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# Patient-Ventilator Interaction During Neurally Adjusted Ventilatory Assist in Low Birth Weight Infants

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**ABSTRACT:** Neurally adjusted ventilatory assist (NAVA), a mode of mechanical ventilation controlled by diaphragmatic electrical activity (EAdi), may improve patient-ventilator interaction. We examined patient-ventilator interaction by comparing EAdi to ventilator pressure during conventional ventilation (CV) and NAVA delivered invasively and non-invasively. Seven intubated infants [birth weight 936 g (range, 676–1266 g); gestational age 26 wk (range, 25–29)] were studied before and after extubation, initially during CV and then NAVA. NAVA-intubated and NAVA-extubated demonstrated similar delays between onset of EAdi and onset of ventilator pressure of 74 ± 17 and 72 ± 23 ms ($p = 0.698$), respectively. During CV, the mean trigger delays were not different from NAVA, however 13 ± 8.5% of ventilator breaths were triggered on average 59 ± 27 ms before onset of EAdi. There was no difference in off-cycling delays between NAVA-intubated and extubated (32 ± 34 *versus* 28 ± 11 ms). CV cycled-off before NAVA (120 ± 66 ms prior, $p < 0.001$). During NAVA, EAdi and ventilator pressure were correlated [mean determination coefficient (NAVA-intubated 0.8 ± 0.06 and NAVA-extubated 0.73 ± 0.22)]. Pressure delivery during conventional ventilation was not correlated to EAdi. Neural expiratory time was longer ($p = 0.044$), and respiratory rate was lower ($p = 0.004$) during NAVA. We conclude that in low birth weight infants, NAVA can improve patient-ventilator interaction, even in the presence of large leaks. **(*Pediatr Res* 65: 663–668, 2009)**

Neurally adjusted ventilatory assist (NAVA) is a new concept in mechanical ventilation, where the patient's respiratory drive—measured from the diaphragm electrical activity (EAdi)—controls the timing and the magnitude of pressure delivered (1). NAVA has been implemented safely in animals, in healthy volunteers, and in critically ill adults, and has been shown to improve patient-ventilator synchrony (2,3), to limit excessive airway pressure and tidal volume (2–5), and to unload the respiratory muscles (2,5). NAVA has also been implemented noninvasively in animals with severe hypoxemic respiratory failure (6). NAVA was found to be effective in delivering noninvasive ventilation even when the interface was excessively leaky (75% leak) and no positive end-expiratory pressure (PEEP) was applied. With these conditions, NAVA was capable of unloading the respiratory muscles and maintaining adequate blood gases, while maintaining synchrony to respiratory demand (6). Whether or not the respiratory drive of the preterm infant is suitable to control mechanical ventilation—both invasively and noninvasively—is unknown. The aim of the present study, therefore, was to evaluate patient-ventilator interaction with NAVA in very low birth weight infants while intubated and when ventilated noninvasively with an extreme leak. Conventional ventilation was used as a reference.

## METHODS

The protocol was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada. Written informed consent was obtained from a parent or guardian.

***Infants.*** Infants were eligible for the study if they were born premature (≤36 wk), recovering from respiratory illness, and deemed to be ready for elective extubation by their attending physician.

***Measurements.*** Electrical activity of the diaphragm (EAdi) was obtained using an array of nine miniaturized electrodes (spaced 6 mm apart) mounted on a conventional (5.5F) feeding tube (Maquet Critical Care AB, Solna, Sweden; Neurovent Research Inc, Toronto, Canada), and positioned in the lower esophagus at the level of the diaphragm.

During conventional ventilation, we measured ventilator-delivered pressure (Pvent) at a side port of the ventilator's flow sensor (at the endotracheal tube). During NAVA, flow and Pvent were measured with a pneumotach (dead space 1.06 mL) placed at the endotracheal tube. Signals for EAdi, Pvent, and flow (when available), were acquired into a personal computer, displayed as waveforms throughout the study on a computer monitor, and stored for later analysis.

Oxygen saturation, transcutaneous $CO_2$, and heart rate were monitored from the displayed monitors throughout the study, and were noted for the last minute of the runs.

***General principles of NAVA.*** A Servo300 ventilator (Maquet, Sweden), modified to deliver NAVA, was used for the NAVA portions of the study. During NAVA, the pressure delivery was controlled by the EAdi waveform, processed according to standardized algorithms (7). Although the ventilator was set in

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Drs. Beck and Sinderby have made inventions related to neural control of mechanical ventilation that are patented. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Drs. Beck and Sinderby through royalties. Drs Beck and Sinderby each own 50% of Neurovent 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. Slutsky is a paid consultant to Maquet Critical Care.

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**Abbreviations: EAdi,** electrical activity of the diaphragm; **NAVA,** neurally adjusted ventilatory assist; **Nte,** neural expiratory time; **PEEP,** positive end-expiratory pressure; **ΔPi,** delta inspiratory pressure above PEEP; **Pvent,** ventilator-delivered pressure (PEEP + ΔPi)

**Table 1.** *Characteristics of the infants at enrollment and conventional ventilation settings*

| Subject | Mode | ΔPi (cm $H_2O$) | $V_t$ (mL/kg) | PEEP (cm $H_2O$) | Backup rate (per min) | $FIO_2$ (%) | Birth weight (g) | GA at birth (wks) | Age at study (d) | Weight at study (g) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | PSVG | 5 | 3.3 | 5 | 20 | 21 | 1266 | 28 | 5 | 1163 |
| 2 | PSV | 7 | 4.7 | 5 | 15 | 21 | 676 | 25 | 3 | 634 |
| 3 | PSVG | 9 | 6.0 | 5 | 6 | 28 | 930 | 26 | 27 | 1325 |
| 4 | PSVG | 10 | 4.6 | 6 | 11 | 21 | 705 | 25 | 13 | 778 |
| 5 | PSVG | 10 | 4.0 | 7 | 20 | 37 | 730 | 25 | 14 | 810 |
| 6 | PSV | 14 | 4.3 | 5 | 25 | 24 | 1150 | 29 | 2 | 1150 |
| 7 | PSV | 7 | 5.2 | 5 | 15 | 24 | 1092 | 27 | 17 | 970 |
| Mean | | 9 | 4.6 | 5 | 16 | 25 | 936 | 26 | 12 | 976 |
| SD | | 3 | 0.9 | 1 | 6 | 6 | 239 | 2 | 9 | 249 |

PSVG, pressure support with volume guarantee; PSV, pressure support ventilation; ΔP, delta inspiratory pressure above PEEP; PEEP, positive end-expiratory pressure; $FIO_2$, fraction of inspired oxygen; GA, gestational age; SD, standard deviation.

"pressure support/CPAP mode," the EAdi overrode the built-in pressure support algorithms. During NAVA, the EAdi signal was used to trigger-on and cycle-off the assist (60% of peak EAdi in the present study). The EAdi was also the controller signal for the amount of pressure delivered during inspiration, and was multiplied by a proportionality factor known as the NAVA level to adjust the level of assist (1).

***Conventional ventilation.*** The catheter was inserted while the infant was ventilated with conventional ventilation. The EAdi and Pvent were then recorded for 60 min, while the infant remained on conventional ventilation. All infants were ventilated with the study center's standard ventilator (Babylog 8000, Draeger, Lubeck, Germany). Infants were ventilated on the settings that were prescribed clinically (see Table 1), and were not adjusted. Study infants were ventilated with either PSV or PSVG. Both modes terminate a breath when 15% of peak flow has been reached. During conventional ventilation, only EAdi and Pvent were measured, as it was not possible to record flow from the conventional ventilator.

***Adjustment of NAVA level.*** During conventional ventilation, the EAdi waveform was multiplied by the NAVA level to produce an estimated NAVA pressure waveform, which, in turn, was overlaid on the actual pressure waveform measured during conventional ventilation. The NAVA level was adjusted (increased or decreased) until peak airway pressures were matched.

***NAVA-intubated.*** NAVA was delivered through the endotracheal tube for 20 min. In the present study, the NAVA level was adjusted to match the peak pressures delivered during conventional ventilation, as described above. PEEP was the same as during conventional ventilation.

Backup conventional ventilation [pressure control mode (10/5, rate 30)] was available in case EAdi was absent for more than 10 s.

An upper pressure limit was set and was 21 ± 2 cm $H_2O$ for the group.

***NAVA-extubated.*** After extubation, NAVA was delivered for 20 min, noninvasively through a single Portex cut endotracheal tube positioned in the nasopharynx (single nasal prong). PEEP could not be applied because of the excessive leak. The NAVA level was adjusted if necessary to reach the same delta inspiratory pressure.

All babies were placed on nasal CPAP with clinically prescribed settings after the study.

***Protocol termination criteria.*** The attending physician was asked to assess the baby for possible termination of the protocol if the following were exhibited: signs of increased respiratory work or distress, requirement for a sustained increase in $FIO_2$ >0.1 to maintain saturation ($SpO_2$) >88%, increased transcutaneous $pCO_2$ by >20 mm Hg, respiratory rate >80 bpm, or an increase in heart rate by more than 20 bpm.

***Analysis.*** Analysis was performed off-line. As described previously (2), for each ventilator condition, breath by breath analysis was performed by placing five time cursors on the displayed EAdi and Pvent waveforms: (i) the onset of ventilator breath; (ii) the end of the ventilator breath; (iii) the onset of EAdi; (iv) the peak of EAdi; and (v) 60% of peak EAdi.

Calculations for the following were made: inspiratory (phasic) EAdi, end-expiratory (tonic) EAdi, neural inspiratory (Nti) and expiratory times (Nte), neural respiratory rate (Nrr, calculated as 60/Nti + Nte), the inspiratory mean airway pressure (MAPi), delta inspiratory pressure above PEEP (ΔPi), trigger delays (onset of Pvent minus onset of EAdi) and cycling-off delays (end of Pvent minus 60% of peak EAdi), and the correlation of EAdi and Pvent. The EAdi-time product (an indication about diaphragm energy expenditure) was calculated per minute as the product of the mean inspiratory phasic EAdi, the neural inspiratory time and the neural respiratory rate. Breaths for Nte that exceeded 5 s were not included in this analysis (these were considered respiratory pauses). For each condition, an average of each variable was calculated for the last minute of the runs. Unassisted efforts were counted and defined as presence of an EAdi effort and no assisted breath delivered.

***Statistical analysis.*** Statistical analysis was performed with Sigmastat 3.2 (Jandel Scientific, San Rafael, CA). For each parameter analyzed, one-way repeated-measures analysis of variance was performed. All pairwise multiple comparisons were performed with the Tukey test. Linear regression analysis was performed between EAdi and Pvent, as well as for Pvent and $V_t$ (only during NAVA-intubated), and the determination coefficient ($R^2$) was calculated to explain how much the dependent variable explained the outcome of the independent variable. A significant difference was defined as $p < 0.05$.

## RESULTS

We enrolled seven infants into the study. All but two babies received surfactant at birth. The clinical characteristics and ventilator settings are presented in Table 1. Only one infant was clinically determined to have a leak while intubated (20–70%). All patients fulfilled the intubated steps of the protocol. Two infants were not studied during NAVA-extubated: in one infant, the nasopharyngeal tube did not fit into either nostril, and in another infant, during a reassessment by the clinical team during the first intubated parts of study, the decision to extubate was revoked.

All infants tolerated the NAVA catheter insertion and demonstrated an EAdi signal that was suitable for implementation of NAVA.

There were no significant differences in ΔPi, $SPO_2$, $TCO_2$, and heart rate between conventional ventilation, NAVA-intubated and NAVA-extubated groups (Table 2). After extubation, $FIO_2$ was higher during NAVA-extubated and the MAPi was lower.

During the analyzed periods, respiratory pauses >5 s occurred in two infants on conventional ventilation [mean duration 11 s (range, 5–21 s)], in one infant during NAVA-intubated, where the mean pause duration was 9 s (range, 7–10 s), and in no infants during NAVA-extubated.

Backup ventilation on NAVA during the 20-min study periods was initiated in one infant, both when intubated and extubated. However, this infant was also the only infant to demonstrate absence of EAdi for periods of more than 10 s even during conventional ventilation.

Expiratory tidal volume measured with the pneumotach during NAVA-intubated was 7.1 ± 2.1 mL/kg (range, 4.5–9.1 mL/kg).

Compared with NAVA-intubated and NAVA-extubated, neural respiratory rate was higher and neural expiratory time was significantly decreased during conventional ventilation (Table 2). Peak inspiratory EAdi and tonic EAdi were not different between ventilator conditions. Figure 1 demonstrates the EAdi-neural timing plots for each ventilator condition.

**Table 2.** *Vital signs, ventilator parameters, neural breathing pattern, and patient-ventilator interaction*

| | Conventional ventilation | NAVA-intubated | NAVA-extubated | *p* |
|---|---|---|---|---|
| | *n* = 7 | *n* = 7 | *n* = 5 | |
| $F_{IO_2}$ (%) | 25.1 (5.8)† | 26.4 (5.9)* | 38.0 (19.1) | 0.0034 |
| $S_{AO_2}$ (%) | 94.6 (2.7) | 94.1 (3.5) | 95.4 (6.5) | 0.961 |
| $T_{CO_2}$ (mm hg) | 53.4 (14.6) | 52.6 (13.0) | 60.6 (12.5) | 0.787 |
| Heart rate (per min) | 160 (15) | 159 (11) | 166 (11) | 0.868 |
| | *n* = 5 | *n* = 7 | *n* = 5 | |
| MAPi (cm $H_2O$) | 12.5 (1.5)* | 9.6 (1.8)* | 5.5 (1.6) | 0.002 |
| ΔPi (cm $H_2O$) | 9.3 (1.3) | 9.9 (1.3) | 9.4 (3.1) | 0.710 |
| EAdi phasic (au) | 27.9 (19.5) | 43.6 (18.7) | 44.8 (32.4) | 0.333 |
| EAdi tonic (au) | 5.5 (2.0) | 4.7 (3.0) | 4.7 (1.4) | 0.157 |
| Nti (msec) | 258 (43) | 406 (131) | 436 (198) | 0.09 |
| Nte (msec) | 712 (139) | 875 (237)† | 1001 (256) | 0.044 |
| Nrr (per min) | 74 (7) | 54 (14)† | 51 (14)† | 0.004 |
| EAdi-time product (au*s/min) | 556.4 (421.2) | 823.4 (444.3) | 670.2 (524.5) | 0.504 |
| Trigger delay (ms) | 74 (17) | 72 (23) | 76 (33) | 0.698 |
| Cycling-off delay (ms) | −120 (66) | 32 (34)† | 28 (11)† | <0.001 |
| $R^2$ for EAdi *vs* Pvent | 0.08 (0.1) | 0.80 (0.06)† | 0.73 (22)† | <0.001 |
| Slope EAdi *vs* Pvent (cm $H_2O$ per au) | 0 (0.01) | 0.19 (0.1)† | 0.2 (0.1)† | 0.007 |

* Statistically different from NAVA-ext.

† Statistically different from Conv.

$F_{IO_2}$, fraction of inspired oxygen; $S_{AO_2}$, oxygen saturation; $T_{CO_2}$, transcutaneous carbon dioxide; MAPi, mean inspiratory airway pressure; ΔPi, delta inspiratory pressure above PEEP; EAdi, electrical activity of the diaphragm; Nti, neural inspiratory time; Nte, neural expiratory time; Nrr, neural respiratory rate; $R^2$, determination coefficient; Pvent, ventilator delivered pressure.

During conventional ventilation, 13 ± 8.5% of the analyzed breaths were initiated before the onset of EAdi (by 59 ± 27 ms). When all breaths were considered (including those that triggered too early during conventional ventilation), no differences were observed in trigger delays for the three conditions (Table 2). On average, 1.8 unassisted efforts (range, 0.8–3) per minute occurred in four infants during conventional ventilation. In all infants, cycling-off during conventional ventilation occurred before the time when NAVA would have cycled-off. There was no difference in cycling-off delays during NAVA-intubated and NAVA-extubated.

There was no correlation between EAdi and Pvent during conventional ventilation, whereas NAVA demonstrated very strong correlations, both when intubated and extubated (Table 2). Figure 2 depicts examples of the relationship between the peak inspiratory EAdi and the peak ventilator pressure, during NAVA-intubated and NAVA-extubated (top panels), and during conventional ventilation (bottom panels). During NAVA-

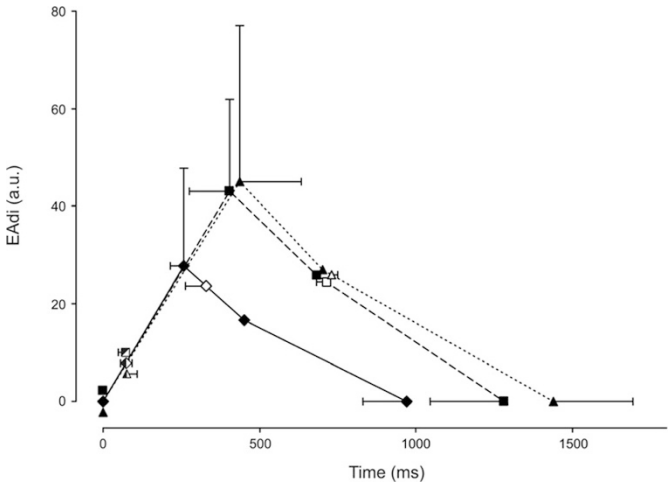


**Figure 1.** EAdi-neural timing profile for the group of infants, plotted for conventional ventilation and NAVA-intubated and NAVA-extubated. Figure depicts neural timing (*x* axis) in relation to EAdi (*y* axis). For each condition, four points of the breathing cycle are plotted (in solid symbols, as they appear from left to right): onset of inspiration, peak of inspiratory EAdi, 60% of peak EAdi, and end of neural expiration. Half-filled symbols indicate where triggering occurred and open symbols describe where off-cycling occurred for the different ventilation modes. Note that the tonic EAdi (baseline) is not zero (see Table 2), but for simplicity, the *y* axis begins at zero.

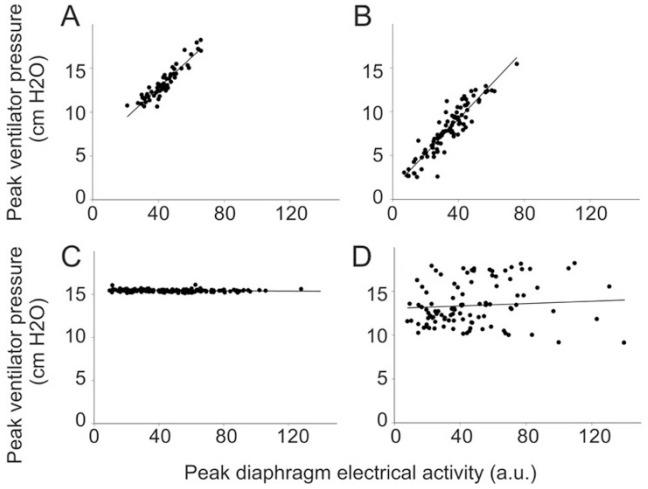


**Figure 2.** Relationship between peak diaphragm activity and peak ventilator pressure. Panels *A* and *B*: Peak diaphragm electrical activity (*x* axis) and peak ventilator-delivered pressure (*y* axis) are plotted breath by breath in one infant breathing on NAVA while intubated (Panel *A*), and while extubated (Panel *B*). Note the strong correlation between EAdi and Pvent. Panels *C* and *D*: Peak diaphragm electrical activity (*x* axis) and peak ventilator-delivered pressure (*y* axis) are plotted breath by breath in one infant breathing on pressure support (panel *C*), and in another infant during pressure support + volume guarantee. Note the poor correlation between EAdi and Pvent.

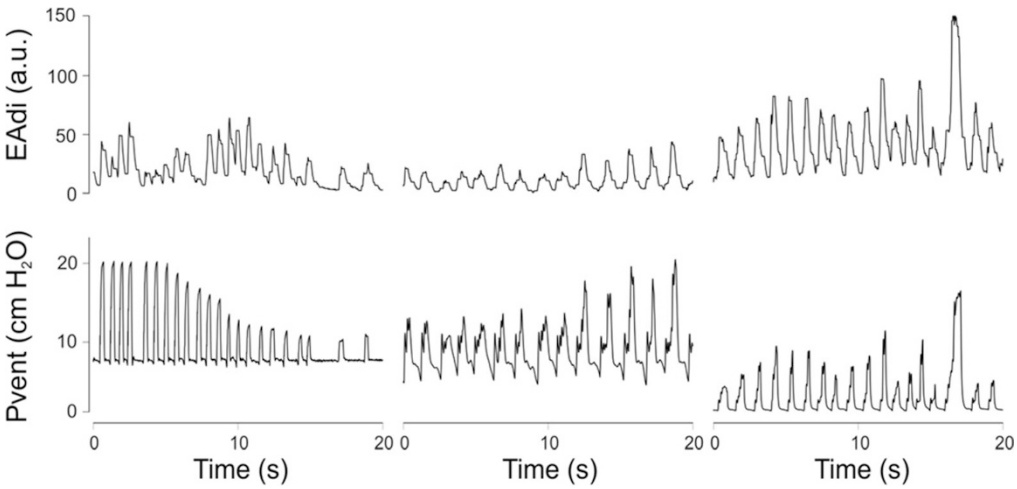


**Figure 3.** Tracings EAdi and Pvent obtained in one subject while breathing on pressure support + volume guarantee, NAVA-intubated and NAVA-extubated. Waveforms of EAdi (top tracings) and ventilator-delivered pressure (bottom tracings) are depicted for one infant breathing on PSV + VG (left), NAVA while intubated (middle), and during non-invasive NAVA (right). Note the synchrony in terms of timing and proportionality, even in the presence of the leak for the NAVA periods.

intubated, the determination coefficient between Pvent and $V_t$ was 0.39 ± 0.15.

Figure 3 demonstrates tracings of EAdi and Pvent in one infant breathing on PSV + VG, and on NAVA while intubated, and on NAVA after extubation.

## DISCUSSION

This small physiologic study demonstrates for the first time in low birth weight infants with variable lung disease that neural control of mechanical ventilation, using the electrical activity of the diaphragm, can synchronize delivery of assist to the patient's inspiratory drive, and that synchrony is maintained regardless of the interface (endotracheal tube or nasal prong) used to deliver assist.

A recent meta-analysis evaluating triggered ventilation in neonates cautioned that most studies did not evaluate patient-ventilator interaction, and hence, the outcomes should not be interpreted as being provoked by synchronous ventilation (8). NAVA is the first mode to use a standardized measurement of the EAdi signal (7) to both monitor *and* control the timing and magnitude of pressure delivery. Monitoring of EAdi and ventilator-delivered pressure is a recommended approach to evaluate patient-ventilator interaction (9). Because NAVA uses the patient's own respiratory signals to control the ventilator, it should offer synchronous ventilation in two dimensions. The first dimension relates to achieving good timing between the beginning/end of the patient's effort and the start/end of the ventilator-delivered breath. The second dimension relates to delivering assist in proportion to the patient's respiratory drive.

In the present study, trigger delays and cycling-off delays during NAVA were in the range, or even less than previously reported (2,6). For all three methods of ventilation (conventional ventilation, NAVA-intubated, and NAVA-extubated), the mean values of trigger delays were not different. However, during conventional ventilation, the assist was triggered before the onset of diaphragm activation in 13% of the breaths. A possible reason for this premature triggering could have been auto-cycling of the ventilator from leaks (10), cardiac oscillations (11), condensation in the ventilator circuit, or simply a mandatory breath (backup rate) occurring before onset of inspiratory effort. Another reason may be that another muscle group generated enough flow to trigger the ventilator; however, in these premature babies, it has been reported that inspiratory flow lags sequentially behind upper airway muscles and diaphragm activity (12). Premature triggering is not possible during NAVA (which uses a neural trigger) because the assist (flow from the ventilator) could only begin after the onset of EAdi. Although infrequent, unassisted wasted efforts were observed during conventional ventilation and not during NAVA.

In the present study, the breath termination criteria during conventional ventilation were 15% of peak inspiratory flow (by default). When the ventilator-delivered pressure waveform was compared with the EAdi waveform, cycling-off in conventional ventilation was found to be consistently earlier than the neural cycling-off criteria used for NAVA. These differences in breath termination criteria might explain why neural respiratory rate was more than 20 breaths per min faster in conventional ventilation than during NAVA-intubated and NAVA-extubated. It has been demonstrated that the timing of cycling-off in relation to the end of neural inspiration has an impact on respiratory rate (13,14), where too early off-cycling reduces neural expiratory time, and hence, increases respiratory rate. As well, the rapid square-wave delivery of pressure during conventional ventilation causes an early increase in flow, and has the effect of terminating inspiration earlier and increasing respiratory rate (15,16). In the present study, the tendency for lower phasic EAdi and shorter neural inspiratory time during conventional ventilation (compared with NAVA) could be explained by the differences in pressure delivery.

Our findings of different cycling-off delays between conventional ventilation and NAVA-intubated and NAVA-extubated, raises the question of which signal is more appropriate for breath termination (flow or EAdi). Conventional ventilation in one patient actually cycled-off the assist while EAdi was still increasing—which is definitely too early—whereas the remainder of the patients showed dispersed timing for off-cycling, albeit after the peak of the EAdi (but earlier than the off-cycling criteria of NAVA). This finding is consistent with the complexity of using flow criteria for off-cycling as theoretically described by Yamada and Du (17)

and clinically described by Tokioka et al. (18), Tassaux et al. (19), and Chiumello et al. (20) in adults.

In the present study, the flow cycling-off criteria during conventional ventilation were fixed at 15% of peak flow, and were not adjustable. If this adjustment had been an option, it may have been possible to reduce the cycling-off differences observed between conventional ventilation and NAVA. However, this would require that the EAdi waveform be monitored to determine the end of neural inspiration (17). The neural cycling-off was likely appropriate because the transition from inspiration to expiration did not reveal zero flow (with a closed exhalation valve) while EAdi was decreasing toward 60% of peak EAdi. In animals, phrenic nerve activity has been shown to persist for 100–200 ms after the peak of neural inspiration (*i.e.*, there is no abrupt inhibition of EAdi, but a gradual one) (21). In the present study, the median time between the peak of EAdi and the 60% cycling-off criteria was 217 ms during NAVA-intubated.

The second dimension to patient-ventilator synchrony relates to delivering assist in response to changes in patient demand. During NAVA, it was possible in these infants, to deliver pressure in proportion to the EAdi. During conventional ventilation (with a fixed target pressure or fixed target tidal volume), the relationship between the infants' neural inspiratory effort and ventilator assist did not correlate at all.

In terms of conventional ventilation, four infants were ventilated on PSV + VG, a mode designed to achieve a set tidal volume by adjusting inspiratory pressure. In the case where inspiratory effort increases (and thus *V*t would increase) the Babylog 8000's response would be a reduction in ΔPi (Fig. 3). This is clearly different from NAVA, where an increased inspiratory effort results in more ΔPi. The fact that NAVA delivers pressure instantaneously (every 16 ms) allowed a high breath-by-breath positive correlation between EAdi and Pvent (Fig. 2). During PSV + VG, the adjustment in ΔPi to reach the target $V_t$ may take up to 6–8 breaths (22). This delay of a few breaths may have masked the anticipated negative relationship between Pvent and EAdi during PSV + VG in Figure 2.

As can be noted by the strong association between patient effort (EAdi) and ventilator assist (Pvent) (Table 2 and Fig. 2), NAVA amplifies the patient's ability to modulate tidal volume within and between breaths. In the population we studied, the spontaneously chosen (expired) tidal volume was on average 7 mL/kg, and was the same as that recently reported in neonates breathing with proportional assist ventilation PAV (23). This shows that, similar to adult patients (3), infants recovering from their respiratory illness do not necessarily adopt excessive tidal volumes when ventilated on modes of mechanical ventilation that amplify patient effort.

It is possible that early cycling-off during conventional ventilation—especially before the peak EAdi in some cases—resulted in insufficient inspiratory time in relation to the inspiratory time constant of the infant. Hence, the later cycling-off during NAVA-intubated might explain the increased $V_t$ (and reduced neural respiratory rate) compared with conventional ventilation. Based on the above discussion, it is clear that further physiologic studies are required to evaluate the complex interaction between assist delivery, patient inspiratory effort, tidal volume, and respiratory reflexes.

Consistent with our previous work using noninvasive NAVA in animals (6) and neurally triggered and cycled pressure support in humans (24), patient-ventilator synchrony was not affected by leaks. Although our study was a physiologic study and cannot draw any conclusive statements about the clinical usefulness of noninvasive NAVA, it demonstrates a clear potential of how EAdi can help to overcome current limitations with regards to synchronizing assist delivery invasively or noninvasively.

Despite that tidal ventilatory assist (ΔPi) could be applied in synchrony with patient effort in the presence of a large leak, the ventilator prototype used in the present study was not able to maintain the set PEEP. During NAVA-extubated, the *M*APi, although lower than NAVA-intubated, was ~5 cm $H_2O$. Even though $F_{IO_2}$ was increased to maintain saturation, the infants did not demonstrate physiologic responses that have previously been observed when PEEP is lowered, such as increased tonic EAdi (6,25) or increased respiratory rate (26). Of note, no signs of increased respiratory drive (phasic EAdi), EAdi-time product or heart rate were observed. One reason to explain why removal of PEEP may not have had an impact on these variables is that the upper airways (liberated after extubation) could have participated in the maintenance of end-expiratory lung volume by "braking" expiratory flow. In the present study, neither upper airway muscle activity nor end-expiratory volume was measured; however, it has recently been reported that most breaths in nonintubated preterm infants are characterized by interruption, or braking, of the expiratory flow (27). It could also be speculated that a fully synchronized mode of ventilation, such as NAVA, may allow the infant to recruit the lung sufficiently during tidal breathing, despite the absence of PEEP.

Although not used routinely, the single nasal prong was the chosen interface for the present study as it represents an extreme leak. The interface used (single nasal prong) could have been replaced by another noninvasive interface, such as binasal prongs. Obviously, using an interface with less of a leak would increase the efficiency of noninvasive ventilation with NAVA.

In conclusion, this first short-term evaluation of patient-ventilator interaction during conventional ventilation in a small group of neonates suggests fairly adequate pneumatic triggering, whereas off-cycling criteria can be asynchronous and suffers from the same limitations as in adult patients. This study shows that NAVA could be implemented for a short-term period, both invasively and noninvasively, in infants as young as 3 days old, and with body weights as low as 640 g. While intubated, NAVA provided adequate and synchronous ventilation. Most importantly, the synchrony with NAVA—both in terms of timing and proportionality—could be maintained even after extubation while ventilating the patient with an excessively leaky interface. At this time, further trials that are suitably powered are required to determine the potential ranges of the clinical use of this technology.

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