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Achieving Patient/Ventilator Synchrony -- Good Luck

Aaron B. Holley, MD | December 13, 2016

Patient/Ventilator Dyssynchrony

What is patient/ventilator synchrony? Broadly speaking, a patient and ventilator are in synchrony when the settings on the ventilator are matched with what the patient's respiratory system is trying to achieve. The respiratory system continually integrates feedback from chemoreceptors, stretch receptors, and baroreceptors to determine intrinsic respiratory drive. Along with cortical input, this feedback is used for breath-to-breath adjustments to respiratory effort, tidal volume, and cycle time. Breath-to-breath adjustments are generally small, assuming there are no major changes to input. If any of several different ventilator settings aren't meeting the patient's respiratory demands, asynchrony can occur.[1]

A concise clinical review published in the *American Journal of Respiratory and Critical Care Medicine*[1] in 2013 provided an excellent summary of patient/ventilator interactions. Breath trigger, gas delivery (target), and cycle settings must provide what the patient needs to prevent dyssynchrony. In the world of low tidal volume ventilation,[2] positive end-expiratory pressure,[3] and driving[4] and plateau pressure targets, other settings are often overlooked. Unfortunately, patient/ventilator dyssynchrony can dramatically increase work of breathing and transpulmonary pressure,[5] negating efforts to rest the respiratory system and protect the lung through recruitment and low tidal volumes.

A recent study published online in the *Annals of the American Thoracic Society*[6] attempted to quantify the effects that tidal volume and mode have on dyssynchrony (defined as lack of simultaneous timing of patient and ventilator trigger, flow, or cycling). Researchers enrolled 19 critically ill, mechanically ventilated patients. Ten of these patients (52.6%) had acute respiratory distress syndrome (ARDS), and all had a PaO_2/FiO_2 ratio < 300 mm Hg (13 [68.4%] had a PaO_2/FiO_2 ratio < 200 mm Hg).

Ventilator targets were adjusted to provide tidal volumes of 6, 7.5, or 9 mL/kg predicted body weight, and two different modes were used: volume assist-control (VC) at a set flow rate of 50 L/min, or adaptive pressure control (APC) mode (Volume Control Plus, Puritan Bennett™ 840).[7] Trigger, flow, and cycle dyssynchronies were measured at each volume, on each mode in every patient.

The researchers calculated a dyssynchrony index (DI) to quantify and compare patient interactions with each volume and mode. "Severe dyssynchronies" were those considered to be "clearly detrimental to patients and most noticeable to clinicians."

Their findings weren't particularly surprising. The DI was inversely related to tidal volume, and APC generally allowed a reduction in the DI at any given tidal volume target. The severe DI followed the same pattern. At the same tidal volume target, patients on APC achieved higher expiratory volumes than those on VC, but this difference was rarely > 1 mL/kg.

The researchers concluded that APC can reduce the DI with minimal increase in risk for volutrauma and ventilator-induced lung injury.

Implications and Limitations

This study is a welcome addition to the literature, and the authors should be commended for their work. It's not easy to control for all of the variables that influence patient/ventilator interactions. Nor is it easy to quantify dyssynchrony and gauge its effects.

The DI, and particularly severe DI, are subjective, however, because they rely on an individual's inspection of the ventilator's flow and pressure tracings. The validity of the study could have been increased by evaluating the tracings and statistically assessing interevaluator agreement. Only one investigator measured dyssynchrony.

In addition, the investigators weren't blinded to mode or volume settings. Granted, blinding would have been difficult to achieve—visual inspection of flow and pressure tracings would provide information on mode, and volume could

be calculated from flow. Nonetheless, the absence of blinding is a study limitation. It helps that neither author has received money from the company that markets the Puritan Bennett ventilator (according to the funding disclosures in the manuscript).

A review of the statistics and visual inspection of the figures and tables show that the DI wasn't normally distributed across the 19 patients. Table 2 shows that the median percentage occurrence was zero for most types of dyssynchrony. In Figure 2, it is evident that patients were clustered at opposite ends of the DI. They were either close to 100% or below 20%, with no "in between." This implies that patients either tolerated the settings well, or not at all. The patients who didn't clearly drove the difference between volume settings and mode, and they should receive special attention.

There is a difference in the median DI between modes and volumes, but there is also a difference in exhaled volumes between VC and APC. Are the same patients who achieved a DI reduction also achieving the largest increase in exhaled tidal volume? If so, perhaps volume is driving all of the dyssynchrony.

Other issues, such as restricting all patients in the VC group to a flow rate of 50 L/min, also limit generalization. Most clinicians would set the flow rate higher at baseline, or simply increase it to reduce the severe flow dyssynchronies seen in this group.[8] An increase in tidal volume or change in mode would not be necessary.

The Richmond Agitation-Sedation Scale scores and PaO_2/FiO_2 varied enough that respiratory drive probably differed significantly across patients. Whenever ventilator settings are standardized without allowing for individual requirements, some patients will be dyssynchronous. It may be that the patients with DI indices close to 100% simply had higher respiratory drives, making compliance with low tidal volumes and fixed flow rates difficult. Such is life when your sample size is only 19 patients and you are trying to control for multiple physiologic variables that can influence dyssynchrony rates.

Limitations aside, the study has value. This is not the first group to draw attention to the effect of tidal volume on synchrony,[9] but in today's world of low tidal volume ventilation, the relationship deserves emphasis. The ARDSNet investigators recognized the effects that the settings they advocated could have on dyssynchrony. They even included a dyssynchrony measure in their protocol and advised adjustments for breath stacking.[2,9,10]

No matter what, clinicians should expect dyssynchrony with severe ARDS when trying to limit pressure and volume (unless you are going to blunt respiratory drive with narcotics or paralyze your patient). In fact, this may be why neuromuscular blockade has the most benefit for those with severe ARDS: Dyssynchrony is eliminated when it would otherwise be present.[11]

On the basis of this study's results, APC is a reasonable mode to start with if your patient needs ventilatory support. For those with severe ARDS, however, I would assume that adjustments will need to be made. I would also watch the tidal volume to ensure that it isn't excessive. We have yet to find a ventilator mode that can mimic the patient's respiratory centers and replace the need for a physician at the bedside.

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Patient–Ventilator Interactions

Implications for Clinical Management

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Assisted/supported modes of mechanical ventilation offer significant advantages over controlled modes in terms of ventilator muscle function/recovery and patient comfort (and sedation needs). However, assisted/supported breaths must interact with patient demands during all three phases of breath delivery: trigger, target, and cycle. Synchronous interactions match ventilator support with patient demands; dyssynchronous interactions do not. Dyssynchrony imposes high pressure loads on ventilator muscles, promoting muscle overload/fatigue and increasing sedation needs. On current modes of ventilation there are a number of features that can monitor and enhance synchrony. These include adjustments of the trigger variable, the use of pressure versus fixed flow targeted breaths, and a number of manipulations of the cycle variable. Clinicians need to know how to use these modalities and monitor them properly, especially understanding airway pressure and flow graphics. Future strategies are emerging that have theoretical appeal but they await good clinical outcome studies before they become commonplace.

Keywords: ventilatory drive; muscle loading; breath triggering; flow synchrony; cycle synchrony

Mechanical ventilatory support can be controlled entirely by the ventilator (controlled ventilation in a passive patient) or can interact with patient breathing efforts (assisted/supported ventilation in an active patient) (1). Controlled mechanical ventilation provides a clinician-set ventilatory pattern and minute ventilation but often requires heavy sedation or even neuromuscular blockade to silence ventilatory muscle activity. Unfortunately, silent ventilatory muscles are at risk for the oxidative stress, muscle atrophy, and proteolysis with loss of force-generating capacity that are characteristic of ventilatory-induced diaphragmatic dysfunction (2, 3). Moreover, heavy sedation use that may be required with controlled ventilation has been shown to lengthen the need for mechanical ventilation (4, 5).

In contrast, assisted/supported ventilation is designed to interact with patient muscle activity and "share" the work of breathing (6–8). If properly done, assisted/supported ventilation facilitates ventilatory muscle recovery and generally requires less sedation (7–9). For this to occur, however, the ventilator's flow and pressure delivery must synchronize with patient effort during all three phases of breath delivery: breath initiation, flow delivery, and breath termination. Synchronous support means that the ventilator's timing and pressure–flow delivery respond promptly to patient effort, provide pressure and flow that avoid excessive muscle loading, and terminate when patient effort ends. Dyssynchronous interactions can overload ventilatory muscles ("imposed" loads), compromise alveolar ventilation, overdistend alveolar units, disrupt sleep patterns, and cause patient discomfort prompting additional sedation. Importantly, dyssynchronies can result from either inappropriate patient ventilatory drive or suboptimal ventilator settings (or both) (7).

The remainder of this article focuses on four aspects of patient–ventilator interactions: (*1*) a brief review of the spontaneous breathing pattern and how the central ventilatory controller (neural drive) is impacted by respiratory failure and mechanical ventilatory support; (*2*) a brief review of ventilatory muscle physiology and the relationship between loading and function in the context of assisted ventilation; (*3*) a discussion on clinical manifestations of synchronous and dyssynchronous interactive breaths; and (*4*) a review of basic and advanced features of modern mechanical ventilators designed to enhance synchronous patient–ventilator interactions.

SPONTANEOUS BREATHING PATTERN AND MECHANICAL VENTILATORY SUPPORT

The ventilatory pattern (tidal volume [V_T], rate, and inspiratory-to-expiratory ratio) is controlled by a collection of neurons located in the brainstem (ventilatory control center). This center has an inherent respiratory rhythm generator that interacts with several inputs. Two important series of inputs come from chemoreceptors (P_{O_2}, P_{CO_2}, and pH receptors) located in the great vessels and fourth ventricle of the brain; and from mechanoreceptors (i.e., stretch and irritant receptors) in the thorax and ventilatory muscles (10–15). The ultimate ventilatory pattern generated by the normal ventilatory control center is generally the one that provides adequate gas exchange (i.e., a physiologic pH and a P_{O_2} that fully saturates hemoglobin) with the least amount of ventilatory muscle loading and air trapping (16). Cortical inputs (e.g., pain, anxiety, stress, artificial airway presence) can also influence this pattern—usually stimulating overall ventilatory drive (10, 11). In contrast, drugs (e.g., sedatives, opioids) and CNS injuries may often depress the overall ventilatory drive. The sleep state can also modulate these responses (10, 11).

The ability of mechanical ventilatory support to provide adequate gas exchange can have profound effects on the ventilatory controller. Increased metabolic demands, acidosis, and hypoxemia all stimulate the ventilatory controller to increase minute ventilation (10–15). The effectiveness of mechanical ventilatory support in addressing these metabolic derangements will clearly modulate these responses.

Mechanical ventilatory support can also affect the ventilatory controller through its effects on muscle loading (10–15). Delayed

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or missed triggers are sensed as an uncomfortable isometric load leading to increased effort intensity and pronounced dyspnea. If excessive muscle loading is sensed during flow delivery, this usually leads to alterations in the spontaneous ventilatory pattern to reduce this loading (e.g., rapid shallow breathing) and also is often accompanied by dyspnea (10–15, 17). Mechanoreceptors can also sense overventilation and overdistention, which often lead to shortening of neural inspiratory time (T_I) and even activation of expiratory muscles (14). It must also be remembered that modes of ventilatory support that provide more than one breath type (e.g., intermittent mandatory ventilation or IMV modes) may have additional effects on the ventilatory control center. Specifically, IMV modes do not allow the patient's ventilatory control center to accurately anticipate the loading pattern of the next breath, and thus adapting to the applied pattern of support may be more difficult to achieve (7, 18, 19).

The timing of set or controlled mechanical breaths can also affect the ventilatory control center. Often a mechanical breath will suppress the generation of spontaneous breaths (10, 15). However, the observation has also been made that "entrainment" can occur during controlled mechanical ventilatory support (20–22). Entrainment is the phenomenon of a machine-triggered mechanical breath eliciting a spontaneous effort. This appears to be mediated through vagal pathways and mechanical stretch receptors, often occurring in heavily sedated patients with high control breath rate settings (20). Entrainment can occur with every control breath or, less commonly, in 1:2 or 1:3 relationships with the control breaths. Moreover, entrainment can be present for varying periods of time. The induced effort from entrainment can result in an augmented V_T if it occurs before the end of a pressure-targeted assisted breath. However, if it occurs after the termination of either a pressure- or a flow-targeted breath, it can trigger a second breath.

Ventilator breath cycling criteria can also impact the ventilatory control center (10, 15, 23, 24). A mechanical breath termination shorter than the neural T_I (machine $T_I <$ neural T_I) can lead to muscle activity beyond the machine's flow delivery phase, which can lead to high muscle loading, excessive V_Ts, and/or triggering of a second breath. In contrast, when mechanical breath cycling terminates after the inspiratory effort has ended (machine $T_I >$ neural T_I), dyspnea and expiratory muscle recruitment may occur in an effort to terminate the breath.

Finally, it is worth noting that because dyssynchronous interactions often result in anxiety and dyspnea, which can stimulate overall ventilatory drive, improving synchrony in one area (e.g., triggering) can help facilitate achieving synchrony in other areas (e.g., flow demand) (18).

VENTILATORY MUSCLE PHYSIOLOGY: LOADING, FUNCTION, AND DYSSYNCHRONY

The most significant and well studied of the muscles of ventilation is the diaphragm. This musculotendinous sheet of skeletal muscle separating the thoracic and abdominal cavities is the primary muscle of ventilation and most used skeletal muscle (25). Although many of the physiologic principles of skeletal muscle can be applied to the diaphragm, including the length–tension relationship, unique adaptations exist. Compared with limb muscles, the diaphragm has a greater proportion of fatigue-resistant type I muscle fibers with increased mitochondrial density, oxidative capacity, and maximal oxygen consumption (25, 26). These smaller muscle fibers have an increased capillary density that facilitates more efficient O_2 diffusion and are further fueled by the potential to augment blood flow up to four times that of limb muscles while shifting regional blood supplies from other skeletal muscle beds (26).

Lung inflation occurs when a sufficient force is generated to overcome the various elastic and resistive loads to effect gas delivery to the alveoli (27). This is largely accomplished by the diaphragm through its piston-like action that expands the thorax and pushes abdominal contents away. In addition, ventilatory demands recruit the external intercostals and accessory muscles of inspiration, which have similar adaptations, to support the diaphragm by lifting and expanding the rib cage (25). Importantly, the role of the intercostal muscles in supporting ventilation is diminished in the supine position (25).

The simplified equation of motion defines the necessary pressure (Ptot) required to overcome the loads of respiratory system elastic recoil (Pel) and airway resistance (Pres) for a given flow ($\dot{V}$) and volume change (ΔV):

$$\text{Ptot} = \text{Pel} + \text{Pres} \quad (1)$$

$$\text{Ptot} = \left(\Delta V/\text{Crs}\right) + \left(\text{R}\times\dot{V}\right), \quad (2)$$

where Crs is respiratory system compliance, and R is airway resistance (27). Individual contributions of inertness and lung tissue resistance are also present but are small and generally disregarded. When present, overcoming intrinsic positive end-expiratory pressure (PEEP) also contributes to the pressure requirements to breathe. Note that Ptot can be supplied entirely by the ventilatory muscles (Pmus) during unassisted breathing or by the mechanical ventilator (Pv) during controlled mechanical ventilation. With interactive breaths Ptot has contributions from both.

Ventilatory muscle failure can be defined as the loss of the ability of ventilatory muscles to generate force (Pmus) in response to these loads to adequately provide for the patient's ventilatory needs. Ventilatory muscle failure with its ensuing alveolar hypoventilation and hypercapnic respiratory failure is thus ultimately related to an imbalance in ventilatory muscle capabilities versus the demands placed on those muscles (28, 29). Ventilatory muscle capabilities are determined by inherent strength and endurance properties, which can be profoundly diminished in critically ill patients with metabolic derangements associated with the systemic inflammatory response syndrome (30–32). Capabilities can also be diminished as a consequence of lung hyperinflation, literally flattening the diaphragm and thereby placing it at a substantial mechanical disadvantage through an unfavorable length–tension relationship (26). Limitations in energy supply imposed by hypoperfusion, anemia, hypoxia, malnutrition, or the inability to extract oxygen such as is seen in sepsis and cyanide poisoning also predispose to ventilatory muscle failure (29, 32, 33). Weak muscles are also less efficient and require more energy in relation to their maximal energy consumption to perform a given task (30).

Increases in ventilatory muscle demands result primarily from increased mechanical loads resulting from abnormal respiratory system mechanics (including assuming the supine position) and/or increased ventilation needs (28–31). Dyssynchronous patient–ventilator interactions can also result in imposed loads on the muscles. Mechanical loads can be described as a single value, work (W), or as a pressure–time product (PTP) (28). Work is the integral of pressure over change in volume and PTP is the integral of pressure over T_I. PTP, with its reliance on the pressure–time component of loading, correlates better with ventilatory muscle energetics and O_2 consumption than work does, and is increasingly used clinically to measure the energy demands on ventilatory muscles (34–36).

Assessing required pressure as a fraction of maximal pressure-generating capabilities and coupling this with the fraction of the ventilatory duty cycle devoted to muscle contraction

(T_I/T_{tot}) has led to the concept of the pressure–time index (PTI):

$$PTI = (P_I/P_{I_{max}})(T_I/T_{tot}), \quad (3)$$

where $P_I/P_{I_{max}}$ is the mean inspiratory pressure required per breath/maximal inspiratory pressure (34). In a normal subject at rest PTI values are generally less than 0.05 and even at high levels of exercise rarely exceed 0.1. However, PTI values greater than 0.15 for the diaphragm and 0.3 for rib cage muscles are related to the development of ventilatory muscle failure (34).

All of the components of the PTI are likely abnormal in patients with respiratory failure. In patients with high resistive loads such as chronic obstructive pulmonary disease, asthma, and/or large airway obstructions; or high elastic loads such as interstitial lung disease, cardiogenic pulmonary edema, and/or acute respiratory distress syndrome (ARDS) the required ventilatory pressures (P_I) can be substantial. As discussed more below, the imposed loads from dyssynchronous interactions in critically ill patients can also contribute to a need for a high P_I. A low $P_{I_{max}}$ reflects the reduced capabilities of ventilatory muscles in the setting of critical illness noted previously. Finally, in acute respiratory failure, the higher minute ventilation requirement may be associated with an increased T_I (larger V_T) and shortened T_{tot} (faster respiratory rate). This combination can greatly increase T_I/T_{tot}.

Taken together, the components of the PTI often change unfavorably in the setting of acute respiratory failure and likely contribute to ventilatory muscle failure. Thus, management of such patients should address all of these factors: minimize disease-imposed loads, minimize ventilator-imposed loads, minimize excessive ventilation demands, minimize inappropriate ventilation patterns produced by patient dyspnea/discomfort, and maximize support of muscle metabolic function. Discussing all of these is beyond the scope of this article. Instead, the final two sections below focus specifically on the role and management of ventilator-induced imposed loads during patient–ventilator interactions.

CLINICAL MANIFESTATIONS OF SYNCHRONOUS AND DYSSYNCHRONOUS INTERACTIVE BREATHS

Interactive breaths can be described as assisted (patient-triggered and time- or volume-cycled breaths) or supported (patient-triggered and flow-cycled breaths). Assisted/supported ventilator breaths interact with patient efforts during all three breath phases: initiation (trigger), gas delivery (target), and termination (cycling) (7). The dyssynchronies associated with each of these phases (Table 1) are discussed below.

Breath Triggering

Trigger dyssynchrony is of two types. The first is missed or delayed triggering. One cause for this is an insensitive or poorly responsive triggering system. On most ventilators a patient's effort is sensed through either a drop in circuit pressure (pressure trigger) or a change in a circuit bias flow (flow trigger) (37, 38). Inherent in all patient-triggering systems is a built-in insensitivity to prevent autotriggering (*see below*). There are also mechanical triggering delays due to the inherent responsiveness characteristics of a ventilator's valving systems.

TABLE 1. PATIENT–VENTILATOR DYSSYNCHRONIES

Phenomenon	Specific Clinical Characteristics*	Possible Interventions
During triggering phase		
Delayed/missed triggers		
Insensitive and/or unresponsive systems	Paw, Pes, flow tracings show delayed/absent response to effort	More sensitive and/or responsive trigger settings
Intrinsic PEEP (PEEPi)	Paw, Pes, flow tracings show delayed/absent response to effort, Pes presence of PEEPi, expiratory flow never reaches 0	Reduce PEEPi Balance PEEPi with PEEPe
Extratriggering		
Autocycling	Extra breaths triggered by artifacts (cardiac, circuit motion)	Less sensitive settings
Entrainment	Efforts triggered by controlled inflations, can add to V_T with pressure target breaths	Fewer controlled breaths, less sedation (?)
Premature cycling of patient-triggered breath	Persistent effort in setting of premature breath cycling initiates second breath	Lengthen cycle criteria (volume, time, flow)
During flow delivery phase		
Inadequate flow	Excessive effort during breath, Paw "sucked down," high Pes PTP during assisted breath, inadequate V_T with pressure target breaths	Increase flow, change flow pattern, use variable flow (pressure targeting), pressure rise time increase Address excessive drive†
Excessive flow	Expiratory efforts to terminate breath, higher V_T with pressure target breaths, reflex neural T_I shortening	Reduce set flow or pressure target or pressure rise time
During cycling phase		
Neural T_I > machine T_I	Effort continues despite breath termination, Paw "sucked down," can trigger second breath	Lengthen cycle criteria (volume, time, flow) Address excessive drive† (including entrainment)
Machine T_I > neural T_I	Expiratory effort to terminate breath	Shorten cycle criteria (volume, time, flow) Address depressed drive†

Definition of abbreviations: Paw = airway pressure; PEEPi and PEEPe = intrinsic and extrinsic or set positive end-expiratory pressure, respectively; Pes = esophageal pressure; PTP = pressure–time product; T_I = inspiratory time; V_T = tidal volume.

* General signs of dyssynchrony include respiratory distress, diaphoresis, tachycardia, anxiety.

† If present.

Engineering advances have produced triggering systems that generally require only a small portion of the total effort of inspiration to initiate assisted/supported breaths. However, in the presence of very vigorous patient efforts, even the best systems may not be sensitive or responsive enough to avoid a significant triggering load (37, 38). Clinically these loads can be identified by an observed patient effort either failing to trigger a breath or having the triggering noticeably delayed. On the airway pressure–time graphic, there may be marked airway pressure deflections present before breath triggering. On the expiratory flow–time graphic, there may be evidence of transient flow reversal during missed trigger efforts.

A second cause of missed or delayed triggers occurs in the presence of intrinsic PEEP (PEEPi). This occurs because the patient's ventilatory muscles must first overcome the PEEPi in the alveoli before any circuit pressure or flow change can occur to trigger a breath (39, 40). This can sometimes be appreciated by noting abrupt expiratory flow termination before a triggered breath or transient expiratory flow reductions or reversals that do not trigger a breath (Figure 1). In some cases, PEEPi can also be detected by measuring airway pressure during an expiratory pause. However, this may not always be evident in the setting of patient inspiratory efforts or in severe airway obstruction with collapsing small airways.

Patient effort and delayed/absent ventilator triggering can be better appreciated if a diaphragmatic EMG or an esophageal pressure (a surrogate for pleural pressure) is available as these techniques directly assess the timing of ventilatory muscle contraction. Coupling these measurements to the onset of flow delivery will clearly demonstrate the missed or delayed trigger (41–43). Moreover, the esophageal pressure–time tracing can be used to quantify any PEEPi present and the muscle PTP related to the imposed triggering load (44). For example, Leung and coworkers used esophageal pressure measurements to show that ventilatory muscle loading (PTP) was 38% higher for missed triggers than for properly triggered breaths (43). In contrast to delayed or missed breaths, a second type of trigger dyssynchrony is excessive triggering. This can be caused by autotriggering, entrainment, or premature cycling of breaths (37, 38). Autotriggering occurs when even small circuit leaks, tube condensation, and/or cardiac oscillations may trigger breaths and produce undesired hyperventilation and/or breath stacking with PEEPi. These extra breaths can result in significant apparent "tachypnea" and hyperventilation. As a consequence, some insensitivity in the triggering system often must be tolerated.

Another mechanism for extra triggering is in the setting of persistent effort after the machine breath has terminated (neural T_I > machine T_I) (37, 38). Under these circumstances, the second breath is tightly linked to the original breath and results in an increase in the measured ventilator rate.

A final mechanism of extra triggering occurs with the entrainment phenomenon described previously (20–22). When this occurs the effects of the stimulated effort depend on the timing and the breath type. If the stimulated effort occurs before the original breath has ended it can result in either an isometric load with airway pressure reductions (flow- and volume-targeted breaths) or as an addition to the V_T (pressure-targeted breath). However, if the stimulated effort occurs after the original breath has ended, a second breath can be triggered. Like the double triggering from a prolonged neural T_I and short machine T_I described previously, the additional triggering from entrainment will often increase the measured breath rate. Similarly, the second breath will graphically be tightly linked to the original breath.

Flow Dyssynchrony

Once a breath is patient effort triggered, diaphragmatic contraction continues to occur (45, 46). If flow is synchronous with that contraction pattern, the inspiratory muscle pressure–volume profile conceptually should resemble a near normal pattern (Figure 2). Note from Figure 2 that flow synchrony does not mean the elimination of the work of breathing. Instead it means providing flow to "reshape" the inspiratory muscle's pressure–time or pressure–volume profile to a more physiologic configuration.

Flow dyssynchrony from inadequate flow delivery can be appreciated clinically by observing inspiratory efforts that appear "flow starved" (vigorous inspiratory efforts unrewarded by adequate flow) and accompanied by marked patient discomfort. Examining the airway pressure–time profile can be useful in assessing flow dyssynchrony (Figure 3). In general, an airway pressure–time tracing that is smooth and consistently positive during inspiration suggests that flow is likely adequate to avoid excessive muscle loading (Figure 3, *left*). In contrast, a pressure–time waveform being "sucked down" by patient effort suggests that the delivered flow is markedly less than patient demand and excessive muscle loading may be developing (Figure 3, *middle*). When flow dyssynchrony is severe, the pressure–time waveform during inspiration can actually be pulled below the baseline airway pressure by high patient flow demands (Figure 3, *right*), an indication that the ventilator is really providing no

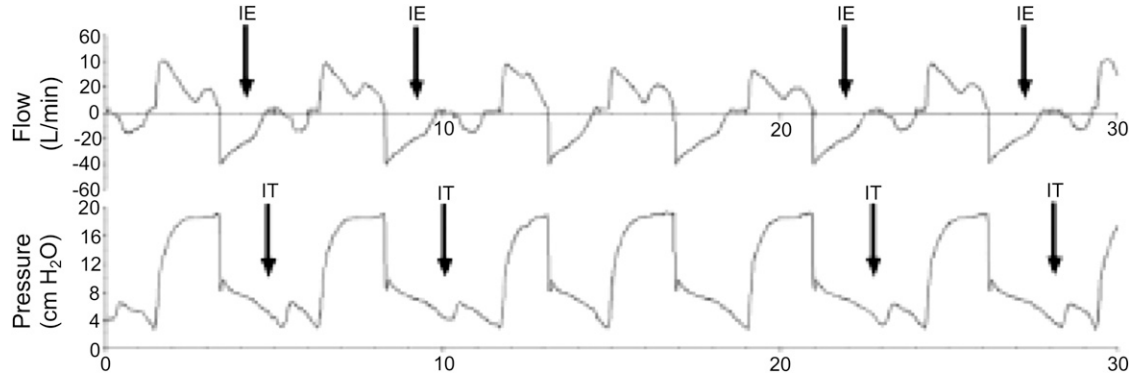

Figure 1. Flow (*top*) and pressure (*bottom*) over time (seconds) in a patient with frequent missed triggers. The missed or ineffective triggers (IT, *arrows*) can be detected on both graphs as transient pressure reductions and expiratory flow reversals. These efforts occur while expiratory flow is still occurring (incomplete exhalation [IE], *arrows*), which suggests that these missed triggers may be the result of intrinsic positive end-expiratory pressure. Adapted by permission from Reference 49.

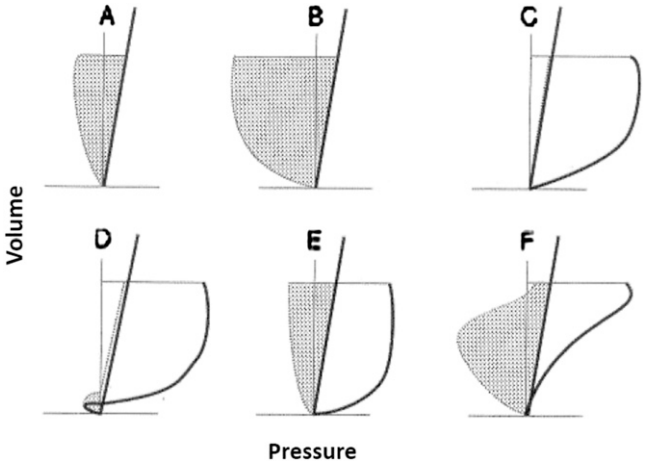

Figure 2. Pressure–volume plots (pressure on the *horizontal axis*, volume on the *vertical axis*) depicting various patient–ventilator flow interactions. Pressure to the *left* of the *thick diagonal line* (chest wall volume–pressure relationship) is patient generated and the work performed by the patient (the area of the curve) is shaded. Pressure to the *right* of the *thick diagonal line* is ventilator generated and the work performed by the ventilator is the open area. (*A*) A normal subject with normal work of breathing and no ventilator assistance. (*B*) A patient with respiratory failure resulting in very high work of breathing without any ventilator assistance. (*C*) This same patient is receiving ventilatory support that has transferred the entire work of breathing onto the ventilator. (*D*) The patient is performing only enough work to trigger an assisted breath—the ventilator does virtually all of the work. (*E*) The assistance provided by the ventilator is such that the patient work pattern resembles normal (*A*). In contrast, *F* illustrates a ventilator assistance pattern that is placing unphysiologic workloads on the patient. Conceptually, the goal of optimizing patient ventilator flow synchrony is to achieve the pattern shown in *E* and avoid that shown in *F*.

inspiratory muscle unloading (43, 46–50). Indeed, by calculating the difference between the area under the curve of the pressure–time tracings of the assisted/supported versus the controlled breath, the actual muscle PTP during the assisted/supported breath can be estimated (46, 51). If an esophageal pressure tracing is available, inspiratory muscle loads can be directly calculated (41).

Flow dyssynchrony from inadequate flow delivery is more common during acute respiratory failure when inspiratory flow demands are high, vary from breath to breath, and ventilator flow delivery is set inappropriately low. Importantly, as noted previously, unmet flow demands drive further discomfort and inspiratory effort (46, 49, 51). Not surprisingly, flow dyssynchrony appears to be more common with ventilatory settings that deliver a fixed flow (flow-targeted breaths) rather than with a flow that can vary with effort (pressure-targeted breaths (48, 52–55).

Flow dyssynchrony can also occur when excessive flow is delivered (high set flow with flow-targeted breaths or high PIS and/or rapid pressure rise time settings with pressure-targeted breaths), especially in patients with reduced inspiratory efforts (56). Under these circumstances, lung expansion occurs faster than desired by the patient's ventilatory control center. This can lead to excessive VTS in pressure-targeted modes, which can result in periodic breathing and adversely impact sleep (57). Excessive flow settings can also result in the ventilatory control center abruptly terminating the inspiratory effort (58) and even activation of expiratory muscles as patients "fight" to turn the breath off (a form of cycle dyssynchrony as described below).

Cycling Dyssynchrony

The ventilator cycles or terminates flow to end the mechanical inspiratory phase and begin mechanical expiration on the basis of different criteria depending on mode settings. Specifically, in flow–volume-targeted modes, the delivered VT and cycle time is clinician set and cannot vary with efforts. In pressure-targeted modes, the cycling criteria are either a set TI in pressure assist control ventilation or a flow cycle setting in pressure support ventilation (PSV).

Cycling dyssynchrony occurs when the neural TI and the machine TI are mismatched (Figure 4) (24, 59). Importantly, the mismatch may be because of an abnormal ventilatory drive or because the cycle criteria are set either too short or too long for an appropriate ventilatory drive.

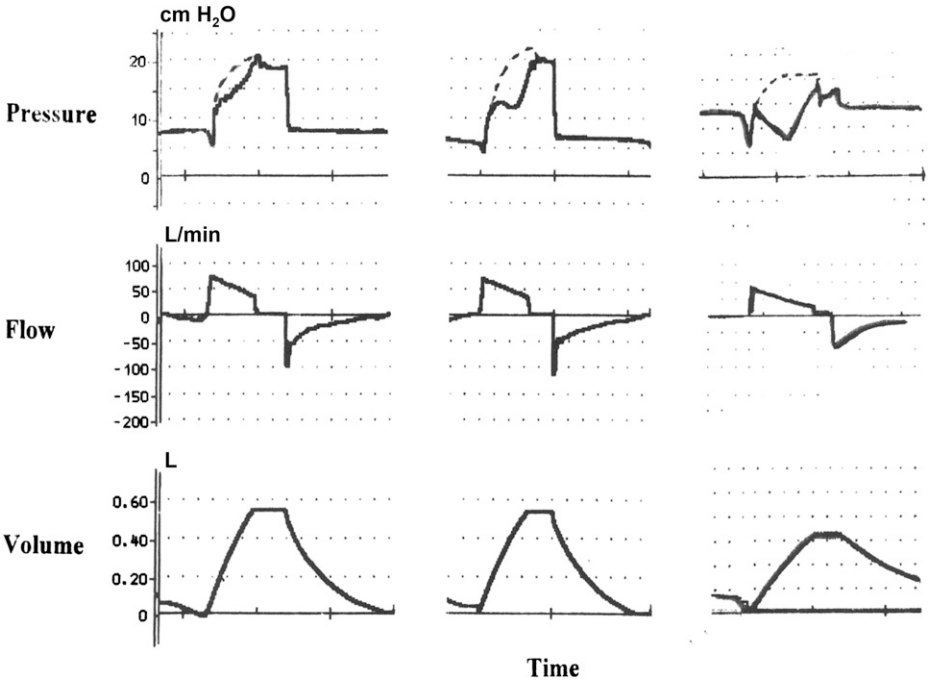

Figure 3. Plotted are airway pressure, flow, and volume over time during three assisted breaths. The *dotted airway pressure line* represents that observed during a control breath with a similar tidal volume as the assisted breath. *Left*: The assisted breath airway pressure profile remains smoothly positive and tracks with the control breath airway pressure profile, suggesting that the inspiratory muscle loading is likely not excessive. *Middle*: The assisted breath airway pressure profile is uneven and appears to be markedly "sucked down" by patient effort during much of the breath. This might suggest that the flow delivery is inadequate for patient demand to the point that inspiratory muscle overload may be present. *Right*: The assisted breath airway pressure profile goes below the baseline (expiratory) pressure. Flow is thus inadequate to provide any inspiratory muscle unloading.

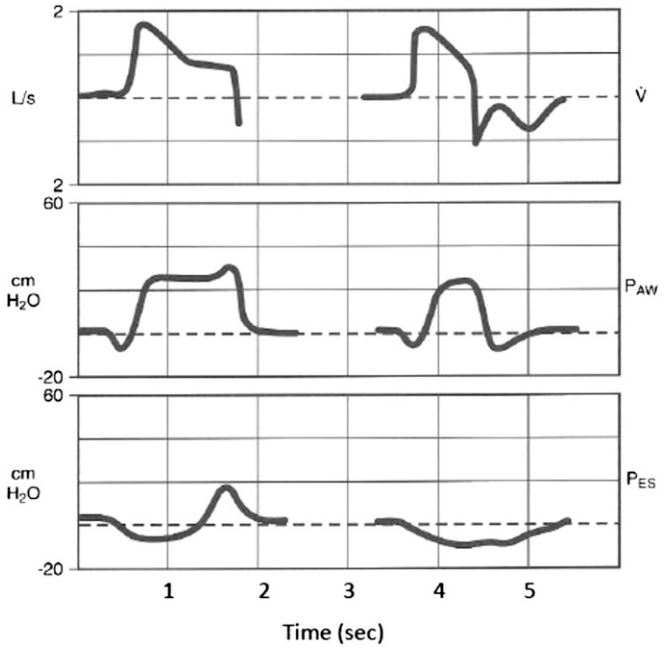

Figure 4. Two examples of cycle dyssynchrony. Depicted are flow ($\dot{V}$), airway pressure (Paw), and esophageal pressure (Pes) over time. *Left*: Machine TI is greater than neural TI. As a consequence, the lung inflation extends into neural exhalation and the patient may activate expiratory muscles to "turn the breath off." This results in an elevation in airway pressure at the end of the inhalation. *Right*: Machine inspiratory time (TI) is less than neural TI. As a consequence the persistent patient effort "pulls" the airway pressure profile downward and reverses expiratory flow after breath termination. This persistent effort may trigger a second breath. Reprinted by permission from Reference 95.

A mechanical TI shorter than neural TI may be necessary to prevent excessive VT values if the neural TI is inappropriately high (e.g., from anxiety, pain, or CNS abnormality). Under these circumstances, in addition to ventilator manipulations, addressing the inappropriate drive should also be done. A mechanical TI shorter than neural TI can also result from an inappropriately short set cycle time in a patient with an appropriate ventilatory drive and neural TI. Regardless of cause, mechanical TI less than neural TI can leave the patient uncomfortable (air hungry) as inspiratory muscles continue to contract into mechanical expiratory time (TE) against the sudden elastic recoil of the chest wall (Figure 4, *right*) (7). Moreover, in the setting of an appropriate neural TI, an inadequate machine TI may result in hypoventilation, which can result in the ventilatory control center both increasing rate and neural TI. Importantly, this persistent effort can also trigger a second breath as noted previously (60, 61).

A machine TI longer than neural TI may sometimes be necessary in patients with reduced ventilatory drive to provide an adequate VT. However, with an appropriate ventilatory drive, an excessive machine TI can lead to discomfort and expiratory efforts may be evident on the pressure–time and flow–time graphics as patients "fight" to turn off the breath (Figure 4, *left*) (56, 59, 61, 62). If the excessive machine TI results in a larger VT, this can lead to overdistention, which can result in the ventilatory control center reducing rate and neural TI (63).

A prolonged mechanical TI can be particularly problematic in patients with obstructive airway disease when using pressure support (23, 64, 65). Under these circumstances, the obstructed airways cause delivered inspiratory flow to decrease slowly and, because pressure support cycles on flow reduction, TI may be inappropriately prolonged. These factors can lead to PEEPi buildup (dynamic hyperinflation) and consequent triggering dyssynchronies.

Effect of Multiple Breath Types

The distribution of controlled/assisted/supported breaths (i.e., the mode of ventilation) may also be important in patient–ventilatory synchrony. Specifically, when more than one breath type is being delivered, the patient's ventilatory control center is unable to anticipate what the loading pattern during the next breath will be, and the potential for all dyssynchronies may go up (7, 18, 19). Thus modes with multiple breath types (i.e., IMV) may be particularly at risk for this. Indeed, as more and more spontaneous breaths with little or no ventilatory assistance are allowed with IMV, ventilatory drive goes up, which can then translate to less synchrony during the assisted mechanical breaths (19, 66).

The Consequences of Patient–Ventilatory Dyssynchrony

Determining the prevalence of patient–ventilatory asynchrony is difficult as studies examining this question have involved varying patient populations, definitions of dyssynchrony, methods of detection, duration and timing of observation, and ventilatory modes (43, 60, 67–69). Triggering dyssynchronies have been the most well studied. Depending on patient population, ventilator settings, and measurement techniques, triggering dyssynchronies have been reported in 26–82% of mechanically ventilated patients (67). Among these patients, anywhere from 20 to 63% have more than 10% of their efforts associated with trigger dyssynchrony (67). Importantly, as many as 20% of patients with triggering dyssynchronies were not detected without measurements of esophageal pressure or diaphragm electrical activity (67). Not surprisingly, trigger dyssynchronies were more common in patients with chronic obstructive pulmonary disease and at risk for PEEPi development (43, 67). Double triggering is the other commonly reported triggering dyssynchrony, but this occurs in generally fewer than 10% of patients in these various studies (67).

The incidence of other forms of dyssynchrony (flow dyssynchrony and cycle dyssynchrony) has not been as well characterized. However, a retrospective evaluation of the National Institutes of Health (NIH) ARDS Network small VT study reported cycling dyssynchronies associated with double triggering in 9.7% of all breaths analyzed (70, 71). Indeed, it is likely that patient–ventilatory dyssynchrony is ubiquitous if any patient is observed long enough during assisted/supported mechanical ventilation.

Although there is no doubt that many dyssynchronies are subtle and of little clinical relevance, significant dyssynchronies can produce patient discomfort and are a frequently cited indication for the administration of sedatives in many intensive care units (ICUs) (9, 72, 73). This may impact ventilator duration as high sedation usage is linked to longer ventilator use (4).

de Wit and colleagues demonstrated a longer duration of mechanical ventilation, worse 28-day ventilation-free survival, and longer ICU and hospital stays but no differences in ICU or hospital mortality in an observational study of 60 patients with various dyssynchronies studied during the first day of mechanical ventilation (68). Thille and colleagues (60) found that efforts associated with trigger dyssynchronies more frequently than 10% of the time (seen in 24% of their patients) were associated with substantially longer durations of mechanical ventilation and even a trend toward worse mortality. Whether the relationship between these additional adverse outcomes and patient–ventilatory dyssynchrony suggests causation or only represent a common link of a poor prognosis remains unclear.

STRATEGIES TO IMPROVE PATIENT–VENTILATORY INTERACTIONS

The challenge with ventilator management in actively breathing patients is to match ventilatory support with patient effort so as to ensure safe and effective support without imposing inappropriate loads. Although there are many ventilatory adjustments that can be made to accomplish this, as described below, attention must first be paid to the appropriateness of the patient's ventilatory drive.

If the ventilatory drive is depressed from disease or drugs, simply supplying an appropriate backup control breath rate and V_T is all that is needed. However, if the ventilatory drive is inappropriately excessive, interactive support settings can become quite challenging (7). Under these circumstances, a search for reversible causes (e.g., pain, anxiety, acidosis, hypoxemia, tube obstructions, mucus plugging, and dyssynchronous settings) should be done initially and corrected if possible, recognizing that achieving synchrony may ultimately require sedation usage.

Achieving the most synchronous settings requires careful assessments and often is a "trial and error" exercise. Ultimately, the proper delivery of assisted/supported breaths must focus on all three phases of interactive breath delivery.

Optimizing Breath Triggering

The clinician should choose the trigger sensor (flow vs. pressure) that is most sensitive and responsive to patient effort (37, 38). Importantly, some ventilators have both types of effort sensors present and will respond to whichever signal is detected first. With either sensor, the clinician should adjust the sensitivity of the triggering system to be as sensitive as possible without producing autotriggering (37, 38).

In the setting of PEEPi trigger dyssynchrony, there are several clinical strategies. First, clinicians should try reducing the PEEPi as much as possible by reducing minute ventilation (e.g., reduce set rate, reduce set P_I, reduce set V_T, reduce ventilation needs driving patient efforts), lengthening the T_E, or improving airway mechanics (17). The triggering load from PEEPi can also be reduced by applying judicious amounts of applied circuit PEEP, which serves to narrow the gradient between circuit (extrinsic) and PEEPi (39, 40). This could be guided by an esophageal pressure tracing with the goal of providing about 70–80% of measured PEEPi as circuit PEEP (19, 65, 73, 74). If an esophageal balloon is not available, an alternative approach is to empirically titrate PEEP and monitor the patient's response (75). If the application of PEEP is benefiting the patient, the delay between effort and ventilatory triggering will shorten and the patient will be observed to be more comfortable. Ironically, the ventilator breathing frequency may actually increase (as will minute ventilation) because more efforts that were previously missed are now being triggered. This may require subsequent adjustments to avoid excessive ventilation. An important sign to look for is the amount of pressure required for the V_T. As long as the applied PEEP is less than the PEEPi this P_I/V_T relationship will not change (19, 65). Excessive PEEP above the PEEPi, however, will either drive the end-P_I up in flow–volume-targeted ventilation or reduce the V_T in pressure-targeted ventilation.

Managing an extra-triggering phenomenon depends on the cause. Ventilator autotriggering can be managed with a careful search for reversible causes (e.g., water in the circuit, small leaks) and/or adjustments to the trigger sensitivity settings (37, 38). Prolonged efforts with short mechanical T_Is that trigger second breaths can be addressed by adjusting cycling criteria (mechanical T_I; *see below*). Managing entrainment effects can be more problematic as this phenomenon is less well studied. Additional sedation seems counterproductive as entrainment is associated with the use of heavy sedation (20). Conceptually, a reduction in sedation and mandatory breath delivery might be useful, but this has not been studied.

Optimizing Flow Delivery

Ventilator setting adjustments for achieving flow synchrony depend on whether flow-targeted volume-cycled breaths or pressure-targeted breaths are being used (18). Flow-targeted volume-cycled breaths are the most common breath type used in modern ICUs (76), and they give the clinician direct control over the flow magnitude, flow delivery pattern, T_I, and the ultimate volume delivered. This can be useful in guaranteeing that a safe and effective V_T is provided. Unfortunately, the fixed flow delivery pattern cannot interact with the patient's ventilatory drive and thus achieving flow synchrony can be a challenge.

When using flow-targeted breaths, the magnitude and the shape of the flow can be adjusted (sinusoidal vs. square vs. decelerating) to enhance synchrony (18, 77, 78). Inspiratory pause times can also be used to help with synchrony. When flow rates are properly titrated, Kallet and colleagues have shown that comfort with flow–volume-targeted breaths appears comparable to variable flow, pressure-targeted breaths (54). Of note is that careful attention to the flow settings with flow-targeted breaths in the NIH ARDS Network small V_T study resulted in no increased sedation use when using small V_Ts compared with large V_Ts (70).

Pressure-targeted breaths may offer synchrony advantages over flow-targeted breaths. This is because pressure targeting allows the ventilator to deliver whatever flow is needed to attain the set pressure target. Flow thus varies with patient effort, and this feature has been shown in many clinical studies to thereby enhance flow synchrony (Figure 5) (18, 19, 48, 52–55, 79).

The pressure-targeted breath also has several additional features that can further enhance flow synchrony. For example, the pressure rise time adjustment (flow acceleration adjustments also known as "pressure slope," "inspiratory percent," and other proprietary names) allows manipulation of the initial flow delivery, thereby increasing or decreasing the rate of rise of P_I (56). In theory, vigorous efforts might synchronize better with a rapid pressurization pattern; less vigorous efforts might synchronize with a slower pressurization pattern. Observational trials suggested this might be the case (56, 80, 81), but no study has shown this manipulation to alter outcome. Another commonly available feature is to have the ventilator adjust the circuit pressure profile to compensate for calculated endotracheal tube resistance and thereby produce a more "square wave" pressure profile in the trachea. Observational trials have suggested this might reduce muscle loads imposed by the artificial airway but, again, no study has shown this feature to alter outcome (82).

A concern with pressure targeting is that V_T control is lost (83). One way to address this is with feedback modes that allow the clinician to set a target V_T and then have the ventilator automatically adjust the pressure to maintain that volume. Although this has theoretical appeal, it is possible that changes in effort from anxiety or pain may create high V_Ts that then result in inappropriate lowering of the P_I (84, 85).

Optimizing Breath Cycling

Achieving breath cycling synchrony involves delivery of an appropriate V_T in accordance with patient demands and matching

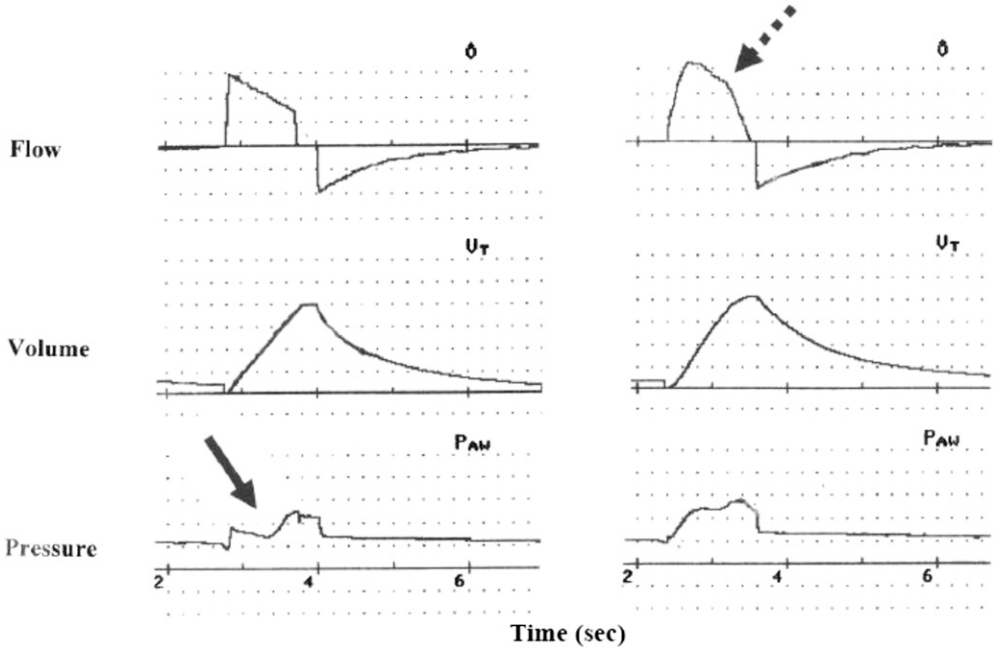

Figure 5. Enhanced flow synchrony with a variable flow, pressure-targeted breath. Depicted are flow ($\dot{V}$), volume (V_T), and airway pressure (Paw) over time (seconds). *Left*: A flow-targeted breath is delivered but the flow is inadequate for patient demand, and dyssynchrony is manifest by the deeply downward coved airway pressure profile approaching the baseline pressure (*solid arrow*). In contrast, the pressure-targeted breath on the *right* is set to deliver a similar tidal volume. However, the variable flow feature (*dashed arrow*) synchronizes better with patient effort, providing a smoother, more constantly positive airway pressure profile. Reprinted by permission from Reference 48.

of neural and machine T_I. With flow–volume targeting, adjusting the V_T and machine T_I is relatively straightforward as these are set independent variables that produce the machine T_I. With pressure targeting, adjusting the V_T and machine T_I is more complex and involves the interactions of applied P_I, respiratory system mechanics, patient effort, and cycling criteria. Altering any of these parameters often results in changes in others. In general, higher P_I settings, better mechanics, increased effort, and longer cycling criteria settings (higher set T_I in pressure assist control ventilation, lower expiratory flow criteria with PSV) extend the machine T_I (56, 59–62, 86). The pressure rise time in PSV can also affect machine T_I depending on its effects on the resulting patient ventilatory drive and its impact on peak flow and the flow cycling criteria (56).

One common cycling management problem is the patient on a pressure-targeted mode with a vigorous inspiratory effort who, despite a low applied P_I, still demands V_Ts that may be considered excessive (e.g., above 8–10 ml/kg ideal body weight) (70). Assuming this patient does not have a reversible cause for excessive inspiratory drive (e.g., pain), is on as low a P_I setting as possible, and is not ready for ventilator withdrawal (e.g., has high fraction of inspired oxygen or PEEP needs), many would argue that the high V_T should be tolerated and not suppressed with sedation.

New Approaches

Two new approaches to improving patient ventilatory interactions have been introduced: proportional assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA) (87). PAV requires that "test breaths" (controlled breaths with fixed flow and volume) be given. This allows for the calculation of respiratory system mechanics, which can be coupled with the measured ventilation to calculate work of breathing (resistive and elastic ventilatory muscle loads). These load calculations are repeated at regular intervals to maintain reliable inputs for the PAV algorithm.

PAV breaths are patient-initiated breaths triggered in a conventional way using circuit pressure or flow sensors. Thereafter, the ventilator continues to monitor flow and volume demanded by the patient and puts a clinician-set "gain" on this demand to augment flow and pressure in proportion to the desired reduction in the patient's work of breathing. The PAV breath cycles when sensed flow demand has ceased.

Like pressure-targeted breaths, PAV flow delivery varies with patient effort; unlike pressure-targeted breaths, pressure also varies with patient effort. The conceptual upside to PAV is that flow and cycle synchrony should be enhanced over conventional assisted/supported breaths. Another conceptual upside is that patient-driven V_T variability with its theoretical lung protective benefits may be enhanced. The downside, however, is that, unlike conventional pressure-targeted breaths, there is no minimal pressure or flow provided. Thus, PAV must be used with caution in patients with unreliable ventilatory drives from either disease or drugs. Indeed, with all patients on PAV, careful monitoring and backup support modes should be available.

Most clinical studies with PAV have shown enhanced synchrony compared with conventional modes (88–90). However, it is not clear what the ideal PAV gain(s) should be in various clinical settings. Moreover, to date, there have been no good randomized trials looking at important outcome benefits (e.g., ventilator duration, sedation needs, mortality) when PAV is compared with properly provided conventional assisted/supported breaths.

NAVA requires a unique esophageal catheter with an array of diaphragm EMG sensors (87). These sensors detect the onset, intensity, and termination of inspiratory efforts directly. Like PAV, a clinician-set gain is then applied that determines flow and pressure delivery in proportion to the EMG signal.

The conceptual upside to NAVA is that synchrony with all three phase of breath delivery (trigger, gas delivery, and cycle) should be enhanced over conventional assisted/supported breaths. Like PAV, another conceptual upside is that patient-driven V_T variability with its theoretical lung protective benefits may be enhanced. Also like PAV, the downside is that there is no minimal pressure or flow provided. Thus, like PAV, NAVA must be used with caution in patients with unreliable ventilatory drives from either disease or drugs. Moreover, with NAVA there is also concern about the stability of the EMG signal coming from a catheter that can move within the esophagus. Thus all patients on NAVA require careful monitoring and backup support modes.

Most clinical studies with NAVA have shown enhanced synchrony compared with conventional modes (91–94). However,

like PAV, it is unclear what the optimal EMG gain setting(s) should be in various clinical settings. To date there have been no good randomized trials looking at important outcome benefits (e.g., ventilator duration, sedation needs, mortality) when NAVA is compared with properly provided conventional assisted/supported breaths.

CONCLUSIONS

Assisted/supported modes of mechanical ventilation offer significant advantages over controlled modes in terms of ventilatory muscle function/recovery and patient comfort (and conceptually sedation needs). Assisted/supported breaths must interact with patient demands during all three phases of breath delivery: trigger, target, cycle. Synchronous interactions match ventilatory support with patient demands; dyssynchronous interactions do not. Dyssynchrony can impose substantial loads on ventilatory muscles, promoting muscle overload/failure, and greatly worsens comfort, driving up sedation needs. On current modes of ventilation there are a number of features that can monitor and enhance synchrony. These include adjustments on the trigger variable, the use of pressure versus fixed flow-targeted breaths, and a number of manipulations of the cycle variable. Clinicians need to know how to use these modalities and monitor them properly, especially understanding airway pressure and flow graphics (48, 94). Future strategies are emerging that have theoretical appeal, but they await good clinical outcome studies before they become commonplace.

Author disclosures are available with the text of this document at www.atsjournals.org.

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