Superiority of NAVA
The Evidence
Introduction

It is our hope that this booklet will increase interest, awareness and understanding of the physiological processes involved in mechanical ventilation, while promoting an individual physiology-based approach to securing gas exchange in the critically ill patient.

By definition, Controlled Mechanical Ventilation is unphysiological and has a large impact on the sensitive interaction between heart and lung in securing homeostasis. Essentially, the only justification for mechanical ventilation is to buy time for other interventions to support the healing process of the organism.

By reading the complementary booklet “Anatomy & physiology of respiration - From brain to breath” some of the concepts presented here may become easier to understand for the reader new to NAVA.

The bedside management of the critically ill patient has by tradition focused on the knowledge of applied physiology. Some physicians will even state that “physiology is always right”. With the increasing complexity of critical care, there has been a trend to favor protocols based on evidence from large randomized clinical trials. This approach may be beneficial for establishing a foundation for the basic treatment of the critically ill population, but it is not necessarily optimized for the treatment of the individual patient. As no large randomized clinical trial has yet been performed with NAVA, this booklet focuses on the findings from small physiology based studies. It emphasizes the concept of supporting normal breathing and minimizing intervention, which are important features of Neurally Adjusted Ventilatory Assist (NAVA).

The assessment of the individual response to an intervention is the classical conduct of critical care. During mechanical ventilation it has only been possible to measure the impact of the strategy chosen by indirect variables based on pressure, flow and blood gases. The availability of the electrical activity of the diaphragm, Edi, opens a window of opportunity for understanding the individual patient’s response to the ventilator settings. It thus completes the loop back to classical physiology and should therefore be regarded as the vital sign of respiration.
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Superiority of – The Evidence

**Electrical activity of the diaphragm – Edi**
Organisms are equipped with regulatory systems that display a variety of dynamic behaviours, ranging from simple stable steady states to switching and multi-stability, and to oscillations. The value of the parameter to be maintained is recorded by a receptor system and conveyed to a regulation module via an information channel. Examples of this regulation are insulin oscillations or gene modulation.

All muscles performing work must be coordinated by the brain or the effort will be inefficient. Respiratory function is a complex motor act involving several types of muscles and functions. To be efficient the contractions of these muscles must be perfectly coordinated (e.g. glottis relaxation and contraction synchronized to inspiration or recruitment of accessory respiratory muscles resulting from increased respiratory demands). This is achieved at the level of the respiratory centers and by the motor neurons that integrate central and peripheral inputs.

The integration of the central command and tight synchronization is obvious as the laryngeal muscles, diaphragm and intercostals are all controlled by motor neurons in the same area of the brain. The electrical activity of the diaphragm (Edi) is the only human bio feedback loop that is possible to study in real time. It is controlled by the respiratory centers, based on the chemical input from the circulating blood levels of pH, P_{aO_2} and P_{aCO_2}, complemented by mechanical pressure and stretch receptors.

Basically the respiratory centers will issue a demand for the respiratory muscles to produce a specific tidal volume for the maintenance of homeostasis.

Sensors in the lungs and the respiratory muscles will continuously feed back the results produced by the respiratory muscles to the brain, and if these muscles do not produce the expected amounts, the respiratory centers will increase the signal (Edi) level.

The increased signal amplitude will result in recruitment of additional muscle fibers and the maintenance of the targeted tidal volume.

**From neural activation to pressure generation**
Clinically, inspiratory effort is frequently associated with the measurement of changes in airway pressure and flow.

The result can be predicted by the equation of motion \[ P=(\text{Flow} \times R)+ (\text{Volume} \times E) + \text{PEEP}. \] The same variables are often referred to when describing the degree of unloading by mechanical ventilation.

Although mechanical effort does not always represent neural effort, the terms are often used interchangeably when referring to inspiratory effort or work.
Simplified, the act of breathing constitutes the transformation of the central nervous system respiratory drive into:

- Neural activity (electrical nerve activity) and muscle excitation (electrical muscle activity), in turn followed by
- Respiratory muscle contraction (development of mechanical muscle tension)
- Pleural pressure generation
- Expansion of the lungs (inspiratory flow)

The pressure-generating capacity of the diaphragm is determined by:

- Its three-dimensional shape and radius of curvature according to Laplace’s law
- The relative degree of apposition to the rib cage and lungs
- The length-force relationship of the muscle
- Diaphragmatic weakness and fatigue

In essence, the pressure-generating capacity is critically related to the position of the diaphragm, which in turn is related to the resting End Expiratory Lung Volume (EELV) or in the spontaneously breathing patient Functional Residual Capacity (FRC).

The transformation of neural activity into inspiratory flow and volume can be referred to as neuro-ventilatory efficiency, measured as the volume generated for a given diaphragm electrical activity (Edi). However, the resultant flow and volume generated by the pressure drop induced by respiratory muscle activation are fed back to the respiratory centers, which continuously corrects output to the respiratory muscles in order to maintain respiratory homeostasis.

- Inspiration is started in the respiratory centers. The signal is transmitted by the phrenic nerve or other nerves
- The tidal volume achieved by the respiratory muscles is continuously fed back to the respiratory centers, which modulate output to achieve the desired volume
- The repeated cycle is referred to as neuro-ventilatory coupling, and involves both neural control and mechanical achievements by the respiratory muscles

**Edi, the vital sign of respiratory monitoring**

Mechanical ventilation will interact with the control system of the respiratory centers, with an excess of mechanical ventilatory assist leading to dissociation between the respiratory centers and the mechanical insufflation of the lung.

At medium levels of Pressure Support, this is frequently seen as neuro-ventilatory asynchrony manifest by missed patient efforts (no trigger response from the ventilator upon neural and diaphragm activation). With increasing Pressure Support levels, a continuous drop of the Edi signal will be seen, and eventually, the disappearance of diaphragm electric activity and patient respiratory effort. This is very interesting, as it shows that the respiratory centers do not care by what means or how the requested tidal volume is delivered. The main function is instead to maintain the

**Lung Volumes and Capacities**

![Fig 4. Static Lung Volumes](image-url)

The position of the diaphragm will affect its strength. It will get progressively weaker during inflation and is most efficient at physiologic Functional Residual Capacity (FRC). During mechanical ventilation with PEEP, FRC is often exchanged for End Expiratory Lung Volume (EELV).
blood chemistry within certain limits. However, as soon as the apnea threshold is passed, spontaneous breathing efforts will cease and the patient will be passively ventilated.\(^3\)

This implies that in mechanically ventilated patients the neural command will reduce its contribution to tidal volume generation progressively with a falling $P_{\text{aCO}_2}$.

With traditional monitoring systems this is very hard to determine, frequently leading to the erroneous assumption that the patient is breathing well, while a semicontrolled respiratory pattern is sustained by auto-triggering or ventilator activation by the intercostal muscles.\(^8\)

An observed flat or low Edi amplitude in this situation, is diagnostic and in most cases easily corrected by lowering the assist level or by reducing excessive sedation.

Edi monitoring will allow immediate detection of dyssynchrony (ventilator delays of mechanical trigger on and trigger off), asynchrony (wasted efforts, double triggering) or auto-triggering.\(^5\)

The potentially injurious consequences of reversed triggering (entrainment), with the patient inhaling after initiation of a controlled breath has been described as impossible to detect other than by largely increased tidal volumes during pressure control ventilation or double triggering during VC. The phenomenon is believed to be linked to deep sedation.\(^5\)

Conditions with any degree of asynchronous respiratory assist are immediately detected and easily analyzed with the aid of the Edi.

- Edi identifies early spontaneous breathing efforts
- Edi allows for the immediate identification of asynchrony, dyssynchrony, and auto-triggering

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**Fig 5.** Absence of diaphragm activity during Pressure Support ventilation. Flow and pressure curves give no indication of the contribution from the patient. Edi easily establishes the diagnosis of patient apnea and autocycling of the ventilator.

**Fig 6.** From top-down; registration of flow, pressure and esophageal pressure. Note how the contraction of the respiratory muscles follows after part of the controlled breath has been delivered (entrainment). Esophageal pressure can be exchanged for Edi monitoring.\(^5\)
Edi and assessment of respiratory muscle function

Edi represents the temporal and spatial summation of neural impulses translated into diaphragm muscle action potentials. The linear relationship of Edi to the pressure-generating capacity of the respiratory muscles has been described both during spontaneous breathing and mechanical respiratory assistance. The amplitude and upstroke slope of the Edi relates to changes in motor unit firing rate and muscle recruitment, thus allowing objective assessment of the neural demand on the respiratory muscles (neural respiratory drive).

The area under the inspiratory part of the Edi curve (Ediauc), gives additional information as it relates to the diaphragm maintenance of force over time, thus representing the mechanical efficiency of the muscle. Ti is the main determinant of Ediauc (P/I index). Edi can be depicted as a perfect right triangle with neural Ti as the base. It is not surprising that neural Ti is closely related to the P/I index. An increase in Edi with a concurrent decrease in the Ediauc (or Ti) is an important sign of a decrease in respiratory muscle efficiency and impending respiratory failure.

Detecting and quantifying PEEPi at the bedside can be quite challenging as the standard expiratory hold may be disturbed by patient activity. Still, PEEPi is relevant to determine, as it will increase the elastic load and ultimately may be an important factor for weaning failure. The Edi value recorded at inspiratory flow onset, represents the Pmusc necessary to counterbalance PEEPi. Bellanis used the esophageal pressure as control to show that the electrical activity of the diaphragm provides a simple and reliable tool for continuously monitoring the presence of dynamic PEEPi.

Edi has been used for several other important purposes e.g. Delisle used Edi to show the influence of apnea occurrence in relation to respiratory variability. Edi has been used to predict extubation readiness in several publications. In babies, Edi has been used to follow the regression of diaphragm stunning due to botulism, diagnosis of diaphragm paralysis, and identification of the physiologic mechanism of neuromuscular control disorders.

Before NAVA and the availability of Edi, respiratory assessment was more of an art or informed guesswork than based on objective conclusions.
Ventilator Induced Diaphragm Dysfunction (VIDD)

Prolonged mechanical ventilation has been found to lead to a reduction in protein synthesis and an increase in protein breakdown. Levin et. al. showed a decline in the muscle area of the diaphragm by 50% in patients after a short time on mechanical ventilation.\(^1\)

The decline in diaphragm force has been described as logarithmically associated with time on mechanical ventilation.\(^2\) Diaphragm force appears to diminish very soon after the start of mechanical ventilation. It has been debated whether the deep sedation associated with mechanical ventilation is an additional factor leading to the fast decline in muscle efficiency. Ventilator Induced Diaphragm Dysfunction may become a severe limitation during weaning, thus complicating and prolonging the process. To prevent muscle atrophy during mechanical ventilation, monitoring of diaphragm function is very important. Edi is a versatile and simple instrument to monitor diaphragm activity, compared to an esophageal balloon catheter, which is influenced by many factors and is often unreliable, even in experienced hands.\(^3\)

The potential of NAVA to reduce Ventilator Induced Diaphragm Dysfunction is based on the continuous coupling between the patient’s neural output and ventilator assistance. In contrast to Pressure Support ventilation, where a gradual increase in the assist level will abolish the electrical activity of the diaphragm, an increase in the NAVA level will unload the muscle, but still maintain muscle activity. Hence, over-assist by Pressure Support will function as a semi-controlled mode where the patient may be triggering the ventilator, by a small activation of the intercostal muscles resulting in a large tidal volume delivery. In contrast, NAVA will maintain the same tidal volume and physiologic diaphragm activation with the degree depending on the NAVA level set.\(^4\)

Preservation of adequate muscle function should target unloading of the pathologic respiratory work by the ventilator, while the patient is still allowed to breathe with his habitual respiratory load.\(^5\) In situations of fever and inflammatory stress this will imply a higher respiratory rate, which is the physiologic response to inflammation. Reloading of the respiratory muscles or the reinstitution of spontaneous breathing after prolonged mechanical ventilation, allows for rather quick reconstitution of the contractile muscular function.\(^6\) Muscle effort can be monitored by the Edi and muscle strength is easily determined by a short occlusion during patient inspiration.\(^7\)

Sepsis Induced Diaphragm Dysfunction (SIDD)

Severe infection is an underdiagnosed cause of diaphragm weakness. Supinski et. al. demonstrated that diaphragm weakness is associated with poor patient outcomes,\(^8\) including significantly increased mortality, an increased transfer to Long Term Acute Care facilities and a markedly longer duration required for weaning from mechanical ventilation. The problem was underdiagnosed by clinicians (5 out of 45 patients were incorrectly assessed). The association between poor outcome and physician unawareness of the problem highlights a need for objective assessment of respiratory muscle function in sepsis and other serious complications in Intensive Care. The problem was further highlighted by Demoule who showed an independent association between sepsis and diaphragm dysfunction.\(^9\)

Demoule defined SIDD as a change in endotracheal tube pressure of ≤ 11 cm H\(_2\)O after bilateral phrenic nerve stimulation during airway occlusion. In their total population, 64% of the patients showed diaphragm dysfunction on the first day after admission resulting in a 50% mortality rate. It seems that the diaphragm, like all striated muscles, is extremely sensitive to sepsis. Hence, diaphragm dysfunction from sepsis should be identified as a prognostic factor for determining patient outcome. Edi analyzed to the pressure drop during an occlusion\(^6\) can be a very important tool in following any disease development involving respiratory muscle function by identifying functional strategies to prevent poor outcomes.

The monitoring of the Edi signal, along with the ventilatory and clinical status of the patient, identifies the relative contributions of central respiratory control, muscle weakness and diaphragm pathology as initiating and aggravating causes for respiratory failure. Thus, Edi monitoring will assist in the identification and individual management of patients with unexpected muscle weakness and respiratory control disorders.

By assessing Edi change over time, either improvement or worsening of the respiratory status can be determined by a maintained VT in the face of reduced or increased Edi.\(^9\) The information from the patient’s current respiratory status will be enhanced by a short inspiratory occlusion while comparing the negative pressure drop to the Edi increase. It is for this reason that monitoring Edi is of outstanding value in conjunction with sedation hold or spontaneous breathing trials, which are the common instruments recommended for determining the respi-
ratory capability of the patient after a severe pulmonary insult. It is even possible to continue monitoring the patient’s respiratory status after extubation.

**What is Neurally Adjusted Ventilatory Assist?**

NAVA is a respiratory mode which adds mechanical assistance to the patient’s respiratory effort in proportion to the electrical activity of the diaphragm. As the controller in NAVA depends on respiratory center feedback, in contrast to randomly set pneumatic trigger points, ventilator assist will be synchronized to patient effort both in time and size. This implies that a patient with an inherent high respiratory rate will continue breathing at the respiratory rate and tidal volume mandated by the respiratory centers. The same is true for the baby who is recruiting collapsed areas by frequent sighing. The distinguishing feature for NAVA in both examples is that it will not interfere with the respiratory regulation, but only provide assist to the respiratory muscles to balance increases in the respiratory load.

The clinician’s role is to determine the appropriate level of ventilator assist required to avoid respiratory muscle failure or fatigue, by setting an appropriate NAVA level. Irrespective of the NAVA level set, tidal volume will remain virtually unchanged indicating that the ventilator will empower the failing respiratory muscles by delivering the required flow at the moment the patient is inhaling.

The response of the respiratory centers following a change in ventilator settings can be immediately assessed by a corresponding change in the Edi.

**Patient indications**

NAVA has been successfully administered to neonatal, pediatric and adult patients, in both noninvasive and invasive ventilation. Ventilator settings and management are essentially the same for these different patient categories, but should always be based on individual patient responses (comfort, RR, VT and Edi) instead of a fixed formula of settings.

NAVA is indicated and can be administered to a wide variety of patients (from ARDS to COPD) suffering respiratory failure. Although apnea episodes are backed up by the ventilator, NAVA, like any other respiratory assist modes, requires a stable respiratory drive. In contrast to other assist modes, objective assessment of the patient’s respiratory status can always be determined during NAVA simply by following Edi. For clinicians new to NAVA it is advisable to start with patients expected to

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**Edi - the vital sign of respiratory monitoring**

- Respiratory muscles are severely affected by infection
- Edi trends analyzed to the pressure drop during short occlusion will identify patients at risk
- SIDD is an important predictor for mortality

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**Fig 10. Monitoring of Edi can be continued after extubation. The effect of interventions like noninvasive respiratory assist can be easily followed.**

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**Fig 9. Pdi twitch represents maximal muscle contraction after stimulation of the phrenic nerve. A low twitch generated force was highly associated with increased mortality, transfer to a chronic respiratory center and prolonged mechanical ventilation.**

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This is a very important diagnostic tool as reliable respiratory monitoring in the non-intubated patient has not been possible before the availability of the Edi signal. The continued assessment of the patient’s respiratory status is of outstanding value, as interventions can be implemented early and with low invasivity, thus constituting an important improvement in the quality of care.

**Fig 9. Pdi twitch represents maximal muscle contraction after stimulation of the phrenic nerve. A low twitch generated force was highly associated with increased mortality, transfer to a chronic respiratory center and prolonged mechanical ventilation.**

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**Fig 10. Monitoring of Edi can be continued after extubation. The effect of interventions like noninvasive respiratory assist can be easily followed.**

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have a fairly predictable course. This is important as there will be many new discoveries along the way.

Before NAVA and the availability of Edi, respiratory assessment was more of an art or informed guesswork than based on objective conclusions. In many cases this can be ascribed to the lack of objective measurements. With added information, traditional thinking may be contradicted which should be discussed and understood before commencing with the more complicated cases.

- In NAVA the ventilator mimics an extra respiratory muscle
- NAVA maintains low tidal volumes irrespective of assist level
- NAVA minimizes the risk of over-assistance and hyperinflation

**Synchrony and breathing variability**

The normal breathing pattern in humans is highly variable and exhibits a chaos-like complexity. In contrast, all conventional modes of respiratory assist tend to impose a monotonic breathing pattern. The high incidence of asynchrony (25-40%) defined as the inability of the ventilator to sense and deliver assist coincidental with patient effort is not surprising. The pneumatic sensing threshold may be small in theory, but it is significantly increased for the patient due to intrinsic PEEP and hyperinflation. Hyperinflation is often induced by patient-ventilator dyssynchrony, the delayed response of the ventilator to patient effort.

The delay in the trigger-on may be quite innocuous, while a delay in the triggering off, may lead to a large increase in lung volume, the weakening of respiratory muscles and after a few breaths be manifest in asynchrony with repeated missed efforts. This pattern is often repeated, with a high level of assist increasing the frequency of occurrence.

NAVA is conceptually different from any other mode of ventilation currently available in that it is controlled by the activity of the respiratory centers and not by pneumatic means. This change in paradigm establishes the markedly lower incidence of asynchrony.

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**Fig 11.** Despite a fourfold increase in assist level, tidal volume remains unchanged. Note also how respiratory center down regulation will offset the expected increase in pressure.

**Fig 12.** Left hand slide shows grave asynchrony due to a volume targeted Pressure Support setting. Right hand side shows NAVA exhibiting perfect synchrony, a small reduction in tidal volume, large reduction in assist pressure and actually a reduction in neural respiratory rate.
of all types of dys- and asynchronous events during mechanically assisted ventilation, representing the primary distinguishing feature of NAVA.

Compared to PSV, the incidences of ineffective efforts, premature end of inspiration and auto-triggering (asynchrony) are negligible or absent.\textsuperscript{25} With patient-ventilator synchrony established, a reduction in PEEPi will follow.\textsuperscript{26} The outcome of these improved physiological conditions is that the respiratory assist will automatically decrease, thus promoting early weaning. Accordingly, physiologic variability of breathing is genuinely reflected by NAVA and represents an added benefit.\textsuperscript{25} Indeed, reduced breathing variability has been associated with an increased rate of weaning failure.\textsuperscript{27}

**NAVA abolishes the double-triggering seen in Assist Control (A/C) and Pressure Support (PSV)**

There is a large international consensus identifying the delivery of small tidal volumes as the cornerstone of lung protective ventilation. However, the routine use of Assist/Controlled (A/C) ventilation may be problematic in the continuous delivery of two tidal volumes in direct succession (i.e. breath-stacking).\textsuperscript{28}

The phenomenon is induced by the ventilator delivering low flow or small tidal volume, resulting in a prolonged neural inspiration extending beyond the time for mechanical insufflation set on the ventilator. The continued inspiratory effort by the patient at ventilator cycle off will immediately trigger another breath from the ventilator, adding an extra tidal volume to the already delivered breath. A similar phenomenon can be seen with Pressure Supported ventilation in patients with a low compliance.

The added risk of double triggering in Assist Controlled modes and Pressure Support is avoided by NAVA even in very stiff lungs,\textsuperscript{29} as cycle time is controlled by Edi and not by time or flow deceleration. Double triggering has been established as a potential risk during low tidal volume lung protective ventilation.

With NAVA, double triggering is described in several publications.\textsuperscript{30} By definition, as NAVA includes a mechanical cycle off by the ventilator, it may be considered double triggering but it has a fundamentally different background and consequences for the patient. The “double triggering” of NAVA is the result of a mechanical cycle off during inspiration caused by a biphasic activation of the diaphragm expressed as an M-shaped Edi signal. Pressure assist will immediately ensue upon the cycle off and rise proportionally to the Edi, suggesting little consequence for the patient. It is always associated with a sigh or a deep breath.\textsuperscript{31}

**Fig 13. Esophageal pressure measured at flow onset. X-axis 0-14 indicate steps in applied external PEEP. PEEPi is lower for NAVA on all levels.**\textsuperscript{26} The reduction in PEEPi by NAVA will improve the position of the respiratory muscles and reduce the work of breathing.

**Mechanism for Double Triggering in NAVA and A/C modes**

**Fig 14. Double triggering in A/C and NAVA.** The prolonged neural inspiratory time during A/C will induce the delivery of an extra tidal volume. With NAVA, the ventilator will cycle to expiration as the end of expiration criteria for the Edi is met. However, it will immediately cycle back to inspiration as the Edi is rising. This is technically a double triggering, but is hardly noticeable for the patient. It is mostly associated with a sigh or a deep breath.\textsuperscript{37}
of the neural inspiratory time and initiate a second tidal volume delivery due to the ventilator sensing the pressure drop induced by the still ongoing inspiration. It should thus be considered a purely mechanical artifact. Circuit leakage will amplify the problem of double triggering as ventilator autocycling will add to the problem.

A very complicated situation can be seen with a pneumothorax, treated by continuous suction. Here the ventilator may be impossible to control as all the factors mentioned above will interact and produce a chaotic breathing pattern with autocycling, double triggering and expiratory muscle recruitment.

NAVA will immediately alleviate these symptoms as triggering and cycling of the ventilator are controlled and synchronized by the patient effort and not by pneumatic sensing. For a treated pneumothorax it is important to set the pneumatic trigger below the suction pressure in order to avoid mechanical triggering.

- NAVA maintains synchrony with low tidal volume
- NAVA maintains synchrony even with large leakage
- NAVA maintains synchrony even in very stiff lungs

**Lung protective ventilation**

There is a large body of evidence that supports mechanical ventilation in critically ill patients has the potential to aggravate or initiate lung injury. The ARMA trial showed VT of 6 ml/kg predicted body weight (PBW) to be associated with a significant improvement in the survival of Acute Respiratory Distress Syndrome (ARDS).19

Two retrospective studies identified high tidal volumes and pressures as independent factors in Acute Lung Injury (ALI) and ARDS for patients with initially relative normal gas exchange.24, 25

Following these studies, an almost universal consensus exists that VT should be limited to 6 ml/kg PBW and a maximum plateau pressure of 30 cm H₂O (as a surrogate for transpulmonary pressure), in patients with ALI or ARDS.

Of course, strong consideration should be given to limiting tidal volume in other clinical settings as well, including short term ventilation in the operating room.26 However, low VT is associated with a decline in oxygenation and may induce lung injury by tidal opening and collapse at the alveolar interface, which is the second important mechanism by which lung injury may occur and propagate. Hence, the recommendation to increase PEEP and administer a recruitment maneuver should both be considered early in the course of mechanical ventilation as adjuncts in a lung protective ventilation strategy.27

**Fig 15. Concentration of Interleukin-8 (IL-8) in bronchoalveolar lavage (BAL) and lung tissues 30 minutes after induction of lung injury in rabbits. Adapted from ref.40**

Patients with a dysfunctional respiratory regulation due to severe ARDS or sepsis may sometimes show an abnormal respiratory drive, with large minute volumes resulting in severe respiratory alkalosis.

**Fig 16. Patient with abnormal respiratory drive after sepsis. Dissociation of patient-ventilator rate during pressure controlled ventilation. Note the continued late inspiratory efforts during insufflation, inducing a dip in the pressure curve. The late peak in the pressure curve is due to diaphragm relaxation.**
Asynchrony is virtually abolished by NAVA.

The reason for this situation has been debated, but it is probably due to a resetting of either the central receptors driving respiration or the peripheral receptors that drive the respiratory centers. Allowing this situation to continue, patients will run the same risk of VILI as if administered excess lung volumes by controlled mechanical ventilation.\(^3\)\(^8\)

The injury may be even worse by using Assist/Control ventilation with a constant low flow, as the eccentric contraction of the diaphragm (no additional volume delivered during contraction) may lead to extremely high pressure gradients (e.g., $P_{pl}$ = -40 cm H\(_2\)O and $PS$ level = 20 cm H\(_2\)O giving a transpulmonary pressure of 60 cm H\(_2\)O), thus immediately putting the lungs at risk of acute injury to both alveolar and muscle cells. These patients should be allowed to rest with controlled mechanical ventilation and even given neuromuscular blockers for a day or two.\(^3\)\(^9\)

The value of EAdi monitoring upon resumption of assisted breathing in patients with dysfunctional respiratory regulation cannot be emphasized enough. The opportunity to objectively assess the status of the respiratory centers with these patients will allow a controlled discontinuation of sedative drugs and mechanical ventilation with a smooth progression until full weaning is possible.

NAVA and lung protection

Preclinical studies show that NAVA has a potential to deliver lung protective ventilation, proven by a reduction in inflammatory markers.\(^4\)\(^0\) This protective effect can be related to how the delivery of high tidal volumes is restricted by neural feedback from the respiratory centers.\(^2\)\(^2\) This restriction will guarantee a maintained low tidal volume, irrespective of the assist level. At the same time, a higher NAVA level setting may in fact be beneficial as it maintains a low tidal volume, but shifts the work over to the ventilator, achieving a more normal breathing pattern.\(^2\)\(^5\)

The practical consequence of the down regulation of diaphragm activity (EAdi) reduces the risk of over assistance and hyperinflation. NAVA will protect the lung and maintain low tidal volumes as an integrated part of the physiologic inflammatory response (e.g., compare the increased respiratory rate in a child with fever). In ARDS patients treated with NAVA, Coisel showed very low tidal volumes (frequently below 6 ml/kg) with maintained $P_{aco2}$ and a large improvement in $P_{ao2}$.\(^4\)\(^1\) This is explained by an improved gas distribution due to the variability in the breathing pattern and frequent sighing to restore collapsed areas.\(^4\)\(^2\) The activation of the diaphragm has been shown to promote penetration of gas into dependent lung areas and improve ventilation-perfusion matching.\(^4\)\(^5\)

**Sedation and breathing**

The drugs used to enhance tolerance to the stress and pain induced by endotracheal intubation and ventilatory support are commonly described in the literature as sedatives. The use of such sedatives is ubiquitous in the ICU and has been associated with increased length of stay, weaning problems, ventilator associated pneumonia (VAP) and increased mortality. Over the last decade, clinical practice seems to favor lighter sedation. This is supported by the 2013 Society of Critical Care Medicine clinical practice guidelines on Pain, Agitation and Delirium.\(^4\)\(^3\)

In contrast to traditional sedation, the SCCM guidelines favor primary pain assessment and relief while avoiding benzodiazepines. However, in clinical practice the term sedation often implies polypharmacy and a mixture of analgo-sedative drugs. With the introduction of EAdi to clinical practice the problem of monitoring patient-ventilator interaction and sedation level are
much relieved. The obvious fact that characteristics and mode of action for the different classes of drugs used in sedation are not exchangeable, indicate different and often conflicting influences on the respiratory centers. There is also a dose-dependent element which tends to aggravate the effects of individual drugs with a sedative-hypnotic drug like Propofol predominantly inducing a rapid and shallow breathing pattern and deterioration in respiratory drive as manifest by rising $P_{CO_2}$.

However, the timing of the breath as measured by the inspiratory duty cycle ($Ti/Ttot$) will not change with Propofol. An increased sedation depth will result in the progressive deterioration of the patient-ventilator synchrony, manifest by a rising Asynchrony Index and an increase in missed efforts.

On the other side of the spectrum, the opioid Remifentanil will induce a slowing of the respiratory rate and an increase in the inspiratory time. The result of mixing the two drugs on patient-ventilator interaction is difficult to predict and depends on the doses administered of the respective drug. Edi monitoring offers the opportunity to directly assess the influence on respiratory timing and drive induced by a change in analgesic-sedative administration.

In a cross-over pediatric study where PSV-NAVA-PSV (optimized by Edi response) was delivered for four hours each, De La Olliva et al. found a deeper sedation level and an improvement in the Comfort Score with NAVA compared to PSV and PSV optimized. The type of sedative drugs was unchanged during the study period. The authors attributed their findings to a decrease in Asynchrony Index, matching of neural breath-to-breath variation and a decrease in neural drive. The authors suggested that lower levels of psychological distress and feelings of dyspnea could explain the decreased need of sedation.

According to their results, 76% of the children in NAVA vs 27% with optimized PSV needed a lower dose of sedation to reach an optimized level of light sedation as verified by the Comfort Score. They concluded that the use of NAVA in children with asynchrony permits a reduction in sedation and therefore may decrease the duration of mechanical ventilation and the length of PICU stay.

These findings were confirmed in a randomized controlled pediatric study by Kallio et al. The authors of this study found that NAVA outscored standard ventilator modes. NAVA enhances oxygenation at lower airway pressures, leading to reduced use of sedatives during longer periods of mechanical ventilation compared to the controls. In the per-protocol analysis, children in the NAVA group left the PICU almost one day earlier. The time of extubation did not differ as the majority (77%) were postoperative patients. However, there is a separation in the Kaplan-Meyer curve after 24 hours, which may be due to a difference in non-operated patients.

Current sedative practices promote the provision of light sedation whenever clinically safe. Therefore, the primary objective should be to minimize pain and administer only light sedation to relieve agitation. Deeper sedation commonly occurs early after initiation of mechanical ventilation and is a strong independent predictor of time to extubation and long-term mortality. Monitoring of the Edi has been recommended for adjusting sedation to an optimal level.

The decrease in sedation need and a concomitant improvement in the Comfort Score may be explained by the findings in a study by Cecchini et al. Activation of accessory muscles (e.g. scalenes, parasternal muscles) will consistently lead to an increase in dyspneic sensation in the patients. By monitoring the electromyograms of the accessory respiratory muscles and Edi, Cecchini found that NAVA was more efficient in restoring a normal breathing pattern with a greater diaphragm contribution to inspiration compared to PSV. Hence, by silencing the accessory muscles the feeling of comfortable breathing was improved by NAVA.

**Sleep**

Sleep disruption is common in critically ill patients and may influence the clinical course of acute illness. Patients receiving mechanical ventilation have severely fragmented sleep, which may be further aggravated by Pressure Support due to awakenings induced by central apnea.

NAVA will promote deep sleep, with ventilator assistance continuously adapting to the variability of the respiratory centers. Delisle compared sleep patterns during PSV and NAVA and reported large improvement in sleep quality with NAVA. PSV showed a low percentage of REM sleep (4.5%) and a high degree of fragmentation (40/h), while NAVA showed a normal percentage of REM sleep (16.5%) with a dramatic decrease in sleep fragmentation (16/h). In addition, the frequent central sleep apneas seen in PSV were totally abolished during NAVA.

- NAVA improves sleep quality by decreasing sleep fragmentation
- NAVA boosts REM sleep
Physiologic patient response to NAVA and PSV

Most published studies have compared NAVA to Pressure Support Ventilation, as this is the most prevalent assisted mechanical ventilation mode. Currently, there is no defined standard for the setting of PSV and no objective way of evaluating the patient response’s patient-ventilator interaction may be extremely poor with prolonged inspiratory cycling, trigger delays and missed inspiratory efforts. The problem may go unnoticed, as assessment of the problem can be almost impossible by inspection of pressure, flow and volume curves. In fact, PSV has a very narrow therapeutic window, where small increments in the assist level may lead to severe asynchrony. This can be explained by the fact that an increase in the PSV level will not only lead to a decrease in the neural drive, indicating unloading, but will also increase the tidal volume. Hence the obvious risk of loss of neural drive. In patients with obstructive respiratory disease, PSV will lead to substantial breath-to-breath variations in PEPI and tidal volume. The predicted instabilities arise entirely independently of patient effort or volition and could affect patient comfort directly, requiring active patient termination of inspiration and recruitment of expiratory muscles.

In contrast to PSV, the physiological response to NAVA is easily quantifiable by monitoring the Edi which is an inherent feature of the technology. Finally, perhaps the most distinguishing feature of NAVA is that the tidal volume and respiratory rate are maintained within physiological limits not sensitive to the assistance level (fig.16).

NAVA only redistributes the mechanical work from the patient to the ventilator. The problem of setting PSV was highlighted again in the study by De La Oliva et. al. They showed a very high Asynchrony Index in the pediatric population, even after the optimization of all settings using the Edi signal. NAVA abolished the asynchrony except for “double triggering” during sighs or periodic neural respiratory hyperactivity. The results have clinical significance as an Asynchrony Index (AI) above 10% is associated with adverse outcomes.

FRC and Pulmonary Vascular Resistance

How to set PEEP has been a subject for intense debate for almost forty years. However, no consensus or guideline for the optimal setting has won acceptance for more general application. From a physiologic perspective, most would agree that the restoration of FRC would be an optimal target to pursue, as this is the point of highest lung compliance and least work of breathing (in absence of severe chest wall impairment). Furthermore, it is the point where the Pulmonary Vascular Resistance is the lowest, as shown many years ago. Edi guided PEEP can be set by increasing the PEEP level in small increments.

If Edi drops with an increase in PEEP, it indicates less work of breathing, unloading of the respiratory muscles and a step closer to physiologic PEEP. If Edi increases, it indicates hyperinflation and that PEEP is set too high. Passath et.al. demonstrated that PEEP titrated by Edi has a profound unloading effect on the respiratory system without influencing other respiratory variables or hemodynamics. They also verified that PEEP can be titrated by Edi incrementally or decrementally with the same result. The PEEP titration in the study by Passath was performed after optimizing the NAVA level. Interestingly, Katz presented a similar physiologic response in patients during weaning from mechanical ventilation after respiratory failure. Katz used an esophageal pressure measurement to assess work of breathing after adjustment of CPAP. They found three different responses: One group where low CPAP (6 cm H2O) seemed optimal, a medium optimum (12 cm H2O) group and a high optimum (18 cm H2O).

This was almost totally replicated by the work by Passath using Edi. Both authors state that it is not possible to predict the response to a PEEP change in the individual patient. An explanation for the findings may be the base line value of FRC. When FRC is normal, further increase (hyperinflation) will decrease lung compliance, thereby increasing elastic work and the O2-cost of breathing. In contrast, when FRC is below normal, atelectasis and decreased compliance will affect pulmonary function. In this situation further lung distension may be beneficial to improve lung mechanics.

Positive pressure ventilation is usually considered a problem for the right heart as it is associated with decreased venous return and increased Pulmonary Vascular Resistance (PVR). Adjusting PEEP by targeting a minimal Edi value seems a very attractive strategy as it can be postulated that it will restore FRC, increase compliance, decrease PVR and right heart energy expenditure. In addition, with NAVA the natural cycle of the intrathoracic pressure gradient will be restored, enhancing venous return.

FRC, the increase in PVR is related to extravascular compression of small intra-alveolar vessels by the surrounding alveoli. The increase in PVR below the FRC is due to mechanical kinking of large extra-alveolar vessels and active hypoxic pulmonary vasoconstriction (HPV).

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**Fig 19. Influence of lung volume on Pulmonary Vascular Resistance.**

An asymmetric U-shaped relationship exists between lung volume and PVR. When lung volume is either increased or decreased from the functional residual capacity (FRC), PVR increases. At lung volumes above FRC, the increase in PVR is related to extravascular compression of small intra-alveolar vessels by the surrounding alveoli. The increase in PVR below the FRC is due to mechanical kinking of large extra-alveolar vessels and active hypoxic pulmonary vasoconstriction (HPV).
Impact on the circulation of mechanical ventilation

Classical teaching used to state that all interventions to improve ventilation will impair circulation. However, it is more useful to see ventilation and circulation as linked and interdependent. This is immediately obvious when instituting controlled mechanical ventilation after a period of spontaneous breathing. CMV will reverse the natural pattern of central venous filling by reversing the natural intrathoracic pressure gradient, where inspiration creates a negative intrathoracic pressure and the expiratory pressure gradient is zero or positive.

CMV will also impede venous return by abolishing the stroke of the diaphragm, which is important for recruiting blood volume from the abdomen. Hence, during CMV, venous return will take place during expiration (as intrathoracic pressure is lower) and the natural sucking effect of a low or subatmospheric inspiratory pressure created by the spontaneous inspiration is lost.

This was highlighted in a recent publication from Berger et al. who found that in patients with impaired cardiac function and clinically stable hemodynamics, the hemodynamic pattern during NAVA closely resembled that of unassisted spontaneous breathing, regardless of the NAVA level used.

In contrast, increased inspiratory assist with Pressure Support Ventilation progressively increased right ventricular outflow impedance, transpulmonary pressure and tidal volume. This physiologic mechanism is supported by Piastra et al., with improved hemodynamic stability and oxygenation after 8 hours of NAVA compared to Pressure Support.

Patients on CMV often receive extra fluid to combat drops in cardiac output and Systemic Blood Pressure. Excess fluid given to the patient is deposited in peripheral tissues which after a few days will show up as an accumulated positive fluid balance. If the intrathoracic pressure gradient is reversed and normalized by switching to spontaneous breathing, it may constitute an added burden for the general circulation and the failure to wean may be mistakenly attributed to primary respiratory failure. However, the resumption of spontaneous breathing imposes several loads on the cardiorespiratory system, such as:

- Venous return increases, thus increasing cardiac preload
- Left afterload increases (especially if low PEEP is used)
- Total body oxygen consumption will increase by 15-25%.
- ZEEP may increase PEEPi and further increase the elastic respiratory load (T-piece trial).

Cardiac ischemia or decompensation may go undetected and the problem is instead ascribed to respiratory failure. Cabello showed that patients failing a first Spontaneous Breathing Trial (SBT) probably had a severe fluid overload, as there was an average difference in the fluid balance between the study day and extubation day of more than 4 liters.

Switching from controlled to spontaneous ventilation may decrease ventricular performance by increasing preload and afterload and unmask latent left ventricular heart failure (LVHF).

Early detection of cardiac origin as a cause of respiratory distress during a weaning trial is relevant since treatment with vasodilators and/or diuretics will usually improve clinical symptomatology and may shorten intubation time. As shown by Berger et al. the natural pressure gradient is preserved with NAVA, and by early institution of NAVA, many problems will never ensue, as the intrathoracic pressure swings are maintained, obviating the need for frequent fluid boluses aimed at stabilizing the hemodynamic situation.

Weaning

Weaning is estimated to represent 40-50% of the duration of mechanical ventilation. Daily screening for extubation readiness is recommended in order to reduce time on mechanical ventilation. However, 20-30% will fail the first extubation trial.

There are two small studies comparing the impact of weaning with NAVA against PSV. The first indicates shorter times spent on mechanical ventilation, lower peak airway pressure, improved oxygenation and improved hemodynamic stability. The second study showed a significant reduction in peak airway pressure, improved oxygenation and in non-postoperative patients, significantly less sedative use with NAVA.

In addition there are a number of reports of complicated weaning, showing success with NAVA, where other ventilation modes have failed. This is hardly surprising, as asynchrony is virtually abolished by NAVA. Roze et al. performed a daily spontaneous breathing trial in patients being weaned from mechanical ventilation during which Edi was measured during a period of CPAP breathing (Edimax). The NAVA level was subsequently set to reduce the Edi by 60% of the Edimax. The NAVA level was progressively decreased from 2.4 to 1.0, resulting in a drop in pressure assist from 20 to 10 cm H2O. The weaning strategy was successfully applied to all patients in the series.

Several indices have been proposed to predict weaning. The Rapid Shallow Breathing Index is probably the most frequently used for comparisons. Mutini et al. used the ratio between Edi and Edimax, called P/I index to predict weaning readiness in 18 patients. In contrast to other weaning indices, they found that the P/I index was unaffected by a decrease or increase in the assist level, as described earlier.
This has potentially useful implications for the weaning decision process as the evaluation of the patient’s ability to wean off the mechanical ventilator could be achieved without the need for a specific intervention like a spontaneous breathing trial. It will also allow comparisons between and within patients irrespective of the ventilator setting at the time of patient assessment.

- The weaning progress is easily assessed by Edi
- NAVA will automatically wean the patient by adapting assist to improvements in muscle function
- NAVA will gradually shift the respiratory load from the ventilator to the patient

**NAVA and auto-weaning**

NAVA can be used for auto-weaning. As the patient controls the tidal volume, an improvement in muscle function is signaled by a maintained NAVA level and a progressive decrease in the Edi. The end result will be a drop of the assist pressure.

As respiratory support pressure during NAVA is directly related to the electrical activity of the diaphragm, which also reflects the patient’s inspiratory effort (Pmus), a drop in assist pressure is a quantitative indicator for the improvement in respiratory muscle function. The patient can be extubated when assist pressure has reached standard extubation criteria.

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Fig 21. Irrespective of the assist level P/I Index was able to separate patients ready for weaning (success) and those who were not (failure). The slope of the curve represents the P/I Index.7

Fig 18. Patient on non-invasive ventilation. Left screen is Pressure Support. Right screen is NAVA. Synchrony is excellent during both conditions. Note the reduction in Edi with NAVA with higher tidal volume and the reduced respiratory rate, despite equal support pressure. The mechanism is probably reflecting the improved coordination of upper airways with inspiratory flow delivery.
Non-invasive ventilation

Non-invasive ventilation (NIV) has assumed an increasingly important role in COPD, congestive heart failure and as an aid for early extubation. It is generally accepted that NIV will reduce intubation and, when used as an aid for early extubation, shorten the time on mechanical ventilation. PSV is the most common mode used for respiratory assistance during NIV. When NIV-PSV is applied with a face mask, leakage will present a problem since the inspiratory phase will depend on flow falling to a predetermined fraction of peak flow. The leakage will exaggerate the oscillatory response of PSV, with prolonged inspiratory time, increased tidal volume and an increased leakage fraction.

A significant percentage of patients will not tolerate NIV, which is often related to the inspiratory interaction between patient’s demand and ventilator response. When NIV NAVA is applied, the incidence of expiratory asynchrony is reduced and problems of asynchrony due to mask leakage are eliminated, as respiratory assistance depends on neural control rather than flow or pressure sensing.

Extubated patients placed on NIV NAVA will usually respond with an increase in Edi. This is not a sign of impending respiratory failure, but a physiological response to an increased dead space (DS). This physiological dead space is reduced by the endotracheal tube and, depending on the size and design of the mask, the rebreathing of exhaled air will influence tidal volume. In addition, contrary to popular belief the removal of the endotracheal tube will induce a rise in respiratory resistance. Increased dead space and increased flow resistance will thus constitute an additional workload after extubation, which explain the higher NAVA level required during NIV NAVA.

In non-invasive ventilation dilator and constrictor muscles in the upper airways are activated to protect the airways and are synchronized with all respiratory activities. An interesting and possibly crucial problem in standard non-invasive ventilation may be that the constrictor muscles in the upper airways will be activated during non invasive ventilation with high assist levels. In fact, abductor muscles (openers) in the upper airway are maximally activated very early in the breath and are not active by the end of the inspiration. Constrictor muscles (adductors) on the other hand, are activated already during late inspiration, and while abduction is relatively weak, adduction tonus is much stronger, indicating the importance of protection both against over-inflation and rapid reductions in the FRC. In fact, upper airway constrictive muscles are activated during inspiration even with low levels of PSV (10/4) and may impede patient compliance and comfort.

The internal coordination between upper airway muscles and flow delivery is affected by the mode of respiratory support. NAVA does not induce active inspiratory glottal closure.

Fig 22. Larynx coordination to Edi. Note maximal opening before inspiratory flow is actually commenced, flow rate is then continuously restricted induced by activation of constrictor muscles. By the end of inspiration the air passage is almost closed, indicating protection against hyperinflation. Note also that during expiration the cords are opening and closing in order to protect FRC.
The absence of inspiratory upper airway constrictor activity is probably related to the physiological interaction between respiratory diaphragm muscle activation—upper airway dilatation—expected delivery of flow. The physiological airway pressurization during NIV NAVA, which tightly follows diaphragm electrical activity, is an important prerequisite for the proper regulation of upper airway constriction.

NAVA and ECMO
Extracorporeal Membrane Oxygenation (ECMO) has been considered a last resort therapy when all other treatment options have proven unsuccessful. With the experience gained during the H1N1 pandemic there has been a reawakened interest in extracorporeal gas exchange as technical progress has substantially reduced complexity and complications associated with the technique. The management of the native lung has been debated in depth, and different ventilatory strategies have been recommended from standard ventilator settings to low frequency-high tidal volume breathing. Currently several centers favor assisted breathing.

However, the logical strategy would be to allow the injured parts of the lungs to rest, as the gas exchange impairment is the reason for the extracorporeal assistance. In the case of the “baby lung”, with large areas unventilated and only a small fraction available for gas exchange, small tidal volumes are the logical choice. As most of the carbon dioxide load is already eliminated by the extracorporeal circuit, the tidal volume produced by the native lungs will be in the range of 2-3 ml/kg PBW with NAVA.

Central respiratory regulation is still active during ECMO and tidal volumes will decline with increased sweep gas flow in the ECMO circuit, which will result in an increase in CO₂ washout. If sweep flow is reduced, minute ventilation will immediately increase to maintain physiological pH and PCO₂. NAVA will thus not only maintain homeostasis and promote lung rest, but also allow for a gradual increase of the gas exchange by the native lung. This will allow for control of the gas exchanging capability of the lung and aid in weaning from the ventilator.

Several studies have confirmed that increasing the NAVA level is not associated with an increase in VT, as Edi is downregulated with an increase in the NAVA level. The net result will be a small increase in driving pressure, but a maintained tidal volume, and a reduced risk of over-assistance and hyperinflation. The interaction between the gas flow of the ECMO circuit, representing oxygenator CO₂-removal, and the additional requirements by the respiratory centers, will thus constitute the tidal volume. Any patient effort to achieve this tidal volume can now be balanced by the setting of the NAVA level.

In situations with extremely impaired gas exchange, allowing the lung time to heal is the primary objective, while ECMO is providing the gas exchange. NAVA can give outstanding lung protection in this situation as it will be synchronous with patient effort, avoid double triggering and allow the patient to adjust tidal volumes. Bearing in mind that most of the carbon dioxide is removed by the extracorporeal circuit.

In summary, ECMO with varying sweep gas flow (graded extracorporeal removal of CO₂ load) consistently results in an increase or decrease in VT in order to maintain normocapnia. Hence, the brain will adapt by issuing an order for a certain tidal volume. As the respiratory muscles and the ventilator receive the same command, they will share the work to deliver the ordered volume. How the work is shared is determined by the NAVA level.

- NAVA will adapt tidal volume according to the CO₂ removed by the ECMO circuit
- Ventilation will primarily take place in the most compliant lung areas allowing the lung to rest and time to heal
- NAVA reduces respiratory muscle effort and large transpulmonary pressure swings
- NAVA maintains baseline work of breathing with the ventilator compensating for disease-induced distress.
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