A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population*

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Objective: **To compare neurally adjusted ventilatory assist ventilation with pressure-support ventilation.**

Design: **Prospective, crossover comparison study.**

Setting: **Tertiary care pediatric and neonatal intensive care unit.**

Patients: **Sixteen ventilated infants and children: mean age = 9.7 months (range = 2 days–4 yrs) and mean weight = 6.2 kg (range = 2.4–13.7kg).**

Interventions: **A modified nasogastric tube was inserted and correct positioning was confirmed. Patients were ventilated in pressure-support mode with a pneumatic trigger for a 30-min period and then in neurally adjusted ventilatory assist mode for up to 4 hrs.**

Measurements and Main Results: **Data collected for comparison included activating trigger (neural vs. pneumatic), peak and mean airway pressures, expired minute and tidal volumes, heart rate, respiratory rate, pulse oximetry, end-tidal CO_2 and arterial blood gases. Synchrony was improved in neurally adjusted ventilatory assist mode with 65% (±21%) of breaths triggered neurally vs. 35% pneumatically ($p < .001$) and 85% (±8%) of breaths cycled-off neurally vs. 15% pneumatically ($p = .0001$). The peak airway pressure in neurally adjusted ventilatory assist mode was significantly lower than in pressure-support mode with a 28% decrease in pressure after 30 mins ($p = .003$) and 32% decrease after 3 hrs ($p < .001$). Mean airway pressure was reduced by 11% at 30 mins ($p = .13$) and 9% at 3 hrs ($p = .31$) in neurally adjusted ventilatory assist mode although this did not reach statistical significance. Patient hemodynamics and gas exchange remained stable for the study period. No adverse patient events or device effects were noted.**

Conclusions: **In a neonatal and pediatric intensive care unit population, ventilation in neurally adjusted ventilatory assist mode was associated with improved patient-ventilator synchrony and lower peak airway pressure when compared with pressure-support ventilation with a pneumatic trigger. Ventilating patients in this new mode seem to be safe and well tolerated. (Pediatr Crit Care Med 2010; 11:7–11)**

Key Words: mechanical ventilation; neonatal; pediatric; diaphragm electrical activity; pressure support; patient ventilator interaction

Modes of mechanical ventilation have evolved from volume- or pressure-targeted, time-cycled modes to patient-cycled modes and onward to increasingly complex automated forms incorporating features of both. Patient-triggered modes have a number of distinct advantages over control modes. As breathing effort is preserved, the physiologic benefits of active diaphragmatic contraction are maintained, with improved ventilation/perfusion ratio matching (1–8), hemodynamics (5, 7, 9–12), and a reduction in required inspiratory pressure (13–15). Additionally, atrophy of the diaphragm arising secondary to mechanical offloading is reduced (16). To operate a patient-cycled mode, a means of synchronization is required. This is most commonly achieved, using sensed changes in pressure or flow, to trigger or terminate a supporting breath. Asynchrony is a widely recognized problem with such triggers, arising from a delay between the neural initiation or termination of a breath, and the ventilator's response (17).

Neurally adjusted ventilatory assist (NAVA) utilizes the electrical activity of the diaphragm (EAdi) to trigger and cycle-off breaths, and therefore presents a means of bypassing the ventilator circuit, and the inherent delays with pneumatic triggering. This is a processed signal, which is not artificially influenced by changes in muscle length, chest wall configuration, and/or lung volume (18–20). It represents the summation of muscle motor unit recruitment and/or firing rate (18), and correlates with phrenic nerve activity (21). Additionally, in this mode, the amount of support pressure is coupled with the magnitude of the EAdi. The proportion of support pressure to EAdi (NAVA level) is adjustable. As an increase

*See also p. 142.

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Compensation was made payable to Dr. Brendan O'Hare on behalf of Our Lady's Children's Hospital Pediatric Intensive Care Department by Maquet Critical Care for the work involved in enrolling patients in the prevalidation study—primarily a safety and efficacy study. As part of the agreement, all study data were freely available to the authors of the submitted manuscript.

None of the authors participating in this study has any financial interest in Neurally Adjusted Ventilatory Assist (NAVA) or associated technology. The study was performed as part of a prevalidation of NAVA in conjunction with Maquet Critical Care AB, Solna, Sweden. A nominal monetary donation was made to the Department of Anaesthesia and Intensive Care of Our Lady's Hospital for Sick Children by Maquet for each patient enrolled.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: cbreatnach@yahoo.com

DOI: 10.1097/PCC.0b013e3181b0630f

in the proportion of supporting pressure may suppress the EAdi, a higher NAVA level may not necessarily result in a higher pressure being delivered by the ventilator.

We sought to test the hypothesis that NAVA mode ventilation would improve patient-ventilator synchrony when comparing pressure-support ventilation (PSV) with a pneumatic trigger.

MATERIALS AND METHODS

A prospective, crossover comparison study of NAVA and PSV modes was conducted from April to August 2007. The site of the study was the pediatric intensive care unit (ICU) of Our Lady's Children's Hospital, Dublin, Ireland. This 20-bed pediatric ICU is the largest in the country and based at the national center for pediatric cardiothoracic surgery. The research was done under the umbrella of a multicentered prevalidation study of NAVA, involving an additional four Swedish centers: University Hospital in Linköping; St. Göran Hospital in Stockholm; The Queen Silvia Children's Hospital in Göteborg; and University Hospital in Lund. All but one of the pediatric patients enrolled were from the Dublin center.

Ethical approval was obtained from the Institutional Review Board. Parents were provided with both an information leaflet and a detailed verbal explanation before they provided their informed consent.

Patients considered for inclusion were required to be: a) ventilated via an endotracheal tube with a nasogastric tube *in situ*; b) ventilatory and hemodynamically stable with not more than one inotropic and/or dilatory infusion ongoing; c) with an intact neuromuscular pathway to the diaphragm; d) >37 wks post conceptional age.

Patients were excluded from enrollment in the study for the following reasons: a) if treated with neuromuscular blocking agents; b) where insertion/exchange of a nasogastric tube was contraindicated; c) where there was a history of heart and lung transplant; d) where there was a history of neurologic trauma or a disorder with increased intracranial pressure; e) patients with a pacemaker.

All patients were ventilated using a ventilator with NAVA option (Servo-i, Maquet Critical Care, Solna, Sweden). Before commencement of the study, the standard nasogastric tube was replaced with a specially modified nasogastric tube with a sensor array. The initial placement was directed by measuring the distance from the patient's xiphisternum, to nose, to the tragus of the ear, and passing the catheter to this depth. Confirmation of appropriate placement was achieved by viewing the online electrical displays from the catheter. The presence of a good quality EAdi trace with p waves displayed by the central electrodes indicates optimal positioning, with the array spanning the diaphragm equally in both caudal and cranial directions.

Where patients were not in PSV, they were converted to this mode. The selection of pressure-support settings was not standardized. Rather, the existing settings—which had been selected on clinical grounds—were continued. Where conversion to PSV mode was required, this was again guided by the existing clinically directed settings with preservation of minute volume.

After 30 mins, patients were changed over to NAVA mode for a maximum period of 4 hrs. Pneumatic triggering was constant during the study period at -1 cm H_2O as was cycling-off at 25% of peak flow. NAVA triggering was titrated to the lowest possible level that avoided false triggering. The magnitude of the proportional assist for NAVA was selected according to the EAdi recorded during the PSV phase of the study, to match the pressure delivered in that mode. A preview window on the ventilator's interface made this possible before change over. The same positive end-expiratory pressure was applied in both modes. General supportive care, including sedation, continued unchanged throughout the study period.

The data recorded manually for each patient included age, weight, diagnosis, type and dose of analgesia and sedation, hemodynamic variables, respiratory variables, pulse oximetry, end-tidal CO_2 and arterial blood gas results. Ventilatory data and electrical signals from the NAVA catheter were recorded continuously and electronically by a computer with a specifically designed software program. We considered delivery of faster triggering and cycling off as consistent with superior synchrony.

Continuous variables were reported as mean ± standard deviation, unless otherwise stated. Student's t test and Wilcoxon rank sums were used to compare parametric and nonparametric variables, respectively. We considered a $p < .05$ as statistically significant. Calculations were performed, using the computer program JMP version 5.1 for windows (SAS Institute, Cary, NC).

RESULTS

A total of 16 infants and children were enrolled in the study. The mean age was 9.7 mos (range = 2 days–4 yrs) and mean weight was 6.2 kg (range = 2.4–13.7 kg). There was a preponderance of children with cardiac pathology in the study population reflecting the workload of the unit. All but one patient was receiving continuous intravenous sedative medication. Demographic data, patient characteristics, and type and dose of sedation are shown in Table 1.

In NAVA mode, operating on a "first serves first" basis with the pneumatic trigger, synchrony was improved with neural triggering for 65% (±21%, $p < .001$) and "cycling-off" for 85% (±8%, $p = .0001$) of all breaths. Triggering and

Table 1. Patient characteristics and sedation

Patient No.	Gender	Age	Weight, kg	Diagnosis	Pao_2/Fio_2	Analgesia, μg/kg/h	Sedation μg/kg/h
1	M	9 mos	8.7	Hypoplastic left heart	122	Morphine 36	—
2	M	9 mos	7.5	Tetralogy of Fallot	185	Morphine 40	—
3	F	14 mos	9.4	Pseudomonas Meningitis	555	Morphine 32	Midazolam 60
4	F	22 days	2.7	TGA	299	Morphine 20	—
5	M	4 days	3.2	Post Coarctation repair	264	Morphine 20	—
6	M	7 days	3.9	Cardiomyopathy	150	—	—
7	M	8 days	3.3	Critical aortic stenosis	324	Morphine 8	—
8	M	2 days	3.3	Diaphragmatic hernia	260	Morphine 12	—
9	M	4 yrs	13.7	Hemolytic anemia	167	Morphine 8	—
10	F	14 days	2.8	Transposition of the great arteries	80	Morphine 20	—
11	F	2 mos	2.4	Hypoplastic left heart	315	Morphine 12	—
12	F	2 mos	3.8	Hypoplastic left heart	195	Morphine 40	—
13	F	14 days	4.0	Hypoplastic left heart	237	Morphine 8	—
14	F	2 yrs	10	Cardiomyopathy	378	Morphine 60	—
15	M	9 mos	4.8	Pneumonia	295	Morphine 12	Midazolam 200
16	M	3 yrs	15	Acute respiratory distress syndrome	231	Remifentanil 66	—

cycling-off results for individual patients are shown in Table 2.

The peak inspiratory pressure for the group, as they were in NAVA mode, was significantly lower than in PSV mode, with a 28% decrease after 30 mins ($p = .0026$) and 32% decrease after 3 hrs ($p < .001$). Individual patient's peak inspiratory pressures in each mode are displayed in Figure 1. Mean airway pressure was reduced by 11% at 30 mins ($p = .13$) and 9% at 3 hrs ($p = .31$) in NAVA mode, although this did not reach statistical significance. Peak pressure, respiratory rate, and expired minute volume after 30 mins in PSV mode and after, 1 and 3 hrs in NAVA mode are shown for individual patients in Table 3.

Patient hemodynamics and gas exchange remained stable for the study period, with no significant differences between pressure support and NAVA mode (Table 4). No adverse patient events or device effects were noted.

Table 2. Neural triggering and cycling off for patients in NAVA mode

Patient No.	Neural trigger, %	Neural cycle off, %
1	22.1	76.1
2	61.8	64.4
3	23.4	91.0
4	73.0	92.4
5	60.2	87.2
6	72.0	87.9
7	79.2	86.2
8	89.7	93.9
9	46.1	79.4
10	91.6	83.7
11	80.5	88.3
12	81.8	91.8
13	60.0	88.8
14	61.5	81.5
15	50.6	73.5
16	85.3	91.2

NAVA, neurally adjusted ventilatory assist.

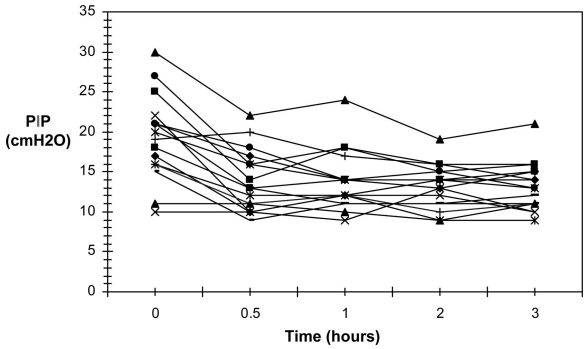

Figure 1. Changes in individual patient peak inspiratory pressure (*PIP*) following commencement of neurally adjusted ventilatory assist (0 hr) after an initial 30-min period of pressure-support ventilation.

DISCUSSION

In our pediatric ICU population, ventilating patients in NAVA mode was associated with improved patient-ventilator synchrony and lower peak airway pressures when compared with PSV. This, while maintaining patient hemodynamic and ventilatory stability. To our knowledge, this is the first published comparison of PSV and NAVA in a pediatric population.

It has been previously demonstrated, that pneumatically cycled, synchronized modes of ventilation, fail to achieve a good match between the patient's neural effort and the supporting mechanical breath. Beck et al demonstrated marked patient-ventilator asynchrony in infants weaning on synchronized intermittent mandatory ventilation mode, using EAdi to identify neural effort (22). This mismatch was most pronounced in expiration, a finding supported by Kondili et al in adults using an indirect mechanical index of muscle activation (23). Furthermore, animal work by Beck et al comparing NAVA and PSV in rabbit models demonstrated significant asynchrony in PSV mode (24), most notably at higher support pressures. They proposed the underlying mechanism to be continued delivery of assist into the neural expiratory phase, with a subsequent reflex prolongation of the neural expiratory time. This approach, particularly at higher respiratory rates—such as those seen in children—leads to dynamic hyperinflation with secondary delay or failure of pneumatic triggering as proposed by Younes et al (25).

We demonstrated superior synchrony in NAVA mode compared with PSV. This superiority was most pronounced during cycling off. The percent of neurally acti-

Table 3. Peak pressures, respiratory rate, and expired minute volume in pressure support and neurally adjusted ventilatory assist mode

Patient No.	PS, PIP, cm H_2O, 30 min	PS, RR, BPM, 30 min	PS, Mve, L/min, 30 min	NAVA, PIP, cm H_2O, 1 hr	NAVA, RR, BPM, 1 hr	NAVA, Mve, L/min, 1 hr	NAVA, PIP, cm H_2O, 3 hr	NAVA, RR, BPM, 3 hr	NAVA, Mve, L/min, 3 hr
1	17	28	1.9	12	28	2.1	14	22	1.3
2	25	22	2.0	18	18	1.6	16	22	1.9
3	11	26	0.4	10	24	0.5	11	29	0.5
4	22	20	0.3	9	26	0.4	10	30	0.3
5	16	20	0.4	12	40	0.5	9	33	0.4
6	21	44	0.7	14	44	0.7	16	43	0.6
7	16	73	0.9	12	65	0.8	11	52	1.1
8	15	50	0.7	11	43	0.6	11	35	0.5
9	21	20	2.6	11	26	2.2	12	23	2.3
10	21	32	0.3	14	40	0.1	15	40	0.1
11	18	47	0.5	14	45	0.4	15	45	0.5
12	30	32	0.6	24	46	0.7	21	45	0.8
13	10	58	0.8	12	33	0.6	10	36	0.6
14	20	19	1.3	14	28	1.2	13	27	1.3
15	27	15	0.6	18	26	0.5	13	38	0.9
16	19	47	4.0	17	31	2.5	14	38	2.8

PS, pressure support; NAVA, neurally adjusted ventilatory assist; PIP, peak inspiratory pressure. RR, respiratory rate; BPM, beats per minute; Mve, expired minute volume.

Table 4. Group hemodynamic and ventilatory parameters on pressure support and neurally adjusted ventilatory assist

Variable	PS, 30 min	NAVA, 1 hr	*p* Value	NAVA, 3 hr	*p* Value
HR, bpm	126 ± 19	121 ± 21	0.51	120 ± 23	0.4
RR, bpm	35 ± 17	35 ± 12	0.74	35 ± 9	0.5
Vte, ml	41 ± 38	36 ± 32	0.58	37 ± 36	0.4
MV, L/min	1.12 ± 1.03	0.96 ± 0.74	0.83	0.99 ± 0.76	0.91
PetCO2, Torr [Kpa]	39 ± 6 [5.2 ± 0.8]	38 ± 5 [5.1 ± 0.7]	0.79	40 ± 5 [5.4 ± 0.7]	0.33
PaCO2, Torr [Kpa]	45 ± 7 [6.0 ± 1.0]	42 ± 7 [5.6 ± 0.9]	0.65	46 ± 8 [6.1 ± 1.1]	0.94
PaO2, Torr [Kpa]	70 ± 21 [9.4 ± 2.8]	88 ± 30 [11.8 ± 4.0]	0.11	72 ± 20 [9.6 ± 2.7]	0.75
Sats, %	93 ± 9	94 ± 7	0.56	94 ± 8	0.33

HR, heart rate; bpm, beats per minute; RR, respiratory rate; MVe, expired minute volume; Vte, expired tidal volume; $PetCO_2$, end-tidal CO_2; Sats, oxyhemoglobin saturation by pulse oximetry.

vated mechanical breaths was only modestly higher than those pneumatically triggered. The reasons for poor neural triggering hinge on problems with signal acquisition, as changes in the EAdi must always precede pneumatic changes. The reasons for this in our study may be varied. No technology is perfect and further modifications were made to the neural trigger based on our findings. Additionally, operator experience may be a factor (the first and third patients studied had the lowest % triggering).

Synchrony is in itself a key factor in decreasing the EAdi (22), and consequently the support pressure in NAVA mode. Previous work has demonstrated that the EAdi often does not decrease in pneumatically cycled support modes. Beck et al found that asynchrony was present during every mandatory breath in synchronized intermittent mandatory ventilation mode, in weaning infants, with no reduction in the amplitude of EAdi when compared with the unsupported pre- and postmandatory effort (22). In more recent work, the same group demonstrated that PSV only offloaded the diaphragm within a narrow range, with increasing support pressures leading to an increase in EAdi associated with worsening synchrony (24). This may explain why the most marked decreases in peak pressure in our group were observed in those on greatest levels of assist. Alternatively, these patients may have been overassisted in PSV, and this was corrected on activation of NAVA, which has been proven to protect against this problem (26). Peak pressure changes for individual patients are shown in Figure 1.

Asynchronous delivery of support breaths interferes with patient's natural breathing pattern, leading to a decrease in the respiratory rate (22). Although our data showed no change in the group's mean respiratory rate, the median breath frequency did reveal a trend toward a higher rate (data not shown). In this way, the patient may demand a minute volume delivered as smaller tidal volumes, requiring lower pressure assist, at an increased frequency. The potential exists for such a response to lead to an increase in dead space ventilation. However, the Hering-Breuer reflex should, in NAVA mode, protect against this. Our study did not demonstrate a statistically significant difference in expired tidal volume.

The observed reduction in airway pressure was consistent with the findings of previous work with animal acute lung injury models (24, 27). There are several potential mechanisms underlying the attainment of a minute ventilation in NAVA similar to PSV but at a significantly reduced peak airway pressure. In addition to those mechanisms outlined above, it should be remembered that in NAVA mode the magnitude of the delivered pressure is the product of the EAdi amplitude and a user adjustable proportionality factor. The result is that assist is adjusted breath by breath, according to the patient demand, rather than an arbitrary fixed pressure being delivered per patient effort, as is the case with PSV. The patient "requests" only that pressure required under the influence of previously described, vagally mediated reflexes, which protect optimum lung recruitment (28, 29). It has been proposed that this technology is best applied to a neonatal population, as they have the most pronounced vagal drive (30). When analyzed as a subgroup, neonatal mean neural triggering and cycling off was greater than the group as a whole at 75% (±12.7%) and 89% (±3.5%), respectively. However, mean and peak inspiratory pressures remained the same as the grouped values. Furthermore, mean expired tidal volume remained unchanged in this subgroup, between each mode.

Perhaps of foremost importance, as NAVA becomes available on the ICU floor, is that we did not observe any adverse patient events or device effects. Additionally, the neural signal remains a viable trigger despite the concurrent use of sedative medication, an absolute prerequisites before any consideration can be given to the widespread clinical application of this technology.

Our study had a number of methodologic limitations. We used a sensitive pressure, rather than a flow trigger. The latter has previously been proven to provide superior reaction times to patient efforts (31). A pressure trigger of -1 cm H_2O was selected, however, to provide a sensitive pneumatic comparison, without the risk of auto-triggering. As the pneumatic trigger remained active during the NAVA phase of the study, artificially activated breaths would have confounded accurate analysis. We identify, however, a comparison of neural and flow triggering in children as an area of future investigation.

The exposure times to PSV and NAVA were unbalanced. As patients were established in a pneumatically triggered mode of ventilation before study commencement, we assumed a steady state had been achieved at the onset of data collection. Therefore, 30 mins was allocated for PSV recordings, reserving a longer interval for the novel mode. Additionally, a crossback phase would have further strengthened our methodology.

The selection of pressure-support settings was not standardized; rather, existing settings, which had been selected on clinical grounds, directed the degree of pressure support in PSV mode.

Although the level of pneumatic cycle-off was not optimized to best fit the time constants of the individual patient's re-

spiratory system, the choice of a fixed cycle-off of 25% of peak flow seemed reasonable and in line with common clinical practice.

With regard to avenues of future research, we identify that the ability to variably offload the respiratory muscles may prove of clinical use in improving the hemodynamic performance of patients, particularly those with a dependence on increased preload, where reducing respiratory muscle offload may provide an intermediary measure between full positive pressure and negative pressure ventilation. Additionally, exploring the impact of this new mode on energy expenditure and oxygen consumption may prove revealing.

CONCLUSIONS

In a neonatal and pediatric ICU population, ventilation in NAVA mode was associated with improved patient-ventilator synchrony and lower peak airway pressure when comparing pressure support with a pneumatic trigger. Ventilating patients in this new mode seems to be safe and well tolerated.

ACKNOWLEDGMENTS

We thank the nursing and physiotherapy teams of the pediatric ICU for their collaboration during this study.

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