13

NEURALLY ADJUSTED VENTILATORY ASSIST

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RATIONALE

BASIC PRINCIPLES AND PHYSIOLOGY OF ELECTRICAL ACTIVITY OF THE DIAPHRAGM
From Brain to Breath
Respiratory Reflexes
Electrical Activity of the Diaphragm
Measurement of Electrical Activity of the Diaphragm
Electrical Activity of the Diaphragm Signal Processing

ELECTRICAL ACTIVITY OF THE DIAPHRAGM AS A MONITORING TOOL
Interpretation of the Electrical Activity of the Diaphragm Waveform
Monitoring Patient–Ventilator Interaction in Conventional Modes of Ventilation Using the Electrical Activity of the Diaphragm
Monitoring Electrical Activity of the Diaphragm during Weaning from Conventional Ventilation

BASIC PRINCIPLES AND PHYSIOLOGY OF NEURALLY ADJUSTED VENTILATORY ASSIST
Concept of Neurally Adjusted Ventilatory Assist
Triggering
Assist Delivery
Cycling-Off
Physiologic Response to Increasing Neurally Adjusted Ventilatory Assist Levels
Weaning
Noninvasive Neurally Adjusted Ventilatory Assist

INDICATIONS AND CONTRAINDICATIONS
Indications
Contraindications

ADJUSTMENTS AT THE BEDSIDE
Electrical Activity of the Diaphragm Catheter Positioning
Setting the Neural Trigger
Initial Setting of the Neurally Adjusted Ventilatory Assist Level
Setting Backup Parameters
Setting Positive End-Expiratory Pressure
Adjustment of the Neurally Adjusted Ventilatory Assist Level during Weaning

TROUBLESHOOTING

ADVANTAGES AND LIMITATIONS

COMPARISON WITH OTHER MODES
Fundamental Differences between Neurally Adjusted Ventilatory Assist and Other Modes
Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Impact on Patient–Ventilator Interaction
Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Impact on Breathing Pattern and Gas Exchange
Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Limitation of Excessive-Assist
Neurally Adjusted Ventilatory Assist and Proportional-Assist Ventilation

SUMMARY AND CONCLUSION

ACKNOWLEDGMENTS

RATIONALE

Mechanical ventilation can be delivered with two extreme approaches: (a) by dictating a flow, volume, pressure, or respiratory timing (or some combination), or (b) by delivering assistance synchronized to and regulated by the patient's neural breathing efforts. Whereas the former approach is advantageous in patients who do not breathe, the latter approach is advantageous in spontaneously breathing patients.

Almost 50 years ago, Gunaratna[1] demonstrated that the problem of patients fighting the ventilator during controlled ventilation could be overcome by the use of patient-triggered ventilation. The patient-triggered ventilation was associated with immediate relief of the respiratory distress, apprehension, and agitation.

Since the 1970s, numerous modes of mechanical ventilation that aim to synchronize the ventilator and the patient have been introduced. Patient-triggered or cycled modes of ventilation are controlled by airway pressure,

flow, and/or volume measured in the respiratory circuit. Significant limitations of these signals to trigger and cycle-off the assist have been documented for decades.[2–12] Despite the term *patient-triggered* ventilation, severe patient–ventilator asynchrony occurs in at least 25% of ventilated patients[13–15] and is associated with prolonged duration of ventilation. Patients with frequent ineffective triggering also tend to receive excessive levels of ventilator support[13] and/or sedation.[16] In newborns, compared to controlled ventilation, patient-triggered ventilation is associated with shorter duration of ventilation.[17–20] Excessive assistance can cause muscle fiber injury and atrophy of the diaphragm.[21,22] Conventional ventilation can induce loss of inspiratory muscle force, as much as 75%.[22,23–27] Promoting spontaneous breathing[28–33] and reducing sedation,[34–39] alone or together,[40] shortens the duration of mechanical ventilation.

Last, but not least, regulation of spontaneous breathing constitutes a very complex interaction between motor-nerve output and sensory feedback.

In summary, conventional modes of ventilation have limitations with regards to (a) synchronizing assist delivery to the patient's neural breathing efforts; (b) bedside monitoring of patient respiratory drive and/or interaction with the ventilator; (c) adjusting the level of assist in response to patient demand; and (d) taking advantage of intrinsic lung protective reflexes.

An ideal approach, therefore, is to connect the patient's respiratory centers to the ventilator, as naturally as the respiratory muscles are connected to the brainstem via the phrenic nerves. This notion is what set the spirit for developing the mode known as neurally adjusted ventilatory assist (NAVA).[41]

BASIC PRINCIPLES AND PHYSIOLOGY OF ELECTRICAL ACTIVITY OF THE DIAPHRAGM

From Brain to Breath

Figure 13-1 (*left*) describes schematically the hierarchy of the steps involved in generating a spontaneous breath. Respiratory neurons originating in the brainstem of the central nervous system send their signals to the diaphragm via the phrenic nerves. After neuromuscular transmission, diaphragmatic excitation occurs, where action potentials propagate along the diaphragm muscle fibers. This is the source of the diaphragmatic electrical activity (Edi) (see "Electrical Activity of the Diaphragm" below). The Edi is generated by the neural respiratory output signal and is modulated by input from multiple respiratory reflexes feeding back to the respiratory centers. The Edi signal is the primary signal used to control NAVA (Figure 13-1, *right side*).

The latency time from stimulation of the phrenic nerve in the neck to the onset of the diaphragmatic compound muscle action potential in healthy subjects is approximately 6 to 8 milliseconds.[42–45] Diaphragmatic excitation stimulates contraction of muscle fibers and causes shortening. The result of diaphragmatic contraction is expansion of the thorax, which causes lung distension and lowers pleural and alveolar pressures, thereby lowering airway pressure creating inspiratory flow. These "pneumatic" signals (pressure, flow, and volume) are used today to control conventional patient-triggered ventilation.

The time between central respiratory output to the generation of inspiratory flow in a healthy subject is approximately 26 to 28 milliseconds.[42–44] Factors such as intrinsic positive end-expiratory pressure (PEEP), increased respiratory load, impaired respiratory muscle function, and reduced respiratory drive (secondary to sedation), alone or in combination, will weaken the flow signal. A weakened flow signal is more problematic to detect by the ventilator, increases the time delay to trigger the assist, and, in the worst case, fails to trigger the ventilator.

In summary, an impairment occurring at any of the steps in the hierarchy described in Figure 13-1 may result in delays, dampening, or even full blockage of the signals used to control the ventilator.

Respiratory Reflexes

Figure 13-2 demonstrates a schematic diagram of the major neural feedback systems to the respiratory centers. Neural feedback to the respiratory centers controls respiratory motor output, and hence the Edi.

FEEDBACK FROM THE LUNGS

For a detailed description of the lung reflexes, the reader is referred to Widdicombe[46,47] and Undem and Kollarik.[48]

Important for NAVA is that the lungs host receptors sensitive to stretch and respond to both lung distension and deflation. Based on the response to sustained lung distension these receptors are divided into slowly adapting receptors and rapidly adapting receptors. The classic experiments by Josef Breuer and Ewald Hering in the mid-nineteenth century[49] showed that lung distension shortens inspiration, or prolongs expiration, the so-called Hering-Breuer inspiratory sensitive reflex.[49] They also noted that deflation of the lungs at end-expiration shortens exhalation and stimulates inspiration, the Hering-Breuer deflation-sensitive reflex.[49] These reflexes are caused by slowly adapting receptors, and rapidly adapting receptors, respectively.

The rapidly adapting receptors are also stimulated by chemical stimuli and changes in lung compliance. When stimulated, the rapidly adapting receptors cause tachypnea, cough, and augmented breaths. Pulmonary edema, mediators of inflammation and immune responses, inhaled irritants, and direct tissue damage stimulate the bronchial C-fiber receptors, causing apnea, rapid shallow

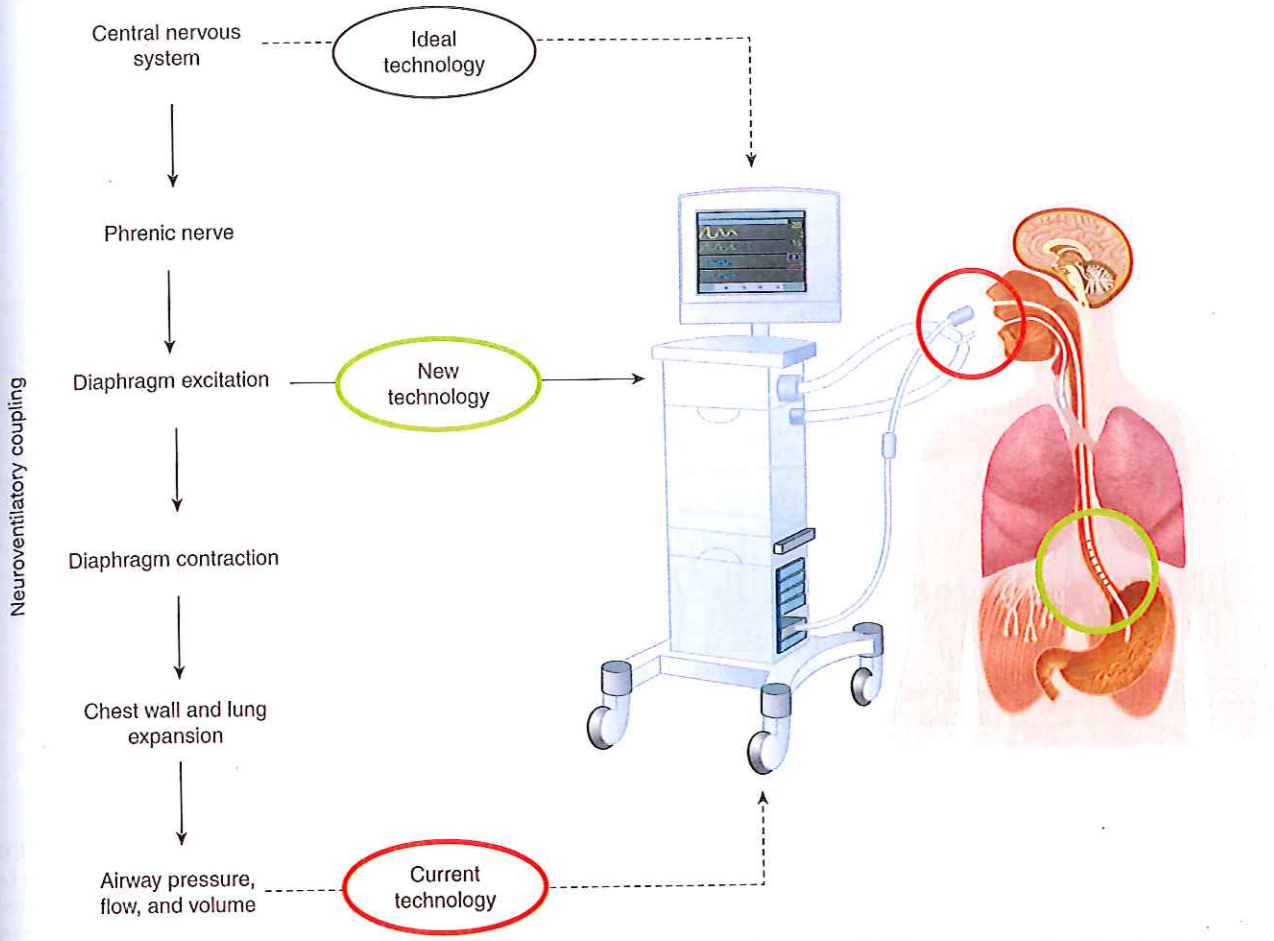

FIGURE 13-1 Overview of neurally adjusted ventilatory assist (NAVA). *Left:* Chain of events involved in spontaneous breathing, beginning with the respiratory centers in the central nervous system, then phrenic-nerve transmission, diaphragmatic electrical activity, diaphragmatic contraction, and ending with airway pressure, flow, and volume (the neuroventilatory coupling). Also indicated are the different levels of signals for ventilator control. During NAVA, electrical activity of the diaphragm is used to control the ventilator. *Right side:* Schematic of setup for NAVA. A feeding catheter equipped with an array of miniaturized electrodes is passed down the esophagus, where the electrical activity of the diaphragm is recorded (*green circle*). Diaphragmatic electrical activity is processed into a waveform, and is used for monitoring neural respiratory drive (in all modes) and for controlling the timing and magnitude of ventilator-delivered pressure during NAVA.

breathing or both, and cough. The above-described reflexes disappear with vagotomy.

FEEDBACK FROM THE RESPIRATORY MUSCLES

Afferent feedback from the respiratory muscles exists and affects neural drive to the different individual muscles.[50–52] Electrical stimulation of the phrenic nerve afferents elicits changes in phrenic efferent activity, breathing pattern, and ventilation, the so-called phrenic-to-phrenic reflex.[53,54] Stimulation of the phrenic afferents can also change neural drive to the intercostal muscles, the so-called phrenic-to-intercostal reflex.[55,56] Golgi tendons and muscle spindles are present in the diaphragm, albeit sparse, and provide feedback related to muscle tension and length, respectively.[57] Respiratory muscle feedback partially controls respiratory drive during unloading[58] and likely influences the sensation of breathing.[59]

JOINT RECEPTORS

Receptors in the costovertebral joints have been suggested as a primary determinant of a load-compensating reflex.[60]

CHEMORECEPTORS

Receptors sensitive to the concentration of oxygen, carbon dioxide, and the pH in the arterial blood are constantly modulating the breathing pattern. Activation of either the hypoxic or hypercapnic chemoreflex elicits hyperpnea (increased respiratory drive and, hence, increased Edi).[61,62]

FEEDBACK FROM THE UPPER AIRWAYS

The larynx contains receptors sensitive to pressure, temperature, and irritants; the laryngeal mucosa also contains C-fiber receptors or J receptors,[46,47] which, when stimulated,

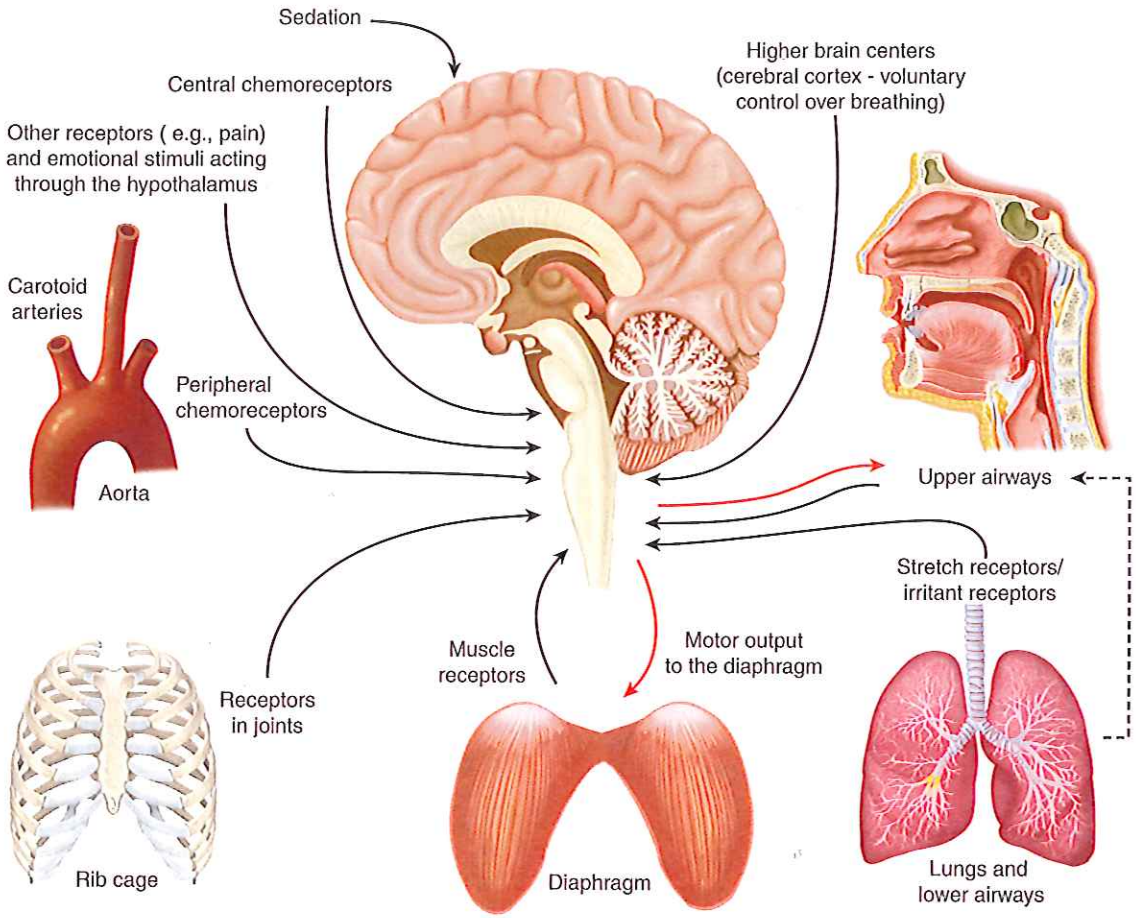

FIGURE 13-2 Respiratory inputs and reflexes important for NAVA. Schematic of the respiratory inputs and reflexes that can affect neural respiratory drive, and hence the motor output to the diaphragm (electrical activity of the diaphragm). The respiratory centers in the brainstem continuously receive information from the peripheral and central chemoreceptors (*upper left side*), receptors in the rib cage and diaphragm (*lower left* and *lower center*), stretch and irritant receptors in the lungs and lower airways (*lower right*), and receptors in the upper airways (*top right*).

cause cough, apnea, bronchoconstriction, and mucus secretion. Recent work by Praud et al[63] suggests that feedback exists from the lungs to the laryngeal muscles.

SEDATION AND ANALGESIA

Increases in sedation and/or analgesia depresses respiratory motor output.[64]

Electrical Activity of the Diaphragm

Petit et al were the first to present, in 1959, a "new technic for the study of functions of the diaphragmatic muscle by means of electromyography in man."[65] Taking advantage of the anatomy of the crural diaphragm, which forms a scarf-like structure around the lower esophageal sphincter, these investigators cleverly obtained the Edi with electrodes on a catheter that was passed down the esophagus.

Considering that nearly all ventilated infants and most intubated adult patients in the intensive care unit are equipped with nasogastric feeding tubes, it was logical to follow up on refining esophageal measurements of Edi for today's clinical use. Some of the obstacles that needed to be overcome included the development of standardized and automated methods to reduce artifacts and filtering effects related to electrode configuration and electrode positioning. Even though Lourenco et al[66] had demonstrated in dogs that the crural electromyogram (EMG) and costal EMG were related to phrenic nerve activity, it was necessary to validate that measurement of Edi with an esophageal electrode relates to global inspiratory effort in ventilated patients.[5]

The Edi signal used for monitoring respiratory drive and for controlling the ventilator during NAVA is an "interference-pattern EMG signal," and constitutes a temporospatial summation of motor-unit action potentials, which, in turn, represent a summation of single-fiber action potentials.

A single-fiber action potential is the extracellular potential generated by movement of ions across the sarcolemma during depolarization of a single muscle-fiber membrane. This current flow can be measured as a voltage difference over time, and when displayed as a waveform, is known as the

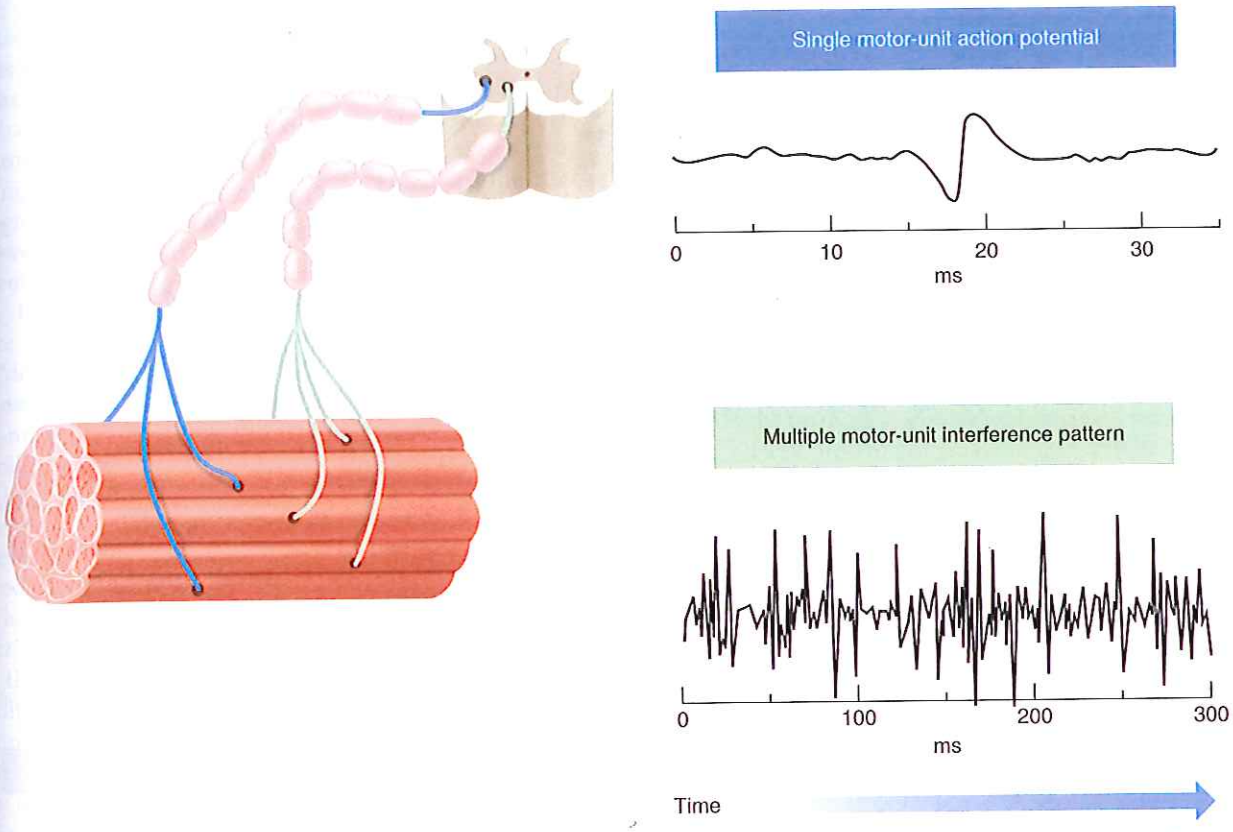

FIGURE 13-3 Skeletal muscle structure and the origin of the interference-pattern EMG. *Left side:* Representation of the structure of skeletal muscle and motor units. Two motor units are demonstrated for simplicity. A motor unit is a single motor neuron and all of the muscle fibers it innervates. Electrical activation of a single motor unit produces a motor unit action potential (*top right*). A spatial and/or temporal summation of the motor-unit action potentials, resulting in an interference-pattern EMG signal (*bottom right*), occurs when several motor units are recruited and/or their firing rate increases. The Edi signal measured during NAVA is an interference-pattern measurement of asynchronously firing diaphragmatic motor units.

action potential. Action potentials are "all or none" in terms of the voltage transient they generate, and they propagate along the muscle-fiber membrane to initiate contraction.

Action potentials occur because of voltage-dependent sodium-potassium channels in the muscle-fiber membrane. In humans, the propagation velocity of an action potential ranges between 2 and 6 meters per second,[67] and depends on the capacitance per unit length (dependent on circumference) and the internal resistance, all passive properties of the muscle fiber. The active properties (e.g., membrane excitability) depend on ion-concentration differences and ion-channel properties, the latter affected by temperature, pH, and electrical field strength. The action potential propagation velocity is dependent on temperature, fiber diameter, pH, fatigue, and ion concentration.[67-71]

Given the muscle innervation scheme, single-fiber action potentials are activated in groups because a single nerve fiber innervates multiple muscle fibers (Fig. 13-3). Thus, a motor-unit action potential represents many single fiber action potentials, which secondary to synchronized initiation, results in mainly a spatial summation of their amplitudes. Motor-unit action potentials are affected by the same factors as single-fiber action potentials, but also the number of muscle fibers within the motor unit, length of the motor unit terminal, fiber-to-fiber differences in action-potential conduction velocity, and dispersion of the motor-unit fibers.[72,73]

Neural breathing effort modulates motor-unit firing rate and recruitment. Hence, when resulting action potentials are summed up in time (temporally) and in space (spatially), the cumulated motor-unit action potential activity (i.e., the interference-pattern EMG) yields a signal where individual motor-unit action potentials can no longer be distinguished (see Fig. 13-3). All factors affecting the individual motor-unit action potentials will influence the interference-pattern EMG, as well as the number of individual motor-unit action potentials, their synchronization, and eventual cancellation of opposite phase potentials.[72,74]

Measurement of Electrical Activity of the Diaphragm

RECORDING ELECTRODES

Optimal Edi signals depend on the use of electrodes with appropriate configuration, maintenance of electrode position and orientation relative to the muscle, and avoidance of signal disturbances.

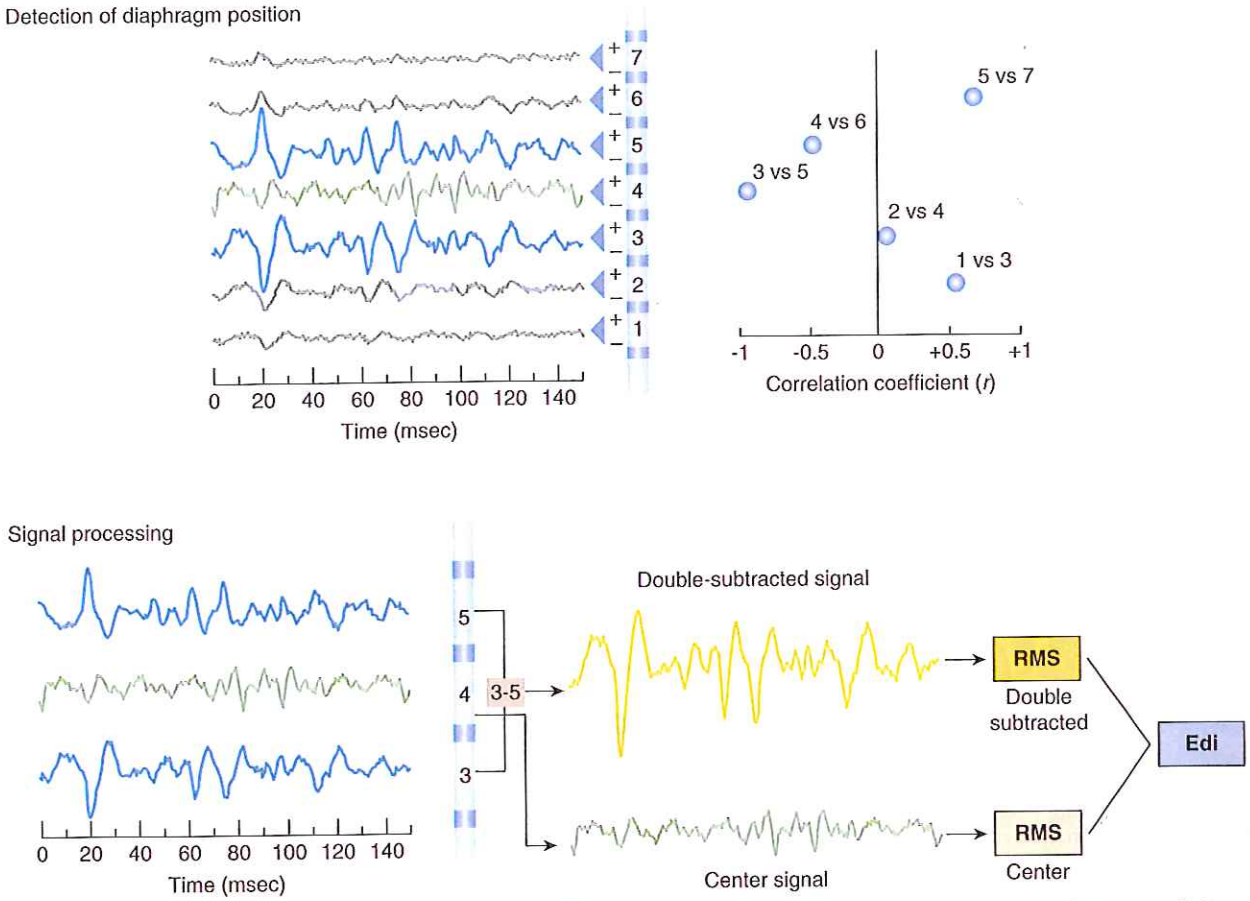

FIGURE 13-4 The double subtraction method. *Top*: Detection of diaphragm position along the array of electrode pairs. *Left:* Raw signals from each electrode pair (electrode array is illustrated in center). *Right*: The electrode pairs closest to the diaphragm are determined by cross-correlating signals from every second pair of electrodes (1 vs. 3, 2 vs. 4, 3 vs. 5, 4 vs. 6, 5 vs. 7, and 6 vs. 8, if eight electrodes are present), and the correlation (r) values are plotted (x axis) for each combination (y axis). Today, the cross-correlation algorithm is applied every 16 ms and eight electrode pairs are used. The two most negatively correlated electrode pairs are tagged (in *blue, left side*) for use in the double subtraction (in this example, electrode pairs 3 and 5). The "center signal" is also tagged (in *green*). *Bottom*: Signal processing. *Left:* The same signals that were tagged in the cross-correlation method as being above and below the diaphragm are displayed (*blue*) as well as the center signal (*green*). *Right*: Signal obtained after subtraction of signal from the most negatively correlated signals (electrode pair 5 and 3 in this example) yields the "double-subtracted signal" (*orange tracing*). The root-mean-square is calculated every 16 ms for this signal (*orange*), as well as the waveform at the center (*green*), and the two root-mean-square (RMS) values are summed (double subtracted + center values) to yield the Edi used during NAVA (*grey*). (Adapted, with permission, from Sinderby et al.[77])

In the context of NAVA, the Edi is measured with an array of electrode pairs placed on a nasogastric or orogastric catheter. The catheter is placed in the esophagus at the level of the gastroesophageal junction such that the direction of the electrode array is perpendicular to the crural diaphragmatic muscle fibers.[75]

The Edi is filtered depending on the electrode's position with respect to the diaphragm[75] (Fig. 13-4). If the electrode pair is centered at the level of the diaphragm (both electrodes receive a similar signal), the frequency increases and the power of the Edi decreases because of a cancellation effect (bipolar electrode filtering). If one of the electrodes of the pair is located at the level of the diaphragm and the second is away from the diaphragm (electrode pairs 3 and 5 in Fig. 13-4), the differential recording will be least influenced by bipolar electrode filtering and muscle-to-electrode distance filtering effects.[75] For the electrode pairs even further away in either direction (channels >6 and <2 in Fig. 13-4), there will be lower signal amplitude, because of muscle-to-electrode distance filtering. Given the sequential configuration of electrodes pairs with respect to the differential amplifiers (indicated by + and – signs in Fig. 13-4, top right panel) and the fact that the diaphragm constitutes an electrical sheet with a direction perpendicular to that of the electrode array, signal waveforms obtained above the diaphragm become inversed to those below the diaphragm (Fig. 13-4 top left panel).

Electrical Activity of the Diaphragm Signal Processing

The specific design of the electrode configuration and the signal processing techniques used with NAVA have been developed and tested since the late 1980s so as to overcome

the inherent difficulties associated with EMG measurements in general, as well as anatomical considerations.[76]

The most significant advance in the development of esophageal measurements of Edi was the use of bipolar electrodes in a sequential order and an automated processing technique to track the displacement of the diaphragm.[77] Implementation of a cross-correlation technique (for every second pair of electrodes) every 16 milliseconds determines the position of the diaphragm along the array (Fig. 13-4), and subtraction of opposite phase signals above and below the diaphragm results in a new signal, the "double-subtracted" signal, free from distance filtering, and enhanced signal-to-noise ratio (Fig. 13-4).[77] The root-mean-square (RMS) of this signal is calculated every 16 milliseconds, and added to the RMS of the center signal (i.e., from the electrode pair closest to the muscle[78,79]), as demonstrated in Figure 13-4. The resultant RMS values for every 16 milliseconds sample can be graphically connected, resulting in the Edi waveform (Fig. 13-5).

The RMS is linearly related to how much the muscle is activated, that is, the number of motor units recruited and their firing rate,[80] and under isometric, nonfatiguing conditions, reflects diaphragmatic force (up to 75% of its maximum).

Several artifacts can potentially influence the Edi waveform and need to be controlled for to avoid misinterpretation of the signal, or in the case of NAVA, miscontrolling the ventilator. Today, this is achieved automatically by the processing of the signal, and the user only needs be made aware of the artifacts' potential impact.

As the diaphragm can move as much as 13 centimeters during spontaneous breathing at large tidal volumes,[81] muscle-to-electrode distance filtering could play a role in amplitude measurements of Edi.[82] Signal processing techniques and design of catheter configuration have enabled automatic control over this factor.

Motion artifacts, induced by physical movement of the electrode, are low in frequency but large in amplitude. Signals that are common to both electrodes in the differential recording (e.g., electrical noise) will be suppressed because of the bipolar electrode configuration and the double-subtraction technique.[77] Esophageal recordings of Edi are particularly affected by the electrocardiogram (ECG) and the artifact should be removed from the Edi waveform, especially for the purpose of controlling the ventilator. The ECG is detected with an adaptive threshold level, and replaced by a value predicted from the previous Edi value. To further reduce electrical noise disturbances (e.g., 50 or 60 Hz) and motion artifacts and to minimize ECG and electrical activity from the esophagus, the signal is filtered with a cascade of filters.

The interelectrode distance affects the Edi signal, and hence catheters of different sizes and interelectrode distances are designed to suit different patient ages and sizes.[75]

A long-lived delusion was that changes in diaphragmatic configuration and length affect the Edi waveform.[83] Studies now confirm that diaphragmatic length[71] and chest wall configuration[80,82] do not affect the Edi waveform, or its frequency content, as long as control is achieved over the above-mentioned influences.

ELECTRICAL ACTIVITY OF THE DIAPHRAGM AS A MONITORING TOOL

Interpretation of the Electrical Activity of the Diaphragm Waveform

The Edi waveform, as any other waveform on the ventilator, such as airway pressure or tidal volume, can be characterized by its amplitude and timing, for both the inspiratory phase and the expiratory phase. The Edi waveform has the units of microvolts (μV), generally ranging between a few μV during resting breathing to above 100 μV during maximal inspiratory efforts. Figure 13-6 provides examples of the Edi waveform in a premature infant and in an adult patient.

Increased Edi amplitude on inspiration ("phasic Edi") indicates greater activation of the diaphragm. The amplitude of the Edi waveform has been shown to be related to global diaphragmatic activation[80] and diaphragmatic power output[84] in healthy subjects, outpatients with chronic obstructive pulmonary disease,[78] and ventilated patients.[5] Edi amplitude increases with worsening of respiratory status,[78] reduced ventilator assist,[5] reduced sedation,[85] increased demand for ventilation such as exercise,[79] and increased dead space.[86] The opposite holds true: Edi decreases within a given subject with respiratory improvement, increased sedation, increasing levels of assist, and reducing the partial pressure of arterial carbon dioxide (Pa_{CO_2}).

In a given subject, the amplitude measures of the Edi waveform can be reliably monitored and quantified, for example, during treatment and interventions. Because of anatomical differences (affecting the muscle-to-electrode distance filtering in particular), absolute Edi values can vary between subjects.[78] When trending Edi values over time, it should also be kept in mind that changes in ventilator settings and sedation level influence the magnitude of Edi. The published literature on Edi monitoring and NAVA using the commercially available $Servo_i$ ventilator demonstrates peak Edi values in the range of 8 to 18 μV in adults under a variety of conditions. In one study, values as low as 2 μV and as high as 50 μV were reported when Pa_{CO_2} was manipulated by extracorporeal membrane oxygenation.[87] Only one study to date has reported Edi values in children (mean values of 7 μV during NAVA).[88]

Edi values can be expressed relative to a maximum inspiratory effort (e.g., maximal inspiration without assist) in patients capable of performing the maneuver.[78,89] Sinderby et al[78] demonstrated that patients with impaired respiratory mechanics require a larger fraction of the maximum Edi to achieve the same mechanical output as healthy subjects

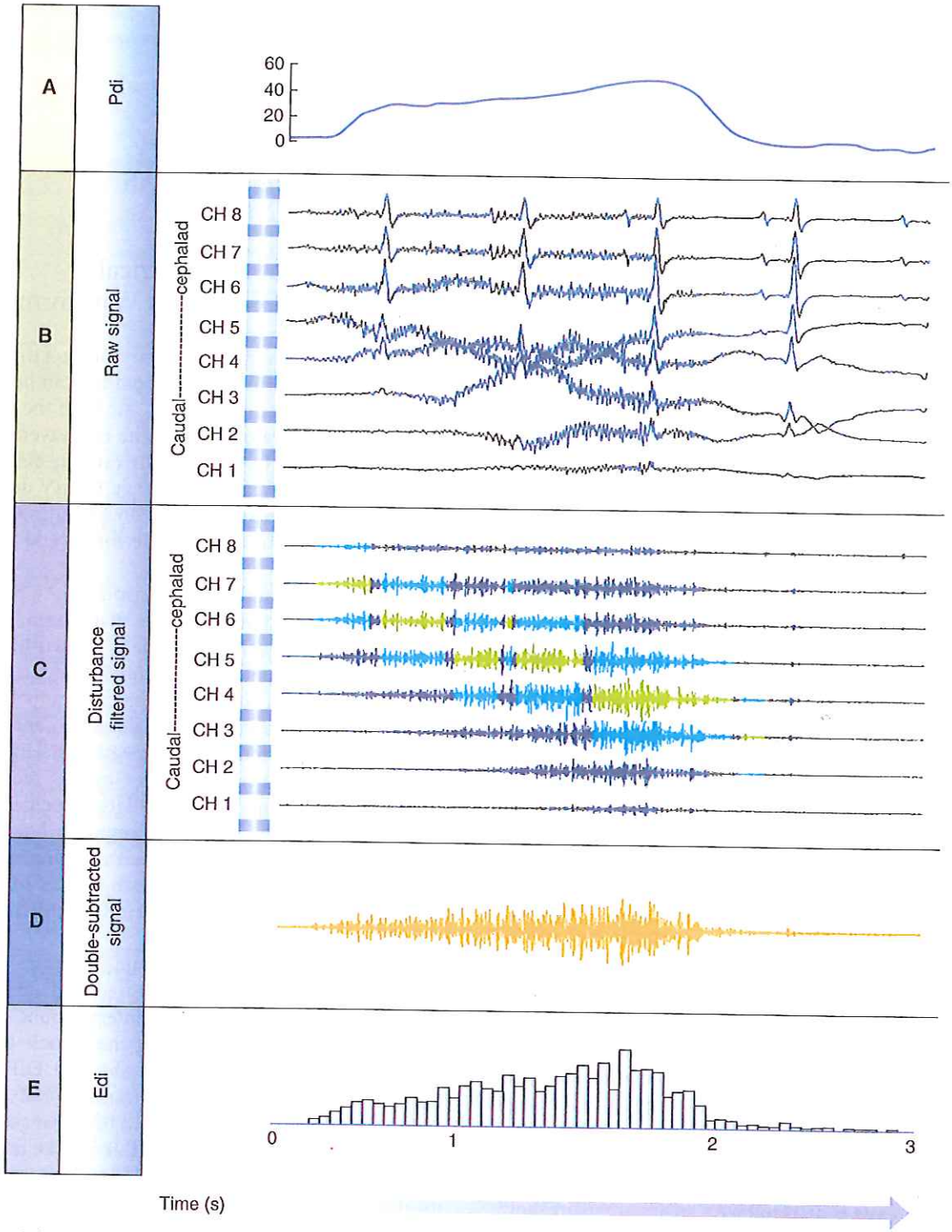

FIGURE 13-5 Edi signal processing during NAVA. **A.** Transdiaphragmatic pressure (Pdi) waveform obtained in a healthy subject performing an inspiration to total lung capacity. **B.** Raw signals obtained from the eight electrode pairs on the esophageal catheter during the same inspiration to total lung capacity. The electrode pair at the top is the most cephalad, whereas the one at the bottom is the most caudal (in the stomach). Note the presence of the electrocardiograms (ECGs) and slow-wave motion artifacts. **C.** Filtered raw signals after processing and removal of ECG and motion artifacts. *Blue* signals show electrode pairs above and below the diaphragm as detected by the cross-correlation algorithm described in Figure 13-4. Signals highlighted in *green* are the center signal as described in Figure 13-4. Note that the intensity of the signals increases throughout inspiration and moves downward with respect to the electrode pairs. **D.** Double-subtracted signal (*orange*) for the same inspiration to total lung capacity. **E.** Root-mean-square (RMS) values from the double-subtracted signal are plotted for every 16-millisecond segment. Note that the RMS values are plotted for the double-subtracted signal in this example from an earlier publication. Presently, the center signal RMS values are also included (as described in Fig. 13-4). (Adapted, with permission, from Sinderby et al.[78])

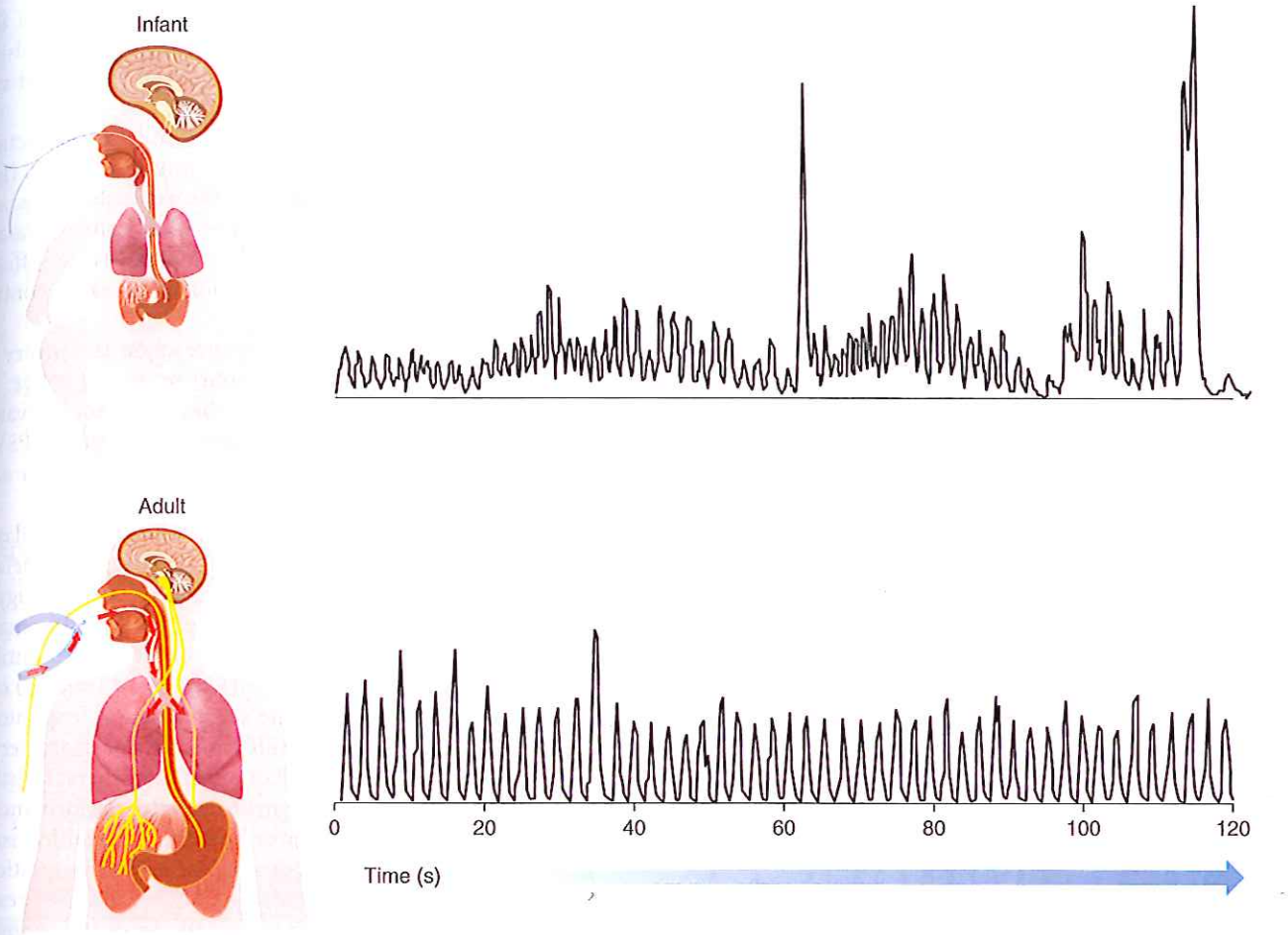

FIGURE 13-6 Examples of the diaphragmatic electrical activity (Edi) waveform in an adult patient and in a premature neonate. *Top panel*: Processed Edi waveform obtained in a nonintubated premature infant. *Bottom panel*: Processed Edi waveform obtained in an intubated adult. The Edi waveform in infants is characterized by larger variability in timing and amplitude, with a distinct amount of changes in the baseline, so-called tonic activity of the diaphragm. The Edi waveform in adults is generally less variable with minimal tonic Edi.

(Fig. 13-7). Statistically, the increase in Edi with respiratory impairment also holds true for absolute values in the same type of patients.[90] In patients with neuromuscular disorders, the Edi during spontaneous breathing, normalized to a maximal effort, can reveal the patient's neural activation reserve, where a ratio at or above 0.5 would indicate extremely little reserve.[78,91] In the same patient group, the absolute Edi observed during a maximal effort can provide information about changes in the total motor-unit pool, that is, a reduced maximal Edi (in μV) as the disorder progresses or vice versa. In patients with late-stage Duchenne muscular dystrophy, the absolute Edi values are low because of a reduced number of available motor units, but in relative terms, they represent approximately 50% of their maximum Edi.[91]

If the Edi persists after the end of an inspiration, the amplitude of the Edi waveform can be quantified (the so-called tonic Edi).[92] The presence of tonic Edi indicates continuous and elevated activation of the diaphragm between respiratory cycles (see Figs. 13-6 and 13-8). Studies in infants and animals suggest that elevated tonic Edi is a reflex response induced by lung derecruitment or removal of PEEP.[92–94] Experimental vagotomy abolishes this reflex.[93,94] Healthy subjects and *adult* mechanically ventilated patients show little, if any, tonic Edi.[78,95,96]

Besides amplitude parameters, the Edi waveform can be used to quantify the timing of the neural breathing pattern, such as neural inspiratory time, neural expiratory time, and neural respiratory rate.

If the catheter position has been deemed appropriate and functioning, a flat Edi waveform at zero μV indicates no diaphragmatic activation. This could be caused by numerous pathologies, including central apnea (no respiratory motor output, or suppressed respiratory drive secondary to mechanical ventilation-induced hyperventilation or sedatives), phrenic nerve damage, or neuromuscular transmission failure.

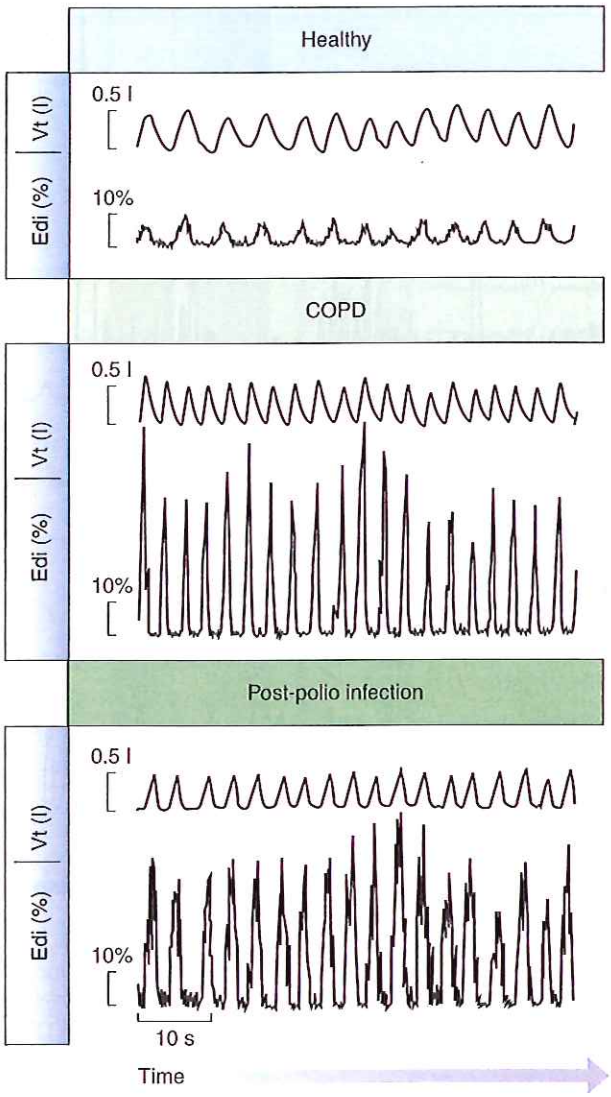

FIGURE 13-7 Examples of the Edi waveform and tidal volume in a healthy subject and in patients. Tidal volume and the Edi waveform are presented for a healthy subject (*top*), a patient with chronic obstructive pulmonary disease (*middle*), and a patient with prior polio infection (*bottom*), all breathing at rest with a mouthpiece (not on a ventilator). Note that all three subjects are breathing with a tidal volume of approximately 500 mL, although diaphragmatic activity required to achieve this tidal volume is eight times higher in the patients than the healthy subject. A higher Edi per milliliter indicates a worsened neuroventilatory efficiency. (Adapted, with permission, from Sinderby et al.[78])

Monitoring Patient–Ventilator Interaction in Conventional Modes of Ventilation Using the Electrical Activity of the Diaphragm

The Edi waveform is considered the reference standard for monitoring patient–ventilator interaction.[4,5,9,15,97,98] During conventional ventilation, when the Edi waveform is simultaneously displayed and superimposed with the airway pressure waveform, it provides immediate bedside information about the interaction between the patient and the ventilator.

An extreme case of poor patient–ventilator interaction is when a patient makes a neural inspiratory effort (Edi waveform starts to increase) and the ventilator does not deliver a breath (Fig. 13-9, *top left*)—often termed "wasted inspiratory efforts." In the example provided, wasted efforts occurred frequently (*red arrows*) during pressure control (PC) ventilation.

At the other extreme of poor interaction is delivery of a ventilator breath when the diaphragm is not active. In Figure 13-9 (*bottom left*), the diaphragm is not activated during the delivery of pressure-support ventilation (PSV). This situation can be a result of too-sensitive trigger settings and too-high levels of assist.

The differences in timing between Edi and ventilator pressure can be quantified for the start (triggering delay) and end (cycling-off delays) of the assisted breaths. Trigger delays are defined as the time interval between the onset of neural inspiratory effort and the onset of the ventilator breath. In Figure 13-9 (*top left*), the assist (*shaded*) can be seen to begin long after the start of neural inspiratory effort. Trigger delays can result from patient characteristics (such as hyperinflation) or ventilator characteristics (trigger sensitivity, trigger algorithms, valve performance).

Cycling-off of a ventilator breath, in healthy subjects, should coincide with the end of neural inspiration. Cycling-off is asynchronous when the ventilator breath terminates while the subject is neurally inspiring (premature cycling-off) or if it cycles-off long after the onset of neural exhalation (delayed cycling-off) (Fig. 13-9, *top left*). In PSV, pneumatic cycling-off algorithms are designed to sense a decrease in flow relative to the peak inspiratory flow. This makes the ventilator cycling-off dependent on the ratio of the time constant of the respiratory system to neural inspiratory time, and the ratio of the pressure support to maximal inspiratory pressure.[99]

Double-triggering can also be detected with the Edi,[98] and can be defined as the delivery of two ventilator breaths for one neural effort. During volume control ventilation or PSV, double-triggering results in the delivery of two full breaths, and could result in "breath stacking" and delivery of higher-than-targeted volumes or pressures.[100]

Monitoring Electrical Activity of the Diaphragm during Weaning from Conventional Ventilation

Monitoring the Edi alone, or in conjunction with other variables, can also be used for decisions about weaning and extubation. The use of daily Edi monitoring during spontaneous breathing trials or during the same fixed level of assist can provide information about changes in

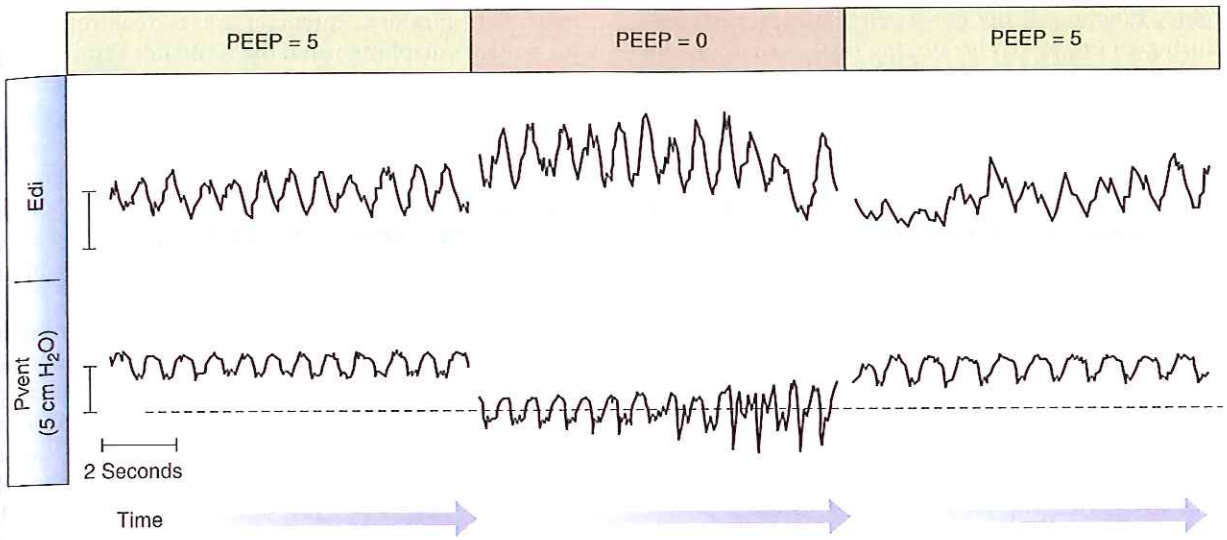

FIGURE 13-8 Impact of removal of positive end-expiratory pressure (PEEP) on tonic Edi. Example of tracings of ventilator-delivered pressure (Pvent) and diaphragmatic electrical activity (Edi) obtained in one intubated and mechanically ventilated infant on synchronized intermittent mandatory ventilation (only the spontaneous breaths in between mandatory breaths are displayed). The amount of tonic Edi (*blue horizontal bars*) increases with brief removal of PEEP (*center*). (Reproduced, with permission, from Emeriaud et al.[92])

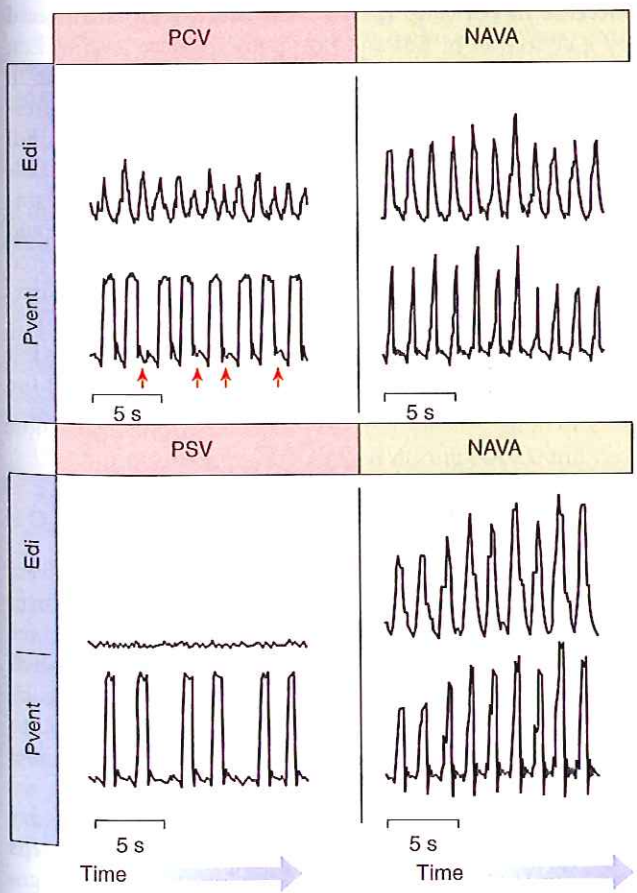

FIGURE 13-9 Patient–ventilator interaction during conventional ventilation and during NAVA. *Top*: Waveforms for Edi and ventilator-delivered pressure (Pvent) for an intubated adult patient breathing on pressure-control ventilation (PCV, *left*) and neurally adjusted ventilatory assist (NAVA, *right*). During PCV, there was a significant amount of wasted efforts (indicated by *red arrows*). During PCV, the delivery of assist (*shaded vertical blue bar*) occurred during neural exhalation, indicating poor patient–ventilator interaction. During NAVA (*right panel*), there were no wasted efforts and the assist was delivered during neural inspiration (*vertical blue shaded bar*). *Bottom*: Waveforms for Edi and ventilator-delivered pressure (Pvent) for an intubated adult patient breathing on pressure-support ventilation (PSV, *left*) and neurally adjusted ventilatory assist (NAVA, *right*). During PSV, too sensitive trigger settings, and too high levels of assist resulted in ventilator-induced hyperventilation and elimination of the Edi. The assist continued to be triggered and delivered (*blue shaded vertical bar*), despite no activation of the diaphragm. During NAVA (*right panel*), Edi controls the ventilator, and cannot be suppressed by ventilator-induced hyperventilation. (Adapted from Sinderby et al,[85] with the kind permission of Springer Science+Business Media.)

respiratory function. If the Edi is referenced to tidal volume during an unassisted breath, the tidal-volume-to-Edi ratio provides an index of the patient's efficiency to generate volume. If an inspiratory occlusion is performed at end-expiration, the ratio of the airway pressure to the Edi expresses the efficiency to generate force. In a recent study, these indices were shown to add important information about extubation failure and success.[101]

BASIC PRINCIPLES AND PHYSIOLOGY OF NEURALLY ADJUSTED VENTILATORY ASSIST

The Edi waveform is today used to control mechanical ventilation in NAVA.[41] NAVA can be delivered by invasive or noninvasive interfaces in all patient ages. Because NAVA uses the Edi waveform to control the assist, the assist is delivered in synchrony and in proportion to the patient's neural respiratory efforts, the latter governed by respiratory demand and reflexes (see Fig. 13-2).

Concept of Neurally Adjusted Ventilatory Assist

NAVA principally works as an artificial respiratory muscle under the same neural control as the patient's respiratory muscles. Figure 13-10 describes how, during NAVA, the patient's respiratory centers serve as the controller for both the patient's diaphragm and the ventilator at the same time. The diaphragm's pressure-generating efficiency depends on its neuromechanical coupling,[80] and is affected by such factors as dynamic hyperinflation and muscle weakness. For the ventilator, the efficiency of pressure generation depends on the NAVA level, a gain factor that controls the amount of pressure for a given Edi. The sum of the patient and ventilator pressures is the transpulmonary pressure, that is, the pressure that distends the lungs.

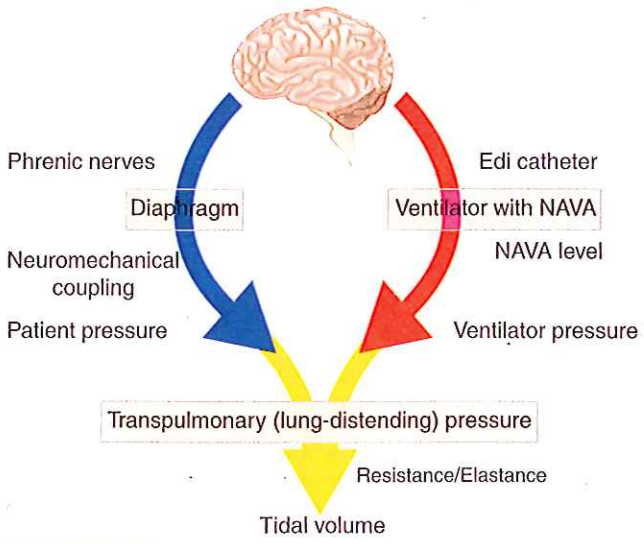

FIGURE 13-10 Concept of NAVA. During NAVA, the respiratory centers control both the patient's own diaphragm (*left*), resulting in a patient pressure, and the ventilator (*right*), creating a ventilator pressure (*right*). Their sum is the transpulmonary (or lung-distending) pressure. Depending on the patient's neuromechanical efficiency (*left*) and on the NAVA level (*right*), the relative contribution of the patient or ventilator to the lung-distending pressure will vary. For a given lung-distending pressure, the tidal volume generated will depend on the elastance and resistance of the patient.

At a fixed NAVA level, the Edi is solely responsible for changes in transpulmonary pressure. If respiratory drive (and hence Edi) is doubled, this doubles the patient pressure *and* doubles the ventilator pressure, therefore doubling transpulmonary pressure. Conversely, reducing the Edi by half reduces the patient pressure by half, *and* the ventilator pressure by half. Therefore, at a constant NAVA level, the patient is in full control of lung-distending pressure.

When the Edi remains constant, an increase in the NAVA level only increases the ventilator's relative contribution to the transpulmonary pressure. Therefore, in relative terms, the patient's contribution to volume is reduced compared to the ventilator.

Triggering

In its current platform, the assist is triggered by the initial increase in Edi (Fig. 13-11). Note that NAVA is triggered by a *deflection* in Edi and not at an absolute level of Edi; the latter would not function when tonic Edi is present. In principle, the Edi signal should precede the airway pressure signal and inspiratory flow signal and trigger on Edi (see Fig. 13-1). There are instances, however, when the filtering of the ECG or artifacts may coincide with the beginning of the Edi, or other inspiratory muscle groups could generate flow first. In this case, the ventilator is triggered by either changes in Edi *or* flow, on a "first-come, first-served" basis. This is to avoid inspiratory occlusions during triggering. If pneumatic triggering occurs (before Edi triggering), a pressure of 2 cm H_2O is delivered until the Edi appears.

Assist Delivery

Throughout neural inspiration, the ventilator delivers pressure in proportion to Edi. The pressure waveform follows the inspiratory portion of the Edi waveform (see Fig. 13-11). This matching of the pressure to the Edi is updated every 16 milliseconds. The Edi is multiplied by a proportionality constant known as the NAVA level, to increase or decrease the assist. The NAVA level has units of cm $H_2O/\mu V$.

The NAVA level is set manually. The range available today is between 0 and 15 cm $H_2O/\mu V$, and can be adjusted in steps of 0.1 cm $H_2O/\mu V$. The response of the ventilator to changes

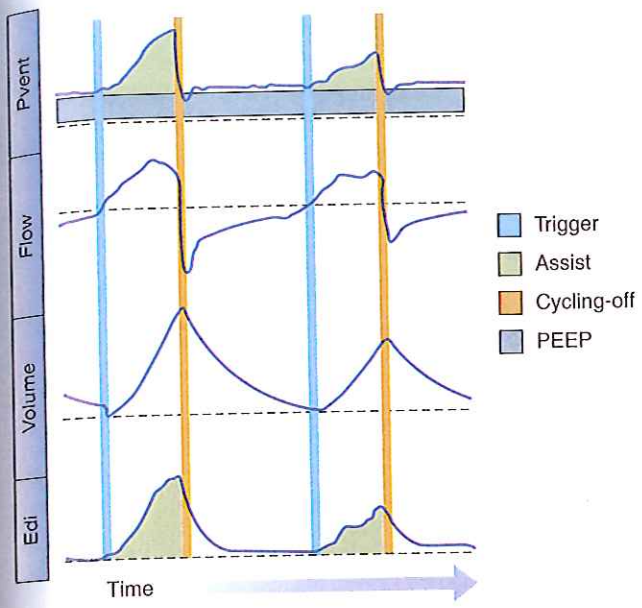

FIGURE 13-11 Features of NAVA. *From top to bottom:* Tracings for ventilator pressure (Pvent), flow, volume, and Edi are displayed for a patient breathing on NAVA. During NAVA, triggering of the ventilator occurs when the Edi exceeds a threshold deflection in Edi, as indicated by the *blue vertical line*. Throughout the inspiration, the ventilator pressure follows the Edi waveform (*green-shaded area*), and the NAVA level determines the proportionality between the ventilator pressure and the Edi. When the Edi waveform has decreased to 70% of the peak, the ventilator cycles off (*orange vertical line*) to a user-defined PEEP (*gray horizontal bar*). During NAVA (and a fixed NAVA level), a larger Edi waveform produces a larger pressure delivery (first breath) and a smaller Edi waveform produces a smaller pressure (second breath).

in the NAVA level is dependent on the absolute level of Edi, which varies between patients. If the Edi is large, it takes only a small change in the NAVA level to produce a large change in ventilator-delivered pressure. For example, an increase in the NAVA level by 1 cm $H_2O/\mu V$ when Edi peak is 10 μV results in an increase in ventilator pressure of 10 cm H_2O, whereas if the Edi is 1 μV, the increase in ventilator pressure is only 1 cm H_2O.

Upper pressure limits are applied during NAVA and can be adjusted. During NAVA the pressure is limited to 5 cm H_2O below the dialed-in limit.

Cycling-Off

During NAVA, the ventilator cycles-off the breath once the Edi drops to 70% of the highest value (see Fig. 13-11). When Edi peak values are low, cycling-off occurs at lower percentages. The breath is cycled off with pressure criteria any time the peak pressure exceeds the predicted NAVA pressure by 3 cm H_2O. In the case of a long neural inspiration, there are time criteria for cycling off: 1.5 seconds in infants and 2.5 seconds in adults.

Physiologic Response to Increasing Neurally Adjusted Ventilatory Assist Levels

If a patient is in respiratory failure, the typical physiologic response to increasing the NAVA level (from zero) is the following (Fig. 13-12).

- "Phase 1": At lowest NAVA levels (see Fig. 13-12, *left*), Edi is highest, indicating a large patient effort with insufficient ventilation. As the NAVA level is progressively increased, ventilator pressure increases, until at some NAVA level, a "patient-desired" transpulmonary pressure (and tidal volume) is reached. This first phase indicates that NAVA supplements the respiratory muscles to restore adequate ventilation.
- "Phase 2": Further increases in the NAVA level result in a constant transpulmonary pressure secondary to a reduction in Edi (see Fig. 13-12).[58,94,96,102,103] This second phase indicates a "comfort zone" where assist levels are adequate to sufficiently unload the respiratory muscles. In this second phase of unloading with NAVA, ventilator pressure, respiratory rate, and tidal volume change minimally.[58,94,96]
- "Phase 3": If the increase in NAVA level continues, the Edi will decrease further until it reaches a plateau (a minimum level). At highest NAVA levels, the Edi is not abolished (see Figs. 13-12 and 13-13),[58,102] but results in an irregular breathing pattern secondary to a too-high loop gain.[96] Even with maximum unloading of the diaphragm, Edi is still present and able to control the ventilator[102] (see Fig. 13-13), without inducing reflex reductions in respiratory rate.[4,15,104–106]

The downregulation of Edi and the avoidance of excessive assist delivery during NAVA have been verified experimentally as preventing ventilator-induced lung injury.[107]

Weaning

Improvement of respiratory function or reduced respiratory demand reduces the Edi waveform. Considering that the pressure delivered during NAVA follows the Edi, as the patient's respiratory status improves and Edi decreases, the pressure delivered will also decrease as long as NAVA levels and sedation management remain constant. Thus, with respiratory improvement, NAVA can—secondary to its close neural integration—be thought of as a "self-weaning" mode.

Noninvasive Neurally Adjusted Ventilatory Assist

The principal difference between invasive and noninvasive NAVA is that the bias flow during PEEP is automatically adjusted (during noninvasive NAVA) and can reach much higher flow levels, ensuring maintained PEEP during the

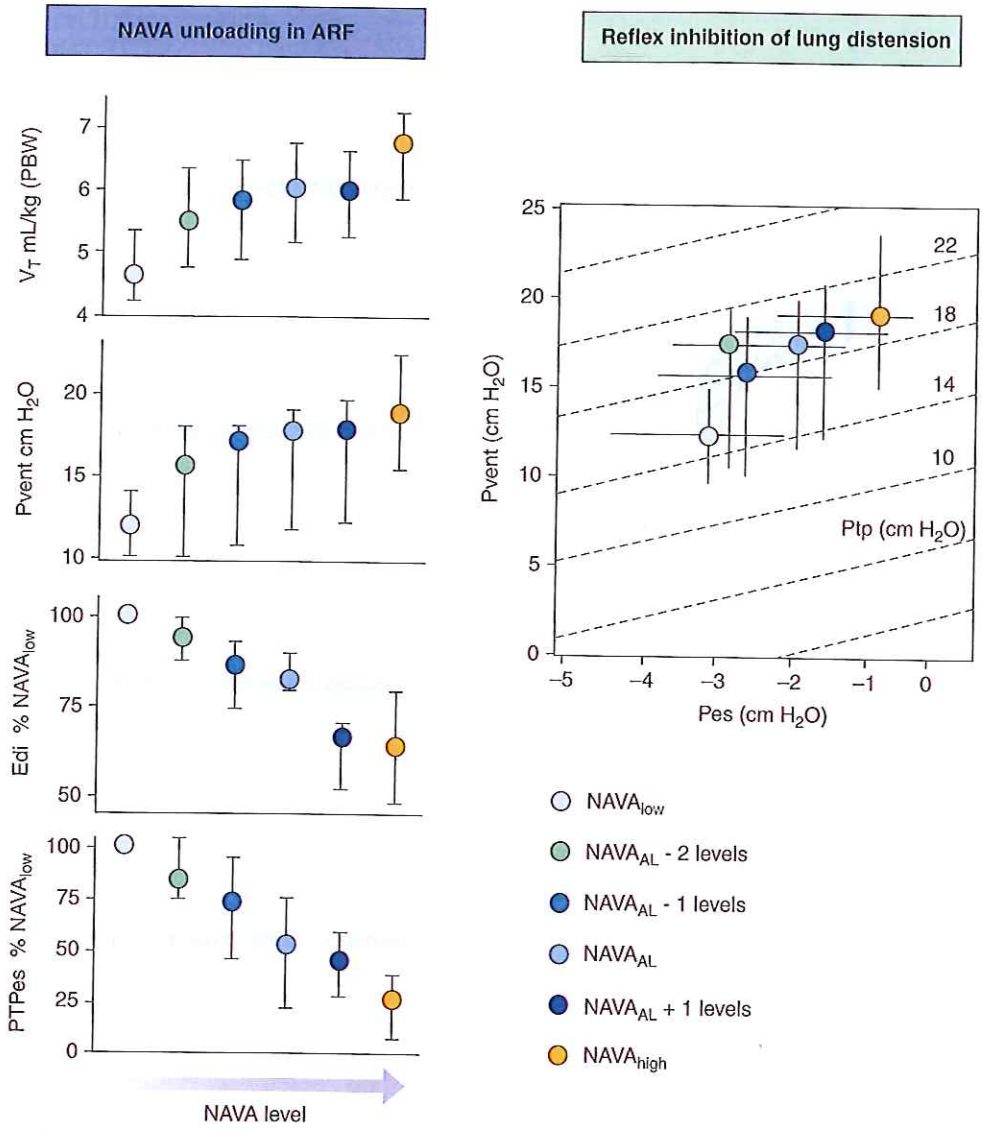

FIGURE 13-12 Physiologic response to increasing NAVA levels. *Left panel:* Changes in tidal volume (V_T) per predicted body weight (PBW), mean inspiratory ventilator pressure (Pvent) including positive end-expiratory pressure (PEEP), electrical activity of the diaphragm (Edi), and esophageal pressure time product (PTPes) for a group of patients during titration of the NAVA level. The initial increase in Pvent and V_T between the lowest NAVA level (*gray dot*, $NAVA_{low}$) and the adequate NAVA level (*royal blue dot*, $NAVA_{AL}$) was associated with a reduction in Edi and PTPes. Thereafter, further increases in the NAVA level did not significantly change either Pvent, V_T, nor minute ventilation (not shown) while the reduction of PTPes and Edi continued from $NAVA_{AL}$ to $NAVA_{high}$ (*orange dot*). *Right:* Interaction between mean inspiratory ventilator pressure (Pvent, *y axis*), esophageal pressure (Pes, *x axis*), and transpulmonary pressure (Ptp, *dashed diagonal lines*) during a NAVA level titration. In this example, from $NAVA_{low}$ (*gray dot*) to one level below $NAVA_{AL}$ ($NAVA_{AL}$–1 level), Pvent increased by 5.0 cm H_2O and reduced the Pes deflection by 0.5 cm H_2O such that transpulmonary pressure increased by 4.5 cm H_2O. Further increasing the NAVA level from $NAVA_{AL}$ to $NAVA_{high}$ resulted in changes of Pvent and Pes that were similar in magnitude and, hence, in an essentially unaltered transpulmonary pressure. PEEP remained unchanged during the NAVA level titration. *ARF*, acute respiratory failure. (Adapted, with permission, from Brander L et al.[96])

neural expiration even in the presence of large leaks. There are also some differences in alarms, which are beyond the scope of this chapter.

In reference to Figure 13-1, Edi precedes inspiratory flow in the chain of events of spontaneous breathing. When a leak is present, Edi is a true indicator of when the breath starts, whereas the flow measurement in itself is affected by the leak. Studies have confirmed that patient–ventilator interaction during NAVA is not affected by severe leaks.[108,109]

Regarding noninvasive ventilation, an important consideration is the anatomical and physiologic consequences of avoiding intubation. Endotracheal intubation conveniently divides the air and food passages such that ventilator assist can be delivered with no interference from upper airway regulation and swallowing. Delivery of assist through the upper respiratory tract using a noninvasive interface, however, introduces a demand to synchronize assist delivery with inspiration for several reasons.

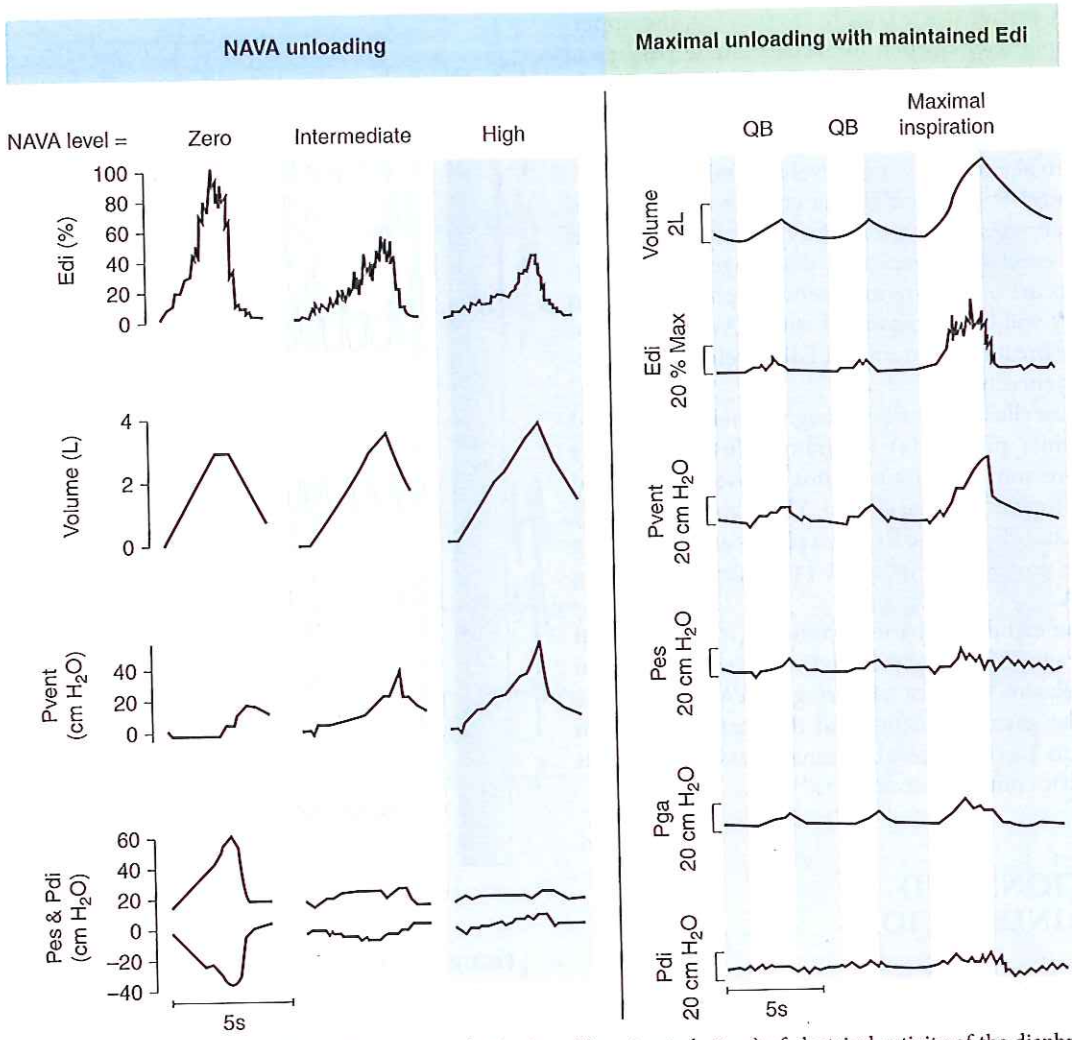

FIGURE 13-13 Respiratory muscle unloading with NAVA. *Left:* Tracings (*from top to bottom*) of electrical activity of the diaphragm (Edi), volume, ventilator pressure (Pvent), and esophageal (Pes) and transdiaphragmatic pressure (Pdi) obtained in one healthy subject performing maximal inspirations with three NAVA levels (zero, intermediate, and high). Increasing the NAVA level resulted in increased ventilator-delivered pressure and deactivation of the diaphragm (by 60%). Note that this was occurring while the Pdi and Pes deflections disappeared, indicating 100% unloading. *Right:* Tracings (*from top to bottom*) of volume, Edi, ventilator pressure (Pvent), esophageal pressure (Pes), gastric pressure (Pga), and transdiaphragmatic pressure (Pdi) obtained in a healthy subject breathing on NAVA at high NAVA levels. The first two breaths were obtained during quiet breathing and the third breath during a maximal inspiration. Note the 100% unloading of the diaphragm (flat Pdi) in all breaths regardless of the level of diaphragm activation, and the remaining Edi, which is still able to control the ventilator at both volumes. (Adapted, with permission, from Sinderby et al.[102])

In humans, the upper airways constitute a common tract allowing ventilation, ingestion, and speech, requiring neural control systems to coordinate respiration with swallowing, speech, cough, and vomiting.[110–113] In 1949, Negus[114] provided the first notation that the glottis opens before inspiration starts. In 1969, Suzuki and Kirchner[115] demonstrated that phasic activity of vocal cord dilators occurs in synchrony with phrenic nerve activity. Kosch et al[116] demonstrated that laryngeal abductors are activated before the diaphragm. The genioglossus is activated and dilates the airway before diaphragmatic activation[117] and airway flow.[118,119] During expiration, activation of, for example, the pharyngeal constrictors also has been suggested to modulate the resistance to airflow.[120,121] Recently, active glottal closure was described during high levels of noninvasive conventional ventilation in nonsedated newborn lambs[122]; active glottal closure is likely mediated by bronchopulmonary receptors.[63]

Another factor complicating the implementation of noninvasive ventilation is swallowing. Swallowing must interact with the inspiratory muscles in a fashion that minimizes disturbances to breathing. In awake human subjects, swallowing is associated with apposed vocal cords and an apneic period,[123] normally followed by expiration.[124] It is suggested that this sequence (swallow followed by expiration) may be protective against aspiration.

The role of the upper-esophageal sphincter is to prevent reflux of food into the airways as well as avoid entry of

air into the digestive tract. During swallowing, the upper-esophageal sphincter is open to accommodate passage of a bolus into the esophagus, and hence delivery of pressure during swallowing increases the risk of gastric distension. During noninvasive NAVA, no gastric distension was observed even at extremely high levels of assist.[108]

Vocal control is achieved by the coordinated efforts of respiratory, laryngeal, and articulatory muscles. Given that speech is an expiratory maneuver, diaphragmatic involvement only occurs on inspirations between phonation, thus assist delivery will be synchronized with NAVA. Abnormal rhythm of the breathing pattern and Edi waveform are anticipated during speech.

In 1937, Coryllos[125] described cough as being composed of three distinct phases: (a) inspiratory, (b) compressive (expiratory pressure generation against a closed glottis), and (c) expulsive (opening of the glottis). The diaphragm is only electrically active during the first two phases and not during the expulsive phase.[121,126] Figure 13-14 illustrates coughing during NAVA.

During the expulsive phase of vomiting, the crural and costal diaphragm dissociate their activities, with the crural diaphragm relaxing (i.e., not triggering NAVA) to allow the ejection of the gastric contents, and the costal diaphragm contracting, to increase the abdominal pressure and thus force the gastric contents outwards.[127–130]

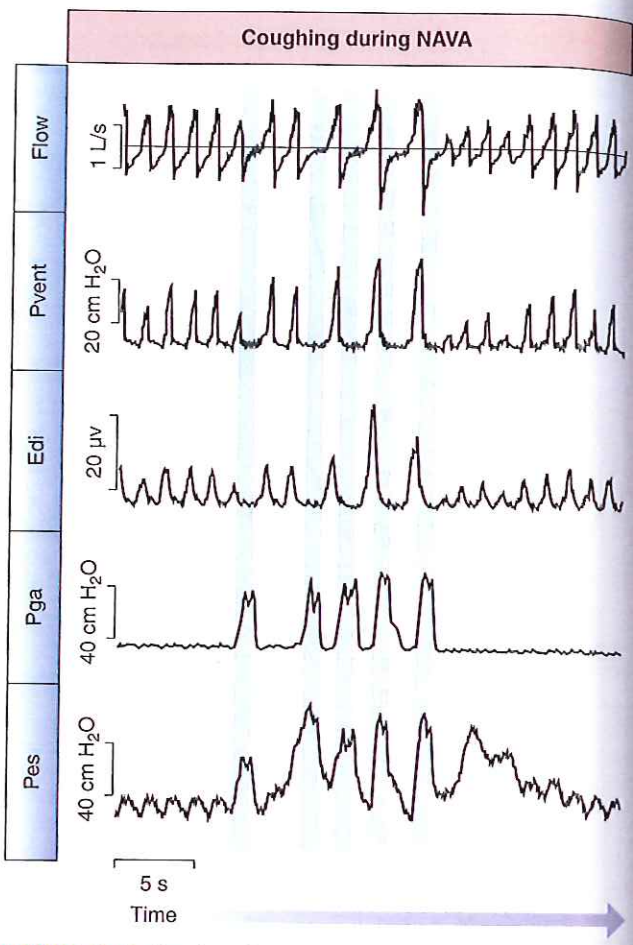

FIGURE 13-14 Coughing during NAVA. Tracings (*from top to bottom*) of flow, ventilator pressure (Pvent), diaphragmatic electrical activity (Edi), gastric pressure (Pga), and esophageal pressure (Pes) in an adult intubated patient ventilated with NAVA who is coughing. The *blue-shaded* vertical areas highlight the coughs (upswing in Pga). The Edi waveform shows termination of Edi during coughs. The functionality of NAVA was not affected by the coughs. (Note that the second compressive phase described in the text is lacking in the intubated patient.)

INDICATIONS AND CONTRAINDICATIONS

Indications

NAVA is indicated for use in patients of all ages who require and qualify for partial ventilator assist, and in whom spontaneous respiratory activity is present. NAVA may prove especially useful in patients at risk for prolonged mechanical ventilation and who fail spontaneous breathing trials.

Monitoring the Edi is indicated in all patients of all ages in any mode of ventilation, invasive or noninvasive, when the goal is to perform bedside evaluation of patient–ventilator interaction and neural breathing pattern, and to ensure that spontaneous breathing is present.

Contraindications

NAVA cannot be applied if (a) Edi is absent, (b) nasogastric and/or orogastric catheters are contraindicated, or (c) ventilatory parameters are unacceptable.

ADJUSTMENTS AT THE BEDSIDE

Implementation of NAVA requires a ventilator with the NAVA option, module, and software, and an Edi catheter.

Electrical Activity of the Diaphragm Catheter Positioning

Catheter positioning is achieved by inserting the tip of the catheter nasally or orally to a predicted distance, and then adjusting the position with feedback from a display showing an Edi curve and four raw signals not filtered for ECG (Fig. 13-15). With the catheter in appropriate position, both P and QRS waveforms should be present at the top and P waves should disappear toward the bottom as illustrated in middle panel of Figure 13-15. The top and bottom panels of Figure 13-15 demonstrate examples of ECG waveforms when the catheter is too far out or too far in, respectively.

A secondary verification method on the same window involves the highlighting of the leads closest to the diaphragm (in blue on the commercially available system), as determined

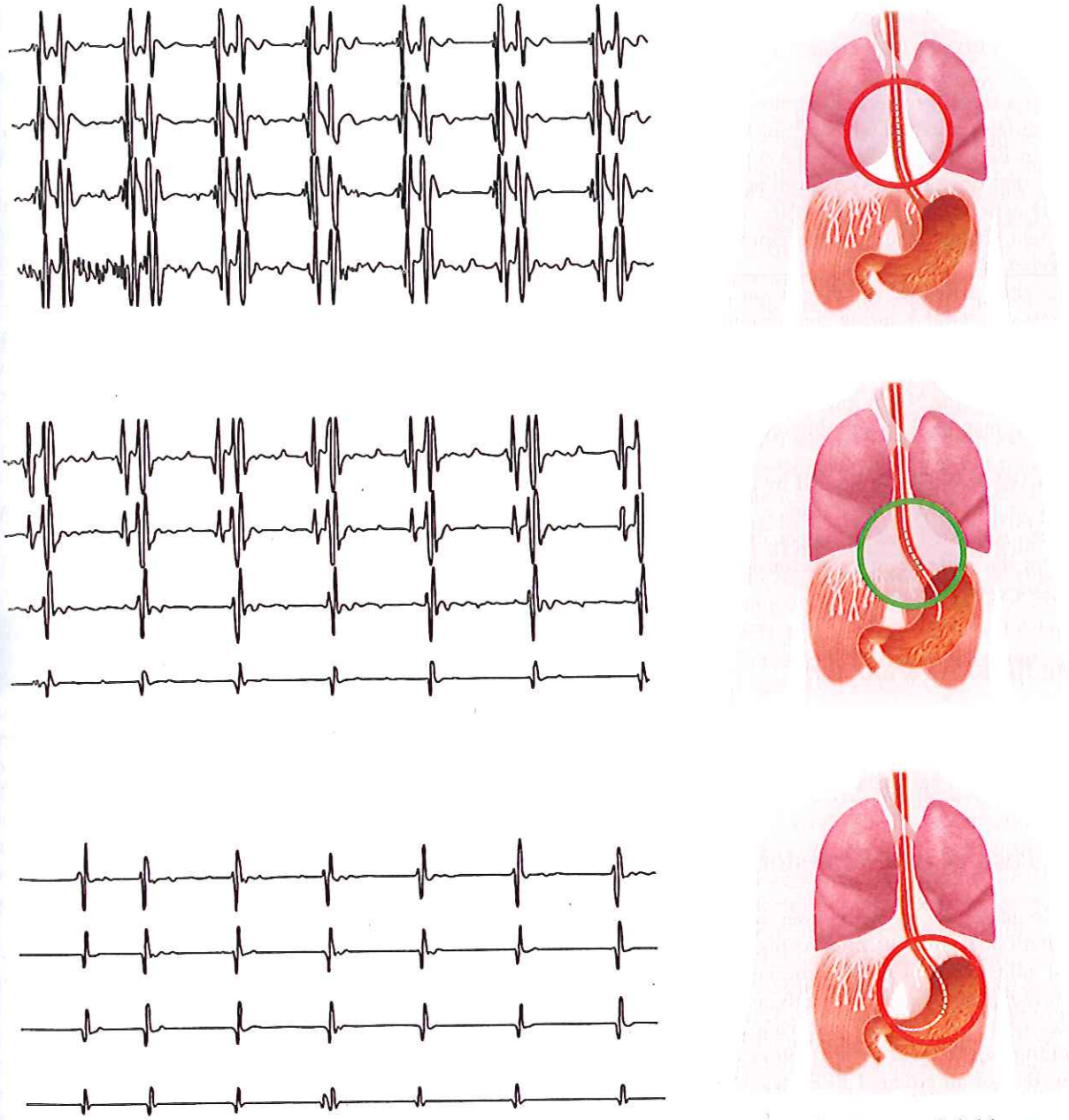

FIGURE 13-15 Electrode positioning during NAVA. Unfiltered tracings obtained from four electrode pairs (top is most cephalad, bottom most caudal) on the Edi catheter when the catheter is too far out (*top*), in good position (*middle*), and too far in (*bottom*). The *middle panels* indicate the correct pattern for the ECG waveforms when the Edi catheter is positioned appropriately (diaphragm located approximately in the middle of the electrode array). This pattern is characterized by distinct P waves and QRS waves whose amplitude is largest at the top, and diminishes more distally. See text for details.

by the cross-correlation method (see Fig. 13-4).[75] Ideally, the two middle leads should be highlighted during inspiration.

The catheter should be fixed after appropriate positioning and the final insertion distance noted. This method has been validated in adult[131] and pediatric[132] patients.

Setting the Neural Trigger

The trigger during NAVA detects a threshold increase in the Edi waveform. The sensitivity of the neural trigger is adjustable, with a default setting of 0.5 μV.

Initial Setting of the Neurally Adjusted Ventilatory Assist Level

To deliver a target pressure, the following formula can be used: Ventilator pressure (above PEEP) in cm H_2O = (peak Edi – min Edi) in μV × NAVA level (cm H_2O/μV). It is possible, that once the NAVA level has been set, and the patient is switched over to the NAVA mode, the Edi waveform might change, and may therefore be different from the targeted pressure.

As an alternative, the NAVA level can be set so that the peak pressure attained during conventional ventilation can be matched. A designated "NAVA preview window" allows feedback for this. It is possible that once the patient is switched over to the NAVA mode, the Edi waveform might change, and may be therefore different from the predicted pressure.

The NAVA level can be titrated by performing stepwise increases in the NAVA level from a minimal level.[58,95,96] It has been suggested that the adequate NAVA level is the one where the increase in ventilator-delivered pressure is slowing—or even plateaus.[96]

Setting Backup Parameters

As in other modes of mechanical ventilation, upper pressure limits and backup parameters should be set for the appropriate patient age and condition.

Setting Positive End-Expiratory Pressure

PEEP should be set as with other modes of mechanical ventilation. In infants, monitoring the tonic Edi may aid with adjustment of PEEP. Emeriaud et al[92] and Allo et al[94] have demonstrated that applying PEEP can reduce tonic Edi (see Fig. 13-8). Monitoring the ratio between tidal volume and Edi (neuroventilatory efficiency) allows identification of an efficient PEEP level.[95] During NAVA, PEEP does not have to be applied to overcome intrinsic PEEP.

Adjustment of the Neurally Adjusted Ventilatory Assist Level during Weaning

NAVA can be combined with any weaning method, for example, daily spontaneous breathing trials, with the advantage that it provides numerical and bedside information about respiratory drive. Any improvement in patient respiratory function (as indicated by a decrease in Edi for the same NAVA level) should be corrected by reducing the NAVA level. The easiest method is to note the Edi value obtained when the patient was comfortable (Edi baseline) and if Edi decreases, reduce the NAVA level until the Edi returns to baseline value. If the patient has undergone a spontaneous breathing trial, another approach is to target an Edi amplitude relative to that observed during a spontaneous breathing trial.[133] Yet another approach is to perform daily titrations of the NAVA level to determine an adequate NAVA level.[96]

TROUBLESHOOTING

The reader is referred to the manufacturer's user manual (Maquet Critical Care AB, Solna, Sweden).

ADVANTAGES AND LIMITATIONS

Table 13-1 lists the advantages and limitations of NAVA.

TABLE 13-1: ADVANTAGES AND LIMITATIONS OF NAVA

Advantages of NAVA
Edi monitoring
Standardized Edi catheter position procedure allows reliable feeding tube placement
Monitoring presence or not of spontaneous breathing during conventional ventilation
Monitoring patient–ventilator interaction during conventional ventilation
NAVA Mode
Improved timing between patient effort and assist delivery independent of
a. Leaks
b. Properties of interface
c. Liquid in respiratory circuit
d. Cardiogenic oscillations in the airway flow
e. Intrinsic PEEP
Neurally integrated with timing of upper airway activity and function
Matching of magnitude assist delivery to patient effort
a. Preservation of respiratory drive
b. No runaway
c. Prevention of excessive assist delivery
d. Responds to changes in respiratory demand
Limitations of NAVA
Cannot use in absence of respiratory drive
Cautious use with uncontrollable respiratory drive
Too-high NAVA levels cause irregular breathing pattern
Cannot be used when feeding tube is contraindicated
Signal disturbances on Edi signal may affect NAVA performance, e.g., ECG leak through

COMPARISON WITH OTHER MODES

Fundamental Differences between Neurally Adjusted Ventilatory Assist and Other Modes

The difference between conventional ventilation (such as PSV, pressure control ventilation, assist-control ventilation, and synchronized intermittent mandatory ventilation) and NAVA lies in the signal used to control the ventilator (see Fig. 13-1). Conventional modes of ventilation control the timing of assist delivery by pneumatic signals (pressure or flow at the airway) or time criteria, and the level of assist is pressure or volume targeted. NAVA, on the other hand, is controlled by the patient's own Edi, occurring at a level proximal to muscle function and respiratory mechanics, and which also responds to respiratory feedback loops.

Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Impact on Patient–Ventilator Interaction

Compared to conventional modes of ventilation, NAVA improves patient–ventilator synchrony in terms of triggering and cycling-off delays.[4,15,98,103,109] The amount of improved synchrony depends on the disease etiology and the settings in the conventional ventilation arm.

The improvement in trigger delays with NAVA is in the 100 millisecond range.[4,98,103] When expressed as a percentage of the neural inspiratory time, NAVA also shows less relative trigger delay (13% to 14% of neural inspiratory time) than PSV (up to 35% of neural inspiratory time at high levels of PSV).[4] One study recently showed that of their twenty-five patients with mixed etiologies, none had trigger delays greater than 150 milliseconds during NAVA.[98] The trigger delay increases with increasing PSV, but is not affected by increasing NAVA levels.[4,15,103,134] In premature infants, 13% of the breaths during conventional ventilation began *before* the onset of Edi.[109]

Wasted efforts are worsened when the PSV level is increased.[3,4,103,134] In contrast, with NAVA, no wasted efforts have been reported in the literature, even when the NAVA level is increased.[4,15,103,134]

Several investigators have reported shorter cycling-off delays during NAVA compared to PSV in adults[4,98] and in rabbits with lung injury.[103] The cycling-off delays are prolonged with increasing PSV, whereas with increasing NAVA, there is no effect.[4,103,134] In premature infants, cycling-off during PSV or PSV with volume guarantee actually occurs *before* the cycling-off during NAVA.[109]

Some investigators have combined the observed asynchronies (trigger delays, wasted efforts, cycling-off delays) to quantify an "asynchrony index," which was found to be significantly lower during NAVA compared to PSV in adults[4,15,98,137] and neonates,[138] and worsened with increasing levels of PSV.[4,15,137]

One challenge for achieving patient–ventilator synchrony is when leaks are present. Figure 13-16 demonstrates airway pressure tracings obtained during noninvasive PSV and noninvasive NAVA, with increasing leak. The worsening asynchrony with increasing leak was accompanied by an eightfold increase in breathing effort (esophageal pressure-time product, not shown). In premature infants and in rabbits with acute lung injury, trigger delays, and cycling-off delays were equal during invasive NAVA and during noninvasive NAVA.[108,109]

Patient-ventilator interaction is difficult to achieve with pneumatically controlled non-invasive ventilation applied with the helmet interface because of its large volume, high compliance, and sensitivity to leaks.[139] Moerer et al[135] examined patient–ventilator synchrony during neurally and pneumatically triggered and cycled-off PSV with the helmet in healthy subjects. Trigger delays, wasted efforts, and cycling-off delays all increased with increasing PSV when pneumatic control was used. During neural triggering and cycling-off, increasing PSV and breathing frequency did not affect trigger and cycling off delays. The comfort of breathing was significantly better during neurally triggered and cycled-off PSV.

By design, NAVA delivers assist in proportion to the Edi, and a few studies have demonstrated a high correlation between Edi and peak airway pressure delivered,[15,103,109] which was superior to the correlation between Edi and pressure during PSV (Fig. 13-17). The high correlation between Edi and peak ventilator pressure was not affected by the presence of a large leak during noninvasive NAVA in premature babies.[109] During PSV plus volume guarantee, Beck and Sinderby demonstrated a negative correlation between Edi and pressure, indicating a reversed proportionality.[140]

As a result of the improved synchrony with NAVA, the pressure-time product of the diaphragm and the Edi-time product are both less during NAVA than during PSV.[4,103] The diaphragmatic work of breathing during the trigger phase was also found to be less for NAVA compared to PSV, which also showed increased diaphragm work when the PSV level was increased.[4]

Double triggering, delivery of two ventilator breaths back-to-back, occurs during NAVA and PSV; while the prevalence is low,[15,16,98,141] it can sometimes be frequent.[13]

Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Impact on Breathing Pattern and Gas Exchange

In studies where peak airway pressure was matched, tidal volume was lower during NAVA compared with

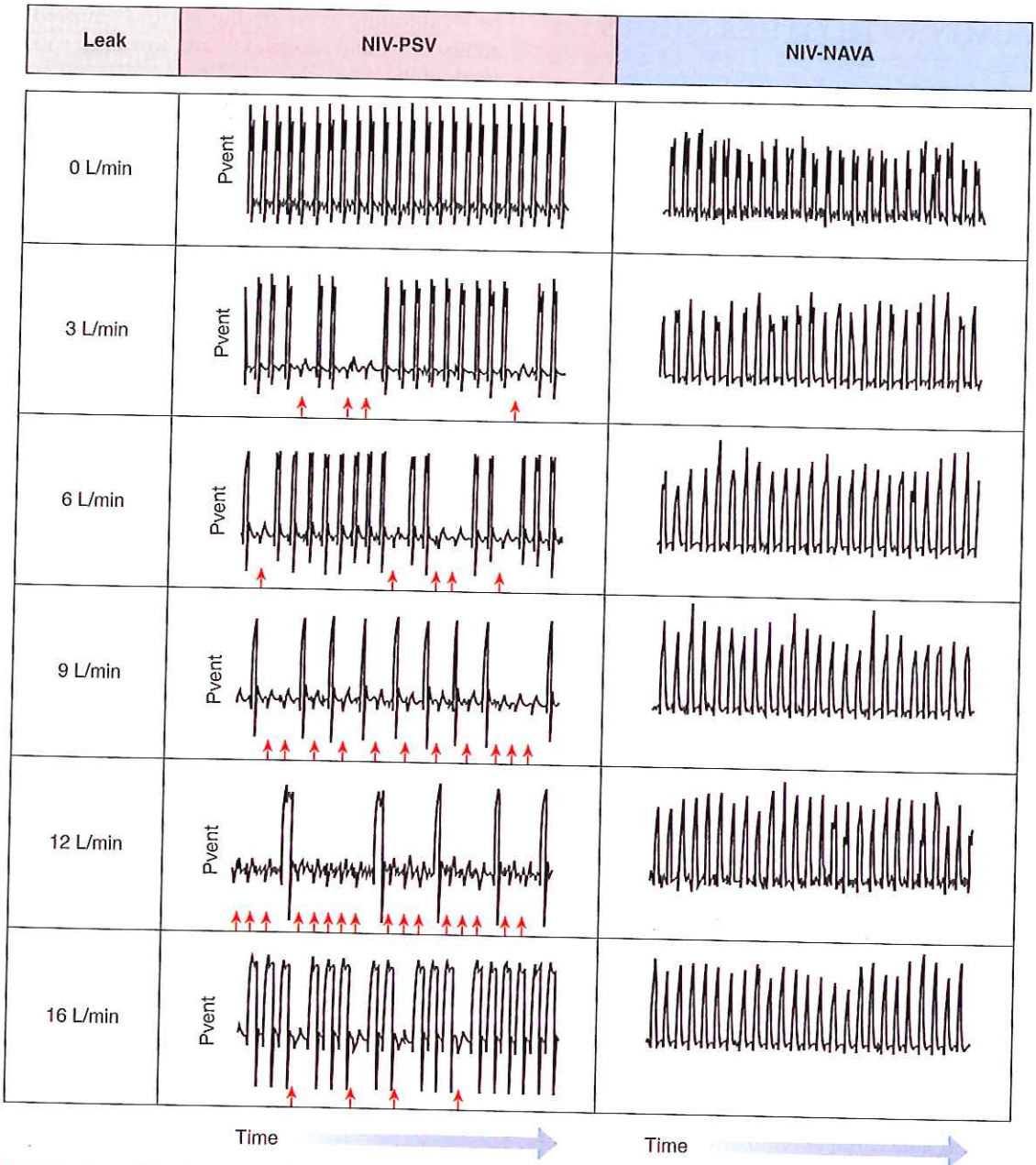

FIGURE 13-16 Patient–ventilator interaction during noninvasive PSV and noninvasive NAVA. Ventilator-delivered pressure (Pvent) is displayed fo noninvasive pressure support (NIV-PSV, *left*) and noninvasive NAVA (NIV-NAVA, *right*), for periods of increasing leak (0 to 16 L/min, *top to bottom* The wasted efforts (*red arrows*) increased with increasing leak during NIV-PSV, whereas wasted efforts were not observed during NIV-NAVA. At th highest leak tested (16 L/min), the ventilator also demonstrated autotriggering and hangup of the ventilator breaths (that were cycled-off by time crite ria). During NAVA, synchrony was maintained in terms of timing and proportionality, despite the increasing leak. The increasing asynchrony durin NIV-PSV with increasing leak was associated with an eightfold increase in effort (not shown).

PSV,[15,96,137,141] usually 6.5 to 8.5 mL/kg of predicted body weight in adult patients of all illnesses and severities. In animal studies, tidal volume during NAVA is lower than during PSV[103] or volume control set to a lung-protective strategy of 6 mL/kg.[104] When attempts are made to systematically increase PSV and NAVA levels, tidal volume increases during PSV but remains more or less unchanged during NAVA, secondary to downregulation of Edi.[4,103,137] In critically ill postoperative patients, Coisel et al[142] demonstrated no significant differences in tidal volume between NAVA an PSV at baseline, although after 24 hours of each, tidal vol ume was lower during NAVA.

Some studies report a higher respiratory rate with NAVA compared to PSV.[4,98,137,141,143] The results, however, should be interpreted with caution because the distinction is no always made between neural respiratory rate and ventila tor rate. Colombo et al[15] and Spahija et al[4] both reported a reduction in neural respiratory rate with increasing PSV

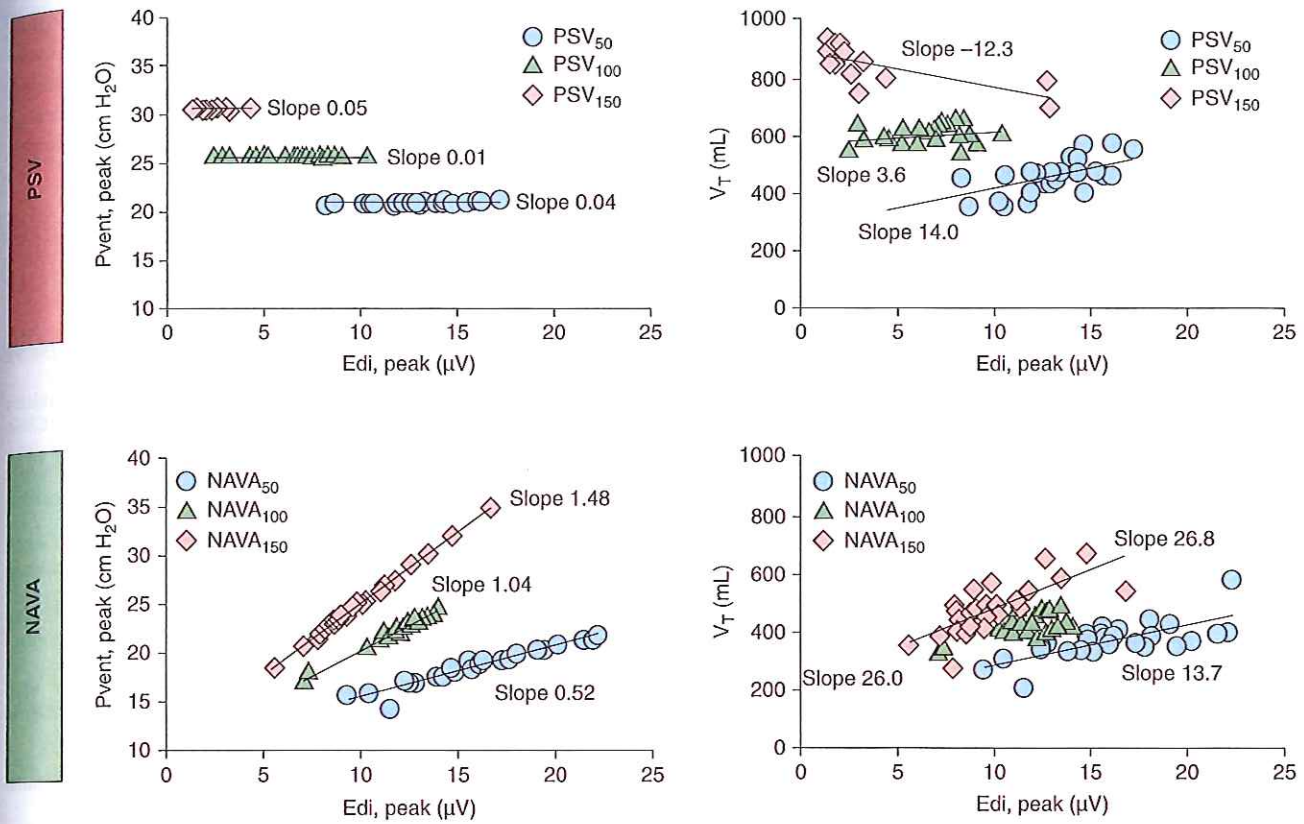

FIGURE 13-17 Proportionality between Edi and ventilator pressure during pressure-support ventilation (PSV) and during NAVA. Relationships between ventilator pressure (Pvent) and Edi (*left panels*), and tidal volume (V_T) and Edi (*right panels*) are depicted for three assist levels with PSV (*upper panels*) and NAVA (*lower panels*), in one patient. The three levels of assist are indicated by different colors. Pvent did not change with varying Edi in PSV. Oppositely, in NAVA, Pvent varied in proportion to Edi. During PSV, V_T slightly rose when increasing Edi only at the lowest level of support. During NAVA, V_T augmented as Edi increased at all levels of assistance. (Adapted, with permission, from Colombo et al.[97])

levels, whereas this was not observed during increasing NAVA levels.[15,96] Another confounding factor in the interpretation of respiratory rate is that, during conventional ventilation, wasted efforts mask the patient's neural respiratory rate. During PSV, the neural respiratory rate can be higher than the ventilator rate.[103] Hence the increased respiratory rate sometimes observed during NAVA may simply be the elimination of wasted efforts. Coisel et al[142] showed no significant differences in ventilator respiratory rate between PSV and NAVA in their group of postoperative patients at baseline or after 24 hours. Beck et al showed a reduced neural respiratory rate during NAVA compared to PSV in preterm infants.[109]

Breathing pattern variability was higher during NAVA compared to PSV[142,143] and was held responsible for improved oxygenation.

All studies comparing NAVA to PSV show maintained clinical stability in terms of heart rate,[109,138] oxygen saturation in both adult[142] and neonatal populations,[109,141,144] minute ventilation,[98,137] and equivalent values of Pa_{CO_2} and partial pressure of arterial oxygen (Pa_{O_2}).[4,15,137,141,143,144] Coisel et al[142] reported an improved Pa_{O_2}/FI_{O_2} (fractional inspired oxygen concentration) ratio after 24 hours of NAVA in postoperative patients. In one pediatric study that measured hemodynamics, NAVA and PSV were equivalent.[138]

Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Limitation of Excessive-Assist

In rabbits with lung injury, Beck et al[103] demonstrated that a fourfold increase in PSV generated four times as much airway pressure, whereas, a fourfold increase in NAVA level resulted only in an increase from 3.5 cm H_2O to 7 cm H_2O, secondary to downregulation of Edi at higher NAVA levels. In adult and critically ill patients, progressively increasing the NAVA level is associated with a deactivation of the diaphragm at higher levels, such that delivered pressure and tidal volume do not increase excessively.[4,15,96,134,137,143] This is in clear contrast to studies with increasing PSV where the targeted pressure (and volume) increases as directed.

In general, the shape of the waveform during PSV is squarer than the triangular shape observed with NAVA.[4] Thus, for matched peak airway pressures, NAVA resulted in lower mean airway pressure as compared with NAVA.[4,15,98,103,143]

Breatnach et al[144] used NAVA for several hours in infants, and found, similar to what Allo et al[94] found in rabbits, that mean airway pressures decreased over time. In premature infants weighing <1500 g, Stein et al[145] also demonstrated reduced mean airway pressures over time when ventilated on NAVA.

High levels of PSV in association with involuntary triggering can produce hyperventilation, and may even eliminate the Edi completely (see Fig. 13-9). In contrast, high levels of NAVA do not eliminate the Edi (see Fig. 13-13).[102]

Neurally Adjusted Ventilatory Assist and Proportional-Assist Ventilation

NAVA and proportional-assist ventilation have not been directly compared. Both modes strive to improve assist delivery in spontaneously breathing patients and both have been found to improve synchrony and physiological variables compared to conventional modes.[140]

SUMMARY AND CONCLUSION

Many patients receiving conventional modes of ventilation receive substandard treatment, which has been associated with prolonged ventilator time. This is secondary to the limitations of conventional ventilators to detect and correct inappropriate timing and delivery of pressure.

Diaphragmatic electrical activity represents the neural output from respiratory centers, a signal which responds to respiratory demand. Diaphragmatic electrical activity is modulated by chemo, muscle, lung and other receptors, which act to ensure adequate ventilation while protecting the lungs. Simply monitoring the diaphragmatic electrical activity waveform is suitable for clinical monitoring of respiratory drive, neural breathing pattern, as well as patient–ventilator synchrony.

NAVA is a mode of ventilator assistance for spontaneously breathing patients, and uses the diaphragmatic electrical activity to trigger, to deliver assist, and to cycle-off the ventilator. Neural triggering and cycling-off improve patient–ventilator synchrony and are unaffected by leaks in the respiratory circuit. Because NAVA is modulated by neural feedback, assist is adjusted instantaneously in response to changes in patient respiratory demand.

NAVA introduces a new avenue for mechanical ventilation, and, different from the conventional deterministic approach of delivering static quantities of assistance, encourages personalized care that takes into account patient's individual differences and needs for every breath.

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Drs. Beck and Sinderby have made inventions related to neural control of mechanical ventilation that are patented. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Drs. Beck and Sinderby through roya ties. Dr. Beck and Dr. Sinderby each own 50% of Neurove Research Inc. (NVR). NVR is a research and developme company that builds equipment and catheters for researc studies. NVR has a consulting agreement with Maqu Critical Care.

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