Ventilation mécanique dans les pathologies obstructives de l'enfant : physiopathologie des interventions ventilatoires et non ventilatoires

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Ventilation mécanique dans les pathologies obstructives de l'enfant : physiopathologie des interventions ventilatoires et non ventilatoires

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RESUME EN FRANCAIS

(187 mots)

Les pathologies respiratoires obstructives de l'enfant (asthme et broncho-alvéolites) sont l'une des principales causes d'admission en réanimation pédiatrique. Depuis plusieurs années, des progrès ont été faits pour réduire l'invasivité des soins se traduisant par une réduction de la morbidité. L'objectif de ce travail de thèse est de s'appuyer sur des mécanismes physiopathologiques pour proposer des stratégies d'optimisation ventilatoire et non ventilatoire chez ces enfants. Nous avons évalué l'impact du décubitus ventral couplé à la ventilation non invasive chez les nourrissons atteints de bronchiolite grave. Le décubitus ventral permet de réduire significativement l'effort inspiratoire et d'améliorer le couplage électromécanique du diaphragme. Ensuite nous avons évalué la « neurally adjusted ventilatory assist » (NAVA) qui est un mode ventilatoire proportionnel basé sur l'activité électrique du diaphragme. Nous avons démontré que la NAVA améliorait la synchronisation patient-respirateur et réduisait le travail respiratoire en comparaison à la « nasal continuous positive airway pressure » (nCPAP). Enfin, dans la pathologie asthmatique nous avons également décrit la faisabilité du haut débit nasal dans cette population. Ces stratégies nécessitent maintenant d'être validées sur des critères cliniques et feront l'objet de deux études multicentriques randomisées.

Mots clés : ventilation mécanique, physiologie respiratoire, travail respiratoire, neurally adjusted ventilatory assist, activité électrique diaphragmatique, bronchiolite, enfants.

RESUME EN ANGLAIS

(187 words)

Obstructive lung disease in children (asthma and bronchiolitis) are one of the main causes of admission to pediatric intensive care units. For several years, progress has been made to reduce the invasiveness of care resulting in a decrease in associated morbidity. The main objective of the thesis was to propose new ventilatory and non-ventilatory strategies based on physiopathology to optimize the care of such children.

In children with severe bronchiolitis we evaluated the impact of prone position associated with non-invasive ventilation. The prone position decreases significantly the inspiratory work of breathing and improves the neuromechanical efficiency of the diaphragm. We also evaluated the effect of neurally adjusted ventilatory assist (NAVA) that is a proportional ventilatory mode based on the electrical activity of the diaphragm. We demonstrated that NAVA improved the patient-ventilator interactions and decrease the work of breathing in comparison with nasal continuous positive airway pressure (nCPAP). We also evaluated the feasibility of high flow nasal cannula as a respiratory support in children with severe asthma attack. These strategies need now to be validated on clinical outcomes and are the subject of two ongoing multicenter randomized trials.

Key words : mechanical ventilation, respiratory physiology, work of breathing, neurally adjusted ventilatory assist, electrical activity of the diaphragm, bronchiolitis, children.

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ABBREVIATIONS

BPCO = Broncho pneumopathie chronique obstructive
CO_2 = Dioxyde de carbone
CPAP = Continuous positive airway pressure ou pression positive continue
nCPAP = CPAP par interface nasale
CRF = Capacité résiduelle fonctionnelle
DD = Décubitus Dorsal
DV = Décubitus Ventral
EAdi = Activité électrique du diaphragme (Ou EDI)
EIT = Tomographie par impédance électrique
FiO_2 = Fraction inspirée en oxygène
GFRUP = Groupe francophone d'urgence et de réanimation pédiatrique
HDN : Haut débit nasal
m-WCAS = Score de Wood pour l'asthme modifié
NAVA = Neurally adjusted ventilatory assist
O_2 = Oxygène
ORL = Oto-rhino-laryngologie
PAC = Pression assistée contrôlée
Pdi = Pression transdiaphragmatique
PEEP = Positive end-expiratory pressure (pression positive de fin d'expiration)
PEEPe = PEEP externe
PEEPi = PEEP intrinsèque
Pes = Pression œsophagienne
Pgas = Pression gastrique
PHRC = Programme hospitalier de recherche clinique
PTP = Produit pression temps
SDRA = Syndrome de détresse respiratoire aigüe
SFMU = Société française de médecine d'urgence
SpO_2 = Saturation pulsée en oxygène
SRLF = Société de réanimation de langue française
Te = Temps expiratoire
Ti = Temps inspiratoire
Ttot = Temps total
VAS = Voies aériennes supérieures
VI = Ventilation invasive
VNI = Ventilation non-invasive
VRS = Virus respiratoire syncytial
VS-AI = Ventilation spontanée en aide inspiratoire

PREAMBULE

La pathologie respiratoire obstructive de l'enfant est un grand cadre nosologique regroupant à la fois la bronchiolite, l'asthme et les broncho-pneumopathies chroniques obstructives de l'enfant. En réanimation pédiatrique, la bronchiolite est un véritable enjeu de santé publique par son incidence très élevée et son coût. Le modèle d'étude dans ce travail de thèse se concentrera sur la bronchiolite aiguë du nourrisson avec quelques ouvertures vers la pathologie asthmatique.

LIENS D'INTERET

Je déclare avoir eu des liens d'intérêt à type de bénéfice financier pour une présentation des résultats lors d'un symposium et non financier (prêt d'un respirateur) avec la société Maquet Critical Care, Solna, Suède.

I. INTRODUCTION

L'enfant et plus particulièrement le nourrisson présente une physiologie respiratoire spécifique qui l'expose aux détresses respiratoires. La broncho-alvéolite aigüe (ou bronchiolite) est une infection virale responsable d'une inflammation des voies aériennes supérieures et inférieures, et notamment des petites bronches (bronchioles) chez le nourrisson [1-3]. La bronchiolite est la pathologie respiratoire la plus fréquente avec près d'un nourrisson sur trois atteint au cours de sa première année de vie (soit près de 450 000 par an en France). Environ 30% des enfants qui consultent aux urgences seront hospitalisés pour bronchiolite [1] représentant entre 20 000 et 30 000 hospitalisations par an en France [2]. Depuis le début des années 2000, on note une diminution du nombre d'hospitalisations mais une augmentation du recours à la ventilation mécanique [3, 4]. Ainsi, parmi les enfants hospitalisés, on estime qu'entre 5 et 22% seront admis en réanimation ou en unité de surveillance continue pour bénéficier d'un support ventilatoire [2, 5, 6]. Les progrès dans la prise en charge ont réduit significativement la mortalité [7] qui est devenue presque inexistante dans les pays industrialisés (< 3/100 000 nourrissons) [2]. Le challenge est maintenant de réduire l'invasivité et la morbidité associée à la prise en charge des formes graves de bronchiolites. La France est particulièrement active dans ce domaine avec de nombreux travaux sur la ventilation non invasive [8-11] et le haut débit nasal [12, 13].

1. SPECIFICITES RESPIRATOIRES DU NOURRISSON

1.1. Spécificités anatomiques

Le poumon fœtal apparaît dès les premières semaines de gestation et va se développer pendant la grossesse pour aboutir à un poumon pouvant être fonctionnel à partir de la 26ème semaine (début du stade sacculaire). Cependant, on considère que la majorité de la formation alvéolaire et bronchiolaire survient après la naissance [14] et le poumon va poursuivre sa croissance même pendant la petite enfance.

L'anatomie des voies aériennes supérieures et du système respiratoire du nourrisson est différente de celle d'un adulte et va évoluer également lors des premières années de vie. Concernant les voies aériennes supérieures, la langue est plus grosse, le larynx antérieur est situé plus haut et l'épiglotte est plus longue et plus flasque. Cette disposition autorise la séparation entre le système naso-pharyngo-laryngé dédié au passage de l'air et le système oropharyngé dédié à l'alimentation permettant au nourrisson de maintenir une respiration pendant l'alimentation [15]. Cette conformation qui présente un avantage en termes de nutrition est responsable d'une augmentation des résistances des voies aériennes supérieures qui totalisent 2/3 des résistances totales. Chez l'adulte, les valeurs en respiration nasale sont approximativement similaires mais sont deux fois moins élevées en respiration buccale [16]. Concernant les voies aériennes inférieures, la trachée est conique, les bronches sont plus compliantes (cartilage plus mou) et les muscles bronchiques sont moins développés [17]. Enfin, la cage thoracique du nouveau-né est souple (peu ossifiée), plus sphérique avec un diaphragme horizontalisé [18]. La proportion de fibres musculaires diaphragmatiques de type 1 (lente) est réduite au profit de fibres de type II (rapide) se traduisant par une plus faible endurance musculaire.

1.2. Spécificités mécaniques

Chez le nourrisson, la respiration nasale est exclusive dans les premiers mois de vie et les résistances respiratoires sont très élevées. Parallèlement à la croissance et aux modifications anatomiques qui concernent à la fois les voies aériennes supérieures et les voies aériennes inférieures, les résistances vont diminuer de moitié au cours de la première année de vie. A la naissance, la compliance pariétale est trois fois plus importante que la compliance thoracique. Suite à l'alvéolisation, la croissance, l'ossification et le développement musculaire ce rapport

va progressivement s'équilibrer (rapport proche de 1 à l'âge adulte) avec une augmentation de la compliance du poumon et une diminution de la compliance thoracique [19].

La capacité résiduelle fonctionnelle CRF est déterminée par le point d'équilibre entre les forces de rétraction du poumon et les forces d'expansion de la cage thoracique [20] et correspond chez l'adulte à environ 1/3 de la capacité pulmonaire totale (Figure 1). Chez le nourrisson en raison du déséquilibre de ces rapports (compliance pulmonaire plus faible et compliance de la paroi thoracique plus élevée), le volume pulmonaire à l'équilibre ne représente que 10 à 15% de la capacité pulmonaire totale [21-23], ce qui est proche du volume critique de fermeture des voies aériennes (Figure 1). Le nourrisson met alors en œuvre des stratégies actives d'élévation de la CRF au-dessus du volume résiduel [24] en particulier un freinage expiratoire au niveau laryngé et une diminution du débit expiratoire par maintien d'une activité diaphragmatique tonique au cours de l'expiration [25-27].

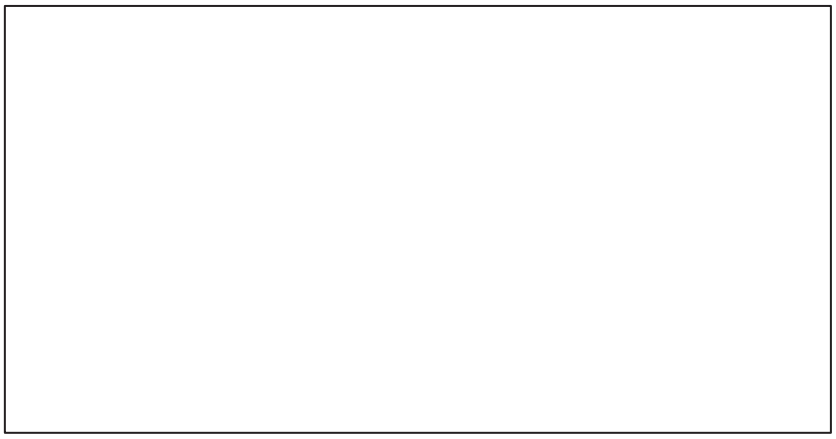

Figure 1 : Courbe pression-volume statique du poumon, de la paroi thoracique et du système respiratoire chez le nouveau-né et chez l'adulte [28]***.***

Le nourrisson est finalement en état permanent d'équilibre précaire et même une faible modification peut entrainer une insuffisance respiratoire.

2. PATHOGENESE ET PHYSIOPATHOLOGIE DE LA BRONCHO-ALVEOLITE

2.1. Microbiologie et histopathologie

2.1.1. Microbiologie

La broncho-alvéolite est une infection virale épidémique et saisonnière essentiellement liée au virus respiratoire syncytial (VRS) qui représente entre 41 et 83% des cas [17, 18].
D'autres virus peuvent être responsables de tableaux de bronchiolites: Rhinovirus [29-31], Entérovirus (picornaviridae) [32], Influenzae et parainfluenzae virus [33], Metapneumovirus humain dont les structures sont proches du VRS [34]. On estime qu'environ 30% des enfants présentent une co-infection virale [30, 35].

2.1.2. Histopathologie

La transmission est essentiellement interhumaine et la contamination se fait par inoculation au niveau des muqueuses rhinopharyngées ou oculaires [37]. L'excrétion virale débute en général 48h après le contage et dure une dizaine de jours. Après contamination, le VRS va se répliquer intensément au sein de l'épithélium nasopharyngé. La propagation du virus de proche en proche lui permet d'atteindre les voies aériennes respiratoires inférieures en 2 à 3 jours [36]. Cette prolifération virale est à l'origine d'une destruction de l'épithélium respiratoire (Figure 2) [36] et d'une infiltration de monocytes et lymphocytes T autour des bronchioles et des vaisseaux [38]. Les voies aériennes inférieures sont le siège d'une intense réaction inflammatoire médiée par les lymphocytes T avec un déséquilibre de la balance Th1/Th2 au profit d'une réponse Th2 [39]. La destruction de l'épithélium respiratoire associée à une infiltration cellulaire et une hyper sécrétion de mucus entrainent une déformation et une obstruction des bronchioles (Figure 2). Enfin, le surfactant pourrait être altéré au cours de l'infection à VRS [40].

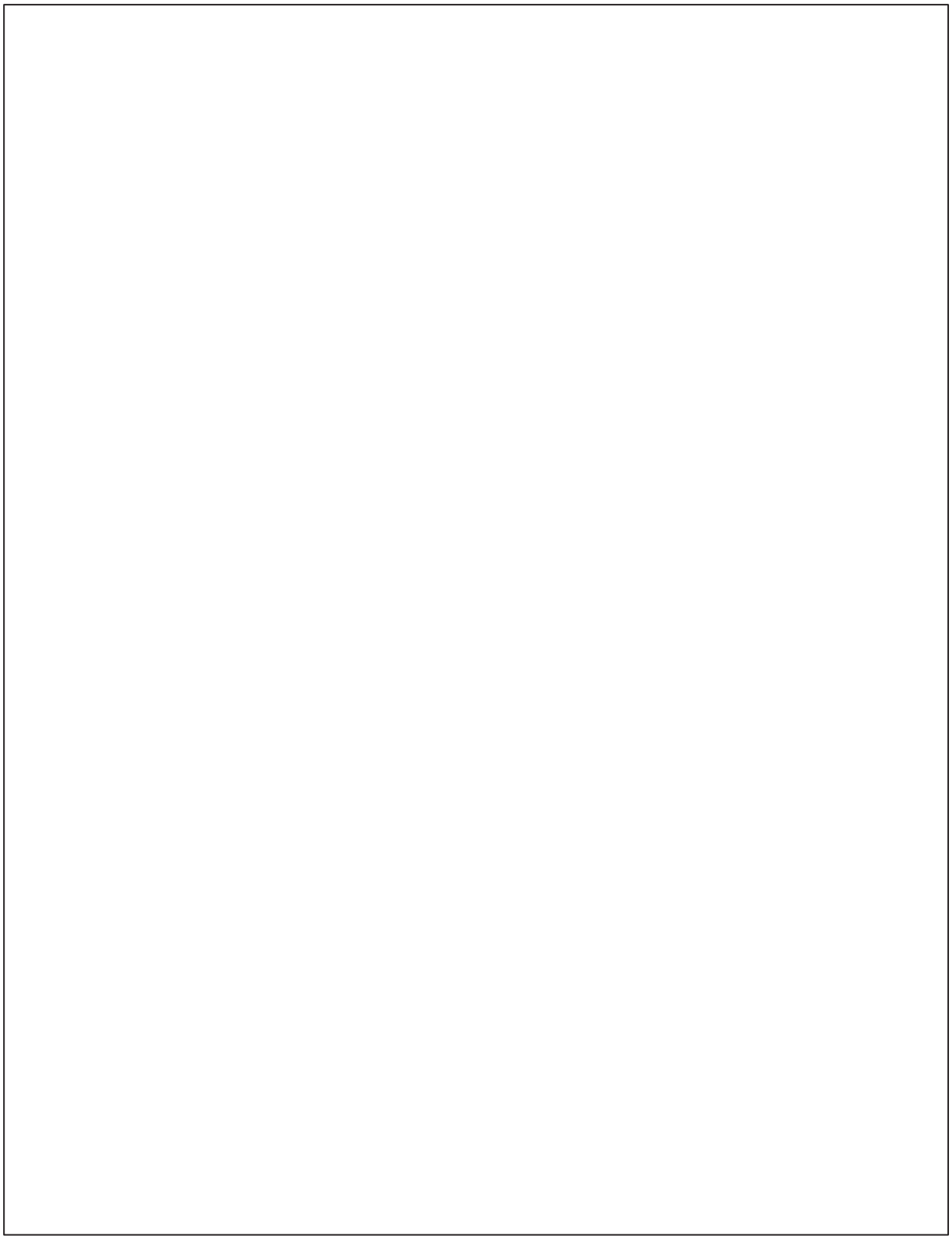

Figure 2 : Pathogenèse de la bronchiolite à VRS d'après Meissner et al. [36]

2.2. Physiopathologie

La bronchiolite est considérée le plus souvent comme une pathologie obstructive. Il s'agit en réalité d'une broncho-alvéolite avec une composante alvéolaire et une composante bronchiolaire. La présence de débris cellulaires, de fibrine et de mucus, associée à une atteinte du système broncho-ciliaire est responsable d'une obstruction intra-luminale. L'infiltration cellulaire péri-bronchiolaire et l'œdème réduisent le diamètre des bronchioles aggravant l'obstruction. Il existe une atteinte alvéolaire pouvant être liée à la destruction des cellules épithéliales mais aussi à une altération directe du surfactant suite à l'infection et l'inflammation [40, 41].

2.2.1. Mécanismes

Le dénominateur commun des pathologies obstructives respiratoires est une augmentation des résistances à l'écoulement de l'air dans les voies aériennes.

- **Augmentation des résistances :**

Les résistances hydrauliques à l'écoulement d'un fluide laminaire sont définies par la loi de Poiseuille [42] (Équation 1):

Équation 1 : $R = 8 \eta l / \pi r^4$

R= résistance, η= viscosité d'un fluide (constante), l= longueur, et r= rayon

L'écoulement de l'air dans l'arbre trachéo-bronchique est complexe et probablement évolutif de bas en haut. La trachée a probablement un flux turbulent et il faut attendre les divisions distales pour obtenir un flux laminaire [42]. Avec l'hypothèse que le flux dans la bronchiole est laminaire, alors les résistances sont inversement proportionnelles au rayon à la puissance quatre. Une réduction de 50% du calibre multiplie par 16 les résistances respiratoires. Au cours de la broncho-alvéolite, l'infiltration et l'œdème péri-bronchiolaire expliquent l'augmentation de résistance.

- **Limitation du débit expiratoire :**

Les bronchioles sont des structures compliantes (absence de cartilage) qui sont maintenues ouvertes grâce aux forces élastiques du tissu conjonctif des alvéoles adjacentes. Elles sont

soumises aux contraintes mécaniques environnantes. Au cours de l'expiration, il peut exister une majoration supplémentaire de l'obstruction liée à une réduction du calibre des voies aériennes appelée limitation du débit expiratoire. Ce phénomène est décrit au cours de la ventilation mécanique chez l'adulte avec une atteinte pulmonaire [43] mais peut également être lié à une expiration active. Au cours de l'expiration forcée, l'augmentation des pressions intra-thoraciques (intra-pleurales) se traduit par une négativation de la pression transmurale responsable d'une réduction du calibre bronchique voir d'un collapsus complet [42].

Nous avons mis en évidence que certains enfants présentent en effet une expiration active comme en témoignent les enregistrements des pressions gastriques et œsophagiennes réalisés au cours de l'étude bronchio-DV [44] (Figure 3). L'expiration active entraine une réduction du diamètre des VAS, responsable d'une majoration expiratoire des résistances à l'écoulement de l'air.

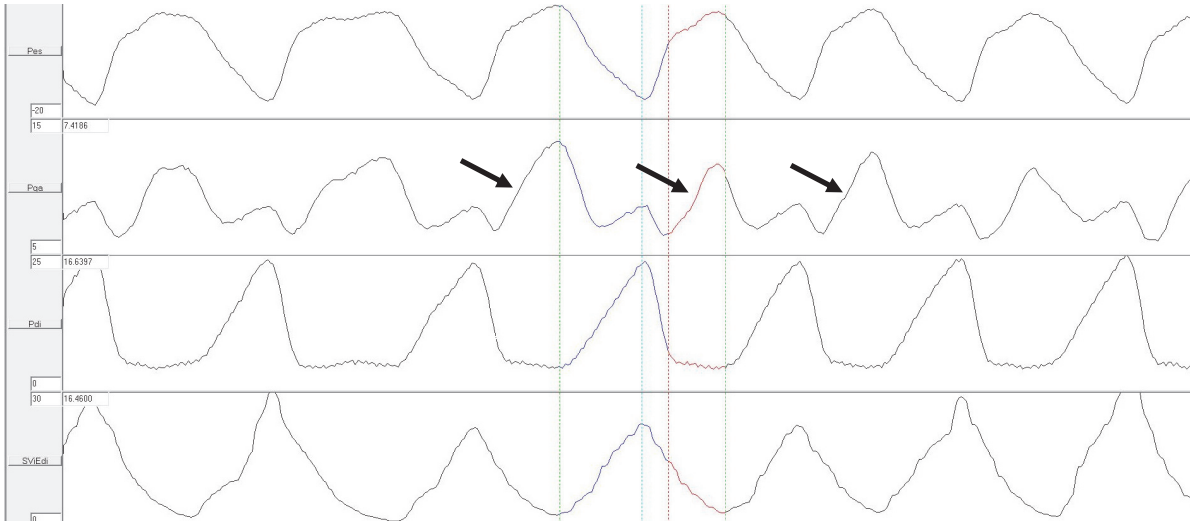

Figure 3 : Exemple d'enregistrement chez un nourrisson âgé de deux mois et ventilé en nCPAP (nasal continuous positive Airways pressure).

On note une augmentation rapide de la pression gastrique au cours de l'expiration (flèche) traduisant une contraction des muscles abdominaux et une augmentation de la pression intra-abdominale. De haut en bas : pression œsophagienne, pression gastrique, pression transdiaphragmatique et activité électrique du diaphragme (EAdi).

- **Hyperinflation dynamique :**

Dans un modèle mono-compartimental et passif, le volume pulmonaire à tout moment de l'expiration est défini par l'équation suivante :

Equation 2: $V= V_0-V^{-kt/\tau}$

V_0 est le volume de fin d'inspiration et τ = constante de temps (résistance x compliance)

Cette formule indique que l'expiration de 96% du volume inspiré est obtenue après trois constantes de temps tau (τ) [45]. L'augmentation des résistances (particulièrement à l'expiration) limite donc la vidange pulmonaire. L'expiration est interrompue par l'inspiration du cycle suivant, avant que le patient n'ait atteint le volume d'équilibre (capacité résiduelle fonctionnelle) et ce d'autant que la fréquence respiratoire augmente. Il en résulte une expiration incomplète avec une augmentation du volume pulmonaire de fin d'expiration appelée hyperinflation dynamique. Cette modification de l'équilibre entre les forces rétractiles du poumon et les forces d'expansion de la cage thoracique [20] se traduit par une augmentation de la pression alvéolaire de fin d'expiration. Cette dernière devient supérieure à la pression atmosphérique définissant la PEEPi (Positive End Expiratory Pressure intrinsèque) [46]. Ce phénomène est amplifié en expiration active [47].

- **Activité tonique du diaphragme :**

Nous avons vu que le nourrisson était dans l'obligation de maintenir activement l'activité de son diaphragme lors de l'expiration (définie comme une activité tonique). Ce mécanisme a récemment été rapporté dans un modèle animal de SDRA par Pelligrini et al. [48] avec l'hypothèse que ce « freinage » par maintien d'une activité diaphragmatique expiratoire permettait de prévenir le collapsus pulmonaire en limitant la fermeture des petites voies aériennes. Dans les pathologies obstructives, une activité tonique particulièrement importante a été décrite au cours des exacerbations d'asthme [49, 50] et de la bronchiolite [51]. Le rôle exact du maintien de cette activité expiratoire reste peu évident. Plusieurs hypothèses ont été proposées selon lesquelles l'activité tonique serait un mécanisme responsable de l'hyperinflation dynamique en réponse à la bronchoconstriction [49, 50] ou inversement un mécanisme d'adaptation à l'hyperinflation dynamique permettant de maintenir le diaphragme dans une meilleure configuration [52]. Dans notre travail nous avons mis en évidence une expiration active chez certains nourrissons atteints de bronchiolite

(Figure 3), et l'on peut émettre l'hypothèse que la mise en œuvre d'une activité tonique permettrait de « freiner » le diaphragme lors de l'augmentation de la pression abdominale afin de prévenir le collapsus expiratoire des voies aériennes. Des travaux physiologiques complémentaires dans ce domaine doivent être menés pour comprendre la finalité de cette activité tonique au cours de la bronchiolite.

- **Atteinte alvéolaire et restrictive :**

Comme décrit précédemment, la broncho-alvéolite n'est pas seulement une pathologie obstructive. En 1997, Hammer et al. décrivaient deux profils avec des formes obstructives (résistances élevées) et des formes restrictives (compliance diminuée), ces dernières évoluant souvent vers un syndrome de détresse respiratoire aiguë (SDRA) [53]. Cette comparaison a été reprise récemment par Cruces et al. par une analyse des courbes du respirateur en ventilation invasive, concluant que les patients intubés pour broncho-alvéolite se présentaient essentiellement avec une forme restrictive [54]. Ce travail présentait de nombreuses limites liées à l'interprétation des courbes du respirateur qui restent dépendantes de certains paramètres réglés par le praticien (débit inspiratoire, ratio temps inspiratoire (Ti) sur temps expiratoire (Te),…).

Finalement, la diminution de la compliance pulmonaire peut être expliquée par plusieurs phénomènes. Premièrement par l'atteinte alvéolaire responsable d'un syndrome de détresse respiratoire aiguë [53], deuxièmement par la possible atteinte du surfactant [40, 41] et troisièmement par la survenue de troubles ventilatoires responsables d'une diminution des volumes pulmonaires. Enfin, l'hyperinflation dynamique et l'augmentation du volume pulmonaire de fin d'expiration sont en elles-mêmes responsables d'une diminution relative de la compliance [55] car le système respiratoire est moins compliant sur les hauts volumes pulmonaires (Figure 1).

2.2.2. Conséquences physiopathologiques

En condition standard, le système respiratoire est soumis à deux contraintes : la contrainte résistive qui s'oppose à l'écoulement de l'air et la contrainte élastique qui s'oppose à l'expansion du poumon et de la paroi thoracique [56]. Au cours de la bronchiolite on observe :

- **Une augmentation du travail résistif**

L'augmentation des résistances à l'inspiration en lien avec la bronchoconstriction et la diminution du calibre des voies aériennes entrainent un surcroit de travail inspiratoire. Il en est de même pour l'obstruction des narines chez les nourrissons ayant une respiration nasale exclusive.

- **Une augmentation du travail élastique**

Les compliances du poumon et de la paroi thoracique sont moins bonnes à haut volume pulmonaire [55]. L'hyperinflation dynamique génère une charge élastique supplémentaire et impose un surcroît de travail musculaire dans des conditions biomécaniques défavorables [55, 57, 58].

- **Une augmentation du travail lié à la PEEPi**

Comme décrit dans les pathologies obstructives de l'adulte, la présence d'une PEEPi entraine une augmentation du travail respiratoire indépendamment des deux autres contraintes. En effet, le nourrisson doit fournir un effort supplémentaire lors de l'initiation de la respiration qui n'est pas assorti d'une variation de volume pulmonaire, pour vaincre la différence entre la pression alvéolaire (PEEP intrinsèque) et la pression atmosphérique [11, 53, 55] (Voir Figure 4).

- **Des anomalies des rapports ventilation et perfusion**

Au cours de la bronchiolite, les troubles ventilatoires (atélectasies) sont responsables d'une inadéquation entre la ventilation et la perfusion d'autant que les pores de Kohn et les canaux de Lambert (permettant une communication entres les alvéoles adjacentes) sont absents chez le nouveau-né [59, 60]. Ils participent à l'insuffisance respiratoire avec les troubles de la diffusion pouvant survenir suite à l'atteinte alvéolaire.

3. PRINCIPE DE PRISE EN CHARGE D'UNE BRONCHIOLITE GRAVE

3.1. Manifestations cliniques et critères de gravité

Le diagnostic de bronchiolite est clinique [61]. La symptomatologie débute par une atteinte des voies aériennes supérieures avec des symptômes ORL puis les signes cliniques d'atteinte des voies aériennes respiratoires inférieures apparaissent secondairement (frein expiratoire, tirage, …) et ne sont pas systématiques [36, 59].

La gravité de la bronchiolite repose sur l'évaluation de deux composantes que sont le terrain et la sévérité de l'atteinte respiratoire et de son retentissement [61-63].

- **Terrain à risque de bronchiolite grave**
    - Prématurité < 34 semaines d'aménorrhée et âge corrigé < 3 mois
    - Age < 6 semaines (indication d'hospitalisation [64])
    - Comorbidité cardiaque et pulmonaire
    - Reflux gastro-œsophagien
    - Déficit immunitaire

- **Facteurs de gravité cliniques et biologiques**
    - Signes de détresse respiratoire (battement des ailes du nez, tirage intercostal et sus claviculaire, balancement thoraco-abdominal, geignement expiratoire)
    - Polypnée avec fréquence respiratoire > 60 /min
    - Altération importante de l'état général, trouble de conscience
    - Présence d'apnées [65]
    - Saturation (SpO_2) < 94% en air ambiant
    - Refus d'alimentation et/ou perte de poids > 5%

Les scores de gravité tel que le m-WCAS (modified Wood Clinical Asthma Score), qui est l'un des plus utilisés [12, 13, 66], permettent de standardiser le degré de détresse respiratoire (Tableau 1)

	0	0,5	1	2
Saturation	$SpO_2 \geq 94\%$ en air	$90\% \leq SpO_2 < 94\%$ en air	$SpO_2 \geq 94\%$ avec $FiO_2>21\%$	$SpO_2 < 94\%$ avec $FiO_2>21\%$
Murmure vésiculaire	Normal	Légèrement variable	Variable	Diminué / absent
Muscles accessoires	Absent	Faible	Modéré	Absent
Frein expiratoire	Absent	Faible	Modéré	Absent
Conscience	Normale	Irritable	Déprimé ou agité	Coma

Tableau 1 : Score m-WCAS (modified Wood's clinical asthma score)

Enfin, la présence d'une acidose respiratoire sur les gaz du sang témoigne de l'incapacité du nourrisson à compenser et il est admis qu'un pH< 7.30 et une pCO_2 > 9KpA est un critère pour débuter une assistance respiratoire [62].

3.2. Prise en charge ventilatoire

Les mesures générales de prise en charge de la bronchiolite visent à prévenir l'épuisement respiratoire du nourrisson atteint de bronchiolite. Il est recommandé [61, 64] de réaliser des désobstructions rhinopharyngées régulières en raison de la respiration nasale exclusive à cet âge, de fractionner les repas (voir de réaliser une alimentation entérale sur sonde oro-gastrique) et de positionner l'enfant en proclive à 30°. Ces mesures sont indispensables et complémentaires de la prise en charge ventilatoire.

3.2.1. Effet de la nCPAP au cours de la bronchiolite

- **Impact de la PEEP externe sur l'effort inspiratoire**

L'application d'une PEEP externe inférieure ou égale à la PEEPi permet de diminuer le gradient entre la pression atmosphérique et la pression alvéolaire et diminue ainsi le travail inspiratoire selon le principe de la cascade d'eau « waterfalls » décrit par Tobin en 1989 (Figure 5).

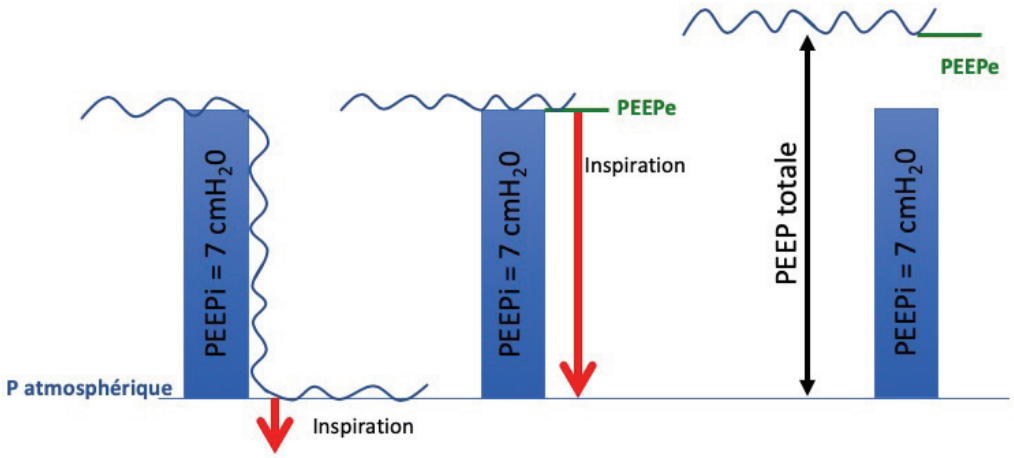

Figure 4 : La théorie du « waterfalls » d'après Tobin et al. [58]

L'application d'une PEEP externe (PEEPe) inférieure ou égale à la PEEP intrinsèque (PEEPi) permet de compenser la hauteur de la cascade d'eau en revanche une PEEP trop élevée va augmenter la PEEP totale et générer une hyperdistension.

D'autre part, l'application d'une PEEP permettrait une stabilisation des VAS qui sont compliantes chez l'enfant [67] et réduirait les résistances.

- **Travaux physiologiques au cours de la bronchiolite**

La première utilisation de CPAP dans la bronchiolite a été rapportée il y a plus de trente ans [68] mais la démonstration de l'effet sur l'effort inspiratoire est récente. En 2008, Cambonie et al. [10] ont montré que la nCPAP permettait une diminution de l'effort inspiratoire (sur le swing œsophagien), réduisait le temps inspiratoire (rapport Ti/Ttot) et le coût métabolique estimé par le produit pression temps (PTP) œsophagien.

Ces travaux étaient confirmés par Essouri et al. en 2011 [8] puis par Milesi et al. [9] en 2012 retrouvant un niveau optimal entre + 6 et + 7cmH_2O. La nCPAP est devenue le mode ventilatoire de référence dans la prise en charge de la bronchiolite en France [69] même si le niveau de preuve reste basé sur les études physiologiques.

3.2.2. Haut débit nasal dans la bronchiolite

Le haut débit nasal (HDN) est l'un des supports ventilatoires les plus récents. Il permet de couvrir les débits inspiratoires du patient tout en offrant un réglage précis de la FiO_2 et aurait pour conséquences [70, 71]:

- un effet « Wash out » de l'espace mort naso-pharyngé
- une diminution des coûts énergétiques par une humidification et un réchauffement des gaz
- un effet « PEEP » qui reste très variable dans le temps et d'un patient à l'autre.

Milési et al. ont montré un bénéfice du haut débit nasal dans une étude physiologique sur la réduction de l'effort inspiratoire et du produit pression temps (PTP) œsophagien. Ces résultats avaient été retrouvés dans une autre étude physiologique [72]. De nombreuses études ont suggéré un bénéfice du haut débit dans la bronchiolite [73-75] et cette modalité ventilatoire est couramment utilisée en raison de sa simplicité et d'un meilleur confort pour le patient. Un travail multicentrique français, auquel nous avons participé, a démontré que le taux d'échec dans la bronchiolite était plus élevé avec le haut débit nasal (50.7%) par rapport à la nCPAP (31.0%) [13] et dans un travail plus récent que le débit (2L/Kg/min vs. 3L/Kg/min) n'influençait pas le taux d'échec [76]. Le haut débit nasal semble se positionner en amont comme un intermédiaire entre l'oxygénothérapie standard et la nCPAP [77, 78].

3.2.3. Ventilation non invasive

La nCPAP reste le mode ventilatoire de référence pour la ventilation non-invasive des bronchiolites. L'avantage principal est l'absence de synchronisation nécessaire et sa simplicité d'utilisation. Environ 20% des enfants dans notre unité sont considérés comme en échec de nCPAP (augmentation de la capnie ou aggravation de la détresse respiratoire) et bénéficient d'un support ventilatoire à deux niveaux de pression [11, 62]. L'ajout d'un deuxième niveau de pression est connu pour diminuer le travail respiratoire [79] mais nécessite une synchronisation entre le patient et le respirateur. Ces modes ont été peu explorés chez les nourrissons et il n'existe pas de recommandations pour leur utilisation notamment au cours de la bronchiolite.

4. JUSTIFICATION ET OBJECTIFS DE LA THESE

4.1. Justification

La bronchiolite est la pathologie la plus fréquente chez le nourrisson et l'une des principales causes d'admission en réanimation pédiatrique. La pathologie asthmatique est son pendant dans l'enfance, l'adolescence avec une incidence et une morbidité élevées [80].

Depuis les années 2000, l'utilisation de la ventilation non-invasive (nCPAP et haut débit inclus) tend à se généraliser dans les réanimations pédiatriques [81, 82] améliorant le pronostic et la prise en charge des enfants [83]. Le niveau de preuve dans la bronchiolite et l'asthme reste limité à des travaux physiologiques et des études rétrospectives [69], même si un bénéfice à court et moyen terme semble se dégager [84, 85].

Ce travail de thèse s'inscrit dans cette dynamique pour explorer et proposer des stratégies thérapeutiques supplémentaires, afin de réduire l'invasivité de la prise en charge et la morbidité, en s'appuyant sur les mécanismes physiopathologiques.

4.2. Objectif du travail de thèse

Ce travail de thèse s'articule autour de trois grands objectifs :

1. Apprentissage et validation des outils d'exploration physiologique en pédiatrie
2. Exploration de l'effet du décubitus ventral au cours de la bronchiolite
3. Utilisation de la neurally adjusted ventilatory assist (NAVA) au cours de la bronchiolite.

II. OUTILS DE MESURE ET METHODOLOGIES

1. EVALUATION DE L'EFFORT RESPIRATOIRE

Le travail respiratoire est l'énergie nécessaire pour assurer la respiration. Cette définition, implique la génération d'un déplacement (volume) lorsqu'une force est appliquée au système respiratoire et repose sur l'analyse de la courbe pression volume au moyen d'une méthode utilisant le diagramme de Campbell [86]. L'analyse du travail respiratoire présente certaines limites notamment lors des efforts isométriques (pas de déplacement ou modification de volume). Le travail est peu adapté lorsqu'une partie du volume est générée par le respirateur. Les physiologistes ont développé, notamment pour la réanimation, d'autres indices permettant de quantifier l'effort musculaire respiratoire [87].

1.1. Mesure des pressions œsophagienne et gastrique

Les indices utilisés pour évaluer l'effort musculaire sont dérivés des mesures des pressions œsophagiennes et gastriques [88, 89]. Utilisée chez l'animal dès la fin du 19ème siècle, la pression mesurée dans l'œsophage (qui est une cavité virtuelle) est une estimation fiable de la pression pleurale chez l'homme [88, 90]

La méthode de référence fait appel à l'utilisation d'un cathéter muni d'un ballon relié à un transducteur de pression. La précision des mesures dépend du type, du volume [91] et de la taille du ballonnet [90]. Le groupe de travail international sur la mesure des pressions œsophagiennes (Pleural Pressure Working Group) recommande l'utilisation de ballons mesurant 5 à 10 cm [90]. En pédiatrie, l'utilisation d'un cathéter muni directement d'un transducteur de pression (Voir Figure 9) est souvent privilégiée autorisant des mesures chez des nourrissons [8, 9, 12, 67, 92, 93]. Cette sonde a été validée (en comparaison à la méthode de référence) dans plusieurs études notamment pour comparer les variations chez un même patient avec probablement une moins bonne précision de mesure en valeur absolue [94, 95]. Enfin, la présence d'une sonde gastrique ne semble pas interférer dans les mesures [96].

1.2. Le produit pression temps (PTP)

Le produit pression temps œsophagien (PTPeso) est l'intégration de la courbe de pression œsophagienne en fonction du temps (Figure 5). Ce paramètre est probablement mieux corrélé

au coût métabolique des muscles respiratoires que la mesure du travail respiratoire [97]. C'est l'un des outils les plus utilisés pour quantifier l'effort respiratoire [86, 87, 98]

Le PTP peut être dérivé à partir de la pression trans-diaphragmatique (PTPdi) en soustrayant la pression œsophagienne à la pression gastrique (Pdi = Pga-Peso) et reflète alors l'activité musculaire du diaphragme.

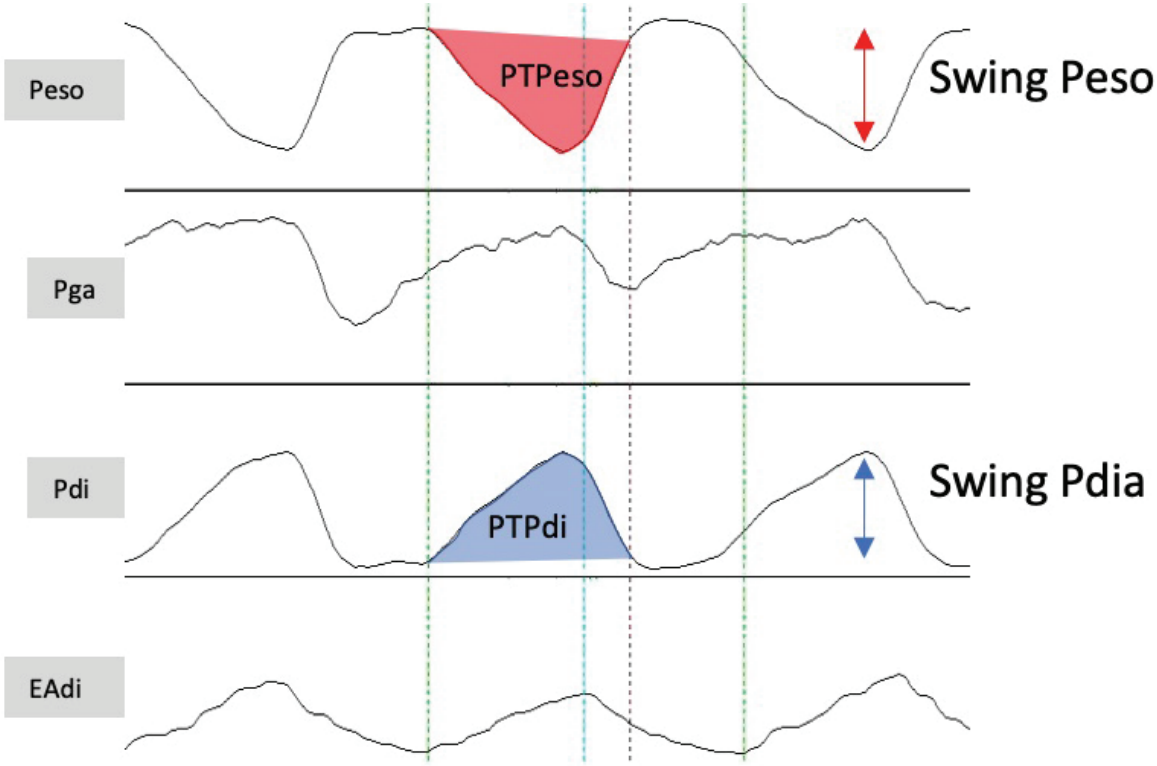

Figure 5 : Principales mesures de l'effort respiratoire.

Peso= pression œsophagienne, Pga=pression gastrique, Pdi = pression transdiaphragmatique, EAdi= activité électrique du diaphragme, PTPeso = produit pression temps œsophagien, PTPdi= produit pression temps transdiaphragmatique

Une des problématiques principales lors de l'utilisation de ce paramètre concerne la détermination du début de l'effort inspiratoire. En ventilation non-invasive, la présence de fuite peut rendre difficile la détermination du début de l'inspiration sur la courbe de débit. Dans notre étude, nous avons utilisé l'activité électrique du diaphragme pour définir le début de l'inspiration comme précédemment décrit [99, 100]. On évalue alors l'effort global en intégrant celui nécessaire pour vaincre la PEEPi.

1.3. Amplitude de la dépression œsophagienne et diaphrgmatique (Swing)

L'amplitude de la dépression générée par le patient (swing) est une mesure informative sur l'effort inspiratoire (Figure 6). Cette mesure peut être dérivée à partir de la pression œsophagienne ou à partir de la pression transdiaphragmatique reflétant l'effort inspiratoire généré par le diaphragme [101].

2. COMMANDE VENTILATOIRE ET NEURALLY ADJUSTED VENTILATORY ASSIST

2.1. Activité électrique du diaphragme

En physiologie respiratoire, le *trigger* automatique de la respiration correspondant à l'initiation de la commande centrale est situé au niveau des portions latérales rostrales et ventrales du bulbe [102]. Deux groupes de neurones (le complexe préBötzinger et le groupe respiratoire parafacial) vont se dépolariser automatiquement produisant le rythme primaire de la ventilation. Ensuite ce message est transmis aux « neurones respiratoires » situés au niveau du bulbe chargé de l'organisation spatiale et temporelle du signal respiratoire. Les informations suivent une voie descendante via des motoneurones (notamment les nerfs phréniques) depuis ces centres respiratoires jusqu'aux muscles de la respiration dont le principal est le diaphragme.

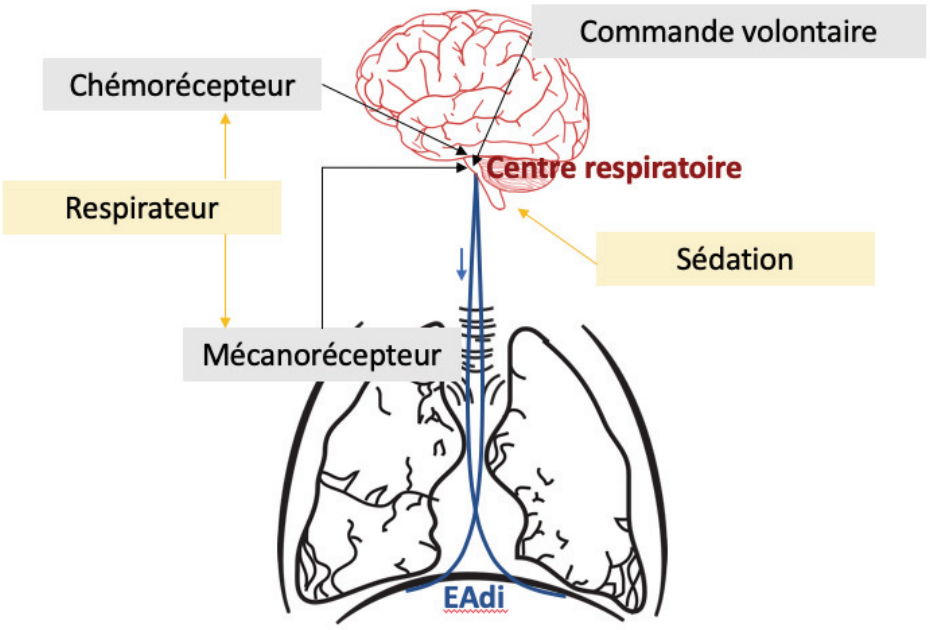

Figure 6 : Schéma récapitulatif de la commande ventilatoire et de l'activité électrique diaphragmatique.

En gris les afférences physiologiques. En Orange les afférences pathologiques

Ce système reçoit de nombreuses afférences, en conditions physiologiques, chargées d'adapter la ventilation (mécanorécepteur, chémorecepteur). Il existe aussi une commande volontaire corticale qui permet de contrôler la respiration à l'éveil (Figure 6). En conditions pathologiques ce système est également soumis aux interventions ventilatoires (respirateur) et médicamenteuses qui peuvent modifier la commande ventilatoire [103, 104]

L'activité électrique diaphragmatique (EAdi) représente seulement une partie de la commande ventilatoire issue des centres respiratoires et transmise via les nerfs phréniques (Figure 6). L'isolement du signal électrique diaphragmatique nécessite une succession de traitements informatiques afin de soustraire les activités électriques interférant avec l'activité du diaphragme (en particulier l'activité cardiaque). La mesure de cette activité à partir d'électrodes œsophagiennes a vu son essor avec le développement de la Neurally adjusted ventilatory assist (NAVA) [105]. A partir d'une sonde gastrique munie de capteurs et d'un respirateur dédié (maquet, Gettinge group, Solna, suède) les praticiens ont accès à cette mesure physiologique.

2.2. Neurally Adjusted Ventilatory Assist

2.2.1. Principe de la NAVA

La Neurally Adjusted Ventilatory Assist est un mode ventilatoire développé à la fin des années 90 qui se base sur l'activité électrique du diaphragme recueillie par voie œsophagienne [105]. Ce signal permettra d'asservir le respirateur avec deux objectifs : synchroniser les cycles ventilatoires et délivrer une ventilation proportionnelle à l'EAdi (Figure 7).

Lors de l'initiation d'un cycle respiratoire, le signal respiratoire va naître au niveau du bulbe puis être transmis via les motoneurones jusqu'aux muscles. Ces derniers vont se contracter et générer une modification du volume de la cage thoracique (responsable d'une variation de pression ou de débit dans le circuit du respirateur) qui sera détectée par le respirateur en ventilation conventionnelle. En NAVA, la détection du signal est effectuée en amont c'est-à-dire lors de la transmission du signal depuis les nerfs phréniques au muscle diaphragmatique.

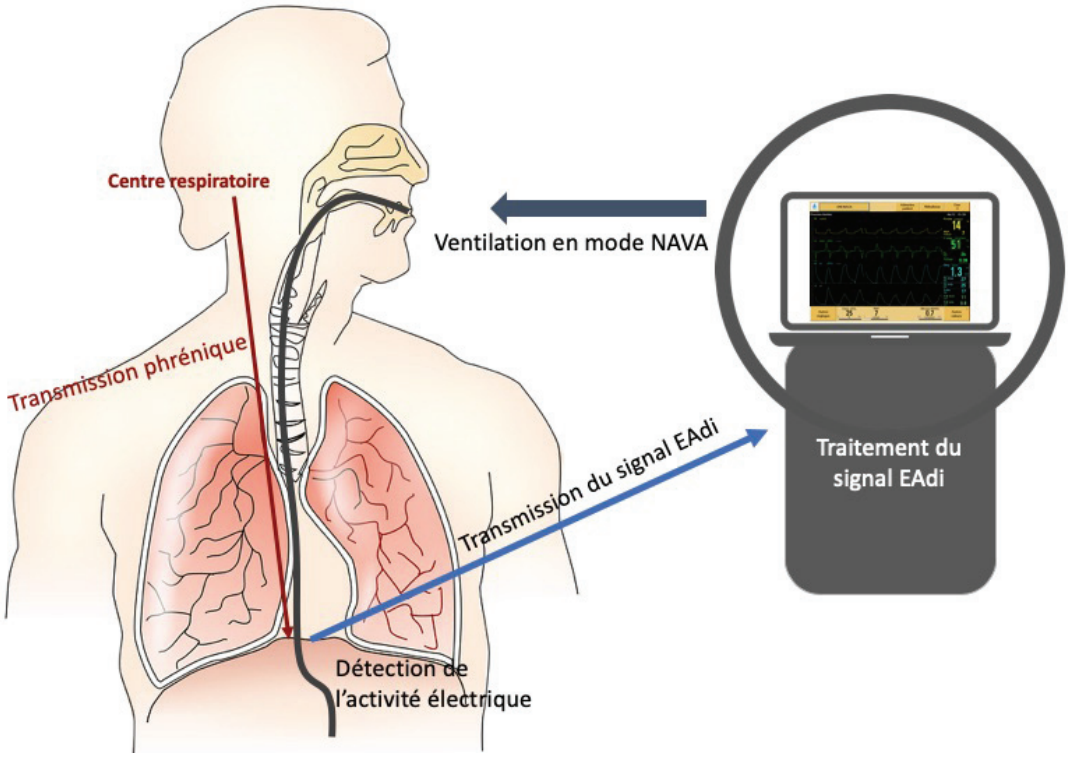

Figure 7 : Principe de la neurally adjusted ventilatory assist [106]

Le principe de la ventilation proportionnelle est d'utiliser les boucles de rétrocontrôle physiologique. En condition normale lors d'une augmentation de la demande ventilatoire, les centres de la respiration vont recruter des motoneurones (recrutement spatial et temporel) [107] se traduisant par une augmentation de l'EAdi [108]. Le respirateur va détecter un signal plus élevé et donc produire une assistance plus importante. En résumé, plus l'effort généré par le patient est important, plus l'assistance délivrée par le respirateur est importante.

2.2.2. Utilisation et réglages

En pratique, ce mode ventilatoire est captif d'une marque de respirateur (Maquet, Getinge, solna, Suède). Un cathéter dédié muni de plusieurs électrodes est positionné en regard du diaphragme à l'aide d'un abaque basé sur la distance nez-oreille-xiphoïde puis de l'écran de configuration [109].

Après positionnement, le signal est recueilli de manière continue via un câble et un module connecté au respirateur. En mode NAVA, le respirateur utilise ce signal pour délivrer une ventilation proportionnelle avec un facteur multiplicateur déterminé par le clinicien selon l'équation 3.

Équation 3

Pressure $_{(t)}$ (cmH_2O) = Niveau NAVA ($\mu V/cmH_2O$) * (EAdi $_{(t)}$ – Eadi $_{minimale}$)

(t)= temps, EAdi=activité électrique diaphragmatique

Le niveau NAVA est réglé directement sur l'écran du respirateur (Figure 8)

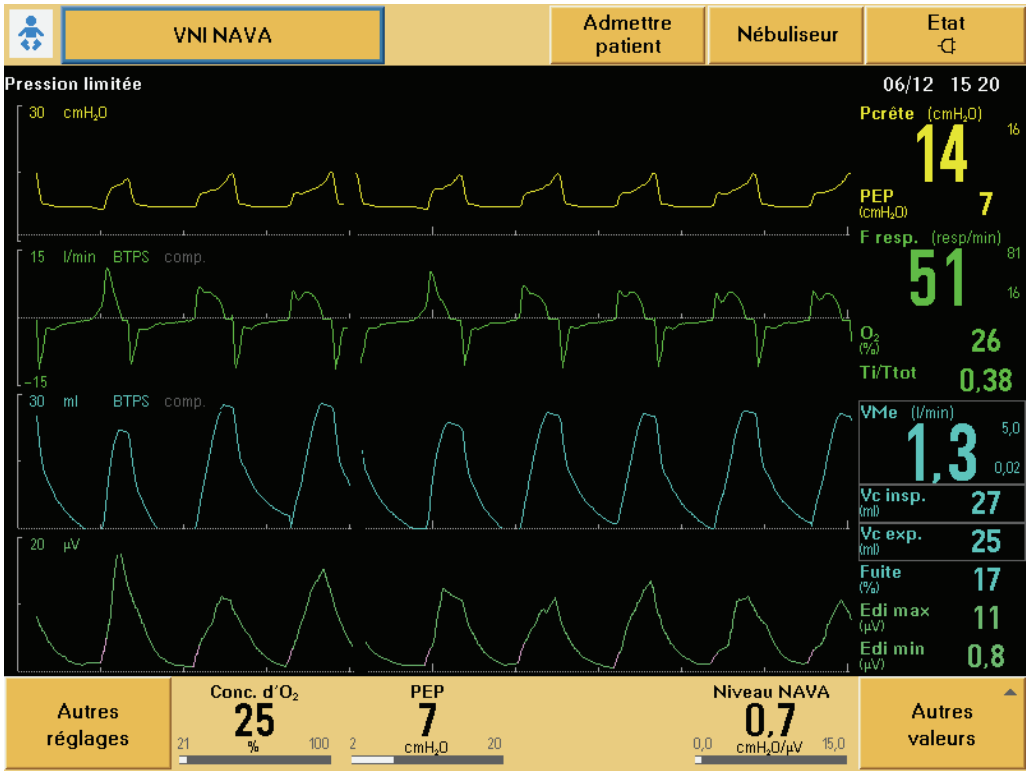

Figure 8 : Capture d'écran en ventilation non invasive NAVA d'un nourrisson.

Le cyclage du respirateur est dit neural car basé sur l'activité électrique. Par défaut, le déclenchement de l'inspiration est détecté pour une variation de 0,5µV de cette activité électrique. Le passage de l'inspiration à l'expiration se fait à 70% de la valeur maximale de l'EAdi (Peak). Il s'agit d'une ventilation assistée uniquement et il existe plusieurs niveaux de sécurité avec la possibilité d'un déclenchement pneumatique (trigger pneumatique), la présence d'une limite maximale de pression qui limitera la pression dans les voies aériennes 5 cmH_2O en dessous de cette limite réglée et une ventilation d'apnée en cas d'absence d'effort du patient.

2.3. Relation entre activité électrique et effort respiratoire

A partir des informations obtenues par l'EAdi, reflet de la commande ventilatoire et des informations à partir des pressions œso-gastriques, reflet de l'effort respiratoire, il est possible d'évaluer la relation entre la commande et l'action mécanique. L'activation des potentiels d'action au niveau diaphragmatique a pour objectif de générer une contraction diaphragmatique et une dépression thoracique permettant la ventilation [110]. Dans des conditions diaphragmatiques constantes (sans modification des propriétés musculaires), l'activité électrique diaphragmatique permet d'évaluer la contractilité diaphragmatique. Plusieurs auteurs ont démontré que chez l'adulte la corrélation entre l'activité électrique et diverses mesures de l'effort inspiratoire est acceptable [111, 112].

A l'inverse, si les conditions de charges changent, le rapport entre la commande et l'effecteur traduit « l'efficacité » de la ventilation. L'efficacité neuro-ventilatoire est définie comme le rapport entre le volume courant et l'activité électrique diaphragmatique[113] et l'efficacité neuro-mécanique comme le rapport entre la force musculaire et l'activité électrique [100, 114]

3. SYNCHRONISATION PATIENT RESPIRATEUR

En dehors de la nCPAP, tous les autres modes ventilatoires requièrent une synchronisation entre le patient et le respirateur c'est-à-dire que le respirateur doit être capable de détecter les efforts respiratoires du patient.

3.1. Le « Trigger » et le délai de réponse du respirateur

Le *trigger* inspiratoire est le seuil à partir duquel le respirateur est capable de détecter un effort inspiratoire du patient. Il peut être en pression (variation de pression nécessaire pour déclencher un cycle ventilatoire) ou en débit. Il joue un rôle fondamental dans la synchronisation inspiratoire patient-respirateur. Le délai de réponse est le temps entre le début de l'effort respiratoire du patient et le début du cycle déclenché par le respirateur. De la qualité du *trigger* dépend le temps de réponse qui peut être extrêmement variable (du simple au double) d'un respirateur à l'autre [115].

3.2. Principales asynchronies

On distingue classiquement cinq types d'asynchronies décrits par Thille et al. [116] :

- **Les efforts inefficaces** sont définis par des efforts générés par le patient mais non détectés et donc non récompensés par le respirateur.
- **Les doubles déclenchements** sont la succession de deux cycles extrêmement rapprochés (dans le même temps inspiratoire).
- **Les auto-déclenchements** sont des cycles produits par le respirateur en l'absence d'efforts du patient.
- **Les cycles courts :** ils apparaissent lorsque le respirateur ouvre sa valve expiratoire alors que le patient n'a pas terminé son cycle inspiratoire.
- **Les cycles prolongés** sont l'inverse des cycles courts avec l'impossibilité pour le respirateur de détecter la fin de l'inspiration. Les fuites sont souvent à l'origine de ce phénomène.

Un index d'asynchronie (AI) peut donc être calculé selon la formule :

AI (%) =Nombre d'évènements (asynchronies) / FR totale x 100

Les descriptions initiales des asynchronies utilisaient les mesures de pression œsophagienne et des débits en ventilation invasive comme référence [116]. L'accès facile à l'activité électrique du diaphragme a permis de simplifier ces explorations et l'EAdi est maintenant largement utilisée comme référence [117-119]. Cette méthode a l'inconvénient de ne prendre en compte que la participation du diaphragme dans la respiration du patient.

3.3. Conséquences des asynchronies en ventilation mécanique

La présence d'asynchronies entraine en plus de l'inconfort du patient, une augmentation significative du travail respiratoire [116, 120] et est associée à une augmentation de la durée de ventilation mécanique [116]. En ventilation invasive, on estime qu'un patient adulte sur quatre présente un taux d'asynchronies élevé (> 10%) [116]. En ventilation non invasive la présence de fuites majore ce risque, malgré l'utilisation d'algorithmes de compensation [121]. Ainsi le taux d'asynchronies peut atteindre 50% des cycles respiratoires [122-124] et jusqu'à 75% en pédiatrie [125-128].

4. MISE EN ŒUVRE DES MESURES

Dans les études réalisées, nous avons utilisé différents systèmes pour analyser les données physiologiques chez les enfants.

4.1. Recueil synchronisé de l'EAdi et des pressions.

La société NeuroVent.inc (Toronto, On, Canada), créée par Jennifer Beck et Christer Sinderby, co-inventeurs de la NAVA a développé plusieurs outils pour l'exploration physiologique respiratoire animale et humaine. Le système utilisé pour l'étude 1 avec le Dr ESSOURI et l'étude 2 (BRONCHIO-DV) permet l'acquisition des signaux issus du respirateur (Servo-I, Maquet, Getingue) de manière simultanée aux autres signaux physiologiques.

4.1.1. Mesure des pressions œsophagiennes

Deux types de sondes ont été utilisées dans le cadre de ce doctorat. Dans l'étude 1 réalisée à Montréal avec le Dr Essouri, une sonde nasogastrique 8F à usage unique a été développée spécialement pour l'étude (Figure 9) permettant le recueil simultané du signal EAdi et des pressions œsophagiennes via un ballonnet. La position était vérifiée à la fois via l'écran dédié sur le respirateur SERVO-I (Maquet, Getinge, Solna, Suède) et via la manœuvre de Baydur [90, 129].

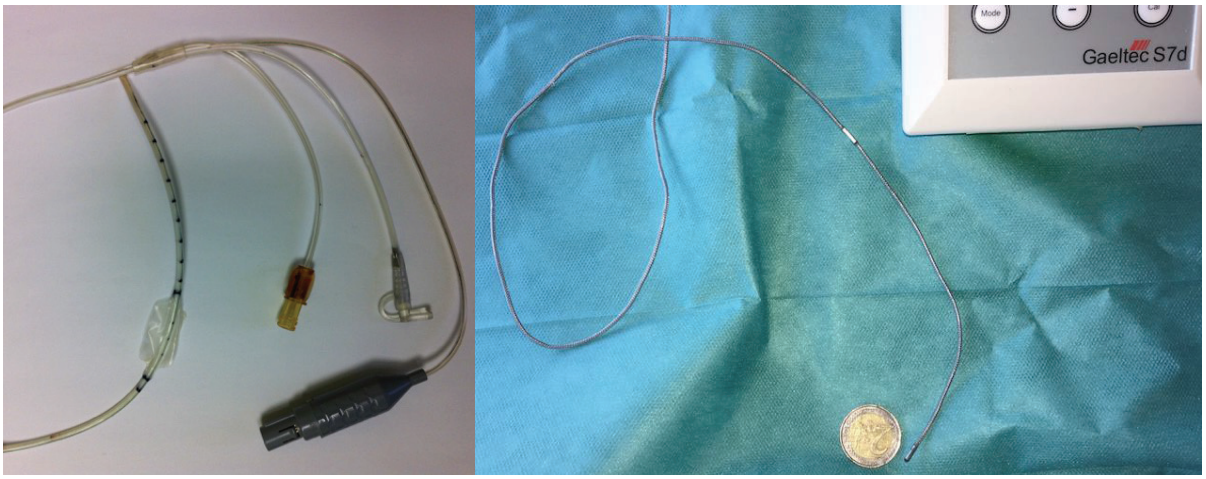

Figure 9 : Sondes de mesure des pressions œsophagiennes utilisées dans les études

A droite une sonde NAVA à ballonnet (Neurovent), à gauche sonde à transducteurs de pressions de 2,3 mm de diamètre (Gaeltec).

La deuxième sonde utilisée était un cathéter souple (Figure 9) réutilisable, de mesure de pressions œsophagienne et gastrique de 2,3 mm de diamètre (CTC, Gaeltec Devices Ltd., Isle of Skye, Scotland - CE 0086) muni de 2 transducteurs de pressions. Les capteurs étaient calibrés selon les recommandations du constructeur à 0 puis à 100 mmHg.

4.1.2. Système d'acquisition Neurovent

Avant tout enregistrement, un fichier de calibration pour les systèmes de pressions était réalisé à 0 puis à 20 cmH_2O. Il n'a pas été utilisé dans ces études de pneumotacographes indépendants. Les données issues du respirateur (débit, pression des voies aériennes, EAdi) étaient recueillies via la prise RS232 du respirateur relié directement au port USB de l'ordinateur et les données des autres dispositifs (pression œsophagienne, pression gastrique, pression des voies aériennes) étaient transmises via le dispositif d'acquisition des données (DAQ) au logiciel. Toutes les données étaient enregistrées et stockées sur un ordinateur. Les données brutes étaient ensuite transformées et exportées avec une fréquence d'échantillonnage de 62,5Hz. Enfin, un logiciel permettait l'analyse des résultats en plusieurs étapes.

La première étape consistait à analyser les timings des cycles respiratoires. Les curseurs de temps étaient automatiquement positionnés à partir du signal EAdi (1) au début de l'inspiration (augmentation de 0,5µV au-dessus de la ligne de base = Niveau de trigger réglé par défaut à 0,5µV), (2) peak (EAdi maximale), (3) début expiration (70% de la valeur maximale de l'EAdi) et (4) à la fin de l'expiration (retour à la ligne de base) (Figure 10). Ils étaient vérifiés cycle à cycle (repositionnement et suppression des cycles aberrants). Quatre autres curseurs étaient ajoutés manuellement au début et à la fin de l'inspiration à partir de la courbe de débit et à partir de la courbe de pression transdiaphragmatique.

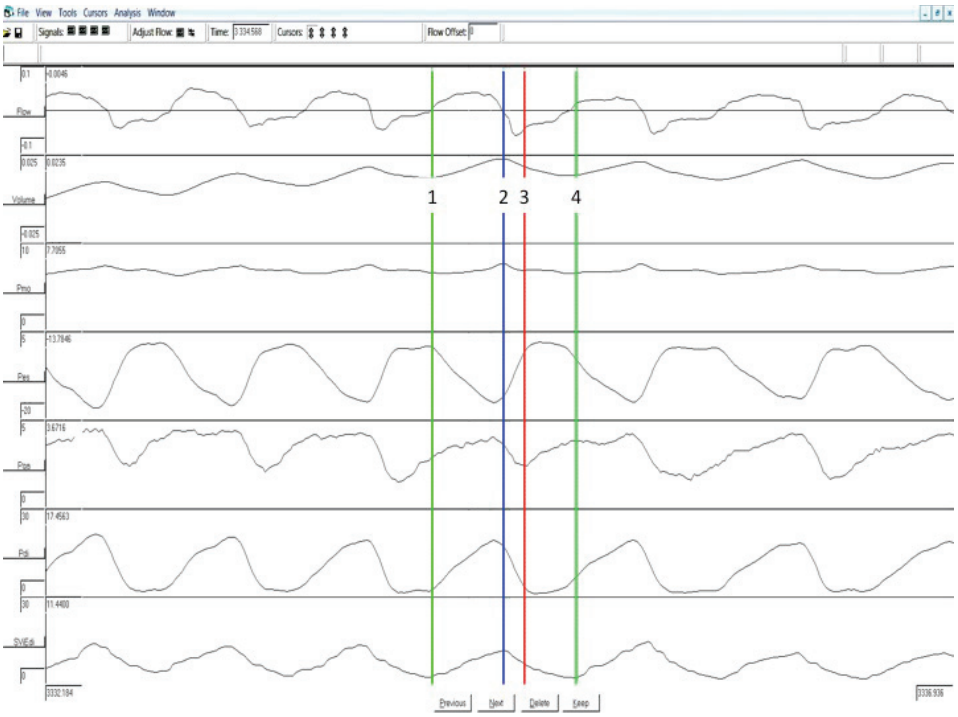

Figure 10 : Exemple d'enregistrement et de positionnement des curseurs de temps à partir de l'activité électrique diaphragmatique.

La deuxième étape consistait à générer les valeurs (valeur initiale, valeur finale, valeur minimale, valeur maximale, valeur moyenne, aire sous la courbe) cycle à cycle à partir de ces curseurs de temps pour chacun des signaux. Enfin, les données étaient exportées dans un tableur, puis moyennées.

4.2. Recueil simplifié des données du respirateur

4.2.1. Acquisition des données avec le logiciel Servo-RCR

Pour l'étude sur les asynchronies, un logiciel fourni par le constructeur (Servo-RCR V 1.7.5, Maquet Critical Care, Solna, Suède) a été utilisé. Les données du respirateur (signaux de pression, de débit et de l'activité électrique diaphragmatique) étaient enregistrées en continue (fréquence 100Hz) à l'aide d'une connexion RS232 et du logiciel Servo RCR software, Maquet (Figure 11).

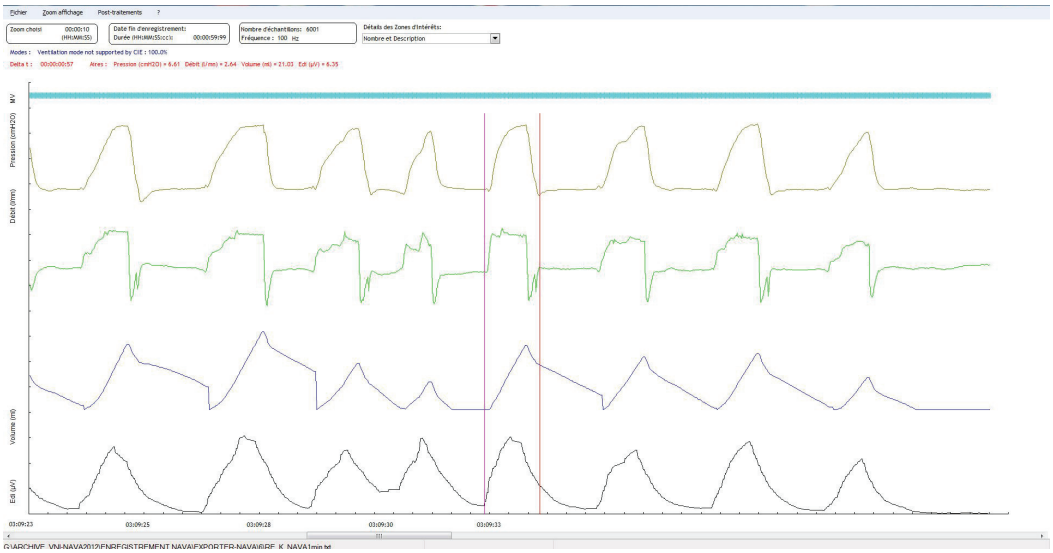

Figure 11 : capture d'écran du logiciel constructeur SERVO-RCR v 3.7.5

4.2.2. Analyses des asynchronies

Les données étaient analysées à postériori cycle à cycle avec le même logiciel. Le délai de trigger a été défini comme le délai entre le début de l'élévation de la courbe d'EAdi et le début de l'élévation de la courbe de débit selon les modalités décrites dans des études précédentes [99]. Seules les trois principales asynchronies facilement identifiables ont été recherchées : effort inefficace, auto-déclenchement et double déclenchement (Figure 12).

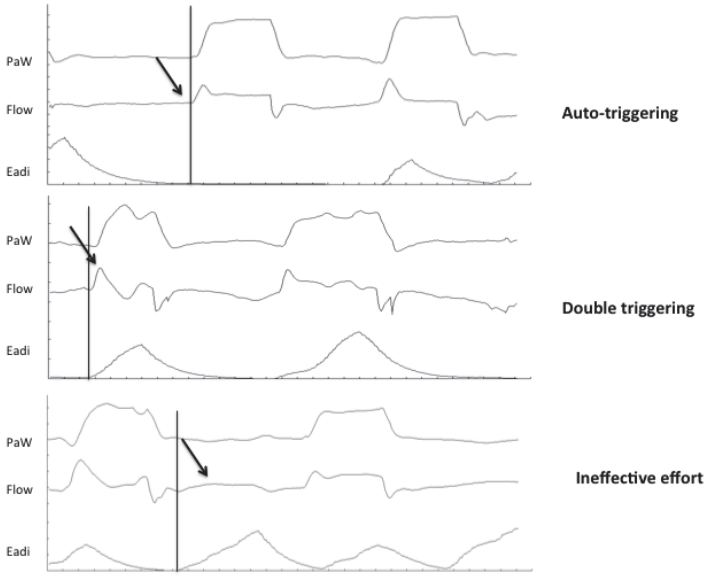

Figure 12 : Exemple des 3 principales asynchronies chez un nourrisson atteint de bronchiolite grave en ventilation non invasive.

La ligne verticale indique le début du cycle et la flèche l'évènement remarquable.

III. RESULTATS ET DISCUSSION DES ETUDES

1. ETUDE 1 : ACTIVITE ELECTRIQUE DIAPHRAGMATIQUE ET EFFORT RESPIRATOIRE CHEZ L'ENFANT SOUS VENTILATION MECANIQUE

1.1. Introduction

Nous avons vu précédemment qu'il existait une relation entre l'activité électrique et l'effort généré par le muscle diaphragmatique chez l'adulte, base du travail ayant abouti à la NAVA. Au-delà de l'utilisation en mode NAVA, le respirateur peut devenir un outil de monitorage simple puisque l'EAdi devient accessible, même chez l'enfant en réanimation pédiatrique.

Notre hypothèse était que chez l'enfant sous ventilation mécanique, il existait une corrélation entre EAdi et effort respiratoire (évalué par le PTP œsophagien). Cette étude permettait d'évaluer cette relation sous différentes conditions et de voir l'évolution des différents indices mesurés.

1.2. Matériel et méthodes

Cette étude a été conduite dans le service de réanimation pédiatrique du CHU Sainte Justine à Montréal, Canada entre octobre 2013 et Août 2014. Après inclusion, signature du consentement, et mise en place de la sonde EAdi avec un ballonnet œsophagien, les enfants étaient randomisés pour être ventilés soit en NAVA puis en ventilation spontanée en aide inspiratoire (VS-AI) ou inversement. La sonde était ensuite laissée en place (durée maximum de 7 jours) et une mesure complémentaire était réalisée dans les 2 heures suivant l'extubation. Tous les paramètres ventilatoires recueillis ont été moyennés sur 100 cycles. Les valeurs ont été ensuite découpées en déciles puis la corrélation entre l'activité électrique et différents marqueurs de l'effort inspiratoire a été évaluée et comparée dans les trois conditions.

1.3. Article 1: "Relationship between diaphragmatic electrical activity and esophageal pressure monitoring in children"

Pediatric Critical Care Medicine

Relationship between diaphragmatic electrical activity and esophageal pressure monitoring in children

--Manuscript Draft--

Manuscript Number:	PCCM-D-18-00838R1
Full Title:	Relationship between diaphragmatic electrical activity and esophageal pressure monitoring in children
Article Type:	Online Clinical Investigation
Keywords:	diaphragmatic electrical activity, esophageal pressure, pressure support ventilation, NAVA, weaning, neuroventilatory efficiency.
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Abstract:	Purpose: Mechanical ventilation is an essential life support technology, but it is associated with side effects in case of over or under-assistance. The monitoring of respiratory effort may facilitate titration of the support. The gold standard for respiratory effort measurement is based on esophageal pressure monitoring, a technology not commonly available at bedside. Diaphragmatic electrical activity (Edi) can be routinely monitored in clinical practice and reflects the output of the respiratory centres. We hypothesized that Edi changes accurately reflect changes in mechanical efforts. The objectives of this study were to characterize the relationship between Edi and esophageal pressure. Methods Children in the weaning phase of mechanical ventilation were eligible in this prospective crossover study. Esophageal pressure and Edi were simultaneously recorded using a specific naso-gastric tube in three conditions: in pressure support ventilation (PSV) and in neurally adjusted ventilatory support (NAVA) in a random order, and then after extubation. The inspiratory esophageal pressure swing (Pesmax) and pressure-time product (PTPes), Edi swing (Edimax), and inspiratory Edi integral (IntEdi) were calculated from 100 consecutive breaths. Neuro-ventilatory efficiency was estimated using the ratio of tidal volume/Edimax. Results Sixteen patients, with a median age of 4 months [IQR 0.5-13], and weight 5.8 kg [IQR 4.1-8] were included. A strong linear correlation between Edimax and Pesmax ($r^2>0.95$), and IntEdi and PTPes ($r^2>0.71$) was observed in all ventilatory conditions.

Relationship between diaphragmatic electrical activity and esophageal pressure monitoring in children

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Key words 4-6: diaphragmatic electrical activity, esophageal pressure, pressure support ventilation, NAVA, weaning, neuroventilatory efficiency.

Manuscripts words counts: 2595

Abstract

Objective: Mechanical ventilation is an essential life support technology, but it is associated with side effects in case of over or under-assistance. The monitoring of respiratory effort may facilitate titration of the support. The gold standard for respiratory effort measurement is based on esophageal pressure monitoring, a technology not commonly available at bedside. Diaphragmatic electrical activity (Edi) can be routinely monitored in clinical practice and reflects the output of the respiratory centres. We hypothesized that Edi changes accurately reflect changes in mechanical efforts. The objectives of this study were to characterize the relationship between Edi and esophageal pressure.

Design and patients: Children in the weaning phase of mechanical ventilation were eligible in this prospective crossover study.

Setting: Esophageal pressure and Edi were simultaneously recorded using a specific naso-gastric tube in three conditions: in pressure support ventilation (PSV) and in neurally adjusted ventilatory support (NAVA) in a random order, and then after extubation.

Intervention and measurements: The inspiratory esophageal pressure swing (Pes_{max}) and pressure-time product (PTPes), Edi swing (Edimax), and inspiratory Edi integral (IntEdi) were calculated from 100 consecutive breaths. Neuro-ventilatory efficiency was estimated using the ratio of tidal volume/Edi_{max}.

Main results: Sixteen patients, with a median age of 4 months [IQR 0.5-13], and weight 5.8 kg [IQR 4.1-8] were included. A strong linear correlation between Edi_{max} and Pes_{max} (r^2>0.95), and IntEdi and PTPes (r^2>0.71) was observed in all ventilatory conditions. This correlation was not modified by the type of ventilatory support.

Conclusion: On a short-term basis, Edi changes are strongly correlated with esophageal pressure changes. In clinical practice, Edi monitoring may help to inform on changes in respiratory efforts.

Introduction

Acute respiratory failure is the main cause leading to admission to Pediatric Intensive Care Unit (PICU). An optimized titration of the mechanical ventilation is essential to minimize the deleterious impact of the ventilation on the lung (ventilation induced lung injury) or the diaphragm (ventilation induced diaphragm dysfunction) [1-4]. Patient active respiratory efforts during mechanical ventilation can prevent diaphragm atrophy [5, 6] but important spontaneous breathing efforts may also lead to lung injury in severe cases (patient self-inflicted lung injury) [7-9]. Thus, the assessment of respiratory muscle function in critically ill children is crucial to provide adequate care and adapt the ventilator settings.

The assessment of the respiratory effort is classically based on the measurement of esophageal pressure, in order to calculate the esophageal (PTPes), or the trans-diaphragmatic pressure-time product but this is not currently used in daily practice in PICU. The diaphragm electrical activity (Edi), which reflects the neural drive, can be relatively easily monitored with a specific naso-gastric tube. The relationship between the Edi (the “demand”) and the inspiratory pressure or the tidal volume that are generated (the “result”) reflects the concept of neuro-mechanical and neuro-ventilatory efficiency (NME and NVE) [10]. Some previous studies suggest that these physiological parameters may be helpful in predicting extubation success in adults [11, 12].

The main objective of the study was to evaluate the relationship between Edi and the breathing effort as estimated with the esophageal pressure, in various ventilatory conditions. We hypothesized that both variables are correlated in critically ill children.

~~Material and method~~Materials and Methods

Study design and patients

This is a prospective physiological crossover study conducted in the PICU at CHU Sainte Justine, a 32-bed university-affiliated pediatric hospital, from October 1, 2013 to August 31, 2014. The study was approved by our local Institutional Ethical Committee (n°3688) and written informed consent was obtained from the parents or legal tutors. This study follows CONSORT recommendations.

Children aged between birth (> 37 gestational age) and 18-year-old, admitted to the PICU and in the weaning phase of invasive ventilation were eligible.

Exclusion criteria included any contraindication to change the naso-gastric tube (severe coagulation disorder, local trauma, recent local surgery, upper airway bleeding). Patient screening was done on a daily basis on weekdays by research staff.

Study protocol

The study protocol consisted in three consecutive phases. Patients were ventilated randomly either in pressure-support ventilation (PSV) first or with NAVA first for a 30-minute period. Then, the ventilator mode was changed to the other mode for a second 30-minute period. During PSV, the settings were those set by the attending physician. During NAVA, the NAVA level was set in order to obtain the same level of total inspiratory pressure support as in PSV. Positive end expiratory pressure (PEEP) and FiO_2 were not modified during the study. In each condition, the data were recorded for 20 minutes after a 10-minute period of stabilization.

After these two recordings, the naso-gastric tube was kept in place until extubation was decided by caregivers, for a maximum of seven days. After the extubation, an additional recording was conducted for five minutes, in the two hours following extubation.

Data acquisition and physiological measurements

At inclusion, patients characteristics (age, sex, weight, gestational age, admission diagnosis, comorbidities) and ventilator settings were collected. The sedation received by patients within the 4 hours preceding the recordings was recorded.

The Edi was recorded using a specific 8F naso-gastric Edi catheter equipped with electrodes (for Edi monitoring) and an esophageal balloon (for Pes monitoring) (Neurovent, Toronto, ON, Canada). After inclusion in the study, the esophageal catheter was inserted and connected to a dedicated Servo-I ventilator (Maquet, Solna, Sweden). The tube position was checked on the ventilator screen according to the procedure suggested by the manufacturer and previously reported [13, 14]. The calibration of esophageal pressure (Pes) was performed using the Baydur maneuver [15, 16].

All patients were recorded in semi-recumbent position. Flow, airway pressure (Paw), Pes and Edi waveforms were simultaneously acquired from the ventilator using a dedicated software (Neurovent monitor, Neurovent, Toronto, Canada) and stored for subsequent analysis. Both catheter position and Edi signal stability were regularly checked throughout the protocol.

In each ventilation condition, Edi and volume waveforms, and esophageal pressure curves were analyzed in a breath-by-breath manner over 100 consecutive cycles exempt of artefacts. Timings of the beginning and the end of cycles were automatically identified, and a visual inspection was performed breath by breath with cursor adjustement, if needed.

Respiratory rate (RR), tidal volume (Vt), maximum Edi (Edi_{max}) and the area under the curve of the Edi during inspiratory time (IntEdi, integrated from baseline to peak) were calculated for 100 consecutive cycles and were averaged for each ventilation condition. On the same 100 consecutive cycles, maximal esophageal swing (Pes_{max}) and esophageal pressure time product (PTP_{es}) were calculated. PTP_{es} was obtained by measuring the area under the esophageal pressure signal between the onset of inspiration effort and the end of inspiration effort defined as the end of the inspiratory flow signal. For the same 100 consecutive cycles, maximal inspiratory pressure (PI_{max}) measured by the ventilator we recorded.

The rapid shallow breathing index (RR/Vt), the neuro-ventilatory efficiency (NVE, estimated with the ratio Vt/Edi_{max} during inspiration) and the Vt/Pes_{max} were also calculated.

Statistical analysis:

Data are expressed as median (interquartile range, IQR) for continuous variables, and number and/or frequency (%) for binary or categorical data. Binary or categorical variables were compared using Chi-square or Fisher's exact test. Differences in continuous variables were assessed by the non-parametric Mann-Whitney test.

To assess the relationship between Edi- and Pes- derived data, in each ventilatory condition, all breaths were grouped by Edi deciles, and the mean values of Edi and Pes data were calculated for each decile [17]. The correlation between Edi_{max} and Pes_{max}, and between IntEdi and PTPes were assessed using the determination coefficient r^2. The impact of the ventilatory condition on this relationship was evaluated by comparing the r^2, the regression slopes and intercepts in the ~~3 three~~ three conditions (Friedman test). All statistical analyses were made with SPSS statistics 24.0.0.0. A bilateral p value < 0.05 was considered significant.

Assuming a correlation coefficient of 0.8 and a bilateral risk of type-1 error of 5%, we estimated that the inclusion of 12 patients was needed to achieve a power of 90% to confirm the correlation between Edi and PTP, based on preliminary data. We included 20 patients to increase the representativeness of the sample.

Results

Study population

During the study period, 100 eligible patients were screened. Among them, 19 patients reached the inclusion criteria and were enrolled (see flow chart diagram, Fig 1). Two patients were excluded from the analysis, because the extubation occurred prior to the first recording. One patient was secondarily excluded because of non-measurable electrical diaphragmatic activity. Sixteen patients were therefore included in the statistical analysis. Post-extubation data were obtained in 13 patients.

The characteristics of the patients are presented in Table 1. Median age of the patients was 4 months [IQR 0.5-13], median weight was 5.8 kgs [IQR 4.1-8]. The primary diagnosis at PICU admission was mainly respiratory failure (11 patients). Seven patients had comorbidities.

Ventilator settings

Table 2 describes the ventilator settings in both assisted ventilation periods. After extubation, 12 patients were on spontaneous breathing while three ~~3 three~~ patients were on non-invasive ventilation and one patient with high-flow nasal cannula. Tidal volume measured in PSV and NAVA were similar (p=0.75). Pressure support level was decreased in three ~~3 three~~ patients at the end of the PSV period, by 2 cmH_20 in two patients and 7 cmH_20 in one patient. None required an increase in pressure support. At the end of the

NAVA period, NAVA level was decreased by 0.2 $cmH_20/\mu V$ in two patients, 0.3 $cmH_20/\mu V$ in one patient, and 0.7 $cmH_20/\mu V$ in one patient.

Neuromuscular coupling

As illustrated in Figure 2 and Table 3, we found a strong linear correlation for the global population between Edi_{max} and Pes_{max} and between IntEdi and PTPes in the three ~~3 three~~ ventilatory conditions (all $r^2 > 0.95$, and $r^2 > 0.71$, respectively). The relationship between the Edi-derived and Pes-derived indices was not statistically different depending on the ventilatory support with similar r^2 (p=0.46), regression slopes (p=0.64) and intercepts (p=0.72).

Individual correlation data are illustrated in supplemental digital content. Overall, the relationship between Edi and Pes swing was relatively strong in all patients and conditions, but some variability was observed when the ventilatory condition was modified in some patients. The Vt/Edi ratio was similar in PSV and NAVA (p=0.49, Table 3).

Respiratory muscles unloading and breathing pattern.

Table 3 provides the breathing pattern variables in the three ~~3 three~~ ventilatory conditions. Breathing pattern was similar during PSV and NAVA. Diaphragmatic activity and Pes_{max} have similar values (Figure 3) during PSV and NAVA periods. However, during spontaneous ventilation all indices of respiratory effort increased as compared to PSV and NAVA ($p < 0.05$).

The tidal volume, the rapid shallow breathing index (RR/Vt), the ratios Edi_{max}/Vt and Vt/Pes_{max} were similar in PSV and NAVA mode.

Discussion

This study describes the relationship between Edi and Pes-derived markers of respiratory effort in children. The main finding is that we confirmed a strong correlation between these two ~~2 two~~ monitoring technologies. This relationship was strong in a given ventilatory condition, and it was overall consistent across the different ventilatory conditions. However, changes in the ventilatory support was in a few cases associated with a change in the Edi – Pes correlation slope.

In clinical practice, respiratory monitoring in mechanically ventilated children is limited and mainly based on clinical exam, and airway pressure and flow monitoring. During assisted ventilation, the amount of work needed to generate the minute ventilation is shared between the patient and the ventilator. The ventilator support is easily measurable at the bedside. However, the effort generated by the patient remains difficult to quantify and monitor. Currently, the ideal level of patient respiratory effort is not known, and maintaining a spontaneous breathing may improve the lung function, decrease some markers of lung inflammation ~~inflammatory~~ [8, 9]. Moreover, spontaneous breathing might improve the diaphragmatic function and success of weaning [18, 19]. On the other hand, in case of severe respiratory failure, excessive work of breathing could lead to diaphragm fatigue and to patient self-inflicted lung injury. This could be one explanation of the survival benefit observed with neuromuscular blockage by Papazian et al. [7] in adult patients with severe acute respiratory distress syndrome. Thus, finding the optimal ventilator settings depending on the stage of the disease would be facilitated by the possibility to assess in real time, easily, and efficiently the patient's respiratory effort.

The reference method to assess the muscular pressure is based on the esophageal pressure monitoring [20]. The pressure-time product (PTP) derived from Pes is well

correlated with work of breathing and oxygen consumption of the respiratory muscles during inspiration. The Pes monitoring can be used in infants and children to assess the work of breathing, and to track the impact of an intervention to unload the respiratory muscles [21-23]. However, it cannot be currently considered as a routine practice monitoring.

The Edi monitoring has been made easily available at the bedside, especially to control the ventilation in NAVA. Besides NAVA ventilation, Edi monitoring provides a direct view of diaphragmatic activation, which carries important information for the clinicians [14]. The relationship between the Edi (the “drive”) and the diaphragmatic pressure (the “effect”) has been called the neuro-mechanical efficiency (NME), initially described by Beck et al. in healthy adult subjects [24], and later by others in mechanically ventilated adults [11, 17]. To our knowledge, our study is the first to report this relationship in the pediatric population. However, NME measurement is influenced by the ventilator support. Ideally, in order to compare NME in different conditions, no support (or at least a perfectly similar level of support) should be applied. In this study, we did not perform an occlusion, and the level of support was clearly different depending on the ventilatory conditions. This precludes us from strictly comparing NME. Nonetheless, we found a strong linear correlation between Edi and the pressure generated by the diaphragm as described previously by Bellani et al. in adults undergoing mechanical ventilation [17]. Of note, Carteaux et al. didn’t find a linear correlation but a curvilinear relationship between Edi and Pmusc, suggesting that the proportionality factor depends on the level of assistance [25]. Akoumianaki et al. also found a weak but linear correlation between Edi and trans-diaphragmatic pressure [26].

Simultaneous recording of tidal volume provides the opportunity to determine the ratio of Vt to Edi, which reflects the ability of the diaphragm to generate an inspiratory volume

normalized to neural drive, the neuro-ventilatory efficiency (NVE). Importantly, the Vt is influenced by the patient effort and by the ventilator, which should be taken into account. In our study, the Vt/Edi ratio and the Vt/Pes_{max} were similar in PSV and NAVA, but they were not assessed after extubation. The NVE index was evaluated in various adult studies as a predictor of weaning failure [11, 12, 27] or to monitor PEEP levels [28]. In 20 mechanically ventilated children undergoing extubation readiness testing, Wolf et al. found a significantly lower Vt/Edi ratio in children who passed the extubation readiness test compared to those who failed [29]. This study was not designed to identify predictor of weaning failure, and only one patient failed the extubation thus we can't conduct this analysis ~~analyze~~.

Interestingly, we observed a good correlation between Edi- and Pes- derived data in all recordings. This strongly suggests that on a short term, NVE is quite stable and a change in Edi closely reflects a change in breathing pattern. Edi monitoring therefore provides important information on the evolution of the work of breathing. However, we observed in a few cases that the relationship could be affected by the change in ventilation conditions (extubation, or mode change). This could be explained by changes in mechanical conditions (variations in lung recruitment, or modified respiratory resistance, different positioning or thoracic conformation), that could lead to different neuro-mechanical efficiency. Importantly, the correlation can also certainly be affected by changes in NME/NVE that may arise with time. For example, Di Mussi et al. [30] reported that prolonged ventilation in adults with PSV was associated with a loss in NME and NVE over time, while these changes were avoided with NAVA.

In this study, we observed normal median level of esophageal pressure swing and of Edi. However some of our patients had low levels of Pes/Edi, although all the patients were deemed to be ready for extubation. This is in keeping with previous observations by our

group or others [31,32]. We might speculate that the lack of monitoring of respiratory effort by most pediatric intensive care providers favors the blunting of the ventilatory drive, through overassistance and/or oversedation.

Study limitations

This study has several limitations. The number of patients enrolled was smaller than targeted. Although this physiological study was able to answer our main objective, the power may have been insufficient to show small differences between the conditions or to conduct subgroup analysis. The population was somehow heterogenous, in age, weight and diagnosis, but the results were consistent in these different conditions. Most patients were infants and toddlers, with a 75th percentile age of 13 months. Although three patients older than 2 years (33 months, 44 months and 12 year old, 70 kg) were also included and had a similar behavior as the rest of the group, younger infants were over-represented in the study. The generalizability of our results to older children therefore deserves further evaluation. The absence of inspiratory occlusion did not allow us to measure the NME independently from the support level. Additional studies would be important to describe the evolution of NME/NVE on a longer period.

Conclusion

This pediatric physiological study indicates that Edi is strongly correlated with esophageal pressure swings. Thus, Edi seems a valuable bedside monitoring tool to provide information on the evolution of the patient's respiratory effort. The clinical impact of this monitoring, if possible combined with automatically calculated NVE/NME indices warrants further evaluation.

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Figure 1

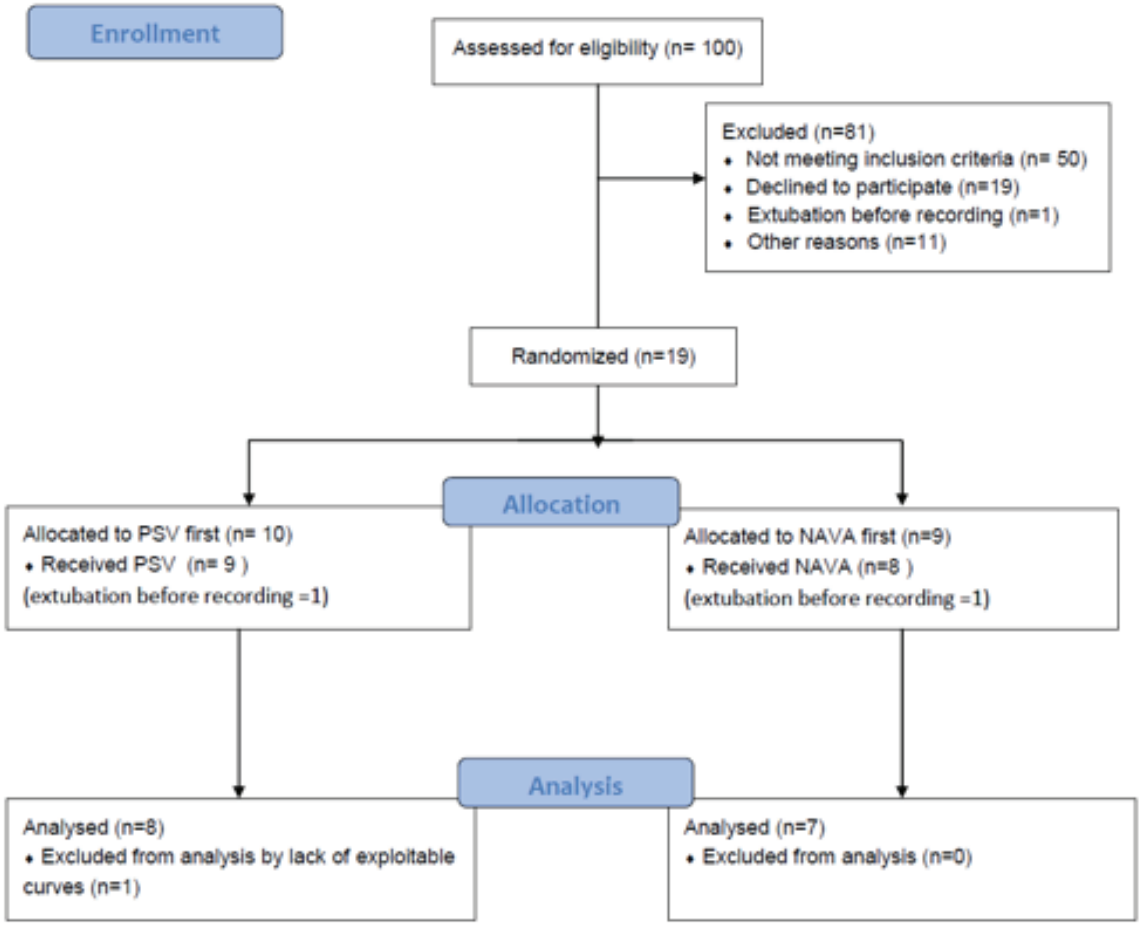

Figure 1 : Flow chart of the study

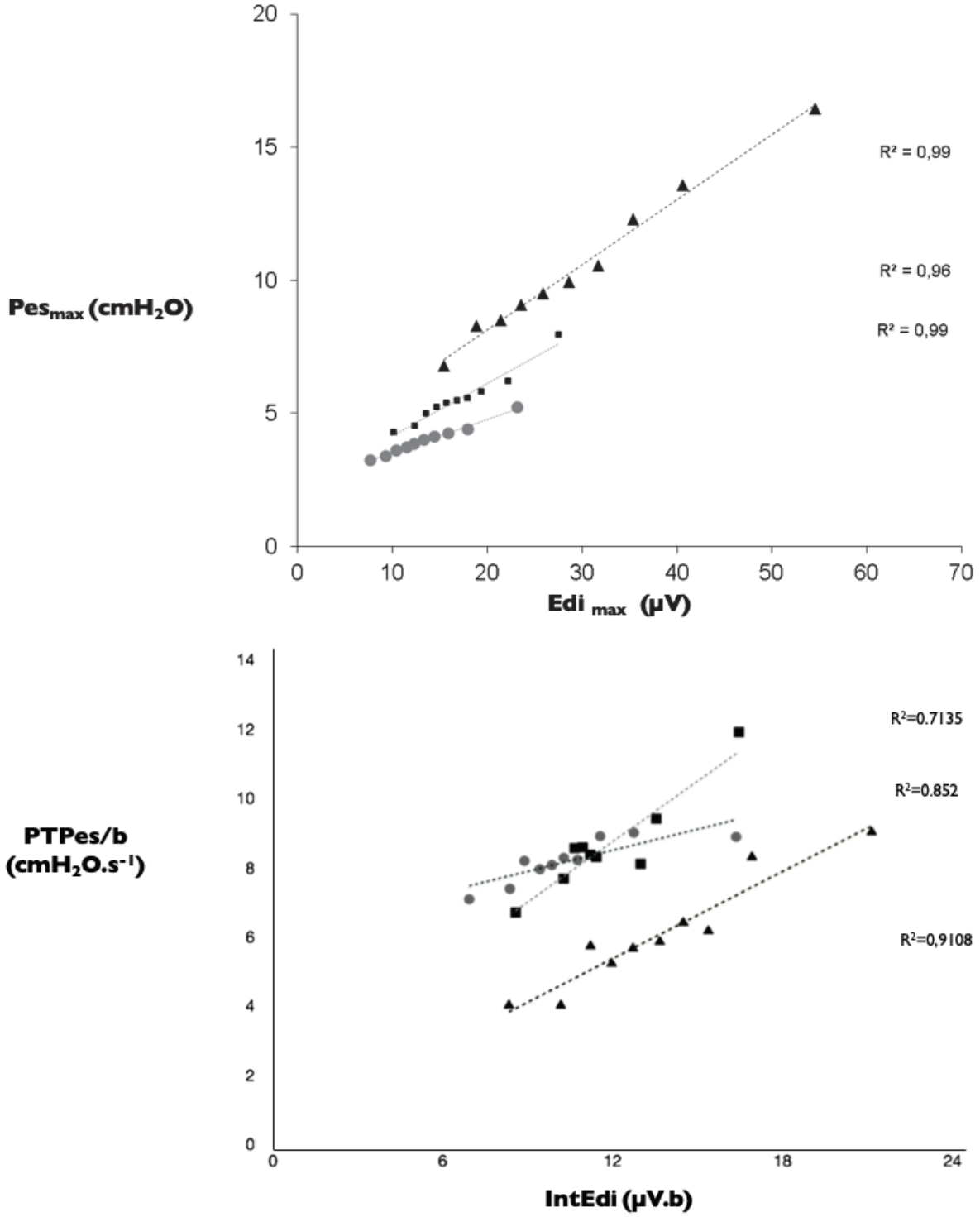

Figure 2: Relationship between Edimax and Pesmax (upper panel) and between IntEdi and PTPes (lower panel) for the group during the 3 periods. Data were grouped by Edi decile, and the group median values are reported, with circles for the pressure ventilatory support period, squares for the NAVA period, and triangles for post-extubation period. Strong linear correlations between Edimax and Pesmax and between IntEdi and PTPes in the 3 ventilatory conditions were found (all r2 > 0.95, and r2 >0.71 respectively).

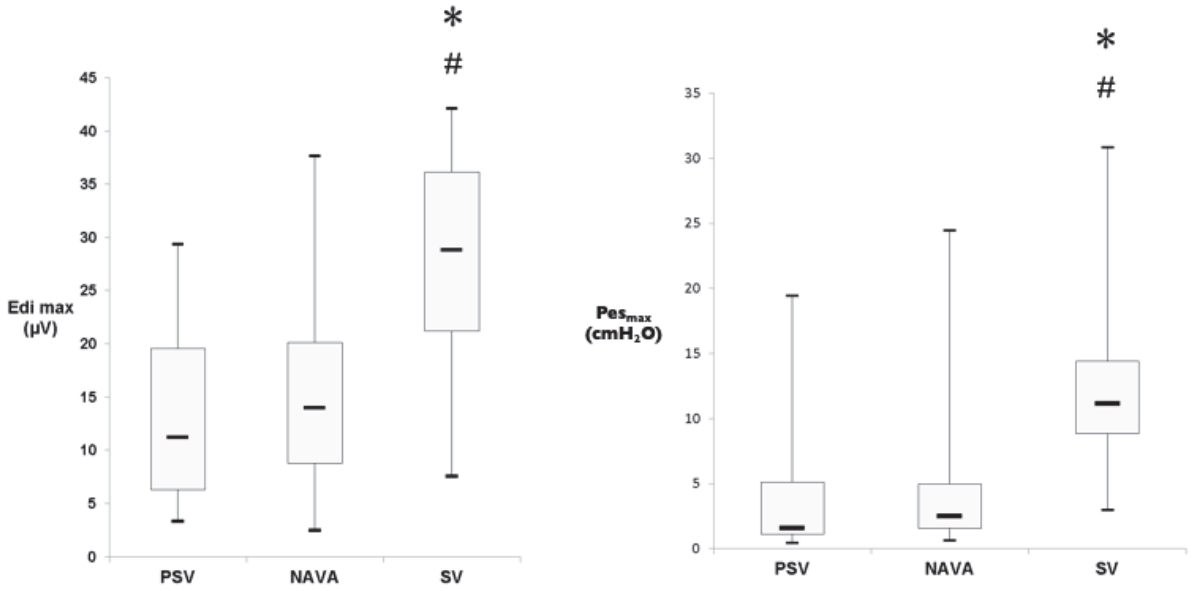

Figure 3: Evolution of the respiratory drive (Edi max) and muscle effort (Pesmax) in the 3 ventilatory conditions. Diaphragmatic activity and Pesmax have similar profiles. Edi and Pesmax were similar during PSV and NAVA periods and increased significantly post-extubation during spontaneous ventilation (SV)

Table 1. Patient characteristics

Parameters	Patients (n=16)
Age (months)	4 [0.5-13]
Sex M/F	10/6
Weight (kg)	5.8 [4.1-8]
Gestational age	39 [35.5-40]
Comorbidities	
- Prematurity	4
- Congenital cardiopathy	2
- Other congenital malformation	2
- Bronchopulmonary displasia	2
PICU admission diagnosis	
- Bronchiolitis	4
- Pneumonia	4
- Sepsis	2
- Cardiac surgery	1
- Neuromuscular disease	2
- Asthma	1
- Bordetella pertussis infection	1
- Foreign body aspiration	1
- Intoxication	1
Days from PICU admission	3 [3-8]
Days from initiation of mechanical ventilation	5 [3-35]

Data are presented as median [interquartile range].

Table 2: Ventilator settings during the two ventilation periods

Parameters	Pressure support ventilation	NAVA
Inspiratory trigger	0.3 L/min	0.5 µV
PEEP (cmH_2O)	5 [5-6]	5 [5-6]
PS level 1 (cmH_2O)	10 [5.5-11]	NA
PS level 2 (cmH_2O)	8 [5.5-10]	NA
NAVA level 1 ($cmH_2O/\mu V$)	NA	0.6 [0.3-0.9]
NAVA level 2 ($cmH_2O/\mu V$)	NA	0.4 [0.3-0.8]
Cycling-off criterion (%)	20 [15-25]	70

Data are presented as median [interquartile range].
PS level 1: initial pressure support used, PS level 2: adapted pressure support based on electrical activity of the diaphragm, PEEP: positive end expiratory pressure, NA: non-applicable.

Table 3: Respiratory parameters in the two assisted ventilation periods and after extubation.

Parameters	Pressure Support Ventilation	NAVA	Post extubation	p
RR	48 [34-61]	53 [34-70]	53 [44-59]	0.6
Vt (ml. kg^{-1})	5.5 [2.5-11.4]	5.6 [1.7-12.2]	NA	0.75
PI_{max} (cmH_2O)	14 [11-15]	14 [11-16]	NA	0.5
Edi max (µV)	11 [3.3-29]	14 [2.5-38¨]	29 [7.5-42]	0.55
Pes_{max} (cmH_2O)	1.6 [0.4-19.4]	2.5 [0.6-24.4]	11.1 [2.9-30.8]	0.76
PTPes/min ($cmH_2O.s.min^{-1}$)	22.8 [13.6-64.8]	37 [16.6-80]	212.7 [141.8-307]	0.2
RR/Vt	9.5 [1-26.7]	5.7 [1.8-12.3]	NA	0.78
Pes_{max}/Edi_{max} ($cmH_2O.\mu V^{-1}$)	0.25 [0.03-1.02]	0.22 [0.03-1.11]	0.47 [0.07-4.09]	0.1
Vt/Edi (ml. kg^{-1}. μV^{-1})	0.57 [0.17-1.75]	0.45 [0.08-2.07]	NA	0.49
Vt/Pes_{max} ($ml.cmH_2O^{-1}$)	3.4 [0.5-9.8]	2.8 [0.5-6.5]	NA	0.55
Correlation between Edi_{max} and Pes_{max}				
R^2	0.89 [0.87-0.97]	0.90 [0.87-0.98]	0.91 [0.86-0.94]	0.46
Regression slope	0.11 [0.06-0.24]	0.14 [0.06-0.25]	0.25 [0.08-0.40]	0.64
Intercept	0.42 [0.07-2.75]	1.35 [0.12-3.40]	3.19 [1.74-5.37]	0.72

Data are presented as median [interquartile range].

RR : respiratory rate, Vt: tidal volume, PI max; maximal inspiratory pressure, Edi: Diaphragmatic electrical activity, Pes: maximal swing in esophageal pressure, PTPes/min: esophageal pressure time product per minute. p are the p-values comparing Pressure Support Ventilation and NAVA.

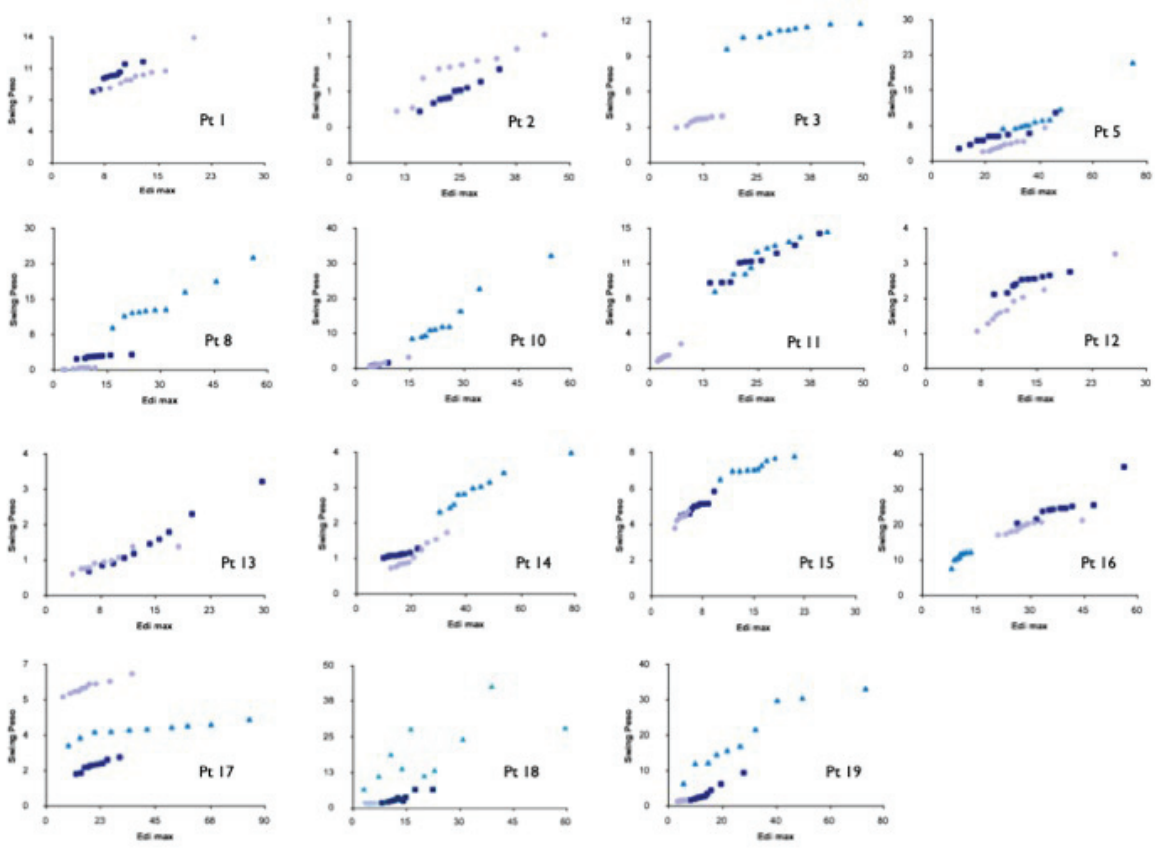

Figure supplemental data: Individual correlation data between Edi_{max} and Pes_{max}. Each point represents the median data for a given Edi decile. Circles represent PSV period, squares represent the NAVA period, and triangle the post-extubation period when available. Overall, the relationship between Edi and Pes swing was relatively strong in all patients and conditions, but in a few cases some variability was observed when the ventilatory condition changed. Post-extubation period in patient 17 was recorded with a 6 cmH_2O nasal CPAP.

1.4. Résultats et Discussion

Ce premier travail nous a surtout permis d'acquérir les connaissances et la technicité nécessaire à l'exploration physiologique en pédiatrie. Il a été l'occasion de se familiariser à l'utilisation du banc de mesures (Neurovent.inc) et au programme d'analyse (calibration, extraction des données, …). Nous avons collaboré avec le Dr Essouri tout au long de l'étude à la fois pour la réalisation des mesures (lors du séjour de Master 2 à Montréal) et des analyses chez quelques patients (double vérification) et enfin pour l'interprétation des résultats et les analyses statistiques.

Cette étude menée en réanimation pédiatrique confirme les résultats trouvés chez l'adulte [100, 112], à savoir une bonne corrélation entre l'activité électrique et l'effort généré par le diaphragme sous certaines conditions. Entre les deux modes ventilatoires (NAVA et VS-AI) la pente de la relation semble globalement non influencée par le mode ventilatoire. Dans leur étude, Carteaux et al. trouvent une relation curvi-linéaire qui est dépendante du niveau d'assistance [130]. Avec des niveaux d'assistance élevés, la variabilité interindividuelle est moindre et le facteur de relation entre pression musculaire et EAdi est plus faible. En ventilation mécanique une partie du volume est générée par le respirateur et un haut niveau d'assistance semble « éteindre » l'activité musculaire. Dans notre étude, nous avons testé un seul niveau d'assistance pour chaque patient dans chacun des deux modes, cependant la pente de la relation qui est assez stable entre les deux modes ventilatoires, tend à être différente en l'absence de support ventilatoire (après extubation). Ce travail suggère comme chez l'adulte que le couplage électro-mécanique est dépendant du niveau d'assistance et du niveau d'effort généré par le patient. Un autre point important est la présence d'une variabilité individuelle importante, rendant difficile la comparaison entre les patients. Cette étude présente un certain nombre de limites, à savoir une population hétérogène, une durée de mesure courte et l'absence de mesure des pressions gastriques. En conclusion, l'activité électrique diaphragmatique ne peut, à elle seule, évaluer l'effort (comparaison interindividuelle) mais reste un outil intéressant pour comparer chez un même patient l'évolution au cours du temps ou encore le support ventilatoire ou le mode ventilatoire (comparaison intra individuelle).

2. ETUDE 2 : EFFET DU DECUBITUS VENTRAL CHEZ LE NOURRISSON ATTEINT DE BRONCHIOLITE GRAVE

2.1. Introduction

2.1.1. Généralités

Le décubitus ventral (DV) est surtout connu pour réduire la mortalité chez les adultes avec un syndrome de détresse respiratoire aiguë (SDRA) grave [131] en modifiant les rapports ventilation-perfusion et en améliorant l'oxygénation [132]. Le décubitus ventral permettrait une réduction de l'effet shunt par une meilleure ventilation des zones perfusées [132].

Le décubitus ventral entrainerait une modification significative de la mécanique respiratoire (résistance, compliance) chez l'adulte comme chez l'enfant. En 1997, Numa et al. ont montré chez l'enfant sous ventilation mécanique, que le décubitus ventral diminuait significativement les résistances à l'écoulement de l'air dans les voies aériennes supérieures , probablement par diminution de l'impact du poids du médiastin sur les voies aériennes [133]. Ils notaient une amélioration significative de l'oxygénation dans le sous-groupe de patients obstructifs mais sans modification de la compliance thoraco-pulmonaire.

Ces résultats ont été retrouvés chez des adultes atteints de broncho-pneumopathie chronique obstructive (BPCO) avec une diminution de l'hyperinflation dynamique et de la PEEP intrinsèque[134]. En décubitus ventral, la ventilation était plus homogène [132] améliorant l'oxygénation et l'élimination du CO_2 chez ces patients BPCO [135].

Enfin en décubitus ventral, la compliance pariétale thoracique du nourrisson diminuait [136] et la synchronisation thoraco-abdominale semblait améliorée [137]. Gouna et al. ont trouvé que chez le prématuré sous CPAP le décubitus ventral améliorait la mécanique ventilatoire et l'hyperinflation dynamique avec une meilleure oxygénation et d'une diminution du CO_2 [137].

Le décubitus ventral est d'ailleurs couramment utilisé en néonatologie afin d'améliorer la ventilation des nouveau-nés prématurés [138] car il est facilement réalisable chez le nourrisson.

Le DV a donc démontré un intérêt chez l'adulte comme chez le prématuré sur :

- La diminution des résistances à l'écoulement de l'air [133, 137]
- La diminution de l'hyperinflation dynamique [134, 137]

- L'amélioration de la synchronisation thoraco-abdominale [137]
- L'oxygénation et de l'élimination de CO_2 [134, 135, 137]

Notre hypothèse était que le décubitus ventral, simple à mettre en œuvre chez le nourrisson, a un impact favorable en termes de réduction de l'effort respiratoire. De plus, le DV pourrait avoir un effet bénéfique sur la composante alvéolaire de la bronchiolite en modifiant les rapports ventilation-perfusion.

2.2. Matériel et méthodes

L'étude a été approuvée par le comité de protection des personnes (Sud Est III - 2015-057 B) et par l'ANSM (151048B-32). Après inclusion, tous les patients bénéficiaient d'une prise en charge standard (sonde naso ou oro-gastrique, désobstruction rhinopharyngée,…) conformément aux recommandations de la conférence de consensus de juin 2000 et aux procédures écrites en vigueur dans le service. Une assistance respiratoire en CPAP avec une interface nasale (Fisher and Paykel Healthcare, New Zélande) était mise en place sur un respirateur Servo-I. Après inclusion et randomisation (Clinsight, Ennov, Paris, France) le cathéter de mesure de pression oesophagienne et gastrique était inséré par la bouche en plus de la sonde oro-gastrique NAVA 8FR 100cm (Maquet, Getinge, Solna, Suède). Les patients étaient évalués successivement dans les deux conditions : 1h en décubitus dorsal et 1h en décubitus ventral dans un ordre aléatoire.

Les paramètres issus du respirateur étaient recueillis simultanément avec les pressions des voies aériennes (contrôle), les pressions œsophagiennes et gastriques via le système d'acquisition. Les analyses étaient réalisées à postériori à l'aide du programme dédié (Figure 10). Les valeurs cycle à cycle étaient moyennées sur 100 cycles.

2.3. Article 2: Physiological Effect of Prone Position in Children with Severe Bronchiolitis: A Randomized Cross-Over Study (BRONCHIO-DV).

ORIGINAL ARTICLES

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Physiological Effect of Prone Position in Children with Severe Bronchiolitis: A Randomized Cross-Over Study (BRONCHIO-DV)

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Objective To assess the effect of the prone position on physiological measures, including inspiratory effort, metabolic cost of breathing, and neural drive to the diaphragm as compared with the supine position in infants with severe bronchiolitis requiring noninvasive ventilation.

Study design Fourteen infants, median age 33 days (IQR [first and third quartiles], 25-58) were randomized to receive 7 cmH_2O continuous positive airway pressure for 1 hour in the prone position or in the supine position, which was followed by cross-over to the supine position and the prone position for 1 hour, respectively. Flow, esophageal, airway, gastric, and transdiaphragmatic pressures, as well as electrical activity of the diaphragm were simultaneously recorded. The modified Wood clinical asthma score was also assessed.

Results Median esophageal pressure–time product per minute was significantly lower in the prone position than in the supine position (227 cmH_2O*s/minute [IQR, 156-282] cmH_2O*s/minute vs 353 cmH_2O*s/minute [IQR, 249-386 cmH_2O*s/minute]; $P = .048$), as were the modified Wood clinical asthma score ($P = .033$) and electrical activity of the diaphragm ($P = .006$). The neuromechanical efficiency of the diaphragm, as assessed by transdiaphramagtic pressure to electrical activity of the diaphragm swing ratio, was significantly higher in the prone position than in the supine position (1.1 $cmH_2O/\mu V$ [IQR, 0.9-1.3 $cmH_2O/\mu V$] vs 0.7 $cmH_2O/\mu V$ [IQR, 0.6-1.2 $cmH_2O/\mu V$], respectively; $P = .022$).

Conclusions This study suggests a benefit of the prone position for infants with severe bronchiolitis requiring noninvasive ventilation by significantly decreasing the inspiratory effort and the metabolic cost of breathing. Further studies are needed to evaluate the potential impact of these physiological findings in a larger population. *(J Pediatr 2019;205:112-9).*

Trial registration Clinicaltrials.gov: NCT02602678.

Viral bronchiolitis is the most common lower respiratory tract illness and the leading cause of hospital admission in infants and young children.[1] Viral bronchiolitis leads to small airway inflammation with edema, epithelium necrosis, and alveolar damage that causes partial or total bronchial obstruction with hyperinflation, atelectasis, and ventilation perfusion mismatch resulting in higher work of breathing and hypoxemia.[2] Between 5% and 22% of all cases require respiratory support in an intensive care unit[3,4] and the management of infants with bronchiolitis remains heterogeneous.[3,5] Prone positioning has been proposed in children with severe bronchiolitis, but without supportive evidence.[6,7] The prone position is easy to perform in small children[8] and is commonly used in neonatal and pediatric intensive care. In adults, the prone position significantly decreases mortality in patients with severe acute respiratory distress syndrome and improves oxygenation.[9] Moreover, the prone position may improve respiratory mechanics and gas exchange in adults with chronic bronchitis[10] as in neonates.[11] The prone position is also able to decrease airway resistance[12] in children invasively ventilated for severe viral bronchiolitis and to decrease apnea occurrence in children with mild bronchiolitis.[13] Therefore, we hypothesized that the prone position may improve respiratory mechanics in children with severe bronchiolitis requiring nasal continuous positive airway pressure (nCPAP). The primary objective was to compare the effort and metabolic cost of breathing in the prone

EAdi	Electrical activity of the diaphragm
m-WCAS	Modified Wood asthma clinical score
nCPAP	Nasal continuous positive airway pressure
NME	Neuromechanical efficiency
PEEP	Positive end-expiratory pressure

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Portions of this study were presented as an abstract at the annual meetings of the French Intensive Care Society, January 11-13, 2017, Paris, France, and the European Society of Paediatric and Neonatal Intensive Care, June 6-9, 2017, Lisbon, Portugal.

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position and the supine position, and the secondary objective was to describe the physiological effects of the prone position in infants with severe acute viral bronchiolitis.

Methods

We conducted a prospective randomized crossover physiological study in a 23-bed pediatric intensive care unit of a tertiary university hospital (Hôpital Femme Mère Enfant, Lyon University Hospital, Bron, France). The study protocol was approved by the institutional review board (CPP SUD-EST3—n° 2015-057B) and by the national medicines authority (ANSM–151048B-32). This clinical trial was recorded in the National Library of Medicine registry ClinicalTrials.gov (NCT 02602678).

Population

Infants <6 months of age with a diagnosis of viral bronchiolitis admitted to the pediatric intensive care unit for respiratory support were eligible if they met the following inclusion criteria: clinical and radiologic diagnosis of bronchiolitis, need for respiratory support by nCPAP based on a modified Wood clinical asthma score (m-WCAS) of >4 and/or hypercapnic acidosis (pH <of 7.30 or partial pressure in carbon dioxide of >8 kPa), and written consent obtained from the parent(s) or guardian(s). Noninclusion criteria were chronic respiratory, neuromuscular, ear-nose-throat, or cardiac underlying disease; a contraindication for the placement of the esophageal probe; need for invasive ventilation (in particular when presenting >3 apneas per hour with heart rate of <90/minute or a pulse oximetry of <90%, or altered level of consciousness); and infants not affiliated with the French social security scheme (according to French regulation).

Measurements and Recordings

After inclusion by an investigator, an esophageal pressure probe of 2.3 mm in diameter with 2 strain gauge pressure transducers (Gaeltec Devices Ltd, Isle of Skye, Scotland), 1 for esophageal (esophageal pressure) and 1 for gastric pressure, was inserted orally together with an orogastric catheter able to detect electrical activity of the diaphragm (EAdi; 8F, 100 cm, Maquet Critical Care, Solna, Sweden). After fixation, the correct positioning was verified by gentle manual pressure on the patient's abdomen to observe gastric pressure fluctuations without effect on the esophageal pressure tracing and negative deflection during inspiration on the esophageal pressure tracing.[14,15] The position of the catheter able to detect the EAdi was also verified using the dedicated screen of the ventilator (SERVO-I, Maquet Critical Care). The position of both catheters was verified after each position change. The bed was set at 30° inclination from the horizontal plane during the entire procedure. Airway pressure, flow, and EAdi were recorded using the SERVO-I ventilator through a RS232 serial port continuously and simultaneously with esophageal pressure and gastric pressure using an analogical/numerical data acquisition system and transferred to a laptop (Neurovent, Inc, Toronto, Ontario, Canada). All data were analyzed offline. Only breaths with available signals for all measures (flow, airway pressure, gastric pressure, esophageal pressure, and EAdi) were analyzed. Time cursors were placed at the beginning of neural inspiration, the maximal inspiratory EAdi value, the end of neural inspiration, and at the end of neural expiration (**Figure 1**; available at www.jpeds.com), as previously described.[16,17]

Heart rate, pulse oximetry, inspired fraction of oxygen, transcutaneous partial pressure of carbon dioxide, and m-WCAS calculated by the caregiver were collected at the beginning and at the end of each study period. Comfort was assessed by the nurse at the end of each study period using the EDIN scale as in a previous study of bronchiolitis.[18]

Study Design

The randomization sequence was generated by the clinical investigation center of the Hospices Civils de Lyon, France. Infants were randomized using an online data management software (Clinsigh, Ennov, Paris, France) to receive the supine position then the prone position, or the converse. They were placed for 1 hour in the first position with nCPAP, followed by a 15-minute washout period (in the supine position under spontaneous breathing with oxygen therapy but no CPAP), and then they were moved to the second position for 1 hour with resumption of nCPAP. Double circuit with heated humidifier and infant nasal masks (Fisher and Paykel Healthcare, Auckland, New Zealand) were used with the noninvasive CPAP mode of the SERVO-I ventilator set at +7 cmH_2O for all infants. Airway pressure, flow, EAdi, esophageal pressure, and gastric pressure from 50 consecutive breaths during the first 5-10 minutes (initial values) and from 100 breaths during the last 50-55 minutes (end values) of each period were analyzed. The primary outcome was the mean of the esophageal pressure time product per minute over 100 breaths during the last 5 minutes of the recording.

Secondary outcomes were transdiaphragmatic pressure time product per minute, esophageal pressure time product and transdiaphragmatic pressure time product per single breath, esophageal and transdiaphragmatic inspiratory pressure swings (maximal amplitude of the inspiratory depression), EAdi at the end of the expiratory time, the difference between the minimum and the maximum EAdi values during inspiration (ΔEAdi), respiratory rate, neural inspiratory time (which corresponds to the interval between the beginning of neural inspiration and end of neural inspiration), expiratory time (which corresponds with the interval between the end of neural inspiration and the end of neural expiration), and inspiratory time to total time ratio (neural inspiratory time/neural total time). Determination of intrinsic positive end-expiratory pressure (PEEP) was attempted using deflection of the esophageal pressure at the time of flow onset from the esophageal pressure baseline,[19] and, in infants without nCPAP, on the value of the pleural pressure at the beginning of inspiration.[14]

Based on the primary outcome, children with a lower esophageal pressure time product per minute in the prone position than in the supine position were considered as responders to the prone position. Post hoc analyses were performed to compare responders and nonresponders with the prone

position and to characterize the impact of the prone position on EAdi during expiration and on diaphragm neuromechanical efficiency (NME) of the diaphragm defined as the ratio between transdiaphramagtic pressure swings and ΔEAdi breath by breath.

Statistical Analysis and Sample Size

Qualitative variables are reported as count and percentage, and quantitative variables are reported as median with IQR (first and third quartiles). Kolmogorov-Smirnov tests was used to assess data distribution. It was calculated that 14 infants were required for a decrease of 25% of the esophageal pressure time product per minute in the prone position as compared with the supine position, assuming an alpha error of 5% and targeting a power of 90%. To take into account technical difficulties in recording physiological measures, a total of 16 patients were included. Clinical and physiological measures were expressed as absolute value and as relative difference over time (100*(End value – Initial value) / Initial value). The nonparametric Wilcoxon signed-rank test was used to compare paired samples. The Fisher exact test was used to compare qualitative variables. Differences were considered statistically significant at $P < .05$. Statistical analysis was performed using SPSS Statistics (V22, IBM, Armonk, New York).

Results

Patients were enrolled between November 2015 and January 2016. Sixteen patients were included in the study and 2 patients were excluded from the analysis owing to a technical problem with the data acquisition system (no EAdi data for 1 patient and no flow data for the other; **Figure 2**; available at www.jpeds.com). No patient received sedative drugs before or during the study, and 2 patients had received caffeine sulfate before admission to the pediatric intensive care unit. The main characteristics of the 14 patients included in the analysis are reported in **Table I**. The median age of infants was 33 days (25; 58), 9 were boys (64%), and respiratory syncytial virus was found in all of them. One-half of the patients received the prone position first. No adverse event was reported in the study.

Effect on Clinical Measures

The median m-WCAS was significantly lower in the prone position (3.0; IQR, 3.0-3.0) than in the supine position (3.5; IQR, 3.0-4.0; $P = .033$) and there was no significant difference in comfort between the prone and the supine position (median EDIN scale, 3.5 (IQR, 2.00-5.75) vs 5.5 (IQR, 2-7); $P = .13$). The transcutaneous partial pressure of carbon dioxide, inspired fraction of oxygen, pulse oximetry, and heart rate are reported in **Table II**, as relative difference over the study period; there was no significant difference in these measures between the prone and the supine position.

Effect on Physiological Measures

Median respiratory rate (66 breaths/minute [IQR, 46-78 breaths/minute] in the prone position vs 59 breaths/minute [IQR, 52-77 breaths/minute] in the supine position; $P = .40$) and respiratory cycle time durations were not different (**Table III**) between the 2 positions. Mean airway pressure measured at the Y-piece was similar in the prone position (6.99 cmH_2O; IQR, 6.98-7.08 cmH_2O) and supine position (7.0 cmH_2O; IQR, 6.96-7.06 cmH_2O; $P = .93$).

The median esophageal pressure time product per minute was significantly lower in the prone position (227cmH_2O*s/minute; IQR, 156-282 cmH_2O*s/minute) than in the supine position (353cmH_2O*s/minute; IQR, 249-386 cmH_2O*s/minute; $P = .048$; **Figure 3**), as were esophageal pressure time product per single breath (3.5 cmH_2O*s [IQR, 2.9-4.2 cmH_2O*s] vs 4.6 cmH_2O*s [IQR, 3.4-5.1 cmH_2O*s]; $P = .048$) and Swing esophageal pressure (9.3 cmH_2O; IQR, 8.3-12.8 cmH_2O] vs 14.9 cmH_2O [IQR, 11.0-16.2 cmH_2O]; $P = .035$;

Table I. Main characteristics of the population

Variables	Supine position first (n = 7)	Prone position first (n = 7)	Overall population (n = 14)
Age (d)	30 (18-39)	44 (30-63)	33 (25-58)
Weight (g)	4060 (3500-4465)	4300 (3630-4630)	4180 (3606-4525)
HFNC before nCPAP, no. (%)	4 (57)	5 (71)	9 (64)
PELOD 2 score	3 (3-4)	3 (3-4)	3 (3-4.5)
Blood gas on admission			
pH	7.29 (7.26-7.31)	7.30 (7.29-7.33)	7.29 (7.27-7.32)
pCO_2 (kPA)	7.7 (7.6-8.5)	7.7 (7.1-8.5)	7.7 (7.3-8.5)
Clinical measures on admission			
m-WCAS	5.0 (4.5-5.0)	4.5 (4.25-5.5)	4.75 (4.5-5.0)
Heart rate (beats/min)	172 (150-175)	159 (154-177)	166 (149-177)
FiO_2 (%)	30 (28-35)	30 (25-38)	30 (25-35)
Time from PICU admission (min)	530 (358-570)	624 (232-674)	540 (282-625)
Duration of nCPAP (h)	19 (18-75)	41 (22-60)	38 (18-69)
Duration of mechanical ventilation (h)	79 (65-119)	64 (58-87)	74 (58-98)
Invasive mechanical ventilation (no.)	0/7	0/7	0/14 (0)
LOS PICU (d)	5 (4-7)	5 (5-6)	5 (4-6)
Total LOS (d)	8 (6.5-9.5)	7 (6-9.5)	7.5 (6-10)

FiO_2, inspired fraction of oxygen; *HFNC*, high-flow nasal cannula; *LOS*, Length of stay; *PELOD*, Pediatric Logistic Organ Dysfunction; *pCO_2*, partial pressure in carbon dioxide; *PICU*, pediatric intensive care unit.
Values are median (IQR [first and third quartiles]) or counts (percent-point in group).

Table II. Clinical data in prone and supine position at the end of each study period

Clinical measures	Supine position	Prone position	*P* value*	Relative difference supine position (%)	Relative difference prone position (%)	*P* value*
$TcPCO_2$ (kPA)	6.5 (6.1 to 6.8)	6.9 (6.1 to 7.7)	.16	–4 (–7.9 to –2.0)	–10.4 (–16.0 to –5.6)	.24
FiO_2 (%)	30 (25 to 35)	27 (25 to 30)	.17	0 (0 to 12.5)	–1.7 (–15.6 to 0.0)	.16
SpO_2 (%)	97.5 (95 to 99)	96.5 (94 to 98)	.46	0 (–2.8 to 0)	–3 (–3.10 to 2.9)	.64
Heart rate (beats/min)	159 (146 to 164)	156 (144 to 163)	.10	–6.3 (–9.7 to –0.2)	–6.8 (–12.2 to –0.5)	.82

SpO_2, pulse oximetry; *$TcpCO_2$*, transcutaneous partial pressure in carbon dioxide.
Data are expressed as median (IQR [first and third quartiles]). Relative difference over the study period was calculated using the formula [100*(End value – Initial value)/ Initial value].
**P* value by paired nonparametric Wilcoxon signed-rank test.

Table III). The esophageal pressure time product decreased over time in all infants while in the prone position and in 10 infants while in the supine position. The decrease in the esophageal pressure time product and transdiaphragmatic pressure time product per single breath or per minute over time as well as the magnitude of decrease in esophageal pressure and transdiaphramagtic pressure swings were significantly greater in the prone position than in the supine position (Table III). During expiration, gastric pressure swing was not different between prone and supine position (3.2 cmH_2O [IQR, 2.3-3.7 cmH_2O] vs 3.1 cmH_2O [IQR, 2.4-3.5 cmH_2O]; $P = .95$). The intrinsic PEEP as determined by deflection of the esophageal pressure did not provide reliable results owing to interface air leaks. After attempting to correct for this leak in the analysis by removing breaths with flow onset before EAdi onset, the median intrinsic PEEP value was 0.9 cmH_2O (IQR, 0.6-1.5 cmH_2O) in the prone position and 1.3 cmH_2O (IQR, 0.9-1.5 cmH_2O) in the supine position ($P = .25$). In infants without nCPAP, it was not possible to obtain analyzable signals owing to agitation after removal of the interface.

Eight infants (57%; defined as responders) had an esophageal pressure time product per minute that was lower in the prone position than in the supine position (Figure 4, A; available at www.jpeds.com). Among them, 5 were placed first in the prone position and 3 in the supine position ($P = .59$). The median esophageal pressure time product per minute was similar in the prone position between responders and nonresponders (227 cmH_2O*s/minute [IQR, 158-280cmH_2O*s/minute] vs 227 cmH_2O*s/minute [IQR, 159-317cmH_2O*s/minute]; $P = .75$) but higher in the supine position in responders (379 cmH_2O*s/minute; IQR, 360; 389 cmH_2O*s/minute) than in nonresponders (204 cmH_2O*s/minute; IQR, 142-284cmH_2O*s/minute; $P = .043$; Figure 3). Comparisons for other variables are available in Tables IV and V (both available at www.jpeds.com).

Effects on EAdi and NME

The maximal inspiratory EAdi value and ΔEAdi were significantly lower in the prone position than in the supine position (Table III and Figure 4, B [available at www.jpeds.com]). The EAdi at the end of the expiratory time was also significantly lower in the prone position (2.1 μV; IQR, 1.6-3.6 μV) than in the supine position (3.5 μV; IQR, 2.4-4.4 μV; $P = .03$) and during all expiration time (Figure 5; available at www.jpeds.com). The diaphragm NME was significantly greater in the prone position (1.1 $cmH_2O/\mu V$; IQR, 0.9-1.3 $cmH_2O/\mu V$)

Table III. Physiological data in prone and supine position at the end of each study period

Physiological measures	Supine position	Prone position	*P* value*	Relative difference supine position (%)	Relative difference prone position (%)	*P* value*
Primary outcome						
Esophageal pressure time product/min (cmH_2O*s/min)	**353 (249 to 386)**	**227 (156 to 282)**	**.048**	**–29.1 (–56.4 to 11.9)**	**–53.6 (–61.5 to –25.2)**	**.013**
Secondary outcomes						
Transdiaphragmatic pressure time product/min (cmH_2O*s/min)	336 (209 to 394)	232 (204 to 324)	.084	**–20.4 (–34.6 to –5.8)**	**–40.3 (–50.8 to –12.0)**	**.022**
Esophageal pressure time product/breath (cmH_2O*s)	**4.6 (3.4 to 5.1)**	**3.5 (2.9 to 4.2)**	**.048**	**–19.7 (–45.2 to 4.6)**	**–40.5 (–52.3 to –23.3)**	**.013**
Transdiaphragmatic pressure time product/breath (cmH_2O*s)	4.5 (3.6 to 5.8)	3.9 (3.0 to 5.0)	.30	**–11.0 (–31.0 to 2.0)**	**–27.1 (–46.6 to –1.3)**	**.035**
Swing esophageal pressure (cmH_2O)	**14.9 (11.0 to 16.2)**	**9.3 (8.3 to 12.8)**	**.035**	**–27.5 (–43.9 to 8.3)**	**–41.6 (–57.7 to –25.8)**	**.008**
Swing transdiaphramagtic pressure (cmH_2O)	13.9 (10.2 to 16.9)	11.3 (9.0 to 15.2)	.096	**–17.0 (–26.8 to –4.1)**	**–40.0 (–42.0 to –10.0)**	**.011**
EAdi min (μV)	**3.5 (2.4 to 4.4)**	**2.1 (1.6 to 3.6)**	**.030**	–48.4 (–64.9 to 30.3)	–62.6 (–77.6 to –36.3)	.51
EAdi max (μV)	**22 (19 to 28)**	**16 (10 to 25)**	**.006**	**–30.2 (–49.4 to –22.4)**	**–57.7 (–68.2 to –43.0)**	**.013**
Δ EAdi (μV)	**17 (15 to 22)**	**13 (8 to 20)**	**.008**	**–30.1 (–44.9 to –15.7)**	**–57.6 (–66.3 to –39.4)**	**.016**
Neural inspiratory time (s)	0.44 (0.38 to 0.53)	0.44 (0.38 to 0.53)	.47	8.1 (–2.1 to 19.7)	16.3 (–4.7 to 29.8)	.64
Neural inspiratory time/neural total time (%)	0.45 (0.43 to 0.48)	0.47 (0.43 to 0.47)	.78	–6.3 (–9.7 to 0.1)	–1.8 (–8.6 to 2.9)	.47
Respiratory rate (/min)	59 (52 to 77)	66 (46 to 78)	.40	–11.9 (–23.5 to 3.1)	–11.3 (–20.5 to –0.9)	.55

EAdi max, maximal inspiratory EAdi value; *EAdi min*, EAdi at the end of the expiratory time; *Δ EAdi*, EAdi max – EAdi min.
Bold text indicates a statistically significant difference, $P < .05$.
Data are expressed as median (IQR [first and third quartiles]). Relative difference over the study period was calculated using the formula [100*(End value – Initial value)/ Initial value].
**P* value by paired nonparametric Wilcoxon signed-rank test.

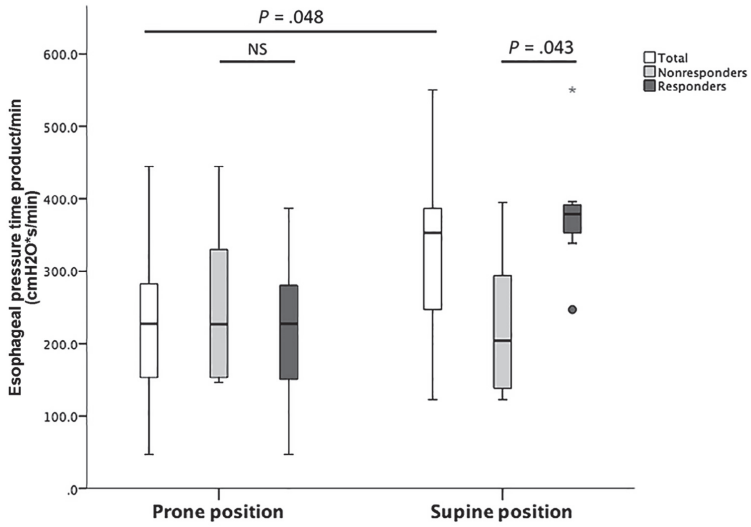

Figure 3. Box plot of esophageal pressure time product per minute in the prone and supine positions in all children and in responders and nonresponders. The esophageal pressure time product per minute was similar in the prone position between responders and nonresponders ($P = .75$) but significantly higher in the supine position in responders than in nonresponders ($P = .043$)

compared with supine position (0.7 $cmH_2O/\mu V$; IQR, 0.6-1.2 $cmH_2O/\mu V$; $P = .022$).

Discussion

The present study described the neural and mechanical consequences of prone positioning in children with severe bronchiolitis and found that the prone position can decrease inspiratory effort (estimated by the esophageal pressure swing) and the metabolic cost of breathing (estimated by the esophageal pressure time product). The measurement of mechanical variables assessing the effort of breathing associated with neural and clinical measures provides robust and original data. These indicators, focused primarily on inspiratory effort, were lower in the prone position as compared with the supine position, and they decreased over time in both positions, but more efficiently in the prone position than in the supine position. Furthermore, the EAdi, which reflects the neural drive to the diaphragm,[16,20] also decreased over time and was significantly lower in the prone position. The m-WCAS, described previously to standardize the scoring of accessory muscles used in bronchiolitis,[18,21] was also significantly lower in the prone position than in the supine position. It is also noteworthy that the decrease in the inspiratory efforts and demand was associated with stable ventilation, with no deterioration in CO_2 measurement. All mechanical, neural, and clinical measures were consistent and showed that breathing was easier in the prone position than in the supine position, as previously reported in neonates.[22] Concerning diaphragm function, there was an increase of transdiaphramagtic pressure/ΔEAdi ratio in the prone position, which corresponds with an improvement of the diaphragm NME.[16,23,24] Rehan et al described that in healthy term infants, the diaphragm was significantly thicker and shorter in the prone position than in the supine position.[25] They hypothesized that this thickening might be attributable to an increased diaphragmatic work in the prone position, which is not in agreement with the findings of the present study. We hypothesize that, in children with severe bronchiolitis, the improvement of NME resulted from lower airway resistance, improved lung recruitment,[26] and therefore an improvement of the dome shape of the diaphragm and its excursion.[27] Echographic assessment of the diaphragm in bronchiolitis will be interesting to confirm this hypothesis.

Among our population, 6 infants were considered as nonresponders to the prone position. We found that the metabolic cost of breathing was similar in the prone position in responders and nonresponders, although a difference was observed in the supine position. Infants who respond to prone positioning had a significantly higher value of esophageal pressure time product per minute in the supine position than nonresponders. These results suggest that the prone position may be particularly beneficial in infants with higher effort in the supine position.

All infants were ventilated using a noninvasive interface (nasal mask) and presence of air leaks was the main limita-

tion for an accurate measurement of flow (and volume) and for the calculation of work of breathing. PTP and amplitude of pleural depression (swing) were used as an estimation of the metabolic cost of the respiratory muscles and inspiratory effort, as has been reported in several studies conducted in adults and children during noninvasive ventilation.[14,28] For calculation, time cursors were placed using the EAdi signal and not the flow signal for several reasons. First, in lower obstructive lung disease, the beginning of inspiration based on flow signal may be delayed and so the PTP does not consider the part owing to intrinsic PEEP.[29] Second, air leaks may also influence the timing of the beginning of inspiration (and expiration). Neural time cursor may, therefore, vary less in these conditions and this may influence the PTP calculation herein. However, pressure swing, which is independent of time, was consistent with PTP results, suggesting that the choice of neural time did not affect the conclusions of the present study.

For expiration, the similar expiratory gastric pressure swing described suggests no change in abdominal muscle recruitment, but the tonic activity of the diaphragm (EAdi at the end of the expiratory time) was lower in the prone position than in the supine position in the present study. The diaphragm may play a role in preserving lung volume and protecting against collapse during mechanical ventilation in acute respiratory distress syndrome, as suggested previously.[30-32] In infants, the diaphragm also remains active during expiration, which is thought to contribute to actively maintain the end-expiratory lung volume.[33,34] Indeed, infants <1 year of age have to actively maintain their end-expiratory lung volume above the relaxation volume,[35,36] owing to the high compliance of their chest wall. Bronchiolitis seems to be a condition in which tonic EAdi is particularly high.[33] The decrease in tonic EAdi is likely to be beneficial when considering the energetic cost and the need for the diaphragm to rest during expiration.

Respiratory conditions also improved over time in the 2 positions. Hough et al have demonstrated in neonates using electrical impedance tomography that "change" in body position leads to an improvement in ventilation distribution, irrespective of the position.[37] Herein, change over time seems to be greater in the prone position than in the supine position. This finding may be explained by the fact that children with bronchiolitis have respiratory mechanics different from neonates (e.g., obstructive lung disease and air trapping with high end-expiratory lung volume)[38] and part of the improvement may be due to the decrease of resistance and compliance, and not only by improvement of ventilation homogeneity. Infants were placed in the supine position (or lateral position) before the study, and, although the study was designed as crossover study with a 15-minute washout period in the supine position between the 2 study periods, it is not possible to exclude an ordering effect. Furthermore, Hough et al investigated lung function improvement in children under CPAP at 2 and 4 hours after change and found that the peak was at 2 hours. We evaluated lung function after 1 hour; thus, the optimal duration of prone positioning in this population needs to be defined.

The beneficial effects of the prone position in bronchiolitis described here are likely to be related to the significant changes in respiratory mechanics provided by this position. Prone position effects oppose the main consequences of the disease, namely, increased airway resistance and dynamic hyperinflation that contribute to the high effort and the ventilation–perfusion mismatch.[2,14] Numa et al demonstrated that, in intubated children with obstructive disease, prone positioning decreased airway resistance.[12] This phenomenon was also reported in adults with chronic obstructive disease in whom prone positioning led to a decrease of resistance and dynamic hyperinflation, resulting in an improvement of work of breathing.[39] In preterm infants, Gouna et al described that the thoracoabdominal synchrony was improved in the prone position, leading to a decrease of dynamic elevation of end-expiratory lung volume.[11] The prone position is also known to improve oxygenation in neonates[40] and in patients with acute respiratory distress syndrome[9,41] by homogenization of the ventilation to perfusion ratio.[26,42] However, we failed to demonstrate a benefit of the prone position on oxygenation measures, although the inspired fraction of oxygen tended to be lower in the prone position. This finding may be related to the limited duration of the investigation that could have been too short to identify such differences.[43]

The present study has several limitations. First, it is a physiological study with a limited sample size and a short-term evaluation. This design was chosen to have no change in the modalities of nCPAP delivery and to allow the investigators to be present during the entire recording to check continuously the interface, air leaks, and position. Second, it was not possible to test the hypothesis of lower intrinsic PEEP in response to a decrease of respiratory airway resistance and dynamic hyperinflation. Third, the change in pressure signals in the prone position may potentially relate to a change in mediastinal pressure transmission or a positioning against the wall of the structure. The position of catheter was checked at the beginning of each recording. Furthermore, esophageal pressure measurement remains the reference for pleural pressure evaluation and has been used in several recent studies investigating the prone position.[44,45] Fourth, the sleeping state that may impact the neural drive and the use of accessory muscles was not recorded. In addition, all patients were already treated by nCPAP and the level of PEEP for both positions was chosen based on previous data in bronchiolitis in the supine position.[14,46] Prone positioning further decreased the esophageal pressure time product by one-third in comparison with the supine position, but it is possible that the level of nCPAP in the prone position may have become higher than the intrinsic PEEP in some infants, and paradoxically increased the effort of breathing based on the waterfalls theory.[39] It would be interesting to compare the effects of the prone position to ventilatory support in itself or with other levels of PEEP.

Further studies are needed to evaluate the potential impact of these physiological findings in infants with severe bronchiolitis. ■

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Conflict of Interest/Funding

F.B. received speaking fees and nonfinancial support from Maquet Critical Care. G.E.'s research program is supported by a research grant from the Fonds de recherche en santé du Québec and recently conducted a feasibility study of a new ventilator, for which costs were supported by Maquet Critical Care. J.B. received travel support from, served as a speaker for, and through Neurovent Research serves as a consultant for Maquet Critical Care (Solna, Sweden) for conference attendance.

The following disclosure was agreed upon by the University of Toronto, Sunnybrook Health Sciences Centre, St-Michael's Hospital, and the REBs of Sunnybrook and St-Michael's to resolve conflicts of interest: Dr. Beck has 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 Dr. Beck through royalties. Dr Beck owns 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. The others authors declare no conflict of interests.

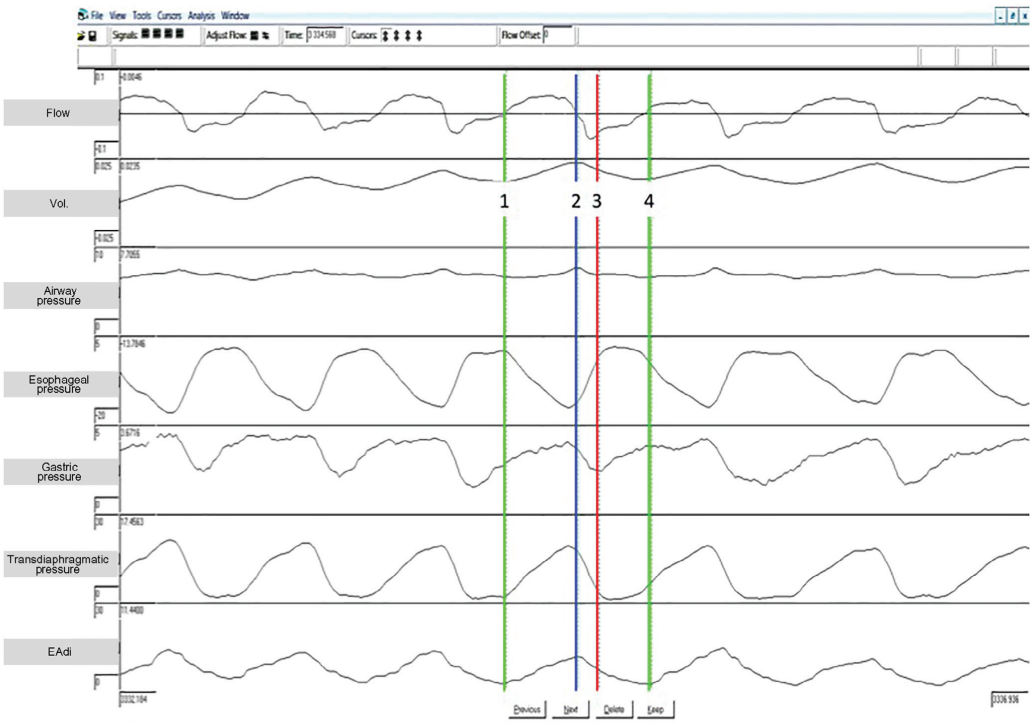


Figure 1. Example of a recording. Flow, volume (Vol.), airway pressure, esophageal pressure, gastric pressure, transdiaphragmatic pressure, and EAdi were recorded simultaneously. Neural time cursors (colored vertical bars) were placed at the beginning of neural inspiration (1), the maximal inspiratory EAdi value (2), the end of neural inspiration (3), and at the end of neural expiration (4).

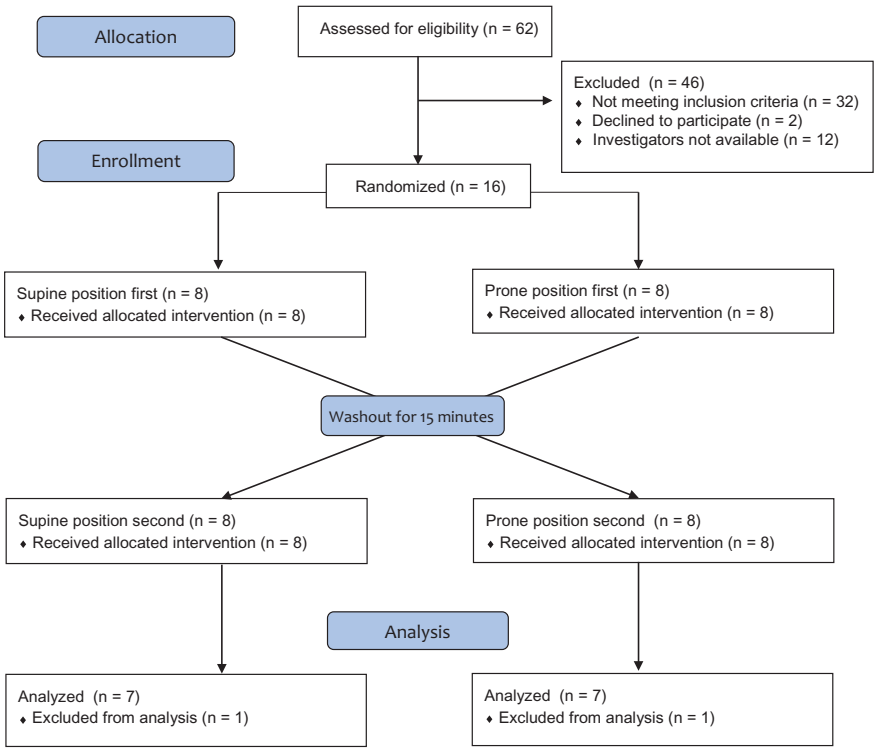


Figure 2. BRONCHIO-DV study flowchart.

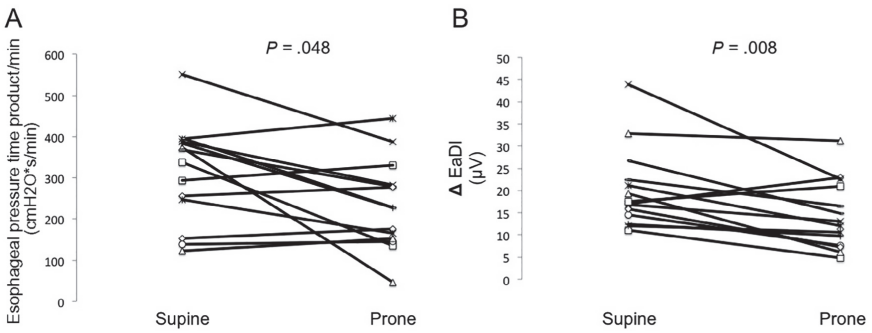
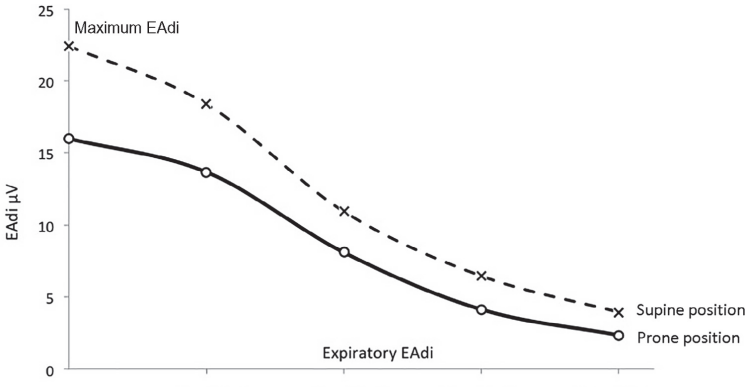


Figure 4. Reduction of the esophageal pressure time product per minute **A,** and change in amplitude of ΔEAdi **B,** in the prone position.



	Quartile 1	Quartile 2	Quartile 3	Quartile 4
EAdi supine position (µV)	22 (19-28)	10.9 (10.2-16.3)	6.5 (5.2-7.5)	3.9 (2.5-4.6)
EAdi prone position (µV)	16 (10-25)	8.1 (5.7-9.9)	4.1 (3.2-5.9)	2.3 (1.8-3.9)

Figure 5. EAdi during expiration. Time between the EAdi peak and the end of expiration was divided into four equally sized quartiles (Q1, Q2, Q3, and Q4). The mean values of each expiratory quartile are presented in the prone position (continuous line) and the supine position (discontinuous line). Values of EAdi in the prone and supine positions are presented at each time as median (IQR; first and third quartiles) below the figure.

Table IV. Demographic and clinical data at admission between responders and nonresponders

	Responders (n = 8)	Nonresponders (n = 6)	*P* value*
Age, d	40 (30-63)	24 (17-40)	.14
Weight (g)	4415 (3620-4710)	3850 (3460-4315)	.34
PELOD 2 score	3 (3-5)	3 (3-3)	.57
pH	7.29 (7.23-7.31)	7.30 (7.27-7.34)	.66
pCO_2 (kPA)	7.65 (7.45-8.56)	7.9 (7.32-8.33)	.95
m-WCAS	5 (4.38-5.10)	4.5 (4.5-4.9)	.66
Heart rate (beats/min)	166 (156-177)	161 (149-175)	.75
FiO_2 (%)	33 (29-36)	28 (25-34)	.41

FiO_2, inspired fraction of oxygen; *pCO_2*, partial pressure in carbon dioxide; *PELOD*, Pediatric Logistic Organ Dysfunction.
Data are expressed as median (IQR [first and third quartiles]).
**P* value by independent samples Mann–Whitney *U* test.

Table V. Physiological data in prone and supine position between responders and nonresponders

	Responders (n = 8)	Nonresponders (n = 6)	*P* value*
Prone position			
Neural inspiratory time/neural total time (%)	0.47 (0.46-0.47)	0.44 (0.43-0.47)	.76
Respiratory rate (/min)	66 (52-77)	62 (44-78)	.76
EAdi max (μV)	16 (13-20)	19 (10-26)	.57
Swing esophageal pressure (cmH_2O)	9.2 (7.9-12.3)	10.2 (9.2-15.9)	.76
Swing transdiaphramagtic pressure (cmH_2O)	10.5 (9.0-14.7)	11.6 (9.4-17.4)	.49
Esophageal pressure time product/breath (cmH_2O*s)	2.9 (2.8-3.9)	3.9 (3.6-4.2)	.14
Transdiaphragmatic pressure time product/breath (cmH_2O*s)	3.4 (2.8-4.4)	4.8 (4.1-5.0)	.36
Esophageal pressure time product/min (cmH_2O*s/min)	227 (158-280)	227 (159-317)	.75
Transdiaphragmatic pressure time product/min (cmH_2O*s/min)	247 (201-321)	213 (204-322)	1.0
Supine position			
Neural inspiratory time/neural total time (%)	0.47 (0.46-0.49)	0.44 (0.41-0.45)	.06
Respiratory rate (/min)	61 (54-76)	58 (49-73)	.66
EAdi max (μV)	25 (23-31)	19 (18-20)	.11
Swing esophageal pressure (cmH_2O)	15.2 (14.4-16.3)	9.2 (6.9-15.0)	.23
Swing transdiaphramagtic pressure (cmH_2O)	15.6 (12.7-17.2)	9.4 (9.1-14.3)	.11
Esophageal pressure time product/breath (cmH_2O*s)	5.0 (4.0-6.3)	3.2 (3.0-4.6)	.081
Transdiaphragmatic pressure time product/breath (cmH_2O*s)	5.3 (4.2-6.5)	3.7 (3.4-4.5)	.14
Esophageal pressure time product/min (cmH_2O*s/min)	**379 (360-389)**	**204 (142-284)**	**.043**
Transdiaphragmatic pressure time product/min (cmH_2O*s/min)	**393 (326-419)**	**209 (172-299)**	**.029**

EAdi max, maximal inspiratory EAdi value.
Bold text indicates a statistically significant difference, $P < .05$.
Data are expressed as median (IQR [first and third quartiles]).
**P* value by independent samples Mann–Whitney *U* test.

2.4. Résultats et Discussion

Cette étude met en évidence une différence significative entre le décubitus ventral et le décubitus dorsal sur différents marqueurs de l'effort inspiratoire chez des nourrissons atteints de bronchiolite grave. Le PTP œsophagien reflet du coût métabolique et l'amplitude de la dépression œsophagienne (swing) sont diminués en décubitus ventral de même que l'amplitude de l'EAdi. Le décubitus ventral semble placer les nourrissons dans une meilleure conformation permettant d'optimiser la ventilation. Pour tenter de décrire les mécanismes pouvant expliquer cette amélioration, nous avons à postériori analysé le couplage électromécanique du diaphragme qui semble amélioré en position ventrale. Cette amélioration pourrait venir à la fois de la resynchronisation thoraco-abdominale comme cela a été décrit précédemment chez le nouveau-né prématuré [137], ou de l'amélioration de la course diaphragmatique. En effet, la contraction diaphragmatique dépend de son activation (activité électrique) et de la relation tension-longueur. Comme démontré chez l'adulte atteint de BPCO, l'hyperinflation entraine un étirement des sarcomères et une modification du rapport tension / longueur et donc une altération du couplage neuro-mécanique [139, 140].
Au sein de la population étudiée, six enfants ne répondent pas au décubitus ventral c'est à dire qu'ils ne diminuent pas leur PTPeso en décubitus ventral. L'analyse de ce sous-groupe est particulièrement intéressante puisque nous avons montré que la différence ne se faisait pas en décubitus ventral mais en décubitus dorsal.
Cette étude présente plusieurs limites. La première est un effectif faible qui peut entrainer un manque de puissance sur certaines analyses statistiques. Deuxièmement, malgré une randomisation et une période de wash-out sans ventilation, il n'est pas possible d'exclure complètement un effet de la séquence d'observation. Les enfants sont par défaut positionnés sur le dos ou en décubitus latéral et nous ne pouvons exclure un effet rémanent de la position. Par conséquent la séquence dorsale (position par défaut) puis ventrale puis dorsale, n'est peut-être pas totalement équivalente à la séquence dorsale (position par défaut) puis dorsale puis ventrale. L'amplitude des résultats suggère que l'impact de cette séquence semble être minime s'il existe.

Ce travail physiologique était une première étape pour l'exploration du décubitus ventral au cours de la bronchiolite grave.

3. ETUDE 3 : NAVA ET SYNCHRONISATION PATIENT - RESPIRATEUR DANS LA BRONCHIOLITE

3.1. Introduction

En ventilation à 2 niveaux de pression, les phases inspiratoires et expiratoires doivent être concordantes pour le confort du patient mais aussi pour l'efficacité de l'assistance respiratoire.

La synchronisation patient-respirateur est un véritable défi en pédiatrie. La fréquence respiratoire élevée (parfois > 100/min), les faibles volumes générés et la présence de fuites (interface nasale) en ventilation non invasive sont sources de nombreuses asynchronies. Comme retrouvé précédemment chez l'adulte notre hypothèse était que la NAVA améliorait la synchronisation et réduisait le délai de réponse du respirateur par rapport à la ventilation conventionnelle au cours de la bronchiolite.

3.2. Matériel et méthodes

Nous avons mené une étude prospective dans la réanimation pédiatrique de l'HFME (HCL, Lyon, France) entre décembre 2012 et mars 2013 après accord du comité de protection des personnes (Sud-est II, Lyon, France -N° 2012-A01409-34).

Après la mise en place de la sonde NAVA, les enfants étaient ventilés en VNI sur le respirateur SERVO-I en mode pression assistée contrôlée (PAC) puis en NAVA. Dans les deux modes, les réglages du respirateur étaient optimisés pendant une vingtaine de minutes avant de débuter l'enregistrement. La PEEP était initialement réglée à 4 ou 5 cmH_2O puis titrée par le clinicien en charge de l'enfant et le même niveau de PEEP était utilisé tout au long de l'étude. En mode PAC, le trigger était ajusté par le respirateur selon son algorithme et non accessible à un réglage par le médecin. Le ratio temps inspiratoire sur temps expiratoire était réglé à ½. Le niveau de pression était adapté par le clinicien afin de trouver le meilleur compromis entre les fuites et la diminution des signes respiratoires. Le trigger en NAVA était laissé sur la valeur par défaut à 0,5 µV et le gain était initialement à 1 $cmH_20/\mu V$ puis titré progressivement pour obtenir le même niveau de pression qu'en PAC sans dépasser 25 cmH_20.

Après vingt minutes de stabilisation, au moins dix minutes étaient enregistrées dans chaque mode. Toutes les analyses ont été réalisées à postériori à l'aide du logiciel Servo RCR. La 5ème minute de chaque enregistrement était analysée manuellement cycle par cycle par un seul investigateur et les trois principales asynchronies (Figure 12) étaient comptabilisées. L'index d'asynchronie (Nombre d'asynchronies / fréquence respiratoire) a été calculé sur ces trois principales asynchronies (critère de jugement principal).

3.3. Article 3 : Non-invasive ventilation in severe viral bronchiolitis with failure of nCPAP: neurally adjusted ventilatory assist versus pressure assist/control ventilation

Pediatric Pulmonology

Neurally Adjusted Ventilator Assist (NAVA) Reduces Asynchrony During Non-Invasive Ventilation for Severe Bronchiolitis

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Summary. Background: To determine the prevalence of main inspiratory asynchrony events during non-invasive intermittent positive-pressure ventilation (NIV) for severe bronchiolitis. Ventilator response time and asynchrony were compared in neurally adjusted ventilator assist (NAVA) and in pressure assist/control (PAC) modes. Methods: This prospective physiological study was performed in a university hospital's paediatric intensive care unit and included 11 children (aged 35.2 ± 23 days) with respiratory syncytial virus bronchiolitis with failure of nCPAP. Patients received NIV for 2 hr in PAC mode followed by 2 hr in NAVA mode. Electrical activity of the diaphragm and pressure curves were recorded for 10 min. Trigger delay, main asynchronies (auto-triggering, double triggering, or non-triggered breaths) were analyzed, and the asynchrony index was calculated for each period. Results: The asynchrony index was lower during NAVA than during PAC (3 ± 3% vs. 38 ± 21%, $P < 0.0001$), and the trigger delay was shorter (43.9 ± 7.2 vs. 116.0 ± 38.9 ms, $P < 0.0001$). Ineffective efforts were significantly less frequent in NAVA mode (0.54 ± 1.5 vs. 21.8 ± 16.5 events/min, $P = 0.01$). Patient respiratory rates were similar, but the ventilator rate was higher in NAVA than in PAC mode (59.5 ± 17.9 vs. 49.8 ± 8.5/min, $P = 0.03$). The $TcPCO_2$ baselines values (64 ± 12 mmHg vs. 62 ± 9 mmHg during NAVA, $P = 0.30$) were the same and their evolution over the 2 hr study period (−6 ± 10 mmHg vs. −12 ± 17 mmHg during NAVA, $P = 0.36$) did not differ. Conclusion: Patient-ventilator inspiratory asynchronies and trigger delay were dramatically lower in NAVA mode than in PAC mode during NIV in infants with severe bronchiolitis. **Pediatr Pulmonol.**

Key words: neurally adjusted ventilatory assist; non-invasive ventilation; bronchiolitis; patient-ventilator interaction; trigger delay.

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Conflict of interest: None.

This work was performed at the Paediatric Intensive Care Unit, HFME – Hospices Civils de Lyon, BRON, France.

An abstract concerning this work has been presented at the "43ème congrès de la Société de Réanimation de Langue Française" (SRLF), Paris 2014 and at EAPS 2014, Barcelona.

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INTRODUCTION

Respiratory syncytial virus bronchiolitis is one of the most important health problems in infants.[1] It is the leading cause of hospitalization in infants less than 1 year old in developed countries, with 2–6% of these infants admitted to a paediatric intensive care unit (PICU).[2,3] Airway inflammation leads to an increase in respiratory muscle load and may lead to respiratory failure.[4–6]

Nasal continuous positive airway pressure (nCPAP) was proposed as an effective treatment for severe bronchiolitis and as an alternative to transtracheal intubation to provide invasive intermittent positive pressure ventilation.[5–7] Several physiological studies have reported that nCPAP decreases the load on inspiratory muscles during breathing.[4–6] A randomized, cross-over study[8] detected a significant improvement in patients treated with nCPAP. nCPAP was also associated with significant reductions in ventilator time, length of stay, and economic burden.[9,10] In our centre, non-invasive intermittent positive pressure ventilation (NIV) is used as rescue assistance when nCPAP fails,[7,11] before the application of transtracheal intubation and invasive ventilation.

Patient-ventilator asynchrony is frequent in adults treated with NIV, affecting up to 43% of them.[12] Asynchrony increases the work of breathing and is associated with longer periods of mechanical ventilation and more NIV failure.[13,14] In a recent study, Vignaux et al. reported an asynchrony rate of 65% for children on NIV pressure support.[15]

Neurally adjusted ventilatory assist (NAVA) is a relatively new assisted ventilatory mode delivering inspiratory pressures in response to the electrical activity of the diaphragm (EAdi).[16] NAVA is routinely used in our PICU both for invasive ventilation and for NIV. In adults, NAVA limits patient-ventilator asynchronies compared to pressure support ventilation[17,18] during NIV. NAVA has also been shown to improve patient-ventilator asynchronies after extubation in premature infants.[19] Recently, a prospective randomized, cross-over study of six infants aged 4 weeks to 5 years demonstrated the effectiveness of NAVA in reducing patient-ventilator asynchrony.[15]

To our knowledge, no data have been published on the use of NAVA in NIV for infants presenting with severe bronchiolitis. The aim of this physiological study was to evaluate the feasibility of NAVA for delivering NIV to patients younger than 6 months with severe bronchiolitis and to compare its effects on patient-ventilator synchronization with NIV delivering pressure assist control (PAC) ventilation.

METHODS

This prospective trial was performed in a 23-bed university-based hospital PICU (Lyon, France) between December 2012 and March 2013. The institutional review board (Comite´ de Protection des Personnes Sud-Est II, Lyon, France) approved the protocol (ref. number: 2012-A01409–34), and informed consent was obtained from the parents or legal guardians of the study subjects.

Population

Patients younger than 6 months of age admitted to the PICU for severe bronchiolitis were first treated with nCPAP. Severe bronchiolitis was defined as acute respiratory failure (tachypnea >60/min or apnea, signs of clinical respiratory distress, and hypercapnia >50 mmHg (6.5 kPa)) associated with clinical and radiological signs of bronchiolitis due to respiratory syncytial virus infection.[5,20] Respiratory syncytial virus was confirmed by the polymerase chain reaction kit Respiratory Multi Well System r-gene (Argene/bioMerieux, Verniolle, France) identification. These patients were included in the present study in the case of failure of nCPAP applied for at least 2 hr, defined as: 1) more than three apnea events per hour or 2) increase of respiratory distress signs associated with worsening of blood acidosis ($pH < 7.30$, pCO_2 or transcutaneous pCO_2 ($TcPCO_2$) > 60 mmHg (8 kPa)). Patients with underlying cardiopulmonary, neuromuscular, or chronic respiratory disease were excluded. According to our PICU protocol, children with altered level of consciousness, FiO_2 requirement above 60%, respiratory fatigue demonstrated by decrease in respiratory distress signs or haemodynamic instability were intubated.

Standard Treatment of Bronchiolitis

All infants included were laid in dorsal 30° proclivity and given chest physiotherapy when judged necessary. They were fed continuously via orogastric tubes or received intravenous fluids. Infants were not sedated. In accordance with French consensus guidelines, corticosteroids and caffeine were never used.

We carried out continuous cardiorespiratory monitoring (heart rate, SpO_2, and intermittent blood pressure) with an Intellivue MP70 cardioscope (Philips Medical Systems, Eindhoven, The Netherlands). We measured $TcPCO_2$ using an SDMS $TcPCO_2$ (SenTec, Therwil, Switzerland) or a $TcPCO_2$ module for an IntelliVue MP70 cardioscope (Philips Medical Systems).

Ventilator and Interface

Infants were ventilated with a Servo-I (Maquet Critical Care, Solna, Sweden) using the NIV software option. A dedicated module was used for NAVA.

To deliver NIV in both modes, double ventilatory circuits with heated humidifier and infant nasal masks (Fisher and Paykel Healthcare, Auckland, New Zealand)

were used. A specific orogastric tube with several electrodes (EAdi catheter, Maquet Critical Care) for recording diaphragmatic activity was positioned according to the manufacturer's instructions.[21]

Study Protocol

After positioning of the EAdi catheter, NIV was started in PAC mode. After 2 hr of PAC, NAVA was applied for an additional 2 hr.

For both modes, the attending physician adjusted the ventilator settings for 20 min. Positive end-expiratory pressure (PEEP) was first set to 4–5 cmH_2O and FiO_2 was set to maintain SpO_2 $\geq$92%. If the inspiratory oxygen fraction (FiO_2) level was above 35%, then the PEEP level was increased by steps of 1 cmH_2O, with a maximum increase of 4 cmH_2O. After optimization, the same level of PEEP was used during all subsequent phases of the study. FiO_2 was then decreased to the lowest possible level. The pressure level was first set to 12 cmH_2O and increased step by step to obtain a compromise between decreasing respiratory distress signs (respiratory rate, use of accessory muscles, nose flaring, intercostal and xyphoid retraction) and increasing leaks. The respiratory rate was initially set between 35 and 40/min during PAC mode and the ratio of inspiratory time to expiratory time (I:E) at 1:2 based on previous physiological study[5,6] which determined a ratio of inspiratory time to total cycle time (Ti/Ttot) between 0.36 and 0.5 in children with bronchiolitis in spontaneous ventilation. Adjustments of I/E ratio and respiratory rate were performed by the attending physician according to the clinical assessment of patient-ventilator synchrony for 20 min. The EAdi trigger was set to the default value of 0.5 μV; the PAC trigger was set automatically in NIV and was non-adjustable. The NAVA gain level was set to 1.0 $cmH_2O/\mu V$, and then increased to obtain a pressure level at least equal to the pressure in PAC mode. In each mode, the airway pressure limit was at 30 cmH_2O.

At the end of the study period, children were left in PAC or NAVA mode based on the physician's judgment. No other changes in practice have occurred.

Recordings and Measurements

Data from the ventilator (EAdi, flow, and airway pressure signals) were acquired continuously on a laptop at 100 Hz using ServoI-RCR software v3.7.5 (Maquet Critical Care, Solna, Sweden). After a 20 min stabilization period, 10 min of operation were recorded in each mode, without any change in ventilator settings. Pressure, EAdi, and flow curve of the fifth minute of operation were blindly analyzed by one investigator, breath by breath. Patient and ventilator rates were determined by analyzing the EAdi and flow curves. Trigger delay was defined as the time between the elevation of the EAdi curve and the elevation of the flow curve, as described previously.[15] The three main inspiratory asynchronies (autotriggering, double triggering, and ineffective effort) were identified (Fig. 1). The index of asynchrony was calculated as the sum of the occurrences of the three asynchrony types divided by the number of triggered and non-triggered cycles, as previously described.[13,23]

Statistical Analysis

Categorical data were expressed as percentages and compared using the chi-squared test or Fisher's exact test when the conditions for application of the chi-squared test were not met. Quantitative variables were expressed as means and standard deviations (SDs). As measures were successively performed on each patient, we used Student's *t*-test for matched pairs to compare these values. Differences were considered statistically significant at 5% ($P < 0.05$). Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Between December and March 2013, 126 patients were admitted for severe bronchiolitis; 14 (11.1%) children were enrolled in our study. Three patients were excluded at the time of analysis, one due to a missing recording in NAVA mode, one due to a missing EAdi curve in PAC mode, and one due to aberrant data from a defect in the RS232 cable.

Patient characteristics appear in Table 1. All patients were aged less than 3 months, with a mean age of 35.2 ± 23 days and a mean weight of 3.73 ± 0.70 kg. Two patients were born preterm (32 and 36 weeks of gestational age). Two children presented co-infection with picornavirus. The mean length of nCPAP use before inclusion was 12.36 ± 10.10 hr. At enrolment, the mean blood-gas values were as follows: pH 7.25 ± 0.06 and pCO_2 71 ± 10 mmHg (9.5 ± 1.3 kPa).

Clinical characteristics at the beginning of the two periods of recording are presented in Table 2. The modified Wood's clinical asthma score (m-WCAS) was the same in the PAC and NAVA periods (3.3 ± 1.0 vs. 3.1 ± 1.9, respectively, $P = 0.87$). The $TcPCO_2$ baselines values (64.5 ± 12 mmHg (8.6 ± 1.6kPa) vs. 62 ± 9 mmHg (8.1 ± 1.2 kPa) during NAVA, $P = 0.3$) and their evolutions during the study period (-6 ± 10 mmHg (-0.8 ± 1.4 kPa) vs. -12 ± 17 mmHg (-1.6 ± 2.3 kPa) during NAVA, $P = 0.36$) did not differ.

All children received NIV with a nasal mask. No sedation was administered. No problem with the EAdi tubing occurred. A total of 22 min and 1431 respiratory cycles of data were analyzed. The main respiratory parameters are presented in Table 3.

The asynchrony index, the primary endpoint of this study, was significantly lower in NAVA mode compared to

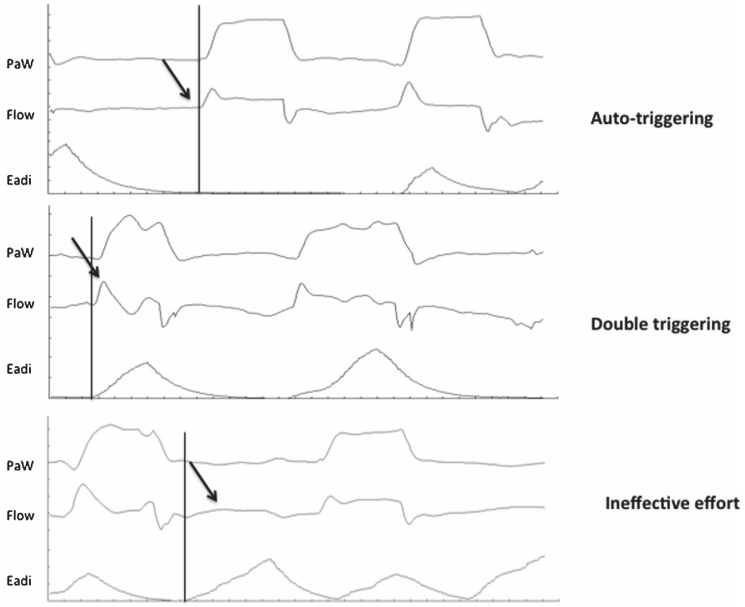

Fig. 1. Examples of the three main asynchronies in a child on non-invasive ventilation.Arrow indicates abnormal events and vertical line indicates the beginning of the cycle. Paw, airway pressure; Eadi, electrical activity of the diaphragm.

PAC mode ($3 \pm 3\%$ and $38 \pm 21\%$ respectively $P < 0.0001$). In addition, the trigger delay was shorter during NAVA than during PAC (116 ± 3.8 ms and 43.9 ± 7.2 ms, respectively, $P < 0.0001$). Only one child had a trigger delay above 50 ms (51.1 ms) during NAVA mode. Ineffective breathing efforts were significantly more frequent in PAC mode than in NAVA mode (21.8 ± 16.5 vs. 0.54 ± 1.5 events/min, respectively; Fig. 2). One child had no ineffective effort during PAC ventilation.

At the end of the study, eight children (63.6%) were left on NAVA ventilation. The mean duration of ventilation

TABLE 1— Characteristics Data at Inclusion and Outcome of the Eleven Children With Severe Bronchiolitis With Failure of Nasal Continuous Positive Airway Pressure

N°	Age (days)	Weight (Kg)	Sex	Length of nCPAP (H)	Length of MV (H)	Final mode	Intubation	PICU stay (Days)
1	35	4.20	M	13	114	NAVA	No	7
2	22	4.00	M	5	118	NAVA	No	8
3	46	3.56	M	12	145	PAC	No	10
4	14	3.45	M	31	196	PAC	No	10
5	63	4.53	F	27	85	NAVA	No	5
6	17	2.50	F	15	226	NAVA	Yes	11
7	27	3.80	M	2	110	NAVA	No	5
8	15	3.50	M	2	184	PAC	Yes	10
9 [1]	56	3.60	M	4	320	PAC	Yes	16
10	80	5.00	M	5	81	NAVA	No	6
11[1]	12	2.90	F	20	288	NAVA	No	14
Mean	35.2	3.73		12.36	170			9.27
SD	23	0.70		10.10	81			3.55

nCPAP, nasal continuous positive airway pressure; MV, Mechanical ventilation; H, hours; NAVA, Neurally adjusted ventilatory assist; PAC, pressure assist/control; PICU, Paediatric intensive care unit.
[1]preterm children

TABLE 2— Characteristics at the Beginning of the Two Periods (Pressure Assist Control and Neurally Adjusted Ventilatory Assist Modes) of Recording in Children (n = 11)

	PAC	NAVA	P^1
Heart rate (n/min)	163.6 (14.4)	169.3 (8.2)	0.18
SpO_2 (%)	95.3 (2.5)	96.7 (2.4)	0.07
$TcpCO_2$ (mmHg)	64 (12)	61 (9)	0.3
m-WCAS	3.3 (1.0)	3.1 (1.9)	0.87

NAVA, neurally adjusted ventilatory assist; PAC, pressure assist/control; SpO_2, pulse oximetry; $TcPCO_2$, transcutaneous pCO_2; m-WCAS, modified Wood's clinical asthma score. Values are expressed as mean (SD).
[1]Student's t-test for matched pairs.

was 7.08 ± 3.38 days for a mean PICU length of stay of 9.27 ± 3.55 days. The rate of intubation in this study was 27%.

DISCUSSION

This physiological study investigated NAVA in NIV in a homogenous paediatric population of children with severe bronchiolitis. NAVA is associated with a significant improvement in patient-ventilator interactions, reducing main asynchrony and ventilator response time three-fold. Studies involving paediatric patients with this new technology in non-invasive ventilation are rare. Only two studies have addressed NAVA in NIV, one in premature children[19] and one in children older than four weeks.[15] Ventilators have difficulties in detecting inspiratory effort in these patients due to leaks, to the physiological characteristics of young children (low tidal volume and high respiratory rate). These studies suggest that NAVA may be a possible alternative to the usual mode of NIV and that patient-ventilator synchronization is improved.

Inspiratory asynchrony is one of the main limitations of NIV in infants and is known to increase the work of breathing during invasive ventilation.[13,24] The observed reductions in the main asynchrony event during the inspiratory phase were impressive, and in accordance with previous reports in children[15,19] and in adults.[17,18,25] In bronchiolitis, dynamic hyperinflation may increase the frequency of ineffective respiratory effort as described in adult patients with expiratory airflow limitation.[13] It was interesting to observe that the ventilator rate was more closely approximated to the patient respiratory rate due to better synchronization.

Reduction of the trigger delay suggests that inspiratory synchronization during NAVA is more effective. Trigger delay is a complex issue and is influenced by numerous factors: ventilator characteristics and setting, patient-ventilator interface and patient respiratory status. In our study, we attempted to limit confounding factors. Water in the circuit and air leaks were frequently monitored. In addition, nasal suctioning was performed and the interface was adjusted before each recording. Nasal airways were left unobstructed as the probe was inserted through the mouth. Respiratory drive may also play a role and high respiratory drive is associated with a shorter trigger delay.[26] In our study, the respiratory drive seemed similar in both groups, as reflected by the similar EAdi[27] ($P = 0.8$). The trigger delay observed during NAVA and PAC was shorter than observed in a previous study on NIV.[15] We attributed the short trigger delay observed in children with bronchiolitis to the high respiratory rate and high respiratory drive (EAdi) in these patients.[22,26,28]

NAVA may be useful in this population because bronchiolitis leads to an airway inflammation with increased airway resistance and auto-peep. Changes in pressure or flow during inspiration could be poorly

TABLE 3— Respiratory Parameters and Measurements During a One Minute Recording in Children (n = 11) under Non-invasive Ventilation

	PAC	NAVA	P^1
Respiratory parameter			
FiO_2 (%)	31.5 (9,4)	29.2 (9.6)	0.22
Trigger	Auto	0.5 (0)	
NAVA Level ($cmH_2O/\mu V$)		1.35 (0.37)	
Neural respiratory rate (n/min)	54.3 (19.7)	60.7 (19.5)	0.16
Ventilator respiratory rate (n/min)	49.8 (8.5)	59.5 (17.9)	0.03
PEEP (cmH_2O)	5.4 (1.1)	5.4 (1.2)	0.95
Pmax (cmH_2O)	15.2 (2.5)	18.7 (4.9)	0.09
EAdi max (μV)	25.3 (15.4)	24.1 (12.8)	0.80
Autotriggerring (n/min)	8.2 (13.3)	0.09 (0.3)	0.07
Ineffective effort (n/min)	21.8 (16.5)	0.54 (1.5)	0.001
Double triggering (n/min)	1.0 (0.89)	1.56 (0.62)	0.28
Asynchrony index (%)	0.38 (0.21)	0.03 (0.03)	<0.0001
Trigger delay (ms)	116.0 (38.9)	43.9 (7.2)	<0.0001

NAVA, Neurally adjusted ventilatory assist, PAC, pressure assist/control, FiO_2, inspiratory oxygen fraction, Pmax, maximal airway pressure, EAdi, electrical activity of the diaphragm. Values are expressed as mean (SD).
[1]Student's t-test for matched pairs.

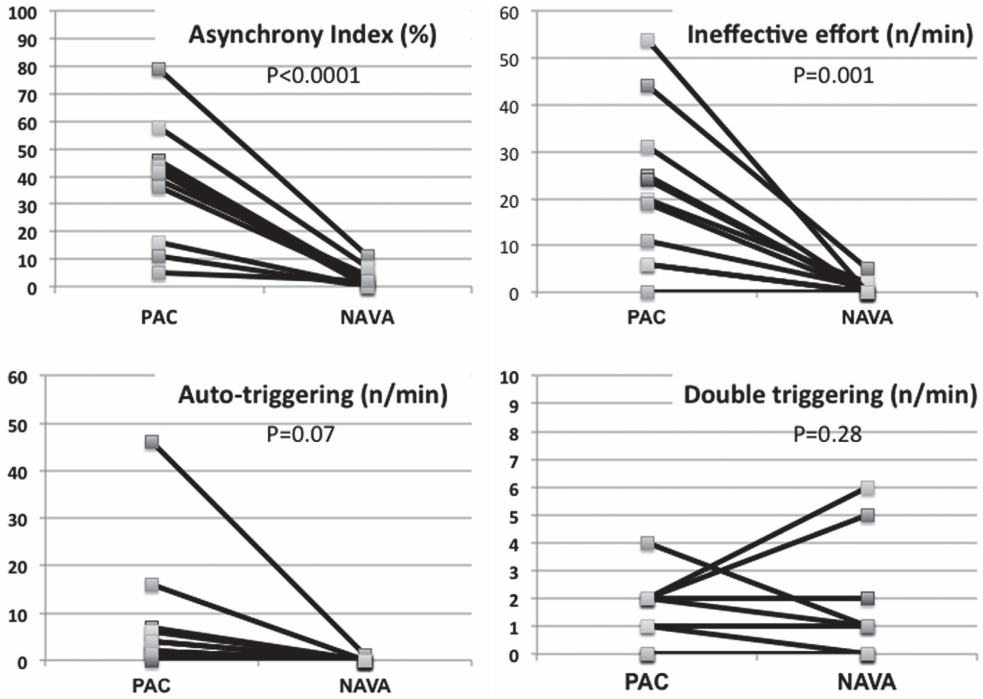

Fig. 2. Three main asynchronies and asynchrony-index children (n = 11) on NIV for severe bronchiolitis in PAC and NAVA modes. NAVA, Neurally adjusted ventilatory assist, PAC, pressure assist/control, n/min, events/min.

transmitted through an obstructed airway to the ventilator, especially during NIV. The EAdi-based triggering with NAVA should theoretically not be influenced by auto-PEEP. Bellani et al. confirmed recently that the effort necessary to overcome auto-PEEP was lower during NAVA than PSV, in COPD patients.[29] This benefit may be the same in children with bronchiolitis and may explain a part of the reduction of trigger delay. We did not measure indices of work of breathing but as suggested in previous studies, the reduction of the trigger delay leads to a decrease in the work needed to activate an assist.[22,30]

For several years, the use of NIV in bronchiolitis has dramatically increased in European countries[10,31,32] and in Australia,[33] and it is now the primary ventilatory support in our unit as reported in 2008.[7] In accordance with our practice, in situations of nCPAP failure, NIV is attempted in order to avoid intubation. Due to patient-ventilator asynchrony, NIV is hard to apply, especially in infants. Rather than switching directly from nCPAP to invasive ventilation, more efficient NIV modes such as NAVA may be attempted.[7,11,31,34] The rate of intubation in our study was 27% despite the fact that our population was representative of severe patients with bronchiolitis.

In the current study, children were not sedated, as sedative drugs are typically avoid in our PICU for this population.[7] This may have facilitated the recording of EAdi and NAVA ventilation as sedation has been shown to decrease the respiratory drive and the intensity of the EAdi signal.[35,36] However, in the study by Vignaux et al.[15] most children received some sedation while on NIV NAVA. Other studies have shown that sedation does not seem to be a limit to use NAVA.[35,36]

The inclusion of two children (number 7 and 8) with significant apnea may be questionable because NAVA is triggered by patients' spontaneous breathing. Previous studies suggested that central apnea could be safely treated with CPAP in bronchiolitis[37] by reducing loop gain.[38] Based on these observations, a trial of NIV was undertaken in our PICU under close clinical monitoring with blood gas analysis every two hours. One out of the two children was ultimately intubated and the other was successfully ventilated with NAVA mode for 4 days.

No adverse events occurred during this study, which is consistent with other studies using NAVA in children for invasive ventilation[39] and NIV.[15,19] In our four years of practice, the primary problem with NAVA during NIV was the probe stability. Some children suck on the orogastric probe, which may lead to a loss of the diaphragmatic signal requiring replacement of the probe by the nurse. Studies with larger samples are needed to demonstrate the safety of this new ventilatory mode in children.

Our study has several limitations. First, we used the data provided by the ventilator itself (EAdi, Flow and pressure signals) and not from independent and proximal sensors. The device does not allow performing independent calibration.

Second, the order of the two observational sessions was not randomized, and was the same (PAC then NAVA) for all patients. Also, respiratory parameters could be improved after 2 hr of ventilation in PAC mode. The blood gas analyses however, were similar at the beginning of the two periods studied. In light of the extent of the improvement of patient-ventilator asynchronies, it is unlikely that this effect was only due to the evolving natural history of ventilated children with bronchiolitis. Since our analysis relied on paired tests and because of the very significant result on synchronization, this bias did not impact the conclusion of our study.

Third, we chose to compare PAC with NAVA due to the difficulties of using pressure-support ventilation during NIV in very young children. Because of very low tidal volume, high respiratory rate, and leaks in NIV, ventilators have difficulties with detecting inspiratory effort. In our experience, alarms and secure apnoea ventilation occurred very frequently during pressure-support ventilation, and we abandoned it for infants with severe bronchiolitis. Ultimately the rate of asynchrony (38%) found in our study during PAC mode was similar to those previously reported in children on pressure support ventilation (40–65.5%).[15]Further more, we cannot exclude that ventilator characteristics and settings may influence the occurrence of asynchrony and the trigger delay. Ventilator settings (I/E ratio, respiratory rate, pressure level,…) however, were optimized before recording which reflects the practices in our unit. During CPAP, the PEEP was set at 7 cmH_2O for all patients, consistent with a previous study.[5] During NIV, the PEEP was lowered (5.4 cmH_2O) during both PAC and NAVA modes to decrease the risks of leaks. Patients were especially hypercapnic and not very hypoxic (FiO_2 = 31.5% in PAC and 29.2% in NAVA). The optimal settings in NAVA are unknown, and settings are employed mainly based on experience. Practices were not modified in this study and reflect the choices of the physicians in charge. Emeriaud et al. suggested an adjustment of ventilator settings based on EAdi values.[40]

Another limitation of the present investigation is that we were interested only in the three main inspiratory asynchrony events (autotriggering, double triggering, and ineffective effort) addressed in a previous study[23] because they were easily and objectively identified. Other asynchronies, especially premature and late cycling, are important to consider during pressure support ventilation. Reductions in these asynchronies seems to be less important in other studies compared to reductions in the three main asynchronies.[13,15,17] Flow asynchronies, defined as a mismatch between the ventilator flow and the patient flow were reported in animals during NAVA.[30] We did not analyze this type of asynchrony in our study.

In conclusion, this study provides an overview of the benefit of NAVA on synchronization, and demonstrates the feasibility of NAVA in a homogenous population of infants with severe bronchiolitis who failed nCPAP. However, in the absence of large studies designed to assess the clinical benefits and the safety of NAVA in children with severe bronchiolitis such a mode must be applied very cautiously. The results of this physiological study are encouraging and could help design a multicentre prospective study on NAVA in non-invasive ventilation in children.

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3.4. Résultats et Discussion

Cette étude était l'une des premières études pédiatriques en ventilation non invasive évaluant la synchronisation patient-respirateur en NAVA. Nous avons démontré que le taux d'asynchronies (3% ± 3% vs. 38 ± 21%) de même que le délai de réponse du respirateur (43.9 ± 7.2 ms vs. 116 ± 3.8 ms) étaient significativement plus bas en NAVA qu'en PAC. Les efforts inefficaces étaient l'asynchronie la plus fréquente et étaient significativement diminués en NAVA (21.8 ± 16.5 vs. 0.54 ± 1.5 /min). Il s'agit d'une population extrêmement sélectionnée que sont les nourrissons atteints de bronchiolite en échec de nCPAP.

Cette étude présente de nombreuses limites. Premièrement le choix du mode de ventilation est discutable car le mode PAC impose un temps inspiratoire qui peut générer des asynchronies, raison pour laquelle nous n'avons pas analysé les asynchronies de cyclage. Ce choix a été fait car la PAC est l'un des principaux modes utilisés dans le service [11]. La VS-AI semble peu adaptée aux nourrissons respirant à très haute fréquence. Deuxièmement, la séquence d'observation est toujours la même, PAC puis NAVA ne permettant pas d'exclure qu'une partie de l'amélioration de la synchronisation puisse être liée à une amélioration clinique. Troisièmement, les réglages n'étaient pas standardisés et basés sur l'expérience du clinicien notamment en PAC alors même qu'ils peuvent être à l'origine des asynchronies [126]. Enfin, la durée d'analyse est courte et n'est pas forcément le reflet de l'ensemble du profil ventilatoire des enfants. La NAVA permettrait de réduire significativement les asynchronies comme confirmée dans une méta-analyse récente chez l'adulte et chez l'enfant [124] incluant notre étude.

La question de l'optimisation de la synchronisation notamment inspiratoire au cours des pathologies obstructives est particulièrement difficile. La NAVA permettrait de restaurer une variabilité cycle à cycle et de délivrer une ventilation proportionnelle permettant dans plusieurs travaux expérimentaux de limiter la sur-distension pulmonaire [141-143] mais également la sur-assistance [144, 145]. De plus, lors de l'utilisation d'un trigger pneumatique, le patient doit vaincre la PEEPi pour générer une variation de débit ou de pression identifiable par le respirateur. Selon la théorie de Tobin et al. [58] le réglage de la PEEP externe est dès lors très importante pour réduire le gap (Figure 4) et donc améliorer le délai de déclenchement. En pratique clinique, l'accès à la valeur de la PEEPi pour titrer individuellement la PEEP externe est impossible à réaliser. Dès lors, les efforts inefficaces sont l'une des asynchronies principales [128]. Il est intéressant de voir qu'en NAVA, cette

problématique est shuntée par le trigger neural. Le déclenchement devient moins dépendant de la différence entre la PEEP externe et la PEEP intrinsèque [99, 146] expliquant la réduction de ce délai dans les études et la réduction des efforts inefficaces.

4. ETUDE 4 : COMPARAISON DE L'EFFORT RESPIRATOIRE ENTRE LA N-CPAP ET LA NAVA AU COURS DE LA BRONCHIOLITE

4.1. Introduction

La NAVA permet d'améliorer la synchronisation y compris lors de la ventilation non invasive au cours de la bronchiolite. Ce critère, certes important, ne permet pas de préjuger de l'impact de ce mode ventilatoire sur l'effort respiratoire du patient. Nous avons conduit une analyse complémentaire lors de l'étude BRONCHIO-DV portant sur la comparaison de l'effort inspiratoire entre la nCPAP considérée comme le mode de référence dans la bronchiolite et la NAVA. Il s'agit d'une étude préliminaire avec un effectif réduit. Notre hypothèse était que la NAVA réduisait l'effort inspiratoire chez le nourrisson atteint de bronchiolite grave en comparaison à la nCPAP.

4.2. Matériel et Méthodes

Cette étude a bénéficié d'un avis favorable du comité d'éthique de la SRLF (CE SRLF 18-48) car les analyses n'étaient pas prévues dans le protocole initial même si les parents étaient informés de la possibilité d'enregistrement à deux niveaux d'assistance.

En fin de période d'enregistrement de l'étude BRONCHIO-DV, certains nourrissons étaient placés en mode NAVA avant le retrait de la sonde de mesure des pressions œsophagiennes et les réglages étaient ajustés par le praticien en charge de l'enfant. Les enfants étaient ventilés en mode nCPAP avec un niveau à 7cmH_2O puis basculés en mode NAVA. Les données étaient enregistrées pendant 2 min avant et après le changement. Huit enfants sur les seize inclus dans l'étude ont été ventilés en mode NAVA et un enregistrement était disponible pour sept d'entre eux. L'analyse était réalisée à postériori et portait sur 25 cycles respiratoires avant et après passage en NAVA.

4.3. Article 4 : Neurally adjusted ventilatory assist improves respiratory unloading in infants with severe bronchiolitis.

Critical Care

Neurally adjusted ventilatory assist decreases work of breathing during non-invasive ventilation in infants with severe bronchiolitis

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Question	**Response**
Is this study a clinical trial?<hr>A clinical trial is defined by the Word Health Organisation as 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.	No

Letter

Title: Neurally adjusted ventilatory assist decreases work of breathing during non-invasive ventilation in infants with severe bronchiolitis

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Dear Editor,

Though neurally adjusted ventilatory assist (NAVA) is known to improve patient-ventilator interactions in infants with bronchiolitis [1,2], its impact on respiratory muscles unloading has not previously been studied.

We conducted a secondary analysis (ethics committee approval CE_SRLF_18-48) of a prospective physiological study [3] which evaluated the impact of body positioning on work of breathing (WOB) in infants with severe bronchiolitis. Seven of the children included (median age 35 [27-63] days), had a respiratory recording during the transition from nasal continuous positive airway pressure (nCPAP, set at 7cmH_2O[4]) to NAVA. Esophageal (Peso), gastric (Pga) and airway (Paw) pressures, as well as Electrical activity of the diaphragm (Edi), and flow were recorded simultaneously. Median NAVA level was set at 0.7 [0.7-0.9] cmH_2O/µV and median positive end expiratory pressure at 5 [4-7] cmH_2O. Twenty-five breaths during the last 2 minutes in nCPAP then during the first 2 minutes in NAVA were analyzed off-line. Metabolic cost of breathing was estimated by the Peso (PTPeso) and diaphragmatic (PTPdi) pressure time product, inspiratory effort by the Peso (ΔPeso) and diaphragmatic (ΔPdi) pressure swings, and respiratory drive by the Edi swing (ΔEdi). Data were expressed as median [IQR] and compared using Wilcoxon two-sample paired sign test. A *p*-value <0.05 was considered significant.

As detailed in Table 1 and illustrated in Figure 1, all indices of WOB (PTPeso, PTPdi, ΔPeso, ΔPdi, Edi swing, and inspiratory time to total time ratio (Ti/Ttot)) decreased significantly in every child with NAVA as compared to nCPAP ($p<0.05$ in all instances), while the mean Paw was increased ($p<0.05$).

In this physiological study, we report an improvement of respiratory unloading by adding a second level of pressure with NAVA in infants with severe bronchiolitis. WOB decreased immediately after switching to NAVA (Figure 1), as reported previously in adults with obstructive lung diseases [5], and was associated with a lower neural drive and Ti/Ttot ratio.
This study has several limitations, including the small sample size, the short study period, the non-randomized order of recordings, and the non-standardized NAVA settings. However, the consistent, rapid, and large improvement in WOB-related indices observed in every infant is an important finding, especially considering the number of infants with severe bronchiolitis who

may benefit from an improvement in non-invasive support. The findings support the need for further evaluation of the potential interest of NAVA to improve the efficiency of non-invasive support in infants with bronchiolitis.

List of abbreviations

Edi: Electrical activity of the diaphragm
IQR: Interquartile Range
NAVA: neurally adjusted ventilatory assist
nCPAP: nasal continuous positive airway pressure
Paw: airway pressure
Peso Esophageal Pressure
Pga: gastric Pressure
PTP: pressure time product
WOB: work of breathing

Declarations:

Ethics approval and consent to participate:

The primary study was approved by the institutional review board (CPP SUD-EST3—n°2015-057B) and by the national medicines authority (ANSM–151048B-32) and written consent was obtained from the parent(s) or guardian(s). The secondary analysis was approved by the ethical committee of the French intensive care society (CE_SRLF_18-48)

Consent for publication: N/A

Availability of data and material:

The datasets generated and/or analyzed during the current study are not publicly available according to the French National Data Protection Commission (CNIL) but are available from the corresponding author on reasonable request.

Competing interests:

FB has received speaking fees and non-financial support from Maquet Critical Care.
GE'S research program is supported by a research grant from the Fonds de recherche en santé du Québec. He also recently conducted a feasibility study of a new ventilator, which costs were supported by Maquet Critical Care.
JB has been reimbursed by Maquet Critical Care (Solna, Sweden) for attending several conferences; JB has participated as a speaker in scientific meetings or courses organized and financed by Maquet Critical Care; JB, through Neurovent Research, serves as a consultant to Maquet Critical Care. The following disclosure was agreed upon by University of Toronto, Sunnybrook Health Sciences Centre, St-Michael's Hospital and the REBs of Sunnybrook and St-Michael's to resolve conflicts of interest: "Dr. Beck has 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 Dr. Beck through royalties. Dr Beck owns 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."
The others authors have no conflict of interests.

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Authors' contributions:
FB, EJ conceived the study, analyzed and interpreted the data and drafted the manuscript. GE, SE, JB, CG analyzed and interpreted the data and revised the manuscript. JB and SE provided technical support. All authors read and approved the final manuscript

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Figure Legend

Figure 1: Decrease of esophageal and trans-diaphragmatic pressure swing and Edi amplitude after switching to neurally adjusted ventilatory assist.

The red arrow indicates the switch from nCPAP to NAVA. nCPAP: nasal continuous positive airway pressure; NAVA: neurally adjusted ventilatory assist; PEEP: positive end expiratory pressure; Paw: airway pressure; Peso: esophageal pressure; Pga: gastric pressure, EAdi: Electrical activity of the diaphragm.

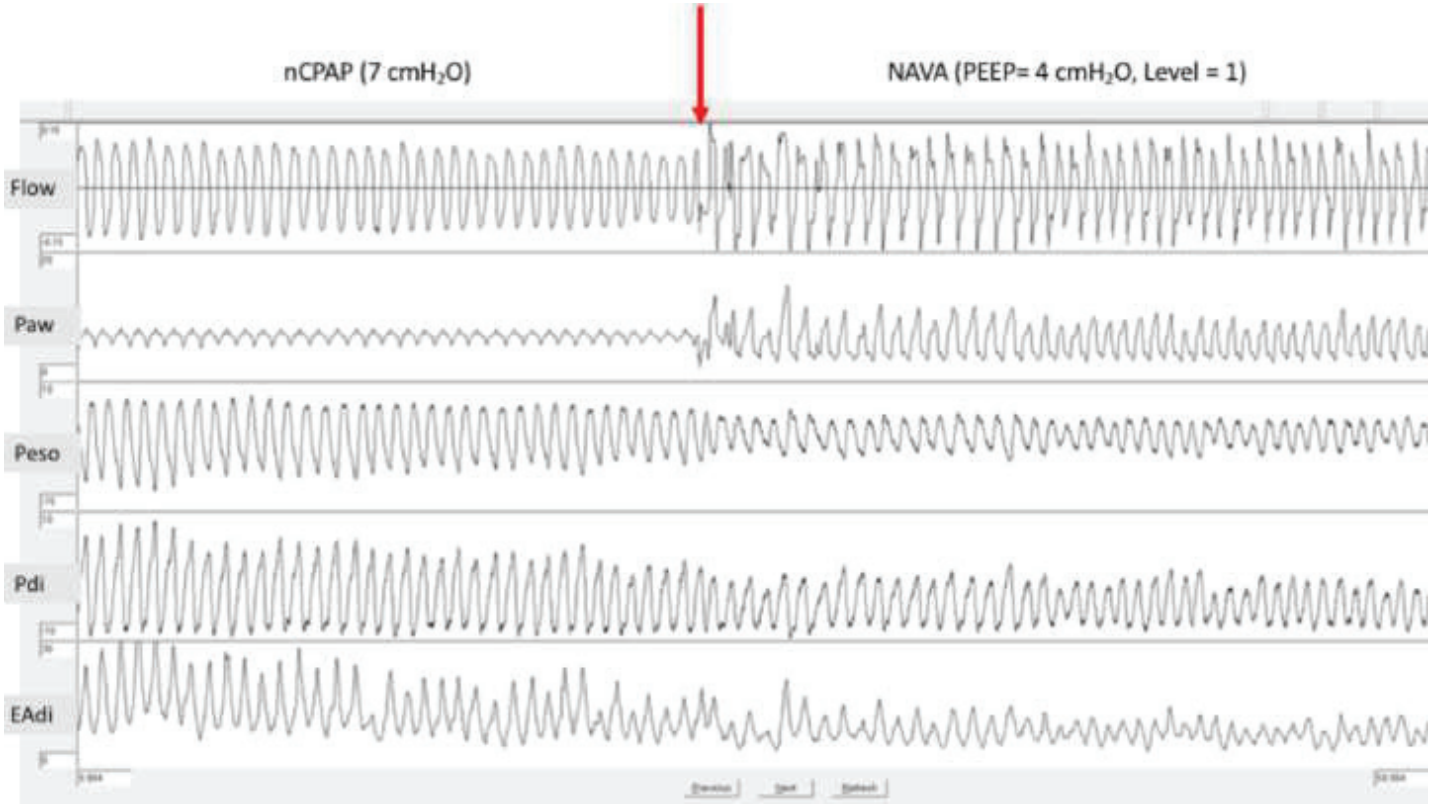
TABLE 1: Comparison of physiological parameters between nasal continuous positive airway pressure and neutrally adjusted ventilatory assist.

	nCPAP	NAVA	p*
Ti/Ttot (%)	0.47 [0.45-0.49]	0.40 [0.37-0.45]	0.02
Respiratory Rate (/min)	71 [64-84]	65 [57-80]	0.31
Mean airway pressure (cmH_2O)	7.0 [6.9-7.1]	10.6 [9.4-11.9]	0.02
ΔEdi (μV)	19 [17-25]	16 [10-19]	0.03
Swing Peso (cmH_2O)	14 [12-18]	8 [8-13]	0.01
Swing Pdi (cmH_2O)	14 [13-15]	10 [9-10]	0.02
PTPeso/breath (cmH_2O*s)	4.7 [3.4-6.1]	2.1 [1.9-3.7]	0.02
PTPdi/breath (cmH_2O*s)	4.2 [3.9-4.4]	2.6 [2.5-2.8]	0.02
PTPeso/min (cmH_2O*s/min)	365 [237-429]	162 [139-226]	0.02
PTPdi/min (cmH_2O*s/min)	298 [256-354]	157 [151-199]	0.02

Data are expressed as median [interquartile range]
* Wilcoxon two-sample paired sign test.
nCPAP: nasal continuous positive airway pressure; NAVA: neutrally adjusted ventilatory assist; PEEP= Positive End Expiratory Pressure; Ti= inspiratory time; Ttot = total time; Peso: esophageal pressure, Pga: gastric pressure, Edi: Electrical activity of the diaphragm; PTP: pressure time product.

Figure1

Click here to access/download;Figure;NAVA_CPAP_Figure1.png



4.4. Résultats et discussion

Ce travail, portant sur un effectif faible de patients, se veut essentiellement descriptif et ne permet pas de tirer de conclusion. Chez tous les nourrissons, l'ajout d'un deuxième niveau de pression, même avec une diminution de la PEEP externe, se traduit par une réduction instantanée de l'effort inspiratoire comme illustré dans la figure 11.

Tous les paramètres reflétant l'effort inspiratoire (EAdi, Amplitude de la dépression œsophagienne et diaphragmatique et PTP œsophagien et diaphragmatique) sont significativement plus bas en NAVA qu'en nCPAP sans modification significative de la fréquence respiratoire mais avec une réduction du rapport Ti/Ttot.

Finalement ce travail n'évalue pas seulement l'impact de la NAVA sur l'effort respiratoire mais plutôt l'apport d'un deuxième niveau de pression par rapport à la PEEP seule. La NAVA réduit le délai de déclenchement du respirateur et améliore la synchronisation patient-respirateur indépendamment de la PEEP externe. Il apparaît que ce mode se justifie (du moins théoriquement) au cours de la bronchiolite. Des résultats similaires pourraient probablement être observés avec un mode ventilatoire en aide inspiratoire avec un ajustement précis des paramètres (Trigger, cyclages, PEEP). D'autres études sont nécessaires pour évaluer pleinement le bénéfice de la NAVA au cours de la bronchiolite d'autant que le coût généré par la technologie (respirateur dédié et sonde NAVA) n'est pas négligeable.

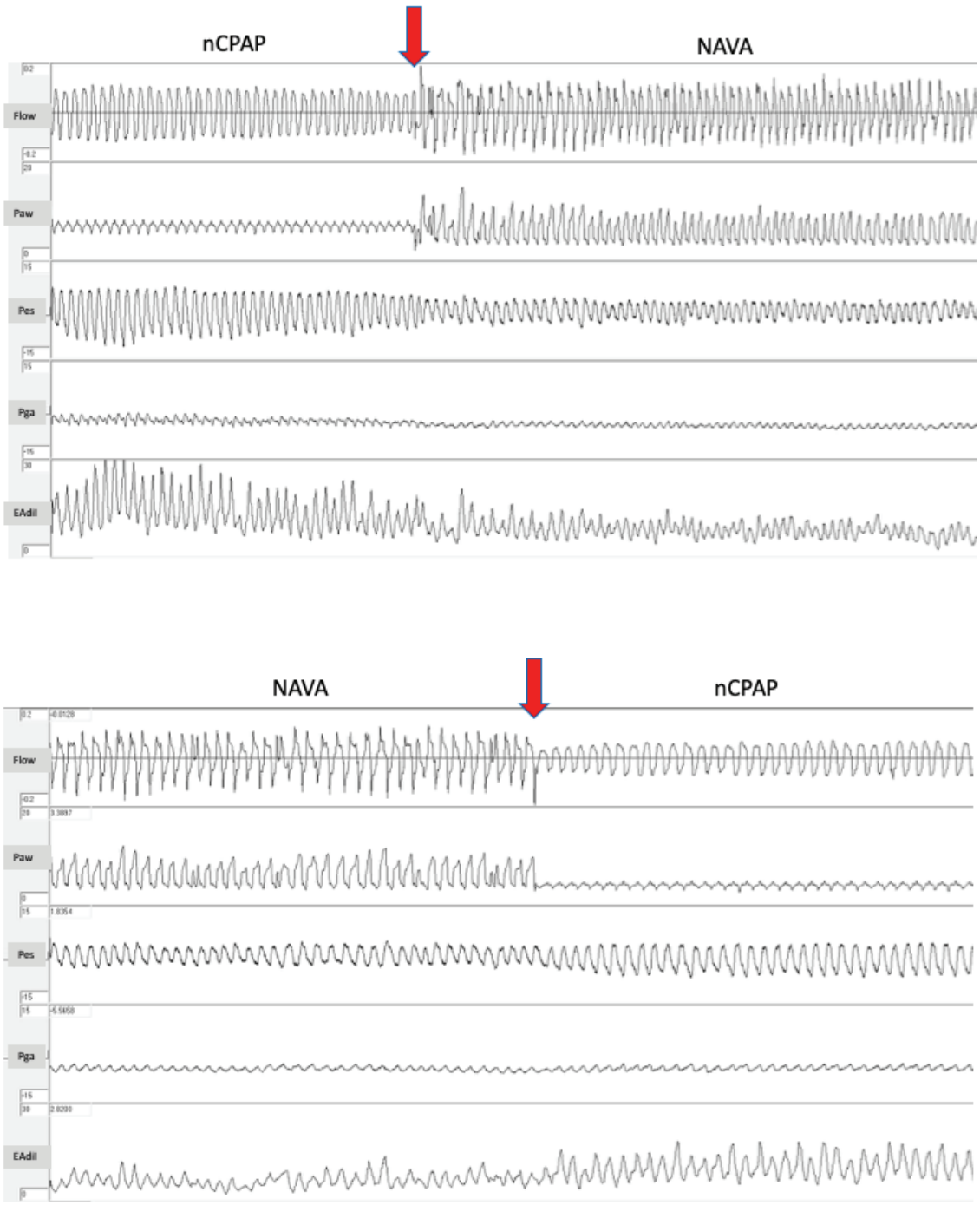


Figure 13 : Exemple d'enregistrement avant et après passage en NAVA chez un nourrisson atteint de bronchiolite.

Flèche rouge = changement de mode. On note une diminution instantanée de l'amplitude de la Peso après passage en NAVA puis une ré-augmentation lorsque l'on retourne en nCPAP NAVA= Neurally adjusted ventilatory assist, nCPAP= nasala continuous positive airway pressure, Peso= pression œsophagienne, Pga= pression gastrique, EAdi = activité électrique du diaphragme.

IV. DISCUSSION GENERALE ET PERSPECTIVES

1. SYNTHESE DES RESULTATS

La broncho-alvéolite du nourrisson est un défi au quotidien pour les réanimateurs et pédiatres qui prennent en charge ces enfants. Elle revêt les caractéristiques d'une pathologie obstructive et d'une atteinte alvéolaire (restrictive) qui peut évoluer vers des syndromes de détresse respiratoire aiguë [53, 54]. Au-delà de la typologie de l'atteinte respiratoire, il est nécessaire de prendre en compte les particularités physiologiques de cette population. Le nourrisson est particulièrement à risque de développer une détresse respiratoire avec une déstabilisation de cet équilibre physiologique précaire responsable d'une altération bruyante de la mécanique respiratoire (balancement thoraco abdominal, trapping, tirage, …). Le raisonnement dans la pathologie respiratoire du nourrisson, de par ses spécificités physiologiques, ne peut être simplement extrapolé ni de la néonatologie, ni des enfants plus grands. Partant de ce constat clinique, nous avons proposé dans ce travail une approche physiopathologique pour répondre à différentes problématiques dans la prise en charge de ces nourrissons atteints de bronchiolite grave.

L'approche basée sur la physiologie nécessite une technicité et une expertise qui s'acquiert avec l'expérience. Dans les études réalisées, nous avons mis en œuvre un monitorage physiologique avancé et tenté de combiner différents indices et paramètres. L'avantage de cette approche est à la fois d'évaluer l'impact de l'intervention sur un effectif faible avec des critères de jugement objectifs mais aussi de tenter de décrypter la mécanique respiratoire et les caractéristiques de ces nourrissons et de proposer un mécanisme explicatif à l'effet observé.

La première stratégie évaluée était autour du positionnement de ces nourrissons au cours de leur prise en charge ventilatoire. Cette étude mettait en évidence un bénéfice « physiologique » au positionnement sur le ventre. Intuitivement, le décubitus ventral est à la fois une réponse à la pathologie obstructive, à l'atteinte alvéolaire et aux spécificités du nourrisson. L'effectif faible, la durée d'observation courte adaptée aux explorations physiologiques ne nous permet pas d'extrapoler vers un bénéfice clinique. D'autre part tous les enfants ne répondaient pas de manière homogène au décubitus ventral. En effet, 6 enfants

ne diminuaient pas leur effort respiratoire en ventral. D'après l'analyse réalisée en sous-groupe, il semblerait que ce soit la position dorsale qui, chez certains nourrissons, pourrait être défavorable pour la mécanique ventilatoire puisque les valeurs de PTP semblent s'homogénéiser en décubitus ventral.

La deuxième partie de ce doctorat s'intéressait à l'optimisation de la ventilation mécanique et l'utilisation de la NAVA dans la bronchiolite. Dans la chronologie de prise en charge, elle se situe en aval du travail précédent et concerne les enfants en échec de prise en charge de première ligne en nCPAP. La ventilation non invasive chez le nourrisson présentant une détresse respiratoire est un défi technologique et clinique. La fréquence respiratoire très élevée, la présence de fuites, les volumes courants très faibles (< 30ml) rendent la synchronisation patient-respirateur difficile. A cela s'ajoute les contraintes liées à la pathologie obstructive et la PEEP intrinsèque connues chez l'adulte pour augmenter le délai de déclenchement du respirateur [99, 146] et les efforts inefficaces [147, 148]. En pratique, les modes spontanés sont délaissés au profit des modes assistés-contrôlés ou intermittents [11] alors même qu'ils sont connus pour améliorer la synchronisation patient-respirateur chez l'adulte [149]. Dans ce contexte, la NAVA présente les avantages théoriques pour répondre à ces questions particulièrement dans cette population de nourrissons.

Dans deux travaux distincts nous avons montré que la NAVA permettait d'améliorer la synchronisation patient-respirateur et permettait de réduire encore (par rapport à la nCPAP) l'effort inspiratoire des nourrissons. Ce mode ventilatoire se place comme une alternative intéressante aux autres modes de ventilation et particulièrement en cas d'échec de nCPAP. Le bénéfice clinique doit être maintenant démontré avant de généraliser cette pratique à l'ensemble des nourrissons. Comme chez l'adulte, la NAVA peine à prouver son bénéfice sur des critères de jugement solides [150, 151]. La technologie est la combinaison d'un mode de synchronisation et d'une ventilation proportionnelle. Autant l'amélioration de la synchronisation a été démontrée largement, autant le bénéfice de la ventilation proportionnelle doit faire ses preuves surtout que la question du réglage du niveau optimal de support reste difficile [152] comme souligné par Rimensberger et al. dans leur article « The top ten unknowns in paediatric mechanical ventilation » [153]. Certains auteurs proposent d'utiliser cette technologie en « aide inspiratoire à trigger neural » c'est-à-dire en augmentant largement le niveau NAVA et en limitant les pressions [146, 154] permettant de garder le

bénéfice de la synchronisation sans être dépendant des réglages. Malgré ces limites, la NAVA apporte une réponse à une problématique jusque-là non résolue qu'est l'interaction patient-respirateur autorisant l'utilisation de deux niveaux de pression en ventilation non invasive.

2. REDUCTION DE L'INVASIVITE : QUEL BENEFICE ?

Les études présentées dans ce doctorat visaient toutes à optimiser la prise en charge non invasive des nourrissons. Malheureusement il n'existe pas de données solides montrant la supériorité de la VNI sur la ventilation invasive en dehors des études physiologiques [69]. L'analyse de la littérature selon la Cochrane en 2015 concluait dans ce sens : « l'effet de la nCPAP chez l'enfant atteint de bronchiolite est incertain du fait du faible nombre d'études disponibles » [155]. La question se pose donc de la pertinence de l'utilisation de ces prises en charge non invasives dans la bronchiolite grave.

Certaines études ont suggéré cependant un bénéfice de la VNI. Borckink et al. [156] retrouvaient dans un travail rétrospectif comparant deux réanimations pédiatriques, une réduction de la durée de ventilation (invasive et non invasive) dans le centre où les enfants bénéficiaient de nCPAP par rapport à une stratégie où seule la ventilation invasive était proposée. Dans un autre travail, l'équipe du Kremlin Bicêtre [157], avait montré sur un modèle avant-après que l'utilisation systématique de la nCPAP était associée à une réduction du recours à la ventilation invasive et permettait une réduction significative des durées de séjour et des coûts d'hospitalisation. Ces données ont été confortées par une étude en Australie et Nouvelle Zélande sur plus de 9000 nourrissons, qui mettait en évidence une réduction du taux d'intubation (de 36,8 à 10,8%), une diminution des durées de séjour avec en revanche une augmentation des coûts. L'hypothèse est celle d'une admission plus précoce de certains enfants [4] notamment pour bénéficier de haut débit nasal.

2.1. Comparaison d'une prise en charge invasive et non invasive

2.1.1. Introduction

De part cette littérature physiologique et les études rétrospectives montrant une réduction des intubations, la tendance en France est donc de favoriser l'utilisation de la ventilation non-invasive pour limiter la ventilation invasive et la morbidité associée [11, 69, 157]. Cette pratique n'est pas systématique notamment en Amérique du nord du fait de l'absence d'un niveau de preuve considéré comme suffisant [155]. Dans une évaluation sur la prise en charge des bronchiolites aux États-Unis, le taux d'utilisation de la VNI variait de 3 à 100% selon les

réanimations pédiatriques soulignant l'extrême variabilité des pratiques [5]. Nous avons mené une étude prospective observationnelle pendant l'hiver 2013/2014 sur deux centres : celui de Montréal au Canada et celui du Kremlin Bicêtre en France afin de comparer le devenir et les complications des patients admis dans chacune des réanimations. Notre hypothèse était que l'utilisation de la VNI n'était pas associée à un moins bon devenir malgré une stratégie moins agressive.

2.1.2. Article 5: "Variability of care in infants with severe bronchiolitis: less-invasive respiratory management leads to similar outcomes."

ORIGINAL ARTICLES

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Variability of Care in Infants with Severe Bronchiolitis: Less-Invasive Respiratory Management Leads to Similar Outcomes

Sandrine Essouri, MD, PhD[1,2], Florent Baudin, MD[3], Laurent Chevret, MD[2], Mélanie Vincent, MD[4], Guillaume Emeriaud, MD, PhD[1], and Philippe Jouvet, MD, PhD[1]

Objective To compare the management of children with severe bronchiolitis requiring intensive care (based on duration of ventilatory support and duration of pediatric intensive care unit [PICU] stay) in 2 countries with differing pediatric transport and PICU organizations.

Study design This was a prospective observational care study in 2 PICUs of tertiary care university hospitals, 1 in France and 1 in Canada. All children with bronchiolitis who required admission to the PICU between November 1, 2013, and March 31, 2014, were included.

Results A total of 194 children were included. Baseline characteristics and illness severity were similar at the 2 sites. There was a significant difference between centers in the use of invasive ventilation (3% in France vs 26% in Canada; $P < .0001$). The number of investigations performed from admission to emergency department presentation and during the PICU stay was significantly higher in Canada for both chest radiographs and blood tests ($P < .001$). The use of antibiotics was significantly higher in Canada both before (60% vs 28%; $P < .001$) and during (72% vs 33%; $P < .0001$) the PICU stay. The duration of ventilatory support, median length of stay, and rate of PICU readmission were similar in the 2 centers.

Conclusion Important differences in the management of children with severe bronchiolitis were observed during both prehospital transport and PICU treatment. Less invasive management resulted in similar outcomes with in fewer complications. *(J Pediatr 2017;188:156-62).*

Viral bronchiolitis is a major health care problem, affecting more than one-third of children aged <2 years, resulting in the hospitalization of nearly 3% of healthy infants in North America.[1] Bronchiolitis can manifest with a range of symptoms and severity, but the youngest infants are prone to developing acute respiratory failure (ARF). Among young infants, 3% may develop severe ARF, necessitating admission to the pediatric intensive care unit (PICU).[2] No clear criteria for PICU admission for severe bronchiolitis are defined in international guidelines, but these criteria are well recognized by physicians worldwide and involve the severity of the acute respiratory failure or recurrent apnea. Despite the availability of practice guidelines for management of mild or moderate bronchiolitis,[3,4] there is tremendous variation in the clinical management of severe viral bronchiolitis worldwide, including significant variation in the rate of intubation.[5,6]

In a prospective descriptive study of 379 patients with bronchiolitis hospitalized between 2007 and 2010 in 16 North-American PICUs, Mansbach et al[7] reported an intubation rate of 40%.[7] Most descriptive studies from Europe have reported lower rates of intubation during the same period.[8] Children receiving mechanical ventilation represent only 2.3% of hospitalized patients with viral bronchiolitis, but account for 18% of the total annual costs related to bronchiolitis.[1] Variations in supportive care begin in the prehospitalization period and persist through the PICU stay. In France, the pediatric transport team, which includes an intensivist, usually manages bronchiolitis with noninvasive ventilatory support (using a nasal or oral interface) and avoids intubation to limit invasiveness.[9] Moreover, first-line ventilatory support in PICUs is most often noninvasive in European centers, with only 12% of infants receiving invasive ventilation as first-line ventilatory support.[8]

A trend toward less-invasive management using nasal continuous positive airway pressure (nCPAP) has been shown to be associated with a low rate of intubation, decreases in the median duration of ventilatory support and length of PICU stay,[10] reductions in diagnostic testing and resource use, and cost reductions.[10]

We performed a bicentric prospective study (1 center in France and 1 center in Canada) to compare the management of children with bronchiolitis admitted to the PICU in the 2 centers. Our primary hypothesis was that management of severe viral bronchiolitis with less-invasive ventilation (defined as a difference

ARF	Acute respiratory failure
HFNC	High-flow nasal cannula
nCPAP	Nasal continuous positive airway pressure
PICU	Pediatric intensive care unit
RSV	Respiratory syncytial virus

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of ≥10% in the rate of invasive ventilation) is associated with a similar outcome on duration of ventilatory support and length of PICU stay. The frequency of additional testing and treatments (eg, antibiotics, blood tests, chest radiography) were evaluated as secondary outcomes.

Methods

We performed a prospective bicentric observational study at 1 French center and 1 Canadian center. The Canadian patients were recruited from the PICU of Centre Hospitalier Universitaire (CHU) Sainte Justine in Montréal, a tertiary care center with 24 specialized pediatric beds and 900-1000 admissions annually. The French patients, were recruited from the PICU of CHU Kremlin Bicêtre (France), a tertiary care center with 20 specialized pediatric beds and more than 800 admissions annually. No specific intervention was introduced during the study.

Patients were included prospectively between November 1, 2013, and March 31, 2014. All patients admitted to the 2 PICUs were screened. Inclusion criteria were age 0-2 years and a clinical diagnosis of viral bronchiolitis requiring any ventilatory support, including nCPAP, bilevel pressure noninvasive ventilation, high-flow nasal cannula, and invasive ventilation. Owing to the observational study design that included all PICU-admitted infants with bronchiolitis, there were no exclusion criteria.

Patient encounters were identified as specific daily screenings performed by a research assistant. The study was approved by the Ethics Committee of CHU Sainte Justine (no. 3817) with a waiver of consent.

Data were collected prospectively from the electronic medical record at CHU Sainte Justine and from the standard medical record at CHU Kremlin-Bicêtre. All therapeutic interventions were performed at the discretion of the PICU providers. The following data were collected: age, sex, weight, and gestational age at birth. Underlying disease, such as congenital heart disease, bronchopulmonary dysplasia, and prematurity, were recorded. Time between emergency department consultation and PICU admission, and transfer mode (eg, French medical transport team, paramedics, intrahospital admission) were recorded.

Disease severity was assessed before the initiation of ventilatory support using clinical scores; the Wood score modified for bronchiolitis, as used in previous studies on bronchiolitis[11]; the Pediatric Risk of Mortality[12]; and objective physiological measurements: respiratory rate, heart rate, pulse oximetry, capillary or venous partial pressure of carbon dioxide, fraction of inspired oxygen, and pulmonary abnormalities on chest radiographs.

Before PICU admission, nonventilatory treatments, such as use of antibiotics, corticosteroids, epinephrine, or beta-2 agonist nebulization and caffeine, were recorded.

Characteristics of respiratory support provided during the PICU stay were recorded: noninvasive ventilation mode and settings, type of interface, intubation rate, duration of ventilatory support (invasive alone, noninvasive alone, and noninvasive + invasive) and PICU length of stay. Data collected during the PICU stay included the use of antibiotics (oral or intravenous), sedation (oral or intravenous), enteral feeding, central line access, and the blood tests and chest radiographs performed.

Healthcare-associated adverse events were recorded: diagnosis of ventilator-associated pneumonia based on Centers for Disease Control and Prevention criteria,[13] pneumothorax, need for transfusion, and acute upper airway obstruction.

Statistical Analyses

With 52 patients in each group (the French and Canadian PICUs), there was a 0.8 chance of detecting a significant difference at a 2-sided 0.05 significance level. This assumed a 10% absolute difference in the endotracheal intubation rate between the 2 groups. This sample size corresponds to 1 season of respiratory syncytial virus (RSV) bronchiolitis in the 2 PICUs.

Baseline and demographic data are expressed as number or percentage for binary or ordinary data, and means for continuous data. Continuous data with a nonnormal distribution are expressed as median and range. Continuous data were compared using the Wilcoxon test; dichotomous data, using the Fisher exact test.

All tests were 2-tailed, with a P values of ≤.05 considered statistically significant. Statistical analyses were conducted using SPSS software (SPSS Inc, Chicago, Illinois).

Results

Data for all children who met our inclusion criteria were collected. The 194 children included 137 patients in the French center (center 1) and 57 patients in the Canadian center (center 2). The number of admitted patients was comparable in the 2 centers when considering the hospital catchment populations. In center 1, the hospital catchment population per PICU was 2 396 000, of which the patients admitted for bronchiolitis represented 0.57% (iledefrance.fr). In center 2, the hospital catchment population per PICU was 943 240, of which the patients admitted for bronchiolitis represented 0.6% (Statistics Canada 2012).

Baseline patient characteristics are reported in **Table I**. The mean age of patients admitted for severe bronchiolitis requiring ventilatory support was similar in the 2 centers (55 ± 59 days in center 1 and 63 ± 63 days in center 2) and comparable with that reported in other studies of severe bronchiolitis necessitating PICU admission. The clinical severity of patients was similar in the 2 centers, with a slightly higher Wood score in center 1 (4.2 ± 0.7 vs 3.8 ± 0.6; $P = .012$), but similar values for PCO_2, the most objective variables assessed. The number of patients with medical comorbidities was similar in the 2 centers, with 43 patients (31.3%) in center 1 and 18 (31.5%) in center 2. Specific conditions are detailed in **Table I**. There was a significant difference between the 2 centers in the admissions of patients with cardiopathy, related to the fact that the Canadian center offers pediatric cardiac surgery, whereas the French center does not.

Delays between first consultation in the emergency department and admission to the PICU were similar in the 2 centers.

Table I. Demographic characteristics of patients

Clinical characteristics	Center 1 (n = 137)	Center 2 (n = 57)	*P* value
Age (days), mean (SD)	55 ± 59	63 ± 63	.4
Male sex n (%)	79 (57.7)	35 (61.4)	.44
Weight (g), mean (SD)	4650 ± 3517	4844 ± 1352	.6
Gestational age (weeks), median [range]	39 [25-41]	39 [34-41]	.46
Prematurity, n (%)	36 (31.3)	12 (21)	.52
RSV confirmed, n (%)	96 (70)	44 (77)	.5
PCO_2 prior to admission (mmHg), mean (SD)	62 ± 13	62 ± 12	.8
mWood score, mean (SD)	4.2 ± 0.7	3.8 ± 0.6	.012
PRISM score, median [range]	5 [4-9]	5 [5-6]	.65
Comorbidities			
Prematurity n (%)	36 (31.3)	12 (21)	.98
Down Syndrome n (%)	1 (0.7)	1 (1.7)	.52
Cardiopathy n (%)	1 (0.7)	5 (8.7)	.003
Bronchopulmonary dysplasia n (%)	2 (14.5)	0	.36

mWood score, the modified Wood score for bronchiolitis; *PCO_2*, capnia level; *PRISM*, Pediatric Risk of Mortality.

In both centers, the largest percentages of children were admitted to the PICU within the first 12 hours of consultation (36% in center 1 and 39% in center 2). The respective percentages of subsequent admissions were 17% and 16% between 12 and 24 hours, 20% and 18% between 24 and 48 hours, and 27% and 27% after 48 hours.

There was a significant difference in the use of invasive ventilation at the 2 sites (3% for center 1 vs 26% for center 2; $P < .0001$. Respiratory management is summarized in **Table II** (available at www.jpeds.com).

In the French center (center 1), nCPAP was the first ventilatory mode used. Invasive ventilation was used in only 4 patients, of whom 1 was intubated for transport and 3 were intubated after failure of nCPAP (**Figure**, A). Two of these latter 3 patients had a coexisting condition, 1 with a double aortic arch and 1 with group B streptococcal meningitis. The third was older (168 days) and presented with RSV infection with severe bronchospasm.

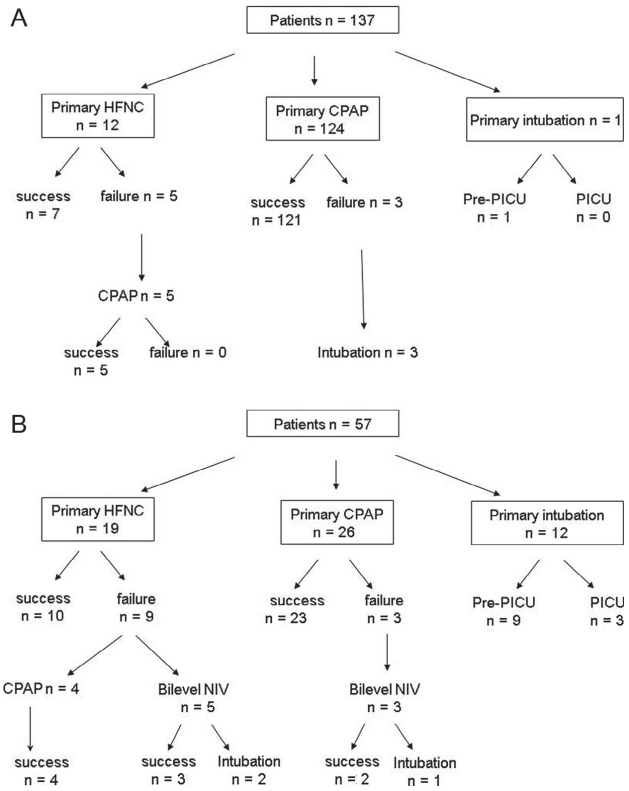

Figure. Ventilatory management of patients with severe bronchiolitis admitted to the PICUs in France (**A,** center 1) and Canada (**B,** center 2). Four patients (3%) in center 1 and 15 patients (26%) in center 2 required tracheal intubation.

Table III. General management before and during the PICU stay

General management	Center 1 (n = 137)	Center 2 (n = 57)	*P* value
Before PICU admission			
Antibiotics, n (%)	38 (27.7)	34 (59.6)	<.001
Corticosteroid, n (%)	17 (10.8)	3 (5.2)	.17
Salbutamol nebulization, n (%)	22 (16)	21 (36.8)	<.001
Epinephrine nebulization, n (%)	5 (3.6)	25 (43.8)	<.001
Oral caffeine, n (%)	27 (19.7)	2 (3.5)	.004
During PICU stay			
Antibiotics, n (%)	45 (32.8)	41 (71.9)	<.001
Blood tests, n, median [range]	1 [1-11]	13 [2-55]	<.001
Chest radiographs, median [range]	1 [0-3]	4 [1-20]	<.001
Central venous catheter, n (%)	1 (0.7)	9 (15.5)	<.001
Intravenous sedation (%)	4 (3)	14 (24.5)	<.001

Table VI. Patient outcomes

Patient outcomes	Center 1 (n = 137)	Center 2 (n = 57)	*P* value
Ventilator-associated pneumonia, n (%)	0	9 (15.5)	<.001
Adult respiratory distress syndrome, n (%)	0	1 (1.8)	.3
Air leak, n	0	0	
Laryngeal postextubation stenosis, n (%)	0	3 (5.1)	.024
PICU length of stay, d, median [range]	4 [1-14]	4 [1-16]	.13
PICU readmission, n (%)	4 (2.9)	3 (5.1)	.4

In the Canadian center (center 2), 15 patients were intubated, 9 before PICU admission (**Figure**, B). For these 9 patients, reasons for intubation included preparation for transport (6 cases) and severity of respiratory failure (3 cases). Of the 6 patients who were intubated in the PICU, 3 received noninvasive respiratory support before intubation (for 1, 3, and 17 hours) and were intubated because of a lack of improvement, and the other 3 were intubated without previous noninvasive support. A high-flow nasal cannula (HFNC) was used more frequently as the first ventilatory support in the Canadian center. The HFNC failure rate was similar at both sites. In cases of HFNC failure, nCPAP was performed in the French PICU without failure, but was not performed in the Canadian PICU.

The use of chest radiography and blood tests before PICU admission and during the PICU stay was significantly higher in center 2 (**Table III**). The number of investigations was significantly associated with the type of ventilatory support in the center 2, but not in center 1 (**Table IV**; available at www.jpeds.com). In the patients who needed invasive support, there was a significant difference between the 2 centers in the number of investigations performed, but not in medication use, before PICU admission (**Table V**; available at www.jpeds.com). Patients with comorbidities were not managed more aggressively in either center. One patient with a comorbidity was intubated in center 1, and 4 patients with comorbidities were intubated in center 2. The median number of chest radiographs in patients with comorbidities compared with other patients was 1 (range, 1-3) vs 1 (range, 1-2) ($P = .98$) in center 1 and 3.5 (range, 1-11) vs 4 (range, 1-20) ($P = .96$) in center 2. For the number of blood tests, we observed the same pattern, with a median of 2 (range, 1-11) vs 2 (range, 1-5) ($P = .78$) in center 1 and 14 (range, 5-41) vs 13 (range, 2-55) ($P = .72$) in center 2.

The use of antibiotics was significantly less frequent before and during the PICU stay in center 1. Use of the intravenous route for antibiotic administration also was significantly less frequent in center 1 (43% vs 81%; $P < .001$). Oral caffeine was used more frequently in center 1 (27% vs 5%). Corticosteroid use was similar in the 2 sites both before and during the PICU stay. Feeding was provided exclusively by the enteral route at both sites using either orogastric or oroduodenal tubes.

The use of nebulized salbutamol was lower in center 1 both before admission (16% vs 37%; $P < .001$) and during the PICU stay (11% vs 44%; $P < .01$). Sedation was used in both centers to ensure comfort and ventilation tolerance. Intravenous sedation was less frequent in center 1 (**Table III**). Central line placement was required for 1 patient in center 1, but in 9 patients in center 2 (**Table III**).

No deaths occurred at either site. The median length of stay was similar in the 2 sites, as was readmission to PICU within 48 hours after discharge. The occurrence of ventilator-associated pneumonia, acute respiratory distress syndrome, pneumothorax, and postintubation laryngeal injury is presented in **Table VI**. There were significantly fewer adverse events in center 1. Postintubation laryngeal injury occurred in 3 patients, all of whom required bronchoscopy and laser intervention. In these 3 patients, intubation was performed before PICU admission.

Discussion

The optimal management of severe viral bronchiolitis remains a matter of debate, with significant variation in the management of patients requiring intensive care, as noted in previous studies.[14] The recent recommendations from the American Academy of Pediatrics,[15] the Canadian Paediatric Society, and the National Institute for Health and Care Excellence highlight the positive impact of reducing diagnostic testing, medications, and interventions in the management of standard viral bronchiolitis.[3,16] Our prospective observational study shows that less-invasive management is not associated with longer duration of ventilatory support or longer length of PICU stay, even in the most severe cases of viral bronchiolitis. Moreover, this study shows a trend toward fewer adverse events and fewer care requirements when less-invasive management is provided. Much work has been done on the underuse and the misuse of care, and there is now movement toward advocating for "safely doing less",[4,17,18] but there is a relative paucity of data on overtreatment in the specific population with the most severe form of bronchiolitis requiring PICU admission. The available data seem to show that in this population, noninvasive ventilation is associated with decreased duration of ventilatory support and length of PICU stay.[10,19,20] Nevertheless, overtreatment represents a major quality problem in medicine and one of the main

sources of waste in health care expenditures.[21] Overtreatment is defined as care that, according to science, has no benefit, including excessive use of antibiotics, blood tests, and radiographic exams. Berwick et al[21] estimated that in 2011, this category represented between $158 and $226 billion in wasteful spending in the US.

Supportive care remains the mainstay of treatment for patients with the most severe form of bronchiolitis. Our data demonstrate a broad variability in care between sites despite similar demographic characteristics, medical history, and disease severity. This variability in ICU patient care was recently noted by Pierce et al[14] in a multicenter study including 16 US PICUs, and was not explained by patient characteristics or severity of illness. Our study confirms this variability and shows that these differences occur all along the course of patient management, starting before PICU admission and continuing during the PICU stay. We observed a large variation in the use of bronchodilators (either salbutamol, used more frequently in France, or epinephrine, used more frequently in Canada). These therapeutics were administered at the clinician's discretion, but neither is recommended by international guidelines. In the French center, oral caffeine was used for apnea-associated bronchiolitis based on its effectiveness in the central apnea of prematurity but a recent randomized controlled study failed to demonstrate any advantage of the use of oral caffeine for apnea associated with bronchiolitis.[22]

One of the main differences between the 2 PICUs was the use of noninvasive ventilation as the primary ventilatory support. This difference was due mainly to differences in prehospital management. In France, a specific pediatric medical transport team is available 24 hours a day/7 days a week with trained physicians and nurses who can initiate and manage nCPAP during transport. All patients in the French center except 1 were transported with noninvasive support, with no failures occurring during transport. In Quebec, prehospital transportation is performed by caregivers with little training in noninvasive ventilation; thus, a large proportion of out-of-hospital patients (6/9) were intubated electively for transport. These differences in capabilities are responsible for the significant difference in standard management in the 2 countries. Several descriptive studies have demonstrated the safety of noninvasive support (HFNC or CPAP) during interhospital ground transportation of neonates and infants,[9,23-25] but this support is mainly provided by transport teams including physicians and/or respiratory therapists. In the present study, the delay between the initial consultation at the primary care hospital and PICU admission was similar in both centers, and thus it cannot be argued that invasive ventilation during transport was safer because of the distance between the primary care center and the PICU. Our results show that in the Canadian center exclusively, intubated patients were subjected to a higher number of chest radiographs and blood tests.

Noninvasive ventilation has been shown to effectively decrease the work of breathing and improve alveolar ventilation. Although there is a lack of large randomized controlled trials to support the use of nCPAP as a first-line therapy, nCPAP is widely used as a primary ventilation mode for bronchiolitis, and large historical studies have confirmed its low failure rate and association with significant decreases in intubation rates.[10,26,27] In our study, criteria for noninvasive ventilation failure were not defined, but were at the discretion of the team of care providers; however, the main criteria were lack of improvement and lack of CO_2 clearance. CPAP and HFNC require special equipment and properly trained staff. The lack of guidelines for physicians regarding the initiation of noninvasive ventilation and the characteristics of children most likely to benefit are of great importance.

In this comparable, severely ill population, variability in care was also observed in the use of antibiotics. The low risk of bacterial coinfections in patients with RSV infection has been reported previously, and investigators have recommended decreasing the use of antibiotics for bronchiolitis.[28,29] In our study, we observed a significant variation in antibiotic use both before PICU admission and during the PICU stay. The increased use of antibiotics perhaps can be explained by differing perceptions of disease severity with the fear of a bacterial coinfection in severe bronchiolitis. Guidelines for the diagnosis and management of mild or moderate bronchiolitis recommend reduced use of chest radiography and blood tests. Use of chest radiography and blood tests should be considered individually for most severely affected patients. In the present study, the numbers of chest radiographs and blood tests during the PICU stay differed significantly between the 2 sites. This variability cannot be explained by patient characteristics or severity of the illness, which were similar at the 2 centers. One major difference between the 2 centers is in the management of children by a more experienced senior physician, including a night shift, in the French center, but by a resident and a fellow supervised by a senior physician in the Canadian center. Intense blood monitoring of PICU-admitted patients in the Canadian center because of the combined pediatric and cardiac surgery units could be another factor influencing this observed difference.

Furthermore, the increased use of invasive ventilation explains the higher numbers of chest radiographs and blood tests at least partially, but not completely, as shown by the similar numbers of these tests performed in patients with either invasive or noninvasive ventilation in the French center, but significantly different numbers in the Canadian center. This study supports the observation that the security of patients is not proportional to the number of investigations performed.

Our study suggests that decreased use of invasive ventilation, medications, chest radiography, and blood tests is not associated with worse outcomes, as demonstrated by the similar duration of ventilatory support, similar length of PICU stay, and similar level of readmission. Differences in hospital-associated pneumonia and laryngeal injury likely are related to the differences in management of invasive ventilation. All patients requiring a procedure for laryngeal injury were intubated before PICU admission; consequently, we can hypothesize that intubation by less-experienced staff is more deleterious for these infants. Other practice differences, such as the use of intravenous sedation and central venous lines, also may be associated with the use of invasive ventilation.

Ralston et al[30-32] proposed an approach to measuring overuse of care using the Achievable Benchmarks of Care, a systematic method for decreasing the uncertainty in defining overuse. Bronchiolitis is one of the most common pediatric pathologies, with abundant literature from which quality metrics can be derived to better define overuse. Defining and measuring actions to treat patients is important, as is defining and measuring restraint of action. For the most severe cases of bronchiolitis, our findings indicate no difference in adverse outcomes with decreased use of medications, chest radiography, and blood testing. These results are promising and could motivate future interventional studies to validate less-invasive but secure approaches. Publication of the American Academy of Pediatrics' evidence-based guidelines for bronchiolitis was associated with significant reductions in diagnostic testing and medication use for non–critically ill children with bronchiolitis.[33] The development of evidence-based guidelines for critically ill children may be associated with reduced variability in care and unnecessary costs.

Our study has several limitations. The use of only 2 centers could affect the power and external generalizability of our results; nonetheless, our cohort represents a large number of cases of severe bronchiolitis in 2 large cities. The limited number of intubations did not allow us to assess the association between invasive ventilation and comorbidities. The impact of pre-PICU management seems relevant, but the small number of intubated patients and the absence of matching weakens the results. The organization of care is different in the 2 countries, which could influence the use of testing for patient monitoring; however, both PICUs had at least a fellow trained in pediatric intensive care in-house, and the caregiver staff per patient ratio is higher in North America compared with Europe.[34] Criteria for PICU admission and site-specific resources may differ across countries, which might have contributed to the difference in the number of severe bronchiolitis cases admitted to the 2 PICUs, recruitment was representative of the hospitals' catchment populations. The Wood score modified for bronchiolitis can provide a subjective evaluation of the intensity of retractions, which explain differences observed between scores by centers. All individuals involved in the management of these children were aware of these scores, but interrater reliability was not examined in this study. Nonetheless, delays between the initial consultation and PICU admission were similar in the 2 groups, as were other baseline patient characteristics, including CO_2 level, the most objective variable recorded.

This 2-center prospective observational study of children with bronchiolitis predominantly due to RSV and requiring ventilatory support and PICU care suggests that less-invasive management, not related to differences in illness severity or patient characteristics, was not associated with less favorable outcomes. Pre-PICU intubation seems to be largely responsible for the incidence of mechanical ventilation in our study, and the benefit of noninvasive support (HFNC or CPAP) during PICU retrieval needs to be addressed in future studies. Our observations provide evidence that, if validated in prospective randomized studies, which could lead to the development of guidelines for this specific population, with the goal of ensuring the best outcomes for infants and children with severe bronchiolitis while decreasing unnecessary resource utilization. ■

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Table II. Respiratory management according to center

Respiratory management	Center 1 (n = 137)	Center 2 (n = 57)	*P* value
Endotracheal Intubation, n (%)	4 (3)	15 (26)	<.0001
Primary HFNC, n (%)	12 (8.7)	19 (33.3)	<.01
Primary CPAP, n (%)	124 (90.5)	26 (45.6)	<.001
HFNC failure, n (%)	5 (41.6)	9 (47.3)	.77
CPAP failure, n (%)	3 (2.1)	3 (11.5)	.002
Length of intubation, hours, median [range]	4.5 [2-144]	84 [17-312]	.06
Length CPAP, hours, median [IQR]	48 [24-96]	33 [20-52]	.04
Length of ventilation, hours, median [IQR]	50 [36-96]	57 [30-84]	.41

CPAP, Continuous Positive Airway Pressure.

Table IV. Differences in management according to ventilatory support

	Center 1			Center 2		
Management	Noninvasive ventilation (n = 133)	Intubation (n = 4)	*P* value	Noninvasive ventilation (n = 42)	Intubation (n = 15)	*P* value
Antibiotics, n (%)	43 (32)	2 (50)	.58	27 (64)	14 (93)	.005
Blood tests, n, median (range)	2 (1-5)	2 (2-11)	.32	9.5 (2-41)	16 (13-55)	.009
Chest radiographs, n, median (range)	1 (1-2)	1 (1-3)	.41	3.5 (1-7)	9 (3-16)	.0003
Central venous line, n (%)	0 (0)	1 (25)	.39	2 (5)	7 (46)	.007
Intravenous sedation, n (%)	1 (7.5)	3 (75)	.06	0 (0)	14 (93)	<.0001

Table V. Differences in management of patients with invasive ventilation according to center

	Center 1 (n = 4)	Center 2 (n = 15)	*P* value
Before PICU admission			
Antibiotics, n (%)	1 (25)	9 (60)	.24
Corticosteroid, n (%)	1 (25)	1 (6.6)	.34
Salbutamol nebulization, n (%)	1 (25)	5 (33.3)	.8
Epinephrine nebulization, n (%)	0 (0)	5 (33.3)	.21
Oral caffeine, n (%)	1 (25)	0 (0)	.07
During PICU stay			
Antibiotics, n (%)	2 (50)	14 (93.3)	.23
Blood tests, n, median (range)	2 (2-11)	16 (13-55)	.002
Chest radiographs, n, median (range)	1 (1-3)	9 (3-20)	.003
Central venous catheter, n (%)	1 (25)	7 (46.6)	.48
Intravenous sedation, n (%)	3 (75)	14 (93.3)	.34

2.1.3. Résultats et Discussion

Dans ce travail prospectif, cent quatre-vingt-quatorze enfants ont été inclus dans l'étude (137 en France et 57 au Canada) avec des caractéristiques à l'admission comparables entre les deux centres. Le recours à la ventilation invasive était significativement plus important au Canada (26%) par rapport à la France (3%, p<0.001), en revanche les durées médianes [Range] de séjour en réanimation étaient comparables 4 [1-14] vs. 4 [1-16] jours, p =0.13. Nous avons noté une différence dans le nombre d'examens paracliniques réalisés au Canada avec une médiane [Range] de 4 radios [1-20] contre 1 [0-3] en France, p<0.01 et une médiane de 13 gaz du sang [2-55] contre 1 [1-11] en France, p< 0.01. Le taux de complication était significativement plus élevé à Montréal avec plus de pneumopathies acquises sous ventilation mécanique et plus de sténoses laryngées.

Cette étude permet d'illustrer deux stratégies de prise en charge qui dépendent à la fois des pratiques et convictions mais également des contraintes locales dans chacun des deux pays (notamment l'absence de médicalisation pré-hospitalière et des durées de transport très importantes au Canada).

2.2. Quel bénéfice à long terme ?

La bronchiolite est devenue une pathologie avec une mortalité quasiment nulle dans les pays industrialisés. Dans le travail précédent, nous avons démontré qu'une prise en charge moins invasive n'était pas associée à un moins bon devenir (à court terme) et réduisait significativement les examens réalisés et certaines complications. L'évaluation à moyen et long terme de nos prises en charge semble nécessaire. Dans une étude rétrospective, analysant plus de 13000 nourrissons à partir de deux bases de données aux États-Unis, Shein et al. [158] démontraient que la morbidité neurologique chez les nourrissons atteints de bronchiolite était loin d'être négligeable. Au-delà de la morbidité immédiate en sortie de réanimation, les auteurs décrivaient que 2,1% des nourrissons avaient développé un retard du développement psychomoteur, 1,6% avaient bénéficié d'une IRM à distance et 1,2% avaient été suivis par un neuropédiatre. Même si cette étude présentait de nombreuses limites en lien avec l'analyse d'une base de données (étude rétrospective, recueil non-exhaustif, biais de confusion), elle posait la question du devenir à long terme de ces patients et de « l'outcome » à utiliser dans les études sur la prise en charge des bronchiolites (Cf. éditorial). Un autre paramètre extrêmement important dans leur analyse multivariée était que

la ventilation mécanique invasive était le seul facteur de risque indépendant associé à la morbidité neurologique (odds ratio 1.92; 95% CI [1.59–2.32] and odds ratio 1.33; 95% CI [1.13–1.56] dans chacune des deux bases de données).

Viral Bronchiolitis in PICUs: Looking Further Than the Acute Phase!*

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Acute viral bronchiolitis (AVB) is the leading cause of acute respiratory distress and is a serious global public health problem, not because of mortality but rather by the sheer number of children infected and requiring hospitalization in all developed countries (1, 2).

In this issue of *Pediatric Critical Care Medicine*, Shein et al (3) have analyzed data from two large U.S. databases (virtual PICU system [VPS] and public health information system) and report that among 13,267 children admitted to a PICU for AVB, about 15% (18.6% and 11.1%, respectively) presented a neurologic and functional morbidity (NFM) at least at the PICU discharge. NFM was assessed using the Pediatric Overall Performance Category (POPC) score (4) at discharge in the VPS database. The use of such a score has some limitations, the main one being the retrospective analysis of a subjective score especially for infants, and may overestimate the neurologic impairment at PICU discharge (in almost all cases, the POPC score increased by only 1 point). However, Shein et al (3) also analyzed a second database that contained information on more precise criteria, such as enteral feeding, rehabilitation, and neurologic evaluation in the subsequent encounter that were used to define NFM. Although enteral feeding and rehabilitation may be directly related to the management of children with AVB, the 2.1% of children with developmental delay or the 1.6% requiring brain MRI is a more concerning issue. Furthermore, as demonstrated for other diseases with early brain injury, neurologic and functional impairment may escape early detection in infants and children (5, 6), and furthermore, injury age, environmental conditions, and injury factors may also influence the outcome (7). Cognitive and especially executive functions should therefore be assessed at school age and sometimes later when the child has to face with more complex reasoning process (8). Despite these limitations, the burden of neurologic morbidity of bronchiolitis seems not to be anecdotal, and NFM should be prospectively evaluated to better explore the consequences of AVB and care given on the neurologic prognosis.

The respiratory syncytial virus is known to have neurologic toxicity (9), which has been reported to be responsible for impaired learning in mice (10); however, Shein et al (3) found that invasive mechanical ventilation was the main independent risk factor of NFM in the two databases (odds ratio [OR], 1.92; 95% CI [1.59–2.32] and OR, 1.33; 95% CI [1.13–1.56], respectively). Mechanical ventilation plays a central role in the care of children with severe bronchiolitis and therefore what is the relation between NFM and mechanical ventilation? At first sight, it is evident that the more severe patients (who are also those requiring mechanical ventilation) are more at risk of NFM, although in the study reported by Shein et al (3), there was no significant difference in severity between ventilated and nonventilated patients (at least on the basis of the Pediatric Index of Mortality 2 score (11): 0.75% vs. 0.78%; $p = 0.175$). The authors propose several hypotheses for the causal relationship between mechanical ventilation and NFM, including the toxicity of sedative drugs and hypoxemia. This raises the issue of less invasive management for these children using noninvasive ventilation or high-flow nasal cannula (HFNC). It is of note that the use of invasive ventilation for bronchiolitis is heterogeneous (2, 12), ranging from 0% to 100% according to the PICU in the United States (2), and that studies evaluating the use of less invasive management (nasal continuous positive airway pressure, noninvasive ventilation, or HFNC) for children in or outside the PICU has increased significantly in the past few years (13). Interestingly, recent studies report that noninvasive ventilation was associated with a shorter duration of ventilatory support (14) and an eight-fold reduction (24.5% vs 3%; $p < 0.001$) in the use of IV sedation (12) and may even reduced mortality (15). However, although on the one hand noninvasive management decreases the use of sedative drugs and adverse events due to intubation, on the other hand it may expose children to more frequent hypercarbia or hypoxic events that are also triggers of NFM. Therefore, in the absence of any obvious solution, the key to the evaluation of such strategies may lie in the long-term neurologic prognosis of the millions of children admitted for bronchiolitis every year to PICUs the worldwide.

In conclusion, the study reported by Shein et al (3) should lead us to consider bronchiolitis as a disease with low mortality but potential neurologic long-term morbidity and suggests that outcomes beyond any short-term benefit of a treatment are of interest for future investigations.

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*See also p. 1106.

Key Words: cognition disorders; mechanical ventilation; morbidity; noninvasive ventilation; pediatric intensive care unit; viral bronchiolitis

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3. QUESTIONS NON RESOLUES ET PERSPECTIVES

3.1. Au cours du décubitus ventral

3.1.1. Répondeurs et non-répondeurs

Certains enfants sont considérés comme non répondeurs au DV selon notre définition (PTP œsophagien égal ou supérieur en DV qu'en DD). Il n'a pas été possible dans cette étude de retrouver des facteurs cliniques (radiographie, âge, …) permettant d'identifier les nourrissons répondeurs des non répondeurs. Même si les résultats de l'analyse en sous-groupe suggèrent que la différence se fait en décubitus dorsal (sous-entendant que le travail respiratoire pourrait être le même en DV chez tous les enfants et augmenté en décubitus dorsal chez certains), il serait intéressant de pouvoir identifier ces groupes de patients *à priori*.

3.1.2. Mécanismes sous-jacents

Dans l'étude bronchio-DV nous avons étudié le couplage électromécanique du diaphragme qui semble amélioré en décubitus ventral et l'activité tonique du diaphragme (activité électrique encore présente en fin d'expiration) qui est significativement plus basse en décubitus ventral. Cette activité peut jouer un rôle dans le maintien de la CRF ou dans le freinage diaphragmatique au cours de l'expiration. Malheureusement, il n'a pas été possible d'évaluer de manière fiable la différence de la PEEP intrinsèque entre les deux positions. Nous avons vu précédemment que cette activité tonique était présente chez le nouveau-né et « réactivée » dans les pathologies obstructives [51]. La combinaison de différents indices et notamment la répartition de la ventilation pourrait permettre de décrypter les mécanismes responsables de cette activité tonique. Une estimation de la répartition de la ventilation peut être accessible de manière totalement non invasive grâce à la tomographie par impédance électrique (EIT). L'application de courants alternatifs de faible intensité à partir d'électrodes disposées de manière circonférentielle sur le thorax permet de générer en temps réel une image qui est dépendante de la composition tissulaire (principalement influencée par l'aération du tissus pulmonaire). A partir de cette technique, certains travaux chez le prématuré suggèrent que la distribution de la ventilation ne serait pas dépendante de la gravité [159] et que les modifications de la distribution de la ventilation après changement de position serait surtout un mécanisme immédiat plus lié à la mobilisation qu'à la position en

elle-même [160]. Il serait très intéressant de pouvoir documenter la distribution de la ventilation chez le nourrisson atteint de bronchiolite grave grâce à l'EIT ce qui permettrait d'évaluer si l'activité tonique est influencée par le volume de fin d'expiration. Il n'existe pas actuellement de dispositif commercial accessible à l'enfant. La société Löwenstein médical (Igny, France) développerait actuellement un système avec une ceinture thoracique adaptée au nouveau-né.

3.1.3. Bénéfice clinique

Les bénéfices physiologiques ne sont pas suffisants pour juger de l'efficacité clinique d'une intervention. Nous avons proposé une étude multicentrique comparant le décubitus ventral au décubitus dorsal sur le recours à la ventilation invasive ou non-invasive chez le nourrisson atteint de bronchiolite grave sous haut débit nasal.

Cette étude se positionnera en amont des réanimations. Les résultats de l'étude Bronchio-DV (amélioration de la mécanique respiratoire) nous laissent supposer que le bénéfice pourrait concerner des enfants avec d'autres supports ventilatoires. D'autre part, de plus en plus de nourrissons sont placés sous haut débit nasal qui est une interface moins encombrante plus souple et présente moins de contraintes et de risques de déplacement lors du positionnement sur le ventre. Cette stratégie permettrait aussi de répondre à un problème majeur de santé publique en autorisant le maintien de certains enfants en unité de surveillance continue dans des hôpitaux de proximité. Le protocole (ANNEXE 2) a été accepté pour un financement en PHRC interrégional et devrait inclure 420 nourrissons.

3.2. Au cours de la NAVA

3.2.1. Le diaphragme n'est pas le seul muscle de la respiration

Le principe de la NAVA est d'utiliser le diaphragme comme muscle principal de la respiration. La NAVA autorise le patient à déclencher le respirateur soit sur son activité neurale (EAdi) soit sur son activité pneumatique (pression). Dans la littérature on retrouve qu'environ 20 à 30% des cycles sont déclenchés sur le signal en pression. Plusieurs hypothèses ont été générées et notamment un effet « indésirable » du traitement de l'activité électrique cardiaque qui pourrait soustraire une partie de l'activité électrique diaphragmatique. Un travail préliminaire

en ventilation invasive, réalisé à Montréal, avait montré que la diminution de la Peso survenait avant l'EAdi dans 15% des cas et pouvait correspondre à la soustraction de l'activité cardiaque (Nuncio-Naud et al. Abstract SRLF 2015). Nous disposons avec l'étude Bronchio-DV de plusieurs heures d'enregistrement et nous avons observé sur certaines séquences que la diminution de la pression œsophagienne survenait en amont du début de l'activité électrique diaphragmatique (Figure 14). Une autre hypothèse serait que les muscles accessoires puissent devancer le diaphragme au cours de la bronchiolite où il existe parfois une asynchronie thoraco-abdominale et une activité expiratoire persistante du diaphragme.

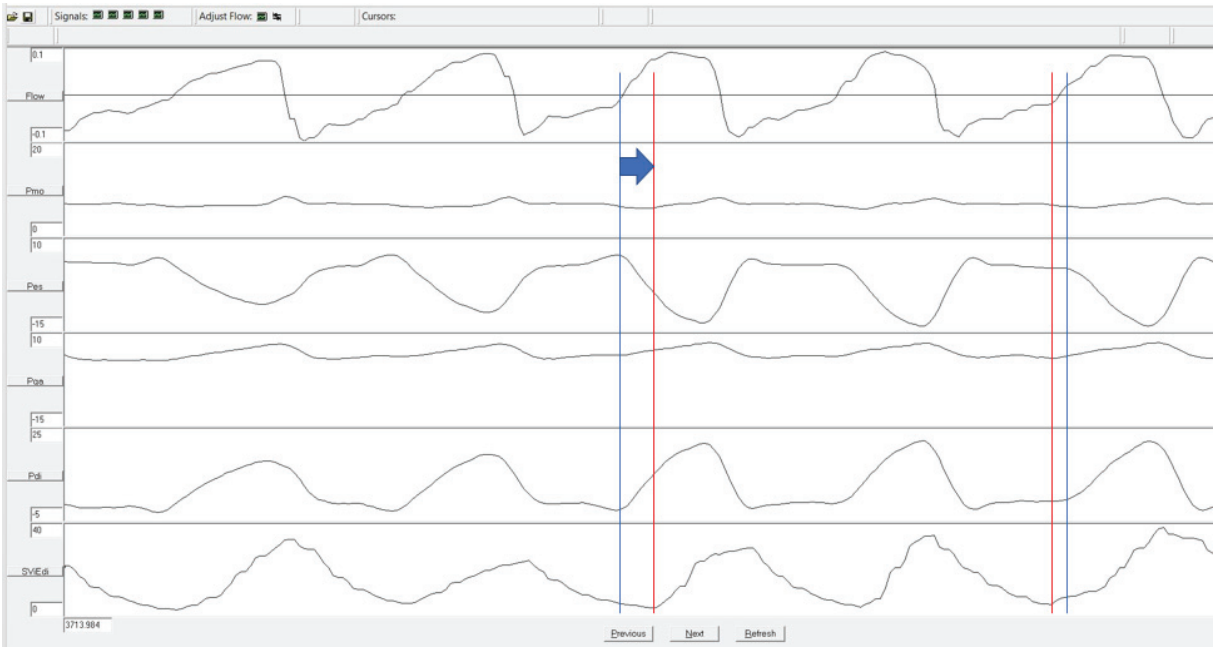

Figure 14 : Exemple de décalage entre le signal électrique diaphragmatique, le signal de pression œsophagien (flèche bleue).

En rouge début du cycle neural. En bleu début du cycle pneumatique.

On peut supposer que dans le cas présenté ci-dessus le trigger pneumatique puisse prendre le pas sur le trigger neural et n'engendre pas ou peu de conséquences pour le patient. Ce phénomène reste rare mais mériterait d'être exploré pour définir s'il s'agit d'une anomalie dans le traitement du signal ou d'un mécanisme propre au nourrisson en détresse respiratoire.

3.2.2. Bénéfice clinique

La NAVA présente donc un intérêt théorique au cours de la bronchiolite. Elle réduit l'effort respiratoire en comparaison à la nCPAP et améliore la synchronisation en comparaison à d'autres modes de ventilation à deux niveaux de pression. Cependant, le coût généré par cette

technologie n'est pas négligeable en raison de l'utilisation d'un respirateur dédié et d'une sonde à usage unique (environ 200€/patient). Dans notre service la NAVA est utilisée en 2ème intention en cas d'échec de la nCPAP, voire en échec des autres modes de ventilation non invasive. Il serait souhaitable d'évaluer l'impact de la NAVA soit précocement en alternative de la nCPAP pour prévenir l'épuisement, en prenant en compte le surcoût généré par la technologie, soit en 2ème intention chez des patients non répondeurs à la nCPAP.

3.2.3. NAVA dans d'autres pathologies

Avec l'expérience acquise dans la prise en charge des bronchiolites nous avons pu élargir le champ d'application et nous avons actuellement en collaboration avec le service de néonatologie une évaluation de la NAVA dans le sevrage ventilatoire des patients opérés de hernie congénitale diaphragmatique (NAVA-DIAPH clinicaltrial.gov NCT03250793). En effet, des travaux sur la NAVA montrent que la ventilation conventionnelle génère le plus souvent une sur-assistance qui « éteint » l'activité électrique diaphragmatique [103]. Au cours de la hernie diaphragmatique, il est évident que le sevrage passe par le reconditionnement diaphragmatique. La synchronisation patient-respirateur en néonatologie revêt les mêmes caractéristiques que pour nos nourrissons. La NAVA pourrait, à la fois par une meilleure synchronisation et par la délivrance d'une assistance proportionnelle, trouver sa place dans le sevrage ventilatoire de ces patients.

4. PERSPECTIVES DANS L'ASTHME

4.1. Introduction

Se basant sur la même approche, nous avons proposé d'évaluer le haut débit nasal dans l'exacerbation sévère d'asthme. La pathologie asthmatique est extrêmement fréquente avec une prévalence de 10% chez l'enfant [161] et représente un nombre important de séjours hospitaliers et en réanimation. L'exacerbation d'asthme est une crise inhabituelle en raison d'une obstruction bronchique sévère pouvant mettre en jeu le pronostic vital. Il s'agit d'un bronchospasme qui ne répond pas aux thérapeutiques habituelles. L'obstruction est la résultante de trois phénomènes immuno-médiés : la bronchoconstriction, l'œdème de la muqueuse respiratoire et l'hyperproduction de mucus. La prise en charge des exacerbations sévères repose sur l'oxygénothérapie et l'administration de béta-2-mimétiques. Dans les recommandations communes de la SRLF et de la SFMU (associée au GFRUP) publiées en 2018, l'utilisation de la VNI et du haut débit nasal ne pouvait être recommandée en l'absence d'un niveau de preuve suffisant. Le haut débit nasal permettrait de répondre à un certain nombre de mécanismes physiopathologiques en cause dans l'exacerbation d'asthme (en diminuant l'hyperréactivité bronchique et la production de mucus par l'administration d'un air réchauffé et humidifié et en diminuant l'effort inspiratoire par l'effet « PEEP » [162] [58]). Il présente l'intérêt de permettre la réalisation des aérosols sans changer d'interface ce qui pourrait améliorer la tolérance [21] et diminuer l'agitation et l'anxiété chez les jeunes enfants. Dans une étude rétrospective nous avons décrit son utilisation dans le service de réanimation pédiatrique de l'hôpital Femme Mère Enfant et démontré sa faisabilité chez trente-neuf enfants même pour des formes sévères avec acidoses hypercapniques.

4.2. Article 6 : Faisabilité du haut débit nasal dans l'exacerbation d'asthme chez l'enfant

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RESEARCH ARTICLE Open Access

Nasal high flow in management of children with status asthmaticus: a retrospective observational study

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Abstract

Background: Asthma is the most common obstructive airway disease in children and adults. Nasal high flow (NHF) is a recent device that is now used as a primary support for respiratory distress. Several studies have reported use of NHF as a respiratory support in status asthmaticus; however, there are no data to recommend such practice. We therefore conducted this preliminary study to evaluate NHF therapy for children with status asthmaticus admitted to our PICU in order to prepare a multicentre randomized controlled study.

Results: Between November 2009 and January 2014, 73 patients with status asthmaticus were admitted to the PICU, of whom 39 (53%) were treated with NHF and among these 10 (26%) presented severe acidosis at admission (pH < 7.30). Thirty-four less severe children (41%) were treated with standard oxygen. For one child (2.6%) NHF failed and was then switched to non-invasive ventilation. NHF was discontinued in another patient because of the occurrence of pneumothorax after 31 h with NHF; the patient was then switched to standard oxygen therapy. Mean ± SD heart rate (165 ± 21 vs. 141 ± 25/min, $p < 0.01$) and respiratory rate (40 ± 13 vs. 31 ± 8/min, $p < 0.01$) decreased significantly, and blood gas improved in the first 24 h. In the subgroup of patients with acidosis, median [IQR] pH increased significantly between hour 0 and 2 (7.25 [7.21–7.26] vs. 7.30 [7.27–7.33], $p = 0.009$) and median [IQR] pCO_2 decreased significantly (7.27 kPa [6.84–7.91 vs. 5.85 kPa [5.56–6.11], $p = 0.007$). No patient was intubated.

Conclusion: This retrospective study showed the feasibility and safety of NHF in children with severe asthma. Blood gas and clinical parameters were significantly improved during the first 24 h. NHF failed in only two patients, and none required invasive ventilation.

Keywords: Asthma, Children, High-flow nasal cannula, Non-invasive ventilation, Paediatric intensive care unit

Background

Asthma is the most common obstructive airway disease in children and adults. Approximately 334 million people around the world and 2.5 million people in France suffer from asthma [1], a third of whom are children [1, 2], and the prevalence of asthma in this subpopulation has increased in recent decades [2]. Supplemental oxygen is commonly administered to children with an asthma exacerbation in the emergency department or intensive care unit in association with beta 2 agonist nebulization [3–5]. Non-invasive ventilation (NIV) may be used as respiratory support in children with status asthmaticus in case of standard treatment failure [6–9]. However, the level of evidence of its efficacy remains low according to the grade system of evidence quality [10].

Nasal high flow (NHF) is a recent device, now used as a primary support for respiratory distress in paediatric and adult intensive care units and in emergency departments [11–16]. It is increasingly used because it is well tolerated [11, 12, 17, 18] especially in infants with bronchiolitis [11, 17, 18]. NHF delivers humidified and heated gas at a rate greater than inspiratory flow [14, 19]. It reduces

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anatomical dead space by flushing the nasopharyngeal cavity and may improve CO_2 clearance. It also provides a certain level of positive end-expiratory pressure (PEEP), between 2 and 7 cm H_2O, depending on the flow rate used [14, 19–22] that may reduce resistance. In children with status asthmaticus, external PEEP may decrease work of breathing [23] based on the "waterfalls" principle published by Tobin and Lodato [24]. HFNC may also reduce the metabolic cost of breathing by supplying adequately warmed and humidified gas. Similarly, in infants with severe bronchiolitis, Milesi et al. demonstrated that HFNC significantly reduced work of breathing, respiratory rate, and Ti/Ttot ratio [25]. By increasing the expiratory time, HFNC may decrease dynamic hyperinflation in patients with obstructive lung disease and break the vicious circle.

There are, however, very few data reported NHF as a primary respiratory support for status asthmaticus, even though some studies have reported its use in the emergency department or intensive care unit in children [11, 12, 15, 16, 26, 27] as in adult patients [28, 29]. Over the previous five years NHF has been commonly used for children admitted to our PICU for acute respiratory failure (ARF) including patients with lower airway obstruction (bronchiolitis or asthma). We therefore conducted this preliminary study to evaluate NHF therapy for children admitted to our PICU with status asthmaticus in order to prepare a multicentre randomized controlled study.

Methods

Study design

We conducted a retrospective observational study in a 23-bed PICU of a tertiary university hospital (Hôpital Femme Mère Enfant, Lyon University Hospital, France). Children aged between 1 and 18 years, without severe comorbidities, admitted between November 2009 and January 2014 to the PICU, and with a diagnosis of status asthmaticus were included. The study was approved by our institutional review board and a waiver of consent given (CPP Sud-Est II N°00009118—2016-08).

Population

Patients were identified in the French hospital information system (PMSI) and the PICU database by using the primary diagnosis of status asthmaticus (International Classification of Diseases—ICD 10 code J46) or ARF associated with asthma (ICD 10 J96.0/J45). Based on the local protocol and French recommendations [5], children were admitted to the PICU after at least 1 h in the emergency department during which they did not response to standard therapy, based on at least three successive beta agonist nebulizations, supplemental oxygen, and oral or intravenous corticosteroids at 2 mg/kg.

In PICU, respiratory support (oxygen, HFNC, NIV, or invasive ventilation—IV) and additional therapy (intravenous salbutamol, magnesium sulphate) were left to the physician's judgment. Patients with severe comorbidities were excluded: cardiopulmonary disease, neuromuscular or metabolic disease, restrictive or chronic respiratory disease (pulmonary fibrosis, cystic fibrosis, bronchodysplasia), ENT disease (laryngo- or tracheo- or broncho-malacia) or children with tracheotomy. For NHF, Optiflow RT330 (Fisher & Paykel Healthcare, Auckland, New Zealand) circuit and nasal prong adapted to the age and the size of the nose were used. The nebulizer system (Aerogen, Inc., Mountain View, CA, USA) was inserted upstream from the electrically heated humidifier [30–32].

Data and outcome

Data were retrospectively collected using the electronic medical record IntelliSpace Critical Care and Anesthesia (Philips Healthcare, Suresnes, France). A patient was attributed to only one group (NHF or standard oxygen), and in case of multiple stays during the period, only the first one was analysed. The primary outcome was defined as failure of the NHF therapy and described as a proportion of all children with asthma having received NHF therapy. The secondary outcome was the change of clinical parameters (respiratory rate, heart rate, SpO_2/FiO_2 ratio) from NHF initiation to 6, 12, 24, and 48 h later, as well as blood gas parameters in children treated with NHF.

Baseline characteristics of the population (age, weight, comorbidity, history of asthma) were collected at admission and compared to those of the standard oxygen group. Data on the medication used before and during PICU stay, and the duration of NHF use and of supplemental oxygen therapy, and length of PICU stay were also collected. Safety of HFNC treatment was assessed by the number of patients with air-leak complications and by the tolerance of the system according to nurse reports. A subgroup analysis of children with severe acidosis treated with NHF was also performed.

Statistical analysis

Qualitative variables are reported as numbers and percentages, and quantitative variables are reported as mean ± standard deviation (SD) or confidence intervals, or as median with interquartile range [IQR], when appropriate. Chi-square test or Fisher's exact test for qualitative variables and Mann–Whitney U test for nonparametric independent sample were used to compare the data between NHF and standard oxygen groups, when appropriate. Repeated-measures analysis of variance (ANOVA) was used to compare clinical variables over time. The assumption of sphericity was tested using Mauchly's test

of sphericity; if sphericity was violated epsilon (ε) was calculated according to Greenhouse and Geisser and used to correct the one-way repeated-measures ANOVA [33]. Post hoc analysis was performed with a Bonferroni adjustment. Wilcoxon signed-rank test was used for non-parametric paired samples. Differences were considered statistically significant at $p < 0.05$. Statistical analysis was performed using SPSS Statistics (V22, IBM, Armonk, NY, US).

Results

Between November 2009 and January 2014, 91 children with diagnosis of status asthmaticus were admitted in our PICU. Sixteen children were excluded because of the presence of severe comorbidities and one because the primary diagnosis was hypoxemic pneumonia. Among the 73 children admitted for status asthmaticus, 39 (53%) were treated with NHF and 30 (41%) received only standard supplemental oxygen therapy (16 with non-rebreathing mask and 14 with standard nasal cannula, Fig. 1). The proportion of children treated by standard oxygen and NHF in each year of the study period was similar ($p = 0.66$) (Fig. 2). A further two children were intubated before admission to PICU (for transport): one was treated with NIV, and one was admitted in the PICU more than 24 h after starting NHF in an intermediate care unit outside of the university hospital (Fig. 1). The median [IQR] age of children treated with NHF was 3.6 years [1.6–5.6], which was similar to that of children treated with standard oxygen (3.6 [2.2–6.7]; $p = 0.72$). All

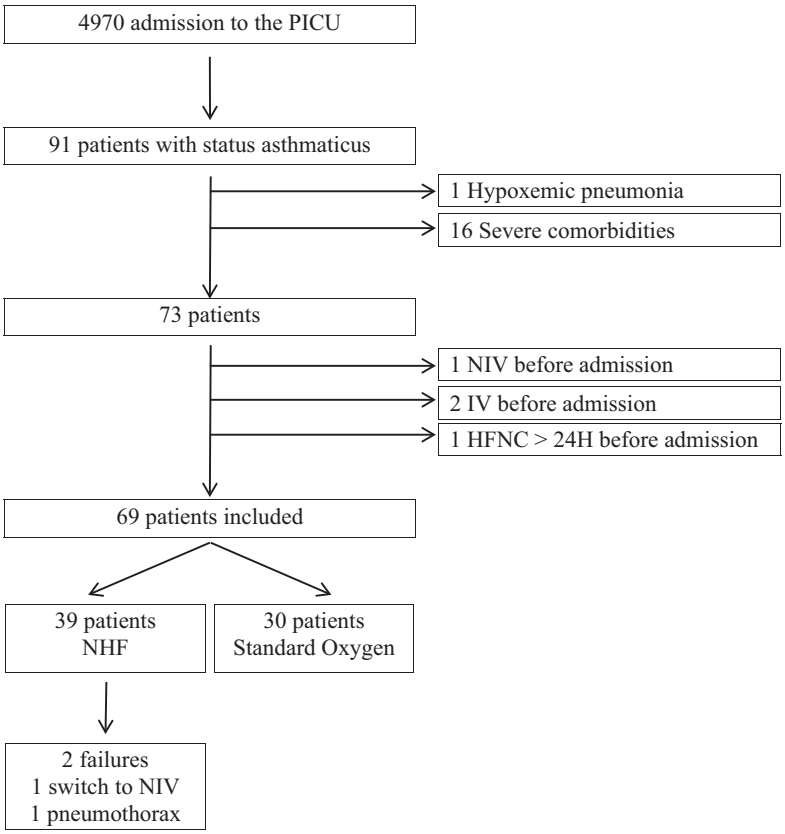

Fig. 1 Patient flow chart. *PICU* paediatric intensive care unit, *NHF* nasal high flow, *NIV* non-invasive ventilation, *IV* invasive ventilation

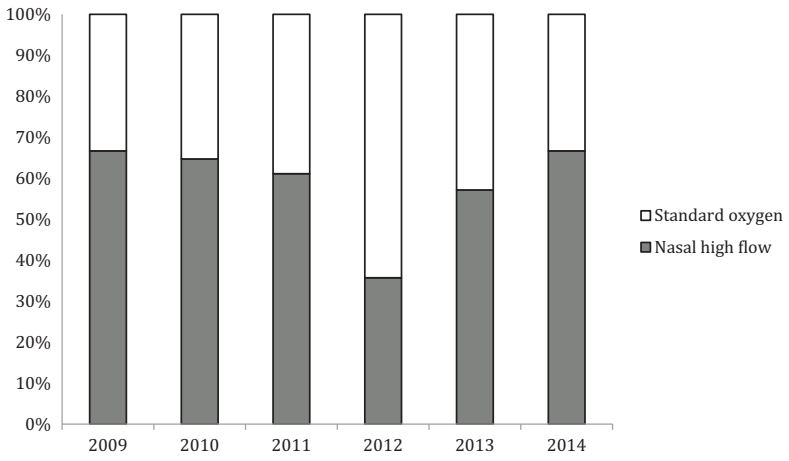

Fig. 2 Proportion of children treated by nasal high flow and standard oxygen from 2009 to 2014 ($p = 0.66$ with Fisher's exact test). *NHF* nasal high flow

children in the two groups received nebulized salbutamol and corticosteroids (intravenous corticosteroid for 79% in NHF and 63% in standard oxygen group). Continuous intravenous salbutamol was used in 13 children (33%) in the NHF group and in 5 (17%); $p = 0.12$. Magnesium sulphate was more often used in the NHF group (59%) than in standard oxygen group (27%, $p = 0.007$; Table 1).

The median [IQR] flow of NHF was initially set at 0.9 L/kg/min [0.75–1] with a median [IQR] FiO_2 of 45% [31–55] (Table 2). NHF failed in only two children. One child required NIV because of worsening blood gas parameters in the first 24 h. NHF was discontinued in another patient because of the occurrence of pneumothorax. The pneumothorax occurred after 31 h with NHF (X-ray at admission without pneumothorax) and requiring chest tube for 24 h. The maximum NHF was 1 L/kg/min. NHF was discontinued and standard oxygen therapy was administered at 0.5 L/min for 22 h. No patient was intubated. The median [IQR] length of NHF treatment was 28 h [21–47], and the median PICU length of stay was 3 days [2.5–5].

Change of heart rate (HR) and respiratory rate (RR) during the first 24 h are presented in Fig. 3. The assumption of sphericity was violated for HR ($p = 0.016$), and a Greenhouse–Geisser correction was applied ($\varepsilon = 0.82$). HR decreased significantly over time $F(2.47, 91.41) = 22.77$, $p < 0.001$, partial $\eta 2 = 0.38$, as did RR $F(3, 111) = 8.65$, $p = 0.001$, partial $\eta 2 = 0.19$. Pairwise post hoc analysis found that mean ± SD HR and RR were significantly lower at hour 24 (141 ± 25 per min and 31 ± 8 per min, respectively) than at hour 0 (165 ± 21 per min, $p < 0.01$ and 40 ± 13 per min, $p < 0.01$). HR was also lower at hour 24 (141 ± 25 per min) than at hour 12 (155 ± 22 per min, $p < 0.01$) and at hour 6 (161 ± 22 per min, $p < 0.01$). For SpO_2/FiO_2 ratio the assumption of sphericity was also violated ($p < 0.01$) and a correction was applied ($\varepsilon = 0.33$). SpO_2/FiO_2 ratio changed significantly over time $F(2.1, 67.0) = 19.7$, $p < 0.001$, partial $\eta 2 = 0.38$. SpO_2/FiO_2 ratio was higher at hour 24 (359 ± 116) than at hour 12 (298 ± 104, $p < 0.01$), at hour 6 (277 ± 116, $p < 0.01$), and at hour 0 (225 ± 81, $p < 0.01$); it was also higher at hour 12 (298 ± 104) than at hour 0 (225 ± 81, $p < 0.01$; Fig. 3). Blood gas (pH and PCO_2) improved in the first 24 h for children treated with NHF (Table 3). Blood gas parameters were available at day 1 for only half of patients treated with standard oxygen ($n = 15$); the median [IQR] pH was 7.41 [7.38–7.42]; and pCO2 was 4.6 kPa [4.2–4.7].

Ten patients treated with NHF (6 boys and 4 girls), who had a median [IQR] age of 3.7 years [2.1–4.4], had at severe acidosis at admission (pH < 7.30). In this subgroup, median [IQR] pH increased significantly between hour 0 (7.25 [7.21–7.26]) and hour 2 (7.30 [7.27–7.33], $p = 0.009$), and pCO_2 decreased significantly (hour 0: 7.27 kPa [6.84–7.91], hour 2: 5.85 [5.56–6.11], $p = 0.007$; Fig. 4). In the patient who failed in the first 24 h (discontinuous line in Fig. 4), blood gases worsened from hour 0

Table 1 Baseline characteristics of children treated with nasal high flow and with standard oxygen therapy for status asthmaticus

	NHF $n = 39$	Standard oxygen $n = 30$	p*
Age (years), median [IQR]	3.6 [1.6–5.6]	3.6 [2.2–6.7]	0.72
Male/female ratio	20/19	21/9	0.11
Weight (kg), median [IQR]	15 [11–24]	15 [13–23]	0.64
PIM2 at admission, median [IQR]	1.5 [1.15–3.3]	1 [0.3–1.37]	<0.001
History of asthma or >2 bronchiolitis, *n* (%)	31 (80)	23 (77)	0.79
Previous admission for asthma, *n* (%)	19 (48)	11 (37)	0.31
In PICU, *n* (%)	4 (10)	2 (6)	0.66
Long-term control medicine, *n* (%)	17 (44)	14 (47)	0.80
Clinical parameters at admission, median [IQR]			
Respiratory rate (/min)	35 [31–47]	35 [30–43]	0.47
Heart rate (/min)	164 [154–185]	168 [153–180]	0.89
SpO_2 (%)	97 [95–98]	98 [97–100]	0.04
SpO_2/FiO_2	216 [175–303]	NA	
Venous blood gas at admission, median [IQR]			
pH	7.35 [7.28–7.39]	7.36 [7.34–7.39]	0.27
pCO_2 (kPa)	5.6 [4.7–7.7]	4.9 [4.4–5.6]	0.02
Bicarbonates (mmol/L)	22 [20–24]	20 [20–23]	0.35
Acidosis (pH < 7.30), *n* (%)	10 (26%)	2 (7%)	0.04
Associated medication, *n* (%)			
Salbutamol—nebulized	39 (100%)	30 (100%)	1.0
Corticosteroids—intravenous[a]	31 (79%)	19 (63%)	0.14
Salbutamol—intravenous	13 (33%)	5 (17%)	0.12
Magnesium sulphate	23 (59%)	8 (27%)	0.007
PICU LOS (days), median [IQR]	3 [2.5–5]	1.5 [1, 2]	<0.001

LOS length of stay, *PIM* Paediatric Index of Mortality, *PICU* paediatric intensive care unit, *NHF* nasal high flow

* Statistical analysis with Chi-square test for qualitative variables or Mann–Whitney *U* test for nonparametric independent sample

[a] All other children received oral corticosteroids

Table 2 Nasal high flow (NHF) parameters of 39 children treated for status asthmaticus

	$n = 39$
NHF settings, median [IQR]	
Initial FiO_2 (%)	45 [31–55]
Initial flow (L/kg/min)	0.9 [0.75–1]
Maximum flow (L/kg/min)	1.0 [0.8–1.1]
Length of NHF (h), median [IQR]	28 [21–47]
NHF failure, *n* (%)	2 (6)

PICU paediatric intensive care unit, *NHF* nasal high flow

to hour 2; the child was switched to non-invasive ventilation with success (Fig. 1).

Discussion

The present study is the largest report to have evaluated the use of NHF as a primary respiratory support for severe status asthmaticus. It showed the feasibility and the safety of management of children with status asthmaticus with NHF; NHF failed in only one patient, and blood gas and clinical parameters were significantly improved during the first 24 h.

During the study period, 39 children were treated with NHF and 30 with standard oxygen. The demographic data were similar in terms of age, weight, and medical history. However, NHF was used according to the physician's judgment (as was the use of additional therapy) and those who received standard oxygen seemed to be less severe at admission (lower PIM2 score, lower pCO_2 values, and less frequently had acidosis) although clinical parameters (heart and respiratory rate) were similar. Another marker of severity is the administration of magnesium sulphate that, in our PICU, is recommended as a second-line therapy before the use of intravenous salbutamol and this was used twice less frequently in the standard oxygen group. Furthermore, the length of PICU stay was also longer in the NHF group, but is of note that both NHF had to be discontinued and nebulization to be scheduled less than

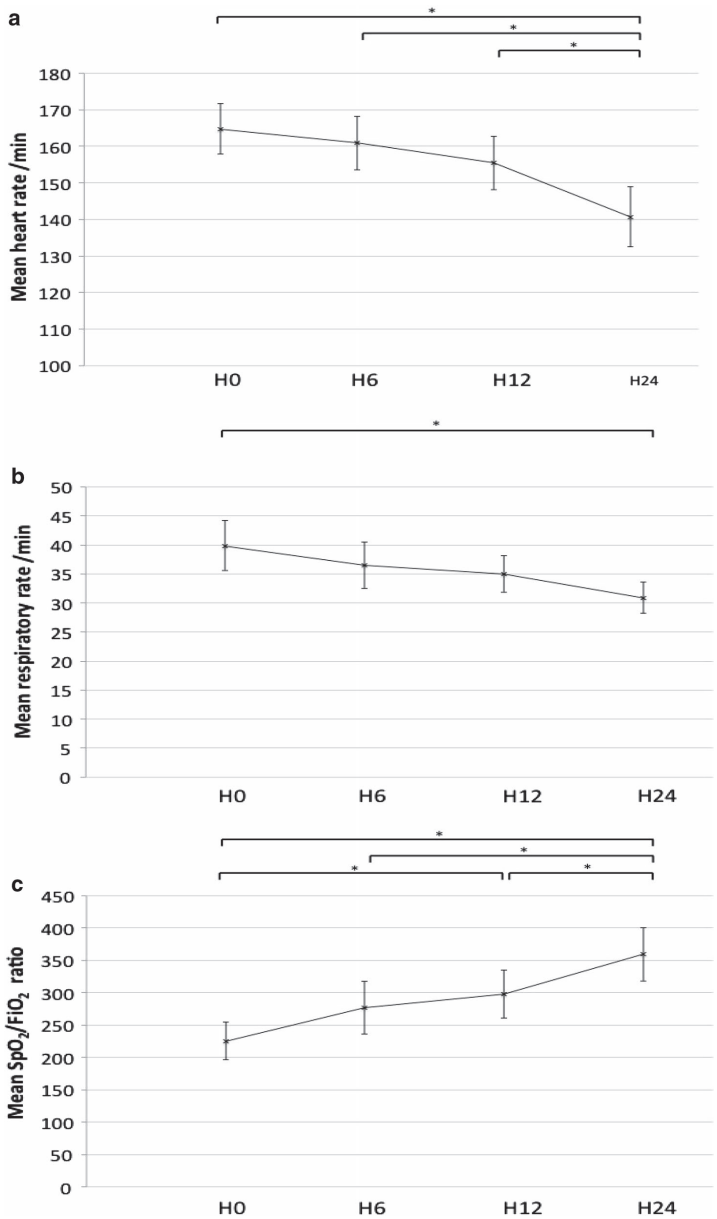

Fig. 3 Change of heart rate (**a**), respiratory rate (**b**), and SpO_2/FiO_2 ratio (**c**) during the first 24 h in 38 children with status asthmaticus treated by nasal high flow. Heart rate, respiratory rate, and SpO_2/FiO_2 ratio significantly change over time according to the repeated-measures analysis of variance (ANOVA). *Significant difference with pairwise post hoc analysis ($p < 0.01$). *Bars* indicate 95% confidence intervals. *H* hours

Table 3 Change of blood gas parameters between hour 0 and 24 in children treated with nasal high flow for status asthmaticus

	Hour 0 $n = 39$	Hour 24 $n = 37$[a]	p
Venous blood gas, median [IQR]			
pH	7.35 [7.28–7.39]	7.42 [7.39–7.44]	$p < 0.001$
pCO_2 (kPa)	5.6 [4.7–7.7]	4.3 [4.0–4.8]	$p < 0.001$
Bicarbonates (mmol/L)	22 [20–24]	21 [19–22]	$p = 0.16$

[a] Nasal high flow failed for one patient during the first 24 h, and one patient had no blood gas at day 1

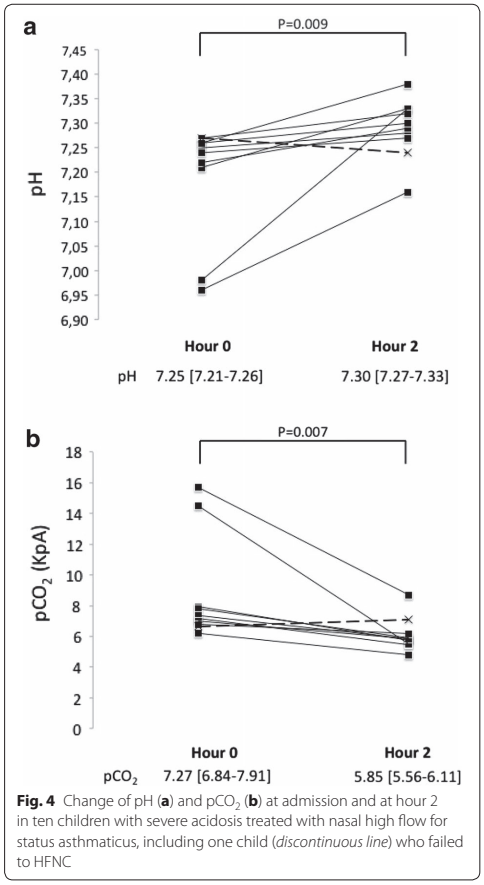

Fig. 4 Change of pH (**a**) and pCO_2 (**b**) at admission and at hour 2 in ten children with severe acidosis treated with nasal high flow for status asthmaticus, including one child (*discontinuous line*) who failed to HFNC

every 3 h for patients to be discharged. These differences preclude any strong conclusions as to the superiority of one technique over the other, which is coherent with the nature of this preliminary retrospective study. It is of note that no patient was intubated (in either group) and only one required NIV. Furthermore, clinical parameters (heart rate and respiratory rate) improved over time with NHF as did blood gas values, even in children with severe acidosis. These results are strengthened by the efforts made to reduce bias related to patient identification and missing data that affect many other retrospective studies. This was limited herein by the use of status asthmaticus and ARF associated with asthma diagnosis codes, and electronic medical records with automatic importation of clinical and biological parameters every 5 min. However, improvement of the physiological parameters may also be due to the normal change over time and more robust conclusions will be made from the results of the multicentre randomized controlled trial that will be implemented later this year.

The place of NHF in the management of ARF is controversial. Several physiological studies have supported that NIV relieves better work of breathing than continuous positive airway pressure [34, 35] and therefore that it is better than NHF [18]. However, the most recent studies in adults suggest either superiority of NHF over conventional oxygen [36], or equivalence [37] and even superiority over NIV [38]. Pulmonary function may be affected by emotion and stress [39, 40], and tolerance to NHF is better than NIV, both in adults [41, 42] and in children [18, 43], and may explain in part the benefit of NHF. It was not possible to assess comfort of children retrospectively. After analysis of nurse report forms, no notable discomfort was reported, and in particular no skin lesions. Clinical improvement observed with NHF in the present study was similar to that previously reported with NIV in children [7], and no patient was intubated. However, although the use of NIV for status asthmaticus in children [6, 7, 9, 44, 45] is common, the level of evidence remains limited [10]. Furthermore, in adults, the Cochrane review published in 2012 found that NIV did not provide additional benefit to medical treatment [46]. At this time, the use of NHF in the most severe asthmatic patients may not be recommended as current guidelines indicate that intubation should never be delayed [47], even though the benefit of NHF in this subgroup was particularly demonstrative and rapid herein. On the other hand, using NHF to treat all children with mild asthma would lead to increase costs but not the benefits. Therefore, it would be of great interest to define the population who would most benefit from NHF, for which the preschool respiratory assessment measure (PRAM) [48] could be of interest. In our PICU, NHF is currently used as the primary respiratory support for children with moderate-to-severe asthma, defined by an acidosis (pH < 7.35) or a PRAM score >7 after optimal care in the

emergency department. For severe patients, a senior physician systematically evaluates children at 1 h and blood gases are measured after 2 h of use to ensure an early detection of patients who do not improve.

NHF allows the delivery of nebulized drugs (i.e. beta agonists) continuously and without changing the interface [30–32, 49, 50] as during NIV. Recent studies suggest greater efficacy of vibrating mesh nebulizers over jet nebulizers [30, 31]. The former was used in association with NHF, and a jet nebulizer was used for children treated with standard oxygen, which further complicates interpretation of the results. More generally, delivery of beta agonist with NHF is heterogeneous and depends on several aspects. According to the manufacturer recommendations and recent studies [30–32], the nebulization system was placed upstream from the active heated humidifier that seems to provide better effectiveness. The gas flow rate is probably the main parameter to take into account the delivery of nebulization drugs. A recent study showed that in infants and toddlers, increasing the flow rate by fourfold decreases tenfold the proportion of lung deposition [32]. For asthma patients, it is necessary to weigh the benefit/risk ratio of a higher flow with higher respiratory support but probably with a decrease of drug delivery. In the present study, the median flow rate was 0.9 L/kg/min [0.75–1] that remains relatively low for paediatric patient [14]. A lower flow rate may participate to a better nebulization drug delivery and a better tolerance in children, older than patient with bronchiolitis.

In conclusion, this study shows that NHF is feasible in children with status asthmaticus, may improve physiological parameters, and prevent the use of subsequent therapeutic steps. Based on these results, a multicentre randomized controlled study will start later this year to evaluate whether early management with NHF may prevent failure in comparison with conventional oxygen (and therefore escalation to NIV or IV) in patients with moderate-to-severe asthma defined as an acidosis (pH < 7.35) or a PRAM score >7 after optimal care in the emergency department.

Abbreviations

ANOVA: analysis of variance; ARF: acute respiratory failure; NHF: nasal high flow; HR: heart rate; ICD: International Classification of Diseases; IQR: interquartile range; IV: invasive ventilation; NIV: non-invasive ventilation; PEEP: positive end-expiratory pressure; PICU: paediatric intensive care unit; RR: respiratory rate; SD: standard deviation.

Authors' contributions

EJ, AB, RP, BM, and EJ participated in the design of the study. FB, AB, and BV collected and analysed the data. FB and EJ drafted the manuscript. BV, RP, and BM reviewed and improved the manuscript. All authors read and approved the final manuscript.

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Competing interests

Dr. Baudin has received speaking fees from Maquet Critical Care. The others authors have no competing interests.

Availability of data and materials

According to the French National Data Protection Commission, we are not authorized to provide the data.

Ethics approval

The study was approved by our institutional review board (CPP Sud-Est II N°00009118—2016-08).

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Le bénéfice clinique est maintenant en cours d'évaluation dans une étude multicentrique française (clinicaltrial.gov NCT03157102) ayant bénéficié d'un financement par un PHRC national évaluant le haut débit nasal par rapport à une prise en charge standard par oxygénothérapie (ANNEXE 3).

V. CONCLUSION

A la lumière de la morbidité associée à la ventilation invasive, il semble légitime de chercher toutes les stratégies visant à prévenir l'épuisement respiratoire chez les nourrissons atteints de bronchiolite comme chez les enfants présentant une exacerbation d'asthme.

Le décubitus ventral permet de réduire encore l'effort inspiratoire chez les nourrissons atteints de bronchiolite grave sous ventilation non-invasive. Cette thérapeutique facilement réalisable chez le nourrisson, a déjà montré son bénéfice dans d'autres populations et semble pleinement justifiée dans une approche purement physiopathologique.

La nCPAP est devenue le mode ventilatoire de référence en ventilation non invasive en raison de sa simplicité. Dans notre unité, environ 20% des nourrissons sont considérés comme en échec de nCPAP et bénéficient d'un support ventilatoire avec deux niveaux de pression ce qui requiert une synchronisation patient-respirateur. En pédiatrie de nombreux facteurs limitent cette interaction (fréquence respiratoire élevée, fuites, volume courant très faible). Au cours de la bronchiolite, nous avons confirmé l'amélioration de la synchronisation avec la Neurally Adjusted Ventilatory Assist (NAVA) et suggéré que l'ajout d'un deuxième niveau de pression réduirait encore l'effort inspiratoire chez le nourrisson en comparaison à la nCPAP. Au cours de la pathologie asthmatique, le haut débit nasal pourrait présenter un intérêt à la fois en répondant à certains mécanismes physiopathologiques et en améliorant la tolérance chez l'enfant. De nombreux mécanismes restent à explorer chez l'enfant pour comprendre et pour optimiser la prise en charge ventilatoire. Toutes ces approches nécessitent maintenant de faire leurs preuves sur des critères de jugement clinique solides avant de pouvoir être intégrées dans la prise en charge des enfants avec une pathologie obstructive. Deux études multicentriques françaises, que nous coordonnons (CANNULASTHME et PROPOSITIS), devraient pouvoir apporter ces résultats et répondre aux attentes des cliniciens.

Finalement, plus qu'une action prise individuellement c'est la combinaison des interventions et surtout le timing de mise en œuvre qui doivent être évalués (Figure 15).

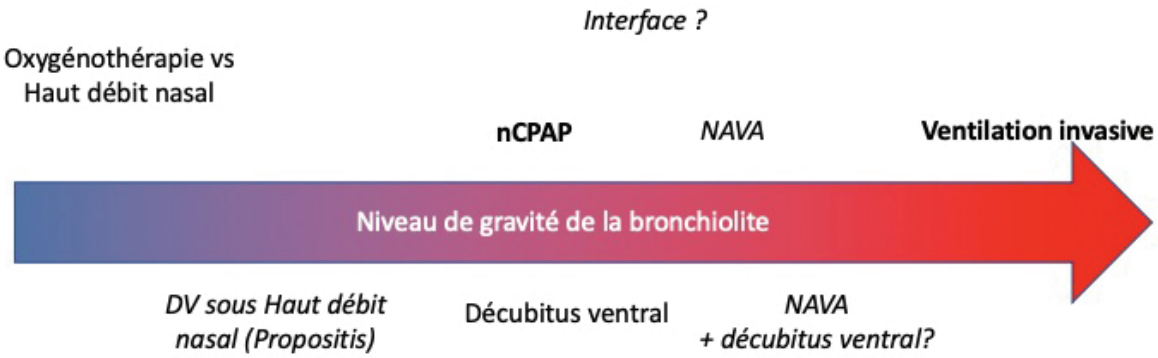

Figure 15 : Réflexions autour des stratégies à évaluer dans la prise en charge des bronchiolites.

Le schéma résume les stratégies et questions actuelles sur la prise en charge de la bronchiolite selon la gravité des enfants - En gras les actions considérées comme validées aux vues des données de la littérature

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ANNEXE 1 : ARTICLES ET COMMUNICATIONS ASSOCIES AU DOCTORAT

ARTICLES :

Article 1: Essouri S, Baudin F, Mortamet G, Beck J, Emeriaud G, Jouvet P. Relationship between diaphragmatic electrical activity and esophageal pressure monitoring in children. Pediatr Crit care Med 2019, in press.

Article 2: Baudin F, Emeriaud G, Essouri S, Beck J, Portefaix A, Javouhey E, Guerin C. Physiological Effect of Prone Position in Children with Severe Bronchiolitis: A Randomized Cross-Over Study (BRONCHIO-DV). J Pediatr 2018 [published ahead of print].

Article 3: Baudin F, Pouyau R, Cour-Andlauer F, Berthiller J, Robert D, Javouhey E. Neurally Adjusted Ventilator Assist (NAVA) reduces asynchrony during non-invasive ventilation for severe bronchiolitis. Pediatr Pulm 2015;50:1320-1327

Article 4 (Letter): Baudin F, Emeriaud G, Essouri S, Beck J, Javouhey E, Guerin C. Neurally adjusted ventilatory assist improves respiratory unloading in infants with severe bronchiolitis. Critical Care 2019, in-press.

Article 5: Essouri S, Baudin F, Chevret L, Vincent M, Emeriaud G, Jouvet P. Variability of Care in Infants with Severe Bronchiolitis: Less-Invasive Respiratory Management Leads to Similar Outcomes. J Pediatr 2017, 188 :156-162.

Article 6: Baudin F, Buisson A, Vanel B, Massenavette B, Pouyau R, Javouhey E. Nasal high flow in management of children with status asthmaticus: a retrospective observational study. Ann Intensive Care 2017;7:55.

EDITORIAL :

Baudin F. Viral bronchiolitis in PICUS: looking further than the acute phase! Ped Crit Care Med 2017; 18 :1178-79.

COMMUNICATIONS

Communication affichée : Baudin F, Emeriaud G, Essouri S, Portefaix A, Beck J, Javouhey E, Guerin C. Prone position reduces work of breathing in children with severe bronchiolitis. Congrès de la Société de Réanimation de Langue française, Paris 2017.

Communication affichée : Baudin F, Essouri S, Beck J, Javouhey E, Emmeriaud G. Nava reduce work of breathing during non-invasive ventilation for severe bronchiolitis. Congress of the World Federation of Pediatric Intensive & Critical Care Societies, Toronto 2016.

Symposium. NIV and intrinsic peep during severe bronchiolitis: benefits of NAVA? Symposium MAQUET, 13th European Conference on Pediatric and Neonatal Mechanical Ventilation, 27 Mai 2016 – Montreux, Suisse.

Communication orale: Baudin F, Pouyau R, Cour-Andlauer F, Berthiller J, Robert D, Javouhey E. Non invasive ventilation in severe bronchiolitis with failure of nCPAP : NAVA versus Pressure Assist Control ventilation. Congrès de l'European Academy Pediatric Society, Barcelone 2014.

Communication orale : Baudin F, Pouyau R, Cour-Andlauer F, Berthiller J, Robert D, Javouhey E. Ventilation non-invasive dans la bronchiolite sévère du nourrisson en échec de CPAP : NAVA versus Pression assistée contrôlée. Congrès de la Société de Réanimation de Langue française, Paris 2014.

ANNEXE 2 : RESUME PROTOCOLE PROPOSITIS

PROPOSITIS

Prone Position in Bronchiolitis

TITRE	Effet du décubitus ventral sur le recours à la ventilation non-invasive et invasive chez le nourrisson atteint de bronchiolite aiguë modérée à grave sous haut débit nasal, une étude multicentrique randomisée, contrôlée « PROPOSITIS »
PROMOTEUR	Hospices Civils de Lyon BP 2251 3 quai des Célestins, 69229 LYON cedex 02
INVESTIGATEUR COORDONATEUR	Dr Florent BAUDIN Réanimation pédiatrique et unité de surveillance continue Hôpital Femme Mère Enfant, Groupement Hospitalier Est 59 Boulevard PINEL, 69500 Bron Tel : 04 72 12 97 35 Fax : 04 27 86 92 70 Email : florent.baudin@chu-lyon.fr
VERSION DU PROTOCOLE	Version 01 du 02/07/2018
JUSTIFICATION / CONTEXTE	La bronchiolite virale aiguë est la première cause d'insuffisance respiratoire aiguë communautaire du nourrisson dans les pays développés (30 000 hospitalisations chaque année en France, PMSI 2009). On estime qu'entre 5 et 22 % de ces enfants seront hospitalisés dans un service de soins critiques (unité de surveillance continue ou réanimation) pour bénéficier d'un support respiratoire par haut débit nasal, ventilation non invasive ou invasive. La ventilation non invasive, en particulier la Continuous Positive Airway Pressure nasal (nCPAP), réduit le travail respiratoire chez l'enfant atteint de bronchiolite et est associée à une diminution de la morbidité et des coûts d'hospitalisation comparativement à la ventilation invasive. Cette technique est aujourd'hui considérée comme la référence en France dans la prise en charge respiratoire des nourrissons atteints de bronchiolite grave mais nécessite une hospitalisation, donc un transfert en réanimation pédiatrique. Le haut débit nasal (HDN) a été proposé comme alternative à la nCPAP en raison de sa meilleure tolérance et de sa simplicité de mise en œuvre, réalisable dans les unités de surveillance continue en particulier. Cependant, la proportion d'échec reste élevée (35 à 50%), n'apportant qu'une réponse partielle à la prise en charge de ces enfants en amont des réanimations. Dans un travail physiologique (NCT02602678, article soumis), nous avons montré que le DV permettait d'améliorer la mécanique respiratoire et de réduire de près de 50% le travail respiratoire chez les nourrissons hospitalisés en réanimation pour une bronchiolite grave. Nous faisons l'hypothèse que le DV au cours du haut débit nasal permettrait une réduction significative de l'usage de la ventilation non invasive (nCPAP et autres modes) ou invasive par rapport au haut débit nasal en décubitus dorsal chez les nourrissons atteints de bronchiolite modérée à grave.
OBJECTIFS	• **Objectif principal :** Démontrer que le décubitus ventral au cours du haut débit nasal réduit significativement le recours à la ventilation (invasive et/ou non invasive) par rapport au décubitus dorsal chez le nourrisson atteint de bronchiolite modérée à grave. • **Objectif(s) secondaire(s) :** Démontrer que le décubitus ventral au cours de la bronchiolite :

	1 Diminue les échecs du haut débit nasal (comité d'adjudication indépendant) et modifie les causes d'échecs 2 Diminue la durée d'utilisation du haut débit nasal et la durée totale de ventilation 3 Diminue la durée de séjour en unité de soins critiques (USC ou réanimation) et de séjour hospitalier 4 Améliore l'oxygénation 5 Est bien toléré sur le plan cutané et sur le plan de l'alimentation 6 Améliore le confort 7 Est réalisable facilement chez l'ensemble des nourrissons
METHODOLOGIE / SCHEMA DE LA RECHERCHE	Étude multicentrique prospective, randomisée contrôlée en ouvert évaluant le décubitus ventral comparativement au positionnement de référence (décubitus dorsal). Qualification : Recherche impliquant la personne humaine du 1°, hors produit de santé
CRITERES DE JUGEMENT	• **Critère principal :** Proportion d'enfants ventilés (invasivement ou non-invasivement) dans chacun des 2 groupes, à tout moment de la prise en charge durant les 7 premiers jours (selon des critères standardisés) • **Critère(s) secondaire(s) :** 1 Échec et causes d'échec du haut débit nasal : - Proportion d'enfants en échec du haut débit nasal durant les 7 premiers jours de prise en charge (critère composite d'échec validé par un comité d'adjudication indépendant) - Proportion d'enfants en échec pour aggravation du score mWCAS de plus de 1 point - Proportion d'enfants en échec pour acidose hypercapnique (pH<7.30 et pCO_2 >8kPa) - Proportion d'enfants en échec pour apnées significatives (apnée avec désaturation < 90% et/ou bradycardie <90/min) 2 Durée de support ventilatoire : - Nombre d'heures cumulées d'utilisation du haut débit nasal - Nombre d'heures cumulées de ventilation VNI et/ou VI 3 Durée de séjour : - Durée de séjour en unité de soins critiques (USC et réanimation) en jours - Durée de séjour hospitalier en jours 4 Oxygénation : - Evolution de la FiO_2 et du rapport SpO_2/FiO_2 entre l'inclusion et H2, entre l'inclusion et H12 et entre l'inclusion et H24 5 Tolérance : - Proportion de patients présentant des lésions cutanées, et grade des lésions selon l'échelle National Pressure Ulcer Advisory Panel jusqu'à la sortie des soins critiques - Nombre de vomissements ou régurgitations rapporté à la durée de haut débit nasal dans les 48 premières heures. - Nombre d'heures entre l'admission et l'instauration d'une alimentation entérale exclusive 6 Confort : - Variation absolue du score EDIN (Echelle de douleur et d'inconfort du nouveau-né) entre H2 et H0 7 Réalisable : - Proportion d'enfants du groupe décubitus ventral repositionnés définitivement en décubitus dorsal avant d'avoir effectué les 24h cumulées de DV

	- Nombre d'heures cumulées de décubitus ventral dans les 48 premières heures
POPULATION CIBLE	Cette étude portera sur les nourrissons de moins de 6 mois, sans antécédent significatif, atteints de bronchiolite virale modérée à grave (nécessitant un support par haut débit nasal) hospitalisés en unité de soins critiques (unité de surveillance continue ou réanimation pédiatrique).
CRITERES D'INCLUSION	- Nourrisson de moins de 6 mois - Hospitalisé en unité de soins critiques (unité de surveillance continue ou réanimation pédiatrique) - Avec un diagnostic clinique de bronchiolite aiguë en période épidémique (critère de l'American Academy of Pediatrics 2014) - Score m-WCAS ≥ 3 et/ou présentant une acidose hypercapnique avec un pH<7.35 et une pCO_2>50mmHg (6,7 kPa) - Consentement éclairé et signé d'au moins un des deux parents avec consentement oral de l'autre parent (et/ou titulaires de l'autorité parentale) consigné dans le dossier médical.
CRITERES DE NON INCLUSION	- Nourrisson ayant des critères de ventilation invasive ou non invasive d'emblée définis par (acidose hypercapnique avec pH<7.25 sans support ventilatoire, hypoxie avec impossibilité de maintenir une SpO_2 > 92% quelle que soit la FiO_2, plus de 2 apnées significatives par heure, trouble de conscience avec Glasgow < 12) - Patient déjà positionné en décubitus ventral avant la randomisation - Comorbidités significatives avec antécédents de pathologie respiratoire (bronchodysplasie), ORL (pharyngo-laryngomalacie) ou neuromusculaire et/ou de cardiopathie congénitale hémodynamiquement significative. - Contre-indication au décubitus ventral : chirurgie abdominale récente (laparoschisis ou omphalocèle) ou sternotomie récente - Patient non affilié à un système de sécurité sociale
CRITERES DE SORTIE D'ETUDE	Il n'y a pas à priori de critères de sortie prématurée d'étude en dehors du retrait de consentement par les parents et/ou titulaires de l'autorité parentale.
PROCEDURES	Après vérification des critères d'inclusion et de non inclusion et du consentement écrit et signé, les enfants seront randomisés pour être positionnés soit en décubitus ventral soit en décubitus dorsal selon le groupe de randomisation. L'intervention évaluée sera l'utilisation du décubitus ventral (durée cumulée de 24h minimum dans les 48 premières heures) combinée au haut débit nasal dans le bras expérimental et comparé au décubitus dorsal combiné au haut débit nasal dans le bras contrôle. **Groupe expérimental = groupe décubitus ventral** : Nourrissons sous haut débit nasal placé en décubitus ventral pendant au minimum 24h dans les 48 premières heures puis selon l'appréciation du médecin en charge de l'enfant. **Groupe contrôle :** Nourrissons sous haut débit nasal positionnés sur le dos (et/ou en décubitus latéral en alternance) comme réalisé habituellement dans les services. La prise en charge et les soins seront standardisés dans les deux groupes : le haut débit nasal sera initié à 2L/Kg/min avec une FiO_2 minimale pour maintenir une SpO_2 entre 92% et 97%. Les nourrissons seront positionnés également en proclive (15 à 30°).
RAPPORT BENEFICES/RISQUES	Le décubitus ventral en tant que stratégie non invasive supplémentaire dans la prise en charge des nourrissons atteints de bronchiolite modérée à grave permettrait un bénéfice individuel en termes de : - Réduction du recours à la ventilation mécanique et de la morbidité - Stabilisation précoce de l'état respiratoire et réduction de la durée d'hospitalisation

	- Réduction des risques liés au transfert en réanimation d'un nourrisson admis dans une unité de surveillance continue d'un centre hospitalier général et maintien à proximité avec son environnement familial. Les bénéfices collectifs attendus sont : une réduction du nombre de séjours en réanimation pédiatrique et de la durée de séjour et des transferts. Le risque de mort inattendue du nourrisson en lien avec le couchage sur le ventre est finalement prévenu dans les conditions de l'étude à la fois par le support ventilatoire (haut débit nasal) et surtout par les conditions d'hospitalisation et de surveillance (unité de soins critiques). Le risque principal semble surtout résider dans la possibilité de remise en cause des conditions de couchage au domicile par les parents après le séjour hospitalier qui sera prévenu par la remise d'une information individuelle ainsi qu'un document validé par le centre de prévention de la mort inattendue du nourrisson. En somme, la balance bénéfice/risque semble favorable au regard des connaissances médicales actuelles et des données de la littérature.
Nombre de sujets	Nombre de sujets nécessaires : 420 patients soit 210 patients dans chaque groupe.
DUREE DE L'ETUDE	Durée de la période d'inclusion : 19 mois Durée de la participation pour chaque sujet : durée d'hospitalisation Durée totale de l'étude : 22 mois
LIEU DE LA RECHERCHE	L'étude sera conduite dans les unités de soins critiques pédiatriques (unité de surveillance continue ou service de réanimation) de 12 centres dont 9 centres appartenant au Comité Régional des Unités de Surveillance Continue : • Réanimation pédiatrique et USC, HFME, Hospices Civils de Lyon • Réanimation pédiatrique, CHU Robert Debré, APHP, Paris • Réanimation pédiatrique, CHU Lenval, NICE • Réanimation pédiatrique et USC, CHU GRENOBLE • Réanimation pédiatrique, CHU MONTPELLIER • Réanimation pédiatrique, CHU SAINT-ETIENNE • Réanimation pédiatrique, CHU CLERMONT FERRAND • USC, CH VILLEFRANCHE SUR SAONE • USC, CH VALENCE • USC, CH BOURG en BRESSE • USC, CH ANNECY • USC, CH CHAMBERY
RETOMBEES ATTENDUES	Chaque hiver, la bronchiolite du nourrisson représente près de 30 000 hospitalisations en France et entre 5 et 22% bénéficient d'un support ventilatoire et seraient donc concernés par les résultats de cette étude (soit entre 1500 et 6000 enfants chaque année en France). Le décubitus ventral, technique simple et non coûteuse, pourrait ainsi, par la réduction du recours à la ventilation (invasive ou non invasive) et donc l'hospitalisation en réanimation et par la réduction des durées de séjour, améliorer la prise en charge de ces patients et apporter une réponse à la problématique de saturation des lits de soins critiques.

ANNEXE 3 : RESUME PROTOCOLE CANULASTHME

Titre	**Haut débit nasal chez l'enfant atteint d'asthme aigu grave: une étude randomisée contrôlée. CANULASTHME**
Promoteur	Hospices Civils de Lyon BP 2251 3 quai des Célestins, 69229 LYON cedex 02
Investigateur coordonnateur	Dr Robin POUYAU Service de réanimation pédiatrique - Hôpital Femme-Mère-Enfant 59, bd Pinel - 69677 Bron Cedex, France Ph. : 04 72 12 97 47 Email : robin.pouyau@chu-lyon.fr
Version du protocole	**Erreur ! Source du renvoi introuvable.**
Justification / Contexte	L'asthme en France atteint plus de 2,5 millions de personnes dont un tiers d'enfants. C'est la maladie respiratoire chronique nécessitant le plus d'hospitalisation. Le moyen de délivrance de l'oxygène classique chez l'enfant est le masque à haute concentration ou les lunettes nasales (oxygénothérapie standard). Actuellement apparaissent de nouveaux systèmes d'assistance ventilatoire non invasive comme le Haut Débit Nasal (HDN). Il s'agit de canules nasales permettant l'administration d'un débit élevé d'air ou d'oxygène, dépassant le débit inspiratoire des malades en insuffisance respiratoire aiguë, permettant de délivrer une légère pression expiratoire positive, tout en assurant une humidification et un réchauffement des voies aériennes. L'administration d'aérosol est possible avec une excellente efficacité et sans interrompre l'assistance respiratoire. Les données physiologiques ou les études cliniques dans d'autres pathologies suggèrent le probable intérêt de cette technique lors de la crise d'asthme mais aucune étude comparative n'existe actuellement dans cette indication. Le HDN pourrait avoir sa place en amont de la Ventilation Non Invasive (VNI) remplaçant ainsi l'oxygénothérapie standard parfois mal tolérée par les enfants. Notre hypothèse est que le HDN permettrait d'améliorer plus rapidement les patients, de réduire le recours à d'autres assistances ventilatoires (VNI, ventilation invasive) et de diminuer la durée d'hospitalisation en réanimation ou en unité de surveillance continue (USC).
Objectifs	**Objectif principal** : Évaluer la capacité du HDN à diminuer le nombre d'échec du traitement de première ligne de l'asthme aigu grave, par rapport à oxygénothérapie standard. **Objectifs secondaires** : quantifier et comparer entre les 2 groupes : - Le recours à une technique de ventilation (VI ou VNI) - La durée de ventilation - Le niveau de confort des enfants - La durée d'oxygénothérapie - Le délai d'amélioration des échanges gazeux - Les doses cumulées des médicaments (aérosols de salbutamol, salbutamol intraveineux, sulfate de magnésium, corticoïdes) - Les durées de séjour en USC ou réanimation et à l'hôpital
Méthodologie / Schéma de la recherche	Etude contrôlée randomisée. Le plan d'étude comprend la randomisation initiale, l'évaluation systématique à H2, H6, H12 et H24 dans chaque bras y compris en cas d'échec de la technique. La période de suivi minimum pour un patient est de 24H. Mise en place d'un comité de relecture des dossiers d'échec par deux experts en aveugle de la randomisation pour vérifier la réalité de l'échec. Aucun comité de surveillance n'est mis en place car les risques encourus sont faibles au regard des techniques qui sont couramment utilisées.

Critères de jugement	**<u>Critère de jugement principal</u>** : Nombre de patients en échec du traitement de première ligne (OS / HDN) dans les 24 premières heures Les critères d'échecs sont définis à priori comme : - Lors des évaluations systématiques de H2, H6, H12 et H24 : o Apparition ou aggravation de l'acidose hypercapnique (pH<7,35 et pCO2>45mmHg) o Ou aggravation du score PRAM (≥+1 par rapport au PRAM initial) o Ou SpO_2<92% sous débit maximal d'oxygène dans le groupe OS ou avec une FiO_2>60% dans le groupe HDN o Ou apparition ou aggravation d'un trouble de conscience avec un Glasgow <12 - Ou à tout moment en cas de nécessité de recours à la ventilation invasive ou non invasive (Glasgow<8, instabilité hémodynamique nécessitant le recours à des amines, hypoxémie réfractaire définie par une SpO_2<90% pendant plus de 5 minutes sous oxygénothérapie maximale) **<u>Critères de jugement secondaire :</u>** - Nombre de patients nécessitant le recours à la ventilation (invasive ou non invasive) - Durée de ventilation en heures. - Confort évalué par l'échelle FLACC - Durée de l'oxygénothérapie en heures - Délai entre l'inclusion et l'obtention d'un score PRAM<8 en heures - Délai entre l'inclusion et la normalisation de la gazométrie si disponible (pCO_2<45 mmHg and pH>7.35) - Doses cumulées de o Salbutamol nébulisé en milligrammes o Salbutamol intraveineux en milligrammes o Corticoïdes en milligrammes o Sulfate de magnésium en milligrammes - Durées de séjour en USC-réa et à l'hôpital en heures
Population cible	Enfant hospitalisé en réanimation ou unité de surveillance continue pour un asthme aigu grave
Critères d'inclusion	- Enfant âgé de 1 an à moins de 18 ans - Hospitalisé en réanimation ou USC pour un asthme aigu grave - avec un score de PRAM > 7 à H+2 du début du traitement conventionnel initial selon le protocole de GINA, c'est à dire : o Oxygénothérapie standard, o bronchodilatateurs inhalés à action rapide en continu pendant 1h puis toutes les heures, o corticothérapie par voie générale (orale ou IV) à 2 mg/kg/j - ou une acidose hypercapnique définie par pCO2 > 45 mmHg et pH < 7,35 - Consentement signé d'au moins un des deux parents avant l'intervention
Critères de non inclusion	- Antécédents de cardiopathie non corrigée, de pathologie neuromusculaire, respiratoire chronique (fibrose bronchique, mucoviscidose, fibrose pulmonaire), de malformation des voies aériennes supérieures symptomatiques (laryngomalacie, trachéomalacie), de déformation de la cage thoracique (cyphoscoliose) ou de maladie métabolique. - Indication de ventilation (instabilité hémodynamique majeure, arrêt cardio respiratoire, trouble de conscience avec Glasgow <8, hypoxie réfractaire). - Pneumothorax documenté - Patient non affilié à un système de sécurité sociale.

Critères de sortie d'étude	Le patient pourra sortir de l'étude en cas de retrait de consentement, sur décision de l'investigateur ou du promoteur. Il n'y a pas *à priori* d'autre condition de sortie d'étude. Les patients, quel que soit le groupe de randomisation, seront suivis selon le protocole.
Procédures	Le recrutement des patients sera fait au fur et à mesure des admissions en réanimation et dans les unités de surveillance continue dans chaque centre après vérification des critères d'inclusion. Apres vérification des critères d'inclusion et de non inclusion et recueil du consentement d'au moins 1 des 2 parents, les enfants seront randomisés pour recevoir : - Dans le bras OS : une oxygénothérapie standard (OS), à bas débit (lunettes nasales ou masque haute concentration) avec aérosols de β_2 mimétiques délivrés par un dispositif à tamis vibrant (aerogen®), selon les modalités habituelles du service et selon le protocole GINA (Global Initiative for Asthma guidelines) - Dans le bras HDN : une oxygénothérapie via un système de haut débit nasal (airvo2®) combinée à l'administration d'aérosols de β_2 mimétiques délivrés par un dispositif à tamis vibrant (aerogen®) directement sur le circuit. Le débit de gaz sera réglé initialement à 1L/kg/mn (max 50L/mn) avec adaptation secondaire possible par le clinicien si nécessaire entre 0,5 et 2L/kg/mn. La FiO_2 sera adaptée pour obtenir une SpO_2>92%. Dans les deux bras l'utilisation des thérapeutiques associées (sulfate de magnésium, salbutamol IV, Bromure ipratropium…) sera laissée à l'initiative du médecin en charge du patient selon les protocoles de chaque service. Une stratification par centre est prévue pour la randomisation.
Rapport bénéfice/risque	L'oxygénothérapie standard est la référence pour l'oxygénothérapie dans l'asthme aigu grave. Le bénéfice de cette technique réside uniquement dans la supplémentation en oxygène. Le HDN semble être une alternative intéressante, confortable et permettant de réduire le recours à des modes ventilatoires plus agressifs (VNI, Ventilation invasive). Cette technique est utilisée de façon habituelle et parfaitement maitrisée par les services participants dans de nombreuses autres indications (bronchiolites, pneumopathies, obstruction hautes des voies aériennes…). Le bénéfice attendu pour le patient atteint d'asthme aigu grave est une amélioration plus rapide, une réduction de la durée d'hospitalisation en réanimation et un confort supplémentaire. Le bénéfice attendu pour la société est une réduction des coûts en lien avec une diminution du recours à la ventilation non invasive et invasive et une réduction des durées de séjour en réanimation ou unité de surveillance continue. Dans le bras oxygénothérapie standard (OS), les risques sont principalement dominés par la mauvaise tolérance avec agitation ou inconfort et le risque d'inefficacité. Dans le bras HDN, les risques attendus pour les participants sont une éventuelle mauvaise tolérance avec inconfort et agitation, de possibles rougeurs cutanées au niveau nasal, et un risque faible de barotraumatisme.
Nombre de sujets	300 inclus pour atteindre 134 patients analysables par groupe
Durée de l'étude	Durée de la période d'inclusion : 24 mois Durée de la participation pour chaque sujet : maximum 1 mois Durée totale de l'étude : 25 mois
Lieux de la recherche	Sélection et suivi des patients : ils s'effectueront dans 12 centres différents (services de pédiatrie, réanimation pédiatrique ou anesthésie/réanimation)
Retombées attendues	Les bénéfices attendus pour les patients souffrant d'asthme aigu seraient une amélioration plus rapide, une réduction du séjour en réanimation et un confort supplémentaire. L'avantage plus général serait de réduire les coûts liés à une réduction de l'utilisation de la ventilation non invasive et invasive et à une réduction de la durée de séjour en réanimation.

Mise en place d'un comité de surveillance ou justification de son absence	Aucun comité de surveillance n'est mis en place car les risques encourus sont faibles au regard des techniques qui sont couramment utilisées. Mise en place d'un comité de relecture des dossiers d'échec par 2 experts en aveugle de la randomisation pour vérifier la réalité de l'échec.