Université de Montréal

**Rôle du diaphragme au cours de l'expiration chez l'enfant
sous ventilation mécanique**

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Mémoire présenté à la Faculté des études supérieures
en vue de l'obtention du grade de
Maîtrise en Sciences Biomédicales (M.Sc.)
Option recherche clinique biomédicale

Août 2006

Université de Montréal

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Ce mémoire intitulé :

**Rôle du diaphragme au cours de l'expiration chez l'enfant
sous ventilation mécanique**

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Résumé

Les nouveau-nés et les nourrissons contrôlent de façon active leur volume pulmonaire de fin d'expiration, à un niveau supérieur au volume du système respiratoire au repos. Différents mécanismes ont été évoqués et notamment le freinage expiratoire par la persistance d'une activité diaphragmatique pendant l'expiration, ou activité tonique diaphragmatique. Cependant, la présence de l'activité tonique du diaphragme reste controversée et peu étudiée, et il n'existe notamment aucune étude réalisée sous ventilation assistée.

L'objectif global de notre travail est de mieux comprendre la façon dont les nourrissons contrôlent le volume pulmonaire de fin d'expiration, et comment la ventilation artificielle interagit avec ce contrôle. Nous présentons dans ce mémoire 2 articles qui reprennent les résultats de 2 études basées sur des enregistrements de l'activité électrique du diaphragme de nourrissons intubés et sous ventilation artificielle.

La 1ère étude permet de confirmer la présence du réflexe de Hering-Breuer chez ces nourrissons, les cycles ventilatoires administrés par le respirateur entraînant bien une augmentation du temps expiratoire. Cette étude montre également que l'asynchronisme patient-respirateur est majeur, correspondant à plus de la moitié du temps. Dans la 2ème étude, nous avons confirmé le maintien d'une partie de l'activité diaphragmatique jusqu'en fin d'expiration. Cette activité tonique s'accroît lorsque la PEEP est supprimée, suggérant un rôle dans le maintien du volume pulmonaire de fin d'expiration.

Ces résultats permettent de mieux comprendre les interactions entre le respirateur et le nourrisson. Dans le futur, la mesure de l'activité diaphragmatique pourrait permettre d'améliorer la synchronisation patient-respirateur et pourrait servir de guide pour l'adaptation du niveau de PEEP chez ces patients.

Abstract – key words

Infants and neonates actively control the end expiratory lung volume (EELV) above the resting lung volume. The persistence of diaphragmatic activity during expiration (or tonic diaphragm activity) with an expiratory flow-braking action has been suggested to contribute to the elevation of EELV. However, this tonic activity of the diaphragm remains controversial and poorly studied. To our knowledge, no studies have been conducted on this topic in mechanically ventilated infants.

The overall objective of this work is to study the role of the diaphragm in the maintenance of EELV in mechanically ventilated infants, and to evaluate the impact of mechanical ventilation on its control. Specifically, we present 2 studies based on diaphragm electrical activity recorded in intubated infants under mechanical ventilation.

The first study provides evidence that prolonged delivery of assist elicits the Hering Breuer reflex, and promotes an expiratory prolongation in mechanically ventilated infants. We also observed a very important asynchrony between neural timing and the ventilatory timing in the infants studied. In the 2nd study, we observed the presence of tonic diaphragmatic activity in every patient. This tonic activity increased when PEEP was briefly suppressed, suggesting its involvement in the control of EELV.

These results provide interesting information on the interactions occurring between mechanical ventilators and infants. Future studies would be necessary to evaluate the electrical diaphragm activity as a tool to improve infant-ventilator synchrony and to assess its potential implications on the management of PEEP in intubated infants.

Key words : infant ; diaphragm ; EMG ; mechanical ventilation ; Hering-Breuer reflex ; expiration ; PEEP

Table des matières

Liste des figures

Manuscrit 1

Manuscrit 2

Liste des tableaux

Manuscrit 1

Manuscrit 2

Abréviations

AEdi, activité électrique du diaphragme

Paw, Pression des voies aériennes (airway pressure)

PEEP, Pression positive de fin d'expiration (positive end-expiratory pressure)

ZEEP, PEEP à zéro

VACI, Ventilation assistée contrôlée intermittente (équivalent à SIMV en anglais)

Te, Temps expiratoire

Ti, Temps inspiratoire

EELV, Volume pulmonaire de fin d'expiration (end-expiratory lung volume)

Remerciements

Je désire remercier particulièrement Jacques Lacroix qui, par sa confiance, est à l'origine de ma venue en tant que « fellow » aux soins intensifs pédiatriques de l'hôpital Sainte-Justine. Je n'oublierai pas son accueil chaleureux, sa passion pour la recherche et son soutien continu.

Un grand merci à Marisa Tucci, qui m'a également accueilli avec chaleur et enthousiasme. Son dynamisme dans les soins, dans la recherche comme dans la vie est un bel exemple. Et un merci particulier d'avoir continué à m'encourager et à m'aider avec toujours autant de disponibilité même de loin après mon retour en France ! Ce mémoire n'aurait pas vu le jour sans cette aide.

Jennifer Beck a contribué à une énorme part du travail présenté dans ce mémoire. Elle est à l'origine des 2 études présentées ici. Merci mille fois de m'avoir fait confiance en me permettant de participer à ce travail, tout en me transmettant une partie de votre grande expérience. J'ai beaucoup apprécié tant votre rigueur scientifique que votre passion pour ce domaine. C'était un plaisir de travailler avec vous.

Je remercie également Christer Sinderby, pour la disponibilité et la patience qu'il m'a accordées pour m'enseigner les principes de la méthode qu'il a progressivement développée et pour la confiance qu'il m'a toujours témoignée.

Je remercie aussi Norman Comtois pour son aide dans la réalisation des enregistrements et des analyses.
Je remercie enfin chaleureusement les parents et les enfants qui ont contribué à la réalisation de ce travail.

Introduction

Chez le nouveau-né à terme ou prématuré, le volume pulmonaire de fin d'expiration (EELV, pour end expiratory lung volume) est maintenu de façon active à un niveau supérieur au volume de relaxation (Kosch 1984 ; Stark 1987). Ce dernier, représentant le volume du système respiratoire au repos, est déterminé par les propriétés mécaniques passives de ce système. Ce n'est qu'après l'âge d'un an que l'EELV correspond au volume de relaxation (Colin 1989). Durant les premiers mois, des réflexes adaptatifs doivent donc permettre d'éviter la diminution de l'EELV.

Chez le nouveau-né, différents mécanismes ont été évoqués pour expliquer le contrôle de l'EELV : le mode respiratoire avec une fréquence haute et un temps expiratoire relativement court (Griffiths 1983), le freinage du débit expiratoire au niveau laryngé (Kosch 1988), ou au niveau diaphragmatique par la persistance d'une activité diaphragmatique pendant l'expiration, ou activité tonique diaphragmatique (Kosch 1984).

Le diaphragme est essentiellement connu comme un muscle inspiratoire actif uniquement durant l'inspiration et au repos lors de l'expiration. Cependant, il a été montré chez des nouveau-nés à terme ou prématurés que l'activité électrique du diaphragme – mesurée par des électrodes sur la surface du thorax – semblait persister tout au long de l'expiration, suggérant une activité « tonique » de ce muscle respiratoire (Prechtl 1977 ; Lopes 1981 ; Stark 1987 ; Eichenwald 1993). Les variations de cette activité tonique étant associées à des variations de l'EELV, Lopes proposa le premier l'hypothèse de l'implication de l'activité diaphragmatique durant l'expiration dans le contrôle de l'EELV chez les nouveau-nés et nourrissons (Lopes 1981). Cependant, cette hypothèse restait controversée, et en outre, aucune étude de l'activité du diaphragme au cours de l'expiration n'a été menée chez des nourrissons intubés et ventilés artificiellement.

L'objectif global des travaux présentés dans ce mémoire est donc d'étudier la façon dont les nourrissons contrôlent leur volume pulmonaire de fin d'expiration, et notamment d'évaluer quelle est la participation de l'activité diaphragmatique dans ce contrôle, et de mieux comprendre l'impact du respirateur sur ce contrôle ventilatoire.

Spécifiquement, après une revue de la littérature qui fera notamment l'état des connaissances actuelles sur le contrôle de l'EELV chez les nourrissons et nouveau-nés, nous présenterons 2 articles : le premier article rapporte une étude du retentissement des cycles de ventilation administrés par le respirateur sur le comportement respiratoire des nourrissons. Cela permettra notamment de démontrer la présence et le rôle du réflexe de Hering-Breuer chez ces patients, réflexe pouvant être impliqué dans le contrôle de l'EELV. Dans le deuxième article, qui constitue l'essentiel de notre travail rapporté dans ce mémoire, nous avons étudié de façon quantitative l'activité diaphragmatique durant l'expiration, et étudié l'impact de la ventilation assistée sur cette activité tonique.

Revue de la littérature

Définitions

- EELV (end expiratory lung volume) : Il s'agit du volume pulmonaire en fin d'expiration.
- Volume de relaxation : volume pulmonaire lorsque le système respiratoire est au repos, c'est à dire qu'il n'y a aucune activité des muscles inspiratoires ni expiratoires, et que les voies aériennes supérieures sont ouvertes.
- Nourrisson : enfant de moins de 2 ans
- Nouveau-né : ce terme s'applique aux enfants de moins de 28 jours.

Particularités du contrôle de l'EELV chez les nouveau-nés et nourrissons

- **Niveau de l'EELV**

Chez l'enfant plus âgé et l'adulte, le volume pulmonaire de fin d'expiration correspond généralement au volume de relaxation. A l'inverse, les nouveau-nés et les nourrissons (au moins la première année) respirent avec un niveau d'EELV relativement élevé, c'est à dire qu'en fin d'expiration, le volume pulmonaire ne redescend pas jusqu'au niveau du volume pulmonaire de relaxation.

Ce maintien d'un volume pulmonaire relativement haut a été bien démontré dans les années 80, notamment par l'équipe de Kosh et Stark au moyen d'enregistrements respiratoires pléthysmographiques (Kosch 1984 ; Stark 1987).

L'EELV rejoint le niveau du volume de relaxation après l'âge de 1 an chez la plupart des nourrissons, un peu plus tôt pour certains, mais toujours après 6 mois (Colin 1989).

L'importance du maintien d'un EELV au dessus du volume de relaxation à cet âge peut s'expliquer notamment par le fait que ces nouveau-nés et nourrissons ont un poumon relativement moins compliant et une cage thoracique non rigidifiée, contrairement à l'enfant plus grand. Au repos, le poumon a donc tendance à se rétracter, et cette tendance ne peut être contrée par la rigidité de la cage thoracique. Or, l'établissement puis le maintien d'un volume pulmonaire suffisant est crucial pour permettre une oxygénation optimale. Il a notamment été montré que des chutes de l'EELV (notamment lors d'apnées ou d'irrégularité respiratoire) étaient associées à des désaturations (Poets 1997 ; Stark 1987).

- **Mécanismes utilisés pour le maintien de l'EELV**

Plusieurs mécanismes sont mis en jeu dans le maintien d'un haut niveau d'EELV par ces nourrissons.

o Le mode respiratoire

Les nouveau-nés et les nourrissons ont une fréquence respiratoire élevée et un temps expiratoire relativement court. Un nouveau cycle inspiratoire peut donc intervenir avant une diminution trop importante du volume pulmonaire. Il est probable que ce mécanisme participe au maintien de l'EELV, comme cela a été suggéré par différentes études (Kosch 1984 ; Mortola 1984 ; Griffiths 1983). Cependant, ce mécanisme ne peut pas expliquer à lui seul le maintien de l'EELV (Griffiths 1983) et des mécanismes de freinage expiratoire sont nécessaires.

o Freinage expiratoire

La présence d'un freinage du débit expiratoire a été mise en évidence chez les nouveau-nés et les nourrissons (Kosch 1984 ; Kosch 1988 ; Mortola 1984). Ce freinage peut se situer à deux niveaux :

- *Freinage expiratoire au niveau laryngé*

Les nouveau-nés exercent un freinage expiratoire en rétrécissant l'ouverture laryngée durant l'expiration. Kosh a notamment pu enregistrer l'activité des muscles crico-aryténoides postérieurs chez certains nouveau-nés (Kosh 1988). L'utilisation de ce freinage est augmentée en présence d'une difficulté respiratoire, ce qui peut entraîner un geignement expiratoire du nouveau-né, un des signes cliniques de la détresse respiratoire néonatale. Par contre, il est évident que ce mécanisme ne peut plus être mis en jeu après une intubation trachéale.

- *Freinage expiratoire par le maintien d'une activité diaphragmatique*
Le diaphragme est le principal muscle inspiratoire, et son activité « classique » est cyclique avec une contraction durant l'inspiration et un relâchement avec un repos des fibres musculaires durant l'expiration. Cependant, plusieurs auteurs ont décrit une activité diaphragmatique persistant au cours de l'expiration chez le nouveau-né à terme ou prématuré (sans détresse respiratoire), suggérant une activité « tonique » du diaphragme (Prechtl 1977 ; Lopes 1981 ; Stark 1987 ; Eichenwald 1993). Ces auteurs ont donc suggéré que la persistance d'une activité diaphragmatique au cours de l'expiration permettait un ralentissement du débit expiratoire, et donc le maintien d'un haut niveau d'EELV. Lopes a d'ailleurs établi une corrélation entre les changements d'activité tonique diaphragmatique et les changements d'EELV (Lopes 1981).

Cependant, dans ces études, l'activité tonique était généralement enregistrée au moyen d'électrodes de surface, ce qui peut laisser craindre une contamination électrique par l'activité musculaire pariétale abdominale ou thoracique.

En outre, aucune étude n'a été réalisée chez des enfants intubés et ventilés artificiellement. Or l'intubation et la ventilation assistée peuvent avoir plusieurs impacts sur le contrôle de l'EELV et sur l'activité tonique diaphragmatique. La présence de la sonde d'intubation supprime la

possibilité d'une contraction laryngée, et on peut supposer que cela rend le nourrisson plus dépendant de son activité tonique diaphragmatique et que celle-ci va donc augmenter. A l'inverse, si la sonde est de petit diamètre, elle peut entraîner des résistances expiratoires et rendre moins important le freinage diaphragmatique. La ventilation artificielle elle-même peut avoir un impact. Le niveau de pression expiratoire positive (PEEP) a un impact direct sur le niveau d'EELV (Thome 1998). Or le réglage optimal du niveau de PEEP reste un challenge important pour les intensivistes (Gentile 2004), et ce réglage est empirique. Il est donc difficile de savoir si le niveau de PEEP habituellement utilisé est suffisant (ou excessif) pour obtenir un niveau de EELV « physiologique » et donc quel est son impact sur l'activité tonique diaphragmatique. Enfin, les cycles ventilatoires administrés par le respirateur peuvent modifier la ventilation du nourrisson, notamment par l'activation du réflexe de Hering-Breuer. L'implication de ce réflexe dans la ventilation artificielle pédiatrique n'a été que très peu étudiée.

- **Importance du réflexe de Hering-Breuer chez le nouveau-né et le nourrisson**

Hering et Breuer (Hering 1868) ont décrit il y a plus d'un siècle sur des animaux nouveau-nés que l'expansion pulmonaire entraînait de façon réflexe une inhibition de l'inspiration et un allongement de l'expiration.

La mise en jeu de ce réflexe a largement été retrouvée dans les études animales (Knox 1973 ; Sammon 1993 ; Clark 1972). Il a été montré que la prolongation réflexe de l'expiration pouvait être obtenue par une prolongation de l'inspiration mais aussi par des inflations pulmonaires survenant au cours de la phase expiratoire (Clark 1972 ; Knox 1973), sauf dans le dernier quartile de l'expiration (Knox 1973). La présence de ce réflexe a également été démontrée depuis de nombreuses années chez le nouveau-né (Cross 1960 ; Bodegard 1969) puis chez le nourrisson (Rabbette 1991).

La mise en jeu du réflexe de Hering-Breuer a également été décrite dans une situation inverse : lorsque le volume pulmonaire de fin d'expiration est artificiellement réduit, par l'application d'une pression nasale continue ou par une distension abdominale, une augmentation de l'activité respiratoire a été observée, chez l'animal (D'Angelo 2002 ; Meessen 1993) puis chez l'homme adulte sain (Meessen 1994). Ces auteurs suggèrent donc l'implication de ce réflexe à la déflation (Hering-Breuer deflation reflex) dans le contrôle de l'EELV.

L'étude de l'impact de ces réflexes sur la ventilation assistée est beaucoup plus limitée. La prolongation de l'expiration a été observée au décours des insufflations artificielles chez des nouveau-nés et des nourrissons (Greenough 1983 ; Giffin 1996), mais sans étude quantitative de ce réflexe.

En outre, l'ensemble des études réalisées chez le nouveau-né ou le nourrisson sont basées sur des temps inspiratoire et expiratoire mesurés de façon très indirecte, sur les courbes de pressions des voies aériennes ou oesophagiennes. Or, il a été démontré récemment que les temps respiratoires mesurés de cette façon étaient insuffisamment précis (Parthasarathy 2000). La voie efférente de ce réflexe est le nerf phrénique et il serait beaucoup plus précis de mesurer les temps respiratoires idéalement au niveau du nerf phrénique (ce qui est impossible en condition clinique) ou au niveau de l'activité électrique du diaphragme (au moyen d'un enregistrement électromyographique). Nous n'avons pas pu retrouver dans la littérature d'étude de ce réflexe chez le nouveau-né ou le nourrisson basée sur ce type d'enregistrement.

Pourtant, l'étude précise de ce réflexe chez le nourrisson sous ventilation assistée serait très importante. En effet, malgré les progrès des respirateurs artificiels, il existe fréquemment un important asynchronisme entre la ventilation spontanée des nourrissons et les cycles respiratoires

administrés par le respirateur. L'asynchronisme peut constituer un stimulus important du réflexe de Hering-Breuer, avec comme conséquence la perturbation de la respiration spontanée du patient et éventuellement l'augmentation de cet asynchronisme.

Enregistrement de l'activité électrique diaphragmatique

Le faible nombre d'études se rapportant à l'activité tonique diaphragmatique chez le nourrisson et les controverses qui persistent à ce sujet s'expliquent en grande partie par les difficultés d'étude de l'activité électromyographique (EMG) du diaphragme dans des conditions cliniques. La plupart des auteurs utilisent des enregistrements à partir d'électrodes EMG de surface. Cependant, il existe un risque important de contamination du signal recueilli par les électrodes de surface par de l'activité ne correspondant pas au diaphragme, mais aux muscles de la paroi abdominale ou aux muscles intercostaux (Sinderby 1996). Cette contamination est d'autant plus risquée chez le nouveau-né et le nourrisson du fait de sa petite taille.

L'enregistrement par voie oesophagienne présente moins de risque de contamination par les muscles pariétaux, mais il présente également de nombreuses difficultés. La proximité du cœur engendre la nécessité d'un traitement du signal pour supprimer le signal ECG (Sinderby 1997). Surtout, le déplacement important du diaphragme au cours de la respiration (Laing 1988) rend impossible le maintien d'une distance muscle-électrode stable dans le temps si on utilise une seule paire d'électrodes, avec donc une impossibilité d'étudier quantitativement l'activité électrique de façon continue (Beck 1995 ; Beck 1996).

En utilisant un faisceau de 8-9 paires d'électrodes miniaturisées placées le long d'un tube naso-gastrique standard, et en développant un algorithme de filtrage puis de traitement du signal de ces électrodes (technique de double-soustraction), Sinderby et Beck *et al.* ont

progressivement mis au point une méthode d'enregistrement EMG peu artéfactée et surtout avec maintien quasi-constant de la distance muscle-électrode, ce qui rend possible l'étude quantitative de ce signal (Sinderby 1997 ; Beck 1997 ; Sinderby 1999 ; Sinderby 1995). De surcroît, cette méthode est très peu invasive et a été utilisée sans problème dans un contexte clinique. Il s'agit donc d'une méthode validée et recommandée par les sociétés savantes (Aldrich 2002).

Objectifs

Dans les études présentées dans les 2 articles qui suivent, nous avons donc utilisé cette méthode récente et peu invasive pour étudier l'activité diaphragmatique des nourrissons sous ventilation assistée et tenter de répondre à plusieurs questions :

- Le 1er article étudie l'impact de la ventilation assistée sur le mode respiratoire spontanée des nourrissons. Spécifiquement, il étudie l'impact des cycles administrés par la machine sur la durée des temps inspiratoire et expiratoire des cycles spontanés suivants. Ceci permettra de confirmer si le réflexe de Hering-Breuer est activé par les cycles respiratoires artificiels et si l'effet de ce réflexe est prolongé à plusieurs cycles, ou porte simplement sur le cycle suivant. Un objectif secondaire est d'évaluer le synchronisme patient-ventilateur dans un mode supposé synchronisé (ventilation assistée contrôlée intermittente, ou SIMV en anglais).

- Dans le 2ème article, notre objectif est (1) de développer une méthode standardisée pour quantifier l'activité diaphragmatique au cours de l'expiration, (2) de mesurer cette activité chez des nourrissons sous ventilation artificielle, et (3) d'étudier les variations de cette activité tonique lorsque la PEEP est supprimée, ce qui reproduit une situation où l'EELV est artificiellement réduit.

Manuscrit 1

Prolonged Neural Expiratory Time Induced by Mechanical Ventilation in Infants

J Beck, M Tucci, G Emeriaud, J Lacroix, and C Sinderby

Pediatric Research 55: 747–754, 2004

Contribution spécifique du candidat : Le candidat n'a pas participé à la conception ni à la mise en place initiale de l'étude, car il est arrivé dans cette équipe de recherche alors que l'étude venait de débuter. Il a par contre participé activement au recueil des données et des enregistrements d'activité diaphragmatique. Il a contribué à la discussion des résultats et à l'élaboration du manuscrit dans sa phase de correction.

Contribution des co-auteurs : J Beck est à l'initiative de la conception de l'étude et a réalisé la majeure partie des enregistrements. Elle a également fait l'essentiel des analyses de données ainsi que la rédaction du manuscrit. M Tucci et J Lacroix ont participé à la conception de l'étude et à l'inclusion des patients, ainsi qu'à la discussion des résultats et la correction du manuscrit. C Sinderby est à l'origine de la méthode d'enregistrement et a réalisé l'ensemble des logiciels de recueil de données. Il a supervisé la conception de l'étude ainsi que sa réalisation, et il a participé à la discussion des résultats et à l'élaboration du manuscrit.

Prolonged Neural Expiratory Time Induced by
Mechanical Ventilation in Infants

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ABSTRACT

Mechanical ventilation may interfere with the spontaneous breathing pattern in infants because they have strong reflexes that play a large role in the control of breathing. This study aimed to answer the following questions: does a ventilator-assisted breath 1) reduce neural inspiratory time, 2) reduce the amplitude of the diaphragm electrical activity, and 3) prolong neural expiration, within the delivered breath? In 14 infants recovering from acute respiratory failure (mean age and weight were 2.3 ± 1.3 mo and 3.95 ± 0.82 kg, respectively), we measured 1) the electrical activity of the diaphragm with a multiple-array esophageal electrode, and 2) airway opening pressure, while patients breathed on synchronized intermittent mandatory ventilation (mean rate, 11.2 ± 6.5 breaths/min). We compared neural inspiratory and expiratory times for the mandatory breaths and for the spontaneous breaths immediately preceding and following the mandatory breath. Although neural inspiratory time was not different between mandatory and spontaneous breaths, neural expiratory time was significantly increased ($p < 0.001$) for the mandatory breaths (953 ± 449 ms) compared with the premandatory and postmandatory spontaneous breaths (607 ± 268 ms and 560 ± 227 ms, respectively). Delivery of the mandatory breath resulted in a reduction in neural respiratory frequency by 28.6 ± 6.4% from the spontaneous premandatory frequency. The magnitude of inspiratory electrical activity of the diaphragm was similar for all three breath conditions. For the mandatory breaths, ventilatory assist persisted for 507 ± 169 ms after the end of neural inspiratory time. Infant–ventilator asynchrony (both inspiratory and expiratory asynchrony) was present in every mandatory breath and constituted 53.4 ± 26.2% of the total breath duration.

ABBREVIATIONS

EAdi, electrical activity of the diaphragm

HB, Hering-Breuer

Pao, airway opening pressure

SIMV, synchronized intermittent mandatory ventilation

Te, expiratory time

Ti, inspiratory time

INTRODUCTION

Newborn infants have strong reflexes that play a large role in the control of breathing (1). The work of Hering and Breuer in 1868 demonstrated in newborn animals that expansion of the lung reflexly inhibits inspiration—the HB inspiratoryinhibiting reflex—and promotes expiration—the HB expiratory- promoting reflex (2). With respect to mechanical ventilation in infants, it is reasonable to expect that delivery of ventilatory assistance should reflexly reduce neural Ti and neural inspiratory activity within the breath delivered. With respect to the HB expiratory-promoting reflex, one would expect an increase in neural Te during the assisted breath, compared with a spontaneous unassisted breath. The expiratory-promoting reflex has been clinically observed in mechanically ventilated infants, but was described with indirect estimates of neural timing (such as airway or esophageal pressure or flow) to gauge its effects (3–5). In addition to the fact that no quantitative evaluation of the reflex was made, the recent work of Parthasarathy *et al.* (6) has demonstrated that indirect estimates of respiratory timing are in poor agreement with more direct measurements of neural activity.

Much of the available literature on reflex control of breathing has been derived from anesthetized healthy animals. There is only very limited information on reflex control of healthy awake humans, and virtually no information on reflex control in patients with lung disease undergoing ventilatory support (adult or pediatric). To our knowledge, there are no studies evaluating the influence of ventilatory assist on neural timing and neural activity in human infants, with direct measurements of respiratory muscle activity.

With this background knowledge, we asked the following questions: In infants, does a single ventilator-assisted breath *1)* reduce neural Ti, *2)* reduce the diaphragm activation, and *3)* prolong neural Te within the

breath delivered? To answer these questions, we studied the EAdi in infants who were breathing on the SIMV mode of mechanical ventilation. Neural timing and inspiratory EAdi were compared for three conditions: *1)* the mandatory breaths, *2)* the spontaneous breaths immediately preceding the mandatory breath (premandatory spontaneous breath), and *3)* the first spontaneous breath after the mandatory breath (postmandatory spontaneous breath). Our hypothesis was that both the inspiratory-inhibiting reflex and the expiratory- promoting reflex would be elicited during the delivery of the mandatory breaths.

METHODS

Subjects. Fourteen patients (11 boys, three girls) with acute respiratory failure were studied. Their mean (±SD) age, postconceptual age, height, and weight were 2.3. ±1.3 mo, 35.8 ±4.5 weeks, 54.3 ±3.4 cm, and 3.95 ±0.82 kg, respectively (Table 1). Seven of the 14 patients were born premature. The ethical and scientific committees of Hôpital Sainte-Justine, Montreal, Quebec, Canada, approved the protocol. Written informed consent was obtained from the parents of all patients. Patients were mechanically ventilated in the SIMV mode with a relatively low rate (rate, 11.2 ±6.5 breaths/min) and long inflation time (754 ±89 ms). Patients had not received sedation for at least 6 h before the test. They were orally or nasally intubated and mechanically ventilated with a Draeger Babylog 8000 ventilator (Drager, Lubeck, Germany) with the ventilator settings as described in Table 2. The ventilator settings had not been adjusted for 12 h before the test. The most sensitive trigger setting ("1") was used. The mandatory breaths were delivered with a continuous flow of 10 L/min.

Measurements. Electrical activity of the crural diaphragm (EAdi) was obtained using nine miniaturized electrodes mounted on a conventional nasogastric (8F) feeding tube (Benlan Inc., Oakville, Ontario, Canada) and spaced 5 mm apart. Pao was measured from a side port of the

endotracheal tube (Sensym Inc., Milpitas, CA, U.S.A.; _350 cm H2O). The
EAdi and Pao signals were fed into a computer for data acquisition and
online display. Expired volumes were noted from the ventilator display in
nine of the 14 patients every minute, for both the spontaneous and the
mandatory breaths. To achieve this, a stopwatch was used to monitor the
time, and every minute, for the 5-min period, one of the investigators would
note the first spontaneous tidal volume displayed on the ventilator monitor
(on the Draeger Babylog this is displayed breath-by-breath), and then the
first mandatory breath. The system for EAdi measurement was approved
by Health Canada for Investigational Testing of Medical Devices.

Protocol. After endotracheal aspiration, the feeding tube with the
electrodes was passed through the nose or mouth and placed such that
the middle of the array of electrodes was located at the level of the crural
diaphragm. Electrode positioning was achieved by online feedback of the
EAdi signals (7). After insertion and placement of the catheter, the infants
continued to breathe on the prescribed ventilator settings. Ten minutes
after catheter placement, recordings of EAdi and Pao were obtained for a
5-min period.

Data analysis. EAdi signals were processed with algorithms as described
by Sinderby *et al.* (8–10). The root-mean-square of EAdi was calculated
and used as a measurement of EAdi signal strength. Timing and
amplitudes of EAdi were evaluated for *1*) the intermittent mandatory
breaths, *2*) the spontaneous breaths immediately preceding the mandatory
breath, and *3*) the first spontaneous breath after the mandatory breath.
Neural Ti was arbitrarily defined as the difference in time between the
onset of EAdi and the peak of the inspiratory EAdi (Fig. 1). Neural Te was
arbitrarily defined as the difference in time between the peak of the
inspiratory EAdi and the onset of the subsequent inspiratory EAdi (Fig. 1).
Instantaneous neural breathing frequency was calculated as 60/(neural Ti
+ neural Te). For quantification of signal strength, the mean inspiratory

EAdi from baseline to peak (mean EAdi) and the inspiratory change in EAdi from baseline (baseline-to-peak EAdi) were calculated for the three breath conditions. For the mandatory breaths, the relative change in neural Te from the premandatory breath value was expressed as the difference between mandatory breath neural Te and premandatory breath neural Te divided by the premandatory breath neural Te, then multiplied by 100.

Statistical analysis. Statistical analysis was performed with commercially available software (Sigmastat, version 2.0; Jandel Scientific, San Rafael, CA, U.S.A.). Data in text and tables are presented as mean ±SD. One-way repeated-measures ANOVA was used to calculate differences in neural Ti, neural Te, mean EAdi, and baseline-to-peak EAdi among the three types of breaths. A $p < 0.05$ was considered to be significant. Linear regression analysis was used to evaluate the relationship between changes in neural Te and the time of ventilator inflation during neural expiration. Variability was evaluated by the coefficient of variation, expressed as percent.

RESULTS

All patients tolerated the experimental protocol and insertion of the catheter. The number of breaths analyzed for the 5-min study period ranged between 6 and 25 per minute for the mandatory breaths (and postmandatory breaths), and between 8 and 48 per minute for the premandatory spontaneous breaths. Table 3 presents the neural timing and EAdi amplitude variables for the mandatory and the premandatory and postmandatory spontaneous breaths. Neural Ti was similar for the three breath conditions ($p = 0.502$). In all subjects, neural Te was significantly increased for the mandatory breaths (953 ±449 ms) compared with the premandatory (607 ±268 ms) and postmandatory spontaneous breaths (560 ±227 ms; $p < 0.001$). There was no difference in neural Te between the premandatory and postmandatory spontaneous breaths. The mandatory breath resulted in a reduction in neural breathing frequency by

28.6 ±6.4% from the premandatory spontaneous neural breathing frequency (73 ±23 breaths/min; Table 3). Figure 2 displays the tracings of EAdi and Pao for one representative subject (patient 9), and shows how delivery of a mandatory breath causes an increase in neural Te.

With respect to inspiratory EAdi amplitude, neither mean EAdi nor baseline-to-peak EAdi was significantly different for the three breath conditions (Table 3). Figure 3 shows peak EAdi–time profiles averaged for the group during the premandatory spontaneous breaths (solid line), the mandatory breaths (dashed line), and postmandatory spontaneous breaths (dotted line). Although the diaphragm activation pattern is oversimplified in this schematic (only three points of the diaphragm activation pattern are presented), the figure indicates the similarity in inspiratory timing and inspiratory EAdi amplitude for the mandatory, the premandatory, and the postmandatory breaths, with a clear prolongation of neural Te for the mandatory breaths.

Mandatory volumes (7.33 mL/kg) were significantly greater than spontaneous volumes (3.8 mL/kg; p <0.001).

For the mandatory breaths, the mean delay between the onset of EAdi and the onset of ventilator assistance was 95 (range, 10–170 ms) ±39 ms (range, 5–110 ms). This inspiratory asynchrony (increasing diaphragm activation with no matching ventilatory assist) was equivalent to 29% of the neural Ti. A comparison of neural timing and the ventilator inflation time (which was 754 ±89 ms) for the mandatory breaths revealed that the ventilator continued to inflate the patient for 507 ±169 ms after the end of the neural Ti (*i.e.* during neural Te). This expiratory asynchrony period represented 53% of the neural Te. Taking both the inspiratory and expiratory asynchrony together, we found that asynchrony was present during every mandatory breath and constituted on average 53.4 ±26.2% of the total breath duration. Figure 4 represents these findings schematically.

The relative increase in neural Te during mandatory breaths (see formula in the "Methods" section) was related to the time that the ventilator inflated during neural Te (*i.e.* the time that the ventilator continued to inflate after the end of neural Ti; $r2 = 0.66$; $p < 0.01$; Fig. 5). In contrast, the relative increase in neural Te during mandatory breaths was not related to the extra volume delivered by the ventilator (*i.e.* the volume above the spontaneous volume; $r2 = 0.42$; $p = 0.258$).

The coefficients of variation for neural Ti, neural Te, mean EAdi, and baseline-to-peak EAdi are presented in Table 4. There was no significant difference in the coefficients of variation for the premandatory spontaneous breaths, and the mandatory and postmandatory spontaneous breaths.

DISCUSSION

Summary of findings. The results of this study provide evidence for an expiratory prolongation reflex elicited during mechanical ventilation in the SIMV mode in infants. This reflex is confined to the mandatory breath, and does not carry over to the next, postmandatory spontaneous breath. The extent of expiratory prolongation was related to the time that the ventilator delivered assist during neural expiration. Despite these findings, there was no reduction in the mandatory breath neural Ti nor was there reduction in diaphragm activity when mandatory breaths were delivered. This suggests that the anticipated inspiratory-inhibiting reflex was not elicited by SIMV. During the mandatory breaths, there was significant asynchrony between the infant's neural timing and the ventilatory timing.

Critique of methods. To our knowledge, this is the first study to use EAdi for the evaluation of neural timings and diaphragm activation during lung inflation in infants. Consequently, it is important to discuss the reliability of this technique. The EAdi signal strength is dependent on accurate methodology for acquisition (*i.e.* electrode configuration), analysis (7), and

electrode positioning (11). With this technology, electrode configuration has been validated (7, 12), and changes in muscle to electrode distance are accounted for (7, 8)—this solution is of critical importance in the EAdi measurements of infants who have large posterior (caudal) displacement of the diaphragm during tidal breathing (13). The EAdi signal strength is also influenced by factors affecting signal quality, such as cardiac activity, electrode motion artifacts, and noise, technical problems that have been overcome (9, 10, 14). A frequently recurring criticism of the measurement of EAdi with esophageal or implanted electrodes during spontaneous breathing is that the signal strength is affected by changes in muscle length or lung volume. This critique is based on studies of evoked diaphragm compound muscle action potentials (15) or outdated methodology that does not control for interelectrode distance (16). Using appropriate methodology, EAdi obtained during spontaneous breathing is not artifactually influenced by changes in muscle length, chest wall configuration, or lung volume (17, 18).

The HB expiratory-promoting reflex was originally characterized in animals by a prolongation of the expiratory period (apnea) after maintained lung expansion at end inspiration (2). This "end-inspiratory occlusion" (sustained inflation) technique is still used today to evaluate the HB expiratorypromoting reflex in infants (19–21). This method has been said, however, to offset the vagally mediated effects by the hypoxic and hypercapnic stimuli that gradually build during the ventilatory inhibition (*i.e.* occlusion) (22, 23). Rapid lung inflation is an alternative approach to evaluate the expiratorypromoting reflex in infants (1), but this method has also been criticized because of claims that the duration of the resultant apnea was dependent on the chemical composition of the inflation gas (23). On the one hand, in the present study, the SIMV mode of mechanical ventilation provided the model of rapid lung inflation. [And in this case, we

believe that the chemical composition of the delivered gas (*e.g.* the fraction of inspired oxygen) during the rapid lung inflation (mandatory breaths) was the same as the control breath (premandatory and postmandatory spontaneous breaths in this model.] On the other hand, because of the poor interaction between the baby's neural breathing pattern and the delivery of assist, the SIMV mode can also be considered a model of end-inspiratory occlusion (assist was being delivered during neural expiration and an elevated lung volume was maintained). In response to the critique of the method described above, we do not believe that any hypoxic or hypercapnic stimuli could have influenced the reflex during this period of overinflation (times ranged from 210 to 750 ms).

Comparison with previous findings. In terms of the expiratory-promoting reflex, studies have shown that vagal stimulation imposed during early expiration in anesthetized animals prolongs the expiratory time of the perturbed cycle (24, 25). Both Clark and von Euler (26) and Knox (24) showed in animals that the responsiveness of Te prolongation was increased when pulse inflations were delivered further into expiration. It has been demonstrated that there is a timedependence to this response and that when ventilator breaths were delivered in the last quartile of expiration, Te remained unchanged (24, 27). Our findings of an augmentation in neural Te in all infants (range, 14–83%) during the mandatory breaths and the fact that the relative increase in neural Te during the mandatory breath was positively correlated to the duration of ventilatory assist during neural Te (Fig. 5) is consistent with the above findings, and supports the notion that SIMV can induce a vagally mediated expiratory-promoting reflex. A similar relationship to that described in Figure 5 was recently reported using an indirect mechanical index of muscle activation in mechanically ventilated adult patients with acute lung

injury (28), suggesting that mechanical ventilation can also elicit this reflex in adults.

Further evidence that the reflex response in neural Te was confined to the mandatory breath was the fact that the effect did not carry over to the postmandatory spontaneous breath neural Te, which was similar to the premandatory spontaneous breath neural Te. Although the data were not shown, Satoh *et al.* (27) also claimed that single ventilator-delivered breaths affected the timing only of the perturbed breath, and not the subsequent spontaneous breath.

Implications for reflex control of breathing pattern by lung inflation.
Why should the HB expiratory-promoting reflex occur without the inspiratory-inhibiting reflex? The HB inspiratory- inhibiting reflex is usually studied in infants by comparing inspiratory duration of a control breath (Ti measured from Pao) to the Ti of the inspiratory effort during airway occlusion at end expiration (29, 30). With surface electromyography of the diaphragm, Witte and Carlo (31) demonstrated in tracheostomized children a clear prolongation in neural Ti (with similar rate of rise of the EAdi) for occluded efforts at end-expiratory lung volume, compared with spontaneous, unoccluded breaths. A lengthening of the occluded effort presumably reflects the removal of afferent signals of lung expansion. In effect, this is a loading technique (*i.e.* occlusion) used to examine the reflex. Mechanical ventilation, which can be considered an unloading technique, should therefore follow the reverse, *i.e.* that inflation by the ventilator should result in an earlier attainment of the volume threshold for inspiratory termination, and a reduction in neural Ti. We expected to observe this effect in our infants, as demonstrated by Younes *et al.* (32) in cats during ventilatory assist. However, our data showed neither changes in neural Ti nor a decrease in EAdi amplitude during the mandatory breaths when compared with premandatory and post mandatory spontaneous breaths.

The delay between the onset of neural Ti and the onset of ventilatory support was 95 ms or approximately 29% of neural Ti. This delay can be explained by *1*) the patient's neuroventilatory coupling process (defined as the time between the onset of diaphragm activation to the onset of flow generation) (10), *2*) the "trigger delay," which includes the time to recognize an inspiratory change and send a trigger signal to the ventilator, and *3*) the "system delay," which is the time from the trigger signal until the onset of positive pressure in the endotracheal tube (approximately 25 ms according to the manufacturers). Considering that eight of the 14 patients had bronchiolitis and were likely hyperinflated, it could be speculated that the neuroventilatory uncoupling (transformation of onset of neural activity into onset of airway flow at the endotracheal tube) contributed to the total delay.

The delay we observed constitutes a significant inspiratory asynchrony between the patient and the ventilator; only the last 230 ms (approximately 71%) of neural Ti was associated with ventilator inflation. We suggest, therefore, that there was insufficient time to elicit the inspiratory-inhibiting reflex because the threshold for triggering the inspiratory-inhibiting reflex progressively increases during inspiration (26).

This timing discrepancy may also explain why Imsand *et al.* (33), in adult patients with chronic obstructive pulmonary disease, found no evidence for an inspiratory-inhibiting reflex during mandatory breaths in SIMV, *i.e.* no instantaneous change in neural Ti and EAdi amplitude. In that study, patients with chronic obstructive pulmonary disease were studied and the mandatory breaths were pressure-triggered, with trigger levels set at _1 to _2 cm H_2O. Only two of the five subjects studied were ventilated with applied positive end-expiratory pressure. Therefore, there was likely a considerable delay between the onset of neural activity and the onset of delivered assist for the mandatory breath in the work of Imsand *et al.* (33). It can be hypothesized, therefore, that if a synchronized mode of

mechanical ventilation were to be implemented (*i.e.* matching the initiation and termination of ventilatory assist with the patient's neural timing), the opposite findings of our study would have been obtained, *i.e. 1)* elicitation of the inspiratory-inhibiting reflex, as demonstrated by Younes *et al.* (32) with a phrenic nerve–controlled (synchronized) respirator, and 2) *no* elicitation of the expiratory-promoting reflex (if the ventilator is cycled off neurally).

Further evidence for a contrast between the two components of the HB inflation reflex (*i.e.* the absence of the inspiratoryinhibiting reflex and presence of the expiratory-prolonging reflex) has been observed in animal studies. Clark and von Euler (26) found that subthreshold inflations, which were able to prolong expiration, were without effect during inspiration. In the present study, however, we obtained volume measurements from the ventilator in nine patients. Despite significantly greater volumes for the mandatory breaths (compared with the premandatory spontaneous breaths), we can only speculate that these greater volumes were not sufficiently timed with the patient's neural inspiration to elicit the inspiratory-inhibiting reflex, but could still elicit the expiratory-promoting reflex. In summary, on the basis of the literature and the present findings, it still remains to be shown that the HB inspiratory-inhibiting reflex is elicited by mechanical ventilation in infants.

Clinical implications. Although not frequently used in adults (34), SIMV is still frequently used as a tool for providing support and for weaning from mechanical ventilation in the infant setting (35). It was originally thought that delivery of the mandatory breath would reflexly deactivate the inspiratory muscles, and that the SIMV mode would allow the combination of unassisted breathing with respiratory muscle rest (36). The present study shows in infants, similar to the findings of Imsand *et al.* (33) in adults, that there is no reflex deactivation of the diaphragm during the delivery of the mandatory breaths. However, neither the study of Imsand *et al.* (33)

nor the present study used modes of mechanical ventilation in which patient and ventilator timings were matched.

In the present work, infant–ventilator asynchrony was present in every mandatory breath and consisted of 53% of the total breath duration (inspiratory and expiratory asynchrony combined). Most of the infant–ventilator asynchrony was associated with expiratory asynchrony, in which the ventilator continued to deliver assist despite the fact that diaphragm activation was decreasing. According to the literature, there are severe consequences of expiratory asynchrony, the most important being that active exhalation against positive-pressure inflation develops pneumothoraces (37), barotrauma (3, 38), and cerebral blood flow fluctuations, which can be associated with intraventricular hemorrhage (39). In extreme cases of expiratory asynchrony, use of sedation or muscle paralysis is sometimes necessary (38, 40, 41). In the adult literature, it is clear that poor off-cycling of mechanical ventilation results in an increased work of breathing (42) and patient discomfort (43). The present work therefore highlights the importance of online monitoring of diaphragm activation during mechanical ventilation, particularly with respect to the adjustment of cycling off ventilatory assist.

Variability in breathing pattern. There are no reports in the literature concerning the variability of timing and amplitude of EAdi in mechanically ventilated infants. Te and Ti measured via flow signals in nonmechanically ventilated preterm infants indicate a larger variability in Te (81%) than Ti (25%) (44). Our data show that there was no significant difference in the coefficients of variation for neural Ti and neural Te. Moreover, there were no significant differences of variability in all measurements for the three breath conditions (premandatory spontaneous breaths, mandatory breaths, and postmandatory spontaneous breaths). On the basis of the observation of a high variability in diaphragm activation variables, in addition to the instantaneous changes in breathing pattern reflexly caused by

overinflation, one could consider the importance of recently developed modes of mechanical ventilation that adapt on a breath-to-breath basis to changes in respiratory drive (*e.g.* proportional assist ventilation and neurally adjusted ventilatory assist) (45).

Acknowledgments. The authors thank M. Norman Comtois, M. Sylvain Morneau, R.T., and Mlle Roxanne Trahan, R.N., for their help during the studies. We also thank Dr. Jim Duffin for his comments on the manuscript.

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Figure 1. Neural Ti was arbitrarily defined as the difference in time between the onset of EAdi and the peak of the inspiratory EAdi. Neural Te was arbitrarily defined as the difference in time between the peak of the inspiratory EAdi and the onset of the subsequent inspiratory EAdi.
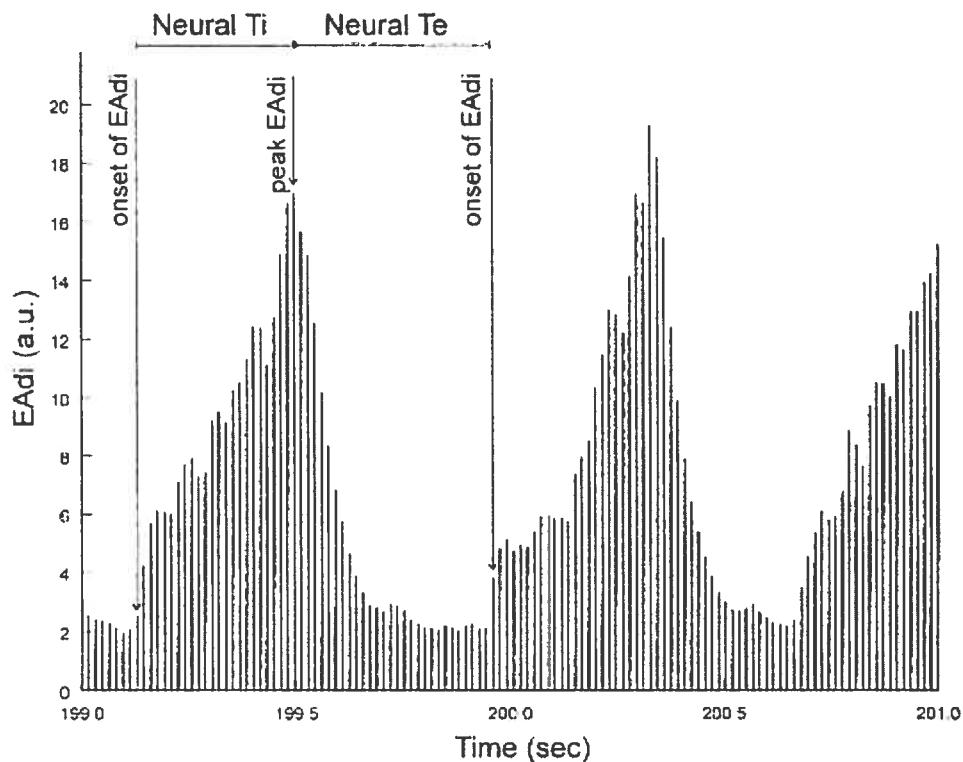
Figure 2. Tracing of Pao with corresponding neural Te in one representative subject. Pao, with shaded areas indicating corresponding neural Te period. Premandatory spontaneous breath neural Te is shaded *light gray* and bound by *small dashed lines*. Mandatory breath neural Te is shaded *dark gray* and bound by *solid lines*. Postmandatory spontaneous breath is shaded *light gray* and bound by *long dashed lines*. This example shows in one subject (no. 9) the increase in neural Te for the mandatory breaths compared with the neural Te for the premandatory and postmandatory spontaneous breaths.
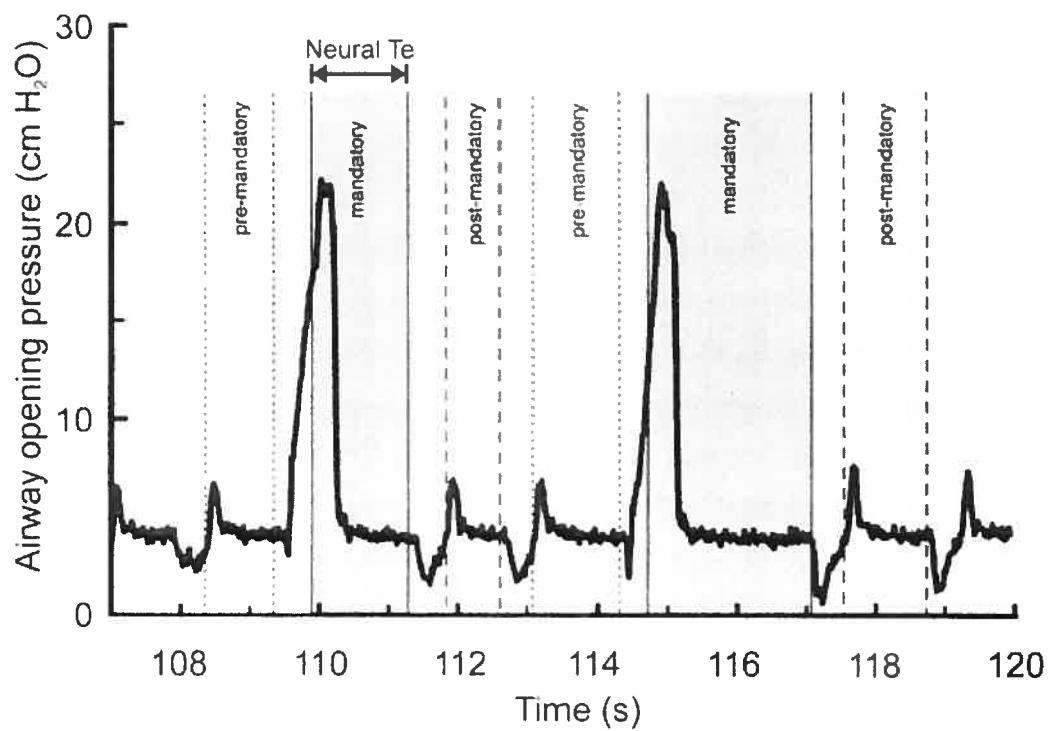
Figure 3. EAdi–time profile for group mean data. Data are presented for group mean values ±SEM. There was no significant difference in neural timing and EAdi amplitude on inspiration for the premandatory spontaneous breaths (*solid line*), mandatory breaths (*dashed line*), or postmandatory spontaneous breaths (*dotted line*). Neural Te was prolonged significantly for the mandatory breaths (*dashed line*). Note that this is not a representation of the shape of the EAdi recruitment pattern, but simply a representation of three points: the onset of EAdi, the peak of EAdi, and the onset of the EAdi for the subsequent breath.
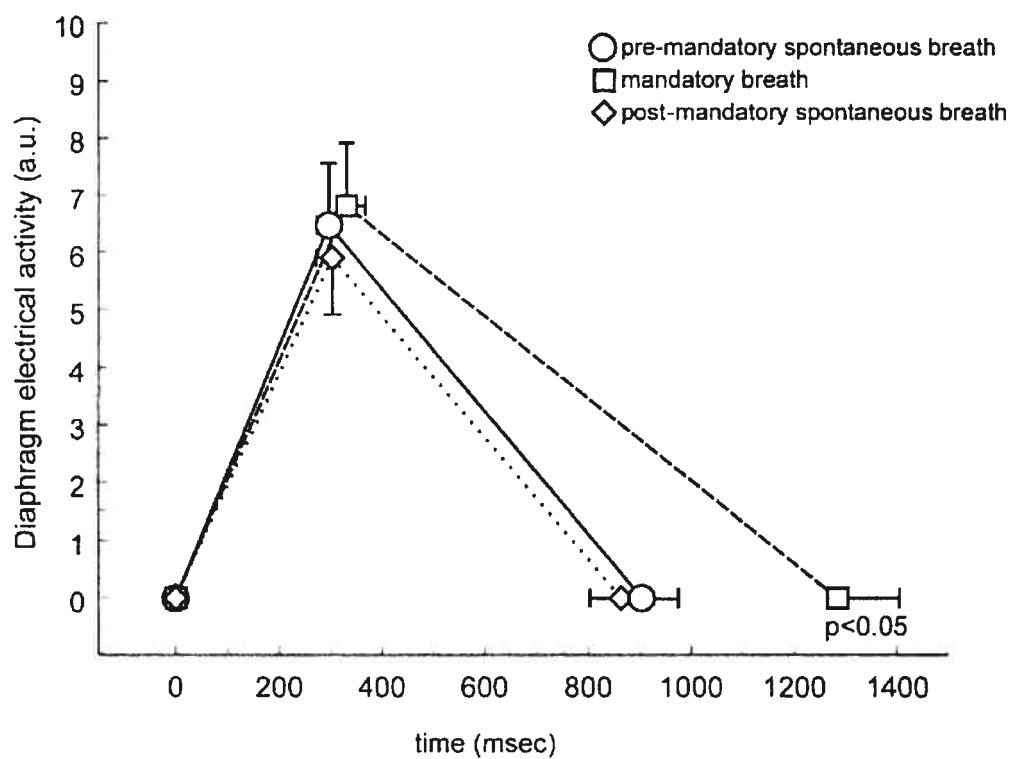
Figure 4. Patient–ventilator interaction during mandatory breaths. Schematic representation of patient neural timing (*upper bar*) and ventilator timing (*middle bar*) during mandatory breaths. *Upper bar,* neural Ti (*gray area*) and neural Te (*white*) for the group data are presented. *Middle bar,* periods describing ventilator timing are displayed, including trigger delay and ventilator Ti. *Bottom bar,* periods of infant–ventilator synchrony (*white*) and asynchrony (*black*).
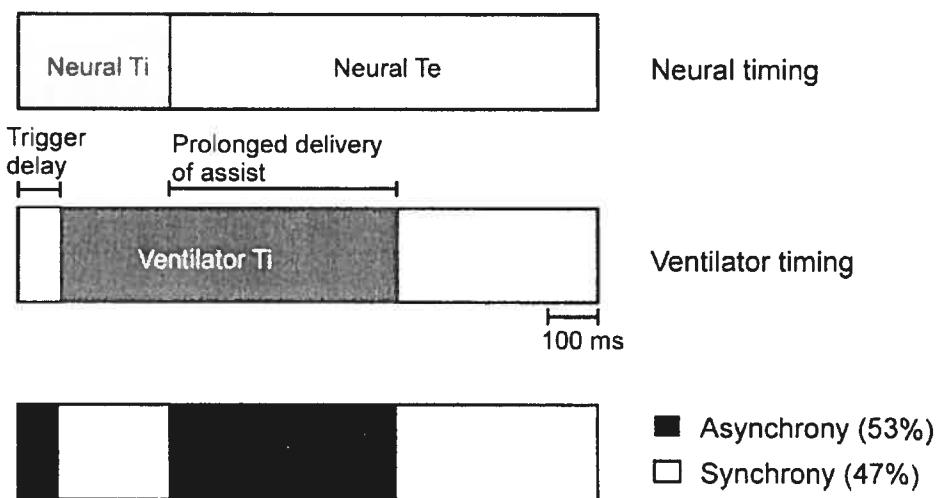
Figure 5. Relationship between change in neural Te and time that ventilator inflation coincides with neural expiration. For the 14 patients studied, figure shows relationship between the relative change in neural Te for the mandatory breaths (from the neural Te of the preceding spontaneous breath; *y* axis) and the time that the ventilator delivers pressure during the neural Te period (*x* axis).
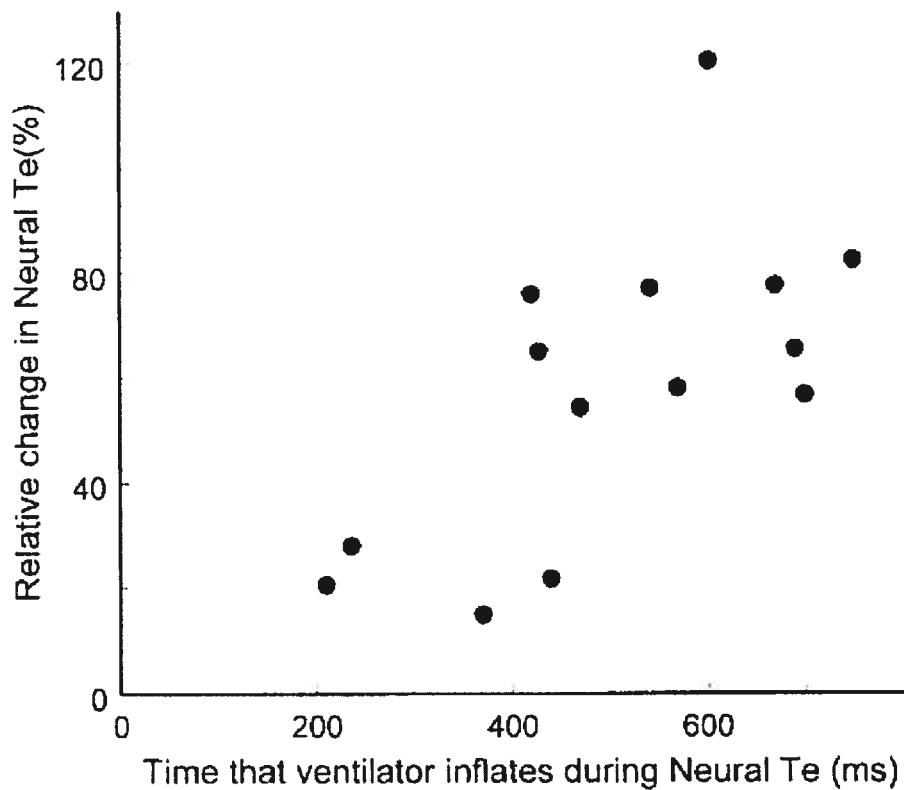
Table 1. *Patient anthropometric data and admission diagnosis*

Patient	Sex	Age (mo)	Postconceptual age (wk)	Height (cm)	Weight (kg)
1	M	4	28	51	2.7
2	M	2	39	57	5.6
3	F	6	35	50	2.9
4	M	1	40	53	4.3
5	F	4	36	60	4.0
6	M	4	29	48	3.7
7	M	4	29	54	4.6
8	M	0.5	40	54	3.3
9	M	2	33	51	2.8
10	F	0.5	40	58	4.6
11	M	2	37	55	4.5
12	M	1.5	40	56	4.3
13	M	3	35	55	4.2
14	M	1	40	58	3.8

Table 2. *Ventilator settings*

Patient	SIMV rate (breaths/min)	PEEP PIP (cm H₂O)	FiO₂ (%)	Measured ventilator T (ms)
1	10	5 35	40	750
2	10	3 33	30	710
3	10	3 21	35	870
4	20	4 35	55	830
5	10	4 32	40	760
6	5	5 22	30	960
7	25	6 29	84	690
8	10	4 21	80	730
9	22	5 27	30	780
10	5	5 21	25	680
11	10	4 14	30	594
12	10	5 24	30	747
13	5	3 28	25	750
14	5	5 33	25	707

Abbreviations used: PIP, peak inspiratory pressure. PEEP, positive end-expiratory pressure. FiO₂, fraction of inspired o

Table 3. *Neural timing and EAdi amplitude for premandatory spontaneous breaths, mandatory breaths, and postmandatory breaths*

	Premandatory spontaneous breath	Mandatory breath	Postma...
Neural Ti (ms)	297 ± 87	331 ± 139	
Neural Te (ms)	607 ± 268	953 ± 449*†	
Neural breathing frequency	73 ± 23	53 ± 18*†	
Baseline-to-peak EAdi (a.u.)	6.47 ± 4.10	6.82 ± 4.11	
Mean EAdi (a.u.)	4.73 ± 2.23	4.70 ± 2.23	

* $p < 0.001$, significantly different from premandatory spontaneous breath value
† $p < 0.001$, significantly different from postmandatory spontaneous breath value
‡ $p < 0.05$, significantly different from premandatory spontaneous breath value
§ $p < 0.05$, significantly different from postmandatory spontaneous breath value
Abbreviation used a.u. arbitrary units

Table 4. *Factor variation expressed as coefficient of variation for the premandatory spontaneous breath, postmandatory spontaneous breaths*

	Coefficient of variation (%)	
	Premandatory breath	Mandatory breath
Neural Ti	30.1 ± 6.9	31.2 ± 15.7
Neural Te	21.2 ± 7.8	26.7 ± 10.2
ΣEAdi	25.3 ± 8.3	29.8 ± 19.6
EAdi	31.7 ± 5.2	39.4 ± 16.7

Abbreviations used: ΣEAdi, mean amplitude of inspiratory EAdi; EAdi, baseline to peak of inspiratory EAdi

Manuscrit 2

Diaphragm Electrical Activity During Expiration in Mechanically Ventilated Infants

G Emeriaud, J Beck, M Tucci, J Lacroix, and C Sinderby

Pediatric Research 59: 705–710, 2006

Contribution spécifique du candidat : Le candidat a participé à la conception et à la mise en place de l'étude. Il a effectué tout le recueil des données cliniques et a participé à tous les enregistrements d'activité diaphragmatique. Il a réalisé la majeure partie du traitement des données recueillies et de l'analyse des résultats. Il a notamment établi la méthode de quantification de l'activité tonique. Il a rédigé la première version de ce manuscrit, puis a participé aux différentes phases de correction.

Contribution des co-auteurs : J Beck est à l'initiative de la conception de l'étude. Elle a participé à la réalisation de tous les enregistrements. Elle a activement participé aux discussions des résultats ainsi qu'à l'élaboration du manuscrit. M Tucci et J Lacroix ont participé à la conception de l'étude ainsi qu'à la discussion des résultats et aux corrections du manuscrit. C Sinderby est à l'origine de la méthode d'enregistrement et a réalisé l'ensemble des logiciels de recueil de données. Il a supervisé la conception de l'étude ainsi que sa réalisation, et a participé à la discussion des résultats et à l'élaboration du manuscrit.

DIAPHRAGM ELECTRICAL ACTIVITY DURING EXPIRATION IN MECHANICALLY VENTILATED INFANTS

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ABSTRACT

The presence of diaphragm electrical activity (EAdi) during expiration is believed to be involved in the maintenance of end expiratory lung volume (EELV) and has never been studied in intubated and mechanically ventilated infants. The aim of this study was to quantify the amplitude of diaphragm electrical activity present during expiration in mechanically ventilated infants, and to measure the impact of removing positive end expiratory pressure (PEEP) on this activity. We studied the EAdi in 16 ready-to-be weaned intubated infants who were breathing on their prescribed ventilator and PEEP settings. In all 16 patients, 5 minutes of data were collected on the prescribed ventilator settings. In a subset of 8 patients, the PEEP was briefly reduced to zero PEEP. EAdi was recorded with miniaturized sensors placed on a conventional nasogastric feeding tube. Airway pressure was also measured. For each spontaneous breath, we identified the neural inspiration, and neural expiration. Neural expiration was divided into quartiles Q1, Q2, Q3 and Q4, and the amplitude of EAdi calculated for each Q1-Q4 represented 95 ± 29 %, 31 ± 15 %, 15 ± 8 %, and 12 ± 7 % of the inspiratory EAdi amplitude (n=16). EAdi for Q3-Q4 significantly increased during zero PEEP, and decreased after reapplication of PEEP ($p < 0.05$) n=8. These findings confirm that the diaphragm remains partially active during expiration in intubated and mechanically ventilated infants, and that removal of PEEP affects this tonic activity. This could have potential implications on the management of PEEP in intubated infants.

ABBREVIATIONS

EAdi, electrical activity of the diaphragm

Paw, airway pressure

PEEP, positive end-expiratory pressure

ZEEP, zero PEEP

SIMV, synchronized intermittent mandatory ventilation

Te, expiratory time

Ti, inspiratory time

EELV, end-expiratory lung volume

INTRODUCTION

The diaphragm is primarily known as an inspiratory muscle that is active during inspiration and relaxed during expiration. However, in healthy premature and full term newborns, it has been demonstrated that electrical activity of the diaphragm - measured with electrodes on the surface of the chest wall- may persist throughout expiration, suggesting a "tonic" activity of the respiratory muscles (1, 2, 3, 4). Lopes demonstrated that changes in tonic activity of the diaphragm were associated with changes in end-expiratory lung volume (EELV), and provided the original physiological explanation that persistent diaphragmatic activity during the exhalation period helps to regulate EELV in infants (1). In healthy full term or premature infants, the EELV is higher than the relaxation volume, the latter being determined by the passive mechanical properties of the respiratory system (1, 3, 5). It is only after one year of age that the EELV coincides with the relaxed lung volume (6); prior to this age, adapting reflexes must compensate for the reduced EELV. In newborns, persistence of diaphragm activity during expiration, in combination with the flow-braking action of the laryngeal adductor muscles (7), a high respiratory rate and a reduced time-constant of the respiratory system has been suggested to contribute to an active elevation of EELV (5, 8, 9, 10, 11). However, in intubated and mechanically ventilated infants, the presence of an endotracheal tube does not allow for expiratory flow braking via the laryngeal muscles and likely increases their dependence on tonic diaphragm activity (i.e. diaphragm activity during exhalation). To our knowledge, no data on this has yet been reported in human infants.

The aims of the present study were to: 1) develop a method to quantify the amplitude of diaphragm electrical activity (EAdi) during expiration in mechanically ventilated infants (i.e. tonic diaphragm activity), 2) determine if tonic EAdi is present during prescribed positive end

expiratory pressure (PEEP) and if removal of PEEP produces changes in tonic EAdi.

METHODS

Subjects

Sixteen patients (11 males, 5 females) with various diagnoses were included (table 1). Patients were intubated and mechanically ventilated in synchronized intermittent mandatory ventilation (SIMV) mode with a Draeger Babylog 8000 ventilator (Draeger, Lubeck, Germany). The patient inclusion criteria were: Infants recovering from acute respiratory failure deemed ready for extubation, aged 3 days–6 months. According to Colin et al (6), the Hering-Breuer reflexes are present and strong for this age range. The patients were breathing with the same ventilator parameters for at least 2 hours prior to the study. Patients with neuromuscular disease, bleeding disorders, cardiovascular instability, depressed central respiratory drive, esophageal malformations, phrenic nerve damage as well as patients having undergone esophageal surgery were excluded.

The protocol was approved by the ethical and scientific committees of Sainte-Justine Hospital, Montreal, Quebec, Canada. Written informed consent was obtained from the parents of all patients.

Measurements

Electrical activity of the crural diaphragm (EAdi) was obtained using nine miniaturized electrodes mounted on a conventional nasogastric (8F) feeding tube (Benlan Inc. Oakville, Ontario, Canada), and spaced 5 mm apart. Airway pressure (Paw) was measured from a side port of the endotracheal tube (Sensym Inc., Milpitas, CA, USA; ±350 cm H_2O). The EAdi and Paw signals were fed into a computer for data acquisition and on-line display.

Protocol

Studies were conducted a few hours prior to extubation, and patients had not received sedation for at least 6 hours prior to the test. Following endotracheal aspiration, the feeding tube with the electrodes was inserted. Optimal electrode positioning was achieved by on-line feedback of the EAdi signals (12).

Following catheter insertion, the infants continued to breathe on the prescribed ventilator and PEEP settings. Ten minutes after catheter placement, recordings of EAdi and Paw were obtained in all 16 subjects during a 5-minute period on the prescribed PEEP.

In 8 patients, a one-minute period of zero end-expiratory pressure (ZEEP) was introduced at the end of the 5-minute period to determine its influence on tonic EAdi. Following this period, the patients were returned to their prescribed PEEP level.

Data acquisition and signal analysis

EAdi and Paw data were acquired, processed on-line and displayed. EAdi signals were continuously and automatically processed with algorithms described by Sinderby et al (13, 14, 15). The EAdi signal strength was quantified by the root-mean-square. The "true" noise level of the signal was estimated during short periods of apnea, defined as periods where both EAdi and Paw signals were flat during more than one second (Figure 1).

For the conditions of prescribed PEEP and ZEEP, we analyzed the spontaneous breaths only, and excluded the mandatory breaths and the post- mandatory breaths. For each spontaneous breath, we identified and placed time cursors for: (i) the onset of EAdi, (ii) the peak of EAdi, and (iii) the onset of the subsequent neural inspiratory effort, as previously described (16) (Figure 1). We excluded all breaths where this identification

was problematic due to interference with ECG signal. Neural inspiratory time (neural Ti) and neural expiratory time (neural Te) were defined from the EAdi tracings (Figure 1). The entire neural Ti was used to calculate the mean inspiratory amplitude of EAdi. In order to quantify the EAdi amplitude during neural expiration, Nte was divided into quartiles (Q1-Q4) (Figure 1), and the mean EAdi amplitude was calculated for each quartile. The mean EAdi of each quartile was expressed in percentage of the mean inspiratory EAdi, after subtraction of the noise level.

Statistical analysis

Data were analyzed by two independent investigators (GE and a technician). The agreement between observers was estimated with the intraclass correlation coefficients (ICC), calculated with Deyo's method (17) for each EAdi quartile. Inter-observer reproducibility is considered to be good when ICC>0.75 (17).

In all 16 patients, the mean inspiratory EAdi, and the mean EAdi for Q1-Q4 were calculated for the 5 minutes of the prescribed PEEP period. In the subgroup of 8 patients, during ZEEP, data were analyzed during the minute preceding ZEEP (Pre-ZEEP), the minute during ZEEP (ZEEP), and the minute following ZEEP (Post-ZEEP). Statistical analysis was performed with commercially available software (Statview 5.0, SAS Institute Inc.). One way repeated measures ANOVA was used to determine differences between the different quartiles during prescribed PEEP, and between Pre-ZEEP, ZEEP, and Post-ZEEP. The difference between a quartile and the common noise level was estimated with a paired t-test. A p-value < 0.05 was considered to be significant.

All data are expressed as mean and standard deviation (mean ± SD).

RESULTS

The patient data is summarized in table 1. Their mean (± SD) age, height, and weight were 2.3 ± 1.3 months, 54 ± 4 cm, and 4.0 ± 0.8 kg, respectively. The baseline ventilator settings are presented in table 1. The mean prescribed FIO2 for the group was 35±13%.

Determination of tonic EAdi at prescribed level of PEEP (n=16)

The average SIMV rate was 10.0 ± 4.3 breaths per minute and the average prescribed PEEP level was 3.9 ± 0.8 cmH_2O.

Figure 1 shows an example of EAdi and Paw tracings for two consecutive spontaneous breaths followed by an apnea period, and depicts how diaphragm activation persists (above the noise level) throughout the neural expiration period. The pattern of tonic EAdi could attain a relatively constant level as in Figure 1, but could also be very variable as depicted in Figure 2 for several patients.

The mean EAdi amplitude calculated during Q1, Q2, Q3 and Q4 is shown in Figure 3 (n=16). The EAdi observed during Q1 was similar to the EAdi observed during the neural inspiratory period. EAdi decreased during Q2 ($p<0.05$), to stabilize at its lowest level during Q3 and Q4 ($p<0.05$). No differences were observed between Q3 and Q4, which constituted 15 ±8 % and 12 ±7 % of inspiratory EAdi, respectively. All quartiles showed significant magnitudes above the noise level ($p<0.05$). The mean noise level for the group was 0.8±0.3 arbitrary units (range 0.3-1.4).

Activity during Q1 was more correlated to the inspiratory EAdi than were the later quartiles, the correlation coefficients between inspiratory EAdi and Q1, Q2, Q3 and Q4 were 0.58 ± 0.20, 0.26 ± 0.26, 0.24 ± 0.26, and 0.19 ± 0.29, respectively ($p<0.01$; one way repeated measure anova).

Individual mean values of EAdi observed during exhalation on prescribed settings of mechanical ventilation are presented in Table 1. Because EAdi stabilized and was comparable during Q3 and Q4, we grouped these 2 quartiles and considered their combined activity as "tonic" activity of the diaphragm. No relationship was found between the level of tonic EAdi and the underlying condition.

The coefficients of variation for EAdi calculated during neural inspiration, Q1, Q2, Q3, and Q4 were 53 %, 44 %, 45 %, 44 %, and 71 % respectively.

The mean neural inspiratory and expiratory times were 0.27 ($\pm$ 0.07) s., and 0.69 ($\pm$ 0.24) s., respectively for all 16 patients for the 5 minute period at the prescribed PEEP.

Impact of removing PEEP on tonic EAdi (n=8)

A subset of the patients (n=8, patients 9-16) were studied for this intervention (Table 1).

The mean and individual levels of tonic EAdi (Q3 and Q4 combined) measured immediately before, during and immediately after the short period of ZEEP are presented in Figure 4. In all infants but one, tonic activity increased during ZEEP ($p<0.05$). Returning PEEP to its baseline level, tonic EAdi returned ($p<0.05$). As indicated in Table 2, the change from baseline PEEP to ZEEP reduced neural Ti and neural Te, and therefore increased instantaneous neural breathing frequency ($p<0.05$). Figure 5 demonstrates in one patient the response of the EAdi to removing PEEP.

Reproducibility

The intraclass correlation coefficients (ICC) calculated for the EAdi timing determinations by two investigators were all above 0.75, and were 0.99, 0.83, 0.94, 0.96, 0.93 for neural inspiration, Q1, Q2, Q3 and Q4, respectively.

DISCUSSION

In the present study we found in intubated and mechanically ventilated infants, that the diaphragm electrical activity (EAdi) after inspiration decreases rapidly during the first half of the neural expiration and plateaus during the second half of the neural expiration to a level which is significantly higher than the noise level. This "tonic" EAdi was observed in every patient and represented 12 – 15 % of the mean inspiratory EAdi at the prescribed level of PEEP (~4 cm H2O). Upon removal of PEEP, the tonic EAdi increased, and immediately returned (decreased) to its initial level when the prescribed PEEP level was re-instituted. Based on these studies, we could anticipate that there should be a relationship between tonic EAdi and PEEP. Studies in intubated rabbits with lung injury show increased tonic diaphragm activity when no PEEP is applied (unpublished data). Systematic increases in PEEP suppressed the tonic diaphragm activation and increased the phasic activation. The interpretation of these data was that during insufficient PEEP, the diaphragm is activated to defend collapse of lung units, perhaps triggered via receptors in the lung. When the PEEP is increased, it recruits the lung and replaces the action of the tonic diaphragm activation, allowing the diaphragm to perform phasic breathing.

Studies in intubated animals show that continuous negative airway pressure, lung deflation (18), abdominal distension (19), and acute lung injury (unpublished data), result in tonic activation of the diaphragm. The tonic activity was abolished by vagotomy (19, unpublished data). Animal

models have also been used to demonstrate that lung deflation (20, 21) and pulmonary edema (22) increase the activity of vagal efferents, and that direct stimulation of vagal afferents causes tonic activation of the diaphragm (23). Application of PEEP to the intubated airway immediately reduces the activity of the vagal efferents (20, 21) and reduces the tonic activity of the diaphragm (unpublished data).

In the clinical setting, infants are frequently provided with CPAP or PEEP to prevent EELV decreases to less than the relaxation volume. Usually this PEEP adjustment is made on an empirical basis. The presence of tonic EAdi in all 16 patients despite applied PEEP levels of 3 to 5 cm H2O, which is considered to maintain EELV above relaxation volume in normal infants (24) suggests that the applied PEEP may have been too low or that some tonic activity always occurs in intubated infants. Based on the above, the authors of the present study suggest that the presence of tonic diaphragm activity and its modulation by PEEP, may describe a vagal reflex acting to adjust EELV and to prevent a derecruitment of the lungs.

Besides its possible role in the maintenance of EELV, another possible explanation for the presence of tonic EAdi in intubated infants is the presence of non-respiratory related activity of the diaphragm, e.g. related to postural activities (25), or upper limb movement (26). As well, crying, micturation, and defecation could potentially cause EAdi to be present during expiration. To our knowledge, the importance of this contribution is poorly described in infants, however, there is little support that any of the above reasons should persist over long periods and that it should be observed in all 16 infants (and that ZEEP would increase the tonic EAdi). Kosh et al (5) reported that electrical activity measured with surface electrodes positioned on the chest wall was not affected by

changes from supine to up-right position. In the present study, infants were studied in supine position, while not agitated. All periods of crying were excluded from analysis and only one baby defecated during the study. Therefore, we do not find it likely that factors unrelated to breathing were the cause for our findings of diaphragm activity during the expiratory phase in all infants.

The presence of tonic diaphragm electrical activity may have important physiological and clinical consequences. The maintained diaphragm activity during expiration likely keeps diaphragm muscle tension higher than if it were relaxed, increasing the diaphragm's metabolism and potentially reducing diaphragm blood circulation (27), both factors which will make the diaphragm more susceptible to peripheral muscular fatigue. In the past, respiratory muscle fatigue was predicted using indices such as the "pressure time product" or "tension time index". Both calculations assume that expiration is passive (28), whereas our findings of EAdi persisting throughout the entire neural expiration may indicate an infinite duty cycle. Diaphragm fatigue could thus be more likely to develop in the case of augmented tonic diaphragm activity. If this is true, this may in part explain the success in treating respiratory failure with CPAP. Monitoring of tonic EAdi could then help in the adjustment of ventilator settings in order to avoid excessive levels.

Another condition that has been associated with tonic EAdi is bronchoconstriction (29). In the present study, there were 8 bronchiolitis patients in whom there were no tendency to have increased tonic EAdi relative to the other infants studied. Moreover, diaphragm activation during the expiratory period was significantly present in all patients (with bronchoconstriction or not).

Despite many studies assuming a specific involvement of the diaphragm in controlling EELV in infants (5, 8, 9, 10), only Reis et al (30) have used esophageal recordings of diaphragm activity and reported that it is uncertain whether the tonic electrical activity measured actually relates to the diaphragm. Esophageal recording of EAdi is the only method currently available to avoid cross-talk interference from muscles other than the diaphragm (31, 32). Reis et al (30), however, reported negligible tonic EAdi from esophageal electrodes, despite the fact that their surface recordings indicated a clear presence of tonic EAdi. These findings are markedly different from the findings of the present study. We can think of at least two possible reasons for the different results obtained by Reis (30) and those obtained in the present study. First, in the present study, a standardized method was implemented to acquire and analyze the diaphragmatic activity (33). The double subtraction technique was used to localize the position of the diaphragm on the electrode array, which eliminates filtering effects related to electrode positioning (13). Reis et al (30) used a single electrode pair on their esophageal catheter and had no method to verify that the electrodes actually remained in the same position with respect to the diaphragm during both inspiration and expiration. In fact, Beck et al (34, 12) demonstrated that electrode filtering is very powerful and that movement of the diaphragm relative to the electrodes disqualifies all quantitative evaluation of EAdi. Moreover, respiratory movement of the crural diaphragm has been demonstrated to be significant in infants (35). The second potential explanation to explain the discrepancy between the results of Reis et al and our findings relate to endotracheal intubation. Non-intubated infants exhibit laryngeal braking of expiratory flow that has been associated with the maintenance of EELV and reduced tonic EAdi (7, 2). Beck et al (unpublished data) have recently demonstrated in rabbits with acid-induced lung injury, that the tonic activity observed during intubation and zero PEEP is reduced after extubation.

Thus, because an endotracheal tube was in place for all patients in the present study, upper airway regulation of EELV was not possible, and it may be speculated that tonic EAdi played a more important role in maintaining EELV.

The data obtained in the present study demonstrates the complexity of defining neural inspiration and neural expiration. Our data shows that EAdi

persists until the end of expiration. We considered the Q3 and Q4 activity as tonic activity because during this period, the EAdi stopped and the activity remained stable and significantly higher than the noise level. Moreover, the correlation coefficients between inspiration and the different quartiles also show that Q3 and Q4 are not related to inspiration, contrary to Q1. We used the peak activity to delimit the beginning of Q1 however some diaphragm motor units may not be deactivated, explaining the relation between Q1 and inspiration. If we believe that the presence of tonic activity is related to the Hering-Breuer deflation sensitive reflex, then it can also explain its presence only during expiration. Moreover, this reflex is involved in a cycle-by-cycle regulation of lung volume could explain the high variability of tonic activity that we measured.

Several problems and potential criticisms inherent to these findings and to the methodology used must be addressed.

Perhaps the most important question that arises from this study is how we can be certain that the signal we measured and quantified during neural expiration was physiological and originated from the diaphragm and did not simply constitute noise. The cross-correlation algorithm (12) was implemented continuously during inspiration and expiration, every 16 ms, and a predictable pattern of EAdi signals representing diaphragm activity

along the array of electrodes (signals were reversed above and below the diaphragm) was observed for both inspiratory EAdi and the Q1-Q4 periods.

The present study showed tonic EAdi in all 16 infants even when PEEP was applied. This could suggest that despite the application of PEEP, certain areas of the lung may not be recruited, and vagal afferents sensitive to lung collapse may be activated. We cannot neglect the fact that the endotracheal tube was suctioned prior to the study, an action that is known to decrease EELV transiently (36). Therefore, we do not know if our patients had a normal EELV, even at the baseline PEEP level.

In the present study, we assumed that removing the PEEP level would reduce EELV, and that this would alter the tonic EAdi. Although we did not measure the EELV in our patients, several studies report a positive correlation between increasing PEEP and EELV in mechanically ventilated infants (24, 37), although the amount of change in EELV per cm H2O of PEEP varies amongst the studies. Regardless of the magnitude, we believe that it is reasonable to assume that the EELV was reduced by the PEEP removal in the present study.

The validity and reliability of esophageal recordings of EAdi has been criticized for various reasons, including possible contamination by non-diaphragmatic activity, variation in signal strength caused by changes in muscle to electrode distance during respiration, or by changes in lung volume (38). However, the methodology that we used for acquisition and analysis of EAdi has been validated to address these problems (33). Contamination of EAdi by non-diaphragmatic activity occurs essentially when surface recording is used (31). Esophageal measurements of EAdi are less subject to contamination, because the distance between electrodes and abdominal or intercostal muscles is larger (39). The problems associated with the muscle-to-electrode distance (12, 34), and

with the influence of cardiac activity and esophageal peristalsis on the signal strength (13, 40) have both been resolved. Thus, the method utilized to analyze and quantify EAdi is reliable and reproducible and accurately provided the data presented in this study.

CONCLUSION

The findings obtained confirm that the diaphragm remains partially active during expiration of spontaneous breaths in mechanically ventilated infants at PEEP levels that are usually prescribed just prior to extubation. The results also show that removal of PEEP increases the tonic activity of the diaphragm. This could have potential implications on the management of PEEP in intubated and mechanically ventilated infants.

Acknowledgments

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FIGURES

Figure 1. *Definition of the periods of analysis for each spontaneous breath.* Neural inspiration and expiration were defined by the diaphragm electrical activity (see text for details). Neural expiration was divided into four quartiles (Q1, Q2, Q3, and Q4). Vertical solid lines identify the onset and the peak of EAdi. Vertical dashed lines separate the quartiles. Horizontal dashed lines represents the noise level. Pao: airway opening pressure.

Figure 1 (Emeriaud et al)
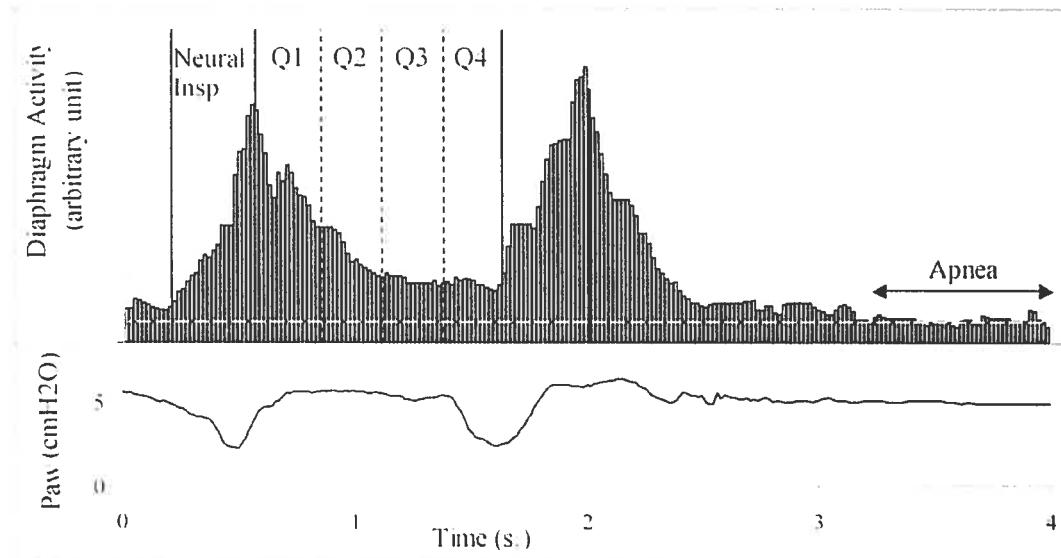
Figure 2. *Tracings of diaphragm activity and airway pressure.*

Representative tracings of diaphragm electrical activity (EAdi) and airway pressure (Paw) in four infants breathing on the prescribed ventilator settings.
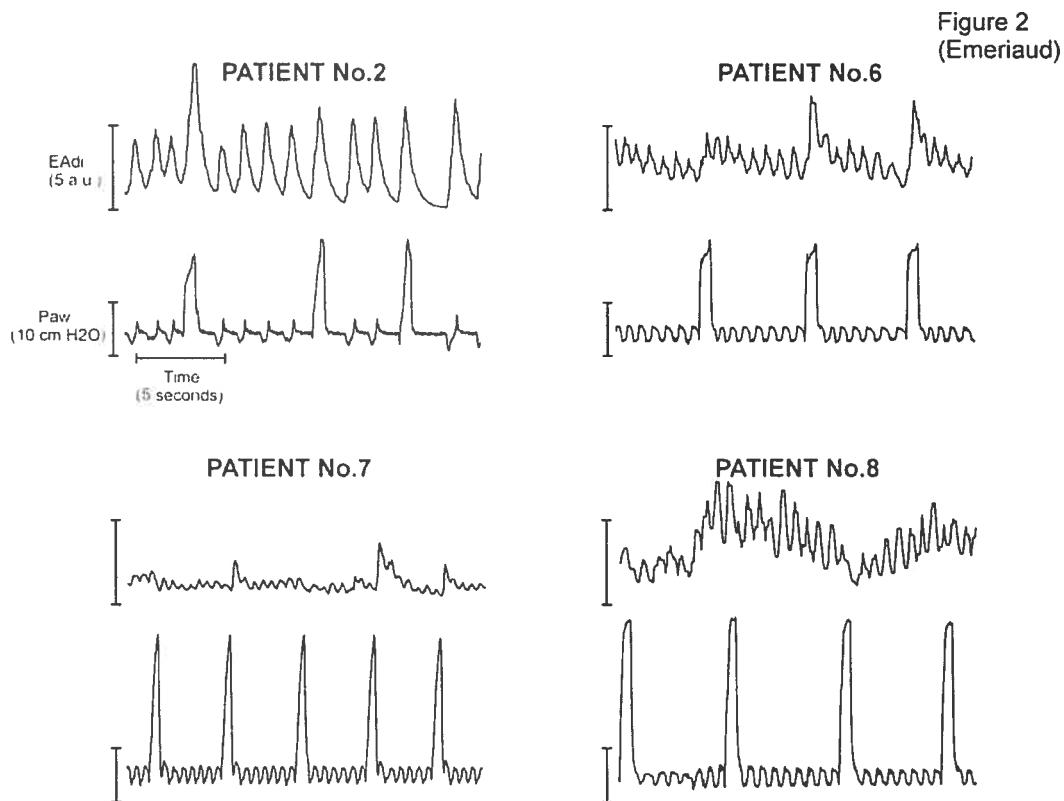
Figure 2
(Emeriaud)

Figure 3. *Group mean (± SD) diaphragm electrical activity during inspiration and the expiratory quartiles (n=16).*

Activity is expressed as a percentage of the mean inspiratory amplitude, after subtraction of noise level. All quartiles showed significant magnitudes above noise level ($p < 0.05$). No difference was observed between inspiratory EAdi and Q1, or between Q3 and Q4. *$p < 0.05$ = significant from Inspiration.

Figure 3
(Emeriaud)
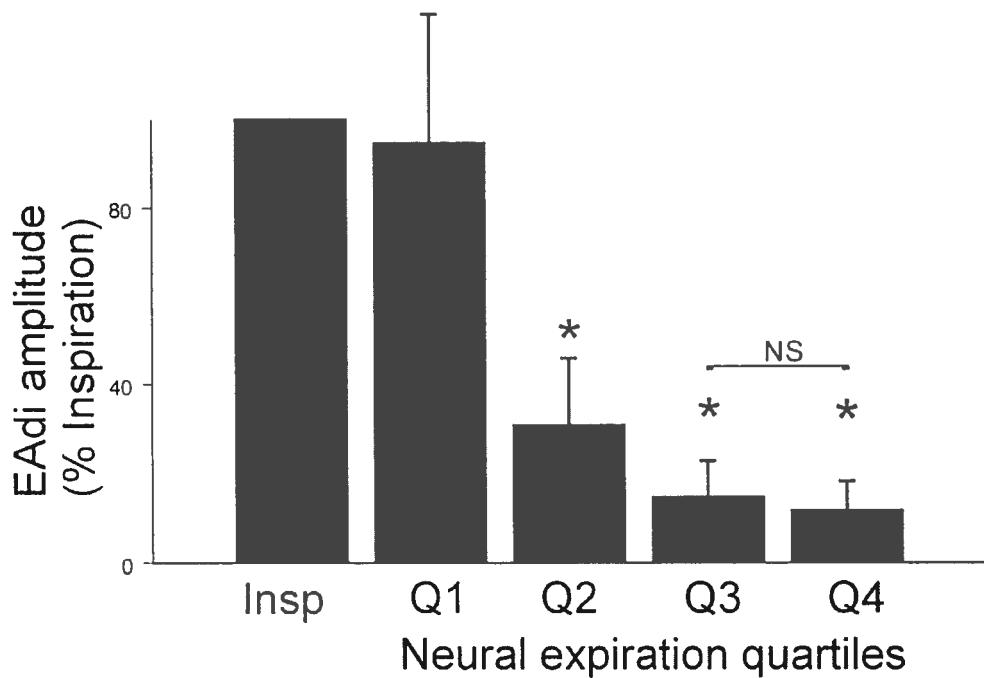
Figure 4. *Impact of ZEEP on tonic electrical activity of diaphragm (n=8).*
Tonic EAdi (combined Q3-Q4) was measured immediately before (black
rectangles), during (white rectangles), and after (grey rectangles) the
ZEEP period. Tonic EAdi significantly increased during the ZEEP period,
and decreased when PEEP was re-applied (p < 0.01).

Figure 4 (Emeriaud et al)
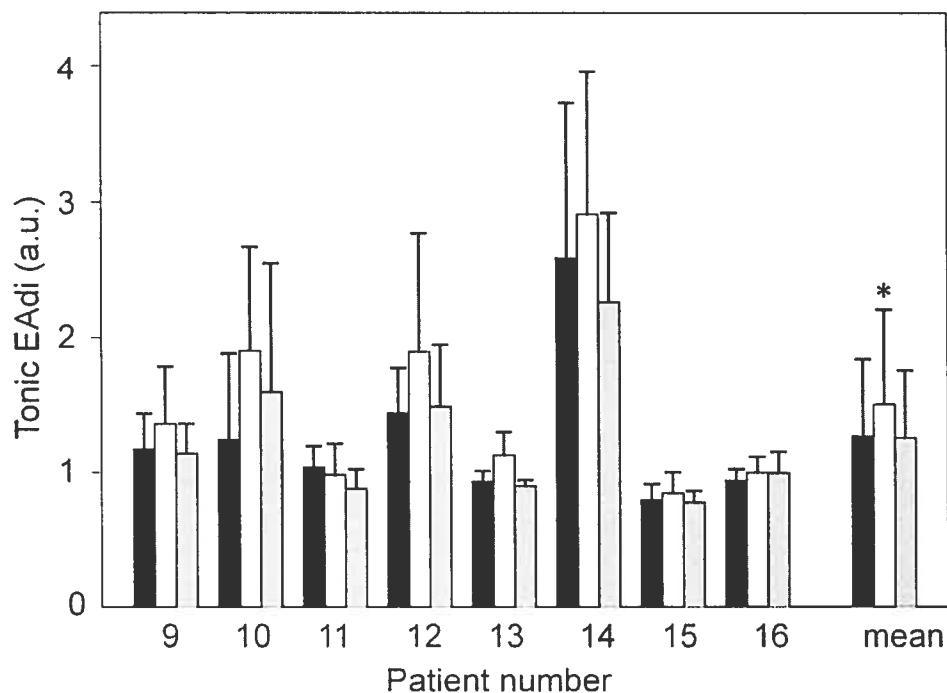
Figure 5. *Experimental record during prescribed PEEP, application of zero PEEP, and after prescribed PEEP was re-applied.*

Example in one infant of how removal of the prescribed PEEP resulted in an increase in the tonic activity of the diaphragm.

Figure 5
(Emeriaud et al)

Pre ZEEP   ZEEP   Post ZEEP

EAdi
(1 a.u.)

Paw
(5 cm H2O)

2 seconds
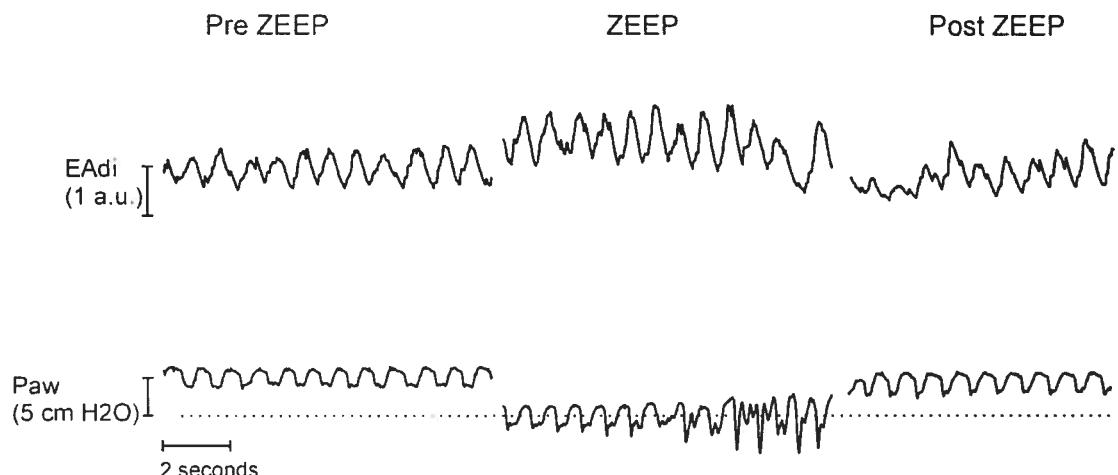
Table 1. *Patient anthropometrical data, ventilator settings, diagnosis, and tonic diaphragm activity* . EAdi are expressed as a percentage of EAdi observed during the pre-peak period, after subtraction of the noise level. GA = gestational age at birth

Patient	Diagnosis	Sex	GA at birth (weeks)	Age at study (mo)	Weight (kg)	SIMV rate	PEEP (cmH₂O)	Tonic EAdi (%)
1	Subglottic stenosis	M	29	4	3.7	5	5	3%
2	Bronchiolitis	F	35	2	2.9	10	3	5%
3	Bronchiolitis	M	39	2	5.6	10	3	26%
4	Head trauma	M	32	2.5	4.6	10	3	24%
5	Bronchiolitis	M	40	1	4.3	20	4	9%
6	Aspiration pneumonia	M	40	0.5	3.3	10	4	14%
7	Aspiration pneumonia	M	28	4	2.7	10	5	14%
8	Bronchiolitis	F	36	4	4	10	4	19%
9	Bronchiolitis	F	40	0.5	4.6	5	5	6%
10	Viral pneumonia	M	37	2	4.5	10	4	14%
11	Pierre-Robin syndrome	F	37	2	3.1	15	4	17%
12	Intestinal stenosis	M	35	3	4.2	5	3	10%
13	Enterocolitis	M	40	1	5.3	5	5	11%
14	Bronchiolitis	M	40	1.5	4.3	10	5	26%
15	Bronchiolitis	M	39	1	3.4	10	5	6%
16	Bronchiolitis	F	37	3.5	4.5	12	5	13%

Table 2: *Effects of ZEEP on neural breathing pattern (n=8)*

	Pre-ZEEP	ZEEP	Post-ZEEP	Significance (p<0.05)
Neural Ti (msec)	347 ± 65	329 ± 60	341 ± 57	ZEEP vs Pre-ZEEP
Neural Te (msec)	567 ± 102	516 ± 115	619 ± 149	ZEEP vs Post-ZEEP
Neural respiratory rate (per min)	66.6 ± 8.5	72.6 ± 11.1	64.4 ± 11.0	ZEEP vs Pre-ZEEP ZEEP vs Post-ZEEP
Inspiratory EAdi (a.u.)	3.45 ± 2.07	4.60 ± 3.51	3.68 ± 2.89	NS

Discussion générale

Résumé des principaux résultats

L'objectif global de notre travail était de mieux comprendre la façon dont les nourrissons contrôlent leur volume pulmonaire de fin d'expiration, notamment lorsqu'ils sont intubés et placés sous respirateur, et comment la ventilation artificielle interagit avec ce contrôle. Plus spécifiquement, les objectifs des travaux présentés dans le cadre de ce mémoire étaient (i) l'étude de la présence et la quantification du réflexe de Hering-Breuer chez le nourrisson sous ventilation artificielle et son interaction avec la ventilation assistée, (ii) de développer une méthode standardisée de quantification de l'activité tonique diaphragmatique, et (iii) de mesurer les variations de cette activité tonique lors de modifications du niveau de PEEP.

Dans le manuscrit 1, nous avons pu confirmer que les cycles ventilatoires administrés par le respirateur entraînent bien une augmentation du temps expiratoire du cycle correspondant, correspondant bien à la réponse expiratoire du réflexe de Hering-Breuer. Cette réponse est limitée à un cycle, et le cycle respiratoire suivant la respiration assistée reprend un profil identique au cycle précédant la respiration assistée. Par contre, il n'a pas pu être montré de modification de la phase inspiratoire du cycle (ni en durée, ni en puissance), ce qui va à l'encontre de l'hypothèse selon laquelle le diaphragme serait au repos lors des cycles avec assistance obligatoire. De même, cette étude a permis de confirmer un asynchronisme majeur entre les cycles respiratoires mesurés par l'activité diaphragmatique et les cycles du respirateur, correspondant en moyenne à plus de la moitié du temps.

Dans le manuscrit 2, nous avons établi une méthode de quantification standardisée de l'activité diaphragmatique au cours de l'expiration. Nous avons ainsi pu confirmer que 12-15 % de l'activité

diaphragmatique inspiratoire reste présente jusqu'à la fin de l'expiration. Cette activité tonique s'accroît encore lorsque la PEEP est supprimée, suggérant le fait que cette activité tonique est un des moyens utilisés chez le nourrisson pour éviter une chute de son volume pulmonaire de fin d'expiration.

Difficultés rencontrées et limites de l'étude

Caractérisation des différentes parties du cycle respiratoire

Une des difficultés principales rencontrées au début de ce travail provient de la difficulté d'identifier précisément le début de l'expiration sur l'enregistrement EMG des nourrissons. Contrairement aux enregistrements réalisés chez l'adulte, la transition inspiration-expiration est moins nette, comme l'illustrent les figures 1 des deux articles. Pour obtenir une identification de l'expiration la plus reproductible possible, nous avons établi la méthode des quartiles. Cette méthode nécessite d'identifier manuellement deux événements : le début et le pic d'activité inspiratoire. L'identification de ces événements est relativement aisée. Le partage en quartile de la période « pic-fin d'expiration » est automatique. Cette méthode est donc reproductible, comme nous avons pu le vérifier en retrouvant des coefficients de corrélation intraclasse > 0.75 pour les analyses réalisées par deux investigateurs différents.

Cette méthode est donc reproductible. Par contre, il est probable que l'activité du premier quartile soit en partie « contaminée » par de l'activité inspiratoire, comme le suggère la corrélation significative retrouvée entre l'activité de Q1 et l'activité inspiratoire. A l'inverse, la corrélation pour les quartiles suivants est beaucoup plus faible. Les deux derniers quartiles étant d'un niveau stable d'activité, nous avons choisi de ne retenir que ces deux quartiles pour quantifier l'activité tonique expiratoire, afin d'être certain que cette activité ne reflète que la période expiratoire.

Validité de l'activité électrique diaphragmatique mesurée durant l'expiration

Une des questions importantes issue de nos travaux est d'être certain que l'activité mesurée durant la période expiratoire correspond réellement à une activité diaphragmatique. La contamination du signal par une activité musculaire abdominale ou intercostale est en effet une des limites de l'EMG. Cette limite est essentiellement retrouvée avec les enregistrements de surface, et est négligeable avec l'EMG par voie oesophagienne (Sinderby 1996). Cependant, le nouveau-né étant plus petit, la proximité de ces muscles reste potentiellement problématique. La méthode de « cross correlation » nous a cependant permis de vérifier en permanence que l'activité mesurée est bien diaphragmatique (Beck 1996). Les signaux enregistrés par toutes les électrodes sont comparés 2 à 2 toutes les 16 ms, et seuls les signaux les plus fortement négativement corrélés (donc intense et de sens opposés) sont retenus, ces signaux correspondant donc au seul muscle situé entre les 2 électrodes retenues : le diaphragme. Ce profil de corrélation était retrouvé durant l'inspiration mais aussi durant toutes les parties de l'expiration, confirmant l'origine diaphragmatique du signal.

La méthode d'acquisition et de filtrage du signal explique probablement en grande partie les résultats contradictoires de notre étude par rapport aux résultats rapportés par Reis et al. (Reis 1994). En effet, ce dernier ne retrouvait pas d'activité diaphragmatique durant l'expiration, chez des nourrissons étudiés par voie oesophagienne. Cependant, l'activité était mesurée par une seule paire d'électrodes. Or, le diaphragme se déplaçant de façon importante chez le nourrisson au cours de la respiration (Laing 1988) et la distance muscle-éléctrode étant très influente sur la qualité du signal EMG (Beck 1995), il est probable qu'une seule paire d'électrodes ne peut mesurer l'activité du diaphragme à la fois durant l'inspiration et l'expiration. La technique que nous avons utilisé permet par contre de

garder une distance muscle-éléctrode stable tout au long du cycle respiratoire (Beck 1995, Beck 1996).

Cependant, notre étude ne permet pas d'établir avec certitude le rôle de l'activité tonique que nous avons mesurée. En effet, tous les enregistrements ont été réalisés chez des nourrissons intubés et ventilés. Plusieurs éléments ont donc pu modifier cette activité. Le tube endotrachéal crée une résistance à l'expiration, mais il supprime également la possibilité du freinage laryngé physiologique de l'expiration. Il est donc difficile de savoir si le fait d'être intubé modifie l'activité tonique. Pour répondre à cette question, il serait intéressant d'étudier l'activité tonique de nourrissons avant et après une extubation. Nous n'avons pas réalisé ces enregistrements, car le protocole ne le permettait pas. En effet, lors de la préparation de l'étude, nous n'avons pas voulu prendre le risque d'augmenter les difficultés respiratoires du nourrisson lors de l'extubation par la présence du matériel d'enregistrement. Le deuxième élément pouvant modifier l'activité tonique est la pathologie présentée par ces nourrissons. En effet, une activité tonique a été retrouvée chez l'adulte dans certaines pathologies, notamment lors de bronchoconstriciton. Le petit nombre d'enfants dans chaque groupe de pathologie rend difficile la comparaison de l'activité tonique en fonction de la pathologie dans notre étude. En outre, les enregistrements étaient réalisés juste avant l'extubation, et on peut penser que l'influence de la pathologie à cette période est faible. Avec ces limites, nous n'avons pas retrouvé de tendance de différence d'activité tonique selon la pathologie. Cependant, pour étudier vraiment cette implication, il faudrait réaliser une étude beaucoup plus large comparant deux groupes de pathologies. Enfin, l'activité tonique est probablement influencée par le niveau de capacité résiduelle fonctionnelle (CRF). En effet, notre hypothèse est que l'activité tonique est un des moyens de contrôle de la CRF. Nous avons pu apporter des éléments en faveur de ce rôle, en confirmant que l'activité tonique

augmente lors du retrait de la PEEP. Cependant, nous n'avons pas mesuré au cours de cette étude le niveau et les variations de la CRF. Il est probable que le retrait de la PEEP abaisse le niveau de CRF, cela ayant été rapporté dans la littérature (Thome 1998). Par contre, il est difficile de savoir si le niveau de CRF maintenu par les réglages du respirateur correspond à la CRF physiologique. Il serait intéressant de réaliser une étude mesurant en parallèle les variations de la PEEP, de la CRF, et de l'activité tonique expiratoire, afin de confirmer le rôle de régulation de cette dernière.

Implications cliniques

Les résultats des travaux présentés ici illustrent les difficultés de réaliser une ventilation assistée optimale : la ventilation assistée utilisée chez les nourrissons que nous avons enregistrés était en grande partie en asynchronisme avec le patient, et la persistance d'une activité tonique diaphragmatique laisse supposer que le nourrisson essaie d'élever activement son niveau de CRF, malgré les paramètres réglés (notamment le niveau de PEEP). Ces études illustrent également le fait qu'une ventilation assistée ajustée sur l'activité diaphragmatique pourrait garantir une meilleur synchronisation patient-respirateur. Un mode respiratoire utilisant ce principe (NAVA) va bientôt être commercialisé chez l'adulte, son intérêt en pédiatrie devrait évidemment être étudié. En outre, et avec toutes les limites que nous avons soulignées, l'activité diaphragmatique au cours de l'expiration pourrait être étudiée comme un reflet des efforts du patient pour maintenir la CRF, et donc pourrait servir de guide à l'ajustement de la PEEP, qui reste un des problèmes les plus difficiles de la ventilation assistée.

Conclusions

L'objectif global de notre travail était de mieux comprendre la façon dont les nourrissons contrôlent leur volume pulmonaire de fin d'expiration, notamment lorsqu'ils sont intubés et placés sous respirateur, et comment la ventilation artificielle interagit avec ce contrôle.

Dans un premier manuscrit, nous avons pu confirmer l'activation du réflexe de Hering-Breuer lors des cycles imposés par le respirateur et nous avons confirmé un asynchronisme majeur entre le respirateur et le patient. Dans le deuxième manuscrit, nous avons pu montrer que 12-15 % de l'activité diaphragmatique inspiratoire reste présente jusqu'à la fin de l'expiration. Cette activité tonique s'accroît lors de la suppression de la PEEP, suggérant que cette activité tonique est un des moyens utilisés par le nourrisson pour éviter une chute de son volume pulmonaire de fin d'expiration.

Dans l'ensemble, ces résultats illustrent d'un côté la grande sensibilité du nourrisson à la ventilation artificielle (dans le contrôle de l'EELV, comme dans les variations du temps expiratoire), et d'un autre côté les grandes difficultés à obtenir une ventilation optimale : synchronisée et à PEEP adaptée. Ces résultats confirment aussi que les progrès obtenus dans l'enregistrement EMG diaphragmatique par voie oesophagienne permettent de suivre au plus près l'activité diaphragmatique y compris chez ces petits patients. Cela permet d'envisager de futurs travaux pour tenter d'optimiser la ventilation artificielle de ces patients en se servant du signal diaphragmatique pour asservir le respirateur (NAVA pour neurally adjusted ventilatory assist), mais aussi pour guider le réglage de la PEEP.

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Accord des co-auteurs

1. **Identification de l'étudiant :**
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   Programme de Maîtrise en Sciences Biomédicales (M.Sc.), option
   recherche clinique biomédicale

2. **Articles :**

   **Prolonged Neural Expiratory Time Induced by Mechanical Ventilation
   in Infants.** J Beck, M Tucci, G Emeriaud, J Lacroix, and C Sinderby
   Pediatric Research 55: 747–754, 2004

   **Diaphragm Electrical Activity During Expiration in Mechanically
   Ventilated Infants.** G Emeriaud, J Beck, M Tucci, J Lacroix, and C
   Sinderby – Pediatric Research 59: 705–710, 2006

3. **Déclarations des co-auteurs :**

A titre de co-auteurs des articles identifiés ci-dessus, je suis d'accord pour que

Guillaume Emeriaud inclue ces articles dans son mémoire de maîtrise qui a pour

titre : Rôle du diaphragme au cours de l'expiration chez l'enfant sous ventilation

mécanique.
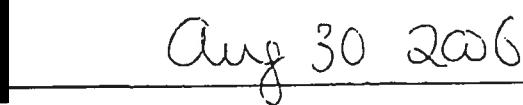
Jennifer Beck   Signature   Aug 30 2006
                                                            Date
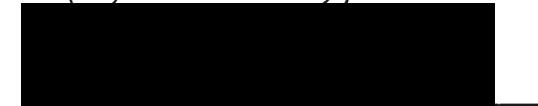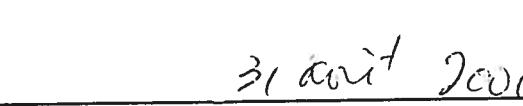
Marisa Tucci   Signature   31 août 2006
                                                            Date

Jacques Lacroix   Signature   31 août 2006
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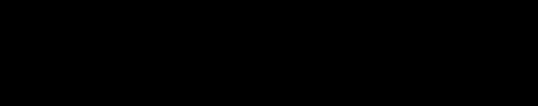
Christer Sinderby   Signature   Aug 30 2006
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