Neurally Adjusted Ventilatory Assist (NAVA): An Update and Summary of Experiences

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Abstract. Neurally adjusted ventilatory assist (NAVA) is a mode of mechanical ventilation delivering pressure in response to the patient’s respiratory drive (measured by the electrical activity of the diaphragm, EAdi). Hence, NAVA acts as an external “respiratory muscle pump” controlled by the patient’s EAdi, which in turn is influenced by respiratory feedback mechanisms. This review describes the “fundamentals” of NAVA and reports results from physiological studies on NAVA in animals and humans. The results demonstrate that NAVA maintains subject-ventilator synchrony, adapts to altered respiratory demand, and delivers tidal volumes and mean airway pressures that can be considered protective. Moreover, there is evidence suggesting that NAVA maintains synchrony even in the presence of leaks, one of the current major limitations of non-invasive positive pressure ventilation. Besides the use of the EAdi to control the respirator, monitoring the EAdi provides information about the neural respiratory drive and breathing pattern and the response of these parameters to various treatments and interventions. In summary, NAVA improves monitoring of respiratory drive, and delivers synchronized assist in relation to patient effort, and the control of assist is not affected by leaks.

Introduction

The “art” of mechanical ventilation began in the 16th century with resuscitation by artificially delivering air to the lungs with positive airway pressure. Mechanical ventilation later developed into maintained ventilation in patients that underwent surgery as well as to treat, with various successes, patients who suffered from respiratory failure.

Not until the large polio epidemics in the 20th century, mechanical ventilation became a successful and widespread method to maintain adequate ventilation using negative pressure ventilators in patients with respiratory failure. Later the use of positive pressure ventilation was reintroduced and mechanical ventilation became standard treatment during acute respiratory failure. Little or no consideration was given to how or if the delivery of the ventilator breaths were synchronized to the patient’s inspiratory efforts. In fact, the first mode to allow a patient to initiate and terminate pressure support was not introduced until the early 1980’s.

In the last decades, research has intensified and contributed to turning mechanical ventilation towards a “science”. A lot of work has been done to improve our understanding of how to ventilate patients with acute lung injury and acute respiratory distress syndrome, however, there appears only to be one consensus which is that gentle lung ventilation must be practiced [1]. Despite this dedicated effort to study how to best use today’s conventional methods of applying mechanical ventilation, there are still controversies about how much positive end-expiratory pressure (PEEP) [2] and tidal volume or pressure [3,4,5] should be applied.

There are three important components of mechanical ventilation: (i) the timing with which breaths are delivered i.e. with what frequency and inspiratory time should the assist be delivered, and (ii) the magnitude of the delivered breath i.e. how much pressure or volume should be delivered to ventilate the lungs, (iii) the magnitude of pressure on expiration, which prevents the lungs from derecruiting between inspirations, i.e. how much PEEP is required.

One new approach to solving the problem of “how much assist” and “when to deliver” is to allow the patient’s own physiological feedback systems to determine “when and how much”. Remmers and Gautier [6] demonstrated in animals the use of a phrenic nerve controlled respirator, and showed that PCO$_2$ remains within the normal limits over a wide range of respirator gain settings. However, this method for neurally controlled mechanical ventilation could not be used in humans because of the invasiveness required to obtain phrenic nerve signals.

In 1959, a landmark publication by Petit, Milic-Emili, and Delhez presented a “New technique for the study of functions of the diaphragmatic muscle by means of electromyography in man”. This paper allowed for new research and eventually led to today’s ability to perform neurally controlled mechanical ventilation in humans [7]. It would however, take another 30-40 years before standardized methodology was developed to adequately measure diaphragm electrical activity via sensing electrodes on a nasogastric tube [8]. During this time, work was performed to demonstrate that the diaphragm electrical activity (EAdi) is related to phrenic nerve activity [9] and that electrical activity of the crural diaphragm is related to global inspiratory efforts in healthy subjects [10,11], in patients with acute respiratory failure [12], and in patients with chronic respiratory insufficiency [13]. Equally important to the success of using EAdi to control mechanical ventilation, however, there appears only to be one consensus which is that gentle lung ventilation must be practiced [1].
ventilation, was the development of new methods to reduce artifacts and filtering effects related to electrode configuration and electrode positioning [14, 15, 16].

In terms of turning the art of mechanical ventilation into science, NAVA uses a method to acquire and process EAdi [17] recommended by the ATS/ERS statement on respiratory muscle testing [8]. In fact, a new era in mechanical ventilation has started where peer-reviewed science initiates new technology and then translates this to be applied at the bedside via industrial collaboration. Examples of these types of developments in mechanical ventilation that are commercially available include Neogamesh [18, 19] proportional assist ventilation, PAV [20, 21, 22] and Neurally Adjusted Ventilatory Assist (NAVA) [17].

**Diaphragm Electrical Activity (EAdi)**

Since NAVA uses the EAdi to control the ventilator, it is important to understand what the signal represents. All muscles (including the diaphragm and other respiratory muscles) generate electrical activity to excite muscle contraction. This electrical excitation is controlled by nerve stimulus and controlled in magnitude by adjusting the stimulation frequency (rate coding) or by adjusting the numbers of nerves that are sending the stimulus (nerve fiber recruitment). Both, the rate coding and nerve fiber recruitment will be transmitted into muscle fiber motor unit action potentials which will be summed both in time and space producing the intensity of the electrical activity measured on the muscle. To reduce the influence of external noise, the measurement of the muscle electrical activity is performed by bipolar differential recordings, where the signal difference between two single electrodes is measured [8]. For example the resting EAdi measured with electrodes in the esophagus in a healthy subject typically ranges between a few and 10 μvolts. Patients with chronic respiratory insufficiency may demonstrate signals 5-7 times stronger (Figure 1) [13, 23]. Due to the differential recording and low signal amplitude, measurement of EAdi is sensitive to electrode filtering, external noise, and cross-talk from other muscles e.g. the heart which produces electrical amplitudes of about 10-100 times that of the diaphragm. Since, the EAdi must always be present to initiate a contraction of the diaphragm it should always be possible to record the signal in healthy subjects – if the electrodes are of adequate design, correctly positioned, and the signals are processed accurately (more on electrode positioning, see below). It should be considered as atypical to not detect EAdi in a healthy subject (similar as failing to measure ECG signals with ECG electrodes placed over the heart in a living subject).

If the EAdi is not detectable, some possible explanations may include anatomical reasons (e.g. diaphragm hernia), central reasons (no central respiratory drive due to e.g. hyperventilation, sedation, or brain injury), and peripheral reasons (action potential conduction failure of the phrenic nerves, neuromuscular junction or diaphragm due to disease or paralytic agents). Hence, if the recording electrodes are in proper position and no EAdi is detected, one should suspect an underlying pathology and refrain from using the EAdi to control the ventilator. Due to anatomical variations, e.g. different distances between the muscle and the electrodes and motor unit density [15], it is not possible to adequately compare absolute levels of EAdi between subjects. It is possible, however, to make intra-subject comparisons over time [13]. Hence, application of a respiratory load, exercise or other reasons that increase respiratory drive should result in an increased EAdi [24], whereas increased assist with mechanical ventilation (unloading) should reduce the EAdi amplitude [25, 26, 12].

Monitoring EAdi over time in the same patient and at the same level of assist (if mechanically ventilated) may hence provide useful information about the progress of the respiratory dysfunction.

**Patient-ventilator synchrony**

As already mentioned, ventilatory assist is related to timing the delivery of pressure to the patient’s effort. A recent study on patient-ventilator synchrony reports that: (i) about 25% of patients have a high incidence of asynchrony during mechanical ventilation, and (ii) such high incidence of asynchrony is associated with prolonged duration of mechanical ventilation, and (iii) patients whose inspiratory efforts are frequently unable to trigger the ventilator may receive excessive levels of ventilatory support [27]. It has also recently been shown that asynchrony causes sleep disruption [22] in mechanically ventilated patients.

Asynchrony can be described as poor timing between inspiratory effort and assist delivery, and poor adjustment of the magnitude of assist in relation to the patient’s needs. The reasons for timing asynchrony are several and for comprehension they require to be divided into inspiratory and expiratory asynchrony.

**Inspiratory asynchrony**

Inspiratory asynchrony is related to situations where the ventilator assist is delayed - or in the worst case absent (wasted inspiratory efforts) with respect to the beginning of the patient’s inspiratory effort and is typically caused by a poor function or setting of the ventilator’s trigger. However, triggering of assist without inspiratory efforts, so called “auto-triggering” is also possible due to a too sensitive trigger setting and/or leak, and probably more common than previously thought [28]. Expiratory asynchrony occurs when the ventilator’s cycling-off algorithm terminates the assist either too early or too late with respect to when the neural inspiratory effort ceases.

Asynchrony (with respect to timing) can be due to pathophysiological and/or technical factors. Pathophysiological factors include suppression of respiratory drive, weak muscles, increased respiratory loads (elastance, resistance, and intrinsic PEEP) whereas, technical factors include leaks in the respiratory circuit, inappropriate trigger or cycling off-settings, inadequate flow, pressure, or volume sensors. It is likely that the pathophysiological and technical factors interact with respect to their effect on asynchrony. For example, it has been demonstrated that increasing the level of pressure support ventilation results in both delayed triggering and increased incidence of wasted inspiratory efforts as well as delays to cycle-off [29, 30].

Reasons for increased asynchrony with increasing levels
of assist could be reduced respiratory drive, dynamic hyperinflation, and a delayed opening of the exhalation valve [31] or too high levels of assist [30]. Another common technical reason for asynchronous trigger and cycling-off is presence of leaks in the respiratory circuit. Uncontrolled triggering due to a leak, so called “auto-triggering”, can occur either with flow trigger because the leak induces a flow higher than the set trigger level or during pressure triggering if the leak causes the pressure to drop below the set PEEP level. Moreover, leaks can cause an inability to cycle-off the assist, so called “hang-up”, if the leak does not allow flow to drop to the targeted percentage of peak flow [32].

Regarding, the second dimension of asynchrony i.e. adjusting the magnitude of assist in relation to changes in the patient’s status, there is minimal literature on this topic. Some studies show that increasing levels of PSV can cause asynchrony and alter breathing pattern during pneumatic triggering and flow cycling-off [33,34] and that altered inspiratory flow rate also affects breathing pattern [35].

Given that variational activity of breathing is high and varies between pathological conditions as well as between states of alertness and is affected by patient-ventilator interaction [36,37,38,39,40,41,42] it is difficult to accept that the most used modes of mechanical ventilation are more or less designed to target fixed volumes or pressures independent of patient’s respiratory effort. Today, only NAVA and PAV offer the possibility to deliver assist proportional to patient effort [20,17]. Figure 2 demonstrates the variability in EAdi in a mechanically ventilated patient with acute respiratory failure. Note in the top panel, that despite large variability of EAdi, pressure support remains at a fixed level. With NAVA, (bottom panel) the assist varies with EAdi, both within the breath, and between breaths, such that larger neural efforts are rewarded with an increase in assist.

From a clinical, perspective, independent of whether asynchrony is related to technical and/or pathophysiologic origins, it does affect the patient’s ability to breathe. For example, delayed cycling-off will cause prolongation of pres-

sure delivery into neural expiration, which due to the Hering-Breuer reflex will cause a prolongation of the neural expiration period and reduce breathing frequency [31,44,45]. Since it is generally believed that a reduction in breathing frequency is a sign of clinical improvement, observing a reduction in breathing frequency with increasing PSV will give a false impression that assist is actually doing something good for the patient, whereas in fact it may only reflect the impact of the asynchronous assist on eliciting the Hering-Breuer reflex. The consequence is likely that the patient will be over-assisted i.e. receive more assist than necessary. The combination of too high levels of PSV (to keep breathing frequency low) with auto triggering (due to a too sensitive trigger) [28], this can cause a situation of neural apnea where the ventilator still triggers every breath and delivers a volume at a frequency purely determined by the caregiver. (Figure 3). In the long term, prolonged diaphragmatic inactivity – when it is assumed that the patient is breathing – is not beneficial for the patient’s respiratory muscles or for the prospect of weaning.

**NAVA**

Today’s modes of mechanical ventilation predominantly use pneumatic control systems to allow the patient to spontaneously initiate and terminate the assist. In contrast, NAVA utilizes EAdi (diaphragm electrical activity), a reflection of the neural respiratory output to the diaphragm, as its primary source to trigger and cycle-off assist in synchrony with neural inspiratory efforts (Figure 4) [17]. The NAVA “trigger” detects increases in EAdi and should be set to a level where random variability in the background noise does exceed the trigger level. The variability of the background noise is typically less than 0.5 microvolt and our experience during paralysis and apnea periods indicates that very few
trigger events occur at this trigger level. It is important to emphasize that NAVA is triggered by a deflection in EAdi and not at an absolute level of EAdi - the latter would not function in situations where the diaphragm is not relaxing between inspirations, so called tonic activation of the diaphragm which is commonly observed in newborns [46]. As a secondary source NAVA also employs a pneumatic trigger, which operates in combination with the neural trigger on first-come-first-served basis.

Once the ventilator is triggered, the pressure delivery above PEEP during inspiration during NAVA is controlled by the EAdi such that the level of assist follows the neural effort within each inspiration. Hence, any change in inspiratory load or inspiratory muscle weakness is immediately sensed and compensated for via neural feedback loops that instantaneously regulate the neural output - the EAdi - and hence the pressure assist level [47]. In other words, NAVA acts as an artificial inspiratory muscle directly regulated by the neural output and feedback system. During the inspiratory period while the inspiratory effort is increasing, the assist is regulated every 16 ms. In its current version, if NAVA is pneumatically triggered, a pressure assist of 2 cm H2O is initially delivered every 16 ms. In its current version, if NAVA is pneumatically triggered, a pressure assist of 2 cm H2O is initially delivered until EAdi dictates higher levels of assist.

Neural cycling-off is performed by determining the decrease in EAdi from its highest value within each inspiration and expressed in percent. Depending on the signal amplitudes a range of 40%-70% of peak EAdi provides a stable off-cycling algorithm. In its current version, the off-cycling is automatically adjusted depending on signal amplitude. The EAdi off-cycling is also combined with a pressure off-cycling which terminates assist if the respiratory circuit pressure increases more than 4 cm H2O above the pressure dictated by NAVA.

NAVA also works interactively with PSV, such that if the electrode is moved out of position or there is no EAdi signal for other reasons, a pneumatically controlled PSV will replace NAVA after half the apnea period, and switch back to NAVA if and when EAdi returns. If the entire apnea period has passed without neural or pneumatic inspiratory efforts, NAVA/PSV will be replaced by pressure control mode. In this case the user is alerted and the ventilator must be switched over to NAVA by manual confirmation. In the case of leaks, it is important to be aware that synchrony with NAVA is not affected by leaks, but since NAVA works interactively with pneumatic triggering, adequate pneumatic trigger sensitivity should be verified during leaks in order to reduce risk of auto-triggering.

Electrode positioning: The EAdi signals are measured with an array of micro-electrodes sensitive to electrical activity, and are situated on a Levin type nasogastric tube with a lumen for feeding and/or suctioning (Figure 5). To allow for simple and maintained positioning, the length of the electrode array covers more than a quarter or more of the thorax. The aim is to insert the catheter so the electrode array is positioned at level where the esophagus passes through the crural diaphragm.

The positioning is achieved in three steps. The first step is based on anatomical measurements [48]. The second step is to verify the position of the electrode array by visual inspection of the ECG signals. Normally, signals recorded with electrodes situated within the proximity of the atrium should show P and QRS waves, whereas signals obtained closer to the stomach would lose the P waves and have a weaker QRS complex. The goal therefore is to position the catheter such that P waves and QRS waves are visible on the upper electrode pairs, with a progressive loss in the P wave and QRS wave amplitude. The third step is to verify that there is a signal and if present that the signal coincides with a negative pressure deflection during an airflow occlusion. If the above steps have been fulfilled, and the signal is present, the electrode array can finally be centered over the diaphragm using a visual feedback based on a cross-correlation method [15].

If the electrode array has the right length and is positioned...
in the esophagus at the level of the diaphragm, the feeding/suctioning holes on the catheter should automatically be placed in the stomach, since the nasogastric tube for use with NAVA is designed such that the distance from the electrode array to the catheter’s tip is sufficiently longer than the abdominal portion of the esophagus.

How does one set the assist level with NAVA? During NAVA, the amount of pressure delivered (in cm H2O) is adjusted by multiplying the EAdi (which is expressed in µV) by a proportionality factor, called the “NAVA level” (expressed as cm H2O/µV). The NAVA level expresses a type of exchange rate i.e. how many cm H2O the patient will receive per µV EAdi. For example a NAVA level of 1 cm H2O/µV will give 5 cm H2O when EAdi is 5 µV. Following the same example, for the same diaphragm activity of 5 µV, increasing the NAVA level to 2 cm H2O/µV will double the pressures delivered and provide 10 cm H2O.

It is important to understand that during NAVA, the patients neural output to the diaphragm (measured as EAdi) is simultaneously determining the pressure generated by the diaphragm [10] and the pressure delivered by the mechanical ventilator. Hence, since the patient controls both his/her own pressure and the ventilator’s pressure, the patient is in control of the transpulmonary pressure i.e. the sum of pressures that acts to inflate the lungs.

This means that if the patient increases or reduces their EAdi at a given NAVA level, it will affect both their diaphragm pressure generation and the ventilator-delivered pressure, hence, providing more or less volume (if the lung mechanics are constant). If for example the elastic and/or resistive loads are increased, the expected response is that the patient’s respiratory drive (and EAdi) will increase, causing both the patient and ventilator pressures to increase, such that volumes can be preserved. If the patient is in respiratory failure and without mechanical ventilation, EAdi is expected to be high (indicating a large patient effort) with insufficient tidal volume and high respiratory rate. If NAVA is applied and the NAVA level is increased, the added ventilator pressure will aid to reach the desired tidal volume and reduce breathing frequency as expected during assisted ventilation. However, with NAVA it has been demonstrated that once the desired tidal volume and breathing frequency (i.e. minute ventilation) have been reached, the EAdi decreases at a rate such that the transpulmonary pressures keeps tidal volume more or less constant [25,49,26]. If the increase in NAVA level continues, the EAdi will decrease further until it reaches a plateau (a minimum level), albeit not absent. Thereafter, any additional increase in NAVA level has little influence on the EAdi, but may result increasing pressure and volume as well as variability in breathing pattern, indicating too high levels of NAVA.

Recall that the impact of increasing pressure support (and other modes using flow cycling-off) on breathing pattern is an increased tidal volume and reduced breathing frequency. With NAVA, an increase in tidal volume and reduction in breathing frequency will occur either when the NAVA level is increased but is still insufficient to compensate for the acute respiratory failure, or when the NAVA level is so high that EAdi no longer decreases. Hence, the traditional expectation that increasing assist results in reduced breathing frequency is not as obvious with NAVA as with current modes. If displayed on a monitor, visual inspection of the responses of airway pressure, tidal volume, breathing frequency, and EAdi to increasing NAVA level can be of help to titrate the level of assist (see below).

This implies a) that the physiological feedback systems can and do control the pressure delivered during NAVA by modulating the EAdi, and b) that traditional views on the response of the breathing pattern to increasing levels of assist may need to be revised. In other words, during NAVA, the subject can control the assist, both in terms of timing and magnitude.

Since NAVA is a mode of spontaneous breathing, many patients will be switched to NAVA from controlled modes of ventilation. The first step would then be to ensure that the catheter is in position (see above) and to evaluate whether or not the EAdi signal is present and is synchronous to inspiration by performing a brief occlusion. Using a display where the predicted NAVA pressure is superimposed on top of the pressure waveform being delivered during the conventional mode, it is possible to adjust the NAVA level to match the current mode’s pressure, and then switch over to NAVA. Given that the patient’s respiratory drive and thus the EAdi, may change when the ventilator mode is switched to NAVA, the pressure delivered by the ventilator may increase or decrease since the respiratory feedback system is now controlling both the EAdi and assist.

When can NAVA be applied? NAVA is similar to other modes of mechanical ventilation in that it can be applied as long as it delivers assist that satisfies the patient needs of adequate ventilation and unloading as well as other criteria used for conventional modes of assisted ventilation. To apply NAVA some specific criteria need to be fulfilled. First and most important, the electrode array must be correctly positioned, and the EAdi signal should be suitable to ventilate with NAVA i.e. the signal should be strong enough to trigger (~0.5 µV to prevent “false” triggering) and control the assist. In some patients the inspiratory EAdi deflection may be as
What if there is no EAdi? To exclude technical problems, verify that the ECG is still present. If technical problems are still no EAdi, then it is not possible to ventilate with NAVA at that time, and the absence of the EAdi should be investigated (e.g., sedation, over assist, etc.).

Based on our current experience, the only confirmed contraindication to using NAVA is the absence of EAdi. As with other triggered modes, patients with problems in their control of breathing and/or regulation of ventilation can still be ventilated with NAVA, however, the mode must be used with precaution (strict upper pressure limits, backup rates and alarms) and with clinical judgment. In these cases, monitoring of EAdi might be of help for diagnosing such problems. In order to limit unnecessary increases in respiratory drive and tidal volume, the use of any device that increases dead space should be minimized. It should also be noted that for reasons discussed above, NAVA may produce higher breathing frequency than conventional modes of ventilatory assist, and increasing NAVA levels may not necessarily reduce breathing frequency (as expected with conventional modes) since it does not interfere with the Hering-Breuer reflex. Therefore, it is not recommended to terminate a NAVA trial based solely on increased breathing frequency. It is important to verify, by monitoring EAdi, that the respiratory rate observed with conventional modes actually is related to the neural respiratory rate and not due to wasted inspiratory efforts reducing ventilator delivered breaths.

Research experience with NAVA

The assumption of NAVA is that, when the EAdi is present, the ventilator receives the same signal as the diaphragm. Thus, the diaphragm and ventilator pressures are synchronously generated to inflate the lungs in response to neural inspiratory drive, whereas the neural feedback adjusts the respiratory drive, which in turn adjusts the ventilator pressure generated to inflate the lungs. We have recently demonstrated that the EAdi is down regulated by increasing NAVA levels and that the esophageal and ventilator pressures - which determine the transpulmonary pressure - are changing equivalently such that transpulmonary pressure is maintained, avoiding over assist and excessive volume delivery (25,49,26).

Physiological response to increasing NAVA levels

NAVA can unload the diaphragm completely (26) while not eliminating the EAdi, during both quiet breathing and maximal inspirations in healthy subjects (Figure 6), and in rabbits with acute lung injury (25,26). It was observed that, despite 100% unloading of respiratory muscles, no runaway (failure to cycle off assist) was observed regardless of whether the inspiratory efforts were generating tidal or maximal inspirations (26). Moreover, tidal volumes and respiratory rate did not change with increasing NAVA levels.

In resistively-loaded rabbits, the response to progressively increasing NAVA levels is an initial increase in airway pressure; at a certain NAVA level, the EAdi and pressure time product of esophageal pressure resemble that observed before the load was applied (50). With further increasing the NAVA level, the EAdi drops at a rate such that there is a slowing in the airway pressure increase, which maintains transpulmonary pressure constant. This occurred until the
EAdi reached its lowest level (albeit still present), where the esophageal pressure time product had been almost abolished. There was a good agreement between observers who were asked to determine the inflection point at which the rate of rise in Paw slowed down. This work suggests - at least in rabbits – that the neural feedback loop regulates EAdi and hence, NAVA, to limit lung distending pressures when the assist is sufficient. The study presents a new possible method to titrate NAVA based on physiological feedback mechanisms.

A similar NAVA level titration method was tested in 15 mechanically ventilated patients with hypoxic respiratory failure [51]. Fourteen patients had EAdi signals suitable for NAVA on the study day, underwent a NAVA titration, and then were ventilated for 3 hours at the titrated level. The study demonstrated that all patients could be successfully ventilated for 3 hours at the titrated level of NAVA. Comparing NAVA to the periods of pressure support or pressure control ventilation (set to maintain low tidal volumes of about 6 ml/kg predicted body weight), NAVA was associated with similar tidal volumes as during the conventional mode, and however, EAdi and esophageal pressure swings per breath were higher. This could suggest that patients were over assisted in the conventional mode. Interestingly, due to changes in inspiratory time the esophageal pressure time product per minute was not increased. This study confirms in patients with hypoxic respiratory failure that the NAVA level can be titrated based on physiological feedback from airway pressure and volume and that the titrated level of assist can be applied for 3 hours without resulting in respiratory failure.

**NAVA and lung protection**

The potential lung-protective features of NAVA were tested in an animal model of respiratory distress [52]. Rabbits with HCl induced lung injury were randomized to NAVA (non-paralyzed) or VC (paralyzed) using VT of 6 (lung-protective strategy) or 15 ml/kg (lung-injurious strategy) (n=9 each group). In the NAVA and VC 6ml/kg group, the highest PEEP level maintaining mean arterial pressure (MAP) >60mmHg was used (and was not different between the groups). PEEP was 1 cmH2O in the VC 15ml/kg group. Cardiac output was measured with echocardiography. Lung injury was assessed by PaO2/FiO2 and lung wet-to-dry (w/d) ratio; IL-8 levels in BAL fluid, lungs, and plasma; remote organ injury by IL-8 levels and apoptosis rate, and creatinine clearance. At baseline, all parameters, anesthesia, and MAP were similar in the three ventilation arms. IL-8 levels in remote organs were highest in the VC 15ml/kg and similar in the other groups. The animals spontaneously chose a tidal volume of 3.4±2.0 3 ml/kg during NAVA. From the ventilatory parameters and the biomarkers measured, it was concluded that NAVA limits ventilation (PSV) in rabbits with lung injury, Beck et al [49] recently demonstrated that when PSV levels are increased, there is an increase in trigger delay, wasted inspiratory efforts and cycling off delays. Moreover, the study showed that with PSV, unloading is only achieved with PSV levels up to 8 cm H2O. Further increases lead to worsening in asynchrony and increased work of breathing. In contrast, with increasing NAVA level, there was minimal impact on trigger and cycling-off delays, and there were no wasted inspiratory efforts. An interesting difference between the two modes is that with PSV, a four fold increase in the setting gives four times as much airway pressure, whereas with NAVA a four-fold increase results in an increase from −3.5 cm H2O to −7 cm H2O, due to down-regulation of EAdi at higher NAVA levels. Moreover whereas tidal volume was increased and respiratory rate decreased with increasing PSV, no effect on breathing pattern was observed with NAVA.

In 14 patients with acute respiratory failure, increasing PSV from a low level of assist (matching the ATS criteria for ventilatory failure) to a level 7 cm H2O higher demonstrated that both trigger and cycling-off delays worsened, that tidal volumes increased and that respiratory rate was reduced [53]. In contrast, matching the same low and high levels of...
airway pressure during NAVA not only showed significantly reduced trigger and cycling-off delays but also confirmed that increasing NAVA levels within this range did neither affect the synchrony nor the breathing pattern.

**EAdi and NAVA in infants and small species**

With regards to smaller species, we have demonstrated that the EAdi signal is sufficient to control NAVA in 350 g rats [54]. In infants, less that 1 year of age, it was demonstrated that asynchrony occurs during more than 50% of the breathing cycle for the mandatory breaths during SIMV [45]. Also, in non-ventilated preterm babies, the EAdi signal can be characterized as variable with a high level of tonic diaphragm electrical activity. This study clearly demonstrated the value of using EAdi to monitor breathing pattern and central apneas [55]. Ongoing studies show that NAVA can be successfully applied in both term and preterm newborns down to a weight of ∼675 grams (at 25 weeks gestational age) [56].

On the topic of tonic EAdi in infants: EAdi can be described in terms of “phasic” activity i.e. periodic increases and decreases in EAdi related to inspiration and exhalation, and as “tonic” which is when EAdi persists during the exhalation period [46,55]. One of our studies showed that acute lung injury provoked tonic EAdi while reducing the phasic activity in absence of PEEP [25]. Increasing PEEP levels demonstrated a normalization of breathing pattern, where tonic EAdi was reduced and phasic increased. In another study, we confirmed the presence of tonic EAdi also in mechanically ventilated babies of less than 1 year of age and demonstrated that removing PEEP increased tonic EAdi [46] (Figure 7).

**Non-invasive ventilation with NAVA**

The greatest challenge to achieving patient-ventilator synchrony is when leaks are present in the respiratory circuit. Since EAdi is a pneumatically independent signal and not affected by leaks, NAVA can deliver assist in synchrony during large leaks (assuming that combined pneumatic trigger is disabled). Administration of NAVA by a single prong inserted into one nostril in rabbits with acute lung injury has been demonstrated [57]. This study showed that NAVA can be successfully applied without PEEP maintaining adequate blood gases and unload respiratory muscles to the same level as when applied with PEEP during intubation [57]. In terms of smaller species, non-invasive NAVA via a single nasal prong has also been implemented in ∼350 g rats [58] and demonstrated to maintain blood gases.

Due to its large volume, compliance, and sensitivity to leaks, the so called helmet interface is a very difficult non-invasive interface to synchronize with inspiratory effort when using pneumatic trigger systems [59]. Patient ventilator synchrony was compared between neural and pneumatic triggered and cycled-off PSV with helmet interface in healthy subjects with breathing efforts that were restrained to normal levels [59]. Results indicated that both increasing PSV levels and breathing frequencies increased trigger delays, frequency of wasted inspiratory efforts, and cycling-off delays with pneumatic triggering and cycling-off algorithms. 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. A second study comparing neural and pneumatic triggered and cycled-off PSV with the helmet interface in healthy subjects with non-restrained breathing efforts showed that increased asynchrony was associated with significant increases in respiratory efforts although yet not sufficient to restore synchrony [60].

Moreover, the value of NAVA to monitor neural inspiratory effort i.e. the neural output necessary for the diaphragm to generate the inspiratory pressure and volume, has been proven very valuable in the studies performed. Considering that patient-ventilator asynchrony distorts the respiratory drive and may invalidate the reliability of breathing frequency as a measure of respiratory drive (45,44,31) the ability to instantaneously monitor synchrony between EAdi and ventilator assist as well as observing the EAdi response to increasing or decreasing assist has been found to be clinically useful [61]. An overlay display showing pressure and EAdi can be used to make online determinations of patient-ventilator synchrony at bedside. Perhaps most important though is that EAdi shows if diaphragm is active or not, which may help to a) diagnose diaphragm paralysis and b) determine over assist (possibly in combination of high sedation levels).

The left panel of Figure 3, shows a patient on PSV, where the ventilator indicated that every assisted breath was triggered and where the flow tracing indicates evidence of wasted inspiratory efforts, however, as indicated in the top left panel of Figure 3 the patient had no EAdi. Our conclusion was that the ventilator triggered so easily that more or less no effort was necessary to obtain a too high level of assist. After switching this patient to NAVA the EAdi activity was restored as depicted on the right panels of Figure 3. Another potentially valuable feature of the EAdi monitoring is the ability to observe the trend of the EAdi during weaning trials. In neonates and newborns central apneas can be detected by EAdi monitoring and it is also possible to determine if there is tonic diaphragm activity i.e. diaphragm is active during exhalation. This tonic activity is likely related to vagal reflexes.
which are activated during lung collapse or edema and has been described to be influenced by PEEP, suggesting a potential tool to assist in titration of PEEP (25,46). More reviews on EAdi monitoring have been recently published (61).

**Conclusion**

NAVA opens up a new era in mechanical ventilation offering a mode of mechanical ventilation which adapts the pressure delivered to changes in the patient’s respiratory drive, which in turn, is regulated by the neural feedback system. Hence, NAVA allows the patient to control breathing frequency, inspiratory time, volume, pressure. With feedback about the neural drive, the caregiver can adjust ventilatory settings to meet patient needs.

Studies have shown that NAVA can improve patient ventilator interaction and unload respiratory muscles, while maintaining diaphragmatic activation and avoiding over-assist which may cause disuse atrophy and prolong weaning. There is also evidence that NAVA will improve non-invasive ventilation and facilitate monitoring of patient effort.

Given that NAVA is in its infancy, most of the presented work depends mostly on physiological studies on animals and humans and larger randomized clinical trials are pending for the future.

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**Statement of conflict of interest**

Dr. Beck and Dr 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 Dr. Beck and Dr Sinderby through royalties. Dr Beck and Dr Sinderby each own 50% of Neurvent Research Inc (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care. Dr Beck and Dr Sinderby are married.

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