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Evaluation and Research Progress of Neonatal Ventilator Weaning Strategies

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Abstract

With the continuous advancement of neonatal intensive care technology, mechanical ventilation has become an important means of neonatal respiratory support therapy. Prolonged mechanical ventilation can lead to ventilator-related problems, lung injury, respiratory muscle fatigue, etc., increasing the incidence of chronic lung disease and the risk of death in neonates; premature weaning can easily lead to weaning failure and increase the risk of re-intubation or repeated intubation. Rationally assessing the timing of weaning and formulating a scientific weaning strategy have become important issues in the management of neonatal respiratory support. This article systematically reviews the latest research progress on the main factors affecting the success of neonatal weaning, clinical evaluation methods, and weaning strategies, aiming to provide evidence-based support for clinicians, optimize the weaning process, improve the success rate of weaning, reduce the occurrence of related complications, and improve neonatal prognosis.

Keywords

Neonate, Mechanical Ventilation, Weaning Assessment, Weaning Strategy

1. Introduction

With the rapid development of perinatal medicine and neonatal intensive care technology, mechanical ventilation has become an indispensable means of life support in the treatment of neonatal respiratory failure and has played a key role in significantly reducing the mortality rate of critically ill neonates [1]-[3]. However, a large number of studies have shown that prolonged mechanical ventilation can lead to many serious complications, including ventilator-induced lung injury (VILI), respiratory muscle atrophy and dysfunction, and ventilator-associated

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pneumonia (VAP) [4] [5]. It not only prolongs the hospitalization time of children and increases the risk of death, but also increases the risk of chronic lung diseases such as bronchopulmonary dysplasia (BPD), seriously threatening the long-term quality of life [6]. It is reported that the annual incidence of mechanical ventilation-related pulmonary complications in the neonatal intensive care unit (NICU) of a secondary care hospital in Sonora, Mexico is as high as 49.05% [7]. For every day of mechanical ventilation in extremely premature infants, their motor function scores decrease by an average of 0.5 points. Long-term ventilation is closely associated with impaired brainstem development, delayed white matter maturation, and decreased motor function in the preschool period [8]. Compared with newborns with mechanical ventilation for no more than 7 days, infants with ventilation for more than 14 weeks have a significantly increased risk of death, which can reach 60% at 16 weeks [9].

Premature weaning can easily lead to weaning failure, while delayed weaning may increase complications and aggravate lung damage. Internationally, few NICUs have weaned according to guidelines, and more decisions are made based on the clinical evaluation of doctors [10] [11]. This is because, while guideline-based weaning checklists can reduce practice variability and shorten ventilation duration, the neonatal population is highly heterogeneous in terms of gestational age, lung maturity, and comorbidities. Strict adherence to guidelines may trigger the risk of insufficient or excessive extubation attempts in infants with physiological abnormalities. Therefore, building a scientific and accurate weaning evaluation system and formulating individualized weaning strategies have become key issues that need to be urgently addressed in clinical practice. This article reviews the research progress on the influencing factors, evaluation methods, and strategies of weaning from neonatal mechanical ventilation, in order to provide clinical physicians with evidence-based theoretical support and practical guidance.

2. Analysis of Factors Affecting Successful Weaning

2.1. The Decisive Role of Individual Differences in Newborns

Gestational age and birth weight are key indicators for assessing lung maturity and are considered to be the core factors affecting the success rate of neonatal weaning [12]. Compared with full-term infants, the failure rate of weaning in premature infants is significantly higher. Liu Xiaoyi *et al.* reported that the failure rate of weaning in premature infants was 17% to 19%, and the failure rate in extremely premature infants was as high as 32% to 50% [13]. This is mainly due to the extremely immature alveolar structure and function of extremely premature infants, especially the lack of ability to synthesize pulmonary surfactant, which makes them more likely to suffer from respiratory failure after weaning. Jensen *et al.* also confirmed that the cumulative duration of mechanical ventilation is closely related to the risk of BPD in extremely low birth weight infants. In other words, the lower the lung maturity, the longer the mechanical ventilation support time required, and the higher the risk of BPD [14].

In recent years, the role of individual genetic factors in affecting the difficulty of weaning has also received increasing attention. Among them, ABCA3 gene mutations have been shown to cause impaired synthesis of pulmonary surfactant, which significantly prolongs the duration of mechanical ventilation. According to relevant studies [15] [16], the average mechanical ventilation time of newborns carrying this gene mutation can be extended several times, which suggests that it should be taken seriously in clinical evaluation and weaning decisions.

2.2. The Complexity of Various Underlying Diseases and Complications

Underlying diseases constitute another important aspect that affects the success of neonatal weaning. Respiratory distress syndrome (RDS) remains one of the most common respiratory diseases in the NICU, accounting for approximately 50% of difficult weaning cases [17]. BPD is another type of chronic lung disease that is highly challenging to the weaning process. A prospective cohort study [18] found that children with BPD are highly susceptible to infections such as RSV, with an RSV-related lower respiratory tract infection rate of up to 56% and a re-hospitalization rate of 62%, significantly increasing the risk of respiratory failure and reintubation after weaning. Poor control of various underlying diseases in the neonatal period will significantly increase the difficulty of weaning, and their influencing mechanisms and management points vary, as shown in **Table 1**.

Table 1. Impact of key underlying diseases on ventilator weaning and management strategies.

Underlying disease	Core pathological changes	Major challenges to weaning
ARDS [19]	Alveolar collapse, hyaline membranes, infection	Decreased lung compliance, oxygenation disorders
BPD [20]	Alveolar simplification,	Fibrosis significant increase in airway resistance, tendency to CO_2 retention
PDA [21]	Left-to-right shunt	Pulmonary edema, heart failure
LCC [22]	Relative adrenal cortex insufficiency	Refractory hypotension, poor tissue perfusion
NEC [23]	Intestinal mucosal damage, intestinal wall gas	Risk of sepsis, metabolic acidosis
PPHN [24]	Abnormal pulmonary vascular contraction	Low cardiac output, hypoxemia, hypercapnia

ARDS: Acute Respiratory Distress Syndrome; BPD: Bronchopulmonary Dysplasia; PDA: Patent Ductus Arteriosus; LCC: Late-Onset Circulatory Collapse; NEC: Necrotizing Enterocolitis; PPHN: Persistent Pulmonary Hypertension of the Newborn.

2.3. Ventilator Parameter Settings and Timing of Weaning

The setting of ventilator parameters and the timing of weaning are another important aspect that affects the success of weaning in neonates [25]. Improper pa-

rameter adjustment, especially during the transition period of weaning, may induce a series of pathophysiological changes, leading to weaning failure. For example, Shi R. *et al.* [26] found that the aggravation of pulmonary edema induced by weaning was closely related to the sudden drop in positive end-expiratory pressure (PEEP), emphasizing that PEEP should be adjusted carefully during weaning to avoid sudden evacuation and prevent acute ventilation disorders caused by redistribution of fluid in the lungs [26]. Gas exchange and spontaneous breathing during weaning are also important parameters for assessing the readiness for weaning. A logistic regression analysis showed that if abnormal indicators such as high carbon dioxide partial pressure ($PaCO_2$ > 55 mmHg) and high spontaneous breathing rate (>60 times/min) were present during weaning, the risk of weaning failure was significantly increased, with relative risks (OR) of 4.2 and 3.8, respectively [17]. Regarding the judgment of the timing of weaning, most studies currently support a comprehensive evaluation strategy based on a series of physiological parameters.

It is generally believed that when the primary disease is effectively controlled, the overall condition of the child is stable, and the results of arterial blood gas analysis are normal, an attempt to wean the patient from the mechanical ventilation can be considered. Commonly used indicators for preparation for weaning include: peak inspiratory pressure (PIP) ≤ 18 cmH_2O, positive end-expiratory pressure (PEEP) maintained at 2 - 4 cmH_2O, respiratory rate (RR) ≤ 10 times/min, inspired oxygen concentration (FiO_2) ≤ 0.4, and no serious abnormalities in blood gas indicators [27]. These parameters provide a basic basis for the clinical formulation of individualized weaning plans and are also important reference standards in the current evaluation of neonatal weaning. However, it may be difficult for some patients to achieve the above parameters and they may face the need for longer invasive ventilation. Therefore, doctors need to make clinical judgments. Currently, NIPPV, non-invasive high-frequency ventilation and other modes can save some children who have failed to be weaned from the mechanical ventilation and help them get rid of invasive mechanical ventilation as soon as possible.

3. Research Progress at Home and Abroad

3.1. Research Progress on Weaning Assessment Technology

3.1.1. Application of Lung Ultrasound Score (LUS) in Prediction of Weaning

In recent years, lung ultrasound (LUS), as a non-invasive, radiation-free, and repeatable bedside imaging assessment tool, has shown important clinical value in the management of neonatal mechanical ventilation and the assessment of the timing of weaning [28] [29]. LUS can not only be used to predict the need for surfactant therapy, the intensity of respiratory support, and assist in judging the risk of progression of BPD [30] [31], but also a number of prospective studies from Italy and the United States have confirmed that the LUS scoring system (especially the modified 12-zone method) is closely related to the oxygenation index

and the intensity of respiratory support, and can effectively predict the success of weaning, with a sensitivity of more than 85% [32] [33]. Rai *et al.* reported that LUS scoring is more accurate than traditional chest X-ray scoring in predicting whether premature infants with RDS need surfactant, suggesting that it has potential advantages in early intervention decisions [34]. In recent years, expert consensus guidelines in related fields have included LUS in the management pathway of neonatal respiratory support as an important supplement to traditional assessment methods (such as blood gas analysis and clinical scoring) to improve the accuracy and safety of weaning judgments [35]. Currently, artificial intelligence (AI)-assisted LUS quantitative analysis technology and multimodal assessment models (such as LUS combined with cardiac ultrasound and electrical impedance imaging) are being explored in order to further improve the sensitivity and specificity of weaning prediction.

3.1.2. Application of Diaphragmatic Function Assessment and Auxiliary Technology in Weaning

Diaphragmatic dysfunction is one of the important mechanisms for failure of mechanical ventilation weaning in extremely low birth weight infants [36] [37]. In recent years, diaphragmatic ultrasound has been widely used in neonatal weaning management as a non-invasive, dynamic functional assessment tool. The contraction capacity of the diaphragm can be quantified by real-time measurement of the diaphragmatic thickness fraction and diaphragmatic displacement amplitude. Marino S. *et al.* found that when the diaphragmatic thickness fraction (DTF) DTF > 30%, the weaning success rate was significantly improved, showing its practical value in predicting weaning [38] [39].

In addition to diagnostic technology, intervention methods related to diaphragmatic function have also made positive progress. Transdiaphragmatic pressure monitoring technology can evaluate the mechanical efficiency of the diaphragm in real time and guide individualized weaning strategies; external diaphragmatic pacing technology enhances the diaphragm contraction function through electrical stimulation, and has also shown stronger advantages than conventional management in children with difficult weaning [40]. Neurally Adjusted Ventilatory Assist (NAVA) is an innovative synchronous ventilation mode that captures diaphragmatic electrical activity to trigger mechanical ventilation in real time, achieving high-precision neural-mechanical synchronization, effectively reducing the patient-ventilator asynchrony in traditional ventilation, and improving ventilation comfort and tolerance to weaning [41]. These advances indicate that dynamic monitoring of diaphragmatic function and related assistive technologies are becoming key means to optimize the neonatal weaning process and improve the success rate.

3.1.3. Application of Multi-Parameter Prediction Model and Artificial Intelligence in Risk Assessment of Weaning

In recent years, the risk prediction model of weaning based on multi-factor Logistic regression analysis has also become a research hotspot, providing a more

objective and quantitative evaluation tool for clinical practice [42] [43]. This model integrates multiple clinical and physiological parameters to comprehensively evaluate the risk of weaning failure, which is superior to the traditional prediction method of a single indicator. The Logistic regression model constructed by Merlin *et al.* takes weaning failure as the dependent variable and incorporates multiple clinical variables such as mechanical ventilation time, spontaneous respiratory rate, blood gas indexes, and ultrasound parameters for analysis [44]. It has high accuracy in predicting weaning failure, showing excellent sensitivity and specificity, and has good clinical guidance significance.

With the development of artificial intelligence technology, the risk prediction model of weaning is gradually moving from traditional statistical methods to intelligent analysis platforms. In neonatal settings, machine-learning models increasingly exploit high-frequency physiologic streams beyond static clinical variables. Typical inputs include beat-to-beat heart rate and heart rate variability metrics derived from ECG; breath-by-breath respiratory mechanics and ventilator waveforms (airway pressure, flow, tidal volume, inspiratory/expiratory time and leak); continuous SpO_2 and plethysmography features; transcutaneous CO_2 or end-tidal CO_2 trends; electrical activity of the diaphragm (EAdi); and lung ultrasound. Fusing these high-resolution signals allows models to capture nonlinear, rapidly evolving patterns in gas exchange and work of breathing, thereby improving extubation-failure prediction over single-time-point metrics and has entered the stage of clinical application verification [45] [46]. The machine learning model constructed by Brasher *et al.* combines the real-time data stream of pulse oximeter and ventilator for modeling, which significantly improves the prediction accuracy of weaning failure in premature infants [47]. This type of algorithm can automatically identify complex nonlinear relationships and interactions between variables, showing a prediction potential far beyond the traditional Logistic model. The decision to wean patients from mechanical ventilation is undergoing a transformation from being based on experience or a single physiological parameter to being intelligent and individualized with multi-parameter integrated models and AI-assisted analysis as the core.

3.2. Research Progress on Weaning Strategies

3.2.1. Optimization of Respiratory Support Mode and Individualized Weaning Pathway

In recent years, the focus of research on neonatal weaning strategies has shifted from the evaluation of a single ventilation mode to the evaluation and dynamic adjustment of individualized and refined combinations. The core goal is to accelerate the weaning process, shorten the mechanical ventilation time, and effectively reduce the occurrence of complications while ensuring respiratory stability and safety [48]. Pressure support ventilation (PSV) can sense the child's inspiratory efforts and provide synchronous pressure support, which helps to exercise respiratory muscles and improve endurance. In recent years, it has also been widely used in clinical practice as a ventilation mode before weaning. Lauret V *et al.* found that

PSV can significantly shorten the weaning time and improve the success rate of weaning compared with synchronized intermittent mandatory ventilation (SIMV) [49]. Bi-level positive airway pressure (BiPAP) and non-invasive positive pressure ventilation (NIPPV) are more effective than nasal continuous positive airway pressure (NCPAP) and high-flow nasal cannula (HFNC) in assisting the weaning of very low birth weight infants. The former can provide higher inspiratory support pressure and positive end-expiratory pressure, and has shown greater potential in preventing respiratory failure after extubation [50] [51]. HFNC is widely used in relatively stable or mildly ill children as one of the means of excessive support after weaning because it is comfortable to wear and easy to operate [52]. In addition, the intelligent closed-loop system has emerged in the field of neonatal respiratory support. The system can automatically adjust the airflow rate, oxygen concentration and pressure support level based on real-time monitoring of respiratory parameters, providing a smoother transition for the weaning process to the greatest extent possible. An example is an automated FiO_2 titration system, which maintains SpO_2 within a predefined target range by gradually increasing or decreasing FiO_2 in response to deoxygenation or hyperoxia events. Another example is a pressure support/PEEP adjustment system, which is guided by real-time signals (such as EAdi or end-tidal/transcutaneous CO_2) and aims to minimize patient-ventilator dyssynchrony and stabilize ventilation with fewer manual adjustments [53].

The decision-making of doctors in clinical practice is very important. A reasonable support mode conversion path should be formulated based on individual factors such as the gestational age, weight, underlying diseases (such as RDS, BPD), neurodevelopmental maturity, and current respiratory mechanical status of the child. For extremely premature infants, a sequential strategy of "high-frequency oscillatory ventilation (HFOV), normal-frequency mechanical ventilation, PSV, NIPPV or HFNC" can be adopted, and the weaning mode can be dynamically selected based on parameters such as respiratory index, lung compliance, blood gas analysis, and transcutaneous carbon dioxide, and the ventilation mode and parameter reduction can be adjusted in a timely manner [2] [54]. The optimization of respiratory support mode and the establishment of an individualized weaning path are expected to further improve the weaning quality and the long-term prognosis of children.

3.2.2. Optimal Application of Drugs in Neonatal Weaning Management

Drug therapy plays a vital role in the management of weaning from mechanical ventilation in neonates, and is gradually moving towards individualization and precision [55]. Caffeine, pulmonary surfactant, and glucocorticoids are the three types of drugs that are currently being studied more. Caffeine has good safety and neurorespiratory stimulant effects, and has a wide therapeutic window, making it one of the first choice drugs for promoting weaning [56]. The timing and dosage of caffeine administration are being further optimized. The currently commonly used regimen is an initial loading dose of 20 mg/kg, and the maintenance dose

starts at 5 mg/kg/day, which can be increased to 10 mg/kg/day based on clinical evaluation [57] [58]. The application of pulmonary surfactant (PS) in weaning has also made important progress in recent years. The new generation of synthetic PS has better characteristics in terms of composition structure and alveolar stability, can improve the oxygenation index faster, reduce lung inflammatory response, and create a more favorable lung function foundation for weaning [59] [60]. In optimizing the management strategy of weaning from neonates, glucocorticoids have attracted attention due to their potential role in promoting the elimination of ventilation dependence. Its mechanism of action is mainly to reduce lung inflammation, edema and exudation through a powerful anti-inflammatory effect, and improve lung compliance; at the same time, it enhances the responsiveness of β-adrenergic receptors to bronchodilators, which helps to reduce airway resistance, thereby creating favorable conditions for smooth weaning. However, this type of drug has significant risks, including inducing hyperglycemia, increasing susceptibility to infection, and possible long-term adverse effects on nervous system development. Therefore, the latest domestic and international consensus emphasizes [61] [62]: the use of glucocorticoids in neonatal weaning must be strictly limited to specific indications to avoid abuse; and blood sugar levels and neurodevelopmental indicators must be closely monitored during use to balance its potential benefits and risks [63].

Furthermore, pharmacological therapy should be accompanied by adequate nutritional support (caloric/protein intake, micronutrients such as phosphate and magnesium) to maintain respiratory muscle strength and reduce fatigue, especially in extremely premature infants with limited reserves. Similarly, using the lowest effective dose and interrupting sedation at appropriate times daily can help maintain respiratory drive and reduce patient-ventilator asynchrony. Attention to anemia, electrolyte and fluid balance should be included in the daily weaning checklist to prevent preventable extubation failures.

4. Conclusions

The success of neonatal ventilator weaning depends on the comprehensive evaluation of multiple factors and the continuous optimization of individualized management strategies. It involves individual differences of newborns, various underlying diseases and complications, and the doctor's reasonable setting of ventilator parameters and judgment on the timing of weaning. It also depends on the progress of clinical evaluation technologies at home and abroad, such as ultrasound scoring, diaphragm function evaluation technology, multi-parameter prediction models, artificial intelligence and other advanced technologies. We look forward to more accurate neonatal ventilator-related diagnosis and support technologies for clinical use.

Future research directions are aimed at:

1) Conducting a multicenter pragmatic trial to test a protocol-based combined clinician intervention versus usual care, with outcomes including extubation fail-

ure, ventilation days, and bronchopulmonary dysplasia (BPD)-free survival.

2) Identifying biological and imaging phenotypes (e.g., BPD subtypes, genetic markers) that predict prolonged ventilation or extubation failure to enable precise weaning pathways.

3) Externally prospectively validating machine learning models using continuous waveform data (e.g., ventilator waveform, SpO_2, CO_2, EAdi, and POC-LUS) with transparent model reporting and bedside integration pathways.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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