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Evolution of Diaphragmatic Function in Children under Mechanical Ventilation

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Résumé

Introduction : La dysfonction diaphragmatique est très fréquente chez des patients adultes aux soins intensifs et elle est associée à des évolutions cliniques défavorables. Il n'y a pour l'instant aucune méthode reconnue pour évaluer la fonction du diaphragme chez l'enfant sous ventilation mécanique (VM), et aucune étude décrivant son évolution dans le temps chez cette population.

Méthodes : Dans ce travail, nous avons évalué la fonction contractile du diaphragme chez des enfants sous ventilation invasive aux soins intensifs pédiatriques (SIP) et en salle d'opération (SOP). Pour ce faire, la pression au tube endotrachéal (Paw) et l'activité électrique du diaphragme (EAdi) étaient enregistrées simultanément lors de respirations spontanées pendant une brève manœuvre d'occlusion des voies respiratoires. Afin de prendre en compte la commande respiratoire, un ratio d'efficience neuro-mécanique (NME, Paw/EAdi) a d'abord été calculé puis validé par une analyse de variabilité. La fonction du diaphragme a ensuite été comparée entre les deux populations, et son évolution dans le temps au sein du groupe SIP décrite.

Résultats : Le NME médian était la mesure de fonction diaphragmatique la plus fiable, avec un coefficient de variation de 23.7% et 21.1% dans les groups SIP et SOP, respectivement. Le NME dans le groupe SIP après 21 heures de VM (1.80 $cmH_2O/\mu V$, IQR 1.25–2.39) était significativement inférieur à celui du groupe SOP (3.65 $cmH_2O/\mu V$, IQR 3.45–4.24, $p = 0.015$). Dans le groupe SIP, le NME n'a pas diminué de façon significative pendant la VM (coefficient de corrélation -0.011, $p = 0.133$).

Conclusion : La fonction diaphragmatique peut être mesurée au chevet des enfants sous VM par de brèves manœuvres d'occlusion. L'efficience du diaphragme était significativement plus élevée dans un groupe sain que dans une cohorte d'enfants critiquement malades, mais elle était stable dans ce groupe avec une commande respiratoire préservée. Dans le futur, les contributions relatives de la maladie critique et de la ventilation mécanique sur la fonction diaphragmatique devront être mieux caractérisées avant de procéder à l'évaluation de potentielles interventions visant à protéger le diaphragme.

Mots-clés : ventilation assistée, diaphragme, dysfonction diaphragmatique, activité électrique du diaphragme, pédiatrie, enfant, soins intensifs

Abstract

Introduction : Diaphragmatic dysfunction is highly prevalent in adult critical care and is associated with worse outcomes. There is at present no recognized method to assess diaphragmatic function in children under mechanical ventilation (MV) and no study describing its evolution over time in this population.

Methods : In this work, we have assessed the contractile function of the diaphragm in children under invasive MV in the pediatric intensive care unit (PICU) and in the operating room (OR). This was done by simultaneously recording airway pressure at the endotracheal tube (Paw) and electrical activity of the diaphragm (EAdi) over consecutive spontaneous breaths during brief airway occlusion maneuvers. In order to account for central respiratory drive, a neuro-mechanical efficiency ratio (NME, Paw/EAdi) was first computed and then validated using variability analysis. Diaphragmatic function was then compared between the two populations and its evolution over time in the PICU group described.

Results : Median NME was the most reliable measure of diaphragmatic function with a coefficient of variation of 23.7% and 21.1% in the PICU and OR groups, respectively. NME in the PICU group after 21 hours of MV (1.80 $cmH_2O/\mu V$, IQR 1.25–2.39) was significantly lower than in the OR group (3.65 $cmH_2O/\mu V$, IQR 3.45–4.24, $p = 0.015$). In the PICU group, NME did not decrease significantly over time under MV (correlation coefficient -0.011, $p = 0.133$).

Conclusion : Diaphragmatic function can be measured at the bedside of children under MV using brief airway occlusions. Diaphragm efficiency was significantly higher in healthy controls than in a cohort of critically ill children, but it was stable over time under MV in this group with preserved respiratory drive. In the future, the relative contributions of critical illness and mechanical ventilation on diaphragmatic function should be better characterized before evaluating potential interventions aimed at protecting the diaphragm.

Keywords : mechanical ventilation, diaphragm, diaphragmatic dysfunction, electrical activity of the diaphragm, pediatrics, children, intensive care

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List of acronyms

CoV : Coefficient of variation

CPAP : Continuous positive airway pressure

EAdi : Electrical activity of the diaphragm

EMG : Electromyogram

ETT : Endotracheal tube

FiO_2 : Fraction of inspired oxygen

ICU : Intensive care unit

IQR: Inter-quartile range

MS : Magnetic stimulation

MV : Mechanical ventilation

NAVA : Neurally-adjusted ventilatory assist

NIV : Non-invasive ventilation

NME : Neuro-mechanical efficiency ratio

NME_{occl} : Neuro-mechanical efficiency ratio generated by maximal inspiratory effort

NME_{twitch} : Neuro-mechanical efficiency ratio generated by phrenic nerve stimulation (*twitch*)

NVE : Neuro-ventilatory efficiency ratio

OI : Oxygenation index

OR : Operating room

PaO_2 : Arterial partial pressure of oxygen

PCO_2 : Partial pressure of carbon dioxide

Paw : Airway pressure

Paw_{max} : Airway pressure at endotracheal tube generated by maximal inspiratory effort

Paw_{twitch} : Airway pressure at endotracheal tube generated by phrenic nerve stimulation (*twitch*)

Pdi : Transdiaphragmatic pressure

Pdi_{max} : Transdiaphragmatic pressure generated by maximal inspiratory effort

Pdi_{twitch} : Transdiaphragmatic pressure generated by phrenic nerve stimulation (*twitch*)

Pes : Esophageal pressure

Pga : Gastric pressure

Ppl : Pleural pressure

$P_{0.1}$: Airway occlusion pressure at 0.1 sec

PEEP : Positive end-expiratory pressure

PEEPi : Intrinsic positive end-expiratory pressure

PELOD : Pediatric logistic organ dysfunction

PICU : Pediatric intensive care unit

PSV : Pressure-support ventilation

PTP_{DI} : Diaphragmatic pressure–time product

PTP_{ES} : Esophageal pressure–time product

RR : Respiratory rate

SBT : Spontaneous breathing trial

SD : Standard deviation

SpO_2 : Oxygen saturation by pulse oximetry

SvO_2 : Mixed venous oxygen saturation

Tdi: Diaphragm thickness

TFdi : Diaphragm thickening fraction

TTI : Tension-time index

V_T : Tidal volume

To my parents Robert & Susan,

who gave me everything I could ever need

for success and happiness

And to all the children,

whose smiles make it all worthwhile

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The author has carried out the following work in the context of this thesis:

- Literature review, determination of the research question and redaction of the protocol (with G Emeriaud)
- Submission to the ethics committee
- Physiological measurements (with G Emeriaud)
- Clinical data collection
- Signal analysis and data interpretation
- Statistical analysis (with A Kawaguchi)
- Presentation of preliminary results as abstracts at the following conferences (see Appendices)
    - Crulli B, Ducharme-Crevier L, Praud J-P, Petrof B, Emeriaud G. Diaphragmatic function in spontaneously breathing children under mechanical ventilation. Journées Québécoises en Santé Respiratoire, Montréal, Canada. 21-22 November 2018. (Appendix 6)
    - Crulli B, Ducharme-Crevier L, Praud J-P, Petrof B, Emeriaud G. Diaphragmatic function in spontaneously breathing children under mechanical ventilation. 17th Annual Congress of the Quebec Society of Intensivists, Montréal, Canada. 9 February 2019. **1st prize, Resident Research Competition.** (Appendix 7)
    - Crulli B, Ducharme-Crevier L, Praud J-P, Petrof B, Emeriaud G. Evolution of diaphragmatic function in mechanically ventilated children. 48th Critical Care Congress, San Diego, USA. 17-20 February 2019. (Appendix 8)
    - Crulli B, Ducharme-Crevier L, Praud J-P, Petrof B, Emeriaud G. Diaphragmatic function in spontaneously breathing children under mechanical ventilation. 34th Annual Research Congress of Graduate and Postdoctoral Students in Research at CHU Sainte-Justine Research Center, Montréal, Canada. 24 May 2019. **Prize for excellence in a poster presentation, "Research in medical technologies" category, TransMedTech Institute.** (Appendix 9)
    - Crulli B, Emeriaud G. Assessment of diaphragmatic function in mechanically ventilated children using the neuromuscular efficiency index. Reanimation 2020, Paris, France. 5-7 February 2020. (Appendix 10)

The author has also contributed to the following related articles

- *Monitoring of respiratory muscle function in critically ill children* (Appendix 4)
    - Contribution (20%): Literature review and manuscript proofreading
- *Mechanical ventilation causes diaphragm dysfunction in newborn lambs* (Appendix 5)
    - Contribution (10%): Manuscript proofreading and laboratory animal experiments for a follow-up project

Introduction

Every year, nearly 300 000 children are admitted to a pediatric intensive care unit (PICU) in North America. Nearly half of these critically sick patients require support with mechanical ventilation (MV) (around 6000 children per year in Canada). MV allows for an improvement in gas exchange and a decrease in work of breathing. It is however imperative to limit its duration because of associated severe complications which can increase length of MV, length of intensive care unit stay, and therefore costs (cost attributed to MV is estimated at 1500$ per day). These complications classically include nosocomial infections, tracheal injury, lung injury, hemodynamic impact of positive intrathoracic pressures, impact of sedation, etc. (1). The impact of ventilation on the function of respiratory muscles, previously overlooked, is now a growing concern. In ICU patients, the function of the diaphragm can be affected by critical illness and therapies (ICU-acquired diaphragm dysfunction, ICU–DD) (2), but also by MV specifically (ventilator-induced diaphragm dysfunction, VIDD) (3, 4). VIDD is highly prevalent in adult critical care (5) and it is associated with worse outcomes, including longer ventilation duration and higher mortality (6, 7). Specificities in pediatric respiratory physiology (namely tonic activity of the diaphragm (8), immature compensatory mechanisms, compliant chest wall, and suppressed respiratory activity (9)) suggest that critically ill children may be at high risk of developing VIDD.

Despite a growing body of literature highlighting the clinical impact of diaphragmatic dysfunction in adult critical care, there are no recognized methods guiding the assessment of diaphragmatic function in children and thus it is rarely done in clinical practice (10). To the best of our knowledge, no study has described the evolution of the pressure-generating capacity of the diaphragm in critically ill children under MV.

The overall goal of the work presented in this thesis is to develop a standardized method to measure diaphragmatic function in mechanically ventilated critically ill children; to

describe its evolution over time under MV; and to compare it with a group of healthy children undergoing general anesthesia for elective surgery. A review of the current literature will first be presented with a focus on respiratory muscle function, diaphragmatic dysfunction, and assessment of diaphragmatic function. The methodology and results of our study will then be detailed. Finally, the implications of these results will be discussed, before concluding.

Literature review

1 Respiratory muscle function

1.1 Neural control

Automatic breathing is a rhythmic phenomenon initiated in the brainstem. Pacemaker neurons located in the pons and the medulla have axons that project down to the spinal cord where they synapse with motoneurons controlling inspiratory and expiratory muscles, notably the diaphragm. The diaphragm is innervated by the phrenic nerves, arising from nerve roots at C3 through C5. The brainstem also receives afferent input allowing it to adapt ventilation to various physiological or pathological triggers. Central and peripheral chemoreceptors detect changes in pH, partial pressure of oxygen PaO_2 and partial pressure of carbon dioxide PCO_2. Peripheral mechanoreceptors located in the airway, lung parenchyma and respiratory muscles inform on the volume and configuration of the respiratory system. For example, lung expansion results in feedback inhibition of inspiration and prolongation of expiration (Hering–Bauer reflex) (11). Finally, analgesia and sedation which are commonly used in intubated patients can decrease respiratory drive and increase asynchrony (12). In the context of critical illness, automatic respiratory drive is therefore modulated by multiple factors, including MV (9).

1.2 Diaphragm

1.2.1 Anatomy and structure

The diaphragm is a dome-shaped structure separating the thoracic cavity from the abdominal cavity. It is composed of a central tendinous aponeurosis and of peripheral skeletal muscular fibers. These myofibers are primarily of the fatigue-resistant slow-

twitch type I and fast-twitch type IIa subtypes (13). When relaxed, the position of the diaphragm depends on the relative pressures of the thoracic and abdominal compartments, which vary with body position and gravity.

1.2.2 Function

The diaphragm is the principal inspiratory muscle, accounting for up to 70% of work required for minute ventilation in humans (14). Following electrical input from the phrenic nerve, its peripheral muscular fibers contract. This results in an increase of abdominal pressure and caudal displacement of abdominal contents, as well as an expansion of the lower rib cage. Accessory inspiratory muscles can also be recruited depending on breathing effort. This increase in thoracic volume decreases pleural pressure which is then transmitted to the alveoli. When alveolar pressure falls below atmospheric pressure, airflow is generated down the pressure gradient. The volume of air that enters the lungs will depend not only on the pressure generated but also on the elastance and on the resistance of the respiratory system. On expiration, diaphragmatic contraction decreases, and it is pulled upwards by elastic lung recoil.

1.2.3 Specificities in children

Although much smaller than in adults, the diaphragm applies its force over a proportionally smaller surface in children, generating similar pleural pressures. Diaphragmatic function in children has some specific features however which may render it particularly susceptible to dysfunction. Because of a more compliant abdomen and a smaller area of apposition between the diaphragm and the rib cage, contraction of the diaphragm in infants does not result in as much expansion of the lower ribs as in adults. Also, the highly compliant chest wall and the weaker intercostal muscles result in chest wall distortion during inspiration (15). This implies that extra energy is required to generate a given tidal volume. Combined with a relatively low pulmonary compliance and small distal airways, this relatively high parietal compliance means that

neonates and infants must maintain an end-expiratory lung volume above the relaxation volume in order to prevent collapse and preserve oxygenation (16). This can be achieved by dynamic hyperinflation resulting from a higher respiratory rate and by expiratory airflow retardation resulting from the contraction of laryngeal muscles or of the diaphragm (16). In this population, the diaphragm is therefore activated during both inspiration and expiration (8, 17). This tonic activity is superimposed on phasic contractions of the diaphragm and this additional load can significantly reduce inspiratory capacity in animals (18). Finally, diaphragm inactivity is very frequent during pediatric conventional MV, even in children considered to be spontaneously breathing: in almost a third of children, respiratory activity is undetectable (9), thereby exposing them to a significant risk of over-assistance myotrauma.

1.2.4 **Specificities under mechanical ventilation**

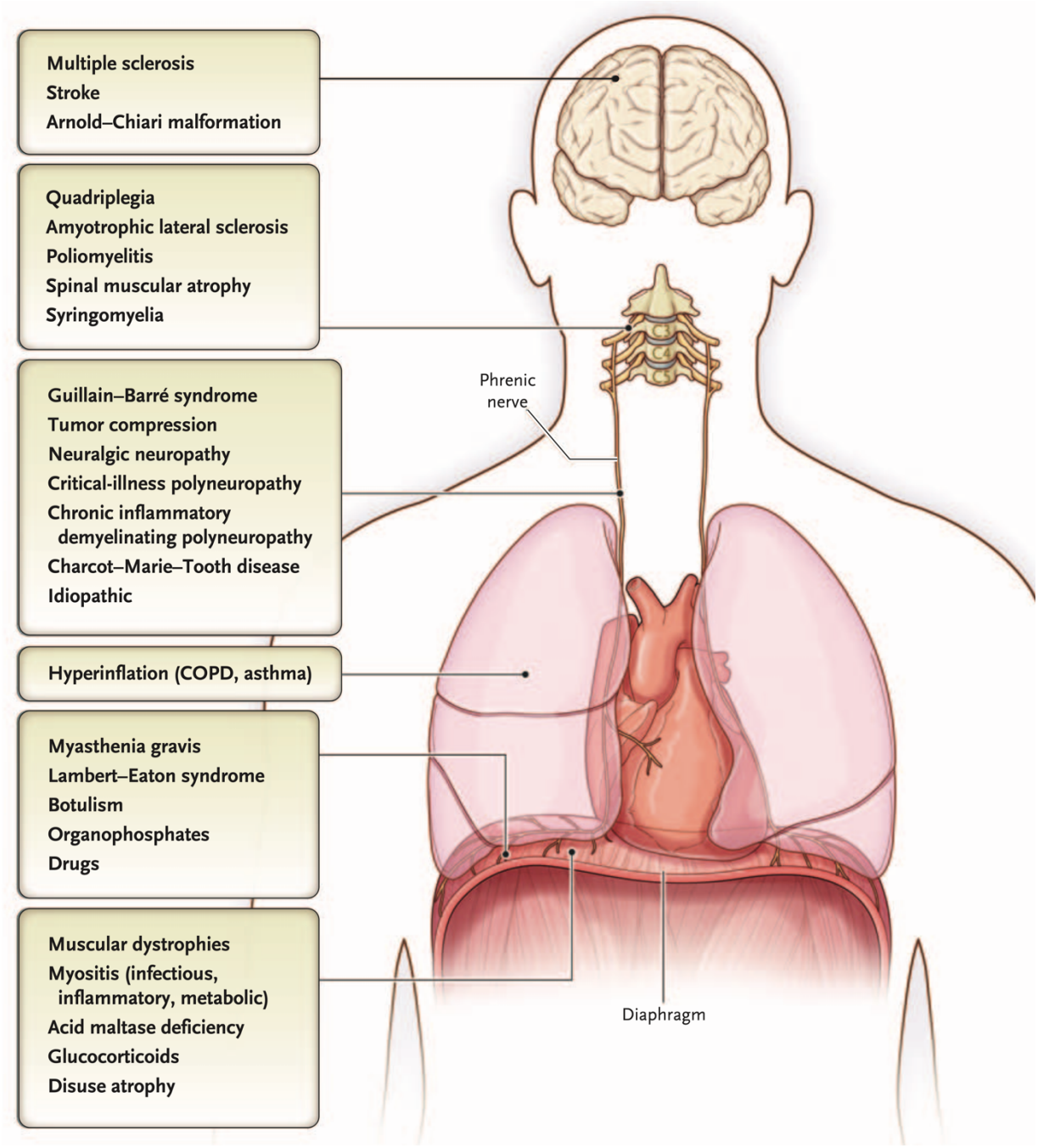
Under MV, inspiratory airflow is generated because of an increase in pressure at the upper airway rather than a decrease in pleural pressure. Expiratory airflow results from passive recoil of the lung and chest wall. Work of breathing is the work necessary to overcome the resistive, elastic, and inertial components of the respiratory system. It can be completely handled by the ventilator (controlled ventilation) or shared between the ventilator and the patient (assisted ventilation). In the latter, work of breathing can be greatly increased if the phases of breathing are not synchronous between the ventilator and the patient and some muscle contractions generate metabolic cost but no effective displacement (19). This asynchrony can be subdivided into trigger, flow, and termination phases. Moreover, MV is often employed in patients in which systemic disease processes result in high respiratory muscle energy demand but low supply. This imbalance can lead to muscle ischemia and fatigue. Although its small diameter may increase airway resistance, the presence of an endotracheal tube prevents laryngeal narrowing during expiration and maintaining end-expiratory lung volume then relies on

the tonic activity of the diaphragm or the application of exogenous positive end-expiratory pressure (PEEP) by the ventilator.

2 Diaphragm dysfunction

Diaphragm dysfunction refers to a decreased capacity of the diaphragm to generate maximal force. It can be uni- or bilateral and can result from multiple conditions that interfere with its innervation, contractile properties, or mechanical coupling to the chest wall (Figure 1). Pathologies that can affect diaphragmatic development and function in infants also include congenital diaphragmatic hernia and anterior wall defects (20). In this thesis, we will focus specifically on diaphragmatic function in the context of critical care.

Figure 1. Causes of diaphragmatic dysfunction



Disorders that occur at various levels can lead to diaphragmatic dysfunction. COPD denotes chronic obstructive pulmonary disease. Reproduced with permission from McCool FD, Tzelepis GE. Dysfunction of the diaphragm. N Engl J Med 2012; 366 (10): 932–942, © Massachusetts Medical Society.

2.1 Definitions

Through various mechanisms, ICU–acquired weakness (ICU–AW) can affect any skeletal muscle. ICU–AW specifically involving the diaphragm can be referred to as ICU-acquired diaphragm dysfunction (ICU–DD), regardless of cause or timing. Although other striated muscles are frequently at rest, the diaphragm usually remains active in a cyclical fashion. Additionally, diaphragmatic myofiber type composition differs from that of other striated muscles such as those found in the limbs. Recent work in adult patients has revealed differences in risk factors and clinical impact between ICU–AW and ICU–DD, which consequently represent distinct entities that can however coexist (21, 22). Although duration of MV was independently associated with both ICU–DD and ICU–AW, age and sedation use were only independently associated with ICU–DD, while exposure to vasoconstrictors was only associated with ICU–AW. With regards to clinical outcomes, only ICU–DD was independently associated with weaning failure, while only ICU-AW was independently associated with ICU mortality (22). Loss of force-generating capacity in the diaphragm as a direct consequence of MV is known as ventilator-induced diaphragm dysfunction (VIDD) (23).

2.1.1 ICU-acquired diaphragm dysfunction (ICU–DD)

ICU–DD is described in both early (5) and late (21, 24) phases of critical illness. Its risk factors are numerous: multiple organ failure and shock (5); sepsis (5, 6, 25); medication such as neuromuscular blockers (26), corticosteroids (27), sedatives such as propofol which adversely affect the diaphragm and promote disuse (28, 29); nutritional deficiency; metabolic disorders such as hypophosphatemia (30), hypomagnesemia, hypokalemia, hypocalcaemia, and thyroid disturbances; surgical lesions which damage the phrenic nerve such as liver transplantation (31), cardiac surgery (32), etc.

These factors undoubtedly play a significant role in ICU–DD, as the majority of adult patients present severe diaphragmatic dysfunction on admission to the ICU, before any

prolonged duration of MV (5). During the ICU stay, it is very difficult to dissociate the impact of MV on diaphragmatic function from these confounding factors as they are almost always present concomitantly.

2.1.2 Ventilator-induced diaphragm dysfunction (VIDD)

The first observations of VIDD in humans were actually reported in neonatal intensive care more than 25 years ago, in a series of autopsies in 7 neonates who received ventilatory assistance for ≥ 12 days. These diaphragms showed diffuse myofiber atrophy not present in other muscles or in diaphragms of infants ventilated for ≤ 7 days (15). More recently, the onset of force loss after initiation of MV was found to be rapid and duration-dependent, occurring as early as 12–18 hours after initiation of MV in two landmark studies done in adult brain-dead organ donors (3, 4).

2.2 Mechanisms

Similar to terms used to describe damage to the lungs secondary to MV, damage to the diaphragm can be referred to as myotrauma. It can result from three main physiological stresses (33). Whereas insufficient inspiratory effort can lead to over-assistance myotrauma (34), excessive inspiratory effort may cause load-induced diaphragm injury (under-assistance myotrauma) (35). When the mechanical load on the respiratory system is important or prolonged, the diaphragm can develop contractile fatigue. This fatigue can be short-term (high-frequency) or long-term (low-frequency). Finally, contractile loading developed while the muscle is lengthening (e.g. during asynchrony or hyperinflation) can be particularly damaging (eccentric myotrauma).

Studies in both animal models and humans have shown that MV results in a series of molecular changes in the diaphragm muscle, as a consequence of myotrauma. Absence of contraction while energetic input is maintained constant leads to imbalance between protein synthesis and proteolysis and an excess of free radicals. In conjunction with

local inflammation, this alters excitation–contraction coupling and results in mitochondrial autophagy and destruction (36). The ubiquitin–proteasome pathway is also activated (37). Our team has published work in a newborn lamb model showing that MV induced a 25–30% decrease in myofibrillar force generation and increased STAT3 transcription factor phosphorylation (see Appendix 5) (38). Ensues a decreased force-generating capacity (4, 5, 29), which is then followed by the development of diaphragm atrophy in both slow- and fast-twitch fibers leading to even greater muscle weakness (3, 4, 39).

2.3 Prevalence

In adult studies using magnetic stimulation (MS), diaphragm dysfunction (defined by twitch airway pressure, $Paw_{twitch} < 11$ cmH_2O) was found to be present in up to 64% of patients within 24 hours after intubation (5), 79–84% in stable ICU patients (6, 40) and 63–80% in ICU patients during weaning (21, 24).

More recent studies have reported that VIDD is likely also common in critically ill children: 47% receiving invasive MV for ≥ 48 hours experienced diaphragm atrophy, defined as $\geq 10\%$ decrease in thickness as assessed by ultrasound (41); and nearly 35% of children had diminished respiratory muscle strength at the time of extubation, defined as maximum inspiratory pressure $\Delta Paw_{max} \leq 30$ cmH_2O (42).

2.4 Clinical impact

In adults, diaphragm atrophy or dysfunction correlates with ventilation weaning failure (21, 24, 43, 44), longer duration of MV (6, 7, 29, 43, 45), prolonged ICU admission (45), higher risk of complications (45), and increased hospital mortality (6, 7, 21). Some authors even report long-term impact with increased mortality at 1 year (46).

In one of the only pediatric studies investigating outcomes of diaphragmatic dysfunction, Khemani et al. found that patients with diaphragmatic dysfunction were

nearly three times more likely to be reintubated than those with preserved strength (42).

3 Assessment of diaphragmatic function

As part of the work accomplished during his master's degree, the author of this thesis contributed to a published review article on monitoring of respiratory muscle function in critically ill children (see Appendix 4). In this section of the thesis, we will focus only on a subset of these tools (Table 1) most relevant to this work. Please refer to Appendix 4 for a more thorough discussion.

3.1.1 Clinical evaluation

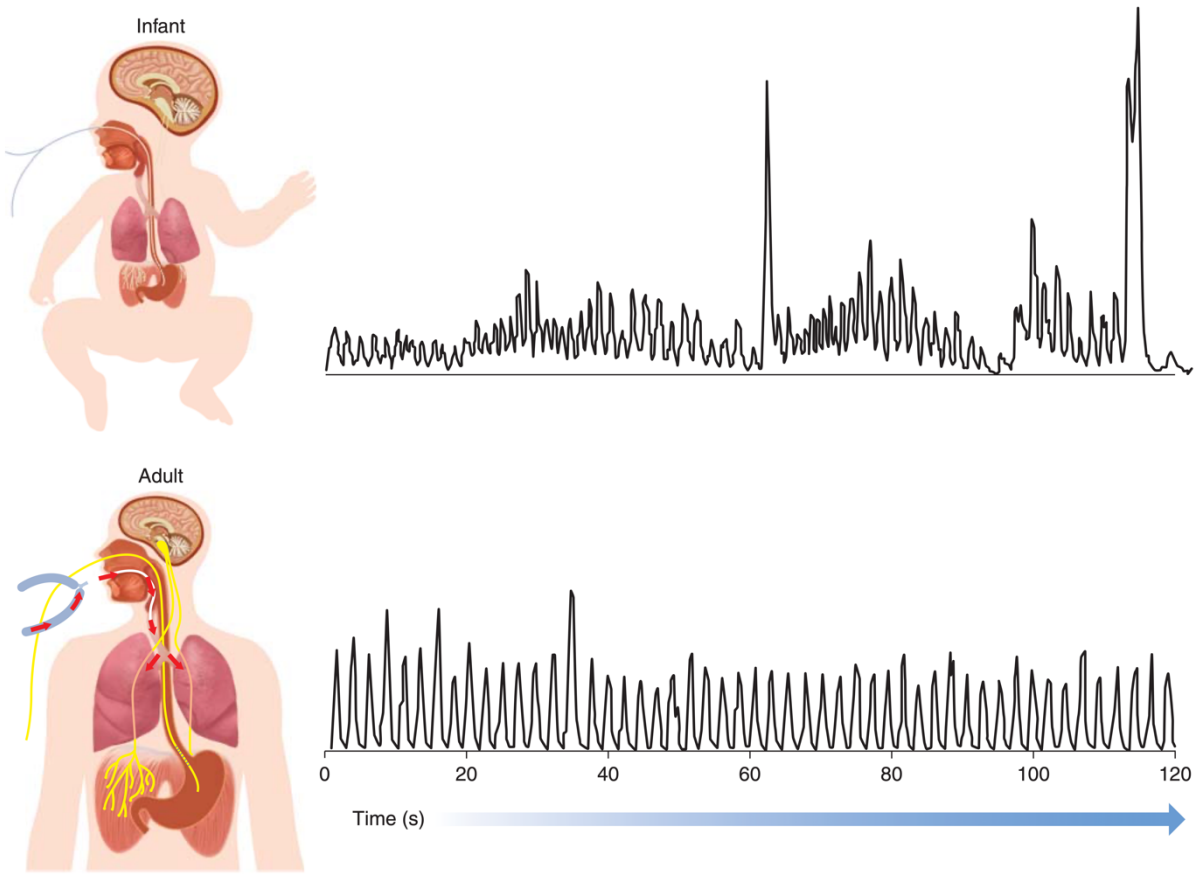
Clinical examination may reveal indirect evidence of diaphragmatic weakness. Accessory inspiratory respiratory muscles, such as the sternocleidomastoid muscle, may be apparent in patients when load exceeds the capacity of the diaphragm. With severe diaphragmatic weakness, a paradoxical inward motion of the abdomen can be observed during inspiration in supine patients. Contraction of the abdominal muscles during expiration and relaxation during inspiration can also reflect respiratory muscle dysfunction. These clinical signs are however not likely to be sensitive to diaphragmatic weakness in the context of critical care, especially under MV. Physiological tools are therefore essential.

3.1.2 Neuromuscular command

Neural impulse from the phrenic nerve is converted into muscle fiber action potentials and can be recorded by electromyography (EMG). Although diaphragm EMG can be measured from surface electrodes, the signal can be contaminated by the activity of other muscles from the thoracic or abdominal wall (47). The use of esophageal electrodes can overcome this crosstalk, but requires filtering out the ECG signal from the

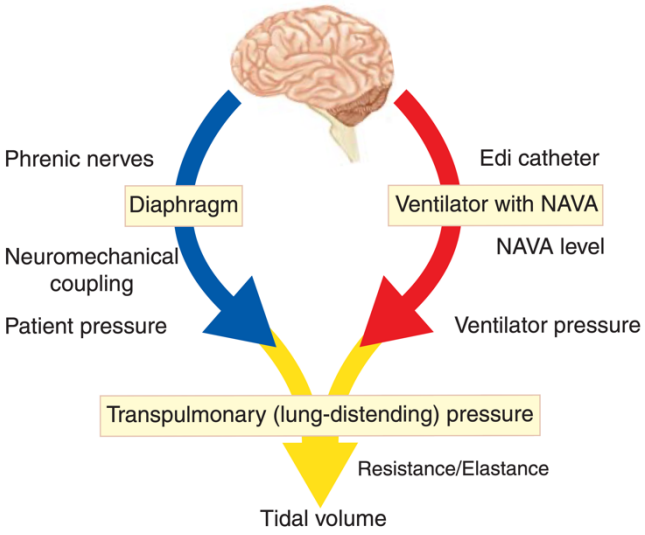
neighboring heart (48) and adjusting for axial displacement of the diaphragm during breathing (49, 50). Using proprietary software developed for neurally-adjusted ventilatory assist (NAVA) mode of ventilation, EMG potentials recorded by each electrode pair are summed temporally and spatially and converted into a single amplitude/time signal (electrical activity of the diaphragm, EAdi, Figure 2) (Maquet critical care, Solna, Sweden). The EAdi signal has many clinical applications, particularly the possibility of delivering ventilation that is synchronized and proportional to neural impulse in NAVA (Figure 3) (51). It can also be useful as a standalone monitoring tool in the PICU (e.g. to monitor respiratory muscle unloading, diaphragm inactivity, and patient–ventilator synchrony) (52). Although they can vary considerably between patients, EAdi values have now been reported for children during a PICU stay (9) and a post-operative course (53). The ratio of actual EAdi to EAdi measured during an occlusion ($EAdi_{max}$) can be used as a measure of patient's effort. The pressure generated after 0.1 sec of occlusion ($P_{0.1}$) also constitutes a marker of respiratory drive and has been found to correlate significantly with EAdi in children (54).

Figure 2. EAdi waveforms



Top panel: Processed electrical activity of the diaphragm (EAdi) waveform obtained in a non-intubated premature infant. *Bottom panel*: Processed EAdi waveform obtained in an intubated adult. The EAdi waveform in infants is characterized by larger variability in timing and amplitude, with a distinct amount of changes in the baseline, so-called tonic activity of the diaphragm. Republished with permission of McGraw-Hill Education, from Principles and Practice of Mechanical Ventilation, Martin J. Tobin, 3rd edition, 2013; permission conveyed through Copyright Clearance Center, Inc.

Figure 3. Concept of Neurally Adjusted Ventilatory Assist (NAVA)



During NAVA, the respiratory centers control both the patient's own diaphragm (*left*), resulting in a patient pressure, and the ventilator (*right*), creating a ventilator pressure (*right*). Their sum is the transpulmonary (or lung-distending) pressure. Depending on the patient's neuro-mechanical efficiency (left) and on the NAVA level (right), the relative contribution of the patient or ventilator to the lung-distending pressure will vary. For a given lung-distending pressure, the tidal volume generated will depend on the elastance and resistance of the patient. Republished with permission of McGraw-Hill Education, from Principles and Practice of Mechanical Ventilation, Martin J. Tobin, 3rd edition, 2013; permission conveyed through Copyright Clearance Center, Inc.

3.1.3 Coupling efficiency

Measured in conjunction with pressures and volumes generated, EAdi is helpful in differentiating between weak muscle contraction and deficient neural or neuromuscular transmission. Recording the diaphragm EMG signal evoked in response to MS specifically allows phrenic nerve function to be assessed (55). Work from Radell et al. has elegantly showed however that neural and neuromuscular transmission are not affected in the context of VIDD, and the loss in pressure-generating capacity therefore resides within the diaphragmatic myofibers themselves (56). The Paw/EAdi ratio provides an estimate of the ability to generate pressure normalized to neural drive (neuro-mechanical efficiency, NME) (57). The Vt/EAdi ratio provides an estimate of the ability to generate volume normalized to neural drive (neuro-ventilatory efficiency,

NVE). Unlike NME, NVE is sensitive to changes in respiratory load (i.e. airway compliance and resistance) and to the work done by the ventilator. It should thus be calculated using tidal volumes generated without any ventilator assistance. A decrease in these ratios indicates that the respiratory muscles are less efficient in converting electrical activity into pressure or volume. NME and NVE have been measured in the context of adult (58-64) and pediatric critical care (54, 65). The key benefit in using such ratios is that inspiratory efforts need not be maximal.

3.1.4 **Diaphragm anatomy**

Chest radiography (66), computed tomography (67), fluoroscopy (68), real-time ultrasonography (43, 69) and respiratory inductive plethysmography (70) have been used historically to investigate diaphragm dome excursion. Importantly, these modalities are mainly qualitative, do not distinguish passive from active movement, and provide no information about actual force production. More recently, various groups have used ultrasound to measure diaphragm thickening fraction (TFdi) at the muscular zone of apposition. TFdi correlates strongly with negative intrathoracic pressure in response to phrenic nerve stimulation (71), with the pressure–time product of the diaphragm (72) and with EAdi (73). Diaphragm thickness (Tdi) and TFdi have recently been evaluated in children under MV (41, 74, 75). The distances measured on ultrasound are nevertheless very small in children and seem prone to a low signal-to-noise ratio.

3.1.5 **Diaphragm specimens**

Landmark studies on VIDD conducted in adults were based on autopsy findings or biopsies (3, 4). These tools are not readily available at the bedside. Moreover, PICU mortality rate is relatively low (<5%) and such studies would therefore be difficult to perform and associated with a strong selection bias. Ultimately, microscopic changes do not necessarily reflect muscle function.

3.1.6 **Pressure generation**

The diaphragm is the only inspiratory muscle for which specific force output can be quantified. The pressure generated across the dome between the thoracic and abdominal cavities is called the transdiaphragmatic pressure (Pdi = Pga – Pes, where gastric pressure estimates abdominal pressure and esophageal pressure estimates pleural pressure). Pdi is proportional to the tension developed within the muscle fibers. The magnitude of the pressure swings on either side of the diaphragm depends on muscle contraction but also on the volume changes it induces and on the elastances of the thorax and abdomen. Pdi further allows the derivation of other variables: the Gilbert index (ΔPga/ΔPdi) can be used to determine the relative contribution of the diaphragm to inspiration (76), the tension-time index is a measure of the load capacity of the diaphragm, and the pressure-time product can estimate the energy expenditure of the diaphragm. Challenges presented by esophageal pressure monitoring include optimal positioning and filling of the balloon. Airway occlusion pressure (Paw) can be easily measured in intubated patients and is directly correlated to Pes in adults (40) and in children (31). In order to estimate Pes using Paw, the glottis must be kept open and pressure must equilibrate rapidly between mouth and alveoli. It is debated whether maximal efforts can be guaranteed in intubated patients (77-79). Non-volitional techniques such as electrical or magnetic stimulation can overcome some of the challenges posed by volitional methods that require subject collaboration, which can be problematic in intensive care and pediatric settings. Electrical stimulation, although precise, is both technically difficult and painful. In contrast, MS is easily applied, painless, and secure (80). The gold standard for assessing diaphragm force in adults is the measurement of Pdi generated by twitch MS, Pdi_{twitch} (40). Rafferty et al. (81) used MS in 25 non-sedated infants, who continued to sleep throughout the study. Antero-lateral neck stimulation seemed to be more specific in stimulating the diaphragm and more supra-maximal than posterior cervical stimulation (81). In adults, anterior pre-

sternal MS has been shown as efficient as bilateral cervical stimulation, and secure (80, 82, 83), but data are lacking in children. As shown in Table 2, MS use has been limited to a few pediatric studies, all performed by the same group, because of the technical challenges it presents.

Table 1. Useful bedside tools used to assess diaphragmatic function in critical care

	Values measured	Specificities
Ultrasound		
Thickness and thickening fraction	Tdi, TFdi	Using a high-frequency linear probe.
Diaphragmatic excursion	EXdi	Using a low-frequency abdominal probe on patients off positive-pressure ventilation.
Pressure generation		
Transdiaphragmatic pressure on occlusion	Pdi_{max}	Requires esophageal and gastric balloons. Low values may reflect poor technique or effort.
Transdiaphragmatic pressure on stimulation	Pdi_{twitch}	Requires magnetic stimulation, technically difficult.
Airway pressure on occlusion	Paw_{max}	Low values may reflect poor technique or effort.
Airway pressure on stimulation	Paw_{twitch}	Requires magnetic stimulation, technically difficult.
Electromyography		
Surface EMG	RMS	Requires offline analysis.
Crural EMG	$EAdi_{max}$, NME	Requires dedicated nasogastric tube and ventilator. Can compensate for respiratory effort.

Tdi denotes diaphragm thickness, TFdi diaphragm thickening fraction, EXdi diaphragm excursion, Pdi_{max} maximal transdiaphragmatic pressure, Pdi_{twitch} transdiaphragmatic pressure induced by bilateral magnetic stimulation of the phrenic nerves, Paw_{max} endotracheal pressure during a maximal inspiratory effort, Paw_{twitch} endotracheal pressure induced by bilateral magnetic stimulation of the phrenic nerves, EMG electromyogram, RMS root mean square, $EAdi_{max}$ electrical activity of the diaphragm during a maximal inspiratory effort.

Table 2. Selection of studies using anterior magnetic stimulation

Author	Population	Results
Rafferty 2000 (81)	25 neonates without respiratory distress or oxygen	Pdi_{twitch} left: 4.5 cmH_2O, right: 4.1 cmH_2O, bilateral: 8.7 cmH_2O
Rafferty 2001 (31)	8 ventilated sedated children after liver transplantation	Pdi_{twitch} left: 7.8 cmH_2O, right: 5.2 cmH_2O, bilateral: 14.8 cmH_2O
Dimitriou 2003 (20)	10 infants with CDH, 26 with AWD and 36 controls, all not requiring support	Paw_{max} (face mask) CDH 45.4 vs control 65.8 cmH_2O AWD 43.9 vs control 53.3 cmH_2O Pdi_{twitch}, bilateral CDH 8.3 vs control 13.1 cmH_2O AWD 5.5 vs control 9.3 cmH_2O
Dimitriou 2003 (84)	29 infants without respiratory distress	Pdi_{twitch} left: 4.4 cmH_2O, right: 3.9 cmH_2O
Rafferty 2005 (85)	23 children anesthetized for minor surgery	Paw_{twitch} (cuffed laryngeal mask airway) left: 7.3 cmH_2O, right: 8.6 cmH_2O, bilateral: 18.2 cmH_2O
Kassim 2011 (55)	18 infants with surgically repaired CDH or AWD	Pdi_{twitch} AWD left: 4.0 cmH_2O, right: 4.4 cmH_2O CDH side with defect: 1.4 cmH_2O, side without defect: 3.9 cmH_2O

Paw_{max} denotes airway pressure by maximal inspiratory effort, Pdi_{twitch} transdiaphragmatic pressure generated by phrenic nerve stimulation, CDH congenital diaphragmatic hernia, AWD abdominal wall defects.

4 Research gap

In summary, mechanical ventilation is often required to maintain homeostasis in critically ill patients, but it can have a deleterious impact on the diaphragm. VIDD is highly prevalent in adult critical care and it is associated with worse outcomes. Specificities in pediatric respiratory physiology suggest that critically ill children may be at high risk of developing VIDD, but there are no validated tools available to assess diaphragmatic function in this population. To the best of our knowledge, no study has described the evolution of diaphragmatic function in critically ill children undergoing mechanical ventilation.

Methods

1 Objectives

The primary objectives of this study were to describe the evolution of diaphragmatic function in mechanically ventilated critically ill children during the first three days of invasive ventilation and to compare it with a group of healthy children undergoing general anesthesia for elective surgery. The secondary objectives were to validate a method to quantify diaphragmatic function in mechanically ventilated children; to identify patient characteristics associated with diaphragmatic dysfunction (in particular, the role of baseline respiratory drive (EAdi)); and to describe any association of diaphragmatic dysfunction with outcomes.

2 Hypothesis

Our main hypothesis was that diaphragmatic function, as assessed by neuro-mechanical efficiency, decreases over time under conventional MV in children.

3 Design

This was a prospective single-center observational study.

4 Setting

This study was performed in a tertiary academic center, in both the PICU and the OR.

5 Population

5.1 Inclusion criteria

In the PICU group, we included children (1 week to 18 years old) admitted to the PICU and under invasive ventilation (since less than 24 hours and planned for more than 24 hours). This was designed to allow for at least two measurements: the first close to intubation (before a possible impact of VIDD), and the later measurement(s) to observe evolution over time. The OR group included children with no chronic or acute respiratory disease (1 week to 18 years old) undergoing endotracheal intubation for elective otorhinolaryngological surgery, without planned neuromuscular paralysis use.

5.2 Exclusion criteria

Because the focus was on ICU-acquired diaphragm dysfunction (ICU–DD), we excluded pre-existing conditions with a possible impact on diaphragmatic function from both groups, namely: neuromuscular disease, cervical spine injury, bi-hemispheric or brain stem lesions, diaphragmatic disease, uni- or bi-lateral phrenic paralysis, recent (<1 month) thoracic surgery, recent (<1 month) multiple costal fractures.

Our protocol required excluding patients where the placement of a new nasogastric tube to measure diaphragmatic electrical activity was contraindicated (trauma or recent surgery in cervical or nasopharyngeal regions, severe coagulation disorder), where magnetic phrenic nerve stimulation was contraindicated (pacemaker or implanted defibrillator, presence of metallic objects in the stimulated field, cervical implants), or where diaphragmatic function was artificially suppressed (use of neuromuscular blockade in the 2 hours prior to inclusion). Finally, patients in whom life-sustaining treatment was withheld were not approached.

6 Outcome measures

As no reference method for assessing diaphragmatic function in this population existed when designing this study, we decided to use the pressure-generating capacity of the diaphragm normalized to respiratory drive as our primary outcome, using a physiological rationale (see Literature review section 3 above). This was measured by the $\Delta Paw_{max}/\Delta EAdi_{max}$ (NME_{occl}) ratio during an occlusion maneuver while patients breathed spontaneously at H_0, H_{12}, H_{24}, H_{48} and H_{72} (PICU group) and at H_0 (OR group). The most reliable method to obtain this ratio was assessed and validated (see Methods section 11.1 below).

Secondary endpoints included the evolution of ΔPaw_{max} at the same timepoints, as well as $\Delta Paw_{twitch}/\Delta EAdi_{twitch}$ (NME_{twitch}) and ΔPaw_{twitch} during bilateral stimulation at expiratory occlusion. Clinical outcome measures such as ventilation duration, extubation failure, requirement of non-invasive ventilation (NIV) for 72 hours post-extubation, PICU length of stay and PICU mortality were also assessed.

7 Study protocol

Approval by the ethics committee of the CHU Sainte-Justine Research Center was granted before initiating enrollment (2017-1534). Written informed consent was obtained from the parents/guardians by a member of the research team. Measurements were performed by one of the two investigators (B Crulli or G Emeriaud).

7.1 PICU group

A dedicated 6Fr or 8Fr nasogastric catheter (Maquet critical care, Solna, Sweden) was inserted to a depth determined by a validated equation and adjusted using dedicated software on the Servo-i ventilator, which then processed and displayed the EAdi signal (52), as per the manufacturer's recommendations.

7.1.1 Timing of measurements

Measurements were conducted at least 2 hours after the use of any neuromuscular blocker, and 1 hour after the last gastric milk bolus in patients with intermittent feeding to minimize the impact of gastric bolus on abdominal compliance. The first measurement of diaphragm contractile strength was conducted as soon as possible after inclusion (within 24 hours of intubation). Measurements were then repeated using the same procedure and timed according to investigator, equipment, and patient availability as close as possible to the following time points after the first measurement: 12 hours, 24 hours, 48 hours and 72 hours or until extubation/death. The duration of MV required to see a statistically significant reduction in diaphragm function in a landmark study in adult ICU patients was 3–4 days (4).

7.1.2 Measurement procedure

Patients were placed in a supine position and the respiratory circuit was assessed for leaks (all had a cuffed endotracheal tube). If needed, an opioid (e.g. fentanyl) dose was administered (as prescribed by the treating team) and the endotracheal tube was suctioned. The EAdi signal from the preceding 60 minutes was extracted from the ventilator to measure baseline respiratory drive, and clinical data were recorded. A low dead space pneumatic occlusion valve (Hans Rudolph, Southport, UK) was installed between the ventilator circuit and the existing endotracheal tube. When patients exhibited a stable spontaneous breathing pattern (i.e. no coughing, hiccups or disproportional differences in respiratory rate), an expiratory occlusion maneuver was performed (at the current level of PEEP), and we simultaneously recorded negative airway pressure generated with the EAdi signal over 5 breaths. The maneuvers were subsequently repeated three times with at least a one-minute interval.

7.1.3 Other procedures

We had initially planned to measure diaphragmatic strength by applying bilateral phrenic nerve MS during 0.1 msec at the anterolateral aspect of the neck (posterior border of sternocleidomastoid at the cricoid level) during an expiratory occlusion maneuver. Two high power magnetic stimulators (Magstim Co., Whitland, Dyfed, UK, approved by Health Canada) were used to simultaneously power two 90-mm circular coils at maximal output. However, this technique posed many technical challenges in infants (see Discussion section 1.1 below) and was abandoned after 14 patients and a protocol amendment.

7.2 OR group

A dedicated 6Fr or 8Fr nasogastric catheter (Maquet critical care, Solna, Sweden) was inserted as described above. Diaphragm contractile strength was measured once, in the same fashion as described for the PICU group (except that no PEEP was applied), immediately after intubation and before surgery.

8 Data collection

8.1 PICU group

8.1.1 Baseline data

- demographic data (gestational age at birth, age, weight, gender)
- previous episode of invasive ventilation (within 7 days)
- admission diagnosis category
- indication for intubation, ETT size

8.1.2 Data collected at each measurement

- PELOD–2 Score (see Appendix 3)

- respiratory status: oxygen saturation by pulse oximetry (SpO_2), respiratory rate (RR), last available capillary or arterial blood gas (pH, PaO_2, PCO_2)
- ventilatory mode and parameters: fraction of inspired oxygen (FiO_2), mandatory respiratory rate, positive end-expiratory pressure (PEEP), driving pressure, tidal volume (Vt)
- hemodynamic status: blood pressure, heart rate, last available lactate, SvO_2
- neurological status: RASS (see Appendix 1), COMFORT–B scale (see Appendix 2)
- suspicion of sepsis (based on inflammatory parameters, cultures), at the time of the recording
- vasoactive drugs, at the time of the recording
- sedative drugs (types and doses), in the last 4 hours
- paralytic drugs (types, dose, timing), since the last recording
- corticosteroids (types, dose, timing), since the last recording

8.1.3 Clinical outcome data

- MV duration (time between the initiation of ventilation and the end of any invasive support, successful for at least 24 hours)
- requirement of NIV for more than 72 hours post-extubation
- length of stay in PICU
- mortality in PICU

8.2 OR group

8.2.1 Baseline data

- demographic data (gestational age at birth, age, weight, gender)
- surgical indication

- ETT size

8.2.2 Data collected at measurement

- induction drugs used for intubation
- respiratory status: oxygen saturation by pulse oximetry (SpO_2), respiratory rate (RR)
- hemodynamic status: blood pressure, heart rate

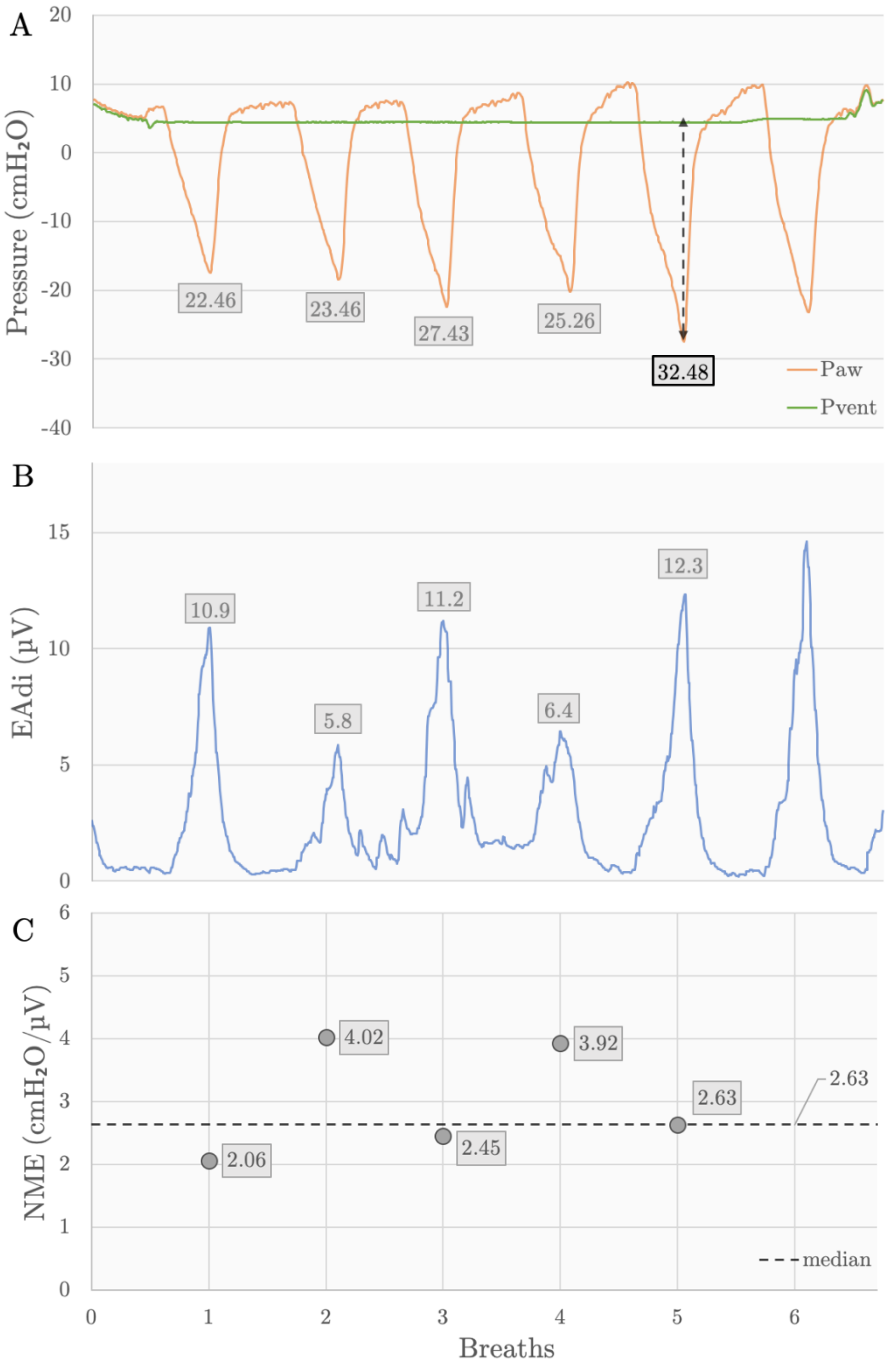
8.2.3 Clinical outcome data

- length of stay in hospital

9 Data acquisition

EAdi waveforms were acquired from the Servo-i ventilator (Maquet critical care, Solna, Sweden) via a RS232 serial port. Pressure measurements were performed with a manometer connected to the endotracheal tube through a low dead space pneumatic occlusion valve. The signals were simultaneously displayed and recorded using dedicated software (NeuroVent Research, Toronto, Canada) (Figure 4). Baseline values of EAdi (maximal EAdi value in each minute) were also extracted from the ventilator for up to 60 minutes before each measurement in the PICU group.

Figure 4. Example of signals recorded during an occlusion maneuver



Paw denotes airway pressure, Pvent pressure on ventilator circuit, EAdi electrical activity of the diaphragm, NME neuro-mechanical efficiency ratio (defined as ΔPaw_{max} divided by $EAdi_{max}$). A: Paw and Pvent over time, with ΔPaw values specified for each breath, dotted arrow shows ΔPaw_{max}. B: EAdi over time, with $EAdi_{max}$ values specified for each breath. C: NME_{occl}. values for each breath, with the median of all 5 values as a dotted line.

10 Sample size

At the time of designing the study, no pediatric data on diaphragmatic function in children under MV was available. In adult patients, data on VIDD is scant but Jaber et al. demonstrated a strong and homogenous decrease in pressure-generating capacity of the diaphragm over time. With only 6 patients, they reported a mean first ΔPaw_{twitch} measurement of 16.5 cmH_2O ± standard deviation of 5.2 cmH_2O and a statistically significant reduction of 32% ± 6% after 5–6 days of MV (4). In this context, and in the absence of pediatric data, a sample size of 20 patients for the PICU group was chosen in order to improve external validity. In the OR group, less heterogeneity was expected and a convenient sample of 10 patients was selected.

11 Data analysis

Data were reported as median ± inter-quartile range (IQR), except as stated otherwise. The level of significance for all statistical tests was set at $p < 0.05$. Statistical analysis was performed using SPSS (SPSS Statistics, Version 25. Armonk, NY: IBM Corp.) and Stata software (Stata Statistical Software, Release 16. College Station, TX: StataCorp LLC.).

11.1 Assessment of diaphragmatic function

For each breath during each occlusion maneuver, the peak value of EAdi was recorded ($EAdi_{max}$) as well as ΔPaw_{max} (the difference in pressure between the lowest P_{aw} during the occlusion and the preceding end-expiratory pressure level). In order to compensate for central respiratory drive and sedation use, a neuro-mechanical efficiency ratio (NME_{occl}) was computed by dividing ΔPaw_{max} by $EAdi_{max}$ (Figure 4).

No standardized method has been described to quantify NME_{occl} in children. In order to determine the optimal measure of ΔPaw_{max} and NME_{occl} to represent each occlusion maneuver, the within-measurement variability over three maneuvers of different

variables (first breath, last breath, breath with largest ΔPaw_{max} deflection, breath with largest NME_{occl} value, and median value over all breaths) was assessed using coefficients of variation in both patient groups. The coefficient of variation (CoV) accounts for the fact that variability can increase as the magnitude of the measured value increases, and was calculated in the following manner:

$$\text{CoV} = \frac{\text{within-subject standard deviation}}{\text{mean}}$$

For both $\Delta Paw_{max,}$ and NME_{occl}, the value with the smallest mean CoV over three occlusion maneuvers in the PICU group (which is larger and the focus of this work) was subsequently used to represent a single occlusion maneuver.

The within-subject correlation between ΔPaw_{max} and $EAdi_{max}$ was also investigated using a correlation coefficient with repeated observations in the OR group (86, 87), in order to corroborate previous results.

11.2 Evolution of diaphragmatic function over time

For each time point measurement, the least variable value according to the method described above was saved for both ΔPaw_{max} and NME_{occl}. In order to assess the impact of MV on diaphragmatic function, these values were then plotted against time under MV and lines of best fit were computed using the method of least squares. A generalized estimating equation with a population-averaged linear model was used to estimate the effects of time under MV on ΔPaw_{max} and NME_{occl}, taking into consideration correlation within individual patients. The model was under the assumption that the effect of MV was consistent over time from intubation.

11.3 Comparison between OR and PICU groups

Aiming to weigh the impact of critical illness on diaphragmatic function, independently from MV, a Mann–Whitney U test was run to determine if there were significant

differences in ΔPaw_{max} and NME_{occl} between the first measurement of the PICU group and the only measurement of the OR group.

11.4 VIDD definition, risk factors and outcomes (PICU group)

Jaber et al. report a reduction in diaphragmatic function of 32% after 5–6 days of MV (4). In our protocol, measurements were performed over a maximum of 72 hours. A cut-off value for the slope of the lines that best fit the evolution of NME_{occl} over time under MV was calculated using this expected decrease (16% in 72 hours), and the PICU group was split *a posteriori* in two subgroups: patients with a slope larger than the cut-off value (stable or improving neuro-mechanical efficiency), and patients with a negative slope below the cut-off value (decreasing neuro-muscular efficiency). Baseline patient characteristics and outcomes were then compared between the two subgroups using Fisher's exact test for categorical variables and a Mann-Whitney U test for non-categorical variables.

11.5 Impact of selected potential confounding factors on diaphragmatic function (PICU group)

Reported in the literature as the main confounding factors affecting diaphragmatic function (see Literature review section 2.2 above and Discussion section 1.2 below), the impact of baseline respiratory drive and PEEP was assessed using the Pearson product-moment correlation. We evaluated both the impact on values measured in those conditions and the long-term impact of these factors on evolution of diaphragmatic function over time.

Results

Patients were recruited between October 2017 and September 2019. In the PICU group, 223 consecutive intubated patients were screened, 50 met the inclusion and exclusion criteria, 36 families provided consent, and measurements were possible in 20 patients. Table 3 describes patient characteristics in the PICU group, in which patients had a median age of 13.7 months (IQR 1.5–34), a median weight of 11 kg (IQR 3.8–17.3), and 12 were male (63.2%). One patient had severe meningitis and was excluded from the analysis because of no detectable spontaneous breathing activity. They were under invasive ventilation for 63.9 hours (IQR 50.4–77.4) and stayed in the PICU for 5.3 days (IQR 4–8.8). There was no PICU mortality, apart from the excluded patient. In the OR group, 12 consecutive eligible patients were approached, 10 families provided consent, and measurements were performed in 10 patients. Table 4 describes patient characteristics in the OR group, in which patients had a median age of 59.3 months (IQR 46.6–65.8), a median weight of 17.9 kg (IQR 13.6–23), and 5 were male (50%). Their hospital stay for elective surgery was 1.5 days (IQR 1–2.8).

In total, 147 occlusions were performed, and 625 breaths were analyzed in the PICU group (19 patients); in the OR group, 30 occlusions were performed, and 150 breaths were analyzed (10 patients). In 3 out of 10 patients in the OR group, the EAdi signal could not be appropriately recorded and NME_{occl} was therefore not computed.

Table 3. Patient characteristics (PICU group, 19 patients)

Age (months), median (IQR)	13.7 (1.5–34)
Weight (kg), median (IQR)	11 (3.8–17.3)
Sex, male (%)	12 (63.2%)
Comorbidity, n (%)	
Prematurity	6 (31.6%)
Previous episode of invasive ventilation (within 7d of intubation)	3 (15.8%)
Reason for PICU admission, n (%)	
Neurological (traumatic brain injury)	1 (5.3%)
Neurological (excluding traumatic brain injury)	4 (21.1%)
Respiratory-Upper airway	4 (21.1%)
Respiratory-Lower airway/pulmonary	7 (36.8%)
Sepsis/shock	1 (5.3%)
Other	2 (10.5%)
Reason for intubation, n (%)	
Neurological	4 (21.1%)
Apnea	3 (15.8%)
Respiratory-Upper airway	4 (21.1%)
Respiratory-Lower airway/pulmonary	6 (31.6%)
Hemodynamics	1 (5.3%)
Procedure	1 (5.3%)
Sedation used less than 4h before measurements, n (%)	
Opioids	19 (100%)
Benzodiazepines	7 (36.8%)
Propofol	1 (5.3%)
Dexmedetomidine	14 (73.7%)
Drugs used during study period, n (%)	
Paralysis (excluding for intubation)	5 (26.3%)
Corticosteroids	8 (42.1%)
Inotropes/vasodilators	5 (26.3%)
Spontaneous mode during admission (NAVA/PSV), n (%)	14 (73.7%)
Duration of MV on first measurement (hours), median (IQR)	20.7 (13.9–21.7)
Maximal ΔPaw_{max} on first measurement (cmH_2O), median (IQR)	35.1 (21–58)
Median NME_{occl} on first measurement ($cmH_2O/\mu V$), median (IQR)	1.8 (1.3–2.4)
Number of measurements, median (IQR)	3 (2.5–4)
Duration of MV (hours), median (IQR)	63.9 (50.4–77.4)
Reintubation within 24 hours of extubation, n (%)	0 (0%)
Rescue NIV for more than 72 hours post-extubation, n (%)	2 (10.5%)
PICU length of stay (days), median (IQR)	5.3 (4–8.8)
Died during PICU admission, n (%)	0 (0%)

PICU denotes pediatric intensive care unit, IQR inter-quartile range, NAVA neurally-adjusted ventilatory assist, PSV pressure-support ventilation, MV mechanical ventilation, ΔPaw_{max} maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm), NIV non-invasive ventilation.

Table 4. Patient characteristics (OR group, 10 patients)

Age (months), median (IQR)	59.3 (46.6–65.8)
Weight (kg), median (IQR)	17.9 (13.6–23)
Sex, male (%)	5 (50%)
Comorbidity, n (%)	
Prematurity	1 (10%)
Sedation used for induction, n (%)	
Sevoflurane	10 (100%)
Opioids	8 (80%)
Benzodiazepines	0 (0%)
Propofol	10 (100%)
Dexmedetomidine	4 (40%)
Ketamine	1 (10%)
Other dugs received before measurement, n (%)	
Corticosteroids	10 (100%)
Duration of MV on first measurement (minutes), median (IQR)	7.6 (2.6–12.4)
Maximal ΔPaw_{max} on first measurement (cmH_2O), median (IQR)	31.3 (28.5–35.5)
Median NME_{occl} on first measurement ($cmH_2O/\mu V$), median (IQR)	3.6 (3.5–4.2)
Hospital length of stay (days), median (IQR)	1.5 (1–2.8)

OR denotes operating room, IQR inter-quartile range, MV mechanical ventilation, ΔPaw_{max} maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm).

1 Assessment of diaphragmatic function

1.1 Validation of diaphragmatic function assessment during an occlusion maneuver

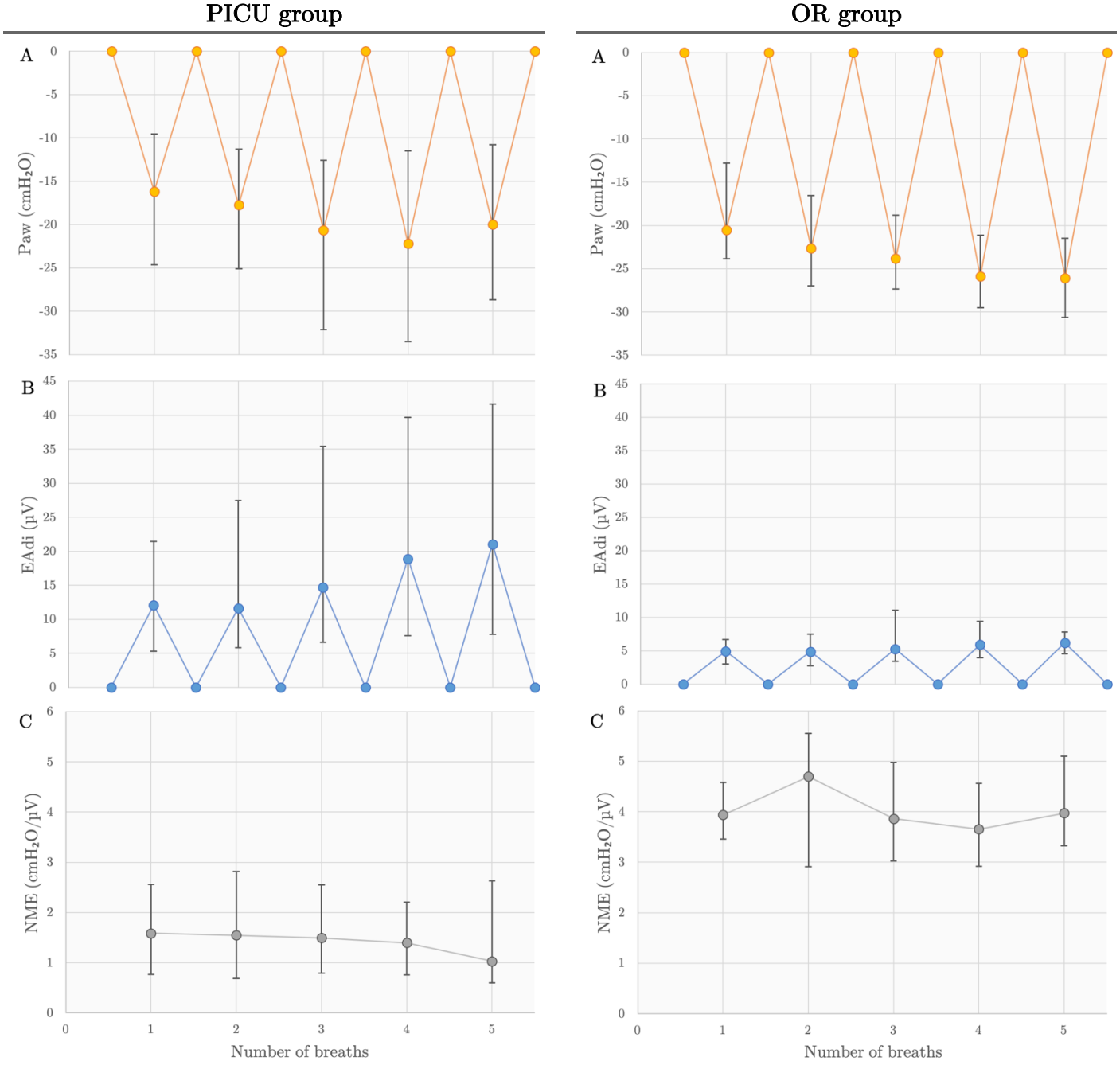
1.1.1 Median values during an occlusion maneuver

The median evolution of ΔPaw_{max}, $EAdi_{max}$ and NME_{occl} over the 5 occluded breaths is represented on Figure 5 for both groups. ΔPaw_{max} tends to increase progressively over each breath of the occlusion maneuver (Figure 5A). This is matched by an increase in respiratory drive and $EAdi_{max}$ (Figure 5B), resulting in a NME_{occl} value which tends to remain stable (Figure 5C, right) or even decrease on the last breath (Figure 5C, left).

1.1.2 Variability of different analysis methods

The variability of different methods assessing ΔPaw_{max} and NME_{occl} for each occlusion maneuver (first breath, last breath, breath with largest ΔPaw_{max} deflection, breath with largest NME_{occl} value, and median value over all breaths) is shown in Table 5 (PICU group) and Table 6 (OR group). For $\Delta Paw_{max,}$ the value corresponding to the breath in each occlusion maneuver with the largest maximal inspiratory airway pressure deflection had the smallest mean CoV over three occlusion maneuvers in both groups. As for NME_{occl}, the median value of all breaths in each occlusion maneuver had the smallest mean CoV of 23.7% over three occlusion maneuvers in the PICU group. In the OR group however, the value corresponding to the last breath in each occlusion maneuver was the least variable, with a CoV of 21.1%. The median value of all breaths in each occlusion maneuver had a mean CoV of 21.4%.

Figure 5. Median evolution of ΔPaw_{max}, $EAdi_{max}$ and NME_{occl} over the 5 occluded breaths (both groups)



Data represented as median ± inter-quartile range. A: ΔPaw_{max}. B: $EAdi_{max}$. C: NME_{occl}. Left: Pediatric intensive care unit (PICU) group, right: Operating room (OR) group.

Table 5. Variability of different measures of ΔPaw_{max} and NME_{occl} (PICU group)

	ΔPaw_{max}			NME_{occl}	
Mean coefficient of variation					
1	Largest ΔPaw_{max}	26.1%	**1**	Median	23.7%
2	Median	26.3%	**2**	Largest ΔPaw_{max}	26.8%
3	Last breath	29.8%	**3**	Largest NME_{occl}	29.8%
4	Largest NME_{occl}	30.3%	**4**	Last breath	33.8%
5	1st breath	35.5%	**5**	1st breath	36.8%

PICU denotes pediatric intensive care unit, ΔPaw_{max} denotes maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm)

Table 6. Variability of different measures of ΔPaw_{max} and NME_{occl} (OR group)

	ΔPaw_{max}			NME_{occl}	
Mean coefficient of variation					
1	Largest ΔPaw_{max}	14.3%	**1**	Last breath	21.1%
2	Last breath	14.3%	**2**	Largest ΔPaw_{max}	21.2%
3	Median	17.3%	**3**	Median	21.4%
4	Largest NME_{occl}	22.7%	**4**	1st breath	26.1%
5	1st breath	23.1%	**5**	Largest NME_{occl}	26.5%

OR denotes operating room, ΔPaw_{max} maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm).

1.1.3 Selected analysis methods

For $\Delta Paw_{max,}$ the value corresponding to the breath in each occlusion maneuver with the largest maximal inspiratory airway pressure deflection was subsequently used to represent ΔPaw_{max} for a single occlusion maneuver, and the largest of all three values corresponding to occlusion maneuvers used to represent ΔPaw_{max} for a single measurement in time. Because this work is mainly focused on the PICU group (which also represents a larger sample) and because the CoV in the OR group were very similar, the median value of all breaths in each occlusion maneuver was subsequently used to represent NME_{occl} for a single occlusion maneuver, and the median of all three values corresponding to occlusion maneuvers used to represent NME_{occl} for a single measurement in time.

1.2 Correlation between ΔPaw_{max} and $EAdi_{max}$ (OR group)

Figure 6 shows a scatter plot correlating ΔPaw_{max} and $EAdi_{max}$ values for all breaths assessed in the OR group. Table 7 compares the ΔPaw_{max} / $EAdi_{max}$ linear regression slope and NME values. There was strong correlation between ΔPaw_{max} and $EAdi_{max}$ in individual patients (slope 1.70, correlation coefficient within subjects 0.81, r ranging from 0.14 to 0.91, $p < 0.0005$).

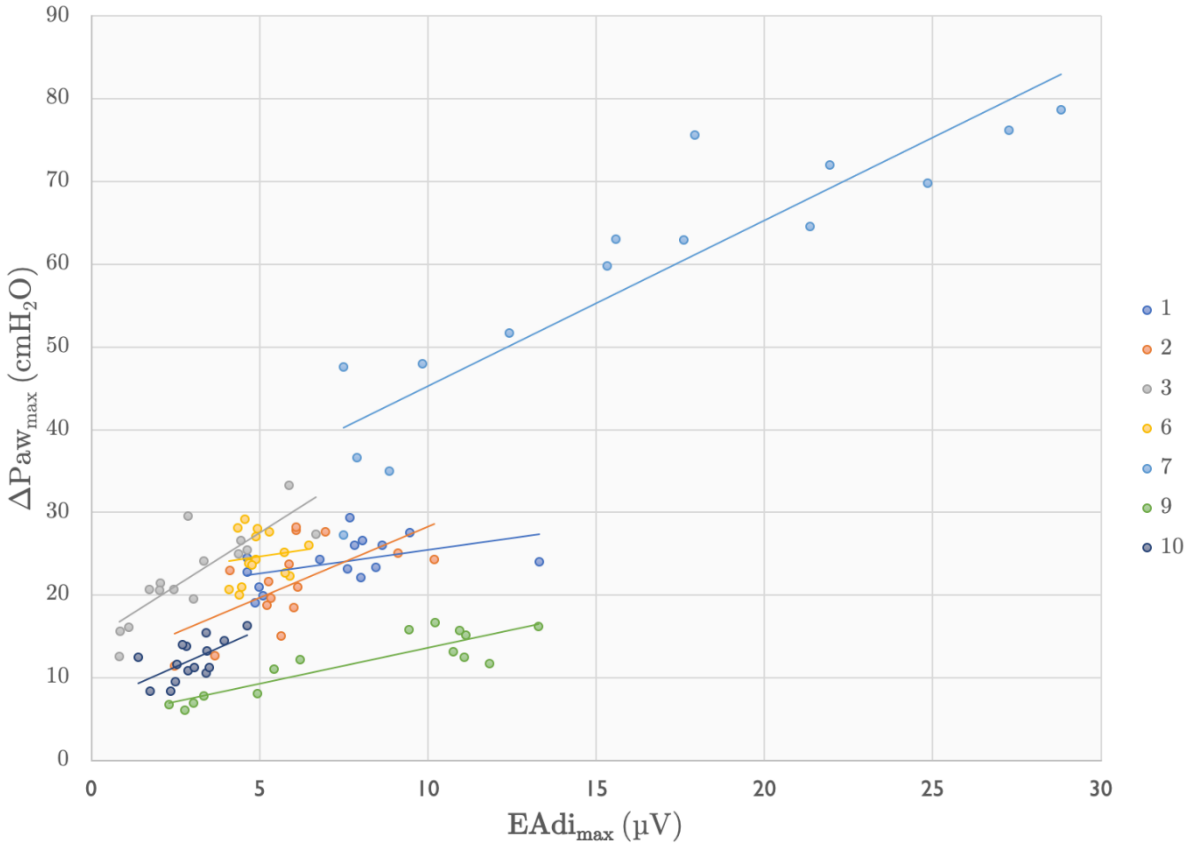
If we assume a linear relationship between ΔPaw_{max} and $EAdi_{max}$, then:

$$\Delta Paw_{max} = (\text{slope} \times EAdi_{max}) + \text{intercept}$$

$$NME_{occl} = \frac{\Delta Paw_{max}}{EAdi_{max}}$$

NME will therefore only correspond to the slope if the intercept is zero. However, as can be seen in Table 7, the intercepts of the linear regressions are different than zero, and thus the slopes differ from the median NME_{occl} values.

Figure 6. ΔPaw_{max} / $EAdi_{max}$ scatter plot (OR group)



Correlation between maximal inspiratory airway pressure deflection (ΔPaw_{max}) and peak electrical activity of the diaphragm $EAdi_{max}$ for all measurements. Each color represents an individual patient with 5 breaths over 3 occlusions (15 dots each) and the corresponding line of best fit (line). OR denotes operating room.

Table 7. Comparison of ΔPaw_{max} / $EAdi_{max}$ linear regression slope and NME (OR group)

Patient	ΔPaw_{max} / $EAdi_{max}$ linear regression intercept	ΔPaw_{max} / $EAdi_{max}$ linear regression slope	ΔPaw_{max} / $EAdi_{max}$ correlation coefficient	Median NME_{occl}
1	19.82	0.57	0.47	3.33
2	11.12	1.72	0.62	3.68
3	14.56	2.60	0.84	8.47
4	N/A	N/A	N/A	N/A
5	N/A	N/A	N/A	N/A
6	21.62	0.61	0.14	4.99
7	25.30	2.00	0.91	3.90
8	N/A	N/A	N/A	N/A
9	5.00	0.87	0.88	1.64
10	6.77	1.81	0.61	3.80

OR denotes operating room, ΔPaw_{max} maximal inspiratory airway pressure deflection, $EAdi_{max}$ peak electrical activity of the diaphragm, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm).

2 Evolution of diaphragmatic function over time

2.1 Clinical condition at measurements

Clinical parameters at each measurement in the PICU group are shown in Table 8. In total, 59 measurements were made in the PICU group, the earliest at 7 hours after intubation, the latest at 104 hours after intubation. The first measurement in each patient was performed at 20.7 hours (IQR 13.9–21.7). A median of 39.2 hours (IQR 22.9–44.9) elapsed between the first and last measurements. The last measurement was obtained a median 4.8 hours (IQR 1.5–25) before extubation. Patients were ventilated with 6.5 ml/kg (IQR 5.2–7.8) of tidal volume, 6 cmH_2O (IQR 5–8) of PEEP, and 35% (IQR 25%–45%) of FiO_2 and physiological ventilation and oxygenation were achieved. Although sedation scores seem similar over the measurements, spontaneous modes of ventilation (PSV/NAVA) were increasingly used in the later measurements. Baseline EAdi in the 60 minutes before a measurement is shown in Figure 11 and was also higher in the later measurements

2.2 Evolution of ΔPaw_{max}

The pressure-generating capacity of the diaphragm (ΔPaw_{max}) for individual patients in both the PICU and OR groups is shown in Figure 7. Lines of best fit for ΔPaw_{max} over time in the PICU group are shown graphically in Figure 7B and textually in Table 9. They had variable slopes ranging from -1.512 to 3.321 cmH_2O/h. Grouped measurements for all patients are displayed in Figure 8. A population-averaged model did not find a significant change in ΔPaw_{max} over time under MV, with a correlation coefficient of 0.10 (95% confidence interval -0.19 – 0.40, $p = 0.495$). In the PICU group, although 8 patients (42%) were not capable of generating a $\Delta Paw_{max} \geq 30$ cmH_2O on their last measurement, only 3/8 could on their earliest measurement.

2.3 Evolution of NME_{occl}

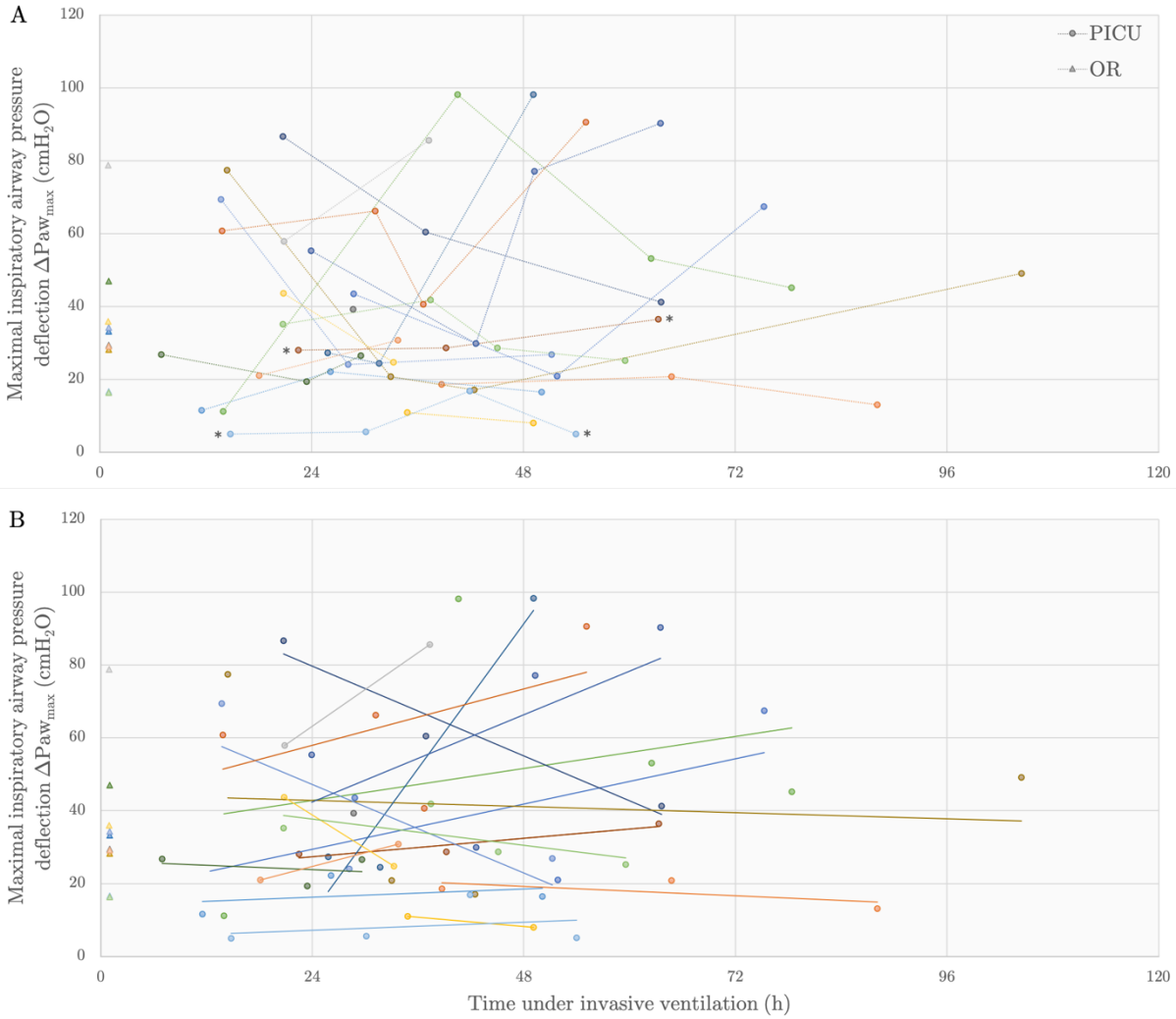
The capacity of the diaphragm to generate pressure from neural input (NME_{occl}) for individual patients in both the OR and PICU groups is shown in Figure 9. Lines of best fit for NME_{occl} over time in the PICU group are shown graphically in Figure 9B and textually in Table 9. They had slopes which were less variable than for ΔPaw_{max} ranging from -0.158 to 0.088 $cmH_2O/\mu V/h$. Grouped measurements for all patients are displayed in Figure 10A and Figure 10C. Because the median NMEoccl is the lowest at the 4^{th} measurement and this measurement was obtained in only 8 patients, we conducted a sensitivity analysis restricted to this subgroup. Figure 10B shows grouped measurements for those 8 patients only, and the pattern is similar to the whole group. A population-averaged model showed a non-significant trend towards a decrease in NME_{occl} over time under MV, with a correlation coefficient of -0.011 (95% confidence interval -0.026 – 0.003, $p = 0.133$).

Table 8. Clinical parameters at each measurement (PICU group)

	All	Measurement 1	Measurement 2	Measurement 3	Measurement 4
Number of measurements	59	19	18	14	8
Duration of MV at measurement (hours), median (IQR)	34.7 (22.9–49.6)	20.7 (13.9–21.7)	33.5 (30.4–38.4)	49.6 (43.1–59.7)	69.3 (58.4–80.8)
PELOD–2 score, median (IQR)	8 (6–9)	9 (7.5–11.5)	7 (5.3–8.8)	7 (5.3–8)	8 (6.5–8.3)
Sedation scores at measurements, median (IQR)					
RASS	-1 (-2 – 1)	-1 (-3 – 0.5)	-1 (-1.5 – -1)	-1 (-1.5 – -0.8)	2 (2 – 2)
COMFORT–B	12 (10–14)	12 (9–13)	12 (9.8–13)	12 (11–13.8)	14 (12–17.3)
Ventilation mode, n (%)					
Assist, volume-control	6 (10.2%)	3 (15.8%)	3 (16.7%)	0 (0%)	0 (0%)
Assist, pressure-control	13 (22%)	5 (26.3%)	4 (22.2%)	3 (21.4%)	1 (12.5%)
Assist, pressure-regulated volume control	13 (22%)	6 (31.6%)	4 (22.2%)	1 (7.1%)	2 (25%)
Support, pressure-control	15 (25.4%)	4 (21.1%)	4 (22.2%)	5 (35.7%)	2 (25%)
Support, neurally-adjusted	12 (20.3%)	1 (5.3%)	3 (16.7%)	5 (35.7%)	3 (37.5%)
Ventilation parameters					
Tidal volume (ml/kg), median (IQR)	6.5 (5.2–7.8)	6.5 (5.4–7.4)	6.9 (6.2–8.6)	6.6 (5.2–8.1)	5.7 (5–6.6)
Respiratory rate above set, for non-spontaneous modes (%), median (IQR)	12.4% (3.3%–28.9%)	8.7% (1.4%–27.9%)	13.3% (7.3%–25.7%)	2.2% (0%–33.3%)	24% (19.1%–93.3%)
Driving pressure (cmH_2O), median (IQR)	11 (6–14.5)	12 (8.5–18)	11 (8.5–14.8)	7.5 (5.3–12)	5.5 (3.8–12)
PEEP (cmH_2O), median (IQR)	6 (5–8)	6 (5–8.5)	7 (5–8)	6.5 (5.3–7)	6 (5.8–6.3)
FiO_2 (%), median (IQR)	35% (25%–45%)	40% (25%–55%)	32.5% (22%–48.8%)	30.5% (25%–40%)	35.5% (30%–43.3%)
Ventilation effectiveness					
SpO_2 (%), median (IQR)	99% (96%–100%)	98% (96%–100%)	100% (99%–100%)	96.5% (96%–98.5%)	99% (96.8%–100%)
pH, median (IQR)	7.39 (7.35–7.42)	7.4 (7.36–7.43)	7.37 (7.34–7.43)	7.39 (7.35–7.41)	7.39 (7.37–7.42)
PCO_2 (mmHg), median (IQR)	43.9 (37.8–52.5)	42.1 (35.7–50.1)	43.1 (37.6–50.2)	44.9 (40.9–54.9)	47.3 (43.1–55.4)
Median baseline $EAdi_{max}$ 60min before measurement (µV), median (IQR)	5.7 (2.9–10)	3.8 (2.9–7.2)	6.5 (2.7–10.5)	5.3 (2.9–11.9)	9.3 (6.6–13.7)
Maximal ΔPaw_{max} (cmH_2O), median (IQR)	28.7 (20.8–55.4)	35.1 (21–58)	26.7 (21.1–43.1)	27.8 (20.9–41.1)	47.2 (22.2–73.1)
Median NME_{occl} (cmH_2O/µV), median (IQR)	1.6 (0.9–2.6)	1.8 (1.3–2.4)	1.9 (1.4–2.6)	1.3 (0.9–2.7)	0.9 (0.7–1.6)

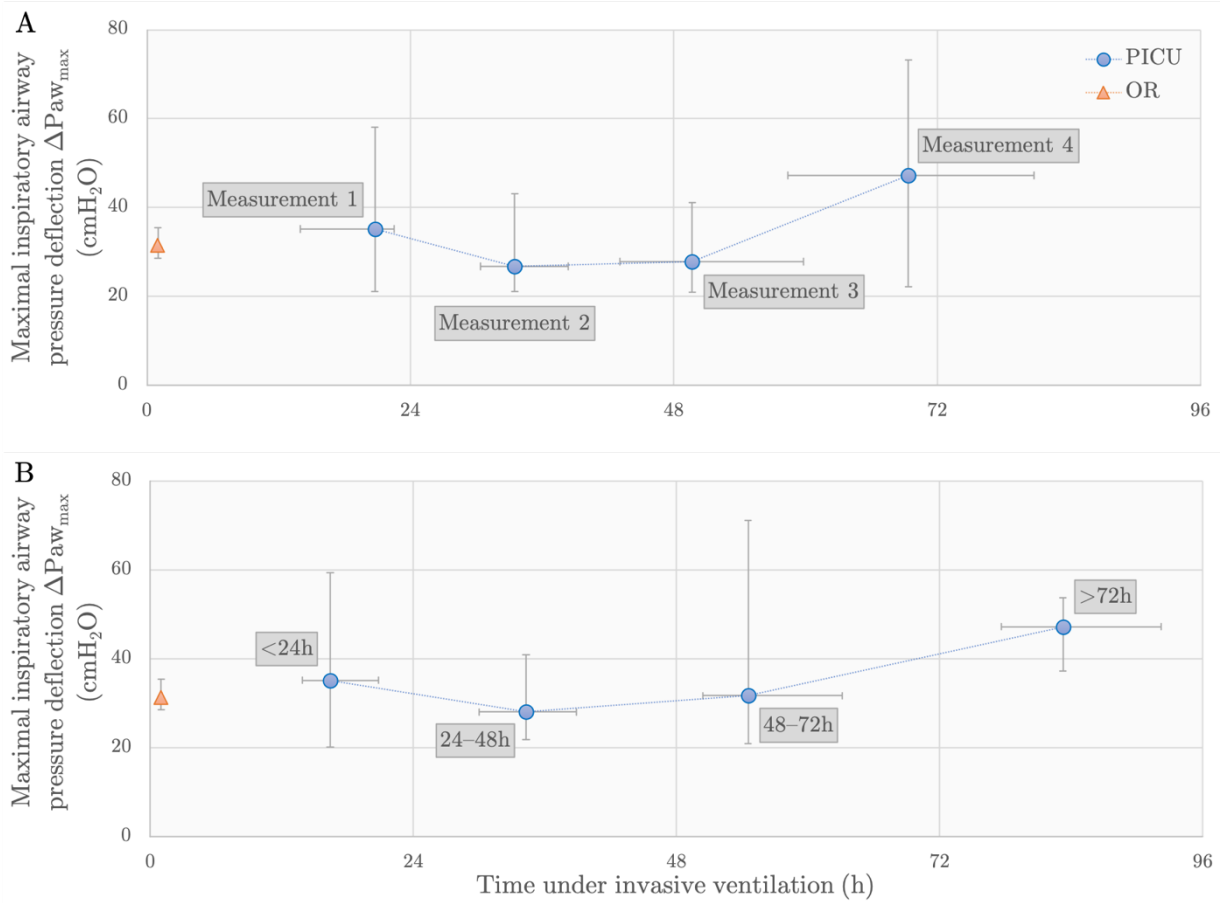
PICU denotes pediatric intensive care unit, IQR inter-quartile range, MV mechanical ventilation, PELOD pediatric logistic organ dysfunction, RASS Richmond agitation–sedation scale, PEEP positive end-expiratory pressure, FiO_2 fractional concentration of inspired oxygen, SpO_2 oxygen saturation, PCO_2 carbon dioxide pressure, $EAdi_{max}$ peak electrical activity of the diaphragm, ΔPaw_{max} maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm).

Figure 7. Maximal inspiratory airway pressure deflection ΔPaw_{max} over time (both groups)



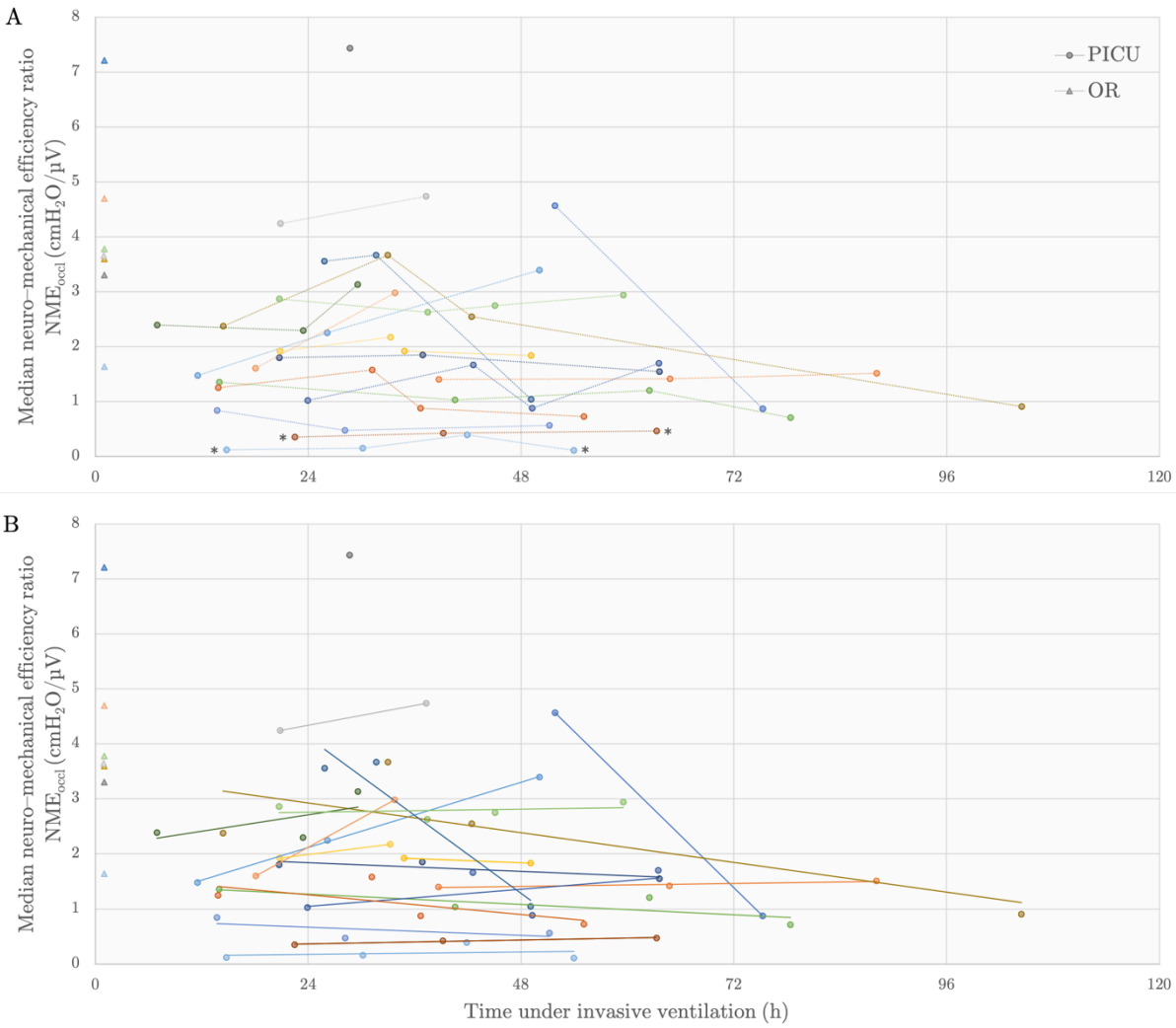
ΔPaw_{max} denotes maximal inspiratory airway pressure deflection, PICU pediatric intensive care unit (data points marked by circles), OR operating room (data points marked by triangles). Time under invasive ventilation starts at intubation. Each color represents an individual patient. A: scatter plot with sequential data points connected by line (dotted). B: scatter plot with lines of best fit according to method of least squares (solid). *: patients who required non-invasive ventilation continuously for 72 hours after extubation.

Figure 8. Maximal inspiratory airway pressure deflection ΔPaw_{max} over time (both groups)



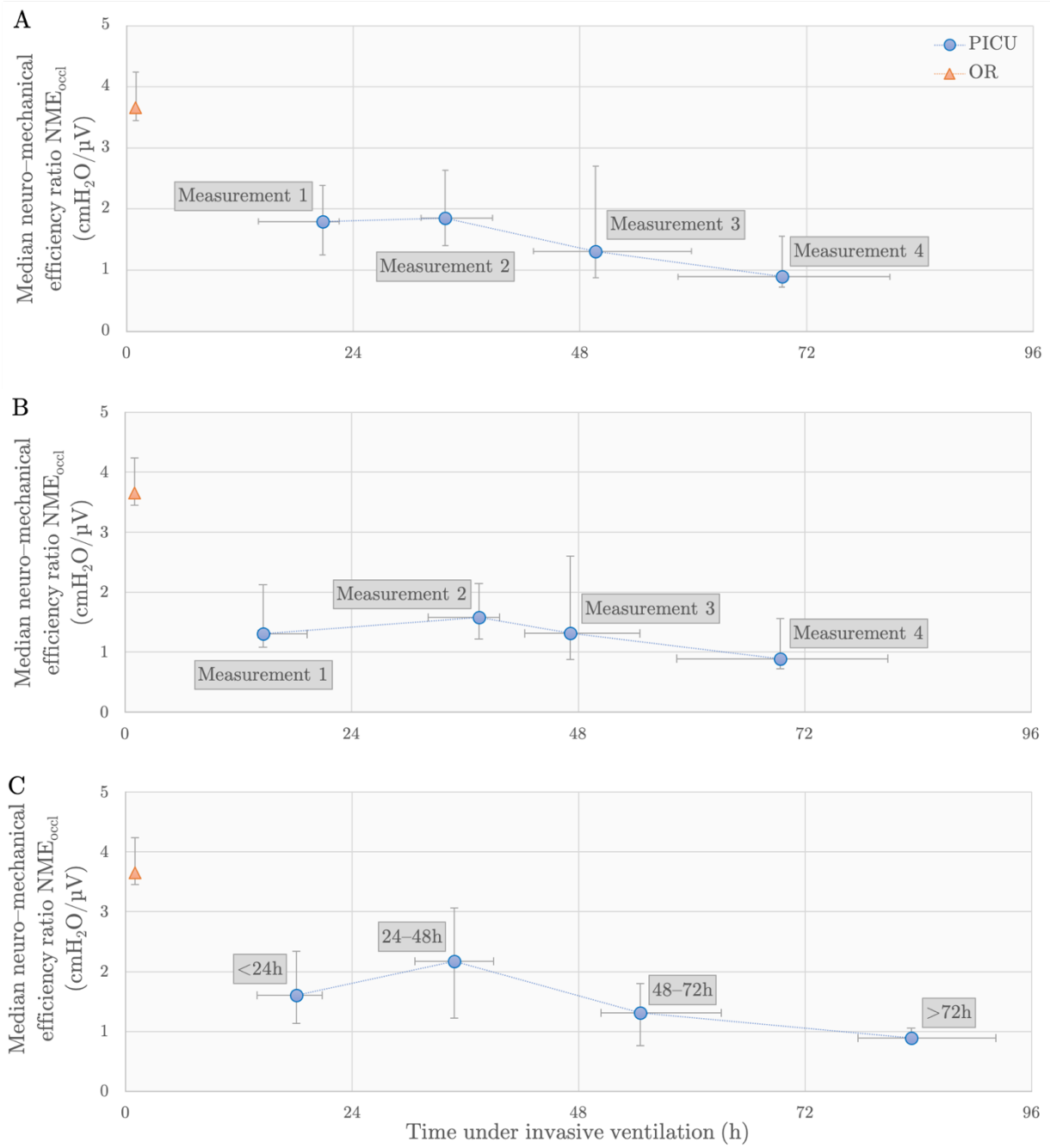
ΔPaw_{max} denotes maximal inspiratory airway pressure deflection, PICU pediatric intensive care unit (data points marked by circles), OR operating room (data points marked by triangles). Time under invasive ventilation starts at intubation. Data represented as median ± inter-quartile range. A: data points grouped by measurement. B: data points grouped by 24–hour blocks.

Figure 9. Median neuro-mechanical efficiency ratio NME_{occl} over time (both groups)



NME_{occl} denotes median neuro-mechanical efficiency ratio, PICU pediatric intensive care unit (data points marked by circles), OR operating room (data points marked by triangles). Time under invasive ventilation starts at intubation. Each color represents an individual patient. A: scatter plot with sequential data points connected by line (dotted). B: scatter plot with lines of best fit according to method of least squares (solid). *: patients who required non-invasive ventilation continuously for 72 hours after extubation.

Figure 10. Median neuro-mechanical efficiency ratio NME_{occl} over time (both groups)



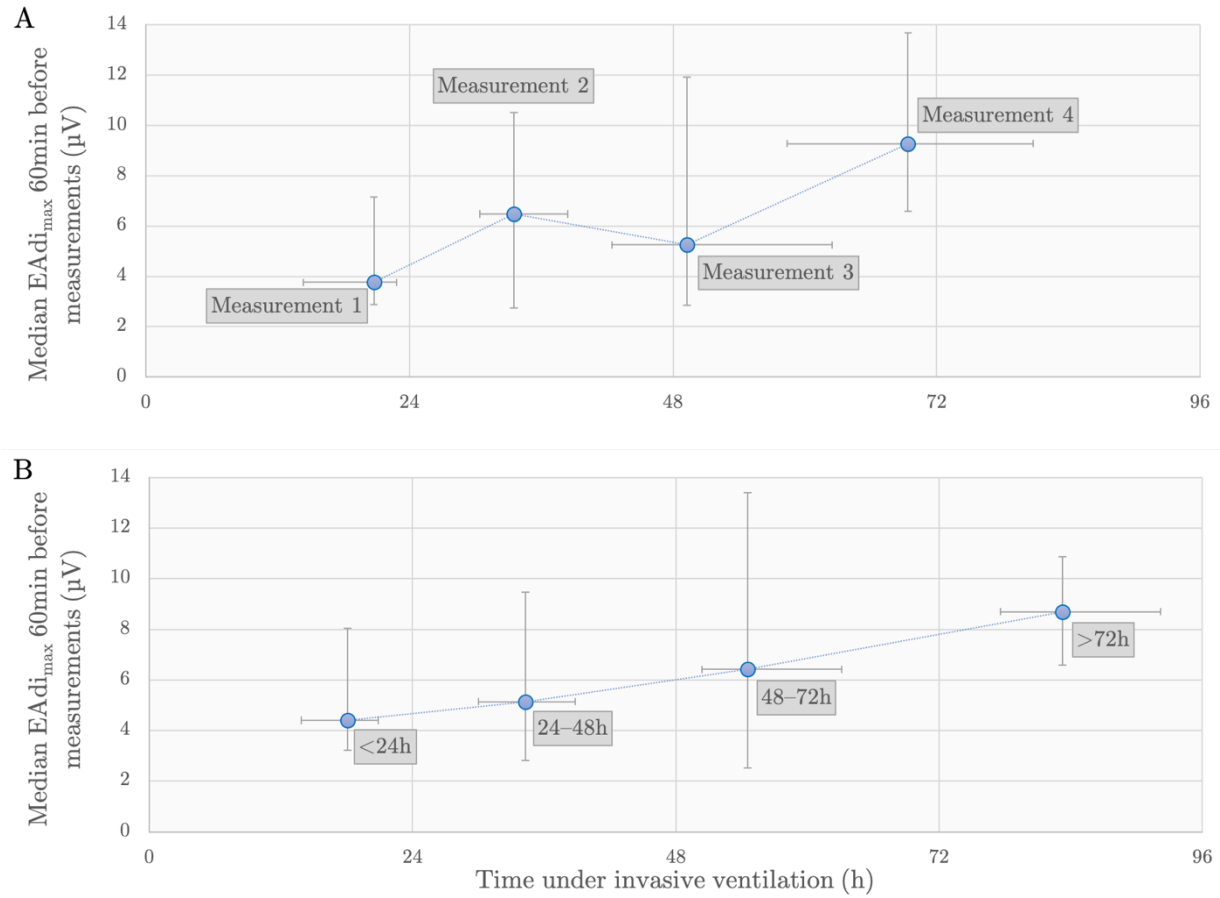
NME_{occl} denotes median neuro-mechanical efficiency ratio, PICU pediatric intensive care unit (data points marked by circles), OR operating room (data points marked by triangles). Time under invasive ventilation starts at intubation. Data represented as median ± interquartile range. A: data points grouped by measurement (all patients). B: data points grouped by measurement (only patients with a 4^{th} measurement, n=8). C: data points grouped by 24–hour blocks.

Table 9. Lines of best fit intercept and slope values (PICU group)

Patient	ΔPaw_{max} over time		NME_{occl} over time	
	intercept (cmH_2O)	slope ($cmH_2O/\mu V/h$)	intercept (cmH_2O)	slope ($cmH_2O/\mu V/h$)
1	17.03	0.518	12.76	-0.158
2	24.42	-0.108	1.30	0.002
3	N/A	N/A	N/A	N/A
4	18.03	-0.203	2.12	-0.006
5	14.10	0.091	0.93	0.050
6	34.13	0.365	1.46	-0.008
7	104.38	-1.028	1.99	-0.006
8	22.19	0.214	0.30	0.003
9	N/A	N/A	N/A	N/A
10	44.61	-0.072	3.47	-0.023
11	-67.97	3.321	6.94	-0.118
12	26.30	-0.103	2.11	0.025
13	71.68	-1.017	0.83	-0.006
14	9.76	0.625	0.02	0.088
15	22.93	1.681	3.63	0.030
16	75.06	-1.512	1.51	0.020
17	4.88	0.093	0.13	0.002
18	45.03	-0.303	2.71	0.002
19	18.61	0.995	0.74	0.013
20	42.56	0.644	1.62	-0.015

PICU denotes pediatric intensive care unit, ΔPaw_{max} maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm). Patient 3 was excluded and patient 9 had only one measurement.

Figure 11. Baseline $EAdi_{max}$ over time (PICU group)



$EAdi_{max}$ denotes peak electrical activity of the diaphragm, PICU pediatric intensive care unit. Time under invasive ventilation starts at intubation. Data represented as median ± inter-quartile range. A: data points grouped by measurement. B: data points grouped by 24–hour blocks.

3 Comparison between OR and PICU groups

ΔPaw_{max} for the first measurement of the PICU group (median 35.14 cmH_2O, IQR 21.05–57.99, $n = 19$) and the only measurement of the OR group (median 31.34 cmH_2O, IQR 28.49–35.48, $n = 10$) were not statistically significantly different, $U = 94$, $z = -0.046$, $p = 0.982$ (Figure 8A), using an exact sampling distribution for U (88). On the other hand, comparing the same measurements, NME_{occl} in the PICU group (median 1.80 $cmH_2O/\mu V$, IQR 1.25–2.39, $n = 19$) was statistically significantly lower than in

the OR group (median 3.65 $cmH_2O/\mu V$, IQR 3.45–4.24, $n = 7$), $U = 108$, $z = 2.399$, $p = 0.015$ (Figure 10A), using an exact sampling distribution for U (88).

4 VIDD (PICU group)

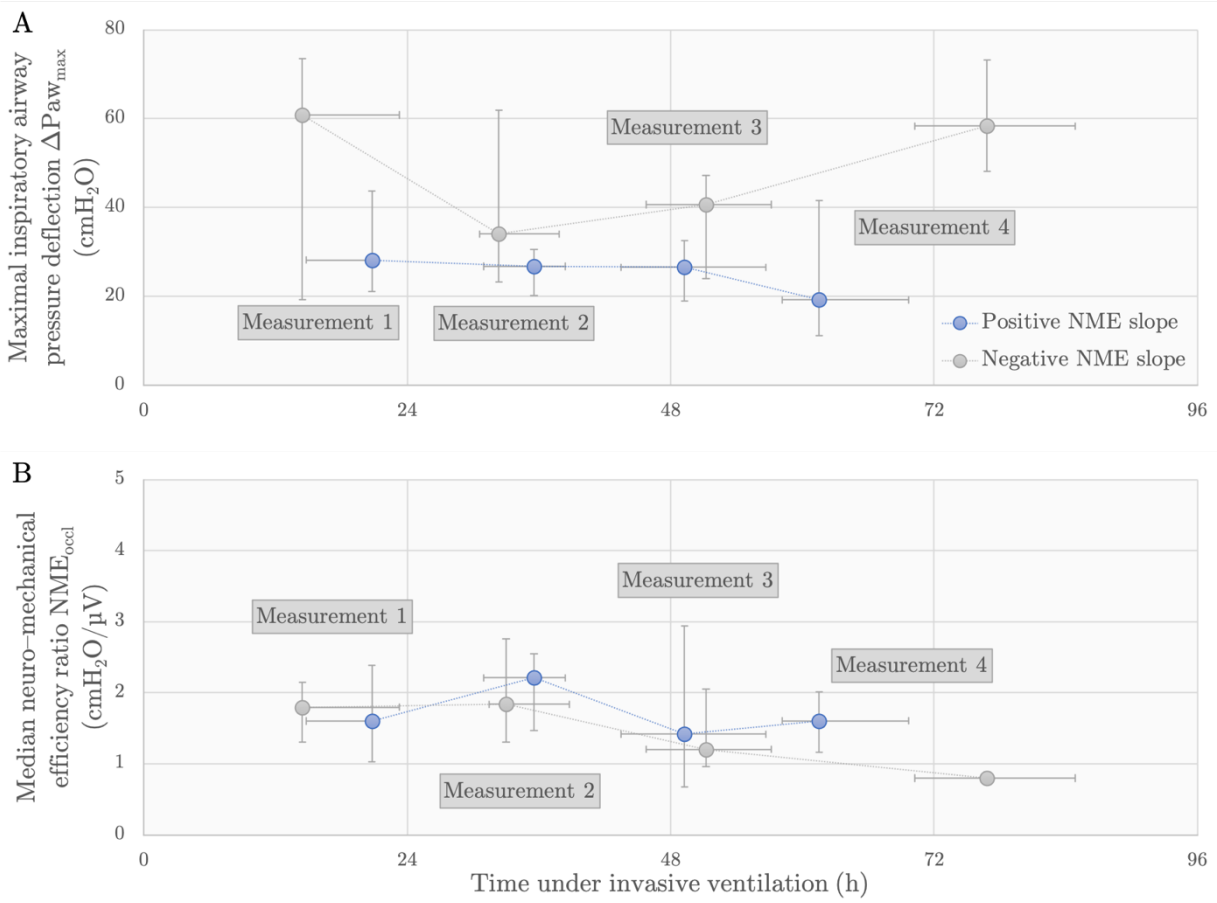
4.1 Definition

With a median NME_{occl} on first measurement of 1.80 $cmH_2O/\mu V$, a decrease of 16% in over 72 hours corresponds to a slope of -0.004 $cmH_2O/\mu V/h$ (see Methods section 11.4 above). All slopes for lines of best fit for the evolution of NME_{occl} over time which were negative were below -0.004 $cmH_2O/\mu V/h$ (Table 9). The PICU group was therefore split into two subgroups corresponding to patients with a negative slope and those with a positive slope. The evolution of maximal inspiratory airway pressure deflection ΔPaw_{max} and median neuro-mechanical efficiency ratio NME_{occl} over time in those two subgroups is shown in Figure 12.

4.2 Risk factors and outcomes

Patient characteristics in the PICU group depending on direction of the NME_{occl} slope are displayed in Table 10. Although our study was not designed with enough statistical power for subgroup analysis (see Methods section 10 above), there were no obvious differences between the two subgroups with regard to patient characteristics, clinical management while on PICU, diaphragmatic function, or clinical outcomes. In the subgroup with a negative slope, there was a non-significant trend towards a greater proportion of male patients. None of the 19 patients required reintubation within 24 hours of extubation, and only 2 patients required NIV continuously for 72 hours after extubation. Interestingly, although both had a positive NME_{occl} slope, these 2 patients actually had the lowest NME_{occl} values of all patients (Figure 9A).

Figure 12. Evolution of maximal inspiratory airway pressure deflection ΔPaw_{max} and median neuro-mechanical efficiency ratio NME_{occl} over time depending of line of best fit slope for NME_{occl} (PICU group)



ΔPaw_{max} denotes maximal inspiratory airway pressure deflection, NME_{occl} median neuro-mechanical efficiency ratio. Time under invasive ventilation starts at intubation. Data represented as median ± inter-quartile range, grouped by measurement.

Table 10. Patient characteristics depending on direction of NME_{occl} slope (PICU group)

	All	Positive slope	Negative slope	p–value
Number of patients	19	10	8	
Age (months), median (IQR)	13.7 (1.5–34)	24.2 (5–65)	3.4 (1.4–15.9)	0.315
Weight (kg), median (IQR)	11 (3.8–17.3)	12.3 (5.3–24.2)	4.6 (3.9–10.4)	0.515
Sex, male (%)	12 (63.2%)	4 (40%)	7 (87.5%)	0.066
Comorbidity, n (%)				
Prematurity	6 (31.6%)	4 (40%)	2 (25%)	0.638
Previous episode of invasive ventilation (within 7d of intubation)	3 (15.8%)	2 (20%)	1 (12.5%)	>0.999
Reason for PICU admission, n (%)				0.54
Neurological (traumatic brain injury)	1 (5.3%)	0 (0%)	1 (12.5%)	
Neurological (excluding traumatic brain injury)	4 (21.1%)	1 (10%)	3 (37.5%)	
Respiratory-Upper airway	4 (21.1%)	2 (20%)	1 (12.5%)	
Respiratory-Lower airway/pulmonary	7 (36.8%)	4 (40%)	3 (37.5%)	
Sepsis/shock	1 (5.3%)	1 (10%)	0 (0%)	
Other	2 (10.5%)	2 (20%)	0 (0%)	
Reason for intubation, n (%)				0.657
Neurological	4 (21.1%)	1 (10%)	3 (37.5%)	
Apnea	3 (15.8%)	1 (10%)	2 (25%)	
Respiratory-Upper airway	4 (21.1%)	2 (20%)	1 (12.5%)	
Respiratory-Lower airway/pulmonary	6 (31.6%)	4 (40%)	2 (25%)	
Hemodynamics	1 (5.3%)	1 (10%)	0 (0%)	
Procedure	1 (5.3%)	1 (10%)	0 (0%)	
Complications during study period, n (%)				
OI $\geq$ 4 at any measurement	3 (15.8%)	3 (30%)	0 (0%)	0.143
Clinical sepsis suspicion	10 (52.6%)	6 (60%)	3 (37.5%)	0.637
Sedation used less than 4h before measurements, n (%)				
Opioids	19 (100%)	10 (100%)	8 (100%)	*
Benzodiazepines	7 (36.8%)	5 (50%)	2 (25%)	0.367
Propofol	1 (5.3%)	1 (10%)	0 (0%)	>0.999
Dexmedetomidine	14 (73.7%)	7 (70%)	6 (75%)	>0.999
Sedation scores at measurements, median (IQR)				
RASS	-1 (-2 – -0.3)	-1 (-2 – -0.3)	-0.8 (-1.8 – -0.4)	>0.999
COMFORT-B	12 (10.5–13)	12 (10.4–13)	12 (10.8–12.3)	0.762
Drugs used during study period, n (%)				
Paralysis (excluding for intubation)	5 (26.3%)	3 (30%)	2 (25%)	>0.999
Corticosteroids	8 (42.1%)	3 (30%)	4 (50%)	0.63
Inotropes/vasodilators	5 (26.3%)	3 (30%)	2 (25%)	>0.999
Spontaneous mode during admission (NAVA/PSV), n (%)	14 (73.7%)	7 (70%)	6 (75%)	>0.999
Proportion of measurements done while patient on spontaneous mode (NAVA/PSV), median (IQR)	50% (12.5%–87.5%)	70.8% (6.3%–100%)	33.3% (18.8%–50%)	0.274
Duration of MV on first measurement (hours), median (IQR)	20.7 (13.9–21.7)	20.7 (15.6–20.9)	14 (13.8–22)	0.633
Baseline $EAdi_{max}$ 60min before first measurement (µV), median (IQR)	3.8 (2.9–7.2)	6.2 (3.4–11.4)	3.1 (2.9–4.5)	0.408
Median baseline $EAdi_{max}$ 60min before all measurements (µV), median (IQR)	5.7 (2.9–10)	5.3 (3–12.4)	6.2 (2.9–8.9)	0.965
Maximal ΔPaw_{max} on first measurement (cmH_2O), median (IQR)	35.1 (21–58)	28.1 (21–43.6)	60.8 (19.3–73.4)	0.237
Median NME_{occl} on first measurement (cmH_2O/µV), median (IQR)	1.8 (1.3–2.4)	1.6 (1–2.4)	1.8 (1.3–2.1)	0.633
Median NME_{occl} slope (cmH_2O/µV/h), median (IQR)	0.002 (-0.008 – 0.018)	0.016 (0.002 – 0.029)	-0.011 (-0.046 – -0.006)	**<0.0005**
Number of measurements, median (IQR)	3 (2.5–4)	3 (2.3–4)	3.5 (3–4)	0.573
Duration of MV (hours), median (IQR)	63.9 (50.4–77.4)	63.4 (45.3–68.8)	74.8 (56.5–81.5)	0.315
Reintubation within 24 hours of extubation, n (%)	0 (0%)	0 (0%)	0 (0%)	*
Rescue NIV for more than 72 hours post-extubation, n (%)	2 (10.5%)	2 (20%)	0 (0%)	0.477
PICU length of stay (days), median (IQR)	5.3 (4–8.8)	5.1 (4.2–8.7)	6.4 (4.6–9.3)	0.633
Died during PICU admission, n (%)	0 (0%)	0 (0%)	0 (0%)	*

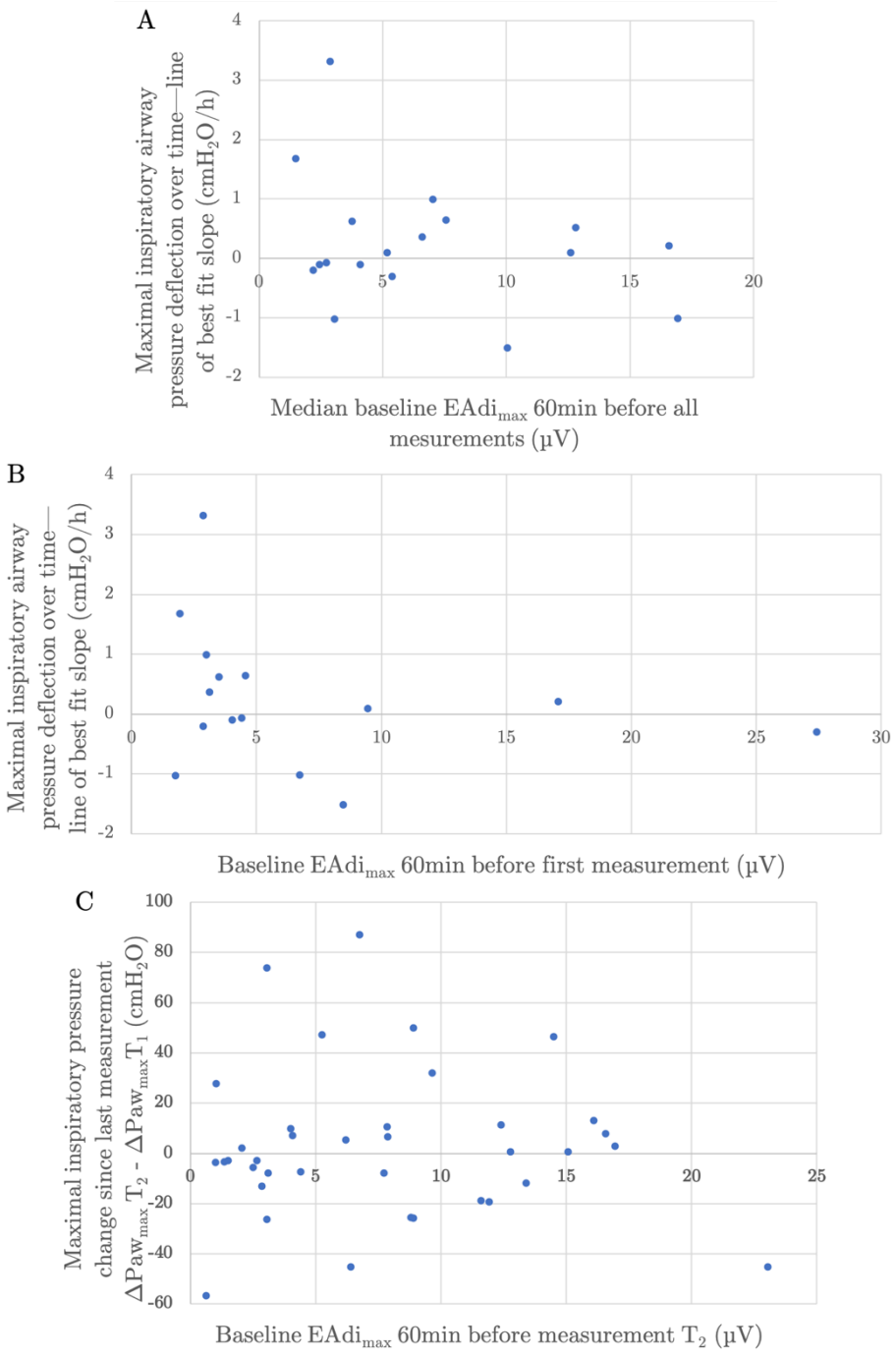
PICU denotes pediatric intensive care unit, IQR inter-quartile range, OI oxygenation index, RASS Richmond agitation–sedation scale, NAVA neurally-adjusted ventilatory assist, PSV pressure-support ventilation, MV mechanical ventilation, $EAdi_{max}$ peak electrical activity of the diaphragm, ΔPaw_{max} maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm), NIV non-invasive ventilation. *: no p–value computed because constant.

5 Impact of selected potential confounding factors on diaphragmatic function (PICU group)

5.1 Impact of baseline respiratory drive on diaphragmatic function

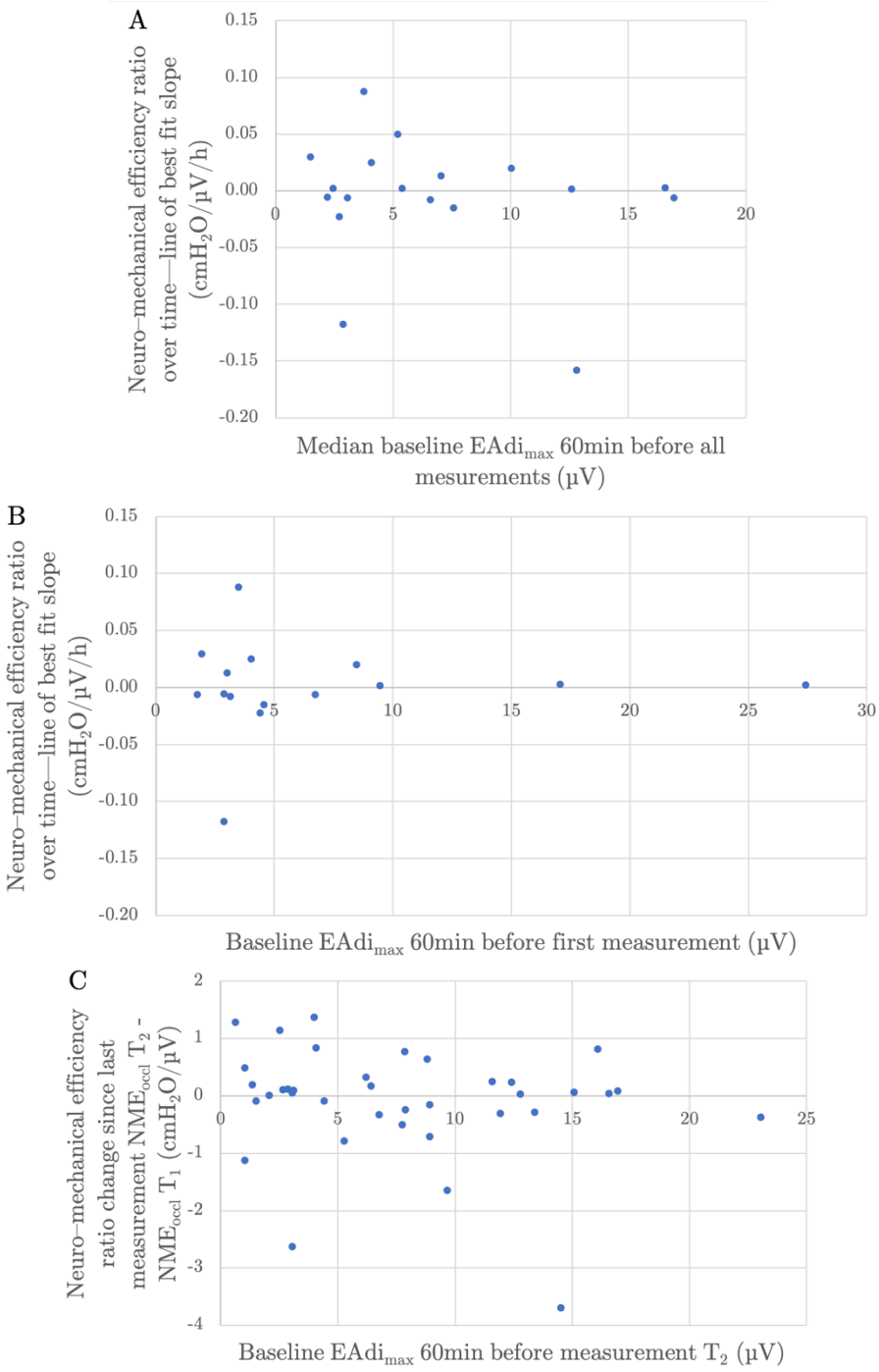
Figure 13 shows the correlation between ΔPaw_{max} and baseline $EAdi_{max}$ in the PICU group. There was poor correlation between the slope of the line of best fit for maximal inspiratory airway pressure deflection over time and baseline peak EAdi, either when considering EAdi before all measurements (Figure 13A, r = -0.30) or EAdi before the first measurement (Figure 13B, r = -0.26). Baseline peak EAdi before any measurement also did not correlate with the change in maximal inspiratory airway pressure deflection since the previous measurement (Figure 13C, r = -0.04). Similarly, there was no correlation between the slope of the line of best fit for median NME_{occl} over time and baseline peak EAdi, either when considering EAdi before all measurements (Figure 14A, r = -0.19) or EAdi before the first measurement (Figure 14B, r = 0.05). Baseline peak EAdi before any measurement also did not correlate with the change in median neuromechanical efficiency ratio since the previous measurement (Figure 14C, r = 0.17).

Figure 13. Correlation between ΔPaw_{max} and baseline $EAdi_{max}$ (PICU group)



ΔPaw_{max} denotes maximal inspiratory airway pressure deflection, $EAdi_{max}$ peak electrical activity of the diaphragm, PICU pediatric intensive care unit. The slopes in A and B are also shown on Figure 7B and Table 9. Pearson correlation coefficients A: -0.30, B: -0.26, C: -0.04.

Figure 14. Correlation between NME_{occl} and baseline $EAdi_{max}$ (PICU group)

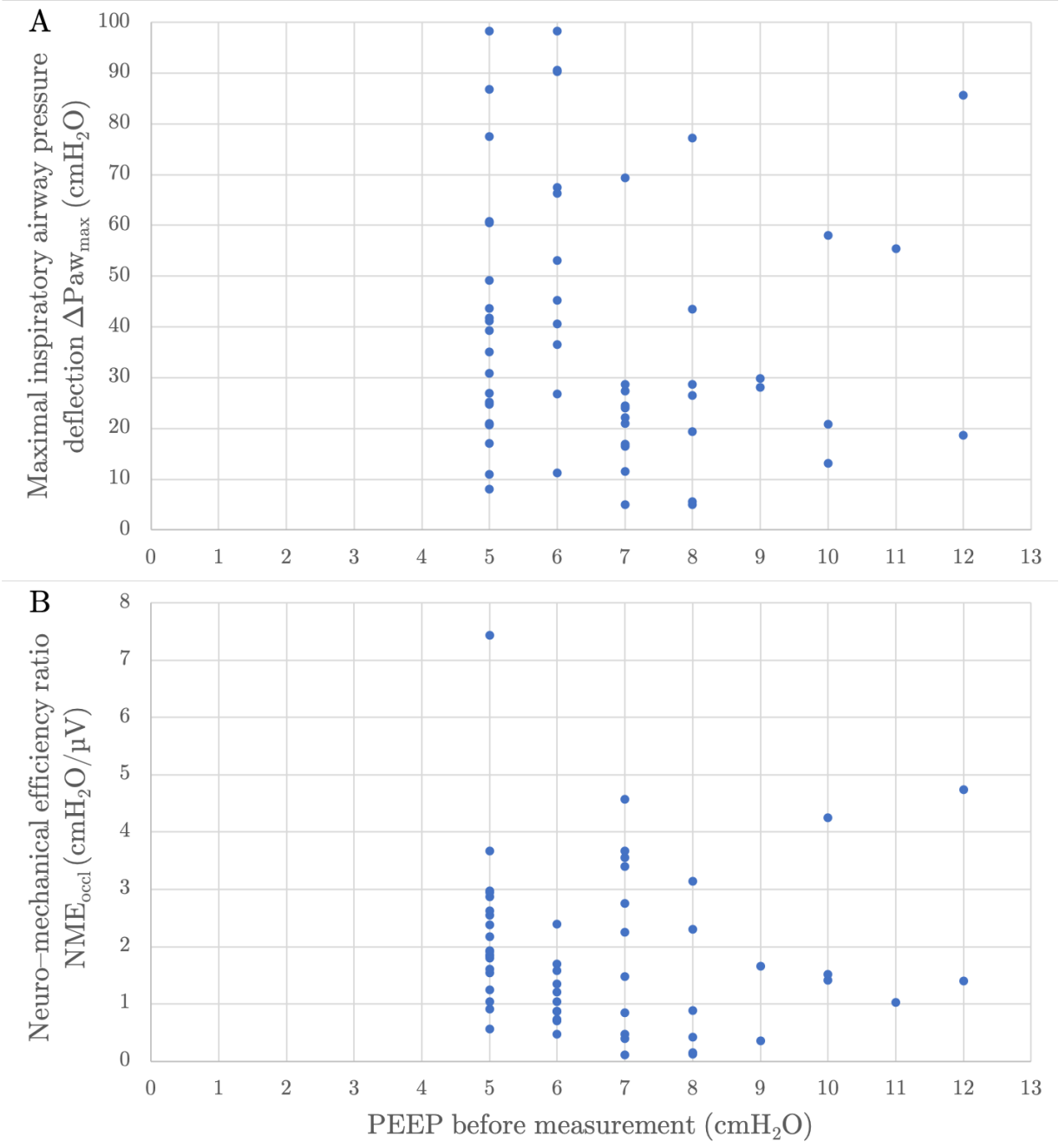


NME_{occl} denotes neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm), $EAdi_{max}$ peak electrical activity of the diaphragm, PICU pediatric intensive care unit. The slopes in A and B are also shown on Figure 9B and Table 9. Pearson correlation coefficients A: -0.19, B: 0.05, C: -0.17.

5.2 Impact of PEEP on diaphragmatic function

The level of PEEP imparted on the respiratory system by the ventilator at the time of measurements did not correlate with ΔPaw_{max} (Figure 15A, r = -0.10) or with NME_{occl} (Figure 15B, r = -0.02).

Figure 15. Correlation between ΔPaw_{max}, NME_{occl} and PEEP before measurement (PICU group)



ΔPaw_{max} denotes maximal inspiratory airway pressure deflection, NME_{occl} neuro-mechanical efficiency ratio (defined as inspiratory airway pressure divided by peak electrical activity of the diaphragm), PEEP positive end-expiratory pressure, PICU pediatric intensive care unit. Pearson correlation coefficients A: -0.10, B: -0.02.

Discussion

1 Summary of main results

In this work, we have validated a method to obtain reliable measurements of diaphragmatic function in mechanically ventilated children. The hypothesis that this function decreases over time under MV could not be confirmed. However, diaphragmatic function in critically ill children after 21 hours of MV was significantly lower than in children undergoing general anesthesia for elective surgery. The only two patients in the PICU group with NME_{occl} below 0.5 $cmH_2O/\mu V$ at all time points were also the only two patients requiring prolonged NIV (for more than 72 hours) after extubation. These results have implications which we will discuss around three key issues: how to measure diaphragmatic function at the bedside, how diaphragmatic function changes over time in the PICU, and how to define diaphragmatic dysfunction.

1.1 How to measure diaphragmatic function at the bedside?

As discussed previously (see Literature review section 3 above), assessing respiratory muscles by measuring the pressure they are able to generate provides a more functional evaluation than other methods focused on macroscopic or microscopic anatomy. It is also easily done at the bedside and can be monitored at repeated time points. These pressures are generally measured during a spontaneous (Paw_{max}) or stimulated (Paw_{twitch}) breath at expiratory occlusion. During a specific breath, Paw is usually measured, but technological innovations now allow for the concomitant measurement of EAdi (and therefore NME).

1.1.1 Stimulated breath or spontaneous breath?

Although this method has been used successfully by one other group (see Table 2), we were not able in this study to obtain reliable diaphragmatic contraction following bilateral anterior MS of the phrenic nerves. A few factors contribute to this technical challenge in small children. The effectiveness of a stimulating coil to result in nerve depolarization depends on its size and design, and the ability to apply it to the desired site. This can prove quite difficult in infants where neck space is limited. MS is also most effective at depolarizing large nerve fibres. When the target nerve fibers are small, as in children and infants, stimulation may not be supramaximal (10). Finally, in children breathing spontaneously at high RR (and therefore with a short expiratory time), it is challenging to coordinate simultaneously occluding the airway at the valve and triggering the MS, ensuring that the negative pressure deflection observed is that of a twitch (stimulated breath) and not simply the next spontaneous breath. Other authors have described a setup where the occlusion valve automatically triggers the MS (85).

Simply measuring Paw_{max} during a spontaneous breath avoids many of the technical challenges of MS, can be done at the bedside with little additional equipment, and is clinically relevant as a physiological surrogate of inspiratory effort. Though we opted to use an occlusion valve with a manometer for accurate pressure measurements and limited impact of circuit compliance, some work in adults has used only the ventilator with no occlusion valve (62). There are however some limitations to using Paw_{max}. It notably requires a preserved spontaneous breathing drive, contrary to MS. Moreover, whereas Paw_{twitch} reflects the function of the diaphragm specifically recruited by phrenic nerve stimulation, Paw_{max} results from the activity of all inspiratory muscles and does not discriminate between various inspiratory muscle groups. Dimitriou et al. showed that ΔPaw_{twitch} was significantly lower in a group of infants with congenital diaphragmatic hernia and abdominal wall defects than in healthy controls, but ΔPaw_{max}

was similar, suggesting that accessory inspiratory muscle groups may help compensate for impaired diaphragmatic function (20).

1.1.2 Paw or NME?

As discussed previously (see Literature review section 3.1.6 above), Paw is easy to measure in intubated patients and is directly correlated to esophageal pressure in children (31). The main issue when measuring Paw as a surrogate of diaphragmatic function is to ensure maximal patient effort. When using MS, this is usually evaluated by verifying that there is a plateau in ΔPaw_{twitch} with increasing stimulator output. This can be quite tedious as it requires using multiple stimulations at varying output in a random order (81). Furthermore, it is possible that by increasing stimulator output aiming for supramaximal stimulation, specificity of stimulation to the phrenic nerve decreases. When assessing Paw_{max} during spontaneous breathing, the number of breaths required for maximal effort must be determined. In our PICU group, ΔPaw_{max} increased progressively over the first four breaths and decreased on the last breath, which would suggest that inspiratory effort was maximal; this was not the case in our OR group however as ΔPaw_{max} continuously increased until the last measured breath (Figure 5A). Other authors have used a unidirectional valve that allows expiration but not inspiration (78, 89). This results in larger values of ΔPaw_{max} because inspiration occurs from progressively smaller lung volumes (see Discussion section 1.2 below) and because increasing PCO_2 and decreasing PaO_2 will result in a gradually higher drive. Harikumar et al. confirmed that ΔPaw_{max} was indeed higher when only inspiratory efforts were occluded compared to occlusions maintained throughout both inspiration and expiration (78). In their work, they found that occlusions should be maintained for 12 seconds or 8 breaths in order to be maximal. When designing tools to be used at the bedside, it is important nonetheless to be minimally disruptive to patient condition and comfort. We therefore opted to aim for 5 consecutive breathing efforts, as commonly done (42, 89).

Another difficulty lies in analyzing the signal obtained from the manometer to determine ΔPaw_{max}. Although the minimum value of Paw is easily defined, multiple baseline Paw values can be considered. We observed that end-expiration airway pressure after an occluded breath was often higher than the initial end-expiratory pressure before the breath. For consistency, we chose to use the initial end-expiratory pressure value (at circuit closure, usually very close to the PEEP set on the ventilator) as a baseline for all breaths in that occlusion maneuver. If diaphragmatic function is considered to be stable at any specific point in time of measurement, a method must then be developed to choose a single value to represent up to 15 breaths (3 occlusions with 5 breaths each). One of the strengths of our work is the number of breaths analysed at each time point, and the fact that this was done in two very different populations (PICU group and OR group), increasing the external validity of our findings. This has allowed a thorough analysis of the variability of both ΔPaw_{max} and NME_{occl}. Guidelines for outpatient respiratory muscle testing recommend choosing the maximum value of three breaths that vary by less than 10% (10). We have shown that selecting the maximal value of ΔPaw_{max} over up to 5 breaths was the most reliable and least variable method (Table 5, Table 6). This also seems a reasonable choice physiologically, corresponding to the maximal negative pressure the diaphragm is capable of generating at that time.

By recording EAdi continuously throughout the occlusion maneuvers, we were also able to compute a NME_{occl} value for each breath. Deriving a ratio is appropriate only if the two components are well correlated. Beck et al. have demonstrated that ΔPaw_{max} and $EAdi_{max}$ are tightly correlated in both healthy adult volunteers (57) and adult patients with acute respiratory failure (90), with similar correlation coefficients as in the present study (Figure 6, Table 7). It has also been shown that the NME in any specific patient does not depend on ventilation mode or level of assistance, and that the NME value derived during an expiratory occlusion in the absence of flow is a good surrogate of the

NME value measured during regular tidal ventilation (albeit overestimated by a factor of about 1.5) (59). In a more recent study however, only moderate correlation was found between $EAdi_{max}$ and ΔPaw_{max} in individual patients (63). Recent work in children during weaning of MV has shown a strong correlation between $EAdi_{max}$ and ΔPes_{max} (65). The major advantage of using NME_{occl} over ΔPaw_{max} as a surrogate of diaphragmatic function resides in how it accounts for respiratory drive by normalizing pressures generated using EAdi. The diaphragm's pressure-generating capacity can therefore be estimated whether or not the inspiratory effort is maximal, solving many of the issues raised above. As can be seen in Figure 10A, NME_{occl} values seem more stable to varying patient conditions than ΔPaw_{max} values (Figure 8A). Interestingly, although ΔPaw_{max} on initial measurement was somewhat higher in our PICU group than in our OR group, the relationship for NME_{occl} was reversed and the difference was statistically significant, supporting the idea that NME_{occl} is a more appropriate variable. A few limits of using NME warrant discussion. Any technical difficulties in measuring the electrical activity of the diaphragm will result in a falsely low EAdi value and consequently an incorrectly high NME ratio. In this study, appropriate catheter positioning was therefore systematically confirmed using the software provided and the EAdi signal was inspected to verify that it varied appropriately with breathing efforts. Furthermore, the relationship between ΔPaw_{max} and $EAdi_{max}$ may not be linear at very high breathing efforts. In Figure 5, it is apparent that an increase in $EAdi_{max}$ between the 4^{th} and the 5^{th} breath does not result in a corresponding increase in ΔPaw_{max}, likely because the diaphragm has reached maximum pressure-generating capacity that cannot be increased with additional respiratory drive, or because the diaphragm is unable to reach its fully relaxed configuration in between breaths. In our PICU cohort, selecting the median value of NME_{occl} over up to 5 breaths was the most reliable and least variable method (Table 5). This also limits the impact of extreme values, and is an acceptable metric considering that respiratory drive is controlled for. Finally, it is

important to note, when considering this ratio during spontaneous breathing, that whereas $EAdi_{max}$ measures the electrical activity generated by the diaphragm only, Paw_{max} includes the pressure generated by the diaphragm as well as accessory muscles (as discussed above).

1.2 How does diaphragmatic function change over time in the PICU?

In a landmark study, Jaber et al. described a progressive decline in diaphragmatic function over time in critically ill adults, with ΔPaw_{twitch} decreasing by 32% after 5–6 days of MV (4). In pediatrics, diaphragm atrophy under MV was only recently demonstrated in studies using ultrasound (41, 74, 75). They found that diaphragm thickness in children receiving MV decreases by 0.68% (74) – 3.4% per day (75). In the current study, which is—to the best of our knowledge—the first to longitudinally assess diaphragmatic function in children under MV, a decrease in pressure-generating capacity normalized to respiratory drive over time was only found in a small number of patients (8/18, 44%), but this decrease was not significant in the whole cohort.

In the absence of a type II error, these findings taken together could imply that diaphragmatic atrophy is not necessarily associated with a loss in diaphragmatic efficiency to convert electrical input into negative pressure. Compensatory mechanisms may be at play, such as the recruitment of accessory muscles in the inspiratory effort, which would mitigate the decrease in ΔPaw_{max} (see Discussion section 1.1.1 above).

There are however multiple reasons why a decrease in diaphragmatic function may not have been observed. Our PICU patient population is quite different from that of the two aforementioned studies. Their cohorts were on invasive ventilation for 140 (75) and 177 hours (41), which is much longer than our cohort with 64 hours of MV. A significant proportion of patients in their cohorts had also received corticosteroids and neuromuscular blockade infusions, both known to affect the diaphragm. The median

daily PELOD–2 score (see Appendix 3) value in our PICU group was 8, with a predicted mortality of 5.5%, which is nonetheless higher than the mean daily PELOD–2 score value on our unit of 4 (unpublished data). Because of time required to screen, consent, and enroll patients, we were not able to perform early post-intubation measurements in our PICU group, the first measurement being at a median of 20.7 hours of MV. Animal data suggest that contractile dysfunction can occur after only 12 hours of MV (91) and studies in adult ICU patients show that ΔPaw_{twitch} decreases early and in a logarithmic fashion (29). It is possible that higher NME_{occl} values would have been obtained with earlier initial measurements. This is unlikely to be significant however as the first diaphragm thickness measurement was done at a median 19 hours of MV in the study by Glau et al., which still found a significant decrease over time (75). If we consider that ICU–DD comprises two concomitant processes, one related to critical illness and therapies, and the other related specifically to ventilation (VIDD), their respective impact on diaphragmatic function may be in opposite directions. As the patient approaches extubation, although the impact of ventilation accumulates over time, his condition has usually vastly improved, and therapies are thus reduced. The relative magnitude of these two processes may cancel out and result in a relatively stable function over time. To illustrate, the last measurement in our PICU group was obtained a median 5 hours before extubation, when patients are predominantly under spontaneous modes of ventilation and with a higher RASS and baseline EAdi than in previous measurements (Table 8, Figure 11). Despite the absence of correlation between baseline EAdi an hour before measurements and NME_{occl} at measurements in our PICU group (Figure 14), low respiratory drive has been shown to be correlated with diaphragmatic atrophy (75). Research in our unit has previously revealed that respiratory drive was severely blunted and EAdi completely absent during 8–12% of the time under assisted modes of ventilation (9). This publication may have since resulted in a change of practice in our unit, with clinicians aiming to preserve respiratory drive,

possibly limiting the impact of VIDD. The clinical team was not blinded to enrolled patients' EAdi signal and this may have affected clinical management. A minority of patients were even switched to NAVA ventilation after being enrolled in the study, once the catheter was in place. It would be interesting to see if results would be different in a study of patients with little to no baseline respiratory drive.

One potential confounding factor to consider is the impact of abdomino-thoracic configuration and lung volume on the relationship between EAdi and Pdi or Paw (92). A very compliant chest wall in young children can result in a smaller ΔPaw should it collapse on inspiration. ΔPaw will also vary with lung volume because of the force–length relationship of the diaphragm and the varying contribution of passive elastic recoil pressure of the lungs. At lower lung volumes, the diaphragm is longer, therefore ΔPaw will usually be larger. It is usually recommended to standardize measurement of ΔPaw at residual volume or at functional residual capacity (77). Increasing lung volume from functional residual capacity to total lung capacity has been found to reduce Pdi by 60% for a specific EAdi (57), and ΔPaw_{max} was shown to be greatly influenced by lung hyperinflation (93), possibly through longitudinal atrophy of the diaphragm at shorter fiber length (94). PEEP was kept relatively constant during all our measurements between 6 and 7 cmH_2O in our PICU group (Table 8), so this was likely not a major confounding factor in our cohort.

Importantly, a sample size could not be calculated as there were no preliminary data available in the literature for our primary outcome (NME_{occl}), and our study was conducted on a small group of 20 patients in a single center. A type II error may therefore have been committed with a p value of 0.133, and the external validity is limited.

1.3 How to define diaphragmatic dysfunction?

At present, there is no recognized definition for critically ill children. In previous studies, cut-off values for diaphragmatic dysfunction have usually been defined in one of the following ways: as predicting negative clinical outcomes (e.g. extubation failure), as compared with healthy subjects (e.g. elective surgery), or arbitrarily (e.g. specific decrease in thickness). These values can then be defined as changes over time (i.e. slopes) or absolute values. This distinction can have significant implications. In our PICU cohort for example, ΔPaw_{max} in the group with a negative NME_{occl} slope seemed high when compared with the group with a positive NME_{occl} slope (Figure 12), and the 2 patients with the lowest NME_{occl} values actually had positive slopes (Figure 9). Lastly, as is often the case in any change associated with critical illness, it is of utmost importance to consider whether this change is a cause, a consequence, or even an adaptive mechanism in the disease process and future outcomes. In a shock state, for example, loss of diaphragmatic function during MV while oxygen supply is redirected to vital organs may in fact be protective.

1.3.1 Diaphragm thickness

Diaphragm atrophy has been *a priori* defined as $\geq 10\%$ decrease in thickness as assessed by ultrasound in the zone of apposition in studies of adult ICU patients, and this atrophy was correlated with poor outcomes (45). The same cut-off value was used in studies of pediatric ICU patients, but not correlated with outcomes (41).

1.3.2 Pressure generation

As discussed previously (see Discussion section 1.1.1 above), ΔPaw_{twitch} cut-off values are specific to the diaphragm and consequently lower than ΔPaw_{max} cut-off values. In a classic adult study, Sahn and Lakshminarayan reported that all patients with a $\Delta Paw_{max} > 30$ cmH_2O were successfully weaned off invasive ventilation, whereas all

patients with a $\Delta Paw_{max} < 20$ cmH_2O failed a weaning trial (95). In later adult studies, ΔPaw_{max} was not found useful in predicting invasive ventilation weaning outcome (96, 97). Jaber et al. reported a baseline ΔPaw_{twitch} value of 16.5 cmH_2O in a long-term MV group compared to 20.1 cmH_2O in a short-term MV group under elective anesthesia, in a design similar to that of the current study (4).

When assessed using MS, ICU-acquired diaphragm dysfunction (ICU–DD) is now defined as $\Delta Paw_{twitch} < 11$ cmH_2O in most adult ICU studies (5, 21, 24), and severe ICU-acquired diaphragm dysfunction (S-ICU–DD) as $\Delta Paw_{twitch} < 7$ cmH_2O (10, 44, 98). Both definitions have been correlated with poor clinical outcomes.

Maximal pressures measured in children are relatively high when compared to adults, likely because of the small radius of curvature of the rib cage, diaphragm, and abdomen (99). In 22 infants and children, ΔPaw_{max} was 30.9 cmH_2O after 4.4 days of MV (78). In a study of 20 neonates before extubation, ΔPaw_{max} was 32 cmH_2O and correlated with gestational age but not with extubation failure (100). Surprisingly, Manczur et al. found that in children judged ready for extubation, ΔPaw_{max} was higher in patients who subsequently failed extubation (43 cmH_2O) than in patients who were then extubated successfully (31.5 cmH_2O) (89). In a recent study by Khemani et al., children with $\Delta Paw_{max} \leq 30$ cmH_2O at the time of extubation were more likely to be reintubated than those with preserved strength (42). We report similar ΔPaw_{max} values of 35.14 cmH_2O for the PICU group and 31.34 cmH_2O for the OR group, and no patients failed extubation in either group.

Values have been reported for ΔPaw_{twitch} after MS in healthy neonates (81), infants (84), and children (85). A major finding of these studies is that maturation and age influence diaphragm function in infants and in older children.

1.3.3 **Pressure generation normalized to respiratory drive**

Multiple studies have recently reported values for NME in adult ICU patients under various conditions. In patients under conventional ventilation for $\geq$ 24 hours, NME_{occl} during an SBT was significantly higher in patients successfully extubated (1.5 $cmH_2O/\mu V$) compared with those who failed extubation (1.0 $cmH_2O/\mu V$) (58). In patients who were transitioned from controlled to assisted breathing, NME_{occl} was 1.04 $cmH_2O/\mu V$, but did not fluctuate over time and was not correlated with outcomes (62). In patients under conventional ventilation for $\geq$ 72 hours, NME_{occl} increased from 1 $cmH_2O/\mu V$ to 2.6 $cmH_2O/\mu V$ after transition to NAVA (61). Finally, in patients under NAVA for 10 hours, NME_{occl} was 1.22 $cmH_2O/\mu V$ and did not change over time (63).

There is—to the best of our knowledge—no study reporting NMEoccl values in children under conventional ventilation. Wolf et al. have nonetheless used NVE, a related variable, to predict successful extubation in PICU patients during SBT (54). When considering clinically relevant outcomes, the only patients in the PICU group who required continuous NIV for 72 hours after extubation were also the only patients who had NME_{occl} values < 0.5 $cmH_2O/\mu V$ at all timepoints. When comparing critically ill children with healthy controls, we report NME_{occl} values of 1.80 $cmH_2O/\mu V$ in the PICU group, significantly lower than values of 3.65 $cmH_2O/\mu V$ in the OR group. Comparison between these two groups must be however interpreted with caution, as they seem quite different (Table 3, Table 4). As the study was not designed to match cases and controls, no p values were computed to compare baseline characteristics. Aside from critical illness, the PICU group included patients that were younger, more patients born prematurely, and some patients who were recently intubated before the current episode. As described above, age has a significant impact on the pressure-generating capacity of the diaphragm. In terms of medication, only patients in the OR group received sevoflurane, but data suggests it does not have a significant effect on

isometric skeletal muscle strength in humans at clinically relevant concentrations (101). A notable difference in measurement procedure was that occlusion maneuvers were performed without PEEP in the OR group, which may have affected diaphragmatic function (see Discussion section 1.2 above). Most importantly, even if we had initially planned to perform measurements rapidly after intubation in both groups to assess the impact of critical illness without a superimposed difference in time under MV, the first measurement occurred only after a median 20.7 hours in the PICU group compared to minutes in the OR group.

2 Clinical implications and perspectives

In light of our results, diaphragmatic function seems impaired in children during critical illness. It is not evident what relative roles critical illness (ICU–DD) and MV (VIDD) play in this process. Nevertheless, a new paradigm emerges in which MV should not only be lung-protective but also diaphragm-protective, aiming to shorten its duration, reduce associated discomfort, and minimize healthcare related costs.

The main tenet of such diaphragm-protective ventilation is to prevent myotrauma by targeting an optimal level of respiratory drive and effort that is synchronized to the ventilator, balancing lung and diaphragm protection at optimal lung volumes, and monitoring diaphragmatic function at the bedside (102). Factors thought to contribute negatively to muscle function can thus be minimized if such bedside monitoring indicates a decline in respiratory muscle function, and care must then be taken to discontinue MV as soon as possible. In the PICU, low or absent respiratory drive is common (9) and this can lead to disuse atrophy of the diaphragm (75). In some patients with acute lung injury however, it may be desirable to suppress respiratory drive with sedation or even neuromuscular blockade in order to achieve permissive hypercapnia and reduce ventilation pressures (103). Spontaneous breathing and excessive respiratory

effort can have a deleterious impact on both lung and diaphragm. The concept of patient self-inflicted lung injury has been introduced whereby spontaneously breathing patients with acute respiratory failure generate potentially damaging transpulmonary pressure swings, injurious regional forces and transmural pulmonary vascular pressure swings (104, 105). Furthermore, supra-physiologic patient effort also appears to have negative effects on diaphragm architecture and function, including through asynchronous efforts (34, 45). The condition of the diaphragm should thus be monitored during critical illness. Point-of-care ultrasound is accessible and seems promising to appreciate dynamic diaphragm movement and anatomy. As we have extensively discussed, EAdi (52) coupled with simple pressure measurements can provide very useful information about baseline respiratory drive, synchrony, and diaphragm efficiency. EAdi variation in response to changes in the level of respiratory assistance in conventional MV as well as in NAVA has been well described (106). Ultimately, it is important to remember that outcomes will not only depend on respiratory muscle strength, but also on the load imparted on the respiratory system. Weaning of ventilatory support will fail only if the respiratory load exceeds the capacity of the muscles, as shown by Khemani et al. (42).

Novel interesting strategies include artificial stimulation of the diaphragm for conditioning in patients when preserving spontaneous activity is impossible (107). There are many potential molecular targets in the signalling pathways responsible for VIDD for which new pharmacologic agents could prove beneficial (36). Once VIDD has occurred, increasing diaphragm inotropy may be possible by inhibiting phosphodiesterase (e.g. theophylline (108, 109)) or by increasing calcium sensitivity (e.g. levosimendan (110)). NAVA is of great interest as it improves synchrony in children under invasive ventilation (111) and non-invasive ventilation (112). By titrating support to the respiratory drive, NAVA is also useful in avoiding over- and under-assistance. Randomised control trials have recently demonstrated that NAVA improves diaphragm efficiency and asynchrony whereas pressure support ventilation

does not (60, 61). The author of this thesis is currently participating in an experimental study evaluating the impact of NAVA on preventing diaphragmatic dysfunction in a newborn lamb model, in which we have already reported a rapid onset of dysfunction under controlled MV (see Appendix 5) (38). An ongoing phase II clinical trial aims to assess the efficacy of a novel computer-based approach in balancing lung- and diaphragm-protective ventilation and possibly in reducing time on MV (113). Their algorithm includes many of the different physiological tools discussed in this thesis.

It is evident that more work is required to better understand diaphragmatic dysfunction in critically ill children, its risk factors, its potential impact on outcomes, and strategies that could potentially limit it. We believe the work presented in this thesis will be helpful in standardizing a method to measure diaphragm function and to allow impact on outcomes and effectiveness of therapies to be assessed.

Conclusion

In this prospective single-center observational study in children, we have described and validated an innovative method to reliably measure diaphragmatic function at the bedside of mechanically ventilated children by computing a NME ratio during an occlusion maneuver. ICU–DD was demonstrated in a cohort of critically-ill children where diaphragm efficiency was significantly lower than in healthy controls undergoing elective surgery. Diaphragmatic function was stable over time under MV in a group of critically ill children with preserved respiratory drive. We believe this method will make it possible to study ICU–DD and VIDD in a standardized fashion and to evaluate effectiveness of therapies such as diaphragm-protective ventilation.

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Appendices

1 RASS (114)

Score	Term	Description
4	Combative	Overtly combative or violent; immediate danger to staff
3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
2	Agitated	Frequent non-purposeful movement or patient–ventilator dys-synchrony
1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

2 COMFORT–Behavior Scale (115)

Alertness	Deeply asleep (eyes closed, no response to changes in the environment)	1
	Lightly asleep (eyes mostly closed, occasional responses)	2
	Drowsy (child closes his or her eyes frequently, less responsive to the environment)	3
	Awake and alert (child responsive to the environment)	4
	Awake and hyperalert (exaggerated responses to environmental stimuli)	5
Calmness–Agitation	Calm (child appears serene and tranquil)	1
	Slightly anxious (child shows slight anxiety)	2
	Anxious (child appears agitated but remains in control)	3
	Very anxious (child appears very agitated, just able to control)	4
	Panicky (child appears severely distressed, with loss of control)	5
Respiratory response ***(score only in mechanically ventilated children)***	No spontaneous respiration	1
	Spontaneous and ventilator respiration	2
	Restlessness or resistance to ventilator	3
	Active breathing against ventilator or regular coughing	4
	Fighting against ventilator	5
Crying ***(score only in children breathing spontaneously)***	Quiet breathing, no crying sounds	1
	Occasional sobbing or moaning	2
	Whining (monotone)	3
	Crying	4
	Screaming or shrieking	5
Physical movement	No movement	1
	Occasional (3 or fewer) slight movements	2
	Frequent (more than 3) slight movements	3
	Vigorous movements limited to extremities	4
	Vigorous movements including torso and head	5
Muscle tone	Muscles totally relaxed, no muscle tone	1
	Reduced muscle tone, less resistance than normal	2
	Normal muscle tone	3
	Increased muscle tone and flexion of fingers and toes	4
	Extreme muscle rigidity and flexion of fingers and toes	5
Facial tension	Facial muscles totally relaxed	1
	Normal facial tone	2
	Tension evident in some facial muscles (not sustained)	3
	Tension evident throughout facial muscles (sustained)	4
	Facial muscles contorted and grimacing	5

3 PELOD-2 Score (116)

Organ Dysfunctions and Variables[a]	Points by Severity Levels						
	0	1	2	3	4	5	6
Neurologic[b]							
Glasgow Coma Score	≥ 11	5–10			3–4		
Pupillary reaction	Both reactive					Both fixed	
Cardiovascular[c]							
Lactatemia (mmol/L)	< 5.0	5.0–10.9			≥ 11.0		
Mean arterial pressure (mm Hg)							
0 to < 1 mo	≥ 46		31–45	17–30			≤ 16
1–11 mo	≥ 55		39–54	25–38			≤ 24
12–23 mo	≥ 60		44–59	31–43			≤ 30
24–59 mo	≥ 62		46–61	32–44			≤ 31
60–143 mo	≥ 65		49–64	36–48			≤ 35
≥ 144 mo	≥ 67		52–66	38–51			≤ 37
Renal							
Creatinine (μmoL/L)							
0 to < 1 mo	≤ 69		≥ 70				
1–11 mo	≤ 22		≥ 23				
12–23 mo	≤ 34		≥ 35				
24–59 mo	≤ 50		≥ 51				
60–143 mo	≤ 58		≥ 59				
≥ 144 mo	≤ 92		≥ 93				
Respiratory[d]							
Pao_2 (mm Hg)/Fio_2	≥ 61		≤ 60				
$Paco_2$ (mm Hg)	≤ 58	59–94		≥ 95			
Invasive ventilation	No			Yes			
Hematologic							
WBC count (× 10^9/L)	> 2		≤ 2				
Platelets (× 10^9/L)	≥ 142	77–141	≤ 76				

[a]All variables must be collected, but measurements can be done only if justified by the patient's clinical status. If a variable is not measured, it should be considered normal. If a variable is measured more than once in 24 hr, the worst value is used in calculating the score. Fio_2: fraction of inspired oxygen.

[b]Neurologic dysfunction: Glasgow Coma Score: use the lowest value. If the patient is sedated, record the estimated Glasgow Coma Score before sedation. Assess only patients with known or suspected acute central nervous system disease. Pupillary reactions: nonreactive pupils must be > 3 mm. Do not assess after iatrogenic pupillary dilatation.

[c]Cardiovascular dysfunction: Heart rate and mean arterial pressure: do not assess during crying or iatrogenic agitation.

[d]Respiratory dysfunction: Pao_2: use arterial measurement only. Pao_2/Fio_2 ratio is considered normal in children with cyanotic heart disease. $Paco_2$ can be measured from arterial, capillary, or venous samples. Invasive ventilation: the use of mask ventilation is not considered invasive ventilation.

Logit (mortality) = −6.61 + 0.47 × PELOD-2 score.

Probability of death = 1/(1 + exp [−logit(mortality)]).

4 Article "*Monitoring of respiratory muscle function in critically ill children*" (117)

5 Article "*Mechanical ventilation causes diaphragm dysfunction in newborn lambs*" (38)

6 Presented abstract (Congrès Québécois en Santé Respiratoire 2018)

Title: Diaphragmatic function in spontaneously breathing children under mechanical ventilation

Authors: B Crulli, L Ducharme-Crevier, J-P Praud, B Petrof, G Emeriaud

Introduction: Ventilator-induced diaphragmatic dysfunction is highly prevalent in adult critical care and associated with worse outcomes. Specificities in pediatric respiratory physiology suggest that critically ill children may be at high risk of developing VIDD.

Methods: 8 children between 1 week and 18 years old under invasive ventilation and without pre-existing neuromuscular disease or recent muscle paralysis were recruited. Brief airway occlusion maneuvers were performed during which airway pressure at the endotracheal tube (Paw) and electrical activity of the diaphragm (EAdi) were simultaneously measured. The largest twitch Paw negative deflection was recorded, along with its corresponding maximal EAdi value. In order to compensate for central respiratory drive and sedation use, a neuro-mechanical efficiency ratio (NME, Paw/EAdi) was computed. Measurements were repeated daily until extubation or death, for up to 3 days.

Results: We excluded one patient which had no spontaneous breathing activity. The 7 remaining patients had a median age of 10.3 months (IQR 1.5-24.4), a median weight of 9.7 kg (3.5-11.7). Three patients (43%) were born prematurely and 2 patients (29%) had been invasively ventilated in the week prior to intubation. Median maximal twitch Paw were 27.8 (19.2-47.9), 39.5 (25.6-57.1), 37.0 (23.6-52.5) and 63.6 cmH_2O (39.3-73.4) on days 1-4 of invasive ventilation, respectively. Median NME ratios were 1.53 (1.11-2.35), 1.80 (1.45-2.20), 2.6 (1.67-4.74) and 2.21 $cmH_2O/\mu V$ (2.03-2.51) on days 1-4 of invasive ventilation, respectively. Linear regression coefficients for evolution of NME over time were slightly positive for all patients but one. Patients were on invasive ventilation for 76 hours (62.4-91.4) and stayed in the PICU for 8.7 days (7.7-11.9).

Conclusion: In this small sample of patients with baseline spontaneous breathing activity, there did not seem to be a decrease in the force-generating capacity of the diaphragm over time.

7 Presented abstract (Quebec Society of Intensivists 2019)

Title: Diaphragmatic function in spontaneously breathing children under mechanical ventilation

Authors: Benjamin Crulli, Laurence Ducharme-Crevier, Jean-Paul Praud, Basil Petrof, Guillaume Emeriaud

Introduction: Ventilator-induced diaphragmatic dysfunction is highly prevalent in adult critical care and associated with worse outcomes. Specificities in pediatric respiratory physiology suggest that critically ill children may be at high risk of developing VIDD.
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8 Presented abstract (Critical Care Congress 2019)

Title: Evolution of diaphragmatic function in mechanically ventilated children
Authors: Benjamin Crulli, Laurence Ducharme-Crevier, Jean-Paul Praud, Basil Petrof, Guillaume Emeriaud

Introduction/Hypothesis: Ventilator induced diaphragmatic dysfunction (VIDD) is highly prevalent in adult critical care and associated with worse outcomes. Specificities in pediatric respiratory physiology suggest that critically ill children may be at high risk of developing VIDD. However, no study has described the evolution of diaphragmatic function in critically ill children undergoing mechanical ventilation in the Pediatric Intensive Care Unit (PICU).
Methods: In this prospective single-center observational study, 8 children between 1 week and 18 years old under invasive ventilation and without pre-existing neuromuscular disease or recent muscle paralysis were recruited. Diaphragmatic function was evaluated using a brief airway occlusion maneuver during which airway pressure at the endotracheal tube (Paw) and electrical activity of the diaphragm (EAdi) were simultaneously measured. The largest twitch Paw negative deflection was recorded, along with its corresponding maximal EAdi value. In order to compensate for central respiratory drive and sedation use, a neuro-mechanical efficiency ratio (NME, Paw/EAdi) was computed. Measurements were repeated daily until extubation or death, for up to three days.

Results: One patient had meningitis with no spontaneous breathing and was therefore excluded from the analysis. The 7 remaining patients had a median age of 10.3 months (interquartile range, IQR 1.5-24.4), a median weight of 9.70 kg (3.51-11.7), and 3 were male (43%). Three patients (43%) were born prematurely and 2 patients (29%) had been invasively ventilated in the week prior to intubation. Median maximal twitch Paw were 27.8 (19.2-47.9), 39.5 (25.6-57.1), 37.0 (23.6-52.5) and 63.6 cmH_2O (39.3-73.4) on days 1-4 of invasive ventilation, respectively. Median NME ratios were 1.53 (1.11-2.35), 1.80 (1.45-2.20), 2.6 (1.67-4.74) and 2.21 $cmH_2O/\mu V$ (2.03-2.51) on days 1-4 of invasive ventilation, respectively. Linear regression coefficients for evolution of NME over time were positive for all patients but one (minimum -0.63, maximum 0.06 $cmH_2O/\mu V/h$). Patients were on invasive ventilation for 76 hours (62.4-91.4) and stayed in the PICU for 8.7 days (7.7-11.9).

Conclusion: Using an innovative method, we were able to assess diaphragmatic function in intubated children. In this small sample of patients with baseline spontaneous breathing activity noted on the EAdi signal, there did not seem to be a decrease in the force-generating capacity of the diaphragm over time under mechanical ventilation.

9 Presented abstract (Congrès des étudiants des cycles supérieurs en recherche au CHUSJ 2019)

Title: Diaphragmatic function in spontaneously breathing children under mechanical ventilation
Authors: B Crulli, L Ducharme-Crevier, J-P Praud, B Petrof, G Emeriaud

Introduction: Ventilator induced diaphragmatic dysfunction (VIDD) is highly prevalent in adult critical care and associated with worse outcomes. Specificities in pediatric respiratory physiology suggest that critically ill children may be at high risk of developing VIDD. However, no study has described the evolution of diaphragmatic function in critically ill children undergoing mechanical ventilation in the Pediatric Intensive Care Unit (PICU).
Methods: In this prospective single-center observational study, 13 children between 1 week and 18 years old under invasive ventilation and without pre-existing neuromuscular disease or recent muscle paralysis were recruited. Diaphragmatic function was evaluated using a brief airway occlusion maneuver during which airway pressure at the endotracheal tube (Paw) and electrical activity of the diaphragm (EAdi) were simultaneously measured. The largest twitch Paw negative deflection was recorded, along with its corresponding maximal EAdi value. In order to compensate for central respiratory drive and sedation use, a neuro-mechanical efficiency ratio (NME, Paw/EAdi) was computed. Measurements were repeated daily until extubation or death, for up to three days.
Results: We excluded from the analysis one patient with no spontaneous breathing, and one patient with a single measurement. The 11 remaining patients had a median age of 5 months (interquartile range, IQR 1.5-24.4), a median weight of 5.3 kg (3.8-11.7). Four patients (36%) were born prematurely and 2 patients (18%) had been invasively ventilated in the week prior to intubation. Median maximal twitch Paw were 35.6 (21.2-70.5), 31 (27.7-39.5), 37 (24.6-61.8) and 64.2 (51.4-69.4) on days 1-4 of invasive ventilation, respectively. Median NME ratios were 2.1 (1.2-3.3), 2.6 (1.7-3.8), 1.8 (1.6-3.1) and 2 $cmH_2O/\mu V$ (1.7-2.4) on days 1-4 of invasive ventilation, respectively. Linear regression coefficients for evolution of NME over time were positive for 8 patients (minimum -0.63, maximum 0.06 $cmH_2O/\mu V/h$). Patients were on invasive ventilation for 73.4 hours (53.9-91.4) and stayed in the PICU for 8.6 days (5-9.8).
Conclusion: Using an innovative method, we were able to assess diaphragmatic function in intubated children. In this small sample of patients with baseline spontaneous breathing activity noted on the EAdi signal, there did not seem to be a decrease in the force-generating capacity of the diaphragm over time under mechanical ventilation.

10 Accepted abstract (Reanimation 2020)

Title: Assessment of diaphragmatic function in mechanically ventilated children using the neuromuscular efficiency index

Authors: Benjamin Crulli, Guillaume Emeriaud

Rationale: Ventilator induced diaphragmatic dysfunction is highly prevalent in adult critical care and associated with worse outcomes. Specificities in pediatric respiratory physiology suggest that critically ill children may be at high risk of developing this complication, but no study has described the evolution of diaphragmatic function in critically ill children undergoing mechanical ventilation. This study aims to validate a method to quantify diaphragmatic function in mechanically ventilated children.

Material and Methods: In this prospective single-center observational study, 10 children between 1 week and 18 years old intubated for elective ENT surgery and without pre-existing neuromuscular disease or recent muscle paralysis were recruited. Immediately after intubation, diaphragmatic function was evaluated using brief airway occlusion maneuvers during which airway pressure at the endotracheal tube (Paw) and electrical activity of the diaphragm (EAdi) were simultaneously measured for 5 consecutive spontaneous breaths. Maneuvers were repeated 3 times. In order to account for central respiratory drive and sedation use, we recorded the neuro-mechanical efficiency ratio (NME, Paw/EAdi), in addition to the maximal inspiratory force (MIF). In order to determine the optimal measure of NME during an occlusion, the variability over three maneuvers of different variables (first breath, last breath, breath with maximal Paw deflection, breath with maximal NME value, and median value) was assessed using coefficients of variation and repeatability coefficients.

Results: Patients had a median age of 4.9 years (interquartile range 3.9-5.5), a median weight of 18 kg (14-23), and 5 were male (50%). The median evolution of Paw, EAdi, and NME ratio over the 5 occluded breaths are represented on Figure 1. NME values corresponding to the last breath and the breath with maximal Paw deflection were the least variable, with median coefficient of variation of 23% and 23% and repeatability coefficients of 3.44 and 3.44, respectively.

Conclusion: Brief airway occlusions can be used to assess diaphragmatic function in intubated children through both MIF and NME ratio, and the latter should ideally be computed on the last breath or the breath with the largest pressure deflection to improve repeatability and decrease variation.