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Guillaume MORTAMET

Evaluation du Travail Respiratoire dans l'Insuffisance Respiratoire Aiguë de l'Enfant

Thèse dirigée par :

Pr Brigitte FAUROUX	**Université de Paris-V**	**Co-Directrice**
Pr Guillaume ÉMERIAUD	**Université de Montréal**	**Co-Directeur**

Membres du jury :

Pr Stéphane DAUGER	**Université de Paris Diderot**	**Président du Jury**
Pr Jordi MANCEBO	**Université de Montréal**	**Pendant du Président**
Pr Nicolas TERZI	**Université de Grenoble-Alpes**	**Rapporteur**
Pr Gilles CAMBONIE	**Université de Montpellier**	**Rapporteur**

Résumé en français

Chez l'enfant, l'insuffisance respiratoire aiguë est responsable de la majeure partie des admissions en soins intensifs. La population pédiatrique étant marquée par une grande hétérogénéité en termes d'âge, de pathologie respiratoire et de maturation pulmonaire, une individualisation de la prise en charge thérapeutique est indispensable. Dans ce contexte, différents outils sont disponibles pour évaluer de manière plus objective le travail respiratoire du patient en insuffisance respiratoire aiguë.

Objectifs - Le principal objectif de la thèse est d'évaluer l'intérêt diagnostique et thérapeutique de la mesure du travail respiratoire dans l'insuffisance respiratoire aiguë hypercapnique de l'enfant.

Méthodes - Trois principaux outils d'évaluation du travail respiratoire ont été utilisés dans nos travaux : la mesure des pressions œsogastriques, la mesure de l'activité électrique du diaphragme et la mesure de la consommation en oxygène par la calorimétrie.

Résultats - Nous avons pu mettre en évidence les intérêts de ces outils de mesure aux différents stades d'évolution de la maladie : (i) à la phase initiale pour indiquer l'initiation d'une ventilation noninvasive et pour optimiser ces réglages ; (ii) à la phase d'évolution de la maladie pour évaluer l'interaction patient-ventilateur ; (iii) à la phase de sevrage ventilatoire pour détecter précocement une augmentation du travail respiratoire.

Conclusion - Tout au long du processus évolutif de la maladie, la surveillance objective du travail respiratoire peut aider à comprendre les mécanismes de la maladie pulmonaire, optimiser les réglages de l'assistance respiratoire, et adapter les interventions thérapeutiques.

Mots-clés en français : ventilation mécanique ; mécanique respiratoire ; travail respiratoire ; insuffisance respiratoire aiguë ; activité électrique du diaphragme ; calorimétrie indirecte ; pression oesophagienne ; enfant ; pédiatrie.

Titre en anglais : Work of breathing assessment in children with acute respiratory failure

Résumé en anglais

Acute respiratory failure is the leading cause of hospital admissions in the pediatric intensive care unit and is associated with significant morbidity and mortality. Since the pediatric population is characterized by a great heterogeneity in terms of age and respiratory pathology, individualization of therapeutic management is essential. Different minimally invasive methods have been described to assess the patient's work of breathing in acute respiratory failure.

Objectives - The main objective of the project was to assess the diagnostic and therapeutic contribution of the measurement of the work of breathing in children with acute hypercapnic respiratory failure.

Methods - We used in the present work three tools to assess the work of breathing: oesogastric pressures, electrical activity of the diaphragm monitoring and oxygen consumption measurements.

Results - We highlighted how these different methods are valuable during the ICU stay: (i) in the early phase of the disease to initiate or withdraw noninvasive ventilation and to optimize its settings; (ii) in the recovery phase to evaluate the patient-ventilator interaction; (iii) during the weaning process to early detect an increase in work of breathing.

Conclusion - Throughout the disease process, the work of breathing assessment can be useful to enhance our understanding of the pathophysiology of lung disease, to optimize mechanical ventilation settings and adapt therapeutic interventions.

Mots-clés en anglais : mechanical ventilation ; respiratory mechanics; work of breathing ; acute respiratory failure ; electrical activity of the diaphragm ; indirect calorimetry ; esophageal pressure ; children; pediatrics.

Lieux où la thèse a été réalisée :

- Unité de Ventilation Noninvasive et du Sommeil de l'Enfant, Hôpital Necker, Unité INSERM U955 Equipe 13, 149 rue de Sèvres, 75015, Paris.

- Service de Réanimation et Soins Continus Médico-Chirurgicaux Pédiatriques, Hôpital Necker, 149 rue de Sèvres, 75015, Paris.
- Service des Soins Intensifs Pédiatriques, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, H3T 1C5, Montréal, QC, Canada.
- Groupe de Recherche Clinique en Soins Intensifs Pédiatriques, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, H3T 1C5, Montréal, QC, Canada.

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Liste des abréviations

AE_{DI} : Activité Electrique du Diaphragme

EMG : Electromyogramme

FR : Fréquence Respiratoire

FiO_2 : Fraction Inspirée en Oxygène

HFNC : *High Flow Nasal Canula*

NAVA : *Neurally Adjusted Ventilatory Assist*

P_{AW} : Pression des Voies aériennes

PCO_2 : Pression Partielle en Dioxyde de Carbone

PO_2 : Pression Partielle en Oxygène

P_{ES} : Pression Œsophagienne

P_{GAS} : Pression Gastrique

P_{DI} : Pression Transdiaphragmatique

P_{PL} : Pression Pleurale

P_{TP} : Pression Transpulmonaire

PPC : Pression Positive Continue

PTP_{DI} : Produit Pression-Temps Diaphragmatique

PTP_{ES} : Produit Pression-Temps Œsophagien

$P_{0.1}$: Pression d'Occlusion des Voies Aériennes à 0,1s

PEEP : *Positive End-Expiratory Pressure*

PEEPi : *Positive End-Expiratory Pressure* intrinsèque

T_E : Temps Expiratoire

T_I : Temps Inspiratoire

TTI : *Tension-Time Index*

VM : Ventilation Mécanique

VNI : Ventilation Noninvasive

V_T : Volume Courant

VO_2 : Consommation en Oxygène

VO_{2resp} : Consommation en Oxygène liée à la Respiration

ETAT DES CONNAISSANCES SUR LE SUJET

A. INTRODUCTION

L'insuffisance respiratoire aiguë est le principal motif d'admission en réanimation pédiatrique et elle est associée à une morbidité et une mortalité non négligeable [1]. Elle apparait dès lors qu'il existe un déséquilibre entre la charge respiratoire et la capacité des muscles respiratoire à assurer leur fonction, à savoir assurer les échanges gazeux. On peut distinguer 2 types d'insuffisance respiratoire : l'insuffisance respiratoire hypoxémique (ou de type 1) et l'insuffisance respiratoire hypercapnique (ou de type 2). Dans le 1er cas, le principal traitement consiste à augmenter l'oxygène dans l'espace alvéolaire. Dans le 2ème cas, le but est de soulager le travail respiratoire, défini par l'effort réalisé par le patient pour assurer une ventilation. La ventilation mécanique (VM), quel que soit sa modalité (invasif ou noninvasif), est le traitement de première ligne de la défaillance respiratoire hypercapnique dans le sens où elle permet d'une part de supporter le patient pour faire face à la charge respiratoire et d'autre part d'assurer les échanges gazeux [2].

Les modalités d'évaluation de la fonction respiratoire ne sont pas clairement déterminées en situation aiguë. Plusieurs outils sont disponibles pour quantifier objectivement le travail respiratoire d'un patient en insuffisance respiratoire hypercapnique [3], mais tous ne sont pas utilisables dans une population d'enfants admis aux soins intensifs pédiatriques, chez qui le degré de coopération est réduit (de par l'âge et la sédation), l'instabilité clinique fréquente et le transport risqué. Ces patients apparaissent alors légitimement comme une population bien spécifique pour qui l'évaluation du travail respiratoire est particulièrement délicate, alors même qu'elle pourrrait avoir un impact clinique majeur.

Ce travail vise à démontrer l'intérêt d'évaluer le travail respiratoire chez l'enfant en insuffisance respiratoire aigue hypercapnique.

Dans la première partie du travail, après quelques rappels physiologiques, nous détaillerons les différentes méthodes d'évaluation du travail respiratoire disponibles chez l'enfant admis en soins intensifs. Ensuite, nous présenterons 4 études dans lesquelles un ou plusieurs de ces outils ont

été appliqués, et ce dans différents contextes cliniques. Enfin, nous discuterons de l'intérêt d'utiliser la mesure du travail respiratoire en pratique clinique.

B. PRINCIPES PHYSIOLOGIQUES DU TRAVAIL RESPIRATOIRE

1. NOTION DE TRAVAIL RESPIRATOIRE

En ventilation spontanée, la respiration est liée à la contraction des muscles respiratoires qui expandent la cage thoracique et génèrent une pression intra-pleurale négative à l'inspiration, autour de -5 à -7 cmH_2O en fin d'inspiration à l'état normal. Cette pression négative entraine une diminution de la pression intra-alvéolaire et aboutit à un débit d'air entrant dans les poumons, permettant ensuite les échanges gazeux. Le travail respiratoire correspond à l'énergie développée par le système respiratoire pour assurer la respiration. Mathématiquement, il équivaut à l'aire dans la boucle pression-volume, représenté de manière dynamique dans le diagramme de Campbell (Figure 1) [4]. Pendant l'inspiration, le travail respiratoire du patient doit surmonter deux forces : les forces élastiques du parenchyme pulmonaire et de la paroi thoracique, et les forces résistives générées par le mouvement du gaz à travers les voies respiratoires. Approximativement, les parts élastique et résistive du travail respiratoire représentent respectivement 2/3 et 1/3 de l'effort total [4, 5]. En cas d'augmentation des résistances des voies aériennes ou de diminution de la compliance pulmonaire, le travail respiratoire est par conséquent augmenté.

Sachant que la pression intra-pleurale (P_{PL}) peut être estimée par la pression œsophagienne (P_{ES}) [6], on peut calculer ces deux composantes (élastique et résistive) en comparant la différence entre la P_{ES} à l'inspiration active et sa valeur dans les conditions passives [7]. La compliance et la résistance pulmonaire peuvent être ensuite déduite de ces mesures [8].

Comme le montre le diagramme de Campbell (Figure 1), deux autres facteurs affectent le travail respiratoire : la Pression Expiratoire Positive en fin d'Expiration, appelée PEEP intrinsèque (PEEPi) et l'expiration active. A la fin de l'expiration normale, la pression des voies aériennes (P_{AW}) et la pression alvéolaire sont équivalentes à la pression atmosphérique, tandis que la pression intra-pleurale est équivalente à -4 cmH_2O. En présence d'une PEEPi, la pression alvéolaire reste positive tout au long de l'expiration, en raison soit d'un obstacle dynamique des voies aériennes, soit d'un temps d'expiration insuffisant. Ce phénomène est particulièrement fréquent chez l'enfant dans certaines pathologies, comme l'asthme aigu grave ou la bronchiolite [9]. A l'inspiration, le patient doit alors d'abord vaincre cette PEEPi avant que l'entrée d'air puisse

débuter. La valeur de PEEPi est mesurée comme la chute de la P_{ES} pendant l'expiration entre le moment où les muscles inspiratoires commencent à se contracter et le moment où le débit devient nul. Alors que l'expiration se produit normalement passivement, la PEEPi peut induire une expiration active chez l'enfant via l'utilisation des abdominaux, comme l'a montré Giovannini *et al.* [10]. Pour éviter de surestimer la valeur de la PEEPi, la variation de pression abdominale résultant de l'expiration active doit donc être soustraite de la variation de P_{ES} [11].

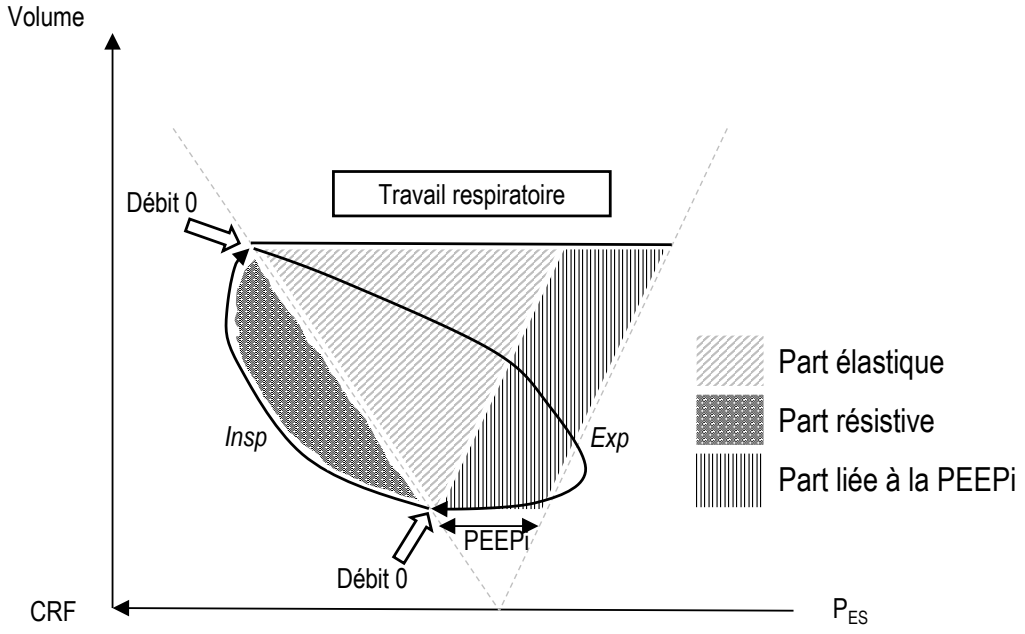

Figure 1 : Diagramme de Campbell.
Analyse graphique du travail des muscles respiratoires pendant un cycle ventilatoire. Le volume pulmonaire généré par le travail respiratoire est en ordonné et la pression pleurale (estimée par la pression œsophagienne) est en abscisse. Les 2 droites représentent la compliance de la cage thoracique (à droite) et du poumon (à gauche) en position statique. Le travail respiratoire total à l'inspiration est la somme du travail résistif et élastique.
CRF : Capacité Résiduelle Fonctionnelle ; Insp : Inspiration ; Exp : Expiration, P_{ES} : Pression Œsophagienne ; PEEPi : Pression Expiratoire Positive en fin d'Expiration intrinsèque.

Le travail respiratoire est normalement exprimé en Joules et un Joule correspond à l'énergie nécessaire pour mobiliser 1 litre de gaz d'un environnement de pression n à un environnement de pression n+10 cmH_2O. Dans la littérature, le terme « travail respiratoire » dépasse sa définition

purement mathématique, et il est utilisé avec un aspect plus clinique comme synonyme « d'effort respiratoire » du patient. Dans notre travail, nous utiliserons le terme « travail respiratoire » au sens large.

2. COMMANDE NEUROMUSCULAIRE DE LA VENTILATION

L'étude du travail respiratoire ne peut être dissociée de la commande ventilatoire, puisque l'adaptation du travail respiratoire pour faire face à une charge respiratoire est commandée par le système nerveux central. Contrairement à la commande volontaire qui nait dans le cortex, la commande ventilatoire automatique est localisée dans le tronc cérébral puis elle est transmise aux muscles inspiratoires et expiratoires (Figure 2) [12]. Le tronc cérébral reçoit de nombreuses afférences dans le but d'adapter la ventilation aux changements de métabolisme au cours de la fièvre, de l'exercice, ou en situation pathologique (hypoxie, hypercapnie, acidose). Les chémorécepteurs sont sensibles aux modifications de pH, de Pression Partielle en Oxygène (PO_2), de Pression Partielle en Dioxyde de Carbone (PCO_2) et à certains médicaments alors que les mécanorécepteurs, localisés principalement dans le parenchyme pulmonaire, les bronches et les muscles respiratoires renseignent sur le volume et l'état des différentes structures pulmonaires. Ainsi, chez le patient en insuffisance respiratoire aiguë, la commande respiratoire est mise en jeu directement pour s'adapter aux contraintes ventilatoires pathologiques et indirectement puisqu'une grande partie des thérapeutiques administrées, à commencer par la ventilation mécanique (VM), ont une influence rétroactive sur le contrôle ventilatoire (*Cf.* ci-dessous).

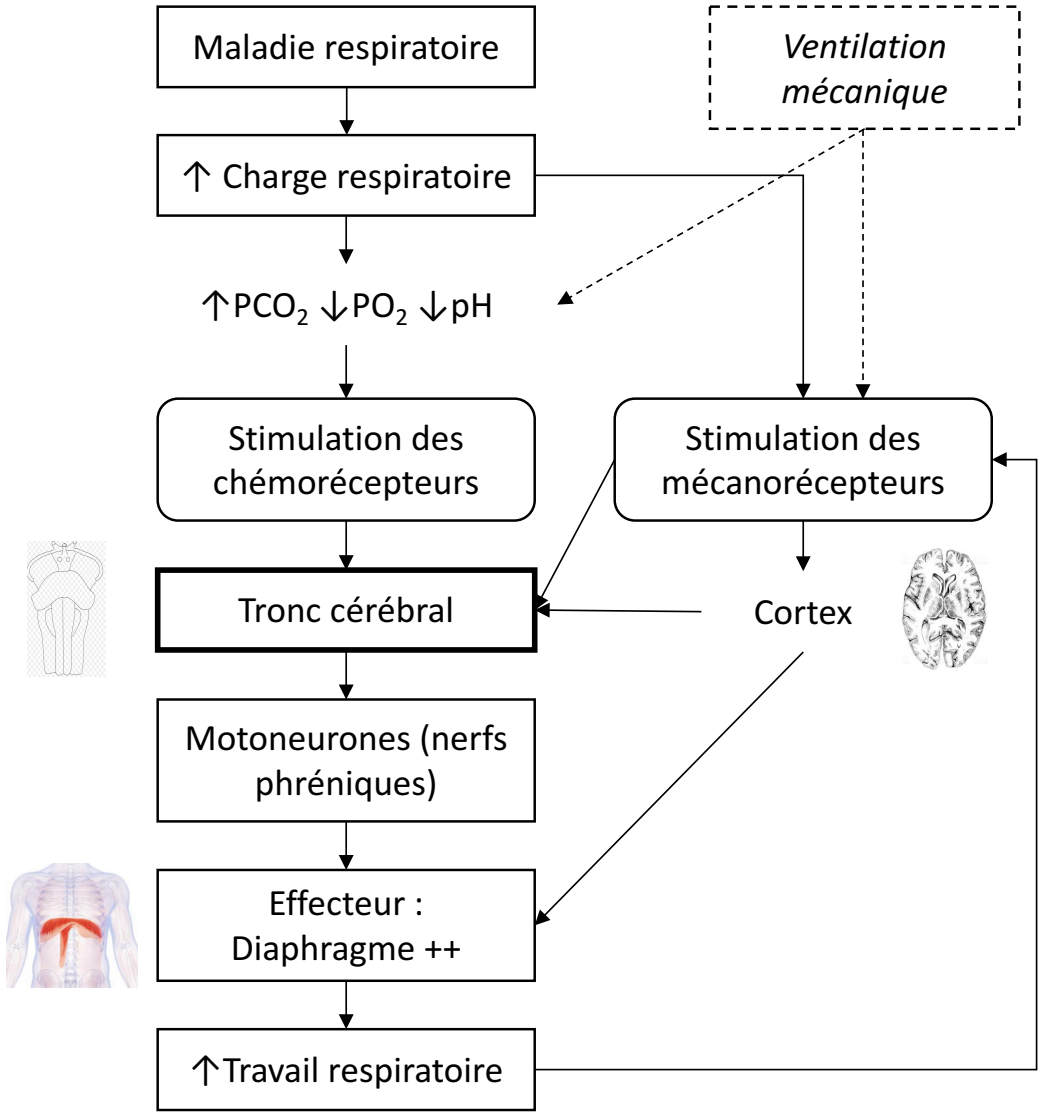

Figure 2 : Représentation schématique de la commande respiratoire.
L'augmentation de la charge respiratoire induit une augmentation du travail par l'intermédiaire du tronc cérébral.
PO_2 : Pression Partielle en Oxygène ; PCO_2 : Pression Partielle en Dioxyde de Carbone.

3. PARTICULARITES PEDIATRIQUES DE LA PHYSIOLOGIE RESPIRATOIRE

Chez l'enfant, *a fortiori* le nourrisson, il existe quelques spécificités à prendre en compte dès lors que l'on s'intéresse à la physiologie ventilatoire, qui expliquent pourquoi la défaillance respiratoire est un phénomène si fréquent en pédiatrie (Tableau 1). La cage thoracique de

l'enfant est plus circulaire que celle de l'adulte et le diaphragme plus aplati, ce qui réduit l'efficacité mécanique du diaphragme [13]. La compliance de la cage thoracique est élevée comparée à la compliance pulmonaire [14]. Les résistances du système respiratoire sont plus importantes, principalement au niveau des voies aériennes supérieures. La capacité fonctionnelle respiratoire (CRF), reflet des réserves d'oxygène, est plus faible et surtout elle est maintenue de manière dynamique par des mécanismes compensateurs : activité post-inspiratoire tonique du diaphragme, PEEPi, contraction laryngée et temps expiratoire augmenté. Ceci contribue à maintenir une hyperinflation pulmonaire en ventilation spontanée. Enfin, bien que la plus grande fatigabilité des muscles respiratoires chez l'enfant comparé à l'adulte reste un élément controversé, le nourrisson est plus sensible à l'hypoxie et à l'acidose, qui sont des facteurs augmentant cette fatigabilité.

Tableau 1 : Particularités physiologiques respiratoires de l'enfant.

Voies aériennes	Diamètre réduit
	Résistances élevées
	Respiration nasale prédominante
	Espace mort anatomique plus élevé
Cage thoracique	Plus circulaire
	Compliance élevée
Parenchyme pulmonaire	Compliance faible
Volumes pulmonaires	Maintien dynamique de la capacité résiduelle fonctionnelle
	Réserve résiduelle plus faible
Commande respiratoire	Contrôle immature chez le nouveau-né
	Fréquence respiratoire plus élevée
Autres	Sensibilité augmentée à l'hypoxie
	Sensibilité augmentée à l'acidose
	Augmentation de la consommation en oxygène

C. PARTICULARITES DU TRAVAIL RESPIRATOIRE EN VENTILATION MECANIQUE

La VM a deux principaux objectifs : assurer les échanges gazeux et supporter le travail respiratoire du patient. Ces objectifs sont atteints par la fonction mécanique du respirateur associée le plus souvent à un apport en oxygène. D'un point de vue physiologique, la VM diffère de la ventilation spontanée, puisque l'entrée d'air se fait grâce à une pression positive à l'inspiration (Figure 3). L'expiration quant à elle est un phénomène passif par l'entremise des forces élastiques du poumon et de la cage thoracique.

Chez les patients en VM, le travail respiratoire est partagé entre le respirateur et le patient et la génèse d'un volume courant peut être soit réalisée totalement (ventilation contrôlée), soit partiellement par le respirateur (ventilation assistée). Cette notion est particulièrement importante dans l'étude du travail respiratoire du patient en VM. La partie effectuée par le respirateur est facilement analysable grâce aux données fournies par la machine, même si cette méthode d'analyse a une sensibilité limitée [15]. En revanche, la part réalisée par le patient est plus difficilement appréciable, à la fois qualitativement (qualité de l'interaction entre le ventilateur et le patient) et quantitativement (importance de l'effort généré par le patient).

Même si la VM est bénéfique, elle peut être responsable de complications. Les pressions générées peuvent engendrer des lésions pulmonaires secondaires, *via* des phénomènes de barotraumatisme, volotraumatisme, et de traumatisme liés aux atélectasies (*atelectrauma*) [16]. En soulageant la contribution respiratoire du patient, la VM peut aussi induire une dysfonction ou une atrophie diaphragmatique [17-19]. Cette atteinte secondaire des muscles respiratoires doit être considérée avec attention car elle prolonge la durée de VM et la durée de séjour et c'est pour cette raison que la VM doit être cessée dès que le patient est capable d'assurer à lui seul une ventilation adéquate [20, 21].

Il existe également une interaction entre la VM et la commande ventilatoire du patient [22] (Figure 2). Si la VM est insuffisante, la commande ventilatoire sera mise à contribution. En agissant sur les échanges gazeux, la VM exerce un effet inhibiteur sur la commande via les chémorécepteurs. Comme l'a montré Georgopoulos *et al.* chez des patients en ventilation assistée, la commande respiratoire, évaluée par des paramètres respiratoires cliniques (Fréquence Respiratoire (FR), Temps Inspiratoire (T_i), Volume Courant (V_T)), est influencée par la

$PaCO_2$ [23]. Mais il semble que ce mécanisme ne soit pas seul, et que d'autres récepteurs non chimiques (musculaires et/ou ostéoarticulaires de la cage thoracique) soient impliqués dans le rétrocontrôle qu'exerce la VM sur la commande respiratoire (réflexe de Hering-Breuer) [24, 25]. L'influence de la VM sur la commande est variable selon les modes et les paramètres de ventilation utilisés. Par exemple, cet effet est limité avec les modes de ventilation dits proportionnels, tels que le mode NAVA (*Neurally Adjusted Ventilatory Assist*), dans lequel le niveau de support fourni est proportionnel à l'intensité de la commande respiratoire du patient évaluée par l'Activité Electrique du Diaphragme (AE_{DI}) [26, 27]. Enfin la sédation et l'analgésie, souvent associés à la VM, peuvent engendrer une dépression de la commande respiratoire et ainsi contribuer à une mauvaise interaction patient-ventilateur et à la prolongation de la durée de sevrage ventilatoire [28].

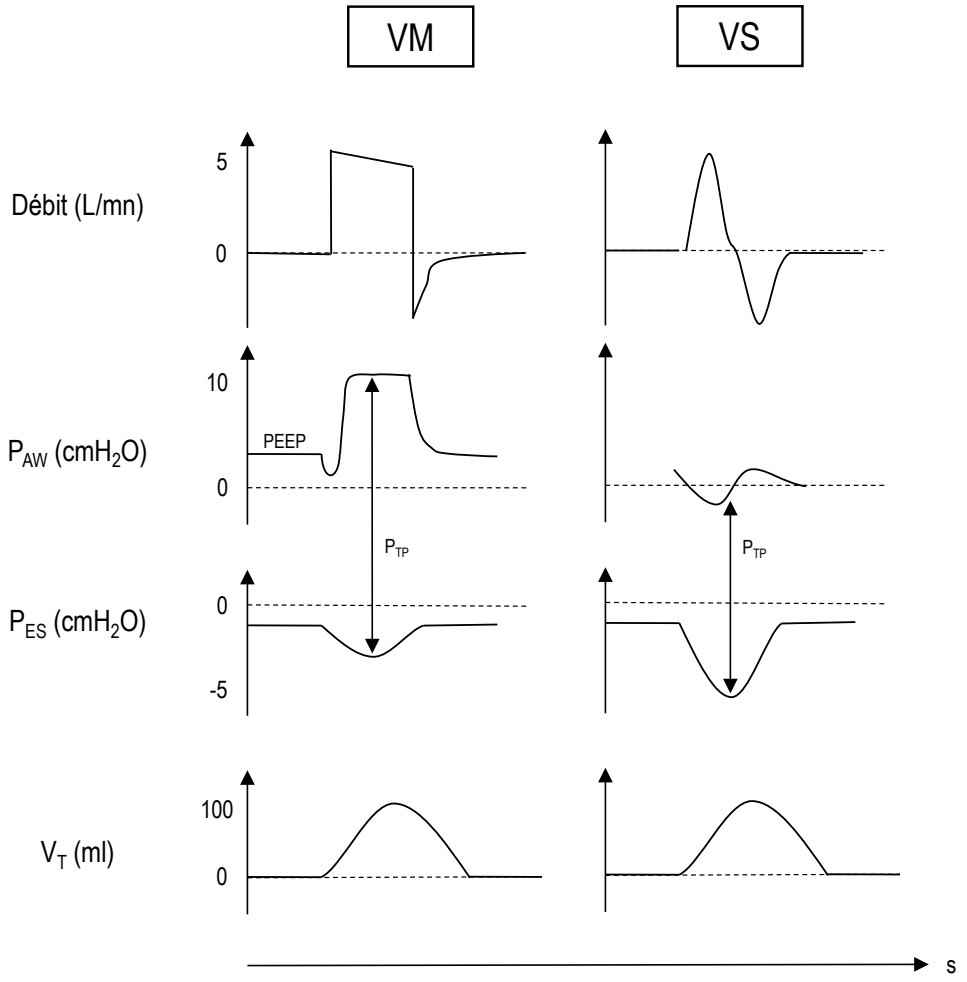

Figure 3 : Physiologie de la ventilation mécanique.
Cycle respiratoire avec débit, volume courant (V_T) et pression des voies aériennes (P_{AW}) générées en ventilation mécanique (VM) et en ventilation spontanée (VS) chez un enfant.
L'effort respiratoire du patient, visualisé grâce à la pression œsophagienne (P_{ES}) est plus important en VS. La pression transpulmonaire (P_{TP}) est définie par la différence entre la P_{AW} et la P_{ES}.

D. EVALUATION CLINIQUE DU TRAVAIL RESPIRATOIRE ET SES LIMITES

Plusieurs éléments cliniques, comme la FR, les signes d'hypoxie et les signes de lutte, sont utilisés au quotidien par les soignants pour évaluer la fonction respiratoire d'un patient [29]. A la phase aiguë, ils sont le plus souvent les seuls éléments dont le clinicien dispose pour guider la prise en charge thérapeutique et en particulier initier une assistance ventilatoire. Dès lors que le patient est ventilé mécaniquement, les paramètres fournis par le spirogramme des respirateurs modernes, comme le $V_{T,}$ le volume minute ($V_M = V_T$ x FR) et le rapport FR/V_T (*Rapid Shallow Breathing Index*) permettent de caractériser plus précisément la ventilation [30]. Le rapport V_T/T_I, définissant la pente de l'activité inspiratoire, évalue quant à lui la transformation mécanique de la commande tandis que le rapport T_i/T_{TOT} ($T_{TOT} = T_I$ + Temps Expiratoire (T_E)) renseigne sur la transition inspiration/expiration, composante active de la commande respiratoire. En plus de fournir des données numériques (pressions, volumes et débits générés, compliance totale, *etc.*), les respirateurs modernes affichent de manière dynamique cycle à cycle ces différents éléments ce qui rend possible l'évaluation de la fonction respiratoire en temps réel et à faible coût, sans nécessiter de dispositif supplémentaire.

L'approche clinique de l'évaluation du travail respiratoire a déjà prouvé sa pertinence. Dans une cohorte de 409 enfants intubés, Khemani *et al.* ont montré que la FR ou le *Rapid Shallow Breathing Index* était significativement plus élevé chez les patients nécessitants une ventilation noninvasive (VNI) après extubation [31]. Chez les enfants stables atteints de mucoviscidose, les réglages de la VNI basés sur des paramètres cliniques étaient comparables aux réglages basés sur des mesures physiologiques en terme de diminution du travail respiratoire [32]. Les paramètres cliniques sont également des éléments déterminants pour le succès de la VNI : la diminution de la FR et de la PCO_2 après 2 heures de VNI sont des facteurs prédictifs de succès de la VNI chez les nourrissons présentant une insuffisance respiratoire aiguë [33]. D'autres travaux ont montré que la variation de la FiO_2 et de la PCO_2 dans les premières heures après l'initiation de la VNI étaient prédictifs de l'échec de la VNI dans cette même population [34, 35].

En revanche, les éléments cliniques d'évaluation de la fonction respiratoire présentent de nombreuses limites. Ils apparaissent comme des signes non spécifiques de détérioration respiratoire, puisqu'ils dépendent de plusieurs mécanismes (stimulation des chémorécepteurs,

volume pulmonaire disponible, fonction corticale, *etc.*) [36]. Ces paramètres peuvent alors être modifiés par d'autres facteurs, comme la fièvre, l'anxiété, une altération de la commande centrale, un déséquilibre acido-basique, *etc*. Les paramètres d'évaluation de la commande respiratoire supposent quant à eux l'intégrité du système respiratoire, rendant leur utilisation difficile chez les patients en insuffisance respiratoire aiguë et/ou en VM. Mais surtout, dès lors que le patient est sous VM les indices cliniques présentent un intérêt bien plus limité puisqu'ils sont complètement (ventilation contrôlée) ou partiellement (ventilation assistée) contrôlés par le respirateur [37]. Par exemple, en ventilation assistée ciblée en pression, le volume inspiré par le patient résulte non seulement de son propre effort respiratoire mais aussi de l'aide inspiratoire fournie par la machine et les paramètres cliniques ne permettent pas de distinguer ces éléments. De plus, il est important de tenir compte d'une éventuelle sédation. Enfin, pour le patient sous VNI, la plupart des éléments fournis par le spirogramme du respirateur ne sont pas fiables en raison notamment des fuites d'air autour de l'interface ou par la bouche.

E. METHODES D'EVALUATION DU TRAVAIL RESPIRATOIRE DANS L'INSUFFISANCE RESPIRATOIRE AIGUË DE L'ENFANT

1. METHODES D'EVALUATION DE LA COMMANDE NEUROMUSCULAIRE

EMG diaphragmatique et Activité Electrique du Diaphragme

Puisque la commande ventilatoire est transmise *via* les nerfs phréniques aux muscles effecteurs, l'étude directe de la fonction des muscles respiratoires reflète la commande centrale. Le signal Electromyographique (EMG) est la méthode de référence pour étudier les muscles respiratoires. En pratique clinique, il n'est pas possible d'enregistrer l'ensemble des muscles respiratoires. Le diaphragme étant le principal effecteur, l'EMG diaphragmatique apporte une bonne évaluation de la commande ventilatoire globale sous réserve de l'intégrité du système neuromusculaire.

Historiquement, l'EMG diaphragmatique a d'abord été réalisé avec des aiguilles insérées dans le muscle. Ensuite, il a pu être réalisé à partir d'électrodes de surface mais avec cette méthode le signal obtenu est contaminé par l'activité des autres muscles [38, 39]. Plus récemment, l'EMG effectué à l'aide d'électrodes œsophagiennes est apparu comme un outil fiable [40, 41]. Il étudie l'activité de la portion crurale du diaphragme, qui apporte une bonne estimation de l'activité diaphragmatique globale. Depuis quelques années, la surveillance en continu de l'activité électrique du diaphragme (AE_{DI}) est apparue comme un outil facilement utilisable au chevet du patient [42], bien que disponible avec une seule compagnie de respirateurs (Maquet, Solna, Suède). Physiologiquement, l'AE_{DI} constitue la sommation temporo-spatiale des potentiels d'action des unités motrices recrutées par le diaphragme [41]. En pratique clinique, la principale application de l'AE_{DI} est son utilisation associée au mode ventilatoire NAVA, qui permet un niveau de support ventilatoire proportionnel aux besoins du patient [43].

Chez l'enfant, l'AE_{DI} présente une variabilité plus importante comparée à l'adulte [27, 44]. Sa valeur habituelle chez l'enfant en VM se situerait entre 3 et 20 µV mais celle-ci dépend grandement du mode ventilatoire, de la pathologie sous-jacente, de la sédation et de la phase d'évolution de la maladie [22, 45, 46]. Etant donné que la variabilité inter-individuelle est aussi importante, le sujet est son propre témoin et les variations d'AE_{DI} importent plus que les valeurs absolues [26].

La mesure de l'AE_{DI} présente plusieurs applications cliniques en dehors du mode NAVA [47] (Figure 4). D'abord, elle permet d'optimiser le niveau de support ventilatoire au chevet du patient. Pour le clinicien, fournir un niveau adapté de support ventilatoire, en évitant la sous-assistance autant que la sur-assistance, est un enjeu important. D'un côté, il est important de maintenir une activité diaphragmatique minimale chez le patient pour limiter une dysfonction diaphragmatique, qui pourrait retarder l'extubation [48]. L'atrophie diaphragmatique est en effet un phénomène très fréquent en réanimation [17] et elle peut survenir très tôt après la mise en place du support ventilatoire [18, 49]. De l'autre côté, une activité diaphragmatique élevée peut traduire un travail respiratoire trop important, comme Ducharme *et al.* l'ont décrit [47]. Dans ce cas, la mesure de l'AE_{DI} incite à augmenter le niveau de support pour répondre à la demande du patient, ce qui se ferait automatiquement en mode NAVA.

L'AE_{DI} peut aussi être utile pour mettre en évidence une activité tonique du diaphragme, c'est-à-dire une activité électrique diaphragmatique en fin d'expiration [22]. Ce phénomène peut augmenter la fatigue musculaire du diaphragme en augmentant son métabolisme [50]. Comme Emeriaud *et al.* l'ont montré, l'activité tonique du diaphragme semble être un bon indicateur de l'effort généré par le patient pour maintenir un volume de fin d'expiration [51] et sa mesure pourrait alors permettre d'adapter les réglages de la VM en titrant le niveau de PEEP.

Enfin, la mesure de l'AE_{DI} a montré son intérêt dans différentes situations cliniques [52, 53]. Par exemple, nous avons montré que la mesure de l'AE_{DI} peut être un outil diagnostic sensible pour détecter une activité respiratoire spontanée chez un patient tétraplégique, contribuant à une adaptation de sa prise en charge [54] (*Cf.* Annexe 1).

La mesure de l'AE_{DI} permet de quantifier et d'améliorer la synchronisation patient-ventilateur. Chez l'adulte, l'asynchronie respiratoire est associée à une augmentation de la durée de ventilation et de la durée de séjour en soins intensifs [55, 56]. Alors que la mauvaise synchronisation patient-ventilateur est difficilement appréciable par la clinique, la mesure de l'AE_{DI} est une technique largement décrite pour évaluer la qualité de cette interaction. Bordessoule *et al.* ont montré que près d'un quart des cycles ventilatoires étaient asynchrones chez des enfants en ventilation conventionnelle [57]. Plusieurs travaux ont montré que la

ventilation en mode NAVA améliorait la synchronisation patient-ventilateur, à la fois en VNI [58-60] et en ventilation invasive [61].

Etant donné qu'une bonne fonction diaphragmatique est un prérequis nécessaire pour respirer spontanément et de manière autonome, la pertinence de la mesure de l'AE_{DI} pendant le processus de sevrage a également été étudiée. Il a été rapporté que les paramètres dérivés de l'AE_{DI} étaient des facteurs prédictifs d'échec de sevrage ventilatoire chez l'adulte [62] et le nouveau-né [63]. L'augmentation de l'AE_{DI} inspiratoire semble être aussi prédictif du succès du test de ventilation spontanée [64, 65]. De plus, en calculant l'index d'efficacité neuro-ventilatoire (V_T/AE_{DI}) pendant le sevrage, Roze *et al.* et Liu *et al.* ont montré que l'AE_{DI} était un outil pertinent pour identifier les patients à risque d'échec de sevrage [65, 66]. Ces mêmes auteurs ont montré que la titration quotidienne du niveau NAVA ciblant 60% de la valeur de l'AE_{DI} enregistrée en l'absence d'assistance ventilatoire était faisable et bien tolérée [67]. Avec une approche un peu différente, Grasselli *et al.* ont utilisé le signal AE_{DI} pour calculer l'indice de contribution ventilatoire du patient [68]. Le niveau d'assistance ventilatoire est réduit à zéro pour un cycle respiratoire (en mode PPC) : le rapport du V_T et de l'AE_{DI} pendant le cycle non assisté et le cycle assisté reflète alors la contribution relative du patient. L'indice est calculé comme suit : Contribution du patient = ($V_{Tnon\text{-}assisté}/AE_{DInon\text{-}assisté}$) / ($V_{Tassisté}/AE_{DIassisté}$). Un indice de contribution proche de 1 indique que le patient génère presque entièrement le V_T, alors qu'un indice proche de zéro indique que le patient contribue peu. Enfin, dans une des rares études pédiatriques sur le sujet, Wolf *et al.* ont observé que la capacité à générer une activité diaphragmatique suffisante pour un V_T donné en ventilation assistée était prédictif du succès de l'extubation [69].

La relation entre les pressions générées par le diaphragme et son activité électrique est un principe physiologique assez bien connu [42, 70]. Bellani *et al.* ont montré une bonne corrélation entre la pression musculaire générée et l'AE_{DI} dans une population d'adultes en ventilation assistée. En revanche, il semble exister une variabilité interindividuelle puisque la pente de cette relation est différente selon les patients [71]. Chez l'enfant, le travail de Essouri *et al.* confirme cette association avec une forte corrélation entre l'AE_{DI} et le produit pression temps œsophagien (PTP_{ES})[72].

Malgré ces différentes applications cliniques, la mesure de l'AE_{DI} présente des limites. D'une part, les valeurs de référence de l'AE_{DI} chez l'enfant sain ou le patient en insuffisance respiratoire aiguë sont limitées. D'autre part, l'AE_{DI} seule permet de juger de l'activité électrique du diaphragme, reflet de la commande respiratoire, et non de sa contractilité effective. Il est alors nécessaire de coupler l'AE_{DI} au volume ou à la pression générée pour évaluer la véritable force diaphragmatique. A ce jour, l'AE_{DI} a encore une place limitée en pédiatrie, en raison d'un manque de données dans la littérature. Une sonde gastrique supplémentaire étant nécessaire, son usage est réservé aux soins intensifs.

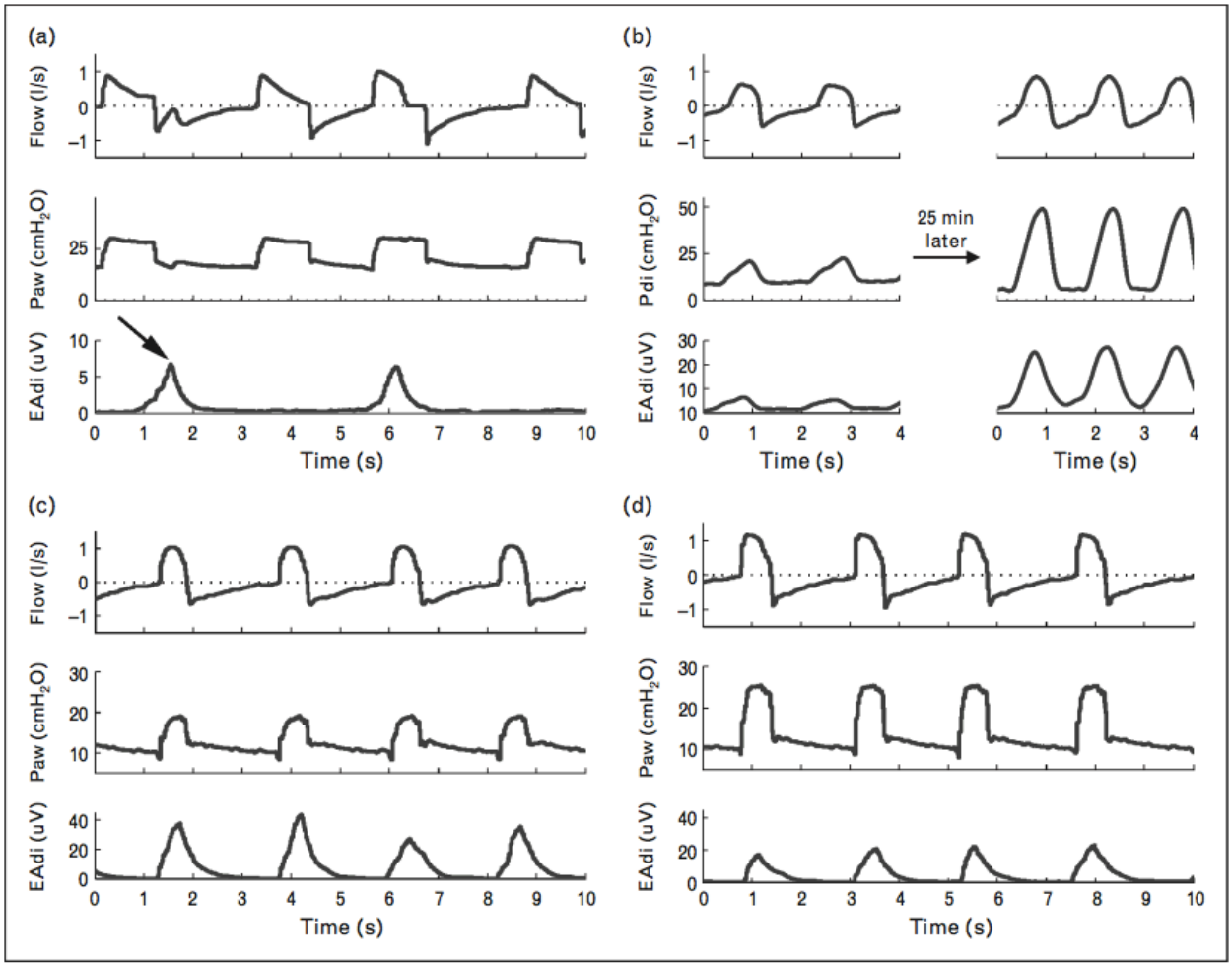

Figure 4 : Evaluation de la fonction diaphragmatique à l'aide de l'AE_{DI}.
Les tracés de débit respiratoire (Flow), de pression des voies aériennes (P_{AW}), d'activité électrique du diaphragme (AE_{DI}) et de pression transdiaphragmatique P_{DI} sont représentés dans différentes conditions : (a) lors d'une asynchronie patient-ventilateur pendant la ventilation assistée (effort non récompensé indiqué par la flèche) ; (b) lors d'un échec d'épreuve de sevrage ventilatoire en ventilation spontanée, où la partie gauche montre le tracé à la 1ère minute du test et la partie droite, l'élévation de l'AE_{DI} et de la P_{DI} 25 minutes plus tard ; les parties (c) et (d) représentent le même patient, ventilé avec un niveau de pression inspiratoire faible (c) et élevé (d), montrant l'AE_{DI} qui diminue suite à une augmentation du niveau de support ventilatoire.
Empruntée à [73] avec autorisation de l'auteur.

Pression d'ouverture des voies aériennes à 0,1s et ses dérivés

La pression d'ouverture des voies aériennes, ou pression d'occlusion à 0.1s ($P_{0.1}$), correspond à la pression négative générée lors des cent premières millisecondes d'une inspiration suivant une occlusion des voies aériennes à la fin d'une expiration normale [74]. Cette mesure reflète principalement la commande respiratoire centrale du patient, mais elle dépend aussi de la qualité des voies motrices contrôlant les muscles inspiratoires et de leur capacité à générer une pression [36]. Une valeur élevée indique une activité centrale augmentée alors qu'une faible valeur ne signifie pas nécessairement une altération de la commande centrale, mais peut aussi être liée à une fatigue musculaire ou une mauvaise intégrité des voies neuronales des muscles respiratoires. De plus, la présence d'une hyperinflation doit être prise en compte dans l'interprétation de la $P_{0.1}$. Mesurée à la pression atmosphérique, la $P_{0.1}$ ne prend pas en compte l'effort que fait le patient pour vaincre la PEEPi. Dans le cas d'un patient asthmatique par exemple, la $P_{0.1}$ sous-estimera l'effort réel que fournit le patient pour assurer un débit inspiratoire.

En pratique, la $P_{0.1}$ est désormais mesurée en temps réel au chevet du patient par la plupart des respirateurs dès lors que le patient est en ventilation assistée. Chez l'adulte en VM, la $P_{0.1}$ a été utilisée pour optimiser le niveau de support apporté au patient [75-77], pour titrer la PEEP [78] et pour prédire le succès de l'extubation, même si son intérêt sur ce point reste controversé [79, 80].

La mesure a été décrite chez l'adulte à 0.1s mais cette durée est très discutable chez l'enfant chez qui le temps inspiratoire est plus court que celui de l'adulte. Chez l'enfant sain, des valeurs de référence ont été proposées [81-83]. En revanche, peu de travaux se sont intéressés à enfant en VM et les valeurs normales n'ont pas été déterminées dans cette population, ce qui rend difficile son utilisation en pratique clinique [84]. Dans une enquête réalisée auprès de 417 pédiatres réanimateurs, seulement 3% d'entre eux déclaraient utiliser la $P_{0.1}$ pour le sevrage des patients, et la majorité considéraient une valeur ≤ 5 cmH_2O comme acceptable. Pour autant, le travail de Wolf *et al.* a mis en évidence une bonne corrélation entre la valeur de $P_{0.1}$ et le delta d'AE_{DI} au cours du sevrage dans une population de 20 enfants [69]. Et comme l'a montré Manczur *et al.* une $P_{0.1}$ faible semble être associée à un risque accru d'échec d'extubation [85].

La $P_{0.1}$ peut également être intégrée dans des indices composites, comme le rapport $P_{0.1}/P_{DImax}$, ce qui permet l'évaluation simultanée de la commande centrale et de la force des muscles respiratoires [3, 86]. Mais à ce jour, il s'avère que ces indices composites ont été étudiés uniquement chez les nouveau-nés [87, 88] et chez des patients neuromusculaires [82, 83, 89], et jamais en situation aigue chez l'enfant plus grand.

2. MESURE DES PRESSIONS GENEREES LORS DE LA VENTILATION : PRESSIONS ŒSOGASTRIQUES ET LEURS DERIVES

Principes de la mesure des pressions œsogastriques

Buytendijk *et al.* ont démontré en 1949 que la P_{ES} estimait de manière fiable la pression pleurale (P_{PL}) [90]. Le principe de cette estimation est basé sur la notion que la pression dans la plèvre adjacente est transmise à l'œsophage [91]. Habituellementt, la P_{ES} est mesurée à l'aide d'un cathéter intra-œsophagien avec un ballonnet rempli d'air ou de liquide, relié à un capteur de pression [91, 92], y compris chez l'enfant [93, 94]. En raison des potentielles sources d'erreurs liées à ce type de sonde (limitations concernant le volume d'air ou de liquide à injecter et position du ballonnet), d'autres sondes ont été développées. Disposant de micro transducteurs de pression, elles permettent de s'affranchir de certaines de ces limites [9, 95, 96]. En particulier la sonde Gaeltec® est bien tolérée et a été utilisée dans plusieurs études pour évaluer le travail respiratoire chez l'enfant [9, 97-99] [100, 101].

Selon le type de cathéter utilisé, la mesure de la pression gastrique (P_{GAS}) peut être réalisée simultanément, apportant davantage d'informations sur la mécanique respiratoire, en particulier sur l'activité du diaphragme et des muscles abdominaux (Figure 5). En effet, la mesure de la P_{GAS} rend possible le calcul de la pression transdiaphragmatique comme suit : $P_{DI} = P_{GAS}-P_{ES}$. Le calcul de l'aire sous la courbe de la P_{DI} et de la P_{ES} au temps inspiratoire permet de calculer le produit pression temps diaphragmatique (PTP_{DI}) et œsophagien (PTP_{ES}), respectivement [102, 103] (Figure 6). Ceux-ci sont exprimés par cycle respiratoire ou par minute en multipliant le PTP par la fréquence respiratoire, et les valeurs habituelles se situeraient entre 50 et 150 $cmH_2O.s/min$ chez l'adulte sain au repos [104, 105].

Ainsi, la mesure des pressions œsogastriques, en quantifiant les efforts générés par le patient, apparait comme une méthode indirecte d'évaluation du travail respiratoire, méthode désormais couramment utilisée en recherche clinique pour des patients en ventilation invasive [31, 106], en VNI [9, 97, 107] ou sous HFNC [108, 109].

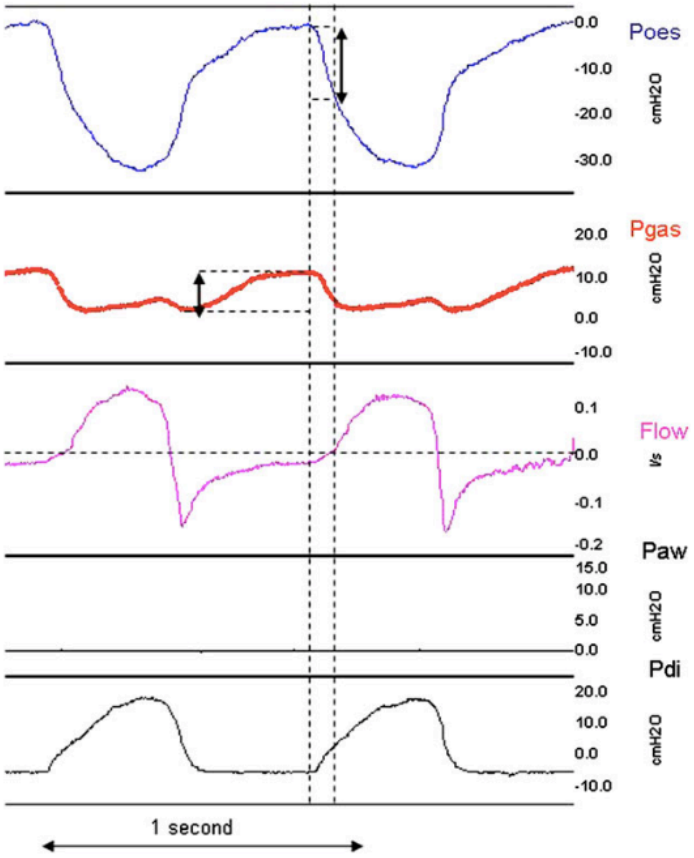

Figure 5 : Représentation de la pression œsophagienne (P_{OES}), de la pression gastrique (P_{GAS}), de la pression transdiaphragmatique (P_{DI}), de la pression des voies aériennes (P_{AW}) et du débit respiratoire en ventilation spontanée chez un patient atteint de bronchiolite oblitérante.
Sur le tracé de P_{OES}, la flèche représente la Pression Expiratoire Positive en fin d'Expiration (PEEPi). On constate non seulement une augmentation de la variation de P_{ES} (ici autour de -35 cm H_2O, alors que la normale est de -5 à -8 cm H_2O) mais aussi une augmentation de la P_{GAS} à l'expiration (ici autour de 10 cmH_2O, alors que la normale est de 0 à 5 cmH_2O) reflétant une participation active des muscles abdominaux (représenté par la flèche sur le tracé de P_{GAS}).
Empruntée à [10] avec autorisation de l'auteur.

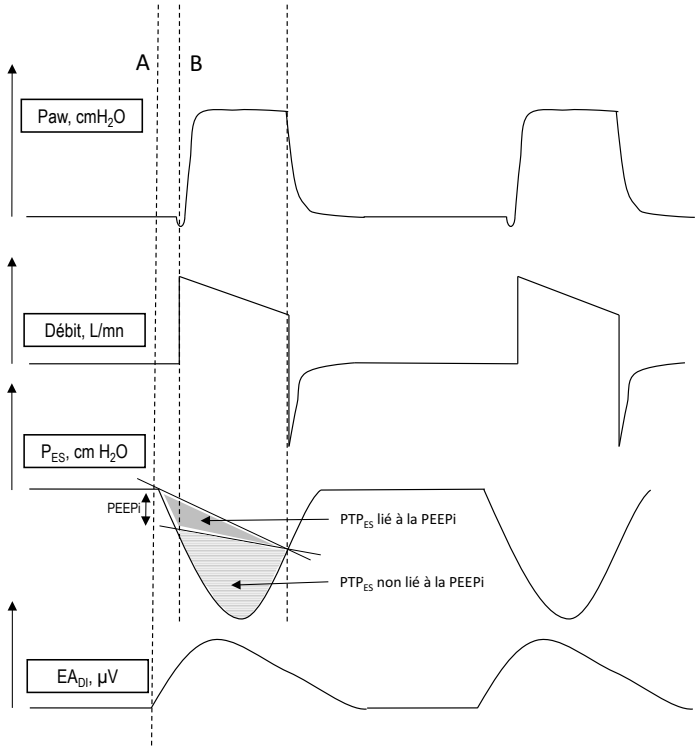

Figure 6 : Représentation du Produit Pression-Temps œsophagien (PTP_{ES}) en ventilation mécanique.
Le PTP_{ES} est mesuré comme étant l'aire sous la courbe de P_{ES} à l'inspiration, dont le début et la fin sont déterminés soit par l'Activité Electrique du Diaphragme (AE_{DI}) (ligne A), tenant en compte l'effort pour vaincre la Pression Expiratoire Positive en fin d'Expiration intrinsèque (PEEPi), soit par le débit (ligne B), ne tenant pas en compte cet effort.
P_{AW} : Pression des Voies Aériennes ; P_{ES} : Pression Œsophagienne

Mesure des pressions œsogastriques pour optimiser la VNI

La mesure des pressions œsogastriques a été utilisée chez l'enfant en VNI et sous HFNC pour vérifier l'efficacité du support ventilatoire sur la décharge des muscles respiratoires, et ce dans différentes situations cliniques, comme l'insuffisance respiratoire hypercapnique [97], la détresse respiratoire post-extubation [110], la mucoviscidose [99] ou la bronchiolite [46, 109, 111]. Par exemple, dans cette pathologie, Milesi *et al.* ont montré qu'une augmentation du débit en HFNC de 1 à 7L/min était associée à une réduction du PTP_{ES} de près de 50% [109].

La mesure des pressions œsogastriques est aussi utile pour optimiser les réglages des paramètres ventilatoires du respirateur. En effet, un « réglage physiologique » de la VNI, basé sur la mesure de la P_{ES} et de la P_{GAS} a montré sa supériorité par rapport au « réglage clinique » basé sur les

paramètres respiratoires non invasifs dans différentes situations cliniques. Dans la bronchiolite, la mesure de ces pressions a permis de déterminer le niveau optimal de Pression Positive Continue (PPC) : le réglage à +7 cmH_2O est associé à une diminution optimale du travail respiratoire [9]. Dans les obstructions sévères des voies aériennes supérieures du nourrisson, Khirani *et al.* ont montré que le niveau optimal de pression positive continue ajusté sur la P_{ES} est en moyenne supérieur de +2 cmH_2O par rapport au niveau de pression réglé sur des paramètres cliniques [107]. Dans ce même travail, la mesure de la P_{GAS} s'est avérée particulièrement utile pour quantifier l'activité des muscles abdominaux. Une activité expiratoire de ces muscles peut être liée à une hyperinflation induite par une PEEP trop élevée [107, 112], mais aussi par une obstruction persistante des voies aériennes sous PPC [113, 114].

Mesure des pressions œsogastriques pour évaluer la synchronisation patient-ventilateur

Puisque les asynchronies respiratoires sont potentiellement délétères pour le patient [55, 115], leur mise en évidence est cruciale, d'autant plus que les paramètres cliniques et ceux fournis par le respirateur ne permettent pas de les identifier correctement [15, 116]. En effet, les mesures de P_{AW} et de débit sous-estiment la plupart des asynchronies patient-ventilateur, alors que la mesure de P_{ES} permet de détecter aisément les efforts du patient à son chevet [117]. Il devient alors plus facile de repérer les efforts inefficaces (*Ineffective Triggering*), les efforts non récompensés (*Wasted Efforts*), les asynchronies d'entrainement (*Reverse Triggering*) et de calculer les délais entre le début de l'inspiration (*Trigger Errors*) ou de l'expiration (*Cycle-off Errors*) commandée par le patient, et le début de l'inspiration ou l'expiration dans le cycle respiratoire effectué par le respirateur (Figure 7).

La mesure de la P_{ES} et de la P_{GAS} a été largement utilisée dans différentes études [55, 118, 119]. Chez l'enfant, Fauroux *et al.* ont montré que la mesure des pressions oesogastriques améliorait la synchronisation du patient avec le ventilateur ainsi que le confort chez des patients atteint de mucoviscidose sous VNI [99].

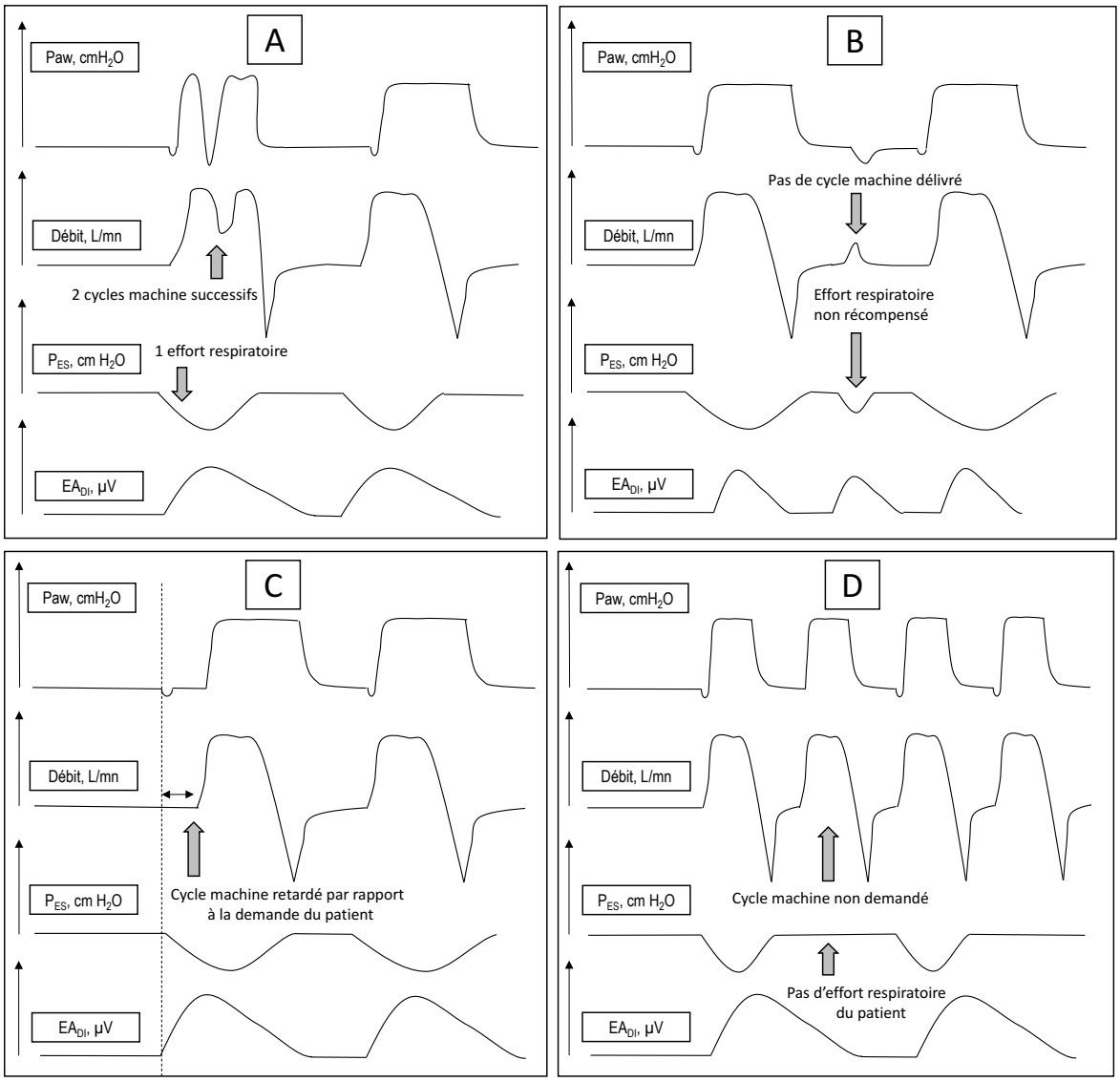

*Figure 7 : Principales asynchronies patient-ventilateur, déterminées à l'aide de la mesure de P_{ES}. La partie A représente un double-déclenchement (*double-triggering*) du ventilateur alors qu'un seul effort respiratoire est réalisé par le patient. Dans la partie B, le patient effectue un effort respiratoire qui n'est pas reconnu par le respirateur et ne déclenche pas de cycle ventilatoire. La partie C met en évidence un retard entre l'effort respiratoire effectué par le patient et l'initiation du cycle ventilatoire par le respirateur (*trigger delayed*). A noter que les asynchronies de délai comprennent aussi les déclenchements prématurés (*premature trigger*), les retards d'expiration (*cycle-off delay*) et les expirations prématurées (*premature cycling-off*), non représentées sur la figure. La partie D montre un auto déclenchement du respirateur, sans qu'existe d'effort respiratoire de la part du patient.*
EA_{DI} : Activité Electrique du Diaphragme ; P_{AW} : Pression des Voies Aériennes ; P_{ES} : Pression Œsophagienne

Mesure des pressions œsogastriques pour optimiser la ventilation invasive

La mesure de la P_{ES} a montré son intérêt au cours du sevrage ventilatoire. A cette étape de la maladie, la capacité du patient à respirer de manière autonome est testée, le plus souvent en réduisant transitoirement les paramètres ventilatoires dans l'idée d'évaluer son autonomie respiratoire. Certains auteurs se sont intéressés aux indices dérivés de la mesure de P_{ES} comme éléments prédictifs du succès de l'extubation [105, 120]. Ainsi, une augmentation du PTP_{ES} au cours du sevrage était associée à un risque plus élevé d'échec d'extubation [105]. Chez les patients pour lesquels l'extubation a été un échec, le PTP_{ES} mesuré pendant le test en ventilation spontanée était 4 fois plus élevé que la valeur normale. Chez l'enfant, on a constaté une association significative entre la valeur de PTP_{ES} post extubation et le risque de réintubation dans une population de 409 enfants intubés et ventilés [31]. En utilisant cet outil, ces mêmes auteurs ont démontré dans un autre travail le bénéfice d'un test de ventilation spontanée effectué en PPC comparé au test réalisé avec une pression inspiratoire [106].

Le *Tension-Time Index*, défini par $TTI = (\Delta P_{ES}/\Delta P_{ES\text{-}OCC}) \times (T_I/T_{TOT})$ a été initialement décrit chez les patients avec une pathologie respiratoire chronique ou une maladie neuromusculaire pour mesurer l'endurance des muscles respiratoires [89, 100]. En réanimation, les variations de P_{ES} ($\Delta P_{ES\text{-}OCC}$) ou de P_{AW} pendant une occlusion inspiratoire peuvent être utilisées pour mesurer le TTI [31]. En situation aigue et chez les patients ventilés, certains travaux ont montré que le TTI était un indice prédictif du succès de l'extubation [121, 122] mais ces résultats n'ont pas été confirmé dans d'autres travaux [31, 88].

Chez les patients en ventilation invasive, la valeur absolue de P_{ES} permet d'apprécier la mécanique du système respiratoire global du patient, incluant le poumon et la cage thoracique [123]. Le calcul de la Pression Transpulmonaire est défini par $P_{TP} = P_{AW} – P_{PL}$ (la P_{PL} étant estimée par la P_{ES}). La P_{TP} permet de distinguer l'effet des pressions agissant sur le poumon d'une part et sur la paroi thoracique d'autre part, alors que l'influence de la cage thoracique dans la mécanique respiratoire varie selon des facteurs propres à chaque patient (obésité, chirurgie abdominale, pathologie pulmonaire, activité respiratoire spontanée, *etc.*) et *a fortiori* en pédiatrie (influence de l'âge, du poids et de la maturation pulmonaire, *etc.*) [124]. Quand une pression de ventilation est fournie par le respirateur, la connaissance de la proportion nécessaire pour expandre le

poumon (potentiellement délétère pour le parenchyme pulmonaire) d'un côté et celle pour distendre la cage thoracique de l'autre est capitale. En ce sens, la P_{TP} permet de déterminer plus précisément le risque de lésions pulmonaires induites par la ventilation [125]. Par exemple, dans le Syndrome de Détresse Respiratoire Aiguë (SDRA), la P_{TP} en fin d'expiration peut être négative (lorsque la P_{PL} est supérieure à la PEEP) et favoriser un collapsus des alvéoles. Cela peut exposer les poumons au phénomène cyclique d'ouverture et de fermeture alvéolaire (recrutement et dérecrutement). Pour protéger les poumons, l'idéal serait de trouver un équilibre en protégeant les alvéoles aérées de la surdistension tout en maintenant un recrutement des alvéoles non aérées [126]. Des études récentes montrant l'intérêt de la mesure de P_{ES} pour optimiser la VM ont été effectuées chez l'adulte [127]. La titration de PEEP basée sur la mesure de P_{ES} a été proposée chez les patients atteints de SDRA [128, 129] et Talmor *et al.* ont montré que les paramètres d'oxygénation et la compliance pulmonaire étaient significativement améliorés en utilisant cette stratégie ventilatoire [130].

Bien que l'estimation de la P_{PL} par la P_{ES} ait été démontrée [6, 131, 132] et soit couramment utilisée dans les études cliniques, il existe plusieurs facteurs confondants pouvant rendre cette estimation inexacte, comme le poids du médiastin [133, 134], la position de la sonde de mesure [131], une pression abdominale élevée [135] ou la posture du patient [136]. Pour ces raisons certains auteurs ont suggéré l'ajout d'un facteur correctif pour valider cette estimation [135, 137-140] mais sa valeur reste controversée [130, 139]. En pédiatrie, les travaux sont plus limités et des études physiologiques sont nécessaires avant d'utiliser la P_{TP} en pratique clinique.

Mesure des pressions œsogastriques pour comprendre les mécanismes physiopathologiques des maladies respiratoires complexes chez l'enfant

La mesure des pressions œsogastriques permet d'évaluer la contribution du diaphragme et des autres muscles respiratoires en ventilation spontanée, en calculant le rapport entre la variation de P_{GAS} et le ΔP_{ES} [141]. Alors que ce ratio est < -1 chez le sujet sain, il peut varier entre -1 et +1 en cas de contribution augmentée des muscles de la cage respiratoire comparé à l'effet du diaphragme. En cas de paralysie diaphragmatique, ce ratio devient égal à 1.

Stimulation magnétique des nerfs phréniques

La stimulation magnétique des nerfs phréniques, initialement décrite chez l'adulte, peut être réalisée chez l'enfant pour évaluer la force diaphragmatique [142]. Elle est utilisable sans risque au chevet du patient et elle ne requiert pas sa participation. La contraction diaphragmatique est évaluée avec le différentiel de pression générée par la stimulation, soit avec la pression transdiaphragmatique (P_{DI}) soit avec la pression endotrachéale en occlusion [143].

Plusieurs travaux chez l'adulte ont utilisé cette technique pour évaluer la fonction diaphragmatique dans différentes situations cliniques [144-147]. Chez l'enfant, les travaux sont plus rares [148-150]. Dans le travail de Rafferty *et al.*, la stimulation phrénique a été utilisée comme méthode pour évaluer la fonction diaphragmatique chez des patients en post-transplantation hépatique, chez qui la mesure des pressions œsogastriques était contre-indiquée [151].

En revanche, la stimulation magnétique des nerfs phréniques ne peut pas être utilisée chez l'enfant sédaté car la sédation est responsable à elle seule d'une diminution de la contraction diaphragmatique [152].

3. MESURES INDIRECTES DU TRAVAIL RESPIRATOIRE

Etude des mouvements thoraco-abdominaux

Etude des mouvements thoraco-abdominaux par pléthysmographie

Une analyse objective des mouvements thoraco-abdominaux peut être réalisée par la pléthysmographie d'inductance, un outil simple, noninvasif et bien toléré chez l'enfant [153] (*Cf.* Annexe 2). Les déplacements de la cage thoracique et de l'abdomen sont évalués par des bandes élastiques thoraciques et abdominales. Le calcul d'angle de phase permet de quantifier une éventuelle asynchronie thoraco-abdominale. Après calibration, la pléthysmographie d'inductance permet aussi de mesurer les volumes pulmonaires, y compris lorsque le patient est sous Ventilation Haute Fréquence (*High Frequency Oscillatory Ventilation,* HFOV) [154, 155]. Même si la pléthysmographie peut orienter vers une dysfonction des muscles respiratoires [156], cet examen n'est pas spécifique et doit être interprété en fonction du contexte. Doivent être pris en compte notamment la maladie sous-jacente, la présence éventuelle d'une obstruction des

voies aériennes supérieures et la compliance et la résistance pulmonaire [157]. En pratique clinique, cette technique peut être réalisée au cours d'une polysomnographie pour caractériser les évènements respiratoires chez l'enfant [158] (*Cf.* Annexe 3) ou au cours de la période de sevrage ventilatoire [31]. Elle permet d'augmenter l'intérêt diagnostic de la polygraphie en identifiant plus précisément le type d'évènement respiratoire survenant pendant le sommeil [159]. Par exemple, une apnée obstructive se caractérise par une diminution du débit respiratoire alors qu'il persiste des mouvements respiratoires (parfois augmentés). Le tracé mettra alors en évidence une opposition de phases, constat similaire en cas de paralysie des muscles intercostaux. En cas de paralysie diaphragmatique, une respiration paradoxale sera observée.

La pléthysmographie optoélectronique, plus récente, permet d'obtenir des résultats comparables tout en s'affranchissant des difficultés de calibration, bien qu'aucun appareil de mesure ne soit disponible sur le marché [161-163]. Cette technique utilise des capteurs disposés sur le thorax et l'abdomen du patient, dont les mouvements tridimensionnels sont analysés par une caméra [164]. Elle a l'avantage de pouvoir analyser la dynamique des différentes parties de la paroi thoraco-abdominale et de distinguer l'activité des 2 hémi-thorax. Chez les patients ventilés de manière invasive, la pléthysmographie optoélectronique a permis d'estimer l'augmentation du V_T induit par la PEEP [165], la répartition des volumes pulmonaires [166] et la variation de la courbe pression-volume [167].

Aussi, une autre méthode d'évaluation des volumes pulmonaires très prometteuse est en cours de développement. Cette technique est basée sur une reconstruction informatique des mouvements respiratoires enregistrés par deux caméras (vidéo 3D) [168].

Tomographie par Impédance Electrique

La tomographie par impédance électrique est une technique d'évaluation de la ventilation et de la perfusion pulmonaire disponible au chevet du malade. Bien que cette technologie date de plus de 30 ans, elle fait l'objet d'un regain d'intérêt [169]. Dans des pathologies complexes comme le SDRA, l'inhomogénéité de la ventilation est un phénomène très fréquent qui contribue au risque de lésions secondaires de la ventilation [170, 171]. Certaines zones pulmonaires sont sujettes au dérecrutement tandis que d'autres régions alvéolaires sont surdistendues. En plus de la

pathologie sous-jacente, d'autres facteurs peuvent intervenir sur la distribution des volumes pulmonaires : l'âge, la mécanique ventilatoire, la position du patient, *etc.* [172]. La multiplicité de ces variables rend l'évaluation de la distribution de la ventilation particulièrement délicate à évaluer au chevet du patient. En tant qu'outil dynamique et continu, la tomographie par impédance électrique peut alors être utile. Chez l'adulte, plusieurs travaux ont évalué l'effet de la PEEP [173], d'une manœuvre de recrutement [174], d'une modification du V_T [175], d'un test en ventilation spontanée [176] ou de changements posturaux [177] sur la ventilation pulmonaire. Mauri *et al.* ont utilisé cette technologie pour mesurer les volumes pulmonaires chez des patients sous HFNC [178]. L'aspect noninvasif et non irradiant de cette technologie la rend séduisante pour une utilisation en pédiatrie. Chez l'enfant prématuré, la tomographie par impédance électrique a été utilisée pour évaluer l'effet sur les volumes pulmonaires de la VNI [179], du décubitus ventral [180] et de l'HFVO [181-183]. Quelques autres travaux ont été effectués chez l'enfant plus âgé [184]. Dans une série de 10 enfants ayant un SDRA, cette technique a permis d'évaluer l'effet d'une manœuvre de recrutement sur le volume pulmonaire en fin d'expiration [185]. De même, l'effet bénéfique du décubitus ventral sur la ventilation a pu être montré [186].

Mesure de la consommation en oxygène (VO_2) par la calorimétrie indirecte

L'estimation de la VO_2 des muscles respiratoires (VO_{2resp}) est indépendante des mesures physiologiques de type pression-volume dont l'analyse est assez complexe. Le travail de Field *et al.* a permis de mettre en évidence que la VO_{2resp} représentait environ 1 à 3% de la VO_2 totale chez le sujet sain [187]. Alors que la VO_2 est d'environ 3 à 4 ml/kg/min chez l'adulte, sa valeur est plus élevée chez l'enfant en raison d'un métabolisme de base plus important. La valeur normale se situe autour de 8-9 ml/kg/mn et diminue avec l'âge jusqu'à atteindre des valeurs comparables à celles de l'adulte autour de l'âge de 10 ans [188-190].

Plusieurs applications respiratoires de la mesure de la VO_{2resp} ont été décrites dans la littérature. Chez l'adulte, il a été démontré que la VM, par la relaxation musculaire qu'elle entraine, était associée à une réduction de près de 20% de la VO_2 [190] et que cette part pouvait varier en fonction des paramètres ventilatoires [191, 192] ou du mode de ventilation utilisé [193]. La mesure de la VO_{2resp} a aussi été réalisée pour évaluer les effets de différentes thérapeutiques

comme les analgésiques [194], les bronchodilatateurs [195] ou la kinésithérapie [196]. Chez l'enfant, l'utilisation de l'utilisation bloqueurs neuromusculaires réduit la VO_2 de près de 10% [197]. Chez le nouveau-né, les rares études conduites ont permis de montrer que la VO_{2resp} était augmentée en cas de pathologie respiratoire sous-jacente alors qu'elle ne semble pas être modifiée par le mode ventilatoire chez les patients intubés [198-200].

Lors de la phase de sevrage ventilatoire, pendant laquelle le travail respiratoire du patient est davantage mis à contribution, Kemper *et al.* ont montré chez l'adulte que la VO_2 augmentaient de l'ordre de 10% [201]. D'autres travaux ont évalué l'intérêt de cette mesure pour prédire le succès de l'extubation [202, 203]. Bellani *et al.* ont testé les effets de la diminution des niveaux d'aide inspiratoire chez des patients prêts à être extubés [191]. Ils ont mis en évidence que non seulement la diminution de l'assistance ventilatoire, mais aussi la sur-assistance étaient associées à une augmentation de la VO_{2resp}. Cette mesure a aussi été utilisée pour comparer deux tests de ventilation spontanée [204].

La relation entre la VO_{2resp} et les autres indices de travail respiratoire a été analysée dans plusieurs travaux physiologiques. En 1984, Field *et al.* ont mis en évidence que la VO_{2resp} était corrélée au PTP_{DI} chez 4 sujets sains [104]. Ces résultats ont ensuite été confortés par d'autres études [205, 206]. La relation entre la VO_{2resp} et la $P_{0.1}$ a aussi été mise en évidence chez les patients en phase de sevrage ventilatoire [191] et chez les patients souffrant d'une bronchopathie chronique [207].

La calorimétrie indirecte est la principale technique pouvant quantifier la VO_2, même si sa principale application aux soins intensifs concerne l'évaluation des dépenses énergétiques au repos [208]. Le principe de base de cet outil est basé sur le fait que le corps humain consomme de l'O_2 et produit du CO_2 pour brûler les nutriments. La calorimétrie indirecte est relativement facile d'utilisation au chevet du patient en ventilation invasive. Le branchement de l'appareil en série du respirateur permet de s'affranchir des fuites rencontrées lors de l'analyse chez le patient non ventilé, même si certains facteurs (FiO_2>60%, présences de fuites sur le tube endotrachéal, température corporelle >38°) altèrent la mesure. Une précision de 96% dans le calcul de la VO_2 a été décrite même si des erreurs minimes dans la mesure du V_T peuvent induire des erreurs significatives dans le calcul de la VO_2 [209, 210].

Imagerie diaphragmatique

La fluoroscopie apporte une vision dynamique du diaphragme, mais les difficultés de son interprétation, son caractère irradiant, et son impossibilité à la réaliser au chevet du patient font qu'elle présente un intérêt limité [211].

Depuis une dizaine d'année, l'échographie est apparue comme une technologie noninvasive facilement utilisable au chevet du patient en insuffisance respiratoire. En plus de pouvoir évaluer le parenchyme pulmonaire et la plèvre, elle peut être utilisée pour étudier les mouvements du diaphragme. Chez l'adulte, différentes applications cliniques de l'échographie diaphragmatique ont été décrites pour le diagnostic d'une dysfonction ou d'une atrophie diaphragmatique [20, 212-214], et pour la prédiction du succès du sevrage ventilatoire [21, 215]. La fonction diaphragmatique évaluée par échographie semble être corrélée au PTP_{ES} [216], au PTP_{DIA} [217] et l'AE_{DI} [218]. Dans ces travaux, deux analyses ont été décrites pour évaluer la fonction diaphragmatique. La première s'intéresse à l'intensité de l'excursion cranio-caudale diaphragmatique à chaque cycle respiratoire [21, 212]. La seconde est basée sur la variation d'épaisseur du diaphragme au niveau de la zone d'apposition au cours de la respiration [213, 217, 219].

Chez l'enfant, les travaux dans ce domaine sont plus limités, mais cette technique est néanmoins faisable pour évaluer la fonction diaphragmatique [220-222]. Récemment, Lee *et al.* ont décrit l'intérêt de l'échographie pour évaluer l'atrophie diaphragmatique et son impact sur le succès d'extubation dans une cohorte de 31 enfants ventilés [223].

Bien que cette technique soit très prometteuse, l'échographie se heurte à un certain nombre de limitations, comme la variabilité inter-observateur ou le manque de valeurs de référence chez l'enfant ventilé [224]. Ensuite, contrairement à la mesure de l'épaisseur du diaphragme, son excursion est plus difficilement interprétable dès lors que le patient est sous VM puisqu'il est impossible de distinguer la part active effectuée par le patient de la part passive secondaire à la pression de ventilation [216, 225].

Le tableau 2 résume les principaux outils d'évaluation du travail respiratoire dans l'insuffisance respiratoire aiguë de l'enfant.

Tableau 2 : Outils d'évaluation du travail respiratoire utilisables dans l'insuffisance respiratoire aiguë de l'enfant.

	Mesure	**Avantages**	**Limites**
Noninvasifs			
Paramètres cliniques	FR, V_T, Temps respiratoires, *etc.*	Utilisables facilement	Facteurs confondants (sédation, ventilation mécanique, *etc.*)
Pléthysmographie	Distribution de la ventilation pulmonaire	Utilisable en continu et en VNI	Pléthysmographie optoélectronique non commercialisée
Calorimétrie Indirecte	VO_2	Temps de mesure court (<30mn) Permet d'autres mesures (DER)	Non utilisable si FiO_2 > 60%, fuites ou VNI Manque de valeurs de référence
Tomographie par impédance électrique	Distribution de la ventilation pulmonaire	Utilisable en continu et en VNI	Difficultés d'interprétation
Echographie diaphragmatique	Epaisseur et incursion diaphragmatique	Disponible au chevet	Requiert une bonne expertise Manque de valeurs de référence
Invasifs			
P_{ES}, P_{GAS} et dérivés	P_{ES}, P_{GAS}, P_{DI}, WOB, PTP_{DI} et PTP_{ES}	Réalisable quel que soit l'âge Méthode de référence	Requiert du personnel formé et du matériel spécifique
EMG diaphragmatique	AE_{DI}	Disponible en continu Peut être intégré à la NAVA	Manque de valeurs de référence Ne reflète pas l'efficacité ventilatoire
Stimulation magnétique des nerfs phréniques	P_{DI} ou Pression endotrachéale	Réalisable quel que soit l'âge	Mesure discontinue

DER : Dépenses Energétiques de Repos ; AE_{DI} : *Electrical Activity of the Diaphragm* ; EMG : Electromyogramme ; FR : Fréquence Respiratoire ; NAVA : *Neurally Adjusted Ventilatory Assist* ; P_{ES} : Pression Œsophagienne ; P_{GAS} : Pression Gastrique ; P_{DI} : Pression Transdiaphragmatique ; PTP_{DI} : Produit Pression-Temps transdiaphragmatique ; PTP_{ES} : Produit Pression-Temps œsophagien ; VO_2 : Consommation en Oxygène ; V_T : Volume Courant ; VNI : Ventilation NonInvasive ; WOB : *Work of Breathing*.

PROBLEMATIQUE DE TRAVAIL

La défaillance respiratoire est un phénomène particulièrement fréquent chez l'enfant et elle est responsable de la plupart des admissions en réanimation. Or, la population pédiatrique est marquée par une grande hétérogénéité en termes d'âge, de maturation pulmonaire et de pathologie respiratoire, ce qui impose une approche plus individualisée de la prise en charge ventilatoire en situation aiguë.

L'évaluation du travail respiratoire est capitale pour optimiser la prise en charge thérapeutique aux différentes étapes de la maladie pour d'un côté garantir l'efficacité de la ventilation mécanique et de l'autre en limiter les complications. Face aux limites de l'évaluation clinique, plusieurs outils utilisables au chevet du patient ont été développés pour apprécier plus objectivement le travail respiratoire. Pour autant dans ce domaine, il existe un manque de données pédiatriques qui a été souligné par la dernière conférence de consensus sur la prise en charge du SDRA [226]. La place de ces outils n'a été que peu étudiée en situation aigue, et en particulier chez l'enfant en VM. Les valeurs normales sont manquantes et le type de patient susceptible de bénéficier de chacun de ces outils n'est pas clairement déterminé.

PRINCIPAL OBJECTIF DE LA THESE

Le principal objectif de la thèse est d'évaluer l'intérêt diagnostique et thérapeutique de la mesure du travail respiratoire dans l'insuffisance respiratoire aiguë hypercapnique de l'enfant.

DEMARCHE SCIENTIFIQUE ET CONDUITE DE LA THESE

La thèse repose sur 4 études principales réalisées entre 2015 et 2017.

1. Mortamet G, Nardi N, Poirier N, Essouri S, Fauroux B, Jouvet P, Emeriaud G. Assessment of esophageal pressure reliability to estimate pleural pressure in critically ill children. Article soumis à *Pediatric Pulmonology* en décembre 2017. Cette 1ère étude avait pour objectif de comparer la P_{PL} mesurée dans un drain thoracique à la P_{ES} chez l'enfant sous VM. Ce travail a montré que la P_{ES} n'est pas un reflet fiable de la P_{PL} pour optimiser les pressions ventilatoires, en particulier titrer la PEEP.

2. Mortamet G, Khirani S, Amaddeo A, Emeriaud G, Renolleau S, Fauroux B. Esogastric pressure measurement to assist noninvasive ventilation indication and settings in infants with hypercapnic respiratory failure. Article publié dans *Pediatric Pulmonology* en 2017. Ce 2ème travail rapporte l'intérêt de mesurer les pressions œsogastriques chez des enfants présentant une insuffisance respiratoire aigue hypercapnique complexe pour poser l'indication on non d'une VNI et optimiser ses réglages.

3. Mortamet G, Larouche A, Ducharme-Crevier L, Fléchelles O, Constantin G, Essouri S, Pellerin-Leblanc AA, Beck J, Jouvet P, Emeriaud G. Patient-ventilator asynchrony during conventional mechanical ventilation in children. Article publié dans *Annals of Intensive Care* en décembre 2017. Ce 3ème travail avait pour but de décrire les asynchronies patient-ventilateur et leur impact dans une cohorte de 52 patients. Nous avons mis en évidence que les patients passaient en moyenne 29% du temps en VM en asynchronie.

4. Mortamet G, Nardi N, Groleau V, Essouri S, Fauroux B, Jouvet P, Emeriaud G. Indirect Calorimetry as a diagnostic tool to assess work of breathing during weaning from mechanical ventilation in children. Article soumis à *Pediatric Pulmonology* en décembre 2017. Dans cette 4ème et dernière étude, nous avons mesuré 3 aspects de la fonction respiratoire lors d'une épreuve de sevrage ventilatoire : la P_{ES} (mesure des pressions

générées), l'AE_{DI} (reflet de la commande) et la VO_2. Nous avons montré que le test en ventilation spontanée était accompagné d'une augmentation du travail respiratoire tel qu'évalué par la P_{ES} et l'$AE_{DI,}$ mais que cette épreuve n'était pas associée à une augmentation de la VO_2.

A ces travaux s'ajoutent 2 publications annexes dans la même thématique :

- Annexe 1 : Mortamet G, Proulx F, Crulli B, Savy N, Jouvet P, Emeriaud G. Diaphragm Electrical Activity monitoring as a breakpoint in the management of a tetraplegic child. Crit Care 2017;21(1):116.
- Annexe 2 : Griffon L, Amaddeo A, Mortamet G, Barnerias C, Abadie V, Olmo J, de Sanctis L, Renolleau S, Fauroux B. Sleep study as a diagnostic tool for unexplained respiratory failure in infants hospitalized in the PICU. J Crit Care 2017;42:317-323.

RÉSULTATS ET DISCUSSION DES ÉTUDES

ETUDE 1 : IS IT POSSIBLE TO HAVE A RELIABLE INDICATOR TO MEASURE TRANSPULMONARY PRESSURE IN CHILDREN?

Hypothèse de travail

Conceptuellement, la P_{TP} permet d'évaluer précisément l'influence respective de la cage thoracique et des poumons dans la mécanique respiratoire. Dans le calcul de la P_{TP} ($P_{TP}=P_{AW}-P_{PL}$), la P_{PL} est estimée par la P_{ES}. Mais il existe plusieurs éléments confondants à prendre en compte dans cette estimation, comme le poids du médiastin [133, 134] ou la position du patient [136], ce qui explique que certains auteurs suggèrent l'ajout d'un facteur correctif [135, 137-140]. *A fortiori* chez l'enfant, la validité de cette estimation, et par conséquent l'utilisation de la P_{TP}, pourraient être limitées par l'hétérogénéité de la population en termes d'âge, de poids ou de pathologies. D'autant plus qu'aucune étude sur ce sujet n'a été conduite chez l'enfant, contrairement à chez l'adulte.

Dans notre travail, nous avions voulu valider l'estimation de la P_{PL} par la P_{ES} en comparant la P_{ES} mesurée par une sonde spécifique (Gaeltec) à la mesure directe de la P_{PL} dans des drains thoraciques. En parallèle, nous voulions mesurer la P_{ES} dans la sonde gastrique préalablement positionnée dans l'œsophage afin de voir si cette technique simple permettaient de s'affranchir de la pose d'une sonde de mesure spécifique.

Méthodes utilisées

Chez des patients intubés, ventilés et sédatés, nous avons mesuré simultanément 3 paramètres :

- La P_{PL} était mesurée via une ligne de pression connectée à une aiguille directement introduite dans le drain thoracique, et ce au plus près possible du patient. Le drain était clampé pour les mesures. Dans l'idée de décoller légèrement le drain de la paroi pleurale, et de le déboucher d'éventuelles sécrétions, 1 ml d'air était systématiquement introduit avant les mesures de pression.

- La P_{ES} était mesurée à l'aide d'une sonde spécifique à transducteurs de pressions (sonde Gaeltec). Cette sonde, de diamètre 2.1 mm, était introduite par le nez. Sa position était d'abord estimée par la distance nez/oreille/xiphoïde puis vérifiée par la présence d'oscillations cardiaques sur le tracé de pression. Dans notre travail, la manœuvre de Baydur [103] (qui consiste à créer une pression négative à l'occlusion inspiratoire) n'a pu être effectuée car nous ne disposions pas de valve d'occlusion. De même, la manœuvre qui consiste à exercer une forte pression sur le thorax pour mesurer le delta de P_{ES} n'a pu être réalisée étant donné que la quasi-totalité des patients venaient de subir une chirurgie cardiaque.
- La P_{ES} était mesurée dans la sonde gastrique après l'avoir mobilisé dans l'œsophage selon la distance évaluée sur la dernière radiographie thoracique disponible. Avant la mesure, une purge de 5 ml d'air était effectuée afin de la déboucher d'éventuelles sécrétions ou dépôts d'alimentation.

Ces 3 signaux étaient convertis, stockés et analysés par un banc de mesure (NeuroVent XIII, Neurovent research Inc, Toronto, Canada). Les données fournies étaient ensuite exportées sous forme de fichiers Excel (Microsoft Excel, Microsoft Corporation, Redmond, WA).

Au préalable, une calibration des capteurs de pression était effectuée selon les recommandations du fabricant.

Article

Does esophageal pressure monitoring reliably permit to estimate transpulmonary pressure in children?

Running title: Esophageal pressure measurement in children

Guillaume Mortamet[1,2,3,4], MD, Nicolas Nardi[1,2,4], MD, Nancy Poirier[2,5], MD, Sandrine Essouri[2,6], MD, PhD, Brigitte Fauroux[2,3,4,7], MD, PhD, Philippe Jouvet[1,2], MD, PhD, Guillaume Emeriaud[1,2], MD, PhD

[1]Pediatric Intensive Care Unit, CHU Sainte-Justine, Montreal (QC), Canada
[2]Université de Montréal, Montréal (QC), Canada
[3]Université de Paris-Est, Créteil, France
[4]Unité INSERM U955, Créteil, France
[5]Department of Cardiac Surgery, CHU Sainte-Justine, Montreal (QC), Canada
[6]Department of Pediatrics, CHU Sainte-Justine, Montreal (QC), Canada
[7]Pediatric Noninvasive Ventilation and Sleep Unit, Hôpital Necker, Paris, France

Corresponding author
Dr Guillaume Mortamet
Pediatric Intensive Care Unit, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, Montreal, Québec, Canada
Email:

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Authors' contribution:

GM, NP, PJ, BF and GE designed the study. GM, NN, SE and GE obtained and analyzed the data from Esophageal and Pleural Pressures. GM and NN wrote the manuscript, which was reviewed, edited, and approved by all authors.

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Abstract

Background - This study aims to determine whether Transpulmonary Pressure can be measured in children using Esophageal Pressure as a surrogate of Pleural Pressure (P_{PL}). To reach this goal, we wanted to validate the reliability of two Esophageal Pressure recording methods compared to direct P_{PL} measurement in situ.

Methods - This is a prospective study. Mechanically ventilated children were included if they had at least one chest tube. P_{PL} was directly measured into the existing chest tube. Esophageal Pressure was measured by two methods: a catheter mounted pressure transducer system ($P_{ES\text{-}REF}$) and the preexisting nasogastric feeding tube pulled out in order to be located in the mid third of the esophagus ($P_{ES\text{-}FT}$).

Results - Twelve patients (median age 3 months, (IQR: 1-4)) were enrolled. For each method, the 2 measurements conducted with the same method were concordant. In the Bland-Altman test, the limits of agreement were wide, larger than +/- 10 cmH_2O for all between-method comparisons.

Conclusion - Prior to consider its use in clinical practice, in particular for the titration of the ventilatory support, it is essential to conduct more research in order to validate the measurement technique of Esophageal Pressure and confirm that it can accurately reflect the P_{PL}.

Introduction

The measurement of Transpulmonary Pressure (P_{TP}), i.e. the difference between alveolar pressure and pleural pressure (P_{PL}), is the best conceptual step to monitor the effective pressure transmitted to the lung itself (1). Because P_{PL} is difficult to measure directly in the clinical setting, several physiological studies suggested that Esophageal Pressure (P_{ES}) could be used as a surrogate of P_{PL} in adults, while airway pressure is measured in the ventilator circuit (2-5).

More recently, a few studies performed in adults demonstrated a potential benefit of P_{ES} monitoring in ventilator management. This measurement has been shown to be helpful in optimizing patient-ventilator interaction (6), for the titration of Positive End-Expiratory Pressure (PEEP) (7), and in the weaning management (8). In children, although the literature in this field is scarce, the recent international consensus conference on pediatric acute respiratory distress syndrome PALICC (9) stresses that P_{ES} measurement could be useful, but there is no evidence regarding the method used to measure and interpret this value.

Despite data demonstrating usefulness of P_{ES} measurement in critically ill patients, several confounding factors that can affect the accuracy of P_{ES} have been highlighted in the literature (10-13). To compensate for these factors, some authors apply a correction factor to estimate P_{PL} (10, 12, 14), but the use and the level of the correction factor is still controversial (15, 16). In addition, due to the pediatric population heterogeneity in terms of age, weight, and conditions modifying the chest wall activity, we hypothesize that P_{ES} varies importantly from a child to another. In this specific population, the way to measure P_{ES} as a tool to estimate P_{PL} needs first to be validated before exploring its potential utility in future clinical studies.

This study aims to determine whether P_{TP} can be measured in children using P_{ES} as a surrogate of P_{PL}. To reach this goal, we wanted to validate the reliability of two P_{ES} recording methods compared to direct P_{PL} measurement in situ.

Methods

This is a prospective study, conducted in the Pediatric Intensive Care Unit (PICU) of CHU Sainte-Justine, a university affiliated pediatric hospital, from November 2016 to September 2017. The study protocol was approved by the Ethics Committee of CHU Sainte-Justine and written informed consent was obtained from the parents or legal tutor.

Patients

Consecutive children aged between 7 days and 18-years old admitted to the PICU, intubated and mechanically ventilated were eligible in the study. The screening was performed by a research assistant every working day. Eligible patients were included if they required invasive ventilation for more than 4 hours according to the prescription of the attending physician and they had at least one chest tube. Patients were excluded if they had one of the following criteria: (i) contraindications to the placement of a new nasogastric tube, (ii) hemodynamic instability, (iii) severe respiratory instability, (iv) persistent pleural effusion or pneumothorax despite the chest-tube, (v) bronchopleural fistula, (vi) recent thoracic hemorrhage, (vii) delayed sternal closure at the time of study, (viii) Significant pericardial effusion and (ix) if a limitation of life support treatments was discussed or decided. Detailed inclusion and exclusion criteria are given in Supplementary Material.

Protocol and data analysis

After verification of the permeability of the chest tube and absence of active air leak or pleural effusion, P_{PL} was directly measured by a pressure transducer connected through a needle inserted into the existing chest tube, as close as possible to the patient, and the tube was occluded distally to the needle. The tube was flushed by 0.5-1 ml of air in order to eliminate potential secretions before the measurements, which were obtained after equilibrium.

Esophageal Pressure was measured by 2 methods. The reference esophageal pressure ($P_{ES\text{-}REF}$) was measured using a 2.1-mm external diameter catheter mounted pressure transducer system with two integrated pressure transducers, mounted 5 and 25 cm from the distal tip (Gaeltec®, Dunvegan, Isle of Skye, the UK) inserted nasally. The placement of the P_{ES} transducer was first estimated with the distance from the bridge of the patient's nose, to the ear lobe and down to the xiphisternum. The appropriate position was checked by the presence of (i) cardiac oscillations on the P_{ES} trace, (ii) a positive P_{GAS} value during a gentle pressure on the abdomen and (iii) a negative deflection during inspiration in spontaneous breathing patients. The occlusion test during a chest compression, as suggested by Baydur *et al.*, was not performed in case of recent cardiac surgery (17).

The second esophageal pressure method tested was based on the feeding tube ($P_{ES\text{-}FT}$). After the removal of the Gaeltec probe, the preexisting nasogastric feeding tube was pulled out in order to

be located in the mid third of the esophagus, according to the feeding tube position checked on the last available chest X-ray. The nasogastric tube was connected to a pressure transducer and gently flushed with 5 ml of air before the pressure measurement. After measurements, the nasogastric tube was repositioned in gastric position.

All the signals were simultaneously recorded using an acquisition system (NeuroVent Monitor XIII), run on a PC computer and displayed and analyzed using a specific software (NeuroVent Research, Toronto, Canada). P_{PL}, $P_{ES\text{-}REF}$, and $P_{ES\text{-}FT}$ were calculated as the mean value at end-expiration during two stable periods of 10 seconds each, with no intervention or artifacts.

The patients were supine, with the head of bed elevated to 30 degrees, as a routine matter, and sedated according to the attending physician instructions. During the entire study, "usual" modifications of settings (*e.g.* adaptation of assist level, changes in FiO_2 or Positive End Expiratory Pressure, etc.) considered by the clinical team were permitted and recorded. Demographic data and patient characteristics, including age, gender, weight, time of measurements, admission diagnostic and comorbidities, Pediatric Risk of Mortality (PRISM) and Pediatric Logistic Organ Dysfunction (PELOD) scores were collected.

Statistical analysis

Data were expressed as median values (with interquartiles, IQR) for continuous variables, and number and/or frequency (%) for categorical data. Pearson's determination coefficient (R^2) was used to evaluate the relationship between the values measured during the 2 periods with a given method. A correlation was considered as poor, moderate, good and excellent if R^2 was lower than 0.5, between 0.5 and 0.75, between 0.75 and 0.9 and greater than 0.9, respectively (18). Comparisons between P_{PL} and $P_{ES\text{-}REF}$, P_{PL} and $P_{ES\text{-}FT,}$ and $P_{ES\text{-}FTL}$ and $P_{ES\text{-}REF}$ followed the method proposed by Bland and Altman, with the calculation of the mean difference and its agreement limit of 95% (19). All p-values are two-tailed and considered significant if $p < 0.05$. Statistical analyses were performed using SPSS 24.0 (SPSS, Inc, Chicago, IL).

Results

Study population

Twelve patients reached inclusion criteria and were enrolled. The exploitable signals were finally available in 11 patients, who were included in the analysis. Median age of patients included was

3 (IQR: 1-4) months and 8 were males. They were studied 2 (1-3) days after PICU admission. The patient characteristics are presented in Table 1. All the patients were deeply sedated or paralyzed and they therefore had no significant spontaneous breathing activity detected according to the P_{ES} or P_{PL} tracing at the time of the study.

Esophageal and pleural pressures analysis

Respectively, for 2 and 1 patient, $P_{ES\text{-}REF}$ and $P_{ES\text{-}FT}$ were impossible to analyze due to technical problems. Median $P_{ES\text{-}REF}$ and $P_{ES\text{-}FT}$ were 2.3 (1.8-5.4) and 7.9 (2.8-9.5) cmH_2O, respectively. The median P_{PL} was 4.0 (0.6-9.6) cmH_2O. For each method, the 2 measurements conducted with the same method were concordant. The determination coefficient was 0.69, 0.95 and 0.83 for P_{PL}, P_{ES} and $P_{ES\text{-}FT}$, respectively (Figure 1).

As shown in Figure 2, the mean difference was 0.8 (-5.7-10) cmH_2O between P_{PL} and $P_{ES\text{-}REF}$, -3.4 (-8.5-2.7) cmH_2O between P_{PL} and $P_{ES\text{-}FT}$, and 0.9 (-0.1-5) cmH_2O between $P_{ES\text{-}FT}$ and $P_{ES\text{-}REF}$. The limits of agreement were wide, larger than +/- 10 cmH_2O for all between-method comparisons.

Discussion

In this study, the observed differences between P_{ES} and P_{PL} are much greater than the value considered as clinically reasonable, especially to guide mechanical ventilation and PEEP titration. Indeed, a cutoff error value < 2 cmH_2O was a priori defined as acceptable to set PEEP, by a panel of pediatric intensive care physicians during the preparation of this study. In our cohort, the difference between P_{PL} and $P_{ES\text{-}REF}$ was > 5 cmH_2O in most patients. We therefore failed to confirm that P_{PL} could be reliably estimated based on the P_{ES}. While P_{ES} measurement is classically based on a specific esophageal probe or balloon, we also tested if a simpler and less invasive method could provide results as accurate as with the Gaeltec probe. As most critically ill children have a nasogastric tube, we attempted to use this device for P_{ES} measurement after appropriate positioning in the mid third esophagus. Again, we failed to show that this simpler method was as reliable with the $P_{ES\text{-}REF}$.

For decades, P_{ES} has been considered a good surrogate of P_{PL}. This assumption is based on the notion that pressure in the adjacent pleura is transmitted to the esophagus (20, 21). Importantly,

P_{ES} measurement is one of the reference method to assess the work of breathing during spontaneous or assisted ventilation. P_{ES} swings and the area under the P_{ES} curve during inspiration (*i.e.* Esophageal Pressure-Time Product) accurately provide a very good reflection of the amount of respiratory muscle work, with several relevant clinical applications in children (22, 23). Those P_{ES}-derived data are not based on the absolute P_{ES} values, but rather on the relative variations. However, the accuracy of the estimation of P_{PL} by P_{ES} when absolute values are used (e.g. for titration of the ventilatory support) is much more complex and questionable, in particular because the zeroing of the method is not simple. Despite P_{ES} changes have been shown to be similar to P_{PL} changes, absolute values of P_{ES} tend in general to be less negative than P_{PL} both in adults (5) and preterm babies (24). Several confounding factors could affect the accuracy of P_{ES} measurement. The position of the balloon in the esophagus (3), the presence of asymmetrical lung disease (4), the amount of air or liquid to inflate the balloon and its compliance (20) or the posture of the patient (25) are factors well-known to impact the estimation of P_{PL} by P_{ES}. Indeed, the pressure vector generated by the weight of the mediastinal structures has a significant influence on P_{ES} (12, 13). To compensate for these artifacts, some authors suggest a correction factor that should be applied to interpret P_{ES} measurement, but the use and the level of the correction factor is still controversial (12, 16, 26). Regardless of uncertainties about the interpretation of P_{ES}, all these artifacts have been considered to be within a clinically acceptable range in adults and P_{TP} measurement is now advocated by some experts to identify the optimal ventilator settings in clinical practice (7, 27). Indeed, P_{TP}, obtained from absolute values of P_{ES}, is the pressure variable that is the most closely correlated with lung strain and the risk of ventilation induced lung injury (28). The monitoring of P_{TP} is therefore attractive to manage mechanical ventilation. As suggested in the study by Talmor *et al*., oxygenation and compliance was improved when PEEP titration was guided by P_{TP} in patients with Acute Respiratory Distress Syndrome (7). Although P_{ES} and P_{TP} could have a greater potential interest to guide mechanical ventilation in children given the heterogeneity of the pediatric population, the literature is scarce in this field (29). We could legitimately hypothesize that some of the confounding factors described in adults could have a great importance in the pediatric population given their anatomical and physiological specificities. The between-method differences were huge in our study, and clearly beyond an acceptable error when titrating the ventilation. For example, pediatric intensivist would not accept an error of 5 cmH_2O when adjusting the level of

PEEP. A systematic bias was not the main issue, but rather the wide limits of agreement. A compensation by a given corrective factor, as sometimes done in adults, would therefore not help.

Of course, our study may be limited by technical issues, but our results confirm that the monitoring of absolute values of P_{ES} as a surrogate of P_{PL} is greatly complex in children. As opposed to the esophageal balloon technique, the use of a catheter-mounted miniature pressure transducer like the Gaeltec probe allows to eliminate the effect of the esophageal wall and the impact of the mechanical properties of the balloon on measurements, as well as the influence of the volume of air injected in the balloon. However, the measurement of absolute values of P_{ES} has been previously questioned by Stell *et al.* (30) and Beda *et al.* (31). In addition, in our study, the protocol to check the position of the Gaeltec probe was limited by the clinical context (no airway occlusion nor chest compression). However, we consider that the impact of such limitation is small as compared to the great difference we observed between P_{PL} and P_{ES}.
The direct measurement of P_{PL} *in situ* is also technically difficult, although some data have been reported in adults (32, 33) and newborns (24, 29). Indeed, the chest tube position, residual volume of pleural effusion, and/or potential secretions occluding the drain could lead to inaccurate measurements.
Other limits of our study include the single-center design, the relatively small sample size, and the heterogeneity of the patients.

Conclusion

The recent international consensus conference on pediatric acute respiratory distress syndrome PALICC (9) stresses that P_{ES} measurement could be useful, mostly based on data extrapolated from adults, although more research and validation in this field were advocated. Our results suggest that prior to consider its use in clinical practice, in particular for the titration of the ventilatory support, it is essential to conduct more research in order to validate the measurement technique of P_{ES} and confirm that it can accurately reflect the P_{PL}. This is far from what we observed in our series. Awaiting those future studies, we argue for prudence, and suggest not using P_{ES} for the titration of ventilation support in children outside a research context.

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Figure legends

Fig. 1 Relationships between the 2 measurements for each method: P_{PL} (panel A), $P_{ES\text{-}REF}$ (panel B) and $P_{ES\text{-}FT}$ (panel C)

Fig. 2 Bland-Altman plot to assess concordance between P_{PL} and $P_{ES\text{-}REF}$ (panel A), between P_{PL} and $P_{ES\text{-}FT}$ (panel B) and between $P_{ES\text{-}FT}$ and $P_{ES\text{-}REF}$ (panel C)

Table 1: Characteristics of the population (n=12)

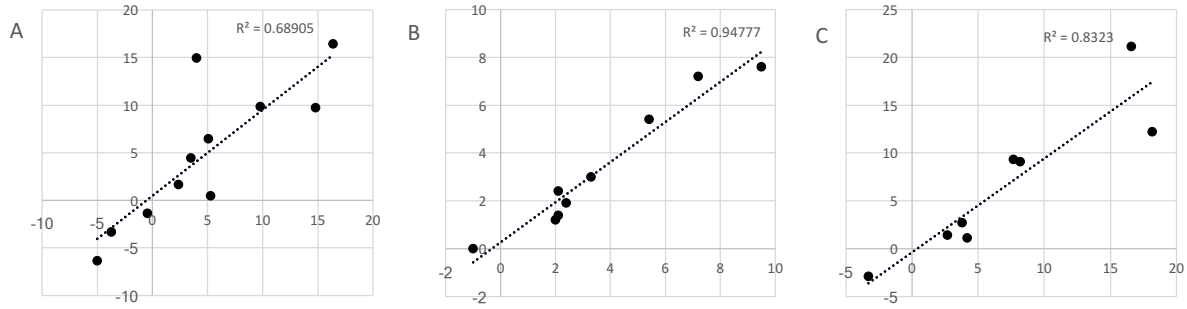
	Total n=12
Age (m)	3 (IQR 1-4)
Weight (kg)	4.9 (3.8-5.4)
Male, n (%)	8 (67)
Days between admission and inclusion	2 (1-3)
Days between MV initiation and inclusion	2 (1-3)
Main reasons for PICU admission, n	
Cardiac postoperative admission	11
Respiratory failure	1
Chronic condition	
Congenital cardiac disease, n (%)	10 (83)
Clinical status	
PIM-2 score	7.5 (4.4-7.5)
PELOD score	11 (2-14)
pH	7.39 (7.35-7.44)
$PaCO_2$, mmHg	43.8 (39.6-47.1)
HCO_{3-}, mmHg	25.7 (23.9-29.2)
Lactates, mmol/L	1.2 (1.0-1.5)
Hemoglobin, g/L	11.4 (10.4-14.1)
Hemodynamic status	
Pulse, min^{-1}	144 (125-155)
Mean Arterial Pressure, mmHg	63 (60-71)
Vasoactive drugs, n (%)	4 (33%)
Ventilator modes and settings	
PRVC, n (%) PC, n (%) VC, n (%) NAVA, n (%)	3 (25) 2 (17) 3 (25) 1 (8)

PSV, n (%)	2 (17)
Positive End-expiratory Pressure, cmH_2O	5 (5-6)
FiO_2	0.40 (0.38-0.53)
Respiratory status	
SpO_2, %	100 (98-100)
Set RR, min^{-1}	28 (24-36)
V_T, ml/kg	6.8 (6.5-7.1)
Outcome	
Duration of mechanical ventilation, d	3 (1-5)
Length of stay in PICU, d	5 (3-10)

MV: Mechanical Ventilation; NAVA: Neurally Adjusted Ventilatory Assist; PC: Pressure Control; PSV: Pressure Support Ventilation; VCRP: Pressure-Regulated Volume Control; VC: Volume Control

Data are expressed as median (25-75 interquartile range) or n (%).

Fig. 1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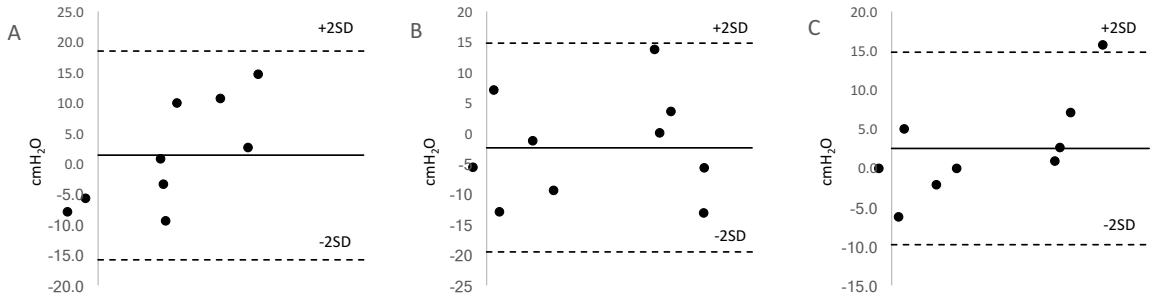
B
R² = 0.94777
C
R² = 0.8323

Fig. 2


A
+2SD
-2SD
cmH2O
B
+2SD
-2SD
cmH2O
C
+2SD
-2SD
cmH2O

Matériel supplémentaire

Subject selection:

Eligibility

All intubated and mechanically ventilated children >7 days and <18 years old, hospitalized in the pediatric intensive care unit will be eligible.

Inclusion criteria:

- Children requiring invasive ventilation for more than 4 hours according to the prescription of the attending physician;
- With at least one chest tube.

Exclusion criteria

- Contraindications to the placement of a new nasogastric tube (*e.g.* trauma or recent surgery in cervical, esophageal, or nasopharyngeal regions, severe coagulation disorder);
- Hemodynamic instability requiring milrinone ≥ 0.5µg/kg/min, dopamine ≥ 5µg/kg/min, epinephrine ≥ 0.03µg/kg/min, norepinephrine ≥ 0.03µg/kg/min, or dobutamine ≥ 5µg/kg/min;
- Severe respiratory instability defined as a severe respiratory failure requiring FiO2 > 60%, or PaCO2 > 80 mmHg on blood gas in the last hour;
- Persistent pleural effusion or pneumothorax despite the chest-tube (>10cc/h);
- Bronchopleural fistula;
- Recent (<12 hours) thoracic hemorrhage;
- Delayed sternal closure at the time of study;
- Significant pericardial effusion;
- Absence of parental or tutor consent;
- Patient for whom a limitation of life support treatments is discussed or decided.

Discussion

Dans ce travail, la différence entre les valeurs observées de P_{PL} et de P_{ES} est nettement supérieure à l'erreur qu'on pourrait considérer comme acceptable. En effet, nous avions préalablement déterminé après sondage d'un échantillon de réanimateurs pédiatres qu'une erreur de ± 2 cmH_2O dans la valeur estimée de P_{PL} pouvait être considérée comme raisonnable en pratique clinique, même si cette valeur reste discutable [107]. Dans l'idée de titrer la PEEP en fonction de la valeur de P_{TP}, comme l'a fait Talmor *et al.* [130], une erreur de ± 2 cmH_2O dans la valeur estimée de P_{PL} équivaudrait à un réglage de PEEP à ± 2 cmH_2O. Or, au vu de nos résultats, l'utilisation de la P_{ES} dans le calcul de la P_{TP} chez l'enfant ne peut être validée pour le moment. D'autres travaux sont donc nécessaires avant d'utiliser cette mesure pour guider les réglages de la VM, notamment la titration de la PEEP en pratique clinique.

Nos résultats alimentent la controverse existante chez l'adulte quant à la validité de l'estimation de la P_{PL} par la P_{ES} [130, 227]. Dans cette population, un facteur correctif variant jusqu'à +5 cmH_2O a été proposé. Or, une marge d'erreur de +5 cmH_2O est très discutable quand on utilise cette donnée pour titrer la PEEP. Les bénéfices potentiels d'une PEEP adaptée sur l'amélioration de l'oxygénation doivent être comparés aux risques de barotraumatisme et aux conséquences hémodynamiques liées à cette modification. On pourrait même se poser la question si le bénéfice de titrer la PEEP selon la P_{TP}, observé par Talmor *et al.* [130], est bien lié à la mesure de P_{TP}, ou simplement secondaire au fait que la PEEP soit augmentée de +5 cm H2O en moyenne dans le bras « titration selon pression trans-pulmonaire ».

Il est vrai que notre étude présente plusieurs limites. D'une part la sonde Gaeltec n'est pas fiable pour mesurer des valeurs absolues de P_{ES} et d'autre part la mesure de la P_{PL} dans les drains peut être faussée par un éventuel épanchement résiduel. Néanmoins, le fait que les mesures soient reproductibles pour chaque méthode démontre leur relative fiabilité.

ETUDE 2 : ESOGASTRIC PRESSURE MEASUREMENT TO ASSIST NONINVASIVE VENTILATION INDICATION AND SETTINGS IN INFANTS WITH HYPERCAPNIC RESPIRATORY FAILURE

Hypothèse de travail

La VNI est classiquement indiquée et ses réglages ajustés au regard d'éléments cliniques et gazométriques [33]. Mais ces paramètres cliniques ont certaines limites. Entre autres, ils manquent d'objectivité dans l'évaluation du travail respiratoire et ils ne permettent pas de juger de la synchronisation patient-ventilateur. La mesure des pressions œsogastriques est un outil qui s'est avéré utile pour optimiser les réglages de la VNI et/ou améliorer la synchronisation patient-ventilateur dans un certain nombre de pathologies chez l'enfant [9, 99, 107]. Dans le cadre des pathologies respiratoires complexes, les paramètres cliniques sont encore plus difficilement interprétables et la mesure des pressions œsogastriques pourrait être un outil potentiellement pertinent pour guider la pratique clinique.

Dans ce contexte, l'objectif de ce travail était de démontrer l'intérêt de la mesure des pressions œsogastriques chez des patients présentant une insuffisance respiratoire hypercapnique dans le cadre d'une maladie respiratoire complexe.

Méthodes utilisées

Dans ce travail, la mesure des pressions œsogastriques était faite en routine au lit du malade chez des nourrissons de moins de 2 ans pour qui l'indication et les réglages de la VNI était difficilement évaluable selon les paramètres cliniques habituels. L'évaluation physiologique était effectuée dans différentes conditions : en ventilation spontanée, en VNI avec les réglages initiaux, et en VNI après ajustement des réglages. Les pressions œsogastriques étaient mesurées grâce à une sonde œsophagienne spécifique (sonde Gaeltec) introduite par le nez. Au préalable, une calibration des capteurs de pression à 0 et +10 cmH_2O était effectuée. La sonde Gaeltec (Gaeltec, Dunvegan, Isle of Skye, UK), de diamètre externe 2.1 mm, est munie de 2 capteurs de pressions œsophagien et gastrique à 0 et 20 cm de l'extrémité distale. La bonne position du capteur gastrique était vérifiée en appliquant une légère pression abdominale, qui montrait une

fluctuation de la P_{GAS} sans augmentation de P_{ES}. La position du capteur œsophagien était quant à lui vérifié en observant une déflection négative à l'occlusion lors de la phase inspiratoire, comme recommandé par Baydur et al [103]. Le signal était converti (MP100 ; Biopac systems, Goleta, CA, USA) échantillonné à 200 Hz, et stocké pour une analyse ultérieure à l'aide du logiciel AcqKnowledge (Biopac systems, Goleta, CA, USA).

Article

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WILEY PEDIATRIC PULMONOLOGY

Esogastric pressure measurement to assist noninvasive ventilation indication and settings in infants with hypercapnic respiratory failure: A pilot study

Guillaume Mortamet MD[1,2,3] | Sonia Khirani PhD[4,5] | Alessandro Amaddeo MD[2,5,6] | Guillaume Emeriaud MD, PhD[3,7] | Sylvain Renolleau MD, PhD[1,6] | Brigitte Fauroux MD, PhD[2,5,6]

[1] AP-HP, Hôpital Necker, Pediatric Intensive Care Unit, Paris, France

[2] INSERM U 955, Equipe 13, 8 rue du Général Sarrail, Créteil, France

[3] Université de Montréal, Bld Edouard Montpetit, Montréal, Canada

[4] ASV Santé, Gennevilliers, France

[5] AP-HP, Hôpital Necker, Pediatric Noninvasive Ventilation and Sleep Unit, Paris, France

[6] Université de Paris Descartes, Paris, France

[7] CHU Sainte-Justine Pediatric Intensive Care Unit, CHU Sainte-Justine, Montreal, Canada

Correspondence
Prof. Brigitte Fauroux, Pediatric Noninvasive Ventilation and Sleep Unit, AP-HP, Hôpital Necke rance.
Email:

Fundi
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Abstract

OBJECTIVE: Noninvasive ventilation (NIV) in usually set on clinical parameters. The aim of the study was to assess the value of esophageal (P_{ES}) and gastric pressure (P_{GAS}) measurements for the indication and optimal settings of NIV in infants with hypercapnic respiratory failure in whom the efficacy of NIV was uncertain on clinical noninvasive parameters.

DESIGN: A retrospective study.

PATIENT-SUBJECT SELECTION: P_{ES} and P_{GAS} measurements were performed in seven infants <2 years old admitted in the Pediatric Intensive Care Unit for an acute or acute-on-chronic hypercapnic respiratory failure.

METHODOLOGY: P_{ES} swing and esophageal pressure time product (PTP_{ES}) during spontaneous breathing, NIV set on clinical parameters (NIVclin) and on P_{ES} (NIVphys) were compared. According to the P_{ES} measurements, NIV was continued if NIV was associated with an at least 20% reduction of the P_{ES} swing and PTP_{ES} and not initiated or withdrawn in the other case.

RESULTS: In all seven patients, the P_{ES} and P_{GAS} measurements were informative and led to the decision to initiate NIV in one patient or continue NIV with different settings in three patients. In the three other patients, NIV was not initiated in one patient and withdrawn in the two last patients because of a lack of improvement in P_{ES} swing and PTP_{ES}.

CONCLUSIONS: P_{ES} and P_{GAS} measurements may be useful for the indication and optimal setting of NIV in a selected group of infants with hypercapnic respiratory failure.

KEYWORDS
esogastric pressure, infants, noninvasive ventilation, respiratory failure

1 | INTRODUCTION

Respiratory failure is the leading cause of hospital admissions in the pediatric intensive care unit (PICU) and is associated with significant morbidity and mortality.[1,2] Mechanical ventilation, preferentially delivered by a noninvasive route, represents nowadays the first-line treatment for acute hypercapnic respiratory failure.[3,4] In adult patients, noninvasive ventilation (NIV) is associated with a reduction in endotracheal complications and mortality.[5] NIV, which comprises both continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV) ventilation, is increasingly used in the PICU, but its expanding use contrasts with the relative limited number of studies in this field.[6–9]

NIV is classically set on a variable association of clinical parameters such as gas exchange, respiratory and heart rates, and the comfort of the patient.[3,5,8,10] However, this "clinical" setting provides no objective data regarding patient's respiratory effort and patient-ventilator synchronization. Esophageal pressure (P_{ES}) and

This work was performed in Hôpital Necker, Pediatric Intensive Care Unit, Paris, France

The study was previously presented as a poster by Guillaume Mortamet at the World Congress on Pediatric Critical and Intensive Care in Toronto, June 2016.

gastric pressure (P_{GAS}) have been shown to be useful to optimize the ventilatory management in adult [11–13] and pediatric patients [10,14–20] with acute respiratory failure by optimizing the decrease in respiratory effort and/or improving the patient-ventilator synchrony. P_{ES} measurements allowed determining the optimal CPAP level in infants admitted to the PICU for an acute bronchiolitis,[16] respiratory distress syndrome,[14,21] severe upper airway obstruction,[17] or the optimal NIPPV ventilation settings in pediatric patients with acute moderate hypercapnic respiratory failure.[10] However, there is a lack of studies evaluating the usefulness of P_{ES} monitoring to initiate, continue or withdraw NIV in infants with hypercapnic respiratory failure.

The aim of the present study was to assess the value of P_{ES} measurements for determining the potential benefit with regard to the reduction of respiratory effort as well as the optimal settings of NIV in infants with hypercapnic respiratory failure admitted to the PICU in whom the efficacy of NIV was uncertain on clinical parameters.

2 | MATERIALS AND METHODS

2.1 | Patients

This retrospective study was performed between January 2014 and June 2015 in the PICU of Necker tertiary university hospital. The PICU comprises 12 beds and admits a mean of 500 children between the age of 1 month and 18 years for acute medical conditions per year with patients <2 years of age representing approximately 50% of the total number of patients. All the consecutive patients <2 years old admitted in the PICU for an acute or acute-on-chronic hypercapnic respiratory failure were eligible and they were included if P_{ES} and P_{GAS} measurements were performed during their stay in PICU. P_{ES} monitoring is not performed on a routine basis in our unit. However, due to the presence of a respiratory physiology unit in our hospital, P_{ES} and P_{GAS} monitoring are performed as "routine care" for patients with hypercapnic respiratory failure and an unpredictable response to NIV on clinical noninvasive parameters such as clinical history and diagnosis, gas exchange, breathing pattern (respiratory rate, symptoms of respiratory distress), and heart rate. The study was approved by the local institutional board (October 12th 2015).

2.2 | NIV equipment

NIV was delivered via a standard ICU ventilator (Evita Infinity v500, Dräger, Lübeck, Germany) or a home ventilator (Trilogy 100, Philips-Respironics, Murrysville, CA) and an individually adapted industrial nasal mask (Soft Baby, Air Liquide Medical Systems, Antony, France, or Nonny pediatric mask, AG Industries, St Louis, MO). In patients already supported by NIV before the study period, NIV was delivered by the ICU or home ventilator.

2.3 | Measurements

P_{ES} and P_{GAS} were measured using a 2.1-mm external diameter catheter mounted pressure transducer system with two integrated pressure transducers, mounted 1 and 21 cm from the distal tip (Gaeltec, Dunvegan, Isle of Skye, UK), inserted pernasally after local anesthesia (Xylocaine, AstraZeneca, Rueil Malmaison, France). Appropriate placement of the pressure transducer was checked as recommended.[22] Transdiaphragmatic pressure (Pdi) was obtained by subtracting on line the P_{ES} signal from the P_{GAS} signal. All the signals were recorded at 200 Hz using an analogical/numeric acquisition system (MP100, BIOPAC Systems, Inc, Goleta, CA), run on a PC computer and displayed using AcqKnowledge software.

2.4 | Protocol

The study was performed during quiet breathing without sedation, preferentially during natural sleep during a daytime nap, which occurred in most infants approximately 1 h after the midday feeding. The presence of the parents was encouraged, in order to decrease the child's anxiety.

After the insertion of the esogastric catheter, the study started with a 5 min-period of spontaneous breathing during which the patient breathed spontaneously with oxygen if necessary to maintain a pulse oximetry (SpO_2) > 92%. After the spontaneous breathing period, if the patient was previously on NIV, NIV was started with the settings determined by the attending physician according to the clinical parameters (NIVclin). This NIVclin had been adjusted on the following criteria: decrease of symptoms such as retractions and/or stridor, a SpO_2 > 95% in room air, the normalization or greatest decrease in heart and respiratory rate, and the best comfort, as assessed by the infant falling asleep or accepting the NIV. After at least 10 min of stable breathing pattern, respiratory parameters with P_{ES} and P_{GAS} were recorded during 5 min. Afterwards, a stepwise protocol was used for NIVphys: the first setting was CPAP, which was progressively increased from 6 cmH_2O to the level associated with the normalization or the greatest reduction in P_{ES} and P_{GAS}.[17] After at least 10 min of stable breathing pattern with the optimal CPAP pressure, respiratory parameters with P_{ES} and P_{GAS} were recorded during 5 min. After this CPAP session, NIPPV ventilation was started with an expiratory pressure corresponding to the optimal CPAP level and an initial inspiratory pressure of 6 cmH_2O, which was progressively increased to the inspiratory pressure associated with the normalization or the greatest reduction in P_{ES} and P_{GAS}.[23] Inspiratory and expiratory triggers were set to optimize patient-ventilator synchronization. After at least 10 min with a stable breathing pattern with the optimal NIPPV settings, respiratory parameters with P_{ES} and P_{GAS} were again recorded during 5 min. During the study period, care was taken to avoid non-intentional leaks, by maintaining the nasal interface firmly on the face and by the use of a pacifier when possible.

Pulse oximetry (SpO_2) was continuously monitored during the study period and venous partial pressure of carbon dioxide ($PvCO_2$) was measured during spontaneous breathing and after at least 24 h with the optimal NIV settings.

The breathing pattern and different P_{ES} and P_{GAS} parameters during spontaneous breathing, NIVclin and NIVphys were compared for each individual patient.

According to the esogastric measurements, NIV (either CPAP or NIPPV) was continued if NIV was associated with an at least 20% reduction of the P_{ES} swing and esophageal pressure time product (PTP_{ES}) (these patients were considered as "NIV responders"), and not initiated or withdrawn in the other case (these patients were considered as "NIV non-responders").

2.5 | Data analysis

After elimination of the cycles with artifacts, such as coughing or esophageal spasms, at least 10 stable breath cycles were used for subsequent analysis. The respiratory rate, P_{ES}, P_{GAS}, and P_{DI} swings were measured. The P_{GAS} swing during expiration was also measured to assess expiratory muscles activity. On the P_{GAS} trace, we measured the decrease from the maximal end-expiratory level to the minimal value.[24] The presence of a positive P_{GAS} swing during expiration was considered as abnormal.[25]

The diaphragmatic and esophageal pressure-time products per breath (PTP_{DI}/breath and PTP_{ES}/breath) were obtained by measuring the area under the P_{DI} and P_{ES} signal between the onset of inspiration, defined as the point at which the deflection occurred on the P_{ES} trace, and the end of inspiration defined as the peak of P_{DI}. Both PTP_{DI} and PTP_{ES} were also expressed per minute by multiplying the pressure-time products per breath by the respiratory rate (PTP_{DI}/min and PTP_{ES}/min).[26] Data for the total group were given as mean ± standard deviation.

3 | RESULTS

3.1 | Characteristics of the population

All the seven patients had a severe underlying condition with an associated lung disease (Table 1). Mean age of the patients was 7.3 ± 3.0 months and the mean weight was 5.6 ± 1.4 kg. Three patients were born before 37 weeks of gestation. All the patients had severe hypercapnic respiratory failure with a mean baseline $PvCO_2$ of 73 ± 7 mmHg (pH 7.32 ± 0.04 and HCO_3- 29.2 ± 4.6 mmol/L) and a high respiratory rate (mean 57 ± 19 breaths/min). Four patients were treated with CPAP at the time of the study (patients #3, #4, #5, and #7), one patient was treated with NIPPV (patient #1) while the two other patients (patients #2 and #6) had no NIV. Fraction of inspired oxygen was <0.4 in all the patients.

3.2 | Breathing pattern, gas exchange, and respiratory effort during spontaneous breathing and NIV

All the patients tolerated the esogastric catheter and exploitable recordings could be obtained in all patients excepted in patient #1 in whom the P_{GAS} was not reliable. The study protocol lasted about 1.5–2 h and all the different NIV (CPAP and NIPPV) settings were tested in every patient.

3.2.1 | Group 1: NIV responders

Respiratory effort improved with NIV as compared to spontaneous breathing in four patients (patients #1, #2, #3, #4). Indeed, NIV was associated with an at least 20% decrease in P_{ES} and P_{DI} swings, PTP_{ES}/min and PTP_{DI}/min (Table 2). This improvement in respiratory effort was greater with NIVphys than with NIVclin (Fig. 1). A decrease in $PvCO_2$ was also observed after 24 h of NIVphys (Table 2).

A positive $P_{GAS\ EXP}$ swing was observed during spontaneous breathing in three patients (patients #2, #3, and #4). This expiratory abdominal activity disappeared in patients #2 and #4 with CPAP but persisted in patient #3 with every NIV setting. Figure 2 shows the decrease in P_{ES}, $P_{GAS\ EXP}$, and P_{DI} swings with a CPAP set at 8 cmH_2O in patient #2.

The optimal NIV mode was CPAP in two patients (patients #2 and #3) but with a different CPAP pressure in patient #3 (Table 2). In the two other patients (patients #1 and #4), the optimal mode was NIPPV but also with different pressure settings. NIV was continued in these four patients. No complications due to NIV, such as skin disorder or barotrauma, were recorded.

During follow-up, patient #1 progressed to an autoimmune scleroderma with multi-organ involvement. The poor evolution of the disease led to the decision of withdrawal of life-sustaining therapy at the age of 24 months and NIV was stopped at this time. The patient died at the age of 30 months. NIV was continued during the sleep periods only in patient #2. This patient was successfully discharged home on long-term CPAP. NIV was stopped at the age of 18 months due to clinical improvement. Patient #3 could be weaned from NIV at the age of 12 months. Finally, NIV was continued in patient #4 after PICU discharge.

3.2.2 | Group 2: NIV non-responders

NIV was not associated with a decrease in respiratory effort in patients #5, #6, and #7 (Fig. 1 and Table 3). Even if NIVphys was associated with a slightly greater decrease in respiratory effort as compared to NIVclin, this was not significantly different from the values observed during spontaneous breathing. Respiratory rate did not decrease with any NIV setting. Finally, NIV was associated with the appearance of a moderate expiratory abdominal activity in patient #6, and a worsening in patient #7.

Subsequently, NIV was not initiated in patient #6 who was naïve to NIV and was withdrawn in the two other patients (patients #5 and #7). Patient #5 died 3 months later because of an acute respiratory infection. Patient #6 was discharged home with oxygen therapy and died 10 months later because of a septic shock. Patient #7's clinical conditions worsened despite corticoid bolus due to major pulmonary hypoplasia, and he died 15 days later.

4 | DISCUSSION

This physiological study shows that P_{ES} and P_{GAS} measurements are informative and clinically useful for the decision of NIV initiation or withdrawal in a selected group of critically ill infants with hypercapnic

TABLE 1 Characteristics of the patients

Patient no.	Sex	Main diagnosis	Associated diagnosis	At PICU admission			Total length of PICU stay (days)[a]
				Chronological age (months)	Weight (kg)	Naive to NIV	
1	F	Undetermined muscular dystrophy	Chronic respiratory failure	13	7.0	No	190
2	M	Omphalocele	Pulmonary hypoplasia	5	6.5	Yes	49
3	F	Severe combined immunodeficiency	Bronchiolitis obliterans	5	6.3	No	134
4	M	IPEX syndrome	Interstitial lung disease	8	5.8	No	15
5	M	Di-George syndrome	Bronchopulmonary dysplasia	6	4.2	No	90
6	F	Tricho-hepato-enteric syndrome	Aspecific broncho-pneumopathy	9	6.1	Yes	45
7	M	Bronchopulmonary dysplasia	Prematurity (27 GA)	5	3.2	No	150

NIV: noninvasive ventilation; PICU: pediatric intensive care unit; GA: gestational age; F: female; M: male
[a]Including stay prior to physiological measurements.

respiratory failure due to complex underlying disorders. Moreover, these measurements were valuable to optimize NIV settings in case of NIV efficacy.

In routine practice, NIV is set on clinical noninvasive parameters such as a decrease in respiratory rate, heart rate and an improvement in tidal volume and gas exchange. This approach has proven its clinical relevance. Indeed, in stable children with cystic fibrosis, the decrease in P_{ES} and P_{DI} and their corresponding PTP was comparable during a NIV setting based on clinical parameters and esogastric measurements.[27] Clinical parameters have also shown to have a predictive value. The decreases in respiratory rate and $PvCO_2$ after 2 h of NIV predicted NIV success in infants and children with acute respiratory failure.[4] Other studies showed that the level of FiO_2 and $PaCO_2$ on admission and their evolution within the 5 h after starting NIV were

TABLE 2 Breathing pattern, gas exchange, and work of breathing during spontaneous breathing (SB) and NIV support in patients in whom indication of NIV was confirmed by P_{ES} measurement

	Patient #1			Patient #2			Patient #3			Patient #4		
	SB	NIVclin	NIVphys	SB	NIVclin	NIVphys	SB	NIVclin	NIVphys	SB	NIVclin	NIVphys
NIV settings												
PS/PEEP (cmH_2O)		10/4	12/4		ND	0/8		0/12	0/7		0/6	14/4
Breathing pattern and gas exchange												
RR (breath/min)	42	48	44	66	ND	60	42	42	52	65	65	45
$PvCO_2$ (mmHg)	84		64	75		64	69		58	64		58
Respiratory muscle output												
Swing P_{ES} (cmH_2O)	19	16	14	28	ND	9	71	62	50	13	9	3
Swing P_{GAS} (cmH_2O)	NA	NA	NA	6	ND	2	4	2	2	3	6	2
Swing P_{GAS} exp (cmH_2O)	NA	NA	NA	6	ND	0.4	34	28	32	4	0	0
Swing P_{DI} (cmH_2O)	NA	NA	NA	28	ND	10	41	34	21	12	6	3
PTP_{ES}/breath ($cmH_2O.s$)	6	5	4	5	ND	2	22	16	15	3	2	0
PTP_{DI}/breath ($cmH_2O.s$)	NA	NA	NA	5	ND	2	10	7	2	2	1	1
PTP_{ES}/min ($cmH_2O.s$/min)	245	237	182	348	ND	111	938	653	765	189	142	12
PTP_{DI}/min ($cmH_2O.s$/min)	NA	NA	NA	318	ND	133	400	294	105	147	49	28

NIV, noninvasive ventilation; SB, spontaneous breathing; NIVclin, noninvasive ventilation settings according to the clinical parameters; NIVphys, noninvasive ventilation settings according to the physiological measurements; PS, pressure support; PEEP, positive end-expiratory pressure; RR, respiratory rate; $PvCO_2$, venous partial pressure of carbon dioxide; PTP_{ES}, esophageal pressure-time product; PTP_{DI}, transdiaphragmatic pressure-time product; NA, data not available; ND, not done.

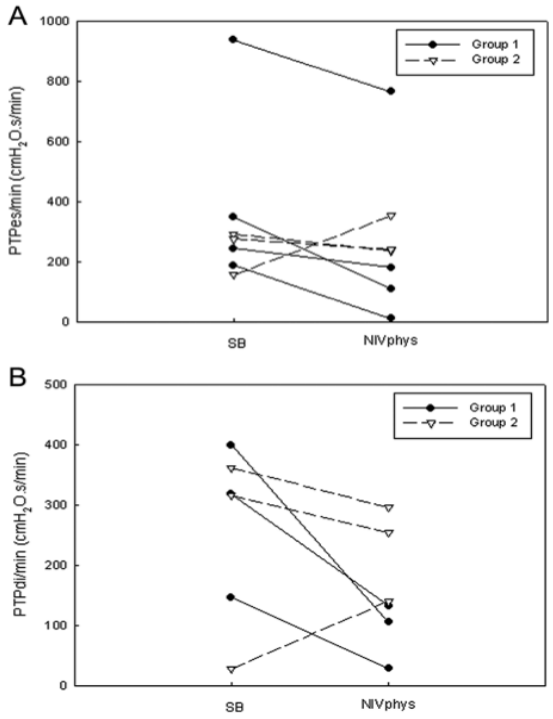

FIGURE 1 Individual values of esophageal (PTP_{ES}) and diaphragmatic (PTP_{DI}) pressure-time products per minute during spontaneous breathing (SB) and noninvasive ventilation set on the recording of esophageal and gastric pressures (NIVphys)

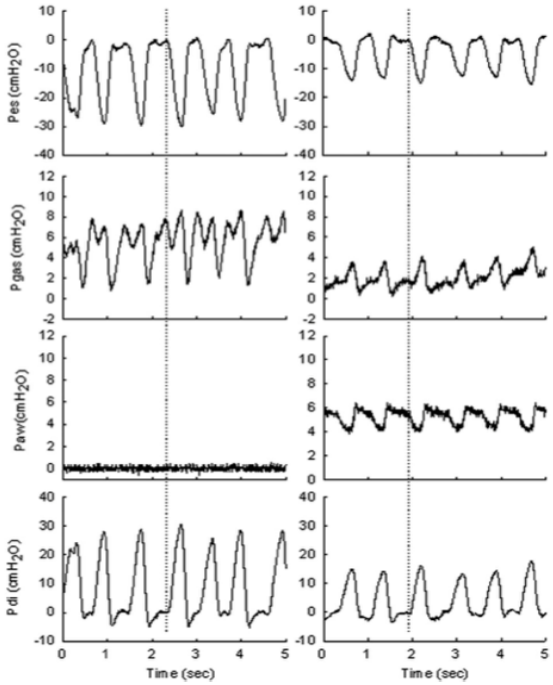

FIGURE 2 Tracings of patient #4 showing the increases in esophageal pressure (P_{ES}) and transdiaphragmatic pressure (P_{DI}) swings during spontaneous breathing. During the physiological setting of NIV, note the important reduction in the P_{ES} and P_{DI} swings and in the breathing rate. P_{GAS}: gastric pressure; P_{AW}: airway pressure

predictive for NIV success or failure in children with acute respiratory failure.[4,28]

The patients in the present study had heterogeneous complex underlying disorders with persistent hypercapnia despite optimal medical therapy and NIV in five patients. The esogastric recording was motivated by the uncertainty of a benefit of NIV and a doubt concerning optimal settings. Our study confirmed the appropriateness of this physiological approach. Indeed, the measurements of markers of respiratory effort, together with clinical assessment, show here to be a reliable tool to confirm or not the indication of NIV, the choice of the optimal mode (CPAP or NIPPV), as well as the optimal settings of NIV. In this group of young infants with hypercapnic respiratory failure, NIV improved breathing pattern and gas exchange, and reduced respiratory effort in four patients. These findings are in agreement with previous studies in pediatric patients showing that CPAP or NIPPV is able to unload the respiratory muscles during severe upper airway obstruction, acute hypercapnic respiratory insufficiency, or acute viral bronchiolitis.[10,14–17]

The lack of efficacy of NIV in Group 2 may be explained by a different physiopathology of respiratory failure with less benefit of an unloading of the respiratory muscles by NIV. Work of breathing and $PvCO_2$ may be increased in these patients but NIV is less efficient or even deleterious in these patients.[29,30] The extreme lung hypoplasia in patient #7 may also explain the lack of benefit of NIV.

Our findings regarding the expiratory P_{GAS} recording are interesting. Indeed, four out of seven patients had an expiratory abdominal activity in spontaneous breathing, which tended to disappear with NIV in two patients, while it appeared or worsened during NIV in two other patients. Expiratory abdominal activity may be due to hyperinflation induced by CPAP overtitration, as shown in healthy awake subjects in whom high levels of CPAP induced an expiratory abdominal activity,[31–33] or may be the consequence of persistent airway obstruction during spontaneous breathing and CPAP.[17,34] We observed this latter condition in a recent study in infants with severe airway obstruction in whom the optimal setting of CPAP was closely related to the decrease or disappearance of the expiratory P_{GAS} swings.[17] This observation underlines the usefulness of P_{GAS} monitoring when possible, which can provide some information regarding the physiopathology of the disease. The two infants with the highest P_{GAS} (#3 and 7) appeared to have primarily obstructive lung disease while the other patients appeared to have primarily restrictive disease.

The present study had several limitations. First, the study was performed at a single center and the number of patients is very

TABLE 3 Breathing pattern, gas exchange, and work of breathing during spontaneous breathing (SB) and NIV support in patients with no indication of NIV proved by P_{ES} measurement

	Patient #5			Patient #6			Patient #7		
	SB	NIVclin	NIVphys	SB	NIVclin	NIVphys	SB	NIVclin	NIVphys
NIV settings									
PS/PEEP (cmH_2O)		0/4	0/10		ND	0/8		0/6	0/10
Breathing pattern and gas exchange									
RR (breath/min)	32	45	46	88	ND	78	64	76	74
$PvCO_2$ (mmHg)	78		64	66		58	72		NA
Respiratory muscle output									
Swing P_{ES} (cmH_2O)	17	19	15	24	ND	20	14	45	27
Swing P_{GAS} (cmH_2O)	4	6	4	2	ND	2	6	2	1
Swing P_{GAS} exp (cmH_2O)	0	0	0	0	ND	2	13	26	17
Swing P_{DI} (cmH_2O)	21	23	18	25	ND	19	11	18	13
PTP_{ES}/breath ($cmH_2O.s$)	9	7	5	3	ND	3	2	10	5
PTP_{DI}/breath ($cmH_2O.s$)	11	8	6	4	ND	3	0	3	2
PTP_{ES}/min ($cmH_2O.s/min$)	293	295	237	276	ND	242	157	796	353
PTP_{DI}/min ($cmH_2O.s/min$)	362	342	296	315	ND	254	28	246	141

NIV, noninvasive ventilation; SB, spontaneous breathing; NIVclin, noninvasive ventilation settings according to the clinical parameters; NIVphys, noninvasive ventilation settings according to the physiological measurements; PS, pressure support; PEEP, positive end-expiratory pressure; RR, respiratory rate; $PvCO_2$, venous partial pressure of carbon dioxide; PTP_{ES}, esophageal pressure-time product; PTP_{DI}, transdiaphragmatic pressure-time product; NA, data not available; ND, not done.

small. However, these patients represent a very selected and small but important and complex population of a polyvalent PICU. Second, we did not measure airflow and thus could not accurately report the onset and end of inspiration. This was explained by the increase in dead space generated by the equipment during spontaneous breathing and the occurrence of high air flows during NIV, which does not allow the measurement of patient's own airflow. Finally, our study is a short-term physiological study performed during daytime. It is difficult to perform measurements of the work of breathing in infants during sleep or during longer periods because these measurements are relatively invasive. Despite these limitations, these findings are important for clinicians, by showing that P_{ES} and P_{GAS} measurements can be helpful for the indication and optimal setting of NIV in critically ill infants with complex respiratory failure.

5 | CONCLUSION

This pilot study showed that a physiological approach, based on the P_{ES} and P_{GAS} measurements, may be useful to initiate or withdraw NIV and to optimize its settings in a specific population of selected critically ill children with complex respiratory failure.

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CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

GM, SK, AA, and BF studied the patients, analyzed the data, and drafted the manuscript. GM, GE, SR, and BF revised the manuscript. BF was the main author and designed the study. All the authors participated to the writing of the manuscript and approved the final version.

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Discussion

Ce travail montre l'intérêt de la mesure des pressions œsogastriques pour guider la prise en charge ventilatoire de patients ayant une insuffisance respiratoire hypercapnique sévère et complexe. Dans ce travail, nous avons montré que ces mesures physiologiques contribuent à la décision d'initiation ou d'arrêt de la VNI, ainsi qu'au réglage optimal d'une éventuelle VNI.

Nos patients avaient une hypercapnie persistante malgré un traitement médical optimal. Il s'agissait de patients présentant des pathologies respiratoires pour la plupart entrant dans le cadre d'une maladie multisystémique, et dont la physiopathologie n'était pas parfaitement définie. Pour ces patients, l'enregistrement des pressions œsogastriques avait initialement été motivé par l'incertitude sur le bénéfice de la VNI ainsi que par un doute concernant les paramètres optimaux. Nos résultats confirment la pertinence de cette approche physiologique.

Bien entendu les mesures physiologiques effectuées ne peuvent être considérées seules en pratique clinique, et elles doivent impérativement être corrélées à l'histoire de la maladie, aux paramètres cliniques et gazométriques pour guider la prise en charge thérapeutique. Néanmoins, l'impact de ces mesures n'est pas négligeable, en particulier pour confirmer l'absence d'indication de VNI pour des patients ayant une maladie sous-jacente sévère.

ETUDE 3 : PATIENT-VENTILATOR ASYNCHRONY DURING CONVENTIONAL MECHANICAL VENTILATION IN CHILDREN

Hypothèse de travail

Dans la population adulte, les asynchronies sont fréquentes et sont associées à une augmentation de la durée de ventilation, des troubles du sommeil, une durée de séjour plus longue et une mortalité plus élevée [55, 56, 228]. Les asynchronies semblent être courantes chez les enfants en VM mais ni leurs facteurs de risque ni leur impact clinique ne sont connus [57, 115, 229-231]. Comme l'enfant a une FR plus élevée, un débit respiratoire et un V_T plus faible comparé à l'adulte, la synchronisation patient-ventilateur est plus difficile à atteindre [232].

Dans le sens où elle reflète la commande respiratoire, l'AE_{DI} permet d'identifier précisément l'effort du patient, à la fois sur un plan qualitatif (temps inspiratoires et expiratoires) et quantitatif (intensité de l'activité électrique). Elle rend donc plus facile la détection des différents types d'asynchronies patient-ventilateur.

Dans ce travail, nous décrivons les asynchronies patient-ventilateur chez les enfants intubés ventilés. Nous avons cherché à identifier les facteurs de risque qui y sont associés ainsi que l'impact des asynchronies sur la morbidité et la mortalité. Nous avons également cherché à valider une méthode automatique de détection des asynchronies.

Méthodes utilisées

L'AE_{DI} était enregistrée via une sonde NAVA (NAVA catheter, Maquet, Solna, Sweden), positionnée selon les recommandations du fabricant comme décrit précédemment [57] et connectée au respirateur Servo-I. Les tracés d'AE_{DI} et les courbes de pression, débit et volume fournies par le respirateur étaient convertis et envoyés au banc d'acquisition (NeuroVent XIII, Neurovent research Inc, Toronto, Canada). Plusieurs types d'asynchronies pouvaient être identifiées : les autodéclenchements (*auto-triggering*), les doubles-déclenchements (*double-triggering*), les efforts inefficaces (*wasted efforts*) et les asynchronies dites de délai (prématuré ou retardé, au temps inspiratoire ou expiratoire).

Les asynchronies patient-ventilateur étaient alors détectées de 2 manières :

- une méthode manuelle, qui consistait à comparer le tracé AE_{DI} obtenu avec la courbe de

pression fournie par le ventilateur, et ce pour chaque cycle ventilatoire, pendant une période de 5 minutes exempt d'artéfacts. Avec cette méthode, les temps inspiratoires et expiratoires étaient obtenus de manière automatique avec une validation et/ou un ajustement manuel si nécessaire.

- une méthode automatique standardisée, réalisée pour la même période que l'analyse manuelle, qui permet une détection automatique des temps inspiratoires et expiratoires basé sur un seuil prédéterminé d'amplitude d'AE_{DI} (0.5 µV), comme précédemment décrit par Sinderby et al [233].

Article

Patient-ventilator asynchrony during conventional mechanical ventilation in children: a prospective study

Guillaume Mortamet[1,2,3], MD, , Alexandrine Larouche[1,3], MD, , Laurence Ducharme-Crevier[1,3], MD, PhD, , Olivier Fléchelles[4], MD, , Gabrielle Constantin[1,3], MD, , Sandrine Essouri[3,5], MD, PhD, , Amélie-Ann Pellerin-Leblanc[6], MD, , Jennifer Beck[7,8,9], PhD, , Christer Sinderby[7,9,10], PhD, , Philippe Jouvet[1,3], MD, PhD, , Guillaume Emeriaud[1,3], MD, PhD,

[1] Pediatric Intensive Care Unit, CHU Sainte-Justine, Montreal, Quebec, Canada
[2] INSERM U 955, Equipe 13, Créteil, France
[3] CHU Sainte-Justine Research Center, Université de Montréal, Montréal, Canada
[4] Pediatric Intensive Care Unit, CHU Fort-de-France, France
[5] Department of Pediatrics, CHU Sainte-Justine, Montreal, Quebec, Canada
[6] Queen's University, Kingston, Canada
[7] Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada
[8] Department of Pediatrics, University of Toronto, Canada
[9] Institute for Biomedical Engineering and Science Technology (iBEST) at Ryerson University and St-Michael's Hospital
[10] Department of Medicine, University of Toronto, Canada

This work was performed in CHU Sainte-Justine, Pediatric Intensive Care Unit, Montreal, Quebec, Canada.

Corresponding author
Dr Guillaume Emeriaud
Pediatric Intensive Care Unit, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, Montreal, Quebec, Canada
Tel: +1(514)345 4931 - 3316
Email:

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Ethics Approval
The study protocol was approved by the local Ethics committee (CHU Sainte-Justine, Montreal, QC, Canada).

Consent for publication

Written informed consent was obtained from the parents or legal tutor.

Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

GM, LDC, OF, GC, SE and AAPL have no conflict of interest to declare. GE's research program is supported by a scholarship award by the Fonds de Recherche du Québec – Santé. He is currently leading a feasibility study in neonatal ventilation which is financially supported by Maquet Critical Care. PJ is supported by a scholarship award by the Fonds de Recherche du Québec – Santé, Ministry of Health and Sainte-Justine Hospital. he was a consultant for Sage Therapeutic inc, was invited to a congress by Medunik Inc and Covidien. JB and CS have made inventions related to neural control of mechanical ventilation that are patented. The patents are assigned to the academic institution(s) where inventions were made. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to JB and CS through royalties. JB and CS each own 50% of Neurovent Research Inc (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care. Neurovent research Inc. provided a recording device. Maquet Critical Care provided the ventilator and catheters for the study. This company was not involved in the result analysis and reporting.

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Authors' contributions:

AL, GE, OF, SE and PJ designed the study. GM, AL, GC, AAPL, OF, JB, CS and GE performed the analysis, carried out the chart review and data collection. GM, JB, CS, PJ and GE wrote the manuscript, which was reviewed, edited, and approved by all authors.

As the corresponding author, GE has full access to all the data in the study and has final responsibility for the decision to submit for publication.

Abstract

Background - We aimed (i) to describe the characteristics of Patient-Ventilator Asynchrony in a population of critically ill children, (ii) to describe the risk factors associated with Patient-Ventilator Asynchrony, and (iii) to evaluate the association between Patient-Ventilator Asynchrony and ventilator free days at day 28.

Methods – In this single-center prospective study, consecutive children admitted to the PICU and mechanically ventilated for at least 24 hr were included. Patient-Ventilator Asynchrony was analyzed by comparing the ventilator pressure curve and the Electrical Activity of the diaphragm (Edi) signal with (i) a manual analysis and (ii) using a standardized fully automated method.

Results – Fifty-two patients (median age 6 months) were included in the analysis. Eighteen patients had a very low ventilatory drive (*i.e.* peak Edi < 2μV on average), which prevented the calculation of Patient-Ventilator Asynchrony. Children spent 27% (interquartile 22-39%) of the time in conflict with the ventilator. Cycling-off errors and trigger delays contributed to most of this asynchronous time. The automatic algorithm provided a NeuroSync index of 45%, confirming the high prevalence of asynchrony. No association between the severity of asynchrony and ventilator free days at day 28 or any other clinical secondary outcomes was observed, but the proportion of children with good synchrony was very low.

Conclusion - Patient-ventilator interaction is poor in children supported by conventional ventilation, with a high frequency of depressed ventilatory drive and a large proportion of time spent in asynchrony. The clinical benefit of strategies to improve patient-ventilator interactions should be evaluated in pediatric critical care.

Key words: mechanical ventilation; patient-ventilator asynchrony; patient-ventilator interaction; diaphragm function; pediatric intensive care unit; pediatrics.

Background

Mechanical ventilation is commonly used in Pediatric Intensive Care Units (PICUs) [1]. Maintaining the patient's own spontaneous breathing effort during ventilation is key. Assisted (or patient-triggered) ventilation may improve ventilation perfusion matching and forestall the development of ventilator-induced diaphragmatic dysfunction [2]. As the patient contributes in the ventilation, good interaction between the patient and the ventilator is essential. Children have higher respiratory rates, smaller tidal volumes and weaker inspiratory efforts when compared with adults, patient-ventilator synchrony is difficult to achieve in pediatric patients [3]. These can lead to a mismatch between the patient and the ventilator, defined as a patient-ventilator asynchrony (PVA). PVA includes the inspiratory and expiratory timing errors (delays between patient demand and ventilator response), efforts undetected by the ventilator, assist delivered in absence of patient demand, and double-triggering (two rapidly successive assists following a single effort).

In critically ill adults, asynchronies occur frequently and are associated with prolonged ventilator support, sleep disorders, poor lung aeration, longer stay in the intensive care unit and mortality [4-9]. Pediatric data in this field are lacking. PVA seems frequent in PICU [10-13], but little is known about the risk factors of PVA and the association with patient outcome.

In the present study, we aimed to describe the characteristics of PVA in critically ill children, to identify risk factors associated with PVA, and to evaluate the association between PVA and patient outcome.

Methods

This prospective observational study was conducted in the PICU of CHU Sainte-Justine, a university affiliated pediatric hospital, from August 2010 to October 2012. The study protocol was approved by the Ethics committee of CHU Sainte-Justine. Written informed consent was obtained from the parents or legal tutor.

Patients

Consecutive children aged between 7 days and 18-years-old admitted to the PICU and mechanically ventilated for at least 24 hours were eligible. The screening was performed daily by a research assistant. Eligible patients reached inclusion criteria when presence of spontaneous breathing was evidenced by clinical respiratory efforts or by a respiratory rate sustainably higher than the set ventilator rate. Patients were excluded if they had one of the following criteria: chronic respiratory insufficiency with prior ventilatory support longer than 1 month, tracheostomy, neuromuscular disease, contraindications to nasogastric tube exchange (i.e., local trauma, recent local surgery, or severe coagulation disorder), suspected bilateral diaphragm paralysis, immediate post-cardiac surgery period, expected death in the next 24 hours, or a limitation of life support treatment.

No modification of the ventilator settings was done for the study. The attending physicians set the ventilator mode and settings according to the local practices. Patients were ventilated with the Evita XL (Dräger, Lubeck, Germany) or the Servo-I ventilator (Maquet, Solna, Sweden). Sedation and analgesia were decided by the treating team, and usually involved a combination of benzodiazepines and opioids. There was no local written protocol regarding the ventilator management or the sedation during the study. The ventilation support was reassessed every 1 or 2 hours

by respiratory therapists according to local practice. At the time of the study, Neurally Adjusted Ventilatory Assist (NAVA) was not routinely used in clinical practice in our unit.

Protocol

PVA was recorded at two different times during the PICU stay. We obtained a first 30-minute recording in acute phase, i.e., as soon as possible after inclusion in the study and an esophageal catheter was installed to record the electrical activity of diaphragm (Edi). The second (pre-extubation) recording was performed during 15 min in the 4 hours preceding extubation, if the Edi catheter was still in place.

Data Recording

PVA was analyzed by comparing the ventilator pressure curve and the Edi signal. Edi was recorded using a specific naso-gastric catheter (Edi catheter, Maquet, Solna, Sweden) connected to a dedicated Servo-I ventilator (Maquet, Solna, Sweden). This ventilator was used only to continuously process and record the Edi signal, the patient being ventilated with his own ventilator as before the study. The catheter was positioned according to the recommendations of the manufacturer as previously described [12, 14].

Demographic data and patient's characteristics, including age, gender, weight, time of measurements, admission diagnostic and comorbidities, Pediatric Index of Mortality (PIM) II and Pediatric Logistic Organ Dysfunction (PELOD) scores were collected. The sedation score was calculated for the 4-hour period preceding the first recording, as suggested by Randolph *et al* [15], using a score for which 1 point was given for the amount of each drug that would be equivalent to 1 hour of sedation in a nontolerant subject. The Comfort B scale was used to determine the level of comfort (comfort is better when score is lower).

Clinical outcomes

The primary outcome was the number of ventilator free days at day 28 (since intubation). Patients who died were considered having zero ventilation free day. The secondary clinical outcomes were first extubation success (no need for invasive ventilation support within 48 hours of extubation), duration of mechanical ventilation, and length of PICU stay.

PVA manual analysis

As previously described [12, 16, 17], for each recording, Edi and ventilator pressure curves were analyzed in a breath-by-breath manner over a continuous 5-minute period exempt of artifacts linked to agitation or patient care. Timings of the beginning and the end of inspiration and expiration phases on the Edi and the ventilatory pressure signals were semi-automatically identified: main timings were automatically identified, and a visual inspection was performed breath by breath, permitting to validate and/or adjust the timing cursors if necessary. All analyses were performed by two independent investigators. By comparing the ventilator and Edi timings, PVA was identified, including wasted efforts (clear effort observed on Edi with no ventilator assist), autotriggered breath (ventilator assist delivered in absence of Edi increase), double-triggering (two rapidly successive assists following a single

effort), and inspiratory trigger and cycling-off errors. As the response of the ventilator for triggering or cycling-off could be frequently either retarded or premature [12], we reported both types of asynchrony.
The main PVA variable of interest was the percentage of time spent in asynchrony, calculated from the total duration spent in each type of PVA (wasted efforts, auto-triggering, double-triggering, trigger and cycling-off errors) divided by the duration of the recording. *A priori*, we defined severe PVA when the percentage of time spent in asynchrony was superior to the 75th percentile of the entire cohort, *i.e.* the quarter of patients with the worst synchrony.

PVA automatic analysis
Asynchrony was also analyzed using a standardized automated method over the same period, to prevent inter-observer variability and to avoid observer subjectivity[18]. Inspiratory and expiratory timings were fully automatically detected on ventilator pressure and Edi signals based on pre-determined thresholds (0.5 µV for Edi amplitude). Asynchrony was quantified using the NeuroSync index, a global index considering both inspiratory and cycling off errors. A higher NeuroSync index reflects worse asynchrony, and synchrony can be considered as poor when NeuroSync index exceeds 20%[19, 20].
Sample size calculation
Based on studies conducted in adults, we expected a difference in ventilator free days of 6 days. With a group distribution of 3/1 and a type-1 error risk of 0.05, the inclusion of 56 patients was necessary to achieve a power of 80%. We planned to enroll a sample of 60 patients to take into account the attrition risk.

Statistical Analysis
Data are expressed as median values (with interquartiles, IQR) for continuous variables, and number and/or frequency (%) for categorical data. Differences for categorical variables were tested using chi-square or Fisher's exact test. Differences in continuous variables were assessed by the non-parametric Mann–Whitney test, the paired t-test, or the Wilcoxon test.
Patients with peak inspiratory Edi <2µV were *a posteriori* excluded in PVA analysis (both manual and automated) because the reality of the spontaneous activity in those patients appeared questionable, and the identification of PVA is complex. Intraclass Correlation Coefficient (ICC, two-way random model) were calculated to assess interobserver reproducibility for manual PVA analysis and to compare the results from the manual and the automatic methods. After confirmation of an excellent inter-observer agreement (ICC > 0.75), the averages of the two observer's results were calculated and used in further analysis.
The association of potential risk factors with severe PVA was studied by univariate logistic regression analysis. Non-collinear factors associated with a univariate association with $p < 0.05$ were included in a multivariate logistic regression. The relationship between PVA and clinical outcomes was described using univariate analysis.
All p values are two-tailed and considered significant if $p < 0.05$. Statistical analyses were performed using SPSS 24.0 (SPSS, Inc, Chicago, IL).

Results

Study population

During the study period, 2,090 patients were admitted in the PICU. Among the 406 eligible patients, 60 patients reached inclusion criteria and were enrolled (Figure 1). Exploitable signals were finally available in 52 patients, who were included in the analysis. Median age of eligible patients who were not included was 8 (1–48) months old, which is similar to analyzed patients (p=0.96). Twenty-two of these patients also had a second recording in the pre-extubation period. The patient characteristics are presented in Table 1. They were studied 4 (IQR: 1-10) days after PICU admission.

Eighteen patients had a very low ventilatory drive (peak Edi < 2µV on average), which prevented the calculation of PVA. As detailed in Table 1, these patients tended to be older, were affected less frequently by a respiratory disease, had a lower $PaCO_2$ and a lower Comfort score as compared to patients with higher drive.

Table 1: Characteristics of population (n=52).

	Total n=52	**Peak-Edi <2 µV n=18**	**Peak-Edi >2 µV n=34**
Age (months)	10 (2-42)	21 (1-135)	6 (2-29)
Weight (kg)	6.5 (4.3-17.4)	11 (4.8-38.4)	5.3 (4.0-12.0)
Male, n (%)	31 (60%)	11 (61%)	20 (59%)
Days between admission and inclusion	4 (1-10)	3 (1-7)	4 (1-10)
Days between MV initiation and inclusion	3 (1-7)	2 (1-6)	4 (2-7)
Main reasons for PICU admission, n (%)			
Respiratory failure	31 (60%)	5 (28%)	26 (76%) *
Including bronchiolitis	11 (21%)	1 (6%)	10 (29%)
Hemodynamic failure	3 (6%)	2 (11%)	1 (3%)
Neurologic disorder	9 (17%)	6 (33%)	3 (9%)
Metabolic disorder	2 (4%)	0 (0%)	2 (6%)
Trauma	2 (4%)	2 (11%)	0 (0%)
Post operative admission	5 (10%)	3 (17%)	2 (6%)
Chronic condition, n (%)			
Respiratory disease	8 (15%)	2 (11%)	6 (18%)
Cardiac disease	9 (17%)	3 (17%)	6 (18%)
Neurogical disease	11 (21%)	4 (22%)	7 (21%)
Immuno-oncologic disease	3 (6%)	0 (0%)	3 (9%)
Clinical status			
PIM-2 score	1.7 (0.8-4.3)	2.3 (0.9-4.5)	1.6 (0.8-4.4)

PELOD score	2 (1-1)	1 (1-11)	1 (1-11)
Set respiratory rate, min^{-1}	25 (20-35)	23 (14-38)	31 (25-42) *
Measured respiratory rate, min^{-1}	29 (20-36)	20 (15-29)	34 (28-40) *
pH	7.40 (7.35-7.42)	7.40 (7.36-7.43)	7.39 (7.34-7.43)
$PaCO_2$, mmHg	46 (42-53)	42 (38-47)	48 (45-57) *
HCO_{3-}, mmHg	28 (24-32)	27 (23-30)	30 (25-33)
PEEP, cmH_2O	5 (5-6)	5 (5-5)	5 (5-6)
FiO_2	0.35 (0.29-0.41)	0.30 (0.24-0.35)	0.35 (0.30-0.50)
Comfort score	13 (10-15)	11 (8-13)	15 (12-16) *
Score sedation	11 (6-21)	10 (1-14)	15 (6-25)
Edi Analysis			
Peak inspiratory Edi, µV	3.6 (1.2-7.6)	1.1 (0.6-1.3)	6.6 (3.8-11.5)
Tonic expiratory Edi, µV	0.7 (0.4-1.9)	0.4 (0.3-0.5)	1.1 (0.7-2.5)

Edi: Electrical activity of the Diaphragm; MV: Mechanical Ventilation; PICU: Pediatric Intensive Care Unit; PEEP: Positive End-Expiratory Pressure.

Data are expressed as median (25-75 interquartile range) or n (%).

*: significant difference between the two groups ($p<0.05$)

Magnitude of PVA

A total of 9,806 breaths were analyzed with the manual method, with a median of 168 (IQR: 123-258) breaths analyzed per recording. The interrater agreement for PVA manual analysis was excellent, with ICC > 0.85 for all PVA parameters. The total proportion of time spent in PVA was 27% (IQR: 22-39) of the time. As illustrated in Figure 2, cycling-off errors and trigger delays contributed to most of this asynchronous time, respectively 12% (IQR: 8-15) and 11% (IQR: 8-16). Auto-triggered cycles, wasted efforts and double-triggering were also highly prevalent, with 2 (IQR: 0-3), 2 (IQR: 1-10) and 1 (IQR: 0-5) events per minute, respectively. In 26 patients (76%), more than 10% of the cycles were either non-detected, double-triggered or auto-triggered.

Characteristics of patients with severe asynchrony

Nine patients were considered as severely asynchronous, with a proportion of time spent in asynchrony > 75^{th} percentile, i.e. > 39% of time (Table 2). Patients with severe asynchrony were younger (p=0.007), had more frequently a narrower and non-cuffed ETT (p=0.001 and p=0.019, respectively), and were less frequently ventilated in pressure-support ventilation (PSV, p=0.034). All but one of these patients were admitted for a respiratory failure as a first reason, and 5 of them had bronchiolitis. In the multivariate logistic regression model in which age, presence of a cuffed ETT, and PSV mode were tested, none of these variables were independently associated with severe PVA (all p>0.17).

The patients with severe asynchrony were enrolled earlier in the PICU course (2 days (1-5) *vs* 8 (2-11), p=0.054), which must be considered while looking at the relationship between PVA and length of stay or ventilation duration.

Evolution of PVA

As illustrated in Figure 3, when comparing the recordings from acute phase and pre-extubation phase, the level of PVA tended to decrease over time (p=0.01), and both period data were correlated (R^2=0.41). Peak Edi increased between the 2 phases (p=0.01).

Automatic analysis of PVA

The automatic algorithm provided a NeuroSync index of 45% (32-70%), confirming the high prevalence of asynchrony. As shown in Figure 4, a good correlation was observed between NeuroSync index and the percentage of time spent in asynchrony derived from the manual analysis, with an ICC of 0.88.

Outcome

We did not observe any association between the level of asynchrony and neither ventilator free days at day 28, nor the secondary outcomes (Table 2). This holds true with the manual classification as severe PVA or not (Table 2), as well as with the automated NeuroSync Index (correlation with ventilation duration: R2= 0.12; p=0.58). None of the patient characteristics were associated with the duration of mechanical ventilation.

Discussion

The incidence of PVA is very high during pediatric conventional ventilation. As a whole, children spend about one third of the time in conflict with their ventilator. We described an a-priori defined group with severe PVA, but marked PVA was present even in the other children, and the proportion of children which could be considered as "well synchronized" is low. Besides, an unexpected form of bad interaction was observed, with the high prevalence of low ventilatory drive.

The magnitude of PVA that we observed is in agreement with those previously described [10-12]. In a recent study conducted in a PICU, Blokpoel *et al* showed that PVA occurred in 33% of breaths [10]. These authors identified PVA using the analysis of ventilator waveforms, a method which has a low sensitivity [6]. We used the Edi signal which clearly facilitates the detection of PVA, in particular the calculation of timing errors for triggering or cycling-off [3, 12, 13, 17, 21, 22]. We were therefore able to show that most of the time spent in asynchrony results from delayed or premature reactions of the ventilator. These timing errors are important, especially when the normal inspiratory time is frequently around 400ms in this population. We hypothesize that this delay in ventilator response is the consequence of small tidal volumes and short inspiratory and expiratory times in children as compared to adults. Although considered as the classical method [12, 17, 23], the breath-by-breath manual analysis of PVA could be criticized because of its dependency on an investigator, as well as being highly time-consuming. However, our findings were supported by the good agreement between the 2 independent investigators, and by the concordance also observed between the automatically calculated NeuroSync index and the manually calculated PVA.

To date, no definition of severe PVA in children had been standardized. Some authors use the specific index described

in adults by Thille *et al* [5, 24] and others the percentage of asynchronous breaths [3, 10, 12]. In the present study, we assessed the magnitude of PVA according to the time spent in asynchrony, because it illustrates well the burden of asynchrony while taking into account different types of patient-ventilator conflict [17]. More than three-quarters of the patients had more than 10% of wasted efforts, double-triggered, or autotriggered breaths, which accounts only for a part of the asynchrony index by Thille *et al* in adults [5]. Similarly, only 2 patients had a NeuroSync index <20%, which corresponds to an adequate synchrony in adults [19, 20]. The non-severe group can therefore not be assumed as "well synchronized". In agreement with Blokpoel *et al*, who observed that only 20% children had an acceptable level of PVA [10], our study highlights that PVA is a major problem in PICU and concerns more than three quarters of the children, as opposed to one quarter of adult patients.

Younger age, smaller tracheal tubes, and absence of a cuff on the tracheal tube were associated with severe PVA, and PSV mode was more frequent in patients with less severe PVA. The smaller size and the absence of cuff may suggest that increased leaks could have played a role, as suggested by Blokpoel *et al* [10]. The magnitude of the leaks was not different between the 2 groups, but the precision of this measure is not perfect [25]. None of the patients ventilated in PSV was classified as severe PVA. We may hypothesize that the patients ventilated in PSV have a stronger ventilatory drive, leading to a better detection of the breathing efforts by the ventilator [5]. However, a confounding factor may also explain this association, PSV being mostly used in our unit in older and less sedated patients.

Overall, we did not observe any association between severe asynchrony and adverse outcomes during the PICU course, in contrast with studies in adults [4, 5, 7]. Similarly, Blokpoel *et al* did not observe prolonged ventilation in patients with higher levels of asynchrony. Several explanations could be hypothesized to explain this difference with adult studies. In adults, adverse outcome was observed in severe PVA groups, while the remaining patients were appropriately synchronized [4, 5, 7]. In contrast, the number of children with good patient-ventilator interaction is quite low. In our study, patients with severe PVA frequently had diseases usually associated with good outcome (*e.g*. bronchiolitis). It is also important to note that the patients with more severe PVA were recorded earlier in the PICU course. This baseline discrepancy makes it difficult to assess the relationship between PVA and ventilation duration.

The question remains whether those children would have a better outcome providing the PVA was improved. Only a controlled interventional trial, for example using a specific mode like NAVA, could confirm the independent role of PVA on outcome. Such evidence remains limited in PICU. In a crossover trial conducted in 12 children, De la Oliva *et al* [13] observed that the improvement of PVA with NAVA was associated with an improvement in Comfort score. This finding is interesting when sedation is sometimes needed in cases of severe asynchrony. An improved synchrony might have the potential to reduce sedation needs and its associated side effects. In a large randomized controlled trial, Kallio *et al* [26] observed an interesting trend for shorter ventilation and ICU length of stay (p=0.03 and p=0.07, respectively).

Finally, some authors hypothesize that improved PVA could also have deleterious effects that counterbalance the

benefits [27]. It is however difficult to retain this hypothesis here while very few patients had good synchrony.

Interestingly, we observed that many patients had low respiratory drive after several days of intubation, while they were deemed to be actively breathing. We consider this finding as a new form of poor patient-ventilator interaction, although not an asynchrony. This low respiratory activity has previously been reported [14, 28]. It could be the consequence of overassistance, oversedation, their combination, or more rarely of an abnormal output by the central respiratory center or by bilateral phrenic nerve palsy [29, 30]. In this study group, many patients were admitted for non-respiratory reasons. Even low level of ventilator support can be sufficient in such conditions to suppress the patient breaths [31]. We previously reported that the ventilatory drive increased in these patients after the extubation, so the central or peripheral neurological explanation seems unlikely [32]. Oversedation may have contributed, as suggested by higher degree of comfort observed in these patients. As described by Vaschetto *et al*, the combination of overassistance and sedation has a synergistic impact on the drive suppression. More attention should be paid to this frequent complication, as such respiratory behavior has clearly been linked to diaphragm dysfunction [33, 34].

Several limitations of our study need to be discussed. We included in the analysis less patients than expected. However, the absence of trend in our observation suggests that our findings are not mainly due to an insufficient power. This is a single-center study and the results may have been influenced by the local practice, especially regarding ventilator settings. NAVA was not used in routine practice during the study period in our PICU. NAVA can improve patient-ventilator interactions [12, 35, 36] and the results of our study would probably be different in population treated with this mode. Many patients were not included, which could limit the external validity of our findings. Certain medical conditions, as chronic respiratory insufficiency with prior ventilatory support, tracheostomy or neuromuscular disease, were a priori excluded, preventing us to generalize our findings to these patients. Due to the study design and the need to observe active breathing for considering patient inclusion, patients were not recorded at the same time after admission. Although the degree of PVA did not seem to change so much over the PICU course, this difference in inclusion timing made it difficult to interpret the relationship between asynchrony and outcome.

Conclusion

Patient-ventilator interaction is poor in critically ill children supported by conventional ventilation. The study did not permit to ascertain if these poor interactions have important clinical consequence. But the magnitude of PVA and the prevalence of low ventilatory drive warrant further studies to assess if strategies to optimize patient ventilator interactions can improve the outcome of PICU patients.

Figure legends

Fig 1 Study flow chart (*patients could be excluded for 2 reasons)

Fig 2 Contribution of the different types of asynchrony in the total time spent in conflict with the ventilator.

Fig 3 Evolution of inspiratory Edi (panel a) and of the time spent in asynchrony (panel b) from inclusion time (time 1) to pre-extubation period (time 2).

Fig 4 Relationship between the asynchrony results obtained using the two methods: the automatic NeuroSync index and the percentage of time spent in asynchrony derived from the manual breath-by-breath analysis

List of abbreviations

Edi: Electrical Activity of the diaphragm

ETT: Endotracheal Tube

NAVA: Neurally Adjusted Ventilatory Assist

PICU: Pediatric Intensive Care Unit

PSV: Pressure Support Ventilation

PVA: Patient-Ventilator Asynchrony

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Table 2: Characteristics of patients depending of the level of asynchrony (in patients with Edi>2 µV, n=34).

	% time spent in asynchrony < 39% (n=25)	**% time spent in asynchrony > 39% (n=9)**	**p value**
Age (m)	14 (2-40)	2 (1-3)	0.007
Weight (kg)	7.0 (4.5-17.3)	4.3 (3.6-5.4)	0.049
Male, n (%)	14 (56%)	6 (67%)	0.70
Days between admission and inclusion	8 (2-11)	2 (1-5)	0.054
Main reasons for PICU admission, n (%)			0.56
Respiratory failure	18 (72%)	8 (89%)	0.40
Including bronchiolitis	5 (20%)	5 (56%)	0.08
Hemodynamic failure	1 (4%)	0 (0%)	1
Neurologic disorder	3 (12%)	0 (0%)	0.55
Metabolic disorder	1 (4%)	1 (11%)	0.46
Trauma	0 (0%)	0 (0%)	1
Post-surgery	2 (8%)	0 (0%)	1
Chronic condition, n (%)			
Respiratory disease	5 (20%)	1 (11%)	1
Cardiac disease	6 (24%)	0 (0%)	0.16
Neurogical disease	6 (24%)	1 (11%)	0.64
Immuno-oncologic disease	3 (12%)	0 (0%)	0.55
Clinical status			
PIM-2 score	2.5 (0.9-4.4)	0.9 (0.5-7.0)	0.40
PELOD score	1 (1-11)	11 (1-12)	0.38
pH	7.40 (7.33-7.42)	7.37 (7.33-7.42)	0.63
HCO_{3-}, mmHg	30.0 (25.1-32.9)	28.8 (24.9-32.0)	0.84
$PaCO_2$, mmHg	48.0 (44.4-53.4)	48.9 (45.8-57.5)	0.57
Hb, g/dL	10.2 (7.3-10.7)	10.4 (7.9-12.3)	0.33
Lactate, mmol/L	1.5 (0.8-2.1)	1.5 (1.2-1.9)	1
Comfort score	15 (13-16)	15 (11-17)	0.95
Sedation score	11 (6-23)	21 (11-39)	0.15
ETT size	4.0 (3.5-4.5)	3.5 (3.5-3.5)	0.013
Cuffed ETT	17 (68%)	2 (22%)	0.019

Ventilatory settings			
Set RR	25 (20-35)	30 (28-38)	0.13
Measured RR	34 (28-40)	35 (29-40)	0.92
Mode PSV	10 (40%)	0 (0%)	0.034
Mode ACV-P	4 (16%)	3 (33%)	0.35
Mode IACV-P	7 (28%)	3 (33%)	1
Mode ACV-V	0 (0%)	0 (0%)	1
Mode IACV-V	1 (4%)	2 (22%)	0.16
Mode PRVC	3 (12%)	1 (11%)	1
PEEP, cmH_2O	5 (5-5)	6 (5-7)	0.06
FiO_2	0.35 (0.26-0.44)	0.35 (0.30-0.60)	0.45
Leaks (%)	7 (4-15)	2 (0 – 7)	0.17
Analysis			
Peak inspiratory Edi, µV	7.2 (3.8-15.3)	5.5 (3.4-7.2)	0.20
Tonic expiratory Edi, µV	0.9 (0.6-2.4)	2.0 (1.1-2.9)	0.058
Type of asynchrony			
Wasted Efforts, % of breath analyzed	4.5 (1.6-15.8)	30.6 (18.7-39.8)	0.002
Auto-triggering, % of breath analyzed	6.1 (1.3-9.9)	8.4 (0.9-23.3)	0.36
Double-triggering, % of breath analyzed	2.1 (0.0-3.2)	0.0 (0.0-0.8)	0.08
Trigger error, ms	136 (104-176)	284 (190-302)	0.008
Cycling-off error, ms	64 (40-131)	255 (184-297)	0.018
Time spent in asynchrony			
Total time spent in asynchrony, %	24 (17-28)	47 (43-50)	<0.001
Wasted Effort, %	0.6 (0.2-3.5)	5.3 (2.8-13.6)	0.03
Auto-triggering, %	1.6 (0.3-2.4)	2.3 (0.3-4.7)	0.40
Double-triggering, %	0.1 (0.0-0.4)	0.0 (0.0-0.1)	0.053
Trigger error			
Delay, %	7.6 (7.6-11.2)	15.5 (12.2-19.1)	0.001
Premature, %	0.8 (0.5-2.1)	2.3 (1.4-2.9)	0.058
Cycle-off error			
Delay, %	3.8 (1.8-6.3)	15.0 (10.2-17.5)	<0.001
Premature, %	4.1 (2.2-5.9)	3.2 (2.0-6.7)	0.98
NeuroSync Index, %	38 (31-47)	81 (69-83)	<0.001
Outcome			
Death in PICU	1 (4.0%)	1 (11.1%)	1

Days in PICU	14 (5-22)	7 (4-14)	0.17
Days in PICU after inclusion	6 (4-12.5)	5 (3-6)	0.66
Days on MV	9 (4-15)	4 (3-12)	0.23
Days on MV after inclusion	2.5 (1-6.5)	3 (1-4)	0.9
NIV post extubation	4 (16.0%)	1 (11.1%)	1
Reintubation	5 (20.0%)	1 (11.1%)	1

Edi: Electrical activity of the Diaphragm; PICU: Pediatric Intensive Care Unit; RR: Respiratory Rate; PEEP: Positive End-Expiratory Pressure; ETT: Endo-Tracheal Tube; MV: Mechanical Ventilation; NIV: Non Invasive Ventilation.

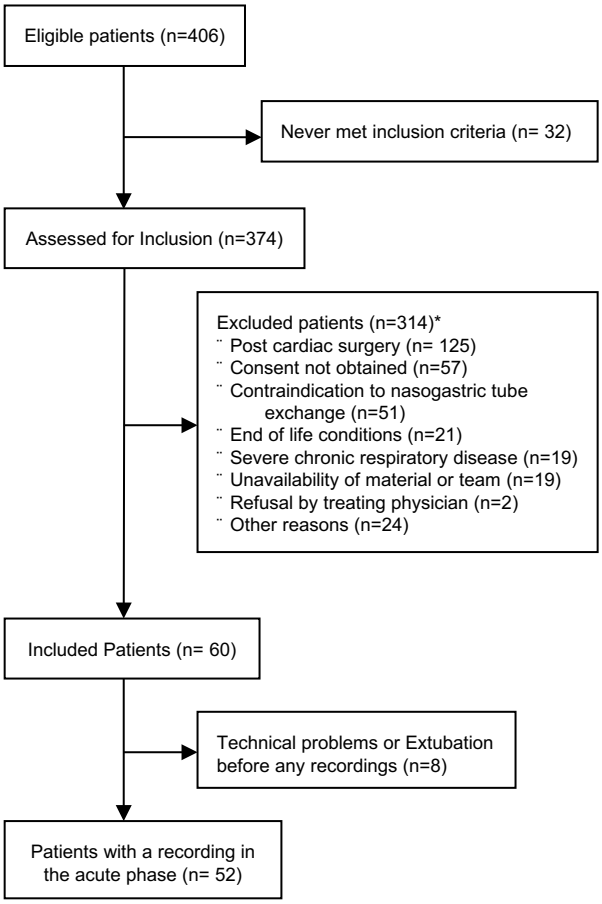


Fig 1

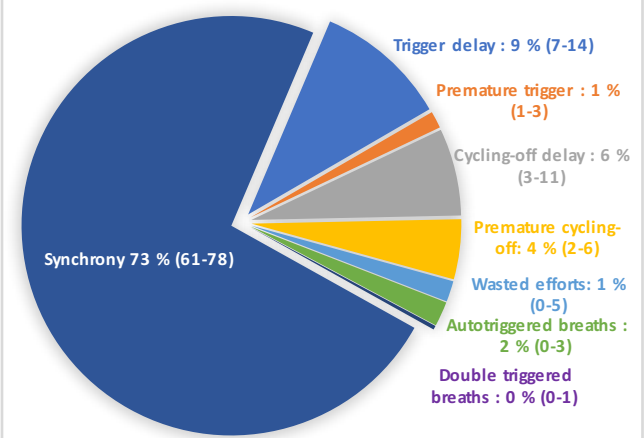


Fig 2

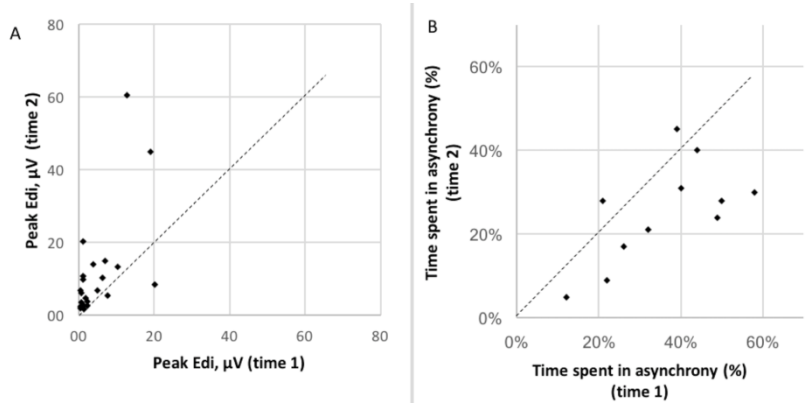


Fig 3

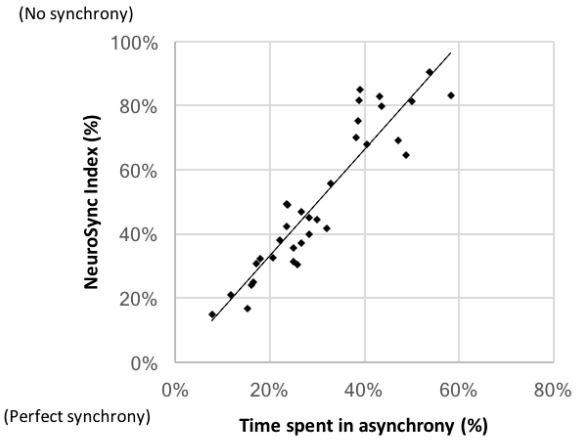
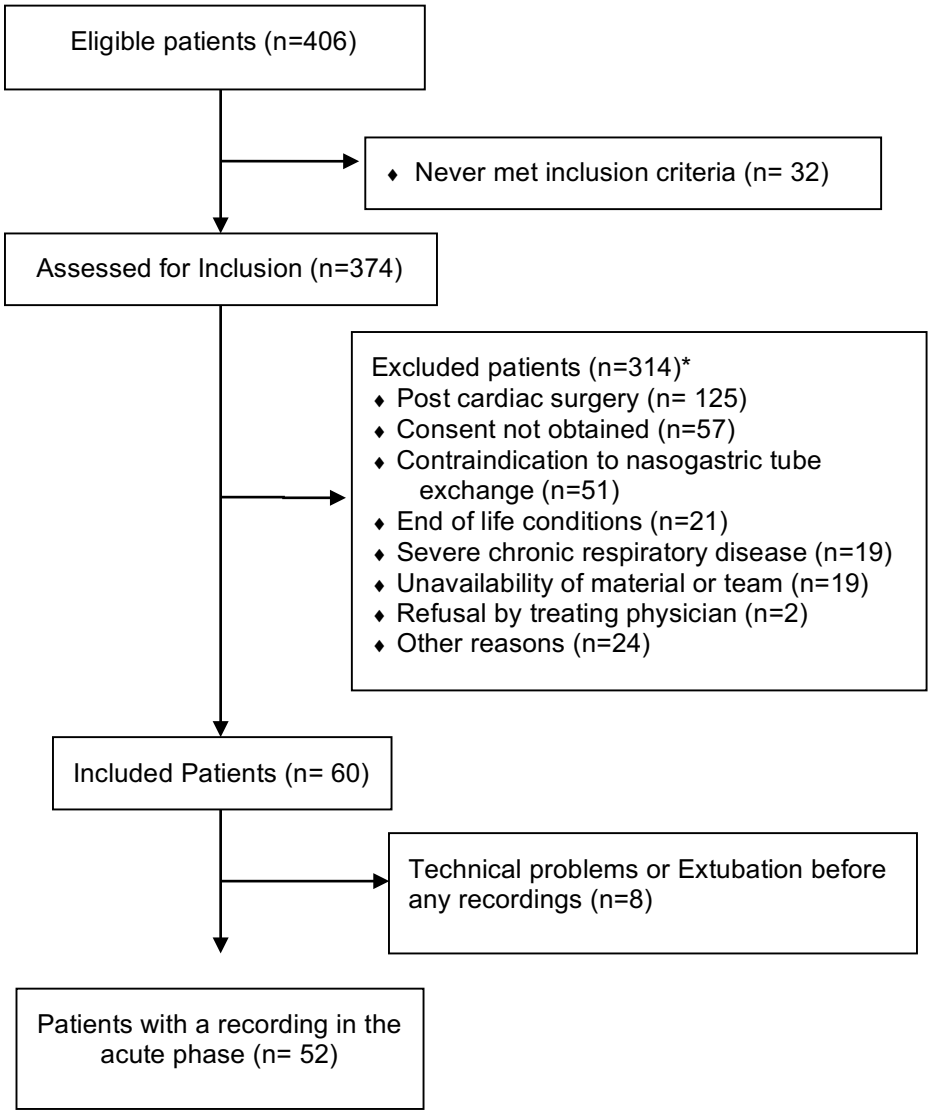


Fig 4

Matériel supplémentaire

Methods

Fig ESM-1. Study flow chart (* patients could be excluded for several reasons)



Discussion

Ce travail a montré que la mesure de l'AE_{DI} permet d'identifier les asynchronies patient-ventilateur chez les patients en VM. L'incidence des asynchronies ventilatoires était importante chez les patients ventilés de manière conventionnelle. Comparée à l'analyse des tracés du respirateur, l'utilisation de l'AE_{DI} permet d'identifier avec plus de fiabilité les asynchronies dites de délai, qui sont le type d'asynchronies le plus fréquent dans notre travail.

En n'observant aucune association significative entre le degré d'asynchronie et le devenir des patients, nous avons soulevé un point important. Certes, l'absence de lien dans notre étude peut être lié à un manque de puissance. Mais il est probable que l'impact clinique des asynchronies dépende de plusieurs facteurs, comme l'âge du patient, sa pathologie et le stade d'évolution de la maladie. Il est aussi possible que le type d'asynchronie rencontré joue un rôle. Par conséquent, une mauvaise interaction patient-ventilateur chez un nourrisson en ventilation assistée pour une pathologie cardiaque ne peut être interprétée de la même manière que chez un patient adolescent avec un SDRA. De plus, nous avons montré de manière intéressante que finalement très peu de patients sont bien synchronisés, ce qui avait déjà été noté par Blokpoel *et al.* [229]. Nous avons donc comparé le devenir des patients très asynchrones avec celui des patients modérément asynchrones. D'autres études, avec un effectif plus important et des patients ayant un nombre d'asynchronies plus important, devraient permettre d'éclaircir ces points.

ETUDE 4 : INDIRECT CALORIMETRY AS A DIAGNOSTIC TOOL TO ASSESS WORK OF BREATHING DURING WEANING FROM MECHANICAL VENTILATION IN CHILDREN

Hypothèse de travail

L'évaluation du travail respiratoire pendant le processus de sevrage est particulièrement importante pour prédire le succès de l'extubation et pour optimiser son déroulement [120]. Plusieurs outils étudiant différents aspects de la fonction des muscles respiratoires ont été développés. La mesure de la P_{ES} est la méthode de référence pour mesurer la pression générée par les muscles inspiratoires du patient et elle s'est avérée être une méthode valable pour prédire le succès du sevrage ventilatoire [106, 234]. La mesure de l'AE_{DI}, reflet de l'activité diaphragmatique, a déjà montré son intérêt dans la phase de sevrage ventilatoire [69, 105]. Enfin, la consommation d'oxygène (VO_2) mesurée par la calorimétrie indirecte semble être un outil pertinent pour quantifier l'activité des muscles respiratoires, même si peu de travaux sur ce sujet ont été publiés chez l'enfant ventilé.

Cette étude visait à comparer 3 éléments de la fonction des muscles respiratoires (P_{ES}, AE_{DI} et VO_2) pendant une épreuve de sevrage ventilatoire.

Méthodes utilisées

Dans ce travail, nous avions utilisé une sonde NAVA modifiée 8Fr (NeuroVent Research Inc, Toronto, Canada) à usage unique, disposant à la fois de capteurs du signal AE_{DI} et d'un ballonnet de pression œsophagien rempli avec 0.5 ml d'air. La bonne position de la sonde était effectuée de la même manière qu'une sonde NAVA classique à l'aide de la fenêtre spécifique sur le respirateur Servo-I (Figures 8 et 9). Le signal fourni était converti et stocké pour être analysé (NeuroVent XIII, Neurovent research Inc, Toronto, Canada).

La VO_2 et les dépenses énergétiques totales au repos étaient calculées par Calorimétrie Indirecte avec le système Vmax Encore (Carefusion Corp, Yorba Linda, CA, USA). Après calibration selon les recommandations du fabricant, le calorimètre était connecté au respirateur et au circuit inspiratoire du patient. Les données étaient recueillies après une période de stabilisation de 10

minutes et les données considérées comme aberrantes (variations supérieures à ±10%) étaient supprimées.

La VO_2, la P_{ES} et l'AE_{DI} étaient mesurées avant, pendant et après une épreuve de ventilation spontanée en PPC. Les valeurs moyennes étaient obtenues sur une période de 10 minutes de stabilité (absence de mouvements du patient, absence de soins médicaux ou paramédicaux).

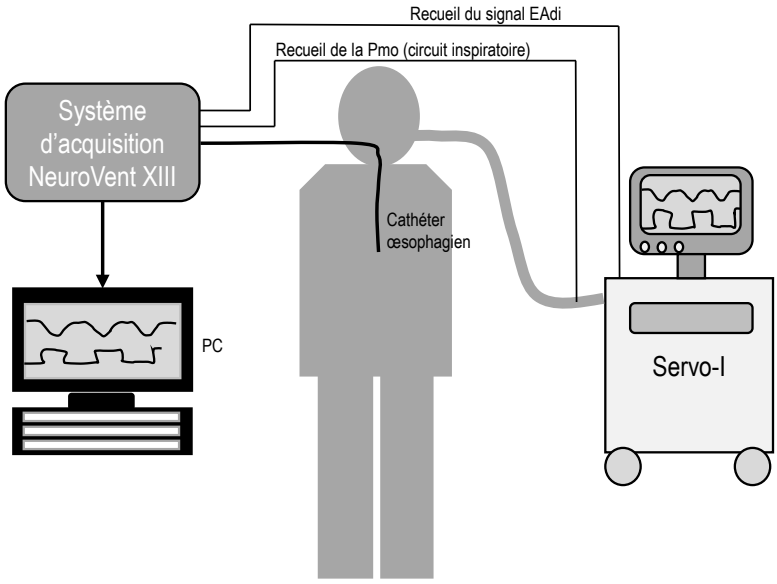


Figure 8 : Représentation du banc de mesure avec recueil du signal d'Activité Electrique du Diaphragme (AE_{DI}) et de Pression Œsophagienne (P_{ES}).
P_{MO} : Pression Moyenne

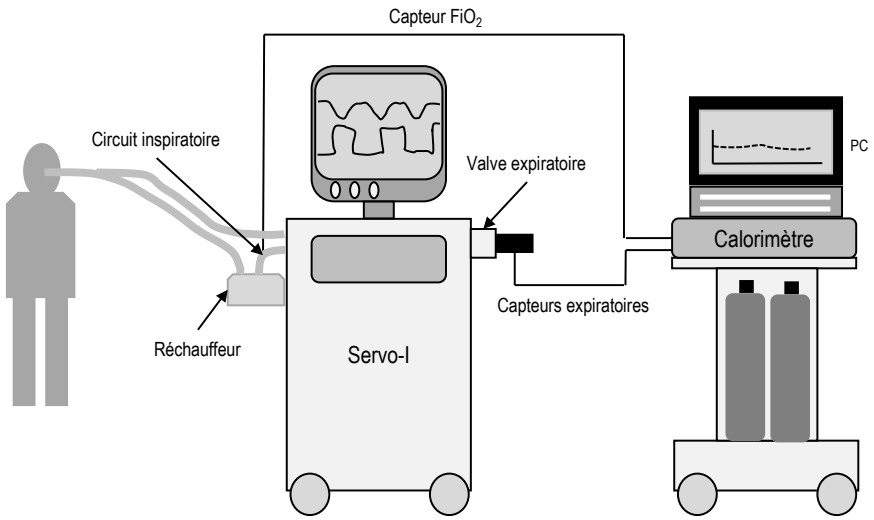


Figure 9 : Schéma de l'installation du calorimètre indirect pour la mesure de la consommation en oxygène (VO_2).
FiO_2 : Fraction Inspirée en Oxygène

Article

Indirect Calorimetry as a diagnostic tool to assess work of breathing during weaning from mechanical ventilation in children

Guillaume Mortamet[1,2,3,4], MD, Nicolas Nardi[1,2], MD, Véronique Groleau[2,5], MD, Sandrine Essouri[2,6], MD, PhD, Brigitte Fauroux[2,3,4,7], MD, PhD, Philippe Jouvet[1,2], MD, PhD, Guillaume Emeriaud[1,2], MD, PhD

[1]Pediatric Intensive Care Unit, CHU Sainte-Justine, Montreal (QC), Canada
[2]Université de Montréal, Montréal, Québec, Canada
[3]Université de Paris-Est, Créteil, France
[4]Unité INSERM U955, Créteil, France
[5]Department of Gastroenterology, Hepatology and Nutrition, CHU Sainte-Justine, Montreal (QC), Canada
[6]Department of Pediatrics, CHU Sainte-Justine, Montreal (QC), Canada
[7]Pediatric Noninvasive Ventilation and Sleep Unit, Hôpital Necker, Paris, France

Corresponding author
Dr Guillaume Mortamet
Pediatric Intensive Care Unit, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, Montreal, Quebec, Canada
Email:

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GM, NN, SE and VG have no conflict of interest to declare. PJ is supported by a scholarship award of the Fonds de Recherche du Québec – Santé, Ministry of Health and Sainte-Justine Hospital. PJ was a consultant for Sage Therapeutic inc, was invited to a congress by Medunik Inc and Covidien. GE's research program is supported by a scholarship award by the Fonds de Recherche du Québec – Santé. He is currently leading a feasibility study in neonatal ventilation which is financially supported by Maquet Critical Care. The research of BF is supported by the Association Française contre les Myopathies (AFM), Assistance Publique-Hôpitaux de Paris, Inserm, Université Paris Descartes, ADEP Assistance, ASV Santé, S2A Santé and IP Santé Domicile.

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Authors' contribution:
GM, PJ, BF and GE designed the study. GM, NN, SE and GE obtained and analyzed the data from Electrical Activity of the Diaphragm and Esophageal Pressure. GM and VG analyzed the data from Indirect Calorimetry. GM

and NN wrote the manuscript, which was reviewed, edited, and approved by all authors.
As the corresponding author, GM has full access to all the data in the study and has final responsibility for the decision to submit for publication.

Location

This work has been performed in Sainte-Justine Hospital, Montreal, Quebec, Canada.

Key words: mechanical ventilation; indirect calorimetry; work of breathing; weaning; pediatric intensive care unit; pediatrics.

Word count of the abstract: 236 words
Word count of the manuscript: 3004 words

Abstract

Purpose - The present study aims to characterize the behavior of three components of the respiratory muscle function during MV weaning in children, to better understand the respective impact of a spontaneous breathing trial on the ventilatory mechanical action (P_{ES}), on the ventilatory demand (EA_{DI}), and on the oxygen consumption (VO_2).

Methods - A prospective single center study. All intubated and mechanically ventilated children >1 months and <18 years old, hospitalized in the pediatric intensive care unit were eligible. Patients considered as ready to extubate were included. Simultaneous recordings of VO_2, P_{ES} and EA_{DI} were performed during 3 steps: before, during and after the spontaneous breathing test.

Results - Twenty patients (median 5.5 months) were included. Half of them were admitted for a respiratory reason. The increase in P_{ES} swings and Esophageal Pressure-Time Product during the spontaneous breathing test was not significant (p=0.3 and 0.7, respectively) and a similar trend was observed with Peak EA_{DI} (p=0.06). Oxygen consumption obtained by Indirect Calorimetry was stable in the 3 conditions (p=0.98).

Conclusion - In these critically ill children, spontaneous breathing trial induced a moderate and non-significant increase in work of breathing, as reflected by the respiratory drive with EA_{DI} and by the respiratory mechanics with P_{ES}. However, indirect calorimetry does not seem to be a sensitive tool to assess respiratory muscle function in mechanically ventilated children during the weaning phase, especially when work of breathing is slightly increased.

Introduction

Respiratory failure is the leading cause of admissions in the pediatric intensive care unit (PICU) and mechanical ventilation (MV) is the first line treatment. While mechanical ventilation is often lifesaving, it can be associated with complications such as ventilator-induced lung injury [1], nosocomial infection, airway trauma, and severe diaphragmatic dysfunction [2]. It is therefore important that MV be discontinued as soon as possible, i.e. as soon as the patient is capable of spontaneous breathing.

During the weaning phase of MV, the ability of the respiratory muscles to cope with imposed load is challenged [3]. The assessment of respiratory muscle function during the weaning process could help to predict the extubation success and optimize its timing [4]. Different tools are available to monitor the different components of the respiratory muscle function during the weaning phase. Esophageal pressure (P_{ES}) measurement is the reference method to measure the pressure generated by the patient's inspiratory muscles and has been shown to be a good method to predict weaning outcome [5, 6]. The Electrical Activity of the Diaphragm (EA_{DI}) reflects the patient ventilatory drive and it has been used to monitor diaphragm activity during weaning trials [7]. The neuro-mechanical or neuro-ventilatory efficiency of the respiratory system can be estimated by the ratio of the muscle pressure or the ventilatory volume divided by the corresponding EA_{DI} [8]. Moreover, oxygen consumption (VO_2) obtained from Indirect Calorimetry (IC) has been shown to change upon adaptations of mechanical ventilation parameters and modes, since the oxygen cost of breathing reflects the output of the respiratory muscles [9]. Whereas in normal subjects, the portion of VO_2 assigned to respiratory load (VO_{2resp}) accounts for 1 to 3% of whole body VO_2 [10], this percentage can be considerably higher in patients being weaned from ventilation [11, 12]. However, pediatric data in this field are lacking, especially about the reliability and reproducibility of IC.

The present study aims to characterize the behavior of three components of the respiratory muscle function during MV weaning in children, to better understand the respective impact of a spontaneous breathing trial on the ventilatory mechanical action (P_{ES}), on the ventilatory demand (EA_{DI}), and on the oxygen consumption (VO_2).

Methods

This is a prospective study, conducted in the PICU of CHU Sainte-Justine, a university affiliated pediatric hospital, from November 2016 to June 2017. The study protocol was approved by the Ethics committee of CHU Sainte-Justine and written informed consent was obtained from the parents or legal tutor.

Patients

Consecutive children aged between 1 month and 18-year-old admitted to the PICU, intubated and mechanically ventilated were eligible. The screening was performed by a research assistant every working day. Eligible patients were included if they were deemed to be ready for an extubation readiness test as per the attending team, providing the research team and the equipment were available. Patients were excluded if they had one of the following criteria: (i) contraindications to the placement of a new nasogastric tube, (ii) hemodynamic instability, (iii) severe respiratory instability, (iv) axillary temperature >38°, (v) cuff leaks >10%, (vi) Nitrite oxide therapy, (vii) ventilation in High Frequency Oscillation and (viii) if a limitation of life support treatments was discussed or decided. Detailed inclusion and exclusion criteria are given in Supplementary Material.

Protocol and data recording

P_{ES}, EA_{DI} and VO_2 data were monitored to characterize the respiratory muscle function. P_{ES} and EA_{DI} were obtained simultaneously by a specific modified 8Fr EA_{DI} catheter (NeuroVent Research, Toronto, Canada) equipped with both microelectrodes (for EA_{DI} monitoring) and an esophageal balloon (for P_{ES} monitoring), installed 30 minutes

before measurement. The catheter was connected to a Servo-I ventilator (Maquet, Solna, Sweden), to gather the EA_{DI} signal. The correct position of the catheter was checked with a specific positioning screen on the Servo-I, following the company recommendation and as done in several previous studies [13]. P_{ES} and EA_{DI} signals were simultaneously recorded using an acquisition system (NeuroVent Monitor XIII) and displayed and analyzed using a specific software (NeuroVent Research, Toronto, Canada).

VO_2 and REE were measured by a portable indirect calorimeter (Vmax Encore, Carefusion, Yorba Linda, CA), which was connected 30 minutes before measurement. Gas and pressure were calibrated according to the manufacturer's instructions.

All data were measured during 3 periods of 30 minutes: before, during and after a Spontaneous Breathing Test (SBT) in Continuous Positive Airway Pressure (CPAP). Patients were supine, with the head of bed elevated to 30 degrees, and not or lightly sedated according to the attending physician instructions.

Demographic data and patient's characteristics, including age, gender, weight, time of measurements, admission diagnostic and comorbidities, Pediatric Risk of Mortality (PRISM) and Pediatric Logistic Organ Dysfunction (PELOD) scores were collected. Rapid Shallow Breathing Index was defined as the ratio of Respiratory Rate to Tidal Volume (V_T). Predicted Energy Expenditure was calculated according to the Schofield equations (kcal/day) (*cf.* Supplementary Material). Clinical indices of increased work of breathing and comfort of the patient, assessed with the « Comfort Behavior » scale, were gathered during the 3 periods. Sedation level was assessed with the sedation score described by Randolph *et al*. [14], which was adapted to include dexmedetomidine according to the study performed by Eren *et al*. [15]. One point was given for morphine or midazolam equivalents of 0.1 mg/kg. PICU outcome data included: SBT success or failure, extubation success or failure (as defined by the need to re-intubate in the 48 hours following extubation) and length of mechanical ventilation.

Data analysis

For P_{ES} and EA_{DI} recordings, after elimination of the cycles with artifacts, such as coughing or esophageal spasms, at least 20 consecutive breath cycles in the 3 different respiratory conditions were used for subsequent analysis. Esophageal Pressure-Time Product (PTP_{ES}) was obtained by measuring the area under the P_{ES} signal between the onset of inspiration and the end of inspiration as determined on EA_{DI} tracing. PTP_{ES} was also expressed per minute by multiplying the pressure-time products per breath by the respiratory rate (PTP_{ES}/min). Neuromechanical and Neuroventilatory efficiency were assessed by the ratio of Swing P_{ES} to peak EA_{DI} and V_T to peak EA_{DI}, respectively. The mean VO_2 and REE were calculated during the 3 periods. Data from the first ten minutes and from periods of documented physical movement or nursing care, as endotracheal suctioning, were excluded. The steady-state was defined as 10 consecutive minutes during which oxygen consumption and carbon dioxide production vary less than ±10% as previously described [16]. VO_{2resp} was defined as the difference between VO_2 during SBT and VO_2 under conventional mechanical ventilation.

Statistical analysis

Data were expressed as median values (with interquartile range, IQR) for continuous variables, and number and/or

frequency (%) for categorical data. Differences for categorical variables were tested using chi-square or Fisher's exact test (when expected frequencies were less than five). Differences in continuous variables were assessed using non-parametric Mann–Whitney test or paired t-test, depending on the variable distribution. Repeated measures analysis of variance (ANOVA) was used to compare the different conditions (before, during and after SBT in CPAP) on the different variables. Pearson's correlation coefficient (R) and determination coefficient (R^2) were used to evaluate the correlation between changes in Swing P_{ES}, PTP_{ES}, EA_{DI} and VO_2. All p values were two-tailed and considered significant if $p < 0.05$. Statistical analyses were performed using SPSS 24.0 (SPSS, Inc, Chicago, IL). Details regarding sample size are given in Supplementary Material.

Results

Study population

During the study period, 568 patients were admitted in the PICU and 280 were ventilated. Thirty-one patients were eligible and approached by the study team. Five did not consent to the study while 4 patients were extubated before inclusion. In 2 patients, measurements were not performed due to clinical deterioration. In total, 20 patients were enrolled (10 males), with a median age of 5.5 (IQR 2-61) months. The patients' characteristics are presented in Table 1. They were studied 7 (3-11) days after initiation of MV. The main reason for admission in PICU was respiratory failure (n=10, 50%) and 3 (15%) patients were admitted after surgery. Before SBT, the median comfort score was 14 (12-16). Five patients (25%) received intermittent analgesic treatments only, whereas 5 (25%) received both sedative and analgesics agents with a continuous infusion. In 2 patients, EA_{DI} could not be measured due to technical problems and for another one, measurements from IC were inaccurate due to air leaks >10% occurring after inclusion.

Breathing pattern and work of breathing during SBT

As detailed in the Table 2, the respiratory rate tended to increase during the SBT, although this did not reach significance (p=0.23). No clear changes in tidal volume, minute ventilation, and rapid shallow breathing index were observed. Unexpectedly, the increase in P_{ES} swings and PTP_{ES}/min during the SBT was not significant (p=0.3 and 0.7, respectively) (Figure 1). P_{ES} swings increased by at least 10% during SBT in 14 (70%) patients. A similar trend was observed with Peak EA_{DI} (p=0.06). Neuromechanical and Neuroventilatory efficiency did not change significantly before, during and after SBT. We did not observe any association between P_{ES} and EA_{DI} changes and the level of comfort or sedation score.

Variables measured by indirect calorimeter

Oxygen consumption obtained by IC was stable in the 3 conditions (p=0.98). In 10 (50%) patients, VO_2 decreased during SBT. REE and VO_{2resp} patterns did not differ according to the comfort and sedation score.

Predicted REE was overestimated as compared to measured REE (47 (40-54) vs 23 (21-29) kcal/kg/day, p<0.001) and the median Respiratory Quotient measured by IC was 0.71 (0.69-0.78).

Correlations between measurements obtained by P_{ES}, EA_{DI} and IC

Overall, changes in VO_2 were not correlated with changes observed with PTP_{ES} and peak EA_{DI} (R^2 = 0.05 and 0.01, respectively). Similarly, only a poor correlation was observed between changes in P_{ES} and changes in EA_{DI} (R^2 = 0.3; Figure 2).

Outcome

SBT was considered a success in 20 (100%) patients and extubation was successful in 17 (89%) patients. One patient was not extubated and died after limitation of life support treatment. Median length of MV and length of stay in PICU were 10 (4-14) and 18 (7-42) days, respectively. After extubation, 9 (45%) patients required no respiratory support while 2 (10%) were reintubated and 8 (40%) were on noninvasive respiratory support within 1h of extubation. The pattern of PTP_{ES}, EA_{DI} or VO_2 during the SBT were not associated with extubation failure, although the number of patients was limited.

Discussion

In this series of 20 critically ill children, we observed that SBT in CPAP was associated with a non-significant increase in P_{ES} derived indices of effort of breathing and of EA_{DI}. However, VO_{2resp} measurements obtained from IC were stable during the maneuver.

In children, the benefit of weaning protocols including SBT to shorten the duration of ventilation has been demonstrated [17] and the recent consensus conference on pediatric Acute Respiratory Distress Syndrome (PALICC) recommends that SBT and/or extubation readiness tests should be performed [18]. For monitoring patient-ventilator interactions during SBT, clinicians rely mostly on patient breathing pattern and waveforms that are available on most ventilators. However, several difficulties remain to assess the patient contribution in the work of breathing with usual clinical monitoring during mechanical ventilation [19]. Measurements of P_{ES} and EA_{DI} provides the clinicians with a bedside evaluation of respiratory effort from two different points of view. Assessment of P_{ES} is the reference method to measure the pressure generated by the patient's inspiratory muscles. The direct monitoring of the respiratory muscle function by P_{ES} has been shown to be helpful in titrating ventilator support in different pathologies [20] and as Jubran *et al.* showed in adults, P_{ES} trend during a SBT can provide an accurate prediction of weaning outcome [5]. On the other hand, EA_{DI} gives the clinician with a bedside evaluation of diaphragm activity [21]. EA_{DI} can be considered as a tool to reflect the patient ventilatory drive, and it consecutively indirectly reflects the evolution of the work of breathing [22]. Because adequate diaphragmatic function is paramount for weaning success, the relevance of monitoring EA_{DI} during the weaning process has also been described [23]. Wolf *et al*. observed that the ability to generate a higher diaphragmatic activity for the same tidal volume in pressure support ventilation was a predictor of successful extubation [7]. Combining EA_{DI} and tidal volume in neuroventilatory index has a great interest since the comparison of the ventilatory demand with the mechanical output informs on the diaphragm efficiency.

Our initial hypothesis was that IC, providing total VO_2 at bedside of critically ill children, could be a reliable and less invasive method to estimate change in work of breathing during weaning from conventional ventilation. We reasonably assumed that no confounding factor except increasing in work of breathing could induce an increase in VO_2 during SBT. We therefore choose 3 periods of 30-minutes recording during which underlying metabolic condition could not change, as suggested in previous studies [12]. Many authors, rather than focusing on the mechanical muscle function, have evaluated the role of VO_{2resp} as a predictor of weaning success [9, 24] and others reported that VO_{2resp} was closely correlated to PTP [25]. In children, the use of IC for respiratory purpose is scarcely reported [26]. In few studies, oxygen consumption has been measured in mechanically ventilated children in different clinical condition to assess effects of therapeutics such as neuromuscular blockers [27] or inhaled salbutamol [28]. To our knowledge, VO_2 measurement during weaning from pediatric MV has never been studied.

As compared with measurements from P_{ES} and EA_{DI}, variables obtained from IC, such as VO_{2resp}, did not tend to accurately reflect changes in work of breathing. We could expect a VO_{2resp} around 10% of VO_2 according to the study by Höher *et al*. who found that patients on assisted ventilation spent 11% more energy than patients on controlled ventilation [29], as supported by another study [12]. Yet, we found in the present study that VO_{2resp} was not influenced by ventilator mode, in agreement with the study published by Briassoulis *et al*. in a population of 11 mechanically ventilated and critically ill children [30]. We suggest several hypotheses to analyze this finding. First, while patients had a low level of support before SBT, VO_{2resp} could not be as sensitive as P_{ES} or EA_{DI} to detect a low work of breathing. According to the study performed by Frankenfield *et al*., measurements from the Vmax Encore Calorimeter can be biased by 5% in the same subject [31]. Second, this finding could be explained by the great heterogeneity of our population, in terms of pathologies, mode of ventilation, ventilator settings, duration of ventilation, time of inclusion and degree of sedation [30]. Third, SBT may induce changes in functional residual capacity, resulting in changes in spirometer volume unassociated with VO_2.

Beside the main study goal, we interestingly observed absolute VO_2 values that were lower than previously reported [26, 32]. Most of these studies have been performed at the early stage of the disease [33]. Moreover, most of the patients in those studies were admitted after trauma and some of them received nutritional therapy, which could explain such difference. In our study, because we performed IC measurements during the weaning phase, we hypothesize that the metabolic rate was low in the recovery period. Although we consider observed VO_2 values as true, we cannot exclude that confounding factors could explain such results. First, although we excluded patients with FiO_2 >0.6 or cuff leaks >10%, values could be less accurate in patients with FiO_2 >0.4 or cuff leaks >5% [34]. In addition, even if we used a standardized and validated approach for IC measurements, we cannot rule out that inaccurate measurements have been caused by technical problems [35].

Both EA_{DI} and P_{ES} are well-known tools to indirectly reflect the respiratory muscle function. Previous studies have shown a tight correlation between EA_{DI} and P_{ES} [22, 36]. However, there is a high inter individual variability [36]. In our study, the changes observed between the 3 periods for these 2 variables were relatively small, and the number of

data was limited, which likely explains the poor correlation observed, due to the limited statistical power. Of note, this relationship can also be affected by sedation [37] or by the level of assistance [38]. These factors, in addition to the great heterogeneity in our population, could also explain the moderate correlation between EA_{DI} and PTP. An impaired neuro-muscular coupling [39] appears unlikely in these patients with almost normalized respiratory condition.

Finally, our findings regarding the difference between predicted and measured REE are in agreement with those reported elsewhere. Indeed, several studies showed that predictive equations overestimated REE in critically ill children with various clinical situations [32, 40]. Our results tend to confirm that such equations cannot substitute for indirect calorimetry measurement of REE.

There are several limitations in the present study. This is a single-center study, which tends to limit its generalizability. Although we included the adequate number of patients, the magnitude of the correlation observed was smaller than expected and the study may have been underpowered to demonstrate the correlation between the variables. We performed measurements during daytime and weekdays only, which could lead to a selection bias. The study population was heterogeneous, in terms of reasons for admission, duration of MV, age and degree of sedation of patients. This may lead to different respiratory behavior during weaning from mechanical ventilation. However, the population does reflect a usual PICU population. In addition, work of breathing indices were assessed during a 30-minute SBT while some authors have suggested longer extubation readiness test [20]. Nevertheless, significant changes in respiratory mechanics occurs rapidly after modification of ventilator settings. Finally, we did not assess respiratory muscle function after extubation.

Conclusion

In these critically ill children, spontaneous breathing trial in CPAP induced a moderate and non-significant increase in work of breathing, as reflected by the respiratory drive with EA_{DI} and by the respiratory mechanics with P_{ES}. However, oxygen consumption measured by IC was stable before, during and after the SBT. Indirect calorimetry does not seem to be a sensitive tool to assess respiratory muscle function in mechanically ventilated children during the weaning phase, especially when work of breathing is slightly increased.

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Figure captions

Fig 1 Work of breathing before, during and after SBT, assessed by Respiratory Rate (panel a), P_{ES} Swing (panel b), PTP_{ES} (panel c), EA_{DI} (panel d) and VO_2 (panel e)

Fig 2 Relationship between the changes of Swing P_{ES} vs peak EA_{DI} (panel a) and Swing P_{ES} vs VO_2 (panel b) from conventional settings to SBT (▲) and from SBT to previous settings (●)

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Fig 1

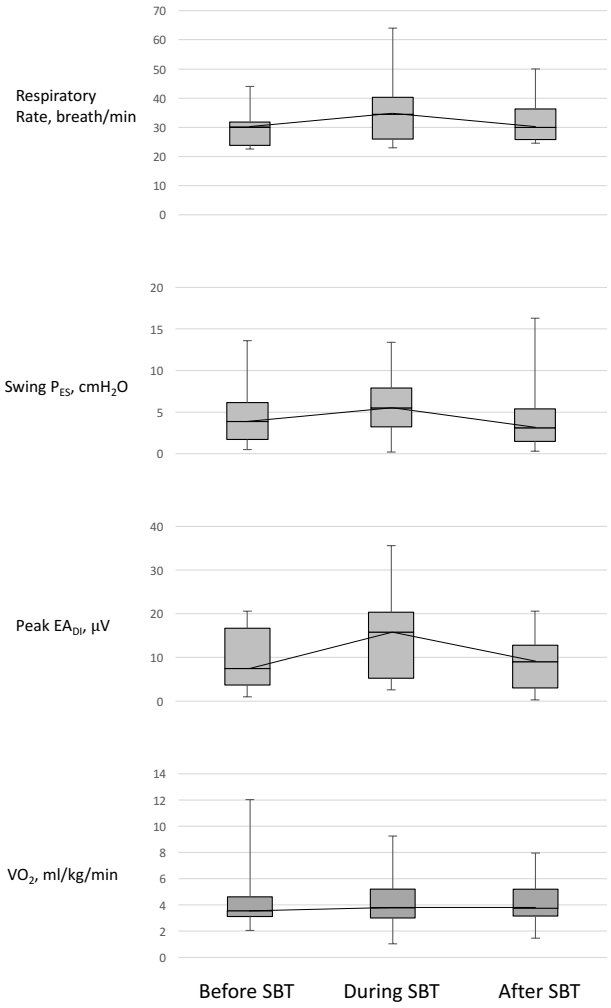
Respiratory Rate, breath/min
70
60
50
40
30
20
10
0
Swing P_{ES}, cmH_2O
20
15
10
5
0
Peak EA_{DI}, μV
40
30
20
10
0
VO_2, ml/kg/min
14
12
10
8
6
4
2
0
Before SBT
During SBT
After SBT

Fig 2

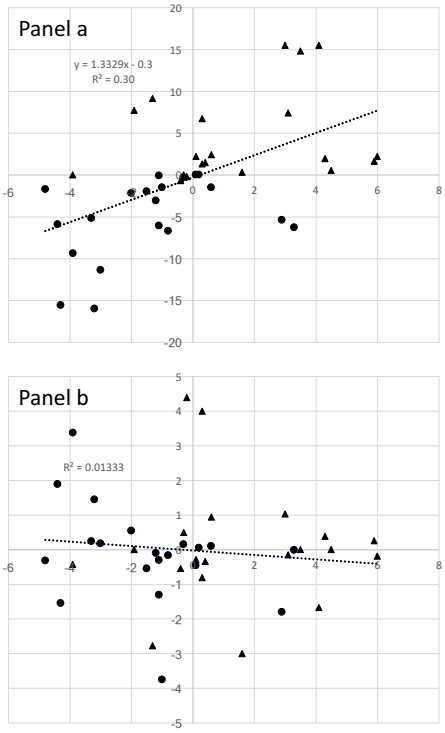

Table 1: Characteristics of population (n=20)

	Total **n=20**
Age (m)	5.5 (2-64)
Weight (kg)	6.4 (4.1-17.6)
Male, n (%)	10 (50%)
Predicted REE, kcal/kg	89 (49-147)
Days between admission and inclusion	7 (3-12)
Days between MV initiation and inclusion	7 (3-11)
Main reasons for PICU admission, n (%)	
Respiratory failure	10 (50%)
Hemodynamic failure	4 (20%)
Neurologic disorder	3 (15%)
Post-operative admission	3 (15%)
Chronic condition, n (%)	
Respiratory disease	7 (35%)
Cardiac disease	4 (20%)
Neurological disease	3 (15%)
Clinical status at baseline	
PIM-2 score (on admission day)	2.8 (0.6-18.8)
PELOD score	7 (1-19)
Temperature, °C	36.9 (36.5-37.2)
pH	7.38 (7.35-7.40)
$PaCO_2$, mmHg	47.4 (44.2-53.3)
HCO_{3-}, mmHg	28.0 (26.0-30.8)
Lactates, mmol/L	1.4 (0.9-1.8)
Hemoglobin, g/L	10.3 (9.6-11.1)
Ventilator modes and settings	
NAVA, n NAVA level, $cmH_2O/\mu V$	7 0.5 (0.3-0.5)
PSV, n PSV, cmH_2O	9 9 (6-11)
PC, n Inspiratory Pressure, cmH_2O	4 14 (11-15)
Positive End-expiratory Pressure, cmH_2O	5 (5-6)
FiO_2	30 (25-40)

Endotracheal tube data	
ETT size, mmID	3.5 (3.5-4.5)
Cuffed ETT	18 (90%)
Air leakage around ETT, %	5 (2-7)
Sedation status	
Comfort score	14 (12-16)
Sedation score	12 (5-26)
Continuous intravenous sedation	14 (70%)
Analgesic bolus only	5 (25%)
Outcome	
SBT failure	0 (0%)
Time between SBT and first extubation, h	18 (1.5-43.5)
Reintubation in the 48h after extubation	2 (10%)

ETT: Endotracheal Tube; MV: Mechanical Ventilation; PICU: Pediatric Intensive Care Unit; REE: Resting Energy Expenditure; SBT: Spontaneous Breathing Test.

Data are expressed as median (25-75 interquartile range) or n (%).

Table 2: Clinical status and respiratory muscle assessment before, during and after SBT.

	Before SBT	During SBT	After SBT	p
Respiratory status				
SpO_2	99 (96-100)	99 (95-100)	97 (95-100)	0.79
Measured Respiratory Rate, min^{-1}	29 (22-31)	35 (26-40)	30 (25-37)	0.23
V_T, ml/kg	7.1 (5.4-7.8)	6.4 (4.4-7.8)	7.8 (5.1-8.1)	0.89
V_M, L/min	1.5 (0.9-2.8)	1.7 (1.1-2.8)	1.6 (0.9-3.2)	0.76
Rapid Shallow Breathing Index (RR/V_T), breath/min/ml/kg	4.1 (3.1-6.3)	5.4 (4.0-7.3)	5.0 (3.9-6.1)	0.76
Comfort Score	14 (12-16)	14 (12-16)	13 (12-16)	0.86
Hemodynamic status				
Cardiac Rate, min^{-1}	115 (97-135)	121 (99-143)	120 (101-141)	0.76
Mean Arterial Pressure, mmHg	69 (59-85)	72 (62-80)	72 (62-83)	0.96
WOB Indices				
P_{ES} derived data				
Swing P_{ES}, cmH_2O	3.9 (1.7-6.2)	5.5 (2.7-8.5)	3.1 (1.1-5.5)	0.33
PTP_{ES}/min, $cmH_2O.s.min^{-1}$	23 (5-89)	83 (24-110)	31 (10-69)	0.75
EA_{DI} derived data				
Peak EA_{DI}, µV	7.5 (3.2-16.3)	15.9 (5.2-22.1)	9.1 (3.0-14.4)	0.059
Neuromechanical efficiency ($\Delta P_{ES}/\Delta EA_{DI}$)	0.6 (0.4-1.1)	0.8 (0.3-1.0)	0.6 (0.2-1.5)	0.56
Neuroventilatory efficiency ($V_T/\Delta EA_{DI}$)	5.1 (2.2-21.4)	3.3 (1.4-6.7)	5.2 (1.8-26.2)	0.3
Indirect Calorimeter derived data				
VO_2/kg, ml/kg/min	3.6 (3.1-4.6)	3.8 (3.0-5.2)	3.8 (3.2-5.2)	0.98
$VO_{2\ resp}$/kg, ml/kg/min	N/A	-0.2 (-0.5-0.44)	N/A	
VCO_2/kg, ml/kg/min	2.8 (2.3-3.3)	2.5 (2.1-3.6)	2.5 (2.3-3.3)	0.57
Resting Energy Expenditure, kcal/kg	23 (21-29)	24 (19-33)	23 (21-33)	0.96
Respiratory Quotient	0.71 (0.69-0.78)	0.72 (0.68-0.78)	0.70 (0.65-0.77)	0.70

EA_{DI}: Electrical Activity of the Diaphragm; N/A: not applicable; NAVA: Neurally Adjusted Ventilatory Assist; PC: Pressure Control; P_{ES}: Esophageal Pressure; PICU: Pediatric Intensive Care Unit; PSV: Pressure Support Ventilation; PTP_{ES}: Pressure-Time Product; SBT: Spontaneous Breathing Test; V_M: Minute Volume; V_T: Tidal Volume; WOB: Work of Breathing.

Data are expressed as median (25-75 interquartile range) or n (%).

Supplementary material

Subject selection:

Eligibility

Consecutive children aged between 1 month and 18-year-old admitted to the PICU, intubated and mechanically ventilated were eligible. The screening was performed by a research assistant every working day. Eligible patients were included if they were deemed to be ready for an extubation readiness test as per the attending team, providing the research team and the equipment were available. In particular, the following criteria were required: (i) improvement in the underlying condition that led to intubation, (ii) presence of spontaneous breathing and adequate oxygenation, (iii) adequate mental status, (iv) effective cough and (v) no planned operative procedure in the next 12 hours.

Inclusion criteria

- The patient is deemed to be ready for an extubation readiness test as per the attending team. In particular, the following criteria should be met:
    - Improvement in the underlying condition that led to intubation;
    - Presence of spontaneous breathing, and adequate oxygenation: $FiO_2 \leq 0.6$ (to obtain a SpO2 between 92 and 97%), with Positive End Expiratory Pressure < 8 cmH_2O;
    - Adequate mental status: Arousal;
    - Effective cough;
    - No planned operative procedure requiring heavy sedation in the next 12 hours.

Exclusion criteria

- Contraindications to the placement of a new nasogastric tube (*e.g.* trauma or recent surgery in cervical, esophageal, or nasopharyngeal regions, severe coagulation disorder);
- Hemodynamic instability requiring milrinone ≥ 0.5µg/kg/min, dopamine ≥ 5µg/kg/min, epinephrine ≥ 0.03µg/kg/min, norepinephrine ≥ 0.03µg/kg/min, or dobutamine ≥ 5µg/kg/min;
- Severe respiratory instability, and in particular PaCO2 > 80 mmHg on the last blood gas in the last 4 hours;
- Axillary temperature >38°;
- Cuff leaks >10%, calculated by the ventilator as mean inspired tidal volume minus mean expired tidal volume divided by inspired tidal volume;
- Absence of parental or tutor consent;
- Patient for whom a limitation of life support treatments is discussed or decided.

Schofield equations calculation (kcal/day):

(0.167*weight) + (1517.4*height) - 617.6 for boys < 3 years-old; (16.25*weight) + (1023.2*height) - 413.5 for girls < 3 years-old; (19.6*weight) + (130.3*height) +414.9 for boys from 3 to 10 years-old; (16.97*weight) + (161.8*height) + 371.2 for girls from 3 to 10 years-old; (16.25*weight) + (137.2*height) + 515.5 for boys > 10 years-old and (8.365*weight) + (465*height) + 200 for girls > 10 years-old

Sample size

We hypothesized that VO_{2resp}, P_{ES} and EA_{DI} data would be correlated with a Pearson's coefficient correlation of at least 0.8. Considering a type-1 error risk of 0.05 (2-tailed), the inclusion of 12 patients was necessary to reach a power of 90% to confirm the correlation between those variables. We planned to study a sample of 20 patients to increase representativeness.

Statistical analysis

Data were expressed as median values (with interquartile range, IQR) for continuous variables, and number and/or frequency (%) for categorical data. Differences for categorical variables were tested using chi-square or Fisher's exact test (when expected frequencies were less than five). Differences in continuous variables were assessed using non-parametric Mann–Whitney test or paired t-test, depending on the variable distribution. Repeated measures analysis of variance (ANOVA) was used to compare the different conditions (before, during and after SBT in CPAP) on the different variables. Pearson's correlation coefficient (R) and determination coefficient (R^2) were used to evaluate the correlation between changes in Swing P_{ES}, PTP_{ES}, EA_{DI} and VO_2. A correlation was considered as poor, moderate, good and excellent if R^2 was lower than 0.5, between 0.5 and 0.75, between 0.75 and 0.9 and higher than 0.9 respectively. All p values were two-tailed and considered significant if $p < 0.05$. Statistical analyses were performed using SPSS 24.0 (SPSS, Inc, Chicago, IL).

Discussion

Nous avons montré dans cette étude physiologique qu'un test de sevrage ventilatoire en PPC était associé à une tendance à l'augmentation des indices reflétant le travail respiratoire, à savoir la P_{ES} et l'AE_{DI}. En revanche, la VO_2 obtenue par calorimétrie indirecte n'était pas modifiée par l'épreuve de sevrage.

Plusieurs hypothèses peuvent expliquer ce résultat. La première est que la calorimétrie indirecte, bien qu'étant un outil fiable et reproductible, pourrait ne pas être suffisamment sensible et précise pour détecter une faible augmentation du travail respiratoire, en particulier chez le jeune nourrisson. Le travail respiratoire était relativement faible chez nos patients, y compris pendant le test de sevrage. La population étudiée était hétérogène en termes de pathologie, degré de sédation et durée de ventilation, pour espérer mettre en évidence une tendance commune chez tous les patients.

Parallèlement à l'étude des différents aspects du travail respiratoire au cours du sevrage ventilatoire, nous avons soulevé un point important dans notre travail concernant les dépenses caloriques mesurées. En effet, nous avons constaté que la dépense énergétique de repos mésurée par la calorimétrie indirecte était nettement inférieure aux valeurs fournies par l'équation prédictive de Schofield, reconnue pour être l'une des équations de référence pour prédire les dépenses caloriques de repos. Déjà, le manque de précision de ces équations chez les patients admis en réanimation avait été prouvé [235, 236]. Mais dans notre étude, les différences étaient relativement importantes et amènent à penser que les dépenses énergétiques de repos des patients à la phase de sevrage, donc à distance de la phase aiguë de la maladie, sont probablement assez faibles, en dépit d'un travail respiratoire augmenté.

DISCUSSION GENERALE

QUEL EST L'INTERET DE MESURER LE TRAVAIL RESPIRATOIRE DANS L'INSUFFISANCE RESPIRATOIRE AIGUË DE L'ENFANT ?

A l'aire de l'individualisation de la stratégie thérapeutique

Jadis dominée par des patients naïfs atteints de pathologies simples et mono-défaillantes (bronchiolites, traumatismes graves, infections, *etc.*), la population admise aux soins intensifs pédiatriques a considérablement évolué au cours des 10 dernières années. Les progrès diagnostiques et thérapeutiques expliquent l'augmentation des patients atteints de pathologies chroniques et multi-organiques aux soins intensifs [237]. Face à une population plus hétérogène et plus complexe, les réanimateurs pédiatriques et les équipements dont ils disposent doivent faire face à ce nouveau défi. La prise en charge thérapeutique doit être individualisée pour chaque malade, tenant compte de son âge, de sa maladie, de son évolution, de sa réponse aux traitements standards, *etc*. Par exemple, un SDRA secondaire à un sepsis chez un patient adolescent immuno-déficient ne peut être traité de la même manière qu'un SDRA secondaire à une pneumopathie chez un nourrisson. Pour surmonter ce nouveau challenge, différentes technologies sont apparues ou réapparues pour assister le clinicien dans la prise en charge ventilatoire de ces patients [2]. L'intérêt potentiel des différents outils au cours du processus de la maladie est représenté sur la Figure 10.

Phase de la maladie		Phase initiale	Phase d'état	Sevrage ventilatoire	Post-extubation
Principaux Enjeux		Choisir le type de support ventilatoire	Assurer l'efficacité de la VM et limiter ses complications	Déterminer le meilleur moment pour le sevrage	Identifier une ré aggravation
Principaux Outils	Paramètres cliniques	✓	✓	✓	✓
	$P_{0.1}$			✓	
	VO_2			✓	
	Pléthysmographie/TIE	✓	✓		✓
	Echo diaphragmatique		✓	✓	
	P_{ES}, P_{GAS}	✓	✓	✓	✓
	EA_{DI}		✓	✓	✓
	Stim des N.phréniques	✓		✓	

Evolution de la maladie

Figure 10 : Intérêt potentiel des différents outils d'évaluation du travail respiratoire au cours du processus évolutif de la maladie.
EA_{DI} : Activité Electrique du Diaphragme ; P_{ES} : Pression Œsophagienne ; P_{GAS} : Pression Gastrique ; Sim des N.phréniques : Stimulation des nerfs phréniques TIE : Tomographie par Impédance Electrique ; VO_2 : Consommation en Oxygène.

Des outils pour améliorer la prise en charge initiale des patients

A cette étape, le principal enjeu est de déterminer s'il y a ou non indication à un support ventilatoire et si oui quel est le mode le plus approprié. Bien que les critères d'intubation soient assez bien définis, les critères d'initiation d'une VNI ou d'un support HFNC ne sont pas validés par des études prospectives randomisées et sont soumis à la subjectivité du clinicien. Alors que des outils objectifs d'évaluation du travail respiratoire seraient conceptuellement pertinents dans ces situations, la réalité clinique rend l'exercice difficile avec les outils dont on dispose actuellement, en dépit de l'importance de cette évaluation soulignée dans notre 2ème article. Le degré d'instabilité clinique et le fait que les patients soient en ventilation spontanée et rarement sédatés limite la place de la plupart des outils de mesure. La prise en charge des patients est alors davantage basée sur des critères cliniques, faciles d'accès et bien maitrisés des cliniciens.

Néanmoins on peut concevoir que certaines mesures non ou peu invasives, utilisables facilement, puissent aboutir à des résultats rapides et informatifs. Par exemple, la pléthysmographie ou la tomographie par impédance électrique permettraient de juger de l'efficacité d'une thérapie (VNI, bronchodilatateurs, physiothérapie, *etc.*). Pour le moment, leur utilisation en pratique clinique est limitée par le peu d'études cliniques sur ce sujet.

Des outils pour optimiser la prise en charge à la phase d'état de la maladie

L'enjeu de la phase d'état de la maladie respiratoire est de garantir l'efficacité des thérapies instituées, principalement la VM, tout en limitant leurs complications. Les différents outils d'évaluation du travail respiratoire prennent ici toute leur place et leur niveau d'invasivité est à pondérer face au fait que le patient est souvent sédaté et instable.

Des outils pour évaluer le risque de complications liées à la VM

En apportant une analyse séparée des deux composantes de la mécanique ventilatoire que sont le poumon et la cage thoracique, la mesure de la P_{TP} permet d'évaluer le risque de lésions pulmonaires induites par la ventilation et d'adapter les réglages de la VM de sorte à minimiser ce risque [123, 130, 227]. Pour autant, les résultats de notre 1er travail ne permettent pas de valider l'estimation de la P_{PL} par la P_{ES} en pédiatrie. Par conséquent l'interprétation de la valeur brute de la P_{ES} (et donc de la P_{TP}) et l'intérêt d'un facteur correctif restent encore discutables chez l'enfant.

Alors que la VM augmente le risque de dysfonction et d'atrophie diaphragmatique [17-20], la surveillance du principal muscle respiratoire au cours de l'évolution de la maladie est importante. L'AE_{DI} fourni des données continues relatives à la fonction diaphragmatique, comme nous l'avons montré dans notre 3ème travail ainsi que dans celui en Annexe 1. Cet outil est utile pour détecter une activité faible, témoignant possiblement d'une sur-assistance ventilatoire, de même qu'une activité trop importante, témoin d'une sous-assistance ou d'une mauvaise interaction patient-ventilateur [47]. Pour autant le niveau optimal d'activité diaphragmatique reste à préciser (même si des valeurs d'AE_{DI} <3 ou >30 µV semblent anormales) [26]. A cette étape de la maladie, la $P_{0.1}$, la stimulation diaphragmatique et l'échographie diaphragmatique pourraient permettre aussi d'obtenir des informations sur la fonction diaphragmatique et son degré d'atrophie, mais à ce jour, les travaux en pédiatrie sont trop limités pour que ces outils soient utilisés en pratique clinique.

Chez les patients en VM, l'impact de la ventilation spontanée sur le parenchyme pulmonaire (concept de *patient self inflicted lung injury*) suscite un intérêt croissant depuis quelques années

[238]. Chez les patients ayant un SDRA modéré à sévère, Papazian *et al.* ont montré un bénéfice de l'abolition de l'activité respiratoire spontanée par des bloqueurs neuromusculaires dans les 48 premières heures de VM [239]. Dans les pathologies moins sévères en revanche, les données de la littérature sont plus controversées [240]. Mais quel que soit la réalité de ses effets, et bien que la relation entre ventilation spontanée et risque de *patient self inflicted lung injury* soit complexe, il semble important d'étudier l'activité respiratoire spontanée du patient ventilé mécaniquement, en particulier dans le SDRA, soit de manière directe (avec l'AE_{DI}), soit indirectement via la mesure des pressions générées. Par exemple, la mesure de $P_{0.1}$ pourrait permettre d'estimer ce risque. Une $P_{0.1}$ élevée, reflet d'une activité inspiratoire importante, associée à un V_T élevé, témoin d'une certaine efficacité mécanique, pourrait alerter sur un risque important de lésions pulmonaires induites par le patient.

Des outils pour garantir l'efficacité de la VM et optimiser ses réglages

Comme nous l'avons montré dans nos 2ème et 4ème travaux, la mesure des pressions œsogastriques permet d'évaluer l'efficacité d'une stratégie thérapeutique sur la décharge des muscles respiratoires. Ces mesures pourraient être aussi judicieuses pour évaluer l'effet d'autres traitements, comme le positionnement du patient, la kinésithérapie respiratoire ou des médicaments.

Pour autant, il reste à déterminer quel est le niveau optimal de travail respiratoire à viser chez les patients ventilés mécaniquement. Il est possible que plusieurs facteurs doivent être pris en compte pour répondre à cette question, comme le type de support, la pathologie et le risque de développer une dysfonction diaphragmatique. De par le moindre risque de complications en VNI, il est recommandable de viser un faible niveau de travail respiratoire, proche de la valeur normale, autrement dit une décharge optimale des muscles respiratoires. En ventilation invasive par contre, il est probable que le maintien d'une activité respiratoire minimale puisse améliorer la fonction diaphragmatique [241, 242].

Des outils pour améliorer l'interaction patient-ventilateur

Notre 3ème travail a mis en évidence que les asynchronies respiratoires sont très fréquentes en pédiatrie. Alors que l'inspection visuelle des tracés du respirateur est une méthode de faible sensibilité [15, 116], leur mise en évidence au chevet avec les mesures de P_{ES} ou d'AE_{DI} est plus fiable. L'AE_{DI} permet de déterminer précisément le début et la fin de l'effort respiratoire neural et peut être alors considérée comme la méthode de référence pour l'identification des asynchronies. Pour autant, nous n'avons pas constaté d'impact clinique important dans cette population pédiatrique, confirmant les résultats d'une étude adulte publiée récemment [243]. Il est donc difficile d'établir si l'amélioration de l'interaction patient-ventilateur doit être un objectif important à viser dans la gestion de la VM. Et si c'est le cas la stratégie thérapeutique pour y parvenir reste à préciser (optimisation des réglages, gestion de la sédation, *etc.*).

Des outils pour optimiser la prise en charge ventilatoire pendant la phase de sevrage

L'apport des mesures physiologiques, comme les pressions œsogastriques ou l'AE_{DI}, pour évaluer le travail respiratoire pendant cette phase a été décrit dans littérature et confirmé dans notre 4ème étude. La mesure de la VO_2, en revanche, ne semble pas une méthode valable pour détecter une augmentation du travail respiratoire pendant cette phase.

Une des applications potentielles de ces outils est d'identifier plus facilement les patients qui ont une atteinte importante des muscles respiratoires et qui pourraient nécessiter un traitement approprié avec mobilisation et réentrainement à l'effort [244]. Alors que le test en ventilation spontanée est une épreuve effectuée tardivement dans le processus de sevrage, nous pourrions supposer qu'une évaluation plus précoce du risque de sevrage prolongé par des outils comme l'échographie, la mesure de $P_{0.1}$ ou l'AE_{DI} pourrait être bénéfique.

QUELS OUTILS POUR QUELS PATIENTS ?

En plus du stade d'évolution de la maladie, plusieurs éléments entrent en compte pour déterminer l'intérêt d'évaluer le travail respiratoire dans l'insuffisance respiratoire aiguë de l'enfant.

Tout d'abord, la sévérité et le degré de stabilité du malade doivent être considérés et le rapport bénéfice-risque mesuré. Bien que ces outils de mesure soient pour la plupart minimalement invasifs, leur utilisation ne doit pas aggraver la situation du patient. Les contre-indications relatives à chaque outil doivent aussi être respectées.

Le bénéfice de l'évaluation du travail respiratoire varie grandement en fonction de la pathologie du patient (Tableau 3). Pour les pathologies communes, comme la bronchiolite, la physiopathologie et l'évolution de la maladie sont suffisamment connus et la prise en charge relativement standardisée, rendant l'évaluation physiologique moins pertinente. En revanche, pour les pathologies plus rares et plus complexes (maladies orphelines, pneumopathies interstitielles, pathologies malformatives, *etc.*) ou dont la présentation est très hétérogène (SDRA), l'intérêt de l'évaluation objective du travail respiratoire est bien plus grand, comme nous l'avons montré dans notre 2ème travail.

Dans le cadre des pathologies interstitielles ou indéterminées, cette analyse aide à mieux comprendre la physiopathologie de la maladie. Elle peut par exemple orienter vers une atteinte obstructive ou restrictive [245].

Pour les patients atteints de SDRA, les mesures physiologiques sont particulièrement intéressantes, et elles pourraient même contribuer à une amélioration de la condition du patient, comme l'ont décrit *Chen et al.* [127]. Elles aident à évaluer plus précisément le risque de lésions pulmonaires induites par la ventilation et de dysfonction diaphragmatique, et à optimiser les réglages de la VM en conséquence. Des outils comme la Tomographie par Impédance Electrique ou la pléthysmographie permettent eux aussi de titrer la PEEP ou le V_T pour les patients avec un SDRA.

Chez les patients pour lesquels l'épisode aigu survient dans le cadre d'une pathologie respiratoire chronique (bronchodysplasie, maladie neuromusculaire, pneumopathie interstitielle, *etc.*), la part aigue de la maladie est parfois difficile à distinguer de l'évolution naturelle de l'insuffisance

respiratoire chronique sous-jacente. Pour ces patients, admis fréquemment en soins intensifs pédiatriques [246], une évaluation précise du travail respiratoire peut être bénéfique pour mieux comprendre la physiopathologie de la maladie.

Pour les patients ayant bénéficié d'une chirurgie lourde, en particulier abdominale, ainsi que pour les patients obèses, la contribution des muscles abdominaux par rapport au diaphragme et l'influence de la cage thoracique dans la mécanique ventilatoire peuvent être appréciées grâce à la mesure des pressions œsogastriques.

Enfin, une évaluation plus précise du travail respiratoire pourrait aider au processus de sevrage chez les patients à risque de neuromyopathie de réanimation. Pour les patients admis en post transplantation d'organe ou pour un choc septique, ou qui ont reçu des curares ou des corticoïdes de manière prolongée, une telle évaluation permettrait d'identifier précocement les difficultés potentielles de sevrage ventilatoire et d'optimiser le plan de traitement en conséquence [31, 247, 248].

Tableau 3 : Principaux intérêts des différents outils de mesure du travail respiratoire en fonction de la pathologie respiratoire.

	Pressions œsogastriques	**AE_{DI}**	**TIE/pléthysmographie**	**Echographie diaphragmatique**
Syndrome de détresse respiratoire Aiguë	-Evaluer le risque de complications de la VM -Titrer PEEP -Optimiser le sevrage	-Optimiser niveau de support -Quantifier les asynchronies -Optimiser le sevrage	-Titrer la PEEP -Evaluer l'effet des thérapies	-Evaluer la fonction diaphragmatique
Décompensation aigue d'une pathologie chronique	-Améliorer la compréhension de la physiopathologie		-Evaluer l'évolution de la maladie -Evaluer l'effet des thérapies	
Chirurgie thoracique ou abdominale lourde	-Evaluer le risque de complications de la VM -Titrer la PEEP -Optimiser le sevrage	-Optimiser niveau de support -Optimiser le sevrage	-Titrer la PEEP -Evaluer l'effet des thérapies	-Rechercher une paralysie diaphragmatique
Patients à risque de sevrage prolongé	-Optimiser le sevrage	-Identifier une dysfonction diaphragmatique -Optimiser le sevrage -Prévenir la surassistance		-Identifier une dysfonction diaphragmatique

AE_{DI} : Activité Electrique du Diaphragme ; PEEP : Pression Expiratoire Positive en fin d'Expiration ; TIE : Tomographie par Impédance Electrique ; VM : Ventilation Mécanique.

QUELLES SONT LES LIMITES DES OUTILS DE MESURES DU TRAVAIL RESPIRATOIRE ?

A ce jour, en dépit des informations physiologiques pertinentes qu'apportent ces technologies, leur impact sur le devenir des patients n'a pas été formellement démontré, en particulier en pédiatrie. Pour la plupart de ces outils, leur intérêt en pratique clinique reste encore à être évalué dans des études autres que descriptives, idéalement des essais randomisés contrôlés.

De manière générale et comme pour toute technologie, les utilisateurs doivent connaitre les principes de base de leur fonctionnement, les avantages et limitations de chaque outil pour garantir un usage approprié [249]. Une mauvaise interprétation des mesures observées peut conduire à des conséquences graves pour le patient, d'autant plus que dans certains cas, les valeurs normales sont manquantes chez l'enfant. Il est admis qu'un certain niveau d'expertise soit requis pour manier ces outils de mesure, bien que certains d'entre eux soient relativement simples d'utilisation. De même, la plupart de ces technologies requièrent du matériel spécifique, souvent couteux.

Enfin, une autre limite à prendre en compte est le degré d'invasivité de ces techniques, qui est néanmoins à relativiser en fonction de la situation du patient (sédaté ou non) et des bénéfices potentiels (*Cf.* Travail n°2 et Annexe 1).

PERSPECTIVES

Dans un 1er temps, pour confirmer l'intérêt de ces différents outils dans la pratique clinique quotidienne en soins intensifs pédiatriques, des études de type « essai randomisé contrôlé » seraient idéales. Pour autant leur réalisation n'est pas toujours possible, pour des raisons éthiques, financières ou à cause d'un nombre limité de patients éligibles. En ciblant les recherches sur les patients les plus complexes ou difficiles, il est probable que les résultats en terme d'impact clinique soient plus probants. Ces futurs travaux permettront d'encourager l'utilisation des différents outils et le financement du matériel nécessaire.

Aussi, le domaine respiratoire n'est pas le seul à voir l'émergence d'outils physiologiques de monitorage. Face à la multiplication de ces technologies souvent complexes, il semble important de développer en parallèle des règles de bonne utilisation et des méthodes d'analyse automatique pour faciliter l'interprétation des données par le clinicien, pour qu'elles puissent ensuite aboutir à un bénéfice pour le patient [250]. Plus globalement, intégrer ces données dans un système d'aide à la décision clinique devrait permettre de générer des informations diagnostiques et thérapeutiques pertinentes directement accessibles au chevet du malade.

Les industriels jouent un rôle majeur dans le développement de nouveaux outils tels que ceux évoqués dans ce travail. Une collaboration entre les soignants, les chercheurs et les industriels est indispensable pour que ces nouvelles technologies répondent à un besoin réel pour les patients. Il est aussi nécessaire que les dispositifs commercialisés par les compagnies prennent en compte non seulement les particularités du patient sévèrement malade, mais aussi les spécificités pédiatriques. Chez l'enfant, les dispositifs utilisant simultanément plusieurs technologies sont à privilégier, car le degré d'invasivité est réduit. La complémentarité permet aussi d'évaluer plusieurs facettes du problème. Par exemple, bien qu'elles ne soient disponibles que pour un but recherche à ce jour, les sondes œsophagiennes disposant d'un ballonnet pour la mesure de P_{ES} et de capteurs pour la mesure de l'AE_{DI} sont d'intérêt majeur. Ce seul dispositif de mesure combine deux des principaux outils d'évaluation.

CONCLUSION

Bien qu'elle soit d'une grande importance dans la prise en charge de l'insuffisance respiratoire aiguë, la VM est potentiellement délétère pour le poumon et le diaphragme. Pour le clinicien, s'assurer de son efficacité et minimiser ses effets néfastes est une tache capitale mais ardue, tant l'évaluation clinique est difficile lorsque le travail respiratoire est partagé entre le ventilateur et le patient. Différentes méthodes ont été développées pour assister le clinicien dans l'évaluation de la mécanique ventilatoire au chevet de l'enfant admis en soins intensifs, et ce aux différents stades d'évolution de la maladie. A la phase aiguë de la pathologie, l'évaluation de la mécanique et de la fonction des muscles respiratoires permet d'améliorer la compréhension des mécanismes physiopathologiques de la maladie et de guider le niveau de support ventilatoire pour garantir son efficacité et limiter ses complications potentielles, tout en assurant une bonne interaction entre le patient et son ventilateur. L'évaluation du travail respiratoire est aussi importante à la phase de sevrage de la VM afin de s'assurer que la fonction respiratoire du patient est compatible avec une décroissance du niveau de support.

Parmi ces outils, la mesure des pressions œsogastriques et la mesure de l'activité électrique du diaphragme sont des outils intéressants pour l'évaluation du travail respiratoire à l'aire de l'individualisation de la prise en charge. Chez les patients atteints d'une maladie respiratoire complexe, d'un SDRA, ou ayant une maladie chronique sous-jacente, ces mesures pourraient avoir un impact pour réduire la durée de ventilation et la durée de séjour en réanimation.

COMMUNICATIONS ECRITES ASSOCIEES AU DOCTORAT

1. Reliability of automatic analysis to quantify patient-ventilator asynchrony in critically ill children. American Thoracic Society Congress, Washington DC, USA. Mai 2017
2. Diaphragm electrical activity monitoring as a breakpoint in the management of a tetraplegic child. American Thoracic Society Congress, Washington DC, USA. Mai 2017
3. Esogastric pressure measurement as a guide for noninvasive ventilation indication and settings in infants with complex hypercapnic respiratory failure. World Congress on Pediatric Intensive and Critical Care, Toronto, Canada. Juin 2016
4. Indirect Calorimetry as a tool to assess work of breathing during weaning from mechanical ventilation in children. International consortium on mechanical ventilation in children, Montreal, Canada, Septembre 2017
5. Assessment of Esophageal pressure reliability to estimate pleural pressure in critically ill children. International consortium on mechanical ventilation in children, Montreal, Canada, Septembre 2017

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ANNEXES

ANNEXE 1 : DIAPHRAGM ELECTRICAL ACTIVITY MONITORING AS A BREAKPOINT IN THE MANAGEMENT OF A TETRAPLEGIC CHILD

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LETTER Open Access

Diaphragm electrical activity monitoring as a breakpoint in the management of a tetraplegic child

Guillaume Mortamet*, François Proulx, Benjamin Crulli, Nadia Savy, Philippe Jouvet and Guillaume Emeriaud

Keywords: Mechanical ventilation, Electrical activity of the diaphragm, Diaphragm function, Pediatric intensive care unit, Pediatrics

Over the last decade, new technology has been developed to continuously record the electrical activity of the diaphragm (EAdi) at the bedside [1]. EAdi monitoring has been shown to be useful in assessing the patient's ventilatory drive, in adjusting ventilatory support, and in detecting patient–ventilator asynchrony [2–4]. In the present case, we highlight how monitoring EAdi could be a sensitive diagnostic tool to detect spontaneous respiratory cycles in a mechanically ventilated child with tetraplegia.

An 8-year-old girl was admitted to our pediatric intensive care unit (PICU) for a rapidly progressive right hemiparesis. The CT scan revealed a large C3–C4 medullary arteriovenous malformation predominantly. An urgent embolization was attempted, but severe edema and hemorrhagic transformation of venous thrombosis developed, leading to tetraplegia with dysautonomia. She underwent tracheostomy on day 12 due to the absence of spontaneous breathing. Three months later, an MRI scan showed extensive cervical cord fibrosis and atrophy at C2–C3–C4 levels (Fig. 1). On day 90, a phrenic nerve stimulation test was conducted to assess the potential for diaphragmatic pacing. No esophageal pressure deflection was induced by the stimulation. However, after a few respiratory pauses applied for the stimulation, we noted some spontaneous cycles on the EAdi recordings (about 5 μV) associated with esophageal pressure deflections (5–10 cmH_2O). Continuous monitoring of EAdi was performed while decreasing the level of ventilator support, thereby confirming an intermittent and small respiratory drive (Fig. 2). Weaning using NAVA was started in order to favor the patient's own respiratory drive, which gradually increased over time (Fig. 2). She was progressively and successfully weaned from the ventilator during daytime on day 162 and the patient was discharged home on day 374.

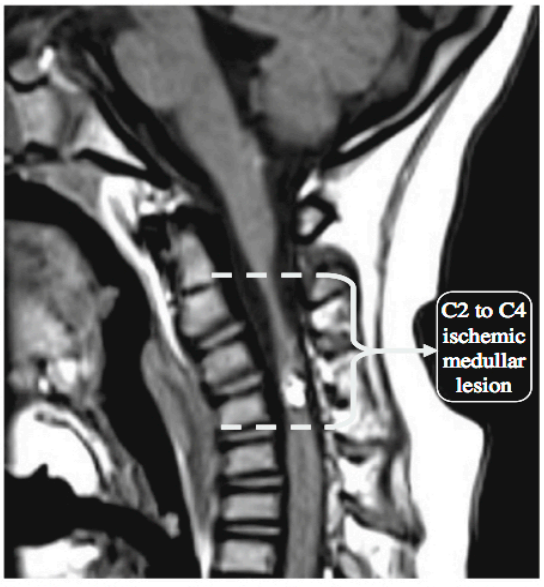

Fig. 1 Brain MRI image (T2-weighted) performed on day 90 showing extensive cervical cord fibrosis and atrophy, which was more severe at C2–C3–C4 levels

* Correspondence: mortam@hotmail.fr
Paediatric Intensive Care Unit, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, Montreal, QC H3T 1C5, Canada

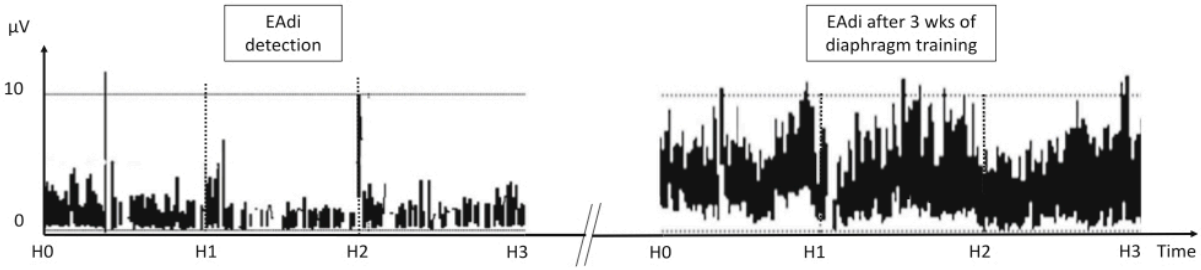

Fig. 2 Evolution of diaphragm electrical activity (*EAdi*) over 3-hour recordings (H0 to H3) at the time of diagnosis of the present ventilatory drive (*left panel*), showing intermittent EAdi at low levels, to 3 weeks (*wks*) later (*right panel*), after weaning in NAVA, showing sustained and higher levels of EAdi

Although it was not observed clinically, residual respiratory activity was evidenced by the EAdi monitoring. We hypothesize that complete ventilatory support during the first 3 months may have induced some diaphragmatic dysfunction [5], making it difficult to detect a respiratory drive. While we were initially considering the implantation of a diaphragmatic pacing device, we instead opted for a ventilation weaning challenge using NAVA, which allowed a gradual decrease in the level of support while preserving spontaneous breathing and diaphragm training.

This case illustrates that clinical assessment could lack sensitivity in detecting spontaneous breathing in patients with low respiratory drive. EAdi monitoring may be considered to precisely assess the presence of spontaneous breathing in complex patients, especially before making important management decisions.

Abbreviations
CT: Computerized tomography; EAdi: Electrical activity of the diaphragm; MRI: Magnetic resonance imaging; NAVA: Neurally adjusted ventilatory assist; PICU: Pediatric intensive care unit

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Availability of data and materials
Not applicable.

Authors' contributions
BC, FP, PJ, and GE were involved in patient care. GM, FP, NS, and BC carried out the chart review and data collection. GE obtained and analyzed the data on EAdi, and led the case report review and submission. GM wrote the manuscript, which was reviewed, edited, and approved by all authors. As the corresponding author, GM has full access to all the data in the study and has final responsibility for the decision to submit for publication.

Competing interests
PJ is supported by a scholarship award of the Fonds de Recherche du Québec—Santé, Ministry of Health and Sainte-Justine Hospital; was a consultant for Sage Therapeutic Inc.; and was invited to a congress by Medunik Inc and Covidien. GE's research program is supported by a scholarship award by the Fonds de Recherche du Québec—Santé; and GE is currently leading a feasibility study in neonatal ventilation which is financially supported by Maquet Critical Care. The remaining authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the patient and her family for publication of their individual details and accompanying images in this manuscript. The consent form is held by the authors and is available for review by the Editor-in-Chief.

Ethics approval and consent to participate
Not applicable.

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ANNEXE 2 : SLEEP STUDY AS A DIAGNOSTIC TOOL FOR UNEXPLAINED RESPIRATORY FAILURE IN INFANTS HOSPITALIZED IN THE PICU

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Sleep study as a diagnostic tool for unexplained respiratory failure in infants hospitalized in the PICU☆

Lucie Griffon, MD [a], Alessandro Amaddeo, MD [a,b], Guillaume Mortamet, MD [b,c,d], Christine Barnerias, MD [e], Véronique Abadie, MD, PhD [b,f], Jorge Olmo Arroyo, BSc [a], Livio de Sanctis, MSc [a], Sylvain Renolleau, MD, PhD [b,c], Brigitte Fauroux, MD, PhD [a,b,d,*]

[a] Pediatric noninvasive ventilation and sleep unit, AP-HP, Hôpital Necker Enfants-Malades, Paris, France
[b] Paris Descartes University, Paris, France
[c] Pediatric intensive care unit, AP-HP, Hôpital Necker Enfants-Malades, Paris, France
[d] Inserm U 955, Team 13, Créteil University, Paris XII, Créteil, France
[e] Pediatric neurology unit, AP-HP, Hôpital Necker Enfants-Malades, Paris, France
[f] General pediatric unit, AP-HP, Hôpital Necker Enfants-Malades, Paris, France

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ABSTRACT

Purpose: The aim of the study was to analyze the diagnostic and therapeutic value of a polygraphy (PG) in infants hospitalized for unexplained respiratory failure or life-threatening events in the PICU.
Material and methods: The PG of 13 infants (4 girls), mean age 6.8 ± 7.7 months, were analyzed.
Results: Eight infants were admitted for unexplained respiratory failure and 5 for life-threatening events. PG showed features suggestive of respiratory muscle weakness in 5 infants whose final diagnoses were nemaline rod myopathy (n = 2), congenital myasthenia (n = 2), and diaphragmatic dysfunction (n = 1). Four of these patients were successfully treated with noninvasive ventilation (NIV). PG was suggestive of brainstem dysfunction in 4 infants; 2 were treated successfully with NIV and another with caffeine. PG showed obstructive sleep apnea in 3 infants; 2 were treated successfully with NIV and one patient was lost during follow up. A typical pattern of congenital central hypoventilation syndrome was observed in the last patient who was treated successfully with invasive ventilation. One patient with diaphragmatic dysfunction and one with brain stem dysfunction died.
Conclusions: PG may assist the diagnosis and guide the management of unexplained respiratory failure or life-threatening events in infants hospitalized in the PICU.

1. Introduction

Respiratory failure is the most common reason of admission to the pediatric intensive care unit (PICU). Indeed, in a recent prospective multicentre survey including more than 10,000 children, the respiratory system was the most common primary system of dysfunction representing 33.5% of admissions [1]. In the majority of patients, the cause of the respiratory failure is obvious such as acute asthma, bronchiolitis or another type of respiratory infection in a previously healthy or an immunocompromised child. More rarely, the respiratory failure is due to the exacerbation of an underlying disease such as a neuromuscular or lung disease. Acute "unexplained" respiratory failure occurring without a precipitating factor or any clinical context (such as fever) that may orientate a diagnosis, in an infant without a known or defined underlying condition, is rare and requires a prompt diagnosis in order to institute the most appropriate treatment.

Respiratory polygraphy (PG) analyzes the breathing pattern and gas exchange during sleep, enabling the diagnosis of central and/or obstructive apneas or hypopneas [2]. But, by recording simultaneously airflow and thoracic and abdominal movements, it may also show tracings evocative of a respiratory muscle dysfunction or a hypoventilation, characterized by a decrease in the amplitude of breathing, which may not fulfill the strict criteria of apnea or hypopnea [3,4]. PG has the advantage that it is totally noninvasive and may be performed at the bedside, inside the PICU. PG, by giving information on the breathing pattern and consequent abnormal gas exchange, may also guide treatment, and in particular noninvasive ventilation (NIV) in case of alveolar

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* Corresponding author at: Pediatric Noninvasive Ventilation and Sleep Unit, Hôpital Necker Enfants-Malades, 149 rue de Sèvres, Paris, France. Tel.: +33 1 71 19 60 92; fax: +33 1 44 49 35 15.
E-mail address: brigitte.fauroux@aphp.fr (B. Fauroux).

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hypoventilation and noninvasive continuous positive airway pressure (CPAP) in case of obstructive events [5].

The aim of the study was to describe the PG findings and the therapeutic implications of this investigation in infants admitted to the PICU with unexplained respiratory failure or life threatening events.

2. Material and methods

2.1. Patients

The PG of all consecutive infants admitted to the medical PICU between September 2013 and September 2015 were analyzed. The PICU comprises 13 beds and admits a mean of 500 children between the age of one month and 18 years for acute medical conditions per year.

The medical records of the patients were systematically reviewed and medical history and demographics data were collected for each patient. Interventions after the PG and the patient's outcome were analyzed. The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval from the Ethical Committee of Necker university hospital (CPP Ile de France II).

2.2. Polygraphy

PG with the recording of nasal pressure by means of a nasal canula, thoraco-abdominal movements by means of inductive plethysmography, respiratory sound, body position, pulse oximetry (SpO_2), and heart rate was performed during spontaneous breathing in room air (Cidelec, Saint Gemme sur Loire, France or Alice 6, Respironics, Carquefou, France). All events were scored according to the American Academy of Sleep Medicine (AASM) manual and following update [2,6]. Obstructive apnea was defined as the absence of nasal airflow, with continued chest wall and abdominal movements for at least two breaths. Central apnea was defined as the absence of airflow with the cessation of respiratory effort, lasting more than 20 seconds or of shorter duration and associated with a bradycardia in infants less than one year of age and/or a 3% desaturation; central apnea occurring after gross body movements or after sighs was not considered as a pathological finding. Mixed apnea was defined as an apnea that usually began as central and ended as obstructive according to changes in the chest, abdominal, and flow traces. Hypopnea was defined as a decrease in nasal airflow of at least 30% with a corresponding decrease in SpO_2 of at least 3% and/or an arousal. The apnea-hypopnea index (AHI) was calculated as the sum of apnea and hypopnea events per hour of total sleep time [2].

Besides these apneic and hypopneic events, other events were looked for:

- progressive simultaneous decrease in airflow and thoracic and abdominal movements accompanied or not by a change in gas exchange, suggestive of a decrease in central drive or global inspiratory muscle weakness [3,4]
- paradoxical breathing with opposition phase on the thoracic and abdominal belts, suggestive of diaphragmatic dysfunction or weakness of the intercostal muscles [4].

Mean, minimal pulse oximetry (SpO_2) values and the percentage of total sleep time spent with $SpO_2 < 90\%$ were calculated. The oxygen desaturation index (ODI) was defined as the number of SpO_2 drops of at least 3% per hour of total sleep time. Transcutaneous carbon dioxide pressure ($PtcCO_2$) was recorded using the SenTec Digital Monitor (software version SMB SW-V06.10; MPB SW-V04.03). Mean and maximal values of $PtcCO_2$ were calculated. All the SpO_2/$PtcCO_2$ data that were not interpretable (probe detachment, outlier data, artifacts) were discarded from the analysis.

2.3. Statistical analysis

Data are expressed as mean ± standard deviation or median [25%–75% interquartiles].

3. Results

During the 2 year period, 19 PGs were performed in children hospitalized in the PICU. Six PG were performed in children with a known underlying disease (bronchopulmonary dysplasia (n = 2), Pierre Robin syndrome (n = 1), Rubinstein-Taybi syndrome (n = 1), tongue hemangioma (n = 1), and brainstem dysfunction (n = 1). Thirteen PG were performed in infants (4 girls), median age 7 months (range 1 to 24 months) without a known underlying condition. The reason for PICU admission was acute respiratory failure in 8 infants and life-threatening events requiring resuscitation maneuvers with hypoxemia ± hypercapnia, and bradycardia in the 5 other patients (Table 1). None of the patients had fever and no precipitating factor was identified for all patients. Chest X-rays, electrocardiography, and echocardiography were normal in all patients. All the infants presented a least one for the following clinical features: peripheral or axial muscle weakness (n = 8, patients #1 to #9 with the exception of patient #5), swallowing difficulties with false passages (n = 4, patients #6 to #9), episodes of bradycardia (n = 5, patients #6 to #9 and patient #12), and/or acute obstructive events (n = 3, patients #10 to #12). Patient #5 presented features of generalized scleroderma and patient #13 was tracheotomised in his country because of recurrent severe episodes of respiratory failure and referred to our center with the suspicion of metabolic disease.

The results of the PG are presented in Table 2. A daytime nap PG was performed in the 10 infants aged less than 6 months whereas an overnight PG was performed in the 3 older patients (Table 2). All the studies were performed in room air with a median analysable time of 146 min (range 64 to 510 min).

Patients #1 and #2 had a high AHI, composed mainly of hypopneas, with severe hypoxemia and hypercapnia. The PG tracings showed tachypnea with repeated episodes associating a simultaneous decrease in airflow and thoracic and abdominal movements followed by a desaturation and an arousal, suggestive of global inspiratory muscle weakness (Fig. 1a and b). Nemaline rod myopathy was confirmed in the 2 patients. Respiratory status improved spontaneously in patient #1 who did not require ventilator support. NIV during night and nap sleep corrected the alveolar ventilation in patient #2. Patient #3 had few respiratory events but repeated episodes of a simultaneous decrease in airflow and opposition phase on the thoracic and abdominal belts followed by a desaturation, occurring at the end of the night, suggestive of a decrease of diaphragmatic endurance (Fig. 2a). Patient #4 had an AHI of 52/h and an ODI of 34/h. The PG tracing showed recurrent episodes of a simultaneous decrease in airflow and thoraco-abdominal belts (Fig. 2b). The PG recordings were suggestive of a respiratory muscle weakness or dysfunction. Further investigations showed that these 2 patients had congenital myasthenia. Both were successfully treated with NIV. Patient #5 had a tracing evocative of diaphragmatic dysfunction. Indeed, when she was awake, airflow was present, with an opposition phase on the thoraco-abdominal belts, which was explained by the fact that she breathed exclusively with her accessory inspiratory muscles. When she felt asleep, because of the reduction of the activity of the inspiratory intercostal muscles during rapid eye movement (REM) sleep, airflow decreased to almost zero, with a simultaneous disappearance of the opposition phase. This lead to a profound desaturation and an arousal, and the cycle restarted again (Fig. 3).

Patients #6, #8, and #9 had extremely high AHI (between 63 and 104 events/h), with mainly obstructive events for patient #6 and central events for patients #8 and #9 (Fig. 4). They spent between 6 and 12% of the recording time with a $SpO_2 < 90\%$, without overt hypercapnia. In these 3 patients, as well in patient #7, breathing pattern was very

Table 1
Anthropometrics, clinical presentation, final diagnosis and outcome of the patients

Patient gender	Age (months)	Weight (kg)	Height (cm)	PICU admission	Associated clinicalfeatures	Final diagnosis	Outcome	Duration of follow up (months)
1 male	3	5	56	Respiratory distress	Peripheral muscle weakness, swallowing dysfunction	Nemaline rod myopathy	Therapeutic abstention	4 - alive
2 female	4	5	40	Respiratory distress	Peripheral muscle weakness	Nemaline rod myopathy	NIV	12 -alive
3 male	24	19	84	Life threatening events	Generalized muscle weakness and fatigability, swallowing dysfunction	Congenital myasthenia	NIV	11 - alive
4 female	3	6	62	Respiratory distress	Axial hypotonia, swallowing dysfunction	Congenital myastenia	NIV	31 - alive
5 female	14	8	75	Respiratory distress	Generalized inflammatory disorder	Diaphragmatic dysfunction	NIV	15 -death
6 female	2	4	60	Life threatening events	Swallowing dysfunction, bradycardia, axial hypotonia, acute obstructive events	Brainstem dysfunction	NIV	2 - death
7 male	4	6	55	Life threatening events	Swallowing dysfunction, bradycardia, axialhypotonia	Brainstem dysfunction	Therapeutic abstention	2 - alive
8 male	1	3	50	Life threatening events	Swallowing dysfunction, bradycardia, axial hypotonia	Brainstem dysfunction	cafeine	5 - alive
9 male	2	5	57	Respiratory distress	Swallowing dysfunction, bradycardia, axial hypotonia	Brainstem dysfunction	NIV	4 - alive
10 male	6	5	60	Respiratory distress	Acute obstructive events	SCID T-B-NK+ and laryngomalacia	CPAP	8 - alive
11 male	3	4	45	Respiratory distress	Acute obstructive events	Laryngomalacia	CPAP	52 -alive
12 male	2	6	59	Life threatening events	Acute obstructive events with bradycardia	Pharyngomalacia	Lost for follow up	Lost for follow up
13 male	21	15	80	Respiratory distress	Recurrent episodes of respiratory failure	CCHS	Invasive ventilation on tracheotomy	14 - alive

Abbreviations: PICU: pediatric intensive care, SCID: severe combined immune deficiency, OSA: obstructive sleep apnea, CCHS: congenital central hypoventilation syndrome, CPAP: continuous positive airway pressure, NIV: noninvasive ventilation.

irregular. The PG findings, in association with swallowing dysfunction, bradycardia, axial hypotonia, and a normal cerebral magnetic resonance imaging led to the diagnosis of brainstem dysfunction in these 4 infants.

Patients #6 and #9 were treated with NIV but patient #6 died when NIV was withdrawn during a traveling abroad. Evolution was spontaneously favorable in patient #7 and patient #8 improved with caffeine.

Table 2
Polygraphic results

	Recording time (minutes)	Respiratory events			Gas exchange							Main polygraphic findings
		CAI (events/h	OAI (events/h)	AHI (events)	Mean SpO_2 (%)	Minimal SpO2 (%)	ODI (events/h)	% time with SpO_2 < 90%	Mean $PtcCO_2$ (mmHg)	Maximal $PtcCO_2$ (mmHg)	% time with $PtcCO_2$> 50 mmHg	
1 male	149	5	0	11	93	75	28	21	51	56	100	Homogeneous decrease in ventilation
2 female	117	0	6	50	91	79	56	27	46	53	1	Homogeneous decrease in ventilation
3 male	420	4	0	7	97	76	21	1	na	na	na	Homogeneous decrease in ventilation at the end of the night with phase opposition on thoracic and abdominal belts
4 female	146	3	5	52	97	78	34	3	41	45	0	Homogeneous decrease in ventilation
5 female	510	0	0	0	95	85	85	2	67	83	100	Tracing evocative of diaphragmatic weakness
6 female	159	8	36	63	94	76	62	6	40	42	0	Obstructive events with decrease in respiratory drive
7 male	85	0	0	6	97	90	13	0	39	43	0	Irregular breathing
8 male	188	34	7	64	95	65	67	10	42	46	0	Central events
9 male	224	71	17	104	94	73	117	12	48	55	33	Central events
10 male	64	0	8	22	96	89	14	0	49	64	39	Obstructive events with hypoventilation
11 male	84	0	31	95	89	51	95	31	54	64	100	Obstructive events with hypoventilation
12 male	113	5	12	20	98	94	3	0	39	41	0	Obstructive events with bradycardia
13 male	120	0	0	0	92	82	30	40	68	70	100	Decrease in central drive during sleep, normalization during awakening

Abbreviations: CAI: central apnea index, OAI: obstructive apnea index, AHI: apnea-hypopnea index, SpO_2: pulse oximetry, $PtcCO_2$: transcutaneous carbon dioxide, na: not available.

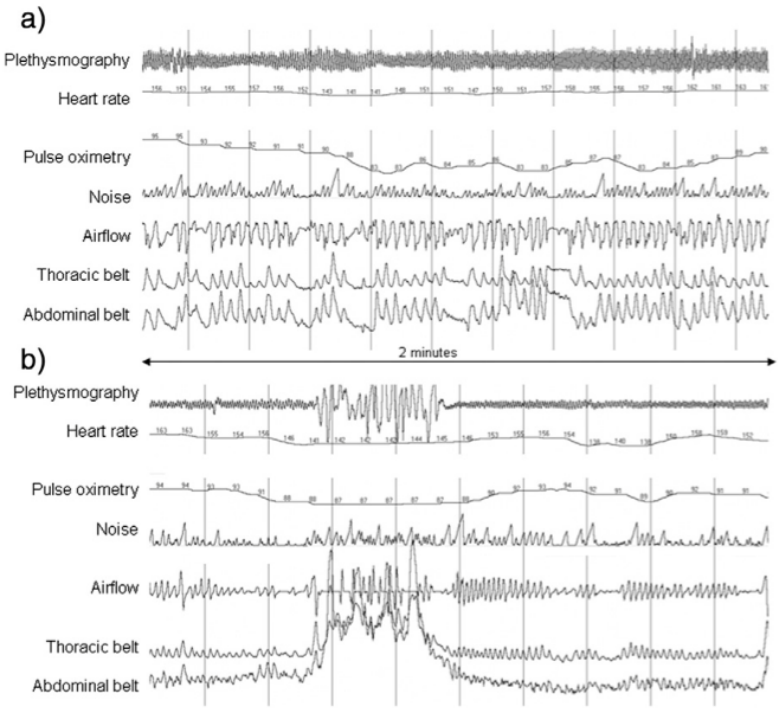

Fig. 1. a) Polygraphy tracing of patient #1 showing an irregular breathing rate of 29/minute with tachycardia (heart rate around 155 beats/minute) and repeated episodes associating a simultaneous decrease in airflow and thoracic and abdominal expansion without opposition phase followed by a desaturation suggestive of global inspiratory muscle weakness. b) Polygraphy tracing of patient #2 showing and irregular breathing pattern with a progressive decrease in airflow and thoracic and abdominal expansion without opposition phase, accompanied by a profound desaturation and an arousal with a repeat of the previous breathing pattern, suggestive of global inspiratory muscle weakness.

PG showed severe obstructive respiratory events in patients #10 to #12 (Fig. 1 online). Patients #10 and #11 were found to have severe laryngomalacia on an endoscopic evaluation and were treated successfully with noninvasive CPAP. The endoscopic evaluation showed severe pharyngeal hypotonia in patient #12 who returned to his country without treatment and was lost during follow up.

Patient #13 was an otherwise healthy infant who had undergone a tracheotomy in Ukraine because of recurrent episodes of severe respiratory failure. His PG showed a severe simultaneous decrease in airflow and thoraco-abdominal movements as soon as he felt asleep, with profound hypoxemia and hypercapnia, without causing an arousal reflex (Fig. 2 online). This tracing was suggestive of central congenital hypoventilation syndrome which was confirmed by a genetic analysis revealing a de novo heterozygous mutation in the PHOX2B gene responsible for a 5 alanine expansion within the 20 alanines on the C-terminal of the PHOX2B protein. This patient is doing well with invasive ventilation on his tracheotomy during sleep.

4. Discussion

To our knowledge, this is the first study showing the diagnostic value of a PG in the PICU in infants admitted for unexplained respiratory failure or life-threatening events. Indeed, sleep studies are generally used to diagnose OSA and prescribed and interpreted within that context. But the analysis of the airflow and thoraco-abdominal breathing pattern can show more very useful information, outside the context of OSA, and in particular in case of respiratory muscle weakness and/or dysfunction, or abnormalities of the respiratory drive. In the present study, the PG tracings showed features suggestive of respiratory muscle dysfunction, abnormal central drive or obstructive respiratory events, guiding appropriate diagnostic investigations and an effective treatment.

Studies on polysomnography (PSG) or PG in the PICU are scarce [7]. None of these studies dealt with the diagnostic value of PG. Indeed, the aim of these studies was to analyze sleep quality in children hospitalized for burns or to evaluate the effects of neuromuscular blockade on sleep quality [7].

PG is rarely used as a diagnostic tool in neuromuscular diseases. However, it may be informative by showing features evocative of respiratory muscle weakness [8]. Global inspiratory muscle weakness is characterized by a decrease in tidal volume, with a simultaneous decrease in airflow and thoraco-abdominal expansion in the PG tracing. These events may be misinterpreted as "central apneas" when the clinical context is not taken into account as neuromuscular patients are unable to generate large inspiratory pressures [3]. On the other hand, other events, such as severe diaphragmatic weakness as observed in patient #5, may be misinterpreted as "obstructive" when the diaphragmatic weakness causes paradoxical movement of the chest and the abdomen even without narrowing of the upper airway [4]. Finally, the high desaturation index in these patients may be explained by the reduction in lung volume and thus the "oxygen reserve" [3]. In order to maintain minute ventilation, breathing rate increases with the appearance of a rapid shallow breathing. This index has been shown to be significantly increased in children with neuromuscular disease requiring NIV [9]. Respiratory muscle fatigue may be evoked when these above mentioned features appear after a certain delay, as in patient #3 in whom features of alveolar hypoventilation appeared at the end of the night and who was shown to have congenital myasthenia. The PG tracing was particularly helpful in patient #5. The disappearance of opposition phase on the thoraco-abdominal belts every time she felt asleep, was explained by

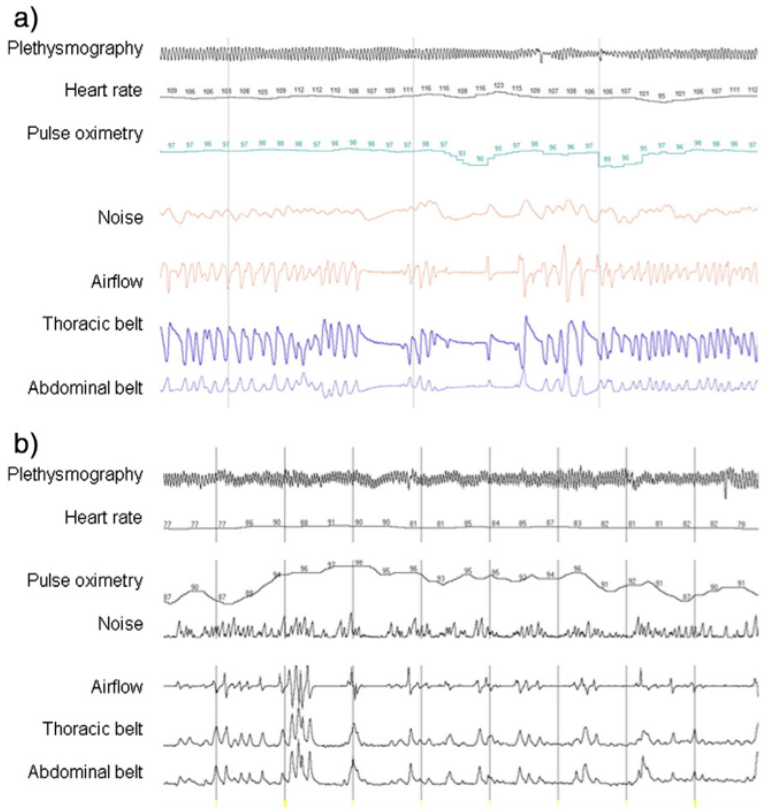

Fig. 2. a) Polygraphy tracing of patient #3 showing repeated episodes of a simultaneous decrease in airflow and opposition phase on the thoracic and abdominal belts followed by a desaturation, occurring at the end of the night, suggestive of a decrease of diaphragmatic endurance b) Polygraphy tracing of patient #4 showing a very irregular breathing pattern with recurrent episodes of a simultaneous decrease in airflow and thoraco-abdominal belts with profound desaturations.

the physiological decrease of the activity of the accessory inspiratory muscles during REM sleep [3,4]. Indeed, during this phase, breathing efficiency relies solely on the diaphragm. As she had severe diaphragmatic dysfunction, sleep resulted in a profound decrease in tidal volume and pulse oximetry, which ended with an arousal.

Brainstem dysfunction in the newborn is an association of symptoms rather than an established disease, originally described in the Pierre Robin sequence [10,11]. Patients present with neonatal suck and swallowing difficulties, pharyngo-oesophageal uncoordination, upper airway obstruction due to upper airway hypotonia, vagal overreactivity, and a normal cerebral magnetic resonance imaging. Abnormalities in central drive are common but have been rarely documented on a sleep study. In these patients, PG showed an irregular breathing pattern, which may concern breathing frequency and/or breathing amplitude with a variable association of central and obstructive events. An extremely high central apnea index was observed in

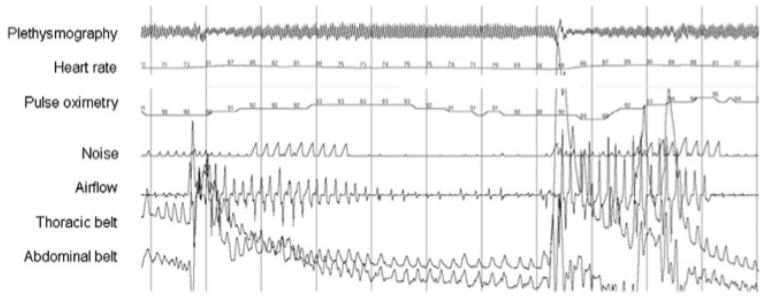

Fig. 3. Polygraphy tracing of patient #5 showing that after an arousal when she is is not still asleep, airflow is present, with an opposition phase on the thoraco-abdominal belts, which is explained by the fact that the patient breathes exclusively with her accessory inspiratory muscles. When the patient falls asleep, because of the reduction of the activity of the inspiratory intercostal muscles during rapid eye movement sleep, airflow decreased to almost zero, with a simultaneous disappearance of the opposition phase. This leads to a profound desaturation and an arousal, and the cycle restarts again.

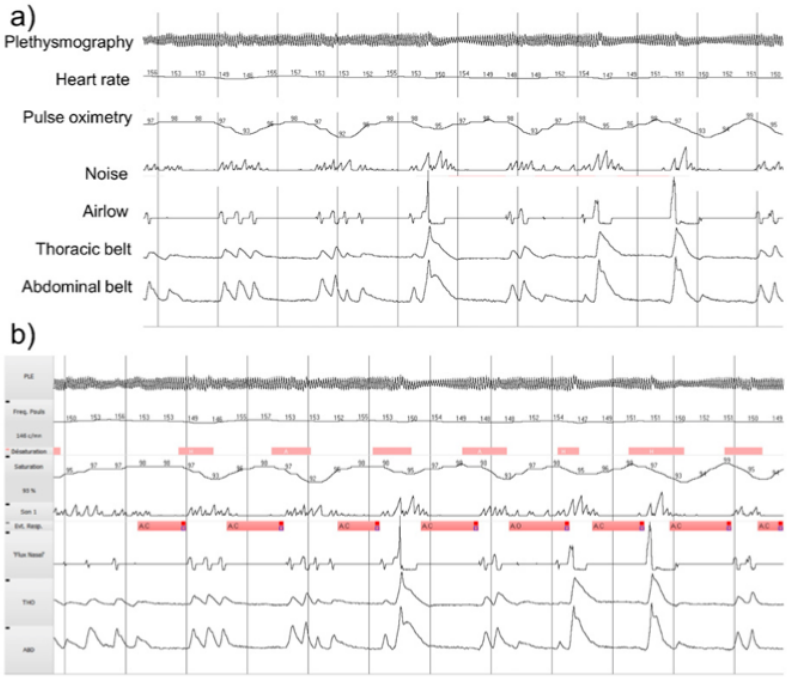

Fig. 4. Polygraphytracing of patient #9 showing repeated central apneas causing severe desaturations.

patients #8 and #9 (Fig. 4) whereas the respiratory were obstructive in patient #6, which may be explained by hypotonia of the upper respiratory airway.

Most infants with obstruction of the upper airways have suggestive clinical symptoms such as stridor, inspiratory retractions, hyperextension of the neck, which predominate during sleep and agitation. However, in the 3 patients in our study, the clinical symptoms were permanent, causing respiratory failure or severe life-threatening events with bradycardia. The observation of severe typical obstructive respiratory events on the PG was in agreement with the endoscopy of the upper airways which showed severe laryngomalacia in 2 patients.

Congenital central hypoventilation syndrome is a rare neurocristopathy with disordered central drive [12]. The clinical presentation is typically during the newborn period with alveolar hypoventilation during sleep, or in more severely affected patients, during sleep and wakefulness. The severity of the clinical presentation is correlated to the number of alanine repeats on the PHOX2B gene. PG tracing, showing an immediate profound decrease in flow and thoraco-abdominal belts as soon as he felt asleep, causing severe hypoxia and hypercapnia without any arousal reflex, was highly suggestive of the diagnosis of congenital central hypoventilation syndrome which was confirmed by the genetic analysis.

Our study has several limitations. Most of the patients had a daytime nap PG and not an overnight recording. It has been showed that nap sleep study parameters are not very sensitive in predicting abnormal overnight sleep findings, but when nap study parameters are abnormal, the chance of an abnormal overnight sleep study is very high [13,14]. As we did not perform a PSG, we were not able to check sleep architecture and quality. Another limitation of PG as compared to PSG is the underestimation of hypopneas due to the impossibility to detect autonomic arousals. However, we do not think that a PSG would have changed the results of our study since the majority of the patients had an extremely abnormal AHI with profound desaturations during respiratory events. Paradoxical breathing is not always an expression of respiratory muscle weakness. Indeed, this breathing pattern is physiological in newborns and infants and decreases with age to disappear around the age of 3 years [15,16]. PG can detect reductions of airflow and thoracic-abdominal respiratory movements during sleep, these findings are graphically displayed and detectable but they are not quantitatively measurable. Finally, the number of patients is small but sufficiently informative to underline the usefulness of PG in infants with unexplained respiratory failure or life-threatening events.

In conclusion, this study shows for the first time the diagnostic usefulness of a PG in infants hospitalized in the PICU for unexplained respiratory failure or life-threatening events. The PG tracings, when interpreted taking in account some pivotal clinical features, can orientate the diagnosis and guide the therapeutic management of these infants. This noninvasive investigation should be integrated in the diagnostic arsenal of these patients.

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