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Neurally adjusted ventilatory assist in patients with critical illness-associated polyneuromyopathy

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Abstract *Purpose:* Diaphragmatic electrical activity (EA_{di}), reflecting respiratory drive, and its feedback control might be impaired in critical illness-associated polyneuromyopathy (CIPM). We aimed to evaluate whether titration and prolonged application of neurally adjusted ventilatory assist (NAVA), which delivers pressure (P_{aw}) in proportion to EA_{di}, is feasible in CIPM patients. *Methods:* Peripheral and phrenic nerve electrophysiology studies were performed in 15 patients with clinically suspected CIPM and in 14 healthy volunteers. In patients, an adequate NAVA level (NAVAal) was titrated daily and was implemented for a maximum of 72 h. Changes in tidal volume (V_t) generation per unit of EA_{di} (V_t/EA_{di}) were assessed daily during standardized tests of neuroventilatory efficiency (NVET). *Results:* In patients (median [range], 66 [44–80] years), peripheral electrophysiology studies confirmed CIPM. Phrenic nerve latency (PNL) was prolonged and diaphragm compound muscle action potential (CMAP) was reduced compared with healthy volunteers ($p < 0.05$ for both). NAVAal could be titrated in all but two patients. During implementation of NAVAal for 61 (37–64) h, the EA_{di} amplitude was 9.0 (4.4–15.2) μV, and the V_t was 6.5 (3.7–14.3) ml/kg predicted body weight. V_t, respiratory rate, EA_{di}, $PaCO_2$, and hemodynamic parameters remained unchanged, while PaO_2/FiO_2 increased from 238 (121–337) to 282 (150–440) mmHg ($p = 0.007$) during NAVAal. V_t/EA_{di} changed by −10 (−46; +31)% during the first NVET and by −0.1 (−26; +77)% during the last NVET ($p = 0.048$). *Conclusion:* In most patients with CIPM, EA_{di} and its feedback control are sufficiently preserved to titrate and implement NAVA for up to 3 days. Whether monitoring neuroventilatory efficiency helps inform the weaning process warrants further evaluation.

Keywords Positive pressure respiration · Breathing pattern · Diaphragm · Electromyography · Respiratory therapy · Polyneuropathy

Introduction

Critical illness-associated polyneuromyopathy (CIPM) is common in long-stay intensive care patients and contributes to ventilator dependency and prolonged rehabilitation [1–5]. Major alterations of the phrenic nerve, including axonal degeneration [6], increased phrenic nerve latency (PNL), and decreased diaphragm compound muscle action potential (CMAP), have been described in CIPM, indicating dysfunction of the phrenic nerve–diaphragm unit [7–10].

Neurally adjusted ventilatory assist (NAVA) delivers pressure to the airways (P_{aw}) in synchrony and linear proportionality to the electrical activity of the diaphragm (EA_{di}) [11], which is a validated measure of global respiratory drive [12–15]. A number of features unique to NAVA may be beneficial in patients with CIPM. For example, using EA_{di} to control the ventilator not only guarantees synchrony with the patient's respiratory demand in each neural breath independent of muscular strength and assist level [16–20], but also allows individual determination of an adequate level of respiratory muscle unloading based on neural feedback control of EA_{di} without overly suppressing respiratory drive [16, 21–27]. Using an assist level titrated to the individual's needs could be helpful in preventing both disuse atrophy and fatigue of respiratory muscles. Furthermore, monitoring neuro-ventilatory efficiency, i.e., tidal volume (V_t) per unit of EA_{di}, provides information on how the patient's ability to translate neural drive into V_t generation progresses over time [24].

NAVA depends on the integrity of complex feedback systems that control EA_{di} [12–15]. It is not known to what extent the function of the phrenic nerve–diaphragm unit is affected in spontaneously breathing CIPM patients and whether the EA_{di} in these patients can be used to control a ventilator.

We aimed to assess the degree of neuromuscular impairment in a group of CIPM patients compared to healthy volunteers and to examine whether titration and application of NAVA for up to 3 days are feasible in these patients.

Methods

Patients and study design

The protocol was approved by the Ethics Committee of the Canton of Bern, Switzerland. Patients were recruited from February 2008 to October 2008. Written informed consent was obtained from the next of kin and from an independent physician. For detailed methods and exclusion criteria see the electronic supplementary material (ESM).

Inclusion criteria

Mechanical ventilation for longer than 48 h, presence of at least one risk factor known to be associated with CIPM, and clinical suspicion of CIPM indicated by a score less than 48 in the Medical Research Council (MRC) scale assessed in 12 muscle groups [28].

NAVA methods

NAVA was used as previously described [11, 16, 22, 24, 25, 29]. Briefly, the EA_{di} was derived via a modified nasogastric feeding tube (Maquet, Solna, Sweden), processed [11, 15, 30–32], multiplied by an adjustable proportionality constant (NAVA level), and used to control P_{aw} delivered by the ventilator (Servo^{i} 3.02.01, Maquet, Solna, Sweden).

Study protocol

Patients were studied in supine position with their head elevated by 30°. Sedation targets according to the Richmond agitation sedation scale (RASS) [33] were prescribed by the clinical team. A schematic study protocol is provided in Fig. E1 (ESM).

Electrophysiological studies

Peripheral nerve conduction and direct muscle stimulation studies were performed before initiation and after completion of the NAVA trial using procedures previously described [34]. The phrenic nerve was stimulated supramaximally with surface electrodes at the posterior edge of the sternocleidomastoid muscle in expiration [35]. CMAPs of the diaphragm were recorded using the electrodes of the nasogastric feeding tube. The most proximally located electrode served as the reference. The electrode depicting the largest CMAP was chosen as the active electrode. Latencies and amplitudes of the maximal CMAP were analyzed off-line. Normal values using the same equipment and technique were established in 14 healthy volunteers.

Baseline measurements and implementation of NAVA

Baseline measurements were performed using the ventilator settings prescribed by the clinical team. NAVA was used for a maximum of 72 h. Steps 1–3 were performed daily.

Step 1: NAVA level titration

A NAVA level titration was performed as previously described [22–24]. Briefly, the NAVA level was reduced

to a minimum of 0 $cmH_2O/\mu V$ (NAVAzero), resulting in virtually no assist. When EA_{di} had stabilized at a maximum, the NAVA level was increased every 20 s in steps of 0.1 $cmH_2O/\mu V$. During the entire titration, the trend graphs for P_{aw} and V_t displayed on the ventilator screen were observed. Using the same procedure, we previously described a characteristic two-phased response, i.e., a transition from an initial steep increase in P_{aw} and V_t (1st response) to a less steep increase in P_{aw} and V_t (2nd response) [22–24]. On the basis of the interpretation that the patients' response pattern would reflect a transition from an insufficient assist level (1st response) to an assist level that meets the subject's respiratory demand (2nd response) [23], a NAVA level early after the transition from the first to the second response was identified by visual inspection of the P_{aw} and V_t trend graphs and was termed adequate assist level (NAVAal).

Step 2: standardized test of neuro-ventilatory efficiency (NVET)

Neuro-ventilatory efficiency refers to the relation between the patient's neural inspiratory effort and the resulting tidal volume (V_t/EA_{di}). Standardized NVETs were performed daily while withholding administration of sedative drugs as part of routine care. Throughout all NVETs an inspiratory assist of 7 cmH_2O (or 3 cmH_2O if tracheotomized) was applied. Each NVET lasted for a maximum of 60 min or was terminated earlier when discontinuation criteria as suggested by MacIntyre et al. were fulfilled [36].

Step 3: implementation of NAVAal

NAVAal as identified in step 1 was implemented until re-titration on the next day. Another mode of ventilation was only used if administration of neuromuscular blocking agents was required or if signs of respiratory failure were detected. Standard procedures, nursing, and physiotherapy were not restricted during the study.

Measurements

P_{aw}, airflow, and EA_{di} were recorded continuously during all NAVA level titrations and during all NVETs, and every 6 h during application of NAVAal. Arterial blood gases were measured twice a day. The amount of sedatives administered was recorded for 48 h prior to and during NAVA.

Data analysis and calculated variables

Breath-by-breath analysis was performed off-line using custom-made software (Neurovent Research Inc., Toronto, Canada) as previously described [24]. For interindividual comparison, EA_{di} is expressed for each patient as a percentage of the maximum inspiratory EA_{di} at the lowest NAVA level during the titration (%NAVAzero).

Statistical analysis

Statistical analysis was performed with SigmaStat™ (version 3.11, Systat Software Inc., San Jose, CA). Data are presented as mean ± SD or median (range) as indicated by assessment of normal distribution (Kolmogorov–Smirnov test). Repeated measurements were analyzed using one- or two-way analysis of variance (ANOVA) or ANOVA on ranks. For two-way ANOVA a between-group factor was chosen as indicated and time was the repeated-measures factor. Tukey's method was used for post-test, pairwise multiple-comparison procedures. Groups with paired data were compared with the *t* test or Wilcoxon signed-rank test. A p value less than 0.05 was considered significant.

Results

Fifteen patients (age 66 [44–80] years; 7 females; APACHE II 19 [10–45]) with clinically suspected CIPM (Table 1) and 14 healthy volunteers who reported no neuromuscular disease were studied. Patients stayed in the intensive care unit for 29 (10–188) days, and were ventilated for 6 (2–25) days prior to enrolment and for 25 (7–185) days in total.

NAVAal was identified and successfully implemented in 13 patients. In patient no. 10 NAVA was terminated after 6.5 h because of high respiratory drive that could not be sufficiently suppressed by increasing the NAVA level, resulting in excessively high P_{aw} and progressive respiratory distress. In patient no. 15 NAVA was terminated after 16 h because of diaphragm myocloni that repeatedly triggered the ventilator's backup mode. These two patients are not included in the analysis of repeated measurements. One patient was transferred to another hospital after 37 h on NAVAal and was lost to follow-up (data included in the analysis).

Electrophysiological studies

At both examinations, motor nerve studies from the median and peroneal nerves showed CMAP amplitudes lower than normal, whereas nerve conduction velocities were within normal limits. Sensory nerve action potentials from the median and sural nerves were severely abnormal or even absent in all patients. Screening for neuromuscular transmission defects by repetitive

Table 1 Patient characteristics

Patient no.	Gender	Age (years)	APACHE II	PBW (kg)	DOIV (days)	Main diagnosis	MRC before NAVA	MRC last day on NAVA	Pressure support (cmH_2O)	PEEP (cmH_2O)	PaO_2/FiO_2	$PaCO_2$ (mmHg)	V_t (ml/kg PBW)	RR (bpm)	RASS	Total hours on NAVAal
1	M	72	19	78	13	Septic shock	4	13	12	10	177	30	10.1	25	–4	51.2[a]
2	F	73	13	47	6	Septic shock	38	36	22	10	320	37	7.5	26	0	61.7[c]
3	F	60	10	56	8	Post cardiac surgery	42	26	24	5	285	34	6.3	30	0	57.3[b]
4	M	45	20	65	9	Heart failure	38	56	20	10	164	58	8.1	11	0	64.3[a]
5	M	74	24	65	3	Septic shock	36	36	16	5	227	54	5.4	32	0	61.3[a]
6	F	63	10	42	6	Post cardiac surgery	18	32	18	10	140	36	6.2	33	–1	38.6[b]
7	M	66	16	65	3	Delirium	12	36	15	15	106	29	11.0	18	−2	60.9[c]
8	F	57	27	51	5	Septic shock	24	36	14	5	300	36	13.5	14	−2	36.8[d]
9	M	71	19	74	4	Septic shock	4	32	15	7	233	29	9.6	24	−3	62.4[c]
10	F	51	17	65	2	Septic shock	18	48	24	10	154	37	8.3	21	0	10.3[e]
11	M	44	36	63	13	Pancreatitis	28	34	28	10	289	28	12.1	13	−1	60.5[c]
12	M	62	23	74	14	Septic shock	32	38	20	5	265	42	7.2	18	0	61.5[c]
13	F	66	23	60	4	Abdominal abscess	36	0	18	8	185	36	7.3	17	−1	53.8[c]
14	F	77	18	60	6	Pancreatitis	36	36	28	10	130	62	6.2	16	−1	61.0[c]
15	M	80	45	69	25	Bilateral pneumonia	0	0	24	5	162	37	7.1	25	−5	16.0[e]

Before implementing NAVA, ventilator settings for pressure support (PSV) and for positive end-expiratory pressure (PEEP) were used as defined by the treating physician *APACHE II* acute physiology and chronic health evaluation score, *PBW* predicted body weight, *DOIV* days on invasive mechanical ventilation before enrolment, *MRC* Medical Research Council (MRC) scale assessed in 12 muscle groups (maximum 60 points; CIPM is likely with a MRC score <48; an MRC of zero indicates that no muscle movements were observed) [28], *Day 0* day before implementing NAVA, *Last day* last day on NAVA, PaO_2 arterial oxygen tension, FiO_2 fraction of inspired oxygen, $PaCO_2$ arterial carbon dioxide tension, V_t tidal volume, *RR* respiratory rate, *RASS* Richmond agitation sedation scale score [33], *NAVAal* adequate level of neurally adjusted ventilatory assist

[a] Successful extubation during NAVA

[b] Failed extubation during NAVA

[c] Return to PSV after completing NAVA

[d] Lost to follow-up

[e] Termination of NAVA and return to PSV within the first 24 h due to excessive respiratory drive (patient 10) and diaphragm myocloni (patient 15)

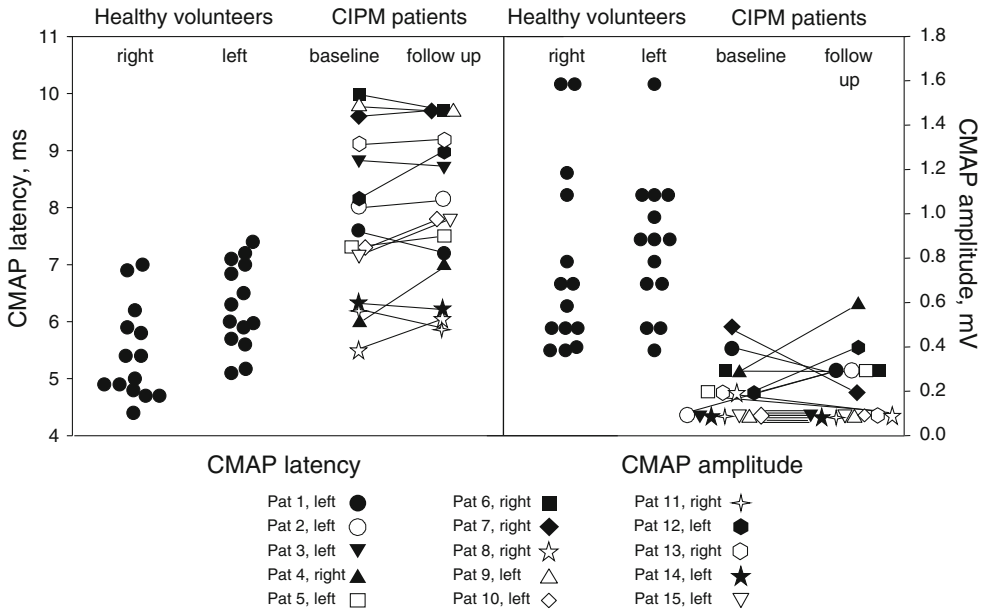

Fig. 1 Compound muscle action potentials (CMAP) of the diaphragm were recorded using the electrodes of a modified nasogastric feeding tube after transcutaneous, cervical stimulation of the phrenic nerve. Phrenic nerve latency (PNL) and CMAP amplitude were determined off-line. Each *data point* represents the average of three measurements. For each patient, the side of cervical stimulation is indicated in the *symbol legend* (*left or right*). Normal values were established in 14 healthy volunteers. PNL was higher and CMAP was lower in our group of 15 patients with established critical illness-associated polyneuromyopathy (CIPM) compared with healthy volunteers. There was no change over time for both parameters in CIPM patients

stimulation at 3 Hz of the median nerve with recording from the abductor pollicis brevis muscle was normal in all patients. Electromyography of the brachioradialis and tibialis anterior muscle revealed fibrillation potentials and positive sharp waves in 3 patients at baseline and in 10 patients at follow-up. Additionally, for the brachioradialis muscle direct muscle stimulation and calculation of the ratio of the nerve and muscle evoked CMAP were performed [34]. In all patients ratios were between 0.7 and 1.0 in both examinations. The electrophysiology findings indicate that CIPM was present in all patients.

Latencies and amplitudes of diaphragm CMAP in healthy volunteers and in patients are given in Fig. 1. CMAP latency was 5.2 ms (4.4–7.0, right side) and 6.2 ms (5.1–7.4, left side) in healthy volunteers and 7.6 ms (5.5–10.0) in CIPM patients at baseline ($p < 0.001$ vs. both sides in volunteers). CMAP amplitude was 0.9 mV (0.4–1.6, right side) and 0.7 mV (0.4–1.6, left side) in healthy volunteers and 0.2 mV (0.1–0.5) in CIPM patients at baseline ($p < 0.001$ vs. both sides in volunteers). Both parameters remained unchanged at follow-up in patients.

Changes observed during NAVAal

In 13 patients NAVAal was implemented for a total of 61 (37–64) h. Changes in cardio-respiratory parameters and clinical scores observed during NAVAal are given in Table 2, and Figs. 2 and E2 (ESM).

NAVA level titrations

Figure 3 depicts a typical example of a NAVA level titration. Such a titration was performed in 15, 13, 11, and 10 patients at 0, 24, 48, and 72 h, respectively (Fig. E3, ESM). V_t and P_{aw} did not change whereas EA_{di} further decreased after reaching NAVAal despite substantial increases in the NAVA level (Table E1, ESM). In those 11 patients who had a NAVA level titration procedure at the beginning of each of the three study days, NAVAal was 1.4 (1.2–2.2) $cmH_2O/\mu V$ at 0 h, 1.7 (1.4–2.3) $cmH_2O/\mu V$ at 24 h, and 1.6 (1.4–2.5) $cmH_2O/\mu V$ at 48 h ($p = 0.332$).

Implementation of NAVAal

From the first to the last measurement on NAVA, PaO_2/FiO_2 increased ($p = 0.007$), while V_t, RR, mean inspiratory EA_{di}, mean inspiratory P_{aw} above PEEP, V_t/EA_{di}, $PaCO_2$, heart rate, and mean arterial pressure remained unchanged ($p > 0.05$ for all) (Table 2).

The average V_t during the entire NAVA period was 6.5 (3.7–14.3) ml/kg predicted body weight (PBW) and

Table 2 Parameters assessed during PSV and during implementation of NAVA

Median (min;max) or mean (±SD)	PSV	NAVAal				ANOVA *p*
	$n = 13$	0 h, $n = 13$	24 h, $n = 13$	48 h, $n = 11$	72 h, $n = 11$	
Respiratory parameters						
NAVAal ($cmH_2O/\mu V$)	–	1.6 ± 0.6	1.9 ± 0.6	1.9 ± 0.8	1.7 ± 0.8	n.s.
SaO_2 (%)	97 (94;99)	95 (92;98)	97 (93;99)	95 (93;96)	94 (90;96)	0.121
PaO_2/FiO_2 ratio	217 ± 71	215 ± 79	219 ± 66	253 ± 77	289 ± 31	0.007
$PaCO_2$ (mmHg)	36 (29;62)	39 (29;68)	39 (35;74)	40 (33;68)	40 (29;59)	0.844
Coefficient of variation for V_t (%)	7.6 (1.9;37.0)	17.5 (12.2;75.3)*	16.6 (10.9;51.9)	19.7 (11.7;26.9)	15.0 (13.0;57.8)	0.615
Minute ventilation (l/kg PBW/min)	0.19 ± 0.05	0.2 ± 0.06	0.19 ± 0.06	0.19 ± 0.05	0.19 ± 0.05	0.494
End-expiratory P_{aw} (cmH_2O)	8.1 ± 2.9	8.6 ± 3.0	9.6 ± 3.2	9.6 ± 3.1	9.4 ± 3.2	0.197
Mean inspiratory P_{aw} (cmH_2O)	25.5 ± 5.4	17.3 ± 4.5*	15.9 ± 3.2	17.0 ± 4.1	17.2 ± 4.5	0.316
Maximal inspiratory P_{aw} (cmH_2O)	29.5 ± 5.3	26.2 ± 6.3	23.8 ± 4.6	25.4 ± 5.4	25.8 ± 5.3	0.428
Mean inspiratory EA_{di} (μV)	3.0 ± 2.9	5.9 ± 2.7*	4.9 ± 2.2	4.7 ± 2.4	5.3 ± 2.1	0.976
Maximal inspiratory EA_{di} (%NAVAzero)	38.5 ± 32.3	71.2 ± 22.0*	68.1 ± 34.9	70.9 ± 30.5	70.0 ± 26.2	0.974
Insp. electrical energy expenditure (μV s/min)	56.3 ± 58.6	118.1 ± 60.3*	100.3 ± 60.0	100.5 ± 66.1	113.2 ± 61.0	0.470
V_t/EA_{di} (ml/kg PBW/μV)	5.9 ± 4.0	1.6 ± 0.8*	1.6 ± 0.8	1.7 ± 1.0	1.5 ± 0.7	0.775
T_i(neural)/T_{tot}(neural)	0.26 ± 0.11	0.33 ± 0.06	0.33 ± 0.11	0.33 ± 0.09	0.34 ± 0.08	0.972
T_i(neural) (s)	0.62 ± 0.22	0.73 ± 0.11	0.76 ± 0.15	0.73 ± 0.11	0.73 ± 0.10	0.694
Hemodynamic and metabolic parameters						
Heart rate (bpm)	95 (70;115)	100 (66;115)	94 (67;122)	93 (66;115)	93 (82;127)	0.260
Mean arterial pressure (mmHg)	64 (42;77)	64 (47;90)	65 (53;80)	67 (61;79)	63 (53;76)	0.408
CVP (mmHg)	10 ± 5	9 ± 4	11 ± 4	10 ± 4	10 ± 5	0.083
Arterial pH	7.47 (7.36;7.50)	7.42 (7.37;7.49)	7.44 (7.34;7.48)	7.44 (7.36;7.49)	7.44 (7.36;7.49)	0.279
Arterial lactate concentration (mmol/l)	1.3 (0.7;3.0)	1.3 (0.7;2.6)	1.4 (0.6;2.1)	1.3 (0.6;2.1)	1.3 (0.6;2.1)	0.368
Clinical scores						
RASS	−0.9 ± 0.9	−0.9 ± 0.9	−0.9 ± 1.6	−0.3 ± 0.9	−0.2 ± 0.7	0.259
MRC	24 ± 14	24 ± 14	28 ± 13	28 ± 13	30 ± 16	0.005
GCS	14 (9;15)	14 (9;15)	14 (7;15)	15 (8;15)	15 (7;15)	0.074
CAM–ICU % delirious	33	33	33	33	27	
SOFA	8.5 ± 3.8	8.2 ± 3.5	6.7 ± 2.9	5.9 ± 3.0	5.3 ± 2.8	0.001

Parameters measured during pressure support ventilation (PSV) and during neurally adjusted ventilatory assist (NAVA) using the NAVA level identified as adequate during the daily NAVA level titration procedure (NAVAal). The level of positive end-expiratory pressure (PEEP) was determined by the clinical team during both conditions. $n = 13$ unless otherwise indicated. Data are reported as group mean (±SD) or as group median (min; max)

SaO_2 arterial oxygen saturation, *PaO_2* oxygen tension in arterial blood, *FiO_2* fraction of inspired oxygen, *$PaCO_2$* carbon dioxide tension in arterial blood, *RR(neural)* neural respiratory rate, *V_t* tidal volume, *PBW* predicted body weight, *P_{aw}* airway pressure, *EA_{di}* electrical activity of the diaphragm, *$\%NAVA_{zero}$* percentage of the value obtained when the lowest NAVA level (NAVAzero) was applied during the NAVA level titration, *ANOVA* analysis of variance for repeated measurements during NAVA, *T_i(neural)* neural inspiratory time, *T_{tot}(neural)* total neural inspiratory cycle time. Inspiratory electrical energy expenditure was calculated as mean inspiratory $EA_{di} \times T_i$(neural) × RR(neural), *GCS* Glasgow coma scale, *CAM-ICU* confusion assessment method for ICU patients [51], *MRC* Medical Research Council scale assessed in 12 muscle groups [28], *RASS* Richmond agitation sedation scale score [33], *SOFA score* sequential organ failure assessment score, *n.s.* not significant

* $p < 0.05$ PSV baseline versus NAVA at 0 h

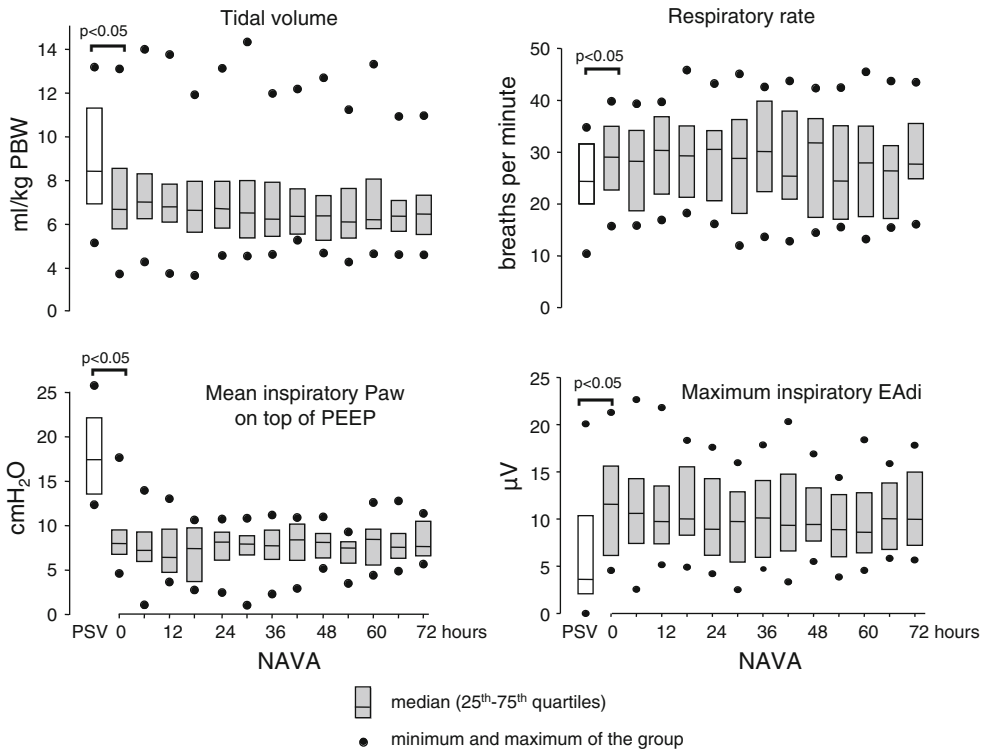

Fig. 2 Changes in tidal volume (V_t), respiratory rate, mean inspiratory airway pressure (P_{aw}) on top of positive end-expiratory pressure (PEEP), and maximal inspiratory electrical activity of the diaphragm (EA_{di}) when implementing NAVA for 72 h. V_t and mean inspiratory P_{aw} on top of PEEP decreased, while respiratory rate and EA_{di} increased when switching from PSV to NAVA. All parameters remained unchanged when NAVA was implemented for a maximum of three consecutive days

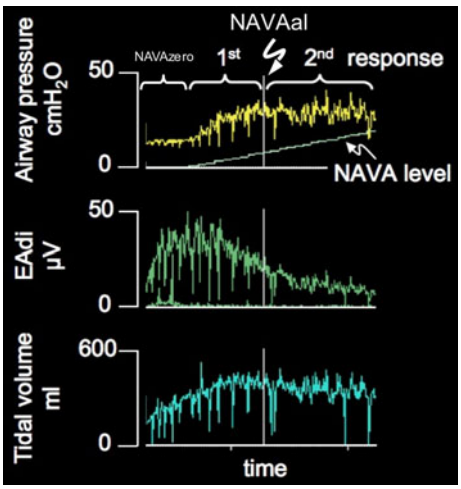

Fig. 3 NAVA level titration in patient no. 11 at baseline. The method used to identify an adequate NAVA level (NAVAal) during systematic increases in the NAVA level has been described previously [22–24]. Briefly, the NAVA level was first reduced to a minimal level of 0 $cmH_2O/\mu V$ (NAVAzero), resulting in virtually no assist and in an increase in the EA_{di}. When EA_{di} had stabilized at a maximum, the NAVA level was increased every 20 s in steps of 0.1 $cmH_2O/\mu V$. A NAVA level early after the transition from an initial steep increase in P_{aw} and V_t (1st response) to a less steep increase in P_{aw} and V_t (2nd response) was identified by visual inspection of P_{aw} and V_t trend graphs displayed on the ventilator screen, and was termed adequate assist level (NAVAal)

was positively correlated with both CMAP latency ($r^2 = 0.305$; $p = 0.033$) and CMAP amplitude ($r^2 = 0.715$; $p = 0.002$) at baseline (Fig. 4). The electrical energy expenditure, a parameter reflecting the respiratory drive spent to generate minute ventilation, did not change during implementing NAVAal. PEEP was 9.7 (4.8–14.7) cmH_2O when starting NAVAal and remained unchanged at 9.0 (5.7–16.0) cmH_2O during the last measurements on NAVAal ($p = 0.25$).

During NAVA the MRC score increased, while the SOFA score decreased, and RASS, GCS, and CAM–ICU remained unchanged (Table 2).

In those patients that received fentanyl, propofol, or midazolam during the 48 h preceding and/or during NAVA the amounts were less during NAVA for fentanyl ($n = 13$; 163 [0–437] µg/patient per day before NAVA and 92 [0–229] µg/patient per day during NAVA) and for midazolam ($n = 7$; 5 [0–15] mg/patient per day before NAVA and 0 [0–4] mg/patient per day during NAVA), and were equal for propofol ($n = 13$, 125 [0–8,640] mg/patient per day before NAVA and 133 [0–4,800] mg/patient per day during NAVA).

Neuro-ventilatory efficiency tests

NVETs were performed daily in all patients. V_t/EA_{di} decreased during the first NVET, from 1.1 ± 0.6 to 0.9 ± 0.4 ml/kg PBW/µV, while it increased from 0.9 ± 0.6 to 1.0 ± 0.8 ml/kg PBW/µV during the last NVET performed ($p = 0.048$; ANOVA time–group interaction) (Table 3). Changes in V_t, RR, and P_{aw} above PEEP were not different between the first and last NVET.

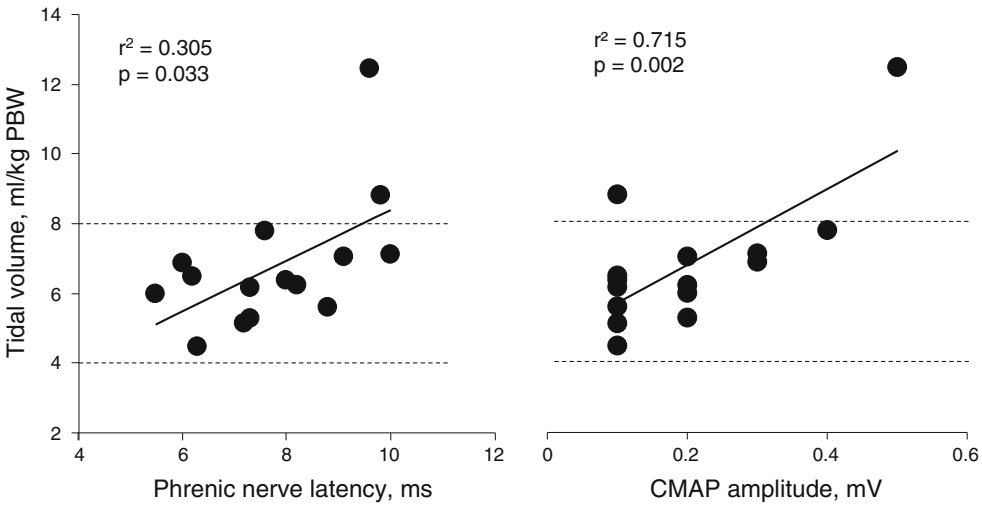

Fig. 4 Relationship between individual average tidal volume (V_t) during NAVA and the phrenic nerve compound muscle action potential (CMAP) latency (PNL) and amplitude. The average V_t during NAVA ranged from roughly 4 to 9 ml/kg PBW (except in one patient), and was correlated to both PNL and CMAP amplitude. This may indicate that feedback control of V_t during NAVA is, to a limited extent, influenced by the degree of phrenic neuropathy

Table 3 Changes in neuro-ventilatory parameters during standardized tests of neuro-ventilatory efficiency (NVET)

$n = 12$		Start of NVET	End of NVET	MANOVA time–group interaction
V_t/EA_{di} (ml/kg PBW/μV)	First NVET	1.1 ± 0.6	0.9 ± 0.4	$p = 0.048$
	Last NVET	0.9 ± 0.6	1.0 ± 0.8	
Tidal volume (ml/kg PBW)	First NVET	6.2 ± 2.6	6.6 ± 2.4	$p = 0.749$
	Last NVET	5.6 ± 1.3	6.0 ± 1.5	
Respiratory rate (breaths/min)	First NVET	33 ± 18	30 ± 11	$p = 0.345$
	Last NVET	30 ± 10	31 ± 10	
Mean insp. P_{aw} above PEEP (cmH_2O)	First NVET	4.8 ± 1.8	4.7 ± 1.9	$p = 0.244$
	Last NVET	4.9 ± 1.8	4.6 ± 2.6	

Changes observed during the first and the last available standardized tests of neuro-ventilatory efficiency (NVET) on pressure support ventilation (PSV). Throughout the NVETs an inspiratory assist of 7 cmH_2O (or 3 cmH_2O if tracheotomized) was applied

V_t tidal volume, *PBW* predicted body weight, *P_{aw}* airway pressure, *EA_{di}* electrical activity of the diaphragm, *PEEP* positive end-expiratory pressure, *MANOVA* multivariate analysis of variance

The proportion of unsuccessful NVETs was 4/15 at 0 h, 5/13 at 24 h, 3/10 at 48 h, and 1/8 at 72 h. Seven patients were not extubated despite successful NVETs due to an impaired level of consciousness (GCS < 9; $n = 3$) or due to a high level of PEEP ($n = 4$). Five patients were liberated from mechanical ventilation during the study, two of whom required re-intubation within 48 h due to progressive respiratory failure.

Discussion

The present study demonstrates for the first time that central respiratory response is adequate such that NAVA can be safely applied for up to 3 days in critically ill patients with established CIPM including phrenic nerve neuropathy.

CIPM was present in all our patients as evidenced by reduced MRC scores and the electrophysiology studies. Our results for both PNL and CMAP in healthy subjects and critically ill patients are comparable to those of previous studies [6–10, 35, 37–40]. Although group mean values in our patients were higher for PNL and lower for CMAP compared with healthy volunteers, the data overlapped between the groups, supporting previous findings that the phrenic nerve–diaphragm unit might be affected to a variable degree in patients with CIPM [41, 42].

Vagally mediated, lung-protective reflexes play a major role in modulating respiratory drive [43–46]. Despite impaired neural function in our patients, the EA_{di} was progressively downregulated via neural feedback control when the NAVA level was increased, resulting in a characteristic two-phase response in V_t and P_{aw} that allows for identification of NAVAal, as previously described in animals and humans [22–25]. At NAVAal, the EA_{di} amplitude averaged about 10 μV and was reduced to approximately 70% of the values observed when only minimal assist was applied (i.e., at NAVAzero).

The positive correlation between V_t and parameters of phrenic nerve function, i.e., PNL and CMAP amplitude, may provide indirect evidence that the neural feedback system is progressively impaired in relation to the degree

of severity of polyneuropathy. However, the fact that during NAVAal our patients chose a V_t within boundaries that are conventionally regarded as lung protective (i.e., 4–9 ml/kg PBW, except for one patient), displayed high V_t variability, kept their RR(neural) stable, controlled $PaCO_2$ levels, improved oxygenation, and maintained the EA_{di} at the titrated level, indicates that vagally mediated feedback to the respiratory centers was sufficiently preserved to use NAVA.

The physiological response during the titration procedures that was similar to what we found in a general population of critically ill patients [22] and the stability during prolonged implementation of NAVAal without evidence of progression to respiratory failure, indicate that NAVA can be safely applied in patients with CIPM. Indeed, individual titration of the assist to a level that maintains muscular function at a comfortable level at all times without inducing fatigue may portend the potential to condition respiratory muscles and hence prevent or attenuate ventilator-induced respiratory muscle dysfunction.

Similar to our previous work [22–25], increasing the NAVA level above NAVAal reduced, but did not abolish, EA_{di}, while the V_t (and hence the transpulmonary pressure) remained constant over a wide range of NAVA levels. Thus, the patient-controlled limitation of V_t with NAVA may also help in reducing the propensity for ventilator-induced lung injury, as recently shown in animals and patients with acute respiratory distress syndrome (ARDS) [20, 47].

Although the majority of our patients were given lower doses of analgesic and sedative drugs during NAVA compared with the preceding PSV period, this might be due to improvement in the patients' condition and not necessarily to the mode of mechanical ventilation. Additional work is required to determine how improved patient–ventilator interaction impacts other aspects of treatment.

NAVA was prematurely terminated in two patients because of suspected uncoupling between respiratory motor output and respiratory demand and because of diaphragm myocloni, illustrating that NAVA might not be suitable for all patients at all times. Conditions associated with excessively high CO_2 production or with disturbed function of breathing centers may result in overexertion of the sensomotor feedback system that controls EA_{di}, and may temporarily require an alternative approach [48] or more controlled modes of ventilation until resolution.

Standardized neuro-ventilatory efficiency tests

The ratio between V_t and EA_{di} during NAVA reflects the conversion of respiratory drive into tidal ventilation [24]. In the present study, V_t/EA_{di} decreased during the first NVET, whereas it slightly increased during the last NVET.

The clinical relevance of the neuro-ventilatory efficiency index is that an increase of the index over time indicates that a patient is able to generate more V_t for a given respiratory drive whereas a decrease in the index over time suggests the opposite. Both components of the index are easily available: V_t is calculated by all mechanical ventilators and the EA_{di} can be reliably acquired using a modified nasogastric feeding tube [22, 49]. In contrast, continuous monitoring of the various components of respiratory system mechanics and respiratory muscle load is not straightforward. Clearly, our index simply indicates that a patient improved or worsened the efficiency in converting electrical neuromuscular activity into tidal ventilation, but does not discriminate between contributing factors such as changes in respiratory muscle force or load, in respiratory system mechanics, in chest wall configuration, in intrinsic PEEP, and in gas tension. Thus, without additional information, changes of the index alone do not allow one to draw conclusions about which combination of factors has been affected and caused the change.

Since a constant level of assist was delivered during all NVETs, our results reflect either an improvement of the respiratory neuromuscular function or a decrease in the respiratory load over time. We did not assess respiratory system mechanics, but a relevant change in the respiratory load during the NVET seems unlikely. Although the changes of V_t/EA_{di} over time during the first and last NVET differed statistically significantly, the magnitude of the changes was small. Further work is required to confirm our results and to evaluate NVET as a weaning predictor.

Limitations

We did not assess inspiratory pressure generation in our patients and are hence unable to determine the extent of respiratory muscle weakness and its eventual association with increased PNL and reduced CMAP amplitude. Luo et al. [39] found a positive correlation between twitch P_{di} and CMAP amplitude (but no relationship between twitch P_{di} and PNL). In another study, CMAP has been suggested to reflect the number of diaphragmatic muscle fibers that can be activated by phrenic nerve stimulation [50].

Conclusions

Our results suggest that the respiratory center's output is accurate and vagally mediated reflexes are sufficient in most critically ill patients with established CIPM, such that implementation of NAVA for up to 3 days results in stable cardiopulmonary function while preserving respiratory drive. Our study confirms that NAVA efficiently limits the risk of excessive assist delivery and patient–

ventilator asynchrony, both frequently observed during pneumatically controlled modes such as PSV. Whether assessment of neuro-ventilatory efficiency helps inform the weaning process requires further evaluation.

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Conflict of interest The Department of Intensive Care Medicine at the Bern University Hospital has a research and development collaboration contract with Maquet Critical Care AB. None of the authors from this department received any personal financial gain from this collaboration. Dr. Sinderby has patented inventions related to neural control of mechanical ventilation. The license for these patents belongs to Maquet Critical Care. Commercial use of this technology provides financial benefit to Dr. Sinderby through royalties. Dr. Sinderby owns 50% of Neurovent Research Inc. Neurovent Research is a research and development company that builds the equipment and catheters for research studies. Neurovent Research has a consulting agreement with Maquet Critical Care. Dr. Brander was an invited speaker at symposiums sponsored by Maquet Critical Care AB but did not receive any personal financial gain.

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