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Patient–ventilator interaction during noninvasive ventilation: practical assessment and theoretical basis

S. Nava
A. Carlucci
P. Ceriana

Respiratory Intensive Care Unit
Fondazione S.Maugeri, I.R.C.C.S.
Istituto Scientifico di Pavia, Pavia, Italy

Correspondence
S. Nava
Respiratory Intensive Care Unit
Fondazione S.Maugeri
Istituto Scientifico di Pavia
Via Maugeri n.10
27100 Pavia, Italy
Fax: 39 382592075
E-mail: stefano.nava@fsm.it

Provenance
Commissioned article, peer reviewed

Competing interests
None declared

Summary

Synchrony refers to the agreement between the patient's own (neural) and the ventilator's (mechanical) inspiratory and expiratory time. Noninvasive ventilation (NIV) is a semi-open system, which means air leaks are common. This greatly affects patient synchrony. In addition to air leaks, there are other factors that affect patient–ventilator mismatching. This review will focus on NIV and on the main forms of asynchrony and mismatching, their causes and methods to eventually identify these problems from the flow and pressure signals.

During spontaneous breathing, there is a physiological time lag between the stimulus to breathe generated by the central nervous system and the contraction of the inspiratory muscles that results in the generation of airflow and tidal volume. This is due to the "long and winding road" that the signal needs to travel before it can reach the site of muscle contraction (figure 1).

When breathing is supported by a ventilator, the lag time is likely to be increased owing to the mechanical and technical characteristics of the machine, the apparatus used (*i.e.* tubing, interfaces and humidification system), the ventilatory settings, and last but not least, by the pathophysiological abnormalities imposed by the patient's underlying condition.

The word synchrony derives from the Greek σύν (with) and χρόνος (time), and, when we are dealing with mechanical ventilation, it refers to the agreement between the patient's own neural respiratory drive and the ventilator's mechanical inspiratory and expiratory time. These phenomena are very difficult to identify in clinical practice, since their detection relies on sophisticated and invasive methods such as the recordings of the electrical activity of the inspiratory muscles (electromyogram (EMG)).

NIV is a "semi-open" system and therefore air leaks around the mask are very likely to occur, in particular in the first few hours of ventilation, when the patient needs to adapt, and later on when prolonged mechanical ventilation is required. Patient–ventilator synchrony may be deeply affected by the:

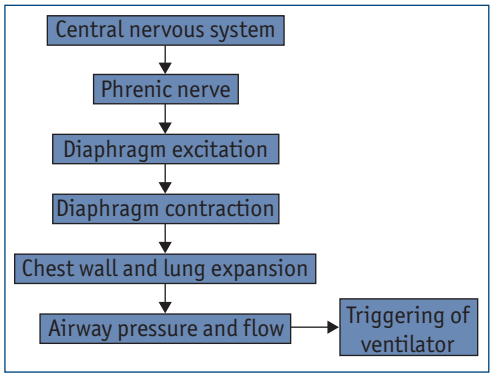
- presence of air leaks
- settings of the ventilator applied to try to correct this problem
- interfaces used
- emotional status of the patient.

All these factors make the problem of patient–ventilator synchrony unique, and even more complex in NIV than in invasive mechanical ventilation.

Some forms of patient–ventilator mismatching may be more easily assessed at the bedside using the ventilator screen, such as the most extreme forms of mismatch between patient effort and ventilator assistance, for example wasted effort, auto-cycled breaths and double triggering.

HERMES syllabus link: modules B.1, B.10,B.19, E.1.6

Figure 1
Mechanisms underlying the generation of spontaneous breathing.



Forms of asynchrony, mismatching and detection

Theoretically, a ventilator should cycle in synchrony with the activity of the patient's respiratory effort. TOBIN *et al.* [1] identified the four major determinants of patient–ventilator synchrony:

- the triggering of the ventilator
- the phase of inspiration after triggering
- the passage from inspiration to expiration
- the end of expiration.

Detailed recordings of neural respiratory timing and ventilator timing are feasible only through the use of sophisticated and invasive measurements such as the diaphragmatic EMG with oesophageal electrode, while the use of transdiaphragmatic pressure (P_{di}) may also be useful even though it is more prone to errors. Both methods of recording are invasive, since a catheter needs to be inserted in the oesophagus, but in clinical practice P_{di} is probably used more, since it requires less sophisticated technologies and provides a more stable signal. Consequently, the examples used in this article will rely on this method.

Figure 2 shows a delay in the inspiratory triggering phase (trigger delay). The onset of diaphragm contraction is represented by positive deflection from the baseline in P_{di}. The time elapsed between the onset of P_{di} and the point of zero flow is due to the presence of intrinsic positive end-expiratory pressure (PEEPi), while the following delay of 360 ms is due to the delayed response of the ventilator machine in starting an inspiratory flow and therefore providing an inspiratory support (*i.e.* opening of the valve, increased dead-space). This delay may also be observed on the flow trace, as an unusually prolonged flat signal before the ventilator pressurisation begins.

Figure 3 represents another common form of asynchrony. In this case, the end of the patient's contraction, as assessed by the peak P_{di}, occurs much before the end of the inspiratory support provided by the machine, so that the ventilator is delivering pressure even when the patient has released his diaphragm.

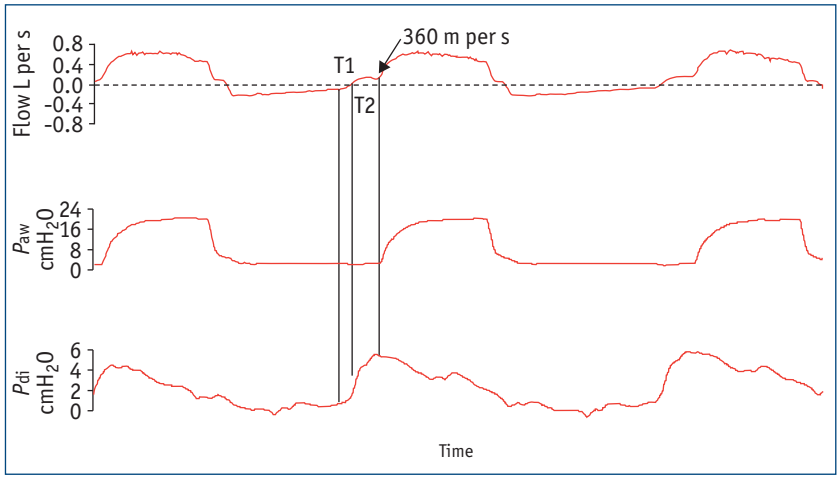
Figure 4 shows the "other side" of the coin, when there is a problem in the pathway from inspiration to expiration. In this case, the ventilator ceases its inspiratory support prematurely, before the patient has inspiration. The diaphragm effort, depicted on the P_{di} trace, continues after the flow provided by the machine has begun decreasing toward zero. This asynchrony may be due either to the ventilator setting (*i.e.* the percentage of flow decay necessary to reach the threshold value to trigger expiration) or to an insufficient flow to support the patient.

These latter two asynchronies are more difficult to read from a ventilator screen. Conversely, the occurrence of patient–ventilator interaction problems such as failure to trigger the ventilator may be detected from the flow and pressure traces on the ventilator screen. However, this still requires expertise on the part of the operator in interpreting the events and close visual monitoring.

Ineffective triggering is defined as an inspiratory effort that is not sufficient to trigger the ventilator (*i.e.* a wasted effort). This phenomenon is easily seen in the P_{di} trace (figure 5) and as a notch on the pressure and flow traces. Ineffective triggering has also been described during the so called assisted inspiratory phase, when the patient wants to exhale but the machine is still providing an inspiratory positive pressure. An inappropriate ventilator setting (*i.e.* high level of support) is often the cause of ineffective triggering.

Double- (or triple-) triggering is defined as two or more cycles separated by a very short expiratory time, where only the first cycle is triggered by the patient. Flow and airway pressure recordings of triple-triggering, defined as three consecutive ven-

Figure 2
Flow, airway pressure (P_{aw}), and P_{di} signals showing a delay in the inspiratory triggering phase. T1 indicates the P_{di} increase required before the ventilator is triggered (i.e. PEEPi). T2 indicates the slow response of the machine to provide an inspiratory flow. Dashed line: zero flow.



tilator cycles separated by an expiratory time less than half the mean inspiratory times are shown in figure 6. Double- and triple-triggering often occur when the ventilator inspiratory time is shorter than the patient's inspiratory time. The patient's effort is not completed at the end of the first ventilator cycle and triggers a second cycle.

Figure 7 shows the phenomenon of auto-triggering, defined as a cycle delivered by the ventilator without a prior airway pressure decrease, indicating that the ventilator delivered a breath that was not triggered by the patient. Common causes of this phenomenon are the presence of air leaks and water in the tubings.

Another form of asynchrony that is a unique feature of NIV occurs when the patient is unable to switch from inspiration to expiration, making the inspiratory time unusually long. This may happen in the presence of large air leaks, when the inspiratory flow remains higher than the threshold value set for the expiratory trigger, because the ventilator tries to compensate for leaks. In this case, the flow signal reaches a plateau after an initial brisk decay (figure 8). Since all ventilators now have a safety feature to avoid what was called the "hang-over" phenomenon, inspiratory time can be no longer than 3 s.

Automatic detection of major patient–ventilator interaction problems has been proposed recently [2–4]. These studies showed that the sensitivity and specificity of the algorithm were good and comparable with those obtained with the recording *P*di traces. The next step will be to implement these algorithms in specific ventilators, in an attempt to warn physicians about the presence of a poor patient–ventilator interaction.

What determines an interaction?

The mode of ventilation and the patient's characteristics

Pressure support ventilation (PSV) is a mode of assisted ventilation, used in intubated patients and especially during NIV ≥80% of NIV patients are ventilated in this way. During PSV, the ventilator delivers a pre-set inspiratory pressure to assist spontaneous breathing efforts. The patient triggers the ventilator by reaching a predetermined pressure or flow, causing the machine to start the delivery of inspiratory support. PSV theoretically allows the patient to control not only the breathing rate but also the duration of inspiration; therefore what distinguishes PSV from other currently available ventilator modes is its capacity to vary

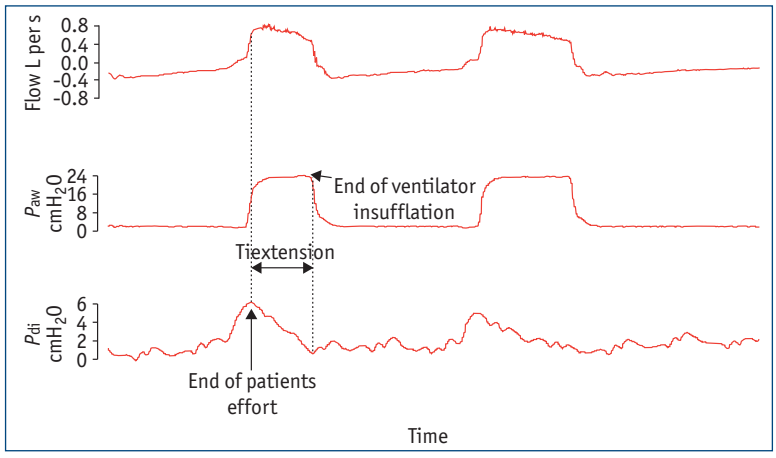


Figure 3

*Flow, airway pressure (*P*aw) and* P*di signals showing the different timings of end of patient effort (neural inspiration) and end of ventilator insufflation (mechanical inspiration). Tiextension is the difference between neural and mechanical inspiratory times.*

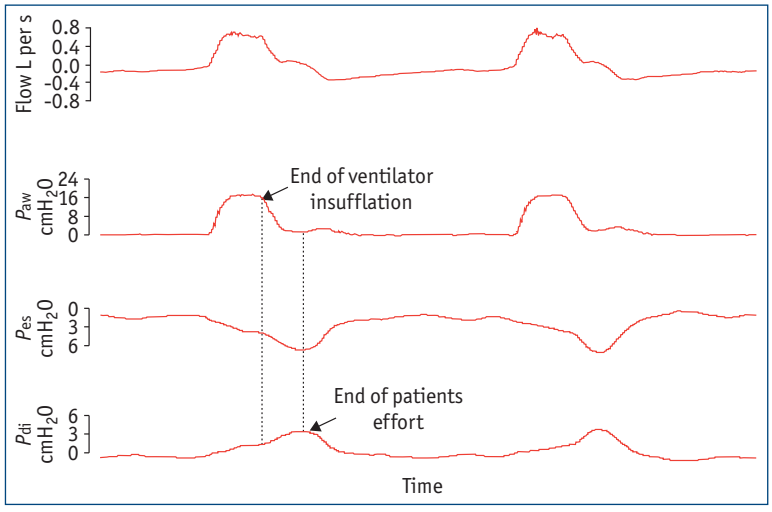


Figure 4

*Flow, airway pressure (*P*aw), oesophageal pressure (*P*es) and* P*di signal the end of ventilator insufflation while the patient is still contracting his inspiratory muscles.*

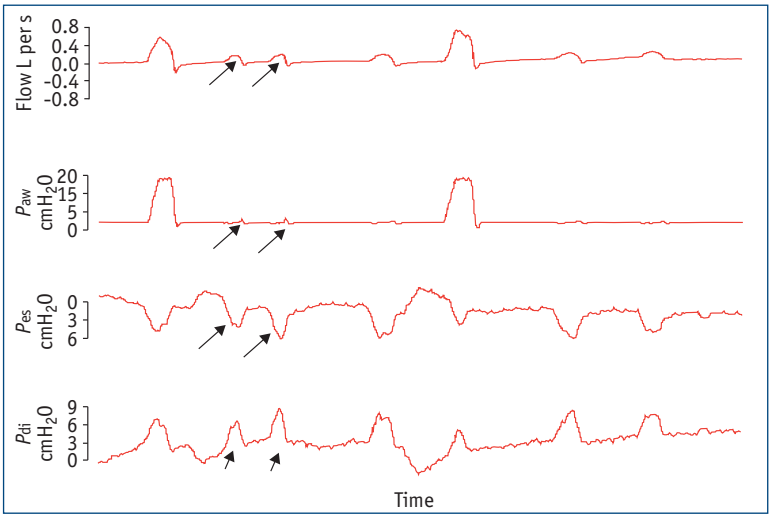


Figure 5

*Flow, airway pressure (*P*aw), oesophageal pressure (*P*es) and* P*di signals showing the occurrence of ineffective efforts (arrows).*

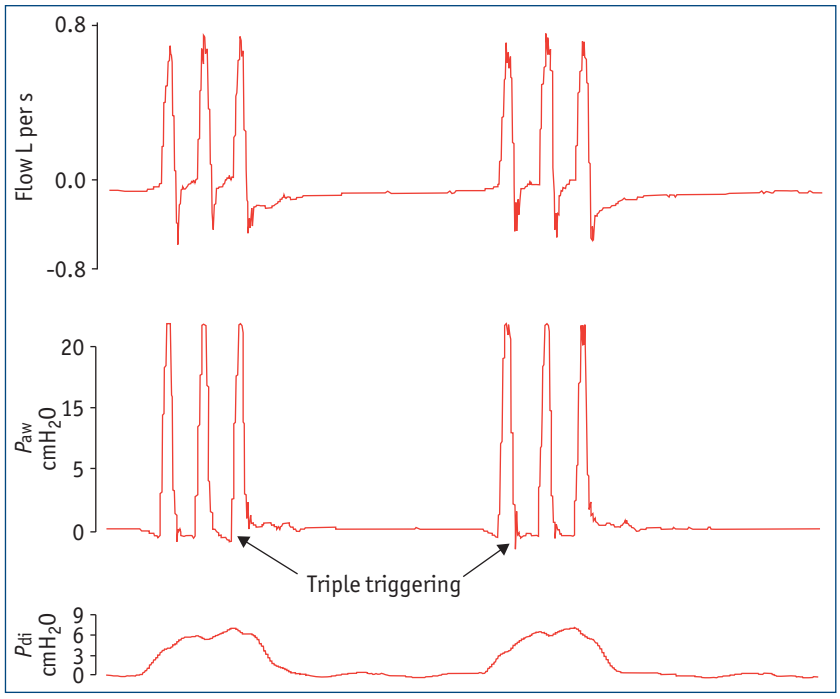


Figure 6

Flow, airway pressure (Paw) and Pdi signals double-triple triggering, defined as three consecutive ventilator cycles separated by an expiratory time less than one-half the mean inspiratory time.

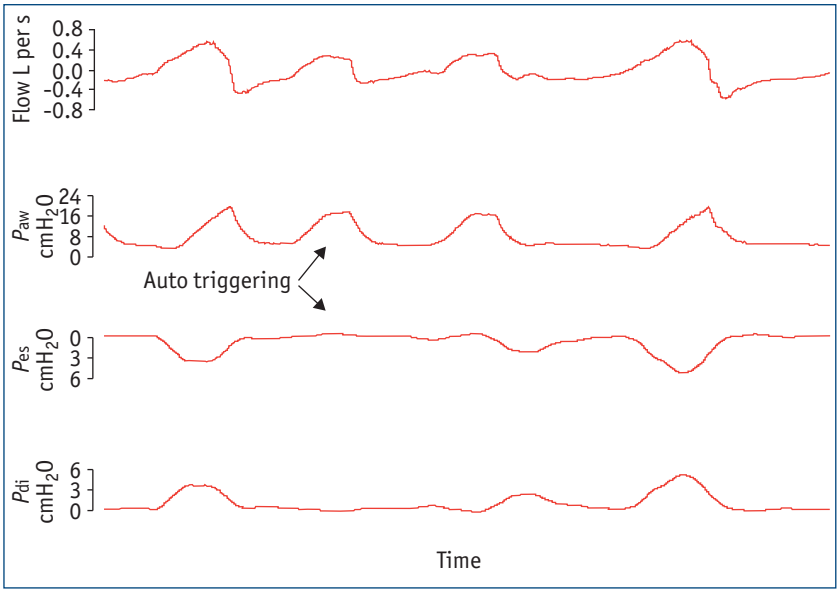


Figure 7

Flow, airway pressure (Paw), oesophageal pressure (Pes) and Pdi signals showing auto-triggering, defined as inspiratory flow delivered by the ventilator that is not triggered by the patient (see the flat Pes and Pdi curve).

inspiratory time breath by breath, permitting close matching with the patient's spontaneous breathing pattern.

Unfortunately this is not always successful. In intubated chronic obstructive pulmonary disease (COPD) patients, it has been shown that during PSV some inspiratory efforts do not trigger the ventilator [5]. These so-called ineffective efforts are very common in ventilator-dependent patients, especially when dynamic hyperinflation is present, and may be caused by an excessive inspiratory pressure delivered by the ventilator [6–7]. In COPD patients, because of the altered mechanical properties of the respiratory system, PSV is associated with important variations in tidal volume and PEEPi, even when the patient's effort is constant [8]. This may lead to very large expired tidal volume (~10 mL per kg) when the elasticity of the respiratory system is low. Therefore, the ventilator inflates long after the inspiratory muscles have stopped their contraction, indicating that part of the inspiration is passively driven by the machine alone. Based on this mechanism, the following breath is likely to happen at a high lung volume, when pressure at the airway opening is still significantly positive, so that inspiratory effort is not sufficient to create a pressure gradient capable of being sensed by the ventilator. VITACCA *et al.* [9] have demonstrated that during NIV, almost half of patients enrolled on home ventilatory programmes showed the presence of ineffective efforts. Interestingly enough, the use of a more sophisticated technique of titration, with the insertion of gastric and oesophageal balloons to record respiratory mechanics, reduced (to 30%) but did not eliminate the problem of asynchrony during NIV.

CALDERINI *et al.* [10] demonstrated that in patients affected by hypoxaemic respiratory failure due to AIDS-related pneumonia, patient–ventilator synchrony and patient effort improved when inspiration was time-cycled to exhalation compared with when it was flow-cycled. In the setting of NIV, where the presence of air leaks is inevitable, especially using "old generation" ventilators, inspiration can be prolonged, with machine cycling to exhalation only after the fixed maximum ventilator inspiratory time has passed (figure 8). As a matter of fact, when the patient's end-inspiratory flow is greater than the flow required to cycle the ventilator to exhalation, as in the presence of massive air leaks, the subject must activate accessory and expiratory muscles to force an increase in system pressure to allow exhalation. In this situation, the patient really "fights" the ventilator and therefore may cause NIV failure and/or intolerance. In the CALDERINI *et al.* [10] study, the synchrony of the patient could easily be improved (and therefore the tolerance) using a time-cycled pressure support that does not differ substantially from pressure-controlled ventilation, which is a pressure-limited, time-cycled ventilatory support that can be used both in controlled or assisted modes.

A challenging approach to improve the interaction between patient and machine would be to match ventilatory support with the neural output of the respiratory centres, so that the patient receives more assistance when demand is high and less assistance when demand is low.

Proportional assist ventilation (PAV) is a ventilatory mode in which inspiratory support stops exactly when the patient's neural output ends, so that a interaction between the two components should be achieved. Several studies have shown both in the acute and chronic settings that PAV delivered noninvasively may improve gas exchange, relieve dyspnoea and decrease inspiratory efforts, in the same fashion as PSV [11–13], but interestingly enough no difference was found in patient–ventilator interaction between PAV and PSV in a study performed in clinically stable COPD patients [14]. Conversely, in intubated patients, the Ranieri *et al.* [15] study showed that after hypercapnic challenge, the capability to increase minute ventilation was achieved at lower diaphragm energy expenditure and greater comfort during PAV than PSV.

A potential problem when using PAV is the fact that the triggering system is the same as that used in PSV or other modes of ventilation. In this setting, the ability to match the patient's effort with the start of the supported breath may be impaired in COPD patients by the presence of PEEPi, which is a threshold to overcome before the preset pressure or inspiratory flow are generated. This problem may be offset by applying extrinsic PEEP, which is able to reduce the trigger delay, but the exact level of PEEP to apply is not easy to determine in clinical practice, so that even during PAV the patient's neural output does not match the ventilatory support.

In an attempt to solve this problem, a new mode of ventilation called neurally adjusted ventilatory assist (NAVA) has recently been developed, in which the patient's neural output is quantified with the electrical activity of the crural diaphragm [16]. In this manner, cycling on and off is determined directly by EMG, whereas the amount of assistance for a given effort depends on the amplification factor set by the operator. With this ventilatory technique, the synchrony between the neural and mechanical inspiratory time should be guaranteed at any phase of respiration, irrespective of PEEPi and respiratory mechanics. Theoretically, it should also not be influenced by the mask "air leaks factor" that, as described before, is one of the main problems for patients undergoing NIV. The insertion of an oesophageal catheter is considered a "semi-invasive" procedure, and therefore, we are unsure whether this may be easily accepted by clinicians and patients when dealing with a "noninvasive" method of ventilation. NAVA is considered a very promising way of avoiding the use of a catheter, but unfortunately up to now we have no data about this particular ventilator.

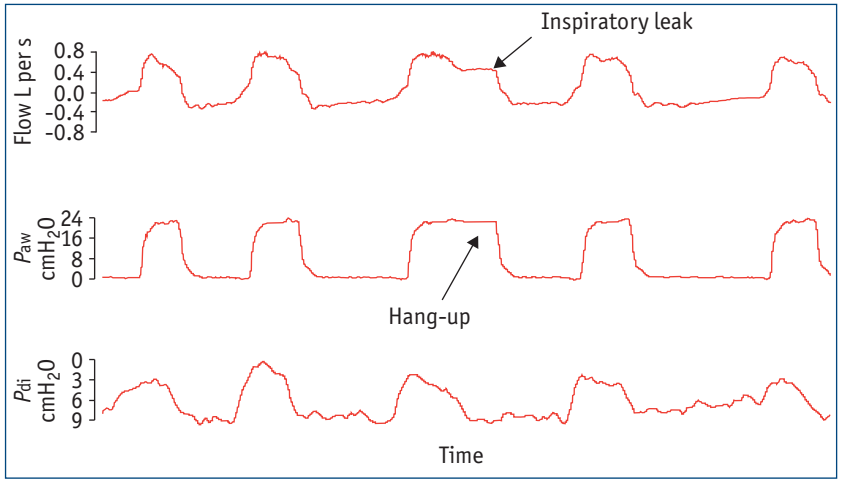


Figure 8
Flow, airway pressure (Paw), and Pdi signals showing an anomalous expiratory cycling due to an inspiratory leak. The end of expiration is obtained in this case by the ventilator reaching a pre-defined maximal inspiratory time value.

Ventilator settings

As described previously, the "neural start" of inspiration and the "ventilator start" are very difficult to match in real patients, and this holds particularly true for NIV. Apart from NAVA, most other ventilatory modes share similar inspiratory triggering systems regulated either by flow, pressure, volume or complex algorithms. Several bench studies have examined "inspiratory trigger variables" using NIV or intensive care unit (ICU) ventilators, but only two have systematically studied the effects of air leaks on trigger efficacy. The Stell *et al.* [17] study, considered 13 types of ventilators specifically designed for NIV against different combinations of tidal volume, airway resistance, functional residual capacity and mask leaks. Three of the ventilators had trigger delays of less than approximately 120 ms at both the beginning and end of expiration under all conditions. The trigger delays of other ventilators were mainly in the range of 120–300 ms, although exceptionally they were as long as 500 ms. Varying the conditions had a variable but generally small effect on triggering times, suggesting that there is a largely unavoidable element to the triggering delays intrinsic to the design of the ventilators. In particular, the authors found that there was a limited effect of leak on triggering delays, explained by the ventilators' cycling criteria at the beginning and end of inspiration being met rapidly. Vignaux *et al.* [18] have studied the performances of eight ICU ventilators with and without

the NIV module and in the presence or absence of air leaks. In the absence of leaks, all machines except two had a trigger delay of ≤100 ms. With leaks, there was wide variation between the machines: some of them increased, others remained unchanged or decreased the delay.

The only *in vivo* study was performed by NAVA *et al*. [19], and demonstrated that the flow triggering system is able to significantly reduce both the inspiratory effort and the delay (89 *versus* 117 ms), compared with the pressure trigger in normal subjects and COPD patients using an ICU ventilator.

However, these studies did not examine in detail the problem of patient–ventilator interaction, and it may be concluded that most of the ventilators commercially available have an "acceptable" intrinsic delay (<120 ms) in the inspiratory trigger, and that the flow triggering system may be more appropriate when using NIV.

The extrapolation of these studies to clinical practice is not easy, since one study [19] was performed on selected stable patients, and the others [17, 8] were bench studies, needing confirmation in patients. Indeed, the *in vitro* studies did not consider that during NIV the amount of leakage may vary within the same respiratory cycle. As a matter of fact, the dimensions of the leaks between the mask and the face would increase together with the rise in mask pressure because of the flexibility of the mask and of facial tissue, thus there is a risk of underestimating the leak that occurs at end-inspiration when the mask pressure may be high.

Lastly, in reality the assumption that the "most sensitive is the best" may not always be true. When setting a very "sensitive" trigger, a mechanical breath may, in some circumstances, be delivered without an inspiratory effort (autotriggering), such as in the presence of air leaks or water in the tubing. Another variable that has to be taken into account when setting NIV is the amount of time needed to reach inspiratory pressure.

The effects of initial flow rate have mainly been studied in intubated patients, where its variation has no effect on tidal volume, respiratory frequency and arterial blood gases, while a high pressure rise time is associated with a reduction in the inspiratory effort [20, 21]. A study by PRINIANAKIS *et al.* [22] assessed the effects of varying this parameter during NIV. In total, 15 patients with COPD recovering from an acute episode of hypercapnic respiratory failure were studied during four randomised trials with different initial flow rates. No significant changes were observed in breathing pattern and arterial blood gases between the different runs. The pressure time product (PTP_{di}/min) of the diaphragm, an estimate of its metabolic consumption, was significantly lower with all pressurisation rates compared with spontaneous breathing, but was significantly lower with the fastest rate. However, air leaks increased and the patients' tolerance of ventilation, measured using a standardised scale, was significantly poorer with the fastest pressurisation rate. Patient–ventilator interaction was assessed by calculating the number of ineffective efforts, which did not differ between the trials, and the ratio between the neural inspiratory time over the mechanical inspiratory time. This ratio was significantly shorter with the highest flow rate, indicating that despite the reduction in inspiratory effort, the mechanical breath delivered by the ventilator exceeded what was required by the patient. Therefore in this study two variables seemed to determine the tolerance to NIV: the presence of higher leaks, and a mismatch between the inspiratory time of the patient and that provided by the ventilator.

The manipulation of the expiratory trigger during PSV may also deeply influence patient–ventilator interaction. During PSV, the ventilator cycles into expiration when inspiratory flow decreases to a given percentage of peak inspiratory flow. In obstructive airways disease, the slower rise and decrease of inspiratory flow entails delayed cycling, an increase in PEEPi and nontriggering breaths. TASSAUX *et al*. [23] demonstrated that setting an expiratory trigger at a higher than usual percentage of peak inspiratory flow attenuates the adverse effects of delayed cycling and therefore improved patient–ventilator synchrony and simultaneously reduced inspiratory muscle effort.

Interfaces for NIV

There are currently six types of commercially available masks that can be used during an episode of acute respiratory failure (figure 9):

- full-face mask.
- total face mask.
- nasal mask.
- mouthpiece.
- nasal pillows or plugs.
- a helmet.

From a clinical point of view, the facial and nasal masks and the helmet have been shown to improve arterial blood gases, while the tolerance to ventilation delivered through the different kinds of interfaces seems to depend more on

the type of patient and severity of the episode of acute respiratory failure.

Physiological studies [25, 26] have compared the helmet and mask using the same ventilator settings, and showed that using the helmet the synchrony between the patient and the ventilator is poor, especially concerning the triggering delay.

VARGAS *et al*. [27] recently challenged the hypothesis that by using specific ventilator settings to apply NIV by helmet, the aforementioned shortcomings could be minimised, if not eliminated. Increasing the baseline inspiratory and expiratory pressures by 50% through both the helmet and oro-nasal mask, and applying the fastest pressurisation rate in NIV, it was observed that, despite a decrease in inspiratory muscle effort, patient–ventilator asynchrony remained higher with the face mask and baseline settings, compared with the baseline helmet settings where an improvement in inspiratory effort unloading and patient–ventilator synchrony was observed. Indeed, the only significant difference in synchrony induced by the higher helmet settings in the study by VARGAS *et al.* [27] was an improvement in the inspiratory trigger delay, an effect that was attributed to improved pressure and flow transmission, consequent to the lower helmet compliance with higher PEEP.

It is well possible that patient tolerance is related to synchrony that the subject is able to achieve with the machine, and therefore when considering the effect of the interface great care should be taken to avoid the presence of leaks.

Several authors, using different models, have studied the impact of air leaks during simulated NIV, but in their models leaks occurred through fixed-diameter holes placed in the circuit, so the leak rate was only defined by airway pressure and hole resistance. For example, in a study performed using a mathematical model, HOTCHKISS *et al.* [8] demonstrated that when PSV is applied in a semi-open system such as NIV, there is a substantial breath-to-breath variation in the duration of the inspiratory phase and auto-PEEP if the respiratory frequency is fixed, or in variability of the total respiratory time, inspiratory time and auto-PEEP if the frequency is allowed to vary. Interestingly, predicted instabilities are entirely independent of patient effort or volition. Since this unstable behaviour is mediated by auto-PEEP, the authors suggested that it is most likely to occur when the respiratory system time constant is long enough, for example in COPD patients. These unstable dynamics could clearly affect both the tolerance to ventilation and/or the matching between the machine and the patient, since an active initiation of expiration may be required. In an interesting laboratory study, SCHETTINO *et al.* [28] measured mask occlusion pressure as the difference between the airway pressure and the mask fit pressure recorded inside the mask's pneumatic cushion. They also measured the air-leak volume as the difference between proximal tidal volume and that distal to the mask. A pressure support level of 15 cmH_2O was the highest level that could be used without the occurrence of asynchrony (*i.e.* failure to cycle to exhalation). When pressure support level of 16 cmH_2O was used the mask occlusion pressure dropped to 1.1 cmH_2O and at this point all flow delivered by the ventilator leaked around the mask. These data, although obtained in a mechanical model, illustrate the possibility of monitoring the mask fit pressure and the mask occlusion pressure, which may be useful to guide mask fit and the inspiratory pressure setting during NIV and avoid leaks.

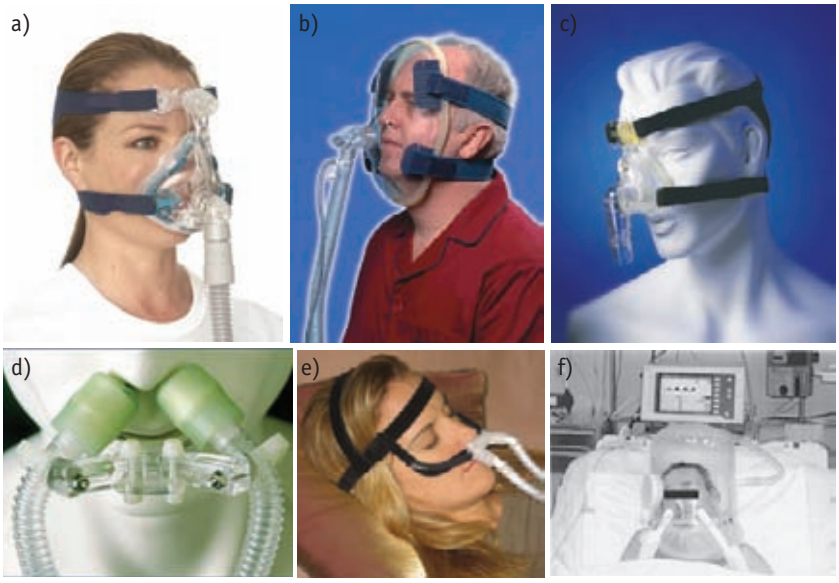


Figure 9
a) Full-face mask. b) Total face mask. c) Nasal mask. d) Mouthpiece. e) Nasal pillows. f) The helmet interface (reproduced from [24], with permission from the publisher).

Humidification

Very little is known about the impact of the humidification system on patient–ventilator synchrony. The recent international consensus conference on NIV stated that inadequate humidification may cause patient distress, but also that available data on humidification devices were too scarce to allow specific recommendations in this area [29]. Mouth leaks with continuous positive airway pressure (CPAP) ventilation have been shown to lead to high unidirectional nasal airflow, which causes a large increase in nasal resistance that may be prevented by humidification of the inspired air [30]. The prevalence of nasal symptoms during NIV is associated with reduced compliance to ventilation using both

noninvasive CPAP or PSV [31]. Therefore, over the years great attention has been paid to the effects of different humidification devices. LELLOUCHE *et al.* [31] have found that in patients receiving NIV for moderate-to-severe acute hypercapnic respiratory failure, the use of heat and moisture exchangers (HMEs) lessens the efficacy of NIV in reducing inspiratory effort compared with heated humidifiers (HHs). This may be due to an increase in dead space, responsible for the negative effects on gas exchange. How the humidification device may influence the triggering functions is unknown; however, the increase in inspiratory effort and dead space may indirectly suggest that using HME may theoretically interfere with the interaction between patient and machine. However, one potential problem using HH is the possibility that condensation of the water in the circuit may interfere with the triggering system, increasing the possibility of auto-triggering.

Sedation

While sedation represents the mainstay of treatment in the care of patients suffering from end-of-life respiratory failure, it can be a dangerous if improperly employed, especially during NIV. Since lack of cooperation is a well-recognised cause of NIV failure, sedation could theoretically improve patient–ventilator interaction; however, if the altered mental status of a fighting or agitated patient is the direct consequence of hypoxia and hypercapnia, then sedation would only cause an already unstable clinical situation to deteriorate.

A recent survey about the use of sedation during NIV [32] showed that most physicians use sedation and analgesic therapy infrequently for noninvasive positive-pressure ventilation to treat acute respiratory failure, but practices vary widely within and between specialties and geographical regions. In particular, sedation, analgesia and hand restraints were more commonly used by North Americans than Europeans. Benzodiazepine alone was the preferred sedation, followed by an opioid alone. Europeans were less likely to use benzodiazepine alone but more likely to use an opioid alone. Sedation was usually administered as an intermittent *i.v.* bolus, outside of a protocol, and was assessed by a nurse using clinical end-points rather than a sedation scale.

Opioids (morphine and fentanyl) have the most powerful analgesic effect but at a usual dosage they cause respiratory depression (which is of particular concern in spontaneously breathing patients) as well as other adverse effects like hypotension, bradycardia, ileus, alteration of the level of consciousness with possible hallucinations and agitation. Newer opiods (sufentanil) with a favourable pharmacokinetic profile are suitable agents for "awake" sedation during partial ventilatory support [34] at a continuous infusion ratio from 0.2–0.3 µg per kg per h without any change of respiratory drive and ventilatory pattern; although this refers to intubated patients, it must be taken into account for its potential application during NIV.

A reasonable choice, at present, is to administer very small doses of opioids (fentanyl and morphine) but only in cases where a moderate blunting of respiratory drive is highly desirable. A pilot study has shown that remifentanil-based sedation was able to improve the tolerance to NIV in patients with acute respiratory failure previously intolerant to the technique [35].

Among the benzodiazepines, a small dose of lorazepam (0.5–1 mg) may be recommended since it has the advantage of fewer drug interactions compared with diazepam and midazolam because of its metabolism *via* glucuronidation. It is indicated for younger patients, for those under chronic benzodiazepine use and for patients with preserved lean mass and muscular force, where a mild muscle relaxant effect elicited by benzodiazepines can be desirable.

Clinical implications of dyssynchrony

As previously explained, the main mechanism underlying dyssynchrony is the mismatch between patient and ventilator inspiratory time that generates "wasted" or ineffective efforts. At the extreme, this can lead to a situation of fighting against the ventilator with increased use of sedatives and prolonged duration of mechanical ventilation. The most immediate and common consequence of these ineffective efforts is the extra load on the respiratory muscles, which have often already adapted to increased elasticity, resistivity and threshold workload due to the underlying respiratory disease. While this increased load can be overcome with ease in patients with well preserved muscular force, in difficult-to-wean patients this force-load imbalance can significantly hamper the process of weaning from mechanical ventilation [36]. One of the most frequently used indicators of the work of breathing is PTP_{di}/min [37]. Both PSV and PAV have demonstrated a capacity to decrease the PTP_{di}/min compared with spontaneous breathing [38,

39], but they may have different effects on the possibility of avoiding gross asynchronies [40]. With PSV, in fact, the higher the inspiratory pressure the greater the number of wasted efforts, because the mechanical inspiratory time outlasts the neural one, worsening lung hyperinflation and hampering lung emptying. With PAV, on the other hand, this risk is theoretically reduced, since airway pressure is continuously adjusted in proportion to the predicted inspiratory muscle effort without a preselected target pressure.

Another clinical aspect closely linked to synchrony between patient and machine is the adaptation of a ventilatory modality to the patient's changing respiratory demand. This issue has been addressed by Ranieri *et al.* [41] and Grasso *et al.* [42] who artificially induced an increase in dead space and in respiratory load. In both cases, the degree of PTP/min reduction was greater with PAV compared with PSV and this also implied a reduced sensation of dyspnoea, thus giving further support to the tight link between synchrony and the comfort of breathing.

Finally, in the majority of cases, synchrony between the patient and the machine has been assessed during the daytime, often overlooking what happens during sleep. However, it must be pointed out that a poor patient–ventilator interaction during sleep can lead to sleep fragmentation, frequent arousals and inadequate correction of nocturnal hypoventilation. This problem was addressed by Fanfulla *et al.* [43], who studied the effect of different ventilator settings on sleep and inspiratory effort in a group of patients affected by neuromuscular disease. The authors found that setting the ventilatory parameters on an empirical basis during the awake state can often lead to dyssynchrony during sleep and to difficult triggering of the mechanical breath, due to an incorrect titration of inspiratory support and PEEP. Conversely, a physiological setting based on the measurement of inspiratory effort allows a reduction of the ineffective efforts with improved sleep quality and gas exchange. In another interesting study, dealing with a group of patients already enrolled in a programme of long-term domiciliary ventilation for both restrictive and obstructive diseases, and apparently reporting good tolerance to NIV, it was evidenced that ineffective efforts were quite common and could be considered a silent phenomen, being detectable only with polysomnography [44]. Patients with the highest index of ineffective efforts were, again, those with the more advanced respiratory diseases and with higher levels of inspiratory assistance, giving a further demonstration of the close link between mechanical overassistance, lung hyperinflation and ineffective efforts.

To date, the presence of dyssynchrony during mechanical ventilation has been described mainly in COPD patients, and especially in those with low elastance and/or high levels of auto-PEEP [5, 26, 36] and in patients with restrictive thoracic disorders [43, 44]. In those affected by different pathologies (*i.e.* acute respiratory distress syndrome or pneumonia) this phenomenon is not frequently observed. This may be partly due to the different mechanical properties of the respiratory system, or just because the published studies were not focused on these populations of patients.

Summary

In summary, this review has discussed the clinical occurrence, the pathophysiology and the possible solutions of a bad interaction between the patient and the ventilator mainly during NIV. Some examples of the most common dyssynchronies that can be easily recognised with a close observation of the flow and airway pressure traces were illustrated, in the hope that this may assist the clinician in the correction of the problems that may determine this bad interaction between the "two brains" (*i.e.* the patient and clinician responsible for the machine settings).

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Educational questions

1. The gold standard to assess the neural inspiratory time is:
a) the transdiaphragmatic pressure (P_{di}).
b) the diaphragm electromyography (EMG).
c) the flow signal of the ventilator.
d) the pressure at the airways opening (P_{aw}).
2. A "reasonable" delay of the inspiratory trigger system is:
a) <20 ms
b) <300 ms
c) <100 ms
d) there is usually no delay, since the trigger is almost instantaneous to the patient's effort
3. Which of the following is NOT true?
a) The presence of ineffective efforts may be detected on the flow trace.
b) There are few noninvasive algorithms able to assess the presence of ineffective efforts.
c) The presence of ineffective efforts is usually associated with a high level of inspiratory support.
d) Using an ICU ventilator, you may easily avoid the occurrence of ineffective efforts.
4. During noninvasive pressure support ventilation, which of the following is true?
a) A high initial flow rate (or fast pressurisation rate) is associated with an increased effort by the patient.
b) A low initial flow rate (or slow pressurisation rate) is associated with the presence of higher air leaks.
c) A high initial flow rate (or fast pressurisation rate) is associated with the presence of higher air leaks.
d) The amount of air leaks and the effort by the patient are not influenced by the setting of the initial flow rate.

Suggested answers
1. b
2. c
3. d
4. c