MECHANICAL VENTILATION
IN CRITICALLY ILL CHILDREN

FROM INTUITION TO EVIDENCE BASED.

Anita Duijndam

Mechanical Ventilation in Critically Ill Children: From intuition to evidence based

Mechanische Beademing bij Kritisch Zieke Kinderen: Van intuïtie naar wetenschappelijk bewijs

Proefschrift

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Anita Agnes Petronella Maria Duijndam
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Promotiecommissie

Promotoren: Prof.dr. D. Tibboel

Prof.dr. M. van Dijk

Overige leden: Prof.dr. D.A.M.P.J. Gommers

Prof.dr. L.N. Tume

Prof.dr. J.B. van Woensel

Copromotor: Dr.W.G. Ista

PROLOGUE

Mechanical ventilation was something magical during my pediatric ICU training in 1992 and later when I was a PICU nurse; all children on the PICU were being ventilated, but few nurses really understood its workings. Only the physicians knew the ins and outs. I tried to understand it, but found that the experienced nurses could not answer my questions. The knowledge was not being shared from physicians to nurses and there was no clear ventilation policy. To get more involved and understand mechanical ventilation better, I joined the respiratory work group on the PICU. This also meant I had to teach at continuing education classes for the nurses – but I still knew too little. Then we heard about the possibility of Ventilation Practitioner (VP) training, a one-year course conducted outside the hospital. During this VP training in 2006, my eyes opened and I got really excited about mechanical ventilation. Although I did not think I was technically minded, I now understood what mechanical ventilation was all about and that, as main treatment in the PICU, it was not only beneficial, but could do harm as well if not applied properly. We also took a pig lung training course from Professor Lachmann and dr. Houmes in Erasmus MC, which made the ''Open lung concept'' clear to us. After that course, we were able to familiarize the nursing team with this concept. A training program for the nursing team was introduced, and more VP joined. However, it became clear to me that many issues regarding ventilation for children were not evidence based, but performed based on intuition and so I wanted to contribute to that with this thesis.

INHOUD

chapter 1

MECHANICAL VENTILATION IN CHILDREN: FROM INTUITION TO EVIDENCE BASED.

…. "Then into it he blew the breath of life,
And man became a living soul. Amen"

From God's Trombones, The Creation,
by James Weldon Johnson, 1927

As long as one breathes, one lives, but sometimes one has to be supported temporarily to breathe. This is done by means of invasive mechanical ventilation (MV) and this is an important part in the treatment of critically ill children in a pediatric intensive care (PICU). However, MV is also associated with complications such as ventilator-induced lung injury, ventilator-associated pneumonia (1-5), problems related to sedation, and post-traumatic stress in individual children and parents. (6-8) These complications can lead to prolonged duration of ventilation and PICU stay. Therefore, it is important to have ventilation strategies that are evidence based to prevent these complications. The duration of ventilation should be kept as short as possible but without needing reintubation, because extubation failure is associated with longer PICU length of stay, increased morbidity and increased mortality. (9-13)

The ventilation taxonomy of Chatburn et al. is used worldwide to classify ventilation modes. (14) See figure 1. A ventilation mode is defined by the control variable (pressure control or volume control), the breath sequence (continuous mandatory ventilation or intermittent mandatory ventilation (initiated by the patient or the ventilator and finished by the ventilator) or continuous spontaneous ventilation (initiated by the patient and finished by the patient). In addition, a targeting scheme can be used that describes how the ventilator will achieve the pre-set targets. Examples are pressure regulated volume control (with a guaranteed tidal volume), neurally adjusted ventilator assist (NAVA), variable pressure support, adaptive support ventilation, and smart care. (14) Furthermore, we have high frequency oscillation (HFO), a form of pressure controlled intermittent mandatory ventilation with a set-point control scheme. In contrast to conventional pressure controlled intermittent mandatory ventilation, in which relatively small spontaneous breaths may be superimposed on relatively large mandatory breaths, HFO superimposes very small mandatory breaths (oscillations) on top of spontaneous breaths. (15)
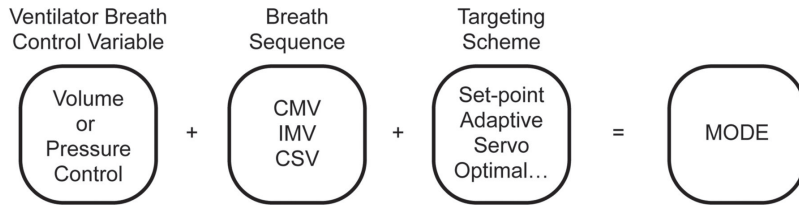
FIGURE1 Building blocks for constructing a ventilation mode according to the taxonomy model of Chatburn

CMV; continuous mandatory ventilation, IMV; intermittent mandatory ventilation, CSV; continuous spontaneous ventilation.
Targeting Scheme:
Set point; The operator sets all parameters of the pressure waveform (pressure control modes) or volume and flow waveforms (volume control modes)
Servo; the output of the ventilator (pressure/volume/flow) automatically follows a varying input
Adaptive; the ventilator automatically sets target(s) between breaths in response to varying patient conditions
Optimal; The ventilator automatically adjusts the targets of the ventilatory pattern to either minimize or maximize some overall performance characteristic (e.g., work rate of breathing)
Intelligent (i); a targeting scheme that uses artificial intelligence programs such as fuzzy logic, rule-based expert systems, and artificial neural networks
Bio-variable (b) The ventilator automatically adjusts the inspiratory pressure or VT randomly

So far, there is too little evidence as to which form of ventilation is best for children and for different lung diseases to guarantee adequate gas exchange with minimal secondary injury and ventilation-related adverse events. (16, 17) Ideally, the ventilation management is based on proven effective strategies. Pediatric intensive care units worldwide use a wide variety of ventilation modes. Nevertheless, a particular mode is often not targeted specifically to the underlying disease, but rather is determined by the intensive care physician's experience, local PICU policy and protocols, or outcomes of studies in adults. An unambiguous international guideline is still lacking. (18-20)

Successful implementation of a protocol or guideline at a PICU takes time, and adherence often proves to be a difficult issue. (21-23) Interdisciplinary collaboration, effective communication and leadership support are necessary for proper implementation and future adherence. (22, 24-26) Multifaceted implementation strategies are needed, such as education tailored to the specific learning needs of the PICU team combined with bedside reminders, audits and visual feedback.

On our search for the best form of MV in children we came across Neurally Adjusted Ventilatory Support (NAVA), which became available on the Servo I, our ventilation machine, around 2009-2010. NAVA was a new form of continuous spontaneous ventilation with a targeting scheme that uses electrical activity of the diaphragm to synchronize the patient's breathing with the machine's breathing cycle. The patient's own respiratory drive, measured by the electrical activity of the diaphragm, controls the timing and the magnitude of the pressure delivered, known as neuroventilatory coupling. NAVA seemed promising, especially in terms of better synchronization of the ventilator with the patient's own activity. So far only a few studies on the application of NAVA in neonates and children have been published but overlooked its practical feasibility in neonates and children and patient comfort. (27-31)

Just as there is little evidence as to which form of ventilation is best for children, there is also no consensus on weaning off ventilation and extubation criteria in children. (16) On average, critically ill children require 5-7 days on ventilation, depended on reason of admission, after which they are extubated after a weaning period. After that, respiratory support such as non-invasive ventilation, high flow nasal cannula or oxygen via a nasal cannula or non-rebreathing mask is sometimes required. (19, 32-35) The weaning period consists of either the gradual reduction of ventilation, or an extubation readiness test in the form of a spontaneous breathing trial. This trial assesses the patient's ability to breathe while receiving minimal or no ventilator support before extubation. Optimal management of mechanical ventilation and weaning requires dynamic and collaborative decision-making to minimize complications and avoid delays in the transition to extubation. If nurses and physicians do not collaborate well enough, ventilation decision-making may be fragmented, inconsistent or delayed. (36-38) The role of nurses may be pivotal for effective decision-making during weaning of ventilation due to their active presence at the patient's bedside 24 hours per day and ability to observe whether the child recovers or deteriorates. (39) The introduction of protocol-based weaning parameters associated with a training of the nurses on ventilator management could be the basis for the hypothesis that a nurse-driven ventilation weaning protocol could optimize this process.

The optimal timing of extubation is still debated. Many invasively ventilated children suffer from respiratory muscle weakness after a period of mechanical ventilation, which is associated with prolonged PICU length of stay and prolonged invasive ventilation duration. Diaphragm thickness and diaphragm thickening fraction (percentage change

in diaphragm thickness from end-expiration to end-inspiration on MV) as assessed with ultrasound are widely used to evaluate diaphragm function in patients with suspected diaphragm weakness, including critically ill children, but mainly in adults. (40-45) In the adult group there is evidence that thickening fraction, measured with ultrasound before extubation, can predict or is associated with failure or success of extubation. (40, 44, 46-48). However, studies of children to evaluate diaphragm thickening fraction on success of extubation are scarce. (49-51)

For children up to the age of 8 years old there are no or not enough reference values of the diaphragm thickness and diaphragm thickening fraction during in- and expiration, unlike older children. (52-55) The availability of reference values can be helpful in studying the clinical relevance of these values in ventilated children. Therefore, ultrasounds of the diaphragm of healthy children in the first place followed by studying the diaphragm of ventilated children can be informative.

OUTLINE OF THE THESIS

The overall aim of this thesis is to seek and enhance evidence for the best way to manage mechanical ventilation in children. The secondary aim is finding the optimal way to ventilate and wean children to extubation from a nursing perspective.

We aimed to providing answers regarding five research questions:

1. Is there evidence of the best ventilation mode in critically ill children?
2. Does a new ventilation strategy lead to more uniformity in the mode of ventilation on a PICU?
3. Is Neurally Assisted Ventilator Assist feasible in ventilated children?
4. Does a larger role for PICU nurses in a nurse-led weaning protocol lead to a shorter length of ventilation?
5. Does assessing the function of the diaphragm through an ultrasound study of the diaphragm thickening fraction help predict whether extubation will be successful in ventilated children?

This thesis is divided in three parts.

PART I

VENTILATION STRATEGIES FOR CRITICALLY ILL CHILDREN

Following the introduction (**chapter 1**), we search for evidence of the best ventilation in children in **chapter 2**, by means of a review that includes RCTs that compare ventilation modes in children and the following parameters: mortality, duration of ventilation (DOV), oxygenation, chronic lung disease and weaning. The outcome could lead to a better understanding of the preferred ventilation mode and could possibly lead to an unambiguous ventilation strategy in the PICU.

Chapter 3 contains an update of the review of 2011, described in chapter 2, in 2020. Again, we compare ventilation modes in children to search for the optimal ventilation mode or strategy for specific diseases. Outcomes are mortality, duration of ventilation, oxygenation, chronic lung disease, weaning and sedation.

As a result of the first review (**chapter 2**), a ventilation policy was set up for the PICU which determines the choice of ventilation mode for children upon admission. In **chapter 4** we examines and describe whether physicians adhere to this protocol, the implementation process and the role of nurses in this implementation process.

PART II

WEANING OF VENTILATION IN CRITICALLY ILL CHILDREN

Part II contains three chapters; **chapter 5,** describing a study of a new form of continuous spontaneous ventilation: neurally adjusted ventilatory assist (NAVA). NAVA is a mechanical ventilation mode controlled by the patient's neurological respiratory drive, measured by the electrical activation of the diaphragm via a probe. This study describes the feasibility and comfort of children during NAVA.

In the study presented in **chapter 6** we investigate the effect of a nurse-led weaning protocol on the duration of ventilation. The nurses could apply an algorithm to wean a

child off ventilation until the moment of extubation. Then, a physician was consulted to determine if the child was really ready be extubated.

This study was followed by a new, Dutch multi-centre study on the same weaning protocol **(chapter 7)**, but with the addition of a spontaneous breathing trial, since in the first weaning study we did not find a shorter duration of ventilation.

PART III

ULTRASOUND OF THE DIAPHRAGM IN HEALTHY CHILDREN AND IN VENTILATED CHILDREN

Part III contains two ultrasound studies, conducted to measure the thickness and thickening fraction of the diaphragm in both healthy children and ventilated children. The study in healthy children serve to establish reference values in children aged 0-8 years **(chapter 8)**.

The study in ventilated children serve to determine whether the thickening fraction of the diaphragm is associated with successful extubation in ventilated children aged 0-18 years. Furthermore, we will describe the change during the ventilation period for diaphragmatic thickening and thickening fraction in ventilated children, **chapter 9**.

Chapter 10 contains the general discussion with the implications of our findings and a comparison with the available literature. The summary of this thesis will be described in **chapter 11.**

LITERATURE

1.   Morinec J, Iacaboni J, McNett M. Risk factors and interventions for ventilator-associated pneumonia in pediatric patients. J Pediatr Nurs. 2012;27(5):435-42.

2.   Srinivasan R, Asselin J, Gildengorin G, Wiener-Kronish J, Flori HR. A prospective study of ventilator-associated pneumonia in children. Pediatrics. 2009;123(4):1108-15.

3.   Klompas M, Branson R, Cawcutt K, Crist M, Eichenwald EC, Greene LR, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 Update. Infect Control Hosp Epidemiol. 2022;43(6):687-713.

4.   Iosifidis E, Pitsava G, Roilides E. Ventilator-associated pneumonia in neonates and children: a systematic analysis of diagnostic methods and prevention. Future Microbiol. 2018;13:1431-46.

5.   Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med. 2019;7(2):115-28.

6.   van Dijk M, Knoester H, van Beusekom BS, Ista E. Screening pediatric delirium with an adapted version of the Sophia Observation withdrawal Symptoms scale (SOS). Intensive Care Med. 2012;38(3):531-2.

7.   Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest. 1998;114(2):541-8.

8.   Colville G, Cream P. Post-traumatic growth in parents after a child's admission to intensive care: maybe Nietzsche was right? Intensive Care Med. 2009;35(5):919-23.

9.   Blackwood B, Burns KE, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. Cochrane Database Syst Rev. 2014(11):CD006904.

10. Burns KEA, Raptis S, Nisenbaum R, Rizvi L, Jones A, Bakshi J, et al. International Practice Variation in Weaning Critically Ill Adults from Invasive Mechanical Ventilation. Ann Am Thorac Soc. 2018;15(4):494-502.

11. Ouellette DR, Patel S, Girard TD, Morris PE, Schmidt GA, Truwit JD, et al. Liberation From Mechanical Ventilation in Critically Ill Adults: An Official American College of Chest Physicians/ American Thoracic Society Clinical Practice Guideline: Inspiratory Pressure Augmentation During Spontaneous Breathing Trials, Protocols Minimizing Sedation, and Noninvasive Ventilation Immediately After Extubation. Chest. 2017;151(1):166-80.

12. Kurachek SC, Newth CJ, Quasney MW, Rice T, Sachdeva RC, Patel NR, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Crit Care Med. 2003;31(11):2657-64.

13. Gaies M, Tabbutt S, Schwartz SM, Bird GL, Alten JA, Shekerdemian LS, et al. Clinical Epidemiology of Extubation Failure in the Pediatric Cardiac ICU: A Report From the Pediatric Cardiac Critical Care Consortium. Pediatr Crit Care Med. 2015;16(9):837-45.

14. Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747-63.

15. Mireles-Cabodevila E, Diaz-Guzman E, Heresi GA, Chatburn RL. Alternative modes of mechanical ventilation: a review for the hospitalist. Cleve Clin J Med. 2009;76(7):417-30.

16. Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med. 2017;43(12):1764-80.

17. Duyndam A, Ista E, Houmes RJ, van Driel B, Reiss I, Tibboel D. Invasive ventilation modes in children: a systematic review and meta-analysis. Crit Care. 2011;15(1):R24.

18. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. Crit Care Med. 2009;37(8):2448-54.

19. Randolph AG, Meert KL, O'Neil ME, Hanson JH, Luckett PM, Arnold JH, et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. Am J Respir Crit Care Med. 2003;167(10):1334-40.

20. Turner DA, Arnold JH. Insights in pediatric ventilation: timing of intubation, ventilatory strategies, and weaning. Curr Opin Crit Care. 2007;13(1):57-63.

21. Sinuff T, Cook D, Giacomini M, Heyland D, Dodek P. Facilitating clinician adherence to guidelines in the intensive care unit: A multicenter, qualitative study. Crit Care Med. 2007;35(9):2083-9.

22. Sinuff T, Eva KW, Meade M, Dodek P, Heyland D, Cook D. Clinical practice guidelines in the intensive care unit: a survey of Canadian clinicians' attitudes. Can J Anaesth. 2007;54(9):728-36.

23. Sinuff T, Muscedere J, Cook DJ, Dodek PM, Anderson W, Keenan SP, et al. Implementation of clinical practice guidelines for ventilator-associated pneumonia: a multicenter prospective study. Crit Care Med. 2013;41(1):15-23.

24. Grol RWM. Implementation; effective improvement of patient care (in Dutch: Implementatie; effectieve verbetering van de patientenzorg). 4th edMaarsen; Elsevier Gezondheidszorg; 2011

25. Stein-Parbury J, Liaschenko J. Understanding collaboration between nurses and physicians as knowledge at work. Am J Crit Care. 2007;16(5):470-7; quiz 8.

26. Davies HT, Nutley SM, Mannion R. Organisational culture and quality of health care. Qual Health Care. 2000;9(2):111-9.

27. Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med. 2010;11(1):7-11.

28. Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med. 2010;11(2):253-7.

29. Sinderby C, Beck J, Spahija J, de Marchie M, Lacroix J, Navalesi P, et al. Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest. 2007;131(3):711-7.

30. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. Nat Med. 1999;5(12):1433-6.

31. Clement KC, Thurman TL, Holt SJ, Heulitt MJ. Neurally triggered breaths reduce trigger delay and improve ventilator response times in ventilated infants with bronchiolitis. Intensive Care Med. 2011;37(11):1826-32.

32. Farias JA, Fernandez A, Monteverde E, Flores JC, Baltodano A, Menchaca A, et al. Mechanical ventilation in pediatric intensive care units during the season for acute lower respiratory infection: a multicenter study. Pediatr Crit Care Med. 2012;13(2):158-64.

33. Wolfler A, Calderoni E, Ottonello G, Conti G, Baroncini S, Santuz P, et al. Daily practice of mechanical ventilation in Italian pediatric intensive care units: a prospective survey. Pediatr Crit Care Med. 2011;12(2):141-6.

34. Mayordomo-Colunga J, Pons-Odena M, Medina A, Rey C, Milesi C, Kallio M, et al. Non-invasive ventilation practices in children across Europe. Pediatr Pulmonol. 2018;53(8):1107-14.

35. Moreel L, Proesmans M. High flow nasal cannula as respiratory support in treating infant bronchiolitis: a systematic review. Eur J Pediatr. 2020;179(5):711-8.

36. Blackwood B, Junk C, Lyons JD, McAuley DF, Rose L. Role responsibilities in mechanical ventilation and weaning in pediatric intensive care units: a national survey. Am J Crit Care. 2013;22(3):189-97.

37. Rose L, Blackwood B, Egerod I, Haugdahl HS, Hofhuis J, Isfort M, et al. Decisional responsibility for mechanical ventilation and weaning: an international survey. Crit Care. 2011;15(6):R295.

38. Tume LN, Kneyber MC, Blackwood B, Rose L. Mechanical Ventilation, Weaning Practices, and Decision Making in European PICUs. Pediatr Crit Care Med. 2017;18(4):e182-e8.

39. Elisa P, Francesca C, Marco P, Davide V, Laura Z, Fabrizio Z, et al. Ventilation Weaning and Extubation Readiness in Children in Pediatric Intensive Care Unit: A Review. Front Pediatr. 2022;10:867739.

40. Dres M, Dube BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. Am J Respir Crit Care Med. 2017;195(1):57-66.

41. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax. 2014;69(5):423-7.

42. Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Crit Care. 2015;19:161.

43. Blumhof S, Wheeler D, Thomas K, McCool FD, Mora J. Change in Diaphragmatic Thickness During the Respiratory Cycle Predicts Extubation Success at Various Levels of Pressure Support Ventilation. Lung. 2016;194(4):519-25.

44. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. Am J Respir Crit Care Med. 2018;197(2):204-13.

45. Weber MD, Lim JKB, Glau C, Conlon T, James R, Lee JH. A narrative review of diaphragmatic ultrasound in pediatric critical care. Pediatr Pulmonol. 2021;56(8):2471-83.

46. Mariani LF, Bedel J, Gros A, Lerolle N, Milojevic K, Laurent V, et al. Ultrasonography for Screening and Follow-Up of Diaphragmatic Dysfunction in the ICU: A Pilot Study. J Intensive Care Med. 2016;31(5):338-43.

47. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. Am J Respir Crit Care Med. 2015;192(9):1080-8.

48. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med. 2015;41(4):734.

49. Montoro DV. Ultrasound assessment of ventilator-induced diaphragmatic dysfunction in mechanically ventilated pediatric patients. Pediatric Respiratory Reviews. 2021;40:58-64.

50. Abdel Rahman DA, Saber S, El-Maghraby A. Diaphragm and Lung Ultrasound Indices in Prediction of Outcome of Weaning from Mechanical Ventilation in Pediatric Intensive Care Unit. Indian J Pediatr. 2020;87(6):413-20.

PART   I

VENTILATION STRATEGIES FOR CRITICALLY
ILL CHILDREN

chapter 2

INVASIVE VENTILATION MODES IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Anita Duyndam, Erwin Ista, Robert Jan Houmes, Bionda van Driel, Irwin Reiss, Dick Tibboel

ABSTRACT

Introduction: The purpose of this study was to critically review the existing body of evidence on ventilation modes for infants and children up to the age of 18 years.

Methods: The databases PubMed and EMBASE were searched using the search terms: 'artificial respiration', 'instrumentation', 'device', 'devices', 'mode', 'modes'. The review included only studies comparing two ventilation modes in a randomized controlled study (RCT) and reporting one of the following outcome measures: length of ventilation (LOV), oxygenation, mortality, chronic lung disease and weaning. We quantitatively pooled the results of trials where suitable.

Results: Five trials met the inclusion criteria. They addressed six different ventilation modes in 421 children: high frequency oscillation (HFO), pressure control (PC), pressure support (PS), volume support (VS), volume diffusive respirator (VDR) and biphasic positive airway pressure. Overall there were no significant differences in LOV and mortality or survival rate associated with the different ventilation modes. Two trials compared HFO versus conventional ventilation. In the pooled analysis, mortality rate did not differ between these modes (odds ratio (OR) 0.83, 95% confidence interval (CI) 0.30 to 1.91). High-frequency ventilation (HFO and VDR) was associated with a better oxygenation after 72 hours than was conventional ventilation. One study found a significantly higher PaO_2/FiO_2 ratio with the use of VDR versus PC ventilation in children with burns. Weaning was studied in 182 children assigned to either a PS protocol, VS protocol or no protocol. Most children could be weaned within two days and weaning time did not significantly differ between the groups.

Conclusions: The literature provides scarce data for the best ventilation mode in critically ill children beyond the newborn period. However, there is no evidence that high-frequency ventilation reduced mortality and LOV. Longer-term outcome measures such as pulmonary function, neurocognitive development, and cost-effectiveness should be considered in future studies.

INTRODUCTION

Ventilator-induced lung injury in critically ill children suffering from acute respiratory failure should be counteracted by adapting ventilation management to the cause of respiratory failure. (1) Ideally, management should be based on proven effective strategies. In a multicenter study bronchiolitis was the most frequent cause of respiratory failure in infants (43.6%); pneumonia that in older children (24.8%). (2) Mortality in that study was rare (1.6%); the median duration of ventilation was 7 days. Randolph and colleagues suggested that in pediatric clinical trials, long-term morbidity would be a more sensitive indicator of the effects of clinical ventilation interventions than mortality or duration of ventilation. (1)

Pediatric intensive care units (PICUs) worldwide use a wide variety of ventilation modes: high frequency oscillation (HFO), pressure control (PC), synchronized intermittent mandatory ventilation (SIMV), pressure support (PS), pressure regulated volume control (PRVC) and, more recently, neurally adjusted ventilator assist (NAVA). (3, 4) The ventilation mode is often not targeted specifically to the underlying disease but rather determined by the intensive care physician's experience, local PICU policy and protocols, or outcomes of studies in adults. (1, 2, 5) An unambiguous international guideline is still lacking. (1, 5)

The objective of this article is to systematically review the randomized controlled trials (RCTs) comparing ventilation modes used in critically ill children (term born up to 18 years of age) on the following outcome measures: length of ventilation, oxygenation, mortality, chronic lung disease and weaning. We aimed to answer the question whether there is sufficient evidence to decide on the better mode.

METHODS

SEARCH AND SELECTION
A systematic search was performed in PubMed and EMBASE in September 2010. MeSH terms and keywords searched for in the titles, abstracts and keywords areas were: 'artificial respiration', 'instrumentation', 'device', 'devices', 'mode', 'modes', combined with Boolean operators AND, OR. (Supplemental file 1 provides the complete search strategy). The search was limited to RCTs or quasi-experimental

studies, with age limit > 28 days until 18 years. Only articles comparing at least two ventilation modes were selected for review. Articles on non-invasive ventilation, studies in premature neonates (< 37 weeks), and articles in other languages than English or Dutch were excluded. No limits were imposed on publication date.

Two authors (AD, EI) independently reviewed abstracts and full-text articles to identify eligible studies. Reference lists of retrieved studies were hand searched for additional articles.

QUALITY ASSESSMENT

Study quality and level of evidence were assessed on criteria established by the Dutch Institute for Healthcare Improvement CBO in collaboration with the Dutch Cochrane library (See Supplemental file 2 and Table 1). (6) The major criteria were: 1) was assignment to study group randomized?; 2) were investigators blinded?; 3) was it an intention-to-treat analysis?; 4) were the study groups comparable?; and 5) was there appropriate report of outcome results for each group and the estimated effect size? Consensus between the authors on the interpretation of the extracted data was achieved.

DATA ABSTRACTION

Authors AD and EI each independently recorded patient characteristics (sample size, age, respiratory failure), details of the ventilation mode and period over which outcome variables were measured. Outcome variables considered were the following: length of ventilation (LOV), oxygenation, chronic lung disease (CLD), mortality and weaning.

STATISTICAL METHODS

We quantitatively pooled the results of individual trials, where suitable. We expressed the treatment effect as an odds ratio (OR) for dichotomous outcomes and as a weighted mean difference (WMD) for continuous outcomes with 95% confidence intervals. The pooled OR was estimated with the Mantel-Haenszel method which is generally the most robust model. (7) Differences were considered statistically significant if $p < 0.05$ or if the 95% confidence interval did not include the value 1. The analyses were performed with Microsoft ® Excel, Office 2007 for Windows.

RESULTS

SEARCH AND SELECTION

After filtering out duplicate studies, titles and abstracts of 461 potentially relevant articles were screened (Figure 1). The reference lists yielded one other study that had been missed because the keywords were not in the title or abstract. Eventually, nine full-text articles were retrieved and assessed for eligibility. Four RCTs were excluded for any of the following reasons: focus on triggering instead of ventilation; inclusion of infants below 37 weeks of gestational age; not comparing two ventilation modes. (8-11) This review therefore includes five RCTs. (12-16)

Tabulated details of these five RCTs are presented in Tables 2 and 3.

TABLE 1   Level of Evidence

Level	Description of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort or studies High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant probability that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
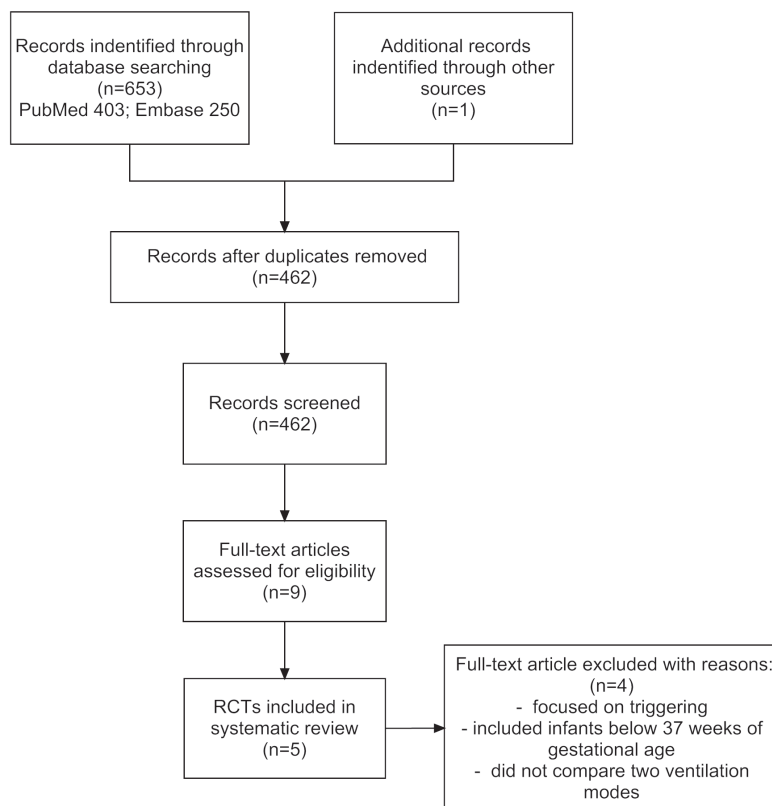
FIGURE 1 Search results

LENGTH OF VENTILATION

The LOV served as outcome measure in four studies (Table 2). First, Arnold and colleagues in a multi-centre trial compared HFO and conventional ventilation (CV) in 58 children with either diffuse alveolar disease and/or air leak syndrome; 29 had been randomized to HFO; 29 to CV. (12) During the first 72 hours of study the mean airway pressure was significantly (p<0.001) higher in the HFO group. The HFO strategy entailed aggressive increases in mean airway pressure to attain the ideal lung volume and to achieve an arterial oxygen saturation of > 90% with FiO_2 < 0.6. The CV strategy entailed stepping up the end-expiratory pressure and inspiratory time to increase mean airway pressure and to limit peak inspiratory pressure increases. Crossover to the alternate ventilator was required if the patient met defined criteria for treatment failure. LOV did not significantly differ between the CV and HFO groups (weighted mean difference (WMD) 2.0 days, 95% confidence interval (CI) -9.61 to 13.61).

2

Second, Dobyns and colleagues in a multicenter study compared HFO and CV in 99 children with acute hypoxemic respiratory failure (14) Seventy-three were treated with CV (38 without iNO, 35 with iNO); 26 with HFO (12 without iNO, 14 with iNO). Mechanical ventilation and FiO_2 were adjusted to maintain SaO_2 at 90% and pCO_2 between 45 and 55 mmHg. Higher pCO_2 values were tolerated as long as the arterial pH was 7.20. In the CV strategy the positive end-expiratory pressure was increased incrementally to improve oxygenation while avoiding clinical and radiographic signs of lung hyperinflation. The peak airway pressure was maintained at < 35–40 cm H_2O by limiting the level of tidal volume and positive end-expiratory pressure. The initial HFO settings were: FiO_2 of 1.0, 33% inspiratory time, frequency of 10 Hz, and mean airway pressure set at 2–4 cm H_2O above that used on CV. Pressure amplitude was set to achieve perceptible chest wall motion and was adjusted if possible to optimize ventilation. In this study HFO did not lead to a significantly shorter LOV (Table 2). However, for the two ventilation groups without iNO, LOV significantly differed between CV and HFO (WMD -30.0 days, 95%CI -45.89 to -14.11).

Third, Carman and colleagues compared the Volume Diffusive Respirator (VDR) with PC ventilation in burned children with inhalation injury. (16) The VDR is a high-frequency, time cycled pressure ventilator that can ventilate, oxygenate and promote secretion removal. SaO_2 was maintained at or above 90%; $PaCO_2$ at <55 mmHg. Thirty-two children with a mean age of 5.5 years ± 0.9 were treated with VDR; 32 children with a mean age of 9.4 years ± 1.0 with PC ventilation (p=0.04 for mean age). The LOV was significantly different between the study groups (WMD -1.0 days, 95%CI -1.98 to -0.02). Fourth, Jaarsma and colleagues randomized 18 children with respiratory failure to either BIPAP (n=11) or PSV (n=7); their median age was 4 months (range 4 weeks to 10 years). (13) Initial ventilator settings depended on age and the cause of respiratory failure and were adjusted according to thoracic excursions and measured tidal volume. Adjustments were made afterwards aiming at a pCO_2 of 4–5 kPa and a pO_2 of 8–11 kPa. LOV did not significantly differ between BIPAP (9.8 ± 9.2 days) and PS (6.4 ± 5.8 days).

Pooled analysis resulted in a significantly shorter LOV after CV in comparison with HFO (WMD -2.3 days, 95%CI= -3. 63, -1.04) (Table 4).

OXYGENATION

Three studies addressed the effects of different ventilation modes on oxygenation.

In the study by Dobyns and colleagues the PaO_2/FiO_2 (PF) ratio improved most in HFO mode with iNO after 4 hrs. (136mmHg ±21 vs. CV 96±6; p=0.2)) and 12 hrs. (HFOV+iNO 184mmHg ±45 vs. CV 107mmHg ±8 and CV+iNO 115mmHg ±9, p=0.023; HFOV 136mmHg ±32). (14) After 24 hrs., HFO treatment both with and without iNO provided better oxygenation than CV both with and without iNO (p<0.05). After 72 hrs., HFO treatment was associated with the best improvement in PF ratio (HFO 259 mmHg ±60 vs. CV 148mmHg ±15 and CV+iNO 150 mmHg ±19, p=0.027; HFOV+iNO 213 mmHg ±9). The two therapies did not differ in failure rate. Arnold and colleagues reported a significant (p=0.001) relationship between time and a decreasing oxygenation index in the HFO group but not in the CV group. (12) After crossover (19 patients crossed over from CV to HFO and 11 patients crossed over from HFO to CV) this relationship was significant in both crossover groups (p=0.03 crossover to CV; p=0.02 crossover to HFO).

Carman and colleagues reported a significantly higher PF ratio in the VDR mode compared with PC (563 mmHg ± 15 vs. 507 mmHg ± 13, p<0.05) but did not specify the time point at which the best PF ratio was measured. (16) As the oxygenation parameters in these three studies were not uniform it was not possible to pool the data.

MORTALITY, SURVIVAL

Three studies focused on the outcome measure mortality or survival.

None found a significant difference in mortality between patients treated with HFO and those treated with CV. Arnold and colleagues reported a mortality rate of 34% (10/29) for HFO versus 41% (12/29) for CV (OR 0.75, 95%CI 0.26 to 2.16). (12) The mortality rate in patients not crossed over to CV from HFO or to HFO from CV, however, was significantly better (p=0.003) than that in patients managed with CV only.

Dobyns and colleagues showed that the survival rate for patients treated with HFO in combination with iNO was higher than that for patients treated with HFO only or with CV (71% vs. 58% in CV, 53% in CV +iNO and 58% in HFO). (14) These differences did not achieve statistical significance. These authors speculated that the improved lung recruitment by HFO enhances the effects of low dose iNO on gas exchange. The

mortality rate for HFO without iNO was 42% (5/12) versus 42% (16/38) for CV without iNO (OR 0.98, 95%CI 0.26 to 3.66). (14) In the study by Carman and colleagues five of 32 (16%) patients in the PCV group died versus two of 32 (6%) in the VDR group (OR 0.36, 95%CI 0.06 to 2.01). (16)

In the pooled analysis, the mortality rates in the HFO mode and in CV did not differ (OR 0.70, 95%CI 0.33 to 1.47) (Table 5).

CHRONIC LUNG DISEASE

Chronic lung disease was examined only in the study of Arnold and colleagues. (12) The proportion of patients treated with HFO and requiring supplemental oxygen at 30 days was lower than that of patients managed with CV (p=0.039; OR 5.4, 95% CI 1.2 to 23.2).

WEANING

Randolph and colleagues randomized 182 children aged from 0 to 17 years to either a Pressure support (PS) protocol (n=62), Volume support (VS) protocol (n=60) or a no ventilation weaning protocol in which weaning was at the discretion of the physician (n=60) (Table 3). (15) The VS and PS protocols dictated that FiO2 and PEEP be adjusted to maintain SpO2 at 95% or higher. In the PS protocol, the amount of pressure support was adjusted to achieve an exhaled tidal volume goal of 5 to 7 ml/kg. In the VS protocol, the ventilator automatically adjusted the level of PS to achieve an exhaled tidal volume of 5 to 7 ml/kg. Two outcome measures were assessed: weaning time and extubation failure (i.e. any invasive or non-invasive ventilator support within 48 hours of extubation). The authors hypothesized that VS would result in shorter weaning time as the inspiratory pressures automatically decrease with improvement of lung compliance. Most children could be weaned within 2 days and the weaning time did not significantly differ for the protocols used: PS (1.6 days), VS (1.8 days) and no protocol (2.0 days). Extubation failure rates were not significantly different for PS (15%), VS (24%) and no protocol (17%).

QUALITY OF STUDIES

These five studies compared six different ventilation modes in 421 children. (12-14, 16) Two studies, based on intention to treat analysis, met all CBO quality criteria. (14, 15) Blinding was not possible in any of these studies, because ventilator displays cannot be masked. In four studies patient characteristics and prognostic variables did not differ

between the intervention groups. In the study of Carman and colleagues the mean age differed significantly. (16) Only one study calculated the estimated effect sizes (relative risk of odds ratio) for continuous outcome variables such as LOV, survival or weaning failure. (15) The study by Dobyns and colleagues (14) is of limited quality because it is a secondary analysis of data obtained from a previous multicenter, randomized trial on iNO treatment in pediatric acute hypoxemic respiratory failure. (8) The mode of ventilation was determined by the attending physician on the guidance of guidelines to maximize oxygenation. The patient was then randomized to treatment with or without iNO. (14) Levels of evidence for the different studies are presented in Tables 2 and 3.

DISCUSSION

This review aimed at identifying the various ventilation modes used in children over the last three decades and searching for any data that would favour a particular mode for paediatric ventilation. The five RCTs included in this review varied in the investigated modes of ventilations, in outcomes and in patient groups.

High-frequency ventilators may use different ventilation modes. Two studies included in this review concerned HFO ventilation (12, 14); a third concerned the volume diffusive respirator (high-frequency time cycled pressure ventilator). (16) The evidence from these studies does not allow making a recommendation on preferred type of high frequency ventilator. Two RCTs compared HFO with CV on the outcomes oxygenation, LOV and mortality. Neither study found significant differences in mortality and LOV. Analysis of the pooled data, however, revealed a significantly lower LOV for the conventional ventilation groups. A confounding factor for this finding is the threefold sample size of conventionally ventilated patients in the study of Dobyns and colleagues. (14) On the other hand, this analysis only concerned the patients treated with HFO and CV without iNO.

In all studies, oxygenation significantly improved over 72 hours for patients treated with high-frequency oscillators. (12, 14, 16) However, lack of uniform data on oxygenation prevented analysis of pooled data. This finding is in contrast with that reported for preterm neonates. The systematic reviews and meta analyses overall provide no evidence that HFO as the initial ventilation strategy offers important advantages over

CV in terms of preventing chronic lung disease in preterm infants with acute pulmonary dysfunction. (17-22)

The level of evidence proved moderate to good in three studies. (12, 14, 15) The study of Jaarsma and colleagues was stopped halfway as both physicians and nurses preferred BIPAP. This was assigned a 1- level of evidence because of the high risk of bias. (13) Likewise, the study of Carman and colleagues was assigned a 1- level of evidence because the randomization failed for the demographic variable age. (16)

The strengths of the present review include a comprehensive search strategy, broad inclusion criteria (resulting in a representative, heterogeneous population), and assessment of clinically important outcomes. In addition, we pooled the data. This statistical approach is also allowed for quasi-experimental, non-randomized studies, such as the study of Dobyns and colleagues (14) in which randomization of groups was not possible or failed. (23) Meta-analytic techniques in the analysis of nonrandomized studies have been criticized for their potential to perpetuate the individual biases of each study and give a false impression of cohesion in the literature thus discouraging further research. (24) The counter-argument is that statistical quantification and pooling of results from many studies helps to identify reasons for variability, inconsistency or heterogeneity in the literature, and thus may encourage further research. (23, 25) Nevertheless, the pooled results of this study should be interpreted cautiously in view of the diversity in patient groups, sample sizes, randomization methods, types of ventilators and ventilation strategies.

The reviewed RCTs cannot easily be compared owing to the heterogeneity in age, underlying disease and study outcomes. We would therefore recommend setting up studies investigating the best ventilation strategy for specific age categories or underlying pathology. (1) Furthermore, as mortality is rather low, longer-term outcome measures others than the short-term outcome measures studied in the present review should be considered, such as pulmonary function, neurocognitive development and cost-effectiveness. Internationally consensus on the most appropriate outcome measures should be reached.

CONCLUSION

The available literature does not provide sufficient evidence on the best ventilation mode in critically ill children beyond the newborn period. High-frequency ventilation (HFO and VDR) provided better oxygenation after 72 hours than did CV. There is no evidence that high-frequency ventilation would reduce mortality and LOV.

KEY MESSAGES

- There is no evidence for the best ventilation mode in critically ill children beyond the newborn period up to 18 years.
- The different modes have not yet been investigated in (large) groups of children.
- Oxygenation significantly improved over 72 hours for patients treated with high-frequency oscillators.
- Longer-term outcome measures such as pulmonary function and neurocognitive development should be considered.

LIST OF ABBREVIATIONS

PF Pao_2/Fio_2 ratio
O.I.   Oxygenation index
FiO_2 Fraction of Inspired Oxygen
SaO_2 Saturation of oxygen
pO_2 Partial pressure of oxygen
pCO_2 Partial arterial pressure of carbon dioxide

ACKNOWLEDGEMENT

REFERENCES

1. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. Crit Care Med. 2009;37(8):2448-54.

2. Randolph AG, Meert KL, O'Neil ME, Hanson JH, Luckett PM, Arnold JH, et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. Am J Respir Crit Care Med. 2003;167(10):1334-40.

3. Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: An observational study. Pediatr Crit Care Med. 2010;11(2):253-7.

4. Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med. 2010;11(1):7-11.

5. Turner DA, Arnold JH. Insights in pediatric ventilation: timing of intubation, ventilatory strategies, and weaning. Curr Opin Crit Care. 2007;13(1):57-63.

6. CBO. Evidence-based Richtlijnontwikkeling. Handleiding voor werkgroepleden: Kwaliteitsinstituut voor de Gezondheidszorg CBO; 2007.

7. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res. 1993;2(2):121-45.

8. Dobyns EL, Cornfield DN, Anas NG, Fortenberry JD, Tasker RC, Lynch A, et al. Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. J Pediatr. 1999;134(4):406-12.

9. Guthrie SO, Lynn C, Lafleur BJ, Donn SM, Walsh WF. A crossover analysis of mandatory minute ventilation compared to synchronized intermittent mandatory ventilation in neonates. J Perinatol. 2005;25(10):643-6.

10. Thiagarajan RR, Coleman DM, Bratton SL, Watson RS, Martin LD. Inspiratory work of breathing is not decreased by flow-triggered sensing during spontaneous breathing in children receiving mechanical ventilation: a preliminary report. Pediatr Crit Care Med. 2004;5(4):375-8.

11. Rojas MA, Lozano JM, Rojas MX, Bose CL, Rondon MA, Ruiz G, et al. Randomized, multicenter trial of conventional ventilation versus high-frequency oscillatory ventilation for the early management of respiratory failure in term or near-term infants in Colombia. J Perinatol. 2005;25(11):720-4.

12. Arnold JH, Hanson JH, Toro-Figuero LO, Gutierrez J, Berens RJ, Anglin DL. Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. Crit Care Med. 1994;22(10):1530-9.

13. Jaarsma AS, Knoester H, van Rooyen F, Bos AP. Biphasic positive airway pressure ventilation (PeV+) in children. Crit Care. 2001;5(3):174-7.

14. Dobyns EL, Anas NG, Fortenberry JD, Deshpande J, Cornfield DN, Tasker RC, et al. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. Crit Care Med. 2002;30(11):2425-9.

15. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA. 2002;288(20):2561-8.

16. Carman B, Cahill T, Warden G, McCall J. A prospective, randomized comparison of the Volume Diffusive Respirator vs conventional ventilation for ventilation of burned children. 2001 ABA paper. J Burn Care Rehabil. 2002;23(6):444-8.

17. Bollen CW, Uiterwaal CS, van Vught AJ. Cumulative metaanalysis of high-frequency versus conventional ventilation in premature neonates. Am J Respir Crit Care Med. 2003;168(10):1150-5.

18. Cools F, Henderson-Smart DJ, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev. 2009(3):CD000104.

2

19. Bollen CW, Uiterwaal CS, van Vught AJ. Systematic review of determinants of mortality in high frequency oscillatory ventilation in acute respiratory distress syndrome. Crit Care. 2006;10(1):R34.

20. Bollen CW, Uiterwaal CS, van Vught AJ. Meta-regression analysis of high-frequency ventilation vs conventional ventilation in infant respiratory distress syndrome. Intensive Care Med. 2007;33(4):680-8.

21. Cools F, Askie LM, Offringa M, Asselin JM, Calvert SA, Courtney SE, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. Lancet. 2010;375(9731):2082-91.

22. Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev. 2008(1):CD000456.

23. MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AM. A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies. Health Technol Assess. 2000;4(34):1-154.

24. Shapiro S. Meta-analysis/Shmeta-analysis. Am J Epidemiol. 1994;140(9):771-8.

25. Greenland S. Can meta-analysis be salvaged? Am J Epidemiol. 1994;140(9):783-7.

TABLE 2   Included RCTs – VENTILATION

Reference	Study population	Intervention/ mode	Outcome measures
			Mortality / survival
Arnold et al, 1994 (12)	58 children (age 2.5±2.5 yrs. versus 3.1±3.3 yrs.) With diffuse alveolar disease and/or air leak syndrome	Multi-centre study (5 centers) Comparison effectiveness of HFO (n=29) with CV (n=29) – crossover Crossover: CV to HFO (n=19) HFO to CV (n=11)	No. survivors at 30 days CV: 17 of 29 (59%); HFO: 19 of 29 (66%); (NS) Death (Ranked) CV: 40% CV to HFO: 42% HFO: 6% HFO to CV: 82% (p=<0.001)
Dobyns et al. (14)	99 children (age 0-23 yrs.) With AHRF Oxygenation index > 15	Multi-centre study (7 centers) Comparisons between patients treated with HFO+iNO (n=14), HFO alone (n=12), CV+iNO (n=35), and CV alone (n=38)	Trend of improved survival in the HFO+iNO. (CV, 22 of 38 (58%); CV+iNO, 20 of 35 (53%); HFO, 7 of 12 (58%); HFO+iNO, 10 of 14 (71%); (p=0.994)
Jaarsma et al. (13)	18 children (age 0-10 yrs.) with respiratory failure for ventilation	Single-centre study Compare BIPAP (n=11) with PS (n=7) determining with mode is effective, safe and easy	ND
Carman et al. (16)	64 children (mean age7.4±0.7 yrs.) with inhalation injury	Single center Compare VDR (n=32) with PC (n=32)	VDR: 2/32 (6%); PC: 5/32 (16%); (NS)

1 - HFO group; 2 - CV group; AHRF - acute hypoxemic respiratory failure; iNO –inhaled NO; CV – conventional mechanical ventilation; HFO –High frequency oscillation ventilation; CLD – chronic lung disease; LOV – length of ventilation; BIPAP- biphasic positive airway pressure; PS- pressure support ventilation; ND – no data; yrs. - years; hrs. – hours; * - mean±sd; VDR – Volume Diffusive Respirator (high-frequency time cycled pressure ventilator); PC – Pressure Controlled Ventilation; NS – not significant; OR – odds ratio; CI – confidence interval; No. – Numbers of

Outcome measures			Level of evidence
LOV (days)*	Oxygenation	CLD	
Total CV: 22±17; HFO: 20±27 Survivors (at 30 days) CV: 29±18; HFO: 27±31. Non survivors (at 30 days) CV: 11±9; HFO: 8±6 (NS)	PaO_2/PAO_2 increase over time (72hrs) in HFO compared to CV group ($p<0.001$) PaO_2/PAO_2: HFO: 0.13 (0 hr.) up to 0.26 (72hr); CV: 0.13 (0 hr.) up to 0.22 (72hrs). After crossover PaO_2/PAO_2 increase over time (72hrs) in CV to HFO group compared to HFO to CV group ($p=0.003$)	CV: n=10 (59%); HFO: n=4 (21%). ($p=0.039$; OR=5.4 95%CI 1.2-23.2) (O_2 at 30 days)	1+
CV: 22±4; CV+iNO: 21±3; HFO: 52±28; HFO+iNO: 17±4; ($p=0.098$)	PaO_2/FiO_2 (PF) ratio: - After 4 hrs.: HFO+iNO 136±21 vs. CV 96±6, $p=0.2$ - After 12 hrs.: HFO+iNO 184±45 vs. CV 107±8 and CV+iNO 115±9, HFO 136±32; $p=0.023$. - After 24 hrs.: treatment both HFO+iNO and HFO resulted in greater improvement in PF ratio than CV or CV+iNO, $p=0.005$. - After 72 hrs.: HFO 259±60 vs. CV 148±15 and CV+iNO 150±19; HFO+iNO 213±29, $p=0.027$		1+
BIPAP: 9.8±9.2; PS: 6.4±5.8; ($p=0.27$)	ND		1-
VDR: 12±2; PCV: 11±2; (NS)	Pao_2/Fio_2 (PF) ratio: VDR: 563±16, PC: 507±13; ($p<0.05$)		1-

2

TABLE 3   Included RCTs WEANING

Reference	Study population	Intervention/ mode
Randolph et al. (15)	182 children (age 0-17 yrs.)	Multicenter study (10 centers)
		To evaluate weaning protocols comparing:
	Weaning of ventilation support for more than 24 hours and who failed a test for extubation readiness on minimal PS	-VS (continuous automated adjustment of PS by the ventilator) (n=59)
		- PS (adjustment by clinicians) (n=61)
		- to standard care (no protocol) (n=59)

* - median (interquartile range); ND – no data; PS-Pressure support; VS –Volume support ; OR – Odds Ratio; CI – Confidence Interval

TABLE 4   Meta-analysis of trials comparing high frequency ventilation to conventional ventilation: length of ventilation

Study	CV		HFOV			
	Mean (SD)	N	Mean (SD)	N	WMD (95%CI)	Z value (p-value)
Length of ventilation						
Arnold (1994)	22 (17)	29	20 (27)	29	2 [-9.61, 13.61]	-0.338 (p=0.74)
Dobyns (2002)	22 (4)	38	52 (28)	12	-30 [-45.89, -14.11]	3.699 (p=0.0002)
Subtotal		67		41	-11.51 [-15.14, -7.88]	-6.221 (p<0.0001)
Carman (2002) (VDR)	11 (2)	32	12 (2)	32	-1 [-1.98, -0.02]	-2.0 (p=0.046)
Overall		99		73	-2.34 [-3.63, -1.04]	-3.542 (p=0.0004)

WMD – weight mean difference; CI – confidence interval; Volume Diffusive Respirator (high-frequency time cycled pressure ventilator); CV – conventional ventilation; HFOV – High Frequency oscillation ventilation; SD –standard deviation

Outcome measures			Level of evidence
Duration of weaning (days)*	Extubation failure rate	Oxygenation	
PS: 1.6(0.9-4.1); VS: 1.8(1.0-3.2); no protocol: 2.0(0.9-2.9), (p=0.75)	PS (15%), VS (24%) and no protocol (17%) (p=.44) Male children more frequently failed extubation (OR, 7.86 95%CI:2.36-26.2; p<.001).	ND	1++

2

TABLE 5   Meta-analysis of trials comparing high frequency ventilation to conventional ventilation: Mortality

Study	CV n/N	HFOV n/ N	OR (95%CI)
Mortality			
Arnold (1994)	12/29	10/29	0.75 (0.26, 2.16)
Dobyns (2002)	6/38	5/12	0.98 (0.26, 3.66)
Subtotal M-H	67	41	0.83 (0.30,1.91)
Carman (2002) (VDR)	5/32	2/32	
Overall M-H	99	73	0.70 (0.33, 1.47)

M-H - Mantel-Haenszel; OR – Odds Ratio; CI – confidence interval; Volume Diffusive Respirator (high-frequency time cycled pressure ventilator); CV – conventional ventilation; HFOV – High Frequency oscillation ventilation
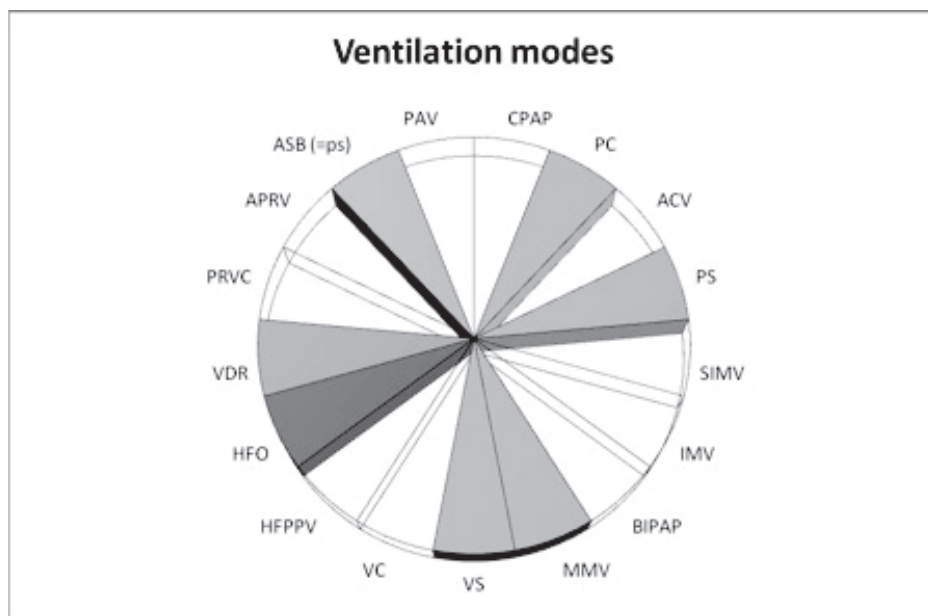
FIGURE 2 Different modes of ventilation

Dark wedges represent a type of ventilation with evidence from a RCT: PS and VS (Randolph et al.), ASB en MMV (Jaarsma et al.), HFO (Dobyns et al. and Rojas et al.), VDR and PC (Carman et al.)

PC	pressure controlled ventilation
ACV	pressure controlled ventilation: patient triggered ventilation-assist control ventilation
CPAP	continuous positive airway pressure
PS	pressure support ventilation
SIMV	synchronous intermittent mandatory ventilation, pressure controlled
IMV	intermittent mandatory ventilation, pressure controlled without possibility of triggering
BIPAP	bi-level or biphasic positive airway pressure
MMV	mandatory minute ventilation: SIMV with pressure support and guarantee of the minute volume
APRV	airway pressure release ventilation
ASB	assisted spontaneous breathing = pressure support
PAV	proportional assist ventilation = **PPV** proportional pressure support
PRVC	pressure regulated volume controlled ventilation
HFPPV	high frequency positive pressure ventilation
HFO	high frequency oscillation
VDR	high frequency percussive ventilation
VC	volume controlled ventilation
VS	volume support ventilation/volume targeted ventilation

SUPPLEMENTAL FILE 1: SEARCH STRATEGY

PubMed

(artificial respiration[mesh] OR artificial respir*[tw] OR mechanical ventil*[tw] OR high frequency respirat*[tw] OR liquid ventilat*[tw] OR pressure respirat*[tw] OR positive airway pressure*[tw] OR pressure breath*[tw] OR pressure ventilat*[tw] OR ventilator wean*[tw] OR ventilation wean*[tw] OR ventilators, mechanical[mesh] OR pulmonary ventilat*[tw] OR respirator*[tw] OR ventilator*[tw]) AND (instrument*[tw] OR device*[tw] OR mode[tw] OR modes[tw]) AND (infan*[tw] OR child*[tw] OR adolescen*[tw] NOT adult[mesh]) AND (randomized controlled trial*[tw] OR randomized controlled trial*[pt] OR rct[tw])

Hits: n=403

EMBASE

(artificial AND 'ventilation'/exp OR (artificial OR mechanical OR 'high frequency' OR 'liquid ventilation' OR 'liquid ventilator' OR pressure OR 'positive airway pressure' OR wean* OR pulmonary) NEAR/3 (breath* OR ventilat* OR respirat*) OR respirator*:de,ab,ti OR ventilator*:de,ab,ti) AND (instrument*:de,ab,ti OR device*:de,ab,ti OR mode:de,ab,ti OR modes:de,ab,ti) AND ([randomized controlled trial]/lim OR 'randomized controlled trial':ti,ab,de OR rct:ti,ab,de) AND ([newborn]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim OR [child]/lim OR [adolescent]/lim) NOT [adult]/lim NOT [aged]/lim AND [humans]/lim

Hits: n=250

SUPPLEMENTAL FILE 2: EVALUATION FORM OF RCTS

Assessment of the quality of a randomized controlled trial (RCT)

1. Was the intervention assignment truly random?
2. The person who includes subjects in the study should be unaware of the randomization order; was that the case?
3. Were patients blinded to treatment allocation?
4. Were caregivers blinded to treatment allocation?
5. Were persons measuring the outcomes blinded?
6. Were the groups comparable at baseline?
7. Was complete follow-up available for a sufficient proportion of all included patients? (loss-to-follow-up)
8. Were all included patients analyzed in the group to which they were randomized? Intention to treat analysis
9. Other than the intervention, was all care that patients received the same?

Intermediate conclusion

10. Are the results of the study valid and relevant?
11. Results. For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% CI)
    Dichotomous outcomes
    Continuous outcomes

Applicability in healthcare

12. Is the result found applicable to the situation in the Netherlands?
13. To which echelon(s) can the result be applied?
14. Conclusion

3

chapter

INVASIVE VENTILATION MODES IN CHILDREN; AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

Anita Duyndam, Robert Jan Houmes, Monique van Dijk, Dick Tibboel, Erwin Ista

ABSTRACT

Objective: We updated a previous systematic review on preferred ventilation modes in critically ill children from 28 days-18 years of age in 2020.

Data Sources: EMBASE, Medline and Cochrane databases were searched on different ventilation modes.

Study Selection: We included studies comparing two ventilation modes in a randomized controlled study or quasi-experimental study and reporting at least one of the following outcome measures: length of ventilation (LOV), oxygenation, mortality, chronic lung disease, weaning, length of stay (LOS) and sedation.

Data Extraction: Two reviewers independently extracted data from the selected studies. A random-effects meta-analysis model was used to synthesize treatment effects. Risk of bias of studies was assessed with the Cochrane Collaboration's tool and the Newcastle-Ottawa scale.

Data Synthesis: Twenty-one studies involving 16,642 children were included. Eight studies addressed: Airway Pressure Release Ventilation (APRV; n=1), Bilevel Positive Airway Pressure (n=1), Neurally Adjusted Ventilator Assist (NAVA; n=5), Pressure Support and Volume Support (VS; n=1). Thirteen studies compared High Frequency Oscillation Ventilation (HFO) with Conventional Ventilation (CV; n=12) or APRV (n=1).

Pooled analysis of HFO versus CV showed a lower mortality rate with CV; OR 0.62 (95%CI 0.42;0.91);p=0.019; I^2=38%(n=11)). PaO_2/FiO_2 ratio significantly differed in favor of CV; SMD 1.55 (95% CI: 0.11;2.99); p=0.0346; I^2 = 89%. (n=3). Both LOV (SMD 0.33 (95%CI 0.02;0.67); p=0.06(n=9)) and LOS (SMD 0.09 (95%CI -0.29;0.12); p=0.39(n=3)) were not significantly different.

Regarding NAVA, one paper found a shorter LOV (9.0 vs. 11.0 days; p=0.032), higher extubation success rate (OR 8.5 (95%CI: 1.01;71.8; p=0.032), shorter median durations of sedation (p<0.0001) and PICU LOS. (HR: 2.49 (95%CI: 1.5;4.07); p<0.001) for NAVA. Another study found a shorter LOV for NAVA; p=0.011 and a higher mean percent change of PaO_2/FiO_2 after 8 hours; p=0.02.

Conclusion: CV in children is associated with lower mortality than HFO. We found no evidence that HFO reduces LOV, LOS or oxygenation. Preliminary findings for NAVA are promising.

INTRODUCTION

Children on a pediatric intensive care unit (PICU) receive mechanical ventilation to bridge a period of illness with respiratory insufficiency or surgery. Complications may arise, however, such as ventilator-induced lung injury, atelectasis, ventilator-associated pneumonia, and ventilator-induced diaphragmatic dysfunction and delirium in heavily sedated children. (1-6)

Mortality rates in children admitted to PICUs have fallen to an all-time low of 1- 3% in developed countries (7-9), and the overall median length of ventilation (LOV) is 5 to 7 days. (10-12) Specific diseases such as acute respiratory distress syndrome (PARDS) (13), sepsis (14) pneumonia (15) and cancer (16) are associated with higher mortality and LOV compared to other indications. Therefore, it is important to apply an optimal ventilation mode or strategy for specific diseases.

PICUs worldwide use a wide variety of ventilation machines and ventilation modes: high-frequency oscillation (HFO), pressure control (PC)- continuous mandatory ventilation, PC -continuous spontaneous ventilation, PC- intermittent mandatory ventilation, volume control (VC)- continuous mandatory ventilation or VC- intermittent mandatory ventilation, airway pressure released ventilation (APRV), or neurally adjusted ventilator assist (NAVA). (17-20) (Supplemental file 1 gives descriptions of APRV and NAVA) The type of ventilation mode is often not targeted to the underlying disease but rather is determined by the intensive care physician's experience, local policy and protocols, or outcomes of studies in adults. (11, 12, 21)

In a previous systematic review and meta-analysis about invasive ventilation modes in children, published in 2011, we found scarce data for the best ventilation mode in critically ill children beyond the newborn period, and no evidence that HFO reduced mortality and LOV. (22)

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In 2017, the European Society for Paediatric and Neonatal Intensive Care developed a European consensus guideline on mechanical ventilation of critically ill children. (23) Since then, two randomized controlled trials (RCT) and five quasi-experimental studies addressing the topic have been published. We updated the previous systematic review – with the ultimate aim to improve ventilation practices in critically ill children.

MATERIALS AND METHODS

A systematic search was performed in the EMBASE, Medline and Cochrane databases from January 1, 2010, to October 1, 2020. The start date was chosen to ensure adequate overlap with the previous review (September 2010). (22) The full search strategy is included in supplemental file 2. The search was limited to RCTs and quasi-experimental studies, with age limit >28 days until 18 years. Only studies comparing at least two ventilation modes were selected. We excluded studies on non-invasive ventilation, studies in premature neonates (< 37 weeks) or studies not comparing ventilation modes, and studies in other language than English. Two authors (AD, EI) independently reviewed abstracts and full-text articles to identify eligible studies. Reference lists of retrieved studies were hand-searched for additional articles. The review was conducted according the PRISMA statement. (24) We contacted investigators if not enough data were provided for meta-analysis.

QUALITY ASSESSMENT
Risk of bias in the included RCTs was assessed independently by two reviewers (AD and EI) using Cochrane Collaboration's tool for assessing the risk of bias. (25) Each study was reviewed and rated as having a high, low or unclear risk of bias. (26) For the other studies we used the Newcastle-Ottawa scale (supplemental files 3 and 4). (27)

DATA ABSTRACTION
Authors AD and EI each independently recorded patient characteristics (sample size, age, respiratory failure), details of the ventilation mode, and the period over which outcome variables were measured. Outcome variables considered were the following: length of ventilation (LOV), oxygenation index (OI), PaO_2/FiO_2, chronic lung disease, mortality, weaning, length of stay (LOS), and sedation.

STATISTICAL METHODS

We quantitatively pooled the results of individual trials, where suitable. Treatment effects are expressed as odds ratio (OR) for dichotomous outcomes and as weighted mean difference for continuous outcomes with 95% confidence intervals (CIs). The pooled OR was estimated with DerSimonian and Laird random-effects models. (28) Heterogeneity among studies was assessed using the Higgins and Thompson I² statistic, which indicates the percentage of variability in the intervention attributable to heterogeneity. (29) We performed subgroup analysis for type of design; e.g. controlled versus propensity matching studies. Publication bias was examined with a funnel plot. A symmetric funnel arises from a well-balanced dataset; an asymmetric plot suggests publication bias. Differences were considered statistically significant if p <0.05. The analyses were performed with Microsoft® Excel Office 2016 and R-statistics. If mean and SD were not provided, we used the median and calculated the SD according to the Cochrane handbook. (30)

RESULTS

SEARCH AND SELECTION

Our previous review of September 2010 included five trials. (31-35) Of the 4819 citations retrieved in this updated search, we reviewed 128 full-text papers and identified sixteen new studies (20, 36-50) as relevant. Thus, this updated review considers 21 studies, including the five from the previous review, comparing five different ventilation modes in 16,642 children (Figure 1).

The studies included 10 RCTs and eight quasi-experimental studies, of which four used propensity score matching based on retrospective observational research (51). One study was a pilot nested study and two were crossover studies. Study characteristics and outcomes are presented in supplemental file 5.

QUALITY OF INCLUDED STUDIES

Of the ten RCTs, three studies scored low on the sources of bias according the Cochrane tool (35, 38, 45); the others moderate. (20, 31, 33, 34, 39, 42, 43) (supplemental file 3) None of the RCTs reported blinding of outcome assessment; only one trial reported partial blinding. (31) Some outcome data were missing in one study. (43) In another study, the mean age differed significantly between treatment modes. (33) Two studies

ended earlier than intended (20, 34); one study used a cross-over design (39); and two trials reported crossovers between groups. (31, 43)

We assessed the methodological quality of the eleven non-randomized trials with the Newcastle-Ottawa scale. (27) Four had used propensity score matching, well described in all cases. (36, 37, 41, 46) Two studies reported differences in median age and or weight between treatment groups. (40, 44) All studies but two scored 7 or more stars on the Ottawa scale, indicating good quality. (32, 36, 37, 40, 41, 44, 46, 47, 50) (Supplemental file 4).

CONTENT OF STUDIES

Eight studies evaluated different ventilation or weaning modes: APRV, BIPAP NAVA, PS and VS. (20, 34, 35, 42, 44, 48-50) (supplemental file 5) Twelve studies in children with PARDS or acute hypoxemic respiratory failure evaluated the effect of HFO ventilation compared to CV, and one compared HFO with APRV. (31-33, 36-41, 43, 45-47) Details of high frequency oscillation and conventional ventilation settings per study are summarized in supplemental file 6.

META-ANALYSIS HFO VERSUS CV

Eleven of thirteen studies comparing HFO with CV were analyzed in the meta-analysis for mortality. Mortality was determined at discharge from hospital (32, 33, 36, 39, 41, 43, 45), or at 28 or 30 days after randomization (31, 38, 46), or in-hospital at 90 days (36). Overall, pooled estimates suggest that CV resulted in a lower risk of mortality compared to HFO (OR 0.62 95% CI 0.42; 0.91;p= 0.019; I^2 = 38%).

In the subgroup analysis for the propensity score studies, CV was again associated with a lower risk of mortality (OR 0.45 95% CI: 0.35- 0.59; I^2=0%) compared to HFO. (figure 2 and table 1) Both LOV (SMD 0.33 95%CI 0.02 to 0.67;p=0.06) (n= 9) and LOS (SMD 0.09 95%CI -0.29 to 0.12;p=0.39) (n=3) were not significantly different between HFO and CV. PaO_2/FiO_2 ratio was significantly different in favor of CV; SMD 1.55 95% CI: 0.11; 2.99; p=0.0346; I^2 = 89%. See table 1 and supplemental file 7 for details about the meta-analysis of LOV, LOS and Oxygenation.

CHRONIC LUNG DISEASE

Chronic lung disease was examined in one study. (31) The proportion of patients treated with HFO and requiring supplemental oxygen at 30 days was lower than that of patients managed with CV; (OR 5.4 95% CI: 1.2 to 23.2; p=0.039). (31)

OTHER COMPARED VENTILATION MODES

BIPAP vs PS (outcome LOV)
Jaarsma et al. randomized 18 children with respiratory failure to either BIPAP (n = 11) or PSV (n = 7); LOV did not significantly differ between the groups. (34)

Airway Pressure Release Ventilation (APRV)
Ganesan et al. performed a RCT comparing the effect of APRV with CV (low tidal volume ventilation) on ventilator-free days in children with ARDS. (20) The trial was terminated after 50% enrollment (n=52) because the 28-day all-cause mortality was 53.8% in the APRV group compared to 26.9% in the CV group (RR 2.0; 95% CI:0.97 to 4.1; Fisher exact p=0.089). (55) Ning et al. compared APRV with HFO in pediatric ARDS and found no significant difference in mortality rate between the HFOV and APRV groups. (47) The PaO_2FiO_2 ratio had significantly improved at 2 and 48 hours in both groups (p<0.001).

Weaning protocols
Randolph and colleagues randomized 182 children aged from 0 to 17 years to either a PS protocol (n = 62), a VS protocol (n = 60) or a no ventilation weaning protocol in which weaning was at the discretion of the physician (n = 60). (35) Most children could be weaned within 2 days, and the median weaning time did not significantly differ for the protocols used: PS, 1.6 (0.9 to 4.1) days; VS, 1.8 (1.0 to 3.2) days; and no protocol, 2.0 (0.9 to 2.9) days. The extubation failure rate was 15% for PS, 24% for VS and 17% for no protocol; p=0.44. The sedatives consumption during the first 24 hours of weaning significantly predicted weaning time; p=0.04 and among extubation success, duration of weaning; p<0.001. (35)

NAVA
Two of the five studies comparing NAVA with CV found a significant difference in LOV in non-randomized studies with historical controls compared with a prospective study population. (44, 50) Sood et al. studied extubation success for ventilatory weaning

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in patients who required prolonged iMV. The NAVA group had a shorter median LOV compared to the CV group (9.0 vs. 11.0 days, p=0.032). The hazard ratio for LOV in the NAVA group was significantly higher than that in the SIMV-PRVC/ PS group (HR: 1.77 95% CI: 1.09 to 2.90), indicating significantly shorter duration of stay on MV for patients ventilated with NAVA. Patients ventilated with NAVA were 8 times more likely to have successful extubation on the first attempt (OR 8.5 95% CI: 1.01 to 71.8) and both duration of sedation and PICU LOS were significantly shorter. (44) Piastra et al. reported a nested study comparing 20 infants with PARDS on PSV with 10 infants with PARDS on NAVA after being weaned directly from HFOV. The two groups were matched on age, weight and PaO_2/FiO_2 ratio and were slightly different at baseline. Extubation succes was comparable between groups, but LOV was significantly shorter in the NAVA group (p=0.011). The NAVA group had a significantly higher mean percent change of PaO_2/FiO_2 after 8 hours (p=0.02). (50)

Kallio et al. compared in a RCT NAVA as a primary ventilation mode with PC in neonates and PRVC in older children. (42) Median LOV was short and not statistically different (3.3 hrs. vs 6.6 hrs.; p=0.17).

Two studies were NAVA-studies with a crossover design in the same patients. (48-49) Bonacina et al. found an improved PaO_2/FiO_2 ratio and oxygenation index in PSV with a sigh compared to PSV (p=0.05), but not in NAVA compared to PSV. NAVA provided the best patient ventilator synchrony with a decrease in asynchrony index (AI) after cardiac surgery (p<0.01). (48) Spinazzola et al. found an improvement in PaO_2/FiO_2 ratio in a pediatric ICU population presenting difficult weaning after PARDS during NAVA vs. PSV 1 and PSV 2 (p=0.004). (49) NAVA was associated with a reduction of AI and an improvement of patient ventilator interaction. The AI during NAVA was 1.7% (0.0-2.4) versus 13.6% (8.0-15.7) during PSV 1, and 10% (6.5-20.0) during PSV 2 (p=0.001). (50) (See supplemental file 5)

DISCUSSION

This updated review includes papers about APRV and NAVA, recent ventilation modes used in PICU patients. We found little evidence to recommend APRV for children with ARDS. Consensus is needed on the recommended ventilation mode and strategies that are effective in PARDS. (52)

Results of our meta-analysis of HFO versus CV in children showed a significantly lower mortality in favor of CV, but LOV and LOS were not significantly different between these modes. The PaO_2/FiO_2 ratio differed significantly between groups in favor for CV. This is in contrast with our former review of 2011, where in the pooled analysis the mortality rates in HFO and CV did not differ, and HFO was associated with a better oxygenation after 72 hours than was CV. (22) A previous systematic review of studies in adults and children likewise concluded, that the PaO2/FiO2 ratio at 24 to 72 hours of ventilation was in favor of HFO. (53) In a systematic review including term-born and premature neonates, Cools et al. also found no evidence of a beneficial effect of HFO on mortality. (54)

Overall, we found that CV in children is favorable for mortality in ARDS and AHRF, but analysis of the available RCT data did not result in a significant difference between HFO and CV in this respect, presumably due to small sample sizes. After our review of 2011, propensity score matching (PSM) studies became available which include far more patients, and may account for the significant effect of CV on mortality. (51, 55) PSM studies require large samples and solid data on both treated and non-treated patient groups, which must have the same characteristics. PSM studies can never fully compensate, however, for the lack of randomization because yet unknown confounders are not matched. (36, 56-57) A drawback of PSM in comparing HFO and CV, is that HFO is supposed to give an upwardly biased effect size because it is often used in more severely ill children. In PSM, the baseline of severity of illness is usually the same for the HFO and CV groups, but the severity of illness scores are measured only at baseline and usually not at the time HFO is started after failing CV. Measuring severity of illness at the time a child needs HFO is recommended to address in future research.

For lack of guidelines for timing, setting and safety features for HFO devices, studies on the use of HFO did not show reduction in mortality. An RCT with an unambiguous protocol and use of one safe HFO machine would be a better option, provided adequate sample sizes can be obtained. (23, 58) So far, PSM studies have proven that the current practice of HFO worldwide does not reduce mortality.

The European consensus guideline on mechanical ventilation of critically ill children (PEM-VECC guideline) provides insufficient evidence to recommend HFO in critically ill children in different conditions. (23) This guideline suggests to consider HFO if CV fails, using an open lung strategy to maintain optimal lung volume. Based on the results

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of this meta-analysis, we cannot yet recommend HFO for PARDS or AHRF until the findings of a robust RCT with a longer follow up than only the time to hospital discharge are known. (59) In this respect, we are awaiting the results of the PROSpect study, a multi-center prone and oscillation pediatric clinical trial. (60)

WEANING STUDIES AND NAVA

After Randolph (2002), the published comparative weaning studies only concerned NAVA. Previous pediatric studies on invasive NAVA, as well as the NAVA crossover studies in this review demonstrate lower peak inspiratory pressures and tidal volumes during NAVA and optimized patient-ventilator interaction compared with other CV modes. (18, 19, 48-50, 61-63) Only two experimental NAVA studies found a positive effect on LOV and extubation success. (44, 50) Kallio et al. found no statistically significant different LOV between NAVA and CV. (42) Other studies have shown much asynchrony during invasive ventilation in children. (62-66) Evidence in adults has shown that asynchrony can lead to a longer ventilator duration (67-68) and even higher mortality, but there is yet no evidence for a worse outcome in children due to asynchrony. (66) A review of mostly crossover studies in adults concluded that NAVA was associated with a significantly lower AI and with a significant decrease in severe asynchrony as compared with PS. (69) More RCTs are needed to evaluate the effect of NAVA on weaning of ventilation in children. This should not be done with a crossover design because then important outcomes such as LOV, extubation success, LOS, neurocognitive development and pulmonary function cannot be measured. (70-72)

We recommend setting up multi-center studies to study the best protocolized ventilation and weaning strategies for specific age categories and underlying pathology. Moreover, these studies should include longer-term outcomes such as pulmonary function, neurocognitive development, and health-related quality of life. (72)

The strengths of the present review include a comprehensive search strategy, broad inclusion criteria (resulting in a representative, heterogeneous population) and assessment of clinically important outcomes. In addition, we pooled the data.

Limitations of this study include the higher numbers of crossovers in two studies, which might have reduced the measured effect of HFO on mortality. Furthermore, not all studies reported HFO and CV settings; reported settings differed between studies; and some studies used recruitment maneuvers for CV and HFO. Pooled results should

be interpreted cautiously in view of the heterogeneity among studies, such as with respect to age, disease and numbers of inclusion. (51, 73-75)

CONCLUSIONS

This review brings evidence that CV in children is associated with lower mortality than is HFO. There is no evidence that HFO reduces LOV, LOS or oxygenation. Preliminary findings for NAVA are promising.

KEY MESSAGES

- Evidence of reduced risk of mortality of CV compared to HFO in children.
- No evidence that high-frequency ventilation (HFO and VDR) is better than CV for the outcomes LOV, LOS and oxygenation in children.
- NAVA provides synchronous ventilation with less sedation and seems associated with shorter LOV and weaning time, but robust RCTs are needed to confirm this.
- APRV is not yet recommended because of too little evidence and lack of an unambiguous protocol.

ABBREVIATIONS

AI: asynchrony index; APRV: Airway pressure released ventilation; BIPAP: bilevel positive airway pressure; CI: confidence interval; CV: conventional ventilation; FiO_2: fraction of inspired oxygen; HFO: high-frequency oscillation; iNO: inhaled nitric oxide; LOV: length of ventilation; NAVA: neurally adjusted ventilator assist; OR: odds ratio; PC: pressure control; pCO_2: partial arterial pressure of carbon dioxide; PF: PaO_2/FiO2 ratio; pO_2: partial pressure of oxygen; PS: pressure support; RCT: randomized controlled trial; SaO_2: saturation of oxygen; VDR: volume diffusive respirator; VS: volume support; WMD: weighted mean difference.

DECLARATIONS

Ethics approval and consent to participate
NA

Consent for publication
All authors agreed with the publication.

Availability of data and materials
NA

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
AD and DT conceived of and designed the study. AD and EI were involved in data acquisition, analysis, and interpretation and drafted the manuscript. DT, MvD and RJ critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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REFERENCES

1. Kollef MH, Levy NT, Ahrens TS, et al: The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998, 114(2):541-548.

2. Srinivasan R, Asselin J, Gildengorin G, et al: A prospective study of ventilator-associated pneumonia in children. *Pediatrics* 2009, 123(4):1108-1115.

3. Hoskote A, Cohen G, Goldman A, et al: Tracheostomy in infants and children after cardiothoracic surgery: indications, associated risk factors, and timing. *J Thorac Cardiovasc Surg* 2005, 130(4):1086-1093.

4. Glau CL, Conlon TW, Himebauch AS, et al: Diaphragm Atrophy During Pediatric Acute Respiratory Failure Is Associated With Prolonged Noninvasive Ventilation Requirement Following Extubation. *Pediatr Crit Care Med* 2020.

5. Lee EP, Hsia SH, Hsiao HF, et al: Evaluation of diaphragmatic function in mechanically ventilated children: An ultrasound study. *PLoS One* 2017, 12(8):e0183560.

6. Ista E, van Dijk M: High Incidence of Pediatric Delirium in PICU; Time for Action! *Pediatr Crit Care Med* 2020, 21(1):96-97.

7. Burns JP, Sellers DE, Meyer EC, et al: Epidemiology of death in the PICU at five U.S. teaching hospitals*. *Crit Care Med* 2014, 42(9):2101-2108.

8. Hartman ME, Saeed MJ, Bennett T, et al: Readmission and Late Mortality After Critical Illness in Childhood. *Pediatr Crit Care Med* 2017, 18(3):e112-e121.

9. Namachivayam P, Shann F, Shekerdemian L, et al: Three decades of pediatric intensive care: Who was admitted, what happened in intensive care, and what happened afterward. *Pediatr Crit Care Med* 2010, 11(5):549-555.

10. Curley MA, Wypij D, Watson RS, et al: Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA* 2015, 313(4):379-389.

11. Randolph AG, Meert KL, O'Neil ME, et al: The feasibility of conducting clinical trials in infants and children with acute respiratory failure. *Am J Respir Crit Care Med* 2003, 167(10):1334-1340.

12. Randolph AG: Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med* 2009, 37(8):2448-2454.

13. Khemani RG, Smith L, Lopez-Fernandez YM, et al: Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. *Lancet Respir Med* 2019, 7(2):115-128.

14. Ross PA, Klein MJ, Nguyen T, et al: Body Habitus and Risk of Mortality in Pediatric Sepsis and Septic Shock: A Retrospective Cohort Study. *J Pediatr* 2019, 210:178-183 e172.

15. Koh J, Wong JJ, Sultana R, et al: Risk factors for mortality in children with pneumonia admitted to the pediatric intensive care unit. *Pediatr Pulmonol* 2017, 52(8):1076-1084.

16. Wosten-van Asperen RM, van Gestel JPJ, van Grotel M, et al: PICU mortality of children with cancer admitted to pediatric intensive care unit a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2019, 142:153-163.

17. Chatburn RL, El-Khatib M, Mireles-Cabodevila E: A taxonomy for mechanical ventilation: 10 fundamental maxims. *Respir Care* 2014, 59(11):1747-1763.

18. Bengtsson JA, Edberg KE: Neurally adjusted ventilatory assist in children: an observational study. *Pediatr Crit Care Med* 2010, 11(2):253-257.

19. Breatnach C, Conlon NP, Stack M, et al: A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. *Pediatr Crit Care Med* 2010, 11(1):7-11.

3

20. Ganesan SL, Jayashree M, Singhi SC, et al: Airway pressure release ventilation in pediatric acute respiratory distress syndrome: A randomized controlled trial. *Am J Respir Crit Care Med* 2018, 198(9):1199-1207.

21. Turner DA, Arnold JH: Insights in pediatric ventilation: timing of intubation, ventilatory strategies, and weaning. *Curr Opin Crit Care* 2007, 13(1):57-63.

22. Duyndam A, Ista E, Houmes RJ, van Driel B, et al: Invasive ventilation modes in children: A systematic review and meta-analysis. *Crit Care* 2011, 15(1).

23. Kneyber MCJ, de Luca D, Calderini E, et al: Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). *Intensive Care Med* 2017, 43(12):1764-1780.

24. PRISMA Statement. Available online at: http://www.prisma-statement.org/PRISMAStatement/Checklist.aspx. Accessed April 25, 2020

25. Higgins JP, Altman DG, Gotzsche PC, et al: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011, 343:d5928.

26. Cochrane Handbook for Systematic Reviews of Interventions version 5.1 Available online at: https://training.cochrane.org/handbook. Accessed April 25, 2020

27. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available online at: http://www.ohri.ca/programs/clinicalepidemiology/oxford.asp. Accessed April 25, 2020.

28. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 1986, 7(3):177-188.

29. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002, 21(11):1539-1558.

30. Cochrane Handbook. Available online at: https:// handbook-5-1.cochrane.org/chapter_7/7_7_3_5_mediansand_interquartile_ranges.htm.

31. Arnold JH, Hanson JH, Toro-Figuero LO, et al: Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med* 1994, 22(10):1530-1539.

32. Dobyns EL, Anas NG, Fortenberry JD, et al: Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. *Crit Care Med* 2002, 30(11):2425-2429.

33. Carman B, Cahill T, Warden G, et al: A prospective, randomized comparison of the Volume Diffusive Respirator vs conventional ventilation for ventilation of burned children. 2001 ABA paper. *J Burn Care Rehabil* 2002, 23(6):444-448.

34. Jaarsma AS, Knoester H, van Rooyen F, et al: Biphasic positive airway pressure ventilation (PeV+) in children. *Crit Care* 2001, 5(3):174-177.

35. Randolph AG, Wypij D, Venkataraman ST, et al: Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. *JAMA* 2002, 288(20):2561-2568.

36. Bateman ST, Borasino S, Asaro LA, et al: Early high-frequency oscillatory ventilation in pediatric acute respiratory failure: A propensity score analysis. *Am J Respir Crit Care Med* 2016, 193(5):495-503.

37. Bojan M, Gioanni S, Mauriat P, et al: High-frequency oscillatory ventilation and short-term outcome in neonates and infants undergoing cardiac surgery: a propensity score analysis. *Crit Care* 2011, 15(5):R259.

38. El-Nawawy A, Moustafa A, Heshmat H, et al: High frequency oscillatory ventilation versus conventional mechanical ventilation in pediatric acute respiratory distress syndrome: A randomized controlled study. *Turk J Pediatr* 2017, 59(2):130-143.

39. Fioretto JR, Batista KA, Carpi MF, et al: High-frequency oscillatory ventilation associated with inhaled nitric oxide compared to pressure-controlled assist/control ventilation and inhaled nitric oxide in children: Randomized, non-blinded, crossover study. *Pediatr Pulmonol* 2011, 46(8):809-816.

40. Guo YX, Wang ZN, Li YT, et al: High-frequency oscillatory ventilation is an effective treatment for severe pediatric acute respiratory distress syndrome with refractory hypoxemia. *Ther Clin Risk Manage* 2016, 12:1563-1571.

41. Gupta P, Green JW, Tang X, et al: Comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *JAMA Pediatr* 2014, 168(3):243-249.

42. Kallio M, Peltoniemi O, Anttila E, et al: Neurally adjusted ventilatory assist (NAVA) in pediatric intensive care - A randomized controlled trial. *Pediatr Pulmonol* 2015, 50(1):55-62.

43. Samransamruajkit R, Rassameehirun C, Pongsanon K, et al: A comparison of clinical efficacy between high frequency oscillatory ventilation and conventional ventilation with lung volume recruitment in pediatric acute respiratory distress syndrome: A randomized controlled trial. *Indian J Crit Care Med* 2016, 20(2):72-77.

44. Sood SB, Mushtaq N, Brown K, et al: Neurally Adjusted Ventilatory Assist Is Associated with Greater Initial Extubation Success in Postoperative Congenital Heart Disease Patients when Compared to Conventional Mechanical Ventilation. *J Pediatr Intensive Care* 2018, 7(3):147-158.

45. Samransamruajkit R, Prapphal N, Deelodegenavong J, et al: Plasma soluble intercellular adhesion molecule-1 (sICAM-1) in pediatric ARDS during high frequency oscillatory ventilation: a predictor of mortality. *Asian Pac J Allergy Immunol* 2005, 23(4):181-188.

46. Wong JJ, Liu S, Dang H, et al: The impact of high frequency oscillatory ventilation on mortality in paediatric acute respiratory distress syndrome. *Crit Care* 2020, 24(1):31.

47. Ning B, Liang L, Lyu Y, et al: The effect of high-frequency oscillatory ventilation or airway pressure release ventilation on children with acute respiratory distress syndrome as a rescue therapy. *Transl Pediatr* 2020, 9(3):213-220.

48. Bonacina D, Bronco A, Nacoti M, et al: Pressure support ventilation, sigh adjunct to pressure support ventilation, and neurally adjusted ventilatory assist in infants after cardiac surgery: A physiologic crossover randomized study. *Pediatr Pulmonol* 2019, 54(7):1078-1086.

49. Spinazzola G, Costa R, De Luca D, et al: Pressure Support Ventilation (PSV) versus Neurally Adjusted Ventilatory Assist (NAVA) in difficult to wean pediatric ARDS patients: a physiologic crossover study. *BMC Pediatr* 2020, 20(1):334.

50. Piastra M, De Luca D, Costa R, et al: Neurally adjusted ventilatory assist vs pressure support ventilation in infants recovering from severe acute respiratory distress syndrome: nested study. *J Crit Care* 2014, 29(2):312 e311-315.

51. Austin PC: An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011, 46(3):399-424.

52. Ganesan SL: Airway pressure release ventilation in children. *Curr Opin Crit Care* 2019:25:63-70.

53. Sud S, Sud M, Friedrich JO, et al: High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2016, 4:CD004085.

54. Cools F, Offringa M, Askie LM: Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2015(3):CD000104.

55. Rubin DB: The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat Med* 2007, 26(1):20-36.

56. Bateman ST, Borasino S, Asaro LA, et al: Reply: Do We Really Know How to Use High-Frequency Oscillatory Ventilation in Critically Ill Children? *Am J Respir Crit Care Med* 2016, 193(9):1068-1069.

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57. Kneyber MC, Markhorst DG: Do We Really Know How to Use High-Frequency Oscillatory Ventilation in Critically Ill Children? *Am J Respir Crit Care Med* 2016, 193(9):1067-1068.

58. Kneyber MC, van Heerde M, Markhorst DG: Reflections on pediatric high-frequency oscillatory ventilation from a physiologic perspective. *Respir Care* 2012, 57(9):1496-1504.

59. Adhikari NK, Slutsky AS: Pediatric High-Frequency Oscillation. The End of the Road? *Am J Respir Crit Care Med* 2016, 193(5):471-472.

60. Kneyber MCJ, Cheifetz IM, Curley MAQ: High-frequency oscillatory ventilation for PARDS: awaiting PROSPect. *Crit Care* 2020, 24(1):118.

61. Alander M, Peltoniemi O, Pokka T, et al: Comparison of pressure-, flow-, and NAVA-triggering in pediatric and neonatal ventilatory care. *Pediatr Pulmonol* 2012, 47(1):76-83.

62. Vignaux L, Grazioli S, Piquilloud L, et al: Optimizing patient-ventilator synchrony during invasive ventilator assist in children and infants remains a difficult task*. *Pediatr Crit Care Med* 2013, 14(7):e316-325.

63. de la Oliva P, Schuffelmann C, Gomez-Zamora A, et al: Asynchrony, neural drive, ventilatory variability and COMFORT: NAVA versus pressure support in pediatric patients. A non-randomized cross-over trial. *Intensive Care Med* 2012, 38(5):838-846.

64. Blokpoel RG, Burgerhof JG, Markhorst DG, et al: Patient-Ventilator Asynchrony During Assisted Ventilation in Children. *Pediatr Crit Care Med* 2016, 17(5):e204-211.

65. Dres M, Rittayamai N, Brochard L: Monitoring patient-ventilator asynchrony. *Curr Opin Crit Care* 2016, 22(3):246-253.

66. Mortamet G, Larouche A, Ducharme-Crevier L, et al: Patient-ventilator asynchrony during conventional mechanical ventilation in children. *Ann Intensive Care* 2017, 7(1):122.

67. de Wit M, Miller KB, Green DA, et al: Ineffective triggering predicts increased duration of mechanical ventilation. *Crit Care Med* 2009, 37(10):2740-2745.

68. Blanch L, Villagra A, Sales B, et al: Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015, 41(4):633-641.

69. Pettenuzzo T, Aoyama H, Englesakis M, et al: Effect of Neurally Adjusted Ventilatory Assist on Patient-Ventilator Interaction in Mechanically Ventilated Adults: A Systematic Review and Meta-Analysis. *Crit Care Med* 2019, 47(7):e602-e609.

70. Ward SL, Turpin A, Spicer AC, et al: Long-Term Pulmonary Function and Quality of Life in Children After Acute Respiratory Distress Syndrome: A Feasibility Investigation. *Pediatr Crit Care Med* 2017, 18(1):e48-e55.

71. Chakdour S, Vaidya PC, Angurana SK, et al: Pulmonary Functions in Children Ventilated for Acute Hypoxemic Respiratory Failure. *Pediatr Crit Care Med* 2018, 19(9):e464-e471.

72. Blackwood B, Ringrow S, Clarke M, et al: A Core Outcome Set for Critical Care Ventilation Trials. *Crit Care Med* 2019, 47(10):1324-1331.

73. Greenland S: Can meta-analysis be salvaged? *Am J Epidemiol* 1994, 140(9):783-787.

74. MacLehose RR, Reeves BC, Harvey IM, et al: A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies. *Health Technol Assess* 2000, 4(34):1-154.

75. Shapiro S: Meta-analysis/Shmeta-analysis. *Am J Epidemiol* 1994, 140(9):771-778.

SUPPLEMENTAL FILE 1: EXPLANATION APRV AND NAVA

APRV-Airway pressure release ventilation	NAVA-Neurally adjusted ventilatory assist
Time triggered, pressure limited, inverse-ratio mode of ventilation that provides continuous positive airway pressure (CPAP) with an intermittent release phases. APRV applies CPAP (P high) for a prolonged time (T high) to maintain adequate lung volume and alveolar recruitment, with a time-cycled release phase to a lower set of pressure (P low) for a short period of time (T low) or release time where most of ventilation and CO_2 removal occurs.	An invasive ventilation mode which provides ventilator support proportional to the electrical activity of the diaphragm (Edi). It enables physiological variations in tidal volume and inspiratory time from breath to breath.

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SUPPLEMENTAL FILE 2: SEARCH STRATEGY

Embase
('artificial ventilation'/exp OR 'ventilator'/exp OR 'assisted ventilation'/de OR (ventilat* OR ((artific* OR pressur*) NEAR/3 (respirat* OR breath* OR control* OR support* OR biphas* OR regulat*)) OR HFO OR ARPV OR PRVC OR NAVA OR SIMV OR VTV):ab,ti) AND ('lung disease'/de OR 'mortality'/exp OR 'survival'/exp OR 'oxygenation'/exp OR (mortalit* OR death* OR survival* OR oxygenat* OR pneumopath* OR ((bronchopulmon* OR lung* OR pulmonar* OR pleuropulmonar*) NEAR/3 (diseas* OR disorder*))):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR pediatrics/exp OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'child death'/de OR 'pediatric ward'/de OR 'pediatric hospital'/de OR 'pediatric intensive care unit'/de OR 'neonatal intensive care unit'/de OR (adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR

trial OR groups):ab,ti) NOT ((animals)/lim NOT (humans)/lim) AND (english)/lim NOT ((Conference Abstract)/lim)

Medline
(exp Respiration, Artificial/ OR exp Ventilators, Mechanical/ OR (ventilat* OR ((artific* OR pressur*) ADJ3 (respirat* OR breath* OR control* OR support* OR biphas* OR regulat*)) OR HFO OR ARPV OR PRVC OR NAVA OR SIMV OR VTV).ab,ti.) AND (Lung Diseases/ OR exp Mortality/ OR Survival/ OR (mortalit* OR death* OR survival* OR oxygenat* OR pneumopath* OR ((bronchopulmon* OR lung* OR pulmonar* OR pleuropulmonar*) ADJ3 (diseas* OR disorder*))).ab,ti.) AND (exp Child/ OR exp Infant/ OR exp Adolescent/ OR exp "Child Health Services"/ OR exp "Child Care"/ OR "Hospitals, Pediatric"/ OR exp "Intensive Care Units, Pediatric"/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti.) NOT (Animals/ NOT Humans/) AND english.la. NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.

Cochrane (RCTs)
((ventilat* OR ((artific* OR pressur*) NEAR/3 (respirat* OR breath* OR control* OR support* OR biphas* OR regulat*)) OR HFO OR ARPV OR PRVC OR NAVA OR SIMV OR VTV):ab,ti) AND ((mortalit* OR death* OR survival* OR oxygenat* OR pneumopath* OR ((bronchopulmon* OR lung* OR pulmonar* OR pleuropulmonar*) NEAR/3 (diseas* OR disorder*))):ab,ti) AND ((adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs):ab,ti)

SUPPLEMENTAL FILE 3: SUMMARY DIAGRAM OF RISK OF BIAS PERCENTILE CHART FOR RCTS
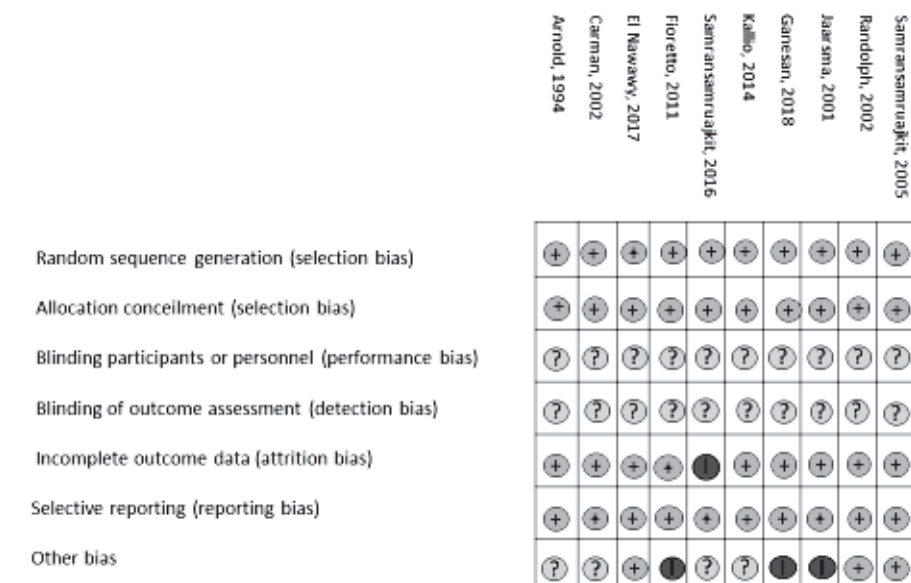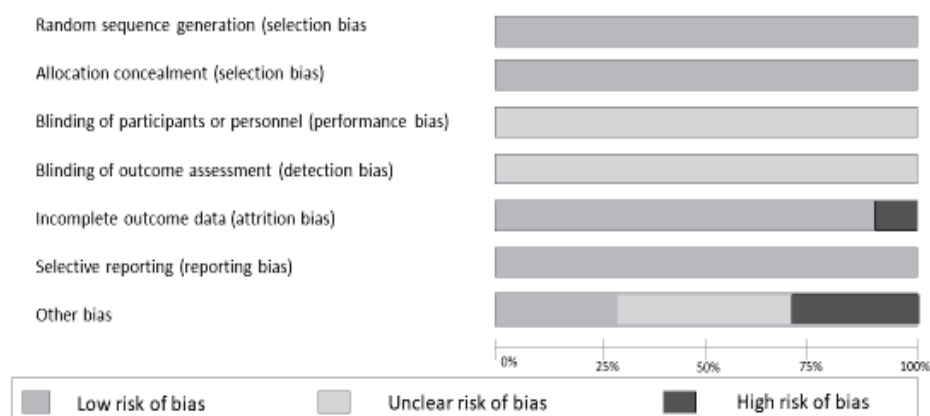
SUPPLEMENTAL FILE 4: NEWCASTLE–OTTAWA SCALE ASSESSMENT OF INCLUDED COHORT STUDIES

Study	Selection			
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at the start of the study
Ning 2020	*	*	*	*
Wong 2020	*	*	*	*
Spinazzola 2020	*		*	*
Bonacina 2019	*		*	*
Dobyns, 2002	*	*	*	*
Gupta 2014	*	*	*	*
Guo 2016	*	*	*	*
Bateman 2016	*	*	*	*
Sood 2018	*	*	*	*
Bojan 2011	*	*	*	*
Piastra 2014	*		*	*

SUPPLEMENTAL FILE 5: SUMMARY OF STUDY CHARACTERISTICS (IN ORDER OF VENTILATION MODE AND YEAR)

Author (year)	Study design and population	Intervention/ mode	Mortality/survival
HFO			
Arnold (1994) USA	RCT/ multicenter (5) n=58 with diffuse alveolar disease and/or air leak syndrome Age: HFO 2.5± 2.5 vs. CV 3.1±3.3 yrs.)	Comparison effectiveness of HFO (n = 29) with CV (n = 29) – crossover Crossover: CV to HFO (n = 19), HFO to CV (n = 11)	Number of survivors at 30 days -CV: 17 of 29 (59%); HFO: 19 of 29 (66%) (NS) Death (ranked) - CV: 40%, CV to HFO: 42%, HFO: 6%, HFO to CV: 82%; (p ≤0.001)
Dobyns (2002) USA	Retrospective analysis of data from a RCT/ multicenter (7) on the use of iNO in patients with AHRF, OI > 15 n=99 Age: 0-23 years	Comparisons between patients treated with HFO + iNO (n = 14), HFO alone (n = 12), CV + iNO (n = 35), and CV alone (n = 38)	Trend of improved survival in HFO + iNO vs CV: CV:22 of 38 (58%); CV + iNO: 20 of 35 (53%); HFO: 7 of 12 (58%); HFO + iNO: 10 of 14 (71%); (p= 0.994)

Comparability	Outcomes			Total score
	Assessment of outcomes	Length of follow-up	Adequacy of follow-up	
*	*		*	7
**	*	*	*	9
*	*			5
*	*			5
*	*	*	*	8
**	*	*	*	9
	*	*	*	7
**	*	*	*	9
	*	*	*	7
**	*	*	*	9
*	*	*	*	7

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LOV (days) Extubation success/AI	Oxygenation	LOS (days)	Sedation
Total CV: 22±17; HFO: 20±27 Survivors (at 30 days)-CV:29±18 vs HFO: 27±31 Non survivors: (at 30 days) CV:11±9; HFO: 8±6 (NS)	PaO_2/PAO_2 increased over time (72 hrs.) in HFO compared with CV (P < 0.001) PaO_2/PAO_2 - CV: 0.13 (0 hrs.) up to 0.22 (72 hrs.) vs HFO: 0.13 (0 hrs.) up to 0.26 (72 hrs.); After crossover - PaO_2/PAO_2 increase over time (72 hrs.) in CV to HFO group compared with HFO to CV group; (p=0.003)	ND	ND
CV: 22±4; CV + iNO: 21±3; HFO: 52±28; HFO + iNO: 17±4; (p=0.098)	PaO_2/FiO_2 ratio (PF ratio) after 24 hrs.: both HFO + iNO and HFO resulted in greater improvement in PF ratio than CV or CV + iNO (P = 0.005); after 72 hrs.: HFO 259±60 vs. CV 148±15 and CV + iNO 150±19; HFO + iNO 213±29; (p = 0.027)	ND	ND

Author (year)	Study design and population	Intervention/ mode	Mortality/survival
Carman (2002) USA	RCT/ single center n=64 with inhalation injury Age: 7.4±0.7 yrs.	Compare Volume diffusive respirator (VDR) (n = 32) with PC (n = 32)	PC: 5/32 (16%) vs. VDR: 2/32 (6%); (NS)
Samransam- ruajkit (2005) Thailand	RCT/single center n=16 children with ARDS Age: >1 months and < 15 yrs.	HFO vs CV To investigate sICAM-1 levels in plasma during HFOV and conventional ventilation	CV:5/9 (56%) vs HFO: 2/7(29%) Overall mortality was 45.7%
Bojan (2011) France	Retrospective cohort study/ single center Data were extracted retrospectively from a prospective database (2001-2010), using propensity score matching. n=3549 children, Neonates and infants who underwent cardiac surgery Age: 28-100 days	HFO vs CV To assess associations between commencement of HFOV on the day of cardiac surgery and the length of mechanical ventilation, ICU stay and mortality. Matching resulted in two well balanced groups of 120 patients HFO vs CV	Died patients: CV 18 (15.8%) vs HFO 10 (8.3%); (p=0.08)
Fioretto (2011) Brasil	Cross-over RCT / single center n=28 with AHRF Time points measured: Before rando-mization and during the 24hr protocol: at T4hr/T8hrs T12hrs/T16hr /T24hr Age: 1 month-14 yrs.	HFO iNO vs PCACV iNO Comparison of the acute oxygenation effects of iNO (5 ppm) during HFOV and PCACV Patients were kept under one of the two ventilation modes for 8 hrs., crossing to the other for 8 hrs. and then back again to the initial mode to complete 24 hrs. observation	Two patients of each group died, with ARDS, Sepsis, MODS and DIC

LOV (days) Extubation success/AI	Oxygenation	LOS (days)	Sedation
PCV: 11±2 vs. VDR: 12±2; (NS)	PF ratio - PC: 507±13 vs VDR: 563±16; ($p< 0.05$)	ND	ND
Survivors: CV: 20 ± 4 (n=4) vs HFO: 13.6±4.0 (n=5)	PaO_2/FiO_2 baseline CV 131.7±26.06 vs HFO 110±30.22 OI baseline: CV 16.4 ± 1.6 vs. HFO 23.9±4.3	ND	ND
CV 5 (9-22) vs HFO 7 (5-11); (P=0.03) The 120 patients switched to HFO on day 0 had longer durations of MV; (P<0.001) Early HFO use was associated with a longer duration of MV after adjusting for risk category (HR 0.75;95%CI, 0.64-0.89; (p=0.001)	No oxygenation measured because of the heterogenic cardiac group with various intracardiac shunting patterns	CV: 14 (9-22) vs. HFO 11 (5-17) (p=0.009)	ND
ND	PF ratio: T baseline compared with T4: CV T base: 111.95±37 vs CV T4: 143.88±47.5 (P<0.05) and HFO T base: 123.76±33 vs HFO T4: 194.61±62.42 (p<0.05) PF ratio at T8: CV 171.21±52.9 vs HFO 227.9±80.7; (p<0.05) PO_2/FiO_2 at T 24: NS, number not mentioned. OI baseline: CV 20.6±14.3 vs HFO 16.7±5.6 OI at T24: CV 6.98±3.7 vs HFO 10.27±3.8; (p<0.05) Either HFOV or PCACV + early iNO improves oxygenation. HFOV causes earlier FiO_2 reduction and increased PaO_2/FiO_2 ratio compared with PCACV at 8 hrs. At 24 hrs.: no significant difference and no clinical improvement derived from HFOV and iNO compared to PCACV plus iNO.	ND	CV comfort score 16 (16–20) vs HFO: 17 (17–19); P < 0.05) No use of neuromuscular blocking agents

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Author (year)	Study design and population	Intervention/ mode	Mortality/survival
Gupta (2014) USA	Retrospective observational, using propensity score matching/Multi center (98), children with ARF, receiving MV, in the virtual PICU system database in the USA n= 902 HFOV (9.8%)/ 8275 (90.2%) CMV Of 902 HFOV: 483 early HFOV and 419 late HFOV 1764 patients were matched to compare HFOV and CMV. 942 patients were matched to compare early HFOV and CMV Age: 1 month till 18 yrs.	HFO vs CV To compare outcomes of HFOV with those of CV in children with AHRF. Propensity score matching was performed as a 1-1 match of HFO and CV patients with similar demographic and clinical characteristics HFOV group: MV ≥ 24 hrs. CV group: MV ≥ 96 hrs. HFOV group was further divided into early and late HFOV, early HFOV: within 24 hrs. of intubation and late HFOV after 24 hrs. of intubation	Mortality CV 74 (8.4%) vs HFO 152 (17.3%); (P<0.001) CV n= 39 (8.3%) vs Early HFOV: n=85 (18.1%); (P<0.001) The SMR (standardized mortality ratio) in the early HFOV group was 1.62; 95% CI:1.31-2.01) vs 0.76; 95% CI: 0.62-1.16)
Bateman (2016) USA	Secondary analysis of a prospective cluster RCT using Propensity score matching/multi center (31). n=2449, with ARF 210 early HFO and 2239 CMV/ late HFO Age: 2 weeks to 17 yrs.	HFO vs CV To compare outcomes of patients from the RESTORE study, with AHRF managed with HFO within 24-48 hrs. of intubation vs CV or late HFO after 48 hrs.	Early HFO was not associated with mortality (OR 1.28;95% CI, 0.92-1.79;) compared to CV/late HFOV, p=0.15 Mortality was high in both groups (CV 17% vs HFO 25%) Within the two highest risk categories early HFOV was associated with higher mortality. OR 1.81(95% CI,1.23-2.65); p=0.00)
Guo (2016) China	Retrospective observational n=48 with severe PARDS (OI ≥ 16) according PALI consensus n=26 HFOV-22 CV Age: 28 days-14 years	Single center study HFO vs CV To estimate whether PARDS patients with refractory hypoxemia who deteriorated on CMV could benefit from HFOV and to identify risk factors contributing to the mortality Age and weight were different HFO: 9 months (21.75) vs CV 40.5 months (48.75) p=0.002 and 6.55 kg. vs. 14.75 kg. (p=0.001)	In hospital mortality was not associated with ventilation mode; p=0.367 OR of survival in HFOV was 2.74 (95% CI, 0.52 to 14.58) compared to CMV; p=0.237 Survival time is not related to the pattern of ventilation; p=0.769 14 of the 48 patients died: CV 5 of 22 (22,7%) vs. HFO 9 of 26 (34.6%). In the mortality analysis HR for weight was 1.198 (p=0.020) and HR for MODS was 17.79; (P=0.006) in the HFOV group

LOV (days) Extubation success/AI	Oxygenation	LOS (days)	Sedation
CV 14.6±15.4 vs HFO 20.3±19; (P<0.001) CV 14.6±16.4 vs Early HFOV: 15.9±15.9; (P<0.001)	ND	CV 19.1±18.5 vs HFO 24.9 ± 22.3%; (p<0.001) CV 19.3±18.0 vs Early HFOV: 19.5±16.9; (p=0.03)	ND
Early HFO use was associated with a longer duration of MV (HR 0.75 (95% CI, 0.64-0.89); p=0.001) compared to CV/late HFOV Within the two highest risk categories early HFOV was associated with longer duration of MV (HR 0.64 (95% CI,0.54-0.76); p<0.001)	The highest risk category representing patients with the most hypoxia, included 52% of the early HFOV patients with an OI > 8 and 13% of the CMV/LHFOV with an OI > 8. In this quintile the worst OI on days 0-1 was higher for the early HFOV patients, median 43.1 (31.0-58.0) vs CV/LHFOV median 32.3 (27.3-43.5); p<0.001	ND	ND
CV 6±7 vs HFOV 18.5±19; (p=0.000) LOV was secondary outcome	Increase in the PF ratio on the first day of HFOV and persisted throughout the remaining study days; (P= 0.005, 0.008, 0.003 and < 0.001 for the first 24 hrs., 48 hrs., 72 hrs. and the last day resp.) PaO_2 showed a remarkable improvement during HFOV; (P=0.013, 0.090, 0.008 and 0.004 for the first 24 hrs., 48 hrs., 72 hrs. and the last day, resp.) The OI and $PaCO_2$ tended to decrease during the first 3 study days on HFOV and on the last day their values improved; (P=0.001 and 0.031, resp.)	CV 264 hrs. (IQR 246) vs HFOV 516 hrs. (IQR 600) (p=0.048)	ND

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Author (year)	Study design and population	Intervention/ mode	Mortality/survival
Samran-samruajkit (2016) Thailand	RCT/ single center n=18 with PARDS according the Berlin definition Age: 1 month-15 yrs.	HFO vs CV to study the clinical benefits of using Lung volume recruitment maneuver (LVRM) with HFOV compared with CV with LVRM in children with severe ARDS	CV: 1/3 (33%) vs HFO: 1/15 (6.6 %) (6 patients switched group from CMV to HFO); ns Overall PICU mortality at 28 days with severe ARDS was 16.7%
El Nawawy (2017) Egypt	RCT/ single center n=200 with PARDS Age: 28 days-108 months	HFO (n=55) vs. CV (n=57)	30 days mortality, no differ between CV: 43% vs HFO: 45%; (p=0.776)
Wong (2020) China	Retrospective study with genetic matching to analyse the association between HFO treatment and 28-day mortality and propensity score matching, inverse probability of treatment weighting and marginal structural modelling to estimate treatment effects Multi center (10) PARDS on a PICU n=328 Age: 0-6 yrs.	HFO vs CV/non HFO For genetic matching 118 pairs were matched	Genetic matching (GM): 28-day mortality: OR 2.3 95%CI (1.3, 4.4) p=0.01 HFO 38/118= 32.2% vs. CV 20/118 = 16.9%; p=0.01

LOV (days) Extubation success/AI	Oxygenation	LOS (days)	Sedation
CMV 17 (10.5-31.5), n=3 vs HFO 15 (11.5-21.7), n= 15 (6 switched group from CMV to HFO)	PF ratio baseline: CV 78.3±27.2 vs HFO 82.4±24 PF ratio at 1 hr. after LVRM: CV 69±56.8 vs HFO 138.5±49.7; (p<0.01) PF ratio at 24 hrs.: CV: 120±30 vs HFO 250±25 ns OI baseline: CV: 23.1±9.3 vs HFO: 25.9±11 OI 24 hrs.: CV: 22.7±4.2 vs HFO: 18.5 (sd unknown) ns 6/9 of the CV group failed to wean oxygen lower than FiO_2 of 0.6 after LVRM and had to switch to HFOV mode at 6 hrs. after enrollment	ND	ND
MV free days: CV 25.0 (23.0-26.0) vs HFO 25.0 (23.0-26.0); (p=0.65) MV days: CV 5.0 (4.0-7.0) vs HFO 5.0 (4.0-7.0); (p=0.65)	OI baseline: CV: 11.8 (9.0-13.9) vs HFO: 16.0 (11.2-22.0); (p=0.001) OI after 24 hrs.: CV: 6.8 (6.1-8.4) vs HFO: 7.5 (6.0-8.5); (p= 0.594) OI decrease percent: CV: 32.2 (24.44-42.37) vs HFO: 50 (40.63-57.85); (p<0.001) PF baseline: CV: 116.0 (98-145.0) vs HFO: 121.0 (91.0-140.0); (p=0.302) PF after 24 hrs.: CV: 191 (161.0-210.0) vs HFO: 221 (191-140.0); (p<0.001) PF increase percent: CV: 37.9 (34.41-72.73) vs HFO: 91.36 (65.0-113.3); (p<0.001)	CV 8.0 (6.0-10.0) vs. HFO: 8.0 (6.0-18.0); (p=0.28)	Midazolam intake: CV 2.69±0.98 mcg/kg/min. vs. HFO: 4.84±1.05; (p<0.001) Atracurium intake: CV: n=10 (10%) vs. HFO: n=85 (85%); p<0.001
Ventilator free days; mean difference; -1.3 (95%CI -3.4, 0.9); p=0.29	OI baseline: HFO en non HFO; 1.8 (12.0-30.2) vs. 7.7 (5.0-13.1); p< 0.001	Intensive care free days lower for HFO: mean difference -2.5 (95%CI -4.9, 0.5); p=0.03	ND

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Author (year)	Study design and population	Intervention/ mode	Mortality/survival
APRV			
Ganesan (2018) India	RCT n=52 with PARDS Age: 1 month-12 years The trial was terminated after 50% of enrollment (n=52) when analysis revealed higher mortality for APRV	Single Center study APRV vs CV To assess if APRV was non inferior to CMV (lung protective low tidal volume with permissive hypercapnia in children with ARDS).	28 day all-cause mortality: CV 26.9% vs APRV 53.8% , Fisher exact P=0.089, accounting for a relative mortality risk of 2.0 (95%CI, 0.97-4.14) Median survival time: CV: 19 days (13.3-24.7) vs APRV 13 days (3.9-22.1) On multivariable analysis , despite adjusting for higher severity of ARDS in the intervention arm, there was a trend toward a higher risk of death in APRV than in the control group (adjusted RR, 2.02 (95%CI, 0.99-4.12); P=0.05) Girls and patients classified as contamination had a significantly higher risk of death Primary cause of death was worsening hypoxemia and MODS
Ning (2020) China	Retrospective observational of children with moderate and severe PARDS who switched to APRV or HFO after failure of CV (SIMV) n= 47 Age: > 6 month and 6 yrs.	Single center study APRV or HFO vs CV	Overall mortality was 34% with no significantly difference between APRV and HFO 10 of 25 (40%) died after transition to APRV 6 of 22 (27%) died after transition to HFO; (p=0.542)
BIPAP			
Jaarsma (2001) The Netherlands	RCT n=18 with respiratory failure for ventilation Age: 0 to 10 years Soon after the introduction of Evita 4 on the ward, physicians and nurses preferred the use of BIPAP over ASB, and inclusion of patients stopped.	Single-center study Compare BIPAP (n = 11) with PS (n = 7), determining which mode is effective, safe and easy	ND

LOV (days) Extubation success/AI	Oxygenation	LOS (days)	Sedation
Ventilator free days (median and mean): CV: 20(0-23) and 14.2±10.2 vs APRV: 0 (0-22.5) and 9.7±10.9; (p=0.23)	PF ratio at baseline: CV: 165±166.4 vs APRV 124.7±52.3; (p=0.02) Oxygenation index 11.7±18.8) vs 17±10.5); (p=0.02) PF and OI were similar except on time of enrollment; p=0.04 APRV showed a greater improvement in PF ratio and OI into the first 12 hrs.; (p=0.08)	ND	ND
ND	PF ratio at 2 hrs. and 48 hrs. in both modes were significantly improved versus CV; (p<0.001) PF ratio at 48 hrs. in the HFO group was better than in the APRV group; (p=0.02)	ND	ND
BIPAP: 9.8±9.2; PS: 6.4±5.8; (p=0.27)	ND	ND	ND

3

Author (year)	Study design and population	Intervention/ mode	Mortality/survival
Weaning			
Randolph (2002) USA	RCT n=182 with weaning of ventilation for more than 24 hrs. and who failed a test for extubation readiness on minimal PS Age: 0 - 17 yrs.	Multicenter study (10) to evaluate weaning protocols comparing VS (continuous automated adjustment of PS by the ventilator) (n = 59) and PS (adjustment by clinicians) (n = 61) with standard care (no protocol) (n = 59)	ND
NAVA			
Kallio (2014) Finland	RCT n=170 who were expected to need MV for at least 30 minutes Age: full term new born-16 years	Single center study NAVA vs CV To evaluate NAVA as an initial ventilation mode and compare it with current standard CV in terms of the duration of MV and the amount of sedation needed	ND
Piastra (2014) Italy	Pilot nested study in PARDS: cases were NAVA-treated patients in 2010 (n=10) Controls were infants selected among those not treated with NAVA in 2008-2009 (n=20) and matched for age, weight and PF ratio. A 2:1 ratio design was chosen to increase the relative power of a small-sized nested study Age: < 1 yr.	Single Center study After HFO switch to PSV or NAVA with PS level targeted to achieve a tidal volume of 6 ml/kg and NAVA level titrated on the PS level which was needed.	ND

LOV (days) Extubation success/AI	Oxygenation	LOS (days)	Sedation
Duration of weaning: PS: 1.6(0.9-4.1); VS: 1.8(1.0-3.2); no protocol: 2.0(0.9-2.9); (p=0.75) days Extubation failure rate: PS (15%), VS (24%); no protocol (17%); (p= 0.44). Male children more frequently failed extubation (OR 7.86 (95% CI: 2.36-26.20; (p< 0.001)	ND	ND	Sedation during the first 24 hrs. of weaning significantly predicted weaning time HR<0.001
CV 6.6 hrs. Vs NAVA 3.3 hrs. (median); (p=0.17)	ND	CV 72.8 hrs. vs NAVA 49.5 hrs. (median); (p=0.10) Per protocol analysis showed a significant shorter LOS in the NAVA group; (p=0.03)	No significant difference in sedation, but when postoperative patients were excluded the amount of sedation needed was significant lower in the NAVA group: Sedation units per hours: CV 2.23 ± 2.54 vs NAVA 0.8 ± 1.16; (p=0.03)
The duration of NAVA (41±17 hrs.) was lower than that of PSV (72.5± 44 hrs.; p=0.011) All babies were successfully extubated, and no reintubation was performed in both groups.	Babies under NAVA had different $\Delta PaO_2/FIO_2$ after 8 hrs.: mean percent change from the baseline: −16.8±5.4 vs. −8.3±4.3; (p=0.02)	LOS in PICU was not different between study groups.	The COMFORT score improved in NAVA 18.1±2.1 versus the PSV group 25.3±7; (p=0.004), while mean dosages of sedatives were similar in NAVA and PSV groups

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Author (year)	Study design and population	Intervention/ mode	Mortality/survival
Sood (2018) USA	Non randomized pilot study. Data were collected prospectively from patients who utilized NAVA during the weaning period of MV to an endpoint of extubation. Data were collected retrospectively for the control group utilized SIMV/ PRVC+PS as a sole strategy to an endpoint of extubation n=75 postoperative congenital heart disease, MV > 96 hours Age: 0-18 yrs.	Single Center study NAVA vs CV To investigate the effects of NAVA compared with SIMV/PRVC+PS (CV) during the weaning phase on initial extubation success in a homogenous group of postoperative cardiac patients who required prolonged MV 40 PRVC/SIMV+PS (CV) vs 35 NAVA	ND
Bonacina (2019) Italy	Prospective physiologic crossover study in infants after cardiac surgery n=14 Three of 14 children had no Eadi signal because of diaphragmatic paralysis Age: median age 11.5 days (8.75-75 days)	Single Center study, three study conditions lasting 1 hour each: PSV vs NAVA vs PSV sigh (1 sigh per minute) in random order, with a washout period of 30 minutes of PSV between them	ND
Spinazzola (2020) Italy	Prospective physiologic crossover study in patients with moderate PARDS n=12 who failed an SBT for 3 times Age: 1 month-2 yrs.	Single-centre study, three study conditions lasting 1 hr. each: PSV 1 vs NAVA vs PSV 2	ND

Data presented as number/total (percentage) or mean ± standard deviation or median and Interquartile range. A(H)RF, acute (hypoxemic) respiratory failure; AI, Asynchrony Index; APRV, airway pressure release ventilation; BIPAP, biphasic positive airway pressure; CI, confidence interval; CV, conventional mechanical ventilation; DIC, disseminated intravascular coagulation; HFO, high-frequency oscillation ventilation; HR; hazard ratio; iNO, inhaled nitric oxide; LOV, length of ventilation; MODS, multiple organ dysfunction syndrome; MV, mechanical ventilation; NAVA, neurally adjusted ventilatory assist; ND, no data; NS, not significant; OR; odds ratio; PC, pressure-controlled ventilation; PS(V), pressure support ventilation; SBT, spontaneous breathing trial; VDR, volume diffusive respirator (high-frequency time-cycled pressure ventilator); VS, volume support ventilation

LOV (days) Extubation success/AI	Oxygenation	LOS (days)	Sedation
CV 11.0 (IQR 7.5) vs NAVA: 9.0 (IQR 4.0) (p= 0.032) days HR ratio for LOV for NAVA compared to CV: 1.77, (95% CI:1.09-2.90), indicating a significant shorter LOV for NAVA. Successfully extubated on initial attempt: CV: 80% vs NAVA: 97% (p=0.03) NAVA group was 8 times more likely to have successful extubation on first attempt; OR, 8.5 (95% CI: 1.01 - 71.80) Extubated at 12 days and 24 days of MV resp.: CV 55% vs NAVA 77% / CV 85% vs NAVA 95%.	ND	Median number of days in PICU was less for NAVA vs SIMV+PS; (p<0.001) (HR:2.49, (95% CI:1.5, 4.07)	Midazolam: CV 11.0 days (IQR 7.5) vs NAVA 8.0 days (IQR 4.0); (P<0.0001) Fentanyl: CV 12.5 days (IQR 7.0) vs NAVA 9.0 days (IQR 5.0);(P<0.0001)
AI decreased in NAVA compared to PSV and PSV sigh; (p<0.01)	PF ratio and OI improved in PSV sigh compared with PSV (p= 0.05) but not in NAVA compared with PSV.	ND	Sedation was deeper for PSV when compared with PSV Sigh; (p<0.05) and for PSV compared with NAVA; (p<0.05), but no differences between PSV Sigh and NAVA
AI improved in NAVA vs PSV 1 and PSV 2; (p=0.001)	PF ratio improved during NAVA vs PSV 1 and PSV 2; (p=0.004)	ND	ND

SUPPLEMENTAL FILE 6: SUMMARY OF HFOV AND CMV SETTINGS PER STUDY

	n	Inclusion	Initial CMV settings
1.Arnold	58	Bodyweight ≤ 35 kg Acute diffuse lung injury needing MV with PEEP Barotrauma OI>13- 2 × in 6 hrs.	Increases in PEEP and inspiratory time to increase mean airway pressure and limit increases in peak inspiratory pressure with servo 900C FiO_2 to be kept < 0.6 Servo 900 or Veolar (Hamilton)
2.Dobyns	99	AHRF requiring MV, OI ≥ 15 × 2 values within 6 hours Choice of ventilation mode was made before randomization to 10 ppm iNO or placebo for 3 days	Permissive hypercapnia with pH ≥ 7.2 Maintain SaO_2 >90% PEEP was increased to improve oxygenation Maintain peak airway pressure at 35-40 cmH_2O by limiting tidal volume and use of PEEP
3.Carman	64	with an acute burn injury and associated respiratory failure	Pressure control mode Inspiratory pressure set to achieve a tidal volume of 6 to 8 ml/kg. Inspiratory time set using the flow vs time waveform to achieve optimal ventilation. Respiratory rate 10 to 16 breaths per minute. FiO_2 titrated to maintain SpO_2 ≥ 90%. PEEP 4 to 6 cm H_2O Puritan-Bennet 7200ae® (Mallinckrodt, St.Louis, MO)
4.El Nawawy	200	PARDS PaO_2/FiO_2 ratio ≤ 200 mmHg -Bilateral pulmonary infiltrates on X ray -No evidence of left atrial hypertension Primary ARDS: pneumonia, aspiration, kerosene toxicity Secondary ARDS: severe sepsis and septic shock	Protective lung strategy Chosen driving pressures to deliver 5-8ml/kg tidal volume I:E ratio was 1:1 during recruitment. Oxygenation goal: to maintain O_2 saturation >90% with a FiO_2 ≤ 0,6 while achieving optimum lung volumes through keeping map constant after which MAP and FiO_2 were allowed to be reduced simultaneously Permissive Hypercapnia (arterial pH ≥7.2 and HCO_3 ≥ 19 mmHg.) Avea and Servo i

Initial HFO settings	Recruitment maneuver
Frequency: 5-10Hz Amplitude: chest wall wiggle MAP 4-8 cmH$_2$O> last MAP on CV Inspiration time 33% FiO2 1.0	No
	Cross-over to the alternate ventilator was required if the patient met defined criteria for treatment failure.
Aggressive increases in mean airway pressure to attain the ideal lung volume and to achieve an arterial oxygen saturation >90% with FiO$_2$ <0.6	
SensorMedics	
Frequency: 10Hz Amplitude: chest wall wiggle MAP 2- 4 cmH$_2$O> last MAP on CMV Inspiration time 33% FiO$_2$ 1.0	No
Frequency between 200- 360 times p/min which allows for optimal alveolar gas mixing and maximizes the percussive effect FiO$_2$ titrated to maintain SpO$_2$ ≥ 90%. inspiratory-expiratory time ratio 2:2 Oscillatory CPAP of 5 to 10 cm H$_2$O Demand CPAP/PEEP of 8 to 10 cm H$_2$O pressure.	No
Volume Diffusive Respirator	
Frequencies: 5-12 Hz, I:E 1:1 Amplitudes were set to assure tidal volumes of 1.5-3 ml/kg MAP set 3-5 cmH$_2$O above MAP on CMV, and increased in a stepwise approach as long as oxygenation improves while FiO$_2$ is fixed. Chest X ray to define optimum lung volume (8-9 ribs posteriorly)	HFO: Applying a constant MAP for a sustained inflation starting with MAP of 20 cmH$_2$O for 20 seconds and increasing MAP in a stepwise approach to 30 cmH$_2$O for 30 seconds and 40 cmH$_2$0 for 40 seconds. CV Increasing PEEP to 15-20 cmH$_2$O and driving pressure 15-10 cmH$_2$O keeping the peak airway pressure no more than 35 cmH$_2$O for 1-2 minutes followed by decremented PEEP titration every 1-2 minutes till achieved best oxygenation.
Fabian	

	n	Inclusion	Initial CMV settings
5.Fioretto	28	ARF Patients were kept under one of the two ventilation modes for 8 hr., crossing to the other for 8 hr. and then back again to the initial mode to complete 24 hours observation	Pip limited ≤ 35 cmH2O Plateau pressure ≤ 30 cmH_2O TV 5-7 ml/kg, accepting hypercapnia PEEP was gradually increased to reach mean airway pressure close to those used in HFOV, while avoiding clinical and radiographic signs of lung hyperinflation. FiO_2 ≤ 0,6 iNo 5 ppm Galileo (Hamilton)
6.Samransam-ruajkit 2016	18	PARDS - Respiratory failure not fully explained by cardiac failure or fluid overload - Full face mask, bi -level ventilation or CPAP > 5 cm_2HO - New pulmonary infiltrates on X ray According the Berlin definition	Before randomization to the treatment arm all patients received CV with: FiO_2 of 1.0 Median PEEP of 12 cmH_2O Servo I and Puritan Bennett 840
7.Samransam-ruajkit 2005	16	ARDS PEEP ≥ 5 H_2O, FiO_2 ≥ 0.6 regardless of PEEP for ≥ 12 hours to maintain oxygen saturation ≥ 92% and OI > 15 for ≥ 4 hours	Time-cycled or Pressure Controlled Ventilation Servo 900/Servo 300 and Puritan Bennett 7200
8.Bateman	2449	ARF	Unreported
9.Bojan	3549	Neonates and infants who underwent cardiac surgery and were ventilated	All patients commenced on PC via a Servo 300 and after 2002 the Servo-i PEEP of 2 cmH_2O TV of 6-8 ml/kg FiO_2 dependent upon the underlying cardiac disease Servo 300/ Servo i

Initial HFO settings	Recruitment maneuver
Frequency 10 Hz for infants ≤1 yr.old and 5-8 Hz for older children. Amplitude: chest wall wiggle MAP 2-4 cmH$_2$O> last MAP on CV to maintain FiO$_2$ ≤ 0,6. Inspiration time 33% FiO$_2$ 1.0 iNO 5 ppm SensorMedics	No
Frequency: weight dependent Amplitude: 3 x mPaw of CV MAP 5-8 cmH2O > last MAP on CV FiO$_2$ gradually reduced stepwise to keep SpO$_2$ > 92%. LVRM was repeated if SpO$_2$ was < 95% with FiO$_2$ of 1.0 SensorMedics	HFO Starting with a MAP at 30 cmH$_2$O (35 cmH2O for p. with IBW > 35 kg) and CDP was sustained for 20 s (or 30 s for > 35 kg), then the piston started together with gradually weaning down MAP to target level (5-8 cmH$_2$O above previous MAP of CV. Other ventilator settings adjusted based on clinical response CV LVRM with 15-20 cmH$_2$O PEEP, driving pressure 20 cmH$_2$O with 2 min decremented PEEP titrate down in each step to get the best compliance and then set above that level, finally wean down PIP to get 6-8 ml/kg of tidal volume
Frequency: weight dependent 4-10 Hz Amplitude: 10 cmH$_2$O above PIP level of CV MAP: 2-3 cmH$_2$O > last MAP on CV Inspiration time 33% FiO$_2$ gradually reduced stepwise to keep SpO$_2$ > 92%. SensorMedics	No
Unreported	No
Switch to HFOV when: -Hypoxemia and acidosis occurred despite increasing alveolar ventilation on CMV -TV exceeded 10 ml/kg -Evidence of Pulmonary hypertension and right ventricular failure. Frequency 8 HZ Amplitude: chest wall vibrations. MAP of 12 cm H$_2$O Inspiration 33% All parameters were adjusted to achieve optimal inflation, a PaCO$_2$ of 35-45 mmHg and a pH of > 7,35 SLE	LVRM by stepwise increase in the MAP

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	n	Inclusion	Initial CMV settings
10. Wong	328	PARDS	CMV:165/206 (80.1%): PIP 25.0 (20.0, 28.0) cmH_2O/ PEEP 7.0 (6.0, 9.0) cmH_2O/ MAP 14.0 (11.8-17.2) cmH_2O/ FiO_2 55.0 (40.0, 80.0)%/ Tv 8.3 (6.6-10.9) ml/kg APRV:41/206 (19.9%), method not mentioned
11. Gupta	9177	ARF	Unreported
12. Guo	48	severe PARDS: OI ≥ 16 cmH_2O/mmHg	All children primarily started on CV. Lung-protective ventilation strategy: small tidal volumes (5–8 mL/kg) Controlled pressures: Insp. plateau pressures < 30-35 cmH_2O Conversion to HFOV when: Refractory hypoxemia with OI > 30 cmH_2O/mmHg Plateau pressure > 30cmH_2O for at least two hours Drager Evita 4 or XL
13. Ning	47	moderate to severe PARDS	SIMV with a minimum PEEP of 5 cmH_2O and 6-8 ml/kg tidal volume and to attempt to reduce FiO_2 to <0.6 Maintain PIP < 30cmH_2O, Oxygen saturation > 88-90% and permissive hypercapnia Conversion to HFO or APRV when: PIP was ≥ 35 cmH_2O, inability to decrease FiO_2 ≤ 0.6 despite increasing PEEP, or ongoing hypercarbia $PaCO_2$ > 80 or pH < 7.25 Drager Evita 4

LVRM, lung volume recruitment maneuver; PARDS, pediatric acute respiratory distress syndrome; mPaw or MAP, mean airway pressure; CDP, continuous distending pressure; SIMV, synchronized mandatory ventilation, APRV, airway pressure released ventilation; CMV, conventional ventilation; HFO, high frequency oscillation

Initial HFO settings	Recruitment maneuver
MAP 25.0 (20.8, 29.3) H_2O Amplitude: 55 (46.5, 62.8) FiO_2 87.9 (71.2, 100)%	No
Unreported	No
Frequency: weight dependent FiO2 1.0 Amplitude: Chest wall wiggle MAP 2-3 cmH_2O > last MAP on CV Permissive hypercapnia policy. HFO failure defined as persisted hypoxemia or refractory hypercapnia. SensorMedics	No
APRV: P high and inspiratory time (T high) to at least match the MAP being delivered by CV, with stepwise increases in mPaw by adjusting P high or T high if unable to reduce FiO_2 ≤ 0.6. Their practice was setting low pressure (Plow) to 0 to facilitate rapid emptying and adjusting expiratory time to terminate at 1 /2- 3/4 of peak expiratory flow. HFO: MAP at least the same as on CV and with escalation until FiO_2 could be reduced to ≤ 0.6 Frequency 6-12 Hz FiO_2 0.4-1.0 Amplitude 25-50 mbar Inspiration 33%	No

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SUPPLEMENTAL FILE 7: META ANALYSIS OF LOV, LOS AND OXYGENATION
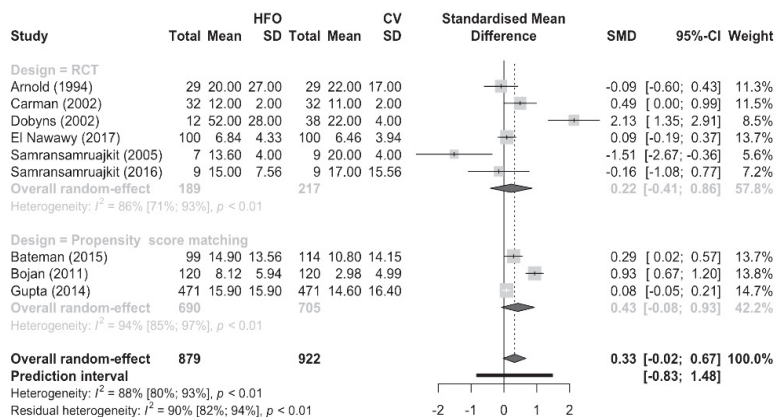
FIGURE 7A Meta-analysis of LOV, (HFO = high frequency oscillation, CV = conventional mechanical ventilation)
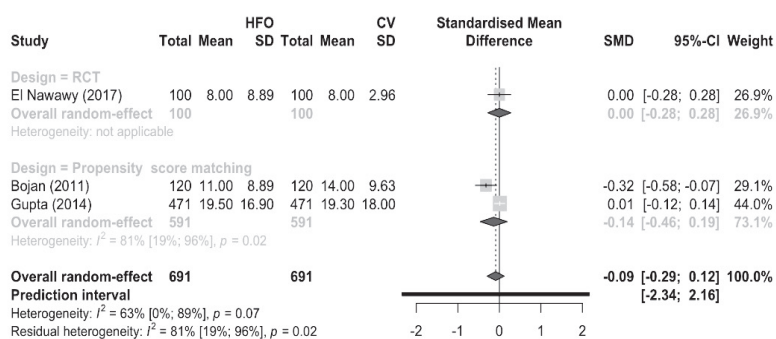
FIGURE 7B Meta-analysis of LOS, (HFO = high frequency oscillation, CV = conventional mechanical ventilation)
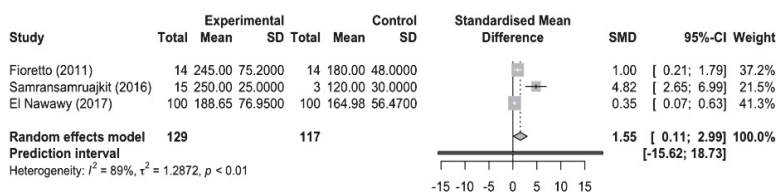
FIGURE 7C Meta-analysis of PaO_2/FiO_2 ratio (Experimental =high frequency oscillation and Control = conventional mechanical ventilation)

Study	Experimental			Control			Standardised Mean Difference	SMD	95%-CI	Weight
	Total	Mean	SD	Total	Mean	SD				
Fioretto (2011)	14	10.27	3.8000	14	6.98	3.7000		0.85	[0.07; 1.63]	36.4%
Samransamruajkit (2016)	.	.	.	.	.	.				0.0%
El Nawawy (2017)	100	13.28	11.6700	100	11.82	8.9700		0.14	[-0.14; 0.42]	63.6%
Random effects model	**114**			**114**				**0.40**	**[-0.27; 1.07]**	**100.0%**

Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.1645$, $p = 0.09$

-1.5 -1 -0.5 0 0.5 1 1.5
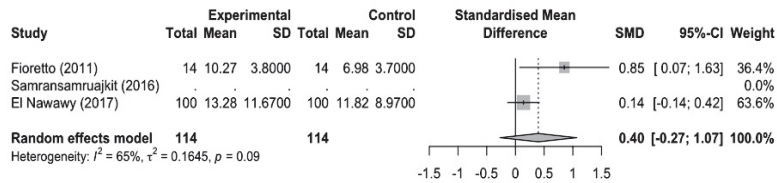
FIGURE 7D Meta-analysis of Oxygenation index (Experimental = high frequency oscillation, Control = conventional mechanical ventilation)

3

chapter

4

HOW TO ACHIEVE ADHERENCE TO A VENTILATION ALGORITHM FOR CRITICALLY ILL CHILDREN?

Anita Duyndam, Robert Jan Houmes, Monique van Dijk PhD, Dick Tibboel, Erwin Ista

ABSTRACT

Aims and Objectives: To evaluate to what extent physicians on a pediatric intensive care unit (PICU) adhered to a newly implemented ventilation algorithm.

Background: PICUs worldwide use different ventilators with wide variety of ventilation modes. We developed an algorithm, as part of a larger protocol, for choice of ventilation mode at time of admission.

Design: This study was performed in a level III PICU of a university children's hospital and had an uncontrolled, pre-post-test design with a period before implementation (T0) and two periods after implementation (T1 and T2).

Methods: An invasive ventilation algorithm targeted at two patient groups was implemented in October 2008. The algorithm distinguished between lung disease, in which pressure control was considered as the preferred mode, and no lung disease, in which pressure-regulated volume control was preferred. Nurses and physicians were instructed in the use of the algorithm before implementation.

Results: During three test periods, a total of 507 children with a median age of 5 months (IQR 0-50) on conventional invasive mechanical ventilation were included. In patients with lung disease, pre-implementation adherence rate was 79% (67/85). At T1 it was 71% (51/72); at T2 84% (46/55). The slight improvement from T1 to T2 was statistically not significant (p=0.092). In patients with no lung disease, the adherence rate rose statistically significantly from 66% at T0 (62/93) to 78% (79/101) at T1, and 84% at T2 (85/101) (p=0.015).

Conclusion: Implementation of a new ventilation algorithm increased physicians' adherence to this ventilation algorithm and the effect was sustained over time. This was achieved by education, reminders and organizational changes such as admission of post cardiac surgery patients with protocolized nursing care including pre-set ventilator settings.

INTRODUCTION

Pediatric intensive care units (PICUs) worldwide use different ventilators with a wide variety of ventilation modes: high frequency oscillation (HFO), pressure control (PC), synchronized intermittent mandatory ventilation (SIMV), pressure support (PS), pressure regulated volume control (PRVC) and, more recently, neurally adjusted ventilator assist (NAVA). (1, 2) An unambiguous international guideline is lacking; ventilator type and ventilation mode are often chosen based on the intensive care physician's experience and preference, financial concerns, or local PICU policy, independent of the underlying disease. (3-5)

The literature is scarce on the best ventilation mode in critically ill children beyond the newborn period. (6) One study found that high-frequency ventilation was associated with better oxygenation after 72 hours than was conventional ventilation. (7) However, there was no evidence of reduced mortality and duration of ventilation. Furthermore, most trials were significantly underpowered as they included small numbers of children. (6)

Because of a lack of a ventilation protocol for clinical practice, we developed an algorithm guiding the choice of the most appropriate mode of ventilation upon admission of a child to our ICU, either PC or PRVC. A different protocol applies in case of need of HFO at admission. HFO is not included in this algorithm because it is not often used.

Separate protocols are in place for HFO and non-invasive ventilation.

This algorithm is based on evidence in the adult literature (8-11) and outcome of consensus meetings of all consultants of our unit. However, adherence to protocols and guidelines remains a difficult issue and successful implementation is time consuming. (12-16) In this study we evaluated to what extent the physicians adhered to the ventilation algorithm.

METHODS

DESIGN:

The study had an uncontrolled, pre-post test design with a pre-test (T0) from January 2008 - July 2008, and two post-tests: from May-November 2009 (T1); and from May-November 2010 (T2). The test periods were chosen to cover seasonal diseases. The T2 measurement served to evaluate the long-term sustainability of the implementation. The Erasmus MC Medical Ethics Review Board approved the study and due to the non-invasive nature of the study waived the need for informed parental consent.

SETTING AND PATIENTS:

The study was performed in the 28-beds ICU of the Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands, a level III referral academic hospital. This ICU consists of four 7-beds units, each with a specific focus: neurology, cardiology, (neonatal) surgery and high dependency care. The ICU also serves as one of the two national ECMO centers and provides all forms of mechanical cardiac support. It is the only one in the Netherlands to provide care to pediatric cardiac transplant recipients.

The annual number of admissions is around 1800, and 30% of patients are ventilated mainly with the Servo-i ventilator of Maquet (Solna, Sweden). Overall, 50% of admitted patients are postoperative patients of all surgical subspecialties. The main reasons for admission are: respiratory insufficiency (20%), general pediatric surgery (20%), cardiac surgery and cardiovascular problems (20%), neurosurgery and neurological problems (10%), injuries and intensive care monitoring (20%), and major congenital anomalies, gastrointestinal and kidney problems (10%). (data retrieved from the electronic patient data management system and the local Quality and Safety Registry)

During the study periods the medical staff included twelve pediatric intensivists, of whom one had a basic training in anesthesiology; four fellows in training for pediatric intensivist; and six physicians in training (pediatrics (n=4) or anesthesiology (n=2).

DEVELOPMENT OF VENTILATION ALGORITHM:

A multidisciplinary team consisting of a pediatric intensivist-anesthesiologist (RJH) and four ventilation practitioners (whose role is similar to that of a respiration therapist) developed a ventilation algorithm for the target population aged from 0 to 18 years. The algorithm is based on lung protective ventilation strategies which are likely to be

of benefit to acute lung injury and acute respiratory distress syndrome: open-lung strategy; low tidal volumes (5-8 ml); and a recruitment maneuver in case of increased oxygen need. (8-11, 17, 18) Furthermore, permissive hypercapnia will avoid high ventilation pressure and thus prevent further lung damage. (8, 11, 19)

The general purpose of our local ventilation strategy, as far as possible based on evidence, is to achieve the following conditions:

- pH: > 7.30 and < 7.48;
- PCO_2: 5-8 kPa;
- PC above Peep ≤ 15cm H_2O;
- Tidal volume: 6 ml/kg; (This was set in PRVC and pursued in PC);
- SpO_2 > 95%; or a lower saturation in case of a cardiac disease with mixed circulation;
- Inspiration time: 0.3-0.6 seconds for neonates and I:E ratio 1:2 for children aged above 6 months with an age-dependent frequency

The algorithm was primarily designed to guide physicians in the choice of ventilation mode upon admission of a patient requiring invasive mechanical ventilation. Also, it accounted for conversion of ventilation mode in case a patient's condition deteriorated. In addition, if ventilation with high pressures was needed (ARDS) some of the above-mentioned conditions were to be modified: pH ≥ 7.20 < 7.48; pCO_2 ≤ 9 kPa; and SpO_2 ≥ 85%. In specific diseases such as pulmonary hypertension and traumatic brain injury (TBI) other target values for pH and PCO_2 are applied, described in different protocols (TBI: pCO_2 values between 4.5 and 5.0 kPa; for pulmonary hypertension initial normocapnia is the aim, provided that the needed inspiratory pressure is not too high. Otherwise permissive hypercapnia is accepted till values of ≥ pH 7.20). I:E ratio is also modified when lung condition deteriorates, dependent on the underlying disease. Extracorporeal membrane oxygenation (ECMO) is indicated at oxygenation index around 40.

The algorithm was developed with two patient groups in mind: 1) those with lung disease, such as acute respiratory distress syndrome, pneumonia, or bronchiolitis; and 2) without lung disease but receiving ventilation for epilepsy, postoperative care or TBI (Figure 1). The PC mode was assumed to be the most appropriate for group 1 because it maintains constant pressure not exceeding 15 cmH_2O above PEEP. Thus, volutrauma is potentially avoided and a tidal volume of 6 ml/kg is achieved.(10, 20) PC

is also suited in children at risk of compression atelectasis, in children with pulmonary hypertension (9), and to compensate for leakage around the tube.

The PRVC mode was considered the most appropriate for group 2 because it provides the lowest possible pressure at a constant tidal volume and achieves a more stable $EtCO_2$ and pCO_2. It has a decelerating inspiratory flow pattern with automatic adjustment of the inspiratory pressure for changes in compliance and resistance, resulting in a guaranteed constant tidal volume. However, volutrauma may occur when the pressure rises in case of deteriorating lungs with different dependent lung regions. Then the aerated lung regions will receive all the volume (higher than 6 ml/kg). There is no evidence for the use of PRVC in case of neurotrauma, although CO_2 has a direct influence on the diameter of the vessels of the brain and the blood volume and therefore influences the intracranial pressure. Because intracranial pressure (ICP) and CO_2 are inter-related, maintaining a constant CO_2 is indicated in case of brain injury. ICUs worldwide mostly use volume controlled ventilation for this purpose, but as PRVC provides constant tidal volume, we opted for this mode in traumatic brain injury. (21)

In the PC mode, ventilation is adjusted to PS as soon as the patient is breathing spontaneously (triggering in the figure); in the PRVC mode, ventilation is adjusted to volume support. Sedation provided at the start of ventilation is reduced stepwise on the guidance of scores on the COMFORT behavior scale.(22)

A protocol for extubation readiness is not in place at our ICU, and a spontaneous breathing trial (SBT) is not used. The following extubation criteria are commonly used: cough/swallowing reflex present, respiration indication solved, $FiO_2 < 0.4$, hemodynamically stable with little inotropic support, sufficient muscle strength, no excessive sputum, PEEP < 8 cmH_2O, proper fluid balance, no edema, Glasgow coma score > 8, no or low-dose sedatives, pH between 7.35 and 7.45, no signs of infection. (23-25) Separate protocols are in place for HFO and non-invasive ventilation.

IMPLEMENTATION:

To enhance adherence, approval of the ventilation algorithm was sought from all medical staff before implementation. In July 2008 the ventilation practitioners instructed all physicians and critical care nurses how to use it. Newly recruited residents after July 2008 also received instruction and in addition were familiarized with the theory of ventilation and the ventilator software. All information was also made available in print

and by email. The algorithm was made available on each unit. A laminated version of the algorithm was placed at each ICU-bed.

The algorithm was put into use in October 2008 after the ventilation practitioners had presented it to all physicians. Since 2010 all ICU staff are provided with a pocket manual that contains all PICU protocols including the ventilation algorithm. Furthermore, in 2010 the protocol for admission of traumatic brain injury patients was changed to the effect that the PRVC mode became the preferred one for these patients. To ensure that this policy was adhered to, a sticker reminding of this ventilation mode was placed on a crash cart for patients with brain injury. For organizational and logistical reasons, from January 2010 cardiac surgery patients were directly admitted to our ICU for postoperative care. The protocol introduced since then prescribed PRVC as the preferred mode for these patients, unless they had serious pulmonary edema. Extubation was attempted in these patients as soon as possible upon arrival at the ICU, usually within 6-12 hours after admission. As such the postoperative cardiac surgery protocol included an algorithm for weaning off the ventilator. Before admission of these patients, nurses prepare the ventilator settings based on the cardiac weaning procedure described in the ventilation algorithm. The nurses are responsible for weaning but need to ask permission from the physician in charge for actual extubation.

STUDY PROCEDURE:

All patients on conventional invasive mechanical ventilation during the three study periods were included. The initial ventilation mode was chosen by the physicians. In all three periods we recorded the initial ventilation mode set for newly admitted patients and recorded the reason for ventilation as an indication to what mode this patient should have been assigned. Patients on HFO and non invasive ventilation were excluded. Patients were not excluded because of their condition. Data were retrieved from the electronic patient data management system that prospectively stores data of all physiological parameters, laboratory results, medication, procedures, assessments and care plans.

OUTCOME MEASURE:

Adherence to the ventilation algorithm was measured as: number of patients with correct ventilation mode according to the algorithm divided by the total number of ventilated patients during the study period in question.

STATISTICAL ANALYSIS:

Patients' characteristics, reason for admission, and initial mode of ventilation are summarized by descriptive statistics. Data are presented as percentages: mean (Standard deviation) for normally distributed data; median and IQR (interquartile range) for non-normally distributed data. Background characteristics for the pre- and posttest groups were compared using chi-squared (categorical variables) and Kruskal-Wallis test for continuous variables. In all three test periods, the difference in adherence to the protocol was compared and tested for the two groups (lung disease versus no lung disease) with the chi-squared test. A p value of 0.05 (two-sided) was considered statistically significant. Data were analyzed with IBM SPSS® version 18.

RESULTS

During the three study periods 615 patients received ventilator support. In total, 108 patients were excluded for analysis (HFO, n=31; non-invasive (home) ventilation, n=87). Thus, analysis was performed on 507 patients, with a median age of 5 months (IQR 0-50) (T0: N=178; T1: N=173; T2: N=156). Age and gender were not significantly different between the three periods. However, the reason for ventilation significantly differed between the periods is the admission of direct postoperative cardiac patients during T2 (Table1).

LUNG DISEASE

Before implementation of the ventilation algorithm (T0), 67 of the 85 patients (79%) with lung disease were ventilated according to the algorithm (PC). After implementation, this held true for 51 of 72 patients (71%) in period T1, and 46 of 55 patients (84%) in period T2 (p=0.215). Adherence to the algorithm slightly improved from T1 to T2 (p=0.092) (Table 2).

NO LUNG DISEASE

At T0, 62 of the 93 patients (66%) with lung disease or no lung disease were ventilated according to the algorithm (PRVC). After implementation this held true for 79 of 101 patients (78%) in period T1, and 85 of 101 patients (84%) in period T2 (Table 2). This means that adherence statistically significantly improved from 66% at T0 to 78% at T1 to 84% at T2 (p=0.015).

RELATED FACTORS FOR (NON) ADHERENCE

Adherence to the algorithm (correct choice of ventilation mode) was not statistically significant associated with patient's age, shift (day versus evening/night), reason for ventilation (lung disease versus no lung disease) and unit (p=0.52, p=0.16, p=0.84 and p=0.06 respectively). In the cardiology unit, however, adherence to the algorithm increased significantly from 74% at T0 to 91% at T2 (p=0.018). Adherence to the algorithm in cardiac and postoperative cardiac surgery patients increased significantly from 68% at T0 to 90% at T2 (p=0.027).

Adherence to the algorithm in TBI patients seems to have increased. In 2010 only one patient was ventilated with PC rather than the prescribed PRVC. This also applies to patients with acute respiratory failure during period T2 who were then mostly ventilated with the prescribed PC.

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DISCUSSION

Implementation of a ventilation algorithm for PICU patients resulted in higher adherence to the ventilation algorithm in comparison to the pretest periods, especially for patients without lung disease. Adherence was not associated with patient factors (e.g. age), shift or reason for ventilation (lung disease vs. no lung disease). Adherence to the ventilation algorithm tended to be best among post cardiac surgery patients, who receive protocolized nursing care including pre-set ventilator settings. The improvement in adherence regarding patients with lung disease is less marked. Before implementation adherence was even better (79%) than during the first post-test period (71%). It would seem that even after education and approval of the algorithm, physicians need time to put personal preferences aside. Still, adherence had increased during the second post-test (84%). Regrettably, still too many postoperative patients with abdominal problems were not ventilated as the algorithm dictated. This violation is perhaps easily overlooked; it would be more easy to remember that the first choice of ventilation for postoperative patients is PRVC, except for those who have undergone abdominal surgery. A reminder sticker on the ventilator, in combination with feedback in case of violations, could perhaps optimize adherence for this patient group. The use of cuffed tubes versus uncuffed tubes might have played a role as well. The data do not indicate, however, if PC in case of no lung disease was chosen on the grounds of leakage along the tube. If so, the choice was right. Any leakage usually occurs later

than in the first hour of ventilation, and therefore we assume that leakage will not have greatly influenced the choice of initial ventilation.

We speculate that the relatively high adherence rates (>80%) in the final post-test period can be ascribed to the fact that all newly appointed physicians and residents were well instructed. Furthermore, nurses – provided with a pocket manual of the ventilation algorithm – reminded physicians of the correct ventilation mode in cardiac surgery patients. We also assume that the use of reminders, such as a sticker on the crash car for traumatic brain injury patients, increased adherence to the ventilation algorithm. This is consistent with the literature in the ICU and other healthcare settings. (26, 27)

Research has shown that consistent use of evidence based guidelines can significantly increase the extent to which patients receive recommended therapies. (12, 13) However, it is a great challenge to stimulate consistent use of these guidelines and protocols. Apart from attempts to change behavior, this requires insight in all influencing factors (e.g. human behavioural, organizational, provider characteristics). Therefore, identifying potential influencing factors, e.g. with the barrier identification and mitigation tool (13), can improve adherence to new protocols. Unfortunately, scarce data are available to guide decisions on optimal strategies to implement guidelines and protocols in the ICU. (12, 14, 28) On the one hand, it has been suggested that guideline implementation strategies tailored to overcome barriers to change might be more effective than the multifaceted "one size fits all" strategy. On the other hand, multi-faceted implementation strategies were considered important enablers of protocol and guideline adherence. (16, 29) One example is education tailored to the specific learning needs of the ICU team combined with bedside reminders, audit, and visual feedback. (15, 29, 30) Also, we believe – and previous studies have demonstrated this – that ICU culture qualities such as interdisciplinary collaboration, effective communication, and leadership support are associated with better quality of care. (31, 32) This is also confirmed in two recent studies about interdisciplinary collaborative decision making regarding ventilation and weaning. (33, 34) Enhanced communication and collaboration between professionals could probably avoid unnecessary prolonged ventilation and weaning. (33, 34) We speculate that manipulating these specific organizational characteristics (interdisciplinary collaboration, effective communication, leadership support and organizational aspects like nurse-to-patient ratio and ongoing education) may be an effective strategy to improve adherence to protocols, which deserves to be

explored and evaluated in further implementation projects. (27) However, ICU culture qualities on our unit also need to be further studied.

Regarding strengths and limitations, a strength of this study is the prospective data collection. A limitation is the lack of a control group or randomization. However, it would have been difficult to blind physicians or other ICU staff to the study. Second, reasons for non-adherence with the algorithm were not documented in the patient data management system.

IMPLICATIONS FOR NURSES IN THE IMPLEMENTATION OF NEW ALGORITHMS
Care for ICU patients will benefit from interdisciplinary collaboration, also when new algorithms or protocols are implemented, related to either nursing care or medical care. To improve physicians' adherence to a medical algorithm, nurses should remind physicians of the steps to take. Nurses are always present at the bedside and as such represent the patient. In summary, the following measures may successfully improve adherence:

- A well thought-out implementation plan, with attention to potential barriers and facilitators is a crucial first step.
- Use reminders as pocket manuals and stickers
- Provide repeated education about the algorithm and the results of its use (performance feedback)
- Provide leadership support at doctor's and nursing level
- Report non-adherence through safety first reports and feedback when protocol violations occur

CONCLUSION

Implementation of a new ventilation algorithm increased physicians' adherence to this ventilation algorithm and the effect was sustained over time. This result was achieved by education, reminders and organizational changes such as protocolized admission of postcardiac surgery patients with protocolized nursing care including pre-set ventilator settings.

Interdisciplinary collaboration between physicians and nurses, effective communication, leadership support and organizational aspects like nurse-to-patient ratio and ongoing education may be effective strategies to improve adherence to protocols.

WHAT IS KNOWN ABOUT THIS TOPIC:

- An unambiguous international ventilation guideline for children is lacking; ventilator type and ventilation mode are often chosen based on the intensive care physician's experience and preference, financial concerns, or local PICU policy, independent of the underlying disease
- The literature is scarce on the best ventilation mode in critically ill children beyond the newborn period
- Adherence to protocols and guidelines remains a difficult issue and successful implementation is time consuming.

WHAT THIS PAPER ADDS:

- Implementation of a new ventilation algorithm in a large PICU increased physicians' adherence to a ventilation algorithm and the effect was sustained over time; this was also accomplished with the help of nurses and the following measures:
- A well thought-out implementation plan, with attention to potential barriers and facilitators is a crucial first step
- Ongoing attempts to improve adherence, for example by performance feedback are crucial to achieve a safety culture.

REFERENCES

1. Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med. 2010;11(2):253-7.

2. Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med. 2010;11(1):7-11.

3. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. Crit Care Med. 2009;37(8):2448-54.

4. Randolph AG, Meert KL, O'Neil ME, Hanson JH, Luckett PM, Arnold JH, et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. Am J Respir Crit Care Med. 2003;167(10):1334-40.

5. Turner DA, Arnold JH. Insights in pediatric ventilation: timing of intubation, ventilatory strategies, and weaning. Curr Opin Crit Care. 2007;13(1):57-63.

6. Duyndam A, Ista E, Houmes RJ, van Driel B, Reiss I, Tibboel D. Invasive ventilation modes in children: a systematic review and meta-analysis. Crit Care. 2011;15(1):R24.

7. Dobyns EL, Anas NG, Fortenberry JD, Deshpande J, Cornfield DN, Tasker RC, et al. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. Crit Care Med. 2002;30(11):2425-9.

8. Haitsma JJ, Lachmann B. Lung protective ventilation in ARDS: the open lung maneuver. Minerva Anestesiol. 2006;72(3):117-32.

9. Logan JW, Cotten CM, Goldberg RN, Clark RH. Mechanical ventilation strategies in the management of congenital diaphragmatic hernia. Semin Pediatr Surg. 2007;16(2):115-25.

10. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342(18):1301-8.

11. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347-54.

12. Cahill NE, Suurdt J, Ouellette-Kuntz H, Heyland DK. Understanding adherence to guidelines in the intensive care unit: development of a comprehensive framework. JPEN J Parenter Enteral Nutr. 2010;34(6):616-24.

13. Gurses AP, Marsteller JA, Ozok AA, Xiao Y, Owens S, Pronovost PJ. Using an interdisciplinary approach to identify factors that affect clinicians' compliance with evidence-based guidelines. Crit Care Med. 2010;38(8 Suppl):S282-91.

14. Ceelie I, de Wildt SN, de Jong M, Ista E, Tibboel D, van Dijk M. Protocolized post-operative pain management in infants; do we stick to it? Eur J Pain. 2012;16(5):760-6.

15. Sinuff T, Cook D, Giacomini M, Heyland D, Dodek P. Facilitating clinician adherence to guidelines in the intensive care unit: A multicenter, qualitative study. Crit Care Med. 2007;35(9):2083-9.

16. Sinuff T, Muscedere J, Cook D, Dodek P, Heyland D, Canadian Critical Care Trials G. Ventilator-associated pneumonia: Improving outcomes through guideline implementation. J Crit Care. 2008;23(1):118-25.

17. Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. Lancet. 2003;361(9354):332-40.

18. Scohy TV, Bikker IG, Hofland J, de Jong PL, Bogers AJ, Gommers D. Alveolar recruitment strategy and PEEP improve oxygenation, dynamic compliance of respiratory system and end-expiratory lung volume in pediatric patients undergoing cardiac surgery for congenital heart disease. Paediatr Anaesth. 2009;19(12):1207-12.

19.   Laffey JG, O'Croinin D, McLoughlin P, Kavanagh BP. Permissive hypercapnia--role in protective lung ventilatory strategies. Intensive Care Med. 2004;30(3):347-56.

20.   Haitsma JJ, Lachmann B. Lung protective ventilation in ARDS: the open lung maneuver. Minerva Anestesiol. 2006;72(3):117-32.

21.   Go SL, Singh JM. Pro/con debate: Should PaCO2 be tightly controlled in all patients with acute brain injuries? Crit Care. 2013;17(1):202.

22.   Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med. 2005;6(1):58-63.

23.   Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA. 2002;288(20):2561-8.

24.   Foronda FK, Troster EJ, Farias JA, Barbas CS, Ferraro AA, Faria LS, et al. The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial. Crit Care Med. 2011;39(11):2526-33.

25.   Newth CJ, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, et al. Weaning and extubation readiness in pediatric patients. Pediatr Crit Care Med. 2009;10(1):1-11.

26.   Cheung A, Weir MC, Mayhew A, Kozloff N, Brown K, Grimshaw J. Overview of systematic reviews of the effectiveness of reminders in improving healthcare professional behavior. Systematic reviews. 2012;1(1):36.

27.   Sinuff T, Muscedere J, Adhikari NK, Stelfox HT, Dodek P, Heyland DK, et al. Knowledge Translation Interventions for Critically Ill Patients: A Systematic Review. Crit Care Med. 2013.

28.   Ista E, de Hoog M, Tibboel D, van Dijk M. Implementation of standard sedation management in paediatric intensive care: effective and feasible? J Clin Nurs. 2009;18(17):2511-20.

29.   Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, et al. Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. Cochrane Database Systematic Reviews. 2010(3):CD005470.

30.   Kastrup M, Nolting MJ, Ahlborn R, Braun JP, Grubitzsch H, Wernecke KD, et al. An electronic tool for visual feedback to monitor the adherence to quality indicators in intensive care medicine. J Int Med Res. 2011;39(6):2187-200.

31.   Davies HT, Nutley SM, Mannion R. Organisational culture and quality of health care. Qual Health Care. 2000;9(2):111-9.

32.   Stein-Parbury J, Liaschenko J. Understanding collaboration between nurses and physicians as knowledge at work. Am J Crit Care. 2007;16(5):470-7; quiz 8.

33.   Blackwood B, Junk C, Lyons JD, McAuley DF, Rose L. Role responsibilities in mechanical ventilation and weaning in pediatric intensive care units: a national survey. Am J Crit Care. 2013;22(3):189-97.

34.   Rose L, Blackwood B, Egerod I, Haugdahl HS, Hofhuis J, Isfort M, et al. Decisional responsibility for mechanical ventilation and weaning: an international survey. Crit Care. 2011;15(6):R295.

TABLE 6   Demographic characteristics

	T0 n=178 n (%)	T1 n=173 n (%)	T2 n=156 n(%)	p-value
Gender (male/female)	91/87 (51.1/ 48.9%)	94/79 (54.3/ 45.7%)	86/70 (55.1/ 45.7%)	0.73 (a)
Age				0.66 (a)
- 0 – 12 months	105 (59%)	97(56.1%)	95(60.9%)	
- 1 – 3 years	33 (18.5%)	27 (15.6%)	19(12.2%)	
- 4- 12 years	26 (14.6%)	32 (18.5%)	25(16%)	
- > 12 years	14 (7.9%)	17 (9.8%)	17(10.9%)	
Median age in months (IQR)	4 (0-211)	8 (0-233)	4.5 (0-218)	0.60 (b)
Reason for ventilation				<0.001
- Cardiac	14	9	13	
- Cardiac - post operative surgery	22	31	50	
- Respiratory failure - acute pulmonology (e.g. bronchiolitis, pneumonia)	36	34	16	
- Respiratory failure - upper airway	2	8	4	
- Respiratory failure - others	6	7	0	
- Neurologic – e.g. trauma injury, epilepsy	16	15	19	
- Hypoplastic lung		1	2	
- Shock/sepsis/ECMO/Resuscitation	18	15	18	
- Trauma	5	7	1	
- Post operative	23	25	12	
- Post operative - abdominal	28	20	17	
- Others (c)	8	1	4	

a Chi-squared test, b Kruskal Wallis test, c congenital diseases like esophageal atresia, pulmonary hypertension, meconium aspiration, metabolic diseases, neuromuscular diseases

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TABLE 7   Adherence rates

	T0 Jan – July 2008 (n=178)	T1 May – Nov 2009 (n=173)	T2 May - Nov 2010 (n=156)	p-value
Lung disease (PC)				
Ventilated according to the algorithm*:	67 (79%)	51 (71%)	46 (84%)	p=0.215
No lung disease (PRVC)				
Ventilated according to the algorithm**:	62 (66%)	79 (78%)	85 (84%)	p=0.015

* p=0.092 (between T1-T2); ** Between T0-T1: =0.072, and between T0-T2: p=0.005
p-value of 0.05 was considered statistically significant.

Ventilation Algorithm

Lung diseases

- ARDS, pneumonia, bronchiolitis
- Leakage along the tube
- Stomach problems, fat belly with compression atelectasis
- Pulmonal hypertension: with or without NO

No lung diseases

- Ventilation because of other reasons than lung disease
- Traumatic brain injury, where PCO2 has to be stable

Pressure Control

Pressure Regulated Volume Controlled

Purpose Conventional ventilation:

- pH > 7.30 < 7.48
- pCO2 5-8 kPa
- PC above PEEP ≤ 15cmH2O
- Vt 6 ml/kg (ideal weight)
- SpO2> 95%
- Ti: 0.3-0.6 sec. neonates
- I:E ratio 1:2 > 6 months

Weaningcriteria reached?*

Weaningcriteria reached?*

*Weaningcriteria

- Cough/swallowing reflex present
- Respiration indication solved
- PaO2/FiO2 > 200mmHg/26.7kPa
- Hemodynamical stable/ little inotropic support
- Sufficient muscle strength
- No excessive mucus
- PEEP < 8 cmH2O
- Proper fluid balance/ no signs of edema
- GCS > 8
- No sedative or low dose
- pH > 7.35 < 7.48
- No signs of infection

Pressure Support

Volume Support

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Extubation

FIGURE1 Ventilation protocol

PC=Pressure Control, PRVC= pressure regulated volume controlled, PS= pressure support, VS= volume support, Ti = inspiration time, SpO_2= oxygen saturation, Vt = tidal volume, NO= nitric oxygen, pCO_2= carbon dioxide partial pressure, ARDS = acute respiratory distress

PART II

WEANING OF VENTILATION IN CRITICALLY
ILL CHILDREN

chapter 5

NEURALLY ADJUSTED VENTILATORY ASSIST: ASSESSING THE COMFORT AND FEASIBILITY OF USE IN NEONATES AND CHILDREN.

Anita Duyndam, Bas Bol, André Kroon, Dick Tibboel, Erwin Ista

ABSTRACT:

Aim: To evaluate the practical feasibility for nurses working with neurally adjusted ventilatory assist (NAVA) and assess patient comfort and safety when NAVA is initiated.

Background: NAVA is a relatively new mode of ventilation. Its application in neonates and children has been widely documented. However, its practical feasibility from a nursing point of view as well as its safety and comfort in these populations compared with conventional modes of ventilation has not been described.

Design: A prospective, observational crossover pilot study

Method: NAVA was compared with the conventional mode of ventilation for 3 hours each and practical feasibility, patient comfort level and safety were assessed.

Results: Twenty-one neonates and children were enrolled into the study. There were no reported adverse events. In most patients the NAVA catheter was placed too shallow, as measured by the distances from the nose, ear, xiphisternum (NEX) method, according to the manufacturer's instructions. Accurate placement was confirmed by visual inspection of the NAVA positioning window. Patients' comfort did not differ between the conventional mode and NAVA.

Conclusions: NAVA is feasible, once an accurate signal of the electrical activity of the diaphragm is achieved and seems safe and well tolerated in both neonates and children. Nurses need to gain experience in placing the NAVA catheter and practical recommendations are given.

Relevance to clinical practice: NAVA is a promising new mode of ventilation. This article contributes to an increasing body of evidence that NAVA is feasible in neonates and children. There are practical considerations when NAVA is applied in these patient groups.

INTRODUCTION

The goal of mechanical ventilation in patients with respiratory insufficiency is to improve and maintain gas exchange, reduce excessive respiratory effort whilst giving the patient time to recover from the underlying disease process. Therefore the ideal ventilator would not diminish the respiratory muscle mass or damage lung parenchyma. Numerous reports describe the potential morbidity and mortality associated with excessive (1-3) or insufficient ventilator support. (3, 4) When considering these aspects, patient triggered modes have a number of clear advantages over machine-controlled modes. As breathing effort is preserved, the physiological benefits of active diaphragmatic contraction are maintained, with improved ventilation/perfusion ratio and hemodynamics; less inspiratory pressure is needed; and there is less chance of muscle atrophy. (3) Mechanical assist level should be lowered to prevent ventilator induced lung injury, in harmony with increasing strength of the patient's respiratory muscles. (4) Synchronisation, which is required to operate a patient cycled mode, is most commonly achieved using sensed changes in pressure or flow, to trigger or terminate a supporting breath. Asynchrony is a widely recognized problem with such triggers, arising from a delay in the ventilator's response after the neural initiation or termination of a breath. (5)

Neurally Adjusted Ventilatory Assist (NAVA) is a relatively new mode of ventilation, in which the patient's own respiratory drive controls the timing and the magnitude of pressures delivered. This neuro-ventilatory coupling is achieved by measuring the electrical activity of the diaphragm (Edi), which controls both initiation and magnitude of the pressure delivered by the ventilator.

Only a few studies on the application of NAVA in neonates and children have been published. (4-10) These studies did not pay attention to its practical feasibility in neonates and children and patient comfort.

Before implementing NAVA in daily practice in neonatal and paediatric intensive care units, it would seem essential to know if nurses can easily place a NAVA catheter and have no problems with fixation and finding the optimal Edi signal. Furthermore, it would be important to know if NAVA is as comfortable for our patients as the conventional modes of ventilation and whether NAVA is a "safe" mode of ventilation. The aim of

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this study was to initiate a pilot study to evaluate the feasibility, comfort and safety of NAVA in patients aged from 0-16 years.

METHODS

A prospective, observational crossover pilot study was conducted from September 2009 till September 2010 on the paediatric and neonatal intensive care units of the Erasmus MC- Sophia Children's Hospital, the Netherlands. (METC number: MEC 2009-213; Dutch trial register number: 2067). Both units are tertiary intensive care units and accommodate 28 and 30 beds, respectively. Total annual number of admissions of both units combined is 2200. The institutional review board approved the study. Patients were enrolled after written informed consent was obtained from the parents or legal representatives.

PATIENTS

Twenty-one mechanically ventilated neonates and children were recruited: 10 neonates (gestational age > 28 weeks, at the moment of inclusion); 5 infants (0 to 24 months), and 6 children older than 24 months. Patients were eligible for the study if:

- Ventilated via an endotracheal tube without complications, and having a nasogastric feeding tube in situ;
- FiO_2 < 40% and Pressure Support (PS) on the paediatric intensive care unit (PICU) with peak pressure ≤ to 15 cmH$_2$O above PEEP; or Volume Support (VS) ventilation on the PICU with a peak pressure < 20 cmH$_2$O and a tidal volume of 6-8 ml/kg, PEEP ≤ to 8 cmH$_2$O and spontaneous breathing efforts;
- Synchronized intermittent mandatory ventilation (SIMV) on the neonatal intensive care unit (NICU) with peak pressure ≤ to 15 cmH$_2$O above PEEP.

Exclusion criteria included:
- No consent from parents/ legal representatives
- Hemodynamic instability: use of inotropics, cardiac arrhythmia.
- Neurological disturbances (e.g. intra-ventricular haemorrhage, asphyxia or epilepsy)
- Congenital diaphragmatic hernia
- Esophageal atresia before surgery

PROCEDURE

The included patients were all ventilated using a ventilator with NAVA option (Servo-i, Maquet, Solna, Sweden). Upon informed consent, the standard nasogastric tube was replaced with a NAVA catheter, in accordance with the manufacturer's manual.

The NAVA catheter is a nasogastric tube with electrode rings mounted in the wall where the electrical diaphragmatic impulse (Edi), which elicits the diaphragm contraction, can be sensed. The Edi signal influences not only the start and end of the breath but also the respiratory frequency and tidal volume. This catheter is also used for feeding or elimination of fluid or air. Proper positioning of the NAVA catheter is identified from signals from the catheter on the Servo-i display. The initial placement of the catheter is directed by measuring the distances from the patient's nose to the tragus of the ear and to the xiphisternum (nose – ear – xiphisternum, NEX method) and passing the catheter to this depth, according to the manufacturer's instructions. Six different sizes of NAVA catheters are available, each one for a specific age category. Sizes and lengths ranged from 6 to 14 French and 49 to 125 centimetres, respectively. Size of NAVA catheter for an individual patient is based on weight (neonates) or height (infants).

Accurate placement was confirmed by visual inspection of the NAVA positioning window. Ease of insertion of the NAVA catheter was evaluated with a short questionnaire (Table 1) filled in by the nurse who inserted the NAVA catheter. The questionnaire requested information relating to the durability of the NAVA catheter, complications of insertion, and ease of understanding the manufacturer's instructions. Complications with fixation of the NAVA catheter were retrieved from the Patient Data Management System (PDMS).

The patients first received PS or SIMV for 3 hours; the mode was then changed to NAVA for the next 3 hours (Figure 1).

NAVA level was set to create the same peak-pressure as in PS/ SIMV.

To guarantee safety during NAVA the following stop-criteria were applicable:

- Peak pressure > 35 cm H_2O for PICU and >25 cm H_2O for the NICU
- Respiratory rate > 80-100 / min for a period longer than 10 minutes
- Distress: children: COMFORT behavior score ≥ 23; for neonates: COMFORT Neo score ≥ 14.

Respiratory data were recorded every minute in the PDMS, but calculated every half an hour.

INSTRUMENTS

Patients' comfort was measured every 30 minutes with the COMFORT behavior scale (11) or COMFORT Neo scale (12) in respectively infants and neonates. Both instruments ask observers to consider intensity of six behavioral manifestations: Alertness, Calmness, Respiratory response (for ventilated children) or Crying (for spontaneously breathing children), Body movements, Facial tension and Muscle tone. For each of these items, five descriptions, rated from 1 to 5, are provided reflecting increasing intensity of the behavior in question. Summation of the item scores yields a total score ranging from 6 to 30.

DATA AND ANALYSIS

The following patient characteristics were collected: age, weight, diagnosis, type and dose of analgesia and sedation, level of distress, and complications.

Descriptive statistics were used to summarize these data and they are presented as percentages, mean (SD) for normal distributed data or median and interquartile range (IQR) for non-normal distributed data. Student's t test and Wilcoxon rank sums were used to compare parametric and nonparametric variables, respectively. Data analyses were performed with SPSS® (Statistical Package for the Social Sciences) version 17.

RESULTS

Twenty-one patients were enrolled in the study. The median gestational age of the NICU patients (n= 10) was 30.8 weeks (range (28.2- 34.7); their median weight was 1370 grams (range 900-2000). Seven neonates suffered from idiopathic respiratory distress syndrome (IRDS). The median age of the PICU patients (n=11) was 30 months (range 1-187 months). The diagnoses of the PICU patients were heterogeneous. (Table 2)

FEASIBILITY AND SAFETY

In all cases, the nurses could easily insert and fixate the NAVA catheter. To ensure good fixation, brown adhesive tape (Leukoplast®,BSN Medical GmbH Hamburg, Germany) was placed on the nose (neonates) or on the cheek and nose (infants) and twisted around the catheter. Fixation of the NAVA catheter presented no problems. The NAVA catheter has a clear scale, divided into centimetres, therefore allowing to achieve optimal depth of insertion. Correct depth of insertion is the main criterion for obtaining an optimal Edi signal. When using the NEX-method, the depth at which a good Edi signal was obtained, was only correctly predicted by the manufacturer's recommendation in 4 patients. In 13 patients it was not deep enough (ranging from 1 to 3.5 cm); and in 4 it was too deep (ranging from 2 to 3 cm). In these latter 17 cases the catheter was repositioned on the guidance of the Edi signal screen. (Table 3)

It was possible to insert the NAVA catheter in combination with a duodenal tube without influencing the signal, even during feeding. The children were fed via a duodenal feeding tube; the nasogastric feeding tube (in this case the NAVA catheter) served to remove excess air from the stomach. In most cases the Edi signal was good, indicating that the NAVA catheter was well positioned in the stomach. Incorrect positioning triggered an alarm in two cases, directly after fixation. The NAVA catheter then was repositioned on the guidance of the Edi signal screen. In both cases, however, the Edi signal did not remain stable after repositioning. It is not clear why this occurred.

None of the patients reached the stop criteria for peak pressure and respiratory rate and no adverse events were recorded.

The neonates' mean peak pressure during SIMV differed significantly from that during NAVA: respectively 15.9 ± 2.14 versus 14.3 ± 2.44 cm H_2O (paired t-test t=2,489, df = 9, p = 0.034). However, the mean respiratory rate did not differ between the SIMV and NAVA periods, 64.6 ± 17.4 versus 54.5 ± 9.4 breaths/min. (p=0.072). Neonates' peak pressures usually remained below 25 cm H_2O. Occasionally, however, during a cough or sigh, the pressure peaked to 27.5 cm H_2O.

The peak pressures of all patients in the PICU remained below 35 cm H_2O; the difference between peak and PEEP remained between 15 cm H_2O except for a 15-year-old boy with herpes pneumonia whose peak pressure was high and PEEP was higher than 8 cm H_2O. The Edi signal increased upon coughing with excessive mucus production, upon which

the peak pressure and difference between peak and PEEP briefly increased. The median airway pressure for each individual patient was nearly the same in PS and NAVA modes.

DISTRESS AND SEDATION DURING NAVA VENTILATION

At the NICU two neonates received continuous intravenous morphine (5 mcg/kg/hr.). In neonates, the median COMFORT Neo score did not differ between the two modes: respectively 11 (IQR 10-12) for SIMV versus 11 (IQR 10-13) for NAVA (Z=-0.178, p=0.858).

At the PICU seven of the eleven patients received midazolam with a median dosage of 178.5 mcg/kg/hr. (range 100-300). Two of these seven patients received both midazolam and morphine (median 5 mcg/kg/hr., (range 5-10)); one received both midazolam and ketamine; one received morphine, midazolam and ketamine. Four of the eleven PICU patients received no analgesics or sedatives because their illness required optimal neurological evaluation. The median COMFORT behaviour score of the PICU patients did not significantly differ between the PS and NAVA periods: 11 (IQR 9-13) versus 12 (Z=-1.187, p=0.235). (10-13)

DISCUSSION

In this study we have established that NAVA appears to be feasible, safe and comfortable for our patient groups. However there are some concerns. For one, insertion depth determined by the NEX-method in most cases deviated from the optimal depth as indicated by the Edi catheter positioning screen. Only one other study, in adults, has compared these two methods. (13) That study found that insertion depth determined by the NEX method was equivalent with the optimal depth as shown on the Edi positioning screen in no more than 16% of cases. In the present study, the NAVA catheter frequently had to be inserted approximately 2 cm more caudal compared with the NEX method. Fixation of the NAVA catheter was never a problem and dislocation would trigger an alarm. No problems were encountered when a NAVA catheter was inserted together with a duodenal tube. Even feeding did not seem to influence the Edi signal.

Another concern is the fact that a suitable catheter was not always available. At the PICU a 10- French NAVA catheter was needed but lacking. For this child we chose

the 8-French NAVA catheter, however, this could have influenced the results. At the NICU, the feeding lumen of the 6 French NAVA catheters was too short: it did not extend to outside the incubator and had to be lengthened. Furthermore, especially in the PICU population converting from a conventional mode to NAVA necessitated raising the pneumatic trigger level to let the NAVA trigger prevail. During NAVA the trigger works on a "first come, first serve" base. As the software in a conventional mode measures more frequently the conventional pressure or flow trigger than the Edi triggering in NAVA mode, this would sometimes mean that the conventional trigger would continually come first. Therefore, if the pneumatic trigger level is not set at the optimal level, NAVA will not be functioning optimally.

We noted that any form of sedation or analgesia had a negative effect on the Edi signal. At the NICU, in one of the patients receiving morphine the Edi signal was absent at a dose of 10 mcg/kg/hr. but was good at a dose of 5 mcg/kg/hr. At the PICU, in one child receiving morphine at 20 mcg/kg/hr. the Edi signal was absent; she was excluded from analysis. Especially in patients receiving a combination of morphine, ketamine and midazolam the Edi signal seemed lower. As opioids and benzodiazepines can cause respiratory depression, this could be a potential drawback of NAVA. The promise of a more "natural" ventilation by NAVA's proportional assist is expected to diminish the need for sedation. Breatnach et al. (2010) concluded that the use of sedatives in their population did not influence the Edi signal as a viable trigger. COMFORT behavior scores in this study were the same during conventional mode and NAVA. This would imply that conversion to NAVA does not affect the patient's comfort.

Some limitations of this study that might have influenced the outcomes need to be addressed. First, all patients were ventilated at moderate to low ventilator settings, so findings cannot be extrapolated to other patients or other stages of disease. Secondly, NAVA was assessed for no more than 3 hours, which may be too short to detect possible benefits such as lower respiratory pressures or respiration rate. Thirdly, the questionnaire, used to assess the NAVA catheter is not a validated instrument.

Nurses and physicians need some time to master NAVA and to understand how patients react to it. Once the catheter was accurately placed, the Edi signal was found, the trigger was set and NAVA level adjusted, NAVA and the patient should be able interact without much interference.

CONCLUSION/ PRACTICAL RECOMMENDATIONS

NAVA seems feasible in neonates and children. In this study no adverse events were seen during 3 hours of NAVA. Inserting the catheter proved as easy as inserting a conventional naso-gastric feeding tube. Placing the NAVA catheter at the right depth requires a good deal of experience.

We recommend using the NEX method to determine a "tentative" insertion depth of the Edi catheter. The correct position will possibly be more caudal, as indicated on the Edi catheter positioning screen. Positioning of the catheter in the stomach should be checked carefully. We advise to increase the conventional trigger, if other triggers than the Edi signal initiate respiration, to prevent auto-triggering and non-neural respiration. However, the conventional trigger should remain at the lowest possible level, because in NAVA back-up mode (Pressure Support/ Pressure Control) the conventional trigger is used. Finally, respiratory therapists or nurse practitioners should teach nurses the essentials needed for NAVA to succeed.

IMPACTS

WHAT IS KNOWN ABOUT THIS SUBJECT
- NAVA is a relatively new mode of ventilation
- NAVA has not been tested extensively in neonates and children
- NAVA is said to deliver a more synchronous respiratory support
- The clinical impact of using NAVA in neonates and children has not yet been established

WHAT THIS PAPER ADDS
- NAVA is a mode of ventilation that can successfully be used in neonates and children
- In NAVA mode, the Edi catheter length should be re-assessed if the NEX method is used to assess catheter length.
- NAVA seems safe and comfortable in neonates and children

REFERENCES:

1.   The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342(18):1301-8.

2.   Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347-54.

3.   Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med. 2008;358(13):1327-35.

4.   Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med. 2010;11(2):253-7.

5.   Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med. 2010;11(1):7-11.

6.   Beck J, Reilly M, Grasselli G, Mirabella L, Slutsky AS, Dunn MS, et al. Patient-ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. Pediatr Res. 2009;65(6):663-8.

7.   Sinderby C, Beck J, Spahija J, de Marchie M, Lacroix J, Navalesi P, et al. Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest. 2007;131(3):711-7.

8.   Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. Nat Med. 1999;5(12):1433-6.

9.   Clement KC, Thurman TL, Holt SJ, Heulitt MJ. Neurally triggered breaths reduce trigger delay and improve ventilator response times in ventilated infants with bronchiolitis. Intensive Care Med. 2011;37(11):1826-32.

10. Stein H, Howard D. Neurally adjusted ventilatory assist in neonates weighing <1500 grams: a retrospective analysis. J Pediatr. 2012;160(5):786-9 e1.

11. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med. 2005;6(1):58-63.

12. van Dijk M, Roofthooft DW, Anand KJ, Guldemond F, de Graaf J, Simons S, et al. Taking up the challenge of measuring prolonged pain in (premature) neonates: the COMFORTneo scale seems promising. Clin J Pain. 2009;25(7):607-16.

13. Barwing J, Ambold M, Linden N, Quintel M, Moerer O. Evaluation of the catheter positioning for neurally adjusted ventilatory assist. Intensive Care Med. 2009;35(10):1809-14.

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TABLES

TABLE 1   Questionnaire requesting information relating to the NAVA catheter

1 Is it clear that the nasal gastric tube is suitable for NAVA?	Yes / No
Is there a clear metric scale on the NAVA catheter?	Yes / No
How does the material feel?	Rigid / Weak / Same as standard nasogastric tubes
How do you experience the flexibility of the NAVA catheter?	Rigid / Same as standard nasogastric tubes / Flexible
Is the catheter easy to manipulate according the guidelines of Maquet?	Yes / No
Is the catheter easy to fixate with common adhesive plaster?	Yes / No
Does the catheter remain in place after fixation?	Yes / No
Is the NEX method appropriate for this child to get the Edi signal well on the screen?	Yes / No, too short/long (....... cm)
What is your overall impression of the use of the Edi catheter?	Weak/ adequate/ good
	Comments:

TABLE 2 Demographics, diagnosis and type and doses of sedation

Category	Gender	GA (weeks)	Age (months)	Diagnosis	Weight (kg)	Midazolam (mcg/kg/h)	Morphine (mcg/ kg/h)	Ketamine (mg/ kg/h)
N	F	35	0	NEC	1.9		5	
N	M	29	0	IRDS	1.2			
N	M	31	0	IRDS	1.5			
N	M	29	0	IRDS	1.5			
N	M	28	0	IRDS/ pneumothorax	1.3		5	
N	M	31	0	IRDS/ PPHN	1.1			
N	F	34	1	IRDS/ dysmaturity	0.9			
N	M	35	1	PDA/ NEC	1.1			
I	F	35	2	IRDS/ NEC/ PDA/ BPD	1.2			
N	M	34	0	Gastroschisis	2			
N	M		1	ARDS	6	100	5	
I	M		2	Post-operative cardiac surgery	3.7	110		
I	F		8	Resp. insufficiency, broncho/ tracheomalacia	7.7	300	5	
I	F		9	Pneumonia	7.6	200	5	
C	M		22	Pneumonia	12.7	157		
C	M		30	Aspiration pneumonia	15.5	100		
C	F		32	Epilepsy, complaints of swallowing and stridor	10	200		0.5
C	F		62	Immuno deficiency	25			
C	F		76	Varicella pneumonia, ARDS	20	300	10	2
C	M		128	Strangulation	66.1			
C	M		187	Herpes pneumonia	42			

– Neonate; I – Infant; C – child; IRDS – Idiopathic respiratory distress syndrome ; NEC – Necrotizing entero-colitis; PPHN –persistent pulmonary hypertension of the Neonate; ARDS – acute respiratory distress syndrome; PDA – Persistent Ductus Arteriosis.; GA – Gestational Age; BPD – Broncho Pulmonary Dysplasia

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TABLE 3   Data from questionnaire requesting information relating to the NAVA catheter

| Patient number | Question numbers | | | | | | | | |
	1	2	3	4	5	6	7	8	9
1	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too shallow	Good
2	yes	yes	Same	Same	Yes	Yes	Yes	Correct acc. NEX	Good
3	yes	yes	Same	Same	Yes	Yes	Yes	1.5 cm too shallow	Good
4	yes	yes	Same	Same	Yes	Yes	Yes	Correct acc. NEX	Good
5	yes	yes	Same	Same	Yes	Yes	Yes	3.4 cm too shallow	Good
6	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too shallow	Good
7	yes	yes	Same	Same	Yes	Yes	Yes	1 cm too shallow	Good
8	yes	yes	Same	Same	Yes	Yes	Yes	Correct acc. NEX	Good
9	yes	yes	Same	Same	Yes	Yes	Yes	Correct acc. NEX	Good
10	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too deep	Good
11	yes	yes	Weak*	Weak*	Yes	Yes	Yes	Correct acc. NEX	Good
12	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too shallow	Good
13	yes	yes	Same	Same	Yes	Yes	Yes	1.5 cm too shallow	Good
14	yes	yes	Same	Same	Yes	Yes	Yes	3 cm too deep	Good
15	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too deep	Good
16	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too deep	Good
17	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too shallow	Good
18	yes	yes	Same	Same	Yes	Yes	Yes	3 cm too shallow	Good
19	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too shallow	Good
20	yes	yes	Same	Same	Yes	Yes	Yes	3 cm too shallow	Good
21	yes	yes	Same	Same	Yes	Yes	Yes	2 cm too shallow	Good

* guide wire was used to insert NAVA catheter; No. 1- 11 PICU patients; No. 12-21 NICU patients

FIGURES
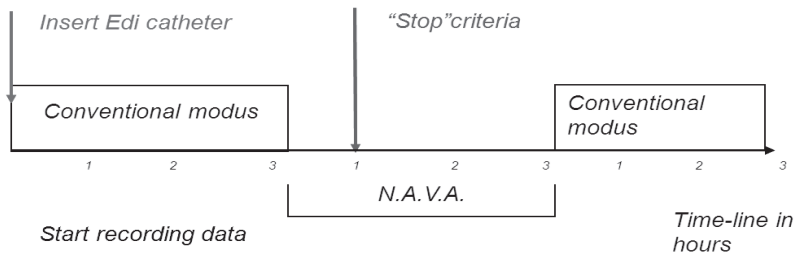
FIGURE 3 Study schedule

chapter 6

IMPLEMENTATION OF A NURSE-DRIVEN VENTILATION WEANING PROTOCOL IN CRITICALLY ILL CHILDREN: CAN IT IMPROVE PATIENT OUTCOME?

Anita Duyndam, Robert Jan Houmes, Joost van Rosmalen, Dick Tibboel, Monique van Dijk,

ABSTRACT

Background: Critically ill children treated with invasive mechanical ventilation in a paediatric intensive care unit (PICU) may suffer from complications leading to prolonged duration of ventilation and PICU stay.

Objective: To find out if the use of a nurse-driven ventilation weaning protocol in a PICU can shorten the duration of mechanical ventilation.

Methods: In a prospective, pretest-posttest implementation study we implemented a nurse-driven ventilation weaning protocol and compared its outcomes with those of the usual physician-driven weaning. In the posttest period, nurses weaned the patients until extubation as per this protocol. The primary outcome was duration of ventilation. The secondary outcomes were length of PICU stay, re-intubation rate and compliance with the protocol (measured by use of the prescribed support mode).

Results: In total, 424 patients aged from 0-18 years (212 pretest and 212 posttest) were included; in both groups the median age was 3 months. The median duration of ventilation did not differ significantly between the pre- and posttest periods: 42.5 hrs. (Interquartile range, IQR 14.3-121.3) vs. 44.5 hrs. (IQR 12.3-107.0), respectively; p=0.589. In the posttest period, the PICU-stay was non-significantly shorter: 5.5 days (IQR 2-11) vs. 7 days (IQR 3-14) in the pretest period; p=0.432. Compliance with the prescribed support mode was significantly higher in the posttest period: 69.9% vs. 55.7% in the pretest period; p=0.005. The re-intubation rate was not significantly different between the pretest and posttest periods (5% vs. 7 %, respectively; p=0.418). The extubation rate during nights was higher in the posttest period, but not significantly different (p=0.097).

Conclusions: Implementation of a nurse-driven weaning protocol did not result in a significantly shorter duration of ventilation, but was safe and successful. The reintubation rate did not significantly increase compared with usual care.

INTRODUCTION

Critically ill children treated with invasive mechanical ventilation (iMV) in a paediatric intensive care unit (PICU) may suffer from complications such as atelectasis and ventilator-associated pneumonia (VAP), and complications related to the administration of sedation. (1-3) These complications may prolong the durations of iMV (DOV) and PICU stay, which in turn could lead to a cascade of extensive complications, especially if more sedation is needed, such as ventilator induced diaphragmatic dysfunction and delirium. (2, 4-6) They may also have a negative psychological impact on both the child and parents. (7) Nevertheless, premature extubation should be prevented, as it may necessitate reintubation, with increased risk of morbidity and mortality. (8) There needs to be a balance between ensuring that iMV is not unnecessarily prolonged and also ensuring that children are not extubated before they are ready. (9) Failure to wean is associated with haemodynamic dysfunction, neuromuscular insufficiency, malnutrition, metabolic disorders and diaphragmatic muscle weakness. (5, 9)

A recent updated systematic review of 17 randomised control trials (RCTs) involving 2434 critically ill adult patients compared protocolised vs. nonprotocolised weaning. Protocolised weaning was associated with a mean 26% reduction of DOV in comparison with nonprotocolised weaning. (10) In four studies, the weaning protocol was computerled. In the other 11 studies it was professional-led, mostly by registered nurses or respiration therapists. Considerable heterogeneity among studies was found, however, concerning the type of protocol and the achieved DOV, which limits generalization of this finding. (10) In a systematic review (n=3 studies) in paediatrics (11-14), one RCT found that protocolised weaning reduced DOV by 32 hours (12); the other two studies did not show a significant effect on DOV. (13, 14)

Effective weaning of ventilation in critically ill children requires effective collaboration between physicians and nurses. From two previous studies we know that key decisions concerning ventilation were mainly made collaboratively, but that nurses were not always able to adjust ventilator settings independently, although they had the autonomy to do so. (15, 16) Reasons brought forward included not being allocated to a 'weanable' patient, high workload, perceived lack of support from medical staff, lack of standardised competency programs and nurse driven weaning protocol. Results of a survey among PICU nurses in 19 European countries showed variability in perceived nursing autonomy and involvement in weaning. (17) The researchers speculated that

the variability could be ascribed to differences in the level of general nursing education and provision of specialist intensive care unit (ICU) nursing education.

PICU nurses take care of ventilated patients night and day. Therefore, they are in an ideal position to determine if a patient is ready for weaning of iMV. The weaning protocols described by Blackwood and colleagues (10) were executed mainly by nurses and respiration therapists, probably because physicians are responsible for more patients, especially during evenings and nights. Our hypothesis was that the well-trained nurses in our PICU, in which the nurse-to-patient ratio is 1:1 or 1:2, should be able reduce the weaning time and length of iMV with the use of a well-thought-out protocol. Before developing the new protocol, we sought the views of nursing and medical staff and took these into account as much as possible. (18, 19) Most of them, especially nurses, were excited to participate.

The primary objective of the study was to investigate if implementation of a nurse-driven ventilation weaning protocol could lead to a shorter DOV and shorter length of PICU stay.

MATERIALS AND METHODS

STUDY DESIGN
We conducted a prospective, pretest-posttest study. Results of this study are reported using the Standards for Quality Improvement Reporting Excellence (SQUIRE) guideline. (20)

CONTEXT
The study involved mechanically ventilated patients in a 28-bed ICU of a tertiary referral academic children's hospital in the Netherlands. This PICU had about 2200 admissions per year, including 700 ventilated patients. The nurse-to-patient ratio was 1:1 or 1:2 during both periods.

In accordance with the ventilation policy, all patients requiring iMV were ventilated with the Servo-i ventilator of Maquet (Solna, Sweden). (21) Patients with lung disease, such as acute respiratory distress syndrome, pneumonia, or bronchiolitis, were ventilated with pressure control (PC). Patients with other conditions, such as epilepsy,

postoperative care or traumatic brain injury, were ventilated with the pressure-regulated volume control mode (PRVC).

INTERVENTION

In the pretest period (December 2013 to September 2014), iMV was weaned off as usual at the time. This implies that a physician assessed a stable patient's iMV and instructed nurses to gradually wean off pressure, tidal volume and positive end-expiratory pressure (PEEP) and change to a support mode. This assessment was made maximally three times daily. Nurses only weaned off oxygen on their own initiative and sometimes changed iMV to a support mode.

A nurse-driven weaning protocol then was implemented over the course of three months (September 2014 up to November 2014). In the posttest period (December 2014 until September 2015) nurses used the weaning protocol. Children up to the age of 18 years receiving iMV were eligible for inclusion in both periods. The exclusion criteria were as follows: airway obstruction, for example, epiglottitis, laryngitis, paralysis of the vocal cord; receiving home ventilation for neuromuscular diseases or obstructive/central apneas; receiving chronic ventilation for longer than 1 month; traumatic brain injury established with intracranial pressure measurement; Glasgow Coma Scale score < 8; unable to swallow or cough; excessive work of breathing and too little physical growth (e.g. cardiac patients); and anticipated death during the study period. In both periods, distress and postoperative pain were treated according as per our sedation and postoperative pain algorithms. [22] Nurses are allowed to increase or decrease sedation and analgesic medication themselves, using these algorithms that are based on the COMFORT behaviour scores. (22) An explicit cut-off level of depth of sedation where extubation is considered has not been set, but sedatives are tapered off or stopped during weaning of ventilation and before extubation, depending on the duration of sedation and the administration of opioids. In case of long-term sedation, intravenous sedatives and opioids are switched to an oral tapering off schedule with lorazepam, methadone or clonidine.

DEVELOPMENT AND USE OF IMV WEANING PROTOCOL

The nurse-led iMV weaning protocol was developed by five PICU nurses who had been trained as ventilation practitioners and a paediatric intensive care physician. The protocol includes a two-step algorithm: first, weaning off oxygen and PEEP, and second, choosing a support mode (volume support in case of PRVC and pressure

support in case of PC) and gradually weaning off pressure or volume (Figure 1). The protocol did not include a spontaneous breathing trial (SBT) or extubation readiness test (ERT) because we could not find a validated method for children in literature. Therefore, we used extubation criteria derived from the paediatric literature and our clinical experience from a former project (unpublished). (12, 23-26) Extubation readiness was determined by these criteria. Nurses were empowered to make the ventilation decision steps without direct supervision of a physician, but approval from a paediatric intensive care physician was needed for the actual extubation. In usual care the physician initiated the weaning but did not perform protocolised steps in stable patients.

IMPLEMENTATION
The implementation of the nurse driven weaning protocol was based on the seven-step Implementation Model of Change of Grol et al. (27) At the end of the pretest period, we identified potential factors influencing its implementation (table 1). We developed the implementation strategy taking into account the barriers and facilitators identified. (19, 28) A full outline of the implementation is described in Supplemental file 1.

STUDY OUTCOMES
The primary outcome was DOV, defined as the time elapsed from either intubation on the PICU or admission on the PICU with iMV (controlled and support modes) in place until the time of extubation.

The secondary outcomes were length of PICU-stay (LOS-PICU), reintubation rate and time of extubation (daytime, evening or night). Further, the following implementation outcomes were determined: time elapsed between meeting the extubation criteria and the actual extubation during the posttest, and protocol compliance. Successful implementation was defined as a compliance rate exceeding 80%.

DATA COLLECTION
Five ventilation practitioners were available to screen patients for eligibility on a daily basis.

For both the pretest and the posttest we collected the following parameters prospectively: patient characteristics, reason for admission, Pediatric Risk of Mortality Score III (PRISM III), DOV and LOS-PICU. Ventilation characteristics were collected 1

hour before extubation, including ventilation mode, PEEP, PC level above PEEP, tidal volume, FiO_2, dosage of continuous sedatives and opiates, COMFORT behavior scale scores, failure of extubation, and clinical signs of fluid overload. Failure of extubation was defined as re-intubation within 48 hours after extubation. Furthermore, times of intubation and extubation were collected (during daytime, evening or night shift). Adverse events were defined as reintubation rate and need for noninvasive ventilation.

For the posttest alone, we collected the times of extubation readiness and reasons for delay of extubation after reaching the extubation criteria.

The following subgroups were distinguished: those ventilated shorter and those ventilated longer than 48 hours and patients belonging to the following admission groups: respiratory failure, postsurgical and postsurgical cardiac patients. We hypothesized that for these groups the impact of the nurse-driven protocol would differ the most.

Furthermore, for both periods, we looked at the difference in outcome (DOV, LOS, reintubation and need for noninvasive ventilation) between patients who were extubated from a controlled versus a support mode.

ANALYSIS
On the basis of a median DOV of 4 days in 2012, the inclusion of at least 170 patients per period would give the study a power of 80% in detecting a decrease in DOV by 1.5 days with a significance level of 0.05.

STATISTICAL METHODS
For children who were ventilated more than once during the current admission, only the first occasion was included for analysis. Data are presented as percentages, mean (standard deviation) for normally distributed data, and as median interquartile range (IQR) for non-normally distributed continuous data. Outcomes were compared between the pre- and posttest periods. Groups were compared using chi-square tests for categorical variables or the Fisher exact test to compare two groups on a dichotomous outcome with small sample sizes. Further, the independent samples t-test (normally distributed data) or Mann-Whitney U test (non-normally distributed data) were applied for continuous variables (e.g. DOV, LOS, age). A p-value of 0.05 (two-

sided) was considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows®, version 21.0 (Armonk, NY: IBM Corp).

ETHICAL CONSIDERATIONS

The Medical Ethics Review Board approved the study and, owing to its non-invasive nature waived the need for informed parental consent. In this medical research the participants were neither subjected to procedures nor required to follow rules of behaviour.

RESULTS

PATIENT CHARACTERISTICS

In the pretest period we screened eligibility of 297 patients. Eighty-five of them were not eligible, and thus 212 patients were included. In the posttest period, the corresponding figures were 319, 107, and 212. Exclusion reasons are shown in Fig. 2. Thus, in each of the predetermined time periods we included more subjects than the 170 calculated from the power analysis.

Demographic characteristics of the patient groups in both periods were not significantly different (Table 2).

Primary outcome: duration of ventilation
In the pretest period, the median DOV was 42.5 h (IQR) 14.3-121.3 h) vs. 44.5 h (IQR 12.3-107.1 h; p=0.589) in the posttest period (Table 3). For the three selected subgroups of patients the DOV was not significantly different between both periods (Table 3).

Secondary outcomes: length of stay, compliance, reintubation
In the pretest period, the median LOS was 7.0 days (IQR 3-14) vs. 5.5 days (IQR 2-11); p=0.432) in the posttest period (Supplemental file 3). The median LOS was not significantly different for the subgroups 'DOV ≤ 48 hours' and 'DOV > 48 hours'. This also held for the three selected patient groups (Table 3).

The compliance rate in the posttest period was significantly higher than that in the pretest period: 69.9% vs. 55.7% (p=0.005).

The rates of adverse events in the pre- and posttest periods were comparable (Supplemental file 3). The reintubation rate did not significantly differ between both periods, respectively 5% (11/212) vs. 7% (15/212); p =0.418. The percentage of patients who needed noninvasive ventilation after extubation was low and not significantly different between groups, respectively 3.3% (7/212 patients) pretest vs. 2.4% (5/212) posttest; p=0.771. In the posttest period, 16.9% of extubations took place in the night, versus 9.4 % in the pretest period (p= 0.097).

Patients in the posttest period were extubated within a median of 2 hours (IQR 0-4) after meeting the extubation criteria. For those not extubated within 2 hours, a median of 7 hours (IQR 3-23) had elapsed before actual extubation. The most frequently reported reasons for later extubation were as follows: insufficient triggering despite low ventilation settings (n=39); too much mucus production according to the physician, but less than three times an hour, particularly in patients with viral airway infections (n=22); need for a low dose nitric oxide in case of pulmonary hypertension while set to sildenafil (n=9) and developing arrhythmias (n=7) (Supplemental file 4).

Sedation levels, COMFORT behavior scores, clinical signs of edema, ventilator settings, pH and bicarbonate before extubation did not significantly differ between the two periods (Supplemental file 5).

Patients who were not changed to support mode were weaned to PC 15 cmH2O (10 cmH2O above PEEP 5 cmH2O) or PRVC with pressures at 15 cmH2O (with PEEP at 5 cmH2O) at a frequency normal for age (or a lower frequency to provoke self-triggering) and an oxygen percentage of 40% or less. There were no significant differences in outcome for patients on a controlled or support mode before extubation in both periods. (see footnote in table 3)

DISCUSSION

SUMMARY

Mechanical ventilation is essential to overcome a period of respiratory insufficiency but its duration should be limited to avoid ventilator-induced lung injury, airway injuries, and high sedatives consumption. (1-3, 7, 8) Although in this study the use of the nurse-driven weaning protocol did not result in a significant shortening of the duration of

ventilation, the application of this nurse-driven protocol was as safe and successful as physician-driven weaning, seeing that the re-intubation rate had not significantly increased. However, the study design does not allow definitive conclusions.

INTERPRETATION

Being 'as good as usual care' is valuable in itself; in this case, because the nurses have more autonomy and not every aspect of weaning needs to be authorized by a physician. In practice, during evenings and nights – when fewer physicians are present – nurses can wean by themselves.

The increased use of a supportive ventilation mode in the posttest period indicates compliance with the protocol to some degree, but implementation success (compliance rate of greater or equal to 80%) was not reached, despite the multifaceted implementation strategy. Of all the strategies, reminders by the ventilation practitioners worked best to improve compliance. The low compliance rate might explain why we could not detect a significant difference in DOV. However, in rare cases, particularly in neonates, a support mode attempt failed because the ventilator was not triggered or the respiratory rate was too high, so that the child was extubated under controlled mode settings. In these cases, compliance was nevertheless intended. It would be useful to ask the nurses how confident they feel, whether they see added value for the patient, and what problems, if any, they encounter with the nurse-driven protocol. (29)

Various authors have recognized that implementation of an intervention is complex, explaining that many factors may influence its success. These include commitment of the management, culture in a ward, staff leadership skills and staff characteristics such as educational level, attitude, autonomy and degree of cooperation. (10, 15-17, 28) The 3 months' period for implementation of the protocol seemed long enough, but in practice its use may not yet have been ingrained in the nurses' work routines. This is why the nurse managers and ventilation practitioners should keep reminding nurses of the protocol, stimulate them to use it and also to educate them if they feel not confident to wean by themselves.

From interviews with physicians in our setting (not published) we know that some physicians are wary of nightly extubation because the staff-per-patient ratio in the night is lower than in the daytime. Although the extubation rate during nights had almost doubled in the posttest period, the number of adverse events had not increased.

We thought that the higher nightly extubation rate in the night might explain a shorter stay, but we cannot demonstrate this with this insignificant result. An option for poorly resourced PICUs may be that the nurses wean and stop the feeding during the night shift, so that extubation can take place early in the morning, before the morning rounds.

There are many approaches to weaning, and not all use a change to support modes of ventilation. In our study we found no significant difference in outcome for the patients weaned from a support mode and those who were extubated from a controlled mode with low settings. Some children may already have been ready for extubation when assessed for being weaning ready. The question is whether a shift to support modes could unnecessarily prolong iMV in these children.

Of all previous pediatric and neonatal studies on the effect of a weaning protocol on DOV, only the study of Foronda et al. found a significant difference in DOV of 1.2 days (3.5 days vs. 4.7 days) compared to usual care without a weaning protocol. (12) Four other studies found a significant earlier weaning time, but no significant difference in DOV. (13, 14, 26, 30) However, only Foronda used an SBT as part of the weaning protocol. This was performed daily by protocol, until extubation. This protocol was not nurse-driven. Fellows who were not involved in the decision to extubate patients assessed how patients in the intervention group performed the SBT and extubated these patients. The control group was weaned by physicians. The ventilator mode used before SBT is not clear in this research, but pressure support, synchronized intermittent mandatory ventilation and pressure- controlled ventilation were applied. Before SBT, the patient had to be on an oxygen percentage equal or under 50%, a positive end-expiratory pressure (PEEP) of equal or less than 8 cmH2O and a peak inspiratory pressure of equal or less than 25 cmH2O. Because that protocol was not nurse-driven, the findings of Foronda et al. are hard to compare with ours, but it is important to realise that a daily evaluation and SBT can lead to a shorter DOV, even when settings of the ventilator are still high and the child is on a controlled mode.

The question remains if a nurse-driven ventilation weaning protocol actually can lead to a shorter DOV. Perhaps DOV is determined to a larger degree by sedation depth, the underlying disease and severity of respiratory failure, waiting time for an operation or magnetic resonance imaging scan, or other reasons. As we showed, extubation can be delayed for many reasons after extubation criteria are reached. The most important reason in this study was a low-ventilation setting, but not triggering the ventilator.

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The patients in question may have been too heavily sedated, although nurses could have weaned sedation themselves, as a sedation protocol is in place. Incidentally, a recent study found no shorter DOV with a nurse-driven sedation protocol. (31) Most of the named reasons for delaying extubation are subjective. An example is 'too much mucus production', as the presence of an endotracheal tube can stimulate mucus production. Fever and neutropenia also are relatively subjective contraindications. Good communication and documentation are needed here for good decision-making.

Studies on extubation criteria vary widely in nature. Some studies describe extubation practices, others are prediction studies or weaning trials, such as an SBT or ERT. (11, 12, 23, 26, 32) Although SBT and ERT have a different focus, they both assess whether a patient is ready for extubation or not. An SBT assesses the patient's ability to breathe while receiving minimal or no ventilator support. An ERT assesses if the weaning is completed, the patient is sufficiently awake with intact airway reflexes, hemodynamically stable and has manageable secretions. (23) There is little evidence for the use of an SBT and ERT in children, in contrast to adults. (33) It is not yet known which of these two methods, SBT or ERT, can best predict extubation success and they are executed differently per study. (24, 32-36) A recent report of a European Paediatric Mechanical Ventilation Consensus Conference recommends a daily ERT in children. (35) A recent quality improvement study in PICU patients found that a protocol with a daily SBT decreased extubation failure, but DOV was not studied here. (37) Our algorithm already includes daily assessment of weaning readiness on the basis of our weaning criteria, but adding an SBT could shorten the weaning period, also considering that there is no proof that pre-extubation ventilator settings have an influence on weaning failure. (12, 38)

In our study the reintubation rate and the use of noninvasive ventilation after extubation were low, and this suggest that the decision to extubate at a peak pressure of 15 cm H_2O and a PEEP of 5 cmH_2O was cautious.

LIMITATIONS

The design of the study was a single-center pre-post study and not a controlled trial. All nurses needed to be familiar with the protocol, and therefore, it was not possible to randomise the study on patient or unit level. As we excluded the patients who died on the ventilator, we could not use the outcome of ventilator-free days (each day alive and free off mechanical ventilation). We did not assess the children's upper airway, although

upper airway obstruction is the main cause of extubation failure. In the pretest, two of the 11 patients who needed reintubation had stridor versus seven of the 15 in the post test. Upper airway obstruction is difficult to predict by an SBT or low ventilation parameters. Measuring compliance with the use of a support mode during weaning does not strictly represent compliance with the whole weaning algorithm. It would be more representative to establish in each case whether nurses were using the protocol and how they experienced it.

DIRECTIONS FOR FURTHER RESEARCH

In the posttest, patients ventilated longer than 48 hours had a shorter LOS-PICU compared with the pretest, although the difference was not statistically significant. Nevertheless, in the future we should focus on patients ventilated for more than 48 hours, as in this group a larger reduction in LOS-PICU might be achieved with the use of a nurse-driven ventilation weaning protocol. This could be studied in a clinical trial. However, it would be difficult to randomise patients in a study on the effects of an intervention such as nurse-driven weaning which requires a change of practice of the whole team. Therefore, a stepped wedge cluster randomised controlled trial would be an appropriate design to study both the effectiveness and implementation outcomes.

To increase the compliance, we should continue with our well-considered multifaceted implementation strategy, including training sessions, reminders and input of local opinion leaders. Especially the local opinion leaders should be present every day to support the nurses and to help them increase their autonomy. The compliance should be measured by the use of a support mode in combination with questionnaires and by having an independent observer monitoring the weaning process.

CONCLUSIONS

Implementation of a nurse-driven weaning protocol in our PICU did not result in a significantly shorter duration of ventilation but was found safe and successful. The greater use of a support mode of ventilation in the posttest period indicates a moderate compliance to the protocol, but still the compliance was not satisfactory enough. Further research is needed with a focus on children ventilated for more than forty-eight hours and on increasing compliance with the protocol.

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ACKNOWLEDGEMENTS

REFERENCES

1. Woodruff DW. How to ward off complications of mechanical ventilation. Nursing. 1999;29(11):34-9; quiz 40.

2. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest. 1998;114(2):541-8.

3. Morinec J, Iacaboni J, McNett M. Risk factors and interventions for ventilator-associated pneumonia in pediatric patients. J Pediatr Nurs. 2012;27(5):435-42.

4. Srinivasan R, Asselin J, Gildengorin G, Wiener-Kronish J, Flori HR. A prospective study of ventilator-associated pneumonia in children. Pediatrics. 2009;123(4):1108-15.

5. Hoskote A, Cohen G, Goldman A, Shekerdemian L. Tracheostomy in infants and children after cardiothoracic surgery: indications, associated risk factors, and timing. The Journal of thoracic and cardiovascular surgery. 2005;130(4):1086-93.

6. van Dijk M, Knoester H, van Beusekom BS, Ista E. Screening pediatric delirium with an adapted version of the Sophia Observation withdrawal Symptoms scale (SOS). Intensive Care Med. 2012;38(3):531-2.

7. Colville G, Cream P. Post-traumatic growth in parents after a child's admission to intensive care: maybe Nietzsche was right? Intensive Care Med. 2009;35(5):919-23.

8. Gomes Cordeiro AM, Fernandes JC, Troster EJ. Possible risk factors associated with moderate or severe airway injuries in children who underwent endotracheal intubation. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2004;5(4):364-8.

9. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. The European respiratory journal. 2007;29(5):1033-56.

10. Blackwood B, Burns KE, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. Cochrane Database Syst Rev. 2014(11):CD006904.

11. Blackwood B, Murray M, Chisakuta A, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients. Cochrane Database Syst Rev. 2013;7:CD009082.

12. Foronda FK, Troster EJ, Farias JA, Barbas CS, Ferraro AA, Faria LS, et al. The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial. Crit Care Med. 2011;39(11):2526-33.

13. Jouvet PA, Payen V, Gauvin F, Emeriaud G, Lacroix J. Weaning children from mechanical ventilation with a computer-driven protocol: a pilot trial. Intensive Care Med. 2013;39(5):919-25.

14. Maloney CG. Computerized weaning of childhood respiratory failure(a dissertation submitted to the faculty of the university of Utah). 2007.

15. Blackwood B, Junk C, Lyons JD, McAuley DF, Rose L. Role responsibilities in mechanical ventilation and weaning in pediatric intensive care units: a national survey. Am J Crit Care. 2013;22(3):189-97.

16. Rose L, Blackwood B, Egerod I, Haugdahl HS, Hofhuis J, Isfort M, et al. Decisional responsibility for mechanical ventilation and weaning: an international survey. Crit Care. 2011;15(6):R295.

17. Tume LN, Kneyber MC, Blackwood B, Rose L. Mechanical Ventilation, Weaning Practices, and Decision Making in European PICUs. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2017;18(4):e182-e8.

18. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. Jama. 1999;282(15):1458-65.

6

19. Grol R, Cluzeau FA, Burgers JS. Clinical practice guidelines: towards better quality guidelines and increased international collaboration. Br J Cancer. 2003;89 Suppl 1:S4-8.

20. Goodman D, Ogrinc G, Davies L, Baker GR, Barnsteiner J, Foster TC, et al. Explanation and elaboration of the SQUIRE (Standards for Quality Improvement Reporting Excellence) Guidelines, V.2.0: examples of SQUIRE elements in the healthcare improvement literature. BMJ Qual Saf. 2016;25(12):e7.

21. Duyndam A, Houmes RJ, van Dijk M, Tibboel D, Ista E. How to achieve adherence to a ventilation algorithm for critically ill children? Nurs Crit Care. 2015;20(6):299-307.

22. Ista E, de Hoog M, Tibboel D, van Dijk M. Implementation of standard sedation management in paediatric intensive care: effective and feasible? Journal of clinical nursing. 2009;18(17):2511-20.

23. Newth CJ, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, et al. Weaning and extubation readiness in pediatric patients. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2009;10(1):1-11.

24. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. Jama. 2002;288(20):2561-8.

25. Rushforth K. A randomised controlled trial of weaning from mechanical ventilation in paediatric intensive care (PIC). Methodological and practical issues. Intensive Crit Care Nurs. 2005;21(2):76-86.

26. Jouvet P, Farges C, Hatzakis G, Monir A, Lesage F, Dupic L, et al. Weaning children from mechanical ventilation with a computer-driven system (closed-loop protocol): a pilot study. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2007;8(5):425-32.

27. Grol R, Wensing M, Eccles M. Improving Patient Care; The Implementation of Change in Clinical Practice. 2013;2nd Revised version.

28. Jordan J, Rose L, Dainty KN, Noyes J, Blackwood B. Factors that impact on the use of mechanical ventilation weaning protocols in critically ill adults and children: a qualitative evidence-synthesis. Cochrane Database Syst Rev. 2016;10:CD011812.

29. Blackwood B, Wilson-Barnett J. The impact of nurse-directed protocolised-weaning from mechanical ventilation on nursing practice: a quasi-experimental study. International journal of nursing studies. 2007;44(2):209-26.

30. Schultz TR, Lin RJ, Watzman HM, Durning SM, Hales R, Woodson A, et al. Weaning children from mechanical ventilation: a prospective randomized trial of protocol-directed versus physician-directed weaning. Respir Care. 2001;46(8):772-82.

31. Curley MA, Wypij D, Watson RS, Grant MJ, Asaro LA, Cheifetz IM, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. Jama. 2015;313(4):379-89.

32. Chavez A, dela Cruz R, Zaritsky A. Spontaneous breathing trial predicts successful extubation in infants and children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2006;7(4):324-8.

33. Valenzuela J, Araneda P, Cruces P. Weaning from mechanical ventilation in paediatrics. State of the art. Arch Bronconeumol. 2014;50(3):105-12.

34. Khemani RG, Hotz J, Morzov R, Flink RC, Kamerkar A, LaFortune M, et al. Pediatric extubation readiness tests should not use pressure support. Intensive Care Med. 2016;42(8):1214-22.

35. Farias JA, Alia I, Retta A, Olazarri F, Fernandez A, Esteban A, et al. An evaluation of extubation failure predictors in mechanically ventilated infants and children. Intensive Care Med. 2002;28(6):752-7.

36. Farias JA, Retta A, Alia I, Olazarri F, Esteban A, Golubicki A, et al. A comparison of two methods to perform a breathing trial before extubation in pediatric intensive care patients. Intensive Care Med. 2001;27(10):1649-54.

37. Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med. 2017;43(12):1764-80.

38. Laham JL, Breheny PJ, Rush A. Do clinical parameters predict first planned extubation outcome in the pediatric intensive care unit? J Intensive Care Med. 2015;30(2):89-96.

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Inclusion: Ventilated patients 0-18 years
Exclusion:
Airway obstruction
Chronical ventilation > 1 months
Traumatic brain injury
GCS < 8, not able to swallow/ cough
'Growing' with ventilation

Start weaning criteria:
F_iO_2 =/< 60%
pH > 7.32
Peak pressure ≤ 23 cmH2O/ PEEP ≤ 8cmH2O*
SpO2 > 95% or adjusted limit*
Hemodynamically stable*
No extra work of breathing*

In doubts: ask physician/VP/NP
Steps 1 and 2 can be done at the same time
Don't reduce PEEP and PC/ VT at the same time
* see appendix

Nurse-driven ventilation weaning protocol

STEP 1
SpO2 > 95%;
Or
Saturation >
adjusted border?

No → Raise FiO2 with 5% until 50%: PEEP back to former setting, consult physician

→ Start the protocol again in the next shift

Yes ↓

Reduce FiO2 with 5% until 40%
then: lower PEEP with 1 cm H2O per hour
Guided by SpO2 until PEEP = 5

STEP 2
1. Patient does his own breathing efforts?
2. pH> 7.32
PCO2< 7.5kPa?

No → 1. Consider to reduce sedation (according sedation protocol)
Does patient have too much support? inspiration time(Ti) too long for a neonate? (Ti 0.4 sec.)
Consider reducing frequency rate (watch Ti!)

2. At pH < 7.32 and PCO2> 7.5:consult physician/VP/NP

Yes ↓

At PC: set Automode PS*
Reduce PC/PS above PEEP with steps of 2 cmH2O
until tidal volume (TV) = minimal 4 ml/kg or
PC/PS minimal 8 cmH2O above PEEP
In case of no automode: reduce frequency rate with 5
I:E to 1:2 (neonate Ti 0.4 sec.)
Guided by PCO2 or EtCO2 < 7.5 kPa
Steps per hour

At PRVC: set automode VS
Reduce TV per step of 1 ml/kg until
minimal 4 ml/kg or
In case of no automode: reduce frequency rate with 5
Steps per hour *

Have extubation criteria been met?

No → Don't extubate until criteria met
Consult physician/report in patient data management system

Yes ↓

Stop feeding*
Dexamethasone**
Maintain at least 1 hour

Consult physician on time of extubation

Extubation

Criteria for Extubation *
Spontaneous breathing
F_iO_2 =/< 40%
pH > 7.32
Peak pressure ≤ 15 cmH2O/ PEEP ≤ 5 cmH2O*
24 hour no raising of ventilator settings (does not apply for O_2)
No new period of fever > 38.5 degrees
No planned operation*
SpO2 > 95% of > custom border*
GCS > 8, able to swallow/cough*
Fluid balance okay*
Suction of sputum ≤ 3 x hour
Hemodynamically stable*

**Consider Dexamethasone In case of Down syndrome/history of difficult intubation: 6 hour and 1 hour before extubation

FIGURE 1 Nurse driven weaning protocol

Legend

Figure 1

* **<u>Start weaning:</u>**
- At PC: peak pressure ≤ 23 cmH_2O/ PEEP ≤ $8cmH_2O$ (=$15cmH_2O$ above PEEP 8)
- At PRVC: peak pressure is not higher than 23 cmH_2O with a set PEEP of 8 cmH_2O.
- SpO_2 ≥ 95% or in neonates: ≥ 92% or adjusted limit:
o Cyanotic heart defect (> 75%)
o Prematurely born with chronic lung disease (CLD) at FiO_2 ≤ 40% (88-96%)
- Hemodynamically stable without or with a low dose inotropics:
(dopamine ≤ 5mcg/kg/min.; dobutamine ≤ 5mcg/kg/min.; milrinone ≤ 0.5mcg/kg/min.)
- No extra work of breathing: frequency < maximum frequency per age

<u>* Extubation criteria</u>
- at PC: peak pressure ≤ $15cmH_2O$/ PEEP ≤ $5cmH_2O$ (=10 cmH_2O above PEEP 5)
- at PRVC: peak pressure is not higher than 15 cmH_2O with a set PEEP of 5 cmH_2O.
- No planned operation within 12 h with need of ventilation or high sedation level.
- SpO2 ≥ 95% or in neonates ≥ 92% or adjusted limit:
o Cyanotic heart defect (> 75%)
o Prematurely born with chronic lung disease (CLD) at FiO2 ≤ 40% (88-96%)
- GCS > 8 with no or low dose sedation and capable to swallow and cough
- Good fluid balance and no clinical signs of edema
- Hemodynamically stable without or with low dose inotropics
- In case of not severely ill neonates: strive for a short inspiration time (0,4 sec.) For own breathing drive.
- **Automode:**
In neonates: Inspiration cycle off (ICO) 5-10% and Trigger time out (TTO) 3-5 sec.
In older children: ICO 30% and TTO 5-7 sec.
- Stop feeding: 2 h before extubation at duodenal feeding and 4 h at gastric feeding. In case of no feeding, maintain low ventilation settings for at least 1 h.
- **Consult physician or VP or NP in case of doubt!**

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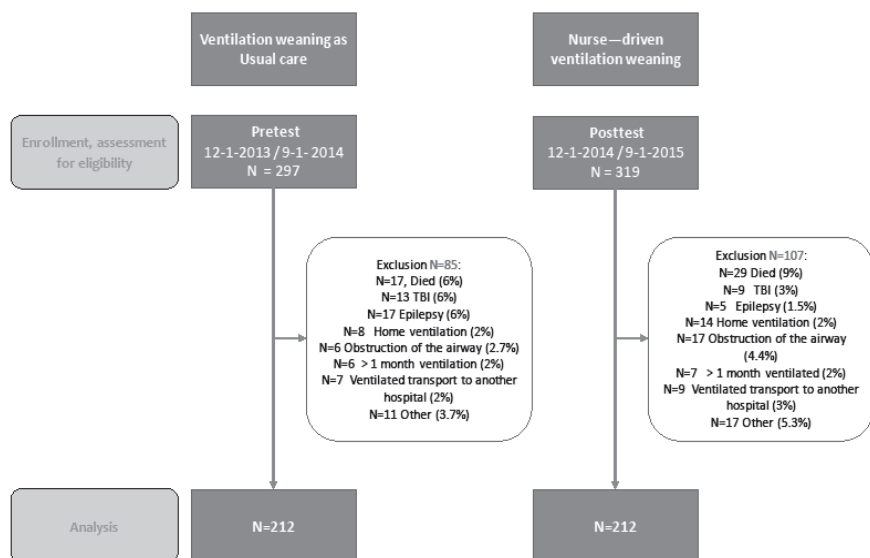
FIGURE 2 Inclusion flowcharts

TABLE 1   Potential factors influencing implementation of a weaning protocol

Level	Barriers	Facilitators	Implementation strategy
Organizational level	- A large unit in which many people have to be educated. - Policy is that patients mainly are extubated following ward rounds in the morning/ early afternoon. Some patients will not be extubated during the night because more controlled situation with more physicians present is needed.	- Availability of ventilation practitioners who can have a stimulating role. - Good nursing leadership - Interdisciplinary collaboration and effective communication.	- Education to nurses. (45 min. sessions) - Bed-side training of nurses. - Medical staff meeting.
Professional level	- Nurses are not always familiar with the medical policy, the last X-ray or the medical intention to reduce ventilator settings. - Resistance of doctors with nurses' autonomy or nurses resistance with changes. - Nurses are concerned they don't get enough support from physicians.	- If physicians do not want to extubate during the night, the nurses will stop feeding anyway, according to the protocol. Extubation will then take place earlier than rounds. - Nurses wishing to have more influence on weaning.	- Medical staff meeting. - Ventilation practitioners supporting the nurses and providing bed-side training.
Protocol- intervention level	- Interpreting the algorithm takes time and the lay-out of the protocol may be not attractive to use. - The moment when to apply the protocol is not clear and patient categories are not well defined.	- Use of the PDMS. - Nurses eager to be taught about ventilation and the algorithm.	- Protocol developed by a physician and 5 ventilation practitioners - Educational sessions - Reminders: pocket manual, checklist in PDMS, laminated protocols on the ward - Bedside training/ support by the ventilation practitioners

Abbreviations: PDMS – patient data management system; min - minutes

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TABLE 2   Demographic characteristics

Characteristics	Pretest (N= 212)	Posttest (N=212)	p-value
Gender, n (%)	M = 121 (57.1%) F = 91 (42.9%)	M = 122 (57.5%) F = 90 (42.5%)	0.90
Age in months *	3 (0-20)	3 (0-32)	0.533
Age groups, n (%) Neonates (0-28 days) >28 days- 1 year 1-3 year 3-12 year >12 year	71 (33.5) 78 (36.8%) 23 (11%) 30 (14%) 10 (4.7%)	66 (31.1%) 79 (37.3%) 18 (8.5%) 36 (17%) 13 (6.1%)	0.610
Reason for admission			0.752
Postoperative - General - Cardiac	71 (33.4%) 53 (25.0%)	53 (25.0%) 70 (33.0%)	
Respiratory failure	54 (25.4%)	51 (24.0%)	
Congenital abnormalities	11 (5.2%)	12 (5.7%)	
Cardiac	7 (3.3%)	4 (1.9%)	
Neurological	1 (0.5 %)	3 (1.4%)	
Sepsis/infection	5 (2.4%)	11 (5.2%)	
Other	10 (4.7%)	8 (3.8%)	
Severity of illness (PRISM III)*	23 (19-30.5)	22.5 (18-28)	0.190

PRISM – Pediatric Risk of Mortality score; * median - IQR- interquartile range

TABLE 3 Primary outcome and subgroup analyses for DOV and LOS

LOS and DOV	Pretest (n=212)	Posttest (n= 212)	p-value
DOV (hours)*	42.5 (14.3-121.3)	44.5 (12.3-107.0)	0.589
Subgroup 'DOV ≤ 48 hours.'	n=110	n=113	
- DOV (hours)*	15.5 (5.0-24.0)	15.0 (6.0-25.0)	0.796
- LOS (days)*	3.0 (1.0-8.0)	3.0 (1.0-5.0)	0.224
Subgroup 'DOV > 48 hours.'	n=102	n=99	
- DOV (days)*	5.0 (2.8-8.0)	4.0 (3.0-7.0)	0.428
- LOS (days)*	12.0 (7.0-27.3)	10.0 (7.0-19.0)	0.455
DOV and LOS for the largest admission groups			
Respiratory failure	n=54	n=51	
- DOV (days)*	4.0 days (2.0-7.0)	3 days (2.0-6.0)	0.210
- LOS PICU (days)*	8.0 days (5.0-13.0)	8 days (4.5-10.5)	0.352
Post-surgical cardiac	n=53	n=70	
- DOV (hours)*	17.5 (4.75-65.3)	20.0 (7.0-72.0)	0.615
- LOS PICU (days)*	6.0 (1.75-13.3)	5.0 (1.5-14.0)	0.224
Post-surgical	n=71	n=53	
- DOV (hours)*	21.5 (11.8-43.5)	21.0 (11.0-40.5)	0.600
- LOS PICU (days)*	4.0 (2.0-11.3)	3.0 days (1.8-6.0)	0.673
Footnote, only for posttest	Support n=118 & Control n=94	Support n=146 & Control n=66	
DOV in hours* for patients on a support mode before extubation vs. patients on a controlled mode before extubation	48.5 (19-143.50) vs 33.50 (8.5-90.50); p=0.202	48.5 (17-111) vs 22 (8.0-88.0); p=0.522	
LOS in days* for patients on a support mode vs. controlled mode	7 (3-14) vs 6 (3-14) p=0.547	6 (2.75-11) vs 5 (2-14.25) p= 0.132	
Reintubation need	Controlled mode: n=5 Support mode: n=6	Controlled mode: n=5 Support mode: n=10	
Non-invasive support need	Controlled mode: n=3 Support mode: n=4	Controlled mode: n= 1 Support mode: n= 4	

*median (IQR), LOS-length of stay; DOV-duration of ventilation; PICU-pediatric intensive care unit

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SUPPLEMENTAL FILE 1: THE IMPLEMENTATION PROCEDURE

The implementation was based on the seven-step Implementation Model of Change of Grol et al. (1) First, we identified the problem and defined the aim of change. In the next five steps, researcher (A.D.) and implementation expert (E.I.) identified potential barriers and facilitators by asking three experienced paediatric intensive care physicians and ten nurses with more than five years of experience about their expectations of a nurse-driven weaning protocol on three levels: organization, professionals and the intervention itself. (see table 1.) Furthermore, implementation strategies were developed taking into account these barriers and facilitators. Thereafter, we focused on executing and evaluating the implementation plan. (2,3)

Implementation activities included 45-min nurse education sessions explaining the protocol and its purpose. Before the new protocol was actually implemented, we trained 15 groups of 5-10 nurses (75% of the whole staff); those who could not attend the group sessions were trained individually after implementation of the protocol, for 45 minutes. Medical staff was informed during a staff meeting and by emails. We added the weaning protocol to the ICU staff's pocket manual that contains all PICU protocols. Several laminated versions of the protocol were placed at each ICU unit. Furthermore, the five nurses who had been trained as ventilation practitioners disseminated the importance of the weaning protocol. They recruited the patients, supported the nurses with bedside teaching and checked if nurses followed the protocol well. We further integrated the protocol in daily practice by means of red flags (reminders) raised in the patient data management system every shift and reading: "start weaning" and "ready for extubation" (supplemental file 2).

Grol and Grimshaw found that education alone resulted in mixed effects when used in healthcare workers. (4) Mixed effects were also found for several commonly used strategies (such as feedback on performance), whereas supportive strategies such as reminders, decision support, use of ICT, and rewards were mostly effective. Furthermore, combined strategies were identified as more effective than were single strategies. (4,5) Nurses are not a uniform target group, as van Achterberg states, but they are professionals with various educational levels, specializations, patient populations to be served, and work settings. All these variations are potentially relevant to implementation. Numerous contextual factors influence successful implementation of evidence into practice. Factors identified in studies of implementation of evidence in nursing include nursing culture and leadership, hospital size, staffing support,

organizational innovativeness, administration responsiveness, access to resources, organizational climate, provision of education, access to research findings, availability of knowledge and skills within organizations, integration of recommendations into organizational structures and processes, inter-organizational collaboration, money, workload, resistance to change, and time. Multiple factors can cause noncompliance, and indicates the need for selecting multiple strategies for improving compliance. For this research we identified potential influencing factors, e.g. barriers and facilitators on our ward to improve adherence to our new protocol. (table 2). We focused on extrinsic motivation (work setting, barriers, a few peer reviews) and intrinsic motivation (competence, attitude, training, feedback, consultation and reminding). After we knew that most nurses were capable and willing to use the protocol, we started the implementation. (5)

1.   Grol R. WM, Eccles M. Improving Patient Care; the implementation of change in clinical practice; 2nd Revised version. 2013.
2.   Grol R, Cluzeau FA, Burgers JS. Clinical practice guidelines: towards better quality guidelines and increased international collaboration. Br J Cancer. 2003;89 Suppl 1:S4-8.
3.   Jordan J, Rose L, Dainty KN, Noyes J, Blackwood B. Factors that impact on the use of mechanical ventilation weaning protocols in critically ill adults and children: a qualitative evidence-synthesis. Cochrane Database Syst Rev. 2016;10:CD011812.
4.   Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003;362(9391):1225-30.
5.   van Achterberg T, Schoonhoven L, Grol R. Nursing implementation science: how evidence-based nursing requires evidence-based implementation. Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing. 2008;40(4):302-10.

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SUPPLEMENTAL FILE 2: REMINDER ITEMS IN PATIENT DATA MANAGEMENT SYSTEM WITH RESPECT TO WEANING AND EXTUBATION CRITERIA

Red flag every 8 hours, in each shift.

<u>Start weaning:</u>

No fever > 38.5

Hemodynamically stable without high dosage of inotropics

Low-dose sedation (midazolam ≤200 mcg and morphine ≤10mcg)

pH ≥ 7.32

SpO2 ≥ 95% or ≥ 75% in case of cyanotic heart defect or ≥ 88% in case of premature birth

No increased breathing efforts; no use of accessory muscles, no use of nostrils, breathing frequency ≤ maximum limit for the age

Red flag in PDMS every 8 hours

<u>Extubation criteria</u>

- Spontaneous breathing efforts.
- $F_iO_2 \leq 0.4$.
- pH ≥ 7.32
- Peak pressure ≤ 15 cm H_2O. Positive End Expiratory Pressure (PEEP) ≤ 5 cm H_2O.
- During past 24 h no raise in ventilation settings.
- No planned surgery in which sedation is needed in the next 12 h
- SpO_2 saturation ≥ 95% before extubation or ≥ SpO2 saturation ≥ 75% dependent on cyanotic heart defect or chronic lung disease in prematurely born neonates
- Glasgow coma scale > 8, capable of swallowing or cough
- Stable fluid balance
- Mucus production normal (≤ 3 x suctioning per hour)
- Hemodynamically stable

SUPPLEMENTAL FILE 3: SECONDARY OUTCOMES

Characteristics	Pretest n=212	Posttest n=212	p-value
Length of stay in days*	7.0 (3.0-14.0)	5.5 (2.0-11.0)	0.432
Compliance by use of support mode	n=118 (55.7%)	n=146 (69.9%)	0.005
Reintubation rate	n=11 (5%)	n=15 (7%)	0.418
Non-invasive ventilation after extubation	n=7 (3.3%)	n=5 (2.4%)	0.771
Extubation rate during day/evening/night			0.097
0-8 a.m.	n=20 (9.4%)	n=36 (16.9%)	
Reintubation rate	0	0	
Non-invasive support after extubation	1	0	
8-12 a.m.	n=68 (32.1%)	n=56 (26.4%)	
Reintubation rate	2	2	
Non-invasive support after extubation	4	2	
12-18 p.m.	n=86 (40.6%)	n=78 (36.9%)	
Reintubation rate	7	10	
Non-invasive support after extubation	1	3	
18-24 p.m.	n=38 (17.9%)	n=42 (19.8%)	
Reintubation rate	2	3	
Non-invasive support after extubation	1	0	

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SUPPLEMENTAL FILE 4: REASONS FOR DELAY OF EXTUBATION > 2 HOURS FROM
EXTUBATION READINESS

Reason	n = 141
Low ventilation setting, but not triggering	39 (27.7%)
Other (e.g. no clear reason found)	35 (24.8%)
Too much sputum according to physician (but less than 3 times an hour)	22 (15.6%)
Need for a low dose nitric oxide (pulmonary hypertension) while set to sildenafil	9 (6.4%)
Arrhythmias	7 (5.0%)
Waiting for ward round	5 (3.5%)
Need for additional support, e.g. blood transfusion, MRI planned after surgery, need for dexamethasone	6 (4.3%)
Too much fluid overload according the physician	4 (2.8%)
Fever	3 (2.1%)
The physicians doubted if the child was ready for extubation	2 (1.4%)
Neutropenia	2 (1.4%)
Muscular disease	2 (1.4%)
Sepsis	2 (1.4%)
Low venous saturation	1 (0.7%)
High lactate	1 (0.7%)
Busy on the ward	1 (0.7%)

MRI, magnetic resonance imaging

SUPPLEMENTAL FILE 5: SEDATION AND PARAMETERS BEFORE EXTUBATION

	Pretest n= 212	Posttest n= 212	p value
Sedation before extubation			
Morphine			0.447
Number of patients	83 (39%)	98 (46%)	
Continuous infusion *	12 mcg/kg/hour (10-20)	10 mcg/kg/hour (6-17)	
Midazolam*			0.541
Number of patients	90 (42%)	86 (40 %)	
Continuous infusion *	100 mcg/kg/hour (57-151)	100 mcg/kg/hour (50-150)	
COMFORT behavior scale score *	12 (11-13)	12 (11-13)	0.128
Parameters before extubation			
Clinical signs of edema *	16 (8%)	17 (8%)	0.856
PEEP *	5 cmH$_2$O (5-5)	5 cmH$_2$O (5-5)	0.218
FiO$_2$ *	25% (21%-30%)	25% (21%-30%)	0.635
PO$_2$ *	74 Torr (61-103) [9.8 (8.1-13.7) kPa]	78 Torr (59-93) [10.4 (7.8-12.4) kPa]	0.358
CO$_2$ *	42 Torr (38-48) [5.6 (5.0-6.35) kPa]	41 Torr (37-46) [5.5 (4.9-6.1) kPa]	0.215
pH *	7.40 (7.35-7.44)	7.41 (7.37-7.45)	0.441
Bicarbonate *	25 (22.0-28.8) mEql/L	25 (22.8-28.2) mEq/L	0.622

*Median (IQR); PEEP, Positive end-expiratory pressure.

chapter 7

DOES A NURSE-LED WEANING PROTOCOL WITH A SPONTANEOUS BREATHING TRIAL IN CRITICALLY ILL CHILDREN LEAD TO A SHORTER DURATION OF VENTILATION? A MULTI-CENTRE STUDY

Anita Duyndam, Marjorie de Neef, Robert Jan Houmes, Joke Smit, Rozalinde Klein-Blommert, Monica van Gestel, Roy Pfeil, Marloes IJland, Joost van Rosmalen, Job van Woensel, Dick Tibboel, Monique van Dijk, Erwin Ista

ABSTRACT

Background: Paediatric studies comparing protocolled weaning and usual care weaning provide little information on reducing duration of ventilation (DOV).

Objective: To determine the effect on DOV of a nurse-led weaning protocol in mechanically ventilated children aged 0-18 years.

Methods: In a multi-centre pre-post study, usual care weaning was compared to nurse-led weaning including a spontaneous breathing trial. Included were children aged 0-18 years with an expected DOV of at least 48 hours. Primary outcome was DOV. Secondary outcomes were length of stay, reintubation rate and nurses' protocol compliance. The three participating PICUs had both medical, surgical and cardiac admissions. Multivariate analysis was performed to analyse the effect of study site, sex, age, admission indication and Pediatric Risk of Mortality score (PRISM III) on DOV. Univariate analysis was performed on pooled data, comparing DOV and PICU-LOS between both weaning approaches.

Results: One hundred and ninety children (median age 1.7 months [IQR 0.5-7.8]) received usual care weaning and 157 (median age 2.0 months [IQR 0.0-10.8]; p=0.14) received nurse-led weaning. Multivariate analysis showed no significant difference in DOV between pretest and posttest periods (p=0.79). Estimated difference in DOV was -0.02 [IQR -0.14 - 0.11] for nurse-led weaning. Study site, sex, age, admission indication and PRISM III score were not significantly associated with a reduction of DOV. Univariate analysis showed a median DOV of 116.0 hours [IQR 81.8-169.0] for usual care and 122.0 hours (IQR 85.0-163.5] for protocolled weaning. Median length of stay did not significantly differ between usual care (8.1 days [IQR 5.7-14.1]) and protocolled weaning (9.9 days [IQR 6.6-15.0]);p=0.43. Reintubation rate was not significantly different between usual care and protocolled weaning (5.7% vs. 8.2%;p=0.602). Rate of compliance was 77.7%.

Conclusion: In this before-after study in three PICUs, a nurse-led weaning protocol in mechanical ventilated children did not lead to a shorter duration of ventilation.

INTRODUCTION

Critically ill children receive invasive mechanical ventilation (MV) to bridge a period of critical illness or to recover from surgery. Deciding when to wean a child off MV requires balancing the potential benefits of early extubation, such as preventing ventilator-induced lung injury or ventilator-associated pneumonia (1-5), or preventing indirect complications related to prolonged sedation and delirium (6-8) against the potential harms of failed extubation with an increased risk of morbidity and mortality. (9-11) The application of a weaning protocol with clear criteria for extubation could help determine the appropriate moment for extubation. Such a weaning protocol could be led by physicians, respiratory therapists, nurses or by a software-driven closed-loop system with an automatic oxygen or peak pressure cut off system.

Until the publication of Blackwood et al. in 2021, studies on the effects of protocolled weaning compared to usual care on the duration of ventilation (DOV) in PICU patients have shown little effect of protocolled weaning. (12) In an earlier systematic review of Blackwood et al. (13), only one of the three RCTs found a reduced DOV with protocolled weaning. This was a study of Foronda et al., in which a spontaneous breathing trial (SBT) was performed on patients after they fulfilled predetermined criteria. The SBT was performed every morning until one of specifically trained medical fellows extubated the patient. These fellows were not involved in the decision to extubate. The question is whether involvement of the whole team would have resulted in a reduced DOV as well. (14) Ferreirea et al. evaluated the usefulness of a SBT for predicting extubation success in children after cardiac surgery compared with weaning based on clinical judgment. A greater extubation success and shorter PICU length of stay were found in the SBT-arm, but not a shorter DOV. (15) Curley et al. found no difference in DOV in a multicentre cluster RCT comparing a sedation weaning protocol and daily extubation readiness test with usual care. (16) However, in a recent randomised cluster trial in 18 PICUs in the United Kingdom, a multi-professional weaning protocol resulted in a significantly shorter median DOV compared to usual care without protocols. (12) This finding had uncertain clinical relevance, however, mostly due to heterogeneity in the population and a low adherence to SBTs. At the same time, guidelines regarding paediatric ventilator liberation are gradually being developed, although still not based on much evidence. In 2020, the Paediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network issued evidence-based recommendations for best practices related to paediatric ventilator liberation. (17) One of the recommendations was comparing

the use of protocolled screening to assess eligibility for extubation readiness. Another recommendation concerned performing a SBT as part of an extubation readiness test (ERT) to objectively assess the patient's ability to independently maintain adequate minute ventilation and gas exchange without excessive respiratory effort if liberated from MV. This can be done with pressure support or continuous positive airway pressure (CPAP). (17) Another study shows evidence of fewer extubation failures when a daily SBT was performed, but no change in DOV with a respiratory therapist-led extubation readiness protocol (18). This was in contrast with another study where a respiratory therapist-led protocol was successfully introduced. This introduction was not associated with reduction of DOV or length of stay (LOS) because adherence to the protocol was not sustained over time. (19)

To date, only one paediatric study has examined the effects of nurse-led protocolled weaning in contrast to physician-led protocolled weaning. The nurse-led protocolled weaning was safe and successful, but was not associated with shorter DOV. (20) Evidence supports that PICU nurses should have a role in decision-making around weaning of ventilation. They are at the child's bedside for 24 hours per day and will note whether the child recovers or deteriorates. (21-23) In a previous study, we implemented a nurse-led weaning protocol without a SBT in a single PICU. (20) The present study was a multi-centre study with a much larger sample, and with the addition of a SBT to the current weaning protocol, as recommended by the PALISI network. (17) The aim was to determine if a nurse-led ventilation weaning protocol with a SBT could shorten the DOV of children aged 0-18 years who received MV for more than 48 hours.

METHOD

STUDY DESIGN AND SETTING

The study was a multi-centre study with a pretest-posttest design in the PICUs of three university medical centres in the Netherlands: the Erasmus MC - Sophia Children's Hospital in Rotterdam, the Emma Children's Hospital Amsterdam UMC in Amsterdam and the Radboudumc-Amalia Children's Hospital in Nijmegen and covered the time period from January 2014 to March 2020.

The total test periods differed between the three centres because of logistical issues with starting up and patient inclusion.

The pretest period was defined as a usual care period, in which weaning was guided by physicians. During the posttest period, weaning was guided by a nurse-led weaning protocol. The study schedule is presented in figure 1 and supplemental file 13. In the Radboudumc-Amalia Children's Hospital, the duration of the study was four months for two pretest periods and four months for the posttest period, because Radboudumc-Amalia Children's Hospital entered the study at a later stage. From 2015 to 2017, another weaning protocol without SBT was used in the Erasmus MC- Sophia Children's Hospital. This period was not included in the study. Data from the different PICUs for the pretest and posttest periods have been pooled.

The trial was not registered and the protocol has not been published.

PARTICIPANTS

Children between 0 months and 18 years of age admitted to one of the three participating PICUs and with an expected duration of MV of at least 48 hours were eligible for inclusion. They were included on day one or two of admission. Exclusion criteria were the following: MV > 1 month, airway obstruction and an expected difficult airway at point of intubation, traumatic brain injury, Glasgow Coma Scale < 8, impaired swallow and/or cough function, need for weight gain on the ventilator in preparation to a surgical procedure, scheduled surgery within 24 hours after extubation criteria are reached, and previous participation in the study.

VENTILATION POLICY

Each PICU applied its own ventilation policy for choice of ventilation mode in both periods. The type of ventilator used in Erasmus MC- Sophia Children's Hospital and Radboudumc-Amalia Children's Hospital was the Servo-I; at the Emma Children's Hospital Amsterdam UMC the Hamilton G5 and C6. (Supplemental file 1)

WEANING STRATEGIES

During the pretest period, nurses weaned the patients off the ventilator by physician's order; i.e., slowly reducing pressure control (PC) level, PEEP level, and frequency, and eventually starting a support mode (Pressure Support of Volume Support (PS and VS)). When low levels of support (PC or PS 10-12 cmH$_2$O above PEEP 5-7 cmH$_2$O) were reached, a physician decided when to extubate.

The nurse-led weaning protocol with an SBT applied in the posttest period consisted of three parts: 1) Checklist for start criteria; 2) Wean algorithm and 3) SBT procedure. (See Supplemental files 2, 3, and 4 for the algorithms and the explanation in text). All PICU nurses were considered competent to perform the protocol after having attended a 45-minute training session given by senior nurses.

Senior nurses guided the nurses in training for the paediatric ICU.

EXTUBATION

Once the child met the extubation criteria (Supplemental file 5), the attending nurse consulted the physician on duty as to whether extubation could take place and when.

PROTOCOL IMPLEMENTATION

An implementation plan for the nurse-led protocol was developed based on the implementation model of Grol et al. (24) It consisted of a combination of different interventions: training sessions for nurses and doctors, printed reminders on the ventilators and appointing opinion leaders. (Supplemental file 6)

OUTCOME MEASURES

The primary outcome was the duration of invasive MV (DOV), defined as the duration from start of MV to the first successful extubation. Extubation failure was defined as requirement for reintubation within 48 hours following extubation.

The secondary outcomes were ventilator free days, defined as the number of days a patient had breathed without invasive MV during a 28-day period after inclusion, LOS on the PICU, nurses' compliance with the protocol (measured by the number of patients put on a support mode before extubation), time of extubation, reintubation rate, accidental extubation rate, violation of the protocol, delay of extubation after a successful SBT and use of non-invasive MV after extubation. Nurses' compliance, violation of the protocol and other secondary outcomes are further explained in Supplemental file 7.

DATA COLLECTION

The following data were collected at the time of inclusion: patient characteristics (age, sex, Paediatric Risk of Mortality (PRISM III-12) score (25), reason for invasive ventilation. Furthermore we collected DOV, PICU-LOS, dosages of sedatives and opiates, COMFORT-B score as a measure of depth of sedation at the time of

extubation. (26) In addition, we recorded use of non-invasive support after extubation. If an accidental extubation had occurred or extubation occurred before the extubation criteria were met, the child's data were still included in the data analysis. If several ventilation episodes had occurred during one admission, only the first episode with the corresponding extubation was included in the data analysis.

SAFETY DATA

Reintubation and accidental extubation were taken to be adverse events. Furthermore, if a patient failed a SBT, the ventilator parameters were reset to prior to SBT-initiation.

SAMPLE SIZE CALCULATION

In the years 2014-2015, the median DOV of children ventilated for more than 48 hours in the PICU of Erasmus MC-Sophia Children Hospital was 4 days (IQR 3-7). To achieve a median DOV reduction of 37.5% (1.5 days) based on this median DOV, a multi-centre, pretest-posttest study would require inclusion of 64 patients per hospital per period (pretest and posttest), with a power of 80% and an alpha level set at 5%. We considered 1.5 days as clinically relevant because aftercare around extubation usually involves 24 hours before a patient is transferred to another unit. We then took this widely and set 1.5 days. To allow for inclusion of a sufficient number of patients ventilated longer than 48 hours, the planned duration of inclusion was one year per hospital because in the Erasmus MC around 500 patients are ventilated per year. Approximately 150-170 of these patients are ventilated for more than 48 hours and the other participating PICUs were smaller with fewer ventilated children during a year.

STATISTICAL ANALYSIS

Data are presented as mean (standard deviation) for normally distributed data and median (IQR) for data that were not normally distributed. Differences in patients' background characteristics between the two periods were tested with independent samples t-tests for normally distributed variables and Mann-Whitney U tests for continuous variables that were not normally distributed. For categorical variables, the chi-square test was used or the Fisher exact test in case of small numbers. A univariate analysis was performed with the data pooled for the three centres, comparing DOV, PICU-LOS and other secondary outcome measures between the pretest period and the posttest period. The natural log (ln) transformation for DOV was used as dependent variable because of the skewed distribution of DOV. Multiple linear regression was performed with ln DOV as dependent variable and period (pretest versus posttest), study site, sex, age category (1=< 1 year;

2= 1-3 years; 3= >3years) admission indication (1=respiratory failure; 2=postoperative general; 3=postoperative cardiac; 4=other) and PRISM III-12 score as independent variables. A two-sided p-value of < 0.05 was considered statistically significant. Data were analysed with IBM SPSS Statistics for Windows version 23.0.Armonk, NY: IBM Corp. Because there were few observations with missing data (around 2%), the multiple linear regressions were performed using a complete case analysis.

ETHICAL CONSIDERATIONS

The Medical Ethics Review Boards of the participating centres approved the study (MEC-2017-1138) and waived the need for informed parental consent because the weaning protocol with SBT was implemented as standard care.

RESULTS

In total 347 patients were included; 190 in the pretest period and 157 in the posttest period (figure 2). The patients' median age was not significantly different between the two periods: median 1.7 months (IQR 0.5-7.8) and 2.0 months (IQR 2.0-10.8), respectively (p=0.14). There was a significant difference in reasons for invasive mechanical ventilation per period. The pretest period included more patients with respiratory failure than the posttest period; 64.2% and 39.5% respectively. The posttest period included more post-operative cardiac patients than the pretest period; 18.5% vs 8.4% respectively (table 1). Other demographics are shown in table 1.

PRIMARY OUTCOME

Multivariate analysis showed no significant difference in DOV between both periods (p=0.79). The estimated difference in DOV was -0.02 (IQR -0.14 - 0.11) for the posttest period, which corresponds to a 2% shorter DOV with a confidence interval of 13% shorter DOV to 12% longer DOV.

In the multivariate analysis, the study site, sex, age, admission indication and PRISM score were not significantly associated with a reduction of DOV. Only reason of MV: 'postoperative cardiac patient' was a significant predictor for shorter DOV, with an estimated effect of -0.23 (95% CI -0.42 to 0.03); p=0.02 compared to admission indication 'other'. This result corresponds on average to a 21% shorter DOV with a confidence interval of 34% shorter DOV to 3% longer DOV (table 2).

Univariate analyses showed that the median DOV in the pretest period (116.0 hours [IQR 81.8-169.0]; n=190) was not significantly shorter than that in the posttest period (122.0 hours [IQR 85.0-163.5]; n=157; p=0.64).

SECONDARY OUTCOMES

Ventilator free days are presented in table 3. The median LOS did not significantly differ between the two periods: respectively 8.11 days [IQR 5.7-14.0] versus 9.9 days [IQR 6.6-15.0] (p=0.43). The median LOS did not significantly differ between patients who underwent an SBT in the posttest period (10.4 days [IQR 6.5-16.4]) versus those who did not undergo an SBT in the posttest period (9.6 days [IQR 6.6-14.1].

Compliance with the protocol in the posttest period was 77.7% (table 3).

One hundred and twenty-two of 157 children (77.7%) in the posttest-period were on a support mode or on PC with a low frequency (equal or below 10 times per minute) before extubation (versus 144 of 190 children (75.8%) in the pretest period; p=0.39. Ninety-one of the 157 (58%) children in the posttest period underwent one to three SBTs, which was successful in 45 cases (59%). Fifty percent of the children (33/ 66) who did not undergo a SBT were already on extubation conditions with pressure support 10 cmH$_2$O above PEEP 5 cmH$_2$O; the most common reasons for the other 33 children were the need of diuretics, an enlarged abdomen, and doubt about swallowing and coughing function. (supplemental file 8; table 4a and 4b).

In 102 of the 157 children who met the extubation criteria, the extubation was delayed with eight hours or more, with a median delay of 27.0 hours [IQR 17.8-53.3]. (supplemental file 9; table 5a). The most frequent reasons for protocol violations were: too much mucus (21.6%), need for additional support (15.7%), need for dexamethasone (13.7%), switch to other sedation medication (12.7%), and too much fluid overload (medical impression) (8.8%) (supplemental file 9; table 5a). Thirty-eight percent of the patients with a more than 8 hours delay of extubation had respiratory insufficiency (supplemental file 9; table 5b).

The extubation rates during day, evening and night were not significantly different between the two periods (p = 0.12) (table 3). In both periods, extubation primarily took place in the morning or afternoon. The use of non-invasive MV after extubation was

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not significantly different between the periods: 4.2% in the pretest period (n=8/190) versus 8.9% in the posttest period (n=14/157); p=0.06.

The reintubation rate was not significantly different between the two periods; 5.7% versus 8.2% (p=0.29). The rate of accidental extubations was significantly different: 3.1% in the posttest period (n=5/157) versus 0.5% in the pretest period (n=1/190; p< 0.001). None of these children needed reintubation.

OTHER PARAMETERS

In both periods, the median COMFORT-B score was 12.0 [IQR 11.0-14.0]. Midazolam and morphine were the most used sedatives in all settings, and dosages at extubation did not differ significantly between the pre- and posttest periods. Consumption of sedatives and analgesics was comparable in both periods (supplemental 10; table 6).

DISCUSSION

In this multi-centre study in the Netherlands, the DOV for critically ill children ventilated for more than 48 hours and weaned of invasive MV according a nurse-led weaning protocol, including an SBT, was not significantly shorter than the DOV in children weaned as usual. In our previous observational single-centre study, we likewise found no shorter DOV in association with a nurse-led weaning protocol. (20) This is in contrast with adults studies, in which a nurse-led weaning protocol led to a significantly shorter DOV and PICU-LOS. (27-30)

Blackwood et al. (12) found in a stepped wedge cluster RCT on protocolled weaning in children a 1.4 hours reduction of DOV to first successful extubation, which reduction was significantly more than that achieved with usual care, although with uncertain clinical significance. The intervention arm concerned physician-led weaning, while nursing staff were encouraged to take part. Engaging the multi-professional ICU team in weaning off sedation and ventilation was the main purpose in this research. Even though this inter-professional approach was associated with little difference in DOV, a more standardized approach and close attention to the patients' need is a big advantage. (23) This was also a conclusion in the multi-centre trial of Curley et al. (16) A recent Australian and New Zealand survey among senior PICU nurses on ventilator weaning and extubation practices in critically ill children found that nurses remain an

underutilized cohort in decision-making on these issues. (31) Most of the respondents favoured more shared decision-making. It was suggested that a collaborative approach and greater engagement of bedside nurses with maximizing the 1:1 nurse-to-patient ratios would allow for an evaluation of the efficacy of this collaborative approach in the paediatric population.

We propose four arguments why nurse-led weaning in the present study had limited efficacy. First, we noted many protocol violations, such as not undertaking a SBT when screening criteria were met, or refusal of physician consent for extubation while the SBT had succeeded. Protocol violations concerned half of the patients, for reasons such as too much mucus, fluid overload, not awake enough to trigger the ventilator and the need for additional support. In a recent study, the primary reason for paediatric intensivists not to extubate after a successful SBT was subjective assessment of unresolved lung pathology. (32) It appears that physicians' subjective assessment and hesitation about the decision to extubate in certain clinical situations play a large role in determining extubation readiness. Changes in guidelines or the introduction of a new protocol often require many physicians to build new experience with the practice change. (33)

We found an overall median delay of 27.0 hours [IQR 17.8-53.3] for patients whose delay was more than 8 hours. See additional file 8, table 5a for the reasons of delay. Assuming that these reasons would be absent and the protocol was strictly adhered to, and thus extubation took place after the SBT was successful, DOV in the post-test period should have been shorter. The question is if a weaning protocol ever really can be nurse-led while nurses are still required to seek medical permission for the last step, extubation. Maybe we should focus on accurately identifying patient readiness for weaning, as evidenced by no need of re-intubation in the accidental extubation group in this study, instead of focusing on shorter DOV. The five children in the posttest who were accidentally extubated had low ventilation parameters and could very likely have been extubated earlier. To answer the question of whether we might be too cautious in extubating children more attention should be paid to inter-professional communication and adherence to the protocol. In addition, we need to look for a valid and reliable extubation readiness test (17, 34)

Second, adherence to the weaning protocol depended on the skills set and availability of nursing staff and unit acuity. A survey among nurses found that a nurse-to-patient

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ratio other than 1:1 was associated with less inter-professional collaboration concerning weaning of ventilation. (21) Nurse-led weaning is reserved for well-trained and experienced PICU nurses and in times of nurses' shortages it will be less well executed. Furthermore, compliance with the protocol may also have been affected by organizational aspects. For example, in one of the participating PICUs, an anaesthetist primarily performs intubation and must be present during extubation as well. In times of pressure on the OR in the evenings and nights, extubation was postponed to the next morning.

Third, the pretest period included more patients with respiratory failure than did the posttest period; 64.2% and 39.5% respectively. The intervention may be more effective in this group, resulting in a shorter DOV. In the Blackwood trial, an exploratory subgroup analysis on the duration of MV found that the intervention favoured medical-respiratory patients, although the finding lacked statistical significance. (12)

Fourth, it may be hard to improve the standard treatment for a paediatric and heterogeneous population through the implementation of a protocol. Strategies for implementation of a protocol should take into account factors such as knowledge, attitudes of the medical and nursing teams, capacity of nurses, opinions, behaviour and resources. (35) For the process of implementation of the nurse-led protocol in the three participating PICUs, see supplemental file 11.

The rate of self-extubations in the posttest period was significantly higher than that in the pretest period, while comfort and sedation regimes did not significantly differ between these periods. The rate was very low, however, and did not lead to more reintubations.

STRENGTH AND LIMITATIONS

The strength of this study is the multi-centre design purely focusing on nurse-led weaning in children. Some limitations of the study need to be addressed. First, in two of the three participating centres, sufficient participant recruitment was not achieved in the planned period, which implied we had to extend the duration. Second, because the study periods between the centres were not of the same length, selection bias may have occurred. In addition, the patient sample may seem relatively small when looking at the entire study period. The reason is that patients from 2015 to 2017 at the PICU of the Erasmus MC-Sophia Children's Hospital were not included to avoid selection bias, because during this period this PICU used a weaning protocol without

SBT. Furthermore, the AMC PICU took into use new ventilation machines during this period. Two PICU departments in Amsterdam meanwhile merged in the AMC, after which training in the weaning protocol was needed again. Third, differences in the population characteristics may have had an impact on the results. Fourth, compliance with the weaning protocol was indirectly measured by means of the ventilator setting at the time of extubation, and not by direct observation. Direct observation might have led to a clearer picture of compliance and reasons for non-compliance. We lacked a person who could be continuously present on the three units to evaluate the study progress and compliance, to remind and encourage physicians and nurses to use the protocol in this multi-centre study.

RECOMMENDATIONS FOR FURTHER RESEARCH

Future studies should focus on an implementation plan including rigorous training on the ventilator management according to the nurse-led ventilation protocol. Preceding the implementation phase all staff should commit to the plan. For example, composing a checklist to determine whether a patient meeting the extubation criteria may indeed be extubated immediately.

Furthermore, someone should be continually present to evaluate the study progress and to encourage staff to adhere to the protocol. Another advice is to develop a valid and reliable extubation readiness test based on the current literature. (17, 36). Furthermore, it is necessary to conduct qualitative research on nurses' perceptions whether a nurse-led protocol can increase their authority and job satisfaction and whether they feel that this protocol increases the quality of ventilator care and safety for patients. It also seems important to study a patient group that has been suggested to benefit most from a weaning protocol; i.e., those with respiratory failure. (12)

CONCLUSION

In this before-after study in three PICUs in the Netherlands, a nurse-led weaning off mechanical ventilation protocol did not lead to a shorter duration of ventilation due to protocol violations and moderate adherence to the protocol. Future research should focus on implementation with commitment of the whole staff to the protocol, on a clear and evidence-based extubation readiness test, and the availability of a well-trained professional to guide the whole process.

REFERENCES

1. Morinec J, Iacaboni J, McNett M. Risk factors and interventions for ventilator-associated pneumonia in pediatric patients. J Pediatr Nurs. 2012;27(5):435-42.

2. Srinivasan R, Asselin J, Gildengorin G, Wiener-Kronish J, Flori HR. A prospective study of ventilator-associated pneumonia in children. Pediatrics. 2009;123(4):1108-15.

3. Klompas M, Branson R, Cawcutt K, Crist M, Eichenwald EC, Greene LR, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 Update. Infect Control Hosp Epidemiol. 2022;43(6):687-713.

4. Iosifidis E, Pitsava G, Roilides E. Ventilator-associated pneumonia in neonates and children: a systematic analysis of diagnostic methods and prevention. Future Microbiol. 2018;13:1431-46.

5. Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med. 2019;7(2):115-28.

6. van Dijk M, Knoester H, van Beusekom BS, Ista E. Screening pediatric delirium with an adapted version of the Sophia Observation withdrawal Symptoms scale (SOS). Intensive Care Med. 2012;38(3):531-2.

7. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest. 1998;114(2):541-8.

8. Colville G, Cream P. Post-traumatic growth in parents after a child's admission to intensive care: maybe Nietzsche was right? Intensive Care Med. 2009;35(5):919-23.

9. Gaies M, Tabbutt S, Schwartz SM, Bird GL, Alten JA, Shekerdemian LS, et al. Clinical Epidemiology of Extubation Failure in the Pediatric Cardiac ICU: A Report From the Pediatric Cardiac Critical Care Consortium. Pediatr Crit Care Med. 2015;16(9):837-45.

10. Kurachek SC, Newth CJ, Quasney MW, Rice T, Sachdeva RC, Patel NR, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Crit Care Med. 2003;31(11):2657-64.

11. Edmunds S, Weiss I, Harrison R. Extubation failure in a large pediatric ICU population. Chest. 2001;119(3):897-900.

12. Blackwood B, Tume LN, Morris KP, Clarke M, McDowell C, Hemming K, et al. Effect of a Sedation and Ventilator Liberation Protocol vs Usual Care on Duration of Invasive Mechanical Ventilation in Pediatric Intensive Care Units: A Randomized Clinical Trial. JAMA. 2021;326(5):401-10.

13. Blackwood B, Murray M, Chisakuta A, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients. Cochrane Database Syst Rev. 2013(7):CD009082.

14. Foronda FK, Troster EJ, Farias JA, Barbas CS, Ferraro AA, Faria LS, et al. The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial. Crit Care Med. 2011;39(11):2526-33.

15. Ferreira FV, Sugo EK, Aragon DC, Carmona F, Carlotti A. Spontaneous Breathing Trial for Prediction of Extubation Success in Pediatric Patients Following Congenital Heart Surgery: A Randomized Controlled Trial. Pediatr Crit Care Med. 2019;20(10):940-6.

16. Curley MA, Wypij D, Watson RS, Grant MJ, Asaro LA, Cheifetz IM, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. JAMA. 2015;313(4):379-89.

17. Abu-Sultaneh S, Iyer NP, Fernandez A, Gaies M, Gonzalez-Dambrauskas S, Hotz JC, et al. Executive Summary: International Clinical Practice Guidelines for Pediatric Ventilator Liberation, A PALISI Network Document. Am J Respir Crit Care Med. 2022.

18. Abu-Sultaneh S, Hole AJ, Tori AJ, Benneyworth BD, Lutfi R, Mastropietro CW. An Interprofessional Quality Improvement Initiative to Standardize Pediatric Extubation Readiness Assessment. Pediatr Crit Care Med. 2017;18(10):e463-e71.

19. Krawiec C, Carl D, Stetter C, Kong L, Ceneviva GD, Thomas NJ. Challenges With Implementation of a Respiratory Therapist-Driven Protocol of Spontaneous Breathing Trials in the Pediatric ICU. Respir Care. 2017;62(10):1233-40.

20. Duyndam A, Houmes RJ, van Rosmalen J, Tibboel D, van Dijk M, Ista E. Implementation of a nurse-driven ventilation weaning protocol in critically ill children: Can it improve patient outcome? Aust Crit Care. 2020;33(1):80-8.

21. Rose L, Blackwood B, Egerod I, Haugdahl HS, Hofhuis J, Isfort M, et al. Decisional responsibility for mechanical ventilation and weaning: an international survey. Crit Care. 2011;15(6):R295.

22. Tume LN, Kneyber MC, Blackwood B, Rose L. Mechanical Ventilation, Weaning Practices, and Decision Making in European PICUs. Pediatr Crit Care Med. 2017;18(4):e182-e8.

23. Elisa P, Francesca C, Marco P, Davide V, Laura Z, Fabrizio Z, et al. Ventilation Weaning and Extubation Readiness in Children in Pediatric Intensive Care Unit: A Review. Front Pediatr. 2022;10:867739.

24. Grol RWM. Implementation; effective improvement of patient care (in Dutch: Implementatie; effectieve verbetering van de patientenzorg). 4th edMaarsen; Elsevier Gezondheidszorg; 2011.

25. Pollack MM, Dean JM, Butler J, Holubkov R, Doctor A, Meert KL, et al. The ideal time interval for critical care severity-of-illness assessment. Pediatr Crit Care Med. 2013;14(5):448-53.

26. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med. 2005;6(1):58-63.

27. Roh JH, Synn A, Lim CM, Suh HJ, Hong SB, Huh JW, et al. A weaning protocol administered by critical care nurses for the weaning of patients from mechanical ventilation. J Crit Care. 2012;27(6):549-55.

28. Hirzallah FM, Alkaissi A, do Ceu Barbieri-Figueiredo M. A systematic review of nurse-led weaning protocol for mechanically ventilated adult patients. Nurs Crit Care. 2019;24(2):89-96.

29. Tonnelier JM, Prat G, Le Gal G, Gut-Gobert C, Renault A, Boles JM, et al. Impact of a nurses' protocol-directed weaning procedure on outcomes in patients undergoing mechanical ventilation for longer than 48 hours: a prospective cohort study with a matched historical control group. Crit Care. 2005;9(2):R83-9.

30. Danckers M, Grosu H, Jean R, Cruz RB, Fidellaga A, Han Q, et al. Nurse-driven, protocol-directed weaning from mechanical ventilation improves clinical outcomes and is well accepted by intensive care unit physicians. J Crit Care. 2013;28(4):433-41.

31. Schults JA, Charles K, Harnischfeger J, Erikson S, Burren J, Waak M, et al. Ventilator weaning and extubation practices in critically ill children: An Australian and New Zealand survey of practice. Aust Crit Care. 2022.

32. Marupudi NK, Steurer-Muller, M. Franzon, D. The decision to extubate: the association between clinician impressions and objective extubation readiness criteria in a pediatric intensive care unit. J Pediatr Intensive Care. 2021.

33. Gupta DM, Boland RJ, Jr., Aron DC. The physician's experience of changing clinical practice: a struggle to unlearn. Implement Sci. 2017;12(1):28.

34. Walz A, Canter MO, Betters K. The ICU Liberation Bundle and Strategies for Implementation in Pediatrics. Curr Pediatr Rep. 2020;8(3):69-78.

35. Grol R, Wensing M. What drives change? Barriers to and incentives for achieving evidence-based practice. Med J Aust. 2004;180(S6):S57-60.

36. Khemani RG, Hotz J, Morzov R, Flink RC, Kamerkar A, LaFortune M, et al. Pediatric extubation readiness tests should not use pressure support. Intensive Care Med. 2016;42(8):1214-22.

37. Pinnock H, Sheikh A. Standards for reporting implementation studies (StaRI): enhancing reporting to improve care. NPJ Prim Care Respir Med. 2017;27(1):42.

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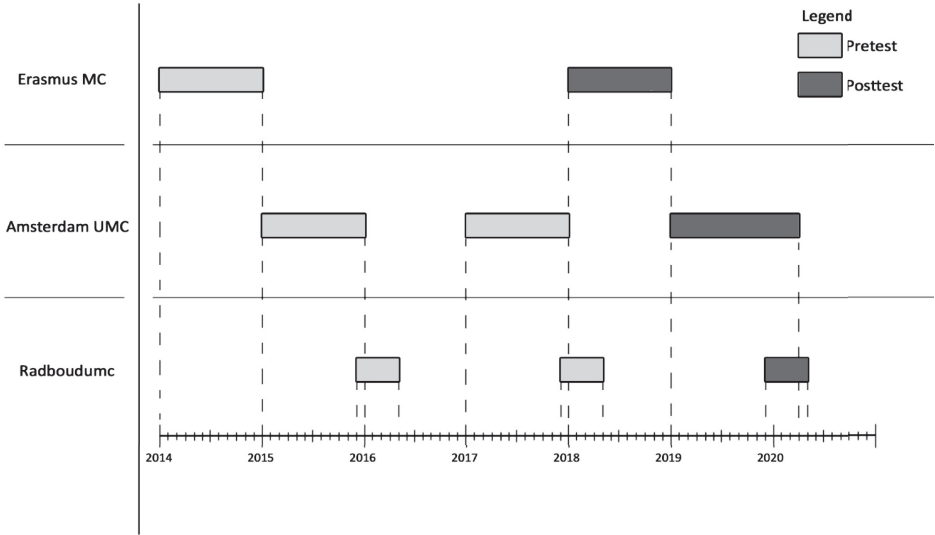
FIGURE 1 Study schedule
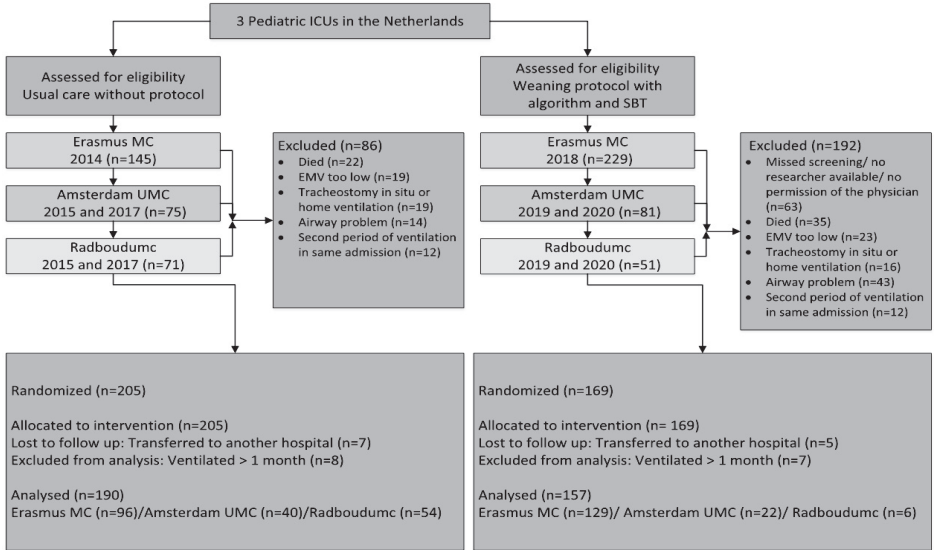
FIGURE 2 Flowchart of patient inclusion (ventilated > 48 hours) and exclusion (conform CONSORT)

TABLE 1 Demographic characteristics of the two groups (pretest, posttest)

Characteristics	Pretest n =190	Posttest n =157	p-value
Sex, n (%)	M=112 (58.9%)	M=88 (56.1%)	0.33
Age in months *	1.7 (0.5 - 7.8)	2.0 (0.0 - 10.8)	0.14
Neonates (0-28 days)	0.4 (0-0.6)	0 (0-2.0)	
>28 days-1 year	2.5 (1.6-5.3)	3.0 (2.0-4.5)	
1-3 year	17.9 (14.4-25.4)	22.0 (15.7-25.8)	
3-12 year	63.0 (68.0-101.1)	81.5 (43.0-102.5)	
>12 year	195.0 (157.0-195.0)	176 (158.6-196.3)	
Body Weight, kg*	4.4 (3.5-8.0)	4.5 (3.5-9.0)	0.41
Neonates (0-28 days)	3.5 (3.0-4.0)	3.4 (2.8-3.9)	
>28 days-1 year	5.0 (4.0-6.0)	5.5 (4.1-6.5)	
1-3 year	10.0 (9.0-12.0)	10.2 (9.8-11.2)	
3-12 year	19.0 (15.0-23.0)	17.5 (7.7-24.6)	
>12 year	59.0 (30.0-59.0)	50.0 (39.4-60.0)	
Age groups, n (%)			0.04
Neonates (0-28 days)	65 (34.2%)	62 (39.5%)	
>28 days-1 year	87 (45.8%)	58 (36.9%)	
1-3 year	20 (10.5%)	13 (8.3%)	
3-12 year	15 (7.9%)	12 (7.6%)	
>12 year	3 (1.6%)	12 (7.6%)	
Reason for admission			< 0.01
Postoperative			
General	17 (8.9%)	17 (10.8%)	
Cardiac	16 (8.4%)	29 (18.5%)	
Respiratory failure	122 (64.2%)	62 (39.5%)	
Congenital abnormalities	10 (5.3%)	13 (8.3%)	
Cardiac	5 (2.6%)	9 (5.7%)	
Neurological	2 (1.1%)	14 (8.9%)	
Sepsis/infection	8 (4.2%)	5 (3.2%)	
Other	10 (5.3%)	8 (5.1%)	
Severity of illness (PRISM III)*	19.0 (11.0 - 29.0)	26.0 (19.0 - 31.5)	0.11

PRISM – Pediatric Risk of Mortality score; * median - IQR- interquartile range

TABLE 2 Primary Outcome (Univariate and Multivariate analysis)

Primary Outcome (Univariate results)	Pretest n =190	Posttest n =157	p-value
DOV (hours)*	116.0 (81.7 - 169.0)	122.0 (85.0 - 163.5)	0.64
DOV (days)*	4.8 (3.4-7.0)	5.0 (3.5-6.8)	

Multiple Linear Regression Analysis - with ln DOV hours (n=347) (multivariate results)

Parameter	B (95% CI)	p-value*
Intercept	4.83 (4.57 - 5.10)	<0.001
Centre		0.14
Erasmus MC-Sophia Children's Hospital	0.20 (-0.23 - 0.43)	0.08
Amsterdam UMC-Emma Children's Hospital	0.17 (-0.04 - 0.39)	0.12
Radboudumc- Amalia Children's Hospital	Reference	
Type of weaning		
Nurse-led weaning (posttest)	-0.02 (-0.14 - 0.11)	0.79
Usual care (pre-test)	Reference	
Reason for admission		0.10
Respiratory failure	-0.02 (-0.17 - 0.14)	0.84
Postoperative general	-0.12 (-0.33 - 0.10)	0.29
Postoperative cardiac	-0.23 (-0.42 - 0.03)	0.02
Other	Reference	.
PRISM value	-0.00 (-0.01 - 0.00)	0.46
Gender-female	0.01 (-0.11 - 0.13)	0.85
Gender-male	Reference	
Age category		
< 1 year	0.12(-0.30 - 0.07)	0.14
1-3 years	0.05 (-0.20 - 0.30)	0.22
> 3 years	Reference	0.68

b = unstandardized regression coefficient, se = se of b, PRISM – Pediatric Risk of Mortality score
*p-values are based on Wald tests for individual coefficients and F tests for categorical variables.
DOV, duration of ventilation

TABLE 3   Secondary outcomes

	Pretest n =190	Posttest n =157	p-value
VFD (days)*	3.3 (2.3-7.0)	4.8 (3.1-8.2)	0.64
LOS (days)*	8.11 (5.7 - 14.0)	9.9 (6.6 - 15.0)	0.43
Compliance by use of a Ventilation mode: controlled or support mode/ PC mode with a low frequency (≤ 10 breaths per minute) before extubation, n (%)	Controlled mode 46 (24.2%) Support mode/ PC with low frequency 144 (75.8%)	Controlled mode 35 (22.3%) Support mode/ PC with low frequency 122 (77.7%)	0.39
Reintubation rate, n (%)	11 (5.7%)	13 (8.2%)	0.29
Accidental extubation	1 (0.5%)	5 (3.1%)	< 0.01
Non-invasive ventilation after extubation, n (%)	8 (4.2%)	14 (8.9%)	0.06
Extubation rate during day/evening/night, n (%)			0.12
0-8 a.m.	10 (5.2%)	9 (5.7%)	
8-12 a.m.	110 (57.9%)	71 (45.2%)	
12-18 p.m.	59 (31.0%)	63 (40.1%)	
18-24 p.m.	11 (5.7%)	14 (8.9%)	

*median (IQR); LOS, Length of Stay; VFD, ventilator free days;

SUPPLEMENTAL FILE 1: VENTILATOR MODES ERASMUS MC, RADBOUD UMC, AMSTERDAM UMC

Machine	Mode
Servo-i	Pressure control Pressure regulated volume control Pressure Support Volume Support
Hamilton G5 en Hamilton C6	Pressure assist control Pressure control- Synchronized Intermittent Mandatory Ventilation (SIMV) Pressure Support

Servo i (Getinge, Sweden) / Hamilton-G5 and Hamilton-C6 (Hamilton Medical, USA)

SUPPLEMENTAL FILE 2: PROTOCOL FOR DETERMINING TYPE OF WEANING

At the beginning of the shift: check patient eligibility for a wean traject
If there is a rapid clinical improvement during the shift, check again

1. Checklist

Exclusion criteria:
- Airway obstruction or expected difficult airway
- Duration of ventilation longer than 1 month
- "Growing on the ventilator" (i.e. before heart surgery)
- Glasgow Coma Scale <8, Traumatic brain injury or not capable to swallow or cough
- Scheduled surgery or MRI
- Previous participation in the study
- Already low ventilation settings

In doubt: consult physician or Nurse Practitioner/Ventilation practitioner
Don't do two steps at once
Use Et CO$_2$ if difference Et CO$_2$ ≤ 1 kPa versus PCO$_2$

Yes → Patient cannot participate

No

Weaning criteria met?
FiO$_2$ ≤ 0.6
Peak pressure ≤ 23 cm H$_2$O
PEEP ≤ 8 H$_2$O
pH ≥ 7.32
Hemodynamic stability (without or with low inotropic dose)
No high work of breathing

Yes | No → Patient cannot start the weaning proces at this moment
Check in the next shift if patient meets inclusion criteria to wean

Time: 8.00-10.00 a.m. or 4.00-5.00 pm? — No → Follow wean-algorithm **2A**

JA

Does patient meet SBT criteria:
FiO$_2$ ≤ 0.45
PCO$_2$ ≤ 7.5 kPa
Patient trigger detected?

In case of no patient triggering:
1. Consider lowering sedation (according sedation protocol)
2. Is PCO$_2$ too low or frequency too high?
3. Is inspiration time too long for a neonate? (Ti= 0.4 sec.)
4. Is triggger sensitivity set sufficiently?
Consider adjusting the points above

Yes | No → Follow wean-algorithm **2A**

Start SBT **2B**

SUPPLEMENTAL FILE 3: WEANING ALGORITHM

2A. Weaning Algorithm

FiO_2 based on saturation: lower oxygen in steps of 5%, a 5 minutes till $F_iO_2 = 0.4$

Lower PEEP level every hour with 1 cm H_2O based on saturation till PEEP ≤ 5 cm H_2O
In case of more oxygen requirement after lowering PEEP: consult physician or practitioner

PC and triggering:
Switch to Pressure Support*

PRVC and triggering:
Switch to Volume Support*

In case of no patient triggering:
1. Consider lowering sedation (according sedation protocol)
2. Is PCO_2 too low or frequency too high?
3. Is Inspiration time too long for a neonate? (Ti= 0.4 sec.)
4. Is triggger sensitivity set sufficiently? Consider changing the points above

Based on $EtCO_2$ or PCO_2 (< 7.5 kPa):
Lower PS above PEEP with steps of 2 cm H_2O per hour until tidal volume is 4 ml/kg (ideal weight)
Or till PS has a minimum of 8 cm H_2O above PEEP

Based on $EtCO_2$ of PCO_2 (< 7.5 kPa):
Lower TV with steps of 1 ml/kg until 4 ml/kg (ideal weight)

Extubation criteria
No high work of breathing
FiO_2 ≤ 0.4
pH > 7.32/ PCO_2 <7.5
SpO_2 > 95% or > 75% in case of cyanotic heart disease or > 88% in case of chronic lung disease or > 92% in case of ARDS.
EMV > 8, capable to swallow or cough
Mucus production ≤ suction 3 x per hour
Hemodynamically stable (with no or low inotropic dose)
No new fever episode> 38.5 degrees
No scheduled surgery/MRI < 24 hrs
No clinical signs of edema

Target reached?

Yes

No

In case of failing weaning, go back to basic values
Use the check list again in the next shift

Stop feeding (2 hours at duodenal feeding and 4 hours at stomach feeding) Dexamethasone needed?

Inform the physician and discuss the time of extubation

EXTUBATION

* At Pressure Support or Volume Support:
Set inspiration cycle off (ICO) at 5-10% in neonates (higher in case of leakage) and at 30% in children > 6 months
Set Trigger time out (TTO) at 3-4 sec. in neonates until a year old and 5-7 sec. in children

*AMC:
P-CMV+ or P-SIMV+ or if possible, Spontaneous mode
In case of tachypnea in Spontaneous mode and children < 1 year old : go back to P-CMV+ mode and lower frequency until patient is triggering well (don't lower less than a frequency of 15 p/m).
Set an apnea time of 5 seconds

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SUPPLEMENTAL FILE 4: SPONTANEOUS BREATHING TRIAL (SBT)

2B. Spontaneous Breathing Trial (SBT)
Start weaning in day shift between 8.00 en 10.00 a.m. and at 4.00 p.m.

Start SBT
Set ventilation mode to Pressure Support
PS 10 cmH2O
PEEP 5 cmH2O;
FiO2 keep at the same level

Testing for 2 hours
Assess per 15 minutes: Is the child able to breathe adequately by himself
If necessary, agree on a longer time frame with the physician for better assessment

Observe: heart rate/work of breathing/comfort/ blood pressure.
Take a blood gas sample after 2 hours and assess Et CO2
(Use Et CO2 only if Et CO2 corresponds to PCO2 with maximum difference of 1 kPa)

SBT is a success and extubation criteria have been met in case of:

No high work of breathing	FiO2 ≤ 0.4	pH > 7.32/ PCO2 <7.5
SpO2 > 95%, > 75%, cardiac > 88%, CLD >92%, ARDS	HF < 20% increase compared to basic value	BP ≤ 10% increase compared to basic value
EMV > 8, inable to swallow or cough	Mucus suction ≤ 3 x per hour	Hemodynamically stable
No new fever episode> 38.5 degrees	No scheduled surgery/MRI < 24 u	No clinical signs of edema

SBT succeeded?
Continue PS 10/5 and prepare on extubation.

SBT failed?
Go back to settings before start SBT and start weaning algorithm (2A) or check patient again with the checklist (1)

Stop feeding
(2 hours at duodenal feeding and 4 hours at stomach feeding)
Dexamethasone needed?

Inform the physician and discuss time of extubation

EXTUBATION

* At Pressure Support:
Set inspiration cycle off (ICO) at 5-10% in neonates (higher in case of leakage) and at 30% in children > 6 months
Set Trigger time out (TTO) at 3-4 sec. in neonates until a year old and 5-7 sec. in older children

Explanation Nurse-led weaning protocol, supplemental file 2-4

1. *Checklist start criteria:* Weaning can be started at any time of the day if the patient meets the start criteria according the checklist (supplemental file 1). PEEP is being decreased in steps of 1 cmH$_2$O every hour when FiO2 is ≤ 40%. If more oxygen is required when PEEP is being decreased, the nurse should consult a physician, nurse practitioner or ventilation practitioner (registered nurse with additional training in ventilation management) about the necessity of increasing PEEP. The saturation limit is ≥ 95% for most children, but ≥ 88% for children with chronic lung disease, ≥ 92% for children with ARDS and ≥ 75% for cardiac patients with mixed circulation. (16)

2. *Wean algorithm:* If the patient breathes spontaneously ('triggers the ventilator'), the wean algorithm can be followed (supplemental file 2). The ventilation mode is set to a support mode; for the Servo i, the 'auto-mode' mode (with pressure support (PS) for pressure control (PC) and volume support (VS) for pressure regulated volume control (PRVC); for the Hamilton the PS mode. If the patient does not trigger the ventilator, the possible reason and a solution have to be found to stimulate triggering. In the Amsterdam UMC, the mode was set to PC or PC-SIMV if the support mode led to tachypnoea, and the frequency was lowered until the patient was triggering well. PS above PEEP can be reduced to a minimum of 8 cmH$_2$O in one-hour steps of 2 cmH$_2$O above PEEP, or the tidal volume can be reduced to a minimum of 4 ml/kg.

3: *Spontaneous Breathing Trial* (Supplemental file 3). For patients meeting the start criteria, an SBT was planned between 8 and 10 a.m. and again in the afternoon around 4 and 6 p.m., with the following ventilation settings during 2 hours: PS 10 cmH2O above PEEP 5 cmH2O, and FiO2 equal to the start of the SBT. During the SBT, the patient was observed to see whether he or she could breathe calmly with the predefined range for respiratory rate, with stop criteria if the SBT fails.

SUPPLEMENTAL FILE 5: EXTUBATION CRITERIA
We have defined the following extubation criteria – all must be met – based on:

1) Respiratory items: no high work of breathing, F_iO_2 ≤ 0.4, pH > 7.32, PCO_2 < 7.5kPa, SpO_2 > 95% or > 75% in case of cyanotic heart disease or > 88% in case of chronic lung disease or > 92% in case of ARDS , mucus production ≤ suction 3 x per hour,

2) Neurological items: Glasgow coma scale > 8, capable to swallow or cough,

3) Hemodynamic items: hemodynamically stable without or with low inotropic dose, no clinical signs of edema,

4) Other items: no new fever episode> 38.5°C, no scheduled surgery/MRI < 24 hours.

If a patient meets the extubation criteria, the attending nurse consults the physician on duty as to whether the patient can be extubated and when. Feeding is stopped by protocol two hours before extubation in case of duodenal feeding and four hours in case of stomach feeding. Dexamethasone is given to all children whose intubation was problematic, and in children with Down's syndrome and a floppy airway. Dexamethasone is given in the Amsterdam UMC in all children with respiratory viruses. Dexamethasone is given as a 0.5 mg/kg bolus, 6 hours and 1 hour before the scheduled extubation.

SUPPLEMENTAL FILE 6: IMPLEMENTATION PLAN

The plan provided 'tailor-made' implementation strategies intended to overcome possible barriers such as nurses being afraid to change ventilation settings because of insufficient knowledge, negative attitude of physicians towards the protocol, no support from the management or physicians, disagreement among physicians about the protocol, not referring to the protocol in case of a heavy workload, no personal gain, etcetera. The implementation plan consisted of a combination of different interventions: training sessions for nurses and doctors, printed reminders on the ventilator, appointing opinion leaders such as the ventilation practitioners at Erasmus MC and Amsterdam UMC and a dedicated nurse in Radboudumc. Members of the nursing respiratory team propagated the importance of adhering to the weaning protocol and the SBT, and integrating these aspects in the daily rounds.

SUPPLEMENTAL FILE 7: EXPLANATION OF SECONDARY OUTCOMES

Compliance of nurses with the protocol was measured by the number of patients put on a support mode or a pressure control mode with a low frequency ($\leq$ 10 breaths per minute) before extubation, divided by the number of patients participating in the study. Compliance was considered sufficient if this outcome exceeded 80%. Applying an SBT was taken to indicate that a patient was put on PS 15 cmH2O above PEEP 5 cmH2O before extubation or earlier in the weaning process. Violation of the protocol was measured by the reasons for no extubation when indicated according the protocol or delayed extubation of 8 hours or more after passing the SBT were analyzed, as

well as the number of patients failing the SBT on respiratory and hemodynamic grounds (supplemental file 3). Extubation failure was defined as need of intubation and ventilation again within 48 hours after extubation. Successful extubation was defined as not requiring invasive respiratory support within 48 hours of extubation. Protocol violation was defined as delay of extubation after extubation criteria were met.

SUPPLEMENTAL FILE 8: TABLE 4A, NUMBER OF SBTS DONE

	Posttest n=157	SBT succeeded	LOV for SBT
SBT done n (%)	91 (58%)	54 (59%)	5.1 days [IQR 3.8-7.2] *
No SBT, only algorithm used	66 (42%)		

*= median, SBT; spontaneous breathing trial

SUPPLEMENTAL FILE 8: TABLE 4B, REASONS FOR WITHHOLDING SBT

Reasons for withholding SBT	n
Already on low ventilation para-meters at the time of planned SBT	33 (50%)
No reasons given	16 (24.3%)
Already on low ventilation parameters but need for more diuretics	4 (6.0%)
Ventilation because of an enlarged abdomen	3 (4.6%)
Inclusion in traumatic brain protocol with measurements of intracranial pressure	2 (3.0%)
Doubting swallow and cough function	2 (3.0%)
Not awake enough	1 (1.51%)
Need for a high PCO_2	1 (1.51%)
Airway problem	1 (1.51%)
Need for NO	1 (1.51%)
A high peak pressure > 20 cmH_2O	1 (1.5%)
Too much mucus during weaning	1 (1.51%)

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SUPPLEMENTAL FILE 9: TABLE 5A, REASONS FOR DELAY OF EXTUBATION IN THE POSTTEST

Reason	
Delay of extubation in hours* ** n=102	27.0 (17.8-53.3)
Reasons for delay (n)	n=102
Need for dexamethasone	14 (13.7)
Switch to other sedation medication	13 (12.7%)
Too much sputum according to physician (but less than 3 times per hour)	22 (21.6%)
Need for additional support***	16 (15.7%)
Too much fluid overload according the physician	9 (8.8%)
Low ventilation setting, but not triggering, not awake enough	8 (7.8)
Arrhythmias/ circulatory insufficiency/PPHN	6 (5.6%)
Increased abdomen (after surgery)	4 (3.9%)
No possibility for HFNC after extubation	3 (2.9%)
Waiting because it is night shift	2 (2.0%)
The physicians doubted if the child was ready for extubation	2 (2.0%)
Need for Nitric Oxide inhalation therapy	1 (1.1 %)
Muscular disease/ doubts whether patient can swallow after extubation	1 (1.1%)
Busy on the ward	1 (1.1%)

* Delay is measured for patients who had a delay of more than 8 hours in the posttest; ** Median (IQR)/ ***Need for additional support: blood transfusion, MRI planned after surgery, surgery or central line insertion scheduled/ PPHN= persistent pulmonary hypertension in the neonate/ HFNC=High flow nasal cannula

SUPPLEMENTAL FILE 9: TABLE 5B, DELAY OF EXTUBATION PER ADMISSION INDICATION

Delay > 8 hours for admission indication	n
Respiratory Insufficiency	39 (38.2%)
Cardiac	7 (6.9%)
Neurologic	10 (9.8%)
Post surgery	10 (9.8%)
Cardiac surgery	18 (17.6%)
Congenital anomaly	8 (7.8%)
Infection/ sepsis	4 (3.9%)
Other	6 (5.9%)
Total	102 (100%)

SUPPLEMENTAL FILE 10: TABLE 6, ANALGOSEDATIVES CONSUMPTION AND COMFORT
BEHAVIOR SCALE SCORE BEFORE EXTUBATION

	Pretest n =190	Posttest n =157	p value
Sedation before extubation n=	111 (58.4%)	86 (54.8%)	0.50
Morphine mcg/kg/hr Continuous infusion *	n=47 (24.7%) 6.5 (5.0-10.0)	n=47 (29.9%) 5.0 (5.0-10.0)	0.15
Midazolam* mcg/kg/hr Continuous infusion *	n=68 (35.7%) 100.0 (60.0-190.0)	n =58 (36.9%) 68.0 (50.0-120.0)	0.35
Esketamine* Mg/kg/hr	n=7 (3.7%) 0.5 (0.5-1.1)	n=11 (7%) 0.2 (0.1-0.4)	0.44
Clonidine* Mcg/kg/hr	n=17 (8.9%) 1.0 (0.9-1.5)	n=9 (5.7%) 0.4 (0.15-0.9)	0.18
Dexmedetomidine*	n=7 (3.7%) 1.0 (0.2-3.0)	n=2 (1.2%) 1.15	0.34
COMFORT behavior scale score * before extubation	12.0 (11.0-14.0)	12.0 (11.0-14.0)	0.07

*median (IQR)

SUPPLEMENTAL FILE 11: THE PROCESS OF IMPLEMENTATION OF THE NURSE-LED
WEANING PROTOCOL IN THE DIFFERENT HOSPITALS

In the Erasmus MC-Sophia Children's Hospital, compliance with the weaning protocol
increased significantly over the years. The researcher (AD) works in this hospital and
could support the study on the floor. In addition, a ventilation practitioner (JS) and the
nurses' respiratory team paid much attention to compliance with the protocol. Although
the SBT succeeded many times, patients were not always extubated according to
the protocol. Nurses liked to have more autonomy but sometimes needed a push to
adhere to the protocol.

In the Amsterdam UMC-Emma Children's Hospital, the study was already initiated in
2018, but inclusions failed. Despite repeated training sessions by the local researcher
(MN) and a ventilation practitioner, inclusion remained difficult.

In 2019, the PICUs of two university hospitals in Amsterdam were merged. The physicians of one of these PICUs did not appreciate the weaning algorithm. The algorithm was modified, after which the study was continued. The nursing team received retraining in clinical classes and were supported by the ventilation practitioners (RK and MG). Inclusion went better when ventilation practitioners started checking for inclusion every day, and decision-making about inclusion was discussed with the physicians.

Nurses were given the prospect that this research could lead to more nursing autonomy in the weaning of mechanical ventilation, and physicians supported the idea that a good algorithm would provide more autonomy for the nurses. For the nurses, working with the protocol was sometimes difficult, despite the laminated versions of the protocol present in all patient rooms. Especially data collection for the study was difficult. But the nurses liked it, though, to wean the patients independently.

In the winter months, progress was less because for some children with bronchiolitis the machine settings had to set back to settings before the SBT. Then the algorithm was adjusted, on further tapering the frequency before an SBT was done.

In Radboudumc- Amalia Children's Hospital, the nurse (RP) who was responsible for the study aimed to train 80% of the nurses' team in working with the nurse-led protocol. Since patients could not be included for some time, repeated training was given several times in the different shifts. The physicians were trained on the job in the same way. To raise awareness of the protocol and to encourage its implementation, the nurse attempted to achieve behavioural changes. The team was not really compliant because several other studies were running at the time that needed attention. Furthermore, nurses were enthusiastic, but also had doubts about the phase-out schedules and were sometimes concerned that the steps were too large.

A laminated protocol/flow chart was placed in the work drawer in each room. A physician (MIJ) helped with data collection and supported the dedicated nurse.

The researcher kept in contact with the sites about the progress.

SUPPLEMENTAL FILE 12: STARI CHECKLIST

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standardsrefers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	1	Title page	Identification as an implementation study, and description of the methodology in the title and/or keywords		
Abstract	2	abstract	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	3	1	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	4	2	The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).	2	The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects).
Aims and objectives	5	2	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	6	3	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	7	4-5 + supplements	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		

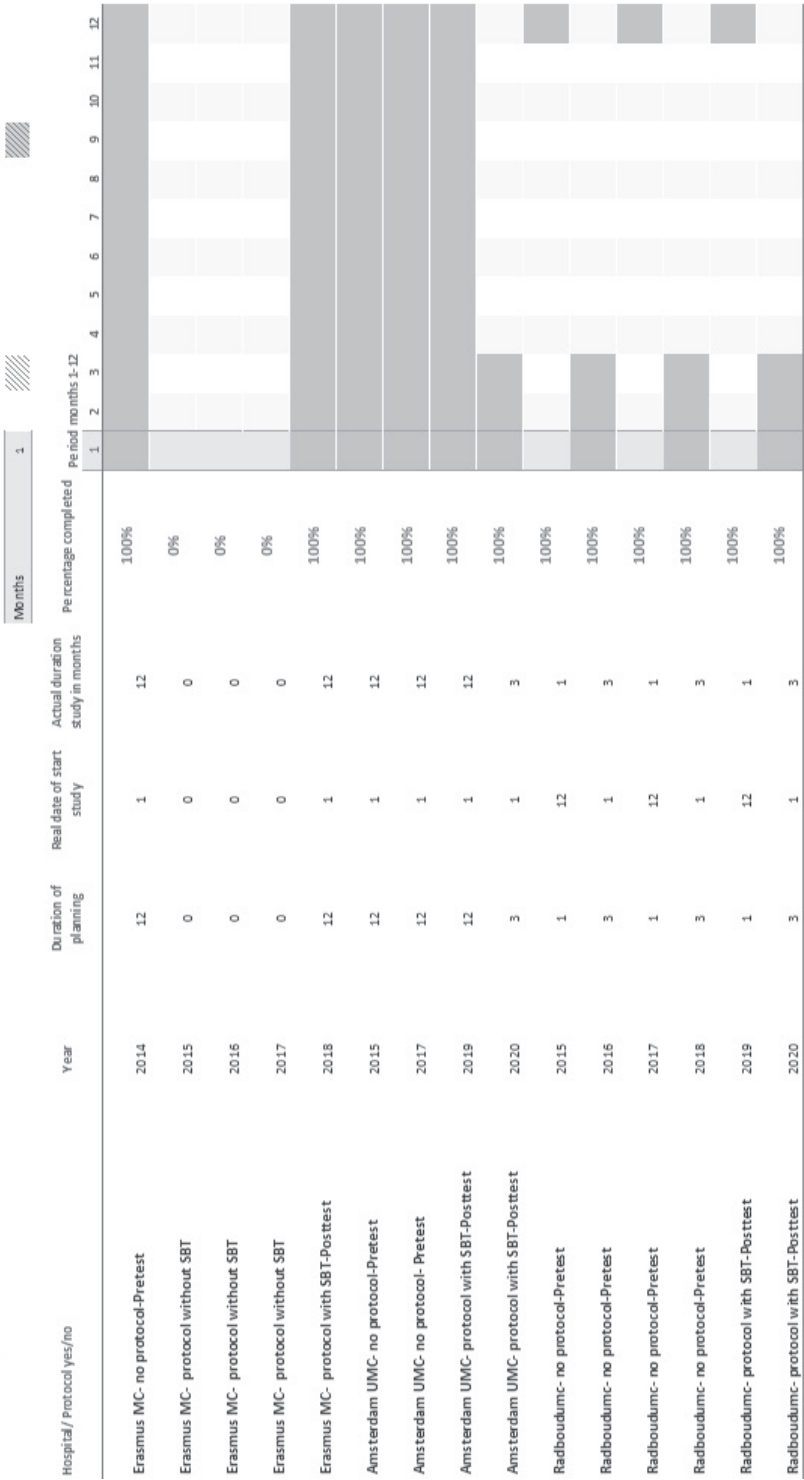| Item	No.	Page	Implementation description	Evaluation description
Targeted 'sites'	8	3-4	The characteristics of the targeted 'site(s)' (e.g locations/personnel/resources etc.) for implementation and any eligibility criteria.	The population targeted by the intervention and any eligibility criteria.
Description	9	5	A description of the implementation strategy	A description of the intervention
Sub-groups	10		Any sub-groups recruited for additional research tasks, and/or nested studies are described	
Methods: evaluation				
Outcomes	11	5-6	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets	Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	12	5 + supple-ments	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work	
Economic evaluation	13	NA	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy	Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	14	6	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)	
Analysis	15	7	Methods of analysis (with reasons for that choice)	
Sub-group analyses	16	NA	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks	

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Results

Section	No.	Page	Implementation strategy	Page	Intervention
Characteristics	17	8	Proportion recruited and characteristics of the recipient population for the implementation strategy	8	Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	18	8-10	Primary and other outcome(s) of the implementation strategy	8-10	Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	19	9-10	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	20	NA	Resource use, costs, economic outcomes and analysis for the implementation strategy	NA	Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	21	NA	Representativeness and outcomes of subgroups including those recruited to specific research tasks		
Fidelity/ adaptation	22	9-10	Fidelity to implementation strategy as planned and adaptation to suit context and preferences	9-10	Fidelity to delivering the core components of intervention (where measured)
Contextual changes	23	9-10	Contextual changes (if any) which may have affected outcomes		
Harms	24	10	All important harms or unintended effects in each group		

Discussion

Section	No.	Page	Implementation strategy	Page	Intervention
Structured discussion	25	11	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	26	12	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)		Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)

General

Section	No.	Page	Implementation strategy	Page	Intervention
Statements	27	8 + title page	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		

(37)

SUPPLEMENTAL FILE 13: STUDY SCHEDULE

Study Schedule

Hospital/ Protocol yes/no	Year	Duration of planning	Real date of start study	Actual duration study in months	Percentage completed
Erasmus MC- no protocol-Pretest	2014	12	1	12	100%
Erasmus MC- protocol without SBT	2015	0	0	0	0%
Erasmus MC- protocol without SBT	2016	0	0	0	0%
Erasmus MC- protocol without SBT	2017	0	0	0	0%
Erasmus MC- protocol with SBT-Posttest	2018	12	1	12	100%
Amsterdam UMC-no protocol-Pretest	2015	12	1	12	100%
Amsterdam UMC- no protocol- Pretest	2017	12	1	12	100%
Amsterdam UMC protocol with SBT-Posttest	2019	12	1	12	100%
Amsterdam UMC- protocol with SBT-Posttest	2020	3	1	3	100%
Radboudumc- no protocol-Pretest	2015	1	12	1	100%
Radboudumc- no protocol-Pretest	2016	3	1	3	100%
Radboudumc- no protocol-Pretest	2017	1	12	1	100%
Radboudumc- no protocol-Pretest	2018	3	1	3	100%
Radboudumc- protocol with SBT-Posttest	2019	1	12	1	100%
Radboudumc- protocol with SBT-Posttest	2020	3	1	3	100%

Months 1

Period months 1-12

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PART III

ULTRASOUND OF THE DIAPHRAGM OF
HEALTHY AND VENTILATED CHILDREN

chapter

8

REFERENCE VALUES OF DIAPHRAGMATIC DIMENSIONS IN HEALTHY CHILDREN AGED 0-8 YEARS

Anita Duyndam, Joke Smit, Leo Heunks, Jeroen Molinger, Marloes IJland, Joost van Rosmalen, Monique van Dijk, Dick Tibboel, Erwin Ista

ABSTRACT

Purpose: Diaphragmatic thickness (Tdi) and diaphragm thickening fraction (dTF) are widely used parameters in ultrasound studies of the diaphragm in mechanically ventilated children, but normal values for healthy children are scarce. We determined reference values of Tdi and dTF using ultrasound in healthy children aged 0-8 years old, and assessed their reproducibility.

Method: In a prospective, observational cohort, Tdi and dTF were measured on ultrasound images across four age groups compromising at least 30 children per group: group 1 (0-6 months); group 2 (7 months-1 year); group 3 (2-4 years); group 4 (5-8 years).

Results: Ultrasound images of 137 healthy children were included. Mean Tdi at inspiration was 2.07 (SD 0.40), 2.09 (SD 0.40), 1.69 (SD 0.30) and 1.72 (SD 0.30) mm for group 1, 2, 3 and 4 respectively. Mean Tdi at expiration was 1.64 (SD 0.30), 1.67 (SD 0.30), 1.38 (SD 0.20) and 1.42 (SD 0.20) mm for group 1, 2, 3 and 4 respectively. Mean Tdi at inspiration and mean Tdi at expiration for groups 1 and 2 were significantly greater than those for groups 3 and 4 (both $p<0.001$). Mean dTF was 25.4% (SD 10.4), 25.2% (SD 8.3), 22.8% (SD 10.9) and 21.3% (SD 7.1) for group 1, 2, 3 and 4 respectively. The intraclass correlation coefficients (ICC) representing the level of inter-rater reliability between two examiners performing the ultrasounds was 0.996 (95% CI 0.982-0.999). ICC of the inter-rater reliability between the raters in 11 paired assessments was 0.989 (95% CI 0.973-0.995).

Conclusion: Ultrasound measurements of Tdi and dTF were highly reproducible in healthy children aged 0-8 years.

INTRODUCTION

The main driver of inspiration, the diaphragm muscle, is a musculo-fibrous membrane separating the thoracic and abdominal cavities. It consists of a non-contractile central fibrous portion (centrum tendineum diaphragmatis) and a peripheral muscular section that is partitioned into the sternal, costal and lumbar muscular groups. The diaphragm has a role in both the low-intensity, perpetual cycle of breathing and in more rapid and strenuous settings, such as talking, singing, sneezing and in situations of acutely increased ventilation. (1, 2) Studies in mechanically ventilated adults have demonstrated rapid development of diaphragm weakness, or: critical illness-associated diaphragmatic weakness. (3-7) This condition reflects the inability of the diaphragm to generate normal levels of maximal force. (8-11) Diaphragmatic thickness (Tdi) and diaphragm thickening fraction (dTF) measured on ultrasound images are widely used to evaluate diaphragm function in patients with suspected diaphragm weakness (4, 11-16), including critically ill children. (16-20) For the sake of comparison, however, limited data is available about normal Tdi and dTF values in healthy children. (21-23)

In children, the chest wall musculature is still immature, with fewer type-1 muscle fibers (slow fibers for quiet breathing) than in adults. Although the proportion of type-1 muscle fibers increases from 9% at 27 weeks gestational age to 25% at term age and already reaches the adult level during the second postnatal year, a child has to develop muscle mass and greater contraction strength during childhood and puberty. (24-26) Studies in ventilated children with a median age between 3 months and 5 years old found evidence of decreases in Tdi during the course of mechanical ventilation compared to baseline values. (17, 18, 20, 27, 28) Decrease in thickness is associated with atrophy, which in turn is associated with diaphragm weakness and worse outcome in adults. (29) Smaller diaphragm thickness is also found at initiation of mechanical ventilation in sick adult patients. (3, 30) The lack of normal values in children makes it hard to establish whether even critical illness already influences changes in respiratory muscle thickness in children.

We performed a study to determine Tdi at end-inspiration, Tdi at end-expiration, and dTF with the use of ultrasound in children aged 0-8 years, and assessed the intra-rater and inter-rater reproducibility. This age group represents the largest patient group in pediatric intensive care units around the world.

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METHOD

We performed a prospective cohort study from September 1, 2020 until March 1, 2021.

STUDY POPULATION:

Healthy children aged 0-8 years old were eligible for inclusion. We created four age subgroups for analysis: 0-6 months; 7 months-1 year; 2-4 years; and 5-8 years. Participants were recruited through healthcare professionals working at the Erasmus MC-Sophia Children's Hospital as well as through the research team members' families, friends and neighbours. In addition, brochures were placed in waiting rooms and elevators in the Erasmus MC Sophia Children's hospital in which parents were invited to have their healthy children participate in this study.

Children who met any of the following criteria could not participate: neuromuscular disease, chronic lung disease, abdominal or thoracic surgery less than 3 months ago, known abnormalities of the diaphragm, and having been mechanically ventilated in the past 6 months.

Informed consent from the parents of each participant was obtained.

DIAPHRAGM MEASUREMENT

After having received thorough training from an experienced ultrasound technician (JM), two researchers (JS and AD) performed ultrasound measurements at the children's homes, supported by a written protocol. Parents were present to keep the child as calm as possible. If necessary, the child was distracted with a video on the phone, a picture book or other toy, and a pacifier.

The procedure did not start until the child lay as much as possible in a 30-degree position with head and shoulders on a pillow either on a sofa, a bed or on the lap of a parent and was breathing quietly.
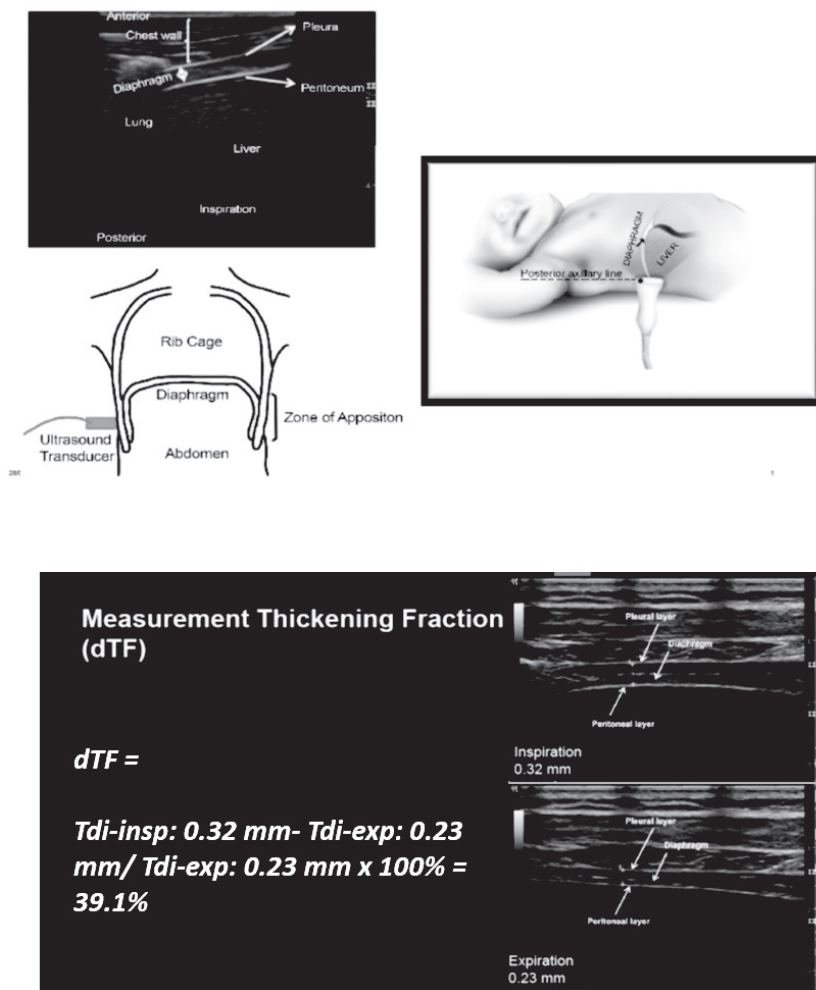
Ultrasound measurement of the diaphragm was performed with a Lumify L 12-4 linear array transducer (Philips Medical Systems B.V., Best, Netherlands) in B mode with the child in a 30-degree supine position, with the head on a pillow. The diaphragm thickness was measured on the right side, with the transducer placed perpendicular

to the ribs in the ninth or tenth intercostal space between the anterior and mid axillary lines, in the zone of apposition between lung and liver. In accordance with the adult literature, we measured only the right hemidiaphragm since the feasibility and repeatability of right hemidiaphragm measurements are superior to those of the left hemidiaphragm. Studies in adults did not show significant differences between Dtf and Tdi between the left and right hemidiaphragms. (13, 31) In the zone of apposition, the diaphragm is observed as a three-layered structure: a non-echogenic central layer bordered by two echogenic layers: the peritoneum and the diaphragmatic pleurae (Fig 1). (12, 13, 15, 32, 33)

Tdi in this position was defined as the vertical distance in millimeters between the midpoint of the diaphragmatic pleura and the midpoint of the parietal peritoneum. dTF was quantified by the percentage change in the right hemi-diaphragm thickness from end-expiration to end-inspiration during tidal breathing. dTF was calculated with the formula: end-inspiratory thickness of diaphragm (Tdi-insp) minus end-expiratory thickness of diaphragm (Tdi-exp) divided by end-expiratory thickness x 100. This index is widely used in various studies and is well applicable (Fig 1). (15, 33, 34)

Per ultrasound moment, three measurements were made when the optimum position was reached with the clearest view. The mean of the three values was used in the head analysis. For participants where it was not possible to do three measurement but only two, the mean of the two values was used and this was used in a sensivity analysis. Short axis Digital Imaging and Communications in Medicine (Dicom) videos were recorded for offline B-mode analysis, and calculations were made with dedicated software (RadiAnt DICOM viewer from Medixant).

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FIGURE1 Ultrasound in the zone of apposition and measurement dTF

Legend: photo above: the diaphragm (black) bordered by the pleura and peritoneal membrane (white); both pictures: ultrasound in the zone of apposition; photo under: calculation of the thickening fraction illustrated by one image at end-inspiration and one at end-expiration with results

OUTCOME MEASURES

Primary outcomes were Tdi at end-inspiration (Tdi-insp), Tdi at end-expiration (Tdi-exp), and dTF in healthy children up to 8 years of age, divided across four age groups: group 1 (0 - 6 months); group 2 (7 months - 1 year); group 3 (2 - 4 years); group 4 (5 - 8 years).

We calculated the inter-rater reliability in terms of 1) performing the ultrasounds and 2) in terms of analyzing the recorded images. The procedure of calculating the inter-rater reliability in performing the ultrasounds was as follows: each examiner independently made ultrasounds of 5 children who came to the hospital with their parents in the same position 5 minutes after each other on the same day. The inter-rater reliability expressed as variability between the two examiners was calculated by analyzing the thickness of the diaphragm of the recorded images of these 5 subjects performed simultaneously. AD analysed these recorded images.

The inter-rater reliability indicates the level of agreement between independent raters who assessed the images. This was calculated from measurements of Tdi at end-inspiration and at end-expiration of eleven randomly selected ultrasound images. These images were assessed at two different times by two raters independently (AD and JS), without knowing each other's results.

PARAMETERS
Each child's age, sex, height, and weight were noted, and Tdi-insp, Tdi-exp (in millimeters) and dTF (as a percentage) were measured during tidal breathing.

SAMPLE SIZE
The desired sample size was based on the available literature and the choice of sample size was not made using a formal sample size calculation. All literature about reference values of the diaphragm were described as mean values. The study of van Doorn et al. described a sample size estimation for reference values of the diaphragm in a population of 0-80 years old. They decided to enroll 10 healthy subjects for regression-based reference limits for each 10 years category. Boon et al. also chose 10 subjects per age category. Vishwanath et al. chose 14-29 subjects per age category. We chose at least the same number of subjects per age group as in these earlier studies and aimed for 30 subjects per age group (120 children in total). (21, 22, 31, 35)

DATA ANALYSIS
Data are presented as mean (standard deviation, SD) for normally distributed data and median (Interquartile range, IQR) for non-parametric data. Differences in patients' characteristics between the four age groups were tested with the one-way ANOVA test for normally distributed variables and the Kruskal-Wallis test for continuous variables that were not normally distributed.

Inter-rater reliability of the results was assessed using the intraclass correlation coefficient (ICC) for average measures with a two-way random effects model for continuous data. An ICC value below 0.5 is considered to indicate poor reliability, between 0.5 and 0.75 moderate reliability, between 0.75 and 0.9 good reliability, and any value above 0.9 excellent reliability. (36)

Correlations between body surface area, age, weight and length with Tdi and dTF were assessed using Pearson correlation coefficients (r_p) with 95% confidence interval.

ETHICAL CONSIDERATIONS
The Medical Ethics Review board at Erasmus MC Rotterdam approved the study (METC No. NL70476.078.19). The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

RESULTS

From 1 September 2020 to 1 March 2021, 137 healthy children were enrolled. In 13 of them, only two measurements instead of three could be performed because of movement artefacts. The two measurements in these 13 children are included in the sensitivity analysis. Age groups 1 and 2 included 30 subjects in each; age group 3 included 29 subjects because we lost the ultrasound image of one. Age group 4 was the largest group, with 48 inclusions. Baseline characteristics are shown in table 1.

TABLE 1   Participants' characteristics

Characteristics	Group 1 (0-6 months) n=30	Group 2 (7 months-1 year) n=30	Group 3 (2 years - 4 years) n=29	Group 4 (5 years- 8 years) n=48	p-value[a]
Sex, F/M (n)	14/16	17/13	13/16	27/21	0.769
Age in years*	0.5 (0.5)	1.0 (0.4)	3.0 (0.8)	6.4 (1.2)	< 0.001
Weight (kg)	5.9 (1.5)	10.0 (1.7)	15.4 (2.5)	23.6 (5.2)	< 0.001
Body surface area (m^2)*	0.30 (0.06)	0.45 (0.06)	0.65 (0.07)	0.89 (0.13)	< 0.001
Height (cm)*	61.1 (7.1)	76.9 (7.0)	100.3 (7.2)	123.6 (9.5)	< 0.001

[a] One-way ANOVA; * mean (SD)

PRIMARY OUTCOME

Mean Tdi-insp ranged from 2.09 (SD 0.40) to 1.69 (SD 0.30) mm; the mean Tdi-exp ranged from 1.64 (SD 0.30) to 1.38 (SD 0.20) across groups. Median dTF ranged from 25.4% (SD 10.4) in the two youngest age groups to 21.3% (SD=7,1) in the oldest age group. Tdi-insp and Tdi-exp differed significantly between groups, with higher values observed in groups 1 and 2 than in groups 3 and 4. dTF did not significantly differ between age groups. (Table 2a, Figures 2a and 2b, Figure 3).

The ICC representing the level of inter-rater reliability between the two examiners performing the ultrasounds was 0.996 (95% CI 0.982-0.999). The ICC of the inter-rater reliability between the raters in 11 paired assessments was 0.989 (95% CI 0.973-0.995).

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TABLE 2A Head analysis *Diaphragm measurements of children with the average of 3 ultrasounds*

	Age group 1 n=28	Age group 2 n=25	Age group 3 n=25	Age group 4 n=44	p-value[a]
Tdi-insp (mm)	2.07 (0.40)	2.09 (SD 0.40)	1.69 (0.30)	1.72 (0.30)	< 0.001
Tdi-exp (mm)	1.64 (0.30)	1.67 (0.30)	1.38 (0.20)	1.42 (0.20)	< 0.001
dTF (%)	25.4 (10.40)	25.2 (8.30)	22.8 (10.90)	21.3 (7.10)	0.201

TABLE 2B. Sensitivity analysis *Diaphragm measurements of all children with the average of 2 and 3 ultrasounds*

	Age group 1 n=30	Age group 2 n=28	Age group 3 n=29	Age group 4 n=48	p-value[a]
Tdi-insp (mm) *	2.07 (0.39)	2.09 (0.38)	1.73 (0.33)	1.70 (0.30)	< 0.001
Tdi-exp (mm)*	1.63 (0.33)	1.67 (0.27)	1.40 (0.23)	1.40 (0.24)	< 0.001
dTF (%)*	27.1 (12.5)	24.7 (8.60)	24.1 (10.40)	21.2 (6.80)	0.167

[a] One-way ANOVA; * mean (SD); Tdi-insp, thickness of diaphragm at inspiration; Tdi-exp, thickness of diaphragm at expiration; dTF, thickening fraction
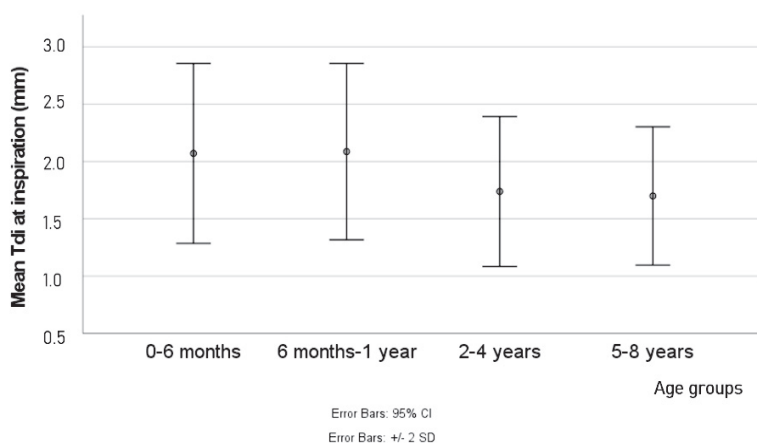
FIGURE 2A Tdi at end-inspiration for age groups

Tdi = thickness of diaphragm
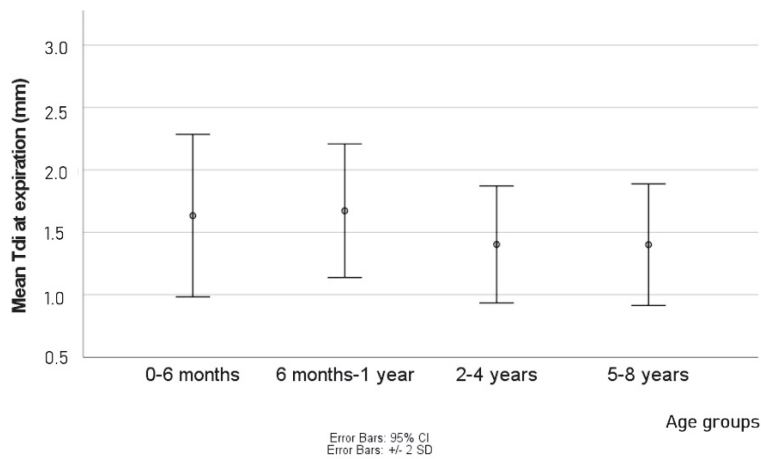
FIGURE 2B Tdi at end-expiration for age groups

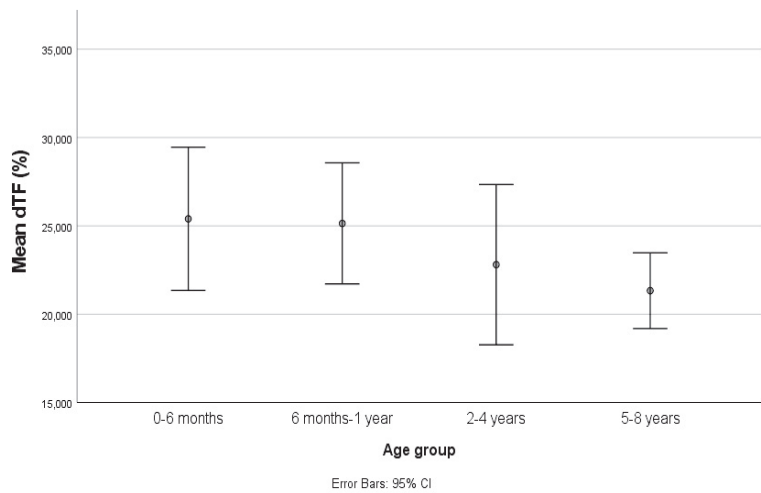Tdi = thickness of diaphragm

FIGURE 3 dTF for age groups

dTF= diaphragm thickening fraction %

Weak to moderate negative correlations between age, body surface area, weight and height on the one hand, and dTF, Tdi-insp and Tdi-exp on the other hand were demonstrated (table 3). For example, the correlation coefficient between Tdi-insp and body surface area was -0.400 (-0.532, -0.246) and the correlation coefficient between Tdi-exp and body surface area was -0.351 (-0.490, -0.193) (figure 4)

TABLE 3   Pearson correlations between age, body surface area, weight, length and Tdi and dTF

	dTF n=135	Tdi-insp n=135	Tdi-exp n=135
Age in years*	-0.180 (-0.338, -0.011)	-0.422 (-0.550, -0.271)	-0.375 (-0.511, -0.219)
Body surface area*	-0.161 (-0.321, 0.009)	-0.400 (-0.532, -0.246)	-0.351 (-0.490, -0.193)
Weight*	-0.148 (-0.309, -0.022)	-0.379 (-0.514, -0.223)	-0.336 (-0.477, -0.176)
Height *	-0.177 (-0.335, -0.008)	-0.424 (-0.552, -0.273)	-0.370 (-0.506, -0.213)

r_p= Pearson product correlation coefficient; CI – confidence interval; *r_p (95% CI)
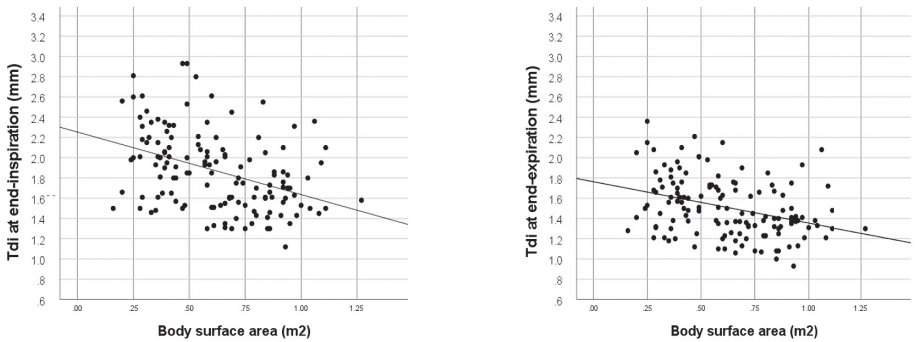
FIGURE 4 Scatter plots presenting Tdi at end-inspiration (left-hand panel) and end-expiration (right-hand panel) for all age groups

Tdi = Thickness of the diaphragm

DISCUSSION

To determine normal values of diaphragm thickness and thickening fraction in young children, we performed measurements in healthy children aged 0 to 8 years old. To our knowledge, this is the largest study in this age group collecting normal values during spontaneous breathing for thickness of the diaphragm at end-inspiration and at end-expiration in combination with thickening fraction. Establishing normal values is important, for example, to be able to judge whether critical illness induces changes in respiratory muscle thickness.

Both the Tdi at end-inspiration and at end-expiration in infants from 0-1 year old were thicker than those of the children from 2-8 years old, a finding we had not expected. Children with the average of 3 ultrasound measurements and children with the average of 2 measurements included, showed small differences. This indicates that even averaging two ultrasounds of the diaphragm results can be fairly accurate.

To relate our findings to those of other studies, it is important to know how the diaphragm muscle measurements were made. It must be taken into account that the membranes are biologically active, and that mechanical forces related to ventilation can lead to inflammation with remodeling and thickening of the tissue. (37) We measured the diaphragm thickness as the vertical distance in millimeters between the midpoint of the diaphragmatic pleura and midpoint of the peritoneal membrane, but other studies measured between the inner lines or outer lines of both membranes. Therefore, thicknesses may differ slightly from each other. (see table 4). (37, 38)

NORMAL DIAPHRAGM VALUES IN RELATION TO OTHER PUBLICATIONS IN HEALTHY CHILDREN AND ADULTS

The diaphragm thickness for children aged 2 to 8 years established in the present study compares well with that found by Vishwanath et al. in healthy children aged 8 to 10 years, while the mean dTF was smaller (Table 4). (35). Of note, however, Vishwanath and colleagues did not describe how dTF and Tdi were exactly measured concerning the pleura and peritoneal membrane.

Rehan et al. measured Tdi at end-expiration in 15 newborns (appropriate for gestational age, and one or two days old) and found greater thickness than we found in our youngest age group, which had a much higher mean age of 5 months. (Table 4). This

finding may tentatively suggest that the thickness is greatest at birth and decreases with the lengthwise growth of the diaphragm. Van Doorn et al. found the same values for Tdi at expiration in 12 children from 0-10 years old (mean age 6.2 years) as in our oldest age group. Tdi at inspiration was higher, because they had measured maximal end-inspiration. (21) Alonso-Ojembarena et al. and recently Yeung et al. found in term newborns diaphragm thickness values comparable with our values for the youngest age group. (23, 39)

El Halaby et al. measured excursion of the diaphragm and thickness of the diaphragm at end-expiration with the M mode of the ultrasound in 400 children from 0-16 years old. (40) In contrast to our finding, they found that the thickness of the diaphragm at end-expiration were much higher for all age groups with means of 3.4 mm (SD= 0.7) for the youngest group (mean age 7 months) to 5.3 mm (SD= 1.2) for the second oldest group (mean age 8.8 years) versus 1.64 mm (SD= 0.30) to 1.38 mm (SD= 0.20) respectively in our study. These differences could be explained by their measurement of the whole peritoneal and pleura membrane instead of the vertical distance between the midpoint of both membranes like we did and more importantly, their recording on a different place than the point of apposition. They placed their probe between the anterior and mid-axillary lines, in the subcostal or lower intercostal area, and directed medially, cranially and dorsally. This is better for measurement of excursion but not for the measurement of thickness of the diaphragm. (38, 41)

The values of Tdi-exp in spontaneously breathing adults, varying from 1.4 mm to 1.9 mm are comparable of those of spontaneously breathing children, varying from 1.4 mm to 1.7 mm across all age groups. Only Boon et al. find higher values in adults, but the lower limit of normal was 1.7 mm. The values of Tdi-insp in spontaneously breathing adults are higher than those in children from 2 to 8 years old, but comparable to those of children from 0-1 year old in our study and in the study of Alonso-Ojembarena et al. (table 3). (21, 23, 31, 35, 42, 43). Older children over ten years appear to have simular thickness of the diaphragm as adults as shown in two studies (21, 35).

NORMAL DIAPHRAGM VALUES (DTF) IN RELATION TO PUBLICATIONS IN VENTILATED CHILDREN

Six studies in ventilated children, with a median age between 3 months and 5 years old, found either a decrease or an increase in Tdi during the ventilation period (table 3). (17-20, 28, 44) Montoro et al. studied ventilated children between 0 and 18 years

old with a median age of 3 months, comparable with that of our youngest age group. (17) The median dTF at baseline was comparable with our finding, but was higher before extubation. The effect of the supporting ventilation mode or the breathing work during spontaneous breathing through an endotracheal tube before extubation could have played a role here. Lee et al. studied 31 ventilated children between one month and 18 years old (median age 3 years). (19) The dTF at baseline in Lee et al. was comparable with our findings, but during the course of ventilation became lower than the values we established, both in the success group and in the three patients who failed extubation. After extubation, dTF in the successfully extubated group was higher and comparable with values in our cohort of children from 2 years to 4 years old. The dTF in the ones who failed extubation was less than 17%, lower than the 24.1% we established for this age group in healthy children. Glau et al. found a linear correlation of a decreasing dTF with less spontaneous breathing via a support ventilation mode in 56 ventilated children between 0 and 18 years old (median age 17 months) (Beta coefficient 9.4, 95% CI 4.2, 14.7, p=0.001). (18) The dTF was very low at baseline and still low before extubation. Notable in that study is the use of neuromuscular blockade infusion (NMB) in one third of the patients, which may have led to this low dTF. The use of NMB in patients in the study of Montoro et al. led to a greater decrease in thickness and increased the daily atrophy rate in the ventilated patients. The dTF values established by IJland et al. at baseline and before extubation in ventilated children with a median age of 4 months were comparable with those of Glau et al. Three children in whom extubation had failed had a very low dTF under 5%. None of the studies in ventilated children had standardized the dTF before extubation for level of sedation or level of ventilation support, so it is difficult to compare all studies. Xue et al. found in 50 ventilated children between 0 and 18 years old, with a mean age of 3 years that a cut-off value for dTF greater or equal to 21% was associated with successful weaning, defined as passing a spontaneous breathing trial of pressure support 8 cm H_2O above PEEP 5 cmH_2O. This cut-off value of 21% is comparable with the normal dTF we found in healthy children in the same age group. (28) Abdel Rahman et al. established a cut-off value of dTF of 23.2% for predicting weaning failure in 106 ventilated children. They did not measure dTF per age group, but per failed weaning group or successful weaning group. (44) Thus, it seems plausible to aim for a normal physiological dTF to estimate the success of extubation. However, various factors may impact diaphragmatic dynamics and thus influence diaphragmatic measurement in ventilated children. They may experience respiratory distress or asynchrony with the ventilator. Moreover, sedation or NMB can influence the diaphragm

dynamics, and the intra-abdominal pressure in ventilated patients will be different from that in spontaneously breathing children. More research is needed assessing the diaphragm and respiratory muscle effort from the initiation of ventilation to extubation in children. (45)

We found that the diaphragm of children from newborn age up to the age of one year was thicker than that of older children and comparable with the diaphragm thickness in adults, which suggests that the diaphragm has already largely been constructed at birth – and becomes notably longer rather than thicker as the child grows. This seems to make sense from the "survival perspective", because the young child has to assure full alveolar ventilation from the first breath onward, but does not need to be able to walk. This scenario is different from growth of the other skeletal muscles in children. (46) The need of a strong diaphragm in newborns is confirmed by the above-mentioned study of Rehan et al. in 15 healthy infants, in which diaphragm thickness was positively associated with body size. (22) The authors stated that thickness has implications for diaphragm strength and found that predicted maximal trans-diaphragmatic pressures were independent of body size and length and were greater than those predicted for adults. (22) In addition, the authors suggested that sufficient transdiaphragmatic pressure is necessary to allow the infant to generate sufficient pressure to overcome substantial elastic and resistive loads at the first breath after birth. (22)

The strength of our study is that this is the largest study that established normal values of the thickness of the diaphragm in combination with the thickness fraction of the diaphragm of healthy children aged 0-8 years. Some limitations can be identified. First, the oldest age group included more participants than did the younger age groups, mainly caused by the fact that older siblings of the younger ones wished to undergo ultrasound examination as well. We found it unethical to discard their results. Second, the method of diaphragm measurement may not have been the optimal one. The current general consensus is to measure just the muscle within the lines of the fascia. This consensus was not yet available at the beginning of our study. (37, 38) On the other hand, we measured healthy children whose membranes are not expected to be affected by disease or mechanical forces related to ventilation as in ventilated children. Third, we did not verify the 30-degree supine position with a degree arc, but approximated this as much as possible by positioning the child with head and shoulders on a pillow. This could have influenced our measurements. Fourth, we only used 5 ultrasounds for calculating inter-rater reliability of performing the ultrasounds. These

results were calculated by one of the two who made the ultrasounds. This may have created bias, however the assessments of the inter-rater reliability of the 11 paired assessments was calculated by two raters.

CONCLUSION

This study provides normal values of diaphragm thickness and thickening fraction in healthy children aged 0 to 8 years. The diaphragm thickness of infants up to 1 year old was significantly greater than that of children from 2 to 8 years old. With an increase in body surface area, the diaphragm thickness decreased. These normal values in healthy children can be used to assess changes in respiratory muscle thickness in ventilated children.

TABLE 4 Results ultrasound measurements of Tdi and dTF in studies of healthy and ventilated children

Studies	Age groups							Measurement Tdi/dTF***
	0-6 months	7 months-1 year	2-4 years	5-8 years	8-10 years	10-20 years	adults	
Healthy children/ Spontaneous breathing								
Tdi-insp (mm)								
Duyndam 2023 (data from this study)	2.07 (0.40) n = 28	2.09 (0.40) n =25	1.69 (0.30) n=25	1.72 (0.30) n =44				midpoint
Vishwanath et al 2016, n=24*					1.88 (0.23)	2.72 (0.43)		NA
Alonso-Ojembarena et al 2020, n=33**	2.6 (2.2-3.2) n=33							innerpoint
Healthy adults/Spontaneous breathing								
Boussuges et al. 2021, n=200							2.5 (0.6)-2.8(0.6)	Midpoint
Vishwanath et al. 2016, n=176							2.6 (0.9)-3.0 (0.6)	NA
Ventilated children								
Montoro et al 2020, n=47** At baseline (PS) Before extubation (PS)	2.20 (1.8-2.5) 1.95 (1.7-2.4)							midpoint
Lee et al 2017, n=31* Before extubation (SIMV + PS)			1.92 (0.48)					midpoint

TABLE 4 (Continued)

Studies	Age groups							Measurement Tdi/dTF***
	0-6 months	7 months-1 year	2 -4 years	5-8 years	8-10 years	10-20 years	adults	
Glau et al 2018, n = 56** Before extubation (Ventilation mode: NA)		2.2 (2.0-2.7)						outerpoint
Tdi-exp (mm)								
Healthy children/ Spontaneous breathing								
Duyndam 2023 (data from this study)	1.64 (0.30) n = 28	1.67 (0.30) n = 25	1.38 (0.20) n = 25	1.42 (0.20) n =44				midpoint
Rehan et al 2003, n=15*	1.90 (0.33)							midpoint
Vishwanath et al 2016, n=24*					1.41 (0.20)	2.00 (0.40)		NA
Van Doorn et al 2022, n=12*				1.4 (0.4)		1.30 (0.40)		innerpoint
Alonso-Ojembarena et al 2020, n=33**	1.9 (1.6-2.4) n=33							innerpoint
Yeung et al 2022, n=55	1.5 (0.4)							innerpoint
Healthy adults/Spontaneous breathing								
Boon et al. 2013, n=150							3.3 (1.0)	Innerpoint
Van Doorn et al. 2022, n=83							1.4 (0.3)- 1.8 (0.3)	Innerpoint

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TABLE 4   (Continued)

Studies	Age groups							Measurement Tdi/dTF***
	0-6 months	7 months-1 year	2 -4 years	5-8 years	8-10 years	10-20 years	adults	
Boussuges et al. 2021, n=200							1.9 (0.4)-2.1 (0.4)	Midpoint (sitting)
Vishwanath et al. 2016, n=176							1.8 (0.5)-2.3(0.6)	NA
Carrillo-Esper et al. 2016, n=109							1.4 (0.3)- 1.9 (0.4)	midpoint
Ventilated children								
Montoro et al 2020, n=47* At baseline (PS) Before extubation (PS)	1.80 (1.5-2.0) 1.40 (1.3-1.7)							midpoint
Lee et al 2017, n=31* Before extubation (SIMV + PS)			1.52 (0.38)					midpoint
Glau et al 2018, n=56** Before extubation (Ventilation mode NA)		2.0 (1.8-2.5)						outerpoint
IJland et al 2020, n=34** Before extubation (PS) Successful extubation group Failed extubation group	1.4 (1.0-1.6) 1.6 (1.0-1.6)							innerpoint

TABLE 4 (Continued)

Studies	Age groups							Measurement Tdi/dTF***
	0-6 months	7 months-1 year	2-4 years	5-8 years	8-10 years	10-20 years	adults	
Thickening fraction (%)								
Healthy children/ Spontaneous breathing								
Duyndam 2023 (data from this study)	25.4 (10.4) n = 28	25.2 (8.3) n = 25	22.8 (10.9) n = 25	21.3 (7.1) n = 44				midpoint
Vishwanath et al 2016, n=24*					34.0 (SD NA)			NA
Ventilated children								
Montoro et al 2020 n=47**								midpoint
At baseline (PS)	24.0 (8.0-36.0)							
Before extubation (PS or SB)	30.0 (23.0-46.0)							
Lee at al 2017, n=31*								midpoint
At baseline (SIMV + PS)			25.8 (3.3)					
Before extubation (SIMV + PS)			15.6 (2.7)					
After extubation (SB)			24.7 (8.6)					
Glau et al 2018, n=56**								outerpoint
At baseline (NA)	9.7 (6.5-16.4)							
Before extubation (NA)	14.8 (10.9-26.8)							

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TABLE 4 (Continued)

| Studies | Age groups | | | | | | | Measurement Tdi/dTF*** |
	0-6 months	7 months-1 year	2-4 years	5-8 years	8-10 years	10-20 years	adults	
IJland et al 2020, n=34**								innerpoint
At baseline (PRVC)	10.7 (9.5-14.4)							
Before extubation (PS)	15.2 (9.6-19.1)							
Xue et al 2019, n=50*								innerpoint
Successful weaning (PS)			30.9 (11.2)					
Failure of weaning (PS)			15.9 (6.7)					
Cut off value			21					

*= mean (SD); ** = median(IQR); Measurement Tdi/ dTF*** between midpoint of diaphragmatic pleura and peritoneal membrane or between inner edges of both layers or between outer edges of both layers; PS= Pressure Support; NA= not available; PRVC = pressure controlled, volume controlled ventilation; SB = spontaneous breathing (through the tube); SIMV= synchronized intermittent mandatory ventilation

STATEMENTS AND DECLARATIONS

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COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

ETHICAL APPROVAL

The Medical Ethics Review board at Erasmus MC Rotterdam approved the study (METC No. NL70476.078.19). The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

CONSENT TO PARTICIPATE

Written informed consent was obtained from the parents.

CONFLICT OF INTEREST

The authors have no competing interests to declare that are relevant to the content of this article.

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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REFERENCES

1.   Dube BP, Dres M. Diaphragm Dysfunction: Diagnostic Approaches and Management Strategies. J Clin Med. 2016;5(12).

2.   Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med. 2008;358(13):1327-35.

3.   Dres M, Goligher EC, Heunks LMA, Brochard LJ. Critical illness-associated diaphragm weakness. Intensive Care Med. 2017;43(10):1441-52.

4.   Dres M, Dube BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. Am J Respir Crit Care Med. 2017;195(1):57-66.

5.   Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, et al. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. Am J Respir Crit Care Med. 2013;188(2):213-9.

6.   Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, et al. Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med. 2003;167(2):120-7.

7.   Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016;42(5):853-61.

8.   Gayan-Ramirez G, Decramer M. Effects of mechanical ventilation on diaphragm function and biology. Eur Respir J. 2002;20(6):1579-86.

9.   Schepens T, Verbrugghe W, Dams K, Corthouts B, Parizel PM, Jorens PG. The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study. Crit Care. 2015;19:422.

10.   Mariani LF, Bedel J, Gros A, Lerolle N, Milojevic K, Laurent V, et al. Ultrasonography for Screening and Follow-Up of Diaphragmatic Dysfunction in the ICU: A Pilot Study. J Intensive Care Med. 2016;31(5):338-43.

11.   DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax. 2014;69(5):423-7.

12.   Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Crit Care. 2015;19:161.

13.   Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med. 2015;41(4):734.

14.   Blumhof S, Wheeler D, Thomas K, McCool FD, Mora J. Change in Diaphragmatic Thickness During the Respiratory Cycle Predicts Extubation Success at Various Levels of Pressure Support Ventilation. Lung. 2016;194(4):519-25.

15.   Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. Am J Respir Crit Care Med. 2018;197(2):204-13.

16.   Weber MD, Lim JKB, Glau C, Conlon T, James R, Lee JH. A narrative review of diaphragmatic ultrasound in pediatric critical care. Pediatr Pulmonol. 2021;56(8):2471-83.

17.   Montoro DV. Ultrasound assessment of ventilator-induced diaphragmatic dysfunction in mechanically ventilated pediatric patients. Pediatric Respiratory Reviews. 2021;40:58-64.

18.   Glau CL, Conlon TW, Himebauch AS, Yehya N, Weiss SL, Berg RA, et al. Progressive Diaphragm Atrophy in Pediatric Acute Respiratory Failure. Pediatr Crit Care Med. 2018;19(5):406-11.

8

19. Lee EP, Hsia SH, Hsiao HF, Chen MC, Lin JJ, Chan OW, et al. Evaluation of diaphragmatic function in mechanically ventilated children: An ultrasound study. PLoS One. 2017;12(8):e0183560.

20. IJland MM, Lemson J, van der Hoeven JG, Heunks LMA. The impact of critical illness on the expiratory muscles and the diaphragm assessed by ultrasound in mechanical ventilated children. Ann Intensive Care. 2020;10(1):115.

21. van Doorn JLM, Wijntjes J, Saris CGJ, Ottenheijm CAC, van Alfen N, Doorduin J. Association of diaphragm thickness and echogenicity with age, sex, and body mass index in healthy subjects. Muscle Nerve. 2022;66(2):197-202.

22. Rehan VK, McCool FD. Diaphragm dimensions of the healthy term infant. Acta Paediatr. 2003;92(9):1062-7.

23. Alonso-Ojembarrena A, Ruiz-Gonzalez E, Estepa-Pedregosa L, Armenteros-Lopez AI, Segado-Arenas A, Lubian-Lopez SP. Reproducibility and reference values of diaphragmatic shortening fraction for term and premature infants. Pediatr Pulmonol. 2020;55(8):1963-8.

24. Serratrice G. Building muscle. Joint Bone Spine. 2009;76(4):324-6.

25. Polla B, D'Antona G, Bottinelli R, Reggiani C. Respiratory muscle fibres: specialisation and plasticity. Thorax. 2004;59(9):808-17.

26. Orsso CE, Tibaes JRB, Oliveira CLP, Rubin DA, Field CJ, Heymsfield SB, et al. Low muscle mass and strength in pediatrics patients: Why should we care? Clin Nutr. 2019;38(5):2002-15.

27. Johnson RW, Ng KWP, Dietz AR, Hartman ME, Baty JD, Hasan N, et al. Muscle atrophy in mechanically-ventilated critically ill children. PLoS One. 2018;13(12):e0207720.

28. Xue Y, Zhang Z, Sheng CQ, Li YM, Jia FY. The predictive value of diaphragm ultrasound for weaning outcomes in critically ill children. BMC Pulm Med. 2019;19(1):270.

29. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med. 2011;183(3):364-71.

30. Dres M, Demoule A. Beyond Ventilator-induced Diaphragm Dysfunction: New Evidence for Critical Illness-associated Diaphragm Weakness. Anesthesiology. 2019;131(3):462-3.

31. Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ. Two-dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects. Muscle Nerve. 2013;47(6):884-9.

32. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. Am J Respir Crit Care Med. 2015;192(9):1080-8.

33. Zambon M, Beccaria P, Matsuno J, Gemma M, Frati E, Colombo S, et al. Mechanical Ventilation and Diaphragmatic Atrophy in Critically Ill Patients: An Ultrasound Study. Crit Care Med. 2016;44(7):1347-52.

34. Vivier E, Muller M, Putegnat JB, Steyer J, Barrau S, Boissier F, et al. Inability of Diaphragm Ultrasound to Predict Extubation Failure: A Multicenter Study. Chest. 2019;155(6):1131-9.

35. Vishwanath TT, Geetha, M.J., Keval, P. J. Evaluation of thickness of normal diaphragm by B Mode Ultrasound. International journal of contemporary Medical Research. 2016;3(9):2658-60.

36. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.

37. Shi ZH, de Vries H, de Grooth HJ, Jonkman AH, Zhang Y, Haaksma M, et al. Changes in Respiratory Muscle Thickness during Mechanical Ventilation: Focus on Expiratory Muscles. Anesthesiology. 2021;134(5):748-59.

38. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, et al. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. Intensive Care Med. 2020;46(4):594-605.

39. Yeung T, Mohsen N, Ghanem M, Ibrahim J, Shah J, Kajal D, et al. Diaphragmatic Thickness and Excursion in Preterm Infants With Bronchopulmonary Dysplasia Compared With Term or Near Term Infants: A Prospective Observational Study. Chest. 2022.

40. El-Halaby H, Abdel-Hady H, Alsawah G, Abdelrahman A, El-Tahan H. Sonographic Evaluation of Diaphragmatic Excursion and Thickness in Healthy Infants and Children. J Ultrasound Med. 2016;35(1):167-75.

41. Dres M, Dube BP, Goligher E, Vorona S, Demiri S, Morawiec E, et al. Usefulness of Parasternal Intercostal Muscle Ultrasound during Weaning from Mechanical Ventilation. Anesthesiology. 2020;132(5):1114-25.

42. Boussuges A, Rives S, Finance J, Chaumet G, Vallee N, Risso JJ, et al. Ultrasound Assessment of Diaphragm Thickness and Thickening: Reference Values and Limits of Normality When in a Seated Position. Front Med (Lausanne). 2021;8:742703.

43. Carrillo-Esper R, Perez-Calatayud AA, Arch-Tirado E, Diaz-Carrillo MA, Garrido-Aguirre E, Tapia-Velazco R, et al. Standardization of Sonographic Diaphragm Thickness Evaluations in Healthy Volunteers. Respir Care. 2016;61(7):920-4.

44. Abdel Rahman DA, Saber S, El-Maghraby A. Diaphragm and Lung Ultrasound Indices in Prediction of Outcome of Weaning from Mechanical Ventilation in Pediatric Intensive Care Unit. Indian J Pediatr. 2020;87(6):413-20.

45. Schepens T, Dres M, Heunks L, Goligher EC. Diaphragm-protective mechanical ventilation. Curr Opin Crit Care. 2019;25(1):77-85.

46. Fricke O, Schoenau E. Examining the developing skeletal muscle: Why, what and how? J Musculoskelet Neuronal Interact. 2005;5(3):225-31.

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chapter

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NO ASSOCIATION BETWEEN THICKENING FRACTION OF THE DIAPHRAGM AND EXTUBATION SUCCESS IN VENTILATED CHILDREN

Anita Duyndam, Joke Smit, Robert Jan Houmes, Leo Heunks, Jeroen Molinger, Marloes IJland, Joost van Rosmalen, Monique van Dijk, Dick Tibboel, Erwin Ista

ABSTRACT

Introduction: In adults, thickening fraction of diaphragm (dTF), measured by ultrasound is used to predict extubation success. Whether dTF can also predict extubation success in children is unclear.

Aim: To investigate the association between dTF and extubation success in children. Second, to assess diaphragm thickness during ventilation and the correlation between dTf, diaphragm thickness (Tdi), age and body surface.

Method: Prospective observational cohort study in children aged 0-18 years old with expected invasive ventilation for >48 hours. Ultrasound was performed on day 1 after intubation (baseline), day 4, day 7, day 10, at pre-extubation, and within 24 hours after extubation. Primary outcome was the association between dTF pre-extubation and extubation success. Secondary outcome measures were Tdi end-inspiratory and Tdi end-expiratory and atrophy defined as < 10% decrease of Tdi end-expiratory versus baseline at pre-extubation. Correlations were calculated with Spearman correlation coefficients. Inter-rater reliability was calculated with intraclass correlation (ICC).

Results: Fifty-three patients, with median age 3.0 months (IQR 0.1-66.0) and median duration of invasive ventilation of 114.0 hours (IQR 55.5 - 193.5), were enrolled. Median dTF before extubation with Pressure Support 10 above 5 cmH2O was 15.2% (IQR 9.7-19.3). Extubation failure occurred in six children, three of whom were re-intubated and three then received non-invasive ventilation. There was no significant association between dTF and extubation success; OR 0.33 (95% CI; 0.06-1.86). Diaphragmatic atrophy was observed in 17/53 cases, in three of them, extubation failure occurred. Children in the extubation failure group were younger: 2.0 months (IQR 0.81-183.0) vs 3.0 months (IQR 0.10-48.0); p=0.045. At baseline, pre-extubation and post-extubation there was no significant correlation between age and BSA on the one hand and dTF, Tdi- insp and Tdi-exp on the other hand. The ICC representing the level of inter-rater reliability between the two examiners performing the ultrasounds was 0.994 (95% CI 0.970- 0.999). The ICC of the inter-rater reliability between the raters in 36 paired assessments was 0.983 (95% CI 0.974-0.990)

Conclusion: There was no significant association between thickening fraction of the diaphragm and extubation success in ventilated children.

INTRODUCTION

Many invasively ventilated children develop respiratory muscle weakness at the time of extubation (1), which is associated with prolonged PICU length of stay, prolonged invasive ventilation (MV) duration, and greater risk of death. (2, 3) Prolonged invasive MV carries the risk of ventilator-associated pneumonia and ventilator-induced lung injury; nevertheless, premature extubation should be prevented. (4-7) The optimal timing of extubation readiness in children is still being debated. (8, 9)

Diaphragmatic thickness (Tdi) and diaphragm thickening fraction (dTF) as assessed with ultrasound are widely used parameters to evaluate diaphragm function in mechanically ventilated patients with suspected diaphragm weakness. In some studies, dTF correlates with diaphragm strength, and absence of diaphragm thickening has been observed in patients with diaphragm paralysis. (10, 11) Several adult studies have provided evidence of diaphragm dysfunction and frequent reintubation if the diaphragm cannot sufficiently thicken with a 19-36% value of dTF cut-off. (12-17) However a new study of Poulard et al. found a weak relation between diaphragmatic strength and dTF. (18)

Studies in ventilated children reported evidence of either a decrease or increase in Tdi after a period of invasive ventilation. (19-23) In addition, Montoro et al. found a strong association between dTF and neuromuscular blockade (NMB). Glau et al. found a longer median length of MV in subjects exposed to NMB and a trend toward increased daily rates of atrophy. In this study, dTF was significantly correlated with spontaneous breathing via a support ventilation mode. (19, 20) However, what this means in practice for failure of extubation is scarce. (20, 24, 25) Lee et al. found a significantly different dTF post-extubation between the 28 children who were successfully extubated and the three children in whom extubation failed (P<0.001). (24) Montoro et al. found no significant differences in dTF at baseline, pre-extubation and post-extubation between the 13 children with extubation failure and the 32 children with successful extubation. (20) Abdel Rahman et al. found a cut-off value for dTF of ≥ 23.2 % with an area under curve of 0.876 for predicting weaning success in 103 children, mostly infants. Xue et al. found that a cut-off value for dTF of ≥ 21% was associated with successful weaning, with a sensitivity of 0.82 and a specificity of 0.81 in 50 ventilated children with a median age of 36 months. The authors did not provide information about extubation failure (26)

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We hypothesized that children with a low dTF would be prone to extubation failure and aimed to investigate the association between dTF before extubation and extubation success in ventilated children aged 0-18 years old. Furthermore, the presence of diaphragm atrophy and the correlation between dTF, end-inspiratory and end-expiratory diaphragm thickness (Tdi-insp, Tdi-exp) and age and body surface area (BSA) were investigated.

METHOD

We performed an observational prospective cohort study from 1 September 2019 till 1 March 2021.

STUDY POPULATION:

We included children, aged 0-18 years old and invasively ventilated for more than 48 hours admitted to a 28-bed ICU of a tertiary referral academic children's hospital with surgical, cardiac and medical beds in Rotterdam, the Netherlands. Excluded were patients after cardiac surgery because these patients are often ventilated for a short time; those who are longer ventilated often have pleural fluid or pericardial fluid affecting the diaphragm (figure 1). (27)

Informed consent from the parents of each participant was obtained.

ULTRASOUND MEASUREMENT OF THE DIAPHRAGM

Ultrasound of the diaphragm was performed with a Sonosite SII, portable system (Secma Holland) and with a Lumify portable ultrasound (Philips Nederland), with the child in a 30-degree supine position. We used the B mode (2-dimensional image) of the ultrasound. For details about the ultrasound measurement, see supplemental file 1 and figure 1.

OUTCOME MEASURES

Primary outcome was the association between thickening fraction (measured on a support ventilation mode), expressed as the index of diaphragm thickness (dTF) before extubation, and extubation success. Extubation success was defined as no reintubation or non-invasive respiratory support was required within 48 hours of

extubation. Only non-invasive ventilation counted as failure; high flow nasal cannula was not considered a failure.

Secondary outcomes were: diaphragm thickness at end-inspiration (Tdi insp) and at end-expiration (Tdi exp) during the period of ventilation (supplemental file 1. Ultrasound measurement and figure 2), the presence of atrophy at the moment of extubation, the association between atrophy and extubation success, and inter-rater reliability. Atrophy was defined as a more than 10% decrease in end-expiratory Tdi at pre-extubation compared to end-expiratory Tdi at baseline (the first day of ventilation).

Other secondary outcomes were presence of respiratory support after extubation, ventilation conditions like ventilation mode (Pressure Control (PC), Pressure Regulated Volume Control (PRVC), Pressure Support (PS) Continuous Positive Airway Pressure (CPAP), PEEP, Pressure above PEEP, frequency rate and FiO_2 at baseline on the first day of ventilation and just before extubation, respiratory support after extubation (non-invasive ventilation (NIV), high flow or low flow oxygen nasal cannula), corticosteroids before extubation or not and dosage of sedatives and opiates (mcg/kg/hour) at time of extubation.

The following patient characteristics were collected: age, sex, weight, length, BSA, reason for admission, severity of illness (Pediatric Risk or Mortality Score III PRISM score), duration of ventilation, length of stay in the ICU (LOS) and reason for invasive ventilation.

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STUDY PROCEDURE

Ultrasounds were performed on fixed days: day 1 after intubation (between twenty-four and forty-eight hours after intubation), on day 4, day 7 and day 10 (depending on the length of ventilation). In addition, ultrasounds were performed prior to extubation when the patient was already on a support mode or at the start of a SBT in a PS mode (PS 10 cmH_2O above PEEP 5 cmH_2O) and when applicable, just before extubation on CPAP with PEEP 5 (if SBT was successful). Finally, we made an ultrasound in the first 8 hours after extubation with a maximum of 24 hours after extubation as an outlier. For more details of the study procedure, see supplemental file 2 with table 1.

The ventilation protocol, extubation criteria and sedation practice protocols are described in supplemental file 3.

SAMPLE SIZE CALCULATION

Based on available literature in 2019, which concerned about 50 inclusions, we aimed at studying a convenience sample of fifty children. (19, 20, 22)

STATISTICAL ANALYSIS

Descriptive continuous data are presented as mean (standard deviation) for normally distributed data, and median (IQR) for non-parametric data. Categorical variables are expressed as numbers and percentages. Thickening fraction (dTF) was compared between pre-extubation on pressure support, pre-extubation on CPAP (whenever possible) and post-extubation. Tdi was compared between baseline, pre-extubation on pressure support, pre-extubation on CPAP (whenever possible), and post-extubation.

These outcomes were also compared between patients who were successfully extubated and those who were not, on day one of ventilation, before extubation and after extubation. Univariable logistic regression analysis was used to analyze the association between dTF (independent variable) and extubation success (dependent variable). Normally distributed variables such as the differences between dTF and Tdi over time, patient characteristics, and dTF and Tdi between the extubation success group and extubation failure group were compared with the paired samples t-test or with the Mann-Whitney U test if these variables were not normally distributed. Categorical variables such as sex and reasons for admission were compared using chi-squared or Fisher exact tests.

We calculated the inter-rater reliability in terms of 1) performing the ultrasounds and 2) in terms of analyzing the recorded images. The procedure of calculating the inter-rater reliability in performing the ultrasounds was as follows: each examiner independently made ultrasounds of 5 ventilated children 5 minutes after each other on the same day. The inter-rater reliability expressed as variability between the two examiners was calculated by analyzing the thickness of the diaphragm of the recorded images of these 5 subjects performed simultaneously. AD analyzed these recorded images. The inter-rater reliability indicates the level of agreement between independent raters who assessed the images. This was calculated from measurements of Tdi at end-inspiration and at end-expiration of 36 randomly selected ultrasound images. These images were assessed at two different times by two raters independently (AD and JS), without knowing each other's results. Inter-rater reliability of the results was assessed using the intraclass correlation coefficient (ICC). The calculation of the ICC was based on a

two-way mixed model with a consistency definition, reporting single measures. An ICC value below 0.5 is considered to indicate poor reliability, between 0.5 and 0.75 moderate reliability, between 0.75 and 0.9 good reliability, and any value above 0.9 excellent reliability. (28)

A Spearman correlation coefficient (rs) with 95% confidence interval was calculated between body surface area (BSA) and diaphragm thickness at baseline, before and after extubation. The r_s between age in months and diaphragm thickness was calculated as well. For dTF the same procedure was applied without inclusion of the baseline values because there is no or little difference in thickness between inspiration and expiration in children who do not spontaneously breathe on the first day of ventilation. Missing data were pairwise deleted. A p-value of < 0.05 was considered statistically significant. Data was analyzed with IBM SPSS version 25.0.

ETHICAL CONSIDERATIONS

The Medical Ethics Review Board of the Erasmus MC Rotterdam approved the study (MEC-2019-0365) and found the study not required to comply with the Medical Research Act, owing to its noninvasive nature. The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

RESULTS

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Fifty-three patients were enrolled, in total 226 ultrasound were acquired, with an average of 4 per patient. Inclusion, exclusion and number of ultrasounds per patient is shown in figure 2. Demographic characteristics of these patients are shown in table 2. We missed six ultrasounds, one for a patient at baseline, three at pre-extubation and two post-extubation. With regard to the latter, in the absence of the investigators (AD or JS), one extubation was performed before the ultrasound could be made and one was re-intubated before the ultrasound was made.

The ICC representing the level of inter-rater reliability between the two examiners performing the ultrasounds was 0.994 (95% CI 0.970- 0.999). The ICC of the inter-rater reliability between the raters in 36 paired assessments was 0.983 (95% CI 0.974- 0.990)
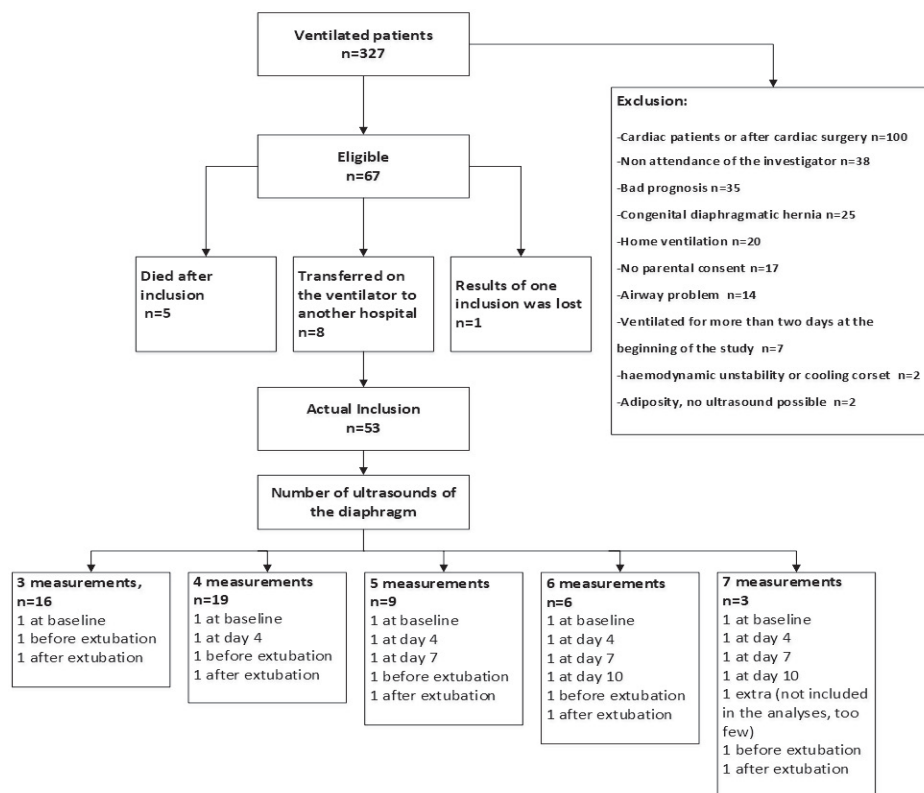
FIGURE 2 Inclusion and exclusion

PRIMARY OUTCOME

Analysis did not reveal a significant association between dTF and extubation success; OR was 0.33 (95% CI; 0.06-1.86). At both pre-extubation and post-extubation, dTF was not significantly different between the failure group and the success group (table 3).

Extubation was unsuccessful in 6 out of the 53 children. Reasons for extubation failure in these 6 patients that could have been predicted with a low dTF were: overall muscle weakness in combination with much mucus production, pleural effusion in combination with hyperventilation and exhaustion, bradypnoea with hypercapnia failure. Other reasons for extubation failure, which, however, could not have been predicted with a low dTF were pneumothorax, airway obstruction, and starting non-invasive ventilation after extubation as a precautionary measure to prevent respiratory failure. Details of the extubation failure group are shown in table 4. Three of the 6 children in whom extubation had failed were re-intubated thereafter (respectively within 1 hour, after twelve hours and twenty-seven hours after extubation) and three received non-invasive ventilation

The median dTF values at pre-extubation and post-extubation are presented in table 3, table 4 and figure 3). There was no significant difference between dTF at pre-extubation with PS or with CPAP (p=0.24), and there was no significant difference between dTF after extubation and dTF at pre-extubation (for PS: p=0.25 and for CPAP: p=0.24).

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TABLE 2   Patient characteristics

Characteristics (n=53)	Total: n=53	Successful extubation n=47	Failed extubation n=6	P value*
Age (months)*	3.0 (0.1-66.0)	3.0 (0.10-48.0)	2.0 (0.81-183.0)	0.045
Weight (kg)*	4.95 (3.3-24.5)	5.20 (3.0-23.5)	4.73 (4.2-62.0)	0.49
Height (cm)*	56.0 (50.5-130.5)	56.0 (50.0-130.0)	59.0 (54.3-162.5)	
Body surface*(m^2)	0.28 (0.2-0.9)	0.28 (0.20-0.9)	0.27 (0.2-1.7)	
Sex, n (%)				
Female	22 (41.5%)	19 (40.0%)	3 (50.0%)	0.49
PRISM III*	14.0 (8.0-16.5)	14.0 (8.0-16.0)	13.5 (9.0-19.8)	0.42
Reason for ventilation				0.80
Respiratory insufficiency	14 (26.4%)	12 (25.5%)	2 (33.3%)	
Postoperative	19 (35.8%)	18 (38.3%)	1 (16.7%)	
Pulmonary hypertension	3 (5.7%)	3 (6.4%)	0	
Traumatic brain injury and trauma	7 (13.2%	6 (12.8%)	1 (16.7%)	
Neuromuscular disease	3 (5.7%)	2 (4.3%)	1 (16.7%)	
Sepsis	1 (1.9%)	1 (2.1%)	0	
Other	6 (11.3%)	5 (10.6%)	1 (16.7%)	
Initial ventilation settings*				
PIP (cmH2O)	12.0 (10.0-14.0)	12.0 (9.8-14.0)	13.0 (9.5-15.0)	0.28
PEEP(cmH2O)	6.0 (5.0-8.0)	5.0 (5.0-8.0)	7.5 (5.0-9.3)	0.19
FiO2 (%)	0.33 (0.3-0.5)	0.33 (0.3-0.5)	0.30 (0.3-0.6)	0.20
Duration of ventilation (hours)*	114.0 (55.5 - 193.5)	114.0 (56.5-190.3)	145.5 (48.0-327.3)	0.73
Length of Stay ICU? (days)*	11.5 (6.7-19.9)	10.2 (6.6-19.5)	30.3 (13.6-81.0)	0.32

TABLE 2   (Continued)

Characteristics (n=53)		Total: n=53	Successful extubation n=47	Failed extubation n=6	P value*
Doses of sedatives and opioids at time of extubation*					
Midazolam	mcg/kg/hrs	71.5 (43.0 – 143.3) n=28	78.0 (48.0-175.0) n=25	42.0 (8.0-42.0)n=3	
Morphine	mcg/kg/hrs	5.8 (5.0-10.0) n=16	5.8 (5.0-10.0) n=16		
Ketamine	mg/kg/hrs	0.5 (0.3-2.1) n=6	0.5 (0.3-2.1) n=6	0.2 (0.2) n=2	
Clonidine	mcg/kg/hrs	0.7 (0.2 – 1.8) n=13	0.7 (0.2-1.8) n=7		
Remifentanyl	mcg/kg/hrs	0.15 (0.1-0.2) n=3	0.1 n=1		
Fentanyl	mcg/kg/hrs	2.5 n=1	2.5 n=1		
Dexamethasone before extubation (n)		7	6	1	
Reintubation		3 (5.7%)			
High flow nasal cannula (therapeutic)		17 (32.1%)			

Median (IQR); p successful extubation versus failed extubation; FiO2; fraction of inspired oxygen, PIP; peak inspiratory pressure, PEEP; positive end expiratory pressure, PRISM; pediatric risk of mortality

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TABLE 3   Measurements of the diaphragm

Measurements of diaphragm	Total: n=53	Successful extubation n=47	Failed extubation n=6	p-value*
Initial Tdi-insp (mm)*	1.82 (1.49-1.82)	1.82 (1.48-2.22)	2.11 (1.65-2.51)	0.70
Initial Tdi-exp (mm)*	1.63 (1.35-2.02)	1.61 (1.34-1.97)	1.93 (1.51-2.32)	0.53
dTF pre-extubation (PS 10/5)*	15.2% (9.7-19.3)	15.8 (10.4-20.1)	12.4 (8.0-15.7)	0.39
dTF pre-extubation (CPAP 5 cmH$_2$O)*	16.1% (12.3-23.2)	17.5 (12.8-23.6) n=15	10.4 (6.5) n=2	0.39
Tdi-insp* Pre extubation	1.83 (1.60-2.30)	1.81 (1.60-2.20)	2.35 (1.60-2.47)	0.36
Tdi-exp* Pre-extubation	1.56 (1.36-2.00)	1.55 (1.35-1.83)	2.06 (1.40-2.25)	0.51
dTF post-extubation*	14.9% (10.9-23.4)	14.9 (10.9-22.9)	19.9 (8.2-31.6)	0.40
Tdi-insp* Post-extubation	1.95 (1.71-2.38)	1.91 (1.71-2.38)	2.32 (1.72-2.58)	0.30
Tdi-exp* Post-extubation	1.68 (1.43-2.08)	1.68 (1.43-2.00)	1.97 (1.34-2.32)	0.14
Atrophy (n)	17	16	1	

Median (IQR); p successful extubation versus failed extubation; Atrophy; more than 10% decrease in Tdi at end expiration compared to baseline; dTF; thickening fraction of the diaphragm, Tdi-insp; thickness of diaphragm at the end of inspiration, Tdi-exp; thickness of diaphragm at the end of expiration

SECONDARY OUTCOMES

Thickening of diaphragm

Tdi-insp and Tdi-exp for baseline, day 4, day 7, day 10, pre-extubation and after extubation are described in table 4. Tdi-insp and Tdi-exp did not change significantly over the duration of ventilation. Overall, at pre-extubation there was no atrophy when considering the baseline thickness (table 4 and figure 5). On the seventh day of ventilation, however, The Tdi-exp of the whole group had decreased 13% versus the baseline value. On day ten, atrophy is no longer apparent. (table 5). Seventeen children had developed atrophy at pre-extubation, and extubation failure had occurred in one of them (table 4).

The dosages of sedatives or analgesics in these 17 children were not significantly higher than those of the children without atrophy at pre-extubation.

At baseline and at pre-extubation and post-extubation, there was no significant correlation (after a Bonferroni correction) between age and BSA on the one hand and dTF, Tdi-insp and Tdi-exp on the other hand. (table 6).

DISCUSSION

THICKENING FRACTION

In this study, we found that the thickening fraction of the diaphragm (dTF) at the time of extubation was not significantly associated with successful extubation in the included ventilated children. From a clinical perspective, this means that the dTF alone cannot predict whether extubation will succeed.

Three of the six children in whom extubation failed had a low dTF (under 10%) in combination with an overall weak state of respiratory muscle function.

We found that most children with a low dTF (10% or lower) before extubation could be successfully extubated. Three children in whom extubation failure occurred had a dTF higher than 10%, which could either reflect greater activity of the diaphragm or high breathing work, which are both possible reasons for extubation failure. Thus so far we demonstrated that a low dTF is not associated with extubation failure, but that the precise cut-off point for successful extubation in either case is not yet clear. Comparing the dTF before extubation for children under 3 months with that of the group above 3 months old revealed no significant difference (p=0.4). Therefore, we assume that with regard to our population the compliant rib cage of infants is not of great influence on dTF when the child is on the ventilator.

Montoro et al. found no correlation between dTF and extubation failure or between dTF and an increased need for non-invasive ventilation post-extubation in ventilated children. (20) Twenty of the 47 patients needed NIV after extubation, and extubation failure occurred in 13 of 47 patients. It is not clear whether these 20 patients had received NIV as a precaution or whether they required NIV post-extubation. Montoro et al. found a higher dTF value pre-extubation than in our study; i.e. 30% versus 15%.

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Median age, dTF and duration of ventilation (DOV) were the same in both cohorts; the only difference was that Montero and colleagues evaluated dTF during pressure support or spontaneous breathing through an endotracheal tube before extubation. The report makes not clear, however, how many patients received pressure support (and at what level of support) and how many breathed without assist. (20)

Our dTF values are more in line with those of Glau et al. with 14.8% pre-extubation in ventilated children. Again, it is not clear how much pressure support was given before extubation. (19) IJland et al. found that a median dTF of 15% was associated with successful extubation in 31 ventilated children and found a median dTF of 4% for failure of extubation in three children. (21) A recent article of Shah et al. explored the feasibility and utility of using dTF during a spontaneous breathing trial for predicting weaning outcomes in ventilated children with a median age of 11 months. (29) Median dTF before extubation with PS 6 above 5 cmH2O was 24% (IQR 12-33). One of the 38 children was reintubated and nine others failed a SBT. No information was given about the dTF value of the reintubated patient. The ones who failed the SBT had a significantly lower dTF (12%) versus the successful SBTs (27%). A dTF lower than 25% had a negative predictive value of 94% to predict SBT failure. This is in line with other studies demonstrating a dTF between 21% and 23% (with equivalent PS before extubation) to predict weaning success. (25, 26) These rates are higher than in our cohort, maybe because of the effect of giving PS 10 above 5 cm H2O before extubation. However, we also found the same values in the 17 children measured with only CPAP (PS 0 above 5 cmH2O). dTF could also be down to the level of sedation as Ijland et al suggested in their study. (21) Sedation remains difficult to standardise and compare between studies. More studies are needed to determine the cut-off point of dTF for successful extubation, both for too low and too high values of dTF, with a standardized ventilator support and level of sedation given just before extubation because the type support will influence the dTF. dTF should be measured within the lines of the pleura and peritoneal membrane. (30)

ATROPHY

On day seven of the ventilation period, we found diaphragm atrophy in the whole group, but not on ventilation day 10 and pre-extubation. The explanation for this may be that on day 7 more children were ventilated with a controlled ventilation mode and higher peak pressures and PEEP than on day 10 and pre-extubation. Seventeen out of 53 children (32%) did have atrophy pre-extubation, and extubation failure occurred

in one of them. Montoro et al. found diaphragm atrophy in 30 out of 47 patients. A possible explanation for this discrepancy includes their use of NMB in 31 out of 47 patients. (20) Glau et al. found atrophy in 19 out of 56 children with NMB. (19) We used NMB in only one patient, for 2 days, and found no atrophy in this patient. Glau et al. found an association between diaphragm atrophy and prolonged NIV after extubation. (31)

Our results are in line with Vivier et al., who highlighted that diaphragmatic dysfunction assessed by ultrasound in adults does not allow predicting extubation failure. Only ineffective cough was associated with extubation failure in this research. (32) This association is also seen in the pediatric study of IJland et al. and in the adult study of Shi et al., in which the expiratory respiratory muscle thickness decreased during mechanical ventilation, and thus coughing power decreased. (21, 30)

The question is what dTF really says about diaphragm function and how high or low it should be. Poulard et al. compared transdiaphragmatic pressure with dTF in both healthy and ventilated adults in different breathing conditions, and found a moderately strong correlation in the healthy ones and a weak correlation in the ventilated ones, while large difference within individuals existed. (18) Since transdiaphragmatic pressure is usually used as a surrogate for diaphragmatic strength, Poulard and colleagues concluded that ultrasound assessment of diaphragmatic function should be used with caution.

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In our cohort we demonstrated an increase in thickness of the diaphragm in 2 of the 6 children who failed extubation, although this was not significantly different from children with extubation success. A recent paper by Shi et al. concluded that an increase in thickness of the diaphragm in ICU patients is usually not due to increase in cross sectional area, but to increase in extracellular matrix (fibrosis or edema). (33) Inspiratory work is redistributed across the various inspiratory muscles and this redistribution could have played a role in the high inter-individual variability of dTF in this study and transdiaphragmatic pressure or esophageal pressure does not solely depend on diaphragm activation. Extra-diaphragmatic muscles such as the parasternal intercostal muscles also thicken during inspiration in healthy and ventilated patients. (34, 35) Weakness of the diaphragm may be compensated with parasternal or expiratory muscle activity. (21, 36, 37) IJland et al. measured thickness of expiratory muscles in children and found a rapidly developing change in diaphragm and expiratory

muscles thickness after initiation of mechanical ventilation, but changes in thickness of the diaphragm and expiratory muscles were not significantly correlated. The decrease in expiratory muscles thickness was significantly higher in the three patients in whom extubation failure occurred than in the successful extubation cases in this study. (21)

In the whole group, twenty-three children showed limb muscle weakness after their illness, but only two of them had failed extubation. These two children had appeared weak and were treated by the pediatric physiotherapist. Apparently, limb muscle weakness does not equal diaphragmatic atrophy. ICU-acquired muscle weakness (ICU-AW) is not often diagnosed in children unlike in adults. (38-40) A retrospective cohort study with 200,000 PICU admissions found an incidence ICU-AW of 0.02%, and ICU-AW was more frequently reported in the children with admission diagnoses of respiratory illness and infection. Furthermore, ICU-AW was associated with a longer length of stay, longer duration of ventilation and longer duration of chronic care. (40) Dres et al. found only limited overlap between ICU-AW and diaphragm dysfunction in adult critically ill patients. (15) Diaphragm dysfunction in that study was twice as frequent as ICU-AW and had a direct negative impact on weaning outcome. "

For future research, assessing all respiratory muscles in children who are prone to muscle atrophy is advisable or should be considered, as Tuinman et al. suggested. (37) By assessing all respiratory muscles with ultrasound, we might have had a good explanation for and at least a completer view of the failed extubations in the five children without upper airway problems in our study. However, although a recent study shows that ultrasound assessment of the parasternal intercostal muscle is feasible in the adult intensive care unit (41) and one study assessed abdominal muscles in ventilated children (21), more studies of ultrasounds of the intercostal and abdominal muscles are needed in ventilated and healthy children before this approach can be used in clinical practice.

The strength of this study is that we looked specifically at the predictive value of dTF on extubation success and failure (not many pediatric studies have done that) and that we also looked at post-extubation, which not many studies have done either. We used a standardized ventilation protocol and also measured 17 patients with CPAP before extubation, which has never been done before.

Some limitations can be identified. First, this was a small and heterogeneous patient population, and extubation failure occurred in only six patients (11.3%). Multivariate analyses were not feasible due to low sample size. We would have done better to base the sample size on a sample calculation instead of taking a convenience sample. Second, due to the occasional absence of the two observers some ultrasounds were missed, this could have influenced the results. Third, the method of diaphragm measurement may not have been the optimal one. The current consensus is to measure just the muscle within the lines of the fascia. This knowledge was not yet available at the beginning of our study. (42, 43) The reason is that because membranes are biologically active, mechanical forces related to ventilation can lead to inflammation with remodeling and thickening of the tissues. This remodeling of the tissues may have caused variation in size of thickness of the diaphragm. (37, 42, 44) Fourth, we measured dTf in 17 children on CPAP before extubation and saw no significant difference in dTF for CPAP versus PS. As Khemani and colleagues have shown that CPAP before extubation better predicts whether extubation could be succesful, maybe we would have done better to set all children on CPAP before extubation. (45) Nevertheless, following our study protocol we standardly applied PS 10 above 5 cmH2O. We only set CPAP when there was time for extubation and the child tolerated it. For future research, it would be better to commence the children on CPAP before extubation as Khemani et al. suggested and then measure dTF. (45) Fifth, with the use of a high frequency (4-10 MHz) linear array transducer the resolution and margin of effort of our measurements are to be taken into account.

For future studies on ultrasounds of the diaphragm, we recommend to measure the diaphragm and extra-diaphragmatic muscles of larger groups of ventilated children and using CPAP before extubation, which could allow to validly compare the successful extubations with the extubation failures. The focus should be on patients with muscle diseases, or with a chronic condition, abnormal lung function, poor nutritional status, or on disabled children who are on the ventilator for five days or more. The extubation failure group should be divided into groups of different causes of extubation failure, in order to find out whether after extubation with ultrasound a good outcome can be predicted. In this research the consensus method of ultrasound should be used, as well as a standardized method with standard mechanical ventilation settings and sedation levels. (42)

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CONCLUSION

There was no significant association between thickening fraction of the diaphragm and extubation success in ventilated children.

REFERENCES

1. Khemani RG, Sekayan T, Hotz J, Flink RC, Rafferty GF, Iyer N, et al. Risk Factors for Pediatric Extubation Failure: The Importance of Respiratory Muscle Strength. Crit Care Med. 2017;45(8):e798-e805.

2. Kurachek SC, Newth CJ, Quasney MW, Rice T, Sachdeva RC, Patel NR, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Crit Care Med. 2003;31(11):2657-64.

3. Edmunds S, Weiss I, Harrison R. Extubation failure in a large pediatric ICU population. Chest. 2001;119(3):897-900.

4. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J. 2007;29(5):1033-56.

5. Gomes Cordeiro AM, Fernandes JC, Troster EJ. Possible risk factors associated with moderate or severe airway injuries in children who underwent endotracheal intubation. Pediatr Crit Care Med. 2004;5(4):364-8.

6. Morinec J, Iacaboni J, McNett M. Risk factors and interventions for ventilator-associated pneumonia in pediatric patients. J Pediatr Nurs. 2012;27(5):435-42.

7. Srinivasan R, Asselin J, Gildengorin G, Wiener-Kronish J, Flori HR. A prospective study of ventilator-associated pneumonia in children. Pediatrics. 2009;123(4):1108-15.

8. Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med. 2017;43(12):1764-80.

9. Abu-Sultaneh S, Iyer NP, Fernandez A, Gaies M, Gonzalez-Dambrauskas S, Hotz JC, et al. Executive Summary: International Clinical Practice Guidelines for Pediatric Ventilator Liberation, A PALISI Network Document. Am J Respir Crit Care Med. 2022.

10. Dube BP, Dres M. Diaphragm Dysfunction: Diagnostic Approaches and Management Strategies. J Clin Med. 2016;5(12).

11. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. Am J Respir Crit Care Med. 2015;192(9):1080-8.

12. Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Crit Care. 2015;19:161.

13. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax. 2014;69(5):423-7.

14. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med. 2015;41(4):734.

15. Dres M, Dube BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. Am J Respir Crit Care Med. 2017;195(1):57-66.

16. Blumhof S, Wheeler D, Thomas K, McCool FD, Mora J. Change in Diaphragmatic Thickness During the Respiratory Cycle Predicts Extubation Success at Various Levels of Pressure Support Ventilation. Lung. 2016;194(4):519-25.

17. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. Am J Respir Crit Care Med. 2018;197(2):204-13.

9

18. Poulard T, Bachasson D, Fosse Q, Nierat MC, Hogrel JY, Demoule A, et al. Poor Correlation between Diaphragm Thickening Fraction and Transdiaphragmatic Pressure in Mechanically Ventilated Patients and Healthy Subjects. Anesthesiology. 2022;136(1):162-75.

19. Glau CL, Conlon TW, Himebauch AS, Yehya N, Weiss SL, Berg RA, et al. Progressive Diaphragm Atrophy in Pediatric Acute Respiratory Failure. Pediatr Crit Care Med. 2018;19(5):406-11.

20. Montoro DV. Ultrasound assessment of ventilator-induced diaphragmatic dysfunction in mechanically ventilated pediatric patients. Pediatric Respiratory Reviews. 2021;40:58-64.

21. MM IJ, Lemson J, van der Hoeven JG, Heunks LMA. The impact of critical illness on the expiratory muscles and the diaphragm assessed by ultrasound in mechanical ventilated children. Ann Intensive Care. 2020;10(1):115.

22. Johnson RW, Ng KWP, Dietz AR, Hartman ME, Baty JD, Hasan N, et al. Muscle atrophy in mechanically-ventilated critically ill children. PLoS One. 2018;13(12):e0207720.

23. Weber MD, Lim JKB, Glau C, Conlon T, James R, Lee JH. A narrative review of diaphragmatic ultrasound in pediatric critical care. Pediatr Pulmonol. 2021;56(8):2471-83.

24. Lee EP, Hsia SH, Hsiao HF, Chen MC, Lin JJ, Chan OW, et al. Evaluation of diaphragmatic function in mechanically ventilated children: An ultrasound study. PLoS One. 2017;12(8):e0183560.

25. Abdel Rahman DA, Saber S, El-Maghraby A. Diaphragm and Lung Ultrasound Indices in Prediction of Outcome of Weaning from Mechanical Ventilation in Pediatric Intensive Care Unit. Indian J Pediatr. 2020;87(6):413-20.

26. Xue Y, Zhang Z, Sheng CQ, Li YM, Jia FY. The predictive value of diaphragm ultrasound for weaning outcomes in critically ill children. BMC Pulm Med. 2019;19(1):270.

27. Salah HM, Goldberg LR, Molinger J, Felker GM, Applefeld W, Rassaf T, et al. Diaphragmatic Function in Cardiovascular Disease: JACC Review Topic of the Week. J Am Coll Cardiol. 2022;80(17):1647-59.

28. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.

29. Shah AJ, Wai K, Sharron MP, Mize M, Cohen J, Basu S. Diaphragmatic Thickening Fraction by Ultrasound in Mechanically Ventilated Pediatric Patients: Pilot Observations During Spontaneous Breathing Trials. J Ultrasound Med. 2022;41(12):3043-50.

30. Shi ZH, de Vries H, de Grooth HJ, Jonkman AH, Zhang Y, Haaksma M, et al. Changes in Respiratory Muscle Thickness during Mechanical Ventilation: Focus on Expiratory Muscles. Anesthesiology. 2021;134(5):748-59.

31. Glau CL, Conlon TW, Himebauch AS, Yehya N, Weiss SL, Berg RA, et al. Diaphragm Atrophy During Pediatric Acute Respiratory Failure Is Associated With Prolonged Noninvasive Ventilation Requirement Following Extubation. Pediatr Crit Care Med. 2020.

32. Vivier E, Muller M, Putegnat JB, Steyer J, Barrau S, Boissier F, et al. Inability of Diaphragm Ultrasound to Predict Extubation Failure: A Multicenter Study. Chest. 2019;155(6):1131-9.

33. Shi Z, van den Berg M, Bogaards S, Conijn S, Paul M, Beishuizen A, et al. Replacement Fibrosis in the Diaphragm of Mechanically Ventilated Critically Ill Patients. Am J Respir Crit Care Med. 2023;207(3):351-4.

34. De Troyer A, Boriek AM. Mechanics of the respiratory muscles. Compr Physiol. 2011;1(3):1273-300.

35. Yoshida R, Tomita K, Kawamura K, Nozaki T, Setaka Y, Monma M, et al. Measurement of intercostal muscle thickness with ultrasound imaging during maximal breathing. J Phys Ther Sci. 2019;31(4):340-3.

36. Dres M, Goligher EC, Heunks LMA, Brochard LJ. Critical illness-associated diaphragm weakness. Intensive Care Med. 2017;43(10):1441-52.

37. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, et al. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. Intensive Care Med. 2020;46(4):594-605.

38. Anekwe DE, Biswas S, Bussieres A, Spahija J. Early rehabilitation reduces the likelihood of developing intensive care unit-acquired weakness: a systematic review and meta-analysis. Physiotherapy. 2020;107:1-10.

39. Dantas CM, Silva PF, Siqueira FH, Pinto RM, Matias S, Maciel C, et al. Influence of early mobilization on respiratory and peripheral muscle strength in critically ill patients Influencia da mobilizacao precoce na forca muscular periferica e respiratoria em pacientes criticos. Rev Bras Ter Intensiva. 2012;24(2):173-8.

40. Field-Ridley A, Dharmar M, Steinhorn D, McDonald C, Marcin JP. ICU-Acquired Weakness Is Associated With Differences in Clinical Outcomes in Critically Ill Children. Pediatr Crit Care Med. 2016;17(1):53-7.

41. Dres M, Dube BP, Goligher E, Vorona S, Demiri S, Morawiec E, et al. Usefulness of Parasternal Intercostal Muscle Ultrasound during Weaning from Mechanical Ventilation. Anesthesiology. 2020;132(5):1114-25.

42. Haaksma ME, Smit JM, Boussuges A, Demoule A, Dres M, Ferrari G, et al. EXpert consensus On Diaphragm UltraSonography in the critically ill (EXODUS): a Delphi consensus statement on the measurement of diaphragm ultrasound-derived parameters in a critical care setting. Crit Care. 2022;26(1):99.

43. MM IJ, Roesthuis LH, van der Hoeven JG, Heunks LM. Diaphragm Atrophy as a Risk Factor for Extubation Failure. Pediatr Crit Care Med. 2021;22(7):e417-e8.

44. Zugel M, Maganaris CN, Wilke J, Jurkat-Rott K, Klingler W, Wearing SC, et al. Fascial tissue research in sports medicine: from molecules to tissue adaptation, injury and diagnostics: consensus statement. Br J Sports Med. 2018;52(23):1497.

45. Khemani RG, Hotz J, Morzov R, Flink RC, Kamerkar A, LaFortune M, et al. Pediatric extubation readiness tests should not use pressure support. Intensive Care Med. 2016;42(8):1214-22.

46. Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747-63.

47. Duyndam A, Houmes RJ, van Dijk M, Tibboel D, Ista E. How to achieve adherence to a ventilation algorithm for critically ill children? Nurs Crit Care. 2015;20(6):299-307.

48. Ista E, de Hoog M, Tibboel D, van Dijk M. Implementation of standard sedation management in paediatric intensive care: effective and feasible? J Clin Nurs. 2009;18(17):2511-20.

49. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med. 2005;6(1):58-63.

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SUPPLEMENTAL FILES

Additional file 1. Ultrasound measurement

Additional file 2. Study procedure

Additional file 3. Ventilation and sedation practice protocol

Additional file 4. Nurse-led weaning protocol, part one

Additional file 5. Nurse-led weaning protocol, part two

Additional file 6. Nurse-led weaning protocol, part three and explanation of file 4-6

Additional file 7. Figure 3. Boxplots of dTF for successful and failure of extubation over time

Additional file 8. Table 4. Cases of failed extubation

Additional file 9.Table 5. Measurements of dTF, Tdi insp, Tdi exp over time

Additional file 10. Figure 4. Thickening fraction over time in percentage

Additional file 11. Figure 5. Thickness of diaphragm at end expiration over time

Additional file 12. Table 6. Spearman correlations between age, body surface area and Tdi and dTF in time

SUPPLEMENTAL FILE 1: ULTRASOUND MEASUREMENT

Ultrasound of the diaphragm was performed with a Sono Site SII, portable system in B mode and M mode or the Philips Lumify portable ultrasound, with the child positioned in a 30-degree supine. We used the B mode (2-dimensional image) of the ultrasound.

The diaphragm thickness was measured on the right side, with a high frequency (4-10 MHz) linear array transducer placed in the ninth or tenth intercostal space between the anterior and midaxillary lines in the zone of apposition between lung and liver. In this area, the diaphragm is observed as a three-layered structure: a non-echogenic central layer bordered by two echogenic layers: the peritoneum and the diaphragmatic pleurae. (11, 12, 14, 17) See figure 1a.

The Tdi in this position was defined as the vertical distance in millimeters between the midpoint of the diaphragmatic pleura and midpoint of the parietal peritoneum. The TF index is expressed as dTF and was quantified by the percentage change in the right hemi diaphragm thickness from end- expiration to end-inspiration during tidal breathing on MV. We measured the vertical distance in percentage between the midpoint of the diaphragmatic pleura and midpoint of the parietal peritoneum. dTF index was calculated, according to international standards, as follows: end-inspiratory

thickness of diaphragm minus end-expiratory thickness of diaphragm divided by end-expiratory thickness x 100. (17, 31, 48) See figure 1b.
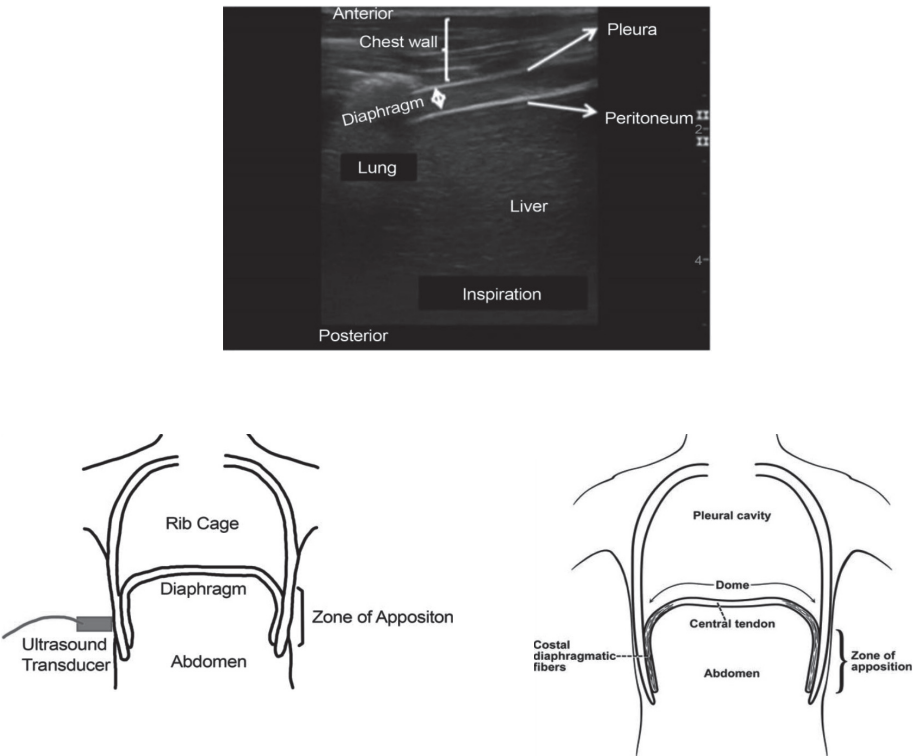
FIGURE 1A Ultrasound in the zone of apposition
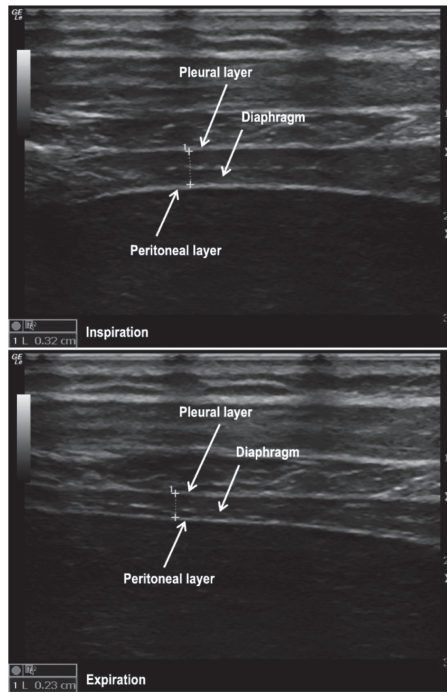
FIGURE 1B Measurement of Thickening fraction (dTF)

SUPPLEMENTAL FILE 2: STUDY PROCEDURE

After having received thorough training from an experienced ultrasound technician (JM), two researchers (JS and AD) performed the ultrasound assessments, supported by a written brief protocol.

Per ultrasound moment, three measurements were made when the optimum position was reached with the clearest view. The mean of the three values was used in the analyses. Short axis Digital Imaging and Communications in Medicine (DICOM) videos were recorded for offline B-mode analysis and calculations were made with dedicated software (RadiAnt DICOM viewer from Medixant). The clinicians involved in patient care were blinded for the outcome of the ultrasounds. No clinical decisions were based on the ultrasound data.

TABLE 1   Ultrasound schedule

Duration of ventilation	Day 1	Day 4	Day 7	Day 10	On the day of extubation After start SBT or already on a support mode	Just before extubation on CPAP	Within 24 hours of extubation
> 48 hours < 4 days	X				X	X	X
5-6 days	X	X			X	X	X
> 6 days <10 days	X	X	X		X	X	X
>10 days	X	X	X	X	X	X	X

SUPPLEMENTAL FILE 3: VENTILATION AND SEDATION PRACTICE PROTOCOL

All patients required ventilation in accordance with a departmental protocol with continuous mandatory ventilation: Pressure Control (PC) or Pressure Regulated Volume Controlled (PRVC). When they started to trigger continuous supported ventilation was applied with spontaneous breaths: Pressure Support (PS) or Volume Support (VS). (49) Nurses reduced support according to the protocol and carried out a Spontaneous breathing trial (SBT) if the patient met the inclusion criteria according to the protocol (see supplemental files 2, 3 and 4). Ventilation was titrated at a tidal volume of 6 ml/kg ideal weight at a pH > 7.30 and PCO_2 within 5-8 kPa, SpO_2 > 95% (unless in cyanotic heart defects ≥ 75% or in neonates with chronic lung disease (CLD): 88-96%). PEEP was given from 5 cm H_2O. We used lung-protective ventilation with small tidal volumes (4-6 mL/kg) and 'permissive hypercapnia' for patients with ARDS. PC above PEEP was kept below 15 cmH$_2$O for acute respiratory distress syndrome and oxygen saturations > 88% and below 92%. (50)

Successful extubation was defined as no invasive or non- invasive respiratory support was required within 48 hours of extubation. Extubation failure was defined as re-intubation or non-invasive ventilation required within 48 hours after extubation. High flow nasal cannulae support after extubation was not seen as an extubation failure.

Sedatives
Sedative administration was protocolized and consisted of a combination of midazolam and morphine in varying concentrations depending on the patient's agitation and

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titrated according to the COMFORT behavior scores and the NISS. (51,52) If necessary, ketamine or clonidine was added as sedatives. In the case of weaning, the sedation was reduced or stopped. If the patient was sedated for more than 5 days and received analgesics, a reduction schedule was made with lorazepam, methadone and/or clonidine orally. (51)

SUPPLEMENTAL FILE 4: NURSE-LED WEANING PROTOCOL, PART ONE

At the beginning of the shift: check patient eligibility for a wean traject
If there is a rapid clinical improvement during the shift, check again

1. Checklist

Exclusion criteria:
- Airway obstruction or expected difficult airway
- Duration of ventilation longer than 1 month
- "Growing on the ventilator" (i.e. before heart surgery)
- Glasgow Coma Scale <8, Traumatic brain injury or not capable to swallow or cough
- Scheduled surgery or MRI
- Previous participation in the study
- Already low ventilation settings

In doubt: consult physician or Nurse Practitioner/Ventilation practitioner
Don't do two steps at once
Use Et CO_2 if difference Et CO_2 ≤ 1 kPa versus PCO_2

Yes → Patient cannot participate

No ↓

Weaning criteria met?
FiO_2 ≤ 0.6
Peak pressure ≤ 23 cm H_2O
PEEP ≤ 8 H_2O
pH ≥ 7.32
Hemodynamic stability (without or with low inotropic dose)
No high work of breathing

Yes | No

No → Patient cannot start the weaning proces at this moment. Check in the next shift if patient meets inclusion criteria to wean

Time: 8.00-10.00 a.m. or 4.00-5.00 pm? — No → Follow wean-algorithm **2A**

JA ↓

Does patient meet SBT criteria:
FiO_2 ≤ 0.45
PCO_2 ≤ 7.5 kPa
Patient trigger detected?

In case of no patient triggering:
1. Consider lowering sedation (according sedation protocol)
2. Is PCO_2 too low or frequency too high?
3. Is inspiration time too long for a neonate? (Ti= 0.4 sec.)
4. Is triggger sensitivity set sufficiently?
Consider adjusting the points above

Yes | No

No → Follow wean-algorithm **2A**

Start SBT **2B**

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SUPPLEMENTAL FILE 5: NURSE-LED WEANING PROTOCOL, PART TWO

2A. Weaning Algorithm

FiO$_2$ based on saturation: lower oxygen in steps of 5%, a 5 minutes till F$_i$O$_2$ = 0.4

Lower PEEP level every hour with 1 cm H$_2$O based on saturation till PEEP ≤ 5 cm H$_2$O
In case of more oxygen requirement after lowering PEEP: consult physician or practitioner

PC and triggering:
Switch to Pressure Support*

PRVC and triggering:
Switch to Volume Support*

In case of no patient triggering:
1. Consider lowering sedation (according sedation protocol)
2. Is PCO$_2$ too low or frequency too high?
3. Is Inspiration time too long for a neonate? (Ti= 0.4 sec.)
4. Is triggger sensitivity set sufficiently? Consider changing the points above

Based on EtCO$_2$ or PCO$_2$ (< 7.5 kPa):
Lower PS above PEEP with steps of 2 cm H$_2$O per hour until tidal volume is 4 ml/kg (ideal weight)
Or till PS has a minimum of 8 cm H$_2$O above PEEP

Based on EtCO$_2$ of PCO$_2$ (< 7.5 kPa):
Lower TV with steps of 1 ml/kg until 4 ml/kg (ideal weight)

Extubation criteria
No high work of breathing
FiO$_2$ ≤ 0.4
pH > 7.32/ PCO$_2$ <7.5
SpO$_2$ > 95% or > 75% in case of cyanotic heart disease or > 88% in case of chronic lung disease or > 92% in case of ARDS.
EMV > 8, capable to swallow or cough
Mucus production ≤ suction 3 x per hour
Hemodynamically stable (with no or low inotropic dose)
No new fever episode> 38.5 degrees
No scheduled surgery/MRI < 24 hrs
No clinical signs of edema

Target reached?

Yes

No

Stop feeding (2 hours at duodenal feeding and 4 hours at stomach feeding) Dexamethasone needed?

In case of failing weaning, go back to basic values
Use the check list again in the next shift

Inform the physician and discuss the time of extubation

EXTUBATION

* At Pressure Support or Volume Support:
Set inspiration cycle off (ICO) at 5-10% in neonates (higher in case of leakage) and at 30% in children > 6 months
Set Trigger time out (TTO) at 3-4 sec. in neonates until a year old and 5-7 sec. in children

SUPPLEMENTAL FILE 6: NURSE-LED WEANING PROTOCOL, PART THREE

2B. Spontaneous Breathing Trial (SBT)
Start weaning in day shift between 8.00 en 10.00 a.m. and at 4.00 p.m.

Start SBT
Set ventilation mode to Pressure Support
PS 10 cmH$_2$O
PEEP 5 cmH$_2$O;
FiO$_2$ keep at the same level

Testing for 2 hours
Assess per 15 minutes: Is the child able to breathe adequately by himself
If necessary, agree on a longer time frame with the physician for better assessment

Observe: heart rate/work of breathing/comfort/ blood pressure.
Take a blood gas sample after 2 hours and assess Et CO$_2$
(Use Et CO$_2$ only if Et CO$_2$ corresponds to PCO$_2$ with maximum difference of 1 kPa)

SBT is a success and extubation criteria have been met in case of:

No high work of breathing	FiO$_2$ ≤ 0.4	pH > 7.32/ PCO$_2$ <7.5
SpO$_2$ > 95%, > 75%, cardiac > 88%, CLD >92%, ARDS	HF < 20% increase compared to basic value	BP ≤ 10% increase compared to basic value
EMV > 8, inable to swallow or cough	Mucus suction ≤ 3 x per hour	Hemodynamically stable
No new fever episode> 38.5 degrees	No scheduled surgery/MRI < 24 u	No clinical signs of edema

SBT succeeded?
Continue PS 10/5 and prepare on extubation.

SBT failed?
Go back to settings before start SBT and start weaning algorithm (2A) or check patient again with the checklist (1)

Stop feeding (2 hours at duodenal feeding and 4 hours at stomach feeding) Dexamethasone needed?

Inform the physician and discuss time of extubation

EXTUBATION

* At Pressure Support:
Set inspiration cycle off (ICO) at 5-10% in neonates (higher in case of leakage) and at 30% in children > 6 months
Set Trigger time out (TTO) at 3-4 sec. in neonates until a year old and 5-7 sec. in older children

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EXPLANATION NURSE-LED WEANING PROTOCOL, SUPPLEMENTAL FILES 4-6

1. *Checklist start criteria:* Weaning can be started at any time of the day if the patient meets the start criteria according the checklist (supplemental file 1). PEEP is being decreased in steps of 1 cmH$_2$O every hour when FiO2 is ≤ 40%. If more oxygen is required when PEEP is being decreased, the nurse should consult a physician, nurse practitioner or ventilation practitioner (registered nurse with additional training in ventilation management) about the necessity of increasing PEEP. The saturation limit is ≥ 95% for most children, but ≥ 88% for children with chronic lung disease, ≥ 92% for children with ARDS and ≥ 75% for cardiac patients with mixed circulation. (16)

2. *Wean algorithm:* If the patient breathes spontaneously ('triggers the ventilator'), the wean algorithm can be followed (supplemental file 2). The ventilation mode is set to a support mode; for the Servo i, the 'auto-mode' mode (with pressure support (PS) for pressure control (PC) and volume support (VS) for pressure regulated volume control (PRVC). If the patient does not trigger the ventilator, the possible reason and a solution have to be found to stimulate triggering. PS above PEEP can be reduced to a minimum of 8 cmH$_2$O in one-hour steps of 2 cmH$_2$O above PEEP, or the tidal volume can be reduced to a minimum of 4 ml/kg.

3: Spontaneous Breathing Trial (Supplemental file 3). For patients meeting the start criteria, an SBT starts between 8 and 10 a.m. and if possible again in the afternoon around 4 and 6 p.m., with the following ventilation settings during 2 hours: PS 10 cmH2O above PEEP 5 cmH2O, and FiO2 equal to the start of the SBT. During the SBT, the patient is observed to see whether he or she can breathe calmly with the predefined range for respiratory rate, with stop criteria if the SBT fails.

SUPPLEMENTAL FILE 7: FIGURE 3. BOXPLOTS OF DTF FOR SUCCESSFUL AND FAILURE OF EXTUBATION OVER TIME
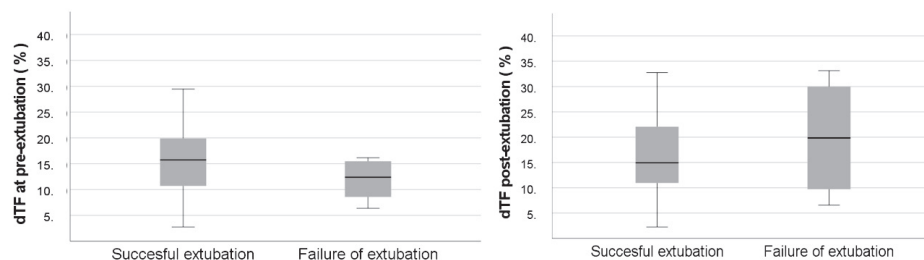
dTF = thickening fraction of the diaphragm; successful extubation: n=47; failure of extubation: n=6

SUPPLEMENTAL FILE 8: TABLE 4. CASES OF FAILED EXTUBATION

case	1. (reintubation)	2.(reintubation)	3. (reintubation)	4.(NIV)	5. (NIV)	6. (NIV)
Age (months)	1	180	0.2	192	3	1
Reason of admission	Respiratory insufficiency (bronchiolitis)	Trauma	Post-operative (correction oesophageal atresia)	Deterioration in Myasthenia Gravis	Pneumonia and pleural effusion	Coronary clot and heart failure
DOV (days)	180.0*	15.1	24.6	36.0	8.9	48.0
Cause of failure	Airway obstruction, mucus and stridor	Pleural effusion Anxiety, hyperventilation and exhaustion	Pneumothorax	Overall weakness and much mucus	Bradypnoea and weakness based on high doses of pyridoxaalfosfaat because of a PNPO deficiency	NIV was a precautionary measure to prevent respiratory failure
dTF at CPAP before extubation	NA	6.5%	15.5%	NA	NA	NA
dTF at pressure support before extubation	16.2%	9.8%	14.3%	8.6%	6.4%	15.1%
atrophy	no	-26.8%	no	no	No	no
Increase of Tdi-exp before extubation	+38%	no	no	no	no	+21%
Sedation before extubation	Midazolam 100 mcg/kg/hour	Midazolam 8 mcg/kg/hour Remifentanil 0.22 mcg/kg/hour	no	Remifentanil 0.15 mcg/kg/ hour	Midazolam 42 mcg/kg/hour	no

NIV: non-invasive ventilation; NA: not available; * this patient needed a trachea cannula and prolonged ventilation, hypertrophy= >10% increase of Tdi-exp versus baseline

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ADDITIONAL FILE 9. TABLE 5. MEASUREMENTS OF DTF, TDI INSP, TDI EXP OVER TIME

	Baseline n=52	Day 4 n=28	Day 7 n=14	Day 10 n=6	Pre-extubation PS n=50	Pre-extubation CPAP n=17	Post-extubation n=51	p* pre-extubation (PS 10/5 cmH2O) vs baseline	p* pre-extubation (CPAP 5 cmH2O) vs baseline	p* post-extubation vs baseline
dTF* Thickening fraction (%)					15.2 (9.7-19.3)	16.1 (12.3-23.2)	14.9 (10.9-23.4)			
Tdi end-inspiration* (mm)	1.82 (1.49-1.82)	1.70 (1.52-1.94)	1.60 (1.44-2.10)	1.58 (1.17-2.20)	1.83 (1.60-2.30)	1.78 (1.50-2.59)	1.95 (1.71-2.38)	0.46	0.25	0.66
Tdi end-expiration* (mm)	1.63 (1.35-2.02)	1.51 (1.41-1.72)	1.44 (1.28-1.96)	1.51 (1.05-2.10)	1.56 (1.36-2.00)	1.53 (1.22-2.13)	1.68 (1.43-2.08)	0.24	0.25	0.18
Atrophy (%) **		-7.9 (-30.0 vs 6.0)	-13.2 (-7.0 vs -6.0)	-7.9 (-30.0 vs 8.0)	-4.5 (-2.0 vs 1.0)	-6.5 (-13.0 vs 11.0)				

Median (IQR); p= Paired samples t test; ** Difference Tdi end-expiration versus Tdi end-expiration at baseline

SUPPLEMENTAL FILE 10: FIGURE 4. THICKENING FRACTION AT PRE-EXTUBATION AND AT POST-EXTUBATION
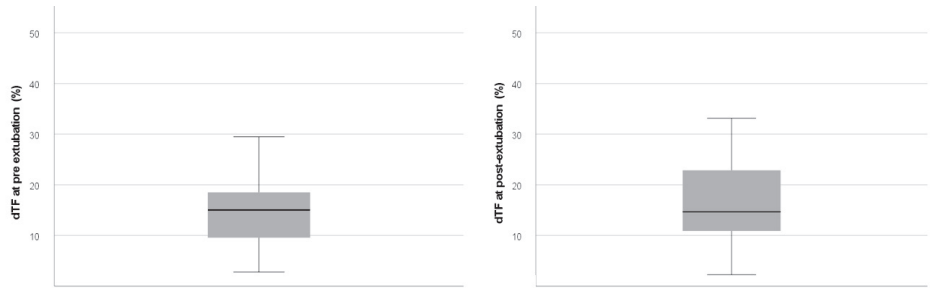
dTF= thickening fraction of the diaphragm; Initial dTF, n=52 ; dTF at pre-extubation, n=50 ; dTF at post-extubation, n=51

SUPPLEMENTAL FILE 11: FIGURE 5. THICKNESS OF DIAPHRAGM AT END EXPIRATION OVER TIME
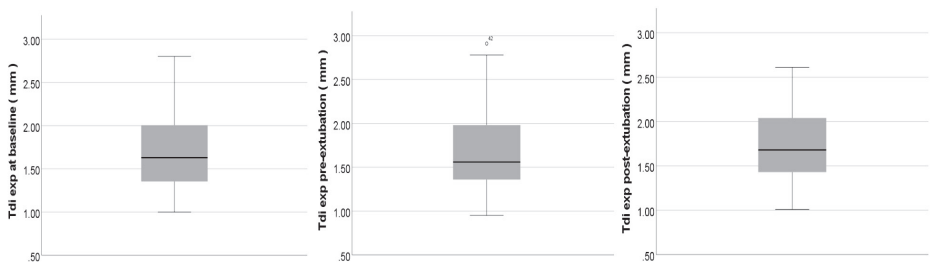
Tdi exp. = Thickness of the diaphragm at end-expiration; Tdi exp at baseline: n=52; Tdi exp pre-extubation: n=50; Tdi exp post-extubation: n=51

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ADDITIONAL FILE 12. TABLE 6. SPEARMAN CORRELATIONS BETWEEN AGE, BODY SURFACE AREA AND TDI AND DTF IN TIME

	BSA (m2	Age in months
dTF Pre-extubation	r= -0.242 n=52 p=0.10 95% CI -0.501 / 0.058	r= -0.219 n=50 p=0.14 95% CI -0.373 / 0.201
dTF Post-extubation	r= -0.256 n=52 p=0.08 95% CI -0.507 / 0.036	r= -0.320 n=51 p=0.02 95% CI -0.555 / -0.037
Tdi insp baseline	r= 0.241 n=52 p=0.09 95% CI -0.046 / 0.491	r= 0.113 n=52 p=0.42 95% CI -0.173 / 0.382
Tdi insp Pre-extubation	r= -0.087 n=52 p=0.56 95% CI -0.366 / 0.208	r= -0.187 n=50 p=0.19 95% CI -0.449 / 0.105
Tdi insp Post-extubation	r= -0.217 n=52 p=0.13 95% CI -0.474 / 0.073	r= -0.323 n=51 p=0.02 95% CI -0.556 / -0.044
Tdi exp baseline	r= 0.256 n=51 p=0.07 95% CI -0.03 / 0.503	r= 0.143 n=52 p=0.31 95% CI -0.143 / 0.408
Tdi exp Pre-extubation	r= 0.020 n=48 p=0.89 95% CI -0.273 / 0.310	r= -0.094 n=49 p=0.52 95% CI -0.373 / 0.201
Tdi exp Post-extubation	r= -0.100 n=50 p=0.50 95% CI -0.375 / 0.192	r= -0.201 n=51 p=0.16 95% CI -0.458 / 0.087

r= correlation coefficient; dTF= thickening fraction of the diaphragm; Tdi insp.= thickening fraction at end-inspiration; Tdi exp. = thickening fraction at end-expiration, BSA = bodysurface area. Bonferroni corrected p-value = 0.0063

chapter 10

GENERAL DISCUSSION

The central aim of the thesis was to seek and enhance evidence for the best way to manage mechanical ventilation in children. The secondary aim was to find the optimal way to ventilate and wean children to extubation from a nursing perspective. I reflect on the main findings, discuss possible difficulties and pitfalls of the weaning from mechanical ventilation, and give directions for future research on the basis of a representative case.

VENTILATION MODE: FIND THE BEST ONE?

CASE

Brit, a 12-year-old girl diagnosed with myotonic dystrophy (long known as Steinert disease) and suffering from acute respiratory distress (ARDS) on account of a bacterial pneumonia is admitted to the PICU. She had a high work of breathing, a low oxygen saturation of 88% and was too weak, due to exhaustion, to cough well enough. Therefore, she needed intubation and mechanical ventilation. In this case, we chose pressure-controlled ventilation with a differential (delta) pressure of max. 15 cmH$_2$O above PEEP to give small tidal volumes (five to six ml per kilo bodyweight) and set a high PEEP because of high oxygen demand. The blood gas test and PO$_2$ were acceptable with pressure-controlled set on a respiratory rate of 40 per minute and a pressure of 31 cmH$_2$O (peak pressure) above PEEP 16 cmH$_2$O, inspiration: expiration ratio 1:1 and FiO$_2$:0.5. To be able to endure the mechanical ventilation, she was sedated with midazolam and morphine doses based on the COMFORT behavior scores. (1) At this point, we are already concerned about Brit's muscle strength after the end of the ventilation period and a period of sedation. Brit is a child with a good quality of life according to her concerned parents, who had never been mechanically ventilated before.

The choice of the ventilation mode in this case, pressure-controlled ventilation was based on the ventilation protocol we had developed (*chapter 3*). Brit's ARDS was characterized by a heterogeneous lung disease, whereby parts of the lung were not ventilated and other parts were moderately or over-ventilated. The best choice to ventilate her according to our protocol is pressure-controlled ventilation *(chapter 3)*. The protocol was made based on adult literature about ventilation since we found no answer on optimal ventilation in pediatric literature in *chapter 2.* Optimal ventilator settings, with recruiting lung volume to participate in gas exchange and ventilating the lung in the least harmful way, should meet the practical concept of Lachmann et al.: "Open up the lung and keep it open". (2) According to this concept, the least harmful way should be with the smallest possible difference between peak pressure and PEEP (delta P). Still, more recent research of Amato et al. showed that decreases in pressure amplitudes were significantly associated with increased survival in adults. (3) This concept still stands in our view, and we translated it to our protocol. We did not opt to ventilate Brit with high frequency oscillation (HFO) ventilation, which is a pressure-controlled mode with very small mandatory breaths (oscillations) on top of

spontaneous breaths. HFO ventilation is another option to ventilate critically ill patients with heterogeneous lung disease. The reason was that we considered HFO ventilation no longer safe, because it was used so rarely that nurses were no longer well-skilled in its use. Considering the absence of evidence of a better outcome for HFO ventilation compared to conventional ventilation (CV) we had stopped using it at our department.

We looked for evidence in our update of the systematic review on preferred ventilation modes in critically ill children as described in chapter 2 and updated in 2020 (chapter 4). The update yielded more studies comparing HFO with CV than in 2011, both RCTs and observational studies. At the time of submitting this review, another review on the same subject from a Brazilian research group was published, (4) focusing on determining the effects of HFO compared to CV when used in children with hypoxemic respiratory failure. (table 1) The Brazilian review also included RCTs and observational studies, but analyzed them by study design. The Brazilian review found no significant difference in mortality rates between HFO and CV in the RCTs, and clinically significant harm or benefit could not be excluded. The duration of ventilation (DOV) was not significantly different between groups. In our review, we concluded that a pooled analysis of HFO ventilation versus CV showed a lower mortality rate for CV, but this result was based on all RCTs and observational studies taken together. When we excluded the observational studies, we found no benefit or harm for the RCTs and DOV was not significantly different for both groups, comparable with the Brazilian study. We acknowledge that there is a significant unexplained residual bias in the observational propensity-matched studies, giving a biased Odds Ratio (OR) suggesting harm through HFO ventilation. This biased OR is almost certainly due to the fact that HFO ventilation is systematically used in sicker patients and used both as primary ventilation therapy as well as rescue therapy. Statistics cannot overcome this degree of confounding by indication. In this review with meta-analysis (chapter 4) we decided to include observational studies in addition to RCTs because of the scarcity of pediatric RCTs on HFO ventilation. We believe that non-randomized studies can provide valuable data since they are analyzed and interpreted cautiously in light of their limitations. Based on both of our reviews, we cannot recommend HFO ventilation for pediatric ARDS or acute hypoxemic respiratory failure until larger RCTs with an unambiguous protocol and adequate sample sizes have shown better outcome effects for HFO ventilation versus CV. We are awaiting the results of the PROSpect study, an international RCT conducted by Kneyber et al. (5) In this RCT, children with moderate-to-severe pediatric ARDS (Oxygenation index > 12) are randomized to prone versus supine positioning

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and HFO ventilation versus CV to compare prone versus supine positioning and HFOV versus conventional mechanical ventilation (CMV) with ventilator-free days. In this trial, CV and HFO ventilation are strictly protocolized, and the HFO ventilation protocol makes use of staircase recruitment maneuvers, high frequencies and daily titration to improve the weaning process.

Finding an answer to the issue of the optimal ventilation mode in children (*chapters 2 and 4*) proved to be difficult for a number of reasons. One of the problems is the heterogeneity of the pediatric population in the PICU. These children have different underlying pathology and different age-related factors such as lung growth and responses from the innate and adaptive immune systems. Since also study outcomes of the different studies vary, it is difficult to compare the studies. In line with Randolph et al., (6) we suggest that long-term morbidity would be a better outcome to compare the impact of MV in children than are mortality, duration of ventilation or ventilator-free days. Randolph et al. showed a low associated mortality rate in children, also in the case of ARDS (4-5%). Nevertheless, the impact of ARDS on children's longer-term pulmonary function or neurocognitive development is unknown and needs further study. The Pediatric Acute Lung Injury Consensus Conference for mechanical ventilation of pediatric patients with ARDS indeed recommended this, and suggested to include long-term outcomes of pulmonary function, neurocognitive development, and health-related quality of life in clinical studies. (7) Regarding long-term outcomes of ventilation, the problem is that ventilation is part of the treatment of a disease or condition. A longer duration of ventilation, however, is a predictor for poorer quality of life in young children. (8, 9)

On the other hand, the choice of ventilation mode in children may be less important for outcome than is lung-protective ventilation, a ventilator strategy aiming to protect the lung. In adults, lung-protective ventilation helps to protect ventilator-induced lung injury. (2, 3, 10). Although this has not yet been proven in children in trials on long-term outcomes, most PICUs worldwide– to our knowledge– apply this strategy in children with respiratory failure. Instead of ventilation modes, future studies should focus on ventilation strategies such as lung-protective ventilation in children and compare the impact of these strategies in specific lung diseases on children's long-term outcome. As the most common causes of respiratory failure are bronchiolitis and pneumonia, we recommend dividing study groups by age. For example, infants up to the age of one year old, which is the group with the highest incidence of bronchiolitis, children

under 4 years old, children under 12 years old and older children till 18 years old with other reasons of respiratory failure. Creating these age groups is important to avoid inconclusive studies about the outcome because of the heterogeneity of the groups. (6) We recommend to seek collaboration with the dedicated follow up staff who already lead a successful longer-term impact program for children with congenital anomalies and children after resuscitation or traumatic brain injury.

CONTINUED CASE

Brit was ventilated according our ventilation protocol for patients with lung disease, and pressure-controlled ventilation was continued the following days of her admission.

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TABLE 1 Comparison of 2 reviews concerning HFO versus CV

Article	Period inclusion	Designs	Number of studies	Inclusion	Outcomes	Conclusion
1.Duyndam A. et al. Invasive ventilation modes in children; an updated systematic review and meta-analysis	January 1. 2010 to October 1, 2020	RCTs and observational studies	21 studies 10 RCT 8 quasi- experimental studies (4 propensity score matching- retrospective observational) 1 pilot nested study 2 crossover studies 12 HFO/1 APRV/ 1 HFO vs APRV/ 1 BIPAP/5 NAVA/ 1 weaning	Age: 28 days-18 years Only studies comparing at least two ventilation modes Excluded: Non-invasive ventilation, premature neonates < 37 weeks, other language than English	Mortality with CV: OR 0.62 (95%CI 0.42;0.91);p=0.019, I^2=38% [n=11]) DOV: (SMD 0.33; 95%CI 0.02 to 0.67; p=0.06) [n=9]) LOS: (SMD 0.09; 95%CI -0.29 to 0.12; p=0.39)[n=3]) Oxygenation, PaO_2/FiO_2 ratio: (SMD 1.55; 95%CI: 0.11 to 2.99; p=0.0346; I^2 = 89%) In the subgroup analysis for the propensity score studies, CV was again associated with a lower risk of mortality (OR 2.2; 95%CI: 1.69 to 2.86; I^2=0%) compared to HFO	CV in children is associated with lower mortality than is HFO. There is no evidence that HFO reduces LOV, LOS or oxygenation. Preliminary findings for NAVA are promising. No evidence for APRV
2. Junqueira M.D. et al. HFO in children; a systematic review and meta-analysis	Before December 2020	RCTs and observational studies	11 studies 6 RCT 5 observational Mean age: 8.2 months, mean Oxygenation index in the RCTs was: 24.4	Age: 28 days-18 years Only studies comparing HFOV vs CMV in patients with hypoxemic respiratory failure No language restrictions	The effect of HFOV on mortality was not significant and clinically significant harm or benefit could not be excluded (RR 0.93; 95% CI 0.72;1.20) I^2 0%,p=0.74) In the subgroup of observational studies the pooled RR was: (1.37; 95%CI 0.84 to 2.22) I^2 85%, p< 0.001) LOV: (RR -2.23; 95%CI -5.07 to 0.61) Treatment failure: (RR 0.28; 95%CI, 0.08 to 1.02)	The scarce evidence available does not allow us to conclude that HFOV has advantages over CMV concerning mortality and DOV. Further studies are needed to clarify its role in the treatment of acute hypoxemic respiratory failure in children Therefore, it should not be routinely used in this population as a primary strategy in place of cv lung protective ventilation until further RCTS are done

APRV: airway pressure release ventilation ; BIPAP: bilevel positive airway pressure; CV: conventional ventilation studies,; HFO: high frequency oscillation ventilation; NAVA: neurally adjusted ventilatory assist ventilation; DOV: duration of ventilation; LOS: length of stay; RCT: randomized controlled trial; RR: relative risk; SMD: standardized mean difference

ADHERENCE TO PROTOCOLS

After the implementation of a ventilation algorithm in our PICU we studied physicians' sustained adherence (chapter 3) during the study period of 2 years. The adherence rate of 84%, two years after introducing the protocol, was obtained by intensive education and training, indicating that implementation strategies tailored to specific circumstances are needed to increase adherence to protocols and guidelines. Physicians' adherence to the ventilation algorithm improved the highest with respect to post cardiac surgery patients without primary pulmonary abnormalities, who received protocolized nursing care including preset ventilator settings. The improvement in adherence in patients with lung disease was less marked, suggesting that physicians' routines and personal preferences play an import role.

Unit culture qualities such as interdisciplinary collaboration, effective communication and leadership, but also organizational aspects such as nurse-to-patient ratio and ongoing education are associated with better quality of care. (11, 12) Manipulating these specific organizational characteristics may be an effective strategy to improve adherence to protocols, which deserves to be explored and evaluated in further implementation projects. (13, 14) Since 2006, we have trained the whole PICU staff (nurses, physicians and other unit staff) in crew resource management to improve communication and cooperation. This training was followed by refresher courses. Crew resource management is a well-recognized need to respond to highly demanding situations where acute situations often occur that require a competent approach with debriefings, to proactively seek to minimize the risk of errors. This is a continuing process and could be applied also to the implementation and evaluation of protocols. Several studies show that team training improves team work competencies; that leadership training improves leader capabilities; and that team debriefings improve team processes. (15-17) A major challenge, however, is sustaining the training effects. Some suggestions are to conduct debriefs directly after training and periodically over time to guide the process of implementation, to appoint people to monitor compliance and people who can lead implementation projects and continue to evaluate them.

CONTINUED CASE
Brit, the 12-year-old girl on mechanical ventilation, continued to have high ventilatory conditions for five days. She turned out to have a gram-negative infection and was treated with antibiotics. Sputum was mobilized with nebulization and the help of

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physiotherapy with thorax compression. After that, oxygen could be gradually decreased and the PCO_2 decreased.

The weaning process could be started. In our PICU, this means that if certain conditions are met (a pressure-controlled level equal or under 15 cmH_2O above PEEP 8 cmH_2O and oxygen level of 60%), the nurses themselves can start to wean according to the ventilation protocol. They can either wean oxygen to 45% and conduct a spontaneous breathing trial (a pressure support mode of 10 cmH_2O above PEEP 5 cmH_2O) or wean the patient gradually and ultimately switch the controlled mode to a supporting mode on the ventilator: pressure support (PS) or volume support (VS= pressure support with a guaranteed tidal volume) to see if this is tolerated.

Weaning can be done in many ways. One way is to support the patient with neurally adjusted ventilator assist ventilation (NAVA).

NAVA- A WEANING MODE

In 2012, we studied the feasibility of NAVA in ten neonates and ten children and how it was tolerated (*chapter 5*). In 2012 this was a relatively new promising ventilation mode and we needed more data about the practical feasibility, Such as placing a NAVA catheter, fixation and finding the optimal electrical activity of the diaphragm (Edi signal). We concluded that NAVA was feasible once an accurate signal of the Edi signal was achieved, and as well was safe and well tolerated in both neonates and children. We gave some recommendations for inserting the NAVA (Edi) catheter and settings of the conventional trigger and advised to teach nurses the essentials needed for NAVA to succeed, because it was a very different approach compared to other conventional ventilation modes.

From the existing pediatric literature on NAVA, we know that invasive and non-invasive NAVA improve patient-ventilator interaction, result in lesser need for oxygen and sedation, less cases of apnea, lower peak pressures and improved comfort. (18, 19) Most of the previous studies had studied the physiological effect of NAVA, like we did in our study. However, there is little evidence about its effects on clinically even more relevant outcomes such as duration of ventilation and length of PICU stay. The systematic review on weaning with NAVA from Sugunan et al. (2021) assessed the

effect of NAVA versus CV on clinical outcomes in invasively ventilated children and included one RCT and two cohort studies. (20) The authors found weak evidence of efficacy in terms of improved clinical outcomes, especially a shorter duration of ventilation and PICU length of stay, as well as reduced needs for sedatives. Further, they found no evidence for lower costs of care and were unable to make recommendations regarding the routine use of NAVA in the weaning process of invasively ventilated children in PICUs. Therefore, the question is whether NAVA holds as much promise in children as that shown in adults, with evidence of a shorter duration of ventilation (21, 22). In premature infants, NAVA also works well with the ability to control the device according to their own rhythm – resulting in greater comfort and lesser need for analgesics and sedatives. (18, 19, 23) Curiously, the effect of asynchrony in children, defined as the inability of the ventilator to detect the patient's breathing efforts, seems to have less effect on outcome of ventilation than in adults or premature neonates. (24-26) Maybe because the group of critically ill children is very heterogeneous in age and reason of admission. Implementation of NAVA requires quite a lot of training as we saw in our feasibility study, and it requires knowledge and skills to make it successful. Moreover, the cost of catheters is high. NAVA needs further investigation in our opinion; we need to evaluate the effect of NAVA on weaning in larger numbers of homogeneous groups of ventilated children who have to be ventilated for a longer period. This should be done in multi-centre comparative effectiveness trials to have enough patient numbers and to measure outcomes such as duration of ventilation, ventilator-free days, extubation success, length of stay, neurocognitive development and pulmonary function.

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CONTINUED CASE

Brit was weaned of ventilation by the physicians to pressure-controlled ventilation: 15 cmH_2O above PEEP 8 cmH_2O (with a peak pressure of 23 cmH_2O), with a respiratory rate of 35 per minute and FiO_2 of 0.5. At that point, the nurses started the weaning algorithm. They weaned Brit gradually and on day 7 performed a spontaneous breathing trial and set the ventilator to PS 10 cmH_2O above PEEP 5 cmH_2O (with a peak pressure of 15 cmH_2O) and FiO_2 to 0.45, which was tolerated well. However, there was still much mucus production. Brit had to be suctioned more than three times an hour. She occasionally was ventilated completely instead of triggering the ventilator, which could be assessed in the trends of the ventilator. In a multidisciplinary meeting we discussed how to proceed. Questions were: was she ready to be liberated from the ventilator

and how would we support her afterwards? With non-invasive ventilation or high flow nasal cannula?

NURSE-LED WEANING

In 2015, we implemented a nurse-led weaning protocol (chapter 6) and primarily measured the effects on duration of ventilation. We found that implementation did not result in a significantly shorter duration of mechanical ventilation on our PICU, but was safe and did not lead to a higher reintubation rate (7% versus 5%) following nurse-led weaning compared to standard care. We think that in a time of shortage of (ICU) nurses every effort must be made to retain them and give them an important fulfilment of their role. This was the only nurse-led weaning study on a PICU till then, although more interdisciplinary weaning protocol studies were published. (27-29) A recent multi-centre study in eighteen British PICUs proved that an interdisciplinary weaning protocol with a spontaneous breathing trial shortens the duration of ventilation. (29) International surveys supports that PICU nurses should have a role in decision-making around weaning of ventilation because they are at the child's bedside for 24 hours per day and will note whether the child recovers or deteriorates. (30-32). Therefore, we decided to conduct another nurse-led weaning study with adding a spontaneous breathing trial to our existing weaning protocol (chapter 7). Even as in our single-centre study (33), we found no significant difference in duration of ventilation. However, the new protocol was safe and successful in terms of no higher reintubation rate. We found that the way of implementation is the most important factor in succeeding to apply a new protocol on the PICU, because although compliance to the protocol by staff was high, it was not high enough in both studies (seventy percent for the single-centre study and seventy-eight percent for the multi-centre study). In addition, it took longer than expected to include enough patients in the participating PICUs in our multi-centre study (chapter 7). Therefore, the time frame of the study could have given bias given the changes in ventilation machines or strategies during the years in the different centres. Strategies to implement a protocol should take into account factors such as knowledge, attitudes of the medical and nursing groups towards the protocol, the nurse-patient ratio, staff opinions, behavior and resources, as described in chapter 3. (34-36) In the future, we should add a process evaluation to understand the effects of the protocol among all nurses and ask nurses how they feel about their autonomy; changing the ventilator settings, involvement in thinking about the next steps, having a

goal each day, and about challenges they encounter. (37) Opinions should preferably be collected directly after their shifts. Senior PICU nurses in Australia and New Zealand, who were surveyed about ventilator weaning and extubation practices in critically ill children, felt that they were an underutilized cohort in decision-making on these issues. (32) Most of the respondents in that survey favored more shared decision-making. We believe that nurses can increase their knowledge, can logically discuss patients with physicians and can become more confident by actively participating in a nurse-led protocol. However, what makes it difficult is that the PICU cannot pursue a one-size-fits-all approach; the pathologies of the patients are heterogeneous as well as their ages. In other words, sometimes a protocol is not well enough tailored to one individual patient. Therefore we think that an experienced ICU staff member, who is involved in the implementation, is needed to guide the process of implementing this protocol – and even more importantly, to sustain the effects. For example, a ventilation practitioner (a nurse with a special education in mechanical ventilation) or a nurse practitioner with knowledge about mechanical ventilation. More attention should be paid to interdisciplinary communication and for everyone to adhere to the protocol in further research. Recently the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) decided to update their recommendations for mechanical ventilation based on the Paediatric Mechanical Ventilation consensus conference with more evidence concerning the practice of pediatric mechanical ventilation. (38). However, more research is definitively needed on how to wean children from ventilation, how to wean when spontaneous breathing trials fail, protocolized weaning, preventing muscle weakness, an accurate and evidence-based extubation readiness test, initiation of non-invasive ventilation after extubation or how to predict extubation failure, to develop these recommendations and enhance the level of evidence. (36, 39-41) These studies should take into account the heterogeneity of the paediatric population – only multi-centre studies will achieve enough numbers of homogenous paediatric groups to generalise the effects.

CARE BUNDLES

Mechanical ventilation, but in fact all critical PICU care, is a team effort which could be improved through the implementation of care bundles. (36, 42, 43) Weaning from mechanical ventilation is also dependent of the use of analgesics and sedatives, the prevention of delirium or the pursuit of early mobilization and this also applies vice

versa. Recently, PICU liberation bundles have been developed according to an ABCDEF approach to avoid post-traumatic stress syndrome (PTSD) or intensive care syndrome. (36, 44) The ABCDEF bundle (A. stands for assess, prevent, and manage pain, B. Both SATs (spontaneous awakening trials) and SBTs (spontaneous breathing trials), C. Choice of analgesia and sedation, D. Delirium: assess, prevent, and manage, E. Early mobility and exercise, F. Family engagement and empowerment) offers guidance for the daily care of critically ill patients and may reduce pain, agitation and delirium, prevent physical, psychological and cognitive morbidities that limit or prolong recovery. Ista et al. evaluated current international practice in PICUs concerning this ABCDEF approach in an international survey, and found that ABCDEF bundle components have been adopted with substantial variability across worldwide regions. (45) Additional research must rigorously evaluate the efficacy of specific elements with a focus on B, D, E, and full ABCDEF bundle implementation. Implementation science is needed to facilitate and understand the barriers to ABCDEF implementation and sustainability with a focus on specific cultural and regional differences. (46) This indicates that while implementation of new protocols needs a lot of attention, it will ultimately improve the quality of care and be beneficial to the critically ill child at risk for a post-intensive care syndrome and their parents.

BEYOND THE ICU PERIOD

In the Netherlands a guideline for follow-up of children after admission to an intensive care unit states that PTSD in children and parents should be prevented as much as possible, and recommends that each PICU has a PTSD prevention guideline in place. (47) Both during PICU admission and after discharge, psycho education is important; information for parents with a young child on a PICU about the possibility of neuropsychological problems after discharge. Both the child and the parents should, at least 3 to 6 months after discharge of the child, be screened for (symptoms of) PTSD and, if necessary, referred for adequate diagnosis and treatment. We also advocate to follow-up children who have been on the ventilator on the PICU, even if this was for a short time, and to monitor lung function in case of persistent problems in this area. At our PICU, we already have outpatient clinics for children with congenital surgical anomalies and children after resuscitation or traumatic brain injury, but not for all children who stayed on the PICU. Before this is realized, it is at least important to contact all parents of (ventilated) patients who were admitted to our PICU and ask

if there are any problems with the child or family that can be traced back to the PICU admission. If so, we can see if follow up is needed and start this up.

CONTINUED CASE

The most important question in the case of Brit was: how weak had her respiratory muscles become after 7 days of mechanical ventilation? Did she develop diaphragmatic weakness or weakness of the other respiratory muscles? To this effect we performed the studies described in chapters 8 and 9.

THICKNESS AND THICKENING FRACTION OF THE DIAPHRAGM IN SPONTANEOUS BREATHING AND IN VENTILATED CHILDREN

In 2020 and 2021, we determined values of normal diaphragm thickness and thickening fraction by B mode ultrasound in 130 healthy children aged 0-8 years, divided in four age groups (*chapter 8*). The diaphragm of the 0-1-year-olds was thicker than that of the older children and remarkably even as thick as that of adults. This goes to show that the diaphragm may have already largely been constructed at birth. The values we found can give an insight in whether critical illness already influences changes in respiratory muscle thickness in critical ill children or can say something about the amount of decrease or increase of diaphragm thickness during mechanical ventilation. Establishing a cut-off point of a normal value for diaphragm thickening fraction per age group before extubation maybe can help estimate successful extubation in different patient groups.

In our next study of the diaphragm in 53 ventilated children (*chapter 9*), the diaphragm thickening fraction was not associated with extubation success, and consequently cannot be used as a standard objective extubation criterion alone. We also measured atrophy in these 53 children; defined as a decrease of more than 10 percent of the expiratory thickness of the diaphragm during the ventilation period. Importantly, seventeen of the fifty-three children had developed atrophy of the diaphragm during the ventilation period, but the majority could be successfully extubated. Two children whose extubation had failed had limb muscle weakness and difficulty coughing. (48) ICU-acquired muscle weakness (ICU-AW) is uncommonly diagnosed in children, unlike in adults. (49-51) An incidence of 0.02% is reported in children and was more

frequently reported in those with admission diagnoses of respiratory illness and infection. (51) ICU-AW in children was associated with a longer length of stay, longer duration of ventilation, and longer duration of chronic care. Dres et al. found only limited overlap between ICU-AW and diaphragm dysfunction in adult critically ill patients. (52) They found that diaphragm dysfunction is twice as frequent as ICU-AW and has a direct negative impact on weaning outcome. (52) Prospective studies in children are needed to better understand ICU-AW in children and the association between ICU-AW and diaphragm dysfunction.

The fact that we found no predictive value by measuring thickening fraction alone suggest that other factors than diaphragm thickness alone play a role in successful self-breathing after extubation. More studies are needed to determine the cut-off point of dTF for successful extubation, with a standardized ventilator support and level of sedation given just before extubatrion because the type of support will also influence the dTF. Some studies suggest to explore extra-diaphragmatic muscles before extubation because patients who have weakness of the diaphragm may compensate with parasternal muscle activity. (53-55) Maybe the combination of assessing parasternal muscles, diaphragm muscles and expiratory abdominal muscles will help predicting extubation success. For the future, we recommend to do more studies using ultrasound of the intercostal and abdominal muscles in combination with the diaphragm thickness in ventilated children. These studies will tell us if assessment of all respiratory muscles before doing a spontaneous breathing trial or before extubation can predict the outcome of extubation, like Tuinman et al. advise in difficult to wean adult patients. (53) These studies should include patient groups with genetic or syndromic conditions, chronic respiratory disorders such as former preterm neonates with bronchopulmonary dysplasia and chronic neurologic conditions because precisely in these categories there is often doubt about the optimal timing of extubation. A special group are newborns with congenital diaphragmatic hernia who can even miss nearly the complete diaphragm on one side. This group is known to need prolonged ventilatory support and is difficult to wean. We further recommend to divide the extubation failure groups of the above-mentioned studies into groups of different causes of extubation failure and underlying pathology, in order to find out whether an ultrasound study can predict a good outcome after extubation. In such research, the consensus method with measuring the diaphragm between the inner lines of the peritoneal membrane and pleura should be used to create more unity in the way of measuring. (53, 56, 57)

In all the ventilation studies we have done, it appears that it is difficult to draw conclusions from a heterogeneous group of ventilated children aged 0 to 18 years. The studies included newborns, infants, children and adolescents with varied reasons of admission, ventilation modes and duration. The diaphragm study again showed this. We learned that we need to look at more homogeneous groups in the future, although it is challenging to obtain enough patients numbers. Therefore, these studies will always have to be multi-centre studies in which scientific societies like the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) should take the lead.

CONTINUED CASE (THE END)

Before Brit was extubated, we made an ultrasound of the diaphragm at PS 10 above 5 cmH$_2$O and found a thickening fraction of 21%. The question was whether 21% was enough to successfully liberate her from ventilation. There was no atrophy of the diaphragm, assessed with ultrasound. The thickness of the diaphragm at end-expiration had decreased before extubation, but no more than 7% compared to the first day of ventilation. We did not assess the intercostal or abdominal muscles. She then was extubated and needed non-invasive ventilation for one and a half week, with a high work of breathing in the first two days of non-invasive ventilation. Afterwards she was supported with high flow nasal cannula and gradually weaned to oxygen by a nasal cannula. Her strength was coming back and she was able to cough and swallow and could be discharged from the hospital without any further support after four weeks of admission.

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CONSIDERATIONS AND FUTURE PERSPECTIVES

How do I see the future of mechanical ventilation of PICU patients?

Looking at Brit's case, it is essential that every PICU should have a ventilation protocol, that the optimal ventilation mode is clear, as well as the strategy to be followed and the goals to achieve.

What could be done better is:

- to improve the weaning protocol and use it with all patients, led by nurses in good collaboration with the PICU physicians.

- to perform a spontaneous breathing trial whenever this is possible and then also extubate if this is successful. When in doubt, and especially in the children with a muscle disease like Brit, or in children who have been ventilated for a long time, it should be advisable to do an ultrasound of the lungs on both sides, the diaphragm, the abdominal muscles and intercostal muscles before extubation, to see if the respiratory muscles are working well, and if there is no pneumothorax or atelectasis. A chest X-ray is then no longer necessary to be sure if one can extubate. This again avoids radiation. Ultrasounds can be made by trained intensivists/fellows, advanced nurse practitioners as well as ventilation practitioners. It is important to make ultrasounds in a standardized way and to record the results in the patient data management system to be able to see the results again.
- to appoint more ventilation practitioners to continually train nurses and improve their autonomy with the latest insights in the field of ventilation.
- to expand nursing research. In the nursing field there is room for improvement in the area of non- invasive ventilation. Currently, a good protocol is in place and nurses can basically start by themselves by following this protocol. However, asynchrony is a very common problem with the ventilation modes and masks we use. Furthermore, nurses and practitioners should think about further implementing and studying a PICU liberation bundle for sedation, preventing ventilator associated pneumonia, weaning and early mobilization with attention to a process evaluation to measure the effects of the bundle among all nurses. Moreover, it needs constant attention to maintain the effects.
- to explore cooperation with the adult intensive care. We can learn from each other in terms of ultrasound of the respiratory muscles, electrical impedance tomography or esophageal pressure measurement.
- to develop follow up for all ventilated patients after the PICU stay. For chronic home ventilation, there is already excellent care and follow up realized through the Centre for home ventilation. For the other ventilated children, one can start with contacting all parents of ventilated patients who were in our PICU and ask if there are any problems with the child or family that can be traced back to the PICU admission. If so, we can see if follow up is needed and start this up. In the future an outpatient clinic for prolonged ventilation patients can study outcomes such as morbidity, lung function and quality of life, and support parents and children with possible problems. The above of course applies to all patients admitted to the PICU, but for most of them follow up is already provided. We now advocate

especially for follow up of the ventilated children because we would like to monitor the longer-term effects of mechanical ventilation.

TAKE HOME MESSAGE

The quality of ventilation care on the PICU is based on interdisciplinary cooperation between dedicated PICU nurses, physicians and practitioners. The ventilation care is evidence-based or at least is there a unity of work formed by preferably evidence-based protocols or bundles and there is attention to monitor children's long-term outcomes after being on the ventilator, irrespective of the underlying disease or reason of PICU admission.

LITERATURE

1.   Ista E, de Hoog M, Tibboel D, van Dijk M. Implementation of standard sedation management in paediatric intensive care: effective and feasible? J Clin Nurs. 2009;18(17):2511-20.

2.   Lachmann B. Open up the lung and keep the lung open. Intensive Care Med. 1992;18(6):319-21.

3.   Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747-55.

4.   Junqueira FMD, Nadal, J.A.H., Brandao, M.D., Nogueira, R.J.N., de Souza, T.H. High-frequency oscillatory ventilation in children: A systematic review and meta-analysis . . Pediatric Pulmonology. 2021(56):1872–88.

5.   Kneyber MCJ, Cheifetz IM, Curley MAQ. High-frequency oscillatory ventilation for PARDS: awaiting PROSPect. Crit Care. 2020;24(1):118.

6.   Randolph AG, Meert KL, O'Neil ME, Hanson JH, Luckett PM, Arnold JH, et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. Am J Respir Crit Care Med. 2003;167(10):1334-40.

7.   World SoCCMat, Societies FoPlaCC. Pediatric Acute Respiratory Distress Syndrome: Consensus Recommendations From the Pediatric Acute Lung Injury Consensus Conference*. Pediatric Critical Care Medicine. 2015;Volume 16(number 5).

8.   Hordijk JA, Verbruggen SC, Buysse CM, Utens EM, Joosten KF, Dulfer K. Neurocognitive functioning and health-related quality of life of children after pediatric intensive care admission: a systematic review. Qual Life Res. 2022;31(9):2601-14.

9.   de Sonnaville ESV, Knigs M, van Leijden O, Knoester H, van Woensel JBM, Oosterlaan J. Intelligence outcome of pediatric intensive care unit survivors: a systematic meta-analysis and meta-regression. BMC Med. 2022;20(1):198.

10.   Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. Am J Respir Crit Care Med. 2013;188(12):1420-7.

11.   Davies HT, Nutley SM, Mannion R. Organisational culture and quality of health care. Qual Health Care. 2000;9(2):111-9.

10

12. Stein-Parbury J, Liaschenko J. Understanding collaboration between nurses and physicians as knowledge at work. Am J Crit Care. 2007;16(5):470-7; quiz 8.

13. Sinuff T, Cook D, Giacomini M, Heyland D, Dodek P. Facilitating clinician adherence to guidelines in the intensive care unit: A multicenter, qualitative study. Crit Care Med. 2007;35(9):2083-9.

14. Sinuff T, Muscedere J, Cook DJ, Dodek PM, Anderson W, Keenan SP, et al. Implementation of clinical practice guidelines for ventilator-associated pneumonia: a multicenter prospective study. Crit Care Med. 2013;41(1):15-23.

15. Lacerenza CN, Reyes DL, Marlow SL, Joseph DL, Salas E. Leadership training design, delivery, and implementation: A meta-analysis. J Appl Psychol. 2017;102(12):1686-718.

16. Salas E, Reyes DL, McDaniel SH. The science of teamwork: Progress, reflections, and the road ahead. Am Psychol. 2018;73(4):593-600.

17. Buljac-Samardzic M, Dekker-van Doorn CM, Maynard MT. What Do We Really Know About Crew Resource Management in Healthcare?: An Umbrella Review on Crew Resource Management and Its Effectiveness. J Patient Saf. 2021;17(8):e929-e58.

18. Beck J, Sinderby C. Neurally Adjusted Ventilatory Assist in Newborns. Clin Perinatol. 2021;48(4):783-811.

19. Beck J, Emeriaud G, Liu Y, Sinderby C. Neurally-adjusted ventilatory assist (NAVA) in children: a systematic review. Minerva Anestesiol. 2016;82(8):874-83.

20. 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. 2021;10(15).

21. Kacmarek RM, Villar J, Parrilla D, Alba F, Solano R, Liu S, et al. Neurally adjusted ventilatory assist in acute respiratory failure: a randomized controlled trial. Intensive Care Med. 2020;46(12):2327-37.

22. Liu L, Xu X, Sun Q, Yu Y, Xia F, Xie J, et al. Neurally Adjusted Ventilatory Assist versus Pressure Support Ventilation in Difficult Weaning: A Randomized Trial. Anesthesiology. 2020;132(6):1482-93.

23. Stein H, Alosh H, Ethington P, White DB. Prospective crossover comparison between NAVA and pressure control ventilation in premature neonates less than 1500 grams. J Perinatol. 2013;33(6):452-6.

24. Blokpoel RGT, Burgerhof JGM, Markhorst DG, Kneyber MCJ. Trends in Pediatric Patient-Ventilator Asynchrony During Invasive Mechanical Ventilation. Pediatr Crit Care Med. 2021;22(11):993-7.

25. Blokpoel RGT, Koopman AA, van Dijk J, Kneyber MCJ. Additional work of breathing from trigger errors in mechanically ventilated children. Respir Res. 2020;21(1):296.

26. Blokpoel RGT, Wolthuis DW, Koopman AA, Kneyber MCJ. Reverse Triggering: A Novel Type of Patient-Ventilator Asynchrony in Mechanically Ventilated Children. Am J Respir Crit Care Med. 2019;200(2):e4-e5.

27. Abu-Sultaneh S, Hole AJ, Tori AJ, Benneyworth BD, Lutfi R, Mastropietro CW. An Interprofessional Quality Improvement Initiative to Standardize Pediatric Extubation Readiness Assessment. Pediatr Crit Care Med. 2017;18(10):e463-e71.

28. Krawiec C, Carl D, Stetter C, Kong L, Ceneviva GD, Thomas NJ. Challenges With Implementation of a Respiratory Therapist-Driven Protocol of Spontaneous Breathing Trials in the Pediatric ICU. Respir Care. 2017;62(10):1233-40.

29. Blackwood B, Tume LN, Morris KP, Clarke M, McDowell C, Hemming K, et al. Effect of a Sedation and Ventilator Liberation Protocol vs Usual Care on Duration of Invasive Mechanical Ventilation in Pediatric Intensive Care Units: A Randomized Clinical Trial. JAMA. 2021;326(5):401-10.

30. Elisa P, Francesca C, Marco P, Davide V, Laura Z, Fabrizio Z, et al. Ventilation Weaning and Extubation Readiness in Children in Pediatric Intensive Care Unit: A Review. Front Pediatr. 2022;10:867739.

31. Rose L, Blackwood B, Egerod I, Haugdahl HS, Hofhuis J, Isfort M, et al. Decisional responsibility for mechanical ventilation and weaning: an international survey. Crit Care. 2011;15(6):R295.

32.   Schults JA, Charles K, Harnischfeger J, Erikson S, Burren J, Waak M, et al. Ventilator weaning and extubation practices in critically ill children: An Australian and New Zealand survey of practice. Aust Crit Care. 2022.

33.   Duyndam A, Houmes RJ, van Rosmalen J, Tibboel D, van Dijk M, Ista E. Implementation of a nurse-driven ventilation weaning protocol in critically ill children: Can it improve patient outcome? Aust Crit Care. 2020;33(1):80-8.

34.   Grol R, Wensing M. What drives change? Barriers to and incentives for achieving evidence-based practice. Med J Aust. 2004;180(S6):S57-60.

35.   Grol RWM. Implementation; effective improvement of patient care (in Dutch: Implementatie; effectieve verbetering van de patientenzorg). 4th edMaarsen; Elsevier Gezondheidszorg; 2011.

36.   Walz A, Canter MO, Betters K. The ICU Liberation Bundle and Strategies for Implementation in Pediatrics. Curr Pediatr Rep. 2020;8(3):69-78.

37.   Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015;350:h1258.

38.   Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med. 2017;43(12):1764-80.

39.   Ramnarayan P, Blackwood B, Khemani RG. What's new in paediatric ventilator liberation? Intensive Care Med. 2022;48(11):1635-7.

40.   van Dijk J, Blokpoel RGT, Abu-Sultaneh S, Newth CJL, Khemani RG, Kneyber MCJ. Clinical Challenges in Pediatric Ventilation Liberation: A Meta-Narrative Review. Pediatr Crit Care Med. 2022.

41.   Abu-Sultaneh S, Iyer NP, Fernandez A, Gaies M, Gonzalez-Dambrauskas S, Hotz JC, et al. Executive Summary: International Clinical Practice Guidelines for Pediatric Ventilator Liberation, A PALISI Network Document. Am J Respir Crit Care Med. 2022.

42.   Phipps LM, Bartke CN, Spear DA, Jones LF, Foerster CP, Killian ME, et al. Assessment of parental presence during bedside pediatric intensive care unit rounds: effect on duration, teaching, and privacy. Pediatr Crit Care Med. 2007;8(3):220-4.

43.   Phipps LM, Thomas NJ. The use of a daily goals sheet to improve communication in the paediatric intensive care unit. Intensive Crit Care Nurs. 2007;23(5):264-71.

44.   Di Nardo M, Boldrini F, Broccati F, Cancani F, Satta T, Stoppa F, et al. The LiberAction Project: Implementation of a Pediatric Liberation Bundle to Screen Delirium, Reduce Benzodiazepine Sedation, and Provide Early Mobilization in a Human Resource-Limited Pediatric Intensive Care Unit. Front Pediatr. 2021;9:788997.

45.   Ista E, Redivo J, Kananur P, Choong K, Colleti J, Jr., Needham DM, et al. ABCDEF Bundle Practices for Critically Ill Children: An International Survey of 161 PICUs in 18 Countries. Crit Care Med. 2022;50(1):114-25.

46.   Wittmeier KD, Klassen TP, Sibley KM. Implementation science in pediatric health care: advances and opportunities. JAMA Pediatr. 2015;169(4):307-9.

47.   Kindergeneeskunde NVv. Follow-up van kinderen na opname op een intensive care: Federatie Medisch Specialisten; 2017 [updated 03-22-2017. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881283&tagtitles=Intensive%2BCare.

48.   Vivier E, Muller M, Putegnat JB, Steyer J, Barrau S, Boissier F, et al. Inability of Diaphragm Ultrasound to Predict Extubation Failure: A Multicenter Study. Chest. 2019;155(6):1131-9.

49.   Anekwe DE, Biswas S, Bussieres A, Spahija J. Early rehabilitation reduces the likelihood of developing intensive care unit-acquired weakness: a systematic review and meta-analysis. Physiotherapy. 2020;107:1-10.

50.   Dantas CM, Silva PF, Siqueira FH, Pinto RM, Matias S, Maciel C, et al. Influence of early mobilization on respiratory and peripheral muscle strength in critically ill patients

10

Influencia da mobilizacao precoce na forca muscular periferica e respiratoria em pacientes criticos. Rev Bras Ter Intensiva. 2012;24(2):173-8.

51. Field-Ridley A, Dharmar M, Steinhorn D, McDonald C, Marcin JP. ICU-Acquired Weakness Is Associated With Differences in Clinical Outcomes in Critically Ill Children. Pediatr Crit Care Med. 2016;17(1):53-7.

52. Dres M, Dube BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. Am J Respir Crit Care Med. 2017;195(1):57-66.

53. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, et al. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. Intensive Care Med. 2020;46(4):594-605.

54. MM IJ, Lemson J, van der Hoeven JG, Heunks LMA. The impact of critical illness on the expiratory muscles and the diaphragm assessed by ultrasound in mechanical ventilated children. Ann Intensive Care. 2020;10(1):115.

55. Newth CJ, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, et al. Weaning and extubation readiness in pediatric patients. Pediatr Crit Care Med. 2009;10(1):1-11.

56. Haaksma ME, Smit JM, Boussuges A, Demoule A, Dres M, Ferrari G, et al. EXpert consensus On Diaphragm UltraSonography in the critically ill (EXODUS): a Delphi consensus statement on the measurement of diaphragm ultrasound-derived parameters in a critical care setting. Crit Care. 2022;26(1):99.

57. Shi ZH, de Vries H, de Grooth HJ, Jonkman AH, Zhang Y, Haaksma M, et al. Changes in Respiratory Muscle Thickness during Mechanical Ventilation: Focus on Expiratory Muscles. Anesthesiology. 2021;134(5):748-59.

chapter

SUMMARY

SUMMARY

PART I. VENTILATION STRATEGIES FOR CRITICALLY ILL CHILDREN

In **chapter 2** we searched the literature for evidence to provide the optimal ventilator modes for mechanical ventilation of pediatric patients. We showed that the available literature (five randomized clinical trials were found) does not provide sufficient evidence on the best ventilation mode in critically ill children beyond the newborn period. With regards to high-frequency ventilation (HFO) we found that it provided better oxygenation after 72 hours than conventional ventilation (CV). However, there is no evidence that HFO would reduce mortality and length of ventilation (LOV). With this knowledge we defined our protocol for ventilation of critically ill children with help of evicence of adult literature.

In **chapter 3** we updated the formal systematic review and meta-analysis on preferred ventilation modes in critically ill children from 28 days up to 18 years of age in 2020. We found twenty one studies (7 RCTs and 14 observational studies) on five different ventilation modes. Pooled analysis of HFO versus CV showed a lower mortality rate with CV while LOV and LOS were not significantly different. When we analyzed the RCTs and observational studies apart we found an OR of 0.99 (no benefit or harm) for the RCTs versus the estimate of an OR of 0.45 (benefit for CV) in the observational cohorts. Of the studies comparing NAVA and CV there was only one small RCT, so this should be studied in larger RCTs.

In **chapter 4** we described the implementation of the ventilation protocol, an algorithm for guiding the choice of ventilation, for use at our PICU. This algorithm improved physician's adherence to the ventilation algorithm and the effect was shown to be sustainable over time; this was also accomplished with the help of nurses. A well thought-out implementation plan with attention to potential barriers and facilitators is a crucial first step and must be followed by ongoing attempts to improve adherence.

PART II: WEANING OFF MECHANICAL VENTILATION IN CRITICALLY ILL CHILDREN

In **chapter 5** we evaluated the practical feasibility for nurses working with Neurally Adjusted Ventilator Assist (NAVA), a mode of assisted ventilation which uses electrical activity of the diaphragm to synchronize the patient's breathing with the machine's breathing cycle. We assessed patient comfort and safety when NAVA was initiated. NAVA was compared with the conventional mode of ventilation for 3 hours each.

Twenty-one neonates and children were enrolled into the study. There were no reported adverse events. In most patients, the NAVA catheter was placed too shallow. Accurate placement was confirmed by visual inspection of the NAVA positioning window. Patients' comfort did not differ between the conventional mode and NAVA. We found that Nava was feasible, once an accurate signal of the electrical activity of the diaphragm was achieved and seemed safe and well tolerated in both neonates and children. Nurses needed to gain experience in placing the NAVA catheter and our practical recommendations were noted in this article.

In **chapter 6** we investigated if implementation of a nurse-led ventilation protocol could lead to a shorter duration of ventilation (DOV) and shorter length of PICU stay (LOS). We conducted a prospective, pretest-posttest study and involved mechanically ventilated patients on our PICU. In the pretest period mechanical ventilation (MV) was weaned off as usual. This implies that a physician assessed a stable patient's MV and instructed nurses to gradually wean off pressure, tidal volume, positive end-expiratory pressure (PEEP) and change to a support mode. A nurse-led weaning protocol was then implemented over the course of three months. In the posttest period nurses used the weaning protocol. Primary outcome was DOV and secondary outcomes were LOS, reintubation rate and compliance with the protocol. In total 424 patients aged from 0-18 years old (212 pre-test and 212 post-test) were included. In both groups the median age was 3 months. Median DOV and LOS did not differ significantly between pre- and posttest periods. Compliance with the prescribed support mode was significantly higher in the posttest period than in the pretest period. Reintubation rate was not significantly different between both periods. Extubation rate during nights was higher in the posttest period but not significantly. Implementation of a nurse-drive weaning protocol did not result in a significantly shorter duration of mechanical ventilation but was safe and successful.

In **chapter 7** we performed a multi-center pre-post study in which DOV was compared between usual care and nurse-led weaning including a spontaneous breathing trial in 3 Pediatric Intensive Care Units in the Netherlands. One hundred and ninety children received usual care and 157 received nurse-led weaning. Multivariate analysis showed no significant difference in DOV between the pretest and posttest periods (p=0.79). Estimated difference in DOV was -0.02 (IQR -0.14 - 0.11) for nurse-led weaning. Study site, gender, age, admission indication and Pediatric Risk of Mortality were not significantly associated with a reduction of DOV. In the univariate analysis, there was

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no significant difference in LOV, LOS and reintubation rate between both periods. Rate of compliance with protocolized weaning was 77.7%.

PART III: ULTRASOUND OF THE DIAPHRAGM IN HEALTHY AND VENTILATED CHILDREN

In **chapter 8** we determined values of normal diaphragm thickness and thickening fraction in healthy children aged 0-8 years old by B mode ultrasound. In total 137 healthy children were included. Mean Tdi-insp ranged from 2.09 mm (sd 0.40) to 1.69 mm (sd 0.30) Mean Tdi-exp ranged from 1.64 mm (sd 0.30) to 1.38 mm (sd 0.20). Mean Tdi for newborns up to 1 year old was significant thicker compared to older children (p<0.001). Median dTF ranged from 25.4% (sd 10.4) to 21.3% (sd 7.10).The intraclass correlation coefficients of inter-observer reproducibility was high. Pearson correlation indicated a significant weak or moderate negative correlation between thickening fraction and diaphragm thickness on the one hand and age groups and body surface on the other hand. These reference values are useful for diaphragm evaluation in clinical practice.

In **chapter 9** we investigated whether thickening fraction of the diaphragm, measured with ultrasound (US) had an association with successful extubation in ventilated children and described the progression of US diaphragmatic thickening and thickening fraction during ventilation. We did a prospective observational cohort study on the PICU in children aged 0-18 years old, ventilated for more than 48 hours. Ultrasounds were performed on day 1 after intubation, on day 4, day 7, day 10, the moment when the patient underwent an SBT in a PS mode, just before extubation on CPAP with PEEP 5 and once in the next 24 hours after extubation. 53 patients were enrolled with a median age of 3.0 months (IQR 0.1-66.0) and underwent 226 ultrasounds. Median dTF before extubation with Pressure Support 10 above 5 cmH2O was 15.2% (IQR 9.7-19.3). Extubation failure occurred in six children, three of whom were re-intubated and three then received non-invasive ventilation. There was no significant association between dTF and extubation success; OR 0.33 (95% CI;0.06-1.86). Diaphragmatic atrophy was observed in 17/53 cases, in three of them extubation failure occured. Children in the extubation failure group were younger: 2.0 months (IQR 0.81-183.0) vs 3.0 months (IQR 0.10-48.0);p=0.045. At baseline, pre-extubation and post-extubation there was no significant correlation between age and BSA on the one hand and dTF, Tdi-insp and Tdi-exp on the other hand.

The intraclass correlation coefficients of inter-observer reproducibility was high.

There was no significant association between thickening fraction of the diaphragm and extubation success in ventilated children.

SAMENVATTING

DEEL 1. BEADEMING STRATEGIEËN VOOR KRITISCH ZIEKE KINDEREN

In **hoofdstuk 2** hebben we in de literatuur gezocht naar bewijs voor de optimale beademingsvorm voor mechanische beademing van pediatrische patiënten. Wij toonden aan dat de beschikbare literatuur (er werden vijf gerandomiseerde klinische studies gevonden) onvoldoende bewijs levert voor de beste beademingsvorm bij kritisch zieke kinderen na de pasgeboren periode. Wat betreft hoogfrequente beademing (HFO) vonden wij dat deze na 72 uur een betere oxygenatie gaf dan conventionele beademing. Er is echter geen bewijs dat HFO het sterftecijfer en de beademingsduur zou verminderen. Met deze kennis hebben wij een protocol met algoritme voor de beademing van kritisch zieke kinderen gemaakt met behulp van bewijs uit volwassen literatuur.

In **hoofdstuk 3** hebben wij het systematische review met meta-analyse naar de voorkeur voor beademingsvorm bij ernstig zieke kinderen van 28 dagen tot 18 jaar geactualiseerd in 2020. We vonden eenentwintig studies (7 RCT's en 14 observationele studies) over vijf verschillende beademingsvormen. De gepoolde analyse van HFO versus conventionele beademing (CB) toonde een lager sterftecijfer met conventionele beademing, terwijl beademingsduur en verblijf op de IC niet significant verschilden. Als we de RCT's en observationele studies apart analyseerden vonden we een Odds Ratio van 0.99 (geen voordeel en geen nadeel) voor de RCT's versus een Odds Ratio van 0.45 (voordeel voor CB) voor de observationele studies. Van de studies waarin NAVA en CB werden vergeleken was er slechts één een kleine RCT, dus dit dient in grotere RCT's te worden onderzocht.

In **hoofdstuk 4** beschrijven we de implementatie van het protocol ontwikkeld n.a.v het review in hoofdstuk 2, een algoritme voor de keuze van beademingsvorm, op onze kinder IC. Dit protocol verbeterde de therapietrouw van artsen aan het beademingskeuze algoritme en het effect bleek aan te houden in de tijd; dit werd ook bereikt met de hulp van verpleegkundigen. Een goed doordacht implementatieplan

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met aandacht voor mogelijke barrières en kansen is een cruciale eerste stap en moet worden gevolgd door voortdurende pogingen om de therapietrouw te verbeteren.

DEEL 2. WEANEN VAN MECHANISCHE BEADEMING BIJ KRITISCH ZIEKE KINDEREN

In **hoofdstuk 5** evalueerden we de praktische haalbaarheid voor verpleegkundigen die werken met Neurally adjusted ventilatory assist (NAVA), een wijze van ondersteunende beademing waarbij gebruik wordt gemaakt van elektrische activiteit van het diafragma om de ademhaling van de patiënt te synchroniseren met de ademhalingscyclus van de machine. Wij hebben het comfort en de veiligheid van de patiënt beoordeeld wanneer NAVA werd gestart. NAVA werd vergeleken met conventionele beademing gedurende 3 uur. Er werd gestart met 3 uur beademing op Pressure Support en daarna werd er 3 uur NAVA gegeven. Eenentwintig neonaten en kinderen werden geïncludeerd. Er werden geen ongewenste voorvallen gemeld. Bij de meeste patiënten was de NAVA-katheter te ondiep geplaatst. Nauwkeurige plaatsing werd bevestigd door visuele inspectie van het NAVA-positionering venster. Het comfort van de patiënten verschilde niet tussen de conventionele modus en NAVA. Wij vonden dat NAVA haalbaar was, zodra een nauwkeurig signaal van de elektrische activiteit van het diafragma was bereikt. Verder was NAVA veilig en kon goed worden verdragen bij zowel neonaten als kinderen. Verpleegkundigen moesten ervaring opdoen met het plaatsen van de NAVA katheter en onze praktische aanbevelingen hiervoor werden in dit artikel meegenomen.

In **hoofdstuk 6** hebben wij onderzocht of implementatie van een door verpleegkundigen geleid ontwen protocol van beademing kon leiden tot een kortere beademingsduur en een kortere verblijfsduur op de IC-Kinderen. Wij voerden een prospectieve, pretest-posttest studie uit en includeerden alle beademde patiënten op de IC-Kinderen. In de pretest werd de beademing zoals gebruikelijk afgebouwd. Dit hield in dat een arts de beademing van een stabiele patiënt beoordeelde en de verpleegkundigen instrueerde om geleidelijk de druk, het teug volume en de positieve eind-expiratoire druk (PEEP) af te bouwen en zo mogelijk over te schakelen op een ondersteunende beademingsvorm. Een door verpleegkundigen geleid ontwen protocol van beademing werd vervolgens in de loop van drie maanden geïmplementeerd. In de posttest gebruikten verpleegkundigen het nieuwe ontwen protocol. In totaal werden 424 patiënten in de leeftijd van 0-18 jaar geïncludeerd (212 pretest en 212 posttest). In beide groepen was de mediane leeftijd 3 maanden. De mediane beademingsduur en het verblijf op de ICK verschilden niet significant tussen de pre- en posttest. De naleving van de voorgeschreven ondersteuningsvorm op de beademing was significant

hoger in de posttest dan in de pretest. Het reïntubatie percentage was niet significant verschillend tussen beide periodes. Het percentage extubaties tijdens de nacht was hoger in de posttest, maar niet significant t.o.v. de pretest. Onze conclusie was dat implementatie van een door verpleegkundigen geleid ontwen protocol van beademing niet resulteerde in een significant kortere duur van beademing, maar wel veilig was en succesvol.

In **hoofdstuk 7** hebben wij een multi-center pre-post studie uitgevoerd waarin beademingsduur werd vergeleken tussen gebruikelijke zorg en een door verpleegkundigen geleid ontwen protocol van beademing inclusief een spontane ademhaling test om te zien of de patiënt al geëxtubeerd kon worden. Deze studie vond plaats in 3 academische centra met kinder-intensive care afdelingen in Nederland. Honderdnegentig kinderen werden afgebouwd van beademing volgens de gebruikelijke zorg welke werd geïnitieerd door artsen en 157 kinderen werden afgebouwd van beademing door het door verpleegkundigen geleide ontwen protocol van beademing. Multivariate analyse toonde geen significant verschil in beademingsduur tussen de pretest en posttest (p=0.79). Het geschatte verschil in beademingsduur was -0.02 (IQR -0.14 - 0.11) voor verpleegkundig geleid afbouwen. Onderzoeklocatie, geslacht, leeftijd, opname-indicatie en Pediatrisch Risico op Sterfte waren niet significant geassocieerd met een afname van beademing. In een univariate analyse was er geen significant verschil in beademingsduur, verblijf op de ICK en reintubatie percentage tussen beide periodes. De mate van naleving van geprotocolleerd ontwennen van beademing was 77,7%.

DEEL 3. ECHOGRAFIE VAN HET DIAFRAGMA BIJ GEZONDE EN BEADEMDE KINDEREN

In **hoofdstuk 8** bepaalden wij waarden van normale diafragma dikte en verdikkingsfractie van het diafragma bij gezonde kinderen in de leeftijd van 0-8 jaar door middel van B mode echografie. In totaal werden 137 kinderen geincludeerd. De gemiddelde dikte eind inspiratoir varieerde van 2.09 mm (sd 0.40) tot 1.69 mm (sd 0.30). De gemiddelde dikte eind expiratoir varieerde van 1.64 mm (sd 0.30) tot 1.38 mm (sd 0.20). De gemiddelde dikte van het diafragma was significant dikker bij pasgeborenen tot 1 jaar oud vergeleken met oudere kinderen (p<0.001). De mediaan van de verdikkingsfractie varieerde van 25.4% (sd 10.40) tot 21.3% (sd 7.10).

De intraclass correlatiecoëfficiënt van inter-observer reproduceerbaarheid van de echografieën was hoog.

Pearson correlation gaf een significant zwakke dan wel matige negatieve correlatie tussen VF, dikte van het diafragma eind-inspiratoir en eind-expiratoir enerzijds en leeftijdsgroepen en lichaamsoppervlakte anderzijds. Deze referentie waarden zijn bruikbaar voor het evalueren van het diafragma van kritisch zieke kinderen in de klinische praktijk.

In **hoofdstuk 9** hebben we onderzocht of verdikkingsfractie van het diafragma, gemeten met echo een associatie heeft met extubatie succes bij beademde kinderen en om de progressie van de dikte en de verdikkingsfractie (VF) van het diafragma tijdens beademing te beschrijven. We deden een prospectieve observationele cohortstudie op de PICU bij kinderen van 0-18 jaar, die langer dan 48 uur werden beademd. Echografieën werden uitgevoerd op dag 1 na intubatie, op dag 4, dag 7, dag 10, het moment waarop de patiënt een SBT onderging in een PS modus, vlak voor extubatie op CPAP met PEEP 5 en eenmaal in de volgende 24 uur na extubatie. 53 patiënten met een mediane leeftid van 3.0 maanden (IQR 0.1-66.0) werden geïncludeerd en ondergingen 226 echo's. De mediane verdikkingsfractie voor extubatie met Pressure Support 10 above 5 cmH2O was 15.2% (IQR 9.7-19.3). Bij 6 kinderen mislukte extubatie; 3 van hen werden gereintubeerd en 3 kregen non invasieve beademing met een mond-neus masker. Er was geen significante associatie tussen verdikkingsfractie en extubatie succes; OR 0.33 (95% CI;0.06-1.86). Diafragma atrofie werd gezien bij 17 van de 53 kinderen. Bij 3 van hen mislukte de extubatie. Kinderen in de mislukte extubatie groep waren jonger: 2.0 maanden (IQR 0.81-183.0) versus 3.0 maanden (IQR 0.10-48.0); p=0.045. Zowel voor de basislijn, als voor- en na extubatie was er geen significante correlatie tussen leeftid en lichaam oppervlakte aan de ene kant en verdikkingsfractie en dikte van het diafragma aan de andere kant.

De intraclass correlatiecoëfficiënt van inter-observer reproduceerbaarheid van de echografieën was hoog.

Er was geen significante associatie tussen verdikkingsfractie van het diafragma en extubatie succes bij beademde kinderen.

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PART IV

FINALLY

chapter 12

LIST OF ABBREVIATIONS

AHRF   Acute Hypoxemic Respiratory Failure

ARDS   Acute Respiratory Distress Syndrome

BIPAP   Biphasic Positive Airway Pressure

BPD   Broncho-Pulmonary Dysplasia

CI   Confidence interval

CHD   Congenital Diaphragmatic Hernia

CIADW   Critical Illness-Associated Diaphragm Weakness

CLD   Chronic Lung Disease

CV   Conventional Mechanical ventilation

DOV   Duration of Ventilation

dTF   Diaphragm thickening fraction

FiO_2 Fraction of inspired oxygen

GA   Gestational Age

GCS   Glasgow Coma Scale

HFO   High-frequency Oscillation Ventilation

ICO   Inspiration Cycle off

IQR   Inter quartile range

LOV   Length of Ventilation

NAVA   Neurally Adjusted Ventilatory Assist

NEC   Necrotizing entero-colitis

NEX   Nose-Ear-Xyphisternum

ND   No data

NO   Nitric Oxide

NP   Nurse Practitioner

NS   Not Significant

O.I.   Oxygenation Index

OR   Odds Ratio

PC   Pressure Controlled Ventilation

PCO_2 Partial arterial pressure of carbondioxide

PDA   Persistent ductus arteriosus

PDMS   Patient Data Management System

PEEP   Positive End Expiratory Pressure

PF PaO_2/FiO_2 ratio

PH   Pulmonary hypertension

PICU   Pediatric Intensive Care Unit

PO_2 Partial pressure of oxygen

PPHN   Persistent Pulmonary Hypertension of the Neonate

PRISM   Pediatric Risk of Mortality Score

PRVC   Pressure Regulated Volume Controlled Ventilation

PS   Pressure Support Ventilation

RCT   Randomized Controlled Trial

SaO_2 Saturation of oxygen

SD   Standard Deviation

Tdi-exp. Thickness of the diaphragm at the end of expiration

Tdi-insp. Thickness of the diaphragm at the end of inspiration

Ti   Inspiration time

TTO   Trigger Time Out

VDR   Volume Diffusive Respirator (high-frequency time-cycled pressure ventilator)

VP   Ventilation Practitioner

VS   Volume Support Ventilation

VT   Tidal Volume

WMD   Weight mean Difference

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PHD PORTFOLIO

SUMMARY OF PHD TRAINING AND TEACHING

General information

Name PhD student	Anita Duijndam
Erasmus MC Department	Intensive Care and Department of Pediatrics
PhD Period	2017-2023
Promotors	Prof. dr. D. Tibboel
	Prof. dr. M. van Dijk
Copromotor	Dr. W.G. Ista
Research school	Hogeschool Leiden, master of science

PHD TRAINING

General academic skills	Year	Workload (ECTS)
Research Integrity Course	2018	0.3
BROK ('Basiscursus Regelgeving Klinisch Onderzoek') Course	2017 and 2021	2.0
Biomedical English Writing Course	2017	2.0
Organise your work, outlook and one note	2021	0.6
Research skills		
Basic introduction on SPSS	2019	1.0
Data analysis, summer course	2017	1.9
Power Point	2020	0.3
Seminars and workshops		
Sophia Research Day	2017/2018/2019	1.0
Research Skills for nursing researchers/ Masterclass program- Implementation and qualitative research	2018	1.0
Presentations		
Ventilation workshops ESPNIC Lissabon	2017	0.5
Ventilation workshops EAPS Parijs	2018	0.5
E poster ESPNIC Salzburg	2019	0.5
Insertion and care of Periferal IV catheters for Pediatric and Neonatal Nurse Practioners (oral presentation)	2019	0.5

	Year	Workload (ECTS)
Contribution to the online Mechanical Ventilation Course of the ESPNIC (2 presentations about curves and loops and bronchiolitis)	2020	0.5
Organisation of a reference evening for Nurse Practitioners about bronchiolitis and high flow nasal cannula	2020	0,3
51th World Congres on Advanced Nursing Research, a Webinar about my research in 2019 (oral presentation)	2021	0.5
E poster EAPS Barcelona	2022	0.5
Presentation about 'ultrasound of the diaphragm in ventilated children" on Venticare Congres S'Hertogenbosch and on Topics in IC (Intensive care congress in Utrecht)	2022	0.5
International and national conferences		
European Academy of Paediatric Societies, Lissabon (two workshops about ventilation)	2017	2.0
National Practitioners day with ventilation courses/ presentations and network meetings with sponsors	2017/2018/2019/2021	1.0
National Children Ventilation Practitioner day (of all Dutch PICUs) with courses/ oral presentations of each participant and network meetings / 2 times a year	2017/2018/ 2019/2021	2.0
National Nurse Practitioner (V&VN VS) congress and network meetings of Nurse Practitioners	2017/2020/2021	1.5
EAPS Paris	2018	2.0
10th ICN NP/APN Conference Rotterdam	2018	1.0
AVA congress 2018 Ohio	2018	2.0
Farewell congress Prof. Dr. D. Tibboel. The Critically ill Child: From Translational Research to Reflection	2018	0.5
ESPNIC Salzburg 2019	2019	2.0
RICS Ventilation Congres Maasstadziekenhuis Rotterdam	2018/2019/2021/2022	0.5
1st International Paediatric Chest Conference: Oxygen, Rotterdam	2019	0.5
EAPS 2020 virtual	2020	2.0
ESPNIC 2021 virtual	2021	2.0
Others		
Member (secretary) of the Association of Nurse Specialists Erasmus MC	2016-2021	2.5

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	Year	Workload (ECTS)
Member of network meetings of the Nursing Advice Board (VAR) every 4 weeks	2017/2018/2019	1.0
Fulfilled Re-registration (KWAR certificaat) according registry Ventilation Practitioners training	2018-2023	0.5
Nursing Advice Board (VAR) Congress Erasmus MC Rotterdam	2018/2019/2020	0.5

Cooperation in international studies
1. VESPER- data collection of ventilated children
2. Covent- consensus meeting
   1. Roles And Responsibilities for mechanical VentilatiOn and weaning practice in European PICus (BRAVO-EPIC) and VEntilator Settings Practices in Europe Registry (VESPER) A prospective, observational, multicentre collaborative study
   2. Blackwood B, et al.,A Core Outcome Set for Critical Care Ventilation Trials, Critical Care Medicine, july 2019
	2016,not published
	Publication: 2019
		0,5
		0,5

Teaching activities		
Training of PICU students in doing a Critically Appraised Topic	2017	0.5
Guidance Co-assistants/ Paediatricians in training ICK	2017-2023	0.5
Didactic courses and workshops		
Advanced life support (APLS) course of three days in Riel	2017	1
Ultrasound course ESPNIC Salzburg	2019	1
Summerschool Bristol initiated by ESPNIC for PhD candidates	2019	1
Mechanical ventilation course ESPNIC exam obtained	2021	1
Advanced Life Support-recertification in Riel	2022	1
Ultrasound of the lung course in LUMC Leiden	2022	0.5
Total ECTS		**45.4**

ECTS=European Credit Transfer and Accumulation System/1 ECTS represents 28 hours

ABOUT THE AUTHOR

Anita Duijndam was born in Delft on June 21th, 1966, with her twin sister Marion, on a dairy farm. After graduating from high school (Atheneum, St. Stanislas college Delft) in 1984, she started her nursing study in Leiden (HBO-V).

In 1988 she received her bachelor degree in nursing. From 1988 till 1989 she worked as a registered nurse in the VU Medical Center in Amsterdam. Next, she started training in nursing of children at the Juliana Children's Hospital in Den Haag. She received her certification for child nursing in 1991 and started in 1992 with the Pediatric Intensive Care Unit (PICU) certification in the Juliana Children's Hospital. From 1995 she has worked as a PICU nurse on the PICU of the Erasmus MC Sophia Children's Hospital Rotterdam.

In 2006 she started training as a ventilation practitioner (a nurse specialized in mechanical ventilation) and completed this in 2007. In this capacity, she supported, together with other ventilation practitioners the nursing and medical teams with knowledge about ventilation. She also started research in mechanical ventilation and published a few articles in cooperation with others.

In 2013, she started with a Master of Advanced Nursing Practice (MANP) and completed this in 2015. Since then, she worked as a nurse practitioner specialized in congenital abnormalities at the pediatric intensive care department of the Erasmus MC Sophia Children's Hospital. She started her PhD trajectory in 2017, and fulfilled the function of honorary secretary of the Society of Nurse Practitioners in Erasmus MC till 2021.

She is married to Gerard Castenmiller; together they have a son (1997) and a daughter (1999).

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LIST OF PUBLICATIONS

- Duyndam A. Flow-volume loop: nuttig hulpmiddel om noodzaak tot endotracheaal uitzuigen bij beademde kinderen te bepalen. Kritiek. 2007;6:3-11.

- Duyndam A, Ista E, Houmes RJ, van Driel B, Reiss I, Tibboel D. Invasive ventilation modes in children: a systematic review and meta-analysis. Crit Care. 2011;15(1):R24.

- Duyndam A, Bol BS, Kroon A, Tibboel D, Ista E. Neurally adjusted ventilatory assist: assessing the comfort and feasibility of use in neonates and children. Nurs Crit Care. 2013;18(2):86-92.

- Duyndam A, Houmes RJ, van Dijk M, Tibboel D, Ista E. How to achieve adherence to a ventilation algorithm for critically ill children? Nurs Crit Care. 2015;20(6):299-307.

- Duyndam A, Houmes RJ, van Rosmalen J, Tibboel D, van Dijk M, Ista E. Implementation of a nurse-driven ventilation weaning protocol in critically ill children: Can it improve patient outcome? Aust Crit Care. 2020;33(1):80-8.

- Duyndam A, de Neef M, Houmes R, Smit J, Klein-Blommert R, van Gestel M, Pfeil R, IJland M, van Rosmalen J, van Woensel J, Lemson J, Tibboel D, van Dijk M, Ista E, Does a nurse-led weaning protocol with a spontaneous breathing trial in critically ill children lead to a shorter duration of ventilation? A multi-centre study. Aust Crit Care. 2023 (in revision)

- Duyndam A, Smit J, Heunks L, Molinger J, IJland M, van Rosmalen J, van Dijk M, Tibboel D, Ista E, Reference values of diaphragmatic dimensions in healthy children aged 0-8 years, European Journal of paediatrics 2023, accepted for publication

- Duyndam A, Smit J, Houmes R, Heunks L, Molinger J, IJland J, van Rosmalen J, van Dijk M, Tibboel D, Ista E, No association between thickening fraction of the diaphragm and extubation success in ventilated children. Frontiers in Pediatrics 2023, accepted for publication

DANKWOORD

Een proefschrift schrijf je niet alleen. Velen leefden met mij mee in het lange proces van onderzoek doen. In de ruim 28 jaar dat ik in het Sophia kinderziekenhuis op de ICK werk, eerst als IC verpleegkundige, later als Ventilation Practitioner en nog later als Verpleegkundig Specialist is er veel veranderd. Door het schrijven van dit proefschrift realiseer ik me nu meer wat er allemaal in gang is gezet en veranderd ten goede.

Bij deze wil ik de volgende mensen bedanken die hebben bijgedragen aan de totstandkoming van dit "boekje":

Allereerst wil ik de patiënten, gezonde proefpersonen en hun ouders bedanken die direct of indirect hebben bijgedragen aan dit proefschrift. Jullie data dragen bij aan betere zorg in de toekomst.

Mijn promotor, prof. Tibboel, beste Dick, wie had gedacht dat ik nog eens bij jou zou mogen promoveren. Toen je met emeritaat ging was ik bang dat je zou stoppen, maar je was nog lang niet klaar en zou mij zeker blijven begeleiden. Ik keek als kinder-IC verpleegkundige tegen jou op als hoofd en intensivist van de Kinder IC en had veel respect voor jouw visionaire blik op de afdeling en op onderzoek. Dat je al eerder een verpleegkundige, een fysiotherapeut en een geestelijk verzorger onder jouw promovendi mocht scharen is vooruitstrevend en ook mij zag jij zitten als promovendus. Ons eerste artikel werd tot mijn verbazing in een hoog gerankt medisch blad gepubliceerd en dat was de eerste stap. Daarna heb je steeds interesse getoond en mij weer op weg geholpen als ik vast zat in een onderwerp. Je liet mij vaak in de waan dat zaken wel even geregeld konden worden, waarna ik er heel veel tijd aan moest besteden en het uiteindelijk lukte. Dat was voor mij een goede tactiek. Dick bedankt voor je vertrouwen in mij en er zit nu een kaft om dit boekje.

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bij jou, dat ging zo snel dat ik aan mezelf twijfelde. Was ik nou zo dom? Later ging ik het steeds beter begrijpen, maar de eerste beginselen waren zwaar. Dank voor je relativeringsvermogen en het mij steeds weer motiveren. Ook als drukke hoogleraar gaf je mij steeds jouw aandacht.

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Dr. R.J. Houmes, beste Robert Jan, bedankt voor de samenwerking en jouw kritische bijdrage in bijna alle onderzoeken in dit proefschrift. Jij was vanaf het begin betrokken bij de opleiding Ventilation Practitioner, beademing specialist, die Joke en ik gingen volgen en later ook bij de ontwikkeling van de VS opleiding op de ICK. Wij probeerden jouw geliefde, maar voor ons erg theoretische ''Open long concept" verder te vertalen naar de verpleegkundigen. Voor ons ging dat "Open long concept" echt leven nadat wij door jou, de cursus van prof. B. Lachmann mochten volgen, met de beademde varkens, ook al was het alleen voor anesthesisten bedoeld. Bedankt voor je inzet voor ons als verpleegkundigen om ons verder te kunnen profileren.

Joke Smit, mijn maatje Ventilation Practitioner. Wij hebben dezelfde passie: beademing. Wat hadden wij vaak een andere mening over een onderwerp, maar we hebben elkaar leren waarderen en respecteren. Wij vulden elkaar heel goed aan met ieder onze eigen kracht. Zonder jou was ik niet zo ver gekomen. Jij hebt mij altijd gesteund in het promotie traject, je hebt me aangehoord en oplossingen bedacht als ik dreigde vast te lopen. Samen werden we enthousiast over het echo onderzoek van het diafragma door de verhalen van Jeroen. En wat leerden we hier veel van. Wat opmerkelijk was het dat het al snel normaal werd gevonden dat wij met het echo apparaat rond liepen en patiënten echoden. Jij was altijd kritisch, maar ook behulpzaam en nam vaak zaken van mij over. Maar vooral van belang is dat jij ziet wat op de afdeling speelt bij de verpleegkundigen en dat jij altijd het belang van het kennis niveau op beademingsgebied voor de verpleegkundigen voor ogen houdt. De kwaliteit van de beademingszorg ligt echt in jouw handen en natuurlijk ook bij het enthousiaste beademingsteam met Mirjam, Suzanne, Jan Willem, de onlangs afgezwaaide Nori en Helma en natuurlijk Judith als nieuwe Ventilation Practitioner in opleiding.

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Mijn verpleegkundige collegae die enthousiast meededen aan onze onderzoeken, die lessen volgden om de beademing zelf af te bouwen, die mij belden als een patiënt geïncludeerd kon worden. Maar die ook kritisch waren en opkwamen voor de rust van hun patiënt. Die zich met grote getale aanmelden met hun eigen of met kinderen van familie voor het echo onderzoek van het middenrif van gezonde kinderen. Ook heel veel artsen, arts- assistenten, pedagogische zorg en zorgassistenten melden zich voor dit onderzoek. Joke en ik zijn in heel veel huizen geweest in de omgeving Rotterdam, Den Haag en Utrecht. Onze fysiotherapeute Tabitha spande de kroon, zij zorgde met haar eigen kinderen en de hele buurt voor wel 19 inclusies. Ook Mariska, Judith, Jeanette, Chantal en Christel zorgden voor huizen vol met kinderen. Teveel mensen om allemaal te noemen. Hartelijk dank iedereen bij deze, het heeft ons onderzoek zoveel makkelijker gemaakt.

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Joke Dunk, onze onderzoeksverpleegkundige, jij was mijn geweten en hielp mij bij het integer onderzoek doen met veel aandacht voor de wet AVG en hielp mij bij de aanvragen voor de METC. Een grote vraagbaak en altijd bereid om mij te helpen, dank je wel. Ook Ellen heeft mij geholpen bij een deel dataverzameling, dank daarvoor. Els Roodbol, nu inmiddels gestopt met werken was heel belangrijk voor mijn beademingsonderzoek. Jij leverde de voor mij zo belangrijke data van alle beademde patiënten.

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De steun die ik kreeg vanuit het verpleegkundig management, Carla, Inge. Altijd een luisterend oor, belangstelling, waardering en motivering. Jullie gezamenlijke motto hielp mij: "Als het even niet lukt, sta dan stil bij de goede dingen van het leven en ga daarna stoïcijns weer door."

De mogelijkheden die ik kreeg in dit academische ziekenhuis, de cadeautjes voor de kinderen die een echo onderzoek ondergingen, die ik kreeg van de Sophia Stichting, het geld voor de huur van die gave lumify echokop via Prof. dr. Wijnen en al die mensen om mij heen die mijn onderzoek verbeterden.

Het werk in de kliniek was overigens een goede afleiding van het onderzoek en het onderzoek direct uitvoeren in de patiëntenzorg was motiverend en gaf het gevoel dat ik het ook daadwerkelijk voor de patiënten en de verpleegkundigen deed.

Alle VS in het Erasmus, die mij voorgingen in een promotietraject. En er komen er steeds meer bij! Met name, Annette en Mirjam, jullie waren een inspiratie voor mij. Dank voor jullie steun en advies.

Mijn paranimfen, Joke en Bionda, vanaf de VP opleiding met elkaar verbonden. Fijn dat jullie mij bij willen staan op deze voor mij zo belangrijke dag.

Al onze vrienden, een groot deel van hen kennen wij al sinds de HBO-V. Jullie zijn met ons meegegroeid. Dank voor jullie meeleven in dit traject. Hier noem ik ook mijn trouwste fan, Idelette, wat heb jij veel meegemaakt met Fokke en ondanks alles blijf je altijd geïnteresseerd en motiverend. Dank ook aan de (midden) groep Nordic Walking, de wandelingen op Kijkduin gaven mij de nodige ontspanning en jullie waren steeds belangstellend naar mijn vorderingen, met name Anita en Marten die mij hielpen met mijn voorbereiding.

Lenie, mijn sport maatje; schaatsen, skaten, suppen, een hele goede afleiding. Bedankt voor al je aanmoedigingen en je enthousiasme.

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Ik was zo blij met mijn volkstuin die onderweg kwam en waar Gerard ook meteen enthousiast over was. Het kwam erbij, als een geit die je neemt en het daar dan vervolgens nog drukker mee hebt dan daarvoor. Het gaf echter ook heel veel ontspanning, rust in mijn hoofd en een project om ook na de promotie aan te werken.

Mijn ouders, allebei gelukkig gezond en bij mijn promotie aanwezig. Jullie leerden mij en mijn vier zussen: Connie, Marion, Jolanda en Sandra om te gaan voor de keuzes die wij maakten en dit vol te houden. Door op een boerderij met melkvee op te groeien leer je ook om door te zetten en de voldoening van gedane arbeid te proeven. Dank jullie wel, pa en ma, zussen en zwagers voor jullie belangstelling en meeleven.

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Mijn kinderen, Fabian en Willemijn, die het hele traject hebben meegemaakt vanaf de VS opleiding tot aan het promoveren. Zij waren bezig met hun eigen studie, maar zijn niet anders gewend dan mij achter de computer te zien op bijna elke (vrije) dag, soms enigszins chagrijnig als het tegen zat. Dank jullie wel voor het geduld. Willemijn, ik hoop jou in de keuze voor het verpleegkundig vak, voorgeleefd te hebben dat je als verpleegkundige heel veel kan bereiken. Jij bent nu al op weg om een geweldige verpleegkundige te worden. Ook jij Fabian kan mooie dingen bereiken met je keuze voor een TU master ''management in the build environment''. Jouw creativiteit is groot. En dan jullie partners, Thomas, jij hielp mij soms met technische en ICT uitdagingen en Mirthe, ook vast van plan ooit te gaan promoveren, dank voor jullie meeleven en succes na jullie studies.

Tenslotte, Gerard, met wie ik al 33 getrouwd ben. Jij steunde mij volledig en wist mij altijd weer te motiveren. Ook kon jij mij het hele project laten relativeren. Beiden werkzaam in de zorg weten we dat het allemaal veel erger kan dan b.v. een afwijzing van een medisch tijdschrift. Jij hield de boel draaiende thuis, moedigde mij aan en bent altijd trots op mij. Zonder jou was dit alles niet gelukt.

EPILOGUE

After I had completed my Ventilation Practitioner training, my PhD program actually began, although it did not become official until 2017 – a few years after I had completed a master's degree in Advanced Nursing Practice.

My fellow VP and I had written a paper on the best ventilation mode in children following a question from Professor Tibboel, who already knew that little research had been done on ventilation modes in children. What I noticed was that the ventilation modes varied from day to day, depending on the preference of the physician on duty. Since that paper on the best ventilation mode in children had not found evidence of the best ventilation, we then worked with Robert Jan Houmes to create a ventilation protocol that included evidence from the adult literature. At the same time, we held a baseline measurement among the nurses on their knowledge gaps in ventilation and then provided training and taught the protocol immediately. They also received retraining in the use of the *servo i* mechanical ventilation machine, with a clear guideline. The introduction of the protocol was followed by a study of the physicians' adherence to it, which seems to have improved over the years. And so the studies followed on.

With this doctoral research, I learned a lot. Not only about how to do research, but also about mechanical ventilation and how communication runs in a PICU. Nurses are the hands and feet of the physicians on the PICU. They observe the patient and can report whether a particular ventilator setting is working. It follows that the quality of ventilation depends both on the insights of the physicians, and the experiences and insights of the PICU nurses. An algorithm for weaning which gives nurses more authority is therefore an important thing. The influence of the nurse in making decisions on weaning and extubation can become greater. The VP keeps nurses' knowledge up to date, introduces innovation and provides education (along with a ventilation team with a physician and interested nurses). The VP can also do research or participate in research together with an NP, who also keeps the respiratory knowledge up to date, and thus also create evidence based protocols together.

My doctoral research shows that doing research in this area is useful and can increase nurses' knowledge and influence. We succeeded in establishing a ventilation policy that is easy to follow. We did not succeed, however, in reducing the duration of ventilation

with the protocol, but we did succeed in giving the nurse a greater voice and allowing him or her to reduce ventilation, which in practice goes well. With better knowledge of the ventilator, the patient is more easily turned and mobilized by the nurses. The NAVA study provided insight into the a-synchrony we often see in the ventilated children. The ultrasound studies have provided reference values in children up to 8 years of age and the insight that an ultrasound of the diaphragm alone can not predict extubation success. However, an ultrasound of the diaphragm in combination with the other respiratory muscles may be can help us predict a difficult trajectory after extubation in doubtful cases.

FINALLY

Nursing development is important. In 2022, it was decided after years of discussion that nurses in our PICU can further professionalize as practitioners in various fields, in order to be able to raise the knowledge level of nurses and keep the quality of care in all fields of the PICU high. Physicians in the past may have sometimes have doubts about the value of further development of PICU nurses. However, we have shown that VPs and NPs are not a threat to the physicians, but an addition to the overall PICU team.