Paradigm shifts in mechanical ventilation – a NAVA session report

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The information about NAVA is being provided for planning purposes. The product is pending 510(k) review, and is not yet commercially available in the U.S. Similar requirements may be valid in other countries.

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Research and practical implementation in regard to patient-ventilator synchrony was the focus of a four hour NAVA lecture session at the recent international symposium in New York August 28-29, 2006. Several hundred physicians and respiratory therapists had the opportunity to hear Christer Sinderby, PhD, and Jennifer Beck, PhD present their latest research about invasive and non-invasive NAVA in regard to different patient categories. Critical Care News also had the opportunity to interview Christer Sinderby and Jennifer Beck about their research in neonatal monitoring.
Can cerebral signaling be utilized for feedback in mechanical ventilation?

The problem of determining the patient’s contribution or degree of inhibition to breathing was illustrated by Dr Sinderby in a series of patient examples. His point to the audience was that without the neural signal, it is very easy to be misled and to misinterpret the situation.

If synchrony is defined as including not only gas delivery, but also the degree of ventilation, this can only be achieved by a mode that allows the patient to control both cycling and volume, according to his/her receptor response. This indicates that respiratory muscles can only be efficiently unloaded by an inspiratory assist in full synchrony with the patient’s own effort. Sensitivity of the respiratory center may be influenced by the administration of sedatives or opioid drugs. If the inspiratory assist is delivered in asynchrony with the patient’s own effort, he may be adequately ventilated, but this does not constitute proof of respiratory muscle unloading.

During both conditions, the breathing pattern and resulting blood gases will be influenced by the administration of respiratory depressant drugs.

After a short review on the history of NAVA development, highlighting the progress of the development of the nasogastric (NG) catheter design, to the current electrode array (Edi catheter), Dr Sinderby proceeded by describing the reflex pathway and the mechanical coupling necessary to achieve respiration. He emphasized the necessity of catching the control signal early in the chain of events to avoid asynchrony and time delays.

Proper positioning of the Edi catheter can be easily achieved by using the standard measurement of nose-ear-xiphoid process as a first assumption. Final optimization of the position can then be determined by looking at the ECG progression, which is always recorded by the Edi catheter, provided that the patient is alive. If there is no Edi signal after proper placement of the catheter has been achieved as determined by the ECG signal, the differential diagnosis of resulting functional apnea has to be determined. The most common explanations are hyperventilation or oversedation, according to Dr. Sinderby. In a severely ill patient it should be expected that the Edi amplitude is high, as a result of the mechanical impairment usually seen due to the disease process, resulting in a much weakened response by the respiratory muscle in spite of intense neural signaling. Experience dictates that the signal amplitude reflects that the Edi amplitude is dependent upon both respiratory drive and the expected mechanical response of the respiratory muscles.

As NAVA by design is a mode that works in synchrony with the diaphragm excitation, and the ventilator effectively uses the same signal as the diaphragm, Dr Sinderby was able to show how the “extra muscle” provided by the ventilator can unload all the inspiratory work, as proven by the abolishment of transdiaphragmatic pressure swing during a vital capacity maneuver in a...
healthy subject (This study is now In Press in Chest, September 2006). Interestingly, the positive pressure delivered by the ventilator was essentially the same as the negative pleural pressure obtained without any assistance.

Dr Sinderby underlined that normal breathing is quite variable, even during resting conditions. It would seem logical to try to mimic this biological variability, by unloading the respiratory muscles in proportion to the extra load induced by the disease process, instead of imposing a breathing pattern that is strictly based on one pressure level or a fixed tidal volume. By delivering a proportional assist in synchrony with the patient effort, the amplitude of the Edi signal can be used to precisely titrate the amount of unloading required for the individual patient. A decrease in the amplitude of the Edi signifies less respiratory work for the patient, coupled with an increasing NAVA level, indicates that the extra muscle provided by the ventilator successively assumes a larger share of the respiratory work.

In summary, Christer Sinderby stated that if the electrode is positioned at the level of the diaphragm, if the patient is breathing, it must be possible to detect an Edi signal. If no diaphragmatic activity is detected and the ECG is still seen, the electrode is working. In the presence of diaphragmatic electrical activity, the diaphragm and ventilator receive the same signal and diaphragmatic and ventilator pressures are synchronously generated. To inflate the lungs in response to neural inspiratory drive, neural feedback will adjust the neural respiratory drive, which in turn will adjust the ventilator pressure generated to inflate the lungs.

**Information captured from the EAdi signal**

Dr Beck clarified that the electrical activity (Edi) of the diaphragm represents the respiratory center output for controlling rhythm, depth and duration of breathing. Depending on the response of the muscle, the signal will be modified as the feedback from the stretch receptors and chemoreceptors send back information to the respiratory centers. Since her research has been directed to the control of breathing in neonates and preterm infants, several distinguishing patterns have emerged, differentiating this patient population from adult patients. The research has been conducted by introducing a small-bore nasogastric (NG) feeding tube fitted with an electrode array. The ECG has been used to determine correct positioning of the tube, with a prominent P-wave at the cranial electrode, and the disappearance of the P-wave at the caudal lead. She emphasized that X-ray was not necessary.

Amplitude of the signals was referred to as phasic electrical activity of the diaphragm, and this phasic activity represents a progressive increase in inspiratory effort. When the signal begins to decline, it indicates that the brain has informed the diaphragm to stop the inspiratory effort. In adults, the signal usually goes back to 0 as there is a pause between breaths. However, in babies, a shift in the baseline represents the presence of diaphragmatic activity during expiration, which is called tonic activity of the diaphragm.

She proceeded to show examples of phasic diaphragm activity in adults, with tonic diaphragm activity. Dr Beck also showed examples of how increasing pressure support leads to a continuous decrease in transdiaphragmatic pressure and Edi amplitude, up to a point where the increase in pressure leads to increasing asynchrony and an increase in Edi amplitude.

On the other hand, with NAVA there is a linear relationship of continuous unloading as the mode does not induce asynchrony. SIMV is a commonly employed mode for neonates. The spontaneous neural inspiratory time for this population is 250-300 ms. In Dr Beck’s example, SIMV time had been routinely set at 700 ms, which resulted in grave respiratory asynchrony. As the average delay for the pneumatic trigger was 100 ms, patient-ventilator synchrony on inspiration resulted in 30% of neural inspiratory time spent trying to trigger the ventilator. When combining the inspiratory and expiratory asynchrony, 50% of the delivered assist was delivered out of phase with patient demand (Published in Ped Res 2004 Beck et al). Dr Beck commented on the paradox that SIMV stands for Synchronized Intermittent Mandatory Ventilation, when in fact it is not a synchronized mode.

Tonic diaphragm activity is nearly always present in neonates as their pliable chest wall is inefficient in maintaining lung expansion. In a situation were no PEEP is administered, there is a risk that the baby has to work continuously as he is not able to rest during expiration, possibly leading to frequent apnea and recruitment periods. Dr Beck elegantly showed how PEEP can more or less abolish this energy consuming and stressful breathing pattern. (Emeriaud et al, 2006 Ped Res).

An example of monitoring apnea and bradycardia in a pre-term baby was also presented. ECG signals were plotted as well as the diaphragm electronic activity. The pre-term infant had a typical chaotic breathing pattern, with a heart rate of 150 and satisfactory saturation one minute, and no diaphragm activity the next. During apnea indicated by absence of diaphragm activity, the heart rate fell to 66 and saturation to 82. When aroused, the baby made a large inspiratory effort and
breathed phasically on top of tonic activation (spontaneous recruitment maneuver), then became apneic again. According to Jennifer Beck, this example shows that monitoring the diaphragm electrical activity in neonates can provide the opportunity of evaluating the impact of the respiratory pattern on the entire organism.

In summary, Jennifer Beck stated that phasic Edi can provide information about changes in respiratory drive, and that the timing of diaphragm activity in relation to mechanical ventilation can provide information about patient-ventilator interaction. She also stated that tonic diaphragm activity can provide information about the diaphragm’s role in maintaining FRC, and that monitoring EAdi can provide insights into mechanisms of apnea of prematurity.

**Practical implementation of NAVA in invasive ventilation**

Christer Sinderby presented aspects of lung protection in relation to NAVA, as research available so far shows much promise. He showed a graph representing three maximum inspirations, with no assist, with NAVA at medium level gain, and with NAVA level at maximum. Pressures were recorded, with peak pressure up to 60, or total lung capacity in that patient. The diaphragm activity went down to only 40% of the initial value. According to Christer Sinderby, this illustrates that you cannot fully suppress neural drive during NAVA. You may suppress it, but cannot remove it. Volumes are minimally affected, since the Hering-Breuer inspiratory inhibiting reflex prevents overinflation. He went on to present unloading with NAVA, by plotting mean airway pressure against mean esophageal pressure to identify the mean transpulmonary pressure. In the example a maximum inspiration created a mean inspiratory pressure of 15 cm H₂O esophageal pressure with a diaphragm activity of 100%. When increasing the NAVA level the same transpulmonary pressure was maintained. The system can be controlled within the whole range of volumes, but maintains proportionality. (In Press Chest 2006, Sinderby et al).

He also presented data from a study of increasing NAVA levels in rabbits with acute lung injury. The spontaneously chosen tidal volume before lung injury was 3.5ml/Kg. After injury, this volume was the same, respiratory rate increased initially, and at 100% unloading, tidal volume was only increased to 4 ml/Kg. He stated that after delivering 100% unloading and increasing the NAVA level as much as possible there was no work of breathing, very little diaphragmatic activity, and only 0.5 ml/Kg change in tidal volume. After four hours, there
were normalized breathing patterns, indicating that after induced injury and application of NAVA, the animals were able to regulate themselves.

He reported from a study of 14 sedated patients with acute lung injury, where NAVA was titrated to assist levels where no changes in breathing frequencies, tidal volumes or airway pressures were observed. Recordings were made over three hours of ventilation with NAVA and compared to pressure support or pressure control settings prior to NAVA. It was interesting to note that the patients chose a tidal volume of about 6 ml/Kg, which was similar to the pressure control or pressure support initial settings, with similar respiratory rates recorded prior to NAVA and during NAVA. PCO$_2$ and pH ratios stayed the same over three hours. However, mean airway pressure decreased to 4 or 5 cm H$_2$O, and diaphragmatic activity increased to double. Christer Sinderby commented that it seems that the patients actually want to use twice as much activity as he was allowed to on pressure support or pressure control, while using a lower pressure to breathe than was delivered. He believes this is due to the limitations of one level of assist in conventional ventilation to cover the peaks in respiratory demand.

With regard to patient-ventilator synchrony, Christer Sinderby referred to a study by Martin Tobin et al, indicating the start and stop of diaphragm activity and ventilator activity, with poor overlap between the two. He then presented information by Dr Spahija et al, showing pressure support levels before switching to NAVA, and after NAVA. After switch to NAVA, the diaphragm activity was totally correlated with flow and airway pressure, in synchrony during both inspiration and expiration.

Christer Sinderby also presented examples from the same study illustrating NAVA compared to pressure support in low and high levels of assist in ARF patients. Breathing frequency in pressure support went from 25 to 17, where in NAVA it stayed at 25 at all times. This is due again to the Hering-Breuer reflex, according to Christer Sinderby. He stated that perhaps it is not generally known that respiratory rate is reduced by increasing levels of pressure support. He stated that this is a fundamental difference between NAVA and PSV.

Christer Sinderby summarized his take-home message by saying that NAVA appears to offer improved trigger/cycling off synchrony, which can be mixed with existing technologies and that NAVA offers an appropriate level of assist that can be indicated by the patient. He stated that there is no runaway aspect to NAVA, and that it appears to offer appropriate ventilation with guaranteed respiratory drive.

Practical implementation of NAVA in non-invasive ventilation

Jennifer Beck introduced her presentation with a film of a healthy subject with an Edi catheter sending diaphragm electrical activity signals to the ventilator, with lung model inflation. Chest
movement and inflation of the lung model were clearly seen, illustrating synchrony in a situation of 100% leak, according to Jennifer Beck. This means that the idea of using an electrical signal to control the ventilator opens up a whole new field of possibilities for non-invasive ventilation. She also illustrated how size does not matter by means of a similar film of a 350 gram anesthetized rat that was spontaneously breathing, with signal to ventilator and inflation of lung model. Tidal volume in this case was around 2 ml. She pointed out that this also was an illustration of synchrony in the presence of a 100% leak.

She presented the helmet as another type of non-invasive interface, with a video of a healthy subject breathing on NAVA with a helmet. She stated that normally this device is hard to synchronize since it is so large, which makes it difficult to detect flow or pressure changes for triggering. Diaphragm activity, pressure delivered and esophageal pressures were displayed.

A study comparing pressure triggering and neural triggering of the helmet device in pressure support mode was presented. During pressure triggering there was asynchrony, with delays between the start of diaphragm activity and the delivery of assist. Every second breath in this case was a wasted effort. When switching to neural triggering, diaphragm electrical activity signaled to the ventilator and an assist was delivered, and synchrony was restored.

She also presented data showing neural control and pressure support in healthy subjects, with inspiratory and expiratory delay times. Different pressure support levels of 5, 10 and 15 were studied, with different respiratory rates of 10, 20 and 30. Independent of which pressure support level or respiratory rate was used, the inspiratory delay between the time the diaphragm becomes active and the time the ventilator delivers an assist, is reduced when you use a neural trigger.

Jennifer Beck stated that this is even more striking when considering that the expiratory delays when cycling off with neural activity are much shorter in neural control. Comfort was rated by the subjects, and when comparing pressure trigger to neural trigger, independent of the pressure support level that was used, in general the neural trigger was more comfortable.

She also presented preliminary data from a study implementing NAVA before and after extubation in a rabbit with lung injury. Diaphragm electrical activity was measured at intubation.
and when the injury was induced. At extubation, a tube was placed 2 cm into one nostril of the rabbit, with mouth open and other nostril free. When ventilating with NAVA using a single nasal prong, the tonic activity disappeared completely. With increased levels of NAVA, the assist was delivered in synchrony and in proportion to the diaphragm electrical activity, despite the fact, as Jennifer Beck pointed out, that only one single nasal prong was used. When increasing NAVA levels 4 times, the respiratory muscles were unloaded by means of synchronized non-invasive positive pressure ventilation. She also pointed out that after extubation, despite that PEEP was removed, the tonic activity was not present. Jennifer Beck presented a graph that she thought would make neonatologists very happy, illustrating baseline gastric pressure during the non-invasive runs. Mean level of assist delivered was depicted during progressive increase of NAVA level, with no evidence of stomach inflation. Even at peak pressures of 40 cm H₂O, there was no effect on gastric distention, according to Jennifer Beck. She also presented an example from her preliminary data of non-invasive pressure support compared to NAVA, which she hoped the audience would observe as an important take-home message. The graph displayed tracings from a rabbit breathing on pressure support with a single nasal prong, diaphragm electrical activity, ventilator delivered pressure, and esophageal pressure swings. With such a substantial leak, the animal could not trigger pressure support, with declining PO₂ levels and increasing PaCO₂. After switching to NAVA, there was an instantaneous continuous recording of synchronized, non-invasive positive pressure ventilation, with immediate reduction of work of breathing and diaphragm activity, resulting in improved blood gases. Jennifer Beck completed her presentation by summarizing the goals of NAVA: improved patient-ventilator interactions, reduced work of breathing, to provide improved and safer ventilation, to reduce the need for sedation and paralysis, to adapt to altered metabolic demand, prevent disuse atrophy of the diaphragm, shorten weaning time and improve non-invasive ventilation.

Critical Care News had an opportunity to speak to Jennifer Beck and Christer Sinderby during the symposium:

You are introducing the concept of tonic activity of the diaphragm, is this essentially a reflex?

Jennifer Beck: That is exactly what it is; it is the Hering-Breuer deflation reflex. We did a study in intubated babies in Montreal in 2004, and we evaluated the interaction they had on the ventilator settings that were prescribed by the physicians and the respiratory therapists. We looked at the patient-ventilator interaction and found a severe amount of ventilator asynchrony. Two years later we published a paper in the same patient population, where we made an intervention when we removed the PEEP for a short period while the patients were on mechanical ventilation, and we evaluated the tonic activation of the diaphragm. The tonic activation of the diaphragm is the presence of diaphragm activity during the exhalation period. We were able to develop a method to quantify how much diaphragm activity there is during the expiratory phase, and to see how application or removal of PEEP affects that. This study has been recently published in Pediatric Research by Emeriaud et al.

Can you tell us more about your research in monitoring of the diaphragm activity to evaluate the feasibility of using the signal in the neonatal patients?

Jennifer Beck: We just recently completed a study where we were monitoring the diaphragm activity in premature babies with respiratory distress. Most received surfactant at birth, and some of them also received mechanical ventilation. When we studied them they were all on room air, still being monitored for apnea due to prematurity. We used our methodology to monitor their diaphragm activity over several days. We were able to look at how much phasic activity they had, and how much tonic activity they had, and look at their apneas.

What were the sizes of these neonatal patients?

Jennifer Beck: The youngest was 28 weeks and they ranged up to 36 weeks gestational age, the smallest baby was one kilo. Most were being treated with caffeine for their apneas, and they were fed by feeding tube.

Can you give us a further differentiation between the phasic activity and tonic activity,
and the types of responses you receive from physicians after hearing about your research?

Christer Sinderby: The breathing activity in itself is a waveform, where background diaphragm activity can occur during the exhalation period; for example you continue to expand the lungs to keep them open, to keep them from collapsing during the exhalation phase, and to keep the chest wall from collapsing. I think that this is something new here, that can actually be detected. The manner of ventilating these small patients is determined by the importance of synchronizing their ventilation, which can be a challenge with leakage from small cuffs. With the conventional ventilation technology, you have a problem to start and stop the ventilator, with the same difficulties in obtaining synchrony in adults and neonates. So if the baby tries to breathe in, he might not get the breath he wants and he might not get assist at all. This system provides the neural feedback to start and stop the ventilator, and to see if the patient needs PEEP or not, or which level of PEEP is required from a recruitment perspective. The most interesting thing we have seen in excessive animal studies is that we can actually tell how much assist and PEEP there should be, and titrate these parameters based on the diaphragm electrical activity. It is to be emphasized that monitoring is not just treatment, but you get the feedback that might be of much value when tailoring the ventilatory treatment. The responses from neonatologists who have heard about our research are usually astonished.

Jennifer Beck: I am asked a lot of questions, like “does the feeding affect the signal”? So we have looked closely at that and have monitored the babies while they are being fed, and there are no artifacts on the signal. I am also asked if the position of the baby affects the signal, and as long as the electrodes in the feeding tube are positioned at the diaphragm, the signal is not affected.

Christer Sinderby: Two studies in neonates have been started and are ongoing in Toronto at Women’s College Hospital at the present time, and we are expecting to see good results. The real challenge, which is already done was to establish that we can actually get signals in these small patients, and that the catheters are the right size for these babies.
What do you think will be the learning curve for clinicians in regard to NAVA?

Christer Sinderby: If you take a look at the set up we are using, for adults and infants, if you put the catheter down and don’t see any signals, you will have to be very suspicious about what is going on, because if the electrode is in the right place you will get a signal. If the catheter is placed and you don’t get a signal but you see that you are getting the ECG, the electrode is working but obviously the catheter is not in the right place and needs to be positioned.

As we find in a lot of patients, when we monitor the diaphragm activity, we can see that they are not using the diaphragm, even though the ventilator is in a patient-triggered mode. Disuse of the diaphragm could potentially lead to problems with weaning. When the patient is switched to NAVA, the diaphragm activity returned. The monitoring aspect that we should really emphasize is that you can flow, pressure and volume waveforms however, without Edi you cannot be sure what the diaphragm is doing.

We have heard from some of the researchers that have been utilizing NAVA, that after experiencing the neural drive and assist, they have come to the realization that they have generally been using much too high pressures with pneumatically driven ventilation modes. Think about it – the only development in spontaneous breathing that has occurred in the past 15-20 years is to improve the sensitivity of the pneumatic trigger to start a ventilator. It has improved to be more and more sensitive, but if you generate less than 1 cm of water in pressure you cannot feel it. The response with NAVA is every 16 milliseconds. The reflex response if I hit my knee is 60 milliseconds. So the neural ventilator response is 4 times as fast. From the neural perspective this gives us the power to have integrated information to make decisions faster, and continuously, and to avoid bad decisions.
Biographies
Christer Sinderby, PhD is Assistant Professor at the Department of Medicine, University of Toronto, Canada, and Research Staff Scientist at St. Michael's Hospital, Department of Critical Care Medicine, Toronto. He received his MS degree from Karolinska Institute in Stockholm, Sweden, and Doctor in Medical Science degree at the Department of Neurosurgery, Sahlgrenska Hospital, University of Gothenburg, Sweden.

Christer Sinderby has won numerous academic committee assignments, including the University of Western Australia, as a peer reviewer for American Journal of Respiratory and Critical Care Medicine and Journal of Applied Physiology, and as a member of the American Thoracic Society/European Respiratory Society task force for the ATS/ERS statement on standardization of respiratory muscle tests. He has won numerous research awards and grants including the Montreal Chest Hospital Research Institute Annual Award, the Parker B. Fellowship in Pulmonary Research and Fonds de la Recherche en Santé du Québec Chercheurs Boursier Scholarship. His research has been extensively published in peer review journals and monographies.

Jennifer Beck, PhD is Assistant Professor at the Department of Pediatrics, University of Toronto, Canada, and Associate Scientist, Clinical and Integrative Biology at the Sunnybrook Health Sciences Centre, Neonatal Intensive Care Unit, Women's College Hospital in Toronto, Canada. She received her MS degree and Doctor of Physiology degree from McGill University in Montreal, Canada, and post-doctoral degrees from McGill University and the University of Montreal.

Jennifer Beck has won numerous research awards, including awards for scientific presentations from the Department of Physiology and the University of Miami, the MRC/Glaxo-Wellcome/Canadian Lung Association bursary in 1998, the FRSQ post-doctoral fellowship in 1999, and was also awarded in 2005 at the University of Toronto Critical Care Research Day. She was awarded an operating grant from the National Institute of Health for her work in Neural Control of Non-invasive Ventilation in the Preterm in 2003. Her research has been extensively published in a number of peer review journals.

References


