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NAVA

Neurally-Adjusted Ventilatory Assist (NAVA) is a novel mode of mechanical ventilation that synchronizes ventilator support with the patient's respiratory efforts by monitoring the electrical activity of the diaphragm (EAdi). Introduced over two decades ago, NAVA has garnered attention for its potential to improve patient-ventilator interaction, reduce ventilator-induced injuries, and enhance clinical outcomes in various patient populations. This review delves into the physiological principles, clinical applications, comparative effectiveness, and challenges associated with NAVA.

Unlike conventional ventilation modes that rely on pneumatic signals such as flow or pressure for triggering, NAVA uses EAdi to initiate and terminate ventilator assistance. The diaphragm's electrical activity, detected via a nasogastric tube equipped with specialized electrodes, reflects the central respiratory drive. This signal provides a precise and dynamic measure of respiratory effort, allowing ventilatory support to be proportional to the patient's needs throughout each breath. By ensuring that the ventilator is in tune with the patient's neural respiratory cycle, NAVA minimizes asynchrony, a common issue in traditional ventilation modes. Studies have consistently demonstrated the ability of NAVA to optimize ventilator-patient interaction, particularly in patients with complex respiratory mechanics, such as those with low lung compliance or high airway resistance.

One of the key advantages of NAVA is its ability to enhance synchrony, even in challenging conditions like acute respiratory distress syndrome (ARDS) or chronic obstructive pulmonary disease (COPD). Conventional modes such as pressure support ventilation (PSV) often struggle to maintain synchrony, leading to asynchrony indices as high as 30% in some populations. In contrast, studies comparing NAVA and PSV show significantly lower asynchrony indices in NAVA, underscoring its superiority in ensuring coordination between neural and mechanical respiratory cycles. This improved synchrony has far-reaching implications, including reduced work of breathing, better gas exchange, and enhanced patient comfort.

NAVA also plays a crucial role in preserving diaphragm function. In traditional ventilation, excessive assistance can suppress respiratory drive, leading to ventilator-induced diaphragm dysfunction (VIDD). By delivering proportional support, NAVA prevents over-assistance and maintains adequate diaphragm activity, reducing the risk of atrophy. This aspect of diaphragm-protective ventilation is particularly important in patients requiring prolonged mechanical support.

Additionally, NAVA contributes to lung protection by minimizing ventilator-induced lung injury (VILI). Conventional modes often deliver fixed tidal volumes or pressures, which can

result in barotrauma or volutrauma in vulnerable patients. With NAVA, the ventilator dynamically adjusts pressure in response to the patient's effort, reducing the likelihood of excessive lung stress or strain. Studies in animal models and human subjects confirm that NAVA helps distribute ventilation more evenly across lung regions, thereby mitigating the risk of localized overdistension.

The versatility of NAVA makes it applicable to diverse patient populations, including adults with acute respiratory failure, pediatric patients, and neonates. In adult intensive care units (ICUs), NAVA has been shown to improve clinical outcomes such as duration of ventilation and patient comfort. A narrative review highlighted that NAVA's proportional support not only ensures adequate gas exchange but also reduces the risk of apnea and asynchrony during noninvasive ventilation (NIV). These benefits are particularly pronounced in patients with ARDS or COPD exacerbations, where traditional modes often fall short.

In pediatric intensive care units (PICUs), NAVA is increasingly being used as a weaning mode for invasively ventilated children. Systematic reviews indicate that NAVA reduces the length of PICU stays and sedation requirements compared to traditional modes. For example, a cohort study involving children recovering from cardiac surgery reported higher extubation success rates and shorter ventilation durations with NAVA. Despite these promising findings, the evidence base remains limited, necessitating further research to establish standardized protocols and optimize outcomes.

The use of NAVA in neonates, particularly preterm infants, presents unique challenges and opportunities. Neonates often require prolonged respiratory support due to immature lungs and respiratory control mechanisms. Traditional ventilation modes frequently fail to achieve synchrony in this population due to their rapid respiratory rates and small tidal volumes. NAVA, by directly responding to neural signals, offers a solution to these issues. Studies have demonstrated that NAVA reduces bronchopulmonary dysplasia (BPD) and improves extubation success rates in preterm infants. However, technical difficulties in acquiring reliable EAdi signals and the prevalence of apnea in this population remain significant barriers to widespread adoption.

When compared to conventional ventilation modes, NAVA consistently outperforms in terms of synchrony, patient comfort, and physiological outcomes. Meta-analyses of studies comparing NAVA and PSV during noninvasive ventilation reveal significantly lower asynchrony indices and fewer ineffective efforts in the NAVA group. However, the data on clinical outcomes such as mortality and length of ICU stay are less conclusive. For instance, while some studies report shorter ventilation durations and reduced sedation requirements with NAVA, others note no significant differences in mortality rates or overall clinical outcomes. These discrepancies highlight the need for larger, multicenter randomized controlled trials (RCTs) to validate the observed benefits and explore their impact on long-term outcomes.

Despite its advantages, NAVA is not without limitations. One of the primary challenges is the reliance on a specialized nasogastric tube for EAdi signal acquisition. This requirement

can lead to discomfort and may not be feasible in all patients. Additionally, the need for trained personnel to manage NAVA settings and interpret EAdi signals has hindered its widespread adoption. Cost considerations also play a role, as NAVA-specific equipment and training represent a significant investment for healthcare facilities.

In neonates, the frequent occurrence of apnea and insufficient triggering of EAdi signals pose specific challenges. These issues necessitate careful titration of NAVA settings and ongoing monitoring to ensure effective ventilation. Furthermore, the limited availability of robust clinical data in this population underscores the need for targeted research.

The future of NAVA lies in expanding its clinical applications and addressing existing limitations. Technological advancements aimed at improving EAdi signal acquisition and patient comfort could enhance the feasibility of NAVA in a broader range of patients. Research efforts should focus on conducting large-scale RCTs to establish evidence-based guidelines for NAVA use across different populations. Additionally, exploring the integration of NAVA with other innovative ventilation strategies could pave the way for personalized respiratory support tailored to individual patient needs.

In conclusion, NAVA represents a significant advancement in mechanical ventilation, offering improved synchrony, diaphragm preservation, and lung protection compared to conventional modes. While challenges remain, the growing body of evidence supporting its physiological and clinical benefits makes NAVA a promising tool in the management of respiratory failure. Continued research and innovation are essential to fully realize its potential and optimize outcomes for patients across the age spectrum.

References:

1- Navalesi P, Longhini F: Neurally adjusted ventilatory assist. Curr Opin Crit Care. 21(1):58-64, 2015
2- Sugunan P, Hosheh O, Garcia Cusco M, Mildner R: Neurally-Adjusted Ventilatory Assist (NAVA) versus Pneumatically Synchronized Ventilation Modes in Children Admitted to PICU. J Clin Med. 10(15):3393, 2021
3- Umbrello M, Antonucci E, Muttini S: Neurally Adjusted Ventilatory Assist in Acute Respiratory Failure-A Narrative Review. J Clin Med. 11(7):1863, 2022
4- Weiyun T, Linli S, Liuzhao C: Neurally-Adjusted Ventilatory Assist Versus Pressure Support Ventilation During Noninvasive Ventilation. Respir Care. 67(7):879-888, 2022
5- Fang SJ, Chen CC, Liao DL, Chung MY: Neurally adjusted ventilatory assist in infants: A review article. Pediatr Neonatol. 64(1):5-11, 2023
6- Lefevere J, van Delft B, Decaluwe W, Derriks F, Cools F: Neurally adjusted ventilatory assist in preterm infants: A systematic review and meta-analysis. Pediatr Pulmonol. 59(7):1862-1870, 2024

Botulinum Toxin for Long Gap Esophageal Atresia

Long gap esophageal atresia (LGEA) is a rare but significant congenital condition, occurring in approximately 1 in 3,000 to 4,500 live births. The defining characteristic of LGEA is the presence of a substantial gap between the proximal and distal esophageal segments, often making primary anastomosis unfeasible. Traditional management approaches include delayed primary repair, organ interpositions, or esophageal replacement procedures, but these are frequently associated with high morbidity, prolonged

hospital stays, and suboptimal functional outcomes. In recent years, the use of botulinum toxin (BTX), a neurotoxin derived from *Clostridium botulinum*, has emerged as a potential adjunct in managing LGEA by facilitating tissue elongation and reducing complications.

The mechanism of action of botulinum toxin lies in its ability to block the release of acetylcholine at neuromuscular junctions. This inhibition results in muscle relaxation, which can be exploited to reduce tissue tension in the esophagus. Initial experimental studies in animal models have demonstrated the efficacy of BTX in elongating esophageal tissue, with mechanical stress that often precludes successful primary anastomosis in LGEA.

Botulinum toxin (BTX) is applied intramurally to the esophageal musculature through precise injections, typically performed under direct visualization during surgery or using endoscopic techniques for minimally invasive delivery. The toxin is injected into multiple points along the esophageal wall, often at a dose of 2 units/kg per site, targeting both proximal and distal esophageal segments. Timing is crucial, with injections planned to allow BTX's peak effect, occurring around two weeks post-administration, to coincide with critical phases of elongation or repair. This method ensures localized muscle relaxation, enhancing tissue compliance and facilitating esophageal elongation while minimizing systemic effects.

Building upon these findings, further research explored the utility of BTX in a clinical context. In one randomized controlled trial, pig models with simulated esophageal atresia were treated with BTX prior to surgical interventions. The results demonstrated not only improved esophageal elongation but also a reduction in stricture formation and leakage rates post-anastomosis. The significant reductions in muscle tension observed in pig models. One study conducted in 2013 evaluated the intramural injection of BTX in piglets, showing that treated esophageal segments exhibited an 18% greater elongation under tension compared to controls. This finding underscored the potential of BTX to reduce the histological analysis further revealed that BTX-treated tissues exhibited more organized muscle regeneration and less collagen deposition at anastomotic sites, suggesting enhanced healing. These outcomes align with the hypothesis that BTX's muscle-relaxing and anti-fibrotic properties can mitigate some of the mechanical and biological challenges associated with esophageal repair.

The integration of BTX into surgical protocols for LGEA has also been studied in conjunction with advanced techniques such as the Foker process. This method, which relies on applying continuous tension to stimulate esophageal growth, is a cornerstone of modern LGEA management. However, its implementation is often limited by the prolonged sedation and immobility required for traction. A 2024 study investigating BTX-enhanced Foker procedures demonstrated that the addition of BTX significantly reduced the duration of traction, from an average of 16.6 days in traditional Foker processes to 12.1 days in BTX-enhanced protocols. This reduction not only minimizes the risks associated with prolonged sedation but also expedites recovery, highlighting the practical benefits of incorporating BTX into clinical practice.

Despite these promising results, challenges remain in translating BTX therapy from experimental and early clinical studies to routine use. One key consideration is the optimal timing of BTX administration. The toxin's peak effect typically occurs two weeks post-injection, suggesting that precise scheduling is crucial for maximizing its benefits during surgical planning. Additionally, concerns about potential side effects, such as transient dysphagia or gastroesophageal reflux due to temporary reductions in esophageal motility, warrant careful monitoring and further research.

The anti-fibrotic effects of BTX are another area of interest. By reducing smooth muscle spasms and the mechanical stress that contributes to scar formation, BTX may lower the incidence of refractory strictures—a common and debilitating complication of esophageal surgery. However, clinical data on long-term outcomes in human subjects remain sparse, and larger cohort studies with extended follow-up are necessary to confirm these findings.

Another intriguing application of BTX lies in its potential to enhance minimally invasive surgical techniques for LGEA. Thoracoscopic approaches, which are gaining popularity due to their reduced morbidity compared to open surgery, could benefit from the muscle-relaxing properties of BTX. Early studies suggest that BTX injections can facilitate the mobilization of esophageal segments, making minimally invasive procedures more feasible even in complex cases of LGEA.

The future of BTX in LGEA treatment appears promising, with ongoing research exploring new frontiers. For instance, the combination of BTX with regenerative medicine techniques, such as tissue engineering and stem cell therapies, could revolutionize the field. By creating bioengineered esophageal tissues pre-treated with BTX, it may be possible to further optimize surgical outcomes and reduce reliance on traditional, high-risk procedures.

In conclusion, botulinum toxin represents a novel and versatile tool in the management of long gap esophageal atresia. Its ability to reduce tissue tension, enhance elongation, and improve anastomotic healing positions it as a valuable adjunct in addressing the challenges of this complex condition. While further clinical studies are needed to refine its applications and establish standardized protocols, the integration of BTX into LGEA management has the potential to significantly improve outcomes for affected infants and their families. With ongoing advancements in both surgical techniques and pharmacological interventions, the role of BTX is likely to expand, offering new hope in the treatment of this challenging congenital anomaly.

References:

1- Ellebæk M, Qvist N, Rasmussen L: Secondary anastomosis after preoperative botulinum type A toxin injection in a case with long gap oesophageal atresia. Eur J Pediatr Surg. 23(4):325-6, 2013

2- Larsen HF, Jensen TS, Rasmussen L, Ellebæk M, Qvist N: Intramural injection with botulinum toxin significantly elongates the pig esophagus. J Pediatr Surg. 48(10):2032-5, 2013

3- Dibbern CB, Rose M, Ellebæk MB, Qvist N: The Effect of Intramural Botulinum Toxin Injections on the Elongation of the Piglet Oesophagus Is Time Dependent. Eur J Pediatr Surg. 27(1):56-60, 2017

4- Pike AH, Zvara P, Antulov MR, et al: Intramural Injection of Botulinum Toxin A in Surgical Treatment of a Long Gap Esophageal Atresia-Rat Model. Eur J Pediatr Surg. 30(6):517-523, 2020

5- Svensson E, Zvara P, Qvist N, et al: The Effect of Botulinum Toxin Type A Injections on Stricture

Formation, Leakage Rates, Esophageal Elongation, and Anastomotic Healing Following Primary Anastomosis in a Long- and Short-Gap Esophageal Atresia Model - A Protocol for a Randomized, Controlled, Blinded Trial in Pigs. Int J Surg Protoc. 25(1):171-177, 2021
6- Izadi S, Koo DC, Shieh HF, et al: Botulinum Toxin Enhanced Foker Process for Long Gap Esophageal Atresia. J Pediatr Surg. 59(12):161628, 2024

Newborn Infant Parasympathetic Evaluation Monitor

The Newborn Infant Parasympathetic Evaluation (NIPE) monitor represents a significant advancement in neonatal and pediatric care, offering a non-invasive means of assessing pain and discomfort in infants under two years of age. The device, developed to measure parasympathetic activity through heart rate variability (HRV), provides an objective pain index, ranging from 0 to 100. This technology addresses longstanding limitations of traditional pain assessment methods, which have relied heavily on subjective observations and behavioral scales, such as the Premature Infant Pain Profile Revised (PIPP-R) and the Face, Legs, Activity, Cry, Consolability (FLACC) scale.

Traditional behavioral scales have several drawbacks, including high interobserver variability, time-intensive scoring, and limited applicability in deeply sedated or anesthetized patients. The NIPE monitor overcomes these issues by continuously analyzing high-frequency HRV to evaluate parasympathetic tone. A decrease in the NIPE score indicates heightened pain or stress, while an increase suggests improved comfort. The monitor generates instantaneous (NIPEi) and mean (NIPEm) indices, allowing real-time and averaged pain assessments, respectively.

Several studies have explored the utility of the NIPE monitor across various clinical settings, including acute pain during procedural interventions, intraoperative nociception, and postoperative pain management. However, the results have been mixed, highlighting both the potential and the limitations of this technology.

The NIPE monitor has been evaluated for its ability to detect acute procedural pain in preterm and term neonates. A 2020 study by Gendras et al. examined its effectiveness during routine painful and stressful procedures in preterm infants. While the NIPE index demonstrated high sensitivity and negative predictive value for predicting severe pain during skin-breaking procedures, no significant correlation was found between NIPE and PIPP-R scores during routine painful interventions. This raised concerns about its ability to fully capture acute pain responses, especially in less invasive procedures.

Other studies have similarly reported mixed findings. For instance, the monitor successfully detected significant decreases in NIPE scores during painful interventions, but its correlation with traditional pain scales like the Neonatal Acute Pain (DAN) scale was inconsistent. These discrepancies may stem from differences in patient demographics, procedural types, and study methodologies.

Intraoperative pain assessment is another area where the NIPE monitor shows promise. Traditional methods of evaluating nociception during surgery, such as observing changes in

heart rate and blood pressure, are empirical and prone to variability. The NIPE monitor offers an objective alternative by continuously measuring parasympathetic activity. A 2024 systematic review highlighted the monitor's ability to detect nociceptive events like skin incisions and intubations during surgery, as well as insufficient analgesia. It also demonstrated high sensitivity and specificity for identifying pain.

However, the device's utility may be limited by the complexity of intraoperative pain management. For example, a study comparing open and laparoscopic inguinal hernia repairs found significant differences in NIPE scores, with laparoscopic procedures associated with greater pain despite similar analgesic regimens. This finding underscores the importance of contextual factors, such as the type of surgical intervention and the adequacy of regional anesthesia.

Postoperative pain assessment has also been explored using the NIPE monitor. A 2023 prospective study demonstrated a weak but statistically significant correlation between intraoperative NIPE indices and postoperative FLACC scores. This association was strongest immediately after surgery but diminished over time, likely due to the administration of postoperative analgesia. The findings suggest that while the NIPE monitor can predict early postoperative pain, its utility may decrease as external factors, such as analgesic interventions, modify the pain response.

Another study compared pain outcomes in infants undergoing open versus laparoscopic hernia repairs. Postoperative NIPE scores were significantly lower in the laparoscopic group, reflecting higher pain levels. These results highlighted the monitor's ability to objectively differentiate pain levels between surgical approaches, providing valuable insights for tailoring postoperative care.

Beyond pain assessment, the NIPE monitor has been used to evaluate comfort and stress levels in neonates. Studies have shown increased NIPE scores during interventions promoting comfort, such as skin-to-skin contact and facilitated tucking. However, these findings are not universal, with some studies reporting no significant changes during specific comfort measures. The variability in results underscores the need for further research to clarify the monitor's role in non-pain-related assessments.

While the NIPE monitor offers several advantages, its adoption in clinical practice faces challenges. One major limitation is its inconsistent correlation with traditional pain scales, which remain the gold standard for pain assessment. The reliance on HRV as a sole indicator of pain may overlook other physiological and behavioral components of the pain response.

Another issue is the heterogeneity of study populations and methodologies. Variations in gestational age, clinical settings, and procedural types make it difficult to generalize findings. Furthermore, the monitor's accuracy in detecting subtle changes in parasympathetic activity may be influenced by confounding factors such as medication use, underlying medical conditions, and environmental stressors.

Finally, the NIPE monitor's primary focus on parasympathetic activity may limit its applicability in conditions were sympathetic responses dominate. For instance, pain responses involving significant sympathetic activation may not be adequately captured, reducing the monitor's overall sensitivity.

Despite these challenges, the NIPE monitor holds promise as a valuable tool for neonatal and pediatric pain assessment. To fully realize its potential, further research is needed to address existing limitations. Large-scale, multicenter studies with standardized protocols are essential for validating its accuracy and reliability. Additionally, integrating the NIPE monitor with other pain assessment methods, such as behavioral scales and biochemical markers, could enhance its clinical utility.

Advances in technology may also improve the monitor's performance. For example, refining the HRV algorithm to account for individual variability and incorporating machine learning techniques could increase its sensitivity and specificity. Expanding its use to other clinical settings, such as the evaluation of chronic pain and stress, could further broaden its applications.

The Newborn Infant Parasympathetic Evaluation monitor represents a significant step forward in the objective assessment of pain and discomfort in neonates and infants. While its utility has been demonstrated in various clinical settings, including procedural pain, surgery, and postoperative care, inconsistencies in findings highlight the need for further research. With continued refinement and validation, the NIPE monitor has the potential to revolutionize pain management and improve outcomes for this vulnerable population.

References:

1- Gendras J, Lavenant P, Sicard-Cras I, Consigny M, Misery L, Anand KJS, Sizun J, Roué JM: The newborn infant parasympathetic evaluation index for acute procedural pain assessment in preterm infants. Pediatr Res. 89(7):1840-1847, 2021

2- Recher M, Boukhris MR, Jeanne M, Storme L, Leteurtre S, Sabourdin N, De Jonckheere J: The newborn infant parasympathetic evaluation in pediatric and neonatology: a literature review. J Clin Monit Comput. 35(5):959-966, 2021

3- Ivanic S, Tong LS, Laird A, Malhotra A, Nataraja RM, Lang C, Pacilli M: The Newborn Infant Parasympathetic Evaluation (NIPE™) monitor predicts post-operative pain in children undergoing day-procedures: A prospective observational study. J Pediatr Surg. 58(4):684-688, 2023

4- Manzar S: Does the Newborn Infant Parasympathetic Evaluation Monitor Predict Post-Operative Pain? J Pediatr Surg. 58(9):1852, 2023

5- Sakthivel M, Su V, Nataraja RM, Pacilli M: Newborn and Infant Parasympathetic Evaluation (NIPE™) Monitor for Assessing Pain During Surgery and Interventional Procedures: A Systematic Review. J Pediatr Surg. 59(4):672-677, 2024

6- Sakthivel M, Bapna T, Ivanic S, Lang C, Nataraja RM, Pacilli M: An Objective Evaluation of Intraoperative and Postoperative Pain in Infants Undergoing Open Inguinal Herniotomy and Laparoscopic Inguinal Hernia Repair Using the Newborn Infant Parasympathetic Evaluation (NIPE™) Monitor. J Pediatr Surg. 60(2):161651, 2025

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