Submitted January 2019; Accepted March 2019

REVIEW

Clinical outcome in neurally adjusted ventilatory assist: a review

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Keywords - NAVA, mechanical ventilation, clinical outcome, review

Abstract

Background: Neurally adjusted ventilatory assist (NAVA) is a support mode of mechanical ventilation in which the ventilator is triggered by an electrical signal from the diaphragm (EAdi). Beneficial effects on physiological parameters are unequivocal. However, the effect of NAVA on clinical endpoints is unclear. The aim of this review was to assess the effect of NAVA on clinical endpoints.

Methods: A systematic review was performed using PubMed. Inclusion criteria were: adult intensive care population, comparison between NAVA and other modes of ventilation and clinical outcome parameters or patient-related outcome measures (PROMs). Exclusion criteria were: animal studies, paediatric studies and language other than English, German or Dutch.

Results: 538 articles were screened and six articles remained. Three used clinical outcome measures and three reported PROMs. No difference in mortality or other primary endpoints could be shown, but beneficial effects in secondary endpoints were seen. In one study positive effects of NAVA seemed to be more associated with measurement of EAdi than with NAVA mode itself. This effect might have biased the results of the other included studies. Regarding PROMs, no clinically relevant increase in comfort could be shown. One study revealed an increase in quality and quantity of sleep.

Conclusions: Studies regarding clinical outcome with NAVA are sparse. No robust advantage of NAVA on primary endpoints was shown. The presented advantages were possibly attributed to asynchrony detection, instead of NAVA mode itself. Future research should aim to differentiate between recognition of asynchrony and the effects of NAVA mode itself.

Background

In 2007 Sinderby and Beck published a review in this journal[1] on the principles of neurally adjusted ventilator assist (NAVA). They described the physiological rationale and effects of NAVA, in particular patient-ventilator interactions.

However, that review did not report on studies with clinical outcome measures or patient-related outcome measures (PROMs). In the past years, several studies have published the effects of ventilation in NAVA mode on clinical outcome. This systematic review provides an overview of published studies on clinical outcome parameters or PROMs in patients ventilated in NAVA mode compared with patients ventilated in other support modes. First, we briefly describe the principles of NAVA.

History

Mechanical ventilation is the cornerstone for the treatment of patients with severe respiratory failure. Conventionally, the initiation of support modes was adapted to the airflow or pressure drop in the ventilatory system. Although effective, researchers kept searching for other methods. In 1959 Petit et al.[2] presented a technique to acquire electromyograms (EMG) of the human diaphragm, but it was not until the late 1990s and early 2000s that Sinderby's group presented a method to measure diaphragm EMG signals by using a dedicated nasogastric tube[3] and a software algorithm that allowed to control the ventilator by electrical activity of the diaphragm.[4]

Principles of NAVA

NAVA is a partially supported mode that uses electrical activity of the diaphragm (EAdi) to control the ventilator.[4] To this end, a nasogastric tube with electrodes that continuously acquire EAdi is positioned in the oesophagus. The EAdi catheter, which is often incorporated in the nasogastric tube, is inserted as a normal nasogastric tube[5] and adequate positioning can be verified with a ventilator software tool. NAVA cannot be used in case of contraindications for nasogastric tube placement or in the absence of diaphragm activity.

The EAdi is used to trigger the ventilator, cycle off the ventilator and determine the level of inspiratory support. The amount of inspiratory support is determined by the electrical activity of the diaphragm and a gain factor, as set by the clinician (in cmH_2O per $_{\mu}$Volt). So in contrast with conventional assist modes, the level of assist is variable with each breath (proportionality). Support setting is titrated based on tidal volume, airway pressures and respiratory rate.[6] NAVA can be used during both invasive and non-invasive ventilation.

Methods

Data search

To find all relevant articles concerning clinical outcome, a search was performed in Cochrane CENTRAL and MEDLINE in November 2018. No restrictions in the search strategy were applied. To avoid missing relevant articles, synonyms of 'neurally adjusted ventilatory assist' were used, as well as synonyms of 'proportional assist ventilation'. Although the latter is a different mode of ventilation, some authors also use 'proportional ventilation' for NAVA. All synonyms were searched for using [Title/Abstract] and [MESH terms]. After this initial search all references were checked for additional articles by one reviewer (MN).

Study selection

All articles retrieved in the initial search were screened in a three-stage process, using title, abstract and full-text. Inclusion criteria were: adult intensive care population, comparison of NAVA versus another spontaneous ventilation mode, clinical outcome measures and PROMs. Clinical outcome was defined as an outcome directly affecting the clinical course of a patient, such as duration of mechanical ventilation, ventilation-free days, length of stay in ICU and mortality. PROMs were defined as outcomes which directly affected patient comfort, such as tolerability, pain, sleep, etcetera.

Exclusion criteria were: animal studies, paediatric studies, studies regarding non-invasive ventilation, studies with only physiological variables and no clinical outcome, studies without a direct comparison between NAVA and another mode of spontaneous ventilation and reviews, case reports and editorials. Studies were also excluded when full-text articles were not available in English, German or Dutch.

Results

Data search and selection

The search in Cochrane CENTRAL revealed no relevant articles. In MEDLINE 538 hits were encountered, of which six remained after the selection procedure. Studies regarding proportional assist ventilation (PAV or PAV+) without neural control were excluded. Two articles were excluded because the full text was only available in Chinese. No direct clinical outcome measures were reported in the abstracts. Checking the references resulted in one additional reference, which turned out to be an abstract of a poster presentation. A full-text version could not be retrieved, despite contacting the authors. Ultimately six studies were included: two randomised controlled trials and four prospective cross-over trials. Three of the selected studies reported on clinical outcome and three reported PROMs. The whole selection process is depicted in *figure 1* and an overview of all included studies can be found in *table 1.*

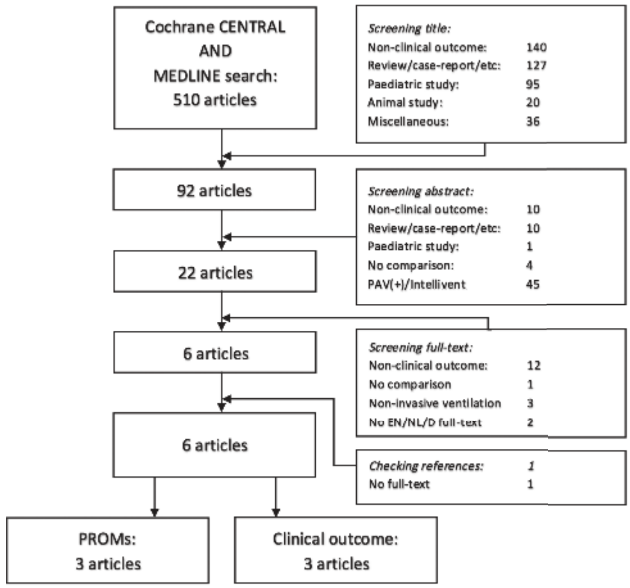

Figure 1. Flowchart of article search and selection

PAV = proportional assist ventilation; PROMs = patient-related outcome measures

Studies reporting clinical outcome measures

Three studies reported clinical outcome measures. The first to discuss is a randomised controlled trial (RCT) from 2016,[7] which is the first and the largest (n=128) of the two RCTs. It was conducted in 11 intensive care units (ICUs) and included patients on mechanical ventilation for acute respiratory failure for more than 24 hours and who were expected to be ventilated for at least another 48 hours. After inclusion, but before randomisation, all patients received an EAdi catheter. Patients in the control group were ventilated in pressure support ventilation (PSV) mode and intervention patients in the NAVA mode. In both groups support was titrated to provide a tidal volume of 6-8 ml/kg. Settings of FiO_2 and PEEP were according to local guidelines and preferences. In case of weaning, a weaning protocol was used in both groups. The primary outcome of this study was the proportion of patients who remained continuously in a support mode (either NAVA or PSV) for the first 48 hours or until extubation. No difference was found between groups, with successful partial ventilator mode in the NAVA group of 67.2% vs 63.3% in the PSV group (p=0.66). There was also no effect on secondary outcomes, such as duration of mechanical ventilation, length of stay (either ICU or hospital) or mortality.

Table 1. Overview of selected studies

Author	Design	Comparator	Population	N	Reported clinical outcome	Results[1]
Demoule 2016	RCT	PSV	ICU patients after with respiratory failure	128	Proportion in support mode during 48h Ventilator-free days Duration of mechanical ventilation Post-extubation NIV ICU and hospital LoS 28-day mortality	Lower incidence and duration of NIV in NAVA group
Kuo 2016	RCT	PSV	COPD patients with pro-longed ventilation	33	Weaning outcome Duration of mechanical ventilation Respiratory Care and hospital LoS 90-day mortality	No differences
Coisel 2010	Prospective cross-over	PSV	ICU patients with ventila-tion > 48h	15	Behavioural Pain Scale (used for comfort)	No differences
Delisle 2011	Prospective cross-over	PSV	ICU patients in weaning phase	14	Sleep quality	Longer REM sleep and less arousals in NAVA group
Vagheggini 2013	Prospective cross-over	PSV	ICU patients weaning with tracheostoma	13	Modified Borg Scale for dyspnoea	No differences
Ferreira 2017	Prospective cross-over	PSV	ICU patients undergoing SBT	20	Success of SBT	No differences

COPD = chronic obstructive pulmonary disease; EAdi = electrical activity of diaphragm; ICU = intensive care unit; LoS = length of stay; NAVA = neurally adjusted ventilatory assist; NIV = non-invasive ventilation; N = number of subjects included; PSV = pressure support ventilation; RCT = randomised controlled trial; SBT = spontaneous breathing trial

[1] Only significant findings are mentioned, see text for details

In the first 7 days, there were more ventilator-free days in the NAVA group, but this difference disappeared on day 14 and day 28. However, a lower rate and duration of post-extubation non-invasive ventilation (NIV) was seen in the NAVA group (43.5 vs 66.6%; 2 vs 0 days).

The other RCT was also conducted in 2016[8] and focused on COPD patients with weaning failure. Patients were included if they had COPD and were ventilated for more than 21 days. Of 33 patients, 14 were assigned to NAVA mode and 19 to PSV mode. An EAdi catheter was inserted in all patients before randomisation. Regarding clinical outcome, no significant effects of NAVA were seen in mortality (7.1% vs 31.6%; p=0.09), duration of mechanical ventilation (20.3 vs 22.1 days; p=0.78) and length of stay in ICU (47.3 vs 49.2 days; p=0.94).

A prospective cross-over study published in 2017[9] compared NAVA with PSV during spontaneous breathing trials (SBTs) lasting 30 minutes and with 5 cmH_2O of PEEP. In the PSV group 5 cmH_2O pressure support was applied, whereas the support in the NAVA group was titrated to peak inspiratory pressures of 10 cmH_2O. Patients (n=20) underwent two SBTs in a randomised order. Three subjects did not pass the SBT in NAVA, while all patients passed the SBT in PSV. Because the protocol mandated to use the results of the SBT in PSV, all patients were extubated after the SBTs. Five patients had to be re-intubated, one of whom failed the SBT in NAVA. Due to the small numbers, no conclusions could be drawn regarding re-intubation rate.

Studies reporting patient-related outcome measures

Two prospective cross-over trials and one RCT reported on PROMs. PROMs were heterogeneous across the studies, and also heterogeneous outcome measures were used.

The study by Coisel et al.[10] included postoperative patients during the weaning phase of ventilation. Among other variables, the authors assessed patient comfort using the Behavioural Pain Scale (BPS). BPS was assessed every four hours during a period of 24 hours, but a difference in BPS between NAVA and PSV was not seen at any of these timepoints.

A comparable study was performed by Vagheggini et al.[11] These authors did not find a difference in patient comfort using the modified Borg score, which is a 11-point scale to rate fatigue.

The study by Delisle et al.[12] investigated quality of sleep in 14 mechanically ventilated patients. Overall, patients had a low percentage of REM sleep and frequent arousals (25 per hour). REM sleep was significantly longer in the NAVA group (16.5 vs 4.5% p=0.001) and the number of arousals per hour was lower in the NAVA group (16 vs 40 per hour, p=0.001). No asynchrony or central apnoea was reported in the NAVA group, compared with 24 asynchronies per hour and 10.5 apnoeas per hour in the PSV group. The apnoea in the PSV mode was thought to be due to over-assistance in non-REM periods in patients on PSV mode. This hypothesis is based on the 15% decline in tidal volume during non-REM periods in NAVA mode, as well as on an increase in tidal volume of about 35% in PSV mode in the three cycles before central apnoea.

The aforementioned RCT by Demoule et al.[7] also reported on PROMs. Dyspnoea was scored daily using a visual analogue scale and was lower on day 1 in the NAVA group (p=0.030). Comfort was assessed using the ATICE comfort score, a score designed to assess the ability of the patient to cope with the ICU environment and especially with mechanical ventilation.[13] No difference was seen in ATICE scores between groups.

Discussion

This is the first paper reviewing the clinical effects of NAVA. Literature on this topic is sparse and studies are relatively small. Based on this limited evidence, no firm conclusions can be drawn, mainly because no significant effect was found in any of the primary outcomes. In the secondary outcomes some advantages of NAVA were found, but studies were underpowered for these endpoints.

Since the introduction of NAVA, studies were conducted to assess the advantages of this mode. Through the years it became clear that NAVA results in a lower asynchrony index (AI),[14-17] which is usually defined as the ineffective efforts divided by the total respiratory rate. Furthermore, NAVA reduces the risk of over-inflation[16,17] and improves physiological parameters. In the included studies reporting on the AI, a lower rate of asynchrony was found in four studies.[7-9,12] What is remarkable is the absence of asynchrony in the NAVA group in two studies.[8,12] On the other hand, one study found no difference at all in the AI[11] which, according to the authors, can be attributed to lower tidal volumes in the PSV group.

The avoidance of asynchrony seems to be important from a physiological perspective, but its importance was also stressed by two studies reporting on adverse outcomes in patients with an AI >10%. Both studies found a longer duration of mechanical ventilation with a higher AI (<10% vs >10%)[20,21] and one of them also found a longer ICU and hospital stay[20] in patients with a reported AI >10%. Moreover, a study with 50 patients reported higher ICU and hospital mortality in patients with an AI >10% compared with patients with an AI <10%.[22]

Based on these results one would expect a shorter duration of mechanical ventilation in patients in NAVA mode because of the large decrease in the AI compared with other assist modes. However, although reporting lower rates of asynchrony in NAVA, none of the studies included in this systematic review can confirm this effect. Although not powered for this outcome, the largest RCT[7] found no reduction in duration of mechanical ventilation. One of the explanations might be that, despite a significant difference, the AI was >10% in both groups, thereby decreasing the difference between groups. Except for a short period of observation for asynchrony, no other explanations for this high AI in the NAVA group were given. This higher AI in both groups was also seen in one of the cross-over studies,[9] but this was at least partially explained by incorporation of triggering delay in the AI.

Another concern is that the EAdi signal was available in all included patients and not only in the NAVA groups. The presence of the EAdi signal, and therefore detection of asynchrony, might have influenced the ventilation strategy in the PSV groups. This effect is seen in the publications from a research group of the Kings College Hospital, London;[23,24] patients with measurement of the EAdi signal had less sedation, less muscle relaxation, less ventilator days and shorter length of stay on the ICU. This effect was independent from mode of ventilation: either PSV or NAVA. Unfortunately, no full-text articles of these studies were available.

Some secondary outcomes in the study by Demoule et al.[7] revealed beneficial effects of NAVA. The number of ventilator-free days was lower in the NAVA group, but only reached significance on day 7. Furthermore, use of post-extubation NIV was more common in the PSV group and also lasted longer. Other secondary outcomes revealed no statistical significance, but nearly all the results showed a trend favouring NAVA. In the other RCT[8] no beneficial effects were seen in other parameters, such as mortality, ventilator-free days, ICU and hospital length of stay. Remarkably, the difference in mortality was quite large (7.1% vs 31.6%), although not reaching statistical significance. The authors do not question the effect and do not have an explanation. Baseline data reveal no significant differences, except for tidal volume per kg ideal body weight, which was larger in the conventional group (6.8 vs 9.4 ml/kg, p=0.01). However, this difference is not likely to cause such an effect in this small population.

Regarding PROMs, heterogeneity characterised study design, outcome measures as well as results. The included studies found no effect on PROMs, but two studies performed in patients on non-invasive ventilation[25,26] found a statistically significant difference in the Numeric Rating Scale (NRS) in favour of NAVA, compared with PSV. Most of the used rating scales (e.g. NRS) are not, of course, validated for the use of comfort assessment in patients on mechanical ventilation. Although the results point towards more patient comfort, no firm conclusions can be drawn. The study with unequivocal results was the one regarding quality of sleep,[13] where patients on NAVA exhibited less arousals and more time in the REM phase of sleep.

As the presented results indicate no consistent advantages in clinical outcome, the possible disadvantages have to be assessed carefully. Two studies reported on safety.[7,10] Demoule et al.[7] recorded four adverse events possibly related to the NAVA catheter, but found no adverse events related to NAVA mode. Coisel et al.[10] described no safety issues, but excluded 2 out of his 15 postoperative patients because of a low EAdi signal, making NAVA impossible. This low rate of adverse events is consistent with other NAVA studies. Concerns regarding ICU acquired weakness were disputed by a study revealing that 13 out of 15 patients with clinically relevant ICU acquired weakness could be ventilated using NAVA.[27]

A major limitation which applies to all selected studies is that difficult weaning from mechanical ventilation may have a cause unrelated to the respiratory system. This is extensively described in a review regarding the management of weaning failure.[28] Changing one of the factors can hardly be translated into large differences in outcome. Furthermore, not all patients with weaning failure can be regarded as one group. Another limitation of the included studies is the low number of participants in all of the studies (median 15). Apart from the limitations of the included studies and the shortcomings of research in weaning, this review also had some limitations. First of all, we only searched MEDLINE database and the Cochrane Library. Although these databases contain the majority of papers, some papers could have been missed. By checking references of selected studies, we minimised this effect. Furthermore, we had to exclude two Chinese studies, which could have been relevant. Due to heterogeneity of methods and outcome variables no meta-analysis could be performed.

Future research on this topic should aim for clarification of the effect of asynchrony monitoring versus the effect of NAVA mode itself. Ideally an RCT should include three groups: one with PSV without EAdi monitoring, one with PSV with EAdi monitoring and one with NAVA including EAdi monitoring. A next step would be incorporation of the effect of maximised support based on EAdi, with adequate pressure limits, thereby increasing inspiratory flow. Use of this method was practised in the NIV studies of Cammarota et al. and Longhini et al.[25,26] resulting in short peak inspiratory flow times and more comfort for the subjects. This method was also used by Liu et al.[29] in intubated COPD patients, where normal PSV was triggered by the measured EAdi signal. Due to faster triggering no external PEEP had to be applied, but this did not result in an increase in mechanical effort. Furthermore, future studies should include patients who are prone for prolonged weaning and the sample size must be powered for clinical relevant endpoints, such as duration of mechanical ventilation.

Conclusion

Besides proven advantages of NAVA in patient-ventilator interaction, the currently available literature shows no beneficial effects of NAVA on primary outcomes, although some beneficial effect was shown for secondary outcomes. Some of the beneficial effects can be attributed to closer detection and observation of asynchrony and not solely to NAVA mode itself. Future research should aim to differentiate between recognition of asynchrony and the effects of NAVA mode itself. Furthermore, NAVA might be associated with increased patient comfort.

Disclosures

L.M.A. Heunks has received speaker's fees and travel expenses from Maquet Critical Care (Sweden), and research grants from Orion Pharma (Finland) and Liberate Medical (USA). The other authors declare no conflict of interest. No funding or financial support was received for this study.

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