

Patient-Ventilator Asynchronies: Clinical Implications and Practical Solutions

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- Introduction**
- Respiratory Physiology and Mechanical Ventilation**
- Asynchronies**
 - Respiratory Drive**
 - Ventilatory Need**
 - Neural Inspiratory Time**
- Types of Asynchronies**
 - Triggering Delay**
 - Ineffective Effort**
 - Auto-Triggering**
 - Double-Triggering**
 - Reverse-Triggering**
 - Flow Asynchrony**
 - Cycling Asynchronies**
- Clinical Implications**
 - Ventilator-Induced Diaphragmatic Dysfunction**
 - Difficult Weaning**
 - Patient Discomfort and Cognitive Dysfunction**
 - Dyspnea**
- How to Monitor Asynchronies**
 - Visual Analysis**
 - Esophageal Pressure**
 - EA_{di}**
 - Diaphragmatic Ultrasound**
 - Automatic Methods**
- Strategies to Improve Patient-Ventilator Interaction**
 - Conventional Ventilator Support**
 - Nonconventional Ventilator Support**
- Summary**

Mechanical ventilation is a supportive treatment commonly applied in critically ill patients. Whenever the patient is spontaneously breathing, the pressure applied to the respiratory system depends on the sum of the pressure generated by the respiratory muscles and the pressure generated by the ventilator. Patient-ventilator interaction is of utmost importance in spontaneously breathing patients, and thus the ventilator should be able to adapt to patient's changes in ventilatory demand and respiratory mechanics. Nevertheless, a lack of coordination between patient and ventilator due to a mismatch between neural and ventilator timing throughout the respiratory cycle may make weaning difficult and lead to prolonged mechanical ventilation. Therefore,

appropriate monitoring of asynchronies is mandatory to improve the applied strategies and thus improve patient-ventilator interaction. We conducted a literature review regarding patient-ventilator interaction with a focus on the different kinds of inspiratory and expiratory asynchronies, their monitoring, clinical implications, possible prevention, and treatment. We believe that monitoring patient-ventilator interaction is mandatory in spontaneously breathing patients to understand, by using the available technologies, the type of asynchrony and consequently improve the adaptation of the ventilator to the patient's needs. Asynchronies are relatively frequent during mechanical ventilation in critically ill patients, and they are associated with poor outcomes. This review summarizes the different types of asynchronies and their mechanisms, consequences, and potential management. The development and understanding of monitoring tools are necessary to allow a better appraisal of this area, which may lead to better outcomes for patients. *Key words:* asynchrony; diaphragm; dyspnea; intensive care units; mechanical ventilation; work of breathing. [Respir Care 2020;65(11):1751–1766. © 2020 Daedalus Enterprises]

Introduction

In critically ill patients, the ideal strategy throughout the duration of mechanical ventilation would be to allow the patient to generate spontaneous breaths as soon as possible to avoid diaphragmatic dysfunction due to prolonged controlled mechanical ventilation.¹ However, during spontaneous breathing, the goal is to maintain synchronous interaction between the patient and the ventilator to reduce the patient's inspiratory effort while adapting the ventilator settings according to the changes in the patient's ventilatory demand and breathing mechanics.²⁻⁴ Nevertheless, patient-ventilator interaction is seldom optimized, causing asynchronies that can be defined as a lack of coordination between patient and ventilator due to a mismatch between neural and ventilator timing throughout the respiratory cycle or the magnitude of support provided and demanded.^{1,3-6}

Respiratory Physiology and Mechanical Ventilation

The effects of mechanical ventilation on gas exchange, respiratory muscle load, and dyspnea depends on the match between the ventilatory setting and patient's respiratory physiology. As described by Ranieri et al,¹ the patient is

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The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.07284

able to interact with the ventilator based on 3 physiologic variables: ventilatory drive, ventilatory need, and neural inspiratory time.⁷⁻¹¹

At the same time, these physiologic variables should match 3 phase variables that define the mechanical breath: (1) the synchronization system (ie, inspiratory trigger) that begins inspiration (ie, trigger variable); (2) the pressure or volume variable that controls the mechanical breath gas delivery (ie, control variable); (3) the cycling-off criteria (ie, cycling variable). The synchronization system defines when the ventilator detects any patient inspiratory effort and activates a mechanical breath. The pressure or volume variable defines the type of control, namely volume or pressure, used by the ventilator to deliver the output. The cycling-off criteria define when the ventilator ends its support of the inspiratory effort, enabling the patient to exhale.^{1,12-20}

Asynchronies

Patient-ventilator asynchrony, as mentioned above, is a lack of coordination between the patient and the ventilator due to a mismatch between neural and ventilator timing throughout the respiratory cycle or the magnitude of support provided and the support demanded.³⁻⁶ Several factors may cause asynchronies (Fig. 1). Asynchronies according to the patient respiratory mechanics are shown in Figure 2. Asynchronies occur whenever there is a mismatch between the physiologic variables and the technological variables characterizing the ventilator functioning: respiratory drive (ie, inspiratory trigger asynchrony), ventilatory need (ie, control variable gas delivery asynchrony), and neural inspiratory time (ie, ventilator cycling variable asynchrony).¹

Respiratory Drive

Inspiratory trigger asynchrony can be defined as a lack of coordination between the ventilator inspiratory start criteria and the patient's respiratory centers output (eg, triggering delay, ineffective trigger, auto-triggering). Asynchrony in

the inspiratory phase may be caused by problems with the inspiratory trigger occurring independent of its algorithm.²¹ Although modern ventilators integrate flow or pressure triggers, the inspiratory effort required to trigger a breath may be a significant part of the total inspiratory effort.^{12-20,22-24} Therefore, the “best” triggering setting should reduce duration and intensity of the respiratory muscles at its minimum level, before the mechanical breath starts, while avoiding auto-triggering. Although the definition of the “best” trigger is still controversial, it is widely recognize that a good response time should be < 100 ms.¹

In a study in which flow and pressure trigger were compared, Aslanian et al²⁵ reported that during a flow trigger the time and the effort for triggering were 43% shorter and 62% lower compared to their percentage during a pressure

trigger. However, the subjects’ effort during the post-triggering phase were not significantly different during either trigger. A neural trigger, as a result of the introduction of a proper nasogastric tube, provided with an array of electrodes in the distal esophageal portion, can significantly improve patient-ventilator interaction.²⁶⁻²⁸

Ventilatory Need

Control variable gas delivery asynchrony can be defined as the ventilator not being able to meet the patient’s ventilatory demand.¹ Ward et al¹² reported that increasing the flow during assisted volume control ventilation mode would result in a reduction of the patient’s respiratory drive and work of breathing. Moreover, in volume control ventilation mode, any leak would decrease the ventilatory output.^{1,29} Conversely, a breath in pressure control ventilation mode better matches the patient’s ventilatory needs because the flow is the dependent variable during the delivery of inspiratory pressure, which means it reproduces the physiologic descendent flow profile better.³⁰

Nevertheless, the setting of pressure-rise time (ie, the time taken to reach the pressure set on the ventilator) may determine the flow output and consequently the asynchrony due to gas delivery.^{31,32} Although leaks are better compensated for in the pressure control ventilation mode than during the volume control ventilation mode, a severe leak, such as occurs during noninvasive ventilation (NIV), may decrease the ventilatory output in assisted pressure control ventilation mode.^{1,29,33-35}

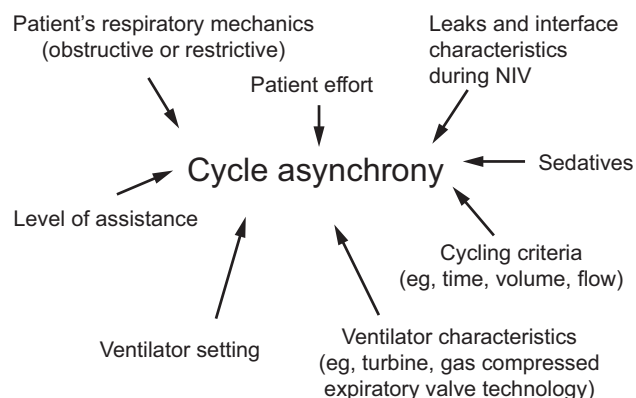


Fig. 1. Several factors may cause asynchrony, some related to patient characteristics (eg, respiratory mechanics, effort), others related to the ventilator (eg, setting, level of assistance, cycling criteria) and to the interface used (ie, invasive or noninvasive). NIV = noninvasive ventilation.

Neural Inspiratory Time

Ventilator cycling variable asynchrony can be defined as a mismatch between the patient’s respiratory center’s

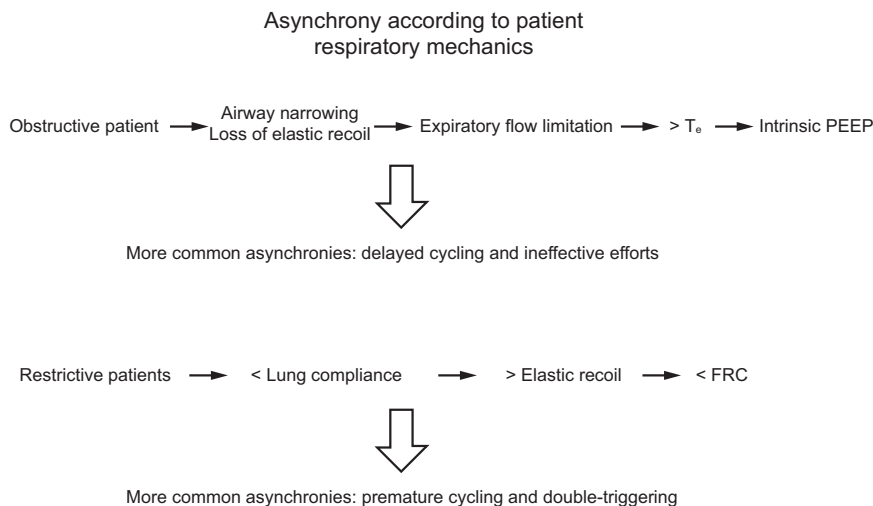


Fig. 2. Asynchronies are common in both obstructive and restrictive patients, although alterations of the underlying respiratory mechanics generate different types of asynchronies. FRC = functional residual capacity; Te = expiratory time constant.

neurologic output and the ventilator's inspiratory time.³⁶ Ventilator cycling asynchrony occurs when, after setting the cycling criteria (ie, pressure, time, volume, or flow), the mechanical breath is longer (ie, delayed cycling) or shorter (ie, premature cycling) than the patient's neural inspiration.^{1,25,32,37,38}

Types of Asynchronies

Longhini et al³⁹ classified asynchronies as major (ie, ineffective triggering, auto-triggering, double-triggering) or minor (ie, premature or short cycling, prolonged or delayed cycling, triggering delay). Table 1 lists different types of asynchronies and their definitions, causes, and strategies to resolve each asynchrony.

Triggering Delay

Triggering delay is a time lag between the onset of the patient's effort and the onset of ventilator pressurization.⁴⁰ This is a typical asynchrony between the respiratory drive and the inspiratory trigger, where the phase lag quantifies the delay between the onset of the inspiratory muscle activity and the beginning of the mechanical breath.^{1,5,10,41}

Giuliani et al⁴² reported that the effort performed by the patient during the triggering phase may interfere with the patient's effort during the remaining part of inspiratory phase. Interestingly, at higher inspiratory demand (ie, high respiratory drive), the trigger delay is shorter and the degree of the negative deflection in airway pressure (P_{aw}) is greater.

Conversely, with a low inspiratory demand (ie, lower respiratory drive), trigger delay is longer and the negative deflection in P_{aw} is smaller.^{7,40} Moreover, a threshold load, such as dynamic intrinsic PEEP, may worsen the triggering phase.¹⁸

Finally, ventilator characteristics such as the position of the flow/pressure sensor (eg, inside the ventilator or proximally to the patient's airway) or a problem related to the valves, the interfaces chosen (endotracheal tube vs face mask or helmet), or the high resistances generated by a heat-and-moisture exchanger (HME) or by the endotracheal tube are all factors that may influence the trigger delay.^{17,20,22,43-47} To detect the triggering delay, the esophageal pressure or electrical activity of the diaphragm (EA_{di}) is necessary. Figure 3 depicts a trigger delay of > 100 ms.

Ineffective Effort

Ineffective effort is defined as a patient's effort being unable to trigger the ventilator breath. Ineffective effort is an asynchrony between respiratory drive and inspiratory trigger. From a clinical point of view, ineffective effort can be detected by analyzing the breathing frequency shown on

the ventilator monitoring system that is lower than the breathing frequency monitored by observing the patient's chest/abdomen movements.¹ Ineffective effort can also be identified by observing flow and P_{aw} tracings on the ventilator monitor; a patient's effort that is unable to trigger the ventilator produces a P_{aw} drop concomitant to a flow increase (Fig. 4).⁴⁸

There are different causes leading to ineffective effort. A less sensitive inspiratory trigger in a patient with a low drive threshold may contribute to ineffective triggering.²⁵ In patients with obstructive lung disease, an inspiratory threshold load, such as intrinsic PEEP as a consequence of air trapping, may cause ineffective triggering.⁴⁹ An external PEEP in spontaneously breathing patients may counterbalance intrinsic PEEP and hence decrease inspiratory muscle effort.^{18,50}

Younes et al⁵¹ reported that ineffective effort may also exacerbate dynamic hyperinflation. Metabolic alkalosis may cause ineffective effort in patients with chronic bicarbonate elevation and low carbon dioxide level due to depression of the neural respiratory drive.⁵² Sedative drugs may affect patients' respiratory drive and may decrease the ability of the respiratory muscles to trigger the ventilator; consequently, deep sedation is likely to produce an increased number of ineffective efforts.⁵³ Several studies reported that a no-sedation protocol in subjects in the ICU was associated with a reduction of the asynchrony index, as well as a reduced duration of mechanical ventilation, in comparison to a daily interruption-of-sedation protocol.^{54,55} de Wit et al⁵⁶ reported that the level of sedation relates to ineffective effort, with a significant increase of ineffective triggering index for every unit decrease on the Richmond Agitation-Sedation Scale. Vaschetto et al⁵³ noted that, compared to light sedation, deep sedation with propofol reduces the respiratory drive and breathing pattern, significantly worsening patient-ventilator interaction.

Another cause of ineffective effort is asynchrony between the neural inspiratory time and the ventilator cycling variable. When the patient inspiratory time is shorter than the mechanical inspiratory time set on ventilator, the ventilator continues to insufflate the patient during neural expiration, thus causing hyperinflation.³ Leung et al⁷ observed that ineffective efforts were common during mandatory breaths in the intermittent mandatory ventilation mode because of the large tidal volume and the prolonged inspiratory time. For these reasons, the use of synchronized intermittent mandatory ventilation, especially in patients with COPD, is ineffective in unloading the respiratory muscles.⁷ Conversely, in a flow-cycled breath (eg, pressure support ventilation [PSV] mode), the duration of the mechanical inspiratory time is determined by the speediness of the pressure rise time and by the set flow threshold value (ie, the expiratory threshold, also called expiratory trigger). Ideally, the ventilator sensor should always track the end of

Table 1. Strategies to Reduce Asynchronies and Improve Patient-Ventilator Interaction

Asynchrony	Type and Definition	Cause of Asynchrony	Solutions
Trigger delay	Type: asynchrony between respiratory drive and inspiratory trigger Definition: a time lag of > 100 ms between the onset of patient effort and the onset of flow delivered by the ventilator	<ol style="list-style-type: none"> 1. Low trigger sensitivity 2. Low respiratory drive 3. Presence of a threshold load such as intrinsic PEEP 4. Presence of partially obstructed ETT or HME 5. Type of NIV interface (eg, mask vs helmet) 	Adjust trigger sensitivity, increase PEEP to counter intrinsic PEEP, replace HME or ETT, change NIV interface
Ineffective efforts	Type: asynchrony between respiratory drive and inspiratory trigger, or asynchrony between neural inspiratory time and ventilator cycling variable Definition: the ventilator is unable to detect the patient's neural effort despite the presence of an inspiratory effort	<ol style="list-style-type: none"> 1. Low trigger sensitivity 2. Weak respiratory drive or weak effort secondary to heavy sedation, excessive respiratory support, or diaphragm dysfunction 3. Presence of highthreshold load such as intrinsic PEEP 4. Delayed cycling, especially in PSV mode or obstructive condition (Fig. 2), or during NIV in presence of intentional leak in a ventilator unable to compensate for them 	Adjust trigger sensitivity, reduce sedation or use drugs with no effect on the respiratory drive, reduce support, correct metabolic alkalosis, increase PEEP to counter intrinsic PEEP, shorten inspiratory time, adjust EET criteria in an obstructive condition (eg, COPD), use appropriate NIV software, consider a neural trigger if the problem persists
Auto-triggering	Type: asynchrony between respiratory drive and inspiratory trigger Definition: a mechanical breath not triggered by the patient's inspiratory effort beyond the mandatory breath (eg, volume control or pressure control continuous mechanical ventilation)	<ol style="list-style-type: none"> 5. Inspiratory time too long in a time-cycled breath 1. High trigger sensitivity 2. Leaks 3. Random noise in the circuit (eg, cardiac oscillations, condensed water in the ventilator circuit, copious tracheobronchial secretions) 	Adjust trigger sensitivity, reduce noise, remove leaks, use appropriate NIV software
Double-triggering	Type: asynchrony between ventilatory need and control variable gas delivery, or asynchrony between neural inspiratory time and ventilator cycling variable Definition: 2 mandatory breaths that may or may not be separated by a very short expiratory time	<ol style="list-style-type: none"> 1. Short cycling due to insufficient assistance: fixed flow or lower tidal volumes in patients with high inspiratory flow demand in assisted/controlled mode 2. Short cycling (ie, premature cycling) due to high expiratory trigger threshold in PSV mode in patients with low respiratory-system compliance and high respiratory drive (Fig. 2) 3. Promote by reverse-triggering 	Increase inspiratory time in a time-cycled breath, increase inspiratory flow, adjust EET in PSV mode, optimize pressure rise time in PSV mode, remove the cause of reverse-triggering

(Continued)

Table 1. Continued

Asynchrony	Type and Definition	Cause of Asynchrony	Solutions
Reverse-triggering	Type: ventilator cycling variable synchrony Definition: ventilator insufflation that triggers diaphragmatic muscle contraction	1. Overassistance 2. Deep sedation	Reduce assistance, reduce sedatives, muscle paralysis if necessary
Cycling asynchrony	Type: asynchrony between neural inspiratory time and ventilator cycling variable Definition: mismatch between patient's respiratory center neurologic output and ventilator's inspiratory time	1. Neural time > ventilator inspiratory time (ie, premature cycling) 2. Neural time < ventilator inspiratory time (ie, delayed cycling) (Fig. 7)	Adjust inspiratory time and EET criteria in PSV mode, check for excessive assistance, reduce leaks or use an appropriate NIV software, use proportional modes
Flow asynchrony	Type: asynchrony between ventilatory need and control variable gas delivery Definition: ventilator's delivered gas flow is less than the patient's inspiratory flow demands	1. Low gas flow ring assisted volume control ventilation 2. Pressure rise time too low in pressure control mode	Increase gas flow or adjust inspiratory flow, decrease respiratory drive with an appropriate drug, increase pressure rise in pressure control mode

EIT = endotracheal tube
HME = heat-and-moisture exchanger
NIV = noninvasive ventilation
EET = end-expiratory trigger threshold
PSV = pressure support ventilation

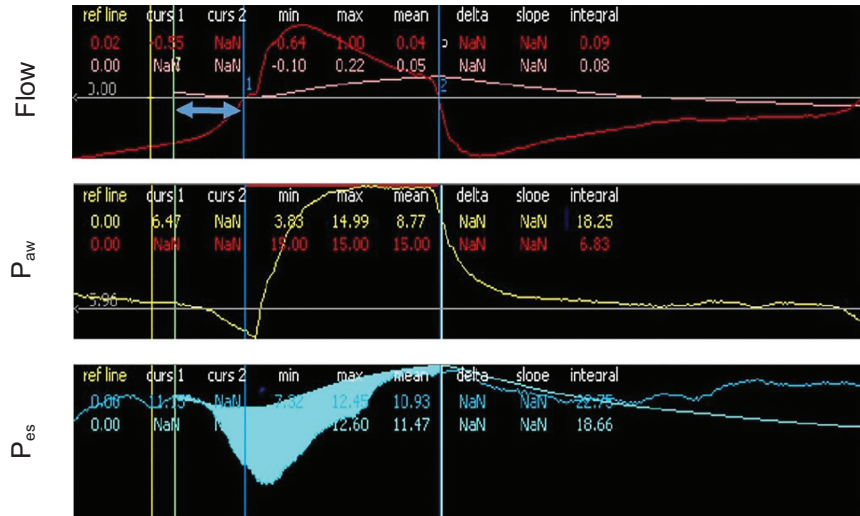


Fig. 3. Representative waveforms of flow (red track), P_{aw} (yellow track), and P_{es} (blue track) in a patient receiving ventilatory support. The blue arrow shows a delay of > 100 ms between the beginning of inspiratory muscle activity and the beginning of mechanical inflation (ie, trigger delay). P_{aw} = airway pressure; P_{es} = esophageal pressure.

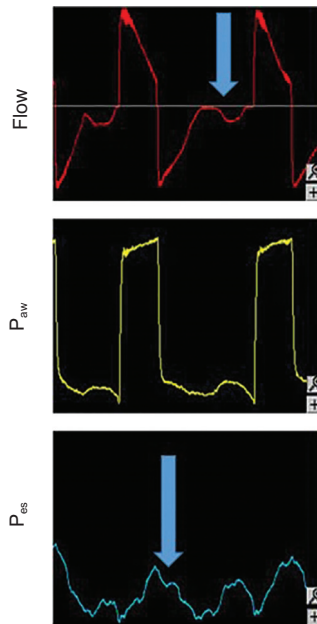


Fig. 4. Representative waveforms of flow (red track), P_{aw} (yellow track), and P_{es} (blue track) in a patient receiving ventilatory support. Arrows indicate ineffective effort. The ventilator is able to detect the patient's effort as a deflection on P_{es} generating only a bump in Flow and P_{aw} tracings. P_{aw} = airway pressure; P_{es} = esophageal pressure.

the patient's flow to assure synchrony.^{57,58} However, several factors may influence this relationship, such as patient respiratory mechanics, ventilator cycling algorithms, and ventilator settings. In patients with COPD, the increased

resistance and compliance produce a slower time-expiratory constant of the respiratory system. The longer time needed for the flow to fall to a low threshold value to trigger the expiration can lead to prolonged mechanical inspiration that persists during neural expiration. An appropriate cycling-off setting may reduce the incidence of ineffective effort.^{5,59,60} In addition, the presence of air leaks may impede a correct cycling in PSV, thus generating prolonged inspiratory time, especially when a dedicated NIV software is not used.⁶¹⁻⁶³

Leung et al⁷ reported that a higher level of assistance might deeply decrease the patient's respiratory drive, prolonging the triggering time as defined by the onset of patient effort and the onset of flow delivery by the ventilator. This causes a prolongation of the ventilator breath into the patient's expiratory phase, thus decreasing the time available for the exhalation.⁴⁴ In patients with COPD, this behavior will produce a larger tidal volume that is associated with a shorter expiratory time, which may determine dynamic hyperinflation and increase intrinsic PEEP.^{7,48,64}

Auto-Triggering

Auto-triggering is a mechanical breath that is not triggered by the patient's inspiratory effort beyond the mandatory breaths (ie, in volume control or pressure control ventilation mode).¹ It is an asynchrony between the respiratory drive and the inspiratory trigger. Auto-triggering can be caused by an extremely sensitive inspiratory trigger threshold or by changes in pressure and flow that may be related to random noise in the ventilator circuit (eg, condensate in the respiratory circuit, leaks, or cardiogenic

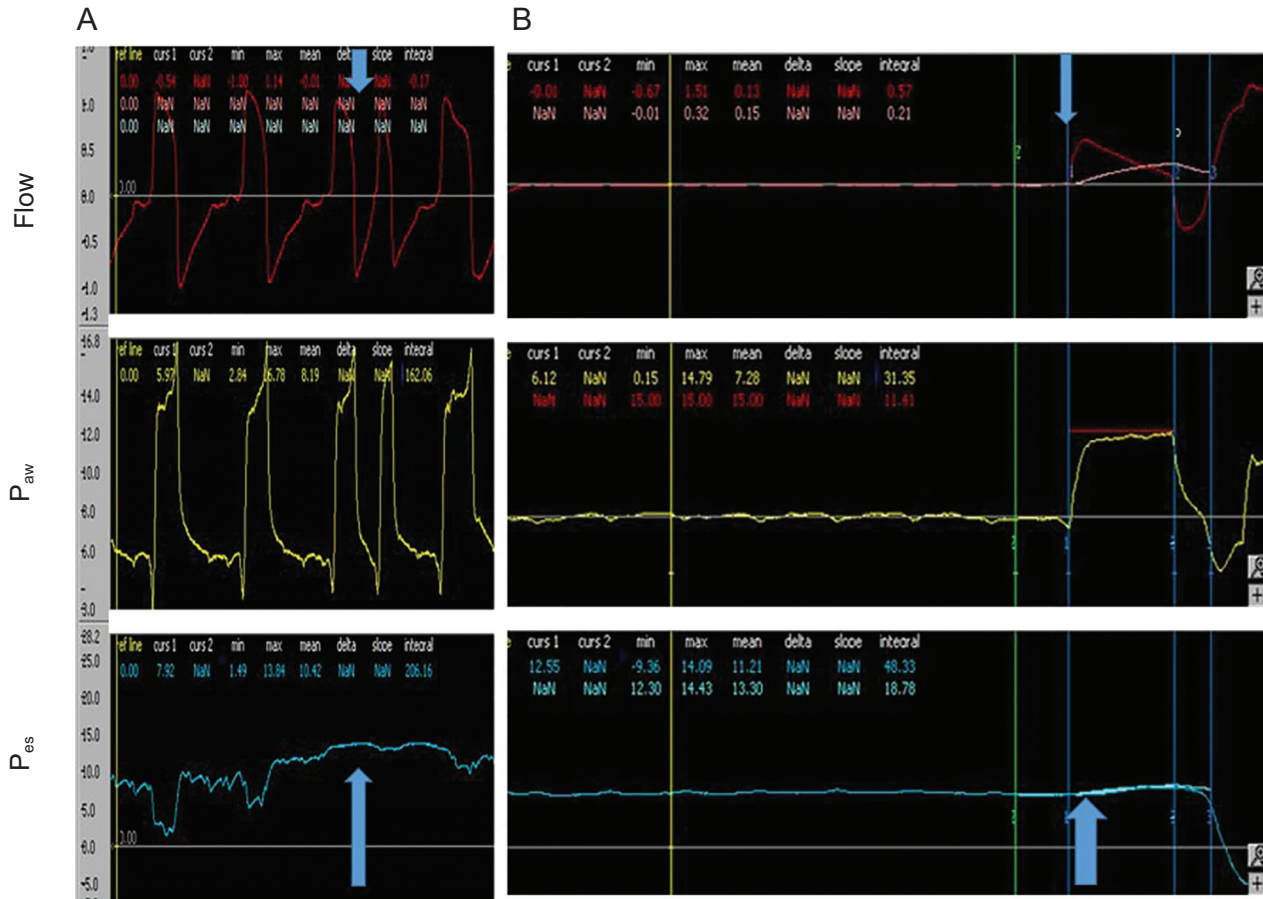


Fig. 5. Representative waveforms of flow (red track), P_{aw} (yellow track), and P_{es} (blue track) in a patient receiving ventilatory support showing 2 samples of auto-triggering (blue arrows). A: 3 mandatory breaths are delivered in the absence of the patient's inspiratory effort, separated by a very short expiratory time. B: A single mandatory breath is delivered in the absence of the patient's inspiratory effort. P_{aw} = airway pressure; P_{es} = esophageal pressure.

oscillations).⁴⁶ In particular, a large stroke volume is able to trigger the breath by cardiac oscillation, especially when the sensitivity of the triggering is too high and the patient's drive is low (eg, a sedated patient).^{53,65} Potential consequences of auto-triggering are respiratory alkalosis, worsening intrinsic PEEP, and cardiac embarrassment.⁶⁶ (Fig. 5).

Double-Triggering

Double-triggering, also called double-cycling or breath-stacking, consists of 2 breaths that may or may not be separated by a very short expiratory time. Double-triggering is caused by high patient ventilatory demand coupled with a too-short ventilator inspiratory time compared to the patient's neural time; this causes 2 inspiratory cycles with a limited expiratory phase (Fig. 6).^{21,66,67}

Double-triggering can be related to an asynchrony between neural inspiratory time and ventilator cycling variable or an asynchrony between ventilatory need and control

variable gas delivery when the ventilator fails to meet the patient's flow demand. This results in the patient's neural effort continuing beyond the ventilator's inspiratory time. If the patient has a high respiratory drive, an additional breath can be generated with or without a very short expiratory time.^{68,69} Double-triggering develops mainly when the ventilator delivers a fixed flow or when lower tidal volumes are set in the presence of high patient inspiratory flow demand. Double-triggering can also occur in the event of poor matching between neural and mechanical inspiratory times (ie, asynchrony between neural inspiratory time and ventilator cycling variable), especially when a high-flow termination criterion is applied to a restrictive lung condition in PSV mode.⁶⁶

In the volume control ventilation mode, double-triggering may be particularly dangerous, especially in patients with ARDS under protective lung ventilation.⁷⁰ Double-triggering can generate high volumes and cause overinflation, thus inducing ventilator lung injury and a possible increase in right-ventricular afterload.^{66,69} Double-

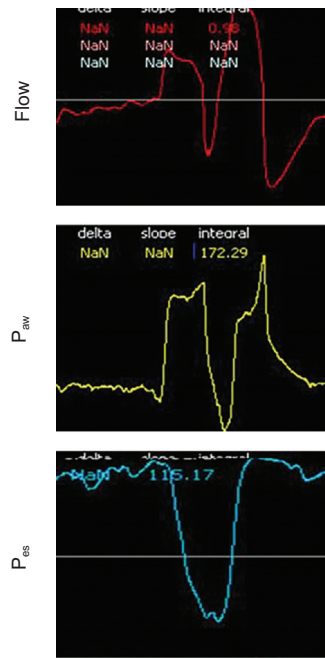


Fig. 6. Representative waveforms of flow (red track), P_{aw} (yellow track), and P_{es} (blue track) in a patient receiving ventilatory support. The figure shows a double-triggering in the pressure support ventilation mode depicted by the presence of 2 inspiratory cycles separated by a very short expiratory time. P_{aw} = airway pressure; P_{es} = esophageal pressure.

triggering in the pressure control ventilation mode seems to be less dangerous because alveolar pressure increases during inspiration with a concomitant decrease in the driving pressure of the next breath.⁷¹

Reverse-Triggering

Reverse-triggering is a type of asynchrony that happens when a patient's effort occurs after the initiation of a ventilator breath (ie, a breath not triggered by the patient). Usually, reverse-triggering represents an underrecognized asynchrony in which the ventilator triggers diaphragmatic muscle contractions through activation of the patient's respiratory center in response to passive insufflation of the lungs.⁷² With reverse-triggering, the effort frequently starts during the insufflation and continues during the expiration. The detection of patient effort that is triggered by a ventilator breath is easier to detect during pressure control ventilation because the flow changes when the effort occurs early enough in the inspiratory phase. Kallet et al⁷³ reported this kind of asynchrony as a common observation during lung-protective ventilation. Because the patient's inspiratory muscles are still active at the beginning of expiration, preventing the elastic recoil of the respiratory system, the peak expiratory flow is markedly reduced.⁷⁴ Reverse-triggering appears in deeply sedated patients, with or without lung

injury, and it seems particularly common in those transitioning from sedated to awakened states.⁷⁵ Interestingly, de Haro et al⁶⁸ reported that one third of double-cycling breaths were reverse-triggered, primarily in association with deeply sedated subjects not triggering the ventilator.

Flow Asynchrony

Flow asynchrony is an asynchrony between ventilatory need and control variable gas delivery. Flow asynchrony occurs when the ventilator flow output does not coincide with the patient's demand.^{73,76} Inadequate gas delivery is common when ventilator flow is set inappropriately low, when the combination between tidal volume and inspiratory time does not result in adequate flow to the injured lung, or when inspiratory flow demands are high and vary from breath to breath.⁷⁷ Flow asynchronies appear to be more common with ventilatory settings that deliver a fixed flow (ie, flow-targeted breaths) rather than with a flow that can vary with effort (ie, pressure-targeted breaths).⁷⁸

Cycling Asynchronies

A cycling asynchrony can be defined as a mismatch between the patient's neurologic respiratory center and ventilator's inspiratory time.^{1,25,32,36-38} If the ventilator's set inspiratory time exceeds the patient's neurological inspiratory time, delayed cycling occurs. On monitor graphics, a pressure spike in PSV mode is detectable, originated by the recruitment of the expiratory muscles as a response to excessive muscle loading.⁷² Delayed cycling may occur because of nonintentional leaks that may prevent the ventilator from cycling from the inspiratory to the expiratory phase (ie, so-called inspiratory hang-up). This is more likely to be seen during NIV when the ventilators do not have software to compensate for air leaks or do not include a time criteria for cycling-off.⁶¹ Delayed cycling, especially in obstructive conditions (Fig. 2), may cause ineffective triggering. If the ventilator's set inspiratory time is less than the patient's neurological inspiratory time, short-cycling (ie, premature cycling) may occur. A high expiratory threshold time in PSV mode may also cause a short inspiration and lead to premature cycling, especially in patients with low compliance, such as in ARDS.^{72,79} If the patient's effort exceeds the time of mechanical support, another breath may also be generated (ie, double-triggering).

Clinical Implications

Asynchronies are often unrecognized, underestimated, and inappropriately treated.^{5,24,27,80,81} The asynchrony rate during invasive ventilation varies, widely ranging from 10% to 50%, with a prevalence of ineffective efforts, especially in patients with COPD.^{48,80,82,83}

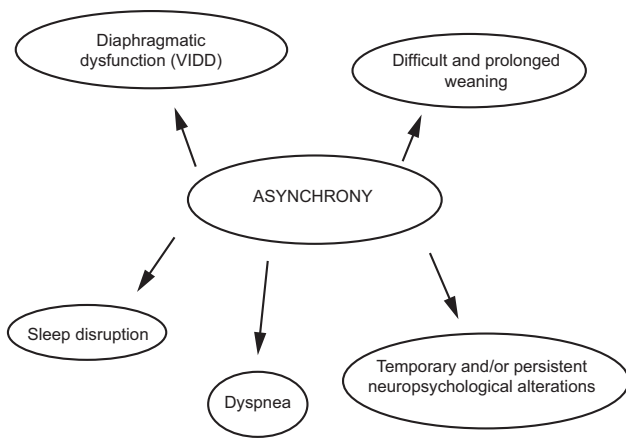


Fig. 7. Clinical implication of poor patient-ventilator interactions. VIDD = ventilator-induced diaphragmatic dysfunction.

The incidence of asynchronies has been defined as the asynchrony index, which is a percentage value of the total number of asynchronous events divided by the sum of the total ventilator cycles plus the ineffective efforts.^{56,84} A high incidence of asynchrony is commonly defined as an asynchrony index > 10%, and it may be related to a patient’s discomfort, increased work of breathing, or prolonged weaning due mainly to wasted diaphragmatic energy.^{8,48,64} Several studies have reported that an asynchrony index > 10% may significantly increase the duration of mechanical ventilation and the risk of tracheostomy, and it may be associated with a higher mortality rate.^{3,56,85} Further studies are needed to define its role in predicting patient prognosis. A schematic representation of the clinical implications of poor patient-ventilator interactions is shown in Figure 7.

Ventilator-Induced Diaphragmatic Dysfunction

Ventilator-induced diaphragmatic dysfunction it is an important risk factor for poor patient-ventilator interaction, contributing to prolonged ventilator dependence and poorer outcome.⁸⁶⁻⁹¹ During partial ventilator support, asynchronies can have an especially important impact on respiratory muscle function, in particular during ineffective efforts occurring in the exhalation phase of the previous mechanical breath, because the inspiratory muscles contract when they should relax as lung volume decreases to functional residual capacity.⁹² The result is a so-called eccentric or plyometric contraction, which leads to ultrastructural muscle damage, cytokine release, and muscle strength reduction with consequent deficit of force and weaning failure.⁹³⁻⁹⁶

Difficult Weaning

Difficult weaning is closely related to asynchronies. Chao et al⁸⁴ reported that the wasted diaphragmatic energy

due to ineffective efforts had negative effects on the weaning process, significantly prolonging mechanical ventilation in subjects with an asynchrony index > 10% compared to those with an asynchrony index < 10%. More recently, de Wit et al⁵⁶ demonstrated that asynchrony index > 10% was related to longer duration of mechanical ventilation and shorter ventilator-free survival, along with lower likelihood of home discharge. A similar trend toward longer mechanical ventilation was confirmed by other studies that also noted an association between an asynchrony index > 10% and a higher mortality rate.^{48,85}

Patient Discomfort and Cognitive Dysfunction

Sleep quality may be deeply influenced by patient-ventilator interaction, and a high percentage of asynchronies appear to be responsible for sleep disruption.⁹⁷ An improvement of sleep quality may be obtained with the reduction of the ventilatory support, which leads to a more stable breathing pattern, fewer missed efforts, and periodic breathing.^{92,98} Furthermore, the type of ventilatory support may play a role in sleep quality by reducing the number of asynchronies.^{66,97,98} However, the relationship between the patient-ventilator interaction and quality of sleep is still controversial. Alexopoulou et al⁹⁹ did not observe improvements in sleep quality during proportional assist ventilation+ compared to PSV, despite the former being able to improve patient-ventilator interaction, whereas neurally adjusted ventilatory assist was found able to improve sleep quality compared to PSV.¹⁰⁰

Dyspnea

Dyspnea, defined as breath discomfort, is a common consequence of poor interaction between the patient and the ventilator and is strongly associated with anxiety in mechanically ventilated patients.¹⁰¹ In up to one third of patients, changes in ventilatory settings are able to reduce dyspnea and the associated anxiety, whereas the inability to reduce dyspnea by modifying ventilator settings seems to be associated with delayed extubation.⁶⁶ The relationship between dyspnea and asynchronies still needs to be thoroughly investigated.⁸¹ Finally, asynchronies are associated with persistent neuropsychological alterations in critically ill patients.¹⁰² A profound sleep disruption with a high frequency of arousals and awakenings is related with acute onset of impaired cognitive function, visual hallucinations, delusions, and illusions.^{103,104}

How to Monitor Asynchronies

The importance of an accurate analysis and quantification of asynchronies is mandatory.^{3,66} However, precise analysis is still challenging in everyday clinical practice.¹⁰⁵

Visual Analysis

Different patterns of asynchrony can be detected by visual inspection of flow/time and pressure/time waveforms in ventilated patients. Ineffective effort and double-triggering are the most common and easily detected asynchronies.⁹² Although a bedside evaluation of respiratory waveforms is a traditionally accepted and reliable method to identify asynchronies,¹⁰⁶⁻¹⁰⁸ this technique requires specific skills and expertise.¹⁰⁹⁻¹¹¹ It has also been suggested that an incorrect estimation of the patient's breathing frequency is one of the consequences of the difficulties in appreciating patient-ventilator asynchronies.^{56,81} Furthermore, while the identification of asynchronies appears easy in extreme situations in which the patient "fights the ventilator," in other circumstances it is more difficult to detect asynchronies because most of them occur without any clinical signs.^{48,56}

Therefore, specific training appears to be crucial for correct asynchrony detection. Colombo et al¹¹⁰ studied the accuracy of experienced ICU physicians in detecting asynchronies in comparison with less experienced physicians (ie, first-year residents); both groups had poor performance because of the absence of specific training. These results are in line with the data reported by Chacòn et al.¹¹¹ In addition, the use of additional signals that reflect the patient's respiratory efforts is often required to increase the ability to recognize the asynchronies.¹¹²

Esophageal Pressure

The use of esophageal pressure allows the clinician to detect every inspiratory effort, thus providing accurate information regarding the patient-ventilator interaction.¹¹³ The simultaneous observation of P_{aw} , inspiratory flow, expiratory flow, and esophageal pressure waveforms allows the clinician to correctly match the patient's inspiratory effort with each mechanical breath. This may enable the identification of ineffective effort as an esophageal pressure deflection that is not followed by a ventilator cycle.¹⁰⁵ However, even if this is the standard technique for asynchrony detection, this measurement is still not available yet for routine use in daily practice due to its invasiveness.^{114,115}

EA_{di}

A specific nasogastric tube provided with a multiple array of electrodes allows the continuous recording of the EA_{di} .^{27,37,116} Only one ventilator uses this signal for triggering. EA_{di} enables the detection of the onset and duration of the neural breath.¹⁰⁵ However, like the esophageal pressure measurement, EA_{di} does not represent a routine measurement in clinical practice.⁶⁶

Diaphragmatic Ultrasound

Another method to detect asynchronies is the diaphragmatic ultrasound. The direct observation of the diaphragm thickening can allow the detection of the patient's inspiratory effort.¹¹⁷ This simple and noninvasive approach is still not standardized, and it requires the synchronization of ventilator waveforms with the diaphragmatic ultrasound signal, so its use still requires investigation.¹¹⁸

Automatic Methods

The real-time automatic detection of asynchronies, based on a machine learning approach, is a promising method aimed at identifying and quantifying asynchronies breath by breath without being affected by any kind of noise, such as secretions and body movements.^{105,115} Most systems today are intended to identify the most common asynchronies, such as ineffective efforts. Chen et al¹¹⁹ evaluated software dedicated to the detection of ineffective efforts, using a computerized algorithm based on the characteristic features of flow and P_{aw} deflections. The investigators applied their software to 14 mechanically ventilated adult subjects demonstrating a sensitivity and specificity > 90% in detecting ineffective triggering.¹¹⁹ Mulqueeny et al¹²⁰ studied an algorithm embedded in a ventilator system that was able to automatically detect the occurrence of ineffective effort and double-triggering in real time. The software was applied during both invasive and noninvasive ventilation, and it showed an overall accuracy of > 95%.¹²⁰ Younes et al¹²¹ developed a new approach for monitoring and improving patient-ventilator interaction that uses a signal generated by the equation of motion. More recently, Blanch et al¹²² validated a software that is able to detect ineffective effort during invasive ventilation, as well as other kinds of asynchronies such as double-triggering, aborted inspiration, and short and prolonged cycling. Other systems aimed at automatically and noninvasively detecting asynchronies have been developed, such as spectral analysis of airway flow, the comparison between P_{aw} and EA_{di} waveforms, and specific algorithms.^{83,123}

Strategies to Improve Patient-Ventilator Interaction

Conventional Ventilator Support

Patient-ventilator interaction is strongly influenced by the ventilatory mode and settings used, as well as by the type and level of sedation. In conventional ventilation, trigger settings may affect patient-ventilator interaction. In fact, a low sensitivity setting for the inspiratory trigger may increase triggering effort, while an oversensitive trigger may cause auto-triggering, especially in cases of decreased

neuromuscular drive like polyneuromyopathy.^{65,89,106} During invasive ventilation, auto-triggering may be caused by noise in the ventilator circuit (eg, condensate in the respiratory circuit), whereas during NIV auto-triggering is caused mainly by nonintentional leak.^{46,63} It is worth noting that, among the new algorithms recently developed to improve patient-ventilator interaction, the neural trigger seems to be able to improve all of the drawbacks of triggering asynchronies, including those due to the presence of inspiratory PEEP and leaks.²⁶⁻²⁸

High levels of support have several detrimental effects on the ventilated patient, most notably hyperventilation, which may cause ineffective efforts, sleep fragmentation, and eventually apnea.⁹⁸ High levels of support should be avoided in patients affected by chronic heart failure, who are particularly exposed to central apnea and abnormal breathing pattern, due to increased chemoreceptor sensitivity. In patients with COPD, a high level of support, especially when associated with a low expiratory threshold, prolongs the mechanical insufflations after the end of the neural inspiratory time, causing dynamic hyperinflation and consequent ineffective efforts.^{48,124} Chao et al⁸⁴ reported that reducing the level of pressure support in subjects with COPD was the most effective strategy to decrease the number of ineffective efforts.

As previously explained, the patient-ventilation interactions worsen because of inappropriate inspiratory flow in continuous mandatory ventilation or an inadequate pressure rise time influencing the duration of a PSV breath.^{12,31} Finally, air leaks may affect both pressure control and volume control ventilatory support, but to a greater extent for the latter.¹

Properly setting the inspiratory time is another important aspect of conventional ventilation. Mechanical breaths that are too long or too short may cause asynchronies due to poor matching between the neural and mechanical inspiratory times.^{3,21,67,92} This could happen during time-cycled modes (eg, volume control or pressure control ventilation) or during a flow-cycled breath (ie, PSV mode) when the expiratory flow threshold is improperly set.^{58,66} Nonintentional leaks during NIV with ventilators that do not have leak-compensation software may increase the time of mechanical breaths, thus worsening patient-ventilator interaction.^{61,63,125} The application of appropriate external PEEP in patients with COPD may help reduce ineffective efforts.^{126,127}

Sedation has as an important effect on patient-ventilator interaction. It is well known that deep sedation may increase the number of missed efforts.¹²⁸ Nonsedated patients often show higher breathing frequency, with a relevant frequency of double-triggering.⁵⁴ Vaschetto et al⁵³ reported that deep sedation with propofol significantly reduce the respiratory drive as assessed with EA_{di}, whereas lower doses of propofol had fewer or no effects on patient-ventilator interaction.⁷ Interestingly, dexmedetomidine

compared with propofol resulted in fewer asynchronies without influencing respiratory timing or drive.¹²⁹ Costa et al¹³⁰ reported no effect of incremental doses of remifentanyl, a potent short-acting opioid drug, on respiratory drive, although there was an increase in the neural expiratory time, which resulted in a parallel reduction of breathing frequency.

Nonconventional Ventilator Support

Proportional assist ventilation and neurally-adjusted ventilatory assist are new modes of ventilation that provide assistance that is proportional to the patient's inspiratory effort; these modes can reduce asynchronies, as demonstrated by an increasing amount of data.^{4,131-134} In comparison with PSV, both proportional assist ventilation and neurally-adjusted ventilatory assist are able to prevent hyperinflation, improve neuro-mechanical coupling, restore the variability of the patient's respiratory pattern, and improve patient-ventilator interaction.^{135,136} It has been suggested that these innovative modes of ventilation should be considered when asynchronies persist after conventional ventilation adjustments.⁸¹

Noisy ventilation, a variable mechanical ventilation mode that is introduced by a variability in the respiratory pattern, is supposed to be beneficial to the respiratory function and to be less harmful to the sick lung than traditional PSV.¹³⁷ Noisy or variable PSV applies a random variation in support levels, thus improving lung function and reducing pulmonary inflammatory response.¹³⁸ Spieth et al¹³⁹ reported that during noisy PSV, with randomly generated pressure support values according to a Gaussian distribution, the number of asynchronies was lower in comparison with conventional PSV. Furthermore, noisy PSV does not require closed-loop mechanisms or the insertion of an esophageal catheter, which make it technically easier to implement.

Summary

The monitoring of patient-ventilator interaction is a crucial aspect in treating spontaneously breathing patients and should be mandatory. Understanding the correct genesis of the various types of asynchronies, independent of available technologies, would improve patient-ventilation interaction and could eventually improve patient outcomes.

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