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Asynchronies during mechanical ventilation are associated with mortality

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Take-home message: Patient–ventilator asynchronies occur frequently around the clock and in the most common modes of mechanical ventilation. A higher frequency of asynchronies is associated with higher mortality.

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Abstract Purpose: This study aimed to assess the prevalence and time course of asynchronies during mechanical ventilation (MV). **Methods:** Prospective, noninterventional observational study of 50 patients admitted to intensive care unit (ICU) beds equipped with Better Care™ software throughout MV. The software distinguished ventilatory modes and detected ineffective inspiratory efforts during expiration (IEE), double-triggering, aborted inspirations, and short and prolonged cycling to compute the asynchrony index (AI) for each hour. We analyzed 7,027 h

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of MV comprising 8,731,981 breaths. *Results:* Asynchronies were detected in all patients and in all ventilator modes. The median AI was 3.41 % [IQR 1.95–5.77]; the most common asynchrony overall and in each mode was IEE [2.38 % (IQR 1.36–3.61)]. Asynchronies were less frequent from 12 pm to 6 am [1.69 % (IQR 0.47–4.78)]. In the hours where more than 90 % of breaths were machine-

triggered, the median AI decreased, but asynchronies were still present. When we compared patients with AI > 10 vs AI ≤ 10 %, we found similar reintubation and tracheostomy rates but higher ICU and hospital mortality and a trend toward longer duration of MV in patients with an AI above the cutoff. *Conclusions:* Asynchronies are common throughout MV, occurring in all MV

modes, and more frequently during the daytime. Further studies should determine whether asynchronies are a marker for or a cause of mortality.

Keywords Patient–ventilator asynchrony · Mechanical ventilation · Mortality · Respiratory monitoring

Introduction

In critically ill patients, appropriate interaction with the mechanical ventilator is of paramount importance throughout ventilatory support. Poor patient–ventilator interaction causes discomfort and dyspnea [1–5], increases the need for sedative and paralytic agents [6–8], prolongs mechanical ventilation (MV) and intensive care unit (ICU) length of stay [9, 10], and increases the likelihood of respiratory muscle injury [11, 12] and tracheostomy [10].

To assess patient–ventilator interaction, critical care professionals need to apply their knowledge of pulmonary physiology to interpret patients’ physical signs together with flow and airway pressure waveforms. Extreme situations in which the patient “fights the ventilator” are usually easily detected and managed [13]. However, less evident manifestations of patient–ventilator asynchrony can be difficult to detect and their frequency remains unknown.

Investigations of patient–ventilator asynchronies in critically ill patients have found that asynchronies occur frequently [7, 9, 10, 14–16]. However, these studies are limited to short evaluation periods (from several minutes to 24 h), focused on patients with a specific disease, related to a particular mode of ventilation, or include patients with different levels of consciousness. Taking into account this information and the results of two clinical pilot studies examining ventilator waveforms of several thousand breaths [17, 18], we hypothesized that the prevalence of different asynchronies in MV patients is higher than previously expected, that asynchronies occur throughout MV, and that asynchronies might affect outcome. Using dedicated software [17], we conducted this prospective, observational study to assess the prevalence and time course of five types of asynchronies: ineffective inspiratory efforts during expiration (IEE), double-triggering, aborted inspirations, short cycling, and prolonged cycling. We also sought to determine if a high proportion of asynchronies is associated with poor outcome. Preliminary results of this study were reported in abstract form [19].

Materials and methods

Fifty patients were studied in a 16-bed intensive care unit (ICU) at a university hospital of Corporació Parc Taulí (Sabadell, Spain) from July 2009 to June 2010. The institutional review board approved the protocol and waived informed consent because the study was non-interventional, posed no added risk to the patient, and did not interfere with usual care. Patients were prospectively included while on MV as soon as the following criteria were met: admitted to one of the four rooms equipped with specific software and intubated with an expectation of invasive MV for more than 24 h. We excluded patients with do-not-resuscitate orders, those admitted for organ donation, less than 18 years old, pregnant patients, and those with chest tubes with suspected bronchopleural fistula. The first two exclusion criteria are related to the fact that MV could be withdrawn as a result of end of life decisions. In patients with suspected bronchopleural fistula and tidal volume loss, the performance of the software will not be accurate. In addition, there were only four ICU beds out of a total of 16 equipped with Better Care. Thus, only patients admitted to these beds could be potentially enrolled if meeting all inclusion criteria. Demographic, clinical, and outcome (duration of MV, reintubation, tracheostomy, and ICU and hospital mortality) data were retrieved from the medical records. The attending ICU team was aware of the study. All patients were managed with similar processes of care and lung-protective MV strategies throughout the study [20].

The software (Better Care™, Barcelona, Spain) captures digital output from different ventilators and associates each acquired waveform with the parameter it represents (airflow, airway pressure, or tidal volume). Signals are then tagged, converted to the digital imaging and communications in medicine (DICOM) standard, formatted, and stored in the hospital picture archiving and communication system (PACS) for analysis. The electronic supplementary material (ESM) explains how the software identifies the beginning of inspiration, the beginning of expiration, and the mode of ventilation for each breath.

The software continuously records airflow, airway pressure, and tidal volume from admission until liberation from the ventilator or death. Interruptions in the recordings due to clinical interventions, out-of-ICU transfers, technical problems, or other issues were excluded from the analysis. We used 1 h of continuous recording of airflow and airway pressure as the basic unit of analysis. Therefore, for the analyses of the different asynchronies and their prevalence related to mode of MV and hours in each mode, patients' contributions varied according to their time under MV. However, for the analysis of the impact of AI on outcome variables, data were normalized so that each patient contributed equally.

The system distinguished the following MV modes: (1) continuous positive airway pressure (CPAP); (2) volume control ventilation (VCV), including both constant and decelerated flow, referred to as "volume control" in Maquet's Servo-i ventilator and as "intermittent positive pressure ventilation" in Dräger's Evita series; (3) pressure-controlled ventilation (PCV), referred to as "pressure control" in Maquet's Servo-i and as "BiPAP assist" in Dräger's Evita 4 and XL; and (4) pressure support ventilation (PSV). Figure S1 in the ESM shows the algorithm the software used to determine the mode of MV.

Each hour was labeled as one of these four modes when more than 75 % of breaths were delivered in that mode. When no single mode was predominated in an hour (whether because a mode different from the four included in the study was used or because the mode changed during the designated hour or because the system could not detect the mode), that hour was labeled as "other modes". Hours labeled as "CPAP" and "other modes" were excluded from subsequent analyses. Inspiratory and expiratory times were computed as the running mean of 20 consecutive breaths. For each breath, the software determined whether the breath was triggered and whether an IEE, double-triggering, aborted inspiration, short cycling, prolonged cycling, or autotriggering was present. Additional details on the methods and algorithms used to detect the different asynchronies are provided in the ESM.

The presence of IEE and double-triggering was investigated in VCV, PCV, and PSV; short cycling, prolonged cycling, and autotriggering were investigated in PSV; aborted inspirations were investigated in VCV and PCV. The software computed the asynchrony index (AI) [7, 10], defined as the number of asynchronous events (IEE+double-triggering+aborted inspirations+short cycling+prolonged cycling) divided by the total number of ventilator cycles (machine or patient triggered) and IEE multiplied by 100. We defined a high incidence of asynchrony as an AI greater than 10 %, based on previous investigations [4, 7, 10].

For each hour, we computed the frequency of each type of asynchrony as a percentage of the total number of breaths registered during that hour. This approach

allowed us to compare the frequency of each asynchrony and the AI in periods (1 h) with different respiratory rates. In addition to computing the AI for all hours of MV, we also separately analyzed hours in which more than 90 % of the breaths were machine triggered excluding PSV breaths.

Categorical variables are presented as proportions. Continuous variables are reported as medians and interquartile ranges (IQR). To compare proportions, we used Pearson's Chi square or Fisher's exact test. To compare quantitative data, we used the Kruskal–Wallis test. When pairwise comparison was necessary, we used the Mann–Whitney *U* with Bonferroni correction for multiple comparisons. Linear regression analysis between asynchronies and airway pressure in PSV was used to determine regression coefficients. All tests were two-sided with $p < 0.05$ considered significant. We used IBM® SPSS® Statistics for Windows version 21 (Armonk, NY) and R for Windows version 2.15.0 (The R Foundation for Statistical Computing) for all analysis.

Results

Table S1 in the ESM reports demographic, clinical, and physiologic data. During the study period, 831 patients were admitted to our ICU. Overall ICU mortality was 26 %. Of the total of 50 patients, 14 (28 %) were ventilated with one mode, 18 (36 %) received two modes, and 18 (36 %) received three modes.

We analyzed 7,027 h, corresponding to 8,731,981 breaths and accounting for a median of 82.6 % [IQR 59.3–100] of the total time each patient received MV. Computing 1 h of ventilator waveforms sampled at 200 Hz takes a mean of 20 s with a 2009 mid-range computer (4 GB RAM, CORE 2 DUO CPU). We split the 7,027 h database into four sets, used four computers to simultaneously analyze data, and reduced the total computation time to 10 h. We excluded 1,308 h from the analysis because they were classified as "other modes" (1,159 h) or "CPAP" (149 h).

Median and interquartile ranges for respiratory rate were 17.9 breaths/min [IQR 15.6–21.1] in VCV, 22.9 breaths/min [IQR 18.7–28.5] in PCV, and 22.9 breaths/min [IQR 19.1–27.4] in PSV (PSV vs PCV $p = 0.96$; PSV vs VCV $p < 0.0001$; PCV vs VCV $p < 0.0001$). Median AI per patient during the entire course of MV was 3.41 % [IQR 1.95–5.77]. Median AI per hour differed significantly between MV modes, being 1.49 % [IQR 0.32–4.68] in VCV, 1.69 % [IQR 0.54–4.37] in PCV, and 2.15 % [IQR 0.90–4.74] in PSV ($p < 0.0001$). Median AI was not significantly different between VCV and PCV (Fig. 1). Table 1 shows the analysis of the different asynchronies in all modes. The most common asynchrony in all modes (PCV, VCV, and

PSV) was IEE (2.38 % [IQR 1.36–3.61]). IEE were more frequent in PSV than in VCV or PCV (Fig. 1). Double-triggering was more frequent in PCV and PSV compared with VCV and IEE was more frequent in PSV compared to VCV and PCV (Table 1). A positive relationship was found between AI and IEE versus airway pressure level ($R^2 = 0.073$; $p < 0.0001$ and $R^2 = 0.084$; $p < 0.0001$, respectively) during PSV.

Asynchronies occurred during the entire course of MV (Fig. 2). The prevalence of AI varied with the time of day, being 1.69 % [IQR 0.47–4.78] from 12 pm to 6 am, 2.14 % [IQR 0.69–5.51] from 6 am to 12 am, 1.97 % [IQR 0.66–5.24] from 12 am to 6 pm, and 1.90 % [IQR 0.56–5.01] from 6 pm to 12 pm. The AI was lower from 12 pm to 6 am than from 6 am to 12 am ($p < 0.0001$) and than from 12 am to 6 pm ($p = 0.0012$). Figure 3 shows the time course of AI in four representative patients. The analysis of the subgroup of hours in which more than 90 % of the breaths were machine triggered, excluding PSV breaths, found that asynchronies were still present.

We also explored the relationship between AI and length of MV, reintubation, tracheostomy, and ICU and hospital mortality by comparing patients with an AI > 10 vs AI ≤ 10 % (Table 2). Reintubation and tracheostomy rates were similar in the groups of patients above and below the cutoff. In patients with an AI above the cutoff, there was a trend toward longer duration of MV, and both ICU and hospital mortality were significantly higher than in patients below the cutoff. Figure S2 in the ESM shows the frequency distribution for AI and individual patients' outcomes.

Discussion

To our knowledge, this is the largest period of patient-ventilator monitoring analyzed to date. The major findings of this study are (1) patient-ventilator asynchronies are common and occur throughout the entire period of MV; (2) asynchronies occur around the clock; (3) asynchronies occur during machine-triggered breaths in seemingly apneic patients; (4) the AI is associated with mortality, although further studies are needed to know whether an elevated AI is an indicator of severity or constitutes a biomarker for another systemic feature that compromises the patient's well-being and perhaps survivability.

In our study, the most prevalent asynchrony overall and in every MV mode was IEE. These findings corroborate those reported by others. For example, Thille et al. [10] used 30-min recordings to show that IEE and double-triggering accounted for more than 98 % of all asynchronies and that most asynchronies occurred during the expiratory period. An AI ≥ 10 % was associated with

longer duration of MV. Similarly, de Wit et al. [9] recorded 10 min within the first 24 h of MV and found that an ineffective triggering index ≥ 10 % was an independent predictor of longer MV and ICU stay. IEE also occurred in up to 80 % of patients with chronic obstructive pulmonary disease, where the prolonged respiratory time constant caused air trapping [21–23]. In general, IEE is associated with an excess of pressure support and the presence of autoPEEP (with or without high levels of ventilator support) which is further aggravated by rapid respiratory rates, and an insensitive inspiratory trigger or an unresponsive system [2, 23–25]. We also found that AI and IEE were slightly more frequent in PSV compared with VCV or PCV and this is in contrast with other short-term studies where PSV achieved better results compared with VCV [10] or synchronized intermittent mandatory ventilation [9]. Since we studied the entire period of MV and the same patient could have been ventilated using different modes, it is difficult to establish conclusions on which mode performed better with the exception that asynchronies may occur during in the entire period of MV irrespective of the mode used. In addition we did not evaluate the specific settings during each mode. It may have been that rise time, termination criteria, and pressure support level were set more frequently inappropriately in PSV than the settings used during VCV or PCV.

Whereas Thille et al. [10] found that double-triggering was more common in VCV than in PSV, we found a higher rate of double-triggering in PSV than in VCV or PCV. A plausible explanation for this discrepancy could be related to differences in respiratory rate, ventilator settings, duration of the study period, and level of consciousness [24]. In the clinical setting, Chanques et al. [26] showed that among all interventions, switching to PSV and increasing the inspiratory time in VCV were the two factors independently associated with decrease of breath-stacking/double-triggering. These results are expected since ventilator assist in PSV continued during the diaphragm deactivation period [27]. In our study, generation of double-triggering could be attributed to the inappropriate setting of cycling-off criteria in PSV. A high flow pressure support cycling-off criterion may result in the ventilator inspiratory time being less than the patients' neuro-inspiratory time thus resulting in double-triggering. We can only speculate that this was the cause of double-triggering in PSV because we did not record the setting of cycling-off criteria. Recently, double-triggering has also been reported in the presence of reverse triggering or entrainment during VCV [28]. Entrainment is the phenomenon of a machine-triggered mechanical breath eliciting a spontaneous effort in highly sedated patients [28]. Interestingly, we found asynchronies in hours in which more than 90 % of breaths were machine triggered. This finding reinforces the idea that new forms of neuromechanical coupling (like reverse triggered

Table 1 Prevalence of different asynchronies in the different modes studied

Modes	PCV	PSV	VCV
Hours	692	2,141	2,886
Aborted inspirations	0.08 [0.000; 0.31]	–	0.06 [0.00; 0.29]
Short cycling	–	0.27 [0.06; 0.70]	–
Prolonged cycling	–	0.07 [0.00; 0.24]	–
Autotriggering	–	1.01 [0.13; 4.60]	–
Double-triggering ^{b,c}	0.11 [0.00; 0.44]	0.12 [0.00; 0.32]	0.06 [0.00; 0.29]
Ineffective inspiratory efforts during expiration ^{a,c}	0.98 [0.23; 3.32]	1.18 [0.49; 2.96]	0.91 [0.15; 3.36]
Asynchrony index ^{a,c}	1.69 [0.54; 4.37]	2.15 [0.90; 4.74]	1.49 [0.32; 4.68]

Data are expressed as medians and interquartile ranges

VCV volume control ventilation, PCV pressure-controlled ventilation, PSV pressure support ventilation

^a *p* significant PSV vs PCV

^b *p* significant VCV vs PCV

^c *p* significant VCV vs PSV

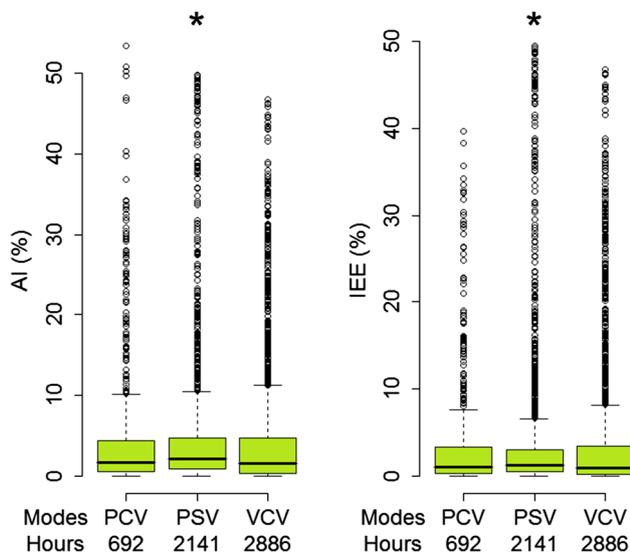


Fig. 1 Box, whiskers, and outliers (*circles*) showing the asynchrony index (AI) and proportion of inefficient expiratory efforts (IEE) during different modes of mechanical ventilation. *Left* percentage of AI in the different modes. The number of hours recorded for each mode is reported below the mode. **p* < 0.001 compared with pressure-controlled ventilation (PCV) and volume control ventilation (VCV). *Right* percentage of IEE in the different modes. **p* < 0.0001 compared with PCV and VCV. PSV pressure support ventilation

breaths) may occur frequently and could be overlooked with potentially important clinical consequences.

We found asynchronies during both day and night time hours. Although day time asynchronies were significantly higher, the small difference between proportions potentially makes this result clinically irrelevant. Alexopoulou et al. [14] examined patient–ventilator asynchrony and sleep quality in non-sedated critically ill patients ventilated with proportional assist ventilation (PAV+) and PSV. They found that PAV+ failed to improve sleep in mechanically ventilated patients despite the fact that this mode was associated with better synchrony. Interestingly,

ineffective efforts, double-triggering, and autotriggering during sleep and wakefulness were similar during PSV, although events per hour were slightly higher during wakefulness. This is in contrast with studies evaluating asynchronies during non-invasive ventilation [29] where several authors have found a higher incidence of ineffective efforts [24, 30, 31] and double-triggering during sleep compared to wakefulness. The fact that the last of these studies [24, 30, 31] only included patients with chronic pulmonary diseases that were not sedated might explain the different results between these studies and Alexopoulou et al. [14] and our study. Actually, a decreased level of consciousness, which is a predictor of ineffective triggering [7, 32], may be a common factor around the clock during invasive MV in the most severely ill.

Mechanistic links between asynchronies and outcome, though speculative, are of interest. Ineffective muscle contractions and increased workload are associated with pro-inflammatory cytokine release and muscle fiber damage [12, 33]. We found lower respiratory rates in VCV compared with other modes. Experimentally, decreased respiratory frequency could diminish the severity of ventilator-induced lung injury [34]. Although drawing parallels between animal models and clinical practice is clearly hazardous, it is conceivable that similar mechanisms could be operative in the early postintubation phase of the acute respiratory distress syndrome where the majority of patients are ventilated with VCV mode [35, 36]. Lastly, persistent asynchronies can cause dyspnea, anxiety, and air hunger, which are known factors for long-term neuropsychological alterations in ICU patients receiving MV [1, 37].

This study has several strengths. First, we used precise definitions of asynchronies. Second, all the analyses were done by computers: it would have been impossible for the human eye to examine the airway pressure and flow signals throughout MV. Third, the study was performed in an ICU with low mortality where certified intensivists manage patients 24 h a day, 7 days a week. Finally, the

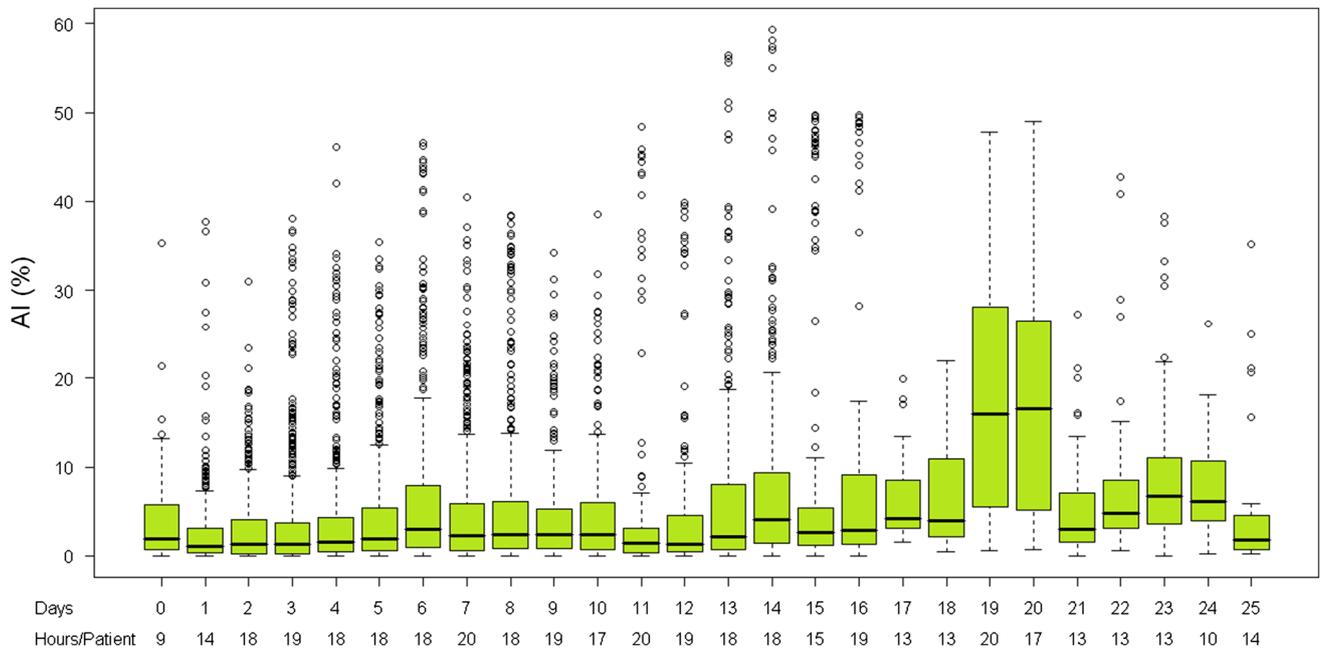


Fig. 2 Box, whiskers, and outliers (*circles*) showing the asynchrony index (AI) for all patients in 24-h periods over 25 consecutive days of mechanical ventilation. Day 0 was the day of intubation. At day 25 only two patients remained on mechanical ventilation. Hours/patient represent mean recorded hours per patient each day

Fig. 3 Asynchrony index (AI), percentage (%) per hour, continuously recorded over several days in four representative patients. Recordings show that periods of almost no asynchronies alternated with periods of high level of asynchronies

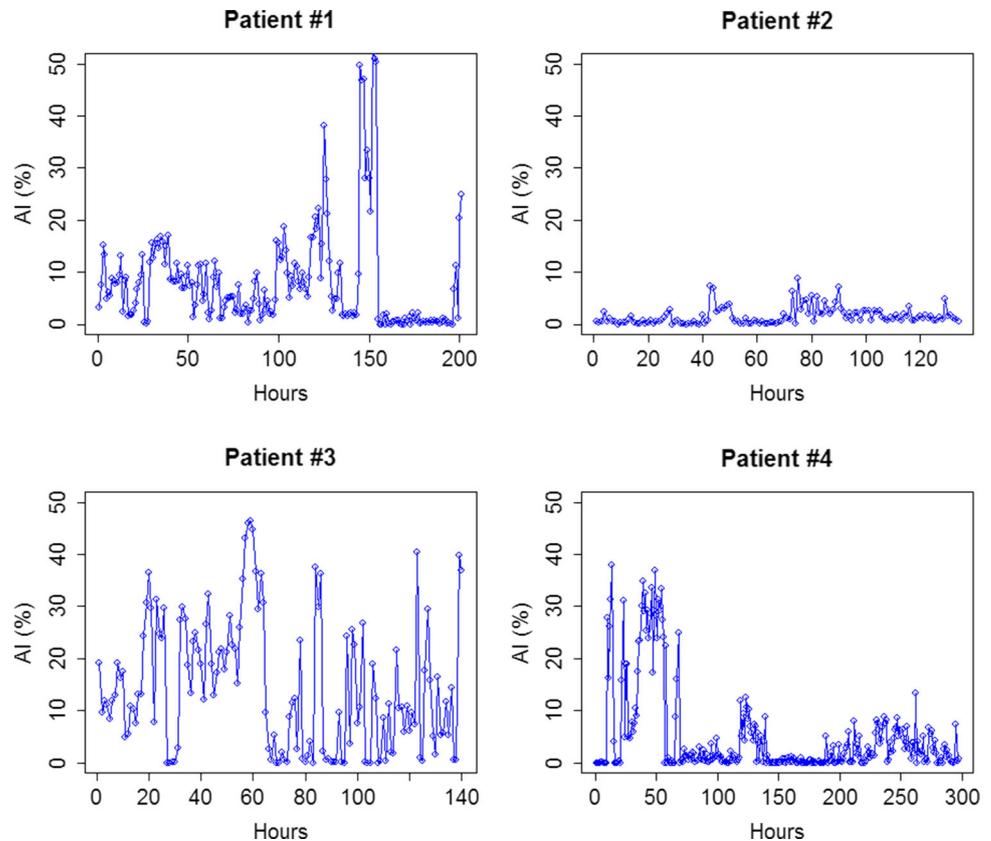


Table 2 Relationship between AI and duration of MV, reintubation, tracheostomy, and ICU and hospital mortality by comparing patients AI \leq 10 vs AI $>$ 10 %

	AI \leq 10 % ($n = 44$)	AI $>$ 10 % ($n = 6$)	p value
Length of MV (days)	6 [5.0; 15.0]	16 [9.7; 20.0]	0.061
Reintubation	9 (20 %)	0 (0 %)	0.57
Tracheostomy	14 (32 %)	2 (33 %)	0.999
ICU mortality	6 (14 %)	4 (67 %)	0.011*
Hospital mortality	10 (23 %)	4 (67 %)	0.044*

Data are expressed as numbers and percentages or as medians and interquartile ranges

MV mechanical ventilation, ICU intensive care unit, AI asynchrony index

* Significant at $p < 0.05$

study deals with a widely recognized clinical problem of unknown magnitude.

The study also has potential limitations. This was a pilot study with a limited power in 50 patients and was not designed to assess the effect of asynchrony on mortality. Moreover, the sample size was not calculated a priori because no data were available regarding the frequency of asynchronies during the entire MV period. Importantly, the study was confined to a single center and the cohort consisted of a mixed population of medical and surgical patients. As the incidence of asynchronies reflects a center's practice and expertise in ventilator settings, it might not be possible to extrapolate our results to other centers. Furthermore, unmeasured covariates such as patient factors (anxiety, dyspnea, ventilator drive, or neuromuscular status), different exposures to pain and sedative medication, and liberal selection of ventilator mode may have affected our results. Likewise, we cannot rule out the possibility that a specific MV mode, specific machine type, or specific sedation strategy contributed to patient-ventilator asynchrony. Moreover, we did not study flow delivery problems during MV; whether flow mismatch is related to asynchronies remains unknown and warrants future investigations. Furthermore, physicians and nurses were aware of the nature of the study; however, since the study was non-interventional and did not interfere with usual patient care, we assume that patients in this study received similar care to other patients in our ICU. Lastly, AI in VCV or PCV as compared to PSV could be underestimated. By definition, no asynchrony occurs during controlled ventilation in patients paralyzed or without spontaneous ventilation and asynchronies only appear after recovering spontaneous ventilation, even for reverse triggering. However, asynchronies can occur during all periods of PSV and this could explain why asynchronies were more frequent during PSV than during VCV or PCV. We also excluded hours classified as CPAP or "other modes", in other words, hours in which patients received ventilatory support in modes other than VCV, PCV, or PSV, hours in which the ventilatory mode was modified, and hours in which the system was unable to determine the ventilatory mode. Therefore, we cannot

assess the impact of asynchronies that can develop in the routine use of dual, proportional, and automated ventilation modes [38–40]. Since proportional modes could potentially lower the prevalence of asynchronies, disregarding hours in those modes might overestimate the prevalence of asynchronies. However, it could also be argued that severe asynchrony might preclude correct ventilatory mode detection.

The algorithm to detect short cycling and prolonged cycling has some limitations. In the context of alterations of respiratory mechanics, the algorithm will identify short cycling or prolonged cycling as an asynchrony only according to variations, half or double the inspiratory time (Ti) from the running mean of the previous 20 breaths. In the extreme case of alternating breaths of very short Ti together with breaths of prolonged Ti, such as in a one to one sequence, the algorithm will not detect short cycling or prolonged cycling as asynchronies. This constitutes a potential major limitation of the algorithm's performance in these circumstances.

The use of pneumatic signals provides information on asynchronies but precludes the understanding of the relative differences in timing between neural output and ventilatory activity, especially in patients with autoPEEP [41]. Although the measurement of esophageal pressure or electrical activity of the diaphragm would have ensured greater accuracy in detecting all asynchronies [42], the nature of the present study precluded the application of these techniques to all patients. Therefore, we focused on the asynchronies that can be easily identified and measured by appropriate algorithms (aborted inspirations, short cycling, prolonged cycling, double-triggering, and autotriggering; see ESM) or mathematically validated algorithms that automatically detect IEE from airflow tracings in close agreement with experts and the EAdi [17].

Conclusions

In summary, we found that patient-ventilator asynchronies occur frequently, round the clock, and in the

most common modes of MV. Further investigations would be necessary to establish a causal relationship between asynchrony and outcome. Diagnosing and correcting asynchronies should be a priority throughout MV.

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Conflicts of interest Blanch, Sales, and Murias are inventors of one Corporació Sanitaria Parc Taulí owned US patent: "Method and system for managed related patient parameters provided by a monitoring device," US Patent No. 12/538,940. Blanch, Sales, Murias, and Lucangelo own stock options of BetterCare S.L., which is a research and development spinoff of Corporació Sanitària Parc Taulí (Spain). Kacmarek is a consultant for Covidien, has received research grants from Covidien and Hollister, and has received honoraria from Maquet for lectures. Villar has received research grants from Maquet. Montanya, Villagrà, Luján, Garcia-Esquirol, Chacón, Estruga, Oliva, Hernandez Abadia, Albaiceta, Fernandez-Mondejar, López-Aguilar and Fernandez have no conflicts of interest.

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