteria were age younger than 18 yr, known pregnancy, participation in another trial within the 30 days preceding the completion of the eligibility criteria, contraindication of the implementation of the esophageal tube (*i.e.*, any contraindication of the implementation of a gastric tube or of the repositioning of a tube already in place: recent gastrointestinal suture or esophageal varicose rupture with gastrointestinal bleeding within 4 days before inclusion), and decision to withhold life-sustaining treatment.

Patient Management

As soon as they were included, patients were connected to a Servo ventilator (Maquet Critical Care, Sweden) equipped with a NAVA mode. The standard nasogastric feeding tube was removed and replaced by an EAdi catheter consisting of a 16-French gastric tube equipped with electrodes. Patients were then randomly assigned to receive either PSV or NAVA. The pressure support level in the PSV group and the NAVA level were set to obtain a tidal volume of 6 to 8 ml/kg of ideal body weight. In both groups, the physician in charge set partial pressure of arterial oxygen (fraction of inspired oxygen) and positive end-expiratory pressure according to local guidelines. NAVA or PSV was continued unless the patients met predefined criteria for switching to controlled mechanical ventilation or for weaning and subsequent extubation. The investigators were not involved in any clinical decisions.

Data Collection

To quantify patient–ventilator asynchrony, airway pressure, airway flow, and EAdi were recorded 12, 24, 36, and 48 h after inclusion. They were acquired for more than 20 min at 100 Hz from the ventilator connected to a computer using commercially available software (Servo-i RCR, version 3.6.2, Maquet Critical Care).

Clinical data included sex, age, Simplified Acute Physiology Score 2, Charlson score, Adaptation to the Intensive Care Environment score, duration of mechanical ventilation before inclusion, cause of acute respiratory failure, ventilator settings, respiratory measure, and blood gas at the time of randomization. Ventilator-free days, need for and duration of postextubation noninvasive mechanical ventilation, duration of mechanical ventilation from either intubation or inclusion in successful extubation (defined as extubation not followed by another intubation within 48 h), ICU and hospital length of stay, and ICU and 28-day mortality were also recorded.

Our main outcome was to evaluate the prognostic impact of patient–ventilator asynchrony. Secondary outcomes were to evaluate the factors associated with patient–ventilator asynchrony and to compare the respective prevalence of

patient–ventilator asynchrony according to the two methods of detection.

The aspects of the plan of analysis that were developed before examination of the data (*i.e.*, *a priori*) were the two methods used to qualify and quantify asynchrony, the comparison of the respective prevalence of patient–ventilator asynchrony according to the two methods of detection, the cutoff of 10% to define severe asynchrony, the risk factors and the major outcome variables analyzed to evaluate the prognosis impact, and the factors associated with patient–ventilator asynchrony.

Quantification of Patient–Ventilator Asynchrony

The following five main patterns of patient–ventilator asynchrony were quantified: (1) ineffective triggering; (2) auto triggering; (3) double triggering; (4) premature cycling; and (5) late cycling, as described in table 1. These patterns of asynchrony were quantified according to two detection methods. The first of these two detection methods, termed hereafter in the article *flow and pressure*, was based on flow and airway pressure signals only, as described previously.[3] Ineffective triggering, auto triggering, and double triggering were detected by visual inspection of the recordings. Premature and late cycling were detected using a MATLAB homemade script in which inspiratory time was compared to a moving mean inspiratory time calculated for more than 20 cycles (Matlab Release 2016a, The MathWorks, Inc., USA).[7] The second method, termed hereafter in the article, *EAdi based*, was based on the analysis of the EAdi signal in addition to the analysis of the flow and pressure signals.[10,14,15] This EAdi-based analysis was performed with the RCR software (Servo-i RCR, version 3.7.5, Maquet Critical Care).

To perform this analysis, for each patient the four 20-min recordings were eventually merged into a single 80-min recording session on which quantification was performed. The five main patterns of asynchrony were quantified offline by the same two investigators (A.D. and C.R-D.), both intensivists, and one of them an expert in the field of patient–ventilator asynchronies, who analyzed all of the breaths. The two experts categorized each analyzed breath as *asynchrony* or *no asynchrony* according to the definitions provided in table 1. A final decision was immediately made when the two readings were concordant. In case of discrepant opinions, the decision relied on consensus discussion between the experts. Each expert was blinded regarding patient data, outcome data, the results derived from the alternative method of quantification, the conclusion of the other expert, the initial ventilatory mode (either PSV or NAVA), and the time of the recording sequence (hour 12, 24, 36, or 48).

Eventually in both methods the asynchrony index (AI) was computed as the number of asynchronous breaths divided by the total number of breaths (both requested and delivered) multiplied by 100.[3] An AI of 10% or higher defined severe patient–ventilator asynchrony.[3]

Statistical Analysis

Because this is an ancillary study, no sample size could be calculated to detect a difference. The sample size was indeed determined by the parent study[14] as follows: assuming 78% of patients remain in partial ventilator support in the PSV group during the first 48 h, 58 patients per group would provide 80% power at a two-sided α level of 0.05 to detect a 17% absolute increase in the probability of continuously remaining on partial ventilator support in the NAVA group without any return to assist–control ventilation. With an estimated 10% failure of ventilator data collection, the final calculated sample size was 128 patients.

Statistical analysis was performed with SPSS (version 19, IBM Corp., USA) and GraphPad (GraphPad Software, USA). Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages). Differences between groups were assessed with the Mann–Whitney test for continuous variables and the chi-square tests for categorical variables. Fisher exact test was performed if the expected value of a group was lower than five. Agreement between observers regarding reliability to detect the presence of severe asynchrony (AI greater than or equal to 10%) was calculated with κ coefficient. Reproducibility in the measurement of the

Table 1. Definition of the Five Patterns of Patient–Ventilator Asynchrony and the Asynchrony Index according to the Method of Detection

	EAdi-based	Flow-and-Pressure
Ineffective triggering	Increases in EAdi greater than 1 μV from basal expiratory EAdi not followed by a ventilator-delivered pressurization	Airway pressure decrease or flow increase not followed by an assisted cycle
Auto triggering	A cycle delivered by the ventilator in the absence of EAdi signal	Cycle delivered by ventilator without previous airway pressure decrease
Double triggering	Aspect of two pneumatic cycles as a consequence of a biphasic EAdi signal	Two cycles separated by a very short expiratory time
Premature cycling	Duration of pressurization at least twice shorter than the patient's neural inspiratory time	Inspiratory time less than a half the mean inspiratory time
Late cycling	Duration of pressurization at least twice as long as the patient's neural inspiratory time	Inspiratory time greater than twice the mean inspiratory time
Asynchrony index	(ineffective triggering + auto triggering + double triggering + premature cycling + late cycling) ×100/(ineffective triggering + pneumatic respiratory rate) × 100	

Patterns of synchrony are quantified per minute. Asynchrony index is expressed as a percentage.
EAdi = electrical activity of the diaphragm.

prevalence of ineffective triggering, auto triggering, and double triggering was calculated with two-way mixed-effects model type A intraclass correlation coefficients using an absolute agreement definition. Because premature and late cycling were detected using a MATLAB homemade script, they were not included in the calculation of the intraclass correlation coefficient. The correlation between the AI measured according to the two methods (flow and pressure and EAdi based) was evaluated by the Spearman rank correlation coefficient. A *P* value less than 0.05 was taken to represent statistical significance.

Results

Study Population

A total of 128 patients were included; 62 had been allocated to the NAVA group and 66 to the PSV group. For technical reasons, flow and pressure and EAdi recordings failed in 9 patients of the NAVA group and in 16 patients of the PSV group. Therefore, data for the prevalence of asynchrony were available for 103 patients, 53 in the NAVA group and 50 in the PSV group. The main characteristics of the patients are indicated in table 2.

Table 2. Baseline Characteristics of the Patients

	n = 103
Men	72 (68)
Age, yr	66 (60–77)
SAPS 2	44 (35–59)
Charlson score	5 (4–6)
ATICE	16 (11–19)
Duration of mechanical ventilation prior to inclusion, days	5 (3–9)
Cause of acute respiratory failure	
De novo ARF, n (%)	62 (58)
Postoperative ARF, n (%)	21 (20)
Acute-on-chronic ARF, n (%)	19 (18)
Acute cardiogenic pulmonary edema, n (%)	5 (4)
Ventilator measurements	
PEEP, cm H_2O	6 (5–8)
PSV level, cm H_2O*	12 (10–15)
NAVA level, cm H2O/μV†	1.6 (1.2–2.3)
Respiratory measure	
Tidal volume, ml	450 (400–525)
Tidal volume, ml/kg	7.34 (6.38–8.51)
Respiratory rate, min^{-1}	24 (20–28)
Minute ventilation, l/min	11 (9–13)
Blood gases	
Pao_2/Fio_2, mmHg	226 (185–268)
$Paco_2$, mmHg	40 (34–48)
pH	7.43 (7.39–7.46)

Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages).

*PSV level is reported for the 50 patients mechanically ventilated with the PSV mode. †NAVA level is reported for the 53 patients mechanically ventilated with the NAVA mode.

ARF = acute respiratory failure; ATICE = adaptation to the intensive care environment; FiO_2 = fractional inspired oxygen tension; NAVA = neurally adjusted ventilatory assist; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation; SAPS = simplified acute physiology score.

Mean of breaths per patient during the four recording sequences was 1,716, and 185,271 breaths during 7,136 min were analyzed. Interobserver reliability of the detection of asynchrony was assessed on a sample of the first 20 patients enrolled in the study while the two observers were blinded to each other's measurements. The κ interrater reliability to detect the presence of severe asynchrony according with the flow-and-pressure method was 100% (95% CI, 100 to 100%). The intraclass correlation was 95% (95% CI, 87 to 98%) for the measurement of the prevalence of ineffective triggering, 98% (95% CI, 96 to 99%) for auto triggering, and 96% (95% CI, 93 to 98%) for double triggering. Discrepant opinion between experts needing consensus discussion was observed in 119 (0.83%) of 14,320 breaths.

Severe Patient–Ventilator Asynchrony during Early Phase of Weaning: Prognosis Impact and Factors Associated

The outcome of patients with and without severe asynchrony as quantified by the EAdi-based method is displayed in table 3. Using the EAdi-based method, severe asynchrony was not associated with alterations of major outcome variables. The outcome of patients with and without severe asynchrony using the flow-and-pressure method is displayed in the Supplemental Digital Content (table SDC1, http://links.lww.com/ALN/B539), as well as the specific association between ineffective triggering and the outcome (tables SDC2 and SDC3, http://links.lww.com/ALN/B539). Using the flow-and-pressure method, severe asynchrony was not associated with alterations of major outcome variables.

Potential factors associated with severe asynchrony (AI greater than or equal to 10%) according to the two distinct quantification methods are evaluated in table 4. Using the EAdi-based method, no factor was associated with severe asynchrony. Using the flow-and-pressure method, no factor was associated with severe asynchrony.

Prevalence of Patient–Ventilator Asynchrony

The prevalence of the five main patterns of patient–ventilator asynchrony according to the two quantification methods is displayed in figure 1. Auto triggering, double triggering, premature cycling, and late cycling were more frequently observed when quantification was performed with the EAdi-based method than with the flow-and-pressure method. By contrast, the prevalence of ineffective triggering was higher when the quantification was performed with the flow-and-pressure method than with the EAdi-based method (fig. 1). Overall, the total prevalence of asynchrony was higher when quantification was performed with the EAdi-based method than with the flow-and-pressure method (4.7 min^{-1} [3.2 to 7.7 min^{-1}] *vs.* 0.3 min^{-1} [0.2 to 0.8 min^{-1}]; $P < 0.0001$). The AI was also higher when quantification was performed with the EAdi-based method than with the flow-and-pressure method (18.5% [12.8 to 31.5%] *vs.* 1.0% [1.0 to 3.3%]; $P < 0.0001$). Among the 103 patients, 7% exhibited severe asynchrony (AI greater than or equal to 10%) when using

Table 3. Impact on Major Outcome Variables on Severe Asynchrony Using the Eadi-based Method

	AI < 10% (n = 17)	AI ≥ 10% (n = 86)	*P* Value	Difference (95%CI)
Duration of invasive MV, days	10 (7–15)	12 (8–21)	0.61	–2.00 (–7.20 to 3.20)
Duration of MV, days*	11 (8–17)	16 (11–25)	0.07	–5.50 (–10.67 to 0.33)
Days of invasive MV from randomization	5 (4–9)	4 (3–11)	0.52	1.00 (–1.87 to 3.87)
Days of MV from randomization*	7 (5–11)	8 (4–14)	0.62	–1.50 (–5.32 to 2.32)
Invasive ventilator-free days, day 7	2 (0–3)	3 (3–6)	0.38	–1.00 (–3.13 to 1.13)
Ventilator-free days, day 7*	0 (0–3)	1 (0–4)	0.79	–1.00 (–2.57 to 0.57)
Invasive ventilator-free days, day 14	9 (4–10)	10 (2–11)	0.39	–1.00 (–3.87 to 1.87)
Ventilator-free days, day 14*	5 (2–10)	5.5 (0–10)	0.83	–0.50 (–5.01 to 4.01)
Invasive ventilator-free days, day 28	22 (11–23)	24 (12–25)	0.22	–2.00 (–5.97 to 1.97)
Ventilator-free days, day 28*	19 (8–23)	19 (5–24)	0.69	0 (–4.51 to 4.51)
Days of ICU stay	16 (11–22)	19 (13–29)	0.36	–2.50 (–9.41 to 4.41)
Days of hospital stay	29 (18–37)	31 (23–40)	0.28	–2.00 (–12.87 to 8.27)
Death before ICU discharge, n (%)	2 (11.8)	15 (17.4)	0.73	NA
Death in the first 28 days, n (%)	4 (23.5)	15 (17.4)	0.51	NA
Use of postextubation NIV, n (%)	8 (47)	48 (56)	0.50	NA
Days of postextubation NIV	0 (0–4)	1 (0–5)	0.28	–1.00 (–2.77 to 0.77)
Proportion of patients with successful partial ventilator support, n (%)†	12 (71)	52 (60)	0.43	NA

Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages), as well as difference (95% CI) or difference between median (CI for difference of medians 95%).

*Data include noninvasive ventilation. †Data show the proportion of patients with successful partial ventilator support who were therefore not switched at least once to assist–control ventilation during the first 48 h after inclusion.

EAdi = electrical activity of the diaphragm; ICU = intensive care unit; MV = mechanical ventilation; NA = not applicable; NIV = noninvasive ventilation.

the flow-and-pressure method and 86% when using the EAdi-based method ($P < 0.0001$).

The concordance analysis showed a poor agreement between the two methods, which was observed in only 22 patients (21%; EAdi table, Supplemental Digital Content 4, http://links.lww.com/ALN/B539). However, in a majority of patients in whom a disagreement was observed (80 of 81), the flow-and-pressure method was underestimating the prevalence of patient ventilator asynchrony as compared to the EAdi-based method. Only one patient was classified as exhibiting severe asynchrony with the flow-and-pressure method, whereas it was not the case with the EAdi-based

Table 4. Factors Associated with Severe Asynchrony

	EAdi-based			Flow-and-Pressure		
	AI < 10% (n = 17)	AI ≥ 10% (n = 86)	*P Value*	AI < 10% (n = 96)	AI ≥ 10% (n = 7)	*P Value*
Men	11 (65)	60 (70)	0.68	67 (70)0.48	4 (57)	0.48
Age, yr	72 (63–77)	66 (60–76)	0.25	66 (57–74)	67 (60–77)	0.76
SAPS 2	43 (37–51)	44 (33–62)	0.88	38 (24–65)	44 (35–59)	0.53
Charlson score	7 (4–10)	5 (4–6)	0.07	4 (4–8)	5 (4–6)	0.82
ATICE	16 (12–19)	16 (11–19)	0.77	16 (11–19)	18 (15–20)	0.12
Duration of MV before inclusion, days	4 (3–7)	5 (3–9)	0.69	4 (2–7)	5 (3–9)	0.61
PEEP, mmHg	6 (5–8)	7 (5–8)	0.29	6 (5–8)	6 (5–8)	0.70
PSV level, cm H_2O*	12 (10–17)	12 (10–14)	0.22	12 (8–14)	12 (10–15)	0.60
NAVA level, cm $H_2O/\mu V$†	1.0 (1.0–2.0)	1.7 (1.3–2.3)	0.07	1.5(1–2)	1.6 (1.2–2.3)	0.51
Tidal volume, ml	450 (406–506)	450 (400–538)	0.98	480 (400–560)	450 (400–521)	0.74
Tidal volume, ml/kg	7.63 (6.48–8.28)	7.31 (6.15–8.53)	0.72	7.31 (6.28–8.44)	8.22 (6.53–9.33)	0.54
Respiratory rate, min^{-1}	26 (22–32)	24 (20–28)	0.07	24 (20–29)	20 (16–23)	0.78
Minute ventilation, l/min	11(10–14)	11 (8–13)	0.20	11 (9–13)	9 (8–11)	0.06
$Paco_2$, mmHg	38 (34–44)	40 (34–48)	0.73	39 (34–47)	45 (37–53)	0.09
Pao_2/Fio_2, mmHg	230 (192–257)	226 (184–271)	0.99	230 (185–268)	213 (169–226)	0.41
pH	7.43 (7.39–7.47)	7.43 (7.39–7.46)	0.67	7.43 (7.39–7.43)	7.40 (7.36–7.43)	0.13

Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages).

*PSV level is reported for the 50 patients mechanically ventilated with the PSV mode. †NAVA level is reported for the 53 patients mechanically ventilated with the NAVA mode.

ATICE = adaptation to the intensive care environment; EAdi = electrical activity of the diaphragm; MV = mechanical ventilation; NAVA = neurally adjusted ventilatory assist; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation; SAPS = simplified acute physiology score.

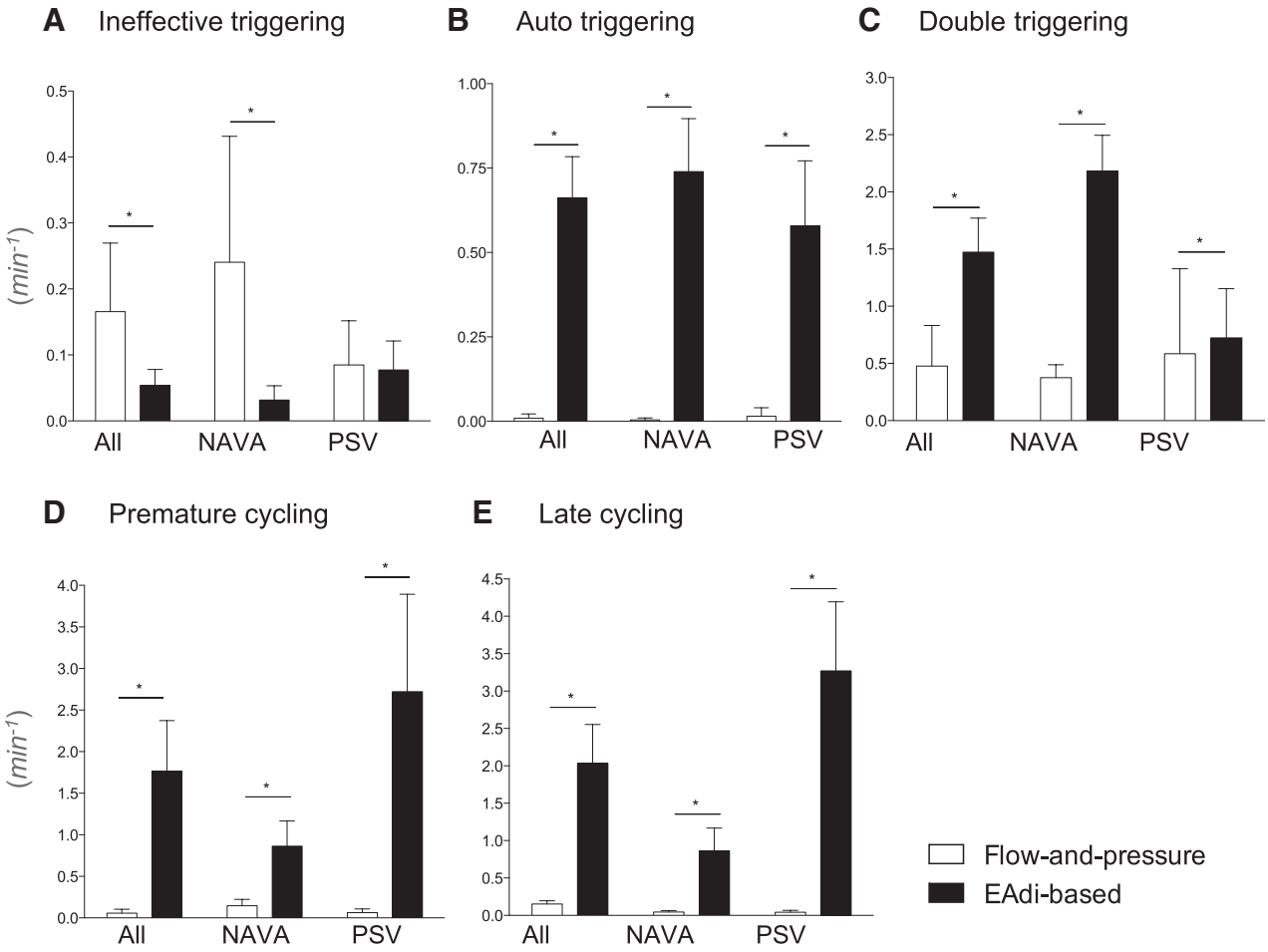

Fig. 1. Prevalence (*min*$^{-1}$) of the five patterns of patient–ventilator asynchrony according to the flow-and-pressure method (*white bar*) and the diaphragm electromyographic activity (EAdi)–based method (*black bar*) in the whole population (n = 103), in the neurally adjusted ventilatory assist (NAVA) group (n = 53), and in the pressure support ventilation (PSV) group (n = 50). Results are expressed as the mean and 95% CI. *P < 0.05.

method. In this patient of the NAVA group, the discrepancy between the two methods was mostly due to ineffective efforts not detected by the EAdi, suggesting that these efforts were probably more generated by extra diaphragmatic inspiratory muscles such as the scalene and intercostal muscles than by the diaphragm. No significant correlation was observed between the measure of the AI by the two methods (ρ = 0.14; P = 0.15).

Post hoc subgroup analyses were performed according to the randomization group (PSV or NAVA). In the NAVA subgroup, the asynchrony pattern was similar to what was observed in the whole population (fig. 1). The prevalence of asynchrony was higher with the EAdi-based method than with the flow-and-pressure method (4.5 min^{-1} [3.2 to 6.2 min^{-1}] *vs.* 0.6 min^{-1} [0.2 to 1.1 min^{-1}]; P < 0.0001). The AI was also higher with the EAdi-based method than with the flow-and-pressure method (14.7% [12.3 to 21.7%] *vs.* 2.1% [1.0 to 4.8%]; P < 0.0001). In the PSV subgroup, the prevalence of each pattern of asynchrony was higher when quantification was performed with the EAdi-based method than with the flow-and-pressure method (fig. 1). The prevalence of asynchrony was higher with the EAdi-based method than with the flow-and-pressure method (6.7 min^{-1} [3.5 to 11.6 min^{-1}] *vs.* 0.2 min^{-1} [0.1 to 0.4 min^{-1}]; P < 0.0001). The AI was also higher when quantification was performed with the EAdi-based method than with the flow-and-pressure method (26.7% [15.8 to 45.1%] *vs.* 1.0% [0.6 to 1.8%]; P < 0.0001). The prevalence of asynchrony was similar among the four 20-min recording periods (Supplemental Digital Content table 5, http://links.lww.com/ALN/B539).

Discussion

The main findings of our study can be summarized as follows: (1) whether the flow-and-pressure method or the EAdi-based method was used, severe asynchrony was not associated with alterations of major outcome variables; (2) whether the flow-and-pressure method or the EAdi-based method was used, no factor was significantly associated with severe asynchrony; (3) the total prevalence of asynchrony and the AI were higher when quantification was performed with the EAdi-based method than with the flow-and-pressure

method; and (4) the patterns of asynchrony were different whether the flow-and-pressure method or the EAdi-based method was used to qualify and quantify asynchrony. To the best of our knowledge, this is the first study to investigate, in such a large population, the risk factors and prognostic impact of severe patient–ventilator asynchrony during the early phase of weaning in patients receiving a partial ventilatory mode and to compare their prevalence using two methods of detection.

Prognosis Impact and Risk Factors of Severe Patient–Ventilator Asynchrony

Whether the flow-and-pressure method or the EAdi-based method was used, severe asynchrony in the early phase of weaning was not associated with alterations of major outcome variables. It suggests that severe patient–ventilator asynchrony is not associated with a poorer prognosis in all circumstances. This is in contrast with the previous reports that observed an association between patient–ventilator asynchrony and adverse outcome, such as duration of mechanical ventilation, requirement for tracheostomy,[3] and mortality.[7,16]

First, the prevalence of patient–ventilator asynchrony, when asynchronies were quantified using flow-and-pressure method, was low in our population and lower than in other studies, especially with the flow-and-pressure method.[3,4,6] This might be explained by the fact that most investigators and teams are deeply involved in research in the field of mechanical ventilation. In addition, half of the patients were ventilated with the NAVA mode, which is known to improve patient–ventilator interactions and to reduce patient–ventilator asynchrony.[10,15,17,18] Finally, the conditions in which the recordings were performed were likely to reduce the prevalence of some given patterns of asynchrony. Indeed, all of the patients were ventilated with a partial mode of ventilatory support, known to reduce certain types of asynchrony, such as double triggering.[3,19] In addition, none of the patients were receiving sedation anymore (see inclusion criteria), which is an important point, because deep sedation is associated with more ineffective triggering with PSV, although this is not the case with NAVA.[4,20]

Second, we quantified asynchrony during the early phase of weaning. We chose to focus specifically on this period because switching from assist–control ventilation to a partial ventilatory mode is a key step in the weaning process. However, we did not record the period during which the patient received assist–control ventilation, which is also associated with a high prevalence of asynchrony[3,19,21] and more precisely with a higher prevalence of double triggering,[19] a pattern of asynchrony that may increase tidal volume and thus expose the lung to overdistension and subsequent ventilator-induced lung injury.[19,22] The aforementioned adverse impact of asynchrony could be less pronounced in individuals who have reached the weaning phase. This may be related to the patient's condition and his ventilatory needs during assist–control ventilation, which differs greatly from those in the early phase of weaning when the patient receives a partial ventilatory mode. Specifically, asynchrony during assist–control ventilation prevents optimal ventilation by limiting muscular passivity, whereas it may have limited impact on the neuromechanical coupling in the early phase of weaning.[3,21]

Finally, by restricting the quantification of asynchrony to four 20-min recording periods rather than over the whole ICU stay, asynchrony may have occurred out of the recording periods and can therefore be ignored, as has been well evidenced recently.[7] For instance, it has been observed that ineffective triggering tends to occur in clusters, between often prolonged uneventful periods, and indexing ineffective triggering over time obviously obscures the presence of clusters. Such clusters are associated with poorer outcome and have a stronger correlation with patient outcome than sporadic ineffective triggering.[16] In the quite short duration of our recordings (20 min), our analyses did not show clusters of ineffective triggering, which does not exclude that such clusters may have occurred outside of the recording periods. However, it is worth noting that, in the present study, whether the flow-and-pressure method or the EAdi-based method was used, the prognosis of patients with ineffective triggering (who subsequently may have clusters of ineffective triggering) is similar to the prognosis of patients without ineffective triggering (who by definition have no cluster of asynchrony). During the past few years, it has been shown that patient–ventilator asynchronies are common and occur around the clock, although daytime asynchrony is significantly higher,[7,23] but the small difference between proportions potentially makes this result clinically irrelevant.[7] This is in contrast with studies evaluating asynchronies during noninvasive ventilation, where several authors have found a higher incidence of ineffective efforts and double triggering during sleep compared with wakefulness.[11,24] Variations of the level of consciousness may explain these temporal fluctuations in the severity of asynchrony.[7] However, this is less likely to happen in our population because a low level of sedation was among inclusion criteria.

Discrepancies between the Two Detection Techniques

Our results are in line with those of previous reports showing that clinicians scoring through ventilator flow-and-pressure signals fail to report up to two thirds of patient–ventilator asynchrony.[8,25] Reports that used EAdi as the gold standard[10] found twice as many patients with severe asynchrony than studies in which asynchrony was quantified using visual detection.[3] Waveform analysis of flow, pressure, and volume tracings seems therefore limited, with monitoring of EAdi providing information about synchrony.[26] In previous reports comparing the two methods, the authors observed that the pneumatic waveform analysis considerably underestimated the prevalence of asynchronies and could not reliably estimate neural inspiratory time onset and duration, which could cause problems in patient care.[8,27] They suggest

the need for additional signals reflecting patients' inspiratory effort, such as esophageal pressure, transdiaphragmatic pressure, or EAdi to facilitate recognition of these events.[8,27]

The EAdi waveform is a reliable signal to monitor the patient's neural respiratory drive[28] as well as patient–ventilator interaction.[27] The method allows for objective evaluation of patient neural breathing pattern and the ventilator performance. Differences in prevalence according to the detection methods result from several causes. First, several factors contribute to discrepancies between the indirect estimates of neural inspiratory time and the reference measurement, the EAdi waveform. These include the presence of dynamic hyperinflation, expiratory muscle activity, activity of accessory muscles of inspiration, postinspiratory activity of inspiratory muscles, and rib cage distortion and diaphragmatic morphometry.[27,28] Second, auto triggering is a very difficult asynchrony to detect with visual inspection because there is no true patient reference to validate the ventilator triggering.[3,26] Finally, the ability of the clinician to identify asynchrony by visual inspection is likely influenced by factors such as the physician's expertise and the prevalence of patient–ventilator asynchrony. ICU staff physicians were able to detect 28% of asynchronies, which was significantly higher than the 16% detection rate by ICU residents.[8] Correct detection of the asynchronous events (*i.e.*, sensitivity) varies inversely with respect to prevalence, indicating that waveform observation reduces its power to disclose asynchronies when the chance for them to occur is higher.[8]

Our results suggest that, although simpler and less invasive, the flow-and-pressure method underestimates the actual prevalence of asynchrony and alters the asynchrony pattern compared with the EAdi-based method. Because the EAdi-based method integrates a physiologic surrogate of the central respiratory drive, this method seems much more reliable, although improvement remains possible. However, our results do not suggest that EAdi should be used systematically to quantify patient–ventilator asynchrony. Nevertheless, our data are confirmatory of previous data regarding an underestimation of the prevalence of asynchrony when flow-and-pressure signals are used alone and the growing need for integration of EAdi indices in ventilatory management in ICUs.

Strengths and Limitations of the Study

The strengths of this study include the unselected character of our population of ICU patients; the multicenter design involving 11 ICUs, which enhances the generalizability of our findings; the fact that all of the patients were studied at given and comparable time points; the use of EAdi as a gold standard to measure neural inspiratory time; and the analysis of the recordings by two investigators to minimize bias. Limitations include the high expertise in mechanical ventilation of most participating centers and the fact that half of the patients were ventilated with the NAVA mode. The fact that asynchrony was quantified at four given time points rather than over the whole weaning phase is also a limitation, which we have discussed previously. Finally, the sample size was not calculated *a priori*.

Conclusions

In some circumstances, namely the very specific early phase of weaning in patients receiving a partial ventilatory mode, patient–ventilator asynchrony quantified in four 20-min recording periods is not associated with adverse clinical outcome, even when taking into account the use of two detection methods. As reported previously, the detection of asynchrony using the EAdi signal was more sensitive than when based on the flow-and-pressure recordings. At this specific moment, our prevalence of patient ventilator asynchrony may be very low and varies according to the definitions and methods used for detection.

Research Support

This study is an investigator-initiated trial that received financial support from Maquet (Orléans, France).

Competing Interests

Dr. Demoule has signed research contracts with Covidien (Dublin, Ireland), Maquet (Orléans, France), and Philips (Amsterdam, The Netherlands); he has also received personal fees from Covidien, Maquet, Resmed (San Diego, California), Fisher and Paykel (Auckland, New Zealand), and MSD (Kenilworth, New Jersey). Dr. Similowski belongs to the board of a research association that has received, over the past 10 yr, unrestricted research grants from Maquet, Hamilton (Bonaduz, Switzerland), Covidien, and Philips; he is the head of a research unit (UMRS 1158) that has signed research contracts with Air Liquide Medical Systems (Anthony, France); he declares no personal conflict of interest with mechanical ventilation firms; he has received personal fees from Lung-pacer (diaphragm pacing in the intensive care unit; Burnaby, Canada); he is listed as inventor or coinventor on several patents, granted or pending, describing a brain–ventilator interface. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Demoule: Service de Pneumologie et de Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière, 47–83 Bld de l'Hôpital, 75651 Paris cedex 13, France. alexandre.demoule@aphp.fr. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, Sinderby C: Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am J Respir Crit Care Med 2001; 164:419–24
2. Sassoon CS, Zhu E, Caiozzo VJ: Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 2004; 170:626–32
3. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L: Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006; 32:1515–22
4. de Wit M, Pedram S, Best AM, Epstein SK: Observational study of patient-ventilator asynchrony and relationship to sedation level. J Crit Care 2009; 24:74–80
5. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK: Ineffective triggering predicts increased

duration of mechanical ventilation. Crit Care Med 2009; 37:2740–5

6. Thille AW, Cabello B, Galia F, Lyazidi A, Brochard L: Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation. Intensive Care Med 2008; 34:1477–86
7. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, García-Esquirol O, Chacón E, Estruga A, Oliva JC, Hernández-Abadia A, Albaiceta GM, Fernández-Mondejar E, Fernández R, Lopez-Aguilar J, Villar J, Murias G, Kacmarek RM: Asynchronies during mechanical ventilation are associated with mortality. Intensive Care Med 2015; 41:633–41
8. Colombo D, Cammarota G, Alemani M, Carenzo L, Barra FL, Vaschetto R, Slutsky AS, Della Corte F, Navalesi P: Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. Crit Care Med 2011; 39:2452–7
9. Blanch L, Sales B, Montanya J, Lucangelo U, Garcia-Esquirol O, Villagra A, Chacon E, Estruga A, Borelli M, Burgueño MJ, Oliva JC, Fernandez R, Villar J, Kacmarek R, Murias G: Validation of the Better Care® system to detect ineffective efforts during expiration in mechanically ventilated patients: A pilot study. Intensive Care Med 2012; 38:772–80
10. Piquilloud L, Vignaux L, Bialais E, Roeseler J, Sottiaux T, Laterre PF, Jolliet P, Tassaux D: Neurally adjusted ventilatory assist improves patient-ventilator interaction. Intensive Care Med 2011; 37:263–71
11. Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille AW, Kossowsky MP, Brochard L, Jolliet P: Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: A multicenter study. Intensive Care Med 2009; 35:840–6
12. Georgopoulos D, Prinianakis G, Kondili E: Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. Intensive Care Med 2006; 32:34–47
13. Gutierrez G, Ballarino GJ, Turkan H, Abril J, De La Cruz L, Edsall C, George B, Gutierrez S, Jha V, Ahari J: Automatic detection of patient-ventilator asynchrony by spectral analysis of airway flow. Crit Care 2011; 15:R167
14. Demoule A, Clavel M, Rolland-Debord C, Perbet S, Terzi N, Kouatchet A, Wallet F, Roze H, Vargas F, Guerin C, Dellamonica J, Jaber S, Brochard L, Similowski T: Neurally adjusted ventilatory assist as an alternative to pressure support ventilation in adults: A French multicentre randomized trial. Intensive Care Med 2016; 42:1723–32
15. Schmidt M, Dres M, Raux M, Deslandes-Boutmy E, Kindler F, Mayaux J, Similowski T, Demoule A: Neurally adjusted ventilatory assist improves patient-ventilator interaction during postextubation prophylactic noninvasive ventilation. Crit Care Med 2012; 40:1738–44
16. Vaporidi K, Babalis D, Chytas A, Lilitsis E, Kondili E, Amargianitakis V, Chouvarda I, Maglaveras N, Georgopoulos D: Clusters of ineffective efforts during mechanical ventilation: Impact on outcome. Intensive Care Med 2017; 43:184–91
17. Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P: Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med 2008; 34:2010–8
18. Spahija J, de Marchie M, Albert M, Bellemare P, Delisle S, Beck J, Sinderby C: Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 2010; 38:518–26
19. Chanques G, Kress JP, Pohlman A, Patel S, Poston J, Jaber S, Hall JB: Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. Crit Care Med 2013; 41:2177–87
20. Vaschetto R, Cammarota G, Colombo D, Longhini F, Grossi F, Giovanniello A, Della Corte F, Navalesi P: Effects of propofol on patient-ventilator synchrony and interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 2014; 42:74–82
21. Schmidt M, Demoule A, Polito A, Porchet R, Aboab J, Siami S, Morelot-Panzini C, Similowski T, Sharshar T: Dyspnea in mechanically ventilated critically ill patients. Crit Care Med 2011; 39:2059–65
22. Pohlman MC, McCallister KE, Schweickert WD, Pohlman AS, Nigos CP, Krishnan JA, Charbeneau JT, Gehlbach BK, Kress JP, Hall JB: Excessive tidal volume from breath stacking during lung-protective ventilation for acute lung injury. Crit Care Med 2008; 36:3019–23
23. Alexopoulou C, Kondili E, Plataki M, Georgopoulos D: Patient-ventilator synchrony and sleep quality with proportional assist and pressure support ventilation. Intensive Care Med 2013; 39:1040–7
24. Fanfulla F, Taurino AE, Lupo ND, Trentin R, D'Ambrosio C, Nava S: Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic non-invasive mechanical ventilation. Respir Med 2007; 101:1702–7
25. Sinderby C, Liu S, Colombo D, Camarotta G, Slutsky AS, Navalesi P, Beck J: An automated and standardized neural index to quantify patient-ventilator interaction. Crit Care 2013; 17:R239
26. Sinderby C, Beck J: Proportional assist ventilation and neurally adjusted ventilatory assist–better approaches to patient ventilator synchrony? Clin Chest Med 2008; 29:329–42, vii
27. Parthasarathy S, Jubran A, Tobin MJ: Assessment of neural inspiratory time in ventilator-supported patients. Am J Respir Crit Care Med 2000; 162(2 pt 1):546–52
28. Society ATSER: ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 2002; 166: 518–624