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REVIEW

Patient-ventilator asynchrony in adult critically ill patients

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ABSTRACT

INTRODUCTION: Patient-ventilator asynchrony is considered a major clinical problem for mechanically ventilated patients. It occurs during partial ventilatory support, when the respiratory muscles and the ventilator interact to contribute generating the volume output. In this review article, we consider all studies published on patient-ventilator asynchrony in the last 25 years.

EVIDENCE ACQUISITION: We selected 62 studies. The different forms of asynchrony are first defined and classified. We also describe the methods used for detecting and quantifying asynchronies. We then outline the outcome variables considered for evaluating the clinical consequences of asynchronies. The methodology for detection and quantification of patient-ventilator asynchrony are quite heterogeneous. In particular, the Asynchrony Index is calculated differently among studies.

EVIDENCE SYNTHESIS: Sixteen studies established some relationship between asynchronies and one or more clinical outcomes, such as duration of mechanical ventilation (seven studies), mortality (five studies), length of intensive care and hospital stay (four studies), patient comfort (four studies), quality of sleep (three studies), and rate of tracheotomy (three studies). In patients with severe patient-ventilator asynchrony, four of seven studies (57%) report prolonged duration of mechanical ventilation, one of five (20%) increased mortality, one of four (25%) longer intensive care and hospital lengths of stay, four of four (100%) worsened comfort, three of four (75%) deteriorated quality of sleep, and one of three (33%) increased rate of tracheotomy.

CONCLUSIONS: Given the varying outcomes considered and the erratic results, it remains unclear whether asynchronies really affects patient outcome, and the relationship between asynchronies and outcome is causative or associative.

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KEY WORDS: Respiration, artificial; Interactive ventilatory support; Treatment outcome.

Introduction

Forms of partial ventilatory assistance are increasingly used in patients with acute respiratory failure (ARF), because they offer, compared to controlled modes, some advantages like reduced need for sedation, decreased risk of hemodynamic impairment, respiratory muscles atrophy and dysfunction. Furthermore, these modes can be applied both in invasive and noninvasive ventilation.[1] These advantages, however, may be limited by poor patient-ventilator interaction causing discomfort, agitation, increased work of breathing and worsening of gas exchange. The lack of coordination between patient effort and ventilator support may result in patient-ventilator asynchrony, which has been increasingly recognized as a major clinical problem for mechanically ventilated critically ill patients. It remains unclear, nonetheless, whether the relationship between occurrence of asynchrony and patient outcome is causative or just associative.[2]

Patient-ventilator synchrony has been reported to be impaired in up to 25% of patient undergoing invasive mechanical ventilation,[3] and in up to 80% of patients receiving non-invasive ventilation (NIV).[4] Indeed, the number of studies published on this topic has constantly increased.[2]

This review article refers to the studies published on patient-ventilator asynchronies during the last 25 years, and aims to provide definitions and classification of asynchronous events, thus describing the methods used to detect such asynchronies, and also focusing on the outcome variables, which outline the clinical consequences of asynchronies.

Evidence acquisition

Search strategy for studies selection

After launching the search strategy in Pubmed ((“1993”[Date - Publication]: “3000”[Date - Publication]) AND “patient-ventilator asynchrony”) OR “asynchrony”) OR “patient-ventilator interaction”) OR “ineffective effort”) OR “wasted effort”) OR “autotriggering”) OR “auto-triggering”) OR “double triggering”) OR “triggering delay”) OR “delayed trigger”) OR “premature cycling”) OR “anticipated cycling”) OR “prolonged cycling”) OR “delayed cycling”) and retrieving all references in the published reviews to identify other studies of interest missed during the primary search, two authors (SC and CP) independently checked all the articles and selected those enrolling adult patients in Intensive Care Unit (ICU), published between September 1st, 1993 and September 1st, 2018 in scientific journals in English language. In case of disagreement, the opinion of a third examiner (FL) was requested for conclusive decision. Case-reports, review articles, editorials and studies available only in abstract forms were excluded (Figure 1). Of the 62 studies included, 12 were multi-centered, while 50 single-centered. All studies but 7 were performed in a university hospital and 42 in European countries. Table I, II report the included studies and their characteristics, separately for invasive ventilation and NIV.[3-64]

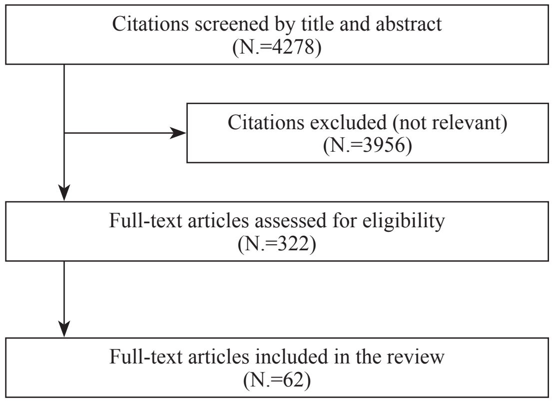

Figure 1.—Flow chart of the studies.

The 62 studies overall enrolled 1747 patients with a median [25^{th}-75^{th} IQR] of 15 [13-28] patients per study. The mean (SD) age of the patients was 63.7 (7.9) years, and the male/female ratio 1090/657.

Classification of asynchronies

Patient-ventilator asynchronies can be arbitrarily classified *a priori* as major or minor. Major asynchronies include ineffective triggering, auto-triggering, and double triggering, while minor asynchronies refer to premature (or anticipated) cycling and prolonged (or delayed) cycling.[2] Thirty-seven studies (58%) considered only major asynchronies, while the remaining 42% also minor asynchronies. Figure 2 depicts representative tracings of wasted effort, auto-triggering, double triggering, premature and delayed cycling (from left to the right). The tracings depicting ineffective triggering and premature cycling are taken from patients receiving invasive mechanical ventilation, while those indicating auto-triggering, double triggering and delayed cycling from patients in NIV. The arrows indicate major asynchronies, while the dotted lines the peak of the inspiratory efforts during minor asynchronies.

Ineffective triggering, also called ineffective or wasted efforts, were considered by 57 stud-

Table I.—*Invasive ventilation.*

Authors	Year of publication	N. of patients	Ventilation mode	Type of asynchronies
Chao *et al.*[3]	1997	174	PSV	Major
Tassaux *et al.*[5]	2005	10	PSV	Major, minor
Thille *et al.*[6]	2006	62	ACV, PSV	Major
Younes *et al.*[7]	2007	21	PAV, PSV	Major, minor
Bosma *et al.*[8]	2007	13	PSV	Major, minor
Chen *et al.*[9]	2008	14	VCV, PCV, PSV	Major
Vagheggini *et al.*[10]	2008	14	NAVA, PSV	Major
Thille *et al.*[11]	2008	12	PSV	Major
de Wit *et al.*[12]	2009	60	ACV, SIMV, PSV	Major
de Wit *et al.*[13]	2009	20	PSV	Major, minor
Terzi *et al.*[14]	2010	11	NAVA, PSV	Major
Spahija *et al.*[15]	2010	14	NAVA, PSV	Major, minor
Costa *et al.*[16]	2011	11	PAV, PSV	Major, minor
Gutierrez *et al.*[17]	2011	110	VCV, PCV, PSV	Major
Liao *et al.*[18]	2011	14	VCV, PCV, PSV	Major
Colombo *et al.*[19]	2011	24	PSV	Major
Piquilloud *et al.*[20]	2011	22	NAVA, PSV	Major, minor
Delisle *et al.*[21]	2011	14	NAVA, PSV	Major, minor
Kondili *et al.*[22]	2012	13	PAV, PSV	Major
Gogineni *et al.*[23]	2012	28	VCV, PSV	Major
Blanch *et al.*[24]	2012	16	VCV, PSV	Major
Chanques *et al.*[25]	2013	30	ACV, PSV	Major
Akoumianaki *et al.*[26]	2013	8	PCV	Minor
Robinson *et al.*[27]	2013	35	PSV, SIMV	Major, minor
Mauri *et al.*[28]	2013	10	NAVA, PSV	Major
Alexopoulou *et al.*[29]	2013	14	PSV	Major
Spieth *et al.*[30]	2013	13	PSV	Major
Vaschetto *et al.*[31]	2014	14	NAVA, PSV	Major
Mellott *et al.*[32]	2014	27	VCV, PSV	Major, minor
Doorduin *et al.*[33]	2015	12	NAVA, PCV, PSV	Major, minor
Blanch *et al.*[34]	2015	50	VCV, PCV, PSV	Major, minor
Chiew *et al.*[35]	2015	11	PCV, SIMV, PSV	Major, minor
Liu *et al.*[36]	2015	12	NAVA, VCV	Minor
Schmidt *et al.*[37]	2015	16	NAVA, PSV	Major
Messina *et al.*[38]	2015	54	PSV	Major
Yonis *et al.*[39]	2015	30	PSV	Major
Vaporidi *et al.*[40]	2016	11	PAV, PSV	Major
Carteaux *et al.*[41]	2016	11	PAV, PSV	Major
Gautam *et al.*[42]	2016	20	PAV, PSV	Major
Figueroa-Casas *et al.*[43]	2016	19	ACV, PSV	Major, minor
Conti *et al.*[44]	2016	20	PSV	Major
Demoule *et al.*[45]	2016	128	NAVA, PSV	Major, minor
Beloncle *et al.*[46]	2017	11	NAVA, PSV	Major, minor
Ferreira *et al.*[47]	2017	20	NAVA, PSV	Major, minor
Rolland-Debord *et al.*[48]	2017	103	NAVA, PSV	Major, minor
Costa *et al.*[49]	2017	13	NAVA, PSV	Major

ies (92%). This mismatch between patient spontaneous inspiration and ventilator delivered assistance is characterized by an inspiratory effort, occurring either during mechanical inspiration or expiration, not supported by the ventilator. The commonest mechanisms promoting the occurrence of wasted efforts are: 1) weak respiratory drive and/or effort, secondary to heavy sedation, or excessive inspiratory support, or diaphragm dysfunction;[65] 2) high intrinsic positive end-expiratory pressure (PEEPi); or 3) an excessively low trigger sensitivity.[6, 13, 31, 66]

Auto-triggering was considered by 45 studies (73%). This asynchrony consists in a mechanical insufflation unrelated to patient's inspiratory activity, with the ventilator triggered by changes

Table II.—*Noninvasive ventilation.*

Authors	Year of publication	N. of patients	Interface	Type of asynchronies
Mulqueeny *et al.*[50]	2007	20	Mask, helmet	Major
Vargas *et al.*[51]	2009	11	Mask, helmet	Major, minor
Vignaux *et al.*[52]	2009	60	Mask	Major, minor
Fraticelli *et al.*[53]	2009	14	Mask	Major
Vignaux *et al.*[54]	2010	65	Mask	Major, minor
Cammarota *et al.*[4]	2011	10	Helmet	Major
Piquilloud *et al.*[55]	2012	13	Mask	Major
Schmidt *et al.*[56]	2012	17	Mask	Major, minor
Bertrand *et al.*[57]	2013	13	Mask	Major, minor
Carlucci *et al.*[58]	2013	69	Mask	Major
Córdoba-Izquierdo *et al.*[59]	2013	24	Mask	Major
Doorduin *et al.*[60]	2014	12	Mask, helmet	Major
Cammarota *et al.*[61]	2016	15	Helmet	Major
Olivieri *et al.*[62]	2016	14	Helmet	Major
Longhini *et al.*[63]	2017	40	Mask, helmet	Major
Longhini *et al.*[64]	2017	14	Mask	Major

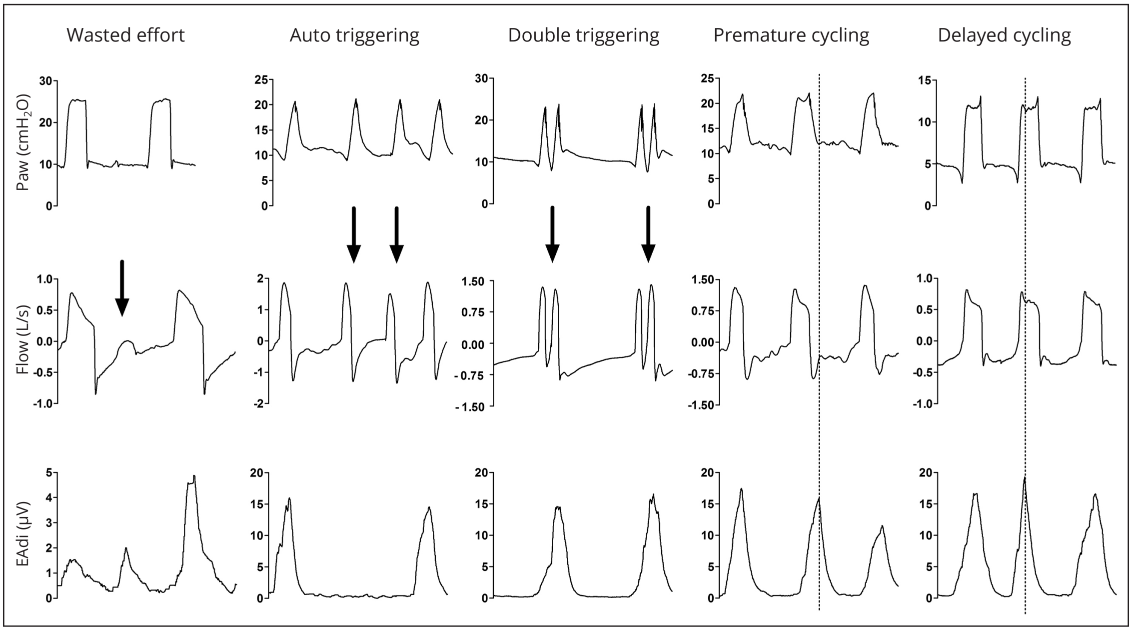

Figure 2.—Examples of the different types of asynchrony.

in airway pressure or flow produced by cardiac oscillations,[67] air-leaks,[52] condensed water in the ventilator circuit,[65] copious tracheobronchial secretions in airways.[65] High trigger sensitivity also promotes occurrence of auto-triggering.[67]

Double triggering, also known as breath-stacking in assist/control (A/C) ventilation, was inspected in 45 articles (73%). This form of altered patient-ventilator interaction, is characterized by two ventilator insufflations, separated by a very short expiratory time (*i.e.*, <30% of the mean inspiratory time), triggered by one single patient's effort. Double triggering is often associated with high respiratory drive.[6] During pressure support ventilation (PSV) it frequently occurs in patients with low respiratory system compliance,[28] and is promoted by low expiratory trigger threshold.[2] During A/C, double triggering nearly doubles the tidal volume, because of the small expiratory time between breaths.[65]

Minor asynchronies were analyzed in 25 studies (42%). Premature cycling occurs when ventilator insufflation ends before patient's effort completion. In general, premature cycling occurs in patients with low lung compliance.[28] Conversely, delayed cycling describes a condition where the end of patient's effort anticipates termination of ventilator insufflation, which then extends into neural expiration. Delayed cycling is more common in patients with high resistance and normal or high lung compliance, such as in chronic obstructive pulmonary disease (COPD) patients.[2] During NIV in PSV, delayed cycling frequently occurs because of air-leaks which prevent the ventilator from cycling from inspiration to expiration, especially in those ventilators without a dedicated software for air-leaks compensation.[68]

Recently, a study has reported a condition characterized by a patient's inspiration triggered by the ventilator insufflation.[26] This condition, considered as a respiratory entrainment, is named reverse triggered breath and is characterized by an established fixed repetitive temporal relationship between the ventilator insufflation and the neural respiratory cycle.[26]

Detection of asynchronies

The methodology for detecting patient-ventilatory asynchrony is not consistent among studies.

Clinical detection

Visual inspection of airway pressure and flow waveforms as displayed on the ventilator screen is the most common approach for recognizing asynchronies, having been used in 24 studies (39%), during both invasive ventilation and NIV. Apparently simple, this approach has been shown to be affected by low sensitivity, denoting a limited ability of ICU physicians to identify asynchronies by observing the signals displayed on the ventilator screen, during both invasive ventilation[19] and NIV.[63]

Detection by adjunctive signals

In 33 studies (53%) adjunctive signals, such as the Electrical Activity of the diaphragm (EAdi) (24 studies) or esophageal (five studies) or transdiaphragmatic pressure (four studies), have been used. EAdi signal is obtained by means of a dedicated feeding tube, mounting a distal array of multiple electrodes, and processed to provide the highest possible quality of signal throughout inspiration. EAdi, which is the closest to respiratory centers available signal for clinical assessment of the respiratory drive, provides an estimate of diaphragm effort.[69] EAdi can be obtained with only one specific ventilator that utilizes this signal for triggering on and off the mechanical breath and to adjust the support delivered throughout each breath. Esophageal and transdiaphragmatic pressure measurements greatly enhance detection of patient-ventilator asynchronies; however, they require placement of dedicated catheters and are quite complex to accomplish in routine clinical practice, which makes them to be presently considered just research tools.[2] Esophageal pressure, as determined through a balloon-tipped catheter, provides an estimate of the pleural pressure, whose variations during spontaneous breathing or partial ventilatory support reflect the effort exerted by the respiratory muscles. Transdiaphragmatic pressure is obtained by subtracting esophageal pressure from gastric pressure, which requires positioning of a second catheter, and indicates the effort exerted during inspiration by the sole diaphragm.

Detection by automatic algorithms

Five studies (8%) proposed algorithms for automatic detection of asynchronies. Chen *et al.* suggested an algorithm to detect wasted efforts during the expiratory phase, based on the analysis of flow and airway pressure waveforms.[9] In order to properly recognize ineffective efforts, the researchers reported that the optimal values for flow and airway pressure deflections were 5.45 L/min and 0.45 cmH_2O, respectively. The algorithm was characterized by good accuracy, as compared to visual assessment of esophageal pressure.[9] Blanch *et al.* tested another computerized algorithm, recognizing and quantifying ineffective efforts during expiration through waveforms analysis.[24] This software estimates the theoretical expiratory flow curve of the patients and calculates the difference between theoretical and actual flow, expressed as percent. The breath is recognized as expiratory ineffective effort when the actual flow curve deviated from the theoretical flow profile for at least 42%. Despite good performances, both these algorithms detect only wasted efforts occurring in the course of the expiratory phase.[24]

An interesting approach for improving patient-ventilator synchrony was proposed by Younes *et al.* who used the equation of motion to generate a real-time signal reflecting respiratory muscles pressure output.[7] When triggering the ventilator through this algorithm, they estimated, from the preexisting files of 21 intubated patients, a noticeable reduction of the occurrence of ineffective triggering.[7]

Mulqueeny *et al.* tested an algorithm capable to identify wasted efforts and double triggering, in 20 patients undergoing PSV, ten in invasive ventilation and ten in NIV.[50] Compared to visual inspection of transdiaphragmatic pressure tracings, this algorithm was characterized by good accuracy.[50]

Gutierrez *et al.* applied airflow spectral analysis for detecting asynchronies, based on the theory that asynchronous events are characterized by a non-organized spectral pattern.[17] The algorithm was tested and validated on 110 patients undergoing invasive mechanical ventilation. The ability to detect asynchronies was determined by comparison with visual inspection of airway pressure and flow waveforms, carried out by three trained observers with no available additional signal.[17]

Quantification of asynchronies

The index most frequently used to quantify the rate of asynchronies, for both invasive ventilation and NIV, is the Asynchrony Index (AI), proposed in 40 studies (65%). AI is the ratio between asynchronous breaths and overall breath count. Prolonged duration of mechanical ventilation,[6, 34] higher rates of weaning failure[3] and tracheotomy[6] characterize patients with AI equal to or greater than 10%. Worth mentioning, the AI is calculated differently among studies. For instance, of the 40 studies that evaluated the rate of asynchrony through this index, 26 considered only major asynchronies in the computation, while 14 also included minor asynchronies.

Five studies (8%) mention the Ineffective Triggering Index (ITI), also referred to as Ineffective Efforts Index, which is the ratio between the sole ineffective efforts and the total breath count.[13, 31]

More recently, three studies (5%) proposed the NeuroSync Index, an automated, objective and standardized method to quantify asynchronies, based on EAdi monitoring.[36, 60, 70] Values of NeuroSync Index ≥20% indicate a critically impaired patient-ventilator synchrony.

Finally, sixteen (26%) studies did not use any index to quantify the rate of asynchrony.

Effects of sedatives on patient-ventilator synchrony

Sedative and analgesic drugs may affect patient-ventilator synchrony by altering either respiratory drive and/or timing. De Wit *et al.* first reported that sedation is in general associated with the rate of ineffective triggering.[13] In 14 intubated patients, Vaschetto *et al.* found heavy sedation by propofol to significantly reduce the respiratory drive, as assessed by EAdi, with no noticeable effect on timing, which deteriorated patient-ventilator synchrony during PSV, while not in NAVA. Lower doses of Propofol, determining lighter sedation, however, had little or no effects on patient-ventilator synchrony.[31] Quite the opposite, Costa *et al.* found that incremental doses of remifentanil do not affect the respiratory drive, while progressively prolong the neural expiratory time, resulting in a parallel reduction of respiratory rate.[49] In 20 difficult-to-wean patients randomized to receive either dexmedetomidine or propofol, compared to the latter, the former resulted in slightly fewer asynchronies, without affecting either respiratory drive or timing.[44]

Outcomes

We found 16 studies evaluating a relationship between patient-ventilator asynchrony and one or more clinical outcomes (Table III).[3, 6, 8, 12, 21, 27, 29, 34, 40, 48, 52, 56, 58, 59, 61, 64] Short-

TABLE III.—*Outcomes.*

Authors	Year of publication	N. of patients	Type of asynchronies	Evaluated outcomes
Chao *et al.*[3]	1997	174	Major	Weaning success
Thille *et al.*[6]	2006	62	Major	Duration of MV, tracheostomy, mortality
Bosma *et al.*[8]	2007	13	Major, minor	Sleep quality
de Wit *et al.*[12]	2009	60	Major	Duration of MV, 28-day ventilator-free survival, reintubation, tracheostomy, ICU stay, mortality, hospital stay, home discharge
Vignaux *et al.*[52]	2009	60	Major, minor	Duration of MV, number and duration of NIV sessions, intubation, mortality, ICU stay, Hospital stay, comfort
Delisle *et al.*[21]	2011	14	Major, minor	Sleep quality
Schmidt *et al.*[56]	2012	17	Major, minor	Comfort
Carlucci *et al.*[58]	2013	69	Major	Tolerance
Robinson *et al.*[27]	2013	35	Major, minor	Duration of MV, ICU stay, hospital stay, home discharge, mortality
Alexopoulou *et al.*[29]	2013	14	Major	Sleep quality
Córdoba-Izquierdo *et al.*[59]	2013	24	Major	Sleep quality
Blanch *et al.*[34]	2015	50	Major, minor	Duration of MV, reintubation, tracheostomy, mortality
Vaporidi *et al.*[40]	2016	110	Major (IE only)	Duration of MV, mortality, ICU stay
Cammarota *et al.*[61]	2016	15	Major	Comfort
Longhini *et al.*[64]	2017	14	Major	Comfort
Rolland-Debord *et al.*[48]	2017	103	Major, minor	Duration of MV, ventilator-free days, ICU stay, hospital stay, mortality, postextubation NIV

age of randomized control trials, inconsistency among studies of the quantification of the rate of asynchrony, heterogeneity of the outcomes and paucity of enrolled patients preclude the possibility to conduct pooled data analysis. Figure 3 depicts the frequency distribution of the clinical outcomes considered in these studies.

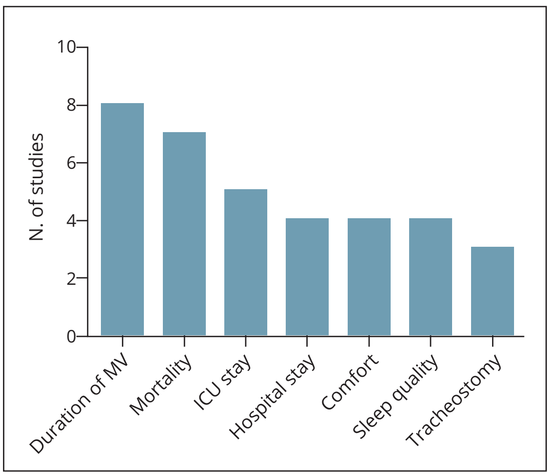

Figure 3.—Outcomes reported in the studies.
MV: mechanical ventilation; ICU: Intensive Care Unit.

Duration of mechanical ventilation

Duration of mechanical ventilation is commonly defined as the time span from intubation to successful extubation. Prolonged mechanical ventilation increases risk of infection, rate of tracheotomy, cost of care, and overall worsens patient's outcome. Some studies consider the association between patient-ventilator synchrony and duration of mechanical ventilation, reporting contrasting results.

In a population of 174 tracheostomized patients with prolonged weaning, Chao *et al.* assessed the prevalence of patient-ventilator asynchronies by detecting ineffective efforts, through visual inspection of ventilator waveforms, and, in a limited number of patients who consented esophageal pressure assessment, by means of an external monitoring device including this measurement. Nineteen (11%) of the 174 patients showed triggering asynchrony. The authors found that only three patients (16%) with asynchronies achieved successful weaning, compared to 88 patients (57%) without asynchronies.[3] Furthermore, the weaning time was more than double for patients affected by asynchronies, compared to those unaffected (72 [70-108] *vs*. 33 [3-182] days, respectively; P=0.013).[3]

Nine years later, Thille *et al.* described the clinical impact of patient-ventilator asynchrony in 62 critically ill patients undergoing invasive mechanical ventilation in PSV or A/C mode.[6] Compared to those with an AI<10%, 11 patients (18%) with an AI≥10% were characterized by longer duration of mechanical ventilation (7 [3-20] *vs*. 25 [9-42] days, respectively; P=0.005). Moreover, the rate of patients with duration of mechanical ventilation ≥7 days was 87% for AI≥10% while only 49% for AI<10% (P=0.01). The illness severity scores (SAPS-II) at ICU admission and the Sequential Organ Failure Score (SOFA) at patient enrolment were similar between the two groups.[6] Noteworthy, these authors included only major asynchronies in the AI computation.[6]

Two other studies considered only wasted efforts. In 60 patients receiving invasive mechanical ventilation, De Wit *et al.* found a high rate of ineffective efforts, as indicated by ITI≥10%, in 16 patients (27%), who showed longer duration of mechanical ventilation, as opposed to those having ITI<10%.[12] A multivariate analysis indicated that ineffective triggering was an independent predictor of prolonged mechanical ventilation duration and lower ventilator-free survival.[12] Very recently, Vaporidi *et al.* assessed in 110 patients the influence of clusters of ineffective effort, *i.e.*, 3-minute periods characterized by at least 30 wasted efforts, on some clinical outcomes, including duration of mechanically ventilation.[40] Forty-two patients (38%) presenting these clusters had an increased risk for prolonged mechanical ventilation (odds ratio 3.4, 95% confidence interval [1.1-10.7]).[40]

In contrast, three studies could not ascertain a significantly negative effect secondary to the occurrence and rate of asynchronies. In a population of 50 patients receiving invasive mechanical ventilation, Blanch *et al.* found that six patients (12%) with an AI≥10% had a non-significantly longer duration of mechanical ventilation, as opposed to 44 patients (88%) with AI<10% (16 *vs*. 6 days, respectively; P=0.061).[34] Robinson *et al.* enrolled 35 critically ill patients with traumatic injuries to investigate the impact of asynchronies on patient's clinical outcomes.[27] Nine patients (26%) who had an AI≥10% did not receive mechanical ventilation for significantly longer than those with AI<10% (7 [3-14] days *vs*. 9 [4-22] days, respectively, P=0.420).[27] In keeping with these findings, the ancillary study of a multicenter randomized controlled trial, including 103 patients, randomized to receive either NAVA or PSV, did not find significantly different duration of invasive mechanical ventilation between patients with AI≥10% and <10% (10 [7-15] *vs*. 12 [8-21] days, respectively; P=0.610).[48] The different results of these three studies could reflect on the one hand the relatively small patient sample, on the other hand the fact that these investigations included also minor asynchronies in the AI computation, which made the index less specific.

Mortality

Six studies investigated the effects of patient-ventilator asynchrony on the survival rate. The observational study by Thille *et al.* reported no difference in ICU mortality between patients with (47%) or without (32%) AI≥10% (P=0.36).[6] In keeping with these results,[6] de Wit *et al.* did not find in patients with ITI≥10%, as opposed to those with ITI<10%, any difference in ICU (25% *vs*. 14%, respectively; P=0.31) and hospital (31% *vs*. 20%, respectively; P=0.39) mortality.[12] However, patients with ITI≥10% were less likely to be discharged at home from the hospital (44% *vs*. 73%, P=0.04).[12]

Conversely, Blanch *et al.* found that patients with AI≥10% had higher rates of mortality, compared to patients with AI<10%, both in ICU (67% *vs*. 14%, respectively; P=0.011) and hospital (67% *vs*. 23%, respectively; P=0.044).[34] Vaporidi *et al.* reported hospital mortality to be significantly higher in patients with clusters of ineffective efforts, compared to those without clusters (57% *vs*. 35%, respectively; P=0.02).[40] However, they also found that the mortality rate of patients with clusters of ineffective efforts was not significantly increased, as opposed to patients not displaying these clusters (36% *vs*. 25%, respectively; P value not reported).[40] Besides, in the online supplement of the same article, they reported ICU and hospital mortality to be not significantly different between patients with and without ITI≥10%, for both ICU (46% *vs*. 27%, respectively; P=0.20), and hospital (61% *vs*. 41%, respectively; P=0.23) mortality.[40] Rolland-Debord *et al.* did not find differences between AI≥10% and <10%, with respect to both ICU (11.8% *vs*. 17.4%, P=0.73) and 28-day (23.5% *vs*. 17.4%, P=0.51) mortality.[48]

The only study assessing mortality in NIV was performed by Vignaux *et al.* who also found no difference in mortality between patients with AI≥10% and <10%.[52]

ICU and hospital lengths of stay

De Wit *et al.* reported longer median ICU and hospital lengths of stay (eight and 21 days, respectively) with an ITI≥10%, as opposed to ITI<10% (four and eight days, respectively), (P=0.01 and P=0.03, for ICU and hospital stay, respectively).[12] Conversely, Robinson *et al.* did not find any difference in ICU and hospital lengths of stay between AI≥10% (13 days and 22 days, respectively) and AI<10% (11 days and 17 days, respectively), (P=0.28 and P=0.46 for ICU and hospital stay, respectively).[27] Rolland-Debord *et al.* also found no significant differences between AI≥10% and <10%, the median ICU length of stay in patients being 19 and 16 days (P=0.36), and the hospital length of stay 31 and 29 days (P=0.28).[48] In patients receiving NIV, Vignaux *et al.* also did not find differences in ICU length of stay between the two groups.[52]

Patient comfort (during NIV)

Patient comfort is one of the most important determinants for NIV success and is influenced by several factors, such as the interface, the mode of ventilation, the ventilator performance, presence and extent of air-leaks and, last but not least, patient-ventilator synchrony. Vignaux *et al.* first reported that poor patient-ventilator synchrony worsens comfort, as assessed on a Visual Analogue Scale (5.7 *vs*. 6.5, P=0.027).[52] In another observational study including 69 acute patients receiving NIV through an oral-nasal mask, patients with AI≥10% were characterized by worsened comfort and reduced NIV tolerance, as assessed by means of a modified 4-point visual analogue scale, compared to patients with AI<10%.[58]

NAVA have been repeatedly shown to improve patient-ventilator synchrony during NIV.[4, 61, 64, 69] Schmidt *et al.* assessed with a cross-over design study patient-ventilator synchrony in four conditions combining the presence or not of a software for air-leaks compensation and two modes of ventilation (PSV and NAVA) in patients receiving postextubation prophylactic NIV through a mask.[56] Regardless of the presence of the algorithm for air-leaks compensation, NAVA improved patient-ventilator interaction and synchrony, as opposed to PSV. However, comfort was no different between trials.[56]

More recently, a new setting of defined "Neurally Controlled Pressure Support" has been proposed during NIV through helmet and mask.[61, 64] This new setting was designed in order to enhance the pressurization and triggering performance, while guarantying optimal patient-ventilator synchrony. In two populations of patients with the indication to receive prophylactic NIV to prevent postextubation respiratory failure, neurally controlled pressure support, compared to PSV, was shown to enhance pressurization and triggering performance, and improve both patient-ventilator synchrony and comfort.[61, 64]

Sleep quality

In critically ill patients, poor sleep quality is associated with increased risk of delirium, which has several negative consequences. The relationship between patient-ventilator asynchrony and sleep quality in ICU patients has been assessed by four studies.[8, 21, 29, 59]

Bosma *et al.* randomized 13 patients in the phase of weaning to receive with a cross-over design either PSV during the first night of the study followed by proportional assist ventilation (PAV) in the second one, or viceversa.[8] Compared to PSV, PAV reduced the overall count of asynchronous events per hour (52.9 *vs*. 23.7, respectively; P<0.05), the number of arousals per hour of sleep time (16 *vs*. 9, P=0.02), and significantly improved sleep quality.[8] Of note, the number of patient-ventilator asynchronies correlated with the number of patient's arousal (R^2=0.65, P=0.0001).[8]

Alexopoulou *et al.* also conducted a study in 14 critically ill patients to assess the relationship between sleep quality and patient-ventilator asynchrony during PSV and PAV.[29] Opposite to Bosma *et al.*,[8] however, compared to PSV, PAV did not improve sleep quality, though it improved patient-ventilator synchrony.[29]

Delisle *et al.* assessed differences in sleep quality with PSV and NAVA[21] in 14 conscious non-sedated ICU patients in the weaning phase. NAVA significantly improved patient-ventilator synchrony and reduced central apneas, compared to PSV. Sleep quality was also improved by NAVA, as defined by a higher proportion of REM sleep (16.5%, range 13-29%), as opposed to PSV (4.5%, range 3-11%; P=0.001) and less sleep fragmentation.[21]

Finally, Córdoba-Izquierdo *et al.* assessed sleep quality in 24 patients with acute hypercapnic respiratory failure receiving NIV, as delivered through an ICU ventilator without air-leak compensation, or a dedicated NIV ventilator compensating for air-leaks.[59] Patient-ventilator asynchrony was responsible for 19% of arousals and awakenings from sleep. Though overall sleep fragmentation and architecture were similar between groups, sleep fragmentation was surprisingly higher during NIV application through the dedicated ventilator equipped with air-leak compensation software. The authors considered these results likely consequent to other factors influencing sleep quality, such as noise, light, pain and staff interruptions.[59]

Tracheostomy rate

Three studies reported the impact of asynchronies on the rate of tracheotomy. Thille *et al.* found that patients with an AI≥10% had higher tracheostomy rate, compared to those with AI<10% (33% *vs*. 4%, respectively; P=0.007).[6] Vice versa, the studies by De Wit *et al.*[12] and Blanch *et al.*[34] observed similar tracheotomy rates in patients with and without AI≥10%, *i.e.*; 7% *vs*. 6%, respectively (P=0.920) for the former, and 33% *vs*. 32%, respectively (P=0.999) for the latter.

Conclusions

Definition and classification of patient-ventilator asynchronies are quite standardized. Conversely, the indexes for quantification of asynchronies are various and unevenly calculated. These discrepancies may in part explain why different studies report unequal and sometimes contrasting results with respect to the clinical outcomes. In particular, the studies that consider only major asynchronies seem more likely to show effects on clinical outcomes, compared to those also including minor asynchronies in AI computation. Moreover, patient samples are quite small in the vast majority of the studies, limiting the possibility to highlight differences.

Before designing further clinical investigations for establishing whether a relationship exists between patient-ventilator asynchrony and clinical outcomes, it appears necessary to achieve a standardization of the manner in which the indexes assessing the rate of asynchrony are calculated. Also, consensus on the meaningful clinical outcomes to consider is warranted. Finally, future studies should be designed to unequivocally ascertain whether the relationship between rate of asynchrony and worsened outcome is causative or just associative.

Key messages

- Patient-ventilator asynchrony occurs in up to 25% of patients undergoing invasive mechanical ventilation, and up to 80% of those receiving noninvasive ventilation.
- While definition and classification of patient-ventilator asynchronies are quite standardized, the indexes for quantification are heterogeneous.
- High rates of asynchrony are apparently associated with worsened patients' outcomes. Because of the different outcomes considered by the various studies and the erratic results, however, it remains unclear whether asynchronies really affect patients' outcome, and whether or not this relationship is causative or just associative.

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Conflicts of interest.—Paolo Navalesi contributed to the development of the helmet Next, whose license for patent belongs to Intersurgical S.P.A., and receives royalties for that invention; Paolo Navalesi's research laboratory has received equipment and grants from Maquet Critical Care, Hillrom, and Intersurgical S.p.A.; he also received honoraria/speaking fees from Maquet Critical Care, Philips, Resmed, Hillrom and Novartis. All other authors have no conflict of interest to declare.

Authors' contributions.—Andrea Bruni and Eugenio Garofalo equally contributed; Andrea Bruni and Eugenio Garofalo were responsible for conception and design of the study, analysis and interpretation of the data and for drafting and revising the article for final approval of the version to be published; Corrado Pelaia and Silvia Corrado were responsible for design of the study, acquisition and analysis of the data and for revising the article for final approval of the version to be published; Antonio Messina was responsible for conception of the study, interpretation of the data and for revising the article for final approval of the version to be published; Gianmaria Cammarota, Paolo Murabito and Luigi Vetrugno were responsible for conception of the study, analysis and interpretation of the data and for revising the article for final approval of the version to be published; Federico Longhini and Paolo Navalesi were responsible for conception and design of the study, acquisition, analysis and interpretation of the data and for drafting and revising the article for final approval of the version to be published.

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